

2-Amino-2-alkyl(aryl)propanenitriles as key building blocks for the synthesis of 5-member heterocycles

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Dedicated to Professor Jaromír Kaválek on the occasion of his 75th birthday

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Abstract

This review article summarizes recent developments and trends in the application of 2-amino-2-alkyl(aryl)propanenitriles as precursors for the syntheses of heterocyclic systems such as imidazole derivatives, oxazoles, isothiazoles and 1,3,2-diazaphospholidines. Also described are less usual examples of applications in which they and their analogies react as monofunctional precursors, or where they have been used as sources of a nitrile carbon atom, or as catalysts or initiators. Their chemical and/or biological properties and potential applications are discussed, along with those of the derived heterocycles.

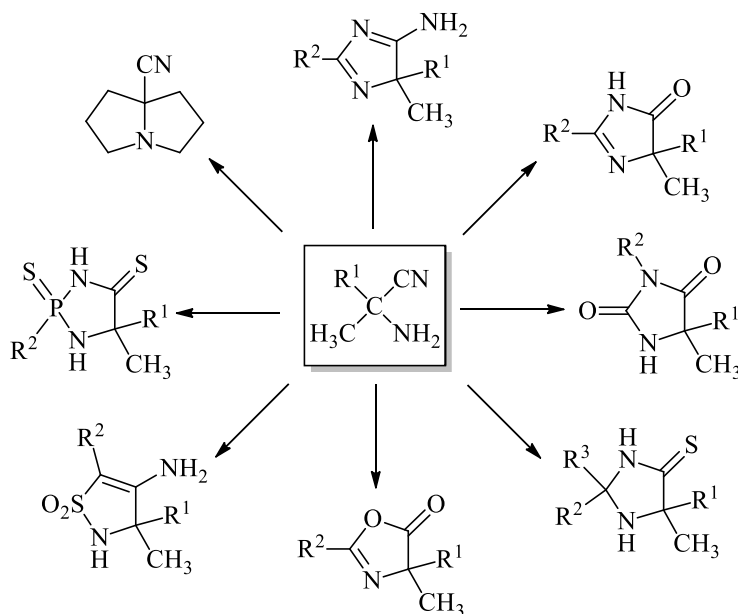
Keywords: α -Aminonitriles, imidazoles, oxazoles, isothiazoles, 1,3,2-diazaphospholidines

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1. Introduction

The reaction of an aldehyde or ketone with ammonia and cyanide ion leads to the corresponding α -aminonitrile.^{1,2} This reaction has been known since 1850 and was named the Strecker synthesis after its author.¹ First of all, α -aminonitriles were used for the syntheses of α -amino acids,² and later they served for preparation of optically pure substituted ethylenediamines.³ Bifunctional 2-amino-2-alkyl(aryl)propanenitriles contain in their molecules both a nucleophilic centre at amino group and an electrophilic centre at cyano group, which is advantageous from the standpoint of their applications as basic synthetic building blocks used for syntheses of a large number of organic compounds.⁴⁻⁷ The aim of this review article is to summarize trends - particularly those appearing during the last decade - in the application possibilities of 2-amino-2-alkyl(aryl)propanenitriles as the key precursors for syntheses of five-membered heterocycles. The paper discusses the conditions of these syntheses, the physico-chemical properties or also the application possibilities of the heterocyclic compounds prepared from 2-amino-2-alkyl(aryl)propanenitriles (Scheme 1).



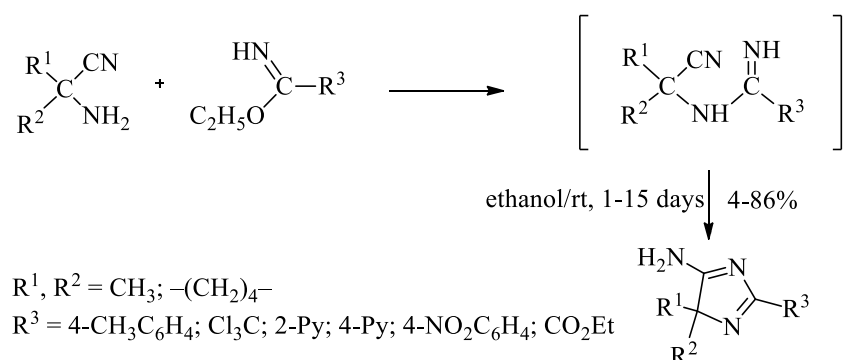
Scheme 1

2. α -Aminonitriles as Bifunctional Reactants

2.1. Derivatives of imidazole

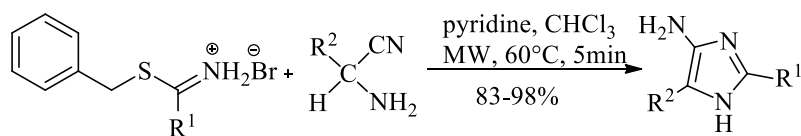
Reactions of substituted α -aminonitriles with imidoesters lead to substituted 5-amino-4H-imidazoles, which represent key components in many bioactive compounds, both natural and

synthetic.⁸⁻¹⁴ The oldest papers describing the syntheses of 5-amino-4*H*-imidazoles from α -aminonitriles were published in the 1980s (Scheme 2).^{11,12}



Scheme 2

The recent work¹³ makes use of the methodology of a microwave-assisted synthesis of 2,4-disubstituted 5-aminoimidazoles, which was realized as a three-step protocol. The total reaction time was markedly shortened, *viz.* to 25 min, as compared with the classical method (53 hours)¹⁴ (Scheme 3).¹³

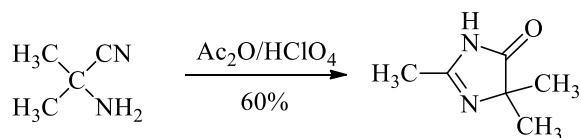


R^1 : CH_3 ; i - C_3H_7 ; Ph; $PhCH_2$; 4- $NO_2C_6H_4$; 3- $NO_2C_6H_4$; 4- $NO_2C_6H_4CH_2$; 4- ClC_6H_4 ; 4- $CH_3OC_6H_4$

R^2 : Ph, CO_2Et

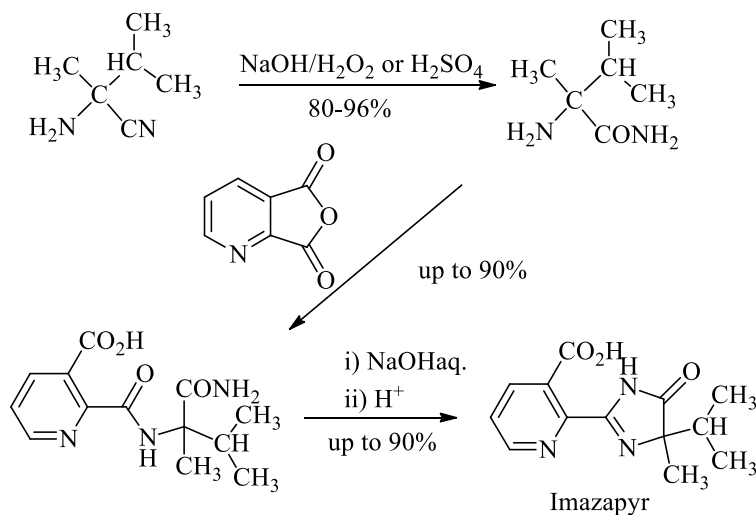
Scheme 3

2,4,4-Trimethyl-4,5-dihydro-1*H*-imidazol-5-one was prepared by the reaction of 2-amino-2-propanenitrile with acetic acid anhydride catalyzed with perchloric acid. The first reaction step is acylation at the amino group of the aminonitrile which is followed by ring closure reaction (Scheme 4).¹⁵



Scheme 4

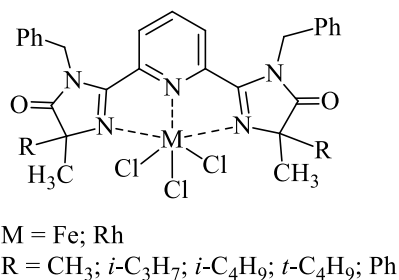
Another method of synthesis of substituted 4,5-dihydro-1*H*-imidazol-5-ones was based on the 2-amino-2-alkylpropanamides obtained from 2-amino-2-alkylpropanenitriles by partial hydrolysis. The 2-amino-2-alkylpropanamides prepared in this way were subsequently acylated and finally submitted to base-catalysed ring closure reaction (Scheme 5).¹⁶⁻¹⁸



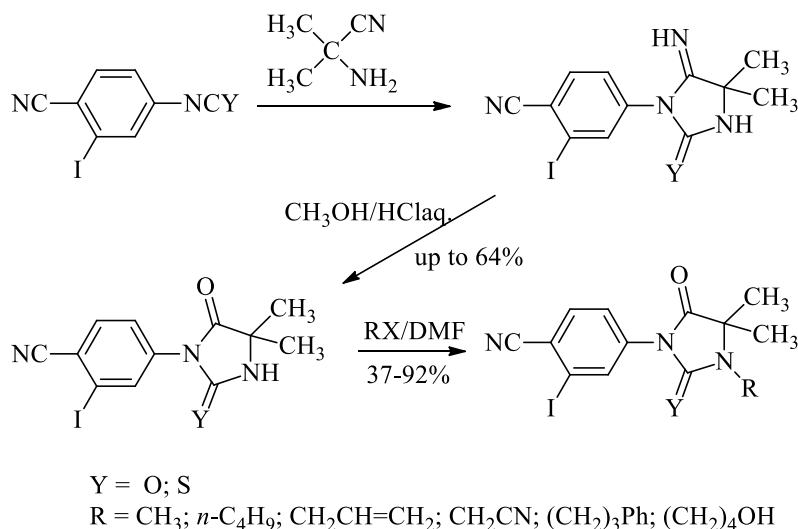
Scheme 5

2-(4-Isopropyl-4-methyl-5-oxo-4,5-dihydro-1*H*-imidazol-2-yl)pyridine-3-carboxylic acid is a well-known total herbicide (Imazapyr) (Scheme 5).¹⁸ Following Imazapyr, suitable chemical modifications of the 4,5-dihydro-1*H*-imidazol-5-one skeleton led to preparation of a varied set of highly selective herbicides of low toxicity.¹⁸ Besides herbicides, the 4,5-dihydro-1*H*-imidazol-5-one ring can also be found as a component of several medical drugs for human use, e.g., Irbesartan, which is an antagonist of angiotensine II type 1 (AII₁) receptor. Inhibition of this receptor plays an important role in the physiology of blood pressure regulation.¹⁹

The published paper²⁰ describes the synthesis and characterisation of a series of the 2-amino-2-alkyl(aryl)propanenitriles derived from acetone, butan-2-one, 3-methylbutan-2-one, 4-methylpentan-2-one, cyclohexanone, acetophenone, and 4-nitroacetophenone. The prepared aminonitriles were partially hydrolyzed to give the respective aminoamides, which were acylated with aromatic acid chlorides; the acylation products were cyclized to prepare several series of substituted 4,5-dihydro-1*H*-imidazol-5-ones.²⁰⁻³⁷ The substituted 4,5-dihydro-1*H*-imidazol-5-ones prepared in this way were used in studies of their physico-chemical properties²⁰⁻²⁸ also including studies of kinetics and mechanism of their formation and decomposition.²³⁻²⁵ The substituted 4,5-dihydro-1*H*-imidazol-5-ones attached to a benzene ring or to a pyridine ring at 2- or 2,6-position(s) were used for preparation and characterization of the corresponding coordination²⁹⁻³⁶ or organometallic³⁷ compounds with the following transition metals: Fe(III),^{29,30-34} Fe(II),³² Rh(III),³⁰ Cu(II),³¹⁻³³ Cu(I),³⁶ Pd(II)³⁷ and also they were used for their potential applications as catalysts in enantioselective syntheses (Figure 1).^{29,30-34}

**Figure 1**

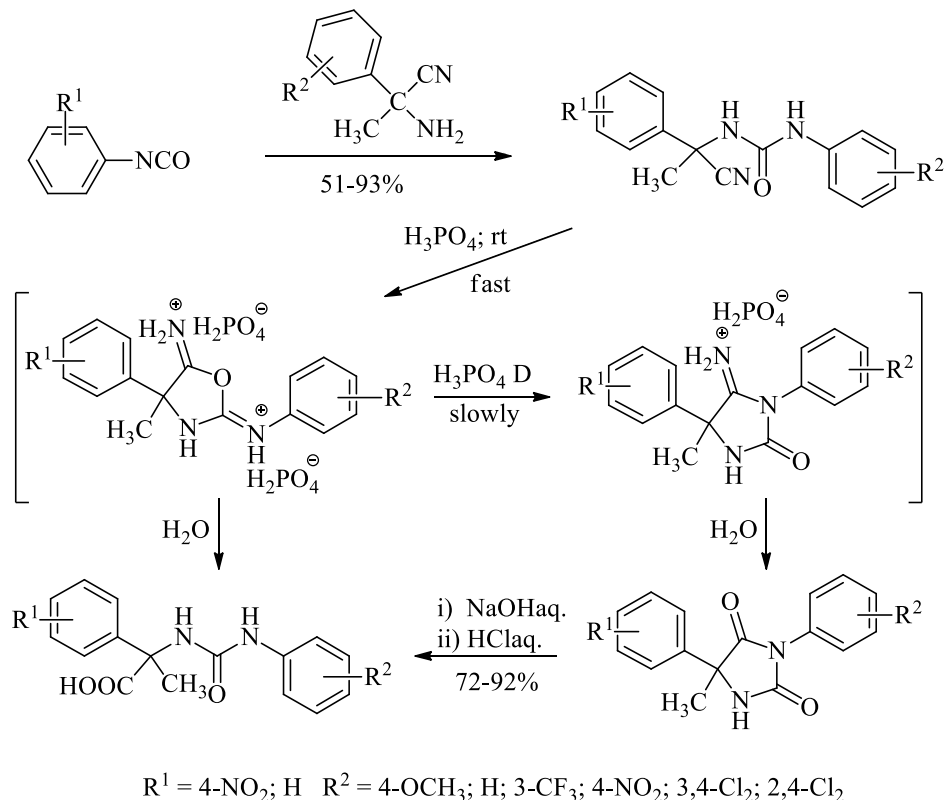
The very long-known^{38,39} substituted imidazolidine-2,4-diones (hydantoin)s represent an important structural component which is present in many natural products^{40,41} and biologically active compounds.^{42–48}

**Scheme 6**

From the period of the last decade it is possible to adduce synthesis and study of biological properties of a series of iodinated arylhydantoin and arylthiohydantoin designed for diagnostic representation of prostate gland carcinoma. It was discovered⁴⁹ that the iodinated arylhydantoin having a methyl or hydroxybutyl group in the side chain exhibit a superior affinity for the androgenic receptor (Scheme 6).⁴⁹

The reaction of substituted phenyl isocyanates with 2-amino-2-phenylpropanenitrile and 2-amino-2-(4-nitrophenyl)propanenitrile was used for preparation of substituted 1-(1-cyano-1-phenylethyl)-3-phenylureas.⁵⁰ These substituted phenylureas react in anhydrous phosphoric acid giving first the phosphates of 5-imino-4-methyl-4-phenyl-2-phenylimino-4,5-dihydro-1,3-oxazoles, which on subsequent hydrolysis provide the corresponding ureidocarboxylic acids. An increase in reaction temperature and time results in rearrangement of the phosphates of 5-imino-

4-methyl-4-phenyl-2-phenylimino-4,5-dihydro-1,3-oxazoles to phosphates of 4-imino-5-methyl-3,5-diphenylimidazolidin-2-ones, which on subsequent hydrolysis provide the corresponding substituted 5-methyl-3,5-diphenylimidazolidin-2,4-diones (Scheme 7).⁵⁰

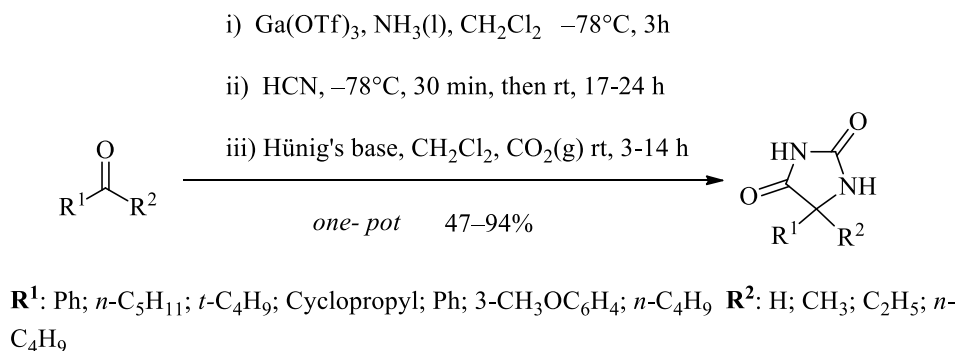


Scheme 7

Ureidocarboxylic acids were also prepared by base-catalysed hydrolysis of 5-methyl-3,5-diphenylimidazolidin-2,4-diones. The structure of 5-methyl-5-(4-nitrophenyl)-3-phenylimidazolidine-2,4-dione was verified by means of X-ray structural analysis. The alkali-catalysed hydrolysis of individual imidazolidin-2,4-diones was studied spectrophotometrically in solutions of sodium hydroxide at the temperature of 25 °C. The rate-limiting step of this base-catalysed hydrolysis is the decomposition of the tetrahedral intermediate. The hydrolysis is accelerated in the cases of derivatives containing electron-acceptor substituents at the 3-phenyl group in the imidazolidin-2,4-dione ring. The kinetically determined pK_a values of individual 5-methyl-3,5-diphenylimidazolidin-2,4-diones varied in the range of 11.0–12.1 (water, 25 °C) (Scheme 7).⁵⁰

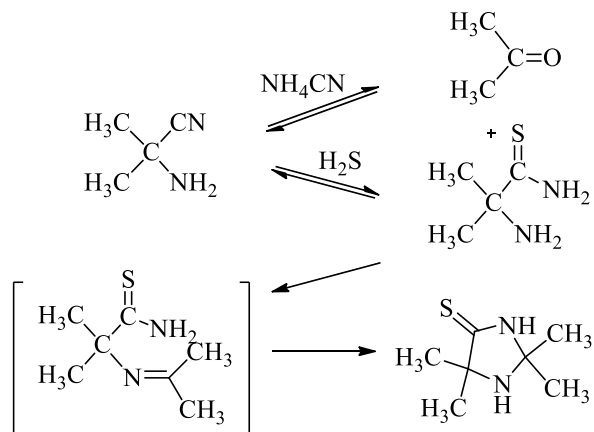
The recently published⁵¹ one-pot methodology of synthesis of hydantoins was realized as a multi-component reaction starting directly from carbonyl compounds, ammonia and carbon dioxide (yields 47–94%). The first step produces the imine, the second step gives the aminonitrile, and the last step provides the required hydantoin. The optimum reaction conditions found were as follows: the imine was formed from the carbonyl compound in liquid ammonia (–

78 °C), the reaction being catalysed with gallium(III) triflate, whereupon there followed addition of hydrogen cyanide which was introduced into the reaction mixture as a solution in dichloromethane at the temperature of –78 °C. Then the reaction mixture was heated to room temperature, the Hünig's base was added and carbon dioxide was introduced into the reaction solution. In the absence of gallium(III) triflate the reaction yield is very low (9%), which was reported as early as 1934⁵² (the Bucherer–Bergs reaction) (Scheme 8).



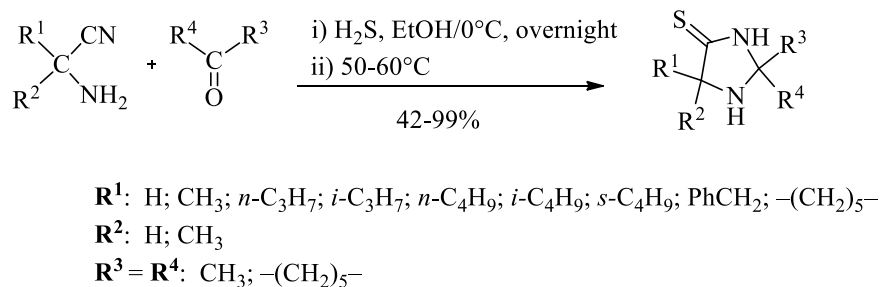
Scheme 8

Attempts at preparing substituted α -aminothioamides by addition of sulfane to α -aminonitriles gave substituted imidazolidin-4-thiones.^{53–57} This reaction course was explained by cyclo-condensation of the corresponding ketone released from α -aminonitrile together with the formed α -aminothioamide (Scheme 9).⁵³



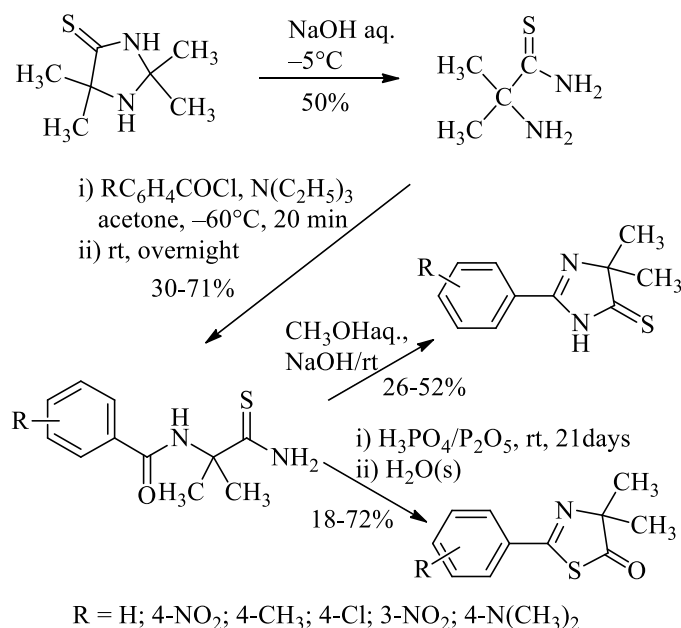
Scheme 9

Later this reaction was modified by addition of other ketones which were prepared from imidazolidine-4-thiones carrying various alkyl substituents (Scheme 10).⁵⁶



Scheme 10

Generally, the corresponding substituted 2-aminothiopropenamides can be prepared by hydrolytic decomposition of imidazoline-4-thiones.⁵³⁻⁵⁷ A particular case of hydrolysis of 2,2,5,5-tetramethylimidazoline-4-thione gave 2-amino-2-methylthiopropenamide (Scheme 11).⁵⁷



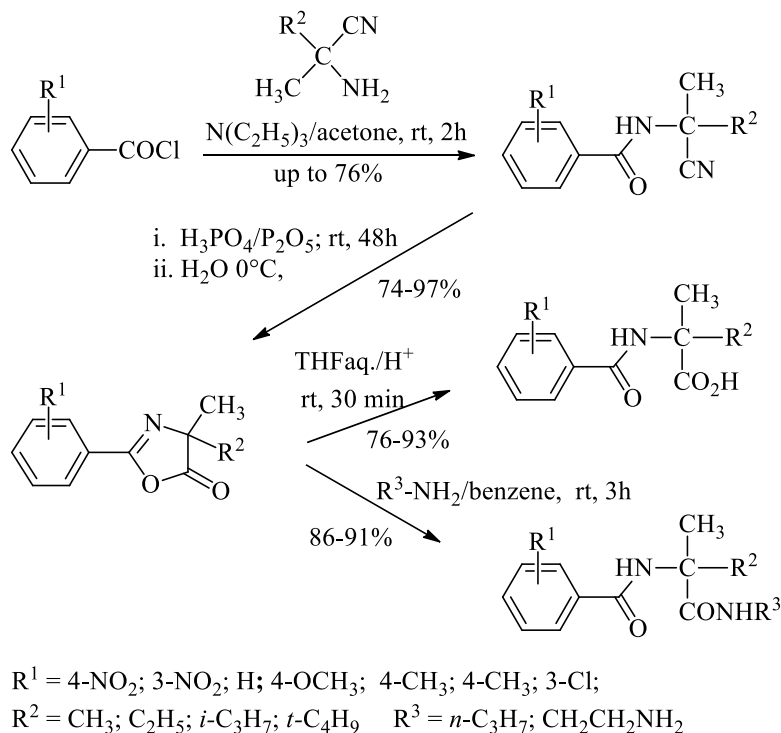
Scheme 11

Subsequent acylation of 2-amino-2-methylthiopropenamide with substituted benzoyl chlorides led to substituted 2-benzoylamino-2-methylthiopropenamides, which were cyclized in basic medium to give the respective 5,5-dimethyl-2-phenylimidazoline-4-thiones. The ring closure reaction of the same compounds was also performed in acidic medium of polyphosphoric acid: however, in this case the reaction gave substituted 2-phenyl-4,4-dimethylthiazolin-5-ones (Scheme 11).⁵⁷ The mechanism of the base-catalyzed ring closure reaction was studied kinetically in aqueous solutions of sodium hydroxide. The reaction constant ρ calculated from Hammett correlation of the cyclization rate constants was 0.45 ± 0.03 . Such a low value of the ρ

constant indicates that the rate-limiting step of the ring closure reaction was decomposition of the tetrahedral intermediate. The kinetically determined pK_a values of individual 2-benzoylamino-2-methylthiopropylamides varied in the range of 12.8–13.2 ($-\text{CS}-\text{NH}_2$; water, 25 °C).⁵⁷

2.2. Derivatives of oxazoles

Substituted 4,5-dihydro-1,3-oxazol-5-ones (azlactones) belong among significant five-membered heterocyclic compounds with a number of applications.^{58–61} The first synthesis of azlactone was described as cyclo-condensation reaction of hippuric acid with benzaldehyde in the presence of acetic acid anhydride.⁵⁸ Generally, oxazol-5-ones are prepared by cyclization dehydration of corresponding α -*N*-acylamino acids, mostly by treatment with acetic acid anhydride or polyphosphoric acid.⁵⁹ Syntheses of oxazolin-5-ones also made use of 2-amino-2-alkylpropanenitriles, which were acylated with chlorides of substituted benzoic acids. The substituted *N*-(1-alkyl-1-cyanoethyl)benzamides prepared in this way were subsequently cyclized to give the corresponding 4-alkyl-2-aryl-4-methyl-4,5-dihydro-1,3-oxazol-5-ones (Scheme 12).⁶⁰

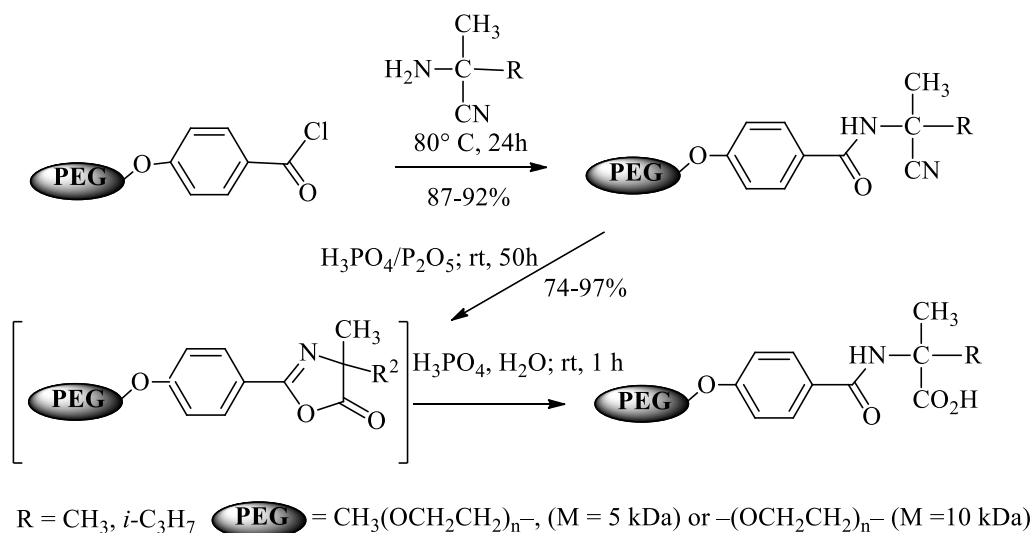


Scheme 12

The paper⁶⁰ was focused on study of kinetics and mechanism of acid- and base-catalysed hydrolysis of substituted 4-alkyl-2-aryl-4-methyl-4,5-dihydro-1,3-oxazol-5-ones to the corresponding 2-alkyl-2-benzoylamino-2-propanoic acids. The Taft correlation for acid-catalysed hydrolysis of 1,3-oxazol-5-one ring carrying various 4-alkyl substituents was not linear. The protonated 4-methyl, 4-ethyl, and 4-isopropyl derivatives underwent a nucleophilic attack by

water predominantly at the carbonyl carbon atom at 5-position of 1,3-oxazol-5-one ring; the hydrolysis proceeded by the $A_{AC}2$ mechanism; the value of Hammett constant $\rho = 0.37$. In the case of the 4-*t*-butyl derivative, the nucleophilic attack by water is increasingly directed to the imine carbon atom at 2-position of 1,3-oxazol-5-one ring; the value of Hammett constant $\rho = 0.77$. In *N*-methylpiperidine buffers, the hydrolysis proceeds with specific base catalysis.

The results of the above-mentioned study⁶⁰ provided a source of inspiration for an elegant synthesis of variously sterically hindered poly(ethylene glycol)carboxylic acids. These acids were prepared by the following reaction sequence (Scheme 13).⁶¹

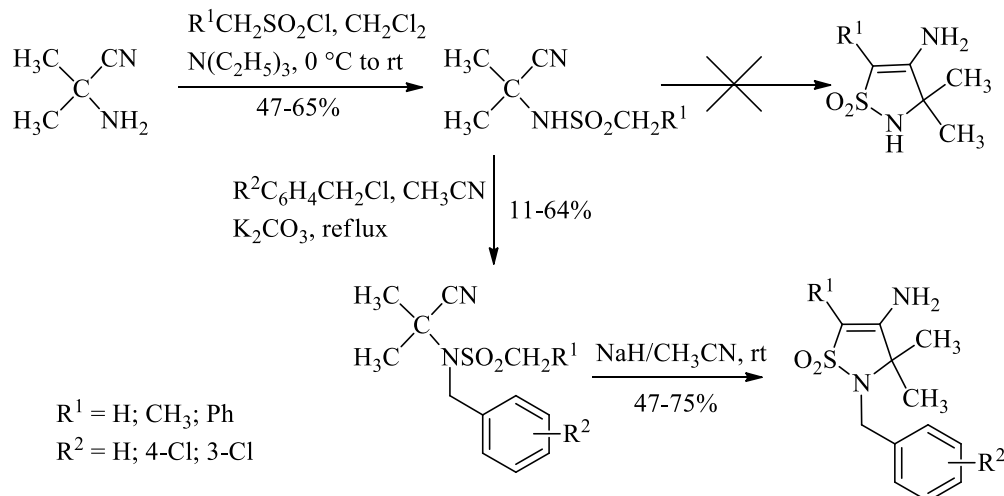


Scheme 13

The poly(ethylene glycols) functionalized with variously sterically hindered carboxylic functional groups find applications in nano-technologies⁶²⁻⁶⁷ as well as in nanomedicine.⁶⁸⁻⁷²

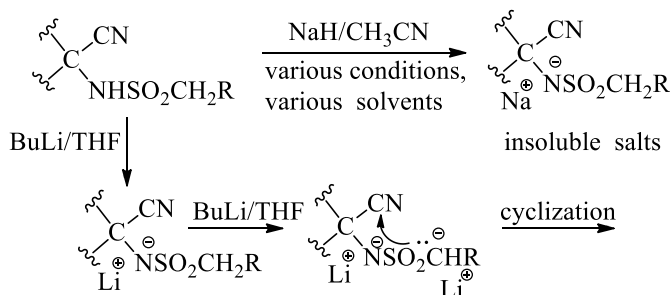
2.3. Derivatives isothiazole

Carbanion-mediated sulfonate intramolecular cyclization⁷³ was first described in 1988. Later this cyclization method was also used for syntheses of derivatives of 4-amino-5,5-dimethyl-2,3-dihydroisothiazole 1,1-dioxide from 2-amino-2-methylpropanenitrile. The reaction sequence consists in transformation of 2-amino-2-methylpropanenitrile into alkylsulfonamides, which after introduction of substituted benzyl group on the nitrogen atom of sulfonamide group were cyclized to provide derivatives of 2-amino-2,3-dihydroisothiazole 1,1-dioxide. (Scheme 14).⁷⁴



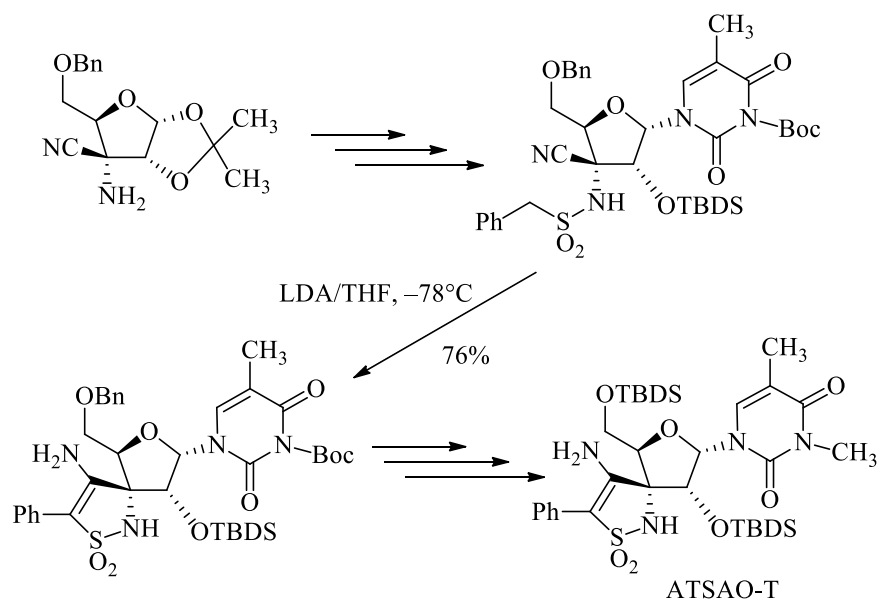
Scheme 14

However, the attempts to carry out base-catalyzed (NaH) cyclization of a secondary sulfonamide ($-\text{NHSO}_2\text{CH}_2\text{R}$) failed.⁷⁴ The failure was explained⁷⁵ by formation of sodium salt which separated from the reaction medium (Scheme 15).



Scheme 15

In recent years it has become clear that the substituted 2-amino-2,3-dihydroisothiazole 1,1-dioxide ring is considerably attractive from the standpoint of potential medical applications.⁷⁶⁻⁷⁹ For that reason, the carbanion-mediated sulfonate intramolecular cyclization of the secondary sulfonamides derived from α -aminonitriles was optimized and then successfully performed in excess butyllithium in tetrahydrofuran (Scheme 15).⁷⁶ In the next years, derivatives were prepared which had the 4-amino-2,3-dihydroisothiazole 1,1-dioxide ring system at the 3-position of furanose ring, among them, e.g., [3'-*N*-methyl-1-{2',5'-bis-*O*-(*tert*-butyl-dimethylsilyl)- β -D-ribofuranosyl}uracil]-3'-spiro-3''-(4''-amino-2''-methyl-2'',3''-dihydroisothiazole-1'',1''-dioxide) (ATSAO-T) (Scheme 16).⁷⁷

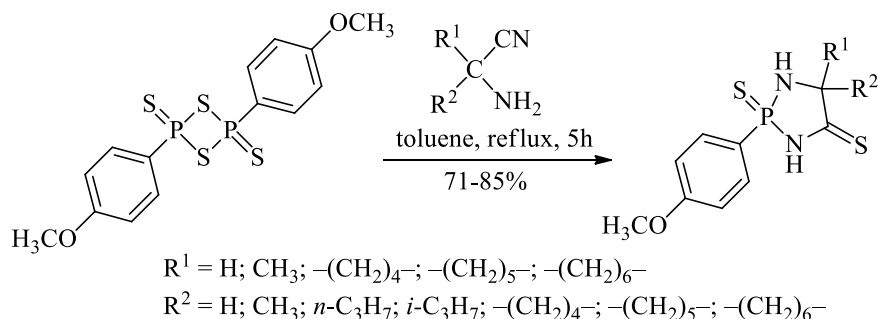


Scheme 16

These types of compound belong to the group of potential medical drugs representing a new prototype of unique analogues with specific inhibition against HIV-1 acting through a non-competitive mechanism against the substrate and template/primer.⁷⁷⁻⁷⁹

2.4. Derivatives of 1,3,2-diazaphospholidine

Other experiments focused on preparation of substituted α -aminothioamides from α -aminonitriles⁸⁰ adopted the Lawesson reagent (LR). The experiments proper were unsuccessful, but they revealed a new and simple access to derivatives of 1,3,2-diazaphospholidine.⁸⁰ The syntheses were accomplished by refluxing a mixture of LR with the respective α -aminonitrile in toluene for a period of *ca* 5 hours. The products were isolated after column chromatography with overall yields of 71–85% (Scheme 17).⁸⁰



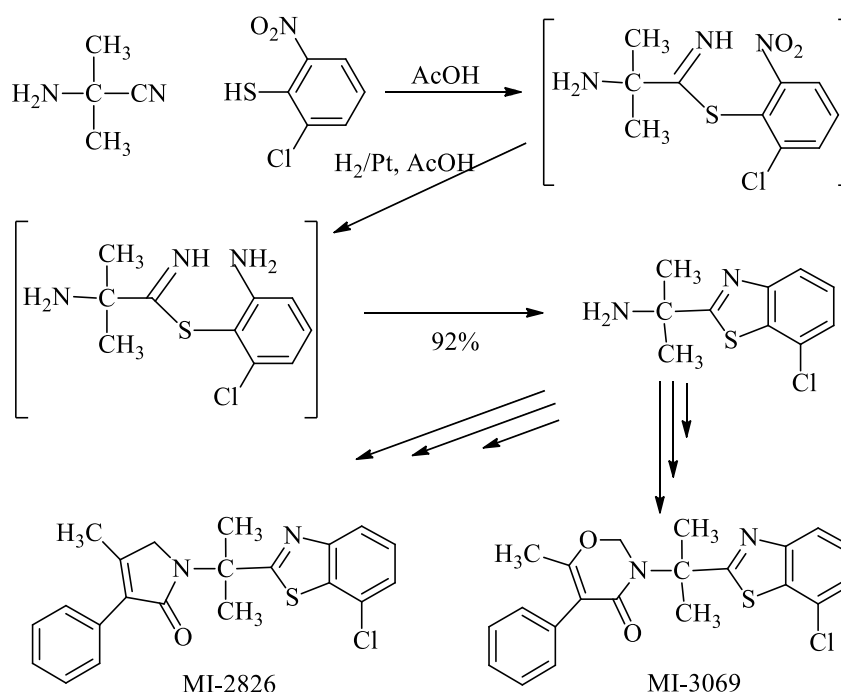
Scheme 17

The prepared 1,3,2-diazaphospholidines were characterized by means of ^1H NMR and ^{31}P NMR spectroscopy, and the structure of spiro-derivative ($\text{R}^1 = \text{R}^2: -(\text{CH}_2)_5-$) was determined by means of X-ray structural analysis.⁸⁰

3. Miscellaneous

3.1. Reactions involving the cyano group in α -aminonitriles

In 2001 was published⁸¹ a synthesis of 2-(2-aminoprop-2-yl)-7-chloro-1,3-benzothiazole as a key building block for syntheses of the herbicides MI-2826 and MI-3069 with long-lasting herbicidal activity against *Echinochloa oryzicola* (Scheme 18).⁸²

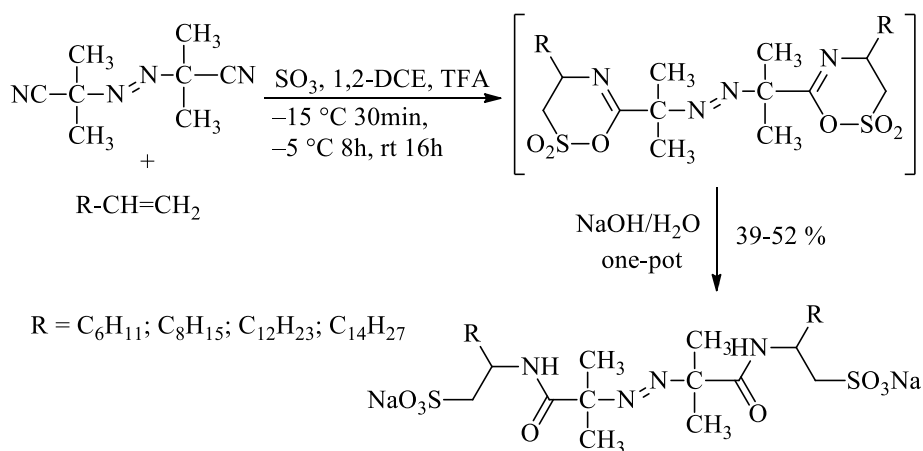


Scheme 18

In this case, 2-amino-2-methylpropanenitrile does not act as a bifunctional reagent. The reaction only involves the acid-catalyzed addition of SH group of 2-chloro-6-nitrothiophenol to nitrile group. The reaction is carried out in reduction medium, which means that the nitro group is reduced to amino group; the latter then attacks the carbon atom of the iminothioester group just formed, the substituted 1,3-benzothiazole being the final product. The reaction yields are very high (92%) (Scheme 18).⁸¹

The well-known source of free radicals, 2,2'-azobisisobutyronitrile (AIBN), can be regarded as a derivative of 2-amino-2-methylpropanenitrile with "protected" amino group and with chemically exploitable cyano group. The transformation of this skeleton to substituted 3,4-

dihydro-1,2,5-oxathiazine-2,2-dioxides can provide compounds that find applications in the intensely developed field of polymeric nanoparticles accessible by the method of emulsion polymerization.⁸³⁻⁸⁸ An example of this kind was the modification of AIBN performed in the way leading to initiators that exhibited properties of surface active compounds (INISURFs).⁸⁵ In order to maintain the initiation properties of AIBN, its modifications have to be based on reactions and processes taking place at the temperatures below 30 °C. The one-pot reaction of AIBN, sulfur trioxide and various alkenes (1-octene, 1-decene, 1-tetradecene and 1-hexadecene), carried out in trifluoroacetic acid and 1,2-dichloroethane, was employed to prepare substituted 3,4-dihydro-1,2,5-oxathiazine-2,2-dioxides, which were then hydrolyzed to give the corresponding disodium 2,2'-azobis[N-(2'-methylpropanoyl)-2-aminoalkylsulfonates] (Scheme 19).⁸⁵

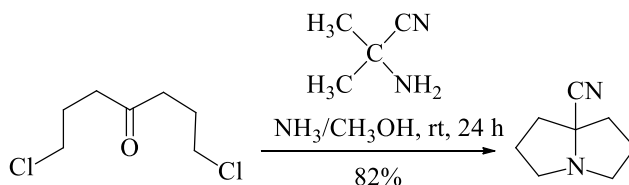


Scheme 19

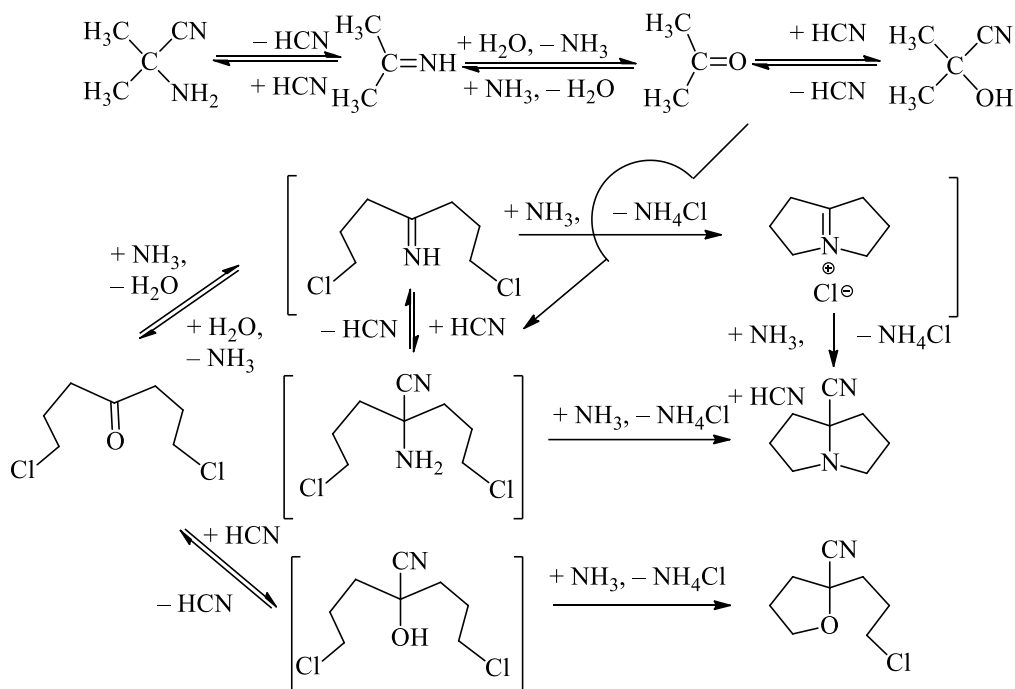
The INISURFs prepared in this way represent geminal surfactants, which were successfully applied in the preparation of a number of polymeric nanoparticles⁸⁶⁻⁸⁸, e.g. also in the first synthesis of biocompatible nanoparticles of poly(2-hydroxyethyl methacrylate).⁸⁸

3.2. Transcyanation

The literature⁸⁹⁻⁹¹ also provides an example of a synthesis in which α -aminonitrile acts as a source of nitrile carbon atom only (transcyanation). In this case, 2-amino-2-methylpropanenitrile reacts with 1,7-dichloroheptan-4-one and ammonia to give 1-azabicyclo[3.3.0]octane-5-carbonitrile in 82% yield (Scheme 20).⁸⁹



Scheme 20

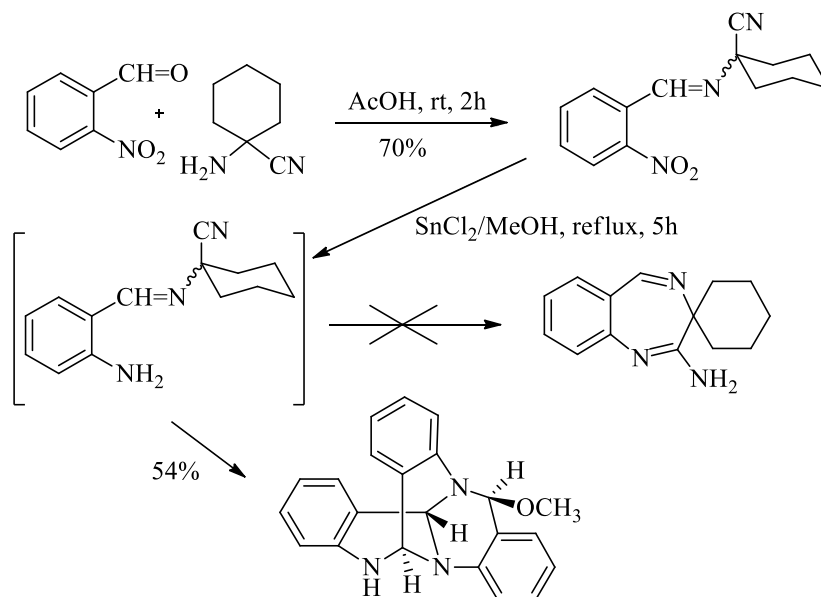


Scheme 21

The suggested⁸⁹ mechanism of formation of 1-azabicyclo[3.3.0]octane-5-carbonitrile consists in the ammonia-catalyzed shift of equilibria between the individual components of equilibrium mixture towards the products. The presence of ammonia plays a key role, only the equilibrium mixture being formed without ammonia. Also the solvent plays a fundamental part here: e.g., in little polar benzene, the reaction does not take place, which is particularly due to the low solubility of ammonia (Scheme 21).⁸⁹ 1-Azabicyclo[3.3.0]octane-5-carbonitrile itself represents a highly significant building block for syntheses of biological active compounds, such as several anti-arrhythmic drugs, activators of cerebral functions, agonists of muscarine M₁ receptor, or drugs against malaria.⁹⁰⁻⁹¹

3.3. Catalysis with α -aminonitriles

Recently, the authors⁹² tried to prepare spiro[1,4-benzodiazepin-3,1'-cyclohexane]-2-amine, namely by a reduction with presumed subsequent ring closure reaction of 1-(2-nitrobenzylideneamino)-cyclohexanecarbonitrile, which was prepared from 2-nitrobenzaldehyde and 1-aminocyclohexanecarbonitrile (Scheme 22).⁹²



Scheme 22

However, the reaction unexpectedly gave 13-methoxy-7,11*b*-dihydro-13*H*-6,12[1',2']-benzeno-6*H*-quinazolino[3,4-*a*]quinazoline, whose structure was determined by means of X-ray structural analysis (Scheme 22).⁹² The reaction course indicates that α -aminonitrile does not become a component of the product formed: it only acts as a catalyst, whose role has not been fully explained yet.⁹²

4. Conclusion

2-Amino-2-alkyl(aryl)propanenitriles continue to represent easily accessible key educts for syntheses of a number of heterocyclic system, which exclusively include substituted imidazoles, oxazoles, isothiazoles, 1,3,2-diazaphospholidines. In most cases, the whole molecule of the respective α -aminonitrile becomes a component of the heterocyclic system, the reaction making use of both the nucleophilic centre at the amino group and the electrophilic centre at the cyano group. In some cases, rather curious ones, the α -aminonitrile only acts as a source of nitrile carbon atom in the synthesis of the heterocyclic system, or exceptionally as a catalytic agent.

Acknowledgment

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