Ring Transformations by Ring-Chain-Transfer. V [1]. Synthesis of Amino-, Hydroxy- and Mercaptoalkyl-pyrazoles by Reaction of 3-Functionalized Acrylonitriles with Hydrazine Hydrate

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Received January 31, 1991

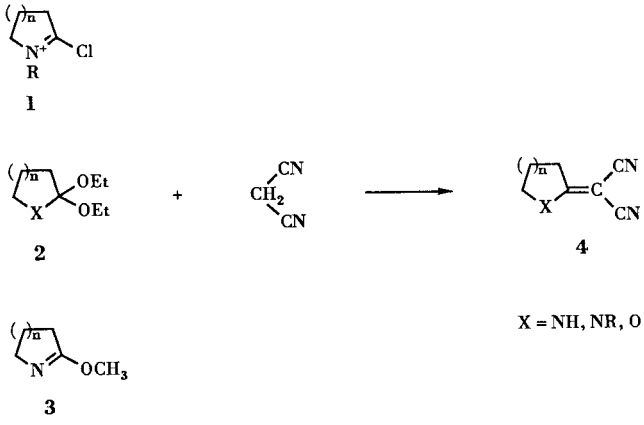
3-Alkylamino, 3-alkoxy or 3-alkylthioacrylonitriles whose leaving group is incorporated in a saturated heterocyclic ring are 1,3-bifunctional electrophiles. They react with hydrazine hydrate at the cyano group by addition as well as at position 3 by opening the saturated ring. By this ring transformation new 5-aminopyrazoles are formed which are additionally substituted by an ω-functionalized alkyl chain in position 3.

J. Heterocyclic Chem., **28**, 1257 (1991).

3-Functionalized acrylonitriles such as 3-amino, 3-alkoxy, and 3-mercaptoacrylonitriles have found a broad application as 1,3-bielectrophilic synthons in syntheses of heterocycles [2a-b]. Bridged derivatives of 3-aminoacrylonitriles **4** (X = NH, NR) are easily available by condensation of amide chlorides **1**, lactam acetals **2** (X = NR) or lactim ethers **3** with cyanoacetic acid derivatives, especially malonodinitrile [3a-c].

In contrast to the open chain enaminonitriles no reactions of bridged derivatives **4** (X = NH, NR) with nucleophiles are reported so far but only with electrophiles (attacks at positions 1 and 3 of the ring) [4].

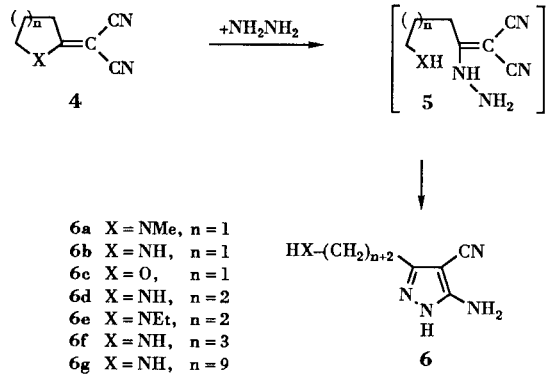
Continuing our investigations of using bridged 1,3-dicarbonyl-heteroanalogs as precursors for the synthesis of ω-functionalized alkylheterocycles [5], we focussed our interest on the reaction of semicyclic 3-aminoacrylonitriles **4** (X = NH, NR) with hydrazines.

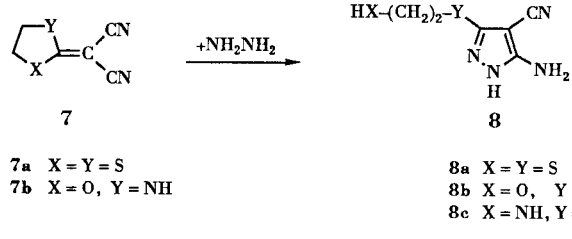


Compounds **4** are surprisingly stable as compared with their open chain analogs. Heating the reactants in organic solvents, like methanol, ethanol, dimethylformamide or acetic acid leaves educts **4** unchanged. In the latter case the hydrazine is acylated. Reflux of compounds **4** in a 10-12 fold excess of 50% hydrazine hydrate however gives a clean reaction affording 5-amino-3-(ω-aminoalkyl)-4-cyanopyrazoles **6** (X = NH, NR) [6].

The formation of these compounds can be explained by primary attack of hydrazine hydrate at the ring-C-atom in position 2 (see **5**) and finally Thorpe analogous cyclization. The whole reaction sequence represents a special type of ring transformation (ring transformation by ring-chain-transfer) where a ring and a chain moiety in the educt are transferred to each other giving the product.

The products **6** are colorless crystalline compounds insoluble in water. They were characterized by spectroscopic methods and by elemental analysis. Only one signal for a CN-group at 2200 cm^{-1} is observed in the ir spectra. Under the conditions of mass spectroscopy the pyrazoles **6** (X = NH, NR) show the typical behavior of aminoalkyl heterocycles [5,7,8]. That means the fragmentation of the aminoalkyl substituent occurs according to α- and β-cleavage as well as to McLafferty rearrangement. In the ^{13}C-nmr spectra of products **6** a signal at 70 ppm is found, which corresponds to the C4-atom of the pyrazole ring. This high field





shift (more than 30 ppm comparing with the unsubstituted pyrazole [9]) can be explained by the enaminonitrile fragment [9] found in **6**.

All attempts failed to extend the above reaction either to aryl hydrazines or to educts **4** derived from other cyanoacetic acid derivatives. Obviously the reactivity is too low in these cases. Investigations to synthesize a corresponding hydroxypropylpyrazole **6** (X = O) were more successful. The necessary precursor **4** (X = O), was obtained from butyrolactone diethylacetal **2** (n = 1, X = O) and malonodinitrile [11]. This compound reacts with hydrazine hydrate already in ethanolic solution demonstrating its higher reactivity. The hydroxypropylpyrazole **6** (X = O, n = 1) formed in this way shows similar spectroscopic properties like the aminoalkyl compounds **6** (X = NH, NHR).

Finally the ring transformation scheme of 3-functionalized acrylonitriles was extended to the syntheses of pyrazoles with an additional heteroatom in the side chain. The cyclic ketene *S,S*-acetal **7a** [11] and the ketene *O,N*-acetal **7b** (X = NH, Y = O) [12] react with hydrazine hydrate in ethanolic solution to the expected ring transformation products **8a** and **8b**. In the latter case also an isomeric structure **8c** (Y = O, X = NH) has to be taken in consideration. But the ^{1}H-nmr signal at 3.4 ppm (O-CH_2) shows no triplet structure, how it is expected for **8c** but a higher multiplicity due to additional coupling of CH_2 with OH. Additional evidences comes from the mass spectra. Finally in reaction of open chain 3-amino-3-alkoxy-2-cyanoacrylonitrile with hydrazine hydrate also the alkoxy substituent serves as the leaving group [14].

The results reported above demonstrate that the general principle [5] of synthesizing ω-functionalized alkyl heteroaromatics by ring transformation of bridged 1,3-dicarbonyl heteroanalogs with binucleophiles can also be applied to semicyclic 3-functionalized acrylonitriles.

In contrast to the known synthesis of 3-aminoalkylpyrazols [8,13] by ring transformation of enaminoketones leading to aryl-substituted compounds, the pyrazoles described here have an amino group at position 5.

EXPERIMENTAL

The melting points were measured with a "Boetius" hot-stage apparatus and are uncorrected. The ^{1}H-nmr spectra were measured with a TESLA BS 587 FT-spectrometer. The ^{13}C-nmr spectra were recorded on a Bruker AC 200. Mass spectra were taken with a Hewlett Packard 599 SA spectrometer and the ir spectra with a Specord 71 (Carl Zeiss Jean).

ω-Functionalized Pyrazoles **6** and **8**.

General Procedures.

Method A:

3-Aminoacrylonitrile **4** (X = NH, NR) (0.01 mole) and 0.1 mole of 50% hydrazine hydrate were refluxed for 10 minutes. After cooling 20 ml of water was added. The product precipitated and was filtered by suction, washed with water and recrystallized.

Method B:

3-Functionalized acrylonitrile **4** (X = O) (0.01 mole) or **7** and 0.015 mole of 50% hydrazine hydrate in 20 ml of ethanol were refluxed for 1 hour. The solvent was evaporated and some water was added to the residue. The precipitate was filtered by suction and recrystallized.

5-Amino-3-(3-methylaminopropyl)-4-cyanopyrazole **6a** (X = NMe, n = 1).

This compound had mp 168-169° (water), yield 55% (method A); ir (potassium bromide): 2210, 3320 cm^{-1}; ms: (m/e) 179 (M^+, 5), 135 (4), 58 (10), 44 (100); ^{1}H-nmr (DMSO-d_6): δ 1.6 (m, 2H, CH_2), 2.8 (m, 4H, 2 x CH_2), 3.1 (s, 3H, NMe), 5.6 (br, 1H, NH); ^{13}C-nmr (DMSO-d_6): δ 24.3, 27.9, 36.0, 50.8, 73.4, 115.6, 151.9, 155.1.

Anal. Calcd. for $C_8H_{13}N_5$ (179.23): C, 53.61; H, 7.31; N, 39.08. Found: C, 53.61; H, 7.18; N, 39.48.

5-Amino-3-(3-aminopropyl)-4-cyanopyrazole **6b** (X = NH, n = 1).

This compound had mp 170-172° (water), yield 78% (method A); ir (potassium bromide): 2225, 3210 cm^{-1}; ms: (m/e) 165 (M^+, 20), 135 (28), 122 (12), 30 (100); ^{1}H-nmr (TFA): δ 2.0 (m, 2H, CH_2), 2.8 (m, 4H, 2 x CH_2), 6.6 (br, 3H, NH, NH_2); ^{13}C-nmr (DMSO-d_6): 23.7, 31.7, 40.9, 72.9, 115.5, 151.7, 154.8.

Anal. Calcd. for $C_7H_{11}N_5$ (165.2): C, 50.89; H, 6.71; N, 42.40. Found: C, 50.96; H, 6.83; N, 42.70.

5-Amino-4-cyano-3-(3-hydroxypropyl)pyrazole **6c** (X = O, n = 1).

This compound had mp 142-144° (acetonitrile), yield 61% (method B); ir (potassium bromide): 2220, 3200 cm^{-1}; ms: (m/e) 166 (M^+, 72), 148 (57), 135 (45), 122 (100); ^{1}H-nmr (DMSO-d_6): δ 1.6 (m, 2H, CH_2), 2.5 (m, 2H, CH_2), 3.3 (m, 2H, CH_2), 4.4 (br, 1H, OH), 7.0 (s, 2H, NH_2), 11.6 (br, 1H, NH).

Anal. Calcd. for $C_7H_{10}N_4O$ (166.2): C, 50.59; H, 6.06; N, 33.71. Found: C, 50.50; H, 5.98; N, 33.24.

5-Amino-3-(4-aminobutyl)-4-cyanopyrazole **6d** (X = NH, n = 2).

This compound had mp 168-169° (water), yield 82% (method A); ir (potassium bromide): 2225, cm^{-1}; ms: (m/e) 179 (M^+, 72), 162 (31), 122 (100), 45 (82).

Anal. Calcd. for $C_8H_{13}N_5$ (179.2): C, 53.61; H, 7.31; N, 39.08. Found; C, 53.30; H, 7.38; N, 39.29.

5-Amino-3-(4-ethylaminobutyl)-4-cyanopyrazole **6e** (X = NEt, n = 2).

This compound had mp 145-146° (water), yield 72% (method A); ir (potassium bromide): 2225, cm^{-1}; ms: (m/e) 207 (M^+, 4), 121 (12), 58 (100), 44 (15); ^{1}H-nmr (DMSO-d_6): δ 1.0 (t, J = 7 Hz, 2H, Me), 1.5 (m, 4H, 2 x CH_2), 2.45 (m, 6H, 3 x CH_2), 5.8 (s, 2H, NH_2); ^{13}C-nmr (DMSO-d_6): 14.9, 25.6, 26.0, 28.8, 43.4, 48.6, 73.0, 115.5, 151.6, 154.8.

Anal. Calcd. for $C_{10}H_{17}N_5$ (207.3): C, 57.94; H, 8.26; N, 33.79. Found: C, 57.75; H, 8.11; N, 33.70.

5-Amino-3-(5-aminopentyl)-4-cyanopyrazole **6f** (X = NH, n = 3).

This compound had mp 165-166° (water), yield 95% (method A); ir (potassium bromide): 2240, cm^{-1}; ms: (m/e) 193 (M^+, 12), 164 (10), 122 (53), 30 (100); ^{1}H-nmr (DMSO-d_6): δ 1.3 (m, 6H, 3 x CH_2), 2.5 (m, 4H, 2 x CH_2), 5.0 (br, 5H, NH, 2 x NH_2); ^{13}C-nmr (DMSO-d_6): δ 25.9, 26.1, 27.7, 32.8, 41.4, 73.2, 115.5; 151.7, 154.8.

Anal. Calcd. for $C_9H_{15}N_5$ (193.25): C, 55.93; H, 7.82; N, 36.24. Found: C, 56.12; H, 7.81; N, 36.09.

5-Amino-3-(11-aminoundecyl)-4-cyanopyrazole **6g** (X = NH, n = 9).

This compound had mp 156-158° (ethanol), yield 78% (method A); ir (potassium bromide): 2215, 3330 cm^{-1}; ms: (m/e) 277 (M^+, 4), 191 (5), 164 (16), 150 (46), 135 (42), 122 (53), 30 (100); ^{13}C-nmr (DMSO-d_6): δ 26.3, 26.6, 27.9, 28.6, 28.7, 29.0, 29.11, 29.15, 29.5, 33.5, 41.7, 73.5, 115.5, 151.8, 155.0.

Anal. Calcd. for $C_{15}H_{27}N_5$ (277.41): C, 64.93; H, 9.81; N, 25.25. Found: C, 65.02; H, 9.70; N, 25.54.

5-Amino-4-cyano-3-mercaptoethylthiopyrazole **8a** (X = Y = S).

This compound had mp 220-225° dec (water), yield 68% (method B); ir (potassium bromide): 2250 cm^{-1}; ms: (m/e) 220 (M^+, 23), 172 (11), 140 (100), 109 (14), 61 (51); ^1H-nmr (DMSO-d_6): δ 2.6 (m, 2H, CH_2), 3.2 (m, 2H, CH_2), 3.5 (br, 1H, SH), 6.3 (s, 2H, NH_2), 12.0 (br, 1H, NH).

Anal. Calcd. for $C_6H_8N_4S_2$ (200.28): C, 35.98; H, 4.03; N, 27.98; S, 32.01. Found: C, 36.78; H, 4.45; N, 27.79; S, 31.56.

5-Amino-4-cyano-3-hydroxyethylaminopyrazol **8b** (X = O, Y = NH).

This compound had mp 142-144° (water) yield 39% (method B); ir (potassium bromide): 2245 cm^{-1}; ms: (m/e) 167 (M^+, 3), 154 (100), 135 (25), 123 (30); ^1H-nmr (DMSO-d_6): 3.1 (m, 2H, NCH_2), 3.4 (m, 2H, OCH_2), 5.6 (br, 2H, NH, OH), 6.6 (br, 3H, NH, NH_2).

Anal. Calcd. for $C_6H_9N_5O$ (167.17): C, 43.10; H, 5.42; N, 41.89. Found: C, 43.56; H, 5.55; N, 41.66.

Acknowledgements.

We thank the Schering AG, Berlin for kind support with chemicals and for the help with nmr spectra.

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