ACETYLENE-BASED FUNCTIONALIZED DIHYDRO-FURANONES AND RELATED BIOMIMETIC ASSEMBLIES

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Abstract - There are overviewed new acetylene-based syntheses of functional dihydrofuran-2-ones and 2-iminodihydrofurans related to naturally occurring and biologically active compounds. Most of the products are synthesized by nucleophilic addition of water, alcohols, amines, azoles, thiols, azide and halogenide ions, etc., as well as multident and multifunctional nucleophiles (thiurea, benzimidazole-2-thione, benzoxazole-2-thione, etc.) to esters, amides or nitriles of α,β-acetylenic γ-hydroxy acids followed by cyclization of the adducts.

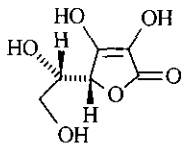
1. Introduction

The functionalized dihydrofuranone (5*H*-furanone-2) structural unit is a key counterpart of a variety of biologically important compounds[1] including tetronic, ascorbic and penicillic acids and related antibiotics, anti-AIDS drugs, such as d4T [1-(2',3'-dideoxy-γ-*D*-glyceropent-2-enofuranosyl)thymine] and AZT {1-[4-azido-5-(hydroxymethyl)tetrahydrofuran-2-yl]-5-methylpyrimidine-2,4-(1*H*,3*H*)-dione}, cardenolides[2] (cardioactive steroid lactones), dysidiolide - the only known natural inhibitor of a protein phosphatase cdc25A[3-5] as well as a great variety of other naturally occurring molecules like sesquiterpenes,[6] pulvinic acid derivatives,[7] etc. (Scheme 1). In strigol and its analogs, the dihydrofuranone parts are primarily responsible for germination stimulation of seeds of parasitics weeds.[8, 9]

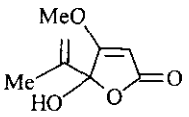
In Table 1, there are listed some more representative examples of polyfunctional furanones and dihydrofuranones isolated from natural sources.[10-26]

The biosynthesis of functional dihydrofuranone derivatives is mostly related to carbohydrates, aromatic polyhydroxy acids and polyketides transformations (Table 1).[10-26]

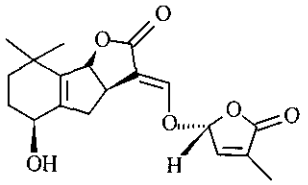
Scheme 1



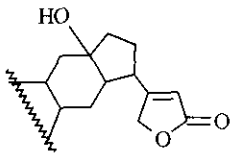
Ascorbic acid



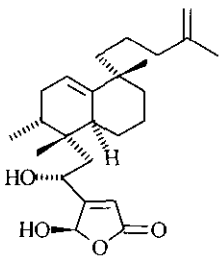
Penicillic acid



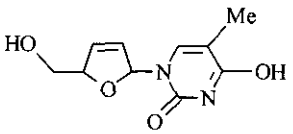
Strigol



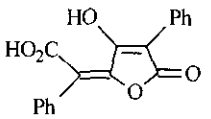
Cardenolides



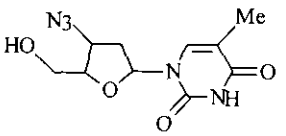
Dysidiolide
(from *Dysidea etheria*)



d4T



Pulvinic acid



AZT

Recently,[27-29] we have found, that α,β-acetylenic γ-hydroxy acids and their derivatives are highly potent building blocks to design heterocyclic compounds due to their activated triple bond and the tendency of the intermediate ethylenic adducts to mild ring-closuring. In particular, they proved to be attractive precursors of the functionalized dihydrofuranones.

Meanwhile, for a long, the chemistry of these acetylenic hydroxy acids was stagnating, because of the absence of general approach to their synthesis.

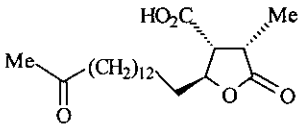
Our steady efforts in this area during the last decade have led to development of a reliable and fairly general method for preparation of both the esters of α,β-acetylenic γ-hydroxy acids and their principal derivatives (amides and nitriles).[30-42]

The method is based on the straightforward carbonylation of available acetylenic alcohols[43] with carbon monoxide and methanol in the presence of Pd/Cu oxidative catalytic systems consisting of $PdCl_2$, $CuCl_2$ and NaOAc, at ambient temperature, under atmospheric pressure, the yields being up to quantitative (Scheme 2).[30-39]

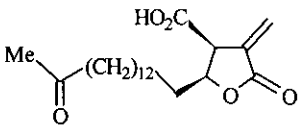
The available methyl esters of the acetylenic hydroxy acids allow the corresponding amides and nitriles to be readily prepared.

Also, adjustment of the known coupling reaction of bromoacetylenes with copper cyanide in DMF to the tertiary acetylenic alcohols has opened another easy transition from the accessible compounds to nitriles of the acetylenic hydroxy acids.[40-42]

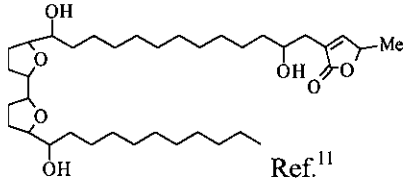
Table 1. Polyfunctional Furanones and Dihydrofuranones from Natural Sources



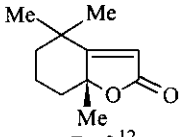
Ref.[10]



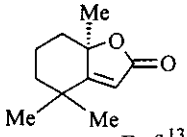
Ref.[10]



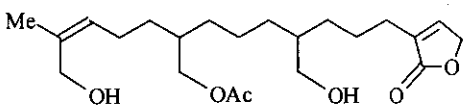
Ref.[11]



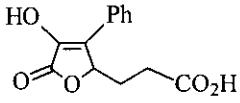
Ref.[12]



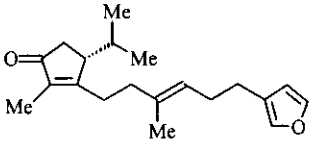
Ref.[13]



Ref.[14]



Ref.[15]



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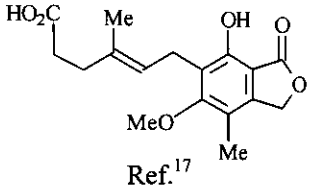
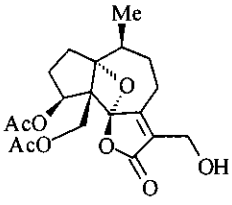


Ref.[17]



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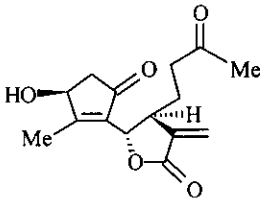

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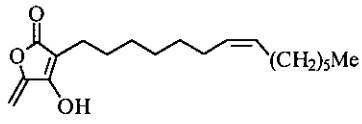
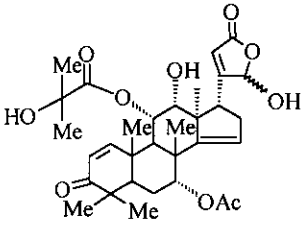
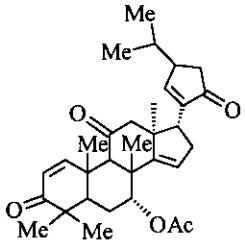


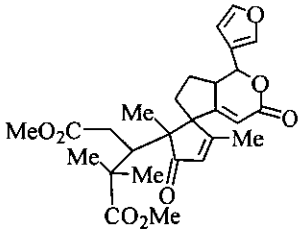
Ref.[20]



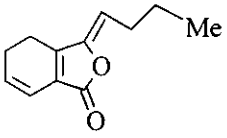
Ref.[21]



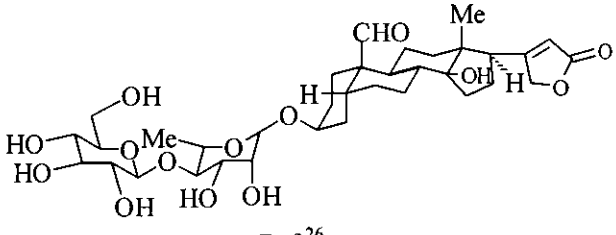
Ref.[22]



Ref.[23]

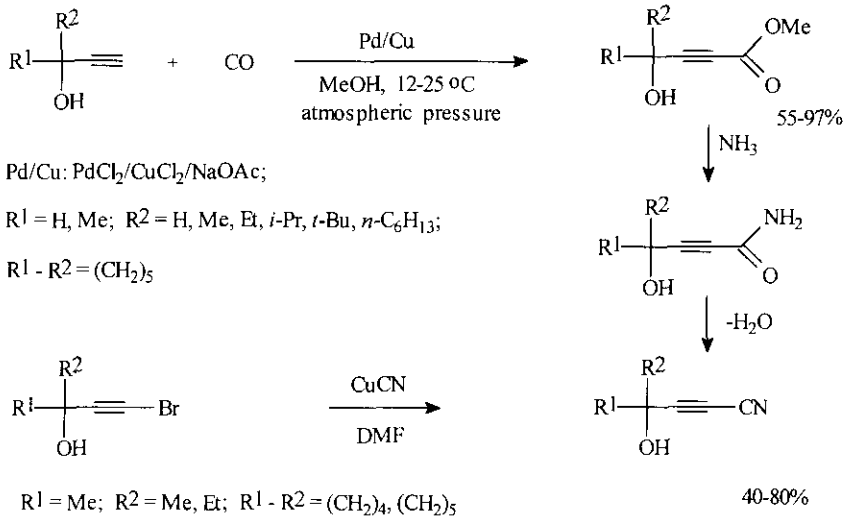


Ref.[24, 25]



Ref.[26]

Scheme 2



Pd/Cu: $PdCl_2/CuCl_2/NaOAc$;

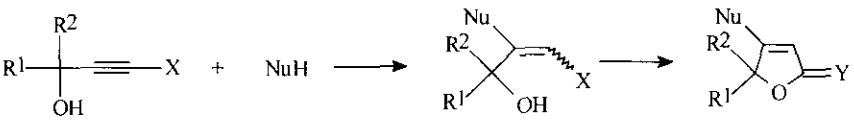
R^1 = H, Me; R^2 = H, Me, Et, *i*-Pr, *t*-Bu, n-C_6H_{13};

R^1 - R^2 = $(CH_2)_5$

R^1 = Me; R^2 = Me, Et; R^1 - R^2 = $(CH_2)_4$, $(CH_2)_5$

This paper is a concise overview of the published results of our systematic study in the synthesis of functionalized dihydrofuranones and related heterocycles from the above acetylenic hydroxy acids derivatives by the nucleophilic addition reactions followed by cyclization of the adducts formed (Scheme 3).

Scheme 3



X = CO_2Me, $CONH_2$, CN;
Nu = OH, OR, NR_2, SR, N_3, azolyl, etc.;
Y = O, NH

Thus, nucleophilic addition-cyclization reactions of the acetylenic hydroxy acids derivatives is a backbone of the strategy.

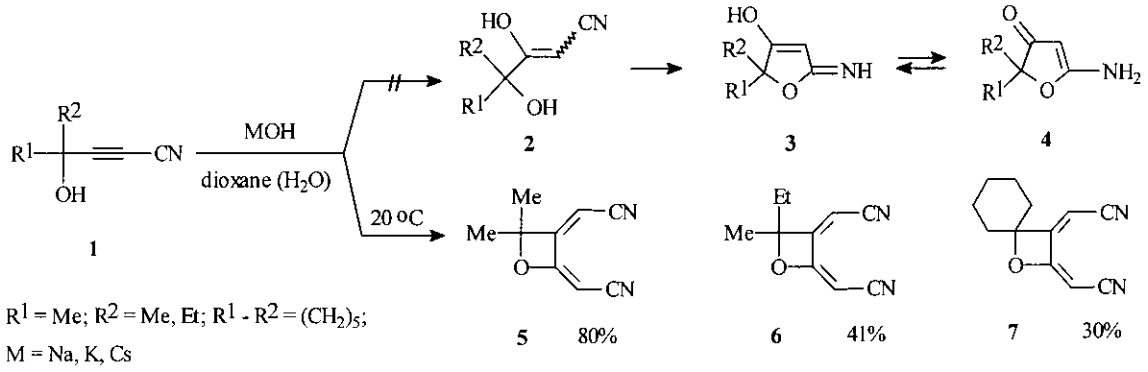
In this line we consider oxygen, nitrogen, and sulfur nucleophiles, multident and multifunctional nucleophilic addends, multi-step biomimetic assemblies and some mechanistic aspects.

2. Oxygen nucleophiles

The simplest oxygen nucleophile, hydroxide ion, might be expected to add to the activated triple bond of the nitriles (**1**). The adducts (**2**) thus formed could further cyclize to iminodihydrofurans (**3**) or

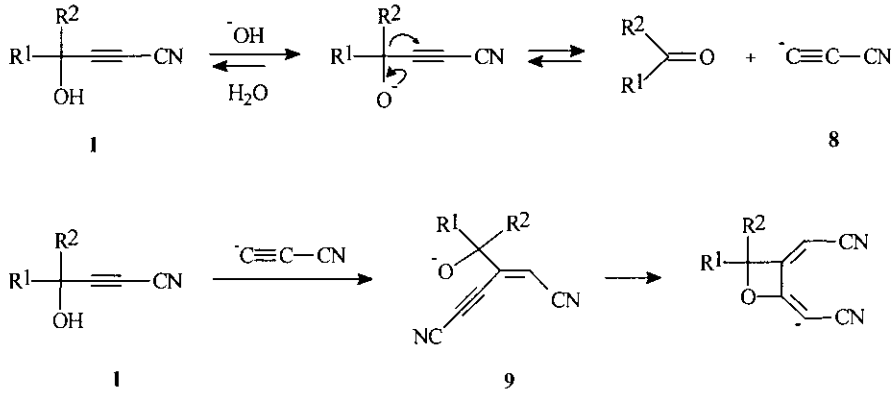
aminodihydrofuranones (**4**). But this does not happen. Instead, the bis(cyanomethylene)oxetanes (**5-7**) of *Z,Z*-configuration are formed. The cyclization proceeds smoothly in ether or dioxane at ambient temperature, the yields of the oxetanes reaching 80%, depending on the structure of starting cyanoacetylenes (**1**) (Scheme 4).[44-47]

Scheme 4



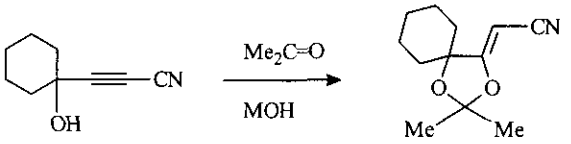
Obviously, in this case, the nucleophilic addition fails to win the competition with the deprotonation, which lead to the Favorsky retroreaction of the tertiary acetylenic hydroxy moiety and the released cyanoacetylide anion (**8**) is trapped by the second molecule of the substrate (**1**) to finally form the oxetane *via* the intramolecular alkoxide anion addition to the triple bond in the intermediate anion (**9**) (Scheme 5). The configuration of cyanomethylene groups has been assigned from comparison of experimental dipole moments with the calculated ones.

Scheme 5

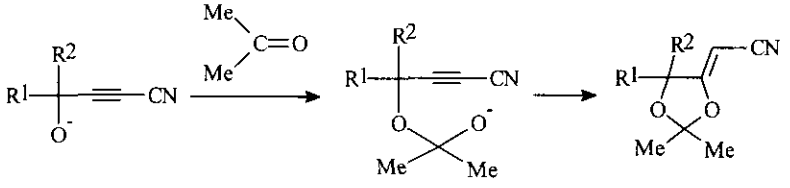


The oxetane formation occurs in ether or dioxane only, whereas in ketones, under the same conditions, the reaction takes another direction leading to cyanomethylene-1,3-dioxolanes (**10**). The latter result from the interception of the deprotonated hydroxy nitrile (**11**) by ketone followed by the intramolecular nucleophilic ring-closure in the intermediate hemiketal anion (**12**) (Scheme 6).[44]

Scheme 6



10 65%



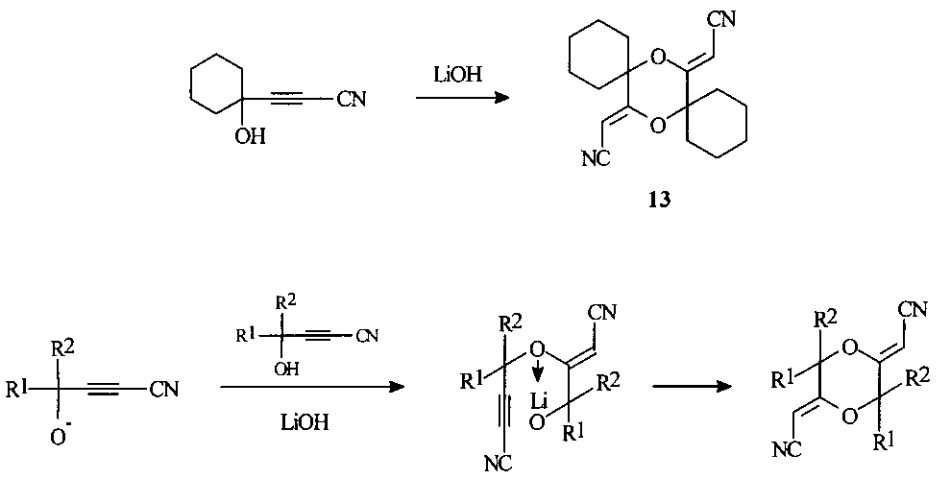
11 **12** **10**

$R^1 = R^2 = Me$; $R^1 - R^2 = (CH_2)_5$

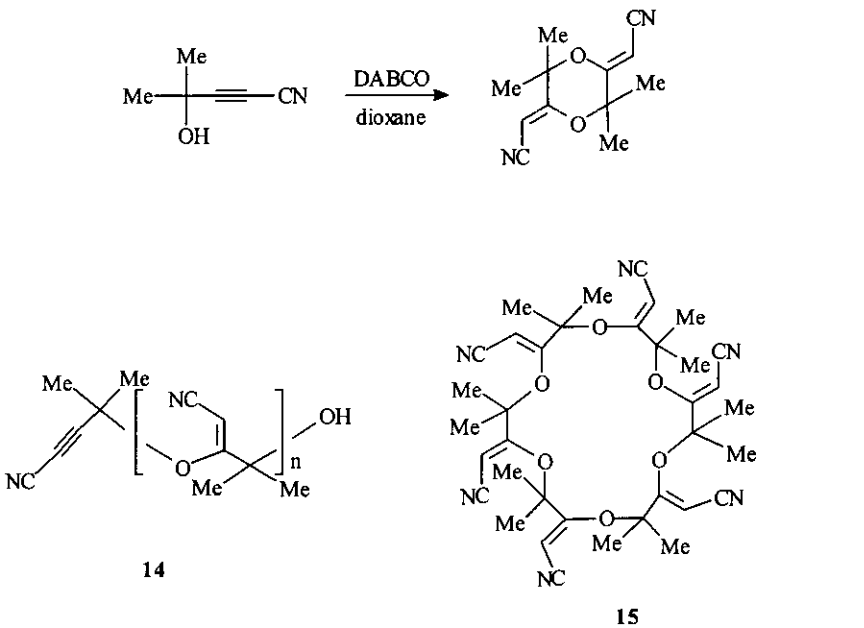
The nature of basic catalyst affects drastically direction of the cyclization. Thus, in the presence of LiOH, neither the oxetanes (**5-7**), nor the dioxolanes (**10**) are formed from the same acetylenic hydroxy nitriles under similar conditions. Instead, dimer 2,5-bis(cyanomethylene)-1,4-dioxanes (**13**) become the only products of the reaction. The LiOH is known to be less active in the Favorsky retroreaction, but still active enough to deprotonate the starting hydroxy nitrile and, therefore, to catalyse the dimerization, where the Li-cation seems to play a template role (Scheme 7).[48-50]

In the presence of DABCO (1,4-diazabicyclo[2.2.2]octane) or other tertiary amines, along with the dimerization, the oligomerization of the head to tail polyaddition type occurs to afford both the open-chain (**14**) and macrocyclic oligomers (**15**) as minor products, the yield of which increasing, when the oligomerization is conducted with sodium or potassium salts as templates. The latter represent a rare polyfunctional crown-ether family with the vinyl ether and acrylonitrile moieties in every unit (Scheme 8).

Scheme 7

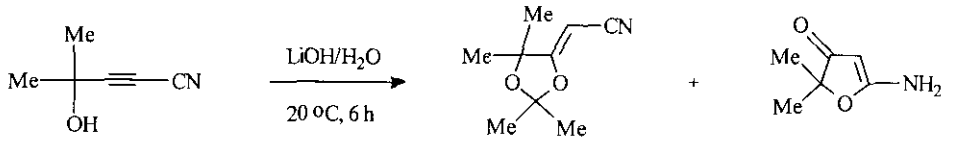


Scheme 8



In water this reaction leads to a mixture of 1,3-dioxolane (**16**) (48%) and 2-amino-4,5-dihydro-5,5-dimethylfuran-2-one (**4**) (27%) (Scheme 9).[51]

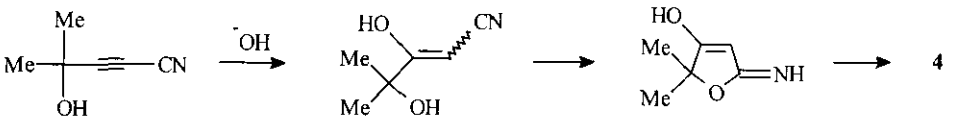
Scheme 9



1 **16** **4**

In this case, the 2-aminofuran-2-one (**4**) is, expectedly, build up by the addition of water to the triple bond and cyclization of the intermediate (**2**) *via* (**3**) (Scheme 10).

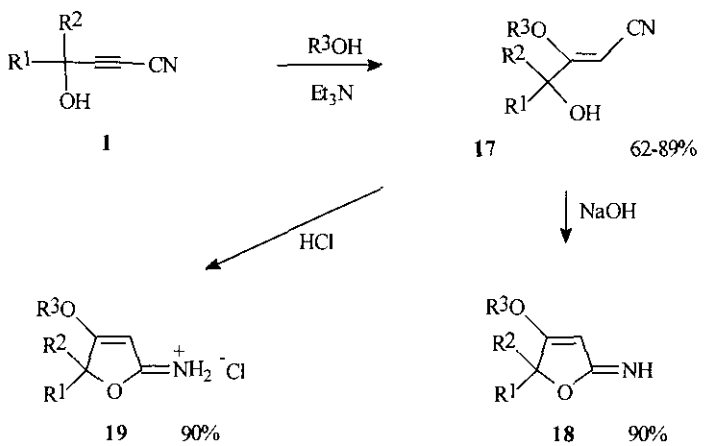
Scheme 10



1 **2** **3**

Alcohols in the presence of tertiary amines add normally to the triple bond of the nitriles (**1**) to afford *Z*-alkoxyalkenenitriles (**17**) capable of further smooth ring-closing with NaOH or HCl to the expected 4-alkoxy-2-imino-2,5-dihydrofurans (**18, 19**) (*via* isomerization to *E*-isomers) (Scheme 11).[52, 53]

Scheme 11



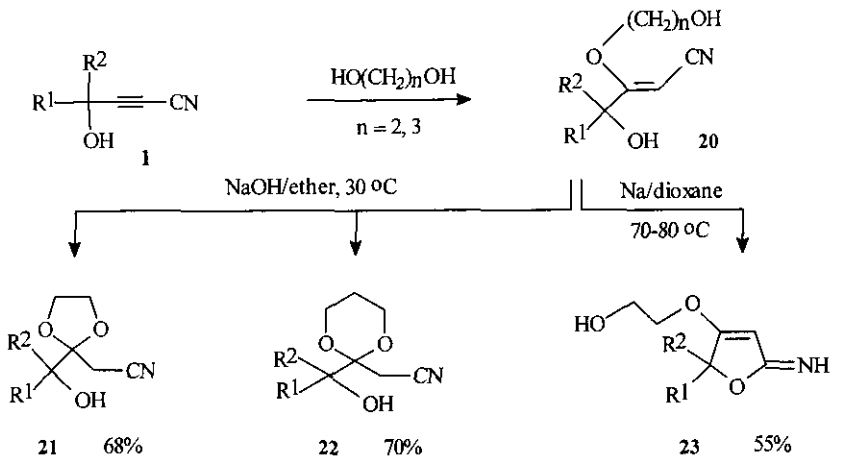
1 **17** **19** **18**

R^1 = Me; R^2 = Me, Et; R^3 = Me, *n*-Pr

With 1,2- and 1,3-diols, the nitriles (**1**) form selectively either hydroxyalkoxy 2-iminodihydrofurans (**23**), or the 1,3-dioxolanes (**21**) and -dioxanes (**22**), depending on the condition favoring the transformation of

the initial adduct (**20**) either with participation of the glycol hydroxyl and the double bond or the tertiary hydroxyl and the cyano groups (after changing the configuration) (Scheme 12).[42, 54]

Scheme 12

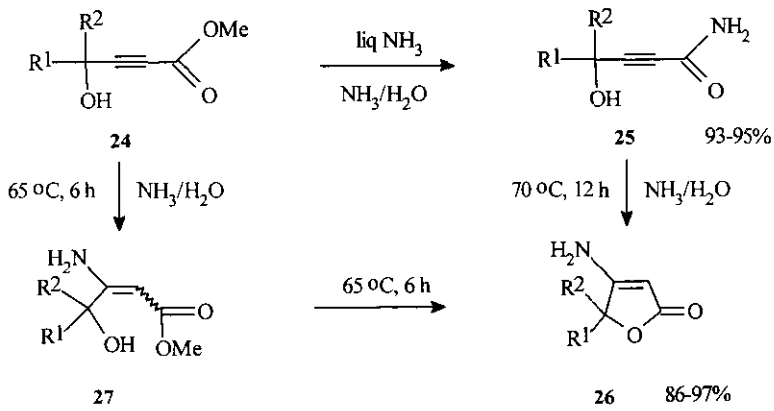


$R^1 = R^2 = Me$, $R^1 - R^2 = (CH_2)_5$

3. Nitrogen nucleophiles

In dry liquid ammonia, the esters of the α,β-acetylenic γ-hydroxy acids (**24**) react by their ester function to quantitatively furnish the amides (**25**), whereas with aqueous ammonia, along with the amides (**25**), the 4-amino-5,5-dialkyl-2,5-dihydrofuran-2-ones (**26**) are formed [*via* the corresponding adducts - aminoacrylic esters (**27**)]. At higher temperature (50-70 °C) both the acetylenic amides (**25**) and the aminoacrylic esters (**27**) quantitatively cyclize to the aminodihydrofuran-2-ones (**26**) (Scheme 13).[55]

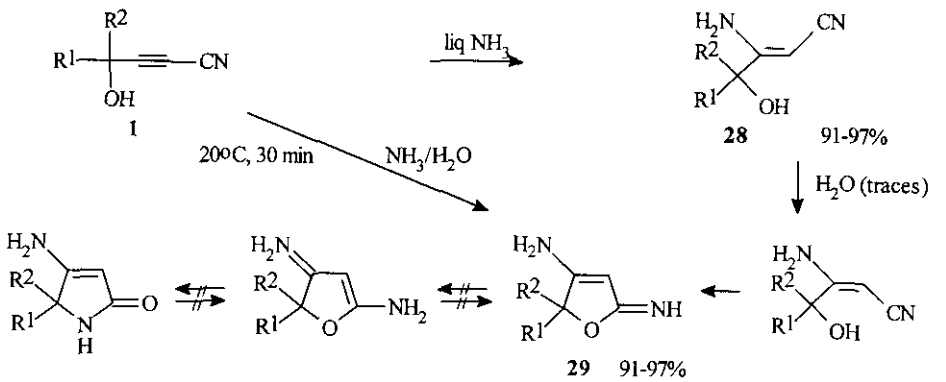
Scheme 13



$R^1 = Me$; $R^2 = Et$; $R^1 - R^2 = (CH_2)_5$

The corresponding nitriles (**1**), in liquid ammonia, form the aminoalkenenitriles (**28**), which, upon storage in air or in the presence of small amount of water acting as catalyst, undergo the quantitative ring-closure to the aminoiminodihydrofurans (**29**).[56-58] The latter are conceived to exist in three tautomeric forms, but, according to NMR spectra, they turned out to be individual compounds and no evidence of the tautomerism was detected, at least under conditions studied (Scheme 14).

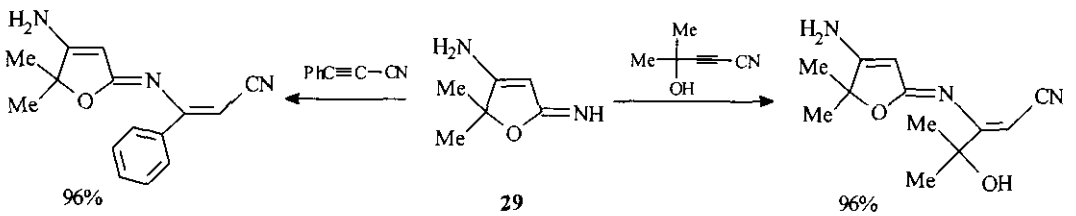
Scheme 14



R^1 = Me; R^2 = Me, Et; R^1 - R^2 = $(CH_2)_5$

The iminodihydrofurans (**29**) proved to be capable of ready adding to the second molecule of acetylenic hydroxy nitrile or to phenylcyanoacetylene (Scheme 15).[57]

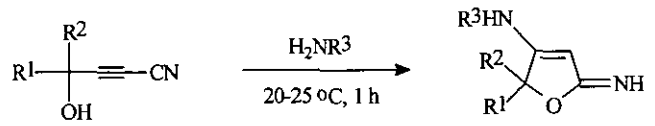
Scheme 15



Noteworthy are biomimetic features of all these transformations: the very mild conditions and quantitative yields.

Primary amines and amino alcohols react with the nitriles (**1**) under the same biomimetic conditions (water, room temperature, 1 h) to quantitatively afford the corresponding alkylaminoiminodihydrofurans (**30**) (Scheme 16).[59-65]

Scheme 16



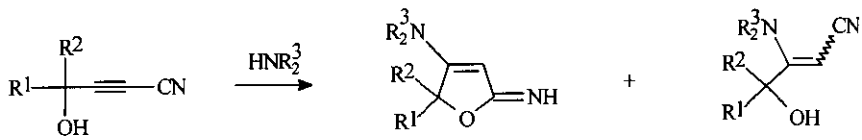
1 **30** ~100%

R^1 = Me; R^2 = Me, Et; R^1 - R^2 = $(CH_2)_5$;

R^3 = Me, Et, *n*-Pr, *i*-Bu, *t*-Bu, $(CH_2)_2OH$, $(CH_2)_3OH$, $(CH_2)_4OH$, etc.

Unlike ammonia and primary amines, secondary amines with the nitriles (**1**) form mixtures of the corresponding iminodihydrofurans (**31**) and *E,Z*-aminoalkenenitriles (**32**). In this case, the reluctance of the *Z*-isomer to the ring-closure still remains poorly understood (Scheme 17).[66, 67]

Scheme 17

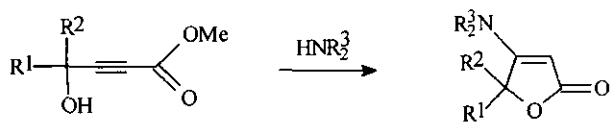


1 **31** **32** *E, Z*

R^1 = Me; R^2 = Me, Et; R^3 = Me, Et, *n*-Pr, *n*-Bu, etc.

Amazingly, that solitary examples of the cyclization of the corresponding esters of α,β-acetylenic γ-hydroxy acids (**24**) to 4-amino-2,5-dihydrofuranones (**33**) under the action of secondary amines was first published, as early as half a century ago (Scheme 18),[68] but since then failed to be further unfolded.

Scheme 18

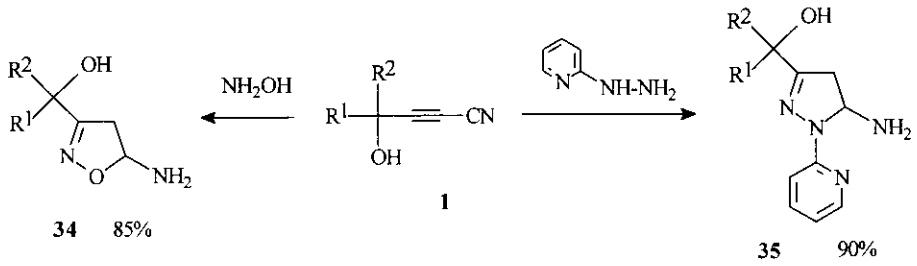


24 **33**

R^1 = H, Me; R^2 = Me, *n*-Pr; R^1 - R^2 = $(CH_2)_5$; R^3 = Et, etc.

Nitriles (**1**) react with hydroxylamine (70-75 °C, 2 h, ethanol) and 2-hydrazinopyridine (0 °C, 1 h) to give the corresponding 3-alkyl-5-aminoisoxazoles (**34**)[63, 69] and aminohydroxypyridylpyrazoles (**35**) (Scheme 19).[70]

Scheme 19

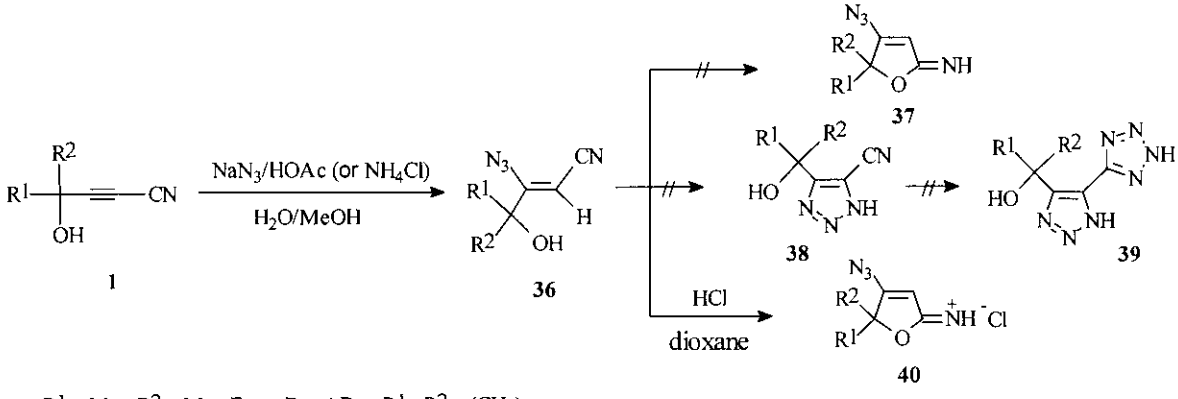


34 85% **35** 90%

R^1 = Me, Et; R^2 = Et

Sodium azide in the presence of acetic acid (or NH_4Cl) adds to the nitriles (**1**) at room temperature to form the azidoalkenenitriles (**36**) in 40-73% yield affording neither the expected iminodihydrofurans (**37**) nor the triazoles (**38**) or the triazolyltetrazoles (**39**). This is quite a rare example when azide adds to the triple bond not as a 1,3-dipole, but as an ordinary nucleophile (Scheme 20).[71]

Scheme 20

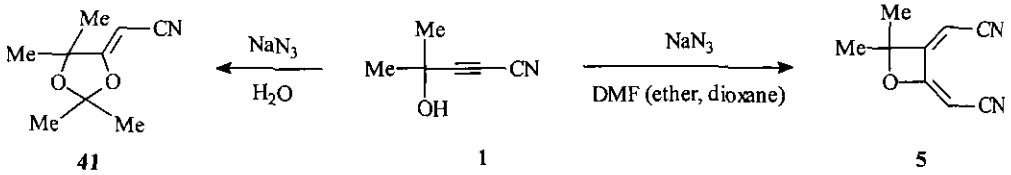


R^1 = Me; R^2 = Me, Et, *n*-Bu, *i*-Bu; R^1 - R^2 = $(CH_2)_5$

The target azidoiminodihydrofurans (**40**) have been easily prepared as hydrochlorides by treatment of the azidoalkenenitriles (**36**) with dry hydrogen chloride (Scheme 20).

Without acid, no azide addition occurs. Instead, the products of base-catalysed autotransformations of the starting materials, bis(cyanomethylene)oxetane (**5**) (in DMF, ether and dioxane) or/and cyanomethylene-1,3-dioxolane (**41**) (in water) are isolated (Scheme 21).[71]

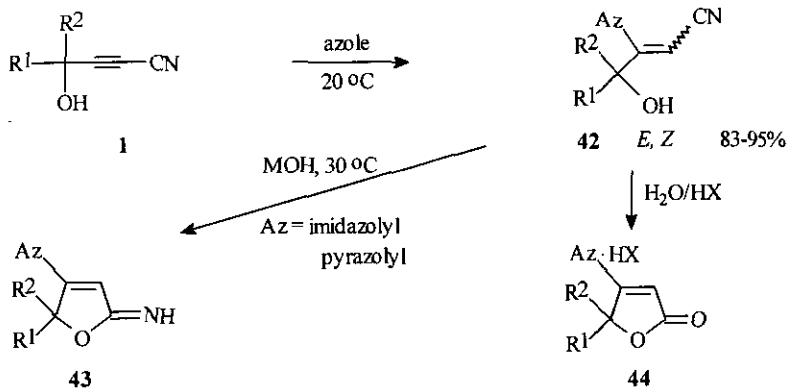
Scheme 21



41 **1** **5**

All-nitrogen azoles, like imidazole, pyrazole, triazole, benzoimidazole and benzotriazole, add to the nitriles (**1**) very smoothly (ambient temperature) to result in azolylalkenenitriles (**42**), mostly of *Z*-configuration, in up to quantitative yield (Scheme 22).[72-77] They are stable and do not cyclize to the expected iminodihydrofurans (**43**) even with tertiary amines, common catalysts for such a cyclization. The exceptions are the imidazolyl and pyrazolyl derivatives, which are cyclized under the action of alkali metal hydroxides in dioxane at 30 °C.[73-76] However, the cyclization occurs with aqueous acids (HCl, HOAc) to give salts of the corresponding dihydrofuranones (**44**) due to simultaneous hydrolysis of the imino group.[74]

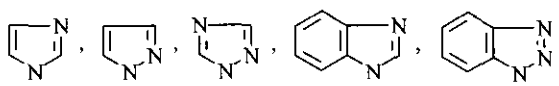
Scheme 22



1 **42** *E, Z* 83-95%

43 **44**

R1 = Me; R2 = Me, Et; X = Cl, OAc; M = Na, K;

Az= 

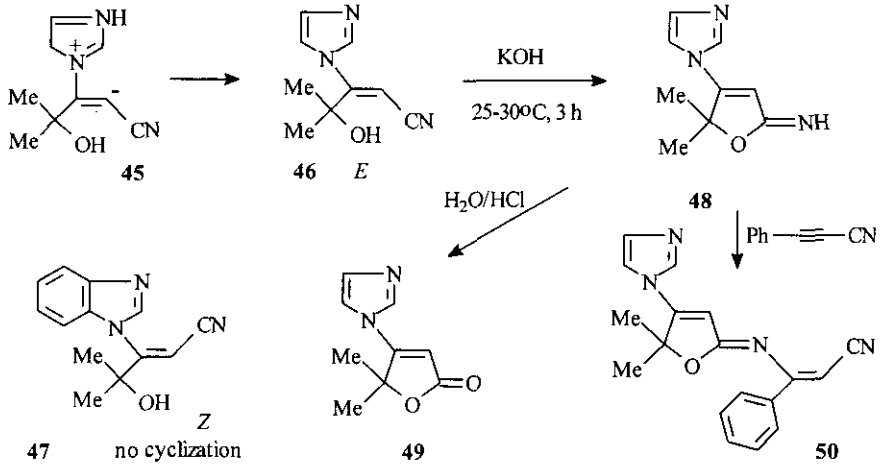
The ready cyclization of the imidazolyl derivatives[73, 74] implies their *E*-configuration (**46**), whereas the benzoimidazole[72] adducts, which are incapable of the cyclizing, should have *Z*-configuration (**47**).

The puzzle is, why the bulkier benzoimidazole follows the classic *trans*-addition mode even forcing the thermodynamically unfavorable configuration while less bulky imidazole breaks this general rule.

Apparently, imidazole, being more basic attacks the triple bond by its "pyridine" nitrogen to form a *cis*-zwitter-ion-like transition state (**45**) stabilized by the negative charge - positive charge attraction.

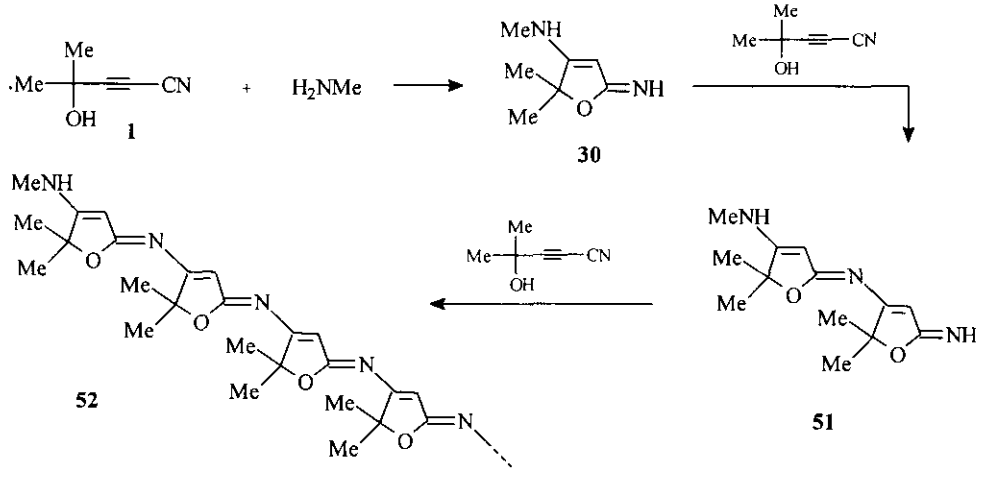
The imidazolyliminodihydrofuran (**48**) is readily hydrolysed to the corresponding furanone (**49**) and adds to phenylcyanoacetylene by its imino group to afford the predicted adduct (**50**) of *Z*-configuration (Scheme 23).[74]

Scheme 23



A similar facile addition takes place, when the iminodihydrofurans (**30**) are allowed to react with the same acetylenic hydroxynitriles, dimers (**51**) and further higher oligomers (**52**) being readily assembled. The polyconjugated oligo(iminodihydrofurans), thus assembled, possess promising electrooptical properties (Scheme 24).[78-81]

Scheme 24



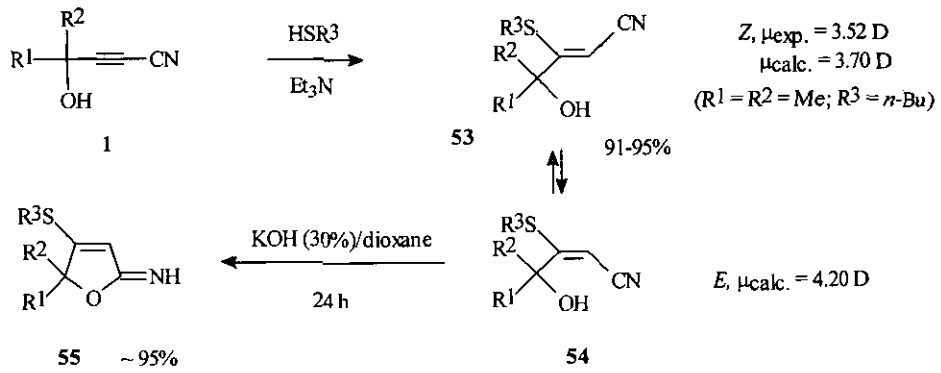
4. Sulfur nucleophiles

Thiols, in the presence of tertiary amines, react with the nitriles (**1**) regio- and stereospecifically, in both protic (alcohols) and aprotic (dioxane) solvents, (requiring no more than a 1-2 h contact at ambient temperature) to form the vinyl sulfides (**53**) of *Z*-configuration (Scheme 25).[82, 83] The latter, unlike their nitrogen analogs, cyclize to the corresponding 2-imino-2,5-dihydrofurans (**55**) with a larger concentration of KOH (30%) and for a longer time (24 h), thus implying the *Z*-*E*-izomerization to be the rate-limiting step of the whole process, although the yield keeping near to quantitative.

In the NMR spectra of the adducts, only one singlet of olefinic proton (at 6.03-6.28 ppm) is observed, that confirms a stereospecific formation of *Z*-isomers. The only spectrum, where the second singlet of the olefinic proton is discernible, is that of the adduct with the most bulky neopentyl radical (6.28 and 6.12 ppm in a ratio of ~ 6:1, respectively). Therefore, there is a breach of the *anti*-addition rule due to steric hindrances in the *Z*-izomer.[82, 83]

The measured dipole moments (3.52 D) and the calculated ones (3.70) for *Z*-izomers of the adducts indeed match much better than for *E*-izomers (**53**) (4.20 D).

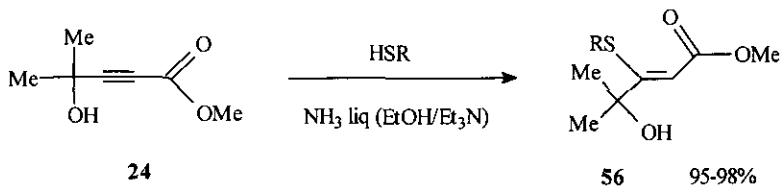
Scheme 25



R^1 = Me; R^2 = Me, Et; R^3 = Et, *i*-Pr, *n*-Bu, *neo*-Am, *n*-$C_{12}H_{25}$, Ph, $PhCH_2$

Thiols add to acetylenic hydroxy esters (**24**) in liquid ammonia or in ethanol in the presence of Et_3N to form *Z*-4-hydroxy-3-organylthio-2-pentenoates (**56**) in near to quantitative yields (Scheme 26).[85]

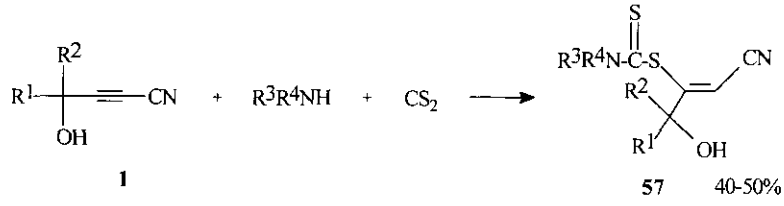
Scheme 26



R = Et, *n*-Pr, *i*-Pr, *n*-Bu, Ph, $PhCH_2$

The reaction of nitriles (**1**) with dithiocarbamic acids, prepared *in situ* from ammonia, primary or secondary amines and carbon disulfide, gives *Z*-3-(dithiocarbamoyl)-2-alkenenitriles (**57**) in 40-50% yields under mild conditions (ambient temperature, 4-5 h, dioxane) (Scheme 27).[86, 87]

Scheme 27

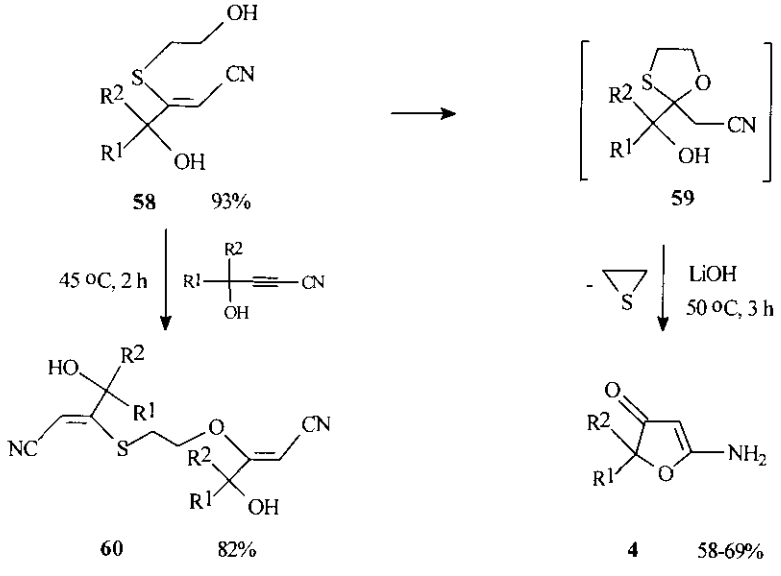


1 **57** 40-50%

R^1 = Me; R^2 = Me, Et; R^3 = H, Et, *n*-Pr, *n*-Bu;
R^4 = H, Me, Et, *n*-Pr, *n*-Bu, *t*-Bu; R^3 - R^4 = $(CH_2)_5$, $(CH_2)_2O(CH_2)$

2-Mercaptoethanol,[88, 89] behaves with the nitriles (**1**) as a sulfur nucleophile, what is predictable. Unpredicted is the behavior of the adducts (**58**), which can eliminate thiirane, presumably, *via* the intermediate 1,3-oxathiolane (**59**), to produce 2-amino-4,5-dihydrofuran-4-ones (**4**). When the *S*-nucleophilicity is spent the monoadduct (**58**) is further attacking the second molecule of the nitrile (**1**) by its hydroxyl group to form the bis-alkenenitrile (**60**) (Scheme 28).

Scheme 28



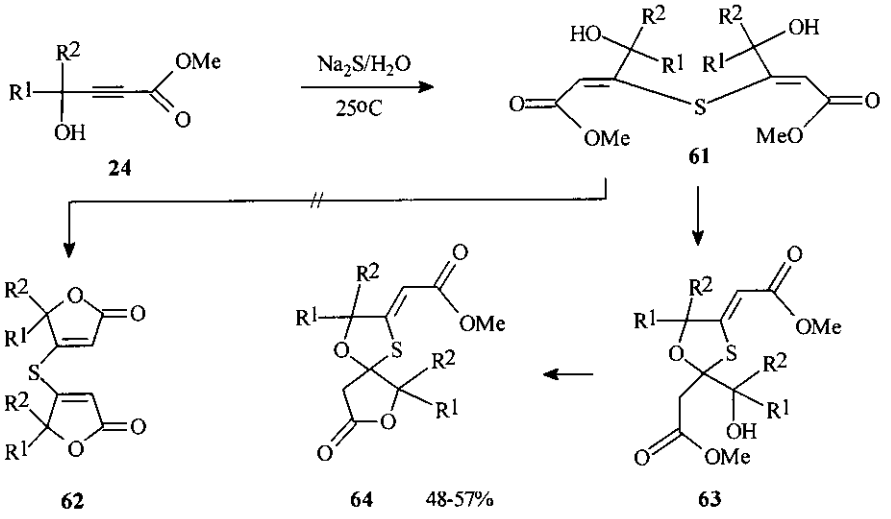
58 93% **59**

60 82% **4** 58-69%

R^1 = Me; R^2 = Me, Et

Sulfide ions smoothly react with two molecules of acetylenic hydroxy esters (**24**) (aqueous medium, room temperature, no catalyst). However, neither the expected divinyl sulfides (**61**), nor the obvious products of their further simple cyclization, bis(dihydrofuranyl)sulfides (**62**), are isolated. Instead, there are fixed the products of a unusual double cross-cyclization of the intermediate divinyl sulfides (**61**) and *via* the next intermediate 1,3-oxathiolane (**63**) - functionalized methyl 3-(2,2,6,6-tetraalkyl-8-oxo-1,7-dioxa-4-thia-spiro[4.4]non-3-yl)prop-2-enoates (**64**), representatives of a novel heterocyclic system (Scheme 29).[91-95]

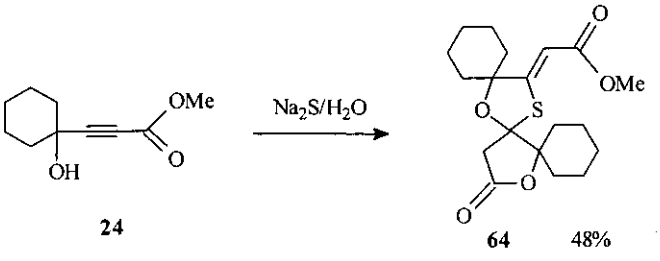
Scheme 29



R^1 = Me; R^2 = Me, Et, *t*-Bu; R^1 - R^2 = $(CH_2)_5$

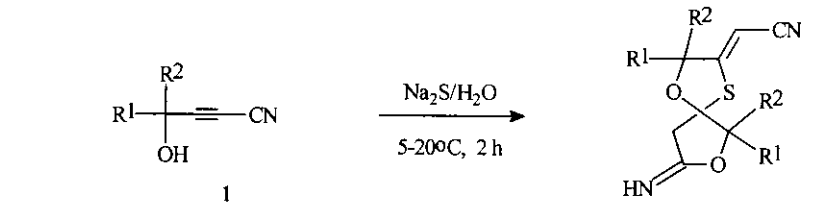
The spiro-annelation can be further extended to synthesize multi-spiro-heterocycles (**64**) by using acetylenic hydroxy esters (**24**) derived from cyclic ketones (Scheme 30).[92]

Scheme 30



Likewise, when the acetylenic hydroxy nitriles (**1**) are treated with aqueous Na_2S, the same spirocyclic skeletons, but bearing the corresponding nitrogen functions (**65**), are built up even more smoothly (at 5-20 °C) in a yield near to quantitative (Scheme 31).[92, 96, 97]

Scheme 31

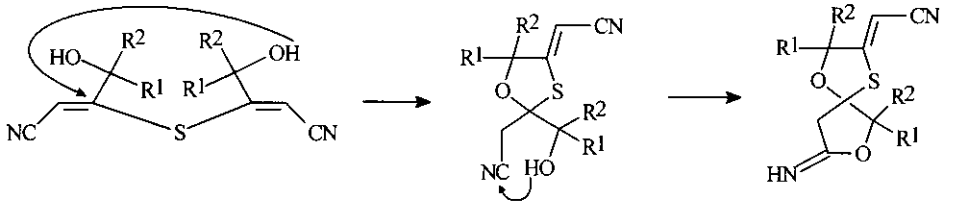


1 **65** 92%

R1 = Me; R2 = Me, Et

Apparently, in both cases, in the intermediate divinyl sulfide (**66**) one of the two hydroxyl groups attacks (in a crossover mode) the double bond of the remote acrylic moiety to close the 1,3-oxathiolane ring (**67**), while the remaining hydroxyl group reacts with the nitrile or ester function to give the imino (**68**) or carbonyl moiety (Scheme 32).

Scheme 32

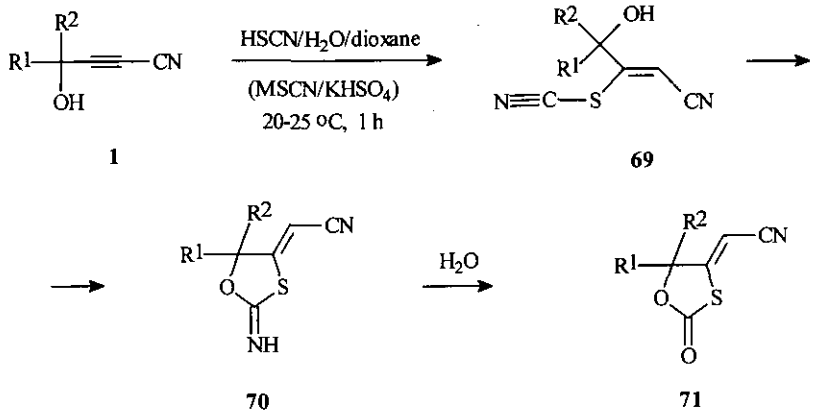


66 **67** **68**

The reaction of thiocyanation of acetylenes was many times approached, but without particular preparative results.[98-103]

It has been found that thiocyanic acid, generated *in situ* from alkali metal thiocyanates, reacts with the acetylenic hydroxy nitriles (**1**) unusually easy (under biomimetic conditions: room temperature, aqueous dioxane, 1 h) and extremely clean, but again not as expected: instead of the normal adducts (**69**), there are formed 1,3-oxathiolan-2-ones (**71**) in high yields, which result from the addition of hydroxyl to cyano group in the normal adduct and subsequent hydrolysis of the imino function in the intermediate 1,3-oxathiolane (**70**) (Scheme 33).[104-106]

Scheme 33

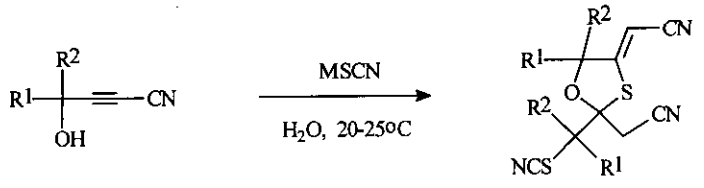


1 **69** **70** **71**

R^1 = Me; R^2 = Me, Et; M = NH_4, Na, K

Unlike thiocyanic acid, thiocyanate anion reacts with the nitriles (**1**) otherwise to form a new family of polyfunctional oxathiolanes, 1-{2-cyanomethyl-4-[(*Z*)-cyanomethylidene]-5,5-dialkyl-1,3-oxathiolan-2-yl}-1-methylethyl thiocyanates (**72**), under the same mild (biomimetic) conditions (aqueous medium, room temperature) in high yields and as smoothly and cleanly as in the former case (Scheme 34).[105, 107-109]

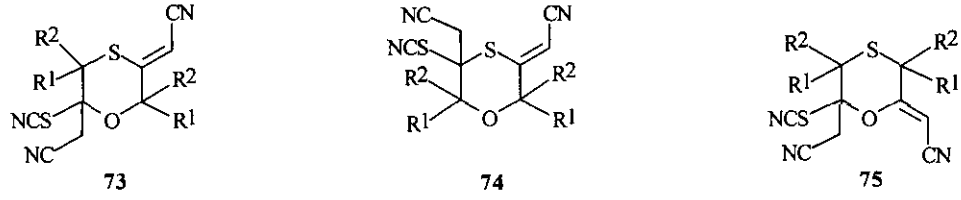
Scheme 34



1 **72** 76-86%

R^1 = Me; R^2 = Me, Et; M = NH_4, Na, K

The following alternative structures (**73-75**) were first thought to be probable for the adduct of Scheme 34 from the common chemistry and all spectral data:



73 **74** **75**

R^1 = Me; R^2 = Me, Et

An unambiguous conclusion of the adduct structure has been made from the X-Ray diffraction examination of the single crystal sample. It shows, that none of the above three structures (**73-75**) are correct and actually there are assembled the oxathiolanes (**72**) with the *syn*-arrangement of the sulfur atom and the cyano group in the cyanomethylene moiety. Besides, fine conformational details of these compounds in the crystalline state are also elucidated (Figure 1).[108]

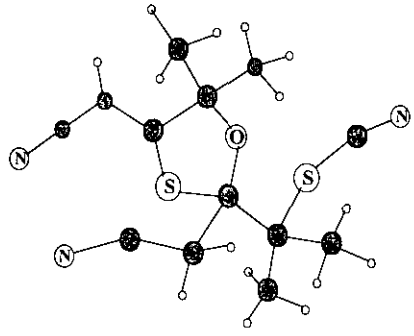
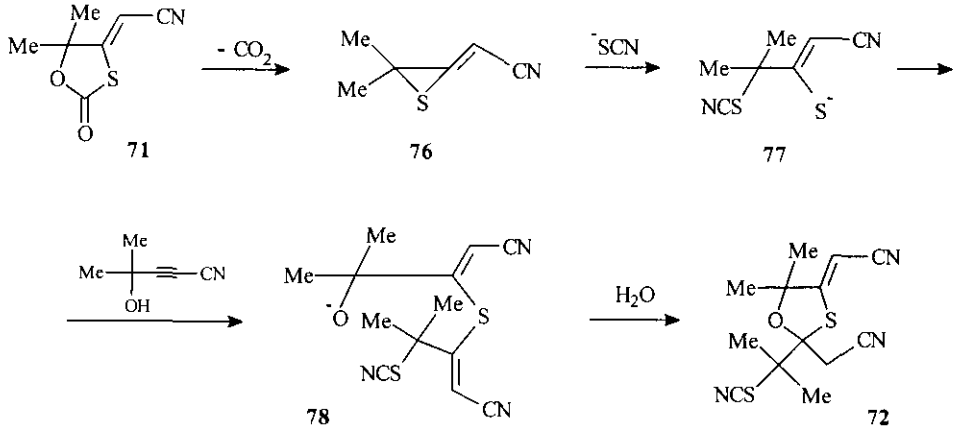


Figure 1. X-Ray structure of 1-{2-cyanomethyl-4-[(*Z*)-cyanomethylidene]-5,5-dimethyl-1,3-oxathiolan-2-yl}-1-methylethyl thiocyanate (**72**) ($R^1 = R^2 = Me$)

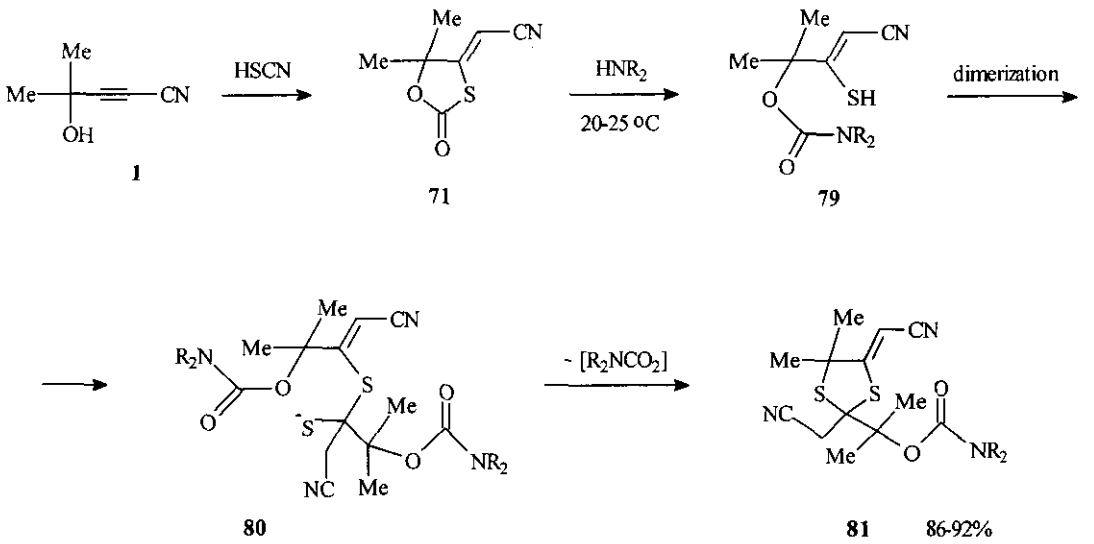
What are the steps involved in building up the structure (**72**)? Apparently, the intermediate oxathiolan-2-one (**71**) eliminates carbon dioxide and the thiirane (**76**) is intercepted by thiocyanate anion to give the new anion (**77**), which is trapped by the second molecule of the acetylenic nitrile and the anion formed (**78**) finally undergoes the ring-closure. Curious features of this self-assembling type reaction are the concerted character and complete selectivity of all its numerous steps proceeding under biomimetic conditions: only one-configuration products are always detected and all the transformations being near to quantitative (Scheme 35).

Scheme 35



The reactivity of the intermediate oxathiolan-2-ones (**71**), which can be prepared as the only products, has been further studied. When reacted with amines, the oxathiolanes (**71**), afford (practically quantitatively) not the expected mercaptocarbamate (**79**), but the heavily functionalized 1,3-dithiolanes (**81**). The cyclization proceeds stereoselectively in a biomimetic way (room temperature, methanol) (Scheme 36).[110, 111]

Scheme 36

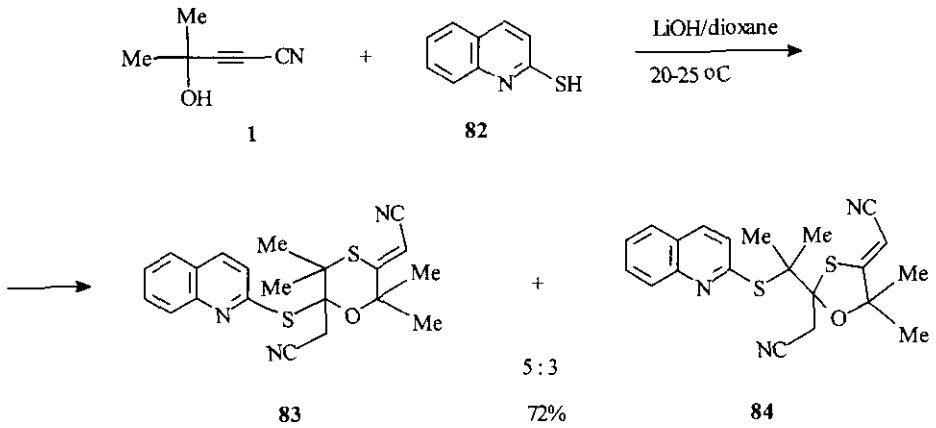


R = H, Et, *n*-Pr, *n*-Bu, *i*-Bu

This complex recyclization seems to include the ring-opening of the cyclic thiocarbonate (**71**), dimerization of the mercaptocarbamate (**79**) and intramolecular substitution of the carbamoyl group in the intermediate (**80**) to finalize the ring-closure. Again, all these transformations are concerted, wonderfully clean, fast, facile and stereoselective as followed from the single crystal X-Ray analysis[110] of the dithiolanes (**81**).

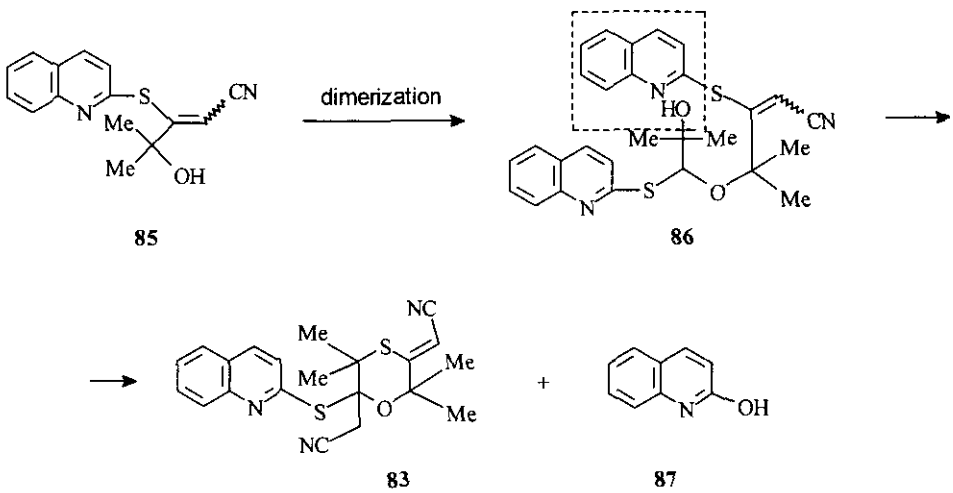
Similar multi-step self-assemblies are observed, when 2-mercaptoquinoline (**82**) reacts with the acetylenic hydroxy nitriles in the presence of LiOH in dioxane at ambient temperature. No the normal addition product is detected. Instead, a mixture of the isomeric functionalized quinolinylthio-1,4-oxathiane (**83**) and 1,3-oxathiolane (**84**) is generally isolated. The ratio of the assemblies depends on the acetylene structure and the reaction conditions, for the dimethyl derivative being 5:3 (according to the 2D-NMR spectra) (Scheme 37).[112, 113]

Scheme 37



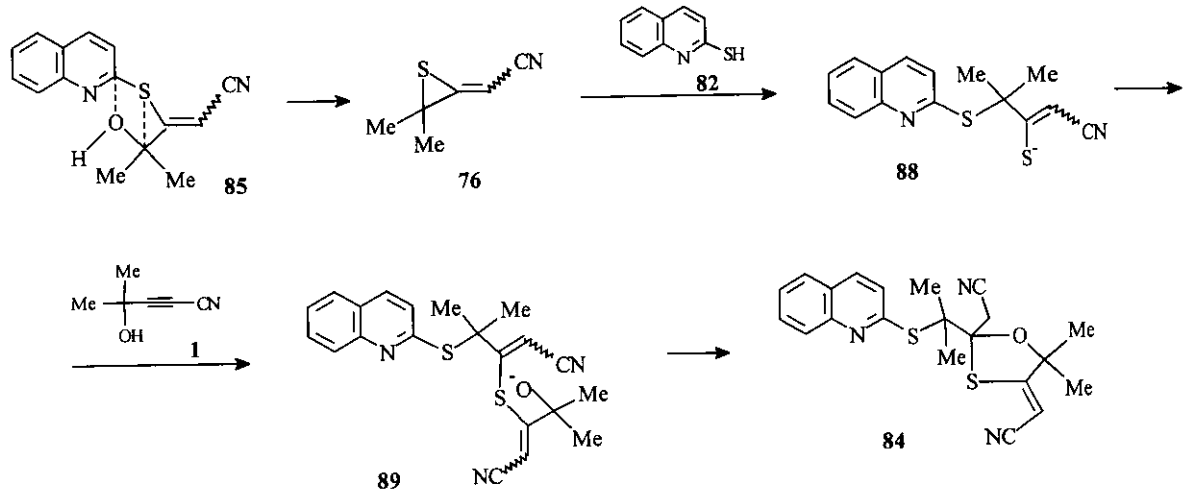
Obviously, the major isomer (**83**) is assembled from two normal adducts (**85**), which dimerise by the hydroxyl to double bond addition to give the intermediate (**86**) which closes the 1,4-oxathiane ring *via* elimination of 2-hydroxyquinoline (**87**), the latter being also isolated from the reaction mixture (Scheme 38).[113]

Scheme 38



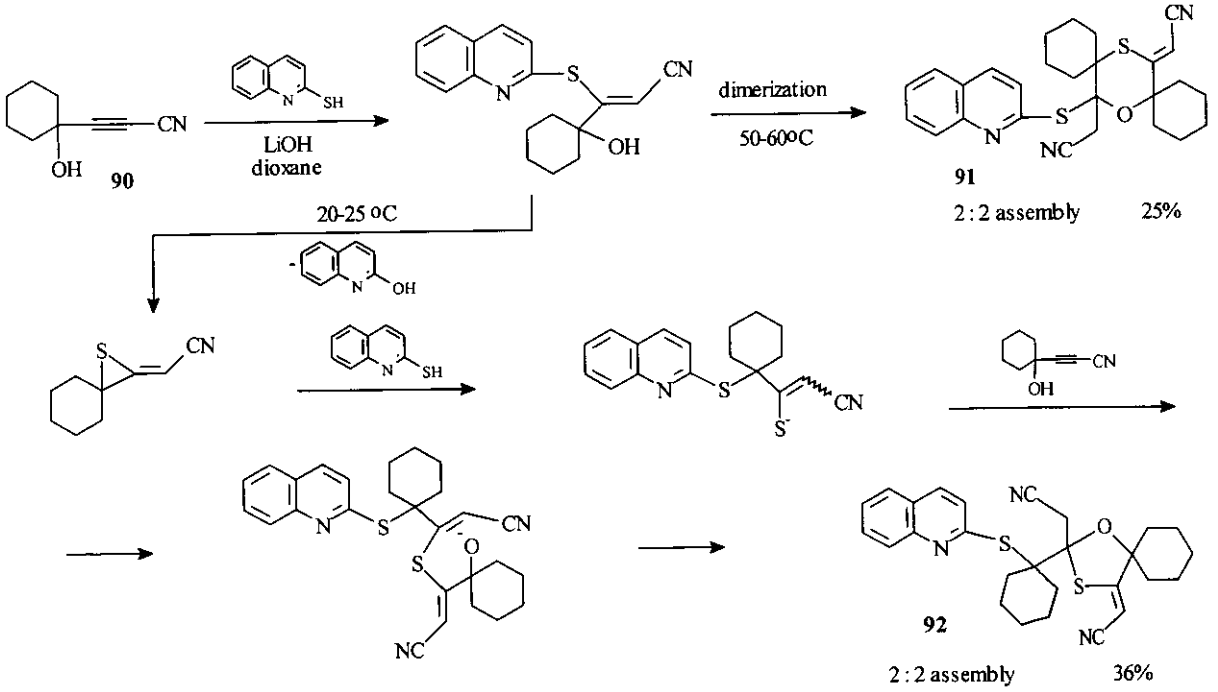
The oxathiolane cycle (**84**) is assembled as follows: the normal adduct (**85**) releases the thiirane (**76**), which is intercepted by mercaptoquinoline (**82**) and the thiolate (**88**) formed adds to the second molecule of the nitrile (**1**). Then there occurs the final intramolecular nucleophilic addition of the alkoxy anion (**89**) to its own double bond (Scheme 39).[113]

Scheme 39



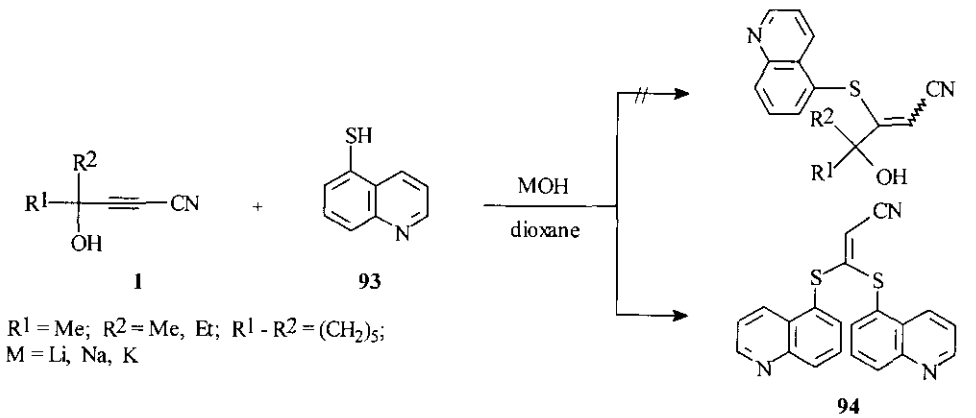
The selective 2 : 2 assembly of either the corresponding oxathiane (**91**) or the oxathiolane (**92**) has been observed for 1-cyanoethynyl-1-cyclohexanol (**90**), which, at 50-60 °C, undergoes the dimerization-elimination to the oxathiane (**91**) or, at room temperature, the dimer follows the above shown more complicated pathway towards the oxathiolane (**92**) (Scheme 40).

Scheme 40



The reaction of 5-mercaptoquinoline (**93**) with the acetylenic hydroxy nitriles (**1**) takes another but again unpredicted pathway to afford di(quinolinylthio)propenenitrile (**94**), the product of a redox process (Scheme 41).[114]

Scheme 41



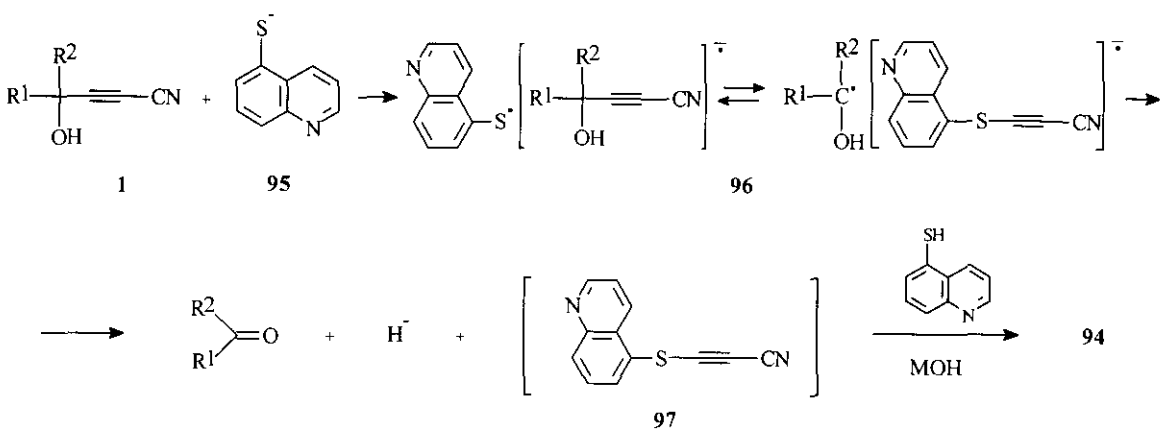
1 **93** **94**

R^1 = Me; R^2 = Me, Et; R^1 - R^2 = $(CH_2)_5$;
M = Li, Na, K

In this case, nucleophilic addition of the bulky and polarizable mercaptoquinoline anion (**95**) to the highly electrophilic and branchy acetylene (**1**) does not progress as far as formation of the classic intermediate carbanion (otherwise, nothing envisaged is to prevent the carbanion from uptaking a proton to give the normal adduct), but stops at the stage of the one electron transfer to form the anion-radical pair.

The anion-radical adduct (**96**) is assumed to be incapable of further recombinating to the classic carbanion due to the steric hindrances. Instead, it decomposes *via* the exchange of radical moieties at the triple bond to form cyanoquinolinylthioacetylene (**97**), which gives, with starting mercaptoquinoline, the final product (**94**). This scheme is supported by the direct observation of the anion-radical species in the ESR spectrum (g = 2.0042, ΔH = 0.8 mT) attributable to the anion-radical pair (**96**) and by identification of ketones (Scheme 42).[114]

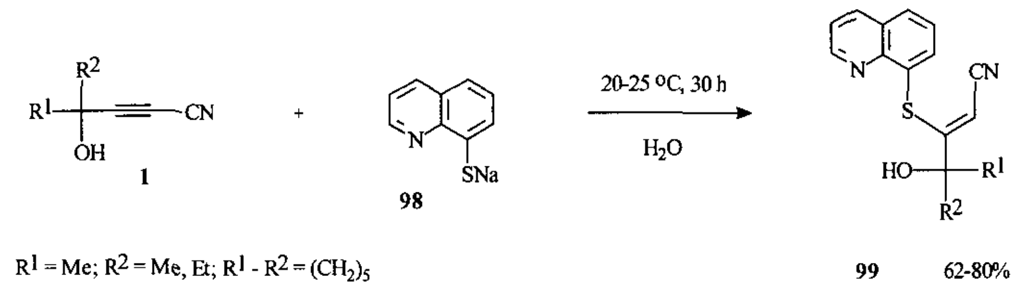
Scheme 42



1 **95** **96** **97**

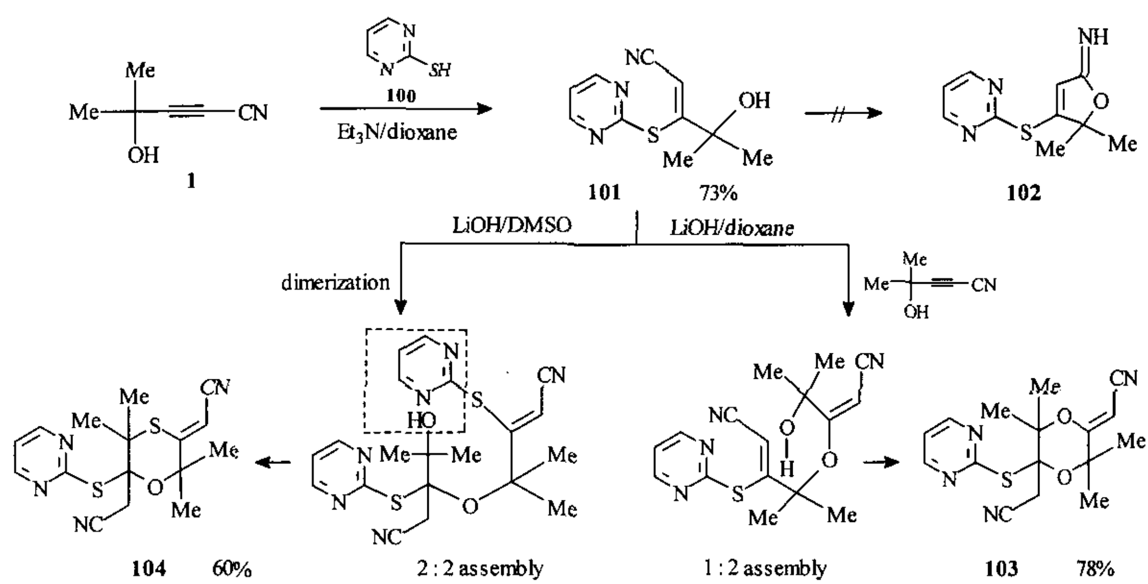
The interaction of sodium 8-mercaptoquinoline (**98**) with acetylenic hydroxy nitriles (**1**) proceeds regio- and stereospecifically under mild condition (20-25 °C, H_2O, LiOH or Et_3N) to yield 4-hydroxy-3-(quinolinyl-8-thio)-2-alkenenitriles (**99**) (Scheme 43).[115]

Scheme 43



2-Mercaptopyrimidine (**100**) under similar very mild conditions (20-25 °C, dioxane, Et_3N) forms with the acetylenic hydroxy nitriles (**1**) the normal 1 : 1 adduct (**101**), seemingly of *Z*-configuration, since it does not convert to the corresponding iminodihydrofuran (**102**). With LiOH, instead of Et_3N, in dioxane, one molecule of the mercaptopyrimidine (**100**) and two molecules of the acetylenic hydroxy nitrile (**1**) are assembled to give finally the functionalized 1,4-dioxane (**103**). Interestingly, that in DMSO, with other reaction conditions being equal, the same reactants are assembled as 2 : 2 to selectively afford the functionalized 1,4-oxathiane (**104**). Such a high sensitivity towards the medium effect at ambient temperature up to entire change of the reaction course is also a typical feature of biochemical transformations (Scheme 44).[116, 117]

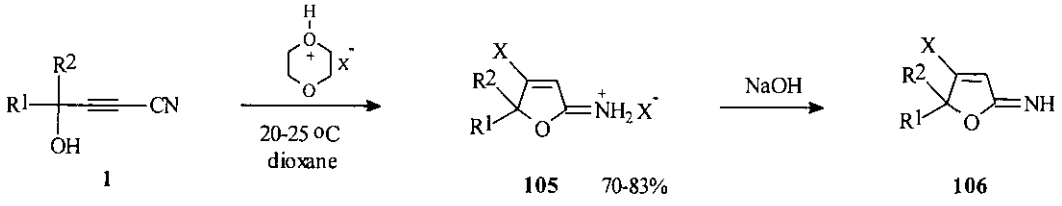
Scheme 44



5. Halogen nucleophiles

Hydrogen halides in dioxane (in fact, dioxanium halides) at room temperature smoothly convert the acetylenic hydroxy nitriles (**1**) into corresponding salts of 4-halo-2-imino-2,5-dihydrofurans (**105**), from which the free bases (**106**) can be readily released (Scheme 45).[118, 119]

Scheme 45

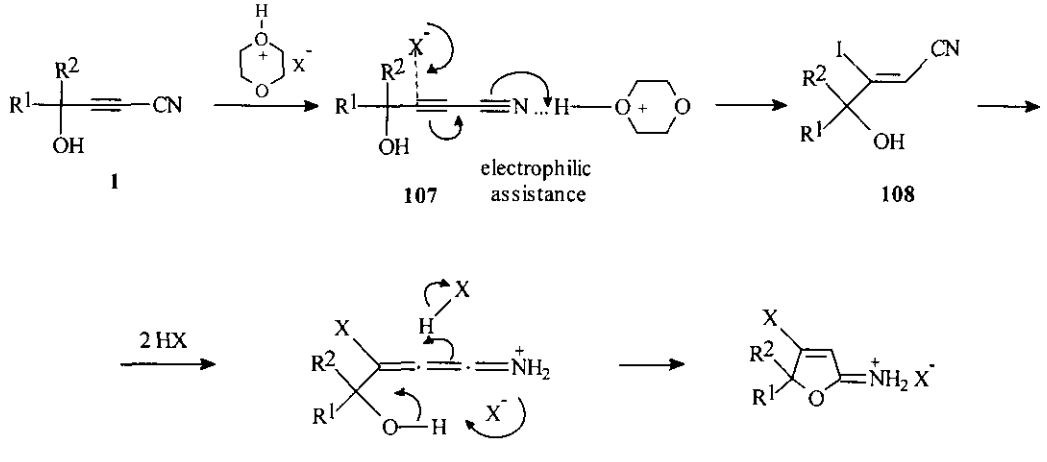


1 **105** 70-83% **106**

R^1 = Me; R^2 = Me, Et; R^1 - R^2 = $(CH_2)_5$; X = Cl (70%), Br (83%), I (75%)

The straightforward formation of the iminodihydrofuran system (skipping by the common intermediate ethylenic adducts) implies a concerted addition mechanism **107** with electrophilic assistance from dioxanium ion. The contribution of the electrophilic assistance should vary depending on nucleophilicity of halogen being the least for the most nucleophilic iodine anion. Indeed, in the latter case, a remaining amount of the corresponding iodoalkenenitrile (**108**) is detectable in the reaction mixture (Scheme 46).

Scheme 46



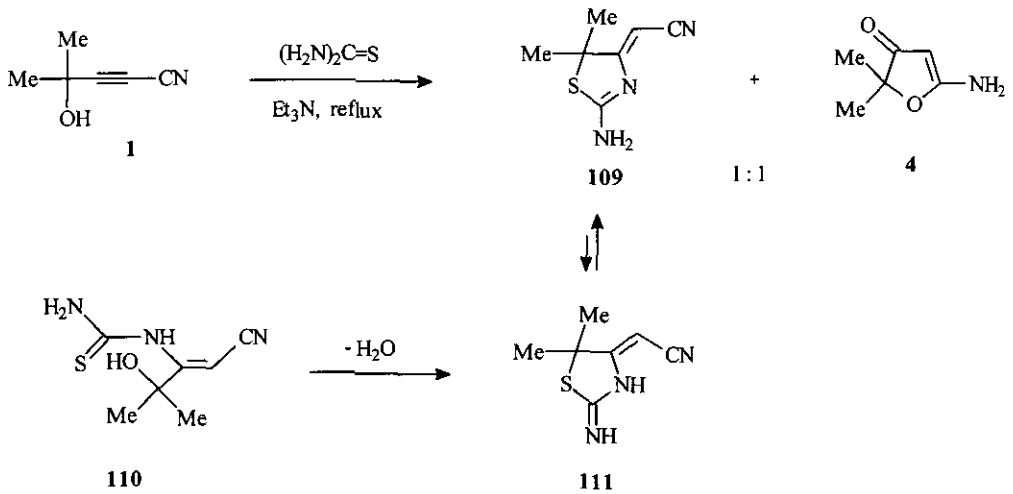
1 **107** **108**

R^1 = Me; R^2 = Me, Et; R^1 - R^2 = $(CH_2)_5$; X = Cl, Br, I

6. Multident and multifunctional nucleophiles

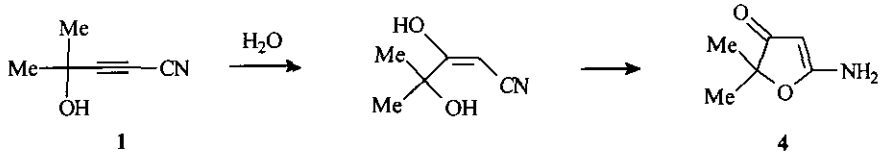
A multident nucleophile, thiourea, when refluxed with the acetylenic hydroxy nitriles (**1**) in Et_3N, gives a 1 : 1 mixture of the aminocyanomethylenethiazoline (**109**) and the aminodihydrofuranone (**4**). Therefore, there takes place the *N*-addition of thiourea to the triple bond, next follows the water elimination from the adduct (**110**) to close the thiazolidine ring (**111**) (Scheme 47).[120, 121]

Scheme 47



The water released adds to another half of the acetylenic nitriles (**1**) to result in the aminodihydrofuranone (**4**) (Scheme 48).

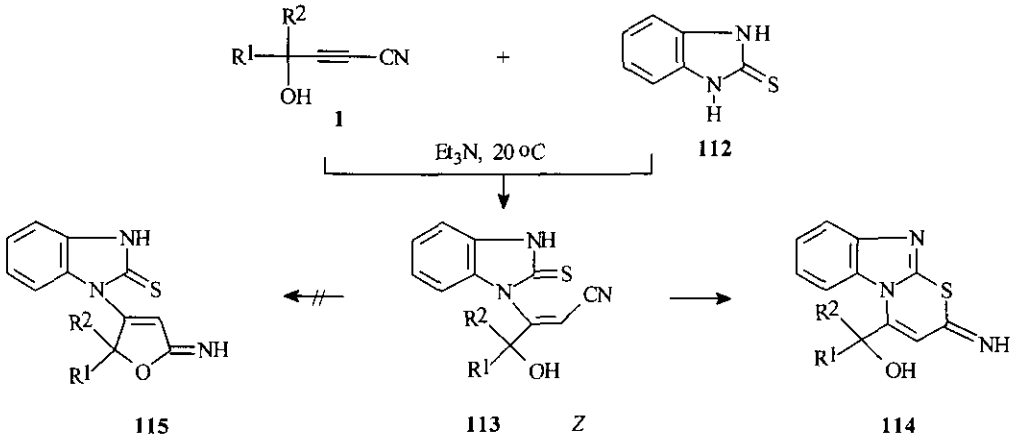
Scheme 48



The thiazoline structure (**109**) is assigned by the X-Ray analysis showing two independent molecules of different conformation in one crystalline cell, with an insignificant geometry variation.[120]

Cyclic thioureas, like, benzimidazole-2-thione (**112**), interact with the acetylenic hydroxy nitriles (**1**) under mild conditions (alkali metal hydroxides, tertiary amines, 20 °C, organic solvent) first by their nitrogen, too, and the intermediate (**113**) further quantitatively closes the thiazine (**114**), but not the iminodihydrofuran cycle (**115**), thus indicating the rigid *Z*-configuration of the adduct (Scheme 49).[122-129]

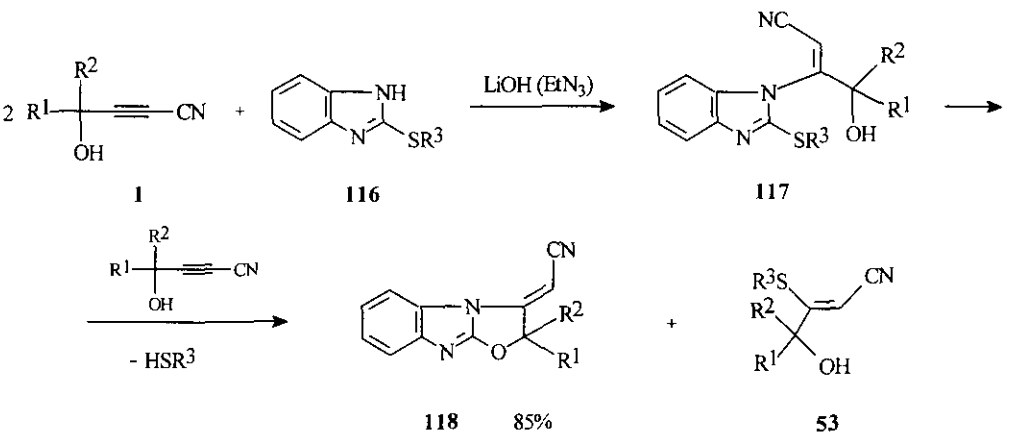
Scheme 49



R^1 = Me; R^2 = Me, Et; R^1 - R^2 = $(CH_2)_5$

A new direction of heterocyclization is observed, when the nitriles (**1**) are allowed to react with substituted thiabenzimidazoles (**116**): the adduct (**117**) eliminates the thiol to result in ring-closure of 1,3-oxazolidinobenzimidazoles (**118**), the thiol adding to the excess acetylenic nitrile (**1**) to form the adduct (**53**) (Scheme 50).[130, 131]

Scheme 50



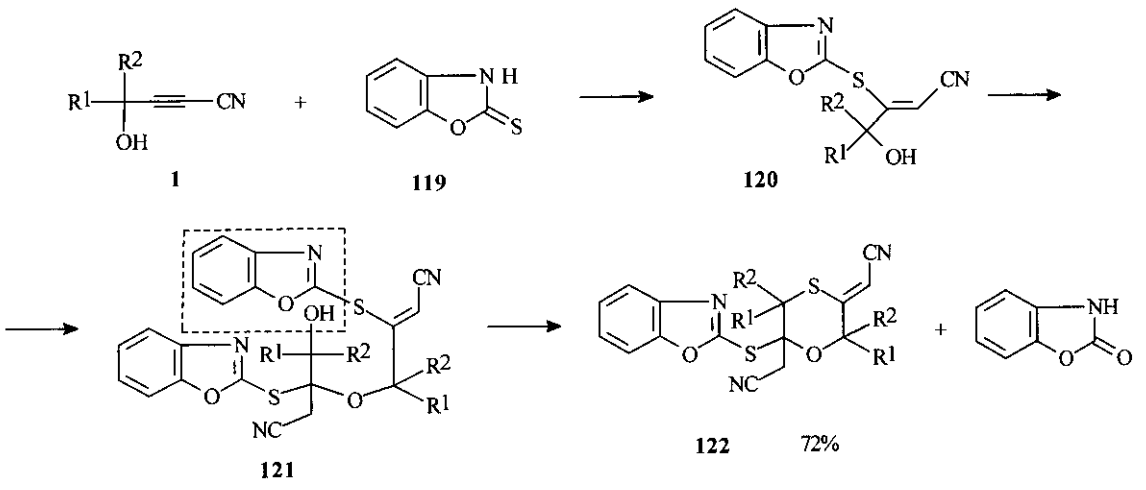
R^1 = Me; R^2 = Me, Et; R^1 - R^2 = $(CH_2)_5$; R^3 = Me, Et, CH=CH_2

Prerequisites of the process selectivity are (i) a two-fold excess of the nitrile (**1**), (ii) initial mixing the reactants at 20-25 °C (8 h) in the presence of LiOH or Et_3N, and (iii) boiling the reaction mixture in the solvent (acetonitrile) for 10 h.

The corresponding oxygen analog, benzoxazole-2-thione (**119**), behaves in the same reaction in a quite different way, using sulfur atom as an initial nucleophilic site. Under the same mild conditions (20-25 °C,

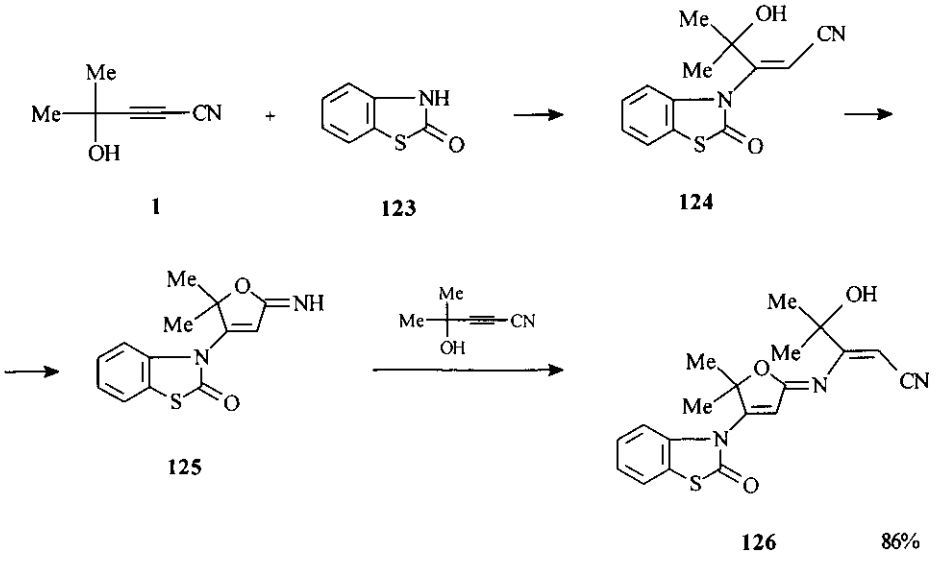
no catalyst, acetonitrile or dioxane), there is assembled 1,4-oxathiane ring (**122**). Therefore, the normal sulfur-adduct (**120**) dimerises through the hydroxyl-double bond nucleophilic addition and then the dimer (**121**) eliminates benzoxazolone to give 1,4-oxathianylthiobenzoxazoles (**122**) (Scheme 51).[132, 133]

Scheme 51



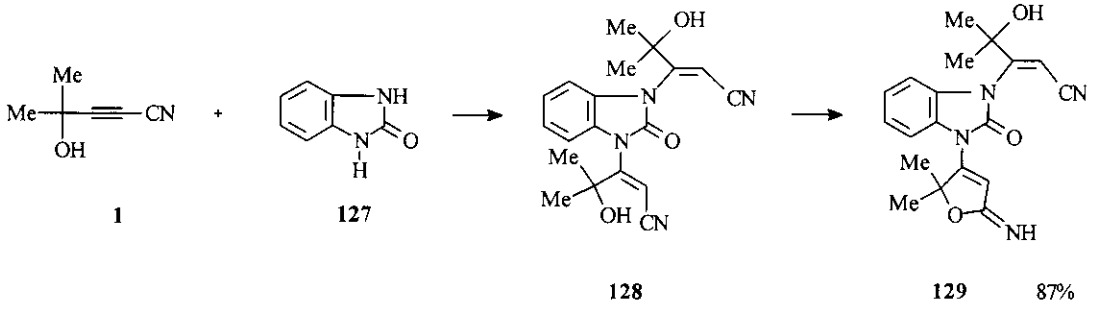
The interaction of benzothiazol-2-one (**123**) and 4-hydroxy-4-methyl-2-pentynenitrile (**1**) (LiOH, DMSO, 20 °C, 1 h) leads to 1 : 2 assembly (**126**) through the consecutive formation of normal adduct (**124**), its cyclization to the iminodihydrofuran (**125**), which adds further to the second molecule of the nitrile (**1**) (Scheme 52).[134]

Scheme 52



The reaction of benzimidazole-2-one (**127**) with the nitrile (**1**) occurs in DMSO or dioxane in the presence of MOH (M = Li, K, 8 h, 20-25 °C) to afford the 1 : 2 assembly of another structure (**129**) (yield 87%) through the open intermediate (**128**), wherein just one of the two moieties capable of cyclizing closes the iminodihydrofuran ring (Scheme 53).[135, 136]

Scheme 53



1 **127** **128** **129** 87%

Thus, the reactions overviewed here show, that every new multident nucleophile behaves with the derivatives of α,β-acetylenic γ-hydroxy acids in its own specific way, thus providing flexible strategies for design of new heterocyclic systems, including dihydrofuranone derivatives.

IN CONCLUSION

Basing on the esters and nitriles of α,β-acetylenic γ-hydroxy acids available from the direct oxidative carbonylation of tertiary acetylenic alcohols with carbon monoxide in the presence of the Pd/Cu system, there have been developed a number of general and highly efficient synthetic approaches employing mild conditions to new families of functional dihydrofuranone derivatives and other polyfunctional heterocycles, prospective drug candidates and agricultural chemicals.[137]

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