SYNTHESIS OF 4-UNSUBSTITUTED ISOTHIAZOLES

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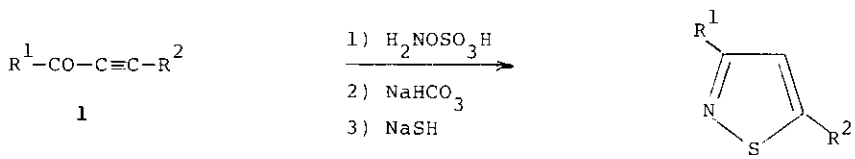
Abstract — A new method for the synthesis of 4-unsubstituted isothiazoles starting from α-acetylenic aldehydes or ketones, hydroxylamine-O-sulphonic acid and sodium hydrosulfide in buffered aqueous solution by one-pot procedure, is described.

Isothiazoles have been intensively studied and numerous preparations have been accomplished.[1] The present work brings a contribution in this field with a new synthesis of 4-unsubstituted isothiazoles. The present method does not require the preparation or separation of N- or S-containing precursors; in fact the introduction of such elements by two commercial reagents is carried out along with the cyclization by one-pot reaction. Yields are comparable and sometimes better than those of more laborious processes for analogous products. The execution of the reaction is extremely simple because it is carried out in water, between 0° and room temperature, in an open vessel. Actually an α-acetylenic aldehyde or ketone is treated with hydroxylamine-O-sulphonic acid and then with sodium hydrosulfide in buffered aqueous solution (Scheme 1).

Scheme 1

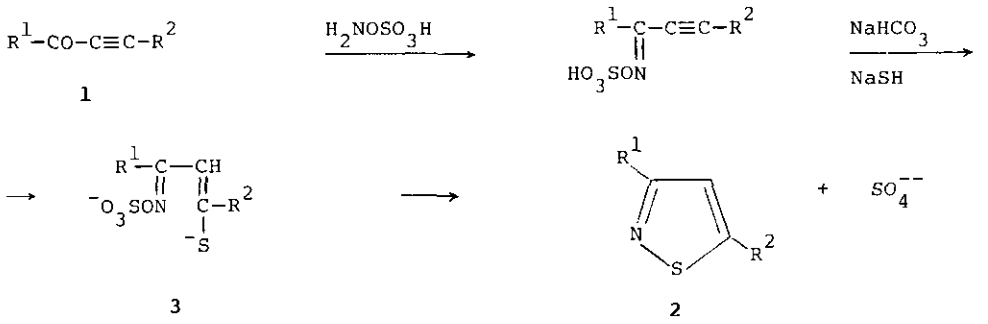


a: $R^1 = R^2 = H$; **b**: $R^1 = CH_3$, $R^2 = H$; **c**: $R^1 = C_2H_5$, $R^2 = H$; **d**: $R^1 = n\text{-}C_3H_7$, $R^2 = H$; **e**: $R^1 = H$, $R^2 = CH_3$; **f**: $R^1 = R^2 = CH_3$; **g**: $R^1 = H$, $R^2 = C_6H_5$; **h**: $R^1 = CH_3$, $R^2 = C_6H_5$; **i**: $R^1 = CH_3$, $R^2 = CH_2OH$; **j**: $R^1 = CH_3$, $R^2 = CHOHCH_3$

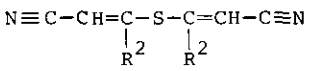
In the initial reaction with hydroxylamine-O-sulphonic acid the characteristic odor of the ynal or ynone disappears and the mixture becomes homogeneous. The subsequent reaction with sodium hydrosulfide affords crude isothiazoles having a fair degree of purity.

A reasonable mechanism scheme foresees the formation of an oxime-O-sulphonic acid from the first reaction which causes the disappearance of the ynal or ynone and then the addition of the sulfide ion to the triple bond as for other activated acetylenes,[2] followed by cyclization through nucleophilic substitution of the sulfate ion at the N atom (Scheme 2).

Scheme 2



It is interesting to note that when acetylenic aldehydes are used the reaction affords a thiobisalkenylnitrile (**4**) as side product. This is in agreement with the known instability of the oxime-O-sulphonic acids derived from aldehydes which easily eliminate sulfuric acid to give nitriles.[3] That part of the sulfide which cannot give rise to the cyclization interacts with the triple bond of a second reagent molecule forming compound **4**.



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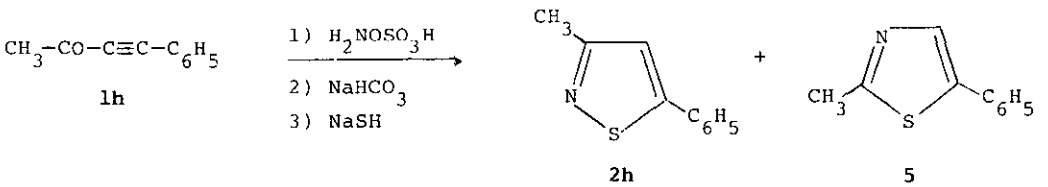
It is relevant that the reaction with 4-phenyl-3-butyn-2-one besides 3-methyl-5-phenylisothiazole also affords 2-methyl-5-phenylthiazole in a poor yield (Scheme 3).

Scheme 3

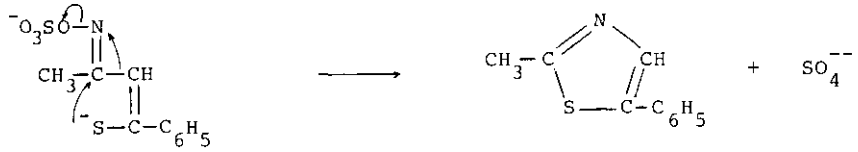


2h **5**

No significant variations in the yields of **2h** and **5** were observed when the in-

itially formed oxime-O-sulphonic acid was left for one day at room temperature both in absence and in presence of sodium hydrogen carbonate before achieving the cyclization as in Scheme 3. Such observations allow to suppose that the rearrangement, which gives rise to the formation of the thiazole derivative, takes place only after the addition of the sulfide ion to the triple bond. This rearrangement could be of Beckman type on the intermediate **3** in which the migration of the alkenyl group towards the nitrogen is favoured by the intramolecular nucleophilic attack of the sulfur anion on the oxime carbon (Scheme 4).

Scheme 4



3h **5**

The molecular structures of the new isothiazoles **2c**, **2d**, and **2j** were unambiguously assigned on the basis of elemental analysis, ir, nmr and Mass spectra. The known isothiazoles showed spectral and physical data in agreement with those reported in the literature.

EXPERIMENTAL

Ir spectra were recorded on a Perkin Elmer 283 spectrophotometer; the reported bands for isothiazoles are tentatively assigned to the ring on empirical basis. ^{1}H-Nmr spectra were run on a Jeol PS 100 spectrometer. Mass spectra were recorded on a Varian MAT CH7 mass spectrometer operating at 70 eV. Preparative layer chromatographies (PLC) were carried out on Merck $PF_{254+366}$ silica gel. Melting points were determined using a Kofler apparatus and are uncorrected. Satisfactory microanalyses of all the new products prepared were obtained: C±0.06; H±0.13; S±0.22.

Materials

Ynals and ynones were prepared according to the known procedures. The ynones **1i** and **1j** were prepared and used with the alcoholic function protected as tetrahydropyranyl derivative.

General procedure for the preparation of isothiazoles

The reagents were used in the molar ratio ynal or ynone : hydroxylamine-O-sulphonic acid : sodium hydrogen carbonate : sodium hydrogen sulfide = 1 : 1 : 1 : 1.1.
An aqueous mixture of ynal or ynone (2.5 mmol/ml) and hydroxylamine-O-sulphonic acid was stirred at 0 °C up to the disappearance of the organic reagent (15-25 minutes for ketones, 3 minutes for aldehydes), and then it was treated carefully with solid sodium hydrogen carbonate. Afterwards the mixture was treated with

the proper volume of a 1.4M aqueous solution of sodium hydrogen sulfide and stirred for 4 h at room temperature. The reaction mixtures from **1b,c,d,f** were extracted with diethyl ether, dried over anhydrous sodium sulfate and distilled to give the corresponding isothiazoles **2b,c,d,f**. The reaction mixture from **1h** was extracted with diethyl ether, dried over anhydrous sodium sulfate, distilled up to the removal of the solvent and chromatographed by PLC with a 80:20 mixture of *benzene/petroleum ether (bp 40-60 °C) as eluent to give the isothiazole* **2h** and the thiazole **5**. The reaction mixtures from the tetrahydropyranyl derivatives of **1i** and **1j** were extracted with diethyl ether and the extracts were evaporated, left for 2 h in presence of an excess of 1M HCl in methanol-water (1:4 v/v) for a complete deprotection of the alcoholic function, neutralized with sodium hydrogen carbonate, extracted with diethyl ether, dried over anhydrous sodium sulfate, distilled up to the removal of the solvent and purified by PLC with a 96:4 mixture of benzene/methanol as eluent to give the corresponding isothiazoles **2i,j**. The reaction mixtures from the ynals **1a** and **1e** were extracted with methylene chloride, dried over anhydrous sodium sulfate, freed from the solvent and distilled up to the collection of the corresponding isothiazoles **2a** and **2e**. The distillation residues were crystallized to give the nitriles **4a** and **4e** respectively using ethyl acetate and acetone as solvents. The reaction mixture from the ynal **1g** was extracted with methylene chloride, dried over anhydrous sodium sulfate, distilled up to the removal of the solvent and chromatographed by PLC with a 80:20 mixture of petroleum ether (bp 40-60 °C)/ethyl acetate as eluent to give the isothiazole **2g** and the nitrile **4g**. Further purification of the new isothiazoles **2c,d,j** was accomplished by precipitation in anhydrous pentane with gaseous HCl, separation of the hydrochlorides and recovery of the bases by treatment with aqueous sodium hydrogen carbonate.

Propynal[4] (**1a**) afforded *isothiazole*[5] (**2a**) (yield 42%) and *1,1'-thiobis[2-cyanoethene]*[6] (**4a**) (yield 18%; mp 141-142 °C, lit.[6] 142-142.5 °C; ir (KBr) ν, cm^{-1} 2220 (CN)).

3-Butyn-2-one[7] (**1b**) afforded *3-methylisothiazole*[5] (**2b**) (yield 45%).

1-Pentyn-3-one[8] (**1c**) afforded *3-ethylisothiazole* (**2c**) in 27% yield; bp 146-148 °C; ir (film) ν, cm^{-1} 1388, 815; ^{1}H-nmr (neat) δ, ppm 8.74(d, J=4.5 Hz, 1H), 7.17(d, J=4.5 Hz, 1H), 2.87(q, J=7.6 Hz, 2H), 1.29(t, J=7.6 Hz, 3H); ms, m/z 113 (68%, M^+).

1-Hexyn-3-one[9] (**1d**) afforded *3-n-propylisothiazole* (**2d**) in 28% yield; bp 93 °C/55 Torr; ir (film) ν, cm^{-1} 1389, 810; ^{1}H-nmr (neat) δ, ppm 8.85(d, J=4.6 Hz, 1H), 7.31(d, J=4.6 Hz, 1H), 3.08(t, J=7.5 Hz, 2H), 2.02(sext, 2H), 1.18(t, J=7.3 Hz, 3H); ms, m/z 127 (8%, M^+).

2-Butynal[10] (**1e**) afforded *5-methylisothiazole*[5] (**2e**) (yield 47%) and *2,2'-thiobis[1-cyanopropene]*[6] (**4e**) (yield 12%; mp 120-121 °C, lit.[6] 119-121 °C; ir (KBr) ν, cm^{-1} 2225 (CN)).

3-Pentyn-2-one[11] (**1f**) afforded *3,5-dimethylisothiazole*[12] (**2f**) (yield 45%).

Phenylpropynal[13] (**1g**) afforded *5-phenylisothiazole*[5] (**2g**) (yield 36%; ir (KBr) ν, cm^{-1} 1414, 810) and *1,1'-thiobis[1-phenyl-2-cyanoethene]*[6] (**4g**) (yield 14%; mp 177-178 °C, lit.[6] 176-178 °C; ir (KBr) ν, cm^{-1} 2215 (CN)).

4-Phenyl-3-butyn-2-one[14] (**1h**) afforded *3-methyl-5-phenylisothiazole*[15] (**2h**) (yield 62% ; ir (KBr) ν, cm^{-1} 1398, 813) and *2-methyl-5-phenylthiazole*[16] (**5**) (yield 11%).

5-(2-Tetrahydropyranyloxy)-3-pentyn-2-one[17] afforded *3-methyl-5-hydroxymethylisothiazole*[18] (**2i**) (yield 35%; ir (film) ν, cm^{-1} 1400, 815; ^{1}H-nmr ($CDCl_3$, TMS int. ref.) δ, ppm 6.87(s, 1H), 4.92(s, 2H), 2.43(s, 3H).

5-(2-Tetrahydropyranyloxy)-3-hexyn-2-one[17] afforded oily *3-methyl-5-(1-hydroxyethyl)isothiazole* (**2j**) in 54% yield; ir (film) ν , cm^{-1} 1398, 812; ^{1}H-nmr ($CDCl_3$, TMS int. ref.) δ, ppm 6.85(s, 1H), 5.23(q(broad), 1H), 2.45(s,3H), 1.61(d, J=6.7 Hz, 3H); ms, m/z 143 (24%, M^+).

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