Synthesis of 3-Methyl-6-phenylamino-substituted-1*H*-pyrazolo[4,3-*d*]pyrimidine-7(6*H*)-ones

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We have recently reported[1] on the reaction of the diketo-piperazine **1** with aliphatic and benzylic amines leading to the corresponding nitro-amides. These intermediates were further converted successfully through reduction and subsequent cyclization to 1*H*-pyrazolo[4,3-*d*]pyrimidine-7(6*H*)-one analogues. In view of these results, we decided to investigate the possibility of further applications of the readily available diketo-piperazine[2] **1** as a potential intermediate in synthetic heterocyclic chemistry.

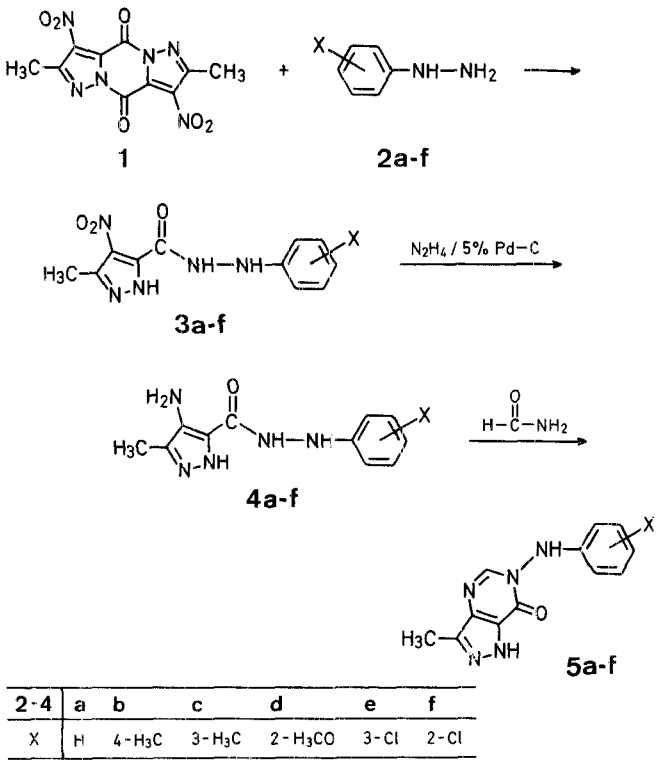
We describe here the results of our studies concerning the reaction of **1** with substituted phenylhydrazines as a new route to 1*H*-pyrazolo[4,3-*d*]pyrimidine-7(6*H*)-ones bearing a phenylamino moiety in the 6-position. Thus, treatment of **1** with different phenylhydrazines **2a–f** allowed to obtain as expected, very high yields of the disubstituted hydrazides **3a–f**.

Reduction of **3a–f** proceeded smoothly with hydrazine in methanolic solution in the presence of 5% palladium-on-carbon[3] to give the corresponding hydrazides **4a–f**.

This reduction procedure proved more efficient, avoiding solubility troubles, as compared to other methods such as catalytic hydrogenation or use of sodium borohydride in presence of palladium on carbon[1]. Moreover, this method was of general applicability and worked well in the presence of reduction-labile substituents such as halogen atoms[4].

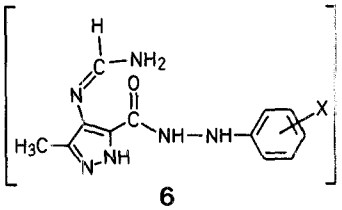
Finally, the cyclization of hydrazides **4a–f** to **5a–f** was achieved by heating with formamide at 180°C in open vessel for 5 h[5] (Scheme A).

Evidence for this ring closure comes from the analytical and spectral data: the ^{1}H-N.M.R. spectra of the cyclic compounds show a characteristic singlet[1,6] in the range $\delta = 8.0$–8.1 ppm. The pyrimidine cyclization of hydrazides **4a–f** presumably proceeds via the amidine intermediate **6**, which undergoes intramolecular attack by the N-1 hydrazide nitrogen atom on the amidine function followed by the loss of ammonia[1].



2-4	a	b	c	d	e	f
X	H	4-H_3C	3-H_3C	2-H_3CO	3-Cl	2-Cl

Scheme A



All of the new derivatives **5** showed interesting pharmacological properties, such as microbiological and anaesthetic activities. These results will be published elsewhere.

N^2-Phenyl-Substituted 3-Methyl-4-nitropyrazole-5-carboxhydrazides 3a–f; General Procedure:

To a methanolic solution (250 ml) of potassium hydroxide (0.05 mol) is added the appropriate phenylhydrazine hydrochloride **2**·HCl (0.05

Table 1. N^2-Phenyl-Substituted 3-Methyl-4-nitropyrazole-5-carboxhydrazides **3a–f**

Product	Yield [%]	m.p. [°C][a]	Molecular[b] formula	I.R. (KBr) ν [cm^{-1}]	^{1}H-N.M.R. (DMSO-d_6) δ [ppm]
3a	82	235–237°	$C_{11}H_{11}N_5O_3$ (261.2)	3300, 3200, 3140, 1650, 1610, 1590, 1510	2.55 (s, 3H); 7.1 (m, 5H); 7.6 (br s, 1H); 10.1 (br s, 1H); 13.7 (br s, 1H)
3b	85	228–230°	$C_{12}H_{13}N_5O_3$ (275.3)	3290, 3200, 3130, 1650, 1610, 1590, 1510	2.2 (s, 3H); 2.55 (s, 3H); 6.9 (dd, 4H, J=9 Hz); 7.85 (br s, 1H); 10.2 (br s, 1H); 13.9 (br s, 1H)
3c	78	232–234°	$C_{12}H_{13}N_5O_3$ (275.3)	3290, 3190, 3130, 1650, 1610, 1590, 1510	2.25 (s, 3H); 2.55 (s, 3H); 6.85 (m, 4H); 7.9 (br s, 1H); 10.2 (br s, 1H); 13.8 (br s, 1H)
3d	75	228–230°	$C_{12}H_{13}N_5O_4$ (291.3)	3300, 3210, 3120, 1650, 1600, 1580, 1500	2.55 (s, 3H); 3.85 (s, 3H); 6.9 (m, 4H); 7.2 (br s, 1H); 10.4 (br s, 1H); 13.7 (br s, 1H)
3e	81	219–221°	$C_{11}H_{10}ClN_5O_3$ (295.7)	3300, 3230, 3140, 1650, 1610, 1600, 1510	2.55 (s, 3H); 6.9 (m, 4H); 7.9 (br s, 1H); 10.1 (br s, 1H); 13.7 (br s, 1H)
3f	85	250–252°	$C_{11}H_{10}ClN_5O_3$ (295.7)	3290, 3220, 3120, 1650, 1600, 1580, 1510	2.55 (s, 3H); 7.0 (m, 4H); 7.8 (br s, 1H); 10.3 (br s, 1H); 13.7 (br s, 1H)

[a] Measured with a Büchi-Tottoli apparatus and not corrected.

[b] Satisfactory microanalysis obtained: C ±0.28; H ±0.20; N ±0.21; Cl ±0.20.

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Table 2. N^2-Phenyl-Substituted 3-Methyl-4-aminopyrazole-5-carboxhydrazides **4a–f**

Product	Yield [%]	m.p. [°C][a] (solvents)	Molecular[b] formula	I.R. (KBr) ν [cm^{-1}]	^{1}H-N.M.R. (DMSO-d_6) δ [ppm]
4a	70	216–218° (1:1 CH_3OH/H_2O)	$C_{11}H_{13}N_5O$ (231.3)	3400, 3340, 3300, 3220, 1670, 1610, 1570	2.10 (s, 3H); 4.3 (br s, 2H); 7 (m, 5H); 7.4 (br s, 1H); 9.3 (br s, 1H); 12.4 (br s, 1H)
4b	62	222–224° (1:1 DMF/H_2O)	$C_{12}H_{15}N_5O$ (245.3)	3400, 3340, 3300, 3240, 1670, 1610, 1580	2.10 (s, 3H); 2.20 (s, 3H); 4.3 (br s, 2H); 6.85 (dd, 4H, J=9 Hz); 7.3 (br s, 1H); 9.3 (br s, 1H); 12.3 (br s, 1H)
4c	65	226–227° (1:1 DMF/H_2O)	$C_{12}H_{15}N_5O$ (245.3)	3390, 3340, 3300, 3240, 1670, 1610, 1580	2.10 (s, 3H); 2.20 (s, 3H); 4.35 (br s, 2H); 6.8 (m, 4H); 7.35 (br s, 1H); 9.25 (br s, 1H); 12.4 (br s, 1H)
4d	71	220–222° (CH_3OH)	$C_{12}H_{15}N_5O_2$ (261.3)	3400, 3300, 3260, 1670, 1600, 1580	2.10 (s, 3H); 3.85 (s, 3H); 4.5 (br s, 2H); 6.9 (m, 4H); 7.6 (br s, 1H); 9.8 (br s, 1H); 12.4 (br s, 1H)
4e	72	225–226° (1:1 DMF/H_2O)	$C_{11}H_{12}ClN_5O$ (265.7)	3390, 3280, 3220, 1670, 1600, 1580	2.10 (s, 3H); 4.1 (br s, 2H); 6.9 (m, 4H); 7.4 (br s, 1H); 9.5 (br s, 1H); 13.0 (br s, 1H)
4f	68	248–250° (1:1 DMF/H_2O)	$C_{11}H_{12}ClN_5O$ (265.7)	3400, 3350, 3300, 3220, 1670, 1600, 1580	2.10 (s, 3H); 4.3 (br s, 2H); 7.1 (m, 5H); 9.5 (br s, 1H); 12.4 (br s, 1H)

[a] Measured with a Büchi-Tottoli apparatus and not corrected.
[b] Satisfactory microanalysis obtained: C ±0.30; H ±0.27; N ±0.22; Cl ±0.18.

Table 3. 6-Phenylamino-Substituted 3-methyl-1H-pyrazolo[4,3-d]pyrimidine-7(6H)-ones **5a–f**

Product	Yield [%]	m.p. [°C][a] (solvents)	Molecular[b] formula	I.R. (KBr) ν [cm^{-1}]	^{1}H-N.M.R. (DMSO-d_6) δ [ppm]
5a	62	285–287° (1:1 CH_3OH/H_2O)	$C_{12}H_{11}N_5O$ (241.3)	3310, 3160, 3060, 1690, 1600, 1580	2.50 (s, 3H); 6.95 (m, 5H); 8.00 (s, 1H); 9.1 (br s, 1H); 13.7 (br s, 1H)
5b	65	281–283° (1:1 CH_3OH/H_2O)	$C_{13}H_{13}N_5O$ (255.3)	3300, 3140, 3060, 1690, 1600, 1580	2.20 (s, 3H); 2.50 (s, 3H); 6.75 (dd, 4H, J=9 Hz); 8.00 (s, 1H); 9.0 (br s, 1H); 13.8 (br s, 1H)
5c	55	256–258° (1:1 CH_3OH/H_2O)	$C_{13}H_{13}N_5O$ (255.3)	3300, 3140, 3060, 1690, 1600, 1580	2.20 (s, 3H); 2.45 (s, 3H); 6.75 (m, 4H); 8.05 (s, 1H); 9.1 (br s, 1H); 13.5 (br s, 1H)
5d	62	257–259° (CH_3OH)	$C_{13}H_{13}N_5O_2$ (271.3)	3300, 3140, 3060, 1700, 1610, 1580	2.50 (s, 3H); 3.90 (s, 3H); 6.3 (m, 1H); 6.9 (m, 3H); 8.05 (s, 1H); 8.5 (br s, 1H); 13.9 (br s, 1H)
5e	64	263–265° (1:1 DMF/H_2O)	$C_{12}H_{10}ClN_5O$ (275.7)	3300, 3160, 3080, 1690, 1600, 1580	2.50 (s, 3H); 6.9 (m, 4H); 8.05 (s, 1H); 9.3 (br s, 1H); 14.2 (br s, 1H)
5f	60	253–254° (1:1 DMF/H_2O)	$C_{12}H_{10}ClN_5O$ (275.7)	3300, 3150, 3060, 1690, 1600, 1580	2.50 (s, 3H); 6.45 (m, 1H); 7.1 (m, 3H); 8.05 (s, 1H); 8.90 (br s, 1H); 14.0 (br s, 1H)

[a] Measured with a Büchi-Tottoli apparatus and not corrected.
[b] Satisfactory microanalysis obtained: C ±0.30; H ±0.28; N ±0.18; Cl ±0.22.

mol) under efficient stirring, the suspension is then stirred for 1 h, and filtered. To the ice-cooled and stirred filtrate is added the diketo-piperazine **1**[2] (0.025 mol) and the resulting solution is stirred overnight at room temperature. The solvent is removed under reduced pressure to give a solid which is purified by crystallization from 1:1 methanol/water (Table 1).

N^2-Phenyl-Substituted 4-Amino-3-methylpyrazole-5-carboxhydrazides 4a–f; General Procedure:

To a methanolic solution (50 ml) of **3a–f** (0.005 mol) is added 5% palladium on carbon (150 mg) and 99% hydrazine (15 ml). The suspension is refluxed for 5 min and then filtered through a small pad of Celite 503. The solvent is removed under reduced pressure to give a solid which is purified by crystallization from suitable solvents (Table 2).

6-Phenylamino-Substituted 3-Methyl-1H-pyrazolo[4,3-d]pyrimidine-7(6H)-ones (4a–f); General Procedure:

A suspension of **4a–f** (0.005 mol) in formamide (8 ml) is heated on an oil bath at 180°C for 5 h in an open vessel. The residue is diluted with dimethylformamide (5 ml), charcoalized, and filtered through a pad of Celite 503. The cyclic compounds **6** are precipitated by addition of water (30 ml) to the filtrate and crystallized from suitable solvents (Table 3).

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