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UNUSUAL COURSE OF CONDENSATION OF 2-BROMO-1-PHENYLETHYLIDENEMALONONITRILE WITH SUBSTITUTED THIOUREAS

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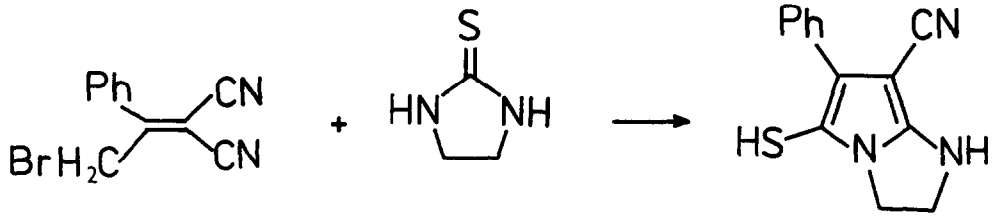
Summary: Condensation of the title compound with 2-mercapto-4,5-dihydroimidazole yields a substituted pyrrolo [1,2-a] imidazole. The reaction with 2-mercapto-3,4,5,6-tetrahydropyrimidine gives an isothiocyanate due to opening of the heterocyclic ring.

2-Bromoalkylidenemalononitriles represent potentially useful precursors for simple construction of the pyrrole or thiophene nucleus.[1] Recent reports on the use of these synthons in the preparation of 7-membered heterocycles[2] prompted us to study the behaviour of 2-bromo-1-phenylethylidenemalononitrile (1) towards ambident nucleophiles. In pursuance of our interest in fused imidazolines[3] we have chosen 5- and 6-membered cyclic thioureas as the object of this study.

Refluxing 1 with 2-mercapto-4,5-dihydroimidazole (2) and triethylamine in ethanol afforded a red solid as the sole product, isolated in a moderate yield.[4] The formula ($C_{13}H_{11}N_3S$ from combustion analysis and high resolution MS) formally corresponds to a 1:1 adduct of 1 and 2 with elimination of hydrogen bromide and hydrogen cyanide. This rules out an imidazothiepine system described previously.[2] The structure of the unexpected product 3 was inferred from the spectral data and chemical modification.

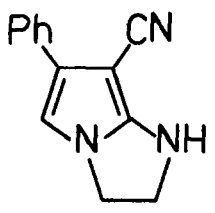


1 2 3

The ^{1}H-NMR spectrum of 3 shows a multiplet of phenyl protons (δ 7.07-7.46, 5H) and a broad singlet of two methylene groups (δ 3.66, 4H). The ^{13}C-NMR spectrum displays two resolved sp^2 methines of the phenyl group (127.78, 127.37), five sp^2 quaternary carbon atoms (155.28,139.54,

131.88, 105.08, 68.63), a nitrile carbon atom (116.43) and two sp^3 methylenes (47.87 and 43.38). The position of the high-field singlet at δ 68.63 is due in part to the shielding effect of the adjacent cyano group. The presence of the latter (2206 cm^{-1}) and of a secondary amine (3290 cm^{-1}) was apparent from the IR spectrum. The mass spectrum showed ions due to loss of hydrogen sulfide, and a $C_9H_7N^+$ fragment which was indicative of a Ph-C-C-CN subunit. These data appeared compatible with the structure of 7-cyano-2,3-dihydro-5-mercapto-6-phenyl-1H-pyrrolo [1,2-a] imidazole, 3, which was further supported by chemical modifications.

Desulfuration of 3 (Raney Ni, 90-100°C, 9 h) yielded compound 4 ($C_{13}H_{11}N_3$, 46%, m.p.181-182 °C) which was characterized by spectral data.[5] The ^{13}C-NMR spectrum showed a high-field signal of C-7 (δ 63.79 sd, ^3J = 7 Hz), while C-5 appeared as a doublet (δ 108.49, ^1J = 191 Hz). The ^{13}C-^1H coupling constants are typical of a pyrrole nucleus.[6] This was confirmed by comparing the ^{13}C-NMR spectrum of 4 with that of a model pyrrole derivative 5 (δ 113.61 d, ^1J = 191 Hz, 70.09 sd, ^3J = 7.5 Hz), prepared according to Gewald.[1]



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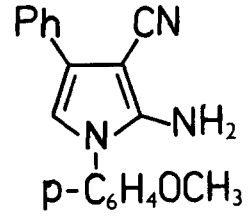

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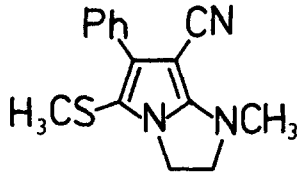
Methylation of 3 (MeI, DMF, K_2CO_3) afforded primarily the dimethylderivative 6, accompanied by side-products 7 and 8, which were characterized by ^{13}C-NMR and mass spectra of the mixture.[8] The presence of the thiol group in 3 was further confirmed by oxidation (I_2, DMF, Et_3N) to a disulfide.



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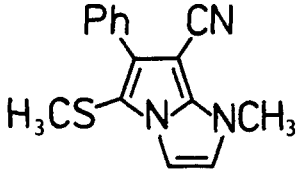

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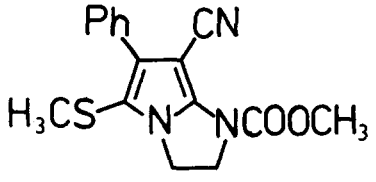

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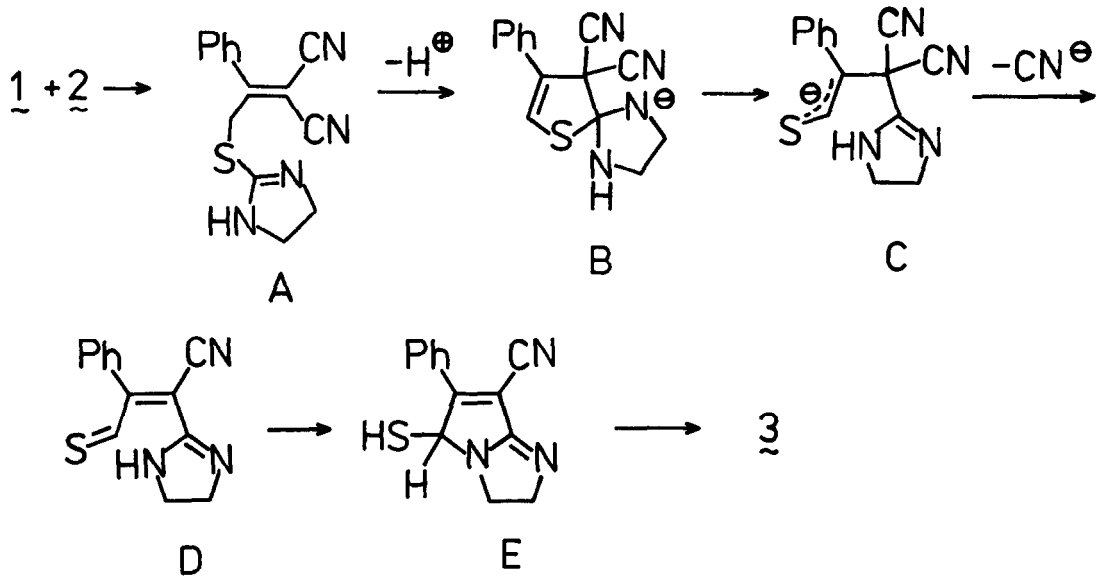
The formation of 3 can be rationalized by the reaction sequence shown in Scheme 1. The reaction is assumed to start with nucleophilic displacement of the bromine atom in 1 by the sulfur nucleophile of 2 (A). Deprotonation of the intermediate A induces intramolecular cyclization (B), forming the carbon-carbon bond. The spirocyclic intermediate B then undergoes a Dimroth-like rearrangement promoted by two electron-withdrawing cyano groups and, possibly, by release of steric strain. The open-ring intermediate C eliminates a cyanide anion, and the sequence is terminated by ring closure (D → E) and prototropic stabilization (E → 3).

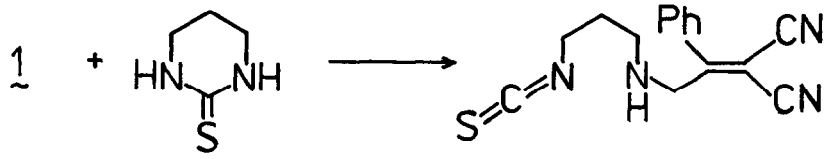
Scheme 1



Since, to our knowledge, there is no literature precedence for the formation of 3, we have examined reactions of 1 with thiourea and 2-mercapto-3,4,5,6-tetrahydropyrimidine (10) as analogs of 2 . Treating 1 with thiourea gave 2-amino-4-phenylthiazole (9)[9] in good yield (86%). In this case the condensation results in a conventional ring closure accompanied by elimination of malononitrile.

The reaction of 1 with 10 proceeded rapidly even at 20°C; the product 11 (86 %, m.p.164-165 °C,dec.) began to separate as a white solid immediately after dropping triethylamine to the reaction mixture. The thermolabile isothiocyanate 11 was characterized through the IR and ^{1}H- and ^{13}C-NMR spectra.[10] The formation of 11 is due to N-alkylation of 10 with the allylic bromide 1. The subsequent fission of the tetrahydropyrimidine ring is reminiscent of the thermal rearrangement of disubstituted 2-mercapto-3,4-dihydropyrimidines.[11]

It should be noted that, although substituted thioureas react mostly as S-nucleophiles,[12] rare cases of N-alkylation have also been described.[13] Nevertheless, the different reactivity of 2 and 10 is remarkable and will be subject to further investigation.



10 11

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2. K. Peseke, H. Kelling and C.N. Castanedo, Ger.(East)Patent 159,339; Chem. Abstr. 99, 53797r (1983).

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4. A typical procedure is as follows: A warm solution of 1 (4 mmol) in ethanol (15 ml, 50°C) was added to a solution of 2 (4 mmol) in ethanol (25 ml). The mixture was stirred for 4 min. cooled rapidly to 20°C and triethylamine (5 mmol) was added dropwise. After refluxing for 45 min. the red precipitate was separated and washed with water and acetone to give 190 mg (20%) of 3, m.p. 232°C, dec. (from DMF, Perkin Elmer DSC-2). MS (m/z,rel.int.) 241(58), 240(43), 239(100), 238(74), 207(26), 184(15), 153(14), 129(38), 77(29).

5. 4: ^{1}H-NMR (DMSO-d_6): 7.54 (m,2H), 7.36 (m,2H), 7.20 (m,1H), 6.76 (s,1H), 6,74)br m,2H), 4.02 (m,2H), 3.83 (m,2H),; ^{13}C-NMR: 155.14 (sm, ^{3}J = 5.5 Hz), 134.43 (sdd), 128.85 (dd), 126.29 (ddd), 125.93 (s), 125.28 (d), 118.37 (s), 108.48 (d, ^{1}J = 191 Hz), 63.79 (sd, $^{3}J \pm 7$ Hz), 48.76 (t), 45.33 (t); MS: 209(100), 181(17), 154(13), 127(28), 77(14).

6. E. Breitmaier and W. Voelter, ^{13}C-NMR Spectroscopy, Verlag Chemie GmbH,Weinheim 1974,p.97.

7. 5: ^{13}C-NMR(DMSO-d_6): 158.89 (sm), 148.63 (sd), 133.66 (sdd), 129.85 (sdd), 128.80 (dd), 126.96 (dd), 126.52 (d), 125.24 (ddd), 122.04 (sm), 118.35 (s), 114.97 (dd), 113.61 (ds), 70.09 (sd), 55.60 (q).

8. 6: MS: 269 ($C_{15}H_{15}N_3S$), 254 ($C_{14}H_{12}N_3S$); ^{13}C-NMR (DMSO-d_6): 154.17 (s), 133.11 (s), 129.30 (d), 128.42 (d), 116.75 (s), 110.64 (s), 66.50 (s), 56.33 (t), 42.96 (t), 35.29 (q), 20.11 (q). 7: MS: 267 ($C_{15}H_{13}N_3S$), 252 ($C_{14}H_{10}N_3S$); ^{13}C-NMR: 132.07 (s), 129.37 (d), 128.71 (d), 127.24 (d), 123.61 (d), 110.64 (s), 106.66 (d), 66.50 (s), 33.11 (q), 19.77 (q); 8: MS: 313, 298, 254; ^{13}C-NMR : 52.99 (q), 49.53 (t), 43.60(t), 19.99 (q).

9. 9: ^{13}C-NMR (DMSO-d_6): 167.70, 150.03, 134.23, 127.80, 126.72, 125.15, 101.11. The product was in all respects identical with an authentic specimen prepared according to R.M. Dodson and L.C. King, J. Am. Chem. Soc. 64, 2242 (1945).

10. 11: ^{1}H-NMR (DMSO-d_6): 8.52 (bs), 7.39, 7.29(m,5H), 3.50 (m,4H), 3.33 (s,2H), 2.12, 1.80 (m,2H); ^{13}C-NMR : 163.24 (sm), 139.08 (sm), 128.74 (dd), 128.26 (ddd), 127.08 (s), 126.79 (ddd), 123.00 (s), 42.78 (tm), 41.36 (tm), 39.18 (tm), 18.61 (tm); IR (KBr): 3430, 3200, 2167, 2107, 1647 cm^{-1}.

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