Synthesis of 1,9-Diazacycl[3.3.3]azine

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2-Methylpyridines substituted in the 6-position with a function containing an activated methylene group adjacent to the ring, *1*, (X = CN or COOEt) react with ethoxymethylenemalononitrile, *2* (Y = CN),[1] or 3-ethoxy-2-cyanoacrylate, *2* (Y = COOEt),[2] to form bicyclic compounds. When these are treated with an acid anhydride (or a second mol of *2*), 7,9-disubstituted 1-azacycl[3.3.3]azines, *3*, result.*

The present communication describes a variation of this approach. The use of *ca.* 3 mol of ethyl *N*-cyanoformimidate, *4*,[3] instead of *2* and the anhydride, leads to the monosubstituted diazacycl[3.3.3]azines *6a* and *6b*.[4,5] Reaction of 2,6-dimethylpyridine, *5*, with *4* analogously yields the unsubstituted diazacycl-[3.3.3]azine, *6* (*cf.* Chart 1).

6-Methyl-2-pyridineacetonitrile, *1a*,[6,7] and ethyl 6-methyl-2-pyridineacetate, *1b*,[8] react with ethyl *N*-cyanoformimidate, *4*, to form 3-cyano- and 3-carbethoxy-1,9-diazacycl[3.3.3]-azine, *6a* and *6b*, respectively. The proposed structures of these green crystalline compounds are confirmed by high resolution mass spectrometrical molecular weights, infrared spectra (C=O and C≡N absorption) and ^{1}H NMR spectra (H-2 singlet, H-4, H-5, and H-6 AMX-type absorption and H-7, H-8 of AX-type in both compounds; *cf.* Experimental). The chemical-shift value for H-4 (δ 7.08) is unusually high due to the effect of the 3-carbethoxy group.

Attempts to decyanate *6a* with PPA [9] to the parent system were unsuccessful due to decomposition of the ring system. Decarbethoxylation of *6b* in diphenyl ether containing traces of *p*-toluenesulfonic acid, on the other hand, gave the unsubstituted cyclazine *6*. 1,9-Diazacycl[3.3.3]azine is a blue-green crystalline compound, rather insoluble in nonpolar solvents and fairly unstable both in air and in solution. The assignment of its structure is supported by an exact mass spectrometrical molecular weight determination and by the presence of one A_2X (H-4, H-5, and H-6) and two AX (H-2, H-3 and H-7, H-8) type absorptions in the NMR spectrum.

1,9-Diazacycl[3.3.3]azine is the first unsubstituted isomer of the seven possible ones in the diaza group.[10] The chemical-shift values for the protons (δ 4.3 – 6.2) are between those for the "corresponding" protons in 2-methyl-1-azacycl[3.3.3]-azine (δ 3.7 – 5.6) [11] and 1,3,4-triazacycl[3.3.3]azine (δ 5.3 – 6.9).[12] This order indicates that the degree of aromaticity increases with the number of peripheral *N*-atoms in the cyclazine.

Treatment of *6* with *N*-bromosuccinimide (NBS) under conditions employed earlier for similar systems [13,14] caused decomposition of the cyclazine, and no brominated products could be isolated.

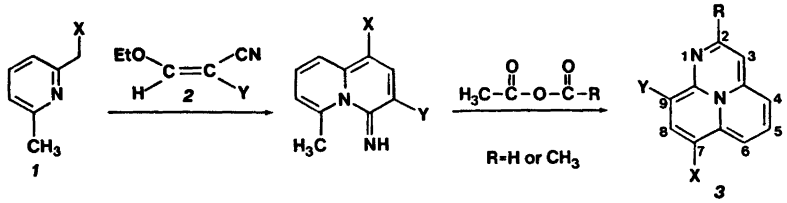
Since the 6-methyl groups in *1a* and *1b*, which are not activated by conjugation, reacted smoothly, we hoped that both methyl groups in *5* would be reactive enough to condense with 2 mol of *4*. This turned out to be the case, and in a one-flask reaction *6* was formed, although in very low yield. This modification should prove to be synthetically useful since methylsubstituted heterocycles are often more stable than their amino analogues and since they are not likely to tautomerize.

Experimental. General. NMR spectra were recorded with a Varian Model A-60 and a Bruker WH 270 spectrometer, using tetramethylsilane (TMS) as internal reference.

Ultraviolet and visible spectra were measured in ethanol with a Beckman DK-2A spectrophotometer. IR spectra were determined in KBr with a Perkin-Elmer 337 spectrophotometer. Mass spectra were obtained with a GEC-AEI 902 mass spectrometer at the Department of Medical Biochemistry, University of Göteborg. TLC was performed on Silica Gel 60F 254 (Merck). For column chromatography, Silica Gel 60 (0.063 – 0.2 mm; Merck) was used.

The cyclazines were obtained in low yields. Attempts to increase them by variation of mol ratios, reaction temperatures and reaction times were not successful as judged from TLC. A detailed study of the reaction conditions could lead to better yields. This has, however, not been pursued since our main object was to synthesize these compounds in amounts sufficient for spectrometric investigations.

* For definitions and nomenclature of cyclazines, *cf.* Refs. 15 and 16.



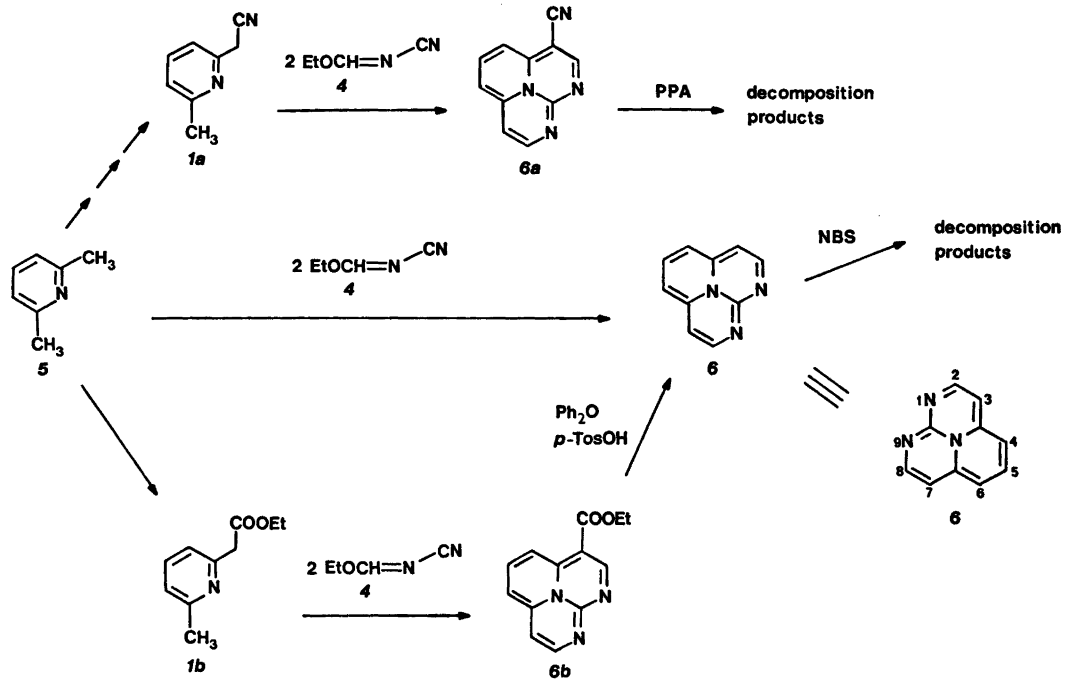


Chart 1.

The ring-closure reactions have been performed at elevated temperatures without solvents which results in large amounts of dark unidentifiable products. Since the cyclazines were easily discovered and isolated by TLC on account of their characteristic colours, no attempts were made to isolate other products from the reaction mixtures.

3-Cyano-1,9-diazacycl[3.3.3]azine, 6a. A mixture of 0.23 g (1.74 mmol) of *1a* [6,7] and 0.60 g (6.12 mmol) of *4* was kept at 110 °C for 15 min. Higher reaction temperature and/or lower *4*/*1a* ratio decreased the yield of *6a*. The reaction product, a dark, oily liquid, was then dissolved in ethyl acetate and chromatographed on 10 g of silica gel. With EtOAc/MeOH (3:1), a dark-green band was eluted. It was further purified by preparative TLC (EtOAc/MeOH; 3:1). Yield: 15 mg (4 %) of *6a* as dark-green needles, m.p. 230 °C. MS: $M^+ = 194.0585 \pm 0.003$. Calc. for $C_{11}H_6N_4$: 194.0592. *m/e* (Rel. int.) 194(100, M^+), 168 (8.4, M−CN), 167 (7.3, M−HCN), 140 (4.6, M−2HCN); *m** (calc.): 145.4 (145.48) 194→168, 143.8 (143.76) 194→167, 117.3 (117.37) 167→140. IR: 2208 cm^{-1} (C≡N). UV: $\lambda_{max}(\varepsilon)$ 254 (28 000), 268 sh. (19 400), 361 (21 600), 391 (19 660), 412 (18 370), 452 (860), 570 sh. (230), 623 (360), 686 nm (420). NMR ($CDCl_3$): δ 5.09 (1 H, d, H-7), 5.43 and 5.58 (2 H, 2d, H-4 and H-6), 6.54 (1 H, t, H-5), 6.67 (1 H, d, H-8), 6.80 (1 H, s, H-2), $J_{4,5} = J_{5,6} = 8.1$, $J_{4,6} = 1.5$, $J_{7,8} = 5.9$ Hz.

3-Carbethoxy-1,9-diazacycl[3.3.3]azine, 6b. A mixture of 0.35 g (1.96 mmol) of *1b* [8] and 0.61 g (6.22 mmol) of *4* was heated at 140 °C for 8 min. Further heating decreased the yield of *6b*. The reaction was followed by TLC (EtOAc/MeOH; 3:1). The product, a very dark, oily liquid, was dissolved in EtOAc and chromatographed on 10 g of silica gel. With EtOAc/MeOH (3:1), a dark-green band was eluted. It was further purified by preparative TLC. The clear, green solution gave on evaporation dark-green crystalline needles. Yield of *6b*: 12 mg (3 %), m.p. 178−179 °C. MS: $M^+ = 241.084 \pm 0.003$. Calc. for $C_{13}H_{11}N_3O_2$: 241.0868. *m/e* (Rel. int.) 241 (97.0, M^+), 213 (100, $M-C_2H_4$), 196 (33.3, M−OEt), 169 (22.7, 196−HCN), 168 (37.9, 196−CO), 141 (17.3, 168−HCN), 114 (16.4, 168−2HCN). *m** (calc.): 188.1 (188.25) 241→213, 180.5 (180.36) 213→196, 144.0 (144.00) 196→168, 118.2 (118.34) 168→141, 92.1 (92.17) 141→114. IR: 1675 cm^{-1} (C=O). UV: $\lambda_{max}(\varepsilon)$ 256 (23 500), 282 sh. (7550), 354 (9400), 384 sh. (7350), 399 (10 700), 420 (11 100), 564 sh. (130), 612 (210), 672 nm (220). NMR ($CDCl_3$): δ 1.28 (3 H) and 4.12 (2 H) [ester group], 5.14 (1 H, d, H-7), 5.52 (1 H, d, H-6), 6.60 (1 H, t, H-5), 6.69 (1 H, d, H-8), 7.08 (1 H, d, H-4), 7.48 (1 H, s, H-2); $J_{4,5} = J_{5,6} = 8.1$, $J_{7,8} = 6.0$ Hz.

Decarbethoxylation of 6b. To a solution of 30 mg (0.12 mmol) of *6b* in 3 ml of diphenyl ether kept at 200 °C, 3 mg of *p*-toluenesulfonic acid

was added. After 2.5 h the reaction mixture was cooled and the diphenyl ether dissolved in petroleum ether. The residue, containing *6*, was then taken up in 2 ml of methanol and purified by preparative TLC (MeOH; $R_F = 0.21$). Yield: 15 mg (71 %) of *6* as blue-green needles, m.p. 216–218 °C (decomp.). MS: $M^+ =$ 169.0637. Calc. for $C_{10}H_7N_3$: 169.0640. *m/e* (Rel. int.) 169 (100, M^+), 143 (17.9, M–CN), 142 (12.5, M–HCN), 116 (6.8, 143–HCN), 115 (10.7, M–2HCN). UV: $\lambda_{max}(\varepsilon)$ 246 (9500), 264 (12 750), 268 sh. (12 000), 365 sh. (10 500), 378 (13 600), 385 sh. (11 300), 399 (5800), 452 sh. (650), 483 (680), 503 sh. (370), 602 sh. (150), 650 nm (240). NMR ($CDCl_3$): δ 4.34 (2 H, d, H-3, H-7), 4.70 (2 H, d, H-4 and H-6), 5.92 (1 H, t, H-5), 6.17 (2 H, d, H-2 and H-8); $J_{2,3} = J_{7,8} = 5.8$, $J_{4,5} = J_{5,6} = 8.0$ Hz.

Preparation of 1,9-diazacycl[3.3.3]azine, 6, from 2,6-dimethylpyridine 5. A mixture of 1 g (9.34 mmol) of *5* and 1.8 g (18.36 mmol) of ethyl *N*-cyanoformimidate, *4*, was kept at 100 °C for 45 min. It was cooled to room temperature and poured onto a column of silica gel. A blue product was eluted with EtOAc/MeOH (4:1) and further purified by preparative TLC (MeOH). Yield: < 5 % of *6*. Mass and NMR spectral data showed it to be identical with the compound obtained by decarbethoxylation of *6b*.

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Synthesis of Methyl-substituted 5-Thia- and 5-Selena-1,3,6-triazacycl-[3.2.3]azines

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For the study of properties of a nonbenzenoid aromatic system the parent compound is usually the most desired member. In many cases, however, available synthetic methods allow only the preparation of derivatives. Of these the phenyl analogues can be of limited value for an investigation of aromaticity.[1,2] The methyl-substituted systems, on the other hand, in general show properties which are very similar to those of the parent compound. Often a methyl group has a stabilizing effect on the system.[3]

We have recently described the synthesis of phenyl-substituted thia- and selena-1,3,6-triazacycl[3.2.3[azines *,[4,5] from 5-phenyl-2,4-diaminothia- and selenazole and ethyl 2-cyano-3-ethoxyacrylate, *2*. We did not succeed then in preparing the unsubstituted thiasystem since 2,4-diaminothiazole reacts with *2* at C-5 in preference to the amino groups,[6] or the methyl-substituted system since 5-methyl-2,4-diaminothiazole is unstable as the free base. Attempts to liberate it from the hydrochloride gave 4-amino-2-hydroxy-5-methylthiazole instead.[7]

In the synthesis of *4b*, the free base of *1b*, which could not be isolated, was instead liber-

* For definitions and nomenclature of cyclazines, *cf.* Refs. 9 and 10.