The Reactions of Benzylmalononitriles with Hydrazine and Hydroxylamine. Synthesis of Pyrazoles, Isoxazoles, and Pyrazolo[1,5-*a*]-pyrimidine Derivatives

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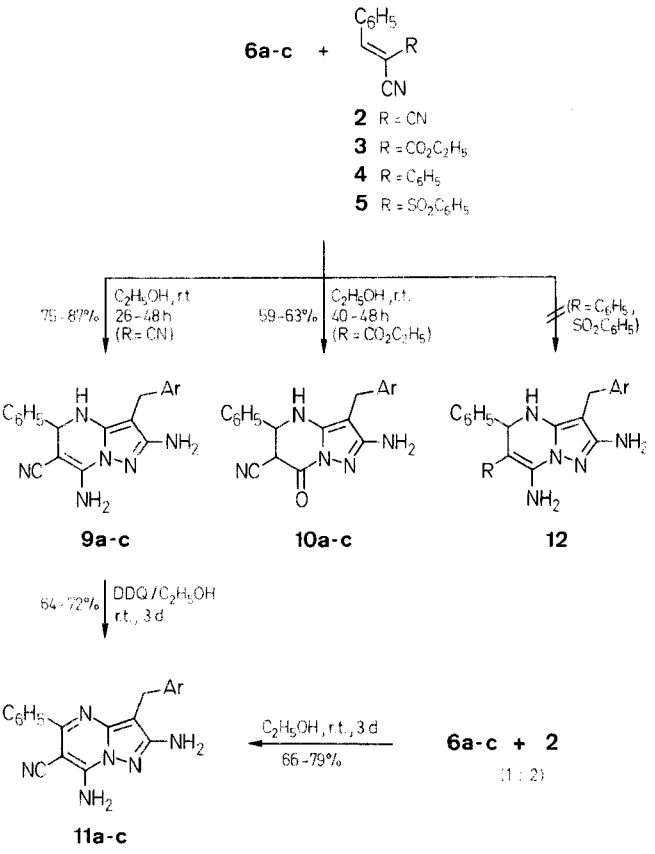
Benzylmalononitriles react with hydrazine or hydroxylamine to give 4-substituted 3,5-diaminopyrazoles or isoxazoles, respectively. Pyrazolo[1,5-*a*]pyrimidine derivatives are prepared by reaction of these pyrazoles with some 2,3-disubstituted propenenitriles (including benzylidenemalononitrile) under mild conditions.

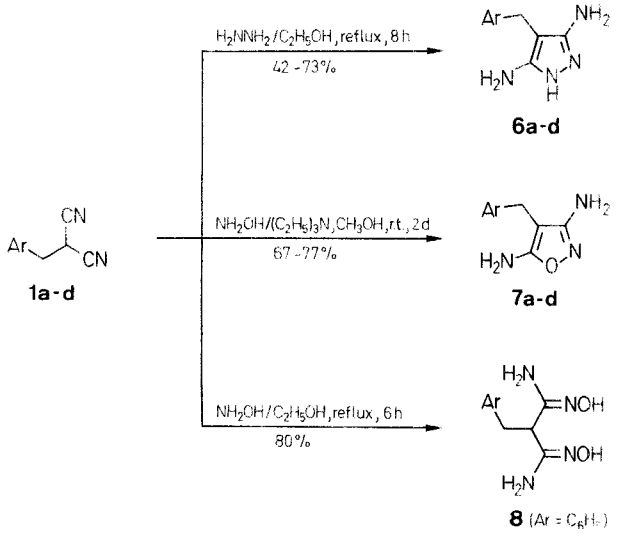
Our previous studies were concerned with the preparation of some 2-amino-4-aryl-3-benzyl-3,5-dicyano-6-methoxy (or ethylthio)-3,4-dihydropyridines by reaction of benzylmalononitriles **(1)** with 3-aryl-2-cyanopropenenitriles **(2)** in methanol/sodium methoxide and isopropanol/sodium ethanothiolate.[1,2]

In view of the continued interest in the chemistry of malononitrile derivatives[3-13] and because of the previously reported potential hypoglycemic activity of some aminoisoxazole derivatives[14,15] as well as the usefulness of aminopyrazoles as intermediates for the preparation of therapeutically interesting pyrazolo[1,5-*a*]pyrimidines,[16-19] we report here the simple syntheses of novel 3,5-diamino-4-benzyl pyrazoles **(6)** and isoxazoles **(7)** by the condensation of **1** with hydrazine and hydroxylamine, respectively. In addition, we describe the subsequent preparation of some pyrazolo[1,5-*a*]pyrimidine derivatives **(9, 10, 11)** from the reaction of **6** with benzylidenemalononitrile **(2)** and ethyl 2-cyano-3-phenylpropenoate **(3)**.

As expected, pyrazoles **6** were obtained in good yield by heating the benzylmalononitrile **1** with excess hydrazine hydrate. However, initial attempts to prepare isoxazoles **7** by a similar procedure failed, the major product being the malonamidedioxime **8**. However, use of the reagent system hydroxylamine/triethylamine in methanol at room temperature gave the desired isoxazoles.

The preparation of the pyrazolo[1,5-*a*]pyrimidine derivatives **9, 10, 11** does not require acidic or basic conditions and the reaction proceeds under mild conditions. In contrast, 2,3-diphenylpropenenitrile **(4)** does not react with **6** under these conditions; extensive decomposition was observed when the reaction was carried out in refluxing acetic acid for two days. Further, a complex mixture was obtained from the reaction of **6** with 3-phenyl-2-benzenesulfonylpropenenitrile **(5)**.





Attempted oxidation of **10** with DDQ failed, whereas similar treatment of **9** afforded the 2,7-diamino-3-benzyl-6-cyano-5-phenylpyrazolo[1,5-*a*]pyrimidines **(11)** in good yield. Additional experiments showed that compounds **11** can also be obtained directly from **6** and a twofold excess of compounds **2**.

All spectral data were in accord with structures **6–11**. Possible isomeric structures for **9** and **10**, resulting from initial alkylation at N-1 and subsequent ring closure onto one of the amine N-atoms, were ruled out on the basis of the ^{1}H-NMR spectra of these compounds and of the analogy to the well established behaviour of 3-aminopyrazoles toward α,β-unsaturated esters and nitriles.[20]

Table 1. Pyrazoles **6** and Isoxazoles **7** Prepared

Product	Ar	Yield (%)	m.p. (°C)	Molecular Formula[a]	IR ν (cm^{-1})	^{1}H-NMR[d] δ (ppm)
6a	C_6H_5	73	150–151	$C_{10}H_{12}N_4$[b] (188.2)	3410, 3360, 3300–3080, 1630, 1600, 1535, 1495, 1430, 1040	3.48 (s, 2H); 4.25 (br., 4H); 7.16 (s, 5H); 9.87 (br., 1H)
6b	4-$CH_3-C_6H_4$	70	176–177	$C_{11}H_{14}N_4$ (202.2)	3410, 3360, 3300–3060, 1625, 1605, 1535, 1495, 1430, 1040	2.33 (s, 3H); 3.63 (s, 2H); 7.13 (s, 4H)
6c	4-Cl–C_6H_4	72	168–169	$C_{10}H_{11}ClN_4$ (222.7)	3410, 3360, 3300–3060, 1630, 1605, 1535, 1495, 1435, 1040	3.63 (s, 2H); 7.26 (s, 4H)
6d	3-$O_2N-C_6H_4$	42	145–146	$C_{10}H_{11}N_3O$ (233.2)	3420, 3310, 3200, 3100, 1630, 1530, 1080, 1050	3.88 (s, 2H); 7.38–7.28 (m, 4H)
7a	C_6H_5	74	114–115	$C_{10}H_{11}N_3O$[c] (189.2)	3450, 3360, 3290, 3170, 1665, 1605, 1490, 1095, 1030	3.46 (s, 2H); 4.27–5.34 (br., 2H); 6.02 (br., 2H); 7.17 (s, 2H)
7b	4-$CH_3-C_6H_4$	67	99–100	$C_{11}H_{13}N_3O$ (203.2)	3460, 3370, 3300, 3180, 1655, 1610, 1490, 1250, 1100, 1030	2.22 (s, 3H); 3.40 (s, 2H); 4.84 (br., 2H); 5.94 (br., 2H); 7.03 (s, 4H)
7c	4-$CH_3O-C_6H_4$	70	131–132	$C_{11}H_{13}N_3O$ (219.2)	3400, 3350, 3200, 3140, 1660, 1605, 1495, 1235, 1170, 1035	3.38 (s, 2H); 3.66 (s, 3H); 4.89 (br., 2H); 5.98 (br., 2H); 6.76, 7.11 (A_2B_2, J = 8.5 Hz, 4H)
7d	4-Cl–C_6H_4	77	144–145	$C_{10}H_{10}ClN_3O$ (207.7)	3450, 3370, 3280, 3140, 1670, 1615, 1490, 1430, 1015	3.45 (s, 2H); 4.98 (br., 2H); 6.07 (br., 2H); 7.23 (s, 4H)

[a] Satisfactory microanalyses obtained: C ±0.41, H ±0.37, N ±0.46.
[b] MS: m/e = 188 (M^+, 100%); 170 (10); 145 (16); 111 (91).
[c] MS: m/e = 189 (M^+, 100%); 171 (31); 128 (28); 103 (35); 91 (95).
[d] Compounds **6a**, **7a–d** in DMSO-d_6, compounds **6b**, **c**, **d** in CF_3COOD.

Table 2. Pyrazolo[1,5-*a*]pyrimidine Derivatives **9, 10 and 11** Prepared

Product	Ar	Yield (%)		m.p. (°C)	Molecular Formula[a]	IR ν (cm^{-1})	^{1}H-NMR (DMSO-d_6) δ (ppm)
9a	C_6H_5	87		182–183	$C_{20}H_{18}N_6$[b] (342.4)	3460, 3400, 3345, 3220, 2190, 1665, 1585, 1490	3.55 (s, 2H); 5.02 (br., 3H, NH_2 + 5-H); 6.40 (br., 2H); 7.20 (s, 5H); 7.30 (s, 5H)
9b	4-$CH_3-C_6H_4$	75		199–200	$C_{21}H_{20}N_6$ (356.4)	3460, 3400, 3340, 3190, 2200, 1670, 1590, 1500	2.20 (s, 3H); 3.50 (s, 2H); 5.00 (br., 3H, NH_2 + 5-H); 6.40 (br., 2H); 7.05 (s, 4H); 7.25 (s, 5H)
9c	4-Cl–C_6H_4	83		212–213	$C_{20}H_{17}ClN_6$ (376.8)	3460, 3330, 3240, 3220, 2200, 1660, 1590, 1490	3.55 (s, 2H); 5.02 (br., 3H, NH_2 + 5-H); 7.20, 7.25 (ds, 9H)
10a	C_6H_5	63		276–277	$C_{20}H_{17}N_5O$ (343.4)	3450, 3300, 3190, 3060, 2240, 1690, 1650, 1500	3.75 (s, 2H); 4.65 (br., 2H); 4.95 (d, 1H, J = 12 Hz); 5.3–5.8 (m, 2H, C–H + NH); 7.25 (s, 5H); 7.40 (s, 5H)
10b	4-$CH_3-C_6H_4$	59		290–291	$C_{21}H_{19}N_5O$ (357.4)	3450, 3300, 3190, 3060, 2240, 1690, 1650, 1510	2.20 (s, 3H); 3.62 (s, 2H); 4.57 (br., 2H); 4.92 (d, 1H, J = 12 Hz); 5.2–5.7 (m, 2H, C–H + NH); 7.10 (s, 5H); 7.32 (s, 4H)
10c	4-Cl–C_6H_4	61		282–283	$C_{20}H_{16}ClN_5O$ (377.8)	3440, 3290, 3185, 3050, 2250, 1680, 1640, 1490	3.65 (s, 2H); 4.67 (br., 2H); 4.90 (d, 1H, J = 12 Hz); 5.2–5.8 (m, 2H, C–H + NH); 7.25 (s, 5H); 7.32 (s, 4H)
		Method A	Method B				
11a	C_6H_5	64	66	218–220	$C_{20}H_{16}N_6$[c] (340.4)	3400, 3280, 3200, 2200, 1620, 1565, 1505	3.87 (s, 2H); 5.72 (br., 2H); 7.0–8.2 (m, 12H, H_{arom} + NH_2)
11b	4-$CH_3-C_6H_4$	72	79	246–247	$C_{21}H_{18}N_6$ (354.4)	3410, 3300, 3200, 2200, 1620, 1505	2.20 (s, 3H); 3.87 (s, 2H); 5.70 (br., 2H); 6.9–8.2 (m, 11H, H_{arom} + NH_2)
11c	4-Cl–C_6H_4	69	76	208–209	$C_{20}H_{15}ClN_6$ (374.8)	3410, 3300, 3200, 2190, 1620, 1480	3.90 (s, 2H); 5.70 (br., 2H); 7.2–7.9 (m, 9H); 8.15 (br., 2H)

[a] Satisfactory microanalyses obtained: C ±0.44, H ±0.33, N ±0.40.
[b] MS: m/e = 342 (M^+, 27%); 341 (39); 340 (100); 265 (43); 263 (61); 187 (20); 128 (25).
[c] MS: m/e = 340 (M^+, 100%); 339 (56); 297 (13); 263 (83).

Melting points were determined on a Büchi SMP-20 and are uncorrected. Mass spectra were recorded on a Varian Mat 711 instrument. IR spectra were recorded on a Perkin-Elmer 700. ^{1}H-NMR spectra were obtained on Varian FT 80 and Bruker WP 60 WC spectrometers.

3,5-Diamino-4-benzylpyrazoles (6); General Procedure:
The benzylmalononitrile **1** (0.01 mol) is added to a solution of hydrazine hydrate (~ 100%; 0.501 g, 0.01 mol) in ethanol (20 ml) and the mixture is heated at reflux temperature for 4 h. Additional hydrazine hydrate (0.25 g, 0.005 mol) is then added and heating is continued for 4 h. The resultant red solution is chilled in ice and the precipitate thus obtained is filtered off. The filtrate is evaporated under reduced pressure and the oily residue is solidified with ethyl acetate (2 ml). The combined solids are recrystallized from ethyl acetate.

3,5-Diamino-4-benzylisoxazoles (7); General Procedure:
To a stirred solution of hydroxylamine hydrochloride (0.695 g, 0.01 mol) and the benzylmalononitrile **1** (0.01 mol) in methanol (60 ml), a solution of triethylamine (1.012 g, 0.01 mol) in methanol (20 ml) is added dropwise. After the addition has been completed (~ 2 h), a second portion of triethylamine (1.012 g, 0.01 mol) is added and the mixture is stirred at room temperature for 2 days. The solution is then concentrated under reduced pressure to a volume of 20 ml and this is poured into cold water (150 ml). The aqueous solution is extracted with chloroform (6 × 30 ml) and the combined organic extracts are dried with magnesium sulfate, filtered, and evaporated to give a crude solid product. Recrystallization from toluene/ethanol affords the pure compound **7**.

Benzylmalonodihydroximic Acid Diamides (Benzylmalonamidedioxime, 8):
Benzylmalononitrile (**1a**; 0.01 mol) is added to a solution of hydroxylamine [0.01 mol, from hydroxylamine hydrochloride (0.695 g, 0.01 mol) and triethylamine (1.012 g, 0.01 mol) in ethanol (15 ml)] and the mixture is heated under reflux for 6 h. Upon cooling of the mixture to 0 °C, a white precipitate is obtained; this is isolated by suction and recrystallized from ethanol; yield: 0.89 g (80%); m.p. 202–203 °C.

$C_{10}H_{14}N_4O_2$	calc.	C 54.04	H 6.35	N 25.21
(222.2)	found	53.67	6.77	25.60

MS: m/e = 222 (M^+, 39%), 205 (36), 190 (56), 91 (100).

IR (KBr): ν = 3400, 3300, 3140, 3080, 1655, 1630, 1490, 1455, 1375, 990, 915 cm^{-1}.

^{1}H-NMR (DMSO-d_6): δ = 3.00 (s, 2H, $CH_2-C_6H_5$); 3.66 (s, 1H); 5.32 (br., 4H, 2 NH_2); 7.16 (s, 5 H_{arom}); 8.95 ppm (br., 2H, 2 OH).

2,7-Diamino-4-benzyl-6-cyano-5-phenyl-4,5-dihydropyrazolo[1,5-*a*]pyrimidines (9): General Procedure:
A mixture of the pyrazole **4a, b, c** (2 mmol) and benzylidenemalononitrile (**2**; 2 mmol) in ethanol (5 ml) is stirred at room temperature until the starting materials can no longer be detected by TLC (26–48 h). The mixture is then cooled, the precipitate isolated by suction, and recrystallized from ethanol/acetone to give the pure product **9a, b, c**.

2-Amino-3-benzyl-6-cyano-7-oxo-5-phenyl-4,5,6,7-tetrahydropyrazolo [1,5-*a*]pyrimidines (10); General Procedure:
A mixture of the pyrazole **6a, b, c** (2 mmol) and ethyl 2-cyano-3-phenylpropenoate (**3**; 2 mmol) in ethanol (20 ml) is stirred at room temperature until the starting materials can no longer be detected by TLC (40–48 h). The mixture is then cooled and the precipitate is isolated by suction and recrystallized from ethanol/acetone.

2,7-Diamino-3-benzyl-6-cyano-5-phenylpyrazolo[1,5-*a*]pyrimidines (11); General Procedure:

Method A: A solution of the compound **9a, b, c** (1 mmol) and DDQ (0.227 g, 1 mmol) in ethanol (5 ml) is stirred at room temperature for 3 days. The precipitate formed is isolated by suction; and recrystallized from ethanol/acetone.

Method B: A mixture of the pyrazole **6a, b, c** (1 mmol) and benzylidenemalononitrile (**2**; 0.309 g, 2 mmol) in ethanol (5 ml) is stirred at room temperature for 3 days, then cooled to 0–4 °C. The precipitate is isolated by suction, and recrystallized from ethanol/acetone.

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