# Synthesis of Pyrazolo[1,5-*a*]pyrimidines in the Reaction of 5-Amino-3-arylpyrazoles with Methoxymethylene Meldrum's Acid Derivatives and Thermolysis of Their Pyrazolylaminomethylene Derivatives

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A series of pyrazolo[1,5-*a*]pyrimidin-3-ones **3** was prepared from Meldrum's acid and 5-amino-3-arylpyrazoles **1** by cyclization in nitrobenzene of the corresponding 5-pyrazolylaminomethylene Meldrum's acid derivatives **2**. The structure of pyrazolo[1,5-*a*]pyrimidin-3-ones and their precursors were determined by nmr measurements.

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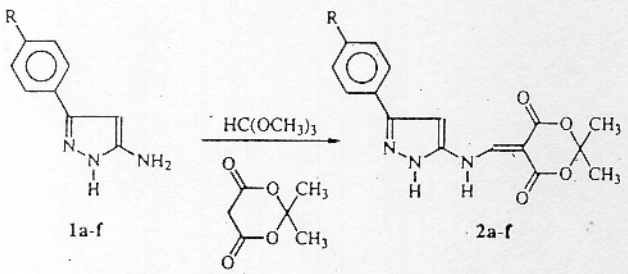
In the last twenty years considerable interest has been focused on derivatives of pyrazolo[1,5-*a*]pyrimidine, due to their physiological and biological activities [1-9]. In our previous work we have described some procedures for the synthesis of aromatic derivatives of pyrazolo[1,5-*a*]-pyrimidine [10,11].

Continuing with the research on aminopyrazoles [10-13] in this work we studied the reaction of 5-amino-3-arylpyrazoles **1** with methoxymethylene derivatives of Meldrum's acid. A solution of Meldrum's acid and methyl orthoformate (1:5) was heated to reflux for 2.5 hours and immediately the 5-amino-3-arylpyrazole **1** was added in an equimolecular amount relative to Meldrum's acid. The reaction mixture was heated for 10-15 minutes, cooled and the precipitate which formed was filtered, to give the corresponding 5-pyrazolylaminomethylene derivative of Meldrum's acid **2**.

Scheme 1




| Compound | R | mp (°C) | Yield, % |
|---|---|---|---|
| **2a** | H | 327-328 | 70 |
| **2b** | $CH_3$ | 341 | 80 |
| **2c** | $CH_3O$ | 245 | 48 |
| **2d** | Cl | 347 | 63 |
| **2e** | Br | 352-353 | 57 |
| **2f** | $NO_2$ | 342 | 57 |

The structures of compounds **2a-f** were established using spectroscopic methods. Thus, the ir spectra of compounds **2a-f** measured in potassium bromide pellets show two bands for the elongation vibrations of C=O groups at 1680-1735 $cm^{-1}$ and two bands for the NH groups at 3150-3330 $cm^{-1}$. The $^1$H-nmr spectra of compounds **2**, measured in dimethyl-$d_6$ sulfoxide, besides the signal of the methylene groups at 1.6-1.7 ppm, showed: two doublets at δ 8.70-9.12 ppm and 11.32-11.40 ppm in a 1:1 relationship, corresponding to the =CH and NH protons of NH=CH group, two singlet for =CH and NH protons of the pyrazole ring at δ 6.90-7.15 and δ 13.20-13.68 ppm respectively and multiplet aromatic protons at δ 7.18-8.29 ppm.

Table 1

$^1$H-NMR Data of **2** (δ values, TMS as the Internal Standard, in Dimethyl-$d_6$ Sulfoxide, 300 MHz)

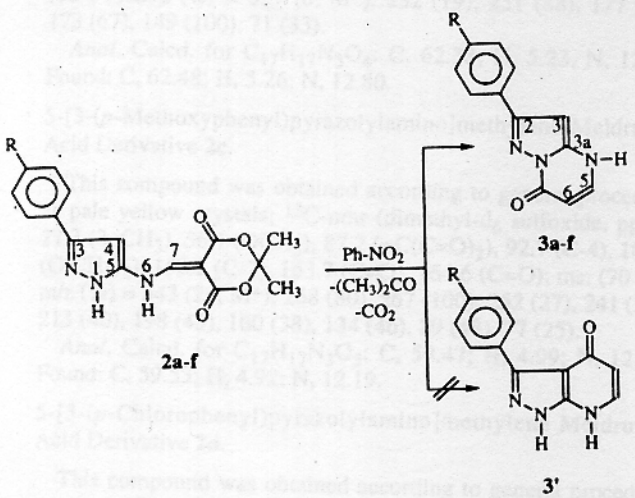
| Compound | 4-H s | 7-H d | 1-NH s | 6-NH d | $CH_3$ s | Ar m |
|---|---|---|---|---|---|---|
| **2a** | 6.90 | 8.72 | 13.30 | 11.32 | 1.70 | 7.58-7.77 |
| **2b** | 6.80 | 8.70 | 13.20 | 11.35 | 1.68 | 7.21-7.62 |
| **2c** | 6.79 | 8.69 | 13.14 | 11.28 | 1.67 | 7.02-7.68 |
| **2d** | 6.95 | 8.74 | 13.39 | 11.38 | 1.60 | 7.98-8.29 |
| **2e** | 6.91 | 8.77 | 13.41 | 11.37 | 1.70 | 7.73-7.75 |
| **2f** | 7.15 | 8.70 | 13.68 | 11.40 | 1.75 | 7.98-8.29 |

$CH_3$ for **2b** 2.32 and $OCH_3$ for **2c** 3.83 ppm.

The cyclization of the compounds **2** was carried out by heating to reflux in nitrobenzene (20% w/w) for 30 minutes to give compounds **3**. The structures of pyrazolo[1,5-*a*]-pyrimidin-3-ones **3a-f** were established from their spectral characteristics.

In the ir spectra of compounds **3** measured in potassium bromide pellets a band for C=O group at 1670-1680 $cm^{-1}$ and a band for NH group at 3120-3145 $cm^{-1}$ were observed.

Scheme 2




| Compound | R | mp (°C) | Yield, % |
|---|---|---|---|
| **3a** | H | 364-365 [a] | 48 |
| **3b** | $CH_3$ | 356 | 44 |
| **3c** | $CH_3O$ | 332-333 | 48 |
| **3d** | Cl | 378-379 | 45 |
| **3e** | Br | 375-376 | 46 |
| **3f** | $NO_2$ | 368 | 47 |

[a] Literature [9] mp 345-348 and [14] mp 303-306.

In the $^1$H-nmr spectra of compounds **3** (Table 2) measured in dimethyl-$d_6$ sulfoxide the signal for the methyl groups disappeared, and two doublets at δ 7.06-7.93 and 5.70-5.81 ppm in a 1:1 ratio, corresponding to the $CH_{(5)}$=$CH_{(6)}$, fragment of pyrimidine ring can be observed together with a singlet for the =CH proton of pyrazole ring at δ 6.70-6.90 ppm. This evidence is to establish the reaction route **2** → **3a-f**, eliminating the formation of compounds **3'**.

Table 2

$^1$H-NMR Data of **3** (δ values, TMS as the Internal Standard, in Dimethyl-$d_6$ Sulfoxide, 300 MHz)

| Compound | 3-H s | 5-H d | 6-H d | NH s | Ar m |
|---|---|---|---|---|---|
| **3a** | 6.69 | 7.41 | 5.73 | 12.39 | 7.41-8.00 |
| **3b** | 6.60 | 7.82 | 5.71 | 12.39 | 7.28-7.86 |
| **3c** | 6.58 | 7.04 | 5.71 | 12.41 | 7.82-7.96 |
| **3d** | 6.68 | 7.86 | 5.75 | 12.42 | 7.52-8.01 |
| **3e** | 6.71 | 7.80 | 5.72 | 12.40 | 7.62-7.90 |
| **3f** | 6.89 | 7.93 | 5.82 | 12.59 | 8.20-8.40 |

$CH_3$ for **3b** 2.36 and $OCH_3$ for **3c** 3.83 ppm.

The $^{13}$C-nmr data for **3** are summarized in Table 3. Signal assignments were made based on DEPT experiments and data from previous work [11,15]. Significant features are as follows: the signal for C-3 appeared at δ 96.6-96.7 ppm, C-5 was observed at δ 143.9-153.7 ppm, C-6 registered at δ 86.5-88.3 ppm and C=O at δ 157.2-160.8 ppm.

Table 3

$^{13}$C-NMR Data of **3** (δ values, TMS as the Internal Standard, in Dimethyl-$d_6$ Sulfoxide, 300 MHz)

| | Compound | **3a** | **3b** | **3c** | **3d** | **3e** | **3f** |
|---|---|---|---|---|---|---|---|
| | C-2 | 140.3 | 139.7 | 140.0 | 140.4 | 140.4 | 144.2 |
| | C-3 | 96.7 | 96.2 | 96.6 | 96.7 | 96.7 | 96.6 |
| | C-3a | 153.8 | 153.4 | 153.7 | 152.6 | 152.7 | 151.6 |
| | C-5 | 143.9 | 143.4 | 143.8 | 143.9 | 143.9 | 148.3 |
| | C-6 | 87.0 | 86.4 | 86.5 | 87.2 | 87.2 | 88.3 |
| | C=O | 157.3 | 156.9 | 157.3 | 157.2 | 157.2 | 157.2 |
| Ar | $C_i$ | 133.3 | 138.9 | 126.3 | 132.2 | 126.3 | 139.6 |
| | $C_{o,m}$ | 127.1 | 126.6 | 115.0 | 128.8 | 129.1 | 124.9 |
| | | 129.6 | 129.8 | 128.4 | 129.7 | 132.6 | 128.1 |
| | $C_p$ | 129.8 | 130.1 | 160.8 | 134.4 | 132.5 | 140.7 |

$CH_3$ for **3b** 2.14 and $OCH_3$ for **3c** 3.83 ppm.

## EXPERIMENTAL

Melting points were taken on a Büchi melting point apparatus and are uncorrected. The ir spectra were obtained in potassium bromide pellets with a Perkin-Elmer 599B spectrometer. The $^1$H- and $^{13}$C-nmr spectra were run on a Bruker DRX 300 spectrometer in dimethyl-$d_6$ sulfoxide. The mass spectra were recorded on a Fison MD-LC 800 (EI) operating at 70 eV. The elemental analysis have been obtained using a LEGO CHNS-900 equipment.

5-[3-(*p*-*R*-Phenylpyrazolylamino]methylene Meldrum's Acid Derivatives **2a-f**.

General Procedure.

A solution of Meldrum's acid (6.94 mmoles) and (34.7 mmoles) of methyl orthoformate was refluxed for 2.5 hours, then 6.94 mmoles of 5-amino-3-(*p*-*R*-phenyl)pyrazoles **1a-f** were added. The reaction mixture was heated for 10-15 minutes and the precipitate was filtered, to give the corresponding 5-[3-(*p*-*R*-phenylpyrazolylamino]methylene Meldrum's acid derivatives **2a-f**.

5-[3-Phenylpyrazolylamino]methylene Meldrum's Acid Derivative **2a**.

This compound was obtained *via* the general procedure as yellow crystals; $^{13}$C-nmr (dimethyl-$d_6$ sulfoxide, ppm): 27.4 (2, $CH_3$), 87.3 (=C(C=O)$_2$), 93.7 (C-4), 105.1 (C($CH_3$)$_2$), 152.8 (C-7), 163.7 (C=O), 164.6 (C=O); ms: (70 eV) m/z (%) 313 (14, $M^+$), 255 (35), 238 (41), 237 (100), 211 (43), 159 (41), 149 (95), 130 (41), 77 (46).

*Anal.* Calcd. for $C_{16}H_{15}N_3O_4$: C, 61.34; H, 4.83; N, 13.41. Found: C, 61.42; H, 4.78; N, 13.46.

5-[3-(*p*-Methylphenyl)pyrazolylamino]methylene Meldrum's Acid Derivative **2b**.

This compound was obtained according to general procedure as pale yellow crystals; $^{13}$C-nmr (dimethyl-$d_6$ sulfoxide, ppm): 21.7 (p-$CH_3$), 27.3 (2, $CH_3$), 87.2 (=C(C=O)$_2$), 93.2 (C-4), 105.1 (C($CH_3$)$_2$), 152.8 (C-7), 163.3 (C=O), 164.6 (C=O); ms: (70 eV) m/z (%) = 327 (5, M$^+$), 252 (19), 251 (88), 177 (25), 173 (67), 149 (100), 71 (33).

*Anal.* Calcd. for $C_{17}H_{17}N_3O_4$: C, 62.38; H, 5.23, N, 12.84. Found: C, 62.48; H, 5.26; N, 12.80.

5-[3-(*p*-Methoxyphenyl)pyrazolylamino]methylene Meldrum's Acid Derivative **2c**.

This compound was obtained according to general procedure as pale yellow crystals; $^{13}$C-nmr (dimethyl-$d_6$ sulfoxide, ppm): 27.3 (2, $CH_3$), 56.1 ($OCH_3$), 87.2 (=C(C=O)$_2$), 92.7 (C-4), 105.1 (C($CH_3$)$_2$), 152.8 (C-7), 163.7 (C=O), 164.6 (C=O); ms: (70 eV) m/z (%) = 343 (28, M$^+$), 268 (80), 267 (100), 252 (27), 241 (33), 213 (40), 198 (45), 160 (38), 134 (46), 89 (48), 77 (25).

*Anal.* Calcd. for $C_{17}H_{17}N_3O_5$: C, 59.47; H, 4.99; N, 12.24. Found: C, 59.53; H, 4.92; N, 12.19.

5-[3-(*p*-Chlorophenyl)pyrazolylamino]methylene Meldrum's Acid Derivative **2d**.

This compound was obtained according to general procedure as pale yellow crystals; $^{13}$C-nmr (dimethyl-$d_6$, ppm): 27.4 (2, $CH_3$), 87.3 (=C(C=O)$_2$), 94.0 (C-4), 105.1 (C($CH_3$)$_2$), 152.8 (C-7), 163.5 (C=O), 164.3 (C=O); ms: (70 eV) m/z (%) = 349/347 (2/6, M$^+$), 289 (12), 273 (31), 271 (100), 182 (19), 149 (85), 71 (23).

*Anal.* Calcd. for $C_{16}H_{14}N_3O_4Cl$: C, 55.26; H, 4.06; N, 12.08. Found: C, 55.20; H, 4.12; N, 12.02.

5-[3-(*p*-Bromophenyl)pyrazolylamino]methylene Meldrum's Acid Derivative **2e**.

This compound was obtained according to general procedure as yellow crystals. $^{13}$C-nmr (dimethyl-$d_6$ sulfoxide, ppm): 27.4 (2, $CH_3$), 87.4 (=C(C=O)$_2$), 94.1 (C-4), 105.1 (C($CH_3$)$_2$), 152.8 (C-7), 163.4 (C=O), 164.6 (C=O); ms: (70 eV) m/z (%) = 393/391 (3/3, M$^+$), 318 (17), 317 (72), 315 (89), 239 (42), 149 (100), 71 (72).

*Anal.* Calcd. for $C_{16}H_{14}N_3O_4Br$: C, 49.00; H, 3.60; N, 10.71. Found: C, 49.06; H, 3.68; N, 10.77.

5-[3-(*p*-Nitrophenyl)pyrazolylamino]methylene Meldrum's Acid Derivative **2f**.

This compound was obtained according to general procedure as yellow crystals. $^{13}$C-nmr (dimethyl-$d_6$ sulfoxide, ppm): 27.4 (2, $CH_3$), 87.5 (=C(C=O)$_2$), 94.8 (C-4), 105.1 (C($CH_3$)$_2$), 152.8 (C-7), 163.5 (C=O), 164.5 (C=O); ms: (70 eV) m/z (%) = 358 (2, M$^+$), 282 (28), 205 (24), 204 (100), 174 (86), 158 (46), 149 (62), 145 (67), 77 (45).

*Anal.* Calcd. for $C_{16}H_{14}N_4O_6$: C, 53.63; H, 3.94; N, 15.64. Found: C, 53.59; H, 3.98; N, 15.58.

Cyclization of 6-[2-R-3-$R_1$-3,4-Dihydro-4-oxopyrimidinyl-amino]methylene Meldrum's Acid Derivatives **2a-f**.

General Procedure.

Compounds **2a-f** (1 mmole) in nitrobenzene (20% w/w) was heated to reflux for 30 minutes. The cyclized products (**3a-f**) were isolated by cooling, followed by filtration, washing with ethanol, and drying.

2-Phenyl-4,7-dihydropyrazolo[2,3-*d*]pyrimidin-7-one **3a**.

This compound was obtained according to general procedure as white crystals; ms: (70 eV) m/z (%) = 211 (72, M$^+$), 177 (23), 154 (24), 149 (100), 97 (27), 71 (47).

*Anal.* Calcd. for $C_{12}H_9N_3O$: C, 68.24; H, 4.29; N, 19.89. Found: C, 68.29; H, 4.33; N, 19.82.

2-(*p*-Methylphenyl)-4,7-dihydropyrazolo[2,3-*d*]pyrimidin-7-one **3b**.

This compound was obtained according to general procedure as pale yellow crystals; ms: (70 eV) m/z (%) = 225 (100, M$^+$), 197 (25), 168 (22), 154 (38), 115 (66), 91 (18), 89 (21), 71 (15).

*Anal.* Calcd. for $C_{13}H_{11}N_3O$: C, 69.32; H, 4.92; N, 18.65. Found: C, 69.38; H, 4.95; N, 18.60.

2-(*p*-Methoxyphenyl)-4,7-dihydropyrazolo[2,3-*d*]pyrimidin-7-one **3c**.

This compound was obtained according to general procedure as pale yellow crystals; ms: (70 eV) m/z (%) = 241 (93, M$^+$), 198 (67), 149 (100), 77 (25), 71 (34).

*Anal.* Calcd. for $C_{13}H_{11}N_3O_2$: C, 64.72; H, 4.60; N, 17.42. Found: C, 64.78; H, 4.55; N, 17.47.

2-(*p*-Chlorophenyl)-4,7-dihydropyrazolo[2,3-*d*]pyrimidin-7-one **3d**.

This compound was obtained according to general procedure as pale yellow crystals; ms: (70 eV) m/z (%) = 247/245 (18/52, M$^+$), 177 (24), 154 (22), 149 (100), 97 (44), 71 (51).

*Anal.* Calcd. for $C_{12}H_8N_3OCl$: C, 58.67; H, 3.28; N, 17.10. Found: C, 58.75; H, 3.33; N, 17.18.

2-(*p*-Bromophenyl)-4,7-dihydropyrazolo[2,3-*d*]pyrimidin-7-one **3e**.

This compound was obtained according to general procedure as yellow crystals; ms: (70 eV) m/z (%) = 291/289 (50/48, M$^+$), 182 (17), 154 (33), 149 (100), 81 (34), 71 (42).

*Anal.* Calcd. for $C_{12}H_8N_3OBr$: C, 49.68; H, 2.78; N, 14.48. Found: C, 49.73; H, 2.81; N, 14.44.

2-(*p*-Nitrophenyl)-4,7-dihydropyrazolo[2,3-*d*]pyrimidin-7-one **3f**.

This compound was obtained according to general procedure as yellow crystals; ms: (70 eV) m/z (%) = 256 (10, M$^+$), 224 (18), 149 (100), 129 (29), 71 (33).

*Anal.* Calcd. for $C_{12}H_8N_4O_3$: C, 56.25; H, 3.15; N, 21.87. Found: C, 56.21; H, 3.10; N, 21.91.

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