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Synthesis of Heterocycles Through Reactions of Nucleophiles with Acrylonitrile Derivatives, Part 10. A conventient one-step synthesis of spirodihydropyridines

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Abstract □ Synthesis of spiro 1,4-dihydropyridines by a novel and facile one-step method is reported. Structures and reaction mechanisms are also reported with a support by another synthetic routes.

Keywords □ Acrylonitriles, spirodihydropyridines.

1,4-Dihydropyridines exhibit analgesic and antihypertensive activity.[1-3] The chemistry of dihydropyridines attracted much attention due to their pharmacological properties especially as calcium antagonists.[4,5] All attempts to prepare 4,4-disubstituted-1,4-dihydropyridines before 1976 had been unsuccessful[6]. Spirodihydropyridines were synthesised from the corresponding spirodialdehydes by Foos *et al.*[7]. Goldmann[8] succeeded to synthesize 4,4-disubstituted 1,4-dihydropyridine by intermolecular addition of carbanions to pyridines. In continuation of our previous work on the synthesis of biologically interesting molecules from α, β,-unsaturated nitriles[9-11], **I** succeeded in preparing 6′-amino-3′,5′-dicyano-1′,4′-dihydro spiro[cyclopentane 1,4′-pyridine]-2′-thione (**5**) by a facile one-step route. Thus, stirring an ethanolic piperidine solution of equimolar amounts of cyclopentanone (**1**), malononitrile and cyanothioacetamide at room temperature yields a product with molecular formula $C_{11}H_{12}N_4S$ (cf. Scheme 1). Structure, **6** was ruled out by the ^{1}H-nmr spectrum of the reaction product which revealed signals at δ 1.3-1.8 ppm (*m*, 8H, cyclic protons), at δ 3.2 ppm (*s*, 2H, NH_2). In addition, one-proton signal at δ 5.3 ppm (*s*, 1H, pyridine H-3) and oneproton signal at δ 7.3 ppm (*s*, 1H, NH) appeared, which expected to be absent in case of **6**. Structure **5** was established for the reaction product on the basis of analytical and spectral data. The ir spectrum of **5** revealed bands for NH, NH_2, C≡N and C=N absorptions and the absence of an SH band at 2600 cm^{-1} which revealed its existance as the thione tautomer.

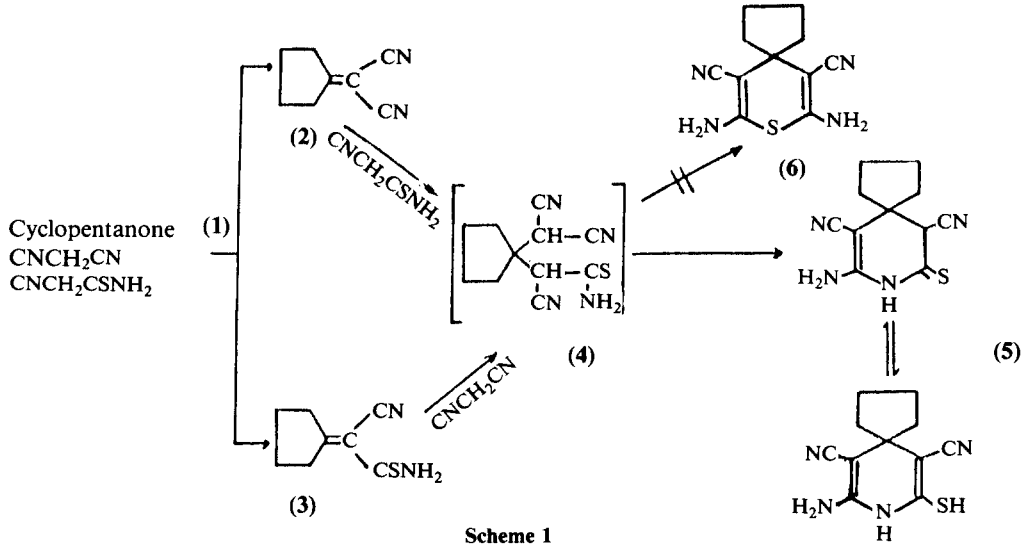
Formation of **5** is rationalized in terms of the initial condensation of cyclopentanone **1** with malononitrile or cyanothioacetamide affording cyclopentylidene malononitrile **2** or cyanocyclopentylidene thioacetamide **3** respectively followed by the Michael addition of the other active methylene compound to the ylidenic bond in **2** or **3** forming the acyclic adduct **4** which cyclised under the applied conditions to **5**.

Structural proof was obtained through another route of synthesis by stirring an ethanolic piperidine solution of equimolar amounts of **2** with cyanothioacetamide at room temperature and also by stirring ethanolic piperidine solution of **3** with malononitrile at room temperature (Scheme 1).

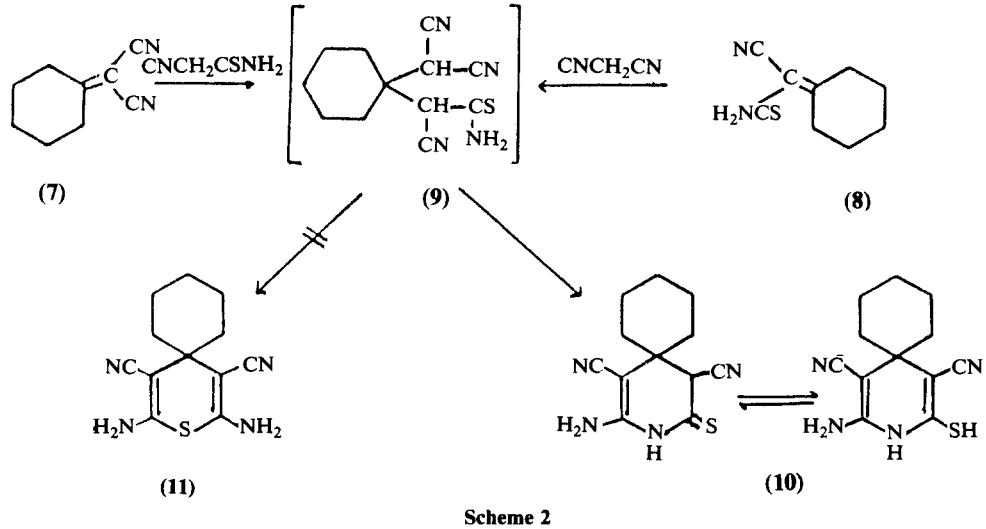
On the other hand, I failed in preparing 6′-amino-3′,5′-dicyano-1′,4′-dihydro spiro[cyclohexane-1,4′-pyridine]-2′-thione (**10**) by using cyclohexanone instead of cyclopentanone in the previous one-step route, while **10** could be synthesised by stirring an ethanolic piperidine solution of cyclohexylidene malononitrile (**7**) with cyanothioacetamide at room temperature. Structure **10** was established for the reaction product on grounds similar to those for **5**.

Formation of **10** is rationalized in terms of the formation of intermediate, **9** which cyclizes under the applied conditions to **10** (Scheme 2).

Furthermore structural proof was obtained through another route of synthesis by stirring an ethanolic piperidine solution of **8** with malononitrile at room temperature. Also structure **11** as an isomer for the reaction product was ruled out



Scheme 1



Scheme 2

based on spectral data.

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded (KBr) on Shimazu 408 spectrophotometer. ^{1}H NMR spectra were measured in DMSO-d6 on a Varian Em-390 spectrometer (90 MHz) using TMS as internal standard and chemical shifts are expressed as δ values. Microanalytical data were obtained from the microanalytical data unit at Cairo University.

Synthesis of 5

Methods A: A suspension of an equimolar amounts (0.01 mol) of cyclopentanone **1**, malononitrile and cyanothioacetamide in ethanol (50 m*l*) and a catalytic amount of piperidine was stirred at room temperature for 10 hrs. The solution was then poured into water and the solid product was collected by filteration.

Method B: A suspension of equimolar amounts (0.01 mol) of **2** or **3** was treated with cyanothioacetamide or malononitrile and a catalytic amount of piperidine was stirred at room temperature for 3 hrs. The reaction mixture was treated as in case of method A.

6′-Amino-3′,5′-dicyano-1′,4′-dihydro spiro[cy-

clopentane-1,4'-pyridine]-2'-thione formed colourless crystals from methanol; m.p.174-176 °C, yield 50% by method A, 70% by method B. IR: 3440, 3350, 3240 cm^{-1} (NH, NH_2), 2930, 2850 cm^{-1} (CH stretches), 2220 cm^{-1} (CN) and 1650 cm^{-1} (C=N, C=C and NH_2). ^1H NMR: 1.3-1.8 ppm (*m*, 8H, cyclic protons); 3.2 (*s*, 2H, NH_2), 5.3 (*s*, 1H, pyridine H-3) and 7.3 (*s*, 1H, NH). $C_{11}H_{12}N_4S$ (M. Wt. = 232): Calcd. C 56.89, H 5.17, N 24.14, S 13.79; Found. C 57.00, H 5.30, N 24.10, S 14.10

Synthesis of 10

Method A: To a suspension of **7** (0.01 mol) in ethanol (50 m*l*) was added 0.01 mol of cyanothioacetamide and a catalytic amount of piperidine. The reaction mixture was stirred for 6 hrs at room temperature. The solid product was collected as in the previous case.

Method B: To a suspension of **8** (0.005 mol) in ethanol (20 m*l*) was added malononitrile (0.005 mol) an a catalytic amount of piperidine. The reaction mixture was stirred for 3 hrs at room temperature. The solid product was collected as in the previous cases.

6-Amino-3',5'-dicyano-1',4'-dihydro spiro[cyclohexane 1,4' pyridine]-2'-thione formed colourless crystals from methanol; m.p. 168-169 °C, yield 65% by method A, 30% by method B. IR: 3450, 3350, 3210 cm^{-1} (NH, NH_2), 2910, 2850 cm^{31} (CH stretches), 2200 cm^{-1} (CN) and 1640, 1630 cm^{-1} (C=N, C=C, δ NH_2). ^1H NMR: 1.2-2.2 (*m*, 10H, cyclic protons); 3.2 (*s*, 2H, NH_2); 5.6 (*s*, 1H, pyridine H-3) and 7.0 (*s*, 1H, NH). $C_{12}H_{14}N_4S$ (M. Wt. 244): Calcd. C 58.53, H 5.69, N 22.76, S 13.01; Found. C 58.50, H 5.50, N 23.00, S 13.20

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