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Synthesis and properties of 3-aminodihydroisoquinolines

L M Potikha, V A Kovtunenko

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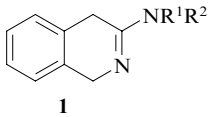
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Abstract. The present review highlights methods for the synthesis of partially hydrogenated 3-aminoisoquinolines and fused heterocyclic systems based on these derivatives. The chemical properties of these compounds are analyzed; in particular, the reactions with electrophilic and nucleophilic agents, oxidation and reduction are considered The bibliography includes 82 references.

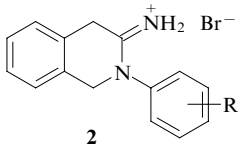
I. Introduction

Isoquinoline derivatives have attracted keen interest because of diverse biological properties. For example, the known alkaloids papaverine and (+)-tubocurarine found in several plants are widely used as a spasmolytic agent and a myorelaxant, respectively. Partially hydrogenated isoquinolines are important group of compounds. For example, fused 1,2,3,4-tetrahydroisoquinoline derivatives, such as benzquinamide, tetrabenazine and butaclamol, are used in clinical practice as neuroleptics; clazolam, as an anxiolytic agent; tofetridine, as an analgesic agent.

According to calculations using the PASS and DRAGON programmes, most of partially hydrogenated 3-aminoisoquinolines should be biologically active. Detailed biological studies were carried out for some of these heterocycles. Thus compounds **1** and **2** exhibit a wide spectrum of neurotropic and antiarrhythmic activities [1] and have a hypotensive effect.[1–4] Compounds **2** were found to be efficient diuretics [4] and antibacterial agents.[4,5] β-Adrenergic effects are observed when these compounds are used at high doses.



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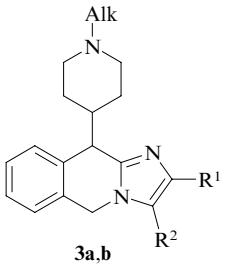


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Compounds **1** (Ref. 6) and **3a**,**b** (Refs 7–9) are histamine H_1 receptor antagonists, and they not only act as antiallergenic agents, but also reduce intracranial pressure.

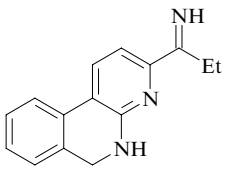


3a,**b**

$R^1 = R^2 = H$ (**a**), $R^1 - R^2$ is benzo (**b**).

Partially hydrogenated derivatives are recommended [7–9] as remedies for the reduction of intracranial pressure and the treatment of secondary anemia caused by traumatic brain injury. A comparative assay showed that the activity level of compounds **3a**,**b** is comparable with that of the known histamine H_2 receptor antagonists, *viz*., cimetidine, *etc*.[8] Compounds **3a**,**b** can reduce the effects of tachykinins on the behavioural processes and hormonal regulation and can influence the release of physiologically active substances.[10] According to the patent,[11] these drugs are poorly absorbed into the gastrointestinal tract although they have a valuable ability [12] to modulate the resistance of tumour cells to cytotoxic agents.

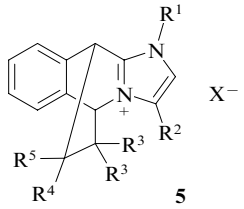
Compound **4** inhibits the neuronal and inducible isoforms of NO synthase (NOS).[13] This enzyme produces nitrogen monoxide as an important mediator of the central nervous system from the guanidine fragment of L-arginine.



4

Cage compounds **5** have affinity for the phencyclidine-binding site of NMDA receptors and are allosteric non-competitive blockers of the effects of stimulating amino

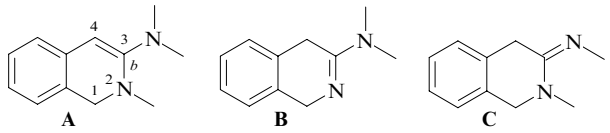
acids. This class of drugs was proposed for the prophylaxis of disorders associated with neuronal degeneration and the treatment of diseases, such as Parkinson's, Huntington's and Alzheimer's diseases, the Down syndrome, amyotrophic lateral sclerosis and other dementias.[14–16]



5

The present review is a continuation of our previous review[17] on the chemistry of 3-aminoisoquinolines. The review highlights methods of synthesis and properties of partially hydrogenated derivatives, *viz*., 3-amino-1,2- and 3-amino-1,4-dihydroisoquinolines. Since reviews on the chemistry of these systems are lacking, we analyze all available data on this topic.

A characteristic feature of these compounds is that they contain the 2-phenylethylene-1,1-diamine (structure **A**) or phenylacetamidine (structures **B** and **C**) fragment responsible for their chemical properties.



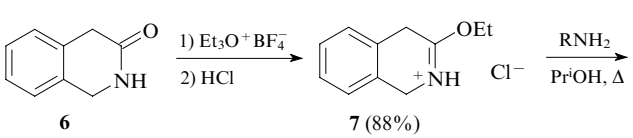
We also consider fused heterocyclic systems based on 3-amino-1,2-dihydroisoquinoline (**A**), 3-amino-1,4-dihydroisoquinoline (**B**) and 1,4-dihydroisoquinoline-3(2*H*)-imine (**C**). The schemes of the construction of the heterocyclic core are classified according to the bond type formed in the final step of the synthesis and the nature of the starting reagents.

II. Methods of synthesis of 3-aminodihydroisoquinolines

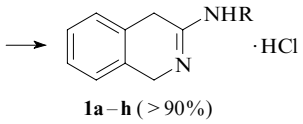
There are two main approaches to the synthesis of 3-aminodihydroisoquinoline derivatives, *viz*., modifications of substituents in the isoquinoline core and cyclization reactions resulting in the dihydropyridine ring.

1. Amination of isoquinoline derivatives

1,4-Dihydroisoquinolin-3(2*H*)-one (**6**) is the simplest and most readily available precursor in the synthesis of 3-aminodihydroisoquinolines. Compound **6** can be synthesized in one step from indan-2-one by the Schmidt reaction.[18] Lactam **6** is transformed into 3-amino-1,4-dihydroisoquinolines **1a**–**r** *via* 3-alkoxy or 3-methylthio derivatives. Thus the reaction of 3-ethoxy-1,4-dihydroisoquinoline hydrochloride (**7**) with an equimolar amount of primary aliphatic amines in refluxing polar solvents affords 3-alkylamino-1,4-



6 **7** (88%)

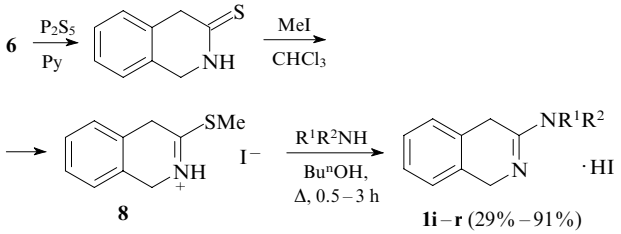


1a–**h** (> 90%)

R = $(CH_2)_2NMe_2$ (**a**), $(CH_2)_2NEt_2$ (**b**), $(CH_2)_2NHMe$ (**c**), $(CH_2)_2NHEt$ (**d**), $(CH_2)_3NEt_2$ (**e**), $(CH_2)_3NHMe$ (**f**), $(CH_2)_3NHEt$ (**g**), cyclo-C_3H_5 (**h**).

dihydroisoquinoline hydrochlorides **1a**–**h** in high yields (> 90%) as a result of nucleophilic substitution.[1–3]

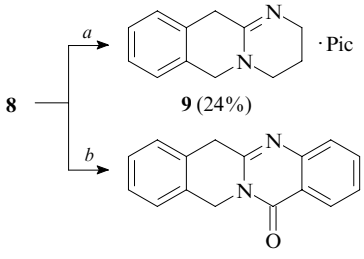
3-Methylthio-1,4-dihydroisoquinoline hydroiodide (**8**) reacts with ammonia and simplest alkylamines at room temperature; however, this reaction requires a 10-fold excess of amines.[11] Products **1p**,**q** were prepared in high yields by the reactions with aromatic amines using an equimolar ratio of the reactants.[11]



8 **1i**–**r** (29%–91%)

R^1 = H: R^2 = H (**i**), Me (**j**), Et (**k**), Pr^i (**l**), Bu^n (**m**), Bn (**n**), $(CH_2)_2Ph$ (**o**), Ph (**p**), 1-naphthyl (**q**); R^1–R^2 = $(CH_2)_2O(CH_2)_2$ (**r**).

3-Amino-1,4-dihydroisoquinoline derivatives fused at the bond *b* can be synthesized according to the same scheme. The reaction of salt **8** with 3-chloropropylamine affords 3,4,6,11-tetrahydro-(2*H*)-pyrimido[1,2-*b*]isoquinoline (**9**) isolated as picrate; the reaction with sodium anthranilate produces 6,11-dihydroisoquino[3,2-*b*]quinazolin-13(13*H*)-one (**10a**).[4]

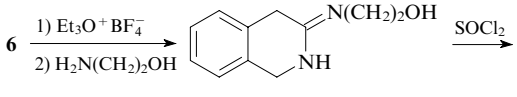


9 (24%)

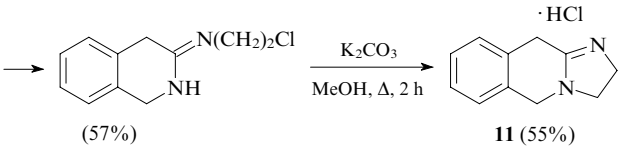
10a (82%)

(*a*) (1) $H_2N(CH_2)_3Cl$, 1 N NaOH in EtOH, Δ, 1 h; (2) picric acid (Pic); (*b*) 4-$H_2NC_6H_4CO_2^-Na^+$, EtOH, Δ, 1 h.

2,3,5,10-Tetrahydroimidazo[1,2-*b*]isoquinoline (**11**) was synthesized from lactam **6** in a similar way.[19] The reaction product of 3-ethoxy-1,4-dihydroisoquinoline (**7**) with ethanolamine exists in the tautomeric form of 1,4-dihydroisoquinoline-3(2*H*)-imine (**12**), which was confirmed by spectroscopic methods.

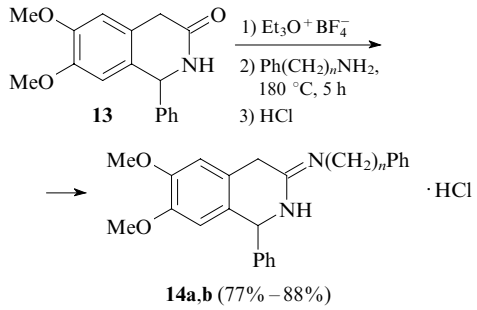


12 (48%)



(57%) **11** (55%)

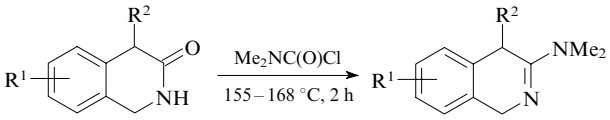
The reaction of 1-phenylisoquinolinone **13** with alkylamines can be performed only under drastic conditions (by fusing a mixture of the reactants). As a result, amino derivatives of 1-phenyl-1,4-dihydroisoquinoline-3(2*H*)-imine **14a**,**b** were prepared in high yields.[20]



13 **14a**,**b** (77%–88%)

n = 1 (**a**), 2 (**b**).

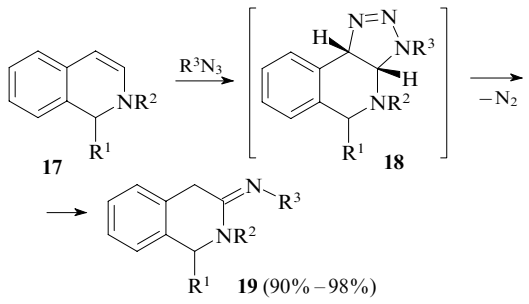
The one-pot synthesis of 3-(dimethylamino)dihydroisoquinolines **15a**–**e** was documented.[6,21] These compounds were obtained as hydrochlorides by heating lactams **16a**–**e** with *N*,*N*-dimethylcarbamoyl chloride.



16a–**e** **15a**–**e**

R^1 = H: R^2 = H (**a**), 4-ClC_6H_4 (**b**), 4-FC_6H_4 (**c**);
R^2 = 2-ClC_6H_4: R^1 = 5-OMe (**d**), 7-OMe (**e**).

The amino group can be introduced in position 3 of dihydroisoquinolines **17** also using aryl, acyl, arylsulfonyl or diarylphosphoryl azides.[22,23] In the first step, azide is attached as a 1,3-dipole at the C(3)–C(4) double bond of a heterocyclic enamine to form 3*a*,4,5,9*b*-tetrahydro-(3*H*)-1,2,3-triazolo[4,5-*c*]isoquinolines **18**. The reaction with 4-nitrophenyl azide proceeds under mild conditions (Et_2O, 0 °C, 1 h), and intermediates **18** can be isolated in the pure form.[22] In the case of other azides, it is necessary to keep a mixture of the reactants at room temperature for 4 h. The

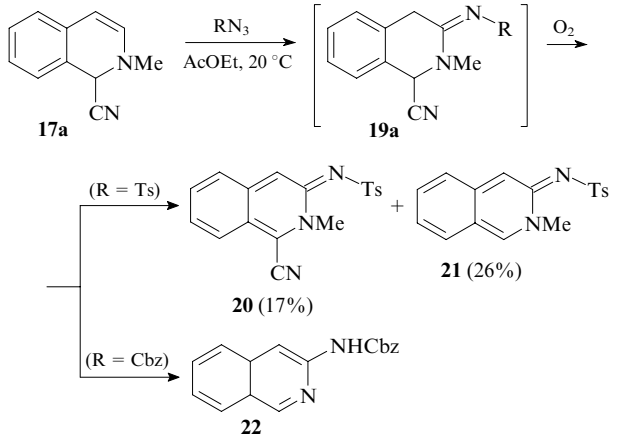


17 **18** **19** (90%–98%)

R^1 = H, Me, Et, Pr^i, Ph; R^2 = Me, Et, Pr^i; R^3 = 4-$O_2NC_6H_4$, 4-$O_2NC_6H_4C(O)$, $(PhO)_2P(O)$, (4-$MeC_6H_4O)_2P(O)$.

conditions for further transformations of compounds **18** into 1,4-dihydroisoquinoline-3(2*H*)-imine derivatives **19** depend on the nature of the azide.

This method has certain limitations. Thus the reaction of dihydroisoquinoline containing electron-withdrawing substituents (**17a**; R^1 = CN, R^2 = Me) with azides is accompanied by aromatization.[23] In this reaction, the electron-withdrawing group either remains intact (compound **20**) or is eliminated (compounds **21** and **22**).

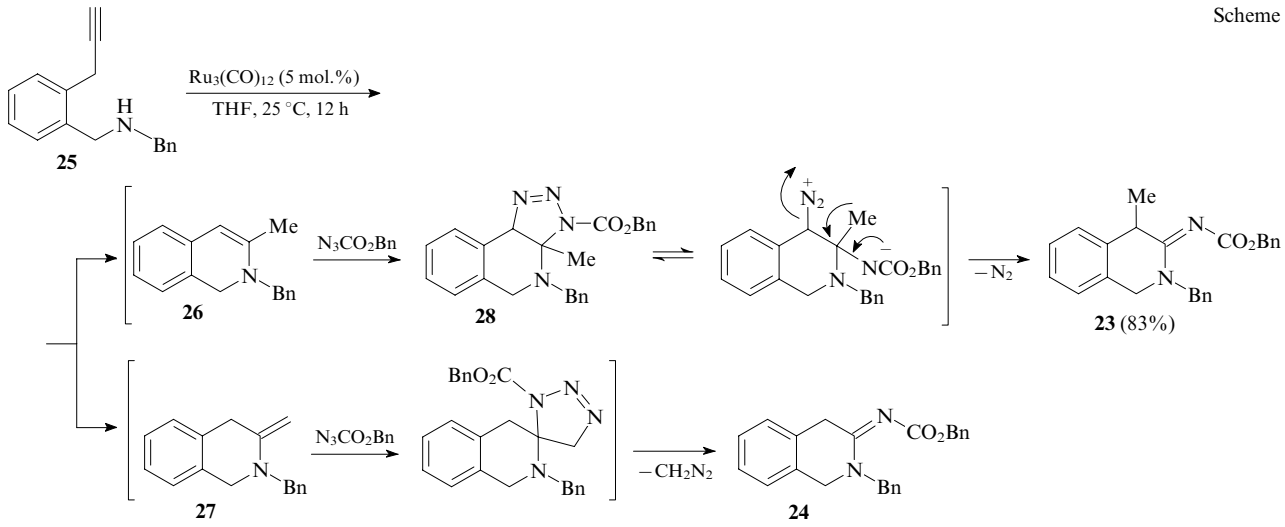


17a **19a** **20** (17%) **21** (26%) **22**

R = Cbz (benzyloxycarbonyl), Ts (*p*-toluenesulfonyl).

The rearrangement in triazolines is the key step in the synthesis of 2-benzyl-1,4-dihydroisoquinolin-3(2*H*)-ylidenecarbamates **23** and **24** (**23**:**24** > 25:1) from substituted dibenzylamine **25**. The reaction of the latter with benzyloxycarbonyl azide proceeds in the presence of a ruthenium complex (Scheme 1).[24] The metal-catalyzed intramolecular

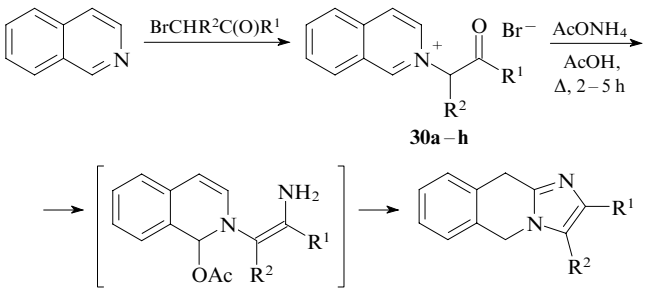
Scheme 1



25 **26** **28** **23** (83%) **27** **24**

hydroamination of compound **25** affords a mixture of enamines **26** and **27**. The azide reacts predominantly with *endo*-adduct **26**. The rearrangement of the resulting triazoline **28** is accompanied by the migration of the methyl group to give 4-methyldihydroisoquinoline **23**. The transformation of *exo*-adduct **27** gives rise to unsubstituted minor product **24**.

The synthesis of 2-aryl-5,10-dihydroimidazo[1,2-*b*]isoquinolines **29a–h** was based on the ability of quaternary isoquinolinium salts to add nucleophiles.[25–28] Thus heating of 2-phenacylisoquinolinium bromides **30a–h** with ammonium acetate in acetic acid affords tricyclic compounds **29** in moderate yields.



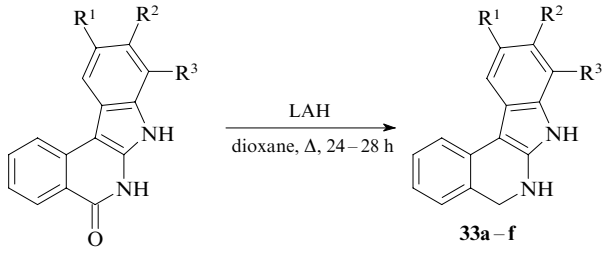
30a–h **31a–h** **29a–h** (17%–49%)

R^2 = H: R^1 = Ph (**a**), 4-BrC_6H_4 (**b**), 4-ClC_6H_4 (**c**), 4-$MeOC_6H_4$ (**d**); R^2 = Ph: R^1 = Ph (**e**), 4-$MeOC_6H_4$ (**f**); R^1 = R^2 = 4-ClC_6H_4 (**g**), 4-$MeOC_6H_4$ (**h**).

It was shown [25] that the reaction mechanism involves the intramolecular amination of intermediate 1,2-dihydroisoquinoline **31** produced upon nucleophilic addition of the acetate ion to salt **30**. Compounds **29a–h** exhibit moderate fungicidal activity.[27]

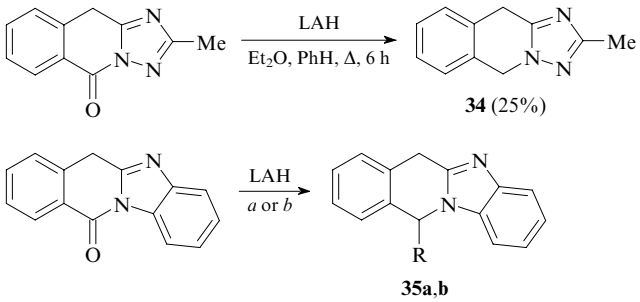
2. Reduction of 3-aminoisocarbostyryls and addition of nucleophiles to 3-aminoisoquinolinium salts

One of the methods for the synthesis of 3-aminodihydroisoquinoline derivatives is based on the reduction of more readily available aromatic or oxo-substituted isoquinolines. For example, the carbonyl group in 3-aminoisocarbostyryls **32** is readily reduced with $LiAlH_4$ (LAH) in non-polar solvents or dioxane. This reaction was used to prepare a series of fused 3-aminodihydroisoquinolines, such as 6,7-dihydro-(5*H*)-indolo[2,3-*c*]isoquinolines (**33a–e**),[29] 6,7-dihydro-(5*H*)-benzo[6,7]indolo[2,3-*c*]isoquinoline (**33f**),[29] 2-methyl-5,10-dihydro-1,2,4-triazolo[1,5-*b*]isoquinoline (**34**)[30] and 7,13*b*-dihydro-(3*H*)-benzimidazo[2,1-*a*]benzo[*de*]isoquinoline (**35a**).[31,32] Under milder conditions, alcohol **35b** was isolated instead of compound **35a**.[32]



32a–f **33a–f**

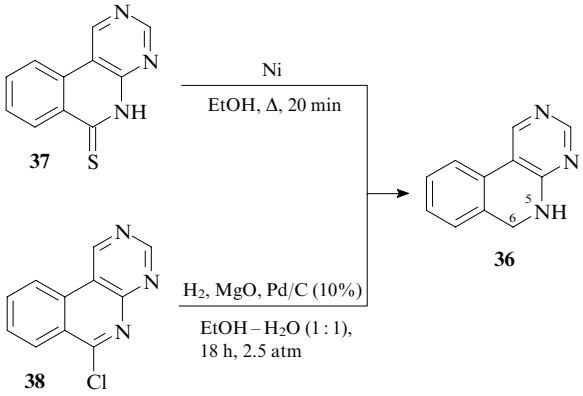
R^2 = R^3 = H: R^1 = H (**a**), Me (**b**), Cl (**c**), Br (**d**), OMe (**e**); R^1 = H, R^2–R^3 is benzo (**f**).



34 (25%) **35a,b**

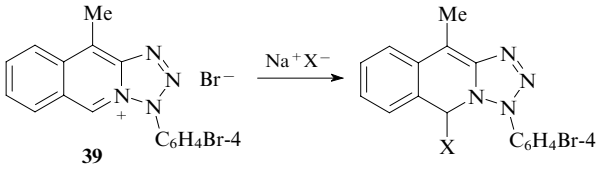
(*a*) dioxane, PhH, Δ, 5 h [for R = H (**a**), yield 93%]; (*b*) Et_2O, PhMe, 25 °C [for R = OH (**b**), yield 37%].

In the framework of the search for new antitumour drugs based on benzo[*f*]quinazoline, methods for the synthesis of 5,6-dihydropyrimido[4,5-*c*]isoquinoline (**36**) were developed.[33] Compound **36** is a convenient precursor for the synthesis of 6-unsubstituted benzo[*f*]quinazoline. The desulfurization of the corresponding thione **37** on the Davison sponge nickel catalyst affords compound **36** in moderate yield (41%). A somewhat higher yield of product **36** (58%) was achieved by the catalytic hydrogenation of 6-chloropyrimido[4,5-*c*]isoquinoline (**38**).



37 **38** **36**

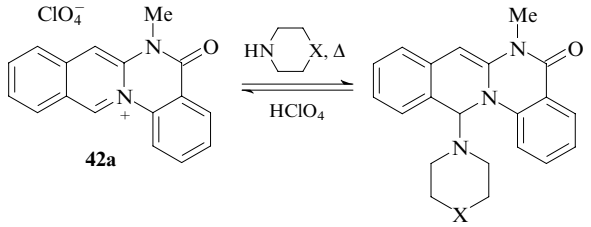
Nucleophiles readily add to isoquinolinium salts at position 1. This method was used to synthesize dihydro derivatives **40a–d** from 1,2,3,4-tetrazolo[1,5-*b*]isoquinolinium bromide **39**, which was prepared in several steps from 3-amino-4-methylisoquinoline.[34]



39 **40a–d** (47%–76%)

X = MeO (**a**), EtO (**b**), EtS (**c**), Bu^{t}S (**d**).

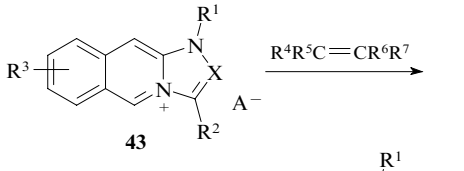
A similar scheme provides the basis for the synthesis of 12-amino-6-methyl-6,12-dihydroisoquino[2,3-*a*]quinazolin-5(5*H*)-ones **41a,b**, which are inaccessible by other methods.[35] Morpholine and piperidine reversibly add to the aromatic system of isoquino[2,3-*a*]quinazolinium **42a** on heating. In an acidic medium, compounds **41a,b** are unstable and easily lose amine.



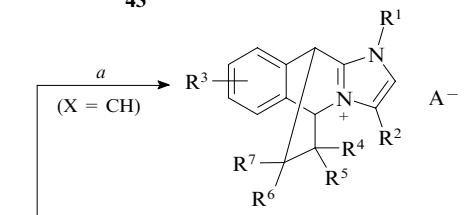
42a **41a**,**b** (33%–41%)

X = O (**41a**), CH_2 (**41b**).

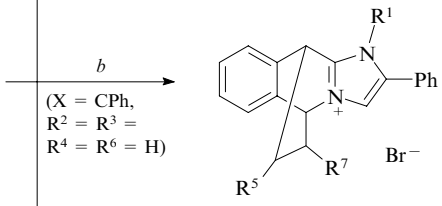
Structure–activity relationships for a new class of NMDA receptor antagonists were studied on a series of derivatives of hetero[*b*]isoquinolinium cations **43** and **44** synthesized from acridizinium salts.[14–16] Salts **43** and **44** give polycyclic derivatives **5** and **45**–**48** as cycloaddition products with reactive electron-rich alkenes.[36]



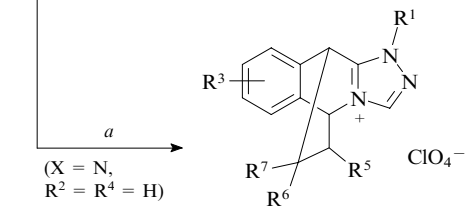
43



5 (R^1 = Alk, $ArCH_2$; R^2 = H, MeO; R^3 = H, 8-CF_3, 8-CCl_3; R^4 = H, Me; R^4–R^5 = CH_2; R^6, R^7 = AlkO, Ar, Het; R^5–R^6 = CH_2Arylene, CH_2Hetarylene)

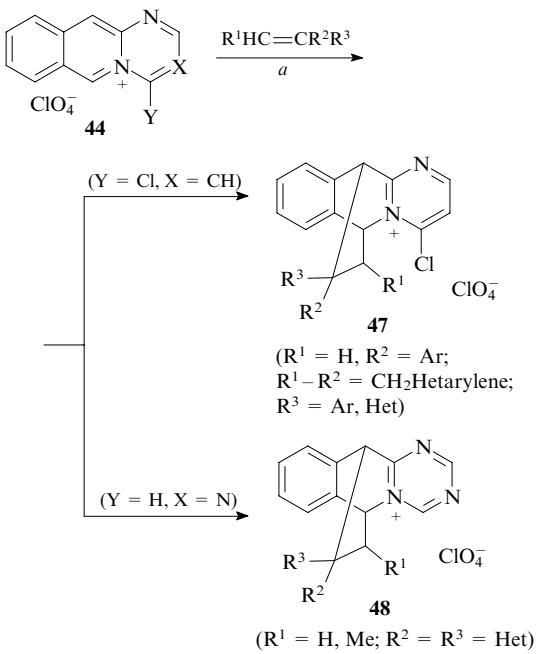


45 (R^1 = Ph, 3-$CF_3C_6H_4$; R^5–R^7 = $CH_2CH{=}CH$; R^7 = H, R^5 is carbazol-9-yl)



46 (R^1 = Me, $ArCH_2$, R^3 = H, F, NO_2, NHAc; R^5 = H; R^6 = Ar, Het; R^5–R^6 = $CH_2C_6H_4$)

(*a*) MeCN or $MeNO_2$, N_2 or Ar, Δ, 8–48 h;
(*b*) MeCN, MeOH, 50–65 °C, 10–12 h; A = PF_6, ClO_4, Cl, Br.



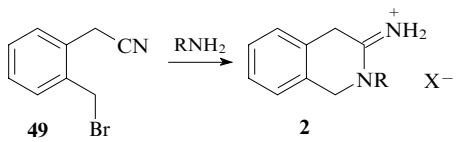
44 **47** (R^1 = H, R^2 = Ar; R^1–R^2 = CH_2Hetarylene; R^3 = Ar, Het) **48** (R^1 = H, Me; R^2 = R^3 = Het)

(*a*) MeCN or $MeNO_2$, N_2 or Ar, Δ, 8–48 h.

The structure of products **45** was proposed[36] based on the authors' experience and experience of other researchers who studied the properties of acridizinium salts. More recently,[14–16] these results were confirmed by spectroscopic studies of derivatives **46**–**48**. Salts **43** and **44** can be synthesized in several steps from the corresponding heterocyclic aldehydes[14–16] or in one step by the reaction of 3-chloro-2-phenacylisoquinolinium salts with anilines.[36] The resulting 3-amino-1,4-dihydroisoquinolinium derivatives **5** were suggested as selective antagonists of the phencyclidine-binding site of NMDA receptors.[16] Compounds **46**–**48** were covered by patents as drugs for treating or preventing neurodegenerative disorders.[14,15]

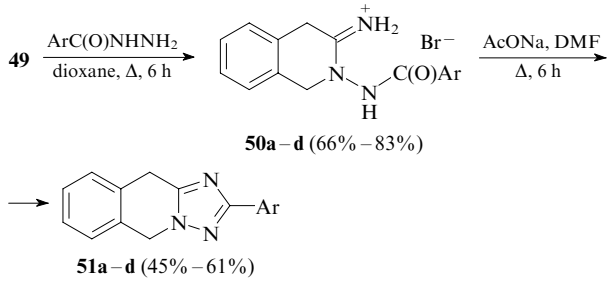
3. Cyclization of (2-bromomethylphenyl)acetonitrile and its derivatives

The main methods for the synthesis of fused 3-aminoisoquinoline derivatives are based on different types of cyclization reactions resulting in the formation of the pyridine ring. The most popular method of heterocyclization involves the introduction of the nitrogen atom into the five-carbon chain (5 C + N). In the majority of cases, (2-bromomethylphenyl)acetonitrile (**49**) is used as a rather simple and readily available synthon to this end. When heated with primary aliphatic or aromatic amines in polar solvents, nitrile **49** gives salts of 2-substituted 1,4-dihydroisoquinoline-3(2*H*)-imines **2**.[5,37] The reaction proceeds most efficiently with less basic arylamines $Y_nC_6H_{4-n}NH_2$ (Y = H, 4-Br, 4-O_2N, 3-O_2N, 2-Cl or 2,6-Cl_2). The reactions of nitrile **49** with alkylamines and basic arylamines (Y = Me or MeO) produce mixtures of cyclic compounds **2** and alkylation products of amines. Hence, additional heating of the reaction mixtures is required to increase the yields of compounds **2**.



R	X	Conditions	Yields (%)
cyclo-C_6H_{11} (Cy), Bn	Br	1) Pr^iOH, Δ, 2 h; 2) 180–190 °C, 0.5 h	20–27
$Y_nC_6H_{4-n}$ (Y = H, 4-Br, 4-O_2N, 3-O_2N, 2-Cl, 2,6-Cl_2)	Br	Pr^iOH, Δ, 2 h	15–68
4-MeC_6H_4, 4-$MeOC_6H_4$	Br	Pr^iOH, Δ, 5 h	28–33
2-MeC_6H_4	ClO_4	1) Pr^iOH, Δ, 2 h; 2) $NaClO_4$, EtOH, Δ	12

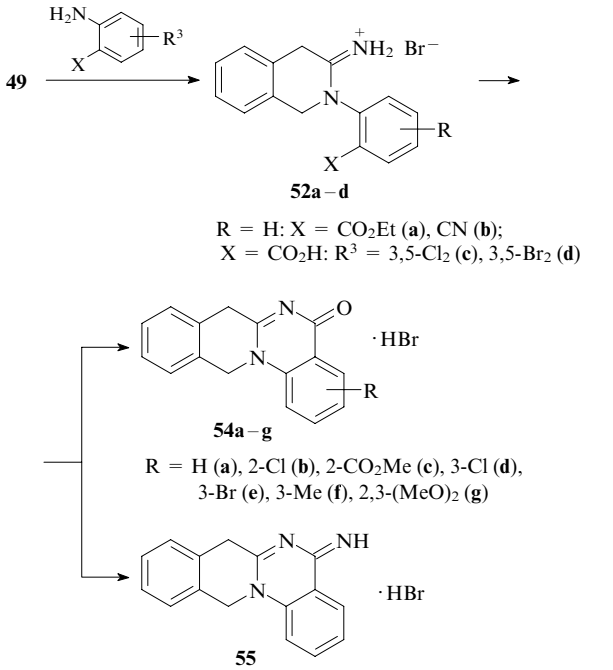
The condensation of nitrile **49** with benzohydrazides affords 2-arylcarboxamido-1,4-dihydroisoquinoline-3(2*H*)-imine hydrobromides **50a–d** in high yields.[38] Upon heating in the presence of AcONa, the latter compounds readily undergo cyclization to 2-aryl-5,10-dihydro-1,2,4-triazolo[1,5-*b*]isoquinolines **51a–d**.[38] This reaction can be performed without isolation of compounds **50** (refluxing in dioxane in the presence of AcONa for 13 h).



Ar = Ph (**a**), 3-BrC_6H_4 (**b**), 2-HOC_6H_4 (**c**), 2-HO-5-BrC_6H_3 (**d**).

The reactions of nitrile **49** with anthranilic acid and its derivatives[39–43] and with 2-aminobenzophenones proceed similarly (Schemes 2 and 3).[44] The possibility of isolation of unstable 2-aryl-1,4-dihydroisoquinoline-3(2*H*)-imine derivatives **52a–d** and **53a–c** is determined by the nature of substituents in the 2-aryl fragment. Thus weakly electrophilic substituents X and the presence of additional *ortho* substituents result in a decrease in the ability of compounds **52** and **53** to undergo intramolecular cyclization to give 7,12-dihydroisoquino[2,3-*a*]quinazoline derivatives **54–56**. Fused products **54a–g**[39,42] and **55**[40,41] are formed under drastic conditions: upon fusion or prolonged heating of the reactants in polar solvents. 5-Arylisoquino[2,3-*a*]quinazolinium salts **56a–c** were prepared only upon heating of compounds **53a–c** in the presence of perchloric acid.[44]

Scheme 2

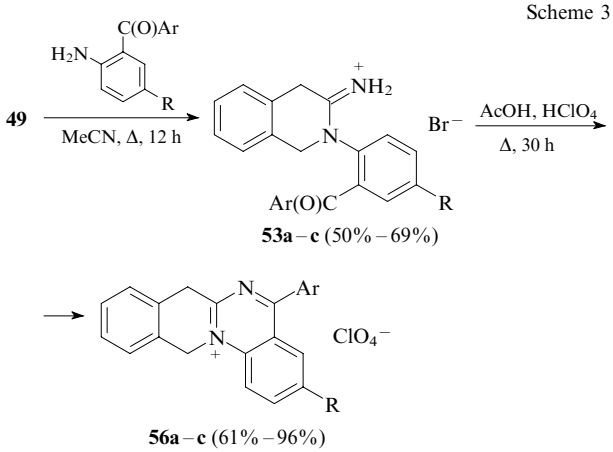


R = H: X = CO_2Et (**a**), CN (**b**); X = CO_2H: R^3 = 3,5-Cl_2 (**c**), 3,5-Br_2 (**d**)

R = H (**a**), 2-Cl (**b**), 2-CO_2Me (**c**), 3-Cl (**d**), 3-Br (**e**), 3-Me (**f**), 2,3-$(MeO)_2$ (**g**)

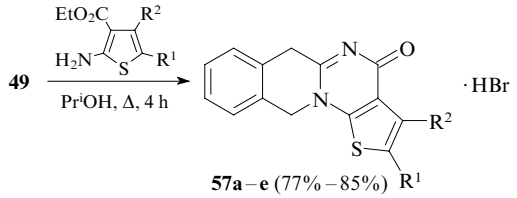
Starting compound	Product	X	Conditions	Yields (%)
49	**52a**	CO_2Et	1) AcOH, Pr^iOH, Δ, 3 h; 2) HBr, Pr^iOH, 50–56 °C, 3 h	32
	52b	CN	Pr^iOH, Δ, 1 h	34
	52c,d	CO_2H	120–140 °C, 3 h	55–60
49	**54a–g**	CO_2H, CO_2Me, CO_2Et	Pr^iOH, Δ, 10–12 h	28–71
	54b,d–f	CO_2H	130–150 °C, 4 h	59–70
	54a	CO_2Et	120–130 °C, 8 h	71
49	**55**	CN	130 °C, 8 h	46
			$MeNO_2$, Δ, 1 h	49
52a	**54a**	CO_2Et	Pr^iOH, Δ, 1 h	58
52b	**55**	CN	Pr^iOH, Δ, 1 h	42

Scheme 3



R = Cl, Ar = Ph (**a**); R = Br: Ar = 4-BrC_6H_4 (**b**), 4-$O_2NC_6H_4$ (**c**).

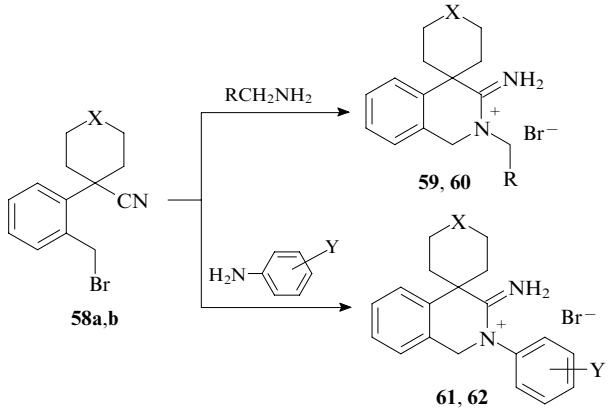
Reactions of 2-aminothiophene-3-carboxylates with nitrile **49** directly afford fused products, *viz*., 6,11-dihydrothieno[3′,2′:5,6]pyrimido[1,2-*b*]isoquinolin-4(4*H*)-one hydrobromides **57a**–**e**.[45] In this case, intermediates **2** could not be isolated.



R^1–R^2 = $(CH_2)_3$ (**a**), $(CH_2)_4$ (**b**); R^1 = R^2 = Me (**c**); R^1 = Et, R^2 = H (**d**); R^1 = H, R^2 = Ph (**e**).

Methods of structural modifications of nitrile **49** were developed[46,47] with the aim of preparing potential biologically active isoquinoline derivatives spiro-fused at position 4. The methylene group of the cyanomethyl fragment was incorporated into the polymethylene chain of cyclopentane or tetrahydropyran. Compounds **58a**,**b** were synthesized by cycloalkylation of (2-methylphenyl)acetonitrile followed by bromination of the corresponding spiro products and coupling with aliphatic and aromatic amines (Scheme 4).

Scheme 4

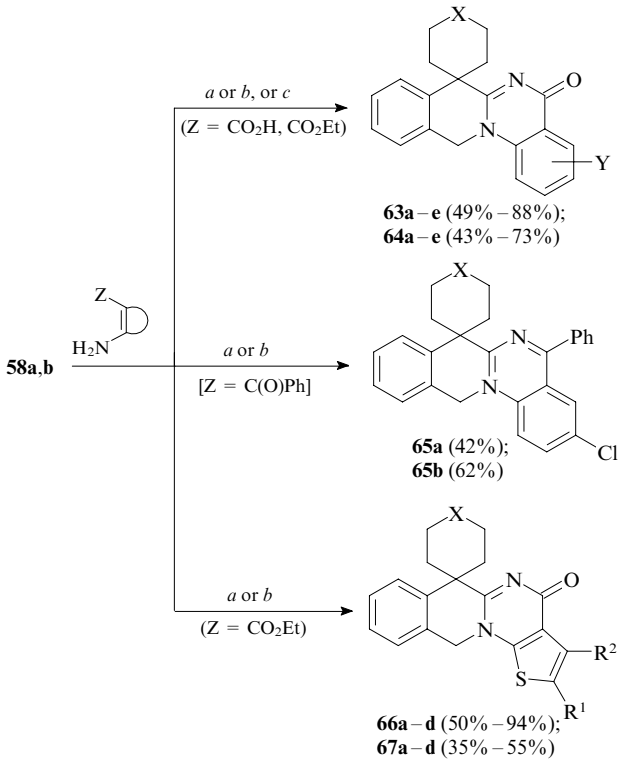


X is absent (**58a**), X = O (**58b**).

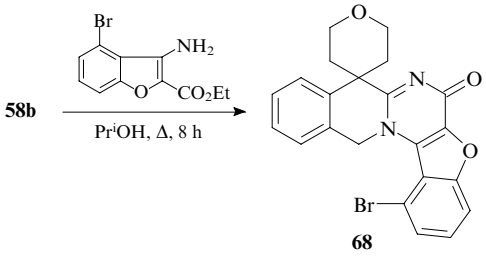
Product	X	R or Y	Conditions	Yields (%)
59	–	Ph, Pr^n, 2-Fu	dioxane, Δ, 8 h	55–93
60	O	Ph, Bu^n	Pr^iOH, Δ, 8 h	60–72
61	–	H, 4-MeO, 4-Me, 2-Cl, 3-Cl, 4-Br, 4-Ac, 3-NO_2, 4-NO_2, 3-F, 4-CO_2Et	dioxane, Δ, 8 h	40–83
62	O	H, 4-MeO, 2-MeO, 4-Me, 2-Cl, 3-Cl, 4-Br, 4-Ac, 3-NO_2	1) Pr^iOH, Δ, 8 h; 2) AcOH, conc. HBr, Δ, 3 h	47–75

Heating of nitriles **58a**,**b** with amines in polar solvents affords 2-substituted 1,4-dihydroisoquinoline-3(2*H*)-imines **59**–**62**.[46,47] On the whole, this reaction has the same features as the reactions of amines with nitrile **49**. The difference is that the reactions of spiro derivatives **58a**,**b** proceed more smoothly and afford products in higher yields.

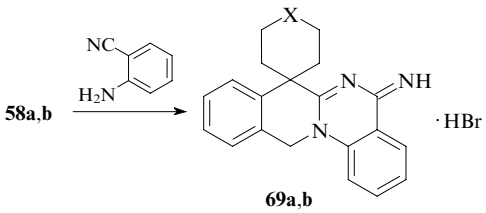
The reactions of nitriles **58a**,**b** with (het)arylamines containing a group in the *ortho* position that can be aminated result in fused dihydroisoquinoline systems **63**–**68** and **69b**.[47,48]



X is absent (**58a**, **63a**–**e**, **65a**, **66a**–**d**), X = O (**58b**, **64a**–**e**, **65b**, **67a**–**d**); Y = H (**a**), 2-Cl (**b**), 3-Br (**c**), 3-Me (**d**), 3-Cl (**e**); R^1 = R^2 = Me (**a**); R^1 = Et, R^2 = H (**b**); R^1–R^2 is benzo (**c**); R^1 = H, R^2 = Ph (**d**); (*a*) dioxane, Δ, 12 h; (*b*) Pr^iOH, Δ, 8 h; (*c*) DMF, Δ, 10 h.

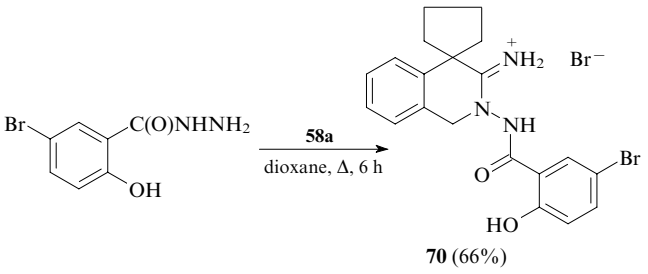


Only the reaction of compound **58a** with anthranilonitrile afforded unexpectedly the alkylation product, which was transformed into 7,12-dihydroisoquino[2,3-*a*]quinazoline derivative **69a** by heating in an ethanolic solution in the presence of concentrated HBr.[47]



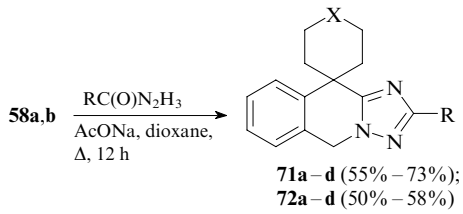
X is absent (**a**): 1) dioxane, Δ, 6 h; 2) HBr (conc.), EtOH, Δ, 0.5 h (yield 42%); X = O (**b**): dioxane, Δ, 12 h (yield 62%).

It is problematic to stop the condensation of nitriles **58a**,**b** with benzohydrazides after formation of the corresponding isoquinoline-3-imines.[38] However, spiro[isoquinoline-4,1′-cyclopentane]-3(2*H*)-imine hydrobromide **70** was prepared by heating compound **58a** with 5-bromosalicylic acid hydrazide.

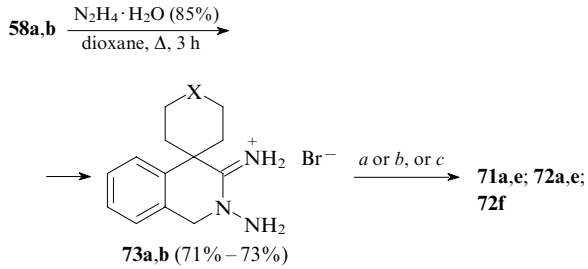


70 (66%)

The analogous reaction performed in the presence of AcONa affords spiro-fused 3-aryl-5,10-dihydro-1,2,4-triazolo[1,5-*b*]isoquinolines **71a**–**d** and **72a**–**d** in good yields.



71a–**d** (55%–73%);
72a–**d** (50%–58%)

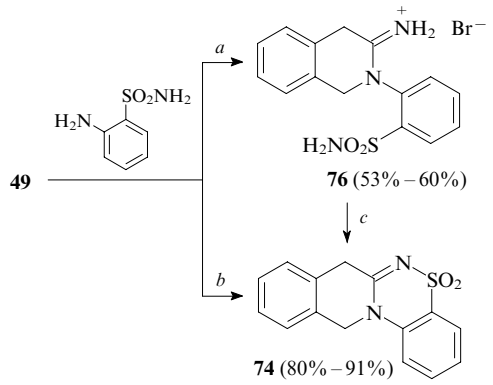


73a,**b** (71%–73%)

X is absent (**58a**, **71a**–**e**, **73a**), X = O (**58b**, **72a**–**f**, **73b**); Ar = Ph (**a**), 3-BrC$_6$H$_4$ (**b**), 2-HOC$_6$H$_4$ (**c**), 2-HO-5-BrC$_6$H$_3$ (**d**), Me (**e**), H (**f**); (*a*) PhC(O)Cl, Et$_3$N, DMF, Δ, 2 h (48%–50%); (*b*) Ac$_2$O, Δ, 12 h (50%–54%); (*c*) 1) HC(OEt)$_3$, DMF, Δ, 6 h; 2) 1-methylmorpholine, Δ, 1 h (48%).

Unlike nitrile **49**, spiro derivatives **58a**,**b** react with hydrazine hydrate to form 2-amino-3-imino-1,2,3,4-tetrahydrospiro[isoquinoline-4,1′-cyclopentane] hydrobromide (**73a**) and 2-amino-3-imino-1,2,2′,3,3′,4,5′,6′-octahydrospiro[isoquinoline-4,4′-(2*H*)-pyran] hydrobromide (**73b**), respectively,[38] which can be used as the starting compounds in the synthesis of 1,2,4-triazolo[1,5-*b*]isoquinolines. This approach was applied to the synthesis of 3-phenyl (conditions *a*) and 3-methyl derivatives (conditions *b*) **71a**,**e** and **72a**,**e**, as well as of compound **72f** (conditions *c*) unsubstituted at position 3 of the triazole ring.

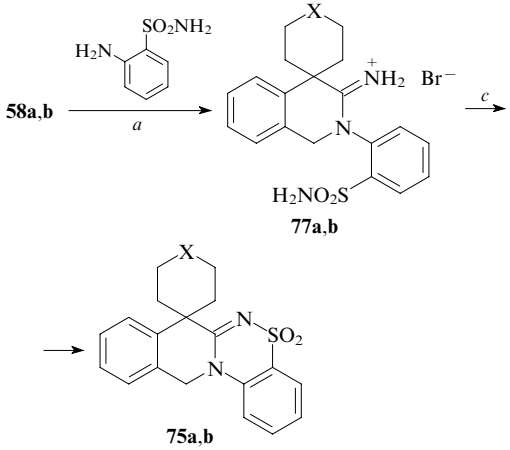
A convenient method for the synthesis of derivatives of the previously unknown 7,12-dihydroisoquino[3,2-*c*]-1,2,4-benzothiadiazine system (**74**, **75a**,**b**) was developed.[49, 50]



76 (53%–60%)

74 (80%–91%)

This method is based on the reaction of nitriles **49** and **58a**,**b** with *o*-aminobenzenesulfonamide. Hydrobromides **76** and **77a**,**b** that are formed in the first step readily undergo cyclization to polycyclic compounds **74** and **75a**,**b** on heating in the presence of triethylamine.

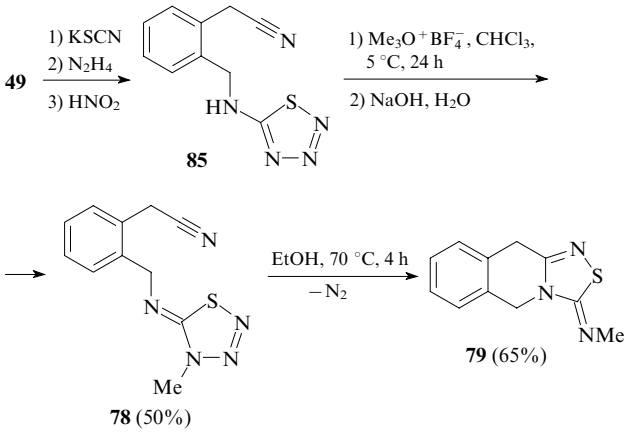


77a,**b**

75a,**b**

X is absent (**a**), X = O (**b**); (*a*) Pr^{i}OH, Δ, 6 h; (*b*) MeCN or dioxane, Δ, 5 h; (*c*) 1) DMF, Δ, 0.5 h; 2) Et$_3$N, DMF, Δ, 15 min.

A novel method of synthesis of fused 1,2,4-thiadiazole derivatives was documented.[51–53] This is based on the ability of the cyano group to undergo 1,3-dipolar cycloaddition reactions. Thus substituted 1,2,3,4-thiatriazole **78**, which is prepared in several steps from (2-bromomethylphenyl)acetonitrile (**49**), undergoes intramolecular addition–elimination on heating. This reaction affords 5,10-dihydro-1,2,4-thiadiazolo[4,3-*b*]isoquinoline **79**.[51, 52]

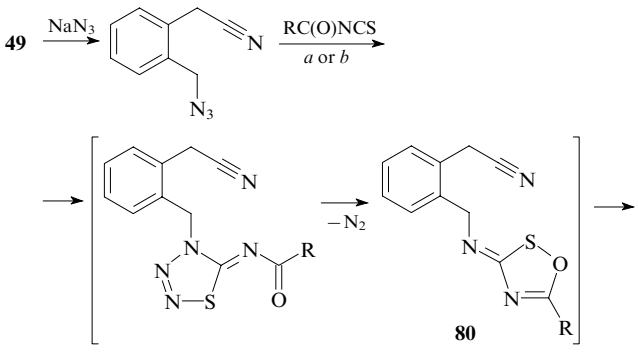


85

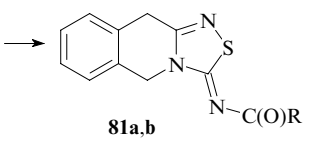
78 (50%)

79 (65%)

An alternative approach to the construction of analogous systems involves the intermediate formation of 1,2,4-oxothiazole-3-imines (**80**). This method was used



80



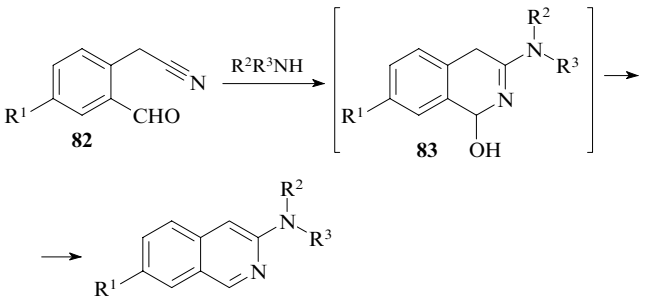
81a,**b**

R = CCl_3 (**a**, 52%), Ph (**b**, 83%); (*a*) CH_2Cl_2, Δ, 16 h; (*b*) 80 °C, 16 h.

for the synthesis of 3-acylimino-5,10-dihydro-1,2,4-thiadiazolo[4,3-*b*]isoquinolines **81a**,**b**.[53]

4. Miscellaneous approaches to the N(2) – C(3) bond formation

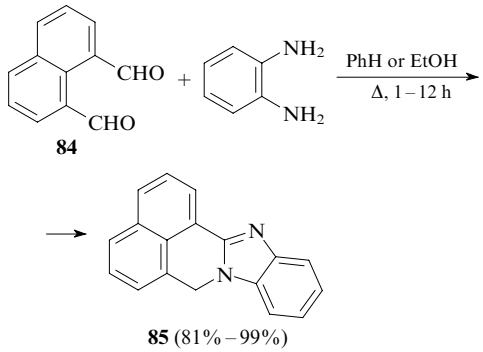
Only a few examples of the use of carbonyl compounds as synthons in 5 C + N cyclization reactions are documented. This method has limitations associated not only with the availability of the starting compounds, but also with the reaction conditions. For instance, the coupling of 2-cyanomethylbenzaldehydes **82** with ammonia, primary or secondary amines in the presence of catalytic amounts of trifluoroacetic acid affords 3-amino-1-hydroxy-1,4-dihydroisoquinolines **83** unstable under these conditions.[54] The latter compounds easily lose a water molecule to form aromatic 3-aminoisoquinolines.



82 **83**

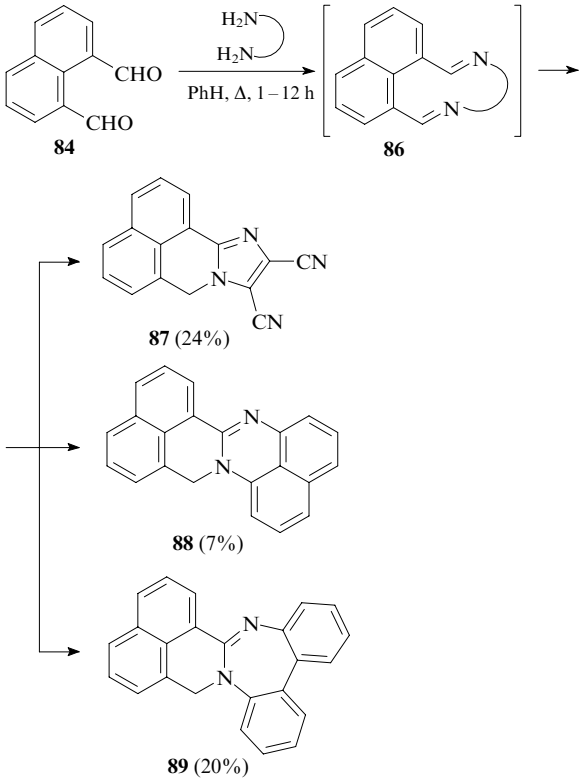
R^1 = H, Cl; R^2, R^3 = H, Alk, Ar.

In the early 1960s, Italian researchers[31, 55] studied the coupling of aromatic aldehydes with *o*-phenylenediamine. The condensation of naphthalene-1,8-dicarbaldehyde (**84**) afforded benzobenzimidazo[2,1-*a*]isoquinoline **85**.



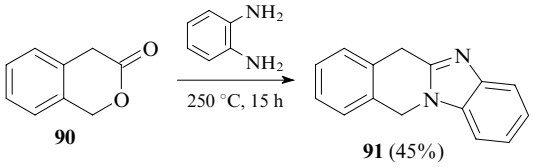
84 **85** (81% – 99%)

More recently, this reaction was studied in detail for other diamines. The intramolecular cyclization of intermediate Schiff bases **86** was shown[56] to result from the polycyclic hydride shift. The reaction of dialdehyde **84** with diamines gave polymeric compounds as the major products; fused isoquinolines **87**,[57] **88** and **89** (Ref. 56) were isolated from the reaction mixture in low yields.



84 **86** **87** (24%) **88** (7%) **89** (20%)

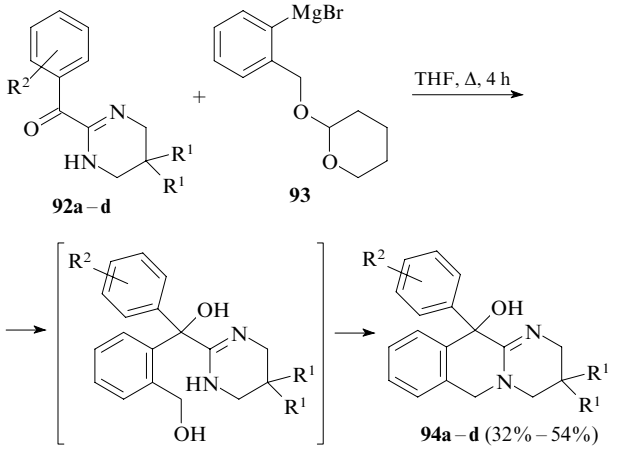
Heating of a mixture of *o*-phenylenediamine and isochroman-3-one **90** in a sealed tube for a long time resulted in amination of the latter compound to give 6,11-dihydrobenzimidazo[1,2-*b*]isoquinoline (**91**).[58, 59]



90 **91** (45%)

5. Methods of C(1) – N(2) bond formation

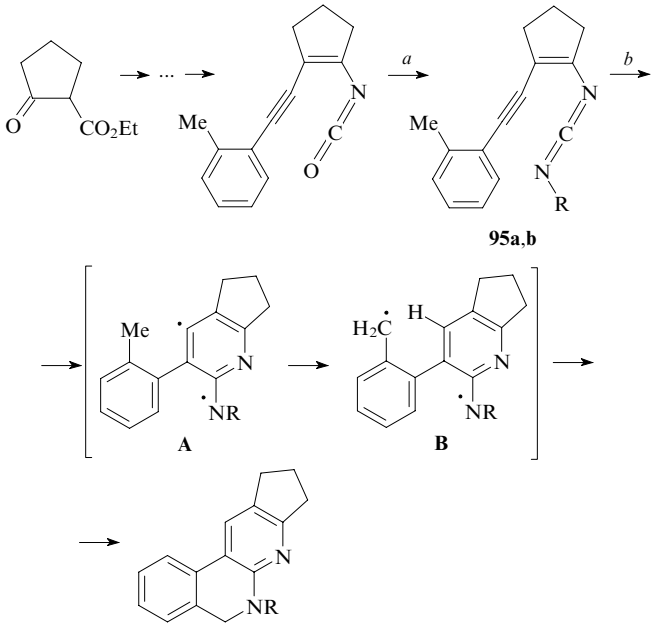
The reactions of substituted 2-benzoyl-1,4,5,6-tetrahydropyrimidines **92a** – **d** with the Grignard reagent **93** are accompanied by heterocyclization yielding 11-aryl-11-hydroxy-3,4,6,11-tetrahydropyrimido[1,2-*b*]-(2*H*)-isoquinolines **94a** – **d**.[60] The latter compounds were covered by a patent as drugs for the reduction of gastric secretion.



92a – **d** **93** **94a** – **d** (32% – 54%)

R^1 = H: R^2 = H (**a**), 4-Cl (**b**), 3-Cl (**c**); R^1 = Me, R^2 = H (**d**).

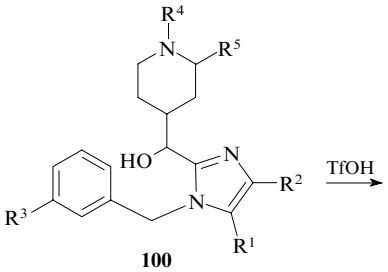
Thermolysis of *N*-{2-[(2-methylphenyl)ethynyl]cyclopent-1-enyl}carbodiimides **95a**,**b**, which were synthesized in several steps from ethyl 2-oxocyclopentanecarboxylate, affords δ,π-biradicals **A**. The latter compounds are readily transformed into π,π-biradicals **B** as a result of the 1,5-hydride shift. The intramolecular recombination of radicals **B** gives 5,8,9,10-tetrahydrobenzo[*f*]cyclopenta[*b*]-[1,8]naphthyridine derivatives **96a**,**b**.[61]

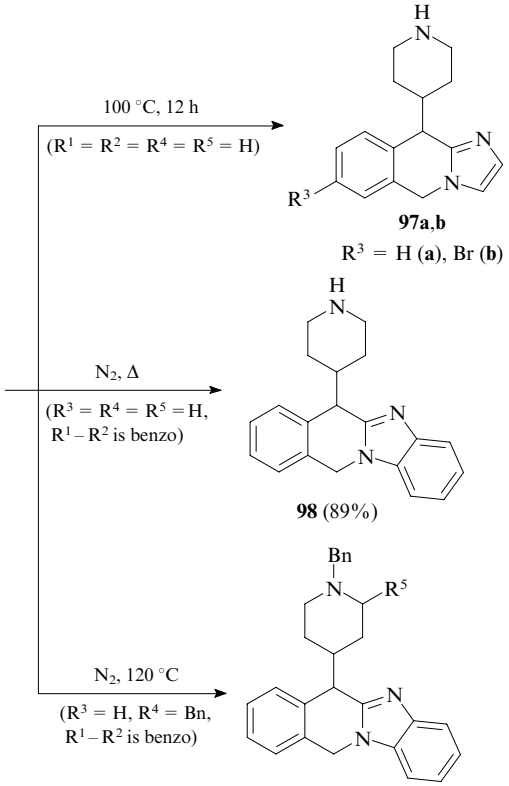


Compounds **95**, **96**	R	Step *a*		Step *b*	
		conditions	yield (%)	conditions	yield (%)
a	Ph	1) $PhNH_2$, CH_2Cl_2, 25 °C, 8 h; 2) Ph_3PBr_2, Et_3N, CH_2Cl_2, 25 °C, 1 h	85	PhCl, 132 °C	56
b	Bn	$Ph_2C{=}NBn$, CH_2Cl_2, −78 °C	86	1,2-$Cl_2C_6H_4$, 180 °C	36

6. Methods of C(4) – C(4a) bond formation

In the context of the programme aimed at designing new efficient antitumour drugs, a series of fused imidazoles and benzimidazoles containing a piperidine fragment were synthesized. The synthesis of the basic structures, *viz*., 10-(piperidin-4-yl)-5,10-dihydroimidazo[1,2-*b*]isoquinolines **97a**,**b**[11,12]

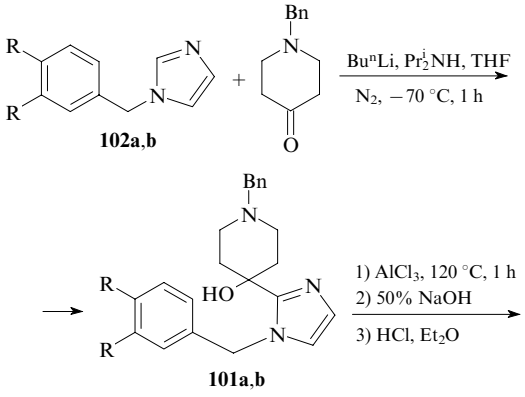


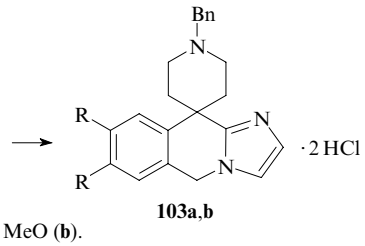


Tf = CF_3SO_2.

and 6-(piperidin-4-yl)-6,11-dihydrobenzimidazo[1,2-*b*]isoquinolines **98** and **99a**,**b**,[8–10] is based on the intramolecular Friedel–Crafts alkylation of the corresponding imidazoles **100**. Their cyclization occurs upon prolonged heating in trifluoromethanesulfonic acid. In the case of benzimidazole derivatives, high yields of the target products are achieved in the reactions performed under argon.

The same idea underlies the synthesis of 10-spiro-fused imidazo[1,2-*b*]isoquinoline derivatives covered by patents as antihistamine drugs. 1-Benzyl-2-(1-benzyl-4-hydroxypiperidin-4-yl)-(1*H*)-imidazoles **101a**,**b**, which have been obtained from 1-benzylimidazoles **102a**,**b**, were fused with $AlCl_3$ to prepare spiro derivatives **103a**,**b**.[62]

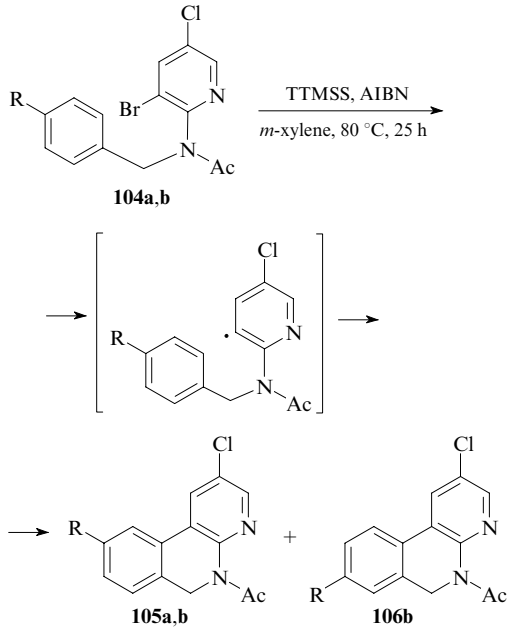




103a,b

R = H (**a**), MeO (**b**).

N-Benzyl-*N*-(3-bromo-5-chloropyridin-2-yl)acetamides (**104a,b**) undergo radical cyclization to form benzo[*c*][1,8]-naphthyridine derivatives **105** and **106** on heating in *m*-xylene in the presence of tris(trimethylsilyl)silane (TTMSS) and α,α′-azobis(isobutyronitrile) (AIBN).[63] This reaction with *para*-substituted benzylamine **104b** afforded a mixture of isomeric products **105b** and **106b** in a ratio of ~1 : 1.



104a,b

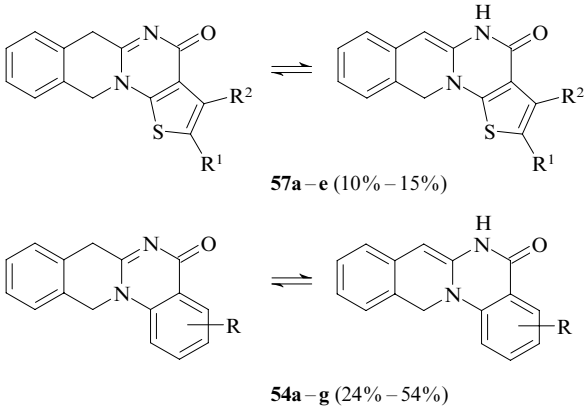
105a,b **106b**

R = H (**a**), Me (**b**).

III. Chemical properties of 3-aminodihydroisoquinolines

First data on chemical transformations of 3-aminodihydroisoquinolines were obtained in the 1960s.[58] However, systematic studies on these compounds have been launched rather recently in relation with the discovery of valuable biological properties of these compounds. Most of the hitherto known reactions of 3-aminodihydroisoquinolines, in which the basic structural fragment is affected, involve transformations of derivatives fused at the bond *b*. Data on the properties of other derivatives are scarce. Four atoms of the pyridine ring [C(1), N(2), C(3) and C(4)] and the amino group in position 3 are the reaction sites in these transformations. The C(4) and N(2) atoms and the 3-amino group are the nucleophilic sites, whereas the C(1) and C(3) atoms are the electrophilic sites.

The reactions of 3-aminodihydroisoquinolines with electrophiles were studied in most detail due to the presence of the acetamidine or ethylene-1,1-diamine fragments, which are tautomeric forms of the 'imine – enamine' equilibrium. The possibility of these transformations was exemplified by 6,11-dihydrothieno[3′,2′:5,6]pyrimido[1,2-*b*]isoquinolin-4(4*H*)-ones **57a – e**[45] and 7,12-dihydroisoquino[2,3-*a*]quinazolin-5(5*H*)-ones **54a – g**.[42]



57a – e (10% – 15%)

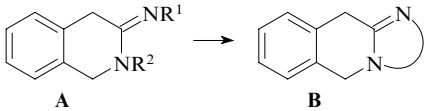
54a – g (24% – 54%)

Compounds **54** and **57**, which exist as amines in the solid state and in non-polar solvents, form two tautomers upon dissolution in a polar solvent (dimethyl sulfoxide). The ratio of tautomers is determined by the electronic properties of substituents.[42] Thus in the case of compounds **54**, the percentage of the enamine form in the reaction mixture increases with increasing electron-withdrawing ability of the substituent R in the benzene ring.

In majority of cases, it is the possibility of the existence of 3-aminodihydroisoquinolines in two tautomeric forms (imine and enamine) that is responsible for the high reactivity of 3-aminodihydroisoquinoline derivatives in reactions with electrophiles and nucleophiles, as well as for the diversity of the employed reaction conditions and reagents.

1. Reactions with electrophiles

Some reactions of 3-aminodihydroisoquinolines with electrophiles were considered above when discussing the methods of their synthesis. These are the cyclizations of 1,4-dihydroisoquinoline-3(2*H*)-imine derivatives **A** giving rise to fused systems **B**.



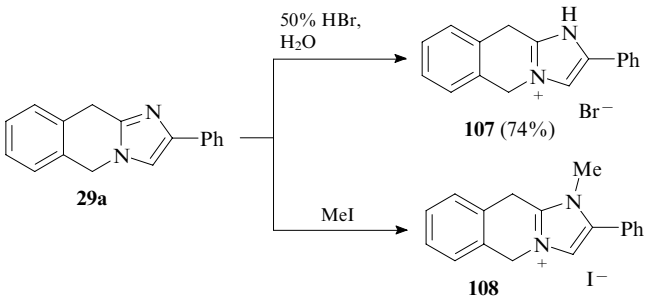
A **B**

R^2 = H: R^1 = $(CH_2)_nCl$, 2-$HO_2CC_6H_4$;

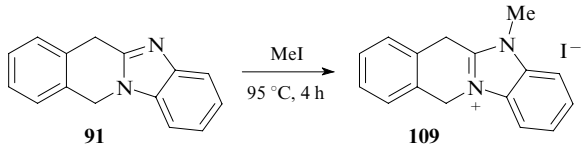
R^1 = H: R^2 =  [X = CO_2H, CO_2Alk, CN, SO_2NH_2, C(O)Ar, HNC(O)Y (Y = H, Alk, Ar)].

In many cases, compounds **A** were formed as intermediates and were not isolated from the reaction mixtures. In these cases, annulation of the ring to the isoquinoline system occurs by two pathways: 1) the intramolecular alkylation[4,19] or acylation[4] at the N(2) atom in the presence of bases; 2) the intramolecular acylation[38–43,47–50] or coupling[38,44,47,48] at the nitrogen atom of the imino group in the presence of acids[39–44,47,48] or bases.[38,49,50]

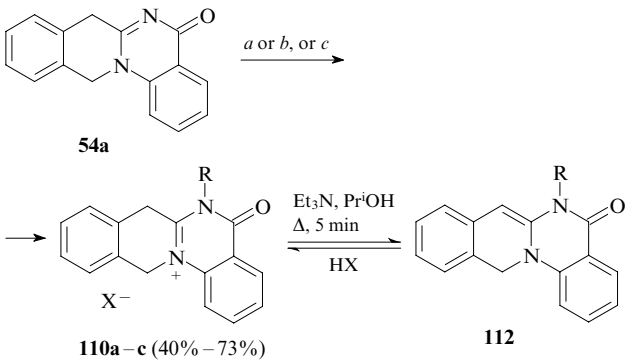
3-Aminodihydroisoquinoline derivatives exhibit high basicity and form stable salts with mineral and carboxylic acids. In many cases, these salts were isolated and characterized (see Sections I.1 and I.3) (Refs 1–6, 19–21, 37–43, 45, 49, 50). The acidity constant of 2-phenyl-5,10-dihydroimidazo[1,2-*b*]isoquinoline (**29a**, pK' = 5.04), which forms water-insoluble hydrobromide **107** in high yield, was estimated.[25]



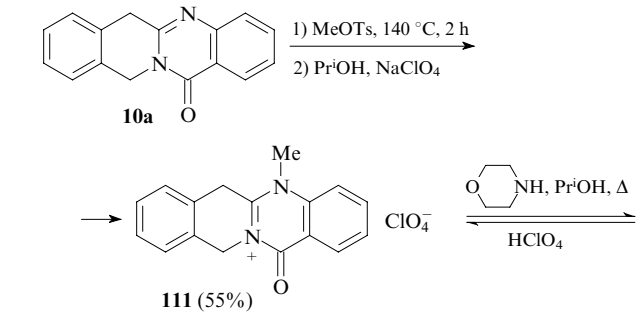
Dihydroimidazo[1,2-*b*]isoquinoline **29a** and 11-dihydrobenzimidazo[1,2-*b*]isoquinoline (**91**) readily undergo quaternization under the action of methyl iodide to form salts **108**[64] and **109**.[58, 59]

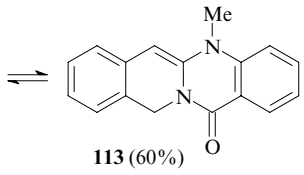


N-Alkyl-5-oxo-7,12-dihydroisoquino[2,3-*a*]quinazolinium salts **110a**–**c** (see Refs 64 and 65) and *N*-methyl-13-oxo-6,11-dihydroisoquino[3,2-*b*]quinazolinium salts (**111**)[67] were prepared from the corresponding bases **54a** and **10a** by fusing with methyl *p*-tolyenesulfonate or by heating with ethyl iodide in nitromethane. The action of bases on compounds **110** and **111** in boiling propan-2-ol results in deprotonation at the methylene group in position 4 of the isoquinoline moieties to form compounds **112** (Refs 66 and 68) and **113**.[67] The latter compounds are readily transformed into the starting quaternary salts on treatment with mineral acids.



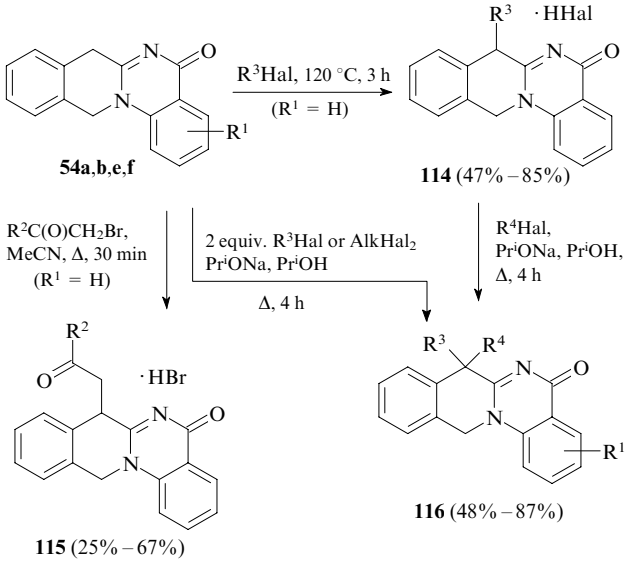
R = Me: X = ClO_4 (**a**), TsO (**b**); R = Et, X = I (**c**); (*a*) EtI, $MeNO_2$ or MeCN, Δ, 2–3 h; (*b*) 1) MeOTs, 120 °C, 40 min; (*c*) 1) MeOTs, 120 °C, 40 min; 2) AcOH, $HClO_4$.





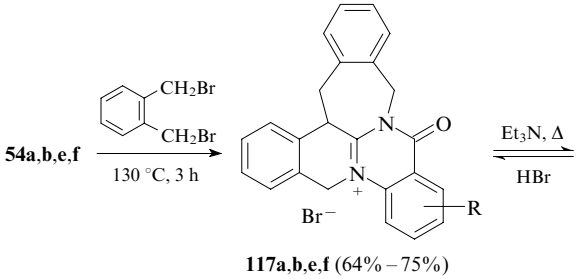
The reactions of isoquinoquinazolines **54** with benzyl halides and α-halocarbonyl compounds afford C-alkylation products **114** and **115**.[66] The repeated alkylation of derivatives **114** or the treatment of compounds **54** with 2 equiv. of alkyl halides or dihaloalkanes can also be performed in the presence of strong bases (for example, of sodium isopropoxide); these reactions give exclusively C,C-dialkyl derivatives **116** (Scheme 5).[66, 69]

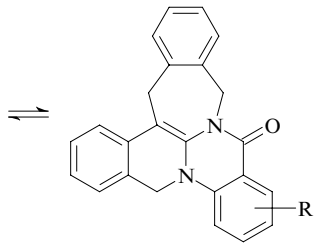
Scheme 5



R^1 = H (**a**), 2-Cl (**b**), 3-Br (**e**), 3-Me (**f**); R^2 = Ph, 4-BrC_6H_4, OMe; R^3 = $X_nC_6H_{4-n}CH_2$ (X = H, 2-Me, 2,4-Me_2, 2-CN, 2-CH_2CN, 3-CO_2H,3-NO_2, 4-Cl); R^1 = H: R^3 = R^4 = Me, Et, Bn; R^3 = Me: R^4 = Bn, 2-$MeC_6H_4CH_2$, 3-$O_2NC_6H_4CH_2$; Alk = R^3–R^4 = *o*-$CH_2C_6H_4CH_2$: R^1 = H, 2-Cl, 3-Br, 3-Me.

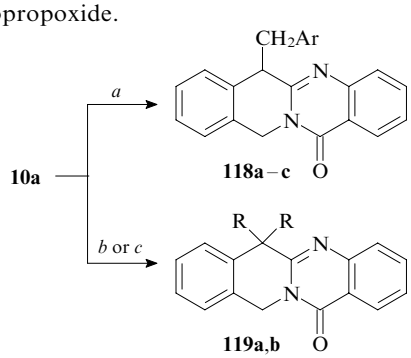
The solvent-free reaction with *o*-xylylene dibromide as the dialkylating agent proceeds at the N(6) and C(7) atoms of dihydroisoquino[2,3-*a*]quinazolines **54** to give 11-oxo-(4*bH*,5*H*,10*H*,11*H*,16*H*)-10*a*-aza-15*b*-azoniadibenzo[*a*,*e*]-pleiadene bromides **117**.[66, 69] Their deprotonation, like that of salts **110** and **111**, results in the generation of the enamine fragment.





R = H (**a**), 2-Cl (**b**), 3-Br (**e**), 3-Me (**f**).

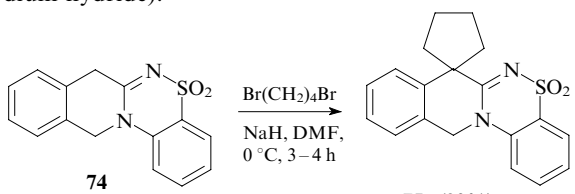
A similar situation is observed in the alkylation of the linear isomer, *viz*., isoquino[3,2-*b*]quinazolinone **10a**.[67] The main difference between compound **10a** and isoquinoquinazoline **54** having an angular structure is that compound **10a** is less reactive. This is manifested in a longer reaction time, more drastic conditions and lower yields of the target products. In some cases, alkylation products cannot be obtained from compound **10a** in the absence of basic catalysts. For example, mono- (**118a–c**) and dibenzyl derivatives (**119a**) are produced only in the presence of sodium isopropoxide.



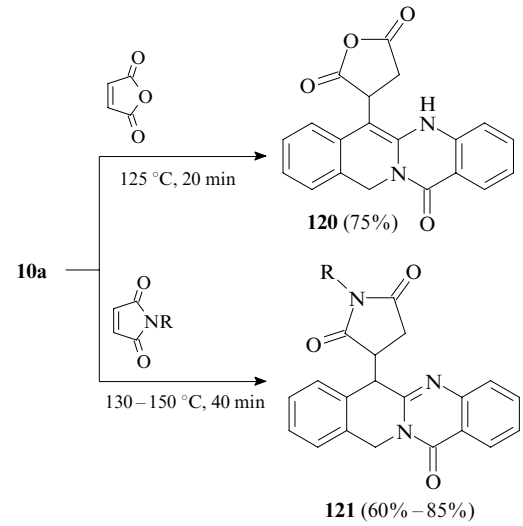
Ar = Ph (**118a**), 2-MeC_6H_4 (**118b**), 3-$O_2NC_6H_4$ (**118c**);
R = Bn (**119a**), R–R = *o*-$CH_2C_6H_4CH_2$ (**119b**);
(*a*) $ArCH_2Hal$, Pr^iONa, Pr^iOH, Δ, 30 min;
(*b*) BnHal (2 equiv.), Pr^iONa (2 equiv.), Pr^iOH, Δ, 30 min (for **119a**, yield 66%); (*c*) *o*-$BrCH_2C_6H_4CH_2Br$, 170 °C, 5 h (for **119b**, yield 63%).

The result of fusion of isoquinoquinazoline **10a** with *o*-xylylene dibromide differs from that of angular isomer **54**, this affords the C,C-dialkylation product, *viz*., spiro derivative **119b**.

7,12-Dihydroisoquino[3,2-*c*]-1,2,4-benzothiadiazine dioxide **74** is even less reactive toward alkyl halides. Compound **75a** can be prepared by the reaction of **74** with 1,4-dibromobutane only in the presence of a strong base (sodium hydride).[50]

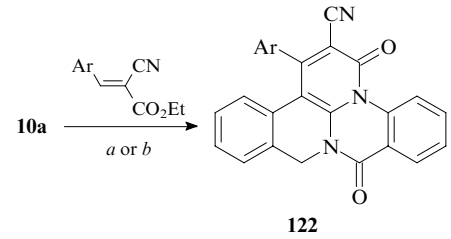


The alkylation of 6,11-dihydroisoquino[3,2-*b*]quinazolin-13(13*H*)-one (**10a**) with activated alkenes was studied.[67] The reactions of **10a** with maleic anhydride and maleimides proceed under drastic conditions (125–130 °C) and afford the Michael adducts **120** and **121**, respectively.



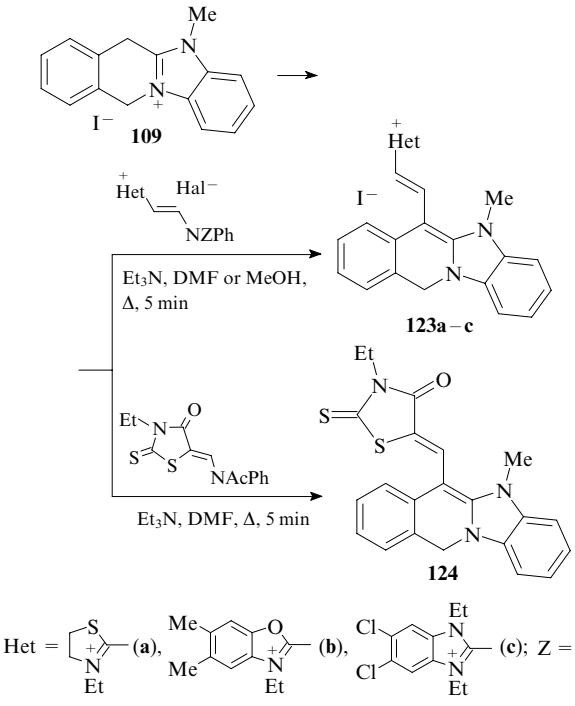
R = H, Bn, Ph, 4-$MeOC_6H_4$, 4-$O_2NC_6H_4$, 1-naphthyl.

The Michael reactions of compound **10a** with arylidenecyanoacetates are accompanied by intramolecular acylation at the N(5) atom followed by oxidation to yield benzo[5,6][1,8]naphthyridino[1,8-*ab*]quinazoline derivatives **122**.[67]



(*a*) Et_3N, DMF, Δ, 5 h (for Ar = 4-$MeOC_6H_4$, yield 35%);
(*b*) 180 °C, 4 h (for Ar = 4-ClC_6H_4, yield 30%).

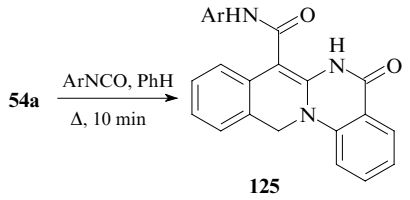
Cyanine dyes of the benzimidazo[1,2-*b*]isoquinoline series (compounds **123a–c** and **124**) were synthesized from 12-methylbenzimidazo[1,2-*b*]isoquinolinium iodide **109** and



Het = (**a**), (**b**), (**c**); Z = Ac, Ts.

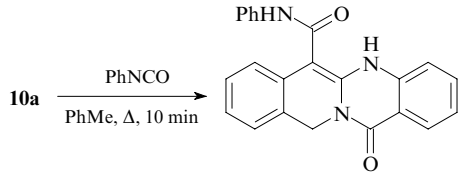
activated enamines.[58, 59, 70] The latter react with salt **109** when heated under reflux for a short period of time in the presence of a base, undergo vinylic substitution with involvement the methylene group in position 6 of the isoquinoline moiety.

3-Aminodihydroisoquinolines react with aryl isocyanates.[68, 71] For example, heating of isoquinoquinazolinones **54a** and **10a** with aryl isocyanates in non-polar solvents (benzene or toluene) affords C-carbamoyl derivatives **125** and **126**. The products exist as enamines stabilized by an intramolecular hydrogen bond.



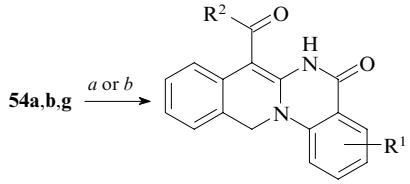
125

Ar = Ph (76%), 4-ClC_6H_4 (73%).



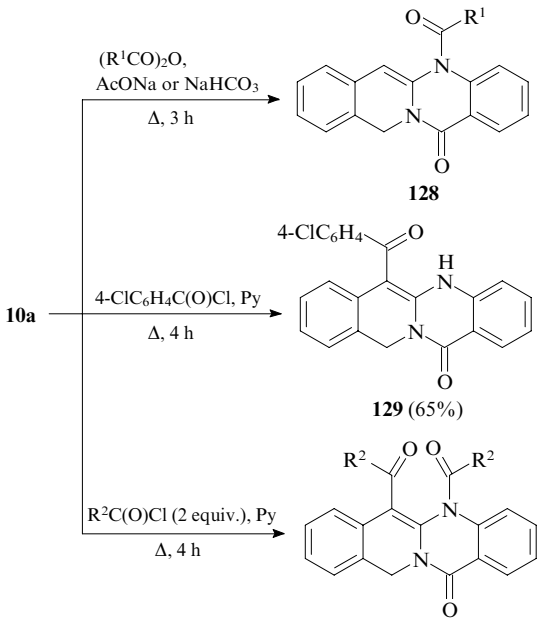
126 (25%)

The acylation of isoquinoquinazolinones **54** and **10a** was studied in detail. It was shown[68, 71] that the acylation of these compounds with carboxylic acid anhydrides and chlorides occurs exclusively in the presence of bases. The reactions of isoquino[2,3-*a*]quinazolinone **54a** and its derivatives **54b**,**g** afford only mono-C-acyl derivatives **127**.[42, 68] By contrast, the acylation of the linear isomer of isoquino[3,2-*b*]quinazolinone **10a** gives the following three types of products depending on the structure of the acylating agent and the ratio of the reactants: N-acyl (**128**), mono-C-acyl (**129**) and C,N-diacyl derivatives (**130**).[71] In addition, as in the alkylation reactions, linear isomer **10a** is less reactive than the angular isomer **54**.



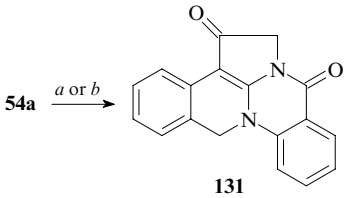
127 (30% – 68%)

R^1 = H: R^2 = Me, Ph, 4-$O_2NC_6H_4$, 4-BrC_6H_4, 4-$MeOC_6H_4$, 2,4-$Cl_2C_6H_3$, 4-Py, 3-Py; R^1 = 2-Cl, R^2 = Me; R^1 = 2,3-$(MeO)_2$, R^2 = Me; (*a*) Ac_2O, AcONa, Δ, 1.5 – 3 h (for R^2 = Me); (*b*) $R^2C(O)Cl$, Py, Δ, 15 min.



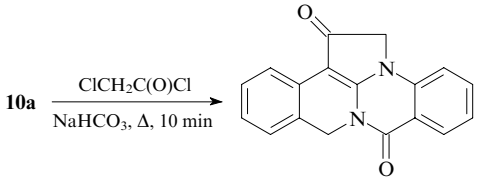
R^1 = Me (35%), Et (47%); R^2 = Me, Ph, 4-MeC_6H_4.

The reactions of compounds **54a** and **10a** with chloroacetyl chloride are accompanied by intramolecular cyclization to yield fused systems, *viz*., 6*a*,11*b*-diazabenzo[*e*]aceanthrylene (**131**)[68] and 2*a*,7*a*-diazacyclopenta[*fg*]naphthacene (**132**).[71]



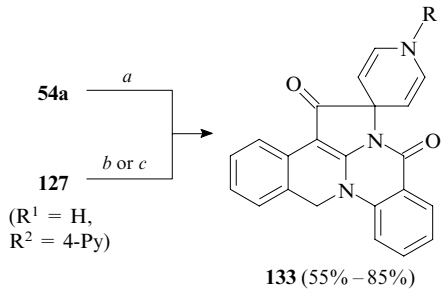
131

(*a*) $ClCH_2C(O)Cl$, Py, dioxane, Δ, 15 min (yield 25%); (*b*) $BrCH_2CO_2Me$, DMF, Δ, 15 min (yield 20%).



132 (45%)

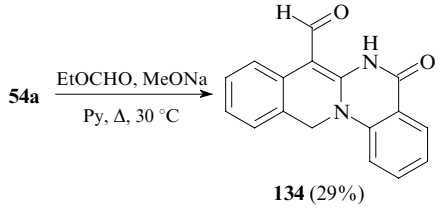
The reaction of isoquino[2,3-*a*]quinazolinone **54a** with excess isonicotinoyl chloride proceeds in an unusual way.[72, 73] In the first step, the reaction produces monoacyl derivative **127** (R^1 = H, R^2 = 4-Py), which undergoes repeated acylation at the pyridine ring in the presence of a base (pyridine) followed by cyclization to yield spiro compound **133** (R = 4-Py). This reaction was used for the synthesis of acyl and alkyl derivatives of spiro[6*a*,11*b*-diazabenzo[*e*]aceanthrylene-6,4′-pyridine] **133**.



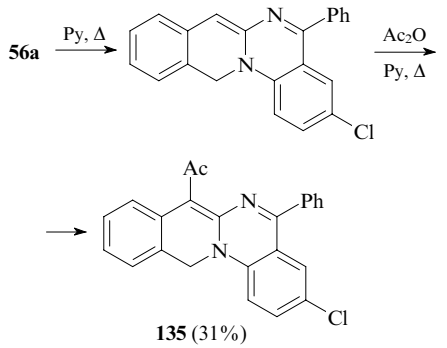
(*a*) 4-PyC(O)Cl (2.5 equiv.), Py, Δ, 15 min (R = 4-PyCO, yield 85%); (*b*) RC(O)Cl, Py, Δ, 15 min [R = MeC(O), 4-MeOC$_6$H$_4$C(O), 4-FC$_6$H$_4$C(O)]; (*c*) 1) RHal, MeNO$_2$, Δ, 4 h; 2) Et$_3$N, Py (R = Me, Et).

Among esters, only methyl bromoacetate was used for the acylation.[66]

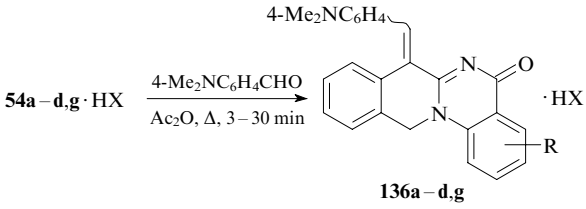
The reaction of isoquino[2,3-*a*]quinazolinone **54a** with ethyl formate in the presence of sodium methoxide produces 5-oxo-6,12-dihydroisoquino[2,3-*a*]quinazoline-7(5*H*)-carbaldehyde (**134**).[68]



Acyl derivatives of isoquinoquinazolines **127** – **130** can also be prepared by the reactions of salts of the starting heterocycles; albeit in low yields.[68] Nevertheless, this approach proved to be useful in the acylation of 5-aryl-(7*H*,12*H*)-isoquino[2,3-*a*]quinazolinium perchlorate **56a**,[74] because the free base is unstable and is easily oxidized to form a complex mixture of products. Compound **135** was synthesized in moderate yield by heating salt **56a** with acetic anhydride in pyridine.

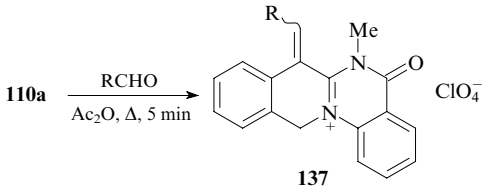


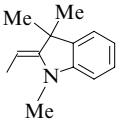
Fused 3-aminodihydroisoquinolines in the form of protic acid salts or free bases react with aromatic aldehydes. For example, isoquino[2,3-*a*]quinazolinone hydrobromides and perchlorates **54a** – **d**,**g** are readily transformed into 7-arylmethylidene derivatives **136a** – **d**,**g** upon heating for a short period of time with *p*-dimethylaminobenzaldehyde in acetic anhydride.[42, 68]



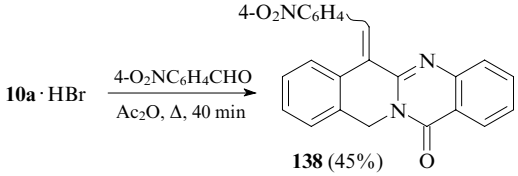
R = H (**a**), 2-Cl (**b**), 2-CO$_2$Me (**c**), 3-Cl (**d**), 2,3-(MeO)$_2$ (**g**).

Under the same conditions, 6-methyl-5-oxotetrahydroisoquino[2,3-*a*]quinazolinium perchlorate **110a** reacted with aldehydes to afford compounds **137**.[68]

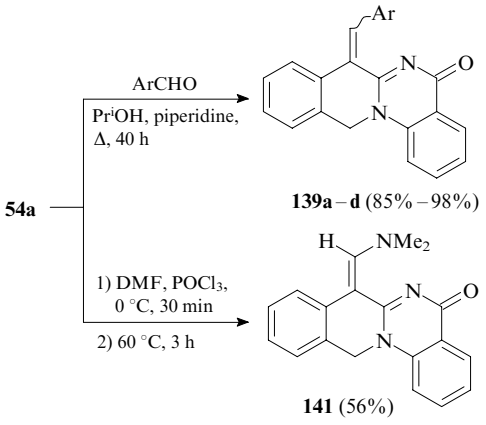


R = 4-Me$_2$NC$_6$H$_4$ (*E* : *Z* = 1 : 1, yield 75%),  (yield 48%).

Coupling of isoquino[3,2-*b*]quinazolinone hydrobromide **10a** with *p*-nitrobenzaldehyde (compound **138**) required heating for a longer time.[71]

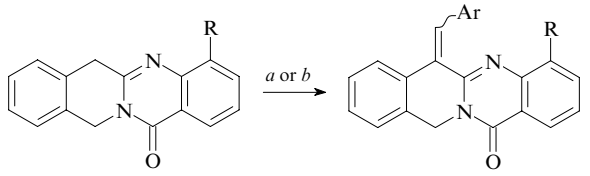


The difference in the reactivity of linear and angular isoquinoquinazolines (**10a**,**b** and **54a**, respectively) is most clearly manifested in the coupling of these compounds in the form of free bases with aldehydes. Thus 7-(arylmethylidene)-7,12-dihydroisoquino[2,3-*a*]quinazolin-5(5*H*)-ones **139a** – **d** were prepared in high yields by the reactions in the presence of piperidine,[75] whereas isomers **140a** – **f** were formed under more drastic conditions (upon heating in acetic anhydride or by carrying out the reaction in the presence of bases for a longer period of time) and in lower yields.[71] An attempt to perform the Vilsmeier formylation



Ar = 4-MeOC$_6$H$_4$ (**a**), 3,4-(MeO)$_2$C$_6$H$_3$ (**b**), 4-BrC$_6$H$_4$ (**c**), 4-O$_2$NC$_6$H$_4$ (**d**).

of compound **54a** resulted in 7-[(*Z*)-(dimethylamino)methylidene]-(5*H*)-isoquino[2,3-*a*]quinazolin-5(12*H*)-one (**141**).[68]



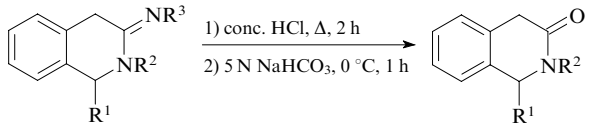
10a: R = H;
10b: R = Cl

140a–f

Ar = 4-$Me_2NC_6H_4$: R = H (**a**), Cl (**b**); R = H: Ar = Ph (**c**), 4-$MeOC_6H_4$ (**d**), 4-BrC_6H_4 (**e**), 4-ClC_6H_4 (**f**);
(*a*) 4-$Me_2NC_6H_4CHO$, Ac_2O, Δ, 40 min (yields 50%–67%);
(*b*) ArCHO, Pr^iOH, morpholine, Δ, 6 h (yields 30%–37%).

2. Reactions with nucleophiles

The carbon atom in position 3 of 3-iminodihydroisoquinoline acts as an electrophilic site, which can be involved in reactions with nucleophiles. Hydrolysis of 1,4-dihydroisoquinoline-3(2*H*)-imine derivatives **19** was documented.[22] 1,4-Dihydroisoquinolin-3(2*H*)-ones **142** were prepared in high yield by refluxing the starting imine in concentrated hydrochloric acid followed by treatment of the residue with sodium hydrogencarbonate.



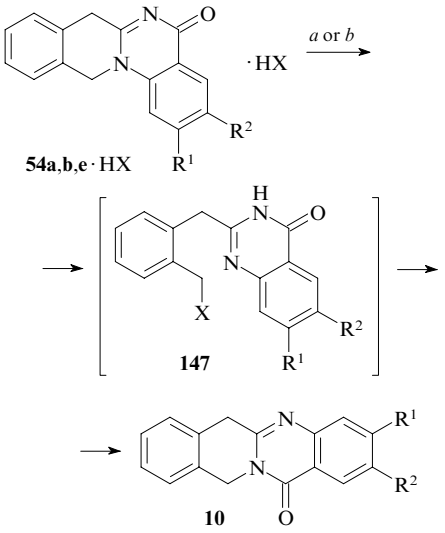
19

142 (90%–95%)

R^1 = H, Me, Pr^i, Ph; R^2 = Me, Et, Pr^i;
R^3 = 4-$O_2NC_6H_4$, 4-$O_2NC_6H_4C(O)$.

At high temperature, 2-aryl-1,4-dihydroisoquinolinium bromides **143**, which were prepared by heating (2-bromomethylphenyl)acetonitrile **49** with substituted anthranilic acids,† undergo nucleophilic substitution reactions in the presence of arylamines (Scheme 6).[76] Fusion of the reactants at >150 °C affords dibenzo[3,4:6,7][1,8]naphthyridino[1,8-*ab*]quinazoline-6,17-diones **144**. The latter compounds are products of the complex transformation involving the nucleophilic substitution and intramolecular bisacylation at both nucleophilic sites of the enamine fragment in intermediate **145**. 6-(4-Methylphenyl)-6,12-dihydroisoquino[2,3-*a*]quinazolin-5(5*H*)-one (**146**) was synthesized by performing the reaction in the presence of a more basic amine (*p*-toluidine).

An unusual transformation of 7,12-dihydroisoquino[2,3-*a*]quinazolin-5(5*H*)-ones **54** with the direct involvement of a nucleophile (halide or perchlorate ions) was studied in several publications.[39,43,77–79] Heating of protic acid salts of compounds **54a**,**b**,**e** at >140 °C results in the C(12)–N(13) bond cleavage and the formation of intermediates **147**, which readily undergo cyclization to thermodynamically more stable 6,11-dihydroisoquino[3,2-*b*]quinazolin-13(13*H*)-one derivatives **10**.

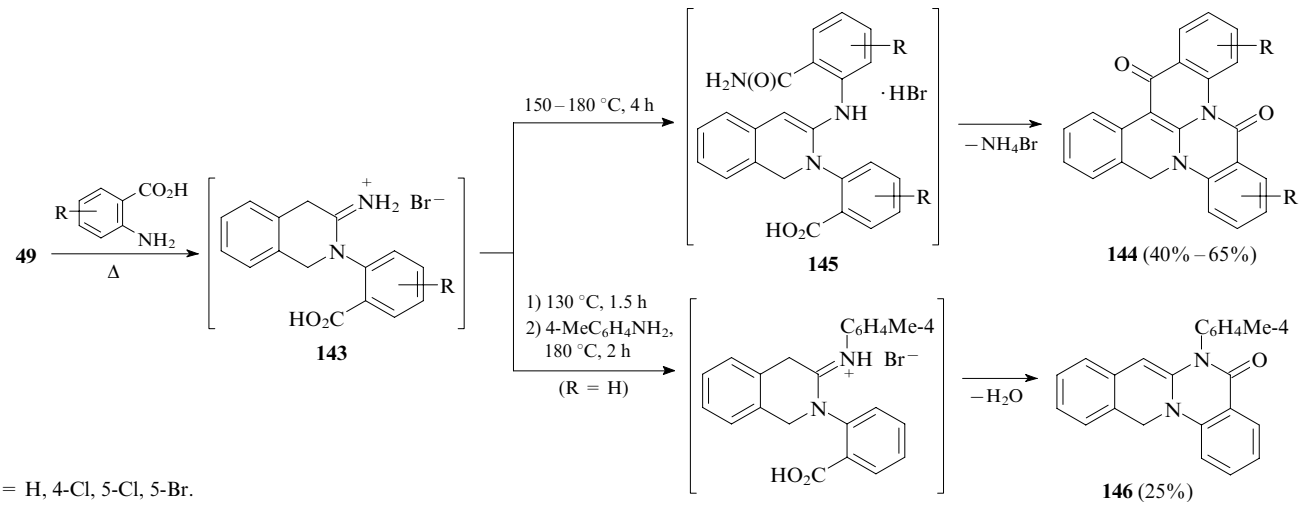


R^1 = R^2 = H (**a**); R^1 = Cl, R^2 = H (**b**); R^1 = H, R^2 = Br (**e**);
X = Br, ClO_4; (*a*) 160–165 °C, 10 h (for **54a**, yield 42%);
(*b*) *N*-methylpyrrolidone, Δ, 2–4 min (for **54b**,**e**, yields 28%–35%).

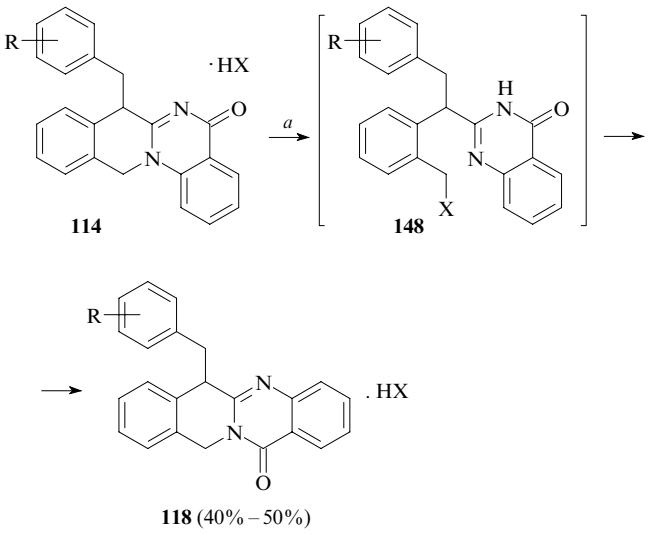
The analogous transformation of salts **114** affords compounds **118**. The reaction proceeds *via* compounds **148**.

† The positions of the substituents in the starting acid are indicated in the scheme.

Scheme 6



R = H, 4-Cl, 5-Cl, 5-Br.



114 **148** **118** (40% – 50%)

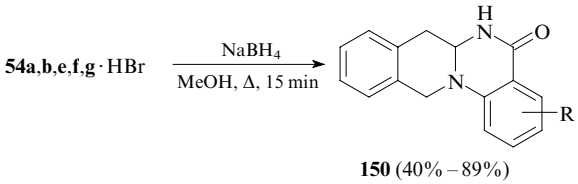
R = H, Me, 2,4-Me_2, 4-Cl, 3-HO_2C, 3-NO_2; X = Cl, Br;
(*a*) 170 – 190 °C, 4 h.

This rearrangement can be performed in the absence of solvents [39, 43, 77, 78] or in high-boiling solvents, such as benzonitrile [43, 79] or *N*-methylpyrrolidone.[39, 43] The reaction in the latter solvent afforded free bases, whereas protic acid salts were isolated in all other cases.

The formation of 2-[2-(bromomethyl)benzyl]quinazolin-4(3*H*)-one derivatives (**147**) is also a key step in the synthesis of 4-chloroisoquino[3,2-*b*]quinazolin-13-ones **10** (Scheme 7).[43] This fact was unexpectedly confirmed in attempting to perform the nucleophilic substitution at the imino group in 3,5-dibromo-2-(3-imino-1,4-dihydroisoquinolin-2-yl)benzoic acid **52d**. Fusion of compound **52d** with N-substituted anthranilic acids affords 2-benzylquinazolin-4(3*H*)-one **149a**,**b** as a result of the C(1) – N(2) bond cleavage in 3-iminodihydroisoquinolines. It was suggested [43] that the cleavage of the isoquinoline ring in sterically hindered 2-arylisoquinolineimines **52** precedes the formation of the quinazoline system. Methyl derivative **149b** easily loses the *N*-methylanthranilic acid molecule upon heating to give isoquinoquinazolinone **10** ($R^1 = R^2 = Br$).

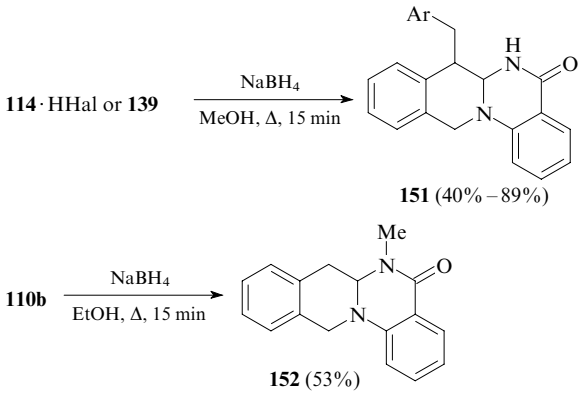
3. Reduction of 3-aminodihydroisoquinolines

The C=N double bond in fused derivatives of 1,4-dihydroisoquinoline-3(2*H*)-imine can be reduced with sodium borohydride. The reaction conditions depend on the structure of the substrate. This reaction proceeds most easily and in high yields with salts of 7,12-dihydroisoquino[2,3-*a*]quinazolin-5(5*H*)-ones **54a**,**b**,**e**,**f**,**g**,[42, 65] monoalkyl derivatives **110b** (Ref. 65) and **114**,[75] and 7-arylidene derivatives **139a** – **c**.[75]



150 (40% – 89%)

R = H (**a**), 2-Cl (**b**), 3-Br (**e**), 3-Me (**f**), 2,3-$(MeO)_2$ (**g**).

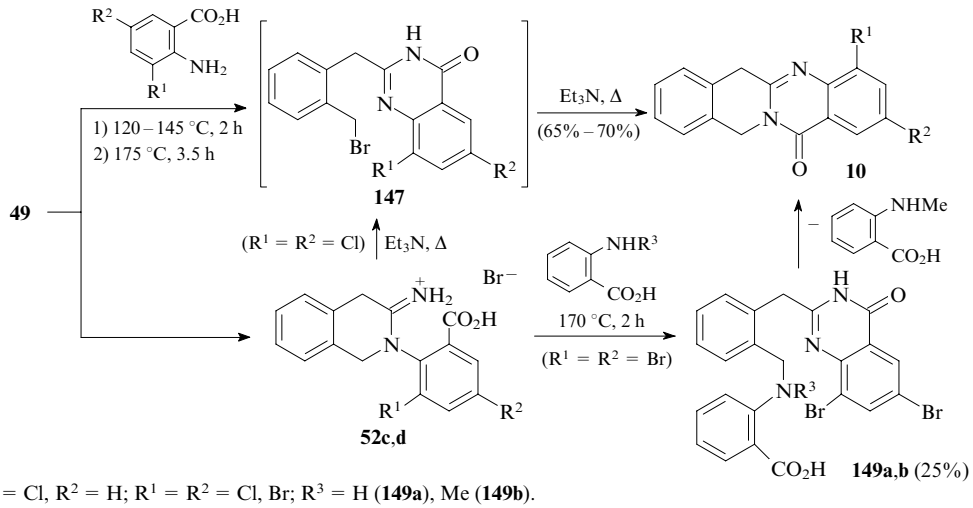


151 (40% – 89%)

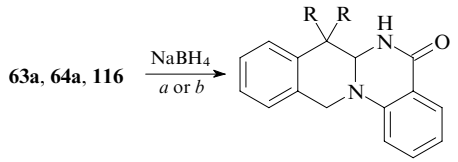
152 (53%)

6,6*a*,7,12-Tetrahydro derivatives **150** – **152** are produced from the corresponding protic acid salts or free bases by heating for a short time with $NaBH_4$ in alcohols. More drastic conditions and a 10-fold excess of $NaBH_4$ are required for the reduction of dialkyl derivatives of isoquino[2,3-*a*]quinazolin-5-ones **63a**,[47] **64a**,[48] **116** (R – R = *o*-$CH_2C_6H_4CH_2$)[75] and **117a**.[69] Reduction products **153** and **154** were obtained in good yields.

Scheme 7

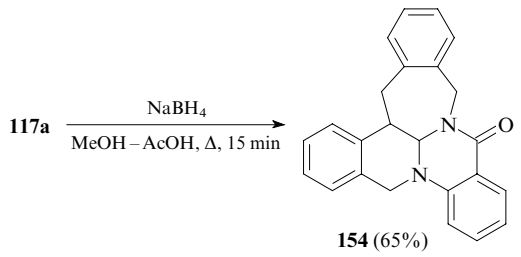


R^1 = Cl, R^2 = H; $R^1 = R^2$ = Cl, Br; R^3 = H (**149a**), Me (**149b**).



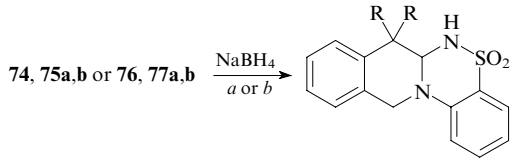
153a–c (73%–97%)

R–R = $(CH_2)_4$ (**63a**, **153a**), $(CH)_2O(CH_2)$ (**64a**, **153b**), *o*-$CH_2C_6H_4CH_2$ (**116**, **153c**); (*a*) dioxane, Δ, 2.5 h (for **63a**); (*b*) MeOH, DMF, Δ, 1–2.5 h (for **64a**, **116**).



154 (65%)

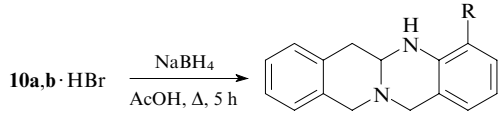
Similar conditions were used in the synthesis of 6,6*a*,7,12-tetrahydro-(5*H*)-5λ^6-isoquino[3,2-*c*]-1,2,4-benzothiadiazine dioxide derivatives **155a–c**.[49,50] It should be noted that compounds **155b**,**c** can be generated directly from isoquinolineimines **77a**,**b**. In this case, $NaBH_4$ acts as a base inducing the cyclization **77** → **75**.



155a–c (80%–88%)

R–R = $(CH_2)_4$ (**75a**, **77a**, **155a**), $(CH_2)_2O(CH_2)_2$ (**75b**, **77b**, **155b**), 2H (**74**, **76**, **155c**); (*a*) MeOH, Δ (for **155a**); (*b*) MeOH, DMF, Δ, 2.5 h (for **155b**,**c**).

6,11-Dihydroisoquino[3,2-*b*]quinazolin-13-(13*H*)-one hydrobromides **10a**,**b** were reduced by heating for a long time in acetic acid with an excess of $NaBH_4$.[43]



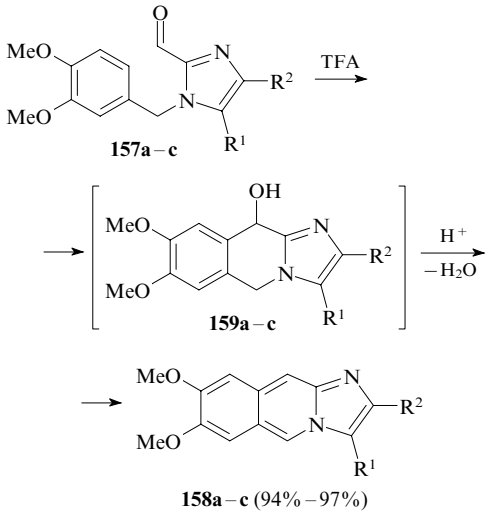
156a,**b**

R = H (**a**, 47%), Cl (**b**, 40%).

4. Oxidation of 3-aminodihydroisoquinolines

The characteristic feature of 3-aminodihydroisoquinoline derivatives is that they are sensitive to oxidation. The aromatization of the isoquinoline ring is facilitated by the presence of electron-withdrawing substituents in positions 1 or 4. This is why some reactions cannot be terminated after the formation of 1,4-dihydro derivatives in the course of constuction of the 3-aminoisoquinolines (see, for example, the synthesis of compound **19**[23]).

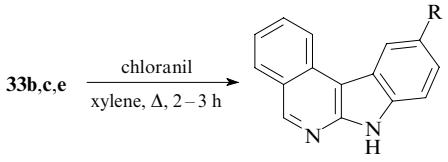
In the presence of the hydroxy or amino group in position 1, the aromatization proceeds under the action of strong acids. Examples are found in the transformations of compounds **41**[35] and **83**.[54] Analogously, the cyclization of 1-benzylimidazole-2(1*H*)-carbaldehydes (**157a–c**) in trifluoroacetic acid (TFA)[80] affords aromatic imidazo[1,2-*b*]isoquinolines **158a–c** through the formation of hydroxy derivatives **159a–c**.



158a–c (94%–97%)

R^2 = Br: R^1 = H (**a**), Br (**b**); R^1–R^2 is benzo (**c**).

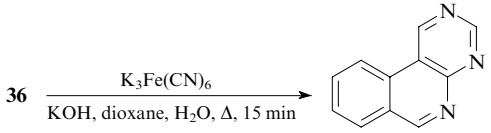
6,7-Dihydroindolo[2,3-*c*]isoquinolines **33b**,**c**,**e** undergo dehydrogenation at the C(1)–N(2) bond upon heating in xylene with chloranil to form compounds **160b**,**c**,**e**.[29]



160b,**c**,**e** (48%–56%)

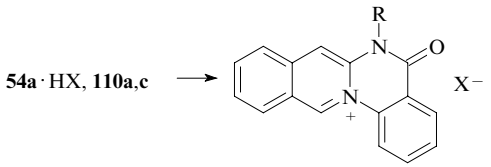
R = Me (**b**), Cl (**c**), OMe (**e**).

The aromatization of 5,6-dihydropyrimido[4,5-*c*]isoquinoline **36** was performed with potassium ferricyanide in refluxing dioxane in the presence of KOH.[33]



(32%)

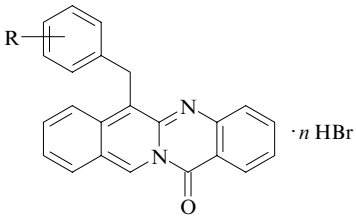
The protic acid salts of 7,12-dihydroisoquino[2,3-*a*]quinazolin-5(5*H*)-one (**54a**) are readily oxidized with atmospheric oxygen in refluxing benzonitrile.[79] For analogous systems **110a**,**c** containing alkyl groups in position 6, nitrobenzene proved to be a more efficient oxidizing agent.[35,68]



42a,**b**, **161**

Compound	R	X	Conditions	Product	Yield (%)
54a	H	I, ClO_4	O_2, PhCN, Δ, 40 min	**161**	61–68
110a	Me	ClO_4	$PhNO_2$, Δ, 30 min	**42a**	92
110c	Et	I	$PhNO_2$, Δ, 30 min	**42b**	65

During heating of 6-unsubstituted isoquino[2,3-*a*]quinazolin-5-ones **54a** and **114** in nitrobenzene, the oxidation is preceded by the rearrangement into isoquino[3,2-*b*]quinazolin-13-one derivatives. Under the same conditions (refluxing for 10 min), identical 6-R-isoquino[3,2-*b*]quinazolin-13(13*H*)-ones **162a–c** were prepared (in 59%–73% yields) from salts of dihydroisoquinoquinazolinones having an angular (**114**; X = H, 2-Me, 3-NO_2) or linear structure (**118a–c**).[81]



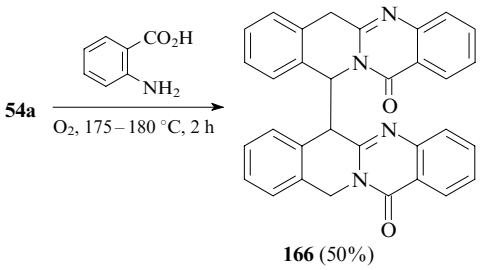
162a–c·*n* HBr

n = 0: R = H (**a**), 2-Me (**b**); *n* = 1, R = 3-NO_2 (**c**).

Nitrobenzene was also used for the oxidation of 5-methyl-6,11-dihydroisoquino[3,2-*b*]quinazolin-13(13*H*)-one perchlorate **111** to the corresponding aromatic salt in 65% yield.[81]

Unlike protic acid salts of angular compounds (for example, compound **54a**), salts of linear isomers {6,11-dihydroisoquino[3,2-*b*]quinazolin-13(13*H*)-one hydrobromide (**10a**·HBr)} undergo oxidation in benzonitrile to give a mixture of compounds, symmetrical dimer **163** being the major product (Scheme 8).[79] Isoquino[3,2-*b*]quinazoline-6,13-dione (**164**) and the oxidative coupling product of the latter with the starting dihydroisoquinoline **10a** (compound **165**) were also isolated from this mixture. It should be noted that compound **165** was obtained as the major product upon attempted acylation of salt **10a**·HBr with isonicotinoyl chloride in pyridine.[71]

It was shown[43] that the oxidative coupling of isoquinoquinazolines proceeds also in the absence of solvents, for example, in melt. Thus fusion of a mixture of dihydroisoquino[2,3-*a*]quinazoline **54a** with anthranilic acid at >170 °C affords unsymmetrical dimer **166**.

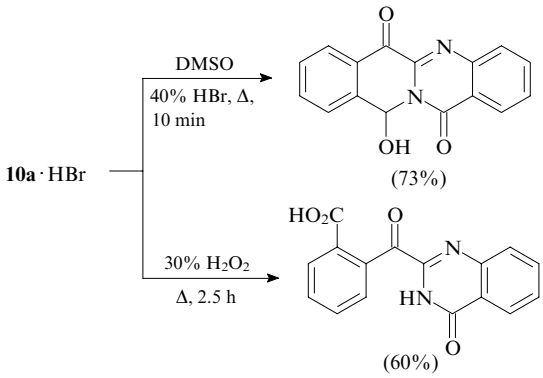


166 (50%)

This can be attributed only to the fact that, under these conditions, compound **54a** is rearranged into isomer **10a**, which undergoes dimerization.

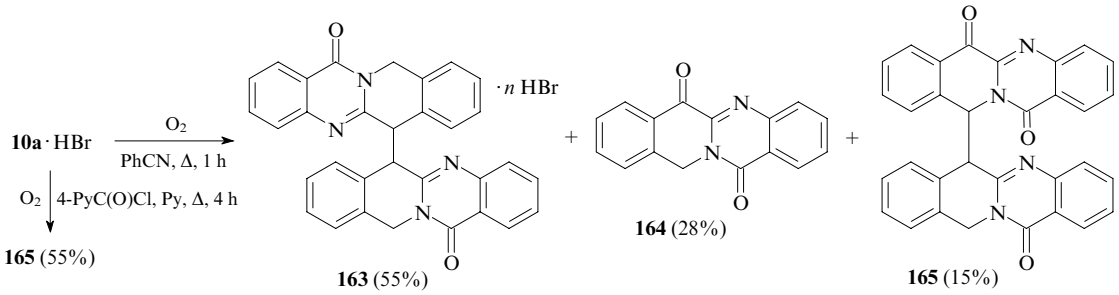
2(3)-Halo-substituted dihydroisoquino[3,2-*b*]quinazolines **149a,b** are more easily oxidized by atmospheric oxygen than unsubstituted compound **10a** and form mixtures of oxidation products **163**, **164** and **166** in melts (at >150 °C).[81]

Dihydroisoquino[3,2-*b*]quinazoline **10a** was oxidized with DMSO and hydrogen peroxide;[81] the reaction proceeds at both CH_2 groups of the molecule. Upon heating with H_2O_2, the oxidation is accompanied by the isoquinoline-ring opening.

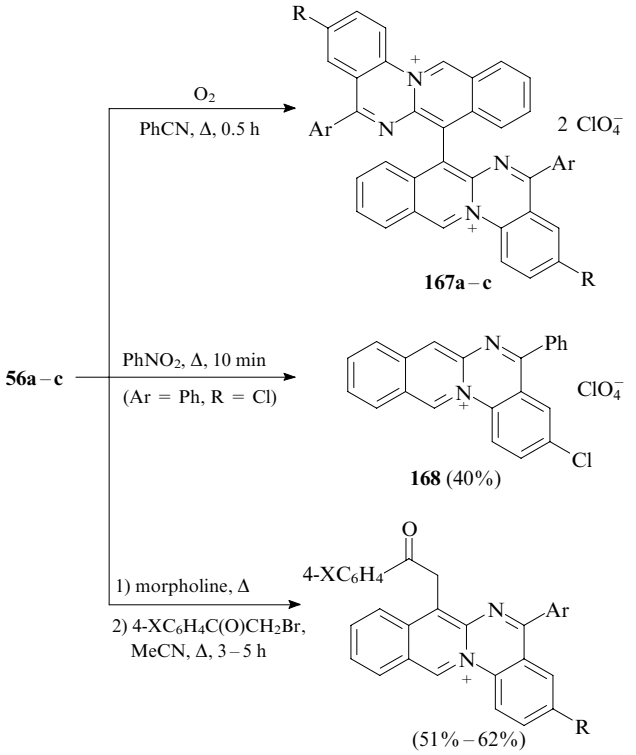


5-Arylisoquino[2,3-*a*]quinazolinium salts **56a–c** readily form the aromatic system in the reaction with atmospheric oxygen.[82] This reaction is also accompanied by oxidative coupling giving rise to symmetrical dimers (**167a–c**). Monomeric product **168** was prepared by refluxing compound **56a** in nitrobenzene.[82] It should be noted that the reaction of

Scheme 8



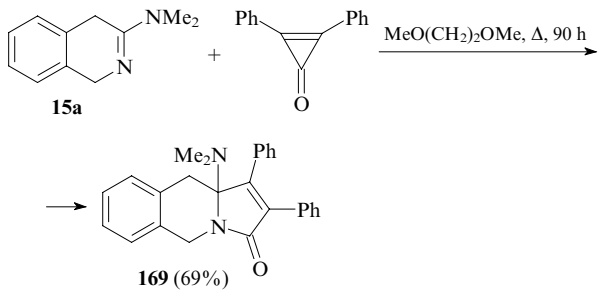
5-arylisoquino[2,3-*a*]quinazolines **56** with phenacyl bromide is also accompanied by oxidation.[74]



Ar = Ph, R = Cl (**a**); R = Br: Ar = 4-BrC_6H_4 (**b**), 4-$O_2NC_6H_4$ (**c**); X = H, Br.

5. Miscellaneous reactions

The reactions of diphenylcyclopropenone with various cyclic amidines, including 3-dimethylamino-1,4-dihydroisoquinoline (**15a**), were studied.[21] Prolonged heating of a mixture of the reactants in dimethoxyethane results in [3 + 2]-cycloaddition at the N(2)=C(3) bond of isoquinoline to form 10*a*-dimethylamino-1,2-diphenyl-10,10*a*-dihydropyrrolo[1,2-*b*]isoquinolin-3(5*H*)-one (**169**).



* * *

To sum up, the known methods for the synthesis of 3-amino-1,2- and 3-amino-1,4-dihydroisoquinolines allow the preparation of not only simple compounds of this series but also rather complex fused heterocyclic systems. Compounds containing the polyfunctional 3-aminodihydroisoquinoline structural fragment are of great synthetic value as an approach to fused isoquinolines containing pharmacophore groups. The most typical reactions of 3-aminodihydroisoquinoline derivatives with electrophiles are those in which these compounds act as ambident nucleophilic reagents. The high activity in reactions with nucleophiles opens a route to the biologically important class of compounds containing the hydrogenated azine fragment.

Preliminary estimates of the biological activity of selected representatives of this class provide evidence for their high pharmacological potential. The available data show that further studies in this field hold considerable promise.

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