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Synthesis of heterocyclic systems based on mono- and dicarbonyl adamantane derivatives

S A Kon'kov, I K Moiseev, M N Zemtsova, K M Bormasheva

Samara State Technical University
ul. Molodogvardeiskaya 244, 443100 Samara, Russian Federation

Examples of the synthesis of various heterocycles containing an adamantane moiety based on mono- and dicarbonyl adamantane derivatives are considered. Systems in which the adamantane cage is spiro-connected to a heterocyclic ring or is a part of substituent in the heterocycle are presented. Data on the biological activities of such derivatives are given. The bibliography includes 85 references.

Contents

I. Introduction 377
II. Synthesis of heterocyclic compounds spiro-connected to adamantane 377
III. Modification of heterocycles using carbonyl derivatives of adamantane 379
IV. Heterocyclization of carbonyl derivatives of adamantane 380

I. Introduction

Heterocyclic compounds containing an adamantane moiety are of special interest. The highly symmetric and balanced adamantane shape makes a significant and often crucial contribution to the properties of molecules, which manifest specific types of interaction with cellular structures of living organisms. Moreover, the introduction of such a moiety into organic compounds often changes their biological activity, in particular, due to increase in the lipophilicity, favouring their transport across biological membranes.

In 1996, Shvekhgeimer [1] described systematically the data on synthesis and properties of adamantane derivatives containing heterocyclic substituents at the bridgehead positions. The present review summarizes data on the synthetic approaches to heterocycles containing the adamantane moiety based on mono- and dicarbonyl derivatives of adamantane.

A separate section is devoted to the synthesis of heterocycles spiro-connected to the adamantane cage. There are few examples of such compounds, all of them having been prepared from commercially available adamantan-2-one in which the carbonyl carbon atom is a member of the polycycle. If one or two carbonyl groups are present in a substituent in adamantane, reactions of such compounds afford heterocyclic derivatives of a different type. In such derivatives, the adamantane moiety is either directly attached to a heterocyclic ring or forms a pendant chain of the substituent in the heterocycle.

The synthetic routes to hetaryladamantanes based on carbonyl adamantane derivatives may be divided into two types. The first type includes few reactions in which the adamantane moiety is introduced into the preformed heterocyclic ring *via* substitution reactions, or the adamantyl-containing substituent in the heterocycle is modified. The second, more frequently encountered type covers heterocyclizations of adamantane mono- and dicarbonyl compounds. As a result of these reactions, rings of different size having different number of heteroatoms and with different location of the adamantane moiety were obtained.

S A Kon'kov Candidate of Chemical Sciences, junior researcher of the SSTU. Telephone (7-846) 332 21 22, e-mail: serge-konkov@yandex.ru
I K Moiseev Doctor of Chemical Sciences, Professor of the same University. Telephone (7-846) 332 21 22, e-mail: ikmoiseev@mail.ru
M N Zemtsova Candidate of Chemical Sciences, Assistant Professor of the same University.
Telephone (7-846) 332 21 22, e-mail: mnzemtova@mail.ru
K M Bormasheva Candidate of Chemical Sciences, assistant of the same University. Telephone (7-846) 332 21 22, e-mail: borks@mail.ru
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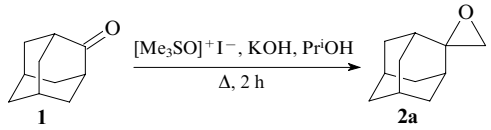
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II. Synthesis of heterocyclic compounds spiro-connected to adamantane

As noted above, heterocyclic compounds spiro-connected to the adamantane cage are synthesized from adamantan-2-one (**1**). Trimethylsulfoxonium iodide (Corey – Chaykovsky reagent), which is formed *in situ* from dimethyl sulfoxide and methyl iodide, was used as the source of methylene group to obtain spiro[oxirane-2,2′-adamantane] (**2a**). The process was carried out by heating the reactants in isopropanol with potassium hydroxide. Under these conditions, the Corey – Chaykovsky reagent yields the corresponding sulfur ylide, which then adds nucleophilically to the carbonyl group of adamantanone **1**. This is followed by

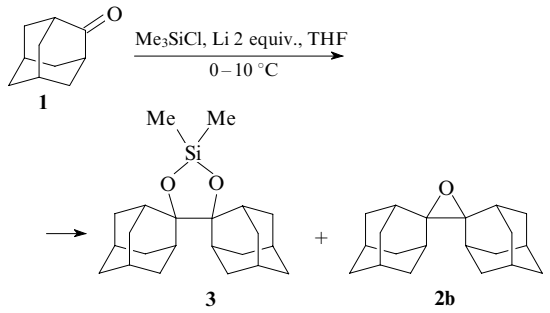
cyclization with elimination of DMSO. Oxirane **2a** was isolated in a nearly quantitative yield (96%) (Scheme 1).[2]

Scheme 1



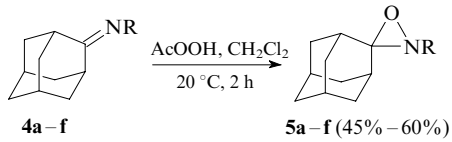
Condensation of ketone **1** with trimethylchlorosilane in the presence of sodium or lithium metal in tetrahydrofuran afforded a mixture of dioxasilolane **3** and oxirane **2b**, bearing two spiro-connected adamantane moieties (Scheme 2).[3] Yields and product ratio are not given in the original study.

Scheme 2



Oxidation of Schiff bases **4a–f** derived from adamantanone **1** with peracetic acid gave a series of spiro[oxaziridine-3,2′-adamantanes] **5a–f** (Scheme 3).[4]

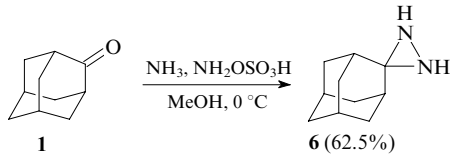
Scheme 3



R = Me (**a**), Bu^n (**b**), Bn (**c**), cyclo-C_6H_{11} (**d**), Ad (**e**), CH_2Ad (**f**);
Ad is 1-adamantyl

Treatment of the adamantan-2-one (**1**) with a methanol solution of ammonia and hydroxylamine-*O*-sulfonic acid under mild conditions yields spiro[diaziridine-3,2′-adamantane] (**6**) (Scheme 4).[5]

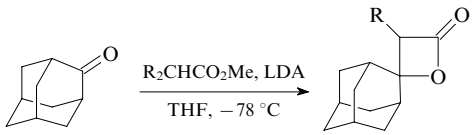
Scheme 4



The reaction between ketone **1** and lithium enolates generated from methyl isobutyrate and methyl estets of substituted acetic acids in the presence of lithium diisopropylamide (LDA) at −78 °C has been reported.[6] The reaction yielded adamantanes **7a–c**, spiro-connected to oxetan-2-ones (Scheme 5). The high product yield was observed only for methyl isobutyrate.

Synthesis of spiro[indol-2-one-3,2′-adamantane] (**8**) in a high yield has been proposed.[7] First, adamantan-2-one reacts with dilithium derivative of *N*-formanilide at

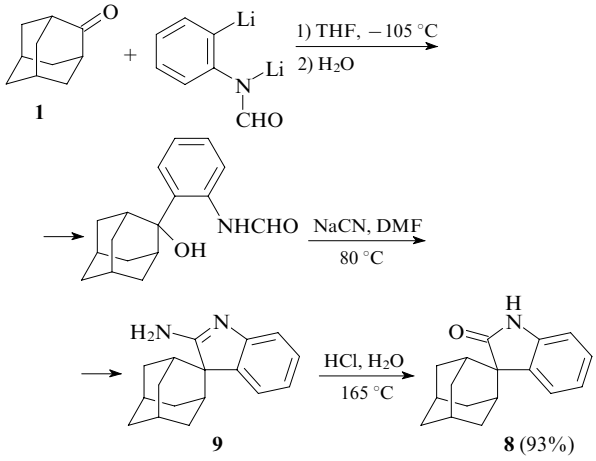
Scheme 5



R = Me (**a**, 85% yield), OPh (**b**, 6%), OBn (**c**, 3%)

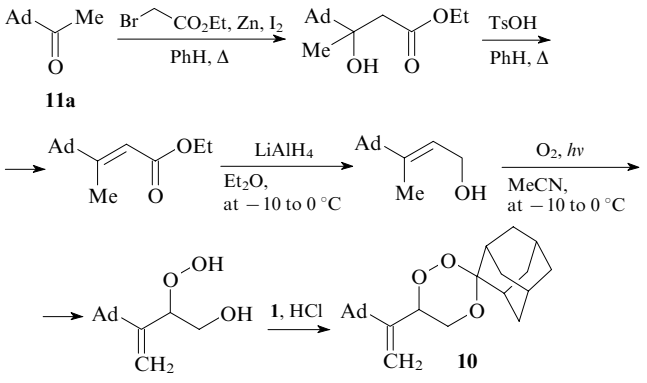
−105 °C in THF affording the corresponding alcohol, which cyclizes under the action of sodium cyanide in DMF to give 3*H*-2-aminoindole **9** spiro-connected to the adamantane. Oxindole **8** was obtained *via* acid hydrolysis of compound **9** (Scheme 6).

Scheme 6



In closing of this section, we present the synthesis of compound **10** having two adamantane moieties (Scheme 7).[8] The first of them is spiro-connected to 1,2,4-trioxane at the 3-position, while the other one is a part of a substituent in the heterocycle. The reaction sequence includes several steps: the Reformatsky condensation involving the adamantyl methyl ketone (**11a**), dehydration yielding a substituted acrylate, reduction to give the corresponding allyl alcohol, photochemical addition of molecular oxygen and ketalization with adamantanone. It should be noted that compound **10** showed a good antimalarial activity in drug-resistant *Plasmodium yoelii nigeriensis* in mice.

Scheme 7

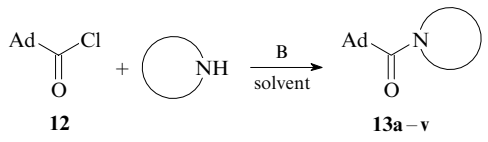


TS is *p*-toluenesulfonyl

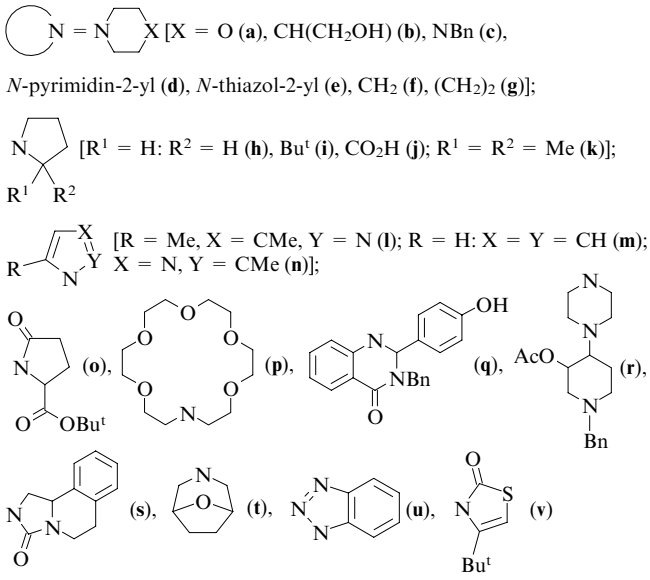
III. Modification of heterocycles using carbonyl derivatives of adamantane

To introduce an adamantane moiety into preformed heterocycle, substitution reactions are generally used. These reactions include, *e.g.*, acylation of heterocyclic compounds having a secondary nitrogen atom in the ring. Adamantane-1-carboxylic acid chloride (**12**) is used as the acylating agent; the reaction is carried out in an organic solvent in the presence of a base (B). This procedure was used to prepare a wide range of saturated nitrogen heterocycles **13a–v** containing the 1-adamantylcarbonyl substituent (Scheme 8).[9–23]

Scheme 8



12 **13a–v**

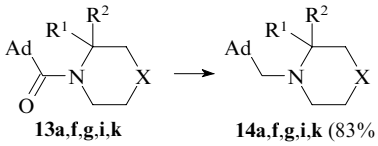


Among these heterocycles, mention should be made of morpholine, substituted pyrroles, pyrrolidines, piperidines and piperazines, aza-crown ethers, benzotriazoles, imidazole and the like. Depending on the nucleophilicy of the nitrogen atom and the N–H bond acidity, the acylation reaction may proceed along two paths. In the case of basic and highly nucleophilic secondary amines, the first step involves the addition of the lone electron pair of nitrogen to the activated carbonyl group of an acid chloride, the base acting as HCl acceptor. For weakly nucleophilic NH-acidic amines (amides and azoles), the reaction begins with the deprotonation under the action of the base, then the N-centred anion attacks the carbonyl group of compound **12**.

Some adamantylcarbonyl-containing heterocycles **13** showed high biological activity. For example, 2-[4-(1-adamantylcarbonyl)piperazino]pyrimidine (**13d**) was shown[24] to actively affect serotonin 5-HT1A and 5-HT2 receptors and to be a potential anxiolytic and antidepressant agent. 1-(1-Adamantylcarbonyl)-3-benzyl-2-(4-hydroxyphenyl)-2,3-dihydroquinazolin-4(1*H*)-one (**13q**) showed moderate antiinflammatory and anticonvulsant activity.[25] 1-(1-Adamantylcarbonyl)pyrrolidine-2-carboxylic acid (**13j**) has an antiamnesic action.[26]

The reduction of the carbonyl group in heterocyclic adamantyl ketones **13a**,**f**,**g**,**i**,**k** gives rise to compounds **14a**,**f**,**g**,**i**,**k** in which the adamantyl moiety is attached to the nitrogen atom *via* the methylene bridge (Scheme 9).[11, 12, 27]

Scheme 9

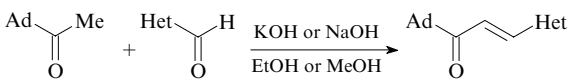


13a,**f**,**g**,**i**,**k** **14a**,**f**,**g**,**i**,**k** (83%–95%)

Compound	R^1	R^2	X	Reducing agent	Solvent
a	H	H	O	$LiAlH_4$	Et_2O (THF)
f	H	H	CH_2	BF_3	MeOH
g	H	H	$(CH_2)_2$	BH_3	THF
i	Bu^t	H	–	BH_3	THF
k	Me	Me	–	$LiAlH_4$	THF

The Claisen–Schmidt condensation is a convenient method for coupling the heterocyclic and adamantane moieties. Thus, the reaction of 1-adamantyl methyl ketone (**11a**) with heterocyclic aldehydes in ethanol in the presence of KOH or NaOH affords adamantyl(hetaryl)-containing chalcones **15a–d** (Scheme 10).[28–30]

Scheme 10



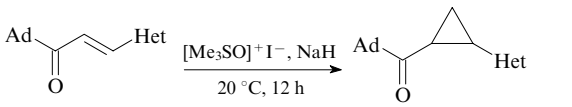
11a **15a–d** (54%–61%)

15: Het is quinolin-3-yl (**a**), pyridin-3-yl (**b**), pyridin-4-yl (**c**), 1,4-benzodioxan-6-yl (**d**)

Compounds **15a**,**d** are potent and selective modulators of metabotropic glutamate receptors (mGluR1), while derivatives **15b**,**c** possess a moderate hepatoprotective action.[28]

Using the Corey–Chaykovsky reaction, *i.e.* the reaction of α,β-unsaturated ketones **15a**,**b**,**e**,**f** with trimethylsulfoxonium iodide, hetarylcyclopropyl ketones **16a**,**b**,**e**,**f** were synthesized (Scheme 11).[29] The authors showed that compounds **16** are selective antagonists of metabotropic glutamate receptors.

Scheme 11

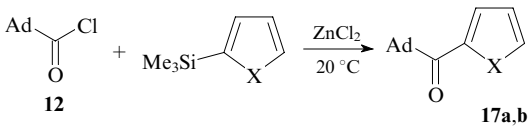


15a,**b**,**e**,**f** **16a**,**b**,**e**,**f** (70%–90%)

Het is quinolin-3-yl (**a**), pyridin-3-yl (**b**), 6-methoxypyridin-3-yl (**e**), 6-morpholinopyridin-3-yl (**f**)

Adamantane-1-carboxylic acid chloride (**12**) reacts with 2-(trimethylsilyl)furan in the presence of $ZnCl_2$ yielding 1-adamantyl 2-furyl ketone (**17a**) (Scheme 12).[31] Thiophene analogue **17b** was also obtained by this route.

Scheme 12

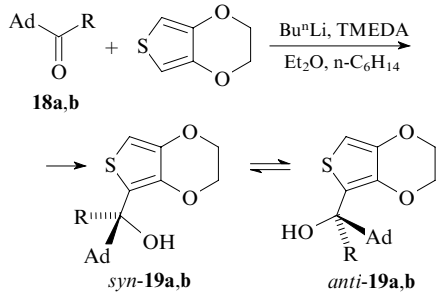


12 **17a**,**b**

X = O (**a**, 61% yield), S (**b**, 82%)

Adamantyl ketones having no acidic hydrogen atoms in the α-position such as 1-adamantyl *tert*-butyl ketone (**18a**) and di(1-adamantyl) ketone (**18b**) form equilibrium mixtures of *syn*- and *anti*-rotamers **19a**,**b** in reactions with 3,4-(ethylenedioxy)thiophene at room temperature in an n-butyllithium–*N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) mixture in diethyl ether and hexane (Scheme 13).[32] The solvent and the temperature influence the position of equilibrium.

Scheme 13



R = But (**a**), Ad (**b**)

Thus, reactions of adamantyl-containing ketones with heterocycles gave rise to various heterocyclic systems bearing the adamantyl substituent.

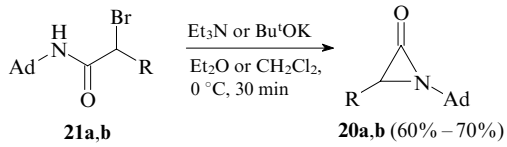
IV. Heterocyclization of carbonyl derivatives of adamantane

Numerous examples of various cyclizations involving mono- and dicarbonyl adamantane derivatives have been reported. This method was used to prepare three-, four-, five- and six-membered heterocycles having nitrogen, sulfur and oxygen atom(s). The subject matter of this section is classified according to the type of the heterocyclic compound formed upon such transformations.

1. Three-membered heterocycles

Aziridine rings, for example, 1-(1-adamantyl)aziridin-2-one derivatives **20a**,**b**, are formed upon the cyclocondensation of α-bromocarboxylic acid *N*-(1-adamantyl)amides **21a**,**b**. The reaction proceeds under the action of a base such as triethylamine or potassium *tert*-butoxide (Scheme 14).[33] Note that compound **20b** comprises two adamantane moieties bonded to the carbon and nitrogen atoms of the heterocycle.

Scheme 14

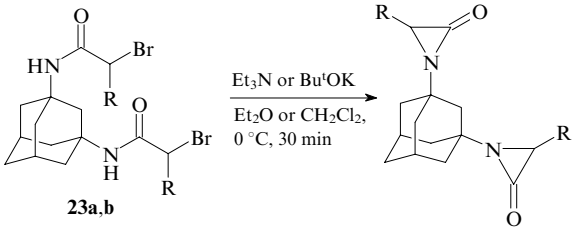


R = Bu^t (**a**), Ad (**b**)

Two aziridine rings in the 1- and 3-positions of adamantanes **22a**,**b** are formed in a similar manner. Diamides **23a**,**b** were used as the starting compounds (Scheme 15).[2] This time the molecule of product **22b** comprises three adamantane cages.

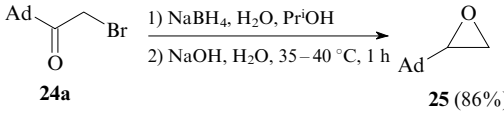
2-(1-Adamantyl)oxirane (**25**) was synthesized starting from 1-adamantyl bromomethyl ketone (**24a**).[34] At the first step, the reaction with sodium tetrahydroborate yields the corresponding alcohol, which cyclizes to give oxirane **25** upon treatment with aqueous sodium hydroxide (Scheme 16).

Scheme 15



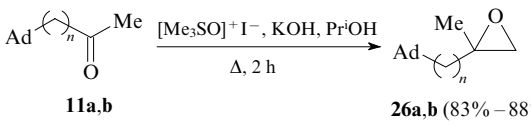
R = Bu^t (**a**), Ad (**b**)

Scheme 16



Adamantyl methyl ketone **11a** and its analogue **11b** reacts with the Corey–Chaykovsky reagent in the presence of an alkali to afford 2-(adamantylmethyl)oxiranes **26a**,**b** in high yields (Scheme 17).[2]

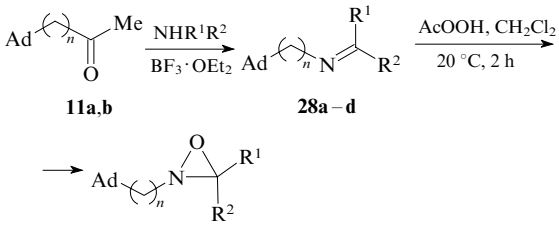
Scheme 17



n = 0 (**a**), 1 (**b**)

Ketones **11a**,**b** also served as the starting compounds in the synthesis of adamantyl-containing oxaziridines **27a**–**d**.[35] First, the ketones were made to react with amines in the presence of boron trifluoride etherate to give Schiff bases **28a**–**d**, which were treated with peracetic acid without isolation (Scheme 18). As a result, products **27a**–**d** are formed in moderate yields.

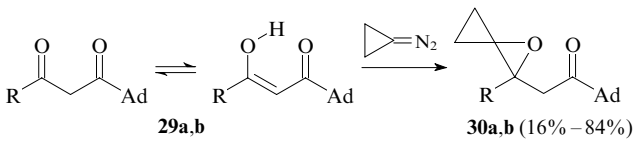
Scheme 18



27, **28**: *n* = 0, R^2 = H: R^1 = Ph (**a**), 2-furyl (**b**);
n = 1: R^1 = Ph, R^2 = H (**c**); R^1–R^2 = (CH$_2$)$_5$ (**d**)

Fluoro-substituted adamantane-derived β-diketones **29a**,**b** obtained by the reaction of 1-adamantyl methyl ketone (**11a**) with ethyl trifluoroacetate and ethyl difluoroacetate were made to react with diazocyclopropane.[36] Obviously, in this case, the reaction involves the enol forms of diketones, resulting in the formation of fluorinated oxaspiropentanes **30a**,**b** (Scheme 19).

Scheme 19

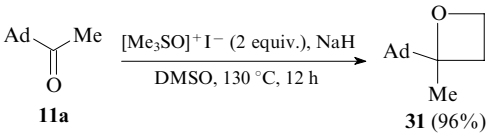


R = CF_3 (**a**), CHF_2 (**b**)

2. Four-membered heterocycles

Representatives of adamantyl-containing four-membered heterocycles were obtained from adamantane-derived ketones and esters of keto acids. Thus, the reaction of ketone **11a** with 2 equiv. of trimethylsulfoxonium iodide in the presence of sodium hydride in DMSO yields 2-(1-adamantyl)-2-methyloxetane (**31**) (Scheme 20).[37]

Scheme 20

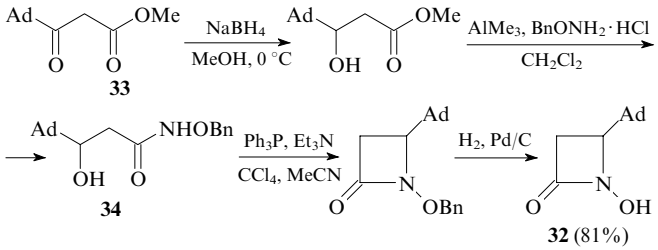


11a **31** (96%)

Evidently, initially formed in this reaction is oxirane **26a** (see Scheme 17) and subsequently an additional methylene group is inserted into it under more drastic conditions.

Synthesis of 4-(1-adamantyl)-1-hydroxyazetidin-2-one (**32**) has been reported.[38] The keto group in methyl 3-(1-adamantyl)-3-oxopropanoate (**33**) is reduced by the action of sodium tetrahydroborate, and then the methoxy group is converted to the hydroxylamine group. The subsequent steps of cyclization–dehydration of alcohol **34** in the presence of triphenylphosphine and triethylamine and removal of the benzyl protecting group by hydrogenation over Pd/C afford product **32** (Scheme 21).

Scheme 21



33 **34** **32** (81%)

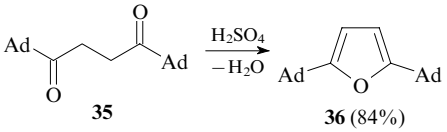
3. Five-membered heterocycles

The synthesis of various five-membered heterocycles starting from adamantane-derived mono- and diketones is widely presented in literature. Heterocyclization reactions provide an approach to adamantyl-containing pyrroles, furans, thiophenes, azoles, azines and their fused derivatives. For convenience, the data concerning these derivatives are given in order of increasing complexity of the product structure.

a. Rings with a single heteroatom

1,4-Disubstituted butane-1,4-diones are known to be convenient starting compounds for one-step heterocyclization to give furan, thiophene and pyrrole derivatives (the Paal–Knorr reaction). Thus cyclocondensation of 1,4-di(1-adamantyl)butane-1,4-dione (**35**) induced by concentrated sulfuric acid yields 2,5-di(1-adamantyl)furan (**36**) (Scheme 22).[39]

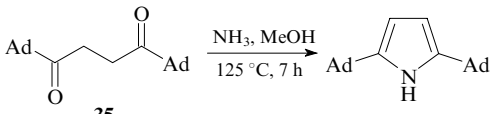
Scheme 22



35 **36** (84%)

Heating of 1,4-diadamantylbutane-1,4-dione **35** with ammonia in a sealed ampoule for 7 h furnishes 2,5-di(1-adamantyl)pyrrole (**37**) in a high yield (Scheme 23).[39]

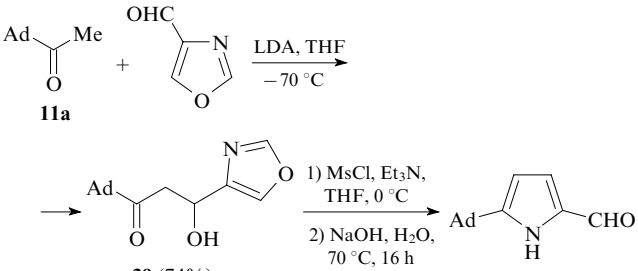
Scheme 23



35 **37** (95%)

Two-step synthesis of 2-(1-adamantyl)-5-formylpyrrole (**38**) starting from the ketone **11a** has been described.[40] First, ketone **11a** adds to 4-formyloxazole to give aldol **39** treatment of which with the methanesulfonyl chloride (MsCl)–Et_3N system followed by hydrolysis with aqueous NaOH affords adamantyl-containing pyrrole-2-carbaldehyde **38** (Scheme 24).

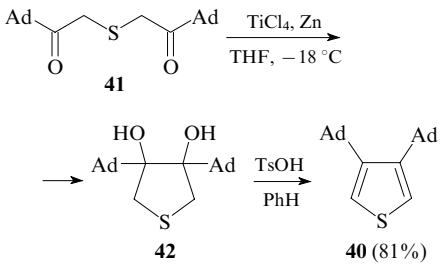
Scheme 24



11a **39** (74%) **38** (72%)

An unusual approach to the synthesis of 3,4-di(1-adamantyl)thiophene (**40**) has been reported.[41] Upon pinacoline reduction under the action of Zn–$TiCl_4$ system, diketo sulfide **41** cyclisizes into diol **42**, which is dehydrated in the presence of *p*-toluenesulfonic acid to give thiophene (Scheme 25).

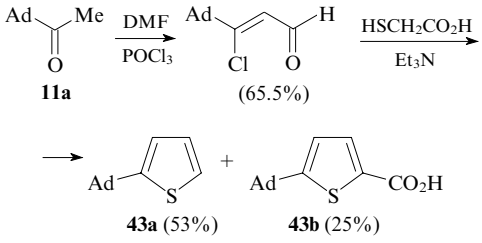
Scheme 25



41 **42** **40** (81%)

When formylated under Vilsmeier conditions, ketone **11a** transformed to 3-(1-adamantyl)-3-chloroprop-2-enal. The latter was made to react with thioglycolic acid. As a result, a mixture of adamantyl derivatives of thiophene **43a**,**b** was obtained (Scheme 26).[42]

Scheme 26

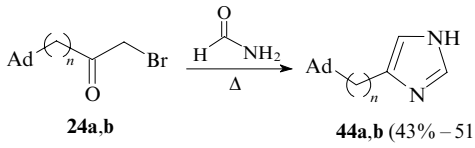


11a (65.5%) **43a** (53%) **43b** (25%)

b. Rings with two or more heteroatoms

Azoles constitute the most numerous group of adamantyl-containing heterocyclic compounds obtained from carbonyl derivatives of adamantane. In most of these compounds, the adamantane cage is directly attached to a five-membered ring, but in some cases, these two moieties are spaced either by the methylene bridge or by a carbonyl group. As cyclization reagents, *e.g.*, adamantyl-containing bromomethyl ketones are used. Heating of ketones **24a**,**b** with formamide affords imidazole derivatives **44a**,**b** (Scheme 27).[43]

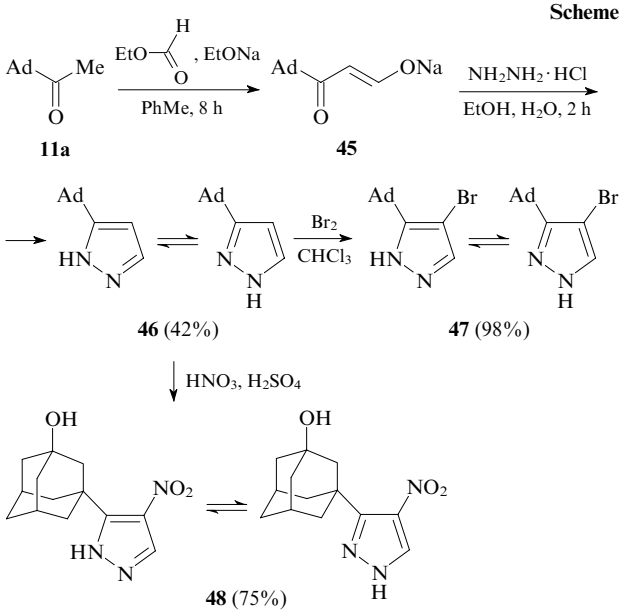
Scheme 27



n = 0 (**a**), 1 (**b**)

To obtain adamantyl-substituted pyrazoles and isoxazoles, the cyclization of hydrazine and hydroxylamine derivatives is performed with sodium enolate **45**. The latter if formed upon the reaction of ketone **11a** with ethyl formate in the presence of sodium ethoxide in toluene. Enolate **45** reacts with hydrazine monohydrochloride to give 3-(1-adamantyl)-2*H*-pyrazole (**46**) (Scheme 28).[44] Treatment of pyrazole **46** with bromine in chloroform affords 3(5)-(1-adamantyl)-4-bromopyrazole (**47**), while treatment of **46** with a mixture of nitric and sulfuric acids yields 3(5)-(3-hydroxy-1-adamantyl)-4-nitropyrazole (**48**) (see Scheme 28). Note that compounds **46**–**48** exist as two equilibrium tautomeric forms due to the migration of the proton at the nitrogen atom.

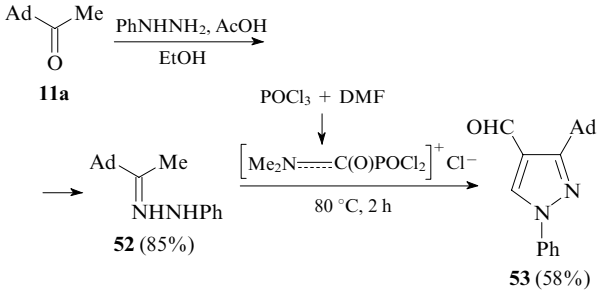
Scheme 28



Sodium enolate **45** serves as a convenient starting compound for the synthesis of a wide range of biologically active heterocycles. Thus its reaction with hydroxylamine hydrochloride and hydrazine dihydrochloride in 50% aqueous methanol affords 5-(1-adamantyl)-5-hydroxy-4,5-dihydroisoxazole (**49**) (41% yield) and 3-(1-adamantyl)-2*H*-pyrazole (**46**) (77% yield). Under the action of methylamine, compound **45** transforms into enamino ketone **50**, which reacts with hydroxylamine hydrochloride to give 3-(1-adamantyl)isoxazole (**51**) in 46% yield (Scheme 29).[45]

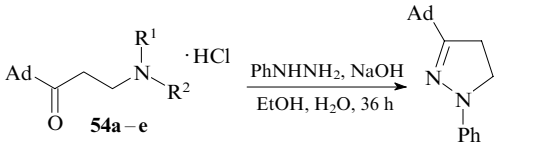
The reaction of ketone **11a** with phenylhydrazine in ethanol with addition of a small amount of acetic acid furnishes phenylhydrazone **52**. The Vilsmeier reaction of the latter yields 3-(1-adamantyl)-1-phenylpyrazole-4-carbaldehyde (**53**) (Scheme 30).[46]

Scheme 30



The reactions of adamantyl 3-aminopropyl ketone hydrochlorides **54a**–**e** with phenylhydrazine in ethanol in the presence of NaOH have been described.[47] The product of these reactions is 3-(1-adamantyl)-1-phenyl-4,5-dihydropyrazole (**55**) (Scheme 31).

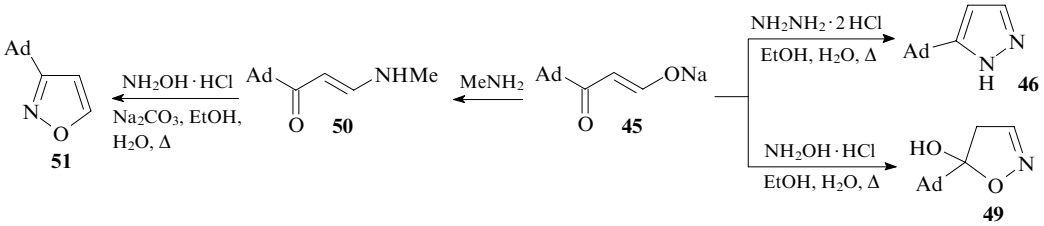
Scheme 31



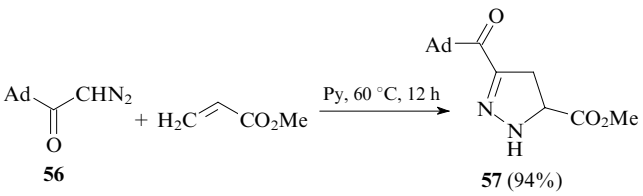
R^1 = Et: R^2 = Et (**a**), Ad (**b**); R^1 = R^2 = Bn (**c**); NR^1R^2 is piperidino (**d**), morpholino (**e**)

A series of adamantyl-containing azoles were obtained from (1-adamantylcarbonyl)diazomethane (**56**) *via* 1,3-dipolar cycloaddition reactions.[48] The starting diazoketone was synthesized by the reaction of acid chloride **12** with diazomethane at room temperature (72% yield) according to a reported[49] procedure. Under the action of methyl acrylate in pyridine (Py), diazoketone **56** cyclisizes to give methyl 3-(1-adamantylcarbonyl)-4,5-dihydro-1*H*-pyrazole-5-carboxylate (**57**) (Scheme 32).[48]

Scheme 29



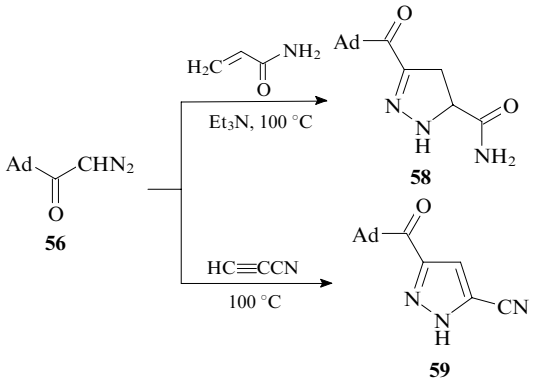
Scheme 32



A series of adamantyl-substituted pyrazoles were obtained from pyrazoline **57**.[48]

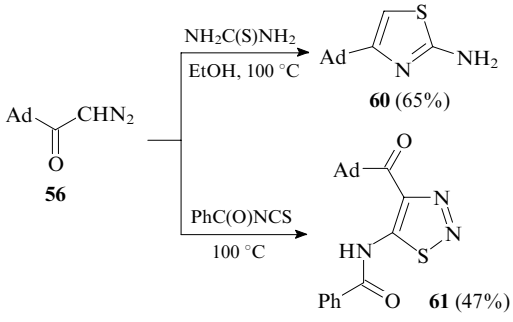
The reactions of diazoketone **56** with the acrylamide and propiolic acid nitrile give 3-adamantylcarbonyl-5-carbamoyl-4,5-dihydropyrazole (**58**) (14% yield) and 3-adamantylcarbonyl-5-cyanopyrazole (**59**) (92% yield) (Scheme 33).[49]

Scheme 33



Heating of diazoketone **56** with thiourea affords 4-(1-adamantyl)-2-aminothiazole (**60**), while a similar reaction with benzoyl isothiocyanate yields 4-(1-adamantylcarbonyl)-5-benzoylamino-1,2,3-thiadiazole (**61**) (Scheme 34).[49]

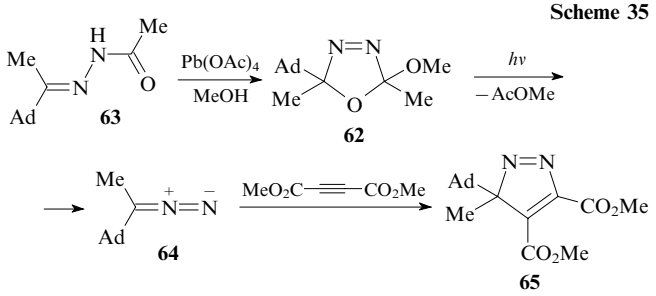
Scheme 34



2-(1-Adamantyl)-2,5-dimethyl-5-methoxy-2,5-dihydro-1,3,4-oxadiazole (**62**) was obtained by cyclization of *N*-[1-(1-adamantylethylidene)]acetohydrazide (**63**) in the presence of $Pb(OAc)_4$ in methanol.[50] During photolysis, oxadiazole **62** eliminates the methyl acetate molecule to be converted to 1-(1-diazoethyl)adamantane (**64**). The latter adds to dimethyl acetylenedicarboxylate yielding unstable dimethyl 3-(1-adamantyl)-3-methyl-3*H*-pyrazole-4,5-dicarboxylate (**65**), which can be detected and identified only at very low temperatures (−78 °C) (Scheme 35).

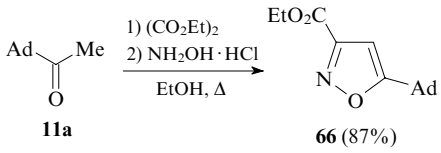
Adamantyl methyl ketone **11a** is acylated by diethyl oxalate in the presence of Bu^tOK in THF; the subsequent reaction with hydroxylamine hydrochloride in ethanol

Scheme 35



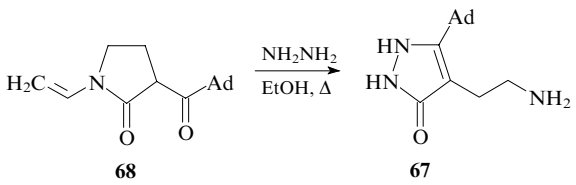
affords ethyl 5-(1-adamantyl)isoxazole-3-carboxylate (**66**) (Scheme 36).[51]

Scheme 36



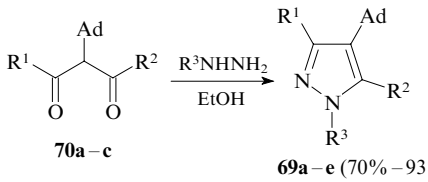
Preparation of 5-(1-adamantyl)-4-(2-aminoethyl)-1,2-dihydro-3*H*-pyrazol-3-one (**67**) has been reported.[52] Condensation of 3-(1-adamantylcarbonyl)-1-vinylpyrrolidin-2-one (**68**) with hydrazine hydrate was carried out in ethanol upon heating, the product yield being 88% (Scheme 37).

Scheme 37



A series of derivatives of 4-(1-adamantyl)pyrazoles **69a–e** were synthesized through the cyclization of adamantyl-containing 1,3-diketones **70a–c** with hydrazines and monosubstituted hydrazines in ethanol upon reflux (Scheme 38).[53]

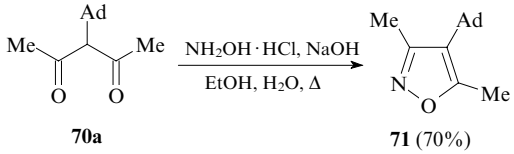
Scheme 38



69: R^1 = Me, R^3 = H: R^2 = Me (**a**), Ph (**b**); R^1 = R^2 = Ph: R^3 = H (**c**), Ph (**d**); R^1 = R^2 = Me, R^3 = Ph (**e**);
70: R^1 = R^2 = Me (**a**), Ph (**b**); R^1 = Me, R^2 = Ph (**c**)

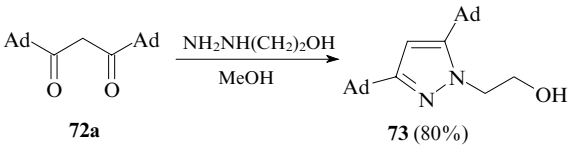
Diketone **70a** reacts with hydroxylamine hydrochloride in aqueous ethanol in the presence of NaOH to yield 4-(1-adamantyl)-3,5-dimethylisoxazole (**71**) (Scheme 39).[53]

Scheme 39



Diadamantylpropane-1,3-dione **72a** reacts with 2-hydrazinoethanol giving rise to 3,5-di(1-adamantyl)-1-(2-hydroxyethyl)-1*H*-pyrazole (**73**) (Scheme 40).[54] This compound is not the only reaction product as cyclization may also involve the hydroxyethyl group (see Section IV.5).

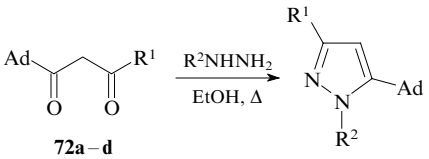
Scheme 40



72a **73** (80%)

The synthesis of a wide range of pyrazoles **74a–l** derived from adamantyl-containing 1,3-diketones **72a–d** has been described.[55,56] Various dinucleophilic reagents such as hydrazine, phenylhydrazine, semicarbazide and its thio analogue and substituted pyrazolyl- and pyridinehydrazines were introduced into the cycloaddition reactions (Scheme 41).

Scheme 41



72a–d **74a–l** (40%–76%)

72: R^1 = Ad (**a**), Ph (**b**), Me (**c**), Et (**d**);
74: R^2 = H: R^1 = Ad (**a**), Ph (**b**); R^1 = Me: R^2 = H (**c**), Ph (**d**), $C(O)NH_2 \cdot HCl$ (**e**), $C(S)NH_2$ (**f**), 3-methyl-4-phenyl-1*H*-pyrazol-5-yl (**g**), 3,5-dichloropyridin-2-yl (**h**); R^1 = Et: R^2 = H (**i**), Ph (**j**), $C(O)NH_2 \cdot HCl$ (**k**), $C(S)NH_2$ (**l**)

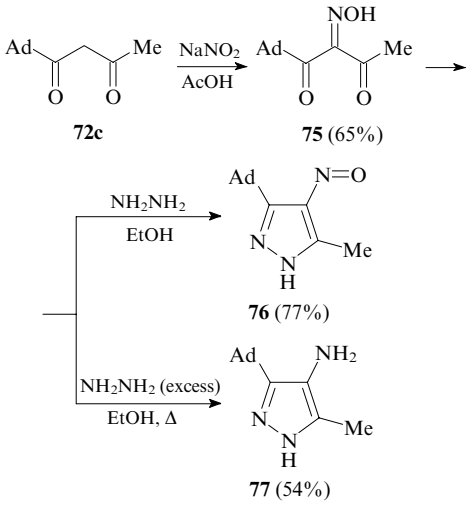
Using quantum-chemical calculations (DFT, B3LYP/6-31G** basis set) and NMR spectroscopy data (heteronuclear HMBC $^1H-^{13}C$ and $^1H-^{15}N$ techniques), the reaction was shown to give only one of the two possible isomers, namely, the product of the initial attack of one of the dinucleophile nitrogen atoms on the carbon atom of the carbonyl group located near the aliphatic substituent.[57] Adamantyl-containing pyrazoles **74** were tested against the vaccinia virus (commercial LIVP strain), cowpox virus (Grishak strain) and mousepox virus (K-1 strain) and showed a moderate activity.[58]

For the synthesis of adamantane nitroso- and aminopyrazoles *via* nitrosation of diketone **72c**, 1-(1-adamantyl)-butane-1,2,3-trione 2-oxime (**75**) was obtained.[59] Compound **75** reacts with hydrazine in an equimolar ratio at room temperature to give 3-(1-adamantyl)-5-methyl-4-nitroso-1*H*-pyrazole (**76**). On heating of oxime **75** with an excess of hydrazine, 3-(1-adamantyl)-4-amino-5-methyl-1*H*-pyrazole (**77**) was isolated. Apparently, this product results from reduction of the NO group in compound **76** with an excess of hydrazine (Scheme 42).

Esters of adamantane keto acids **78a**,**b** were converted to 5-adamantyl(methyl)pyrazolones **79a–d**[60,61] and 3-(1-adamantyl)isoxazol-5(4*H*)-one (**80**) in which prototropic tautomerism was detected (Scheme 43).[60]

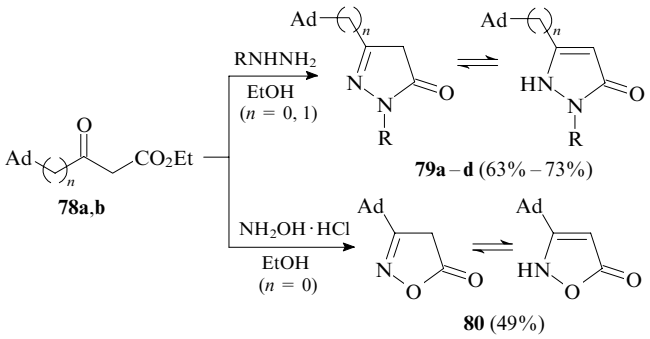
When ethyl di(adamantylcarbonyl)acetate (**81**) reacts with hydrazine hydrate, both ketone groups are involved. Ethyl 3,5-di(1-adamantyl)-1*H*-pyrazole-4-carboxylate (**82**) is formed in a high yield as a single reaction product (Scheme 44).[61]

Scheme 42



72c **75** (65%) **76** (77%) **77** (54%)

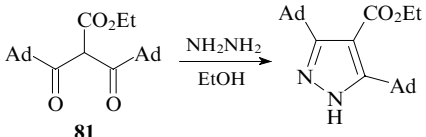
Scheme 43



79a–d (63%–73%) **80** (49%)

78: n = 0 (**a**), 1 (**b**);
79: n = 0: R = H (**a**), $C(O)NH_2$ (**b**), 4-$O_2NC_6H_4$ (**c**);
n = 1, R = H (**d**)

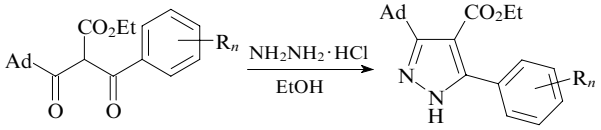
Scheme 44



81 **82** (86%)

The reactions of structurally similar fluorinated diketo esters **83a–c** with hydrazine hydrochloride, resulting in pyrazoles **84a–c**, have been reported.[62] In this case, only keto groups participate in cyclization, whereas the ester functionality in compounds **84** remains unchanged (Scheme 45).

Scheme 45

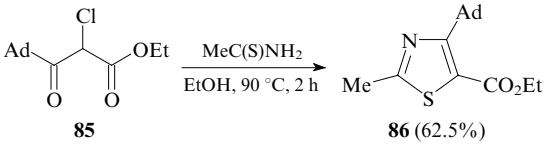


83a–c **84a–c** (63%–80%)

R_n = 4-F (**a**), 2,3,4,5-F_4 (**b**), 2-Cl-4-F (**c**)

Ethyl α-(1-adamantylcarbonyl)-α-chloroacetate (**85**) reacts with thioamide in ethanol yielding ethyl 4-(1-adamantyl)-2-methylthiazole-5-carboxylate (**86**) (Scheme 46).[63]

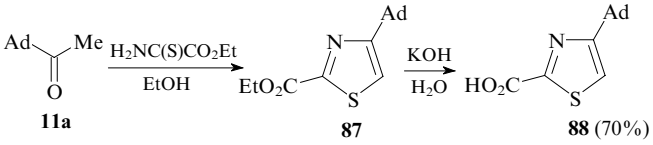
Scheme 46



85 **86** (62.5%)

A series of five-membered heterocyclic compounds having two or more heteroatoms were prepared based of adamantyl methyl ketone **11a**. For instance, the reaction of ketone **11a** with ethyl thiocarbamoylformate affords ethyl 4-(1-adamantyl)-1,3-thiazole-2-carboxylate (**87**). Under the action of aqueous KOH, the latter is hydrolyzed to give 4-(1-adamantyl)-1,3-thiazole-2-carboxylic acid (**88**) (Scheme 47).[64]

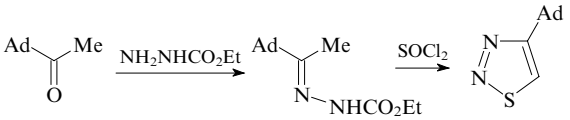
Scheme 47



11a **87** **88** (70%)

4-(1-Adamantyl)-1,2,3-thiadiazole (**89**) was obtained[65] by the procedure of Hurd and Mori. First, ketone **11a** was made to react with ethoxycarbonylhydrazine yielding adamantyl-containing hydrazone, which cyclized under the action of thionyl chloride to give thiadiazole **89** (Scheme 48).

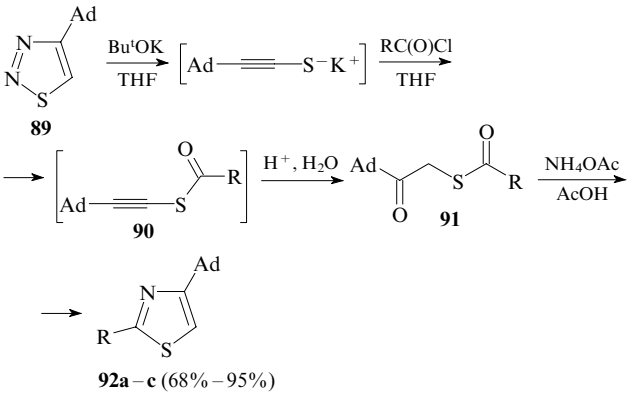
Scheme 48



11a (94%) **89** (72%)

The reaction of thiadiazole **89** with potassium *tert*-butoxide leads to generation of potassium 2-(1-adamantyl)ethynethiolate, which reacts with aromatic carboxylic acid chlorides to give unstable *S*-[2-(1-adamantyl)ethynyl]arenecarbothioates **90**. Upon acid hydrolysis, intermediates **90** are converted to *S*-[2-(1-adamantyl)-2-oxoethyl]arenecarbothioates **91**. The latter react with ammonium acetate in acetic acid to afford 4-(1-adamantyl)-2-aryl-1,3-thiazoles **92a–c** (Scheme 49).[66]

Scheme 49

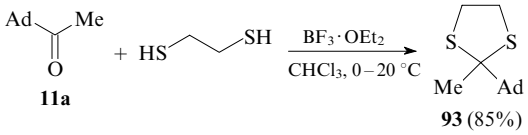


89 **90** **91** **92a–c** (68%–95%)

R = 4-ClC_6H_5 (**a**), 1-benzofuran-2-yl (**b**), 3-O_2N-4-ClC_6H_3 (**c**)

The reaction of ketone **11a** with ethane-1,2-dithiol in $CHCl_3$ in the presence of boron trifluoride etherate yields 2-(1-adamantyl)-2-methyl-1,3-dithiolane (**93**) in high yield (Scheme 50).[67]

Scheme 50



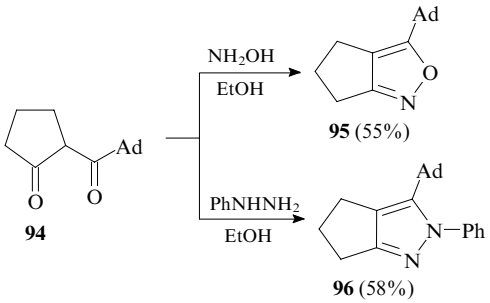
11a **93** (85%)

c. Fused five-membered rings

Examples of heterocyclization of the carbonyl derivatives of adamantane, giving rise to fused heterocycles with a heteroatom in the five-membered ring or at the bridgehead position, have been reported in the literature.

The reactions of a cyclic diketone, 2-(1-adamantylcarbonyl)cyclopentanone (**94**), with hydroxylamine and phenylhydrazine afford fused heterocycles such as 3-(1-adamantyl)-5,6-dihydro-4*H*-cyclopenta[*c*]isoxazole (**95**) and 3-(1-adamantyl)-2-phenyl-2,4,5,6-tetrahydrocyclopenta[*c*]pyrazole (**96**), respectively (Scheme 51).[68]

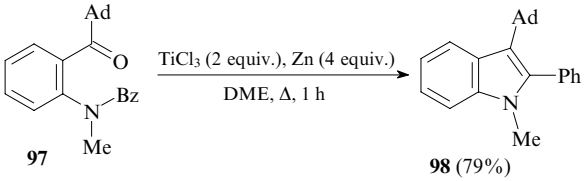
Scheme 51



94 **95** (55%) **96** (58%)

The intramolecular cyclization of *N*-[2-(1-adamantylcarbonyl)phenyl]-*N*-methylbenzamide (**97**) (reductive oxygenation) under conditions of the McMurry reaction ($Zn-TiCl_3$ system) was carried out.[69] This procedure was used to obtain 3-(1-adamantyl)-1-methyl-2-phenyl-1*H*-indole (**98**) (Scheme 52).

Scheme 52

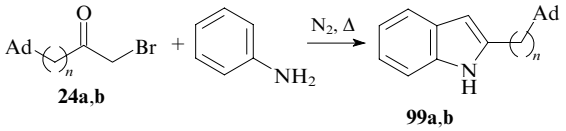


97 **98** (79%)

DME is dimethoxyethane

Adamantyl-containing indoles **99a**,**b** were also synthesized from aniline and α-bromomethyl ketones **24a**,**b** according to Bischler (Scheme 53).[43]

Scheme 53

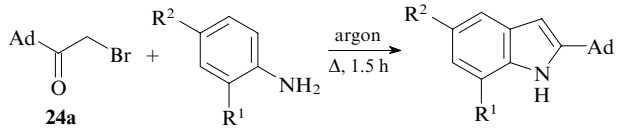


24a,**b** **99a**,**b**

n = 0 (**a**, 94% yield), 1 (**b**, 48%)

The synthesis of 2-(1-adamantyl)-1*H*-indoles **100a–c** by the reaction of α-bromomethyl ketone **24a** with substituted anilines has been described[70] (Scheme 54). The process takes place on refluxing of the reactants for 1.5 h. Under the same conditions, indole **99a** unsubstituted in the benzene ring was also obtained in 91% yield.

Scheme 54

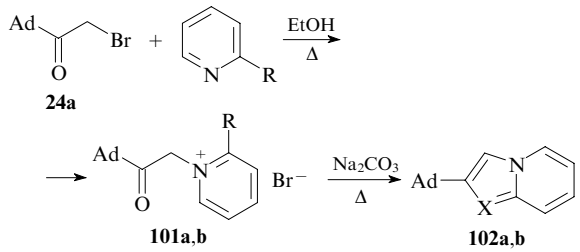


24a **100a–c**

100: $R^1 = R^2 = Me$ (**a**, 85% yield);
$R^2 = H$: $R^1 = Me$ (**b**, 89%), OMe (**c**, 39%)

The reaction of ketone **24a** with 2-methylpyridine was found to afford quaternary salt **101a** (yield of up to 50%), which cyclizes upon heating in the presence of a base (sodium carbonate) to give 2-(1-adamantyl)indolizine (**102a**) through the intermediate anhydro-base formation (Scheme 55).[71] Following the same scheme, salt **101b** and 2-(1-adamantyl)imidazo[4,2-*a*]pyridine (**102b**) were obtained starting from 2-aminopyridine.

Scheme 55

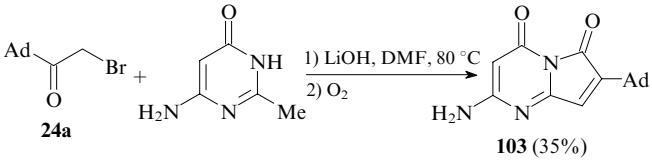


24a **101a,b** **102a,b**

101, **102**: R = Me, X = CH (**a**, 58% yield);
$R = NH_2$, X = N (**b**, 28%)

In a similar way, bromoketone **24a** reacts also with 6-amino-2-methylpyrimidin-4(3*H*)-one yielding 7-(1-adamantyl)-2-aminopyrrole[1,2-*a*]pyrimidine-4,6-dione (**103**) (Scheme 56).[72] However, the mechanism of this transformation is quite different. The significantly reduced nucleophilicity of the nitrogen atoms of pyrimidone impedes the direct quaternization, but the strong base (LiOH) present in the medium generates an anion from the amide moiety, and this anion is alkylated at the N^- atom. The keto group in the pyrrole ring is formed upon oxidation by the atmospheric oxygen. The total mechanism of this transformation is given in the original article.[72]

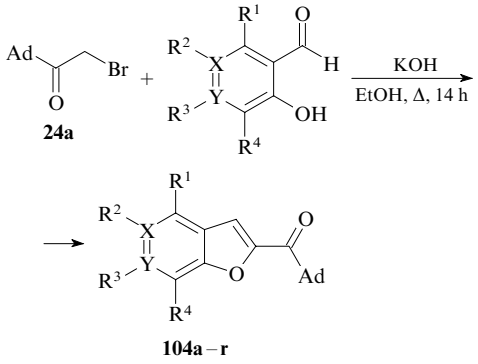
Scheme 56



24a **103** (35%)

Adamantyl-containing annulated furans have also been described in the literature. The reaction of α-bromoketone **24a** with derivatives of salicylaldehyde in the presence of a base produces the corresponding benzofurans **104a–n**, while the reaction of **24a** with derivatives of 3-hydroxypyridine-4-carbaldehyde and 4-hydroxypyridine-3-carbaldehyde yields furopyridines **104o–r** (Scheme 57).[28] Obviously, the reaction begins with the O-alkylation of the *ortho*-hydroxyaldehyde moiety followed by the cyclization step.

Scheme 57



24a **104a–r**

104: X = Y = C: $R^1 = R^2 = R^3 = H$: R^4 = H (**a**), OEt (**b**);
$R^1 = R^2 = R^4 = H$: $R^3 = NEt_2$ (**c**), F (**d**), OMe (**e**), Br (**f**), morpholino (**g**), piperidino (**h**), pyrrolidino (**i**), pyridin-3-yl (**j**);
$R^1 = R^3 = R^4 = H$: R^2 = OMe (**k**), Br (**l**), NO_2 (**m**);
R^1 = OMe, $R^2 = R^3 = R^4$ = H (**n**);
X = C, R^3Y = N: $R^2 = R^4 = H$, $R^1 = CH_2OH$ (**o**); $R^2 = H$, $R^1 = R^4$ = Me (**p**); $R^2 = H$, $R^1 = CH_2OMe$, R^4 = Me (**q**);
R^2X = N, Y = C, $R^1 = R^3 = R^4 = H$ (**r**)

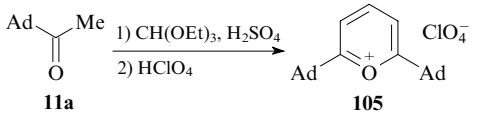
4. Six-membered rings

There exist numerous synthetic routes to six-membered heterocycles contining an adamantane substituent based on cyclization of adamantane ketones. In this way, adamantyl-containing azines (pyridines, pyrimidines, pyridazines) and pyrylium salts as well as their fused analogues were obtained.

a. Rings with one and two heteroatoms

Condensation of two molecules of ketone **11a** with ethyl orthoformate in the presence of sulfuric acid followed by treatment with perchloric acid gives 2,6-di(1-adamantyl)-pyrylium perchlorate (**105**) in 22% yield (Scheme 58).[73]

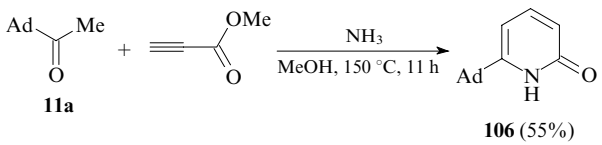
Scheme 58



11a **105**

6-(1-Adamantyl)pyridin-2(1*H*)-one is formed (**106**) upon the reaction of ketone **11a** with methyl propiolate and ammonia in methanol at 150 °C over a period of 11 h (Scheme 59).[74]

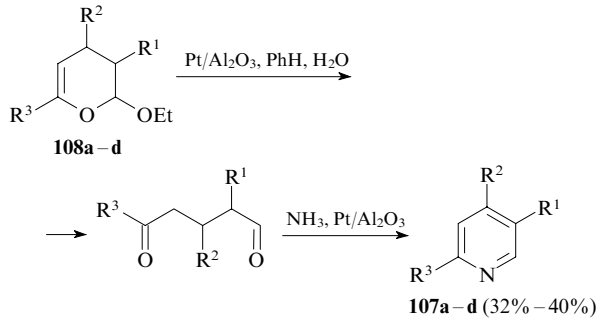
Scheme 59



11a **106** (55%)

Adamantyl-containing pyridines **107a–d** were synthesized from 1,5-dicarbonyl compounds obtained *in situ* upon ring opening in the corresponding 2,3-dihydropyrans **108a–d**.[75] The reaction with ammonia in the presence of platinum catalyst affords products **107a–d** in moderate yields (Scheme 60).

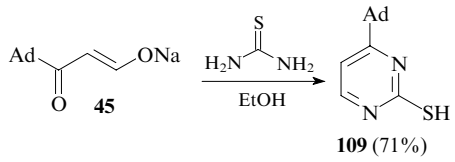
Scheme 60



$R^2 = R^3 = H$: R^1 = Ad (**a**), CH_2Ad (**b**); $R^1 = R^3 = H$, $R^2 = CH_2Ad$ (**c**); $R^1 = R^2 = H$, R^3 = Ad (**d**)

4-(1-Adamantyl)pyrimidine-2-thiol (**109**) was obtained by cycloaddition reaction between sodium enolate **45** and thiourea (Scheme 61).[45]

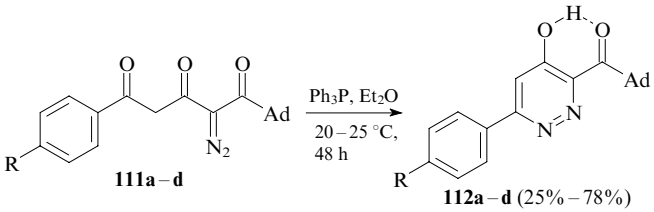
Scheme 61



The synthesis of 2-(1-adamantylethynyl)pyrimidine-5-carbaldehyde (**110**) has been described.[76] The researchers used the Sonogashira cross-coupling reaction between adamantylacetylene and 5-bromo-2-iodopyrimidine followed by formylation. The starting components were synthesized from ketone **11a** and 2-hydroxypyrimidine hydrochloride (Scheme 62).

A study [77] considers intramolecular cyclization of 5-aryl-2-diazo-1,3,5-pentanetriones **111a–d** having an adamantyl substituent in the 1-position. The heterocyclization was carried out in anhydrous Et_2O in the presence of triphenylphosphine during 48 h. As a result, 3-(1-adamantylcarbonyl)-4-hydroxy-6-arylpyridazines **112a–d** were isolated (Scheme 63).

Scheme 63

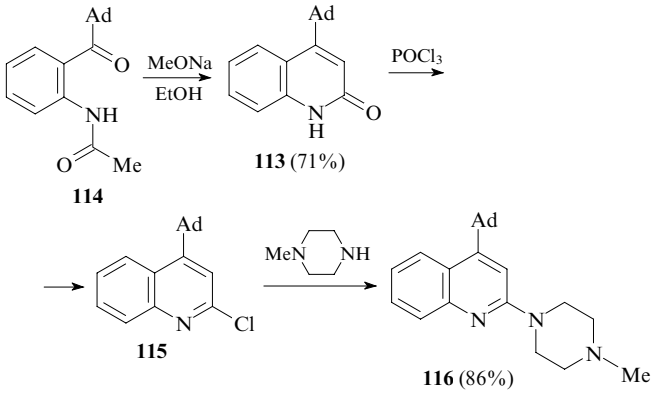


R = H (**a**), Me (**b**), OMe (**c**), Cl (**d**)

b. Fused six-membered heterocycles

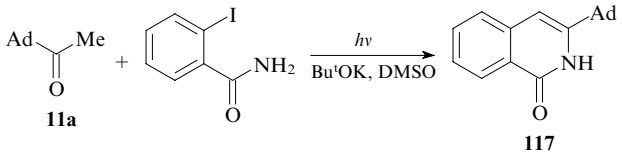
4-(1-Adamantyl)quinolin-2(1*H*)-one (**113**) was synthesized [78] by treatment of *N*-[2-(1-adamantylcarbonyl)phenyl]acetamide (**114**) with sodium methoxide in ethanol. Chlorination of quinolinone **113** with phosphorus(V) oxychloride affords 4-(1-adamantyl)-2-chloroquinoline (**115**), which subsequently reacts with *N*-methylpiperazine to yield 4-(1-adamantyl)-2-(4-methylpiperazino)quinoline (**116**) (Scheme 64).

Scheme 64



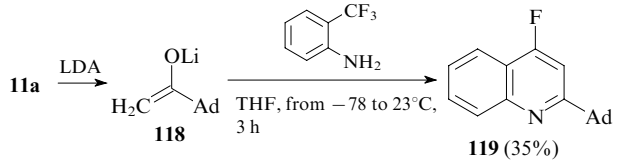
There are several examples of the synthesis of fused six-membered heterocycles based on adamantyl methyl ketone **11a**. The reaction of ketone **11a** with 2-iodobenzamide photoinitiated in the presence of Bu^tOK in DMSO produced 3-(1-adamantyl)isoquinolin-1(2*H*)-one (**117**) in 86% yield (Scheme 65).[79]

Scheme 65

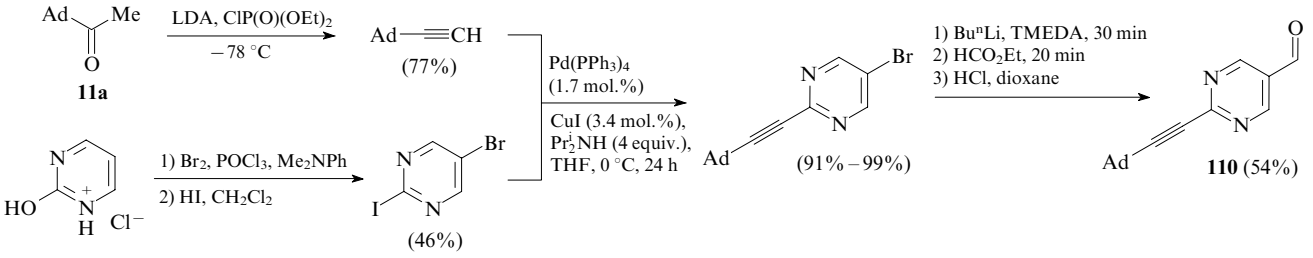


The reaction of ketone **11a** with 2-(trifluoromethyl)aniline has been described.[80] First, on treatment with LDA in tetrahydrofuran at −78 °C, the ketone is converted to enolate **118**, which reacts with 2-(trifluoromethyl)aniline to give 2-(1-adamantyl)-4-fluoroquinoline (**119**) (Scheme 66).

Scheme 66

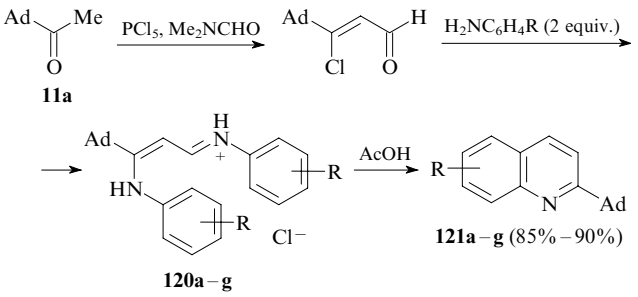


Scheme 62



As has been shown above (see Scheme 26), the Vilsmeier reaction of adamantyl methyl ketone **11a** with $POCl_3$ and DMF furnishes 3-(1-adamantyl)-3-chloroprop-2-en-1-al (see Scheme 26). Under the action of primary aromatic amines, the latter transforms into iminium salts **120a–g**, which undergo cyclization upon refluxing in glacial acetic acid to give 2-(1-adamantyl)quinolines **121a–g** (Scheme 67, the positions of substituents in the parent aniline are indicated).[81]

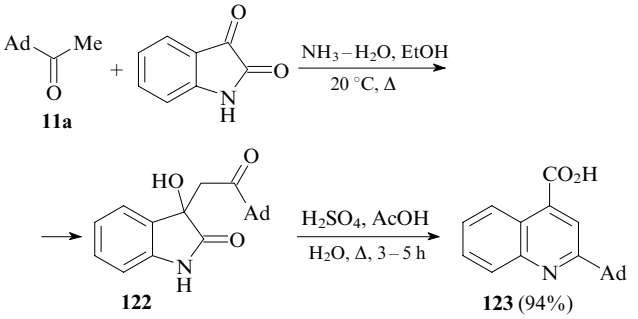
Scheme 67



R = H (**a**), 4-Br (**b**), 4-I (**c**), 4-CO_2Et (**d**), 4-OEt (**e**), 4-Me (**f**), 3-Me (**g**)

Ketone **11a** reacts with isatin in the presence of ammonia yielding compound **122**, which is converted upon heating in a mixture of acetic and sulfuric acids to 2-(1-adamantyl)quinoline-4-carboxylic acid (**123**) in high yield (Scheme 68).[82]

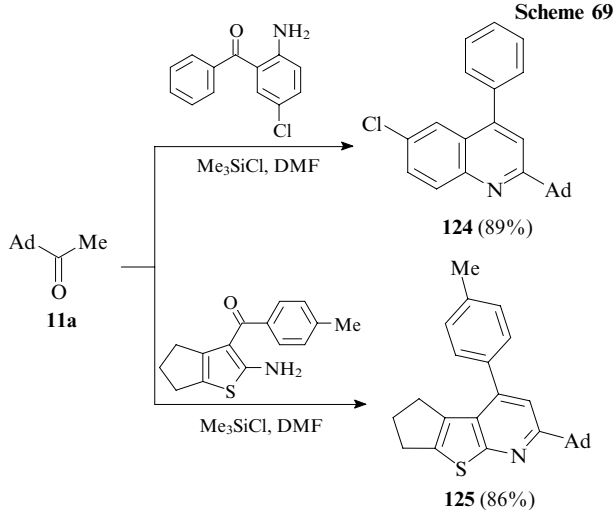
Scheme 68



Compound **123** showed satisfactory antimicrobial activity against bacteria *Staphylococcus aureus* 209F and *Escherichia coli* 675.

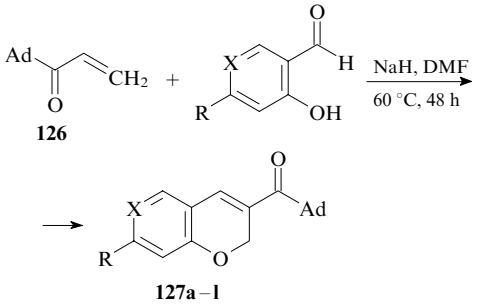
Using the Friedlander reaction promoted by trimethylchlorosilane in DMF and starting from ketone **11a** and *o*-aminoaryl ketones such as 2-amino-5-chlorobenzophenone and 2-amino-5,6-dihydro-4*H*-cyclopenta[*b*]thiophene-3-yl *p*-tolyl ketone, 2-(1-adamantyl)-4-phenyl-6-chloroquinoline (**124**) and 2-(1-adamantantyl)-4-(*p*-tolyl)-6,7-dihydro-5*H*-cyclopenta[4,5]thieno[2,3-*b*]pyridine (**125**), respectively, were obtained (Scheme 69).[83, 84]

Scheme 69



The reaction of 1-adamantyl vinyl ketone (**126**) with salicylaldehyde and its derivatives was used to synthesize the corresponding 1-adamantyl 2*H*-chromen-3-yl ketones (**127a–k**), while the reaction of **126** with 4-hydroxypyridine-3-carbaldehyde yielded 1-adamantyl 2*H*-pyrano[3,2-*c*]-pyridin-3-yl ketone (**127l**) (Scheme 70).[28]

Scheme 70

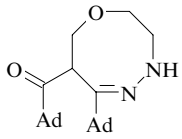


X = CH: R = H (**a**), OMe (**b**), Br (**c**), NHAc (**d**), NMe_2 (**e**), pyrrolidino (**f**), piperidino (**g**), morpholino (**h**), 4-methylpiperazino (**i**), oxazol-2-yl (**j**), thiazol-2-yl (**k**); X = N, R = H (**l**)

5. Miscellaneous heterocycles

In conclusion, we shall cite several examples of seven- and eight-membered heterocycles having three heteroatoms in the ring and one or two adamantyl moieties in the peripheral substituent. Section IV.3.b considered the synthesis of adamantyl-containing pyrazoline from ketone **72a** (see Scheme 40). As a side product (20% yield), this reaction gave 3,4,7,8-tetrahydro-2*H*-1,4,5-oxadiazacine **128** in which one adamantane moiety is attached directly to the heterocycle and the second one is linked through the carbonyl carbon atom.[54]

Structure 128

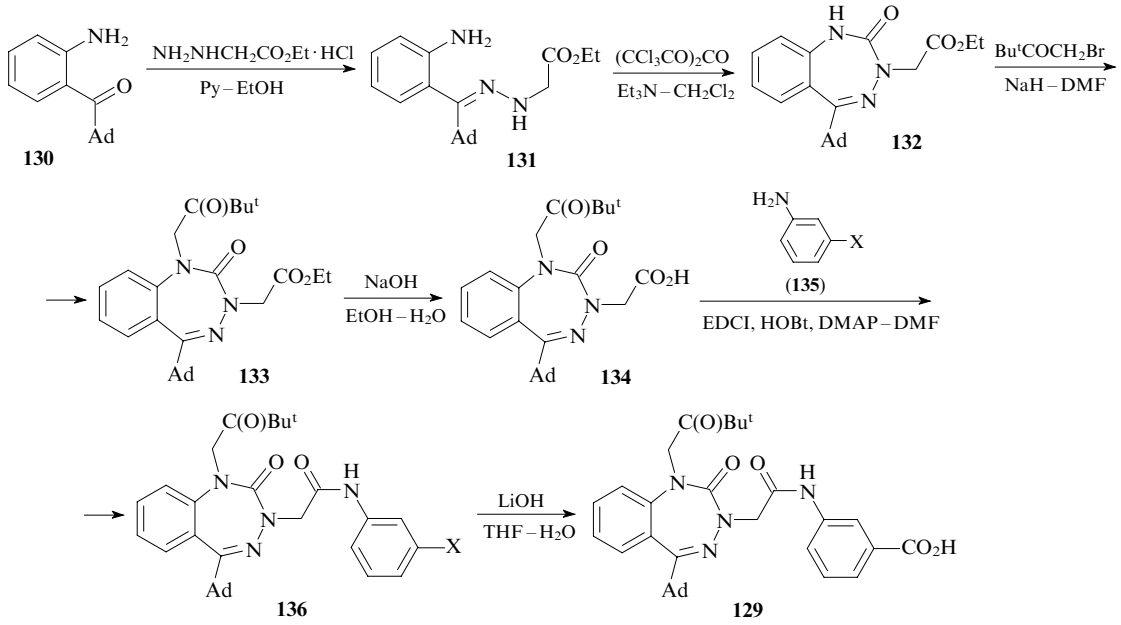


128

The synthesis of the 5-(1-adamantyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepine derivative **129** from 1-adamantyl 2-aminophenyl ketone (**130**) has been described.[85] The authors isolated an extensive range of adamantyl-containing 1,3,4-benzotriazepines having different substituents. Thus the reaction of ketone **130** with substituted hydrazine gave hydrazone **131**, which was made to react with trichloroacetic acid anhydride to give 1,3,4-benzotriazepine **132**. A substituent in the 1-position was introduced by alkylation of compound **132**; then ester **133** was hydrolyzed to give carboxylic acid **134**. For reaction of the latter with aniline **135**, carbodiimide activation was used. Deprotection of the anilide moiety resulted in product **129** (Scheme 71).

Compound **129** was shown to exhibit biological activity as a hormone cholecystokinin (CCK2) inhibitor.[85]

Scheme 71



X = $(CH_2)_2CO_2Bu^t$; EDCI is 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, HOBt is 1-hydroxybenzotriazole, DMAP is 4-dimethylaminopyridine

* * *

As is evident from the foregoing, heterocyclic compounds having an adamantane moiety are currently intensively studied. Adamantyl-containing ketones were used to synthesize a wide range of heterocyclic compounds, *e.g.* aziridinone, oxirane, diaziridine and oxaziridine, oxetane, oxetanone, azetidinone, indole, indolizine, imidazole, pyrrole, pyrazole, pyrazoline, pyrazolone, izoxazole, thiazole derivatives and so on. Among the heterocyclic systems having the adamantane cage discussed above, the compounds showing antimicrobial, antimalarial, antipox, anti-inflammatory and anticonvulsant activities, cholecystokinin CCK2 inhibitors, potential anxyolitics, antidepressants, *etc.* were found. A broad spectrum of biological activities draws attention of various research groups to the development of effective synthetic routes to such derivatives.

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