Syntheses of 3(5)-Substituted-4-(*N*-methylanilino)-5(3)-aminopyrazoles by Reaction of β-Hydroxy-α-cyanoenamines with Hydrazines

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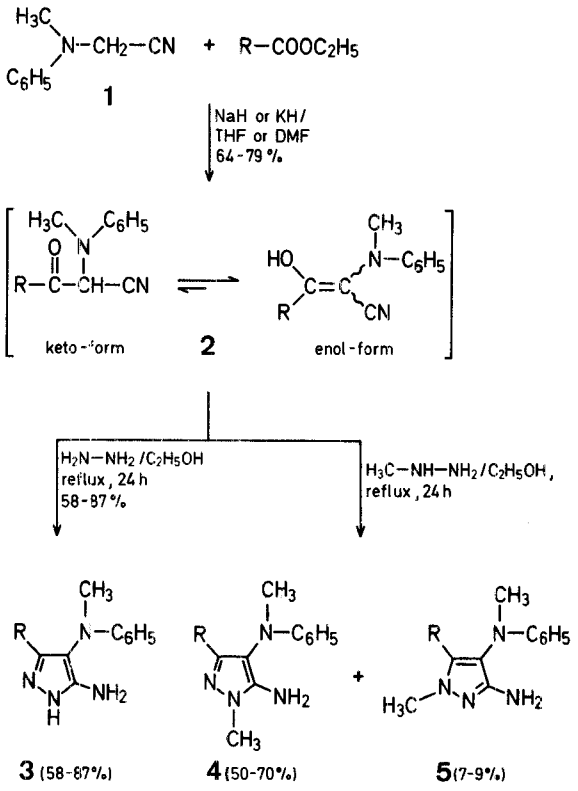
Aminopyrazoles **3–5** are prepared by the reaction of β-hydroxy-α-cyanoenamines **2** with hydrazine hydrate and monomethylhydrazine.

In our previous paper[1], the reaction of α-(*N*-methylanilino)-acetonitrile (**1**) with esters has been reported to give new β-hydroxy-α-cyanoenamines **2** in good yields. We now report on the use of **2** for the synthesis of some new aminopyrazoles **3–5**.

Syntheses of pyrazoles by the reaction of β-ketonitriles with hydrazines have been reported[2,3,4]. There is, however, no information on the synthesis of pyrazoles using β-hydroxy-α-cyanoenamines **2**. We describe here an efficient sequence for the syntheses of new pyrazoles. The method reported here is based on the reaction of β-hydroxy-α-cyanoenamines **2** with hydrazine hydrate and monomethylhydrazine.



2-5	R	2-5	R
a		d	
b		e	H
c		f	C_2H_5

β-Hydroxy-α-cyanoenamines **2**[1] exist as a mixture of keto- and enol-forms. Refluxing a solution of **2** in ethanol with hydrazine hydrate or monomethylhydrazine gave **3**, or **4** and **5**, respectively. For example, when a mixture of **2a** and hydrazine hydrate was refluxed, 5(3)-amino-4-(*N*-

Table. Pyrazoles **3**, **4** and **5** prepared

Product	Yield [%]	m.p. [°C]	Molecular Formula[a]	M.S. (*m/e* (M^+) (rel. intensity %)	I.R. (KBr) ν_{NH} [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS) δ [ppm]
3a	74	94–96°	$C_{16}H_{16}N_4$ (264.3)	264 (100)	3500–3100	3.12 (s, 3H, NCH_3); 6.30 (br., 2H, NH_2); 6.5–7.6 (m, 11H, NH + H_{arom})
3b	82	123.5–125°	$C_{17}H_{18}N_4$ (278.4)	278 (100)	3500–3100	2.29 (s, 3H, CH_3); 3.13 (s, 3H, NCH_3); 5.86 (br., 2H, NH_2); 6.5–7.6 (m, 10H, NH + H_{arom})
3c	58	77–79°	$C_{17}H_{18}N_4O$ (294.4)	294 (100)	3450–3100	3.11 (s, 3H, NCH_3); 3.73 (s, 3H, OCH_3); 6.06 (br., 2H, NH_2); 6.5–7.7 (m, 10H, NH + H_{arom})
3d	79	92–94°	$C_{16}H_{15}ClN_4$ (298.8)	300 (M^+ + 1, 41); 298 (M^+ − 1, 100)	3450–3100	3.12 (s, 3H, NCH_3); 6.31 (br., 2H, NH_2); 6.5–7.7 (m, 10H, NH + H_{arom})
3f	87	oil	$C_{12}H_{16}N_4$ (216.3)	216 (100)	3450–3100[b]	1.09 (t, 3H, J = 7.2 Hz, CH_2CH_3); 2.41 (q, 2H, J = 7.2 Hz, CH_2CH_3); 3.16 (s, 3H, NCH_3), 6.19 (br., 3H, NH + NH_2); 6.4–7.4 (m, 5H_{arom})
4a	59	144–146°	$C_{17}H_{18}N_4$ (278.4)	278 (100)	3425, 3180	3.13 (s, 3H, NCH_3); 3.31 (br., 2H, NH_2); 3.73 (s, 3H, 1-NCH_3); 6.5–7.8 (m, 10H_{arom})
4d	50	147.5–148.5°	$C_{17}H_{17}ClN_4$ (312.9)	314 (M^+ + 1, 39); 312 (M^+ − 1, 100)	3350, 3190	3.11 (s, 3H, NCH_3); 3.35 (br., 2H, NH_2); 3.69 (s, 3H, 1-NCH_3); 6.5–7.8 (m, 9H_{arom})
4f	70	90–91.5°	$C_{13}H_{18}N_4$ (230.3)	230 (100)	3380, 3200	1.08 (t, 3H, J = 7.6 Hz, CH_2CH_3); 2.36 (q, 2H, J = 7.6 Hz, CH_2CH_3); 3.17 (s, 3H, NCH_3); 3.41 (br., 2H, NH_2); 3.60 (s, 3H, 1-NCH_3); 6.4–7.4 (m, 5H_{arom})
5a	9	151–152°	$C_{17}H_{18}N_4$ (278.4)	278 (100)	3425, 3280, 3190	2.98 (s, 3H, NCH_3); 3.42 (br., 2H, NH_2); 3.69 (s, 3H, 1-NCH_3); 6.5–7.5 (m, 10H_{arom})
5d	9	175–177°	$C_{17}H_{17}ClN_4$ (312.9)	314 (M^+ + 1, 39); 312 (M^+ − 1, 100)	3420, 3270, 3180	2.98 (s, 3H, NCH_3); 3.33 (br., 2H, NH_2); 3.68 (s, 3H, 1-NCH_3); 6.5–7.5 (m, 9H_{arom})
5f	4	78–80°	$C_{13}H_{18}N_4$ (230.3)	230 (100)	3450, 3310, 3210	1.04 (t, 3H, J = 7.3 Hz, CH_2CH_3); 2.41 (q, 2H, J = 7.3 Hz, CH_2CH_3); 3.15 (s, 3H, NCH_3); 3.59 (s, 3H, 1-NCH_3); 4.26 (br., 2H, NH_2); 6.4–7.4 (m, 5H_{arom})

[a] Satisfactory microanalyses obtained; C ± 0.30, H ± 0.27, N ± 0.29.
[b] Measured as film.

methylanilino)-3(5)-phenylpyrazole **(3a)** was obtained in 74% yield. Likewise, the reaction of **2b, 2c, 2d,** and **2f** with hydrazine hydrate gave 3(5)-(*p*-tolyl)-, 3(5)-(*p*-anisyl)-, 3(5)-(*p*-chlorophenyl)- and 3(5)-ethyl-5(3)-amino-4-(*N*-methylanilino)-pyrazoles **(3b, 3c, 3d,** and **3f)**, respectively. The reaction using **2e**, however, did not give the corresponding 5(3)-amino-4-(*N*-methylanilino)-pyrazole **(3e)**, but a substantial amount of *N*-methylaniline and unknown products. Under similar conditions, treatment of **2a** with monomethylhydrazine led to 5-amino-4-(*N*-methylanilino)-3-phenyl-1-methylpyrazole **(4a)** and 3-amino-4-(*N*-methylanilino)-5-phenyl-1-methylpyrazole **(5a)**; **4a** being predominant. Likewise, the reaction using **2d** and **2f** gave 3-(*p*-chlorophenyl)- and 3-ethyl-5-amino-4-(*N*-methylanilino)-1-methylpyrazoles (**4d** and **4f**), and 5-(*p*-chlorophenyl)- and 5-ethyl-3-amino-4-(*N*-methylanilino)-1-methylpyrazoles (**5d** and **5f**).

Definitive evidence for the structural assignments of **4** and **5** is obtained from the mass spectra: cleavage of **4** results in the fragment $[H_3C{-}N{=}C(NH_2){-}C{=}N{-}C_6H_5]^{\oplus}$ whereas cleavage of **5** results in the fragment $[H_3C{-}N{=}C(R){-}C{=}N{-}C_6H_5]^{\oplus}$.

The melting points were determined with a Yanagimoto MP-32 melting point apparatus. I.R. spectra were taken on a JASCO A-202 spectrometer, and ^{1}H-N.M.R. spectra were recorded on a Hitachi R-24 or R-600 spectrometer (60 MHz). α-(*N*-Methylanilino)-acetonitrile **(1)** was prepared according to Ref.[5] and compounds **2a–d** according to Ref.[1].

2-(*N*-Methylanilino)-3-hydroxyacrylonitrile (2e):

To a mixture of tetrahydrofuran (17 ml) and potassium hydride (0.553 g, 13.8 mmol) cooled in an ice bath, is added dropwise a mixture of **1** (0.644 g, 4.41 mmol) and ethyl formate (0.517 g, 6.98 mmol) dissolved in tetrahydrofuran (6 ml) under a nitrogen atmosphere. The mixture is stirred for 4 h, the ice bath is removed and the mixture is stirred for 1 h at room temperature. The mixture is then poured into saturated ammonium chloride solution (20 ml) and the product is extracted with dichloromethane (2 × 50 ml). The organic layer is washed with water (2 × 50 ml), dried with anhydrous magnesium sulfate and the solvent is removed. The residue is purified by column chromatography on silica gel using a 6:1 mixture of benzene and hexane as eluent; yield: 0.608 g (79%); m.p. 82.5–84°C.

$C_{10}H_{10}N_2O$ (174.2) calc. C 68.95 H 5.79 N 16.08
found 68.93 5.81 16.06

I.R. (KBr): ν = 3350 (OH); 2220 cm^{-1} (CN).

M.S. (70eV): *m/e* = 174 (M^+, 100%); 157 (38%), 145 (92%).

^{1}H-N.M.R. ($CDCl_3$/TMS): δ = 2.89 [s, N—CH_3 of (*Z*)-isomer]; 2.97 [s, N—CH_3 of (*E*)-isomer]; 6.60–7.50 ppm (m, =CH— + H_{arom}).

1-Cyano-2-hydroxy-1-(*N*-methylanilino)-1-butene (2f):
Analogously, the reaction of **1** (0.641 g, 4.38 mmol) with ethyl propanoate (0.528 g, 5.17 mmol) in the presence of sodium hydride (0.237 g, 9.88 mmol) in dimethylformamide gives **2f**; yield: 0.567 g (64%); m.p. 111–112 °C.

$C_{12}H_{14}N_2O$	calc.	C 71.26	H 6.98	N 13.85
(202.3)	found	71.30	6.96	13.86

I.R. (KBr): ν = 3200 (OH); 2220 cm^{-1} (CN).

M.S. (70 eV): *m/e* = 202 (M^+, 71%); 146 (49%); 145 (100%); 131 (32%); 118 (22%); 104 (30%).

^{1}H-N.M.R. ($CDCl_3$/TMS): δ = 1.25 (t, J = 7.0 Hz, CH_2—CH_3); 2.49 (q, J = 7.0 Hz, CH_2—CH_3); 2.94 (s, N—CH_3); 6.50–7.60 ppm (m, H_{arom} + OH).

3(5)-Amino-4-(*N*-methylanilino)-5(3)-phenylpyrazole (3); Typical Procedure:
A mixture of **2a** (0.502 g, 2.01 mmol) and hydrazine hydrate (1.39 g, 27.8 mmol) in ethyl alcohol (15 ml) is gently refluxed for about 24 h until the disappearance of **2a** is confirmed by means of T.L.C. The mixture is cooled, and poured into water (50 ml) and extracted with dichloromethane (2 × 50 ml). The organic layer is washed with water (2 × 50 ml) and dried with magnesium sulfate. After filtering off mangesium sulfate and distilling off dichloromethane, the residue is purified by means of column chromatography on silica gel using a 4 : 1 mixture of benzene and ethyl acetate as eluent; yield: 0.393 g (74%) (Table).

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