Synthesis of 3-Substituted 7-Methyl-5*H*-pyrazole[4,3-*d*]-1,2,3-triazin-4(3*H*)-ones and Amide-*N*-Substituted 3-Methyl-4-diazopyrazole-5-carboxamides

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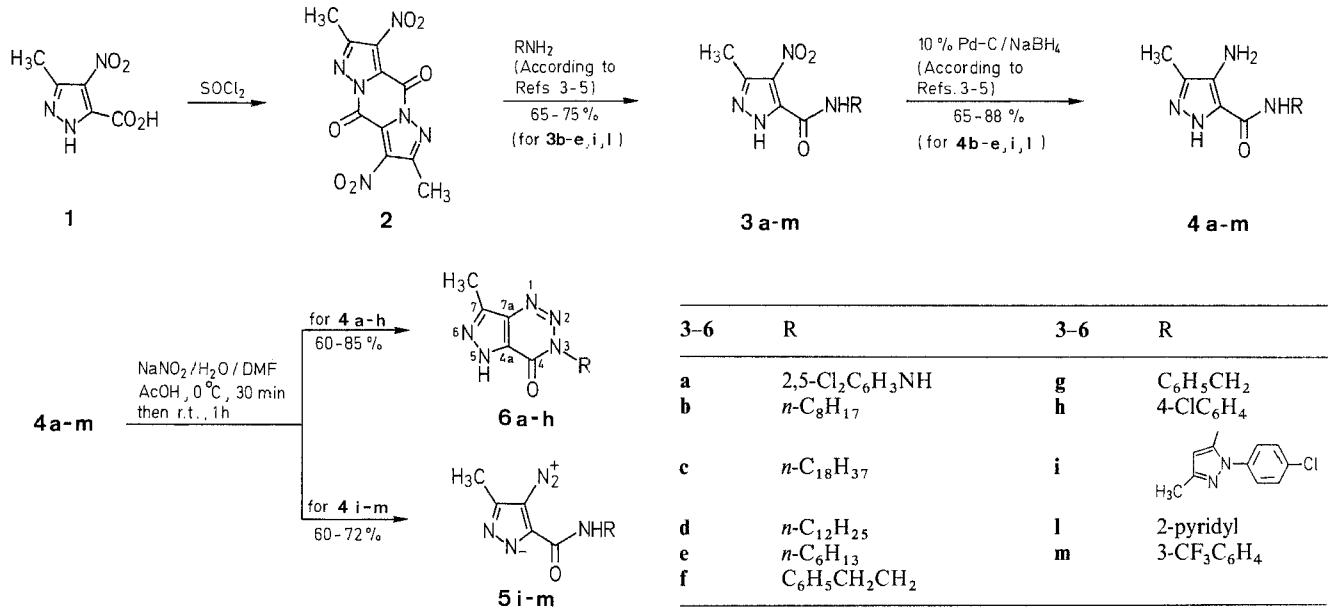
Diazotization of amide-*N*-substituted 4-amino-3-methylpyrazole-5-carboxamides **4** with sodium nitrite and acetic acid produces 3-substituted 7-methyl-5*H*-pyrazolo[4,3-*d*]-1,2,3-triazin-4(3*H*)-ones **6** or amide-*N*-substituted 3-methyl-4-diazopyrazole-5-carboxamides **5**, depending on the substitution pattern.

Diazonium ion condensation into an adjacent functional group has proven a valuable tool for the synthesis of five- and six-

membered rings in a wide variety of nitrogen heterocycles.[1] Thus hetero-fused 1,2,3-triazin-4(3*H*)-ones are formed via intramolecular attack of the electrophilic nitrogen of a diazo group on a carboxamide function.[2]

As an extension of our continuous interest[3-6] in the synthesis of biologically active heterocyclic compounds incorporating the pyrazole nucleus, we required substantial quantities of various 7-methyl-5*H*-pyrazolo[4,3-*d*]-1,2,3-triazin-4(3*H*)-ones bearing



3–6	R	3–6	R
a	2,5-$Cl_2C_6H_3NH$	**g**	$C_6H_5CH_2$
b	*n*-C_8H_{17}	**h**	4-ClC_6H_4
c	*n*-$C_{18}H_{37}$	**i**	
d	*n*-$C_{12}H_{25}$	**l**	2-pyridyl
e	*n*-C_6H_{13}	**m**	3-$CF_3C_6H_4$
f	$C_6H_5CH_2CH_2$		

Table 1. Amide-*N*-substituted 3-Methyl-4-nitropyrazole-5-carboxamides **3b–e, i, l** Prepared

Product	Yield[a] (%)	mp (°C) (solvent)	Molecular Formula[b]	IR (KBr) ν (cm^{-1})	^{1}H-NMR (DMSO-d_6/TMS)[c] δ
3b	69	174–175 ($CHCl_3$/PE[d])	$C_{13}H_{22}N_4O_3$ (282.3)	3280, 3120, 1640, 1610, 1590, 1500	0.85 (br t, 3H); 1.3–1.51 (m, 12H); 2.50 (s, 3H); 3.21 (m, 2H); 8.51 (br s, 1H); 13.95 (br s, 1H)
3c	74	162–164 (THF)	$C_{23}H_{42}N_4O_3$ (422.6)	3290, 3110, 1650, 1600, 1590, 1500	0.86 (br t, 3H); 1.25–1.48 (m, 32H); 2.50 (s, 3H); 3.18 (m, 2H); 8.51 (br s, 1H); 13.8 (br s, 1H)
3d	72	169–171 (THF)	$C_{17}H_{30}N_4O_3$ (338.4)	3280, 3120, 1640, 1600, 1580, 1500	0.83 (br t, 3H); 1.25–1.48 (m, 20H); 2.55 (s, 3H); 3.15 (m, 2H); 8.45 (br s, 1H); 13.4 (br s, 1H)
3e	70	176–178 ($CHCl_3$/PE)	$C_{11}H_{18}N_4O_3$ (254.3)	3280, 3120, 1630, 1600, 1590, 1500	0.87 (br t, 3H); 1.27–1.48 (m, 8H); 2.50 (s, 3H); 3.18 (m, 2H); 8.54 (br s, 1H); 13.89 (br s, 1H)
3i	65	220–221 (MeOH/H_2O)	$C_{15}H_{13}ClN_6O_3$ (360.7)	3220, 1690, 1580, 1560	2.22 (s, 3H); 2.49 (s, 3H); 6.43 (s, 1H); 7.1–7.6 (m, 4H); 8.50 (br s, 1H); 10.58 (br s, 1H)
3l	75	271–273 (THF)	$C_{10}H_9N_5O_3$ (247.2)	3310, 1680, 1600, 1570	2.44 (s, 3H); 7.21 (m, 1H); 7.84 (m, 1H); 8.18 (m, 1H); 8.25 (m, 1H); 8.51 (br s, 1H); 13.7 (br s, 1H)

[a] Yield of isolated product; not optimized.
[b] Satisfactory microanalyses obtained: C ±0.24, H ±0.11, N ±0.28, Cl ±0.23.
[c] Recorded on a Bruker WP80 spectrometer.
[d] PE = petroleum ether (30–40).

Table 2. Amide-*N*-Substituted 4-Amino-3-methylpyrazole-5-carboxamides **4b–e, i, l** Prepared

Product	Yield[a] (%)	mp (°C) (solvent)	Molecular Formula[b]	IR (KBr) ν (cm^{-1})	^{1}H-NMR (DMSO-d_6/TMS)[c] δ
4b	84	103–105 (AcOEt)	$C_{13}H_{24}N_4O$ (252.3)	3410, 3200, 1640, 1560, 1520	0.87 (br t, 3H); 1.22–1.51 (m, 12H); 2.1 (s, 3H); 3.15 (m, 2H); 4.25 (br, 2H); 7.80 (br s, 1H); 12.51 (br s, 1H)
4c	88	129–130 (AcOEt)	$C_{23}H_{44}N_4O$ (392.6)	3400, 3200, 1650, 1550	0.86 (br t, 3H); 1.23–1.50 (m, 32H); 2.07 (s, 3H); 3.15 (m, 2H); 4.20 (br, 2H); 7.80 (br s, 1H); 12.51 (br s, 1H)
4d	80	115–116 (AcOEt)	$C_{17}H_{32}N_4O$ (308.4)	3410, 3200, 1640, 1560, 1520	0.85 (br t, 3H); 1.22–1.50 (m, 20H); 2.1 (s, 3H); 3.12 (m, 2H); 4.1 (br, 2H); 7.6 (br s, 1H); 12.4 (br s, 1H)
4e	85	98–99 (AcOEt)	$C_{11}H_{20}N_4O$ (224.3)	3400, 3200, 1640, 1560, 1520	0.85 (br t, 3H); 1.25–1.50 (m, 8H); 2.07 (s, 3H); 3.15 (m, 2H); 4.39 (br, 2H); 7.75 (br s, 1H); 12.34 (br s, 1H)
4i	65	218–219 (THF)	$C_{15}H_{15}ClN_6O$ (330.7)	3200, 3110, 1690, 1590, 1560	2.06 (s, 3H); 2.2 (s, 3H); 3.37 (br, 2H); 6.3 (s, 1H); 7.5–7.69 (m, 4H); 9.25 (br, 1H); 12.59 (s, 1H)
4l	66	208–209 (THF)	$C_{10}H_{11}N_5O$ (217.2)	3310, 1690, 1600, 1570	2.15 (s, 3H); 4.54 (br s, 2H); 7.15 (m, 1H); 7.84 (m, 1H); 8.33 (m, 1H); 9.29 (br s, 1H); 12.7 (br s, 1H)

[a] Yield of isolated product, not optimized.
[b] Satisfactory microanalyses obtained: C ±0.24, H ±0.11, N ±0.28, Cl ±0.23.
[c] Recorded on a Bruker WP80 spectrometer.

alkyl, aryl and phenylamino substituents on the nitrogen atom at the three position, a class of compounds with little precedent in the literature.[7,8]

To this end we decided to carefully investigate the diazotization reaction of the 4-amino-5-carbamoylpyrazoles **4a–m** in order to find the best conditions to achieve cyclization (Scheme).

These compounds were easily prepared in multigram scale starting from the readily accessible dioxopiperazine derivative **2**,[9] a versatile intermediate in synthetic heterocyclic chemistry. A two-step sequence is employed involving the reaction of **2**, with nitrogen nucleophiles followed by reduction of the resulting nitro-amides **3a–m** with sodium borohydride in the presence of 10% Pd–C. When the amino-amides **4a–m** were exposed to the action of one equivalent of sodium nitrite in acetic acid followed by neutralization of the acidic solution, the reaction takes different courses depending on the substituents pattern.

Thus diazotization of **4a–h** led to the formation of the expected 7-methyl-5*H*-pyrazolo[4,3-*d*]-1,2,3-triazin-4(3*H*)-ones **6a–h** in good yield, the structural assignment being based on microanalysis and spectral data (Table 3). The same conditions applied to **4i–m**, however, gave the diazo-amides **5i–m** in excellent yield. Their structures were established on the basis of ^{1}H-NMR and ^{13}C-NMR data and by the presence of a sharp, intense infrared absorption peak at 2180 cm^{-1}, indicating the diazo group.

It is well known[10] that diazotization of 4-aminopyrazoles, unsubstituted at the nitrogen atom, followed by alkalinization of the diazonium salt solution gives rise to the formation of a neutral zwitterionic diazopyrazole. Our results indicate that the diazonium ion condensation on the adjacent carboxamido function occurs only when the amide nitrogen doesn't bear an electron-withdrawing group.

In conclusion we have demonstrated the utility of the diazotization of 4-amino-5-pyrazole-carboxamides as a way to obtain two classes of rather uncommon compounds, namely, 3-substituted 7-methyl-5*H*-pyrazolo[4,3-*d*]-1,2,3-triazin-4(3*H*)-ones **6a–h** and amide-*N*-substituted 3-methyl-4-diazopyrazole-5-carboxamides **5i–m** through the appropriate choice of the substitution pattern.

In view of the interesting antitumoral activity showed by structurally related condensed pyrazolotetrazinone systems,[11] studies aimed to define the biological profile of these compounds are in course.

Amide *N*-Substituted 3-Methyl-4-nitropyrazole-5-carboxamides 3a–m:
All unknown nitro-pyrazoles **3b–e, i, l** are prepared according to the general procedure previously described;[3–5] in the cases of **3i, l**, the reaction is performed in refluxing toluene for 10 h (Table 1).

Amide-*N*-Substituted 4-Amino-3-methylpyrazole-5-carboxamides 4a–m:
All unknown aminopyrazoles **4b–e, i, l** are prepared according to the general procedure previously described[3–5] (Table 2).

3-Substituted 7-Methyl-5*H*-pyrazolo[4,3-*d*]-1,2,3-triazin-4(3*H*)-ones 6a–h and Amide-*N*-Substituted 3-Methyl-4-diazopyrazole-5-carboxamides (5i–m); General Procedure:
The appropriate amino-carboxamide **4a–m** (4.1 mmol) is dissolved in a mixture of water (3 mL), DMF (3 mL) and AcOH (6 mL) at 0°C.

Table 3. 3-Substituted 7-Methyl-5*H*-pyrazolo[4,3-*d*]-1,2,3-triazin-4(3*H*)-ones **6a–g** and Amide-*N*-substituted 3-Methyl-4-diazopyrazole-5-carboxamides **5i–m** Prepared

Product	Yield[a] (%)	mp (°C) (solvent)	Molecular Formula[b]	IR (KBr) ν(cm^{-1})	^{1}H-NMR (DMSO-d_6/TMS)[c] δ, J(Hz)	^{13}C-NMR (DMSO-d_6/TMS)[c] δ C–CH$_3$, C-4a, C-7a, C-7, C-4
6a	80	193–195 (MeOH)	$C_{11}H_8Cl_2N_6O$ (311.1)	3500, 3420, 1700, 1590	2.6 (s, 3H); 6.6 (d, 1H, J = 1.8); 6.94 (dd, 1H, J = 1.8, 8.6); 7.4 (d, 1H, J = 8.6); 8.5 (br, 1H); 14.5 (br, 1H)	9.56, 130.60, 134.22, 144.04, 150.56
6b	85	113–114 (MeOH/H$_2$O)	$C_{13}H_{21}N_5O$ (263.3)	3180, 1670, 1590	0.84 (br t, 3H); 1.11–1.35 (m, 10H); 1.79 (m, 2H); 2.62 (s, 3H); 4.3 (m, 2H); 14.6 (br, 1H)	10.91, 128.66, 135.66, 144.86, 150.81
6c	85	109–110 (MeOH)	$C_{23}H_{41}N_5O$ (403.6)	3180, 1670, 1590	0.85 (br t, 3H); 1.1–1.36 (m, 30H); 1.92 (m, 2H); 2.77 (s, 3H); 4.57 (m, 2H); 14.5 (br, 1H)	10.99, 128.51, 135.51, 142.27, 150.50
6d	81	114–115 (EtOH)	$C_{17}H_{29}N_5O$ (319.4)	3180, 1670, 1590	0.86 (br t, 3H); 1.1–1.3 (m, 18H); 1.81 (m, 2H); 2.6 (m, 3H); 4.38 (m, 2H); 14.52 (br, 1H)	9.99, 128.31, 135.16, 141.62, 150.5
6e	82	112–113 (EtOH)	$C_{11}H_{17}N_5O$ (235.3)	3180, 1670, 1590	0.86 (br t, 3H); 1.29 (s, 6H); 1.8 (m, 2H); 2.62 (s, 3H); 4.37 (m, 2H); 14.5 (br, 1H)	10.9, 128.34, 135.2, 142.34, 150.52
6f	65	185–187 (AcOEt)	$C_{13}H_{13}N_5O$ (255.3)	3180, 1690, 1560	2.60 (s, 3H); 3.14 (t, 2H, J = 7); 4.6 (t, 2H, J = 7); 7.27 (m, 5H); 13.8 (br, 1H)	9.95, 128.42, 135.03, 141.36, 150.58
6g	85	171–173 (AcOEt)	$C_{12}H_{11}N_5O$ (241.2)	3180, 1690, 1560	2.63 (s, 3H); 5.59 (s, 2H); 7.3 (s, 5H); 14.5 (br s, 1H)	10.03, 128.86, 135.29, 141.56, 150.59
6h	60	300 (AcOEt)	$C_{11}H_8ClN_5O$ (261.6)	3150, 1690, 1560	2.63 (s, 3H); 7.6 (s, 4H); 14.7 (br, 1H)	9.77, 128.85, 135.20, 142.35, 150.55
5i	72	193–194 (AcOEt)	$C_{15}H_{12}ClN_7O$ (341.7)	2180, 1720, 1680, 1550	2.36 (s, 3H); 2.5 (s, 3H); 6.59 (s, 1H); 7.42–7.5 (m, 4H); 8.6 (br s, 1H)	
5l	60	148–150 (H$_2$O)	$C_{10}H_8N_6O$ (228.2)	3380, 2180, 1680, 1580, 1550	2.3 (s, 3H); 7.09 (m, 1H); 7.7 (m, 1H); 8.2 (m, 1H); 8.36 (m, 1H); 9.51 (br s, 1H)	
5m	65	150–152 (AcOEt)	$C_{12}H_8F_3N_5O$ (295.2)	3300, 2180, 1700, 1680, 1610, 1560	2.64 (s, 3H); 7.4 (m, 1H); 7.7 (m, 2H); 8.09 (s, 1H); 9.81 (br s, 1H)	

[a] Yield of isolated product; not optimized.
[b] Satisfactory microanalyses obtained: C ±0.24, H ±0.11, N ±0.28, Cl ±0.23.
[c] Recorded on a Bruker WP80 spectrometer.

Sodium nitrite (4.5 mmol, 0.31 g) in water (3 mL) is added slowly to this cooled solution; stirring is continued at 0 °C for 0.5 h and then at room temperature for 1 h. The solvents are evaporated under vacuum, water (20 mL) is added, and the suspension is extracted with CH_2Cl_2 (3×25 mL). The organic extracts are washed with sat. aq. $NaHCO_3$ (20 mL), dried ($MgSO_4$) and evaporated to give a solid residue, which is crystallized from suitable solvents (Table 3).

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