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# 2-METHYLTHIO-4,5,6,7-TETRAHYDRO-1,2,4-TRIAZOLO[1,5-*a*]PYRIMIDIN-5- AND -7-ONES

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*The cyclocondensation of methylcinnamates and arylidene derivatives of Meldrum's acid with 3-amino-5-methylthio-1,2,4-triazole in DMF gives 2-methylthio-4,5,6,7-tetrahydro-1,2,4-triazolo[1,5-a]-pyrimidin-5-ones. The reaction involving arylidene derivatives of Meldrum's acid or its synthetic equivalents in ethyl acetate with a catalytic amount of pyridine gives a mixture of 2-methylthio-4,5,6,7-tetrahydro-1,2,4-triazolo[1,5-a]pyrimidin-5- and -7-ones.*

**Keywords:** 3-amino-5-methylthio-1,2,4-triazole, arylidene derivatives of Meldrum's acid, methylcinnamates, partially hydrogenated 1,2,4-triazolo[1,5-*a*]pyrimidinones, cyclocondensation.

The question of the regiodirection of the reaction occupies one of the key roles in a study of the cyclocondensation of α-aminoazoles with carbonyl 1,3-biselectrophiles [1-4]. Despite the large number of investigations of the direction of formation of condensed azoloazine systems they have not lost current interest because of the variety of both the conditions for carrying out similar reactions and of the reagents used.

In this work we have studied the reaction of 3-amino-5-methylthio-1,2,4-triazole (**1**) with the methylcinnamates **2a-c**, substituted benzaldehydes **3a-e**, and Meldrum's acid **4** and also the products of intermolecular condensation of the latter – the arylmethylene derivatives of Meldrum's acid **5a-e** and the Michael adducts **6a-e** in a variety of conditions.

We have found that refluxing amine **1** in DMF with an equimolar amount of the esters **2a-c** gives the 2-methylthio-4,5,6,7-tetrahydro-1,2,4-triazolo[1,5-*a*]pyrimidin-5-ones **7a-c**. Similar results were also obtained using as biselectrophiles the arylidene derivatives of Meldrum's acid **5a-e** and the adducts **6a-e** or their synthetic precursors (the benzaldehydes **3a-e** and Meldrum's acid **4**).

The IR spectra of compounds **7a-e** (Table 1) show bands typical of an amide $\nu_{N-H}$ fragment (3480-2750 $cm^{-1}$) and $\nu_{C=O}$ (1720-1708 $cm^{-1}$) and the $^1H$ NMR spectra show signals for the aryl protons, the NH group, and an ABX system for the protons of the –CH–$CH_2$– fragment in the pyrimidine ring (Table 2). The location of the NH group signals at low field (11.6-11.7 ppm) is typical for tetrahydroazolopyrimidinones which contain the NH–C=O fragment [5] and indicates that the direction of formation of the pyrimidine ring corresponds to acylation of the amino group in the azole molecule **1** and not of its endocyclic reaction center which would have given the isomers **8a-e**.

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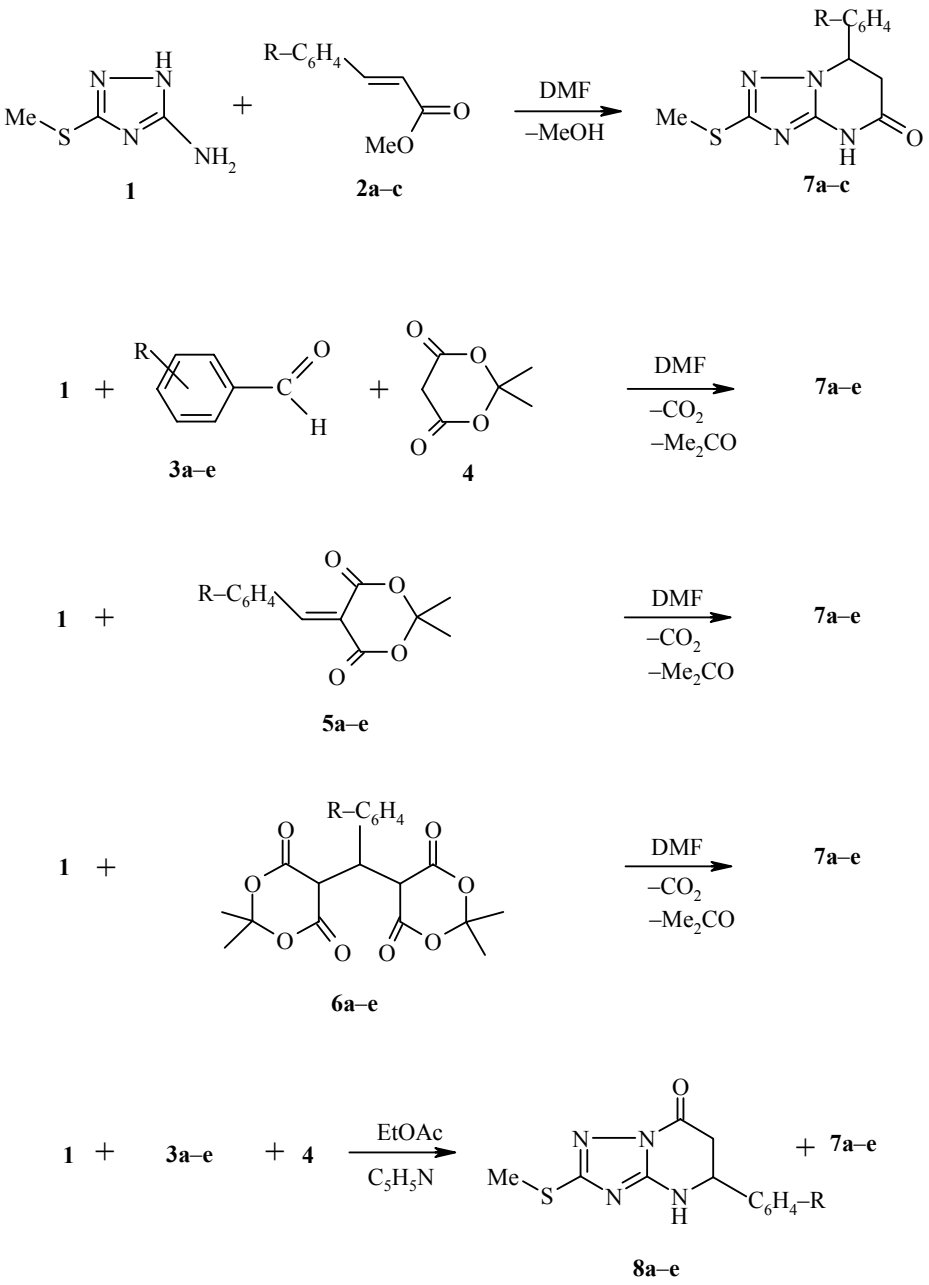


**2**, **3, 5–8** **a** R = H, **b** R = 4-OMe, **c** R = 4-Cl, **d** R = 2,4-$(Cl)_2$, **e** R = 4-$NO_2$

It is known that treatment of the amine **1** with ethoxymethylene derivatives of Meldrum's acid in an ethyl acetate–pyridine medium gives (1,2,4-triazol-3-ylamino)methylenedioxanediones which then cyclize to 6-carboxy-7-hydroxy-2-methylthio-1,2,4-triazolo[1,5-*a*]pyrimidines [6]. In similar conditions the reaction of the aminoazole **1** with benzaldehydes **3a-e** and Meldrum's acid **4** and also with the products of its intermolecular condensation **5a-e** and **6a-e** gave mixtures of the tetrahydro-1,2,4-triazolo[1,5-*a*]pyrimidin-5- and -7-ones. The ratio of the 5- and 7-oxo isomers **7a-e** and **8a-e** in the mixtures was measured using NMR. Separation was carried out by means of fractional crystallization from methanol or 2-propanol. Compounds **7a-e** were identical to those obtained in DMF medium. The composition and structure of the products **8a-e** were shown by means of elemental analysis and by spectroscopic methods.

TABLE 1. Characteristics for Compounds **7a-e** and **8a-e**

| Compound* | Empirical formula | Found N, % / Calculated N, % | mp, °C | IR spectrum (KBr), ν, $cm^{-1}$ | Yield, % (method) |
|---|---|---|---|---|---|
| **7a** | $C_{12}H_{12}N_4OS$ | 21.48 / 21.54 | 254-256 | 3400-2750, 1708, 1608, 1560 | 29 (A), 27 (B), 33 (C), 33 (D) |
| **7b** | $C_{13}H_{14}N_4O_2S$ | 19.28 / 19.31 | 272-274 | 3400-2800, 1712, 1608, 1556, 1516 | 34 (A), 32 (B), 34 (C), 28 (D) |
| **7c** | $C_{12}H_{11}ClN_4OS$ | 18.94 / 19.02 | 265-268 | 3400-2750, 1714, 1618, 1558 | 37 (A), 34 (B), 34 (C), 30 (D) |
| **7d** | $C_{12}H_{10}Cl_2N_4OS$ | 16.95 / 17.02 | 157-160 | 3400-2800, 1714, 1602, 1558 | 68 (B), 65 (C), 59 (D) |
| **7e** | $C_{12}H_{11}N_5O_3S$ | 22.91 / 22.95 | 214-217 | 3400-2750, 1720, 1604, 1520, 1348 | 36 (B), 40 (C), 35 (E) |
| **8a*** | $C_{12}H_{12}N_4OS$ | 21.46 / 21.54 | 179-182 | 3440-2800, 1740, 1620, 1540 | 42 |
| **8b** | $C_{13}H_{14}N_4O_2S$ | 19.27 / 19.31 | 208-210 | 3450-2900, 1744, 1640 | 30 |
| **8c** | $C_{12}H_{11}ClN_4OS$ | 19.04 / 19.02 | 212-215 | 3450-2900, 1744, 1640 | 63 |
| **8d** | $C_{12}H_{10}Cl_2N_4OS$ | 16.93 / 17.02 | 255-258 | 3480-2900, 1760, 1612 | 42 |
| **8e** | $C_{12}H_{11}N_5O_3S$ | 22.86 / 22.95 | 228-231 | 3360-2900, 1748, 1628, 1524, 1352 | 46 |

* Relative content of the 7-oxo isomers, %: **8a** = 75; **8b** = 83; **8c** = 92; **8d** = 66; **8e** = 91.

Compounds **8a-e** have the same nitrogen content as **7a-e** (see Table 1) but have different melting points and spectroscopic parameters. In the IR spectra of the triazolopyrimidinediones **8a-e** the $\nu_{C=O}$ band is shifted to 1760-1740 $cm^{-1}$. When compared with those of compounds **7a-e** the $^1H$ NMR NH group signal is shifted to higher field by 2.8-2.7 ppm and this points to a change in the mutual positioning of the NH and C=O groups. The nature of the splittings in the proton signals for the –CH–$CH_2$– fragment is also changed and corresponds to an $A_2X$ rather than ABX system (Table 2). On this basis the compounds **8a-e** are assigned the structures of 5-aryl-2-methylthio-4,5,6,7-tetrahydro-1,2,4-triazolo[1,5-*a*]pyrimidin-7-ones.

Hence the reaction of amine **1** with arylidene derivatives of Meldrum's acid **5a-e**, their synthetic equivalents **6a-e**, or precursors **3a-e** and **4** in DMF occurs selectively and gives exclusively the 5-oxo derivatives of tetrahydrotriazolo[1,5-*a*]pyrimidine. In ethyl acetate–pyridine medium a mixture of the 5- and 7-oxo derivatives is formed with the latter predominating. A similar dependence of the direction of formation of a pyrimidine ring on reaction conditions has previously been reported by us for the cyclocondensation of 3-amino-1,2,4-triazole and 2-aminobenzimidazole with Meldrum's acid derivatives [7, 8]. However, the formation of a mixture of isomeric azolopyrimidinones has not been reported in any of the previously reported cases [7, 8].

TABLE 2. $^{1}$H NMR Spectra of Compounds **7a-e** and **8a-e**

| Compound | Chemical shift, δ, ppm (spin-spin coupling constants, *J*, Hz)* | | | | |
|---|---|---|---|---|---|
| | NH (1H, br. s) | $H_{Ar}$ | CH ($H_X$) | $CH_2$ ($H_A$, $H_B$) | $CH_3$ (3H, s) |
| **7a** | 11.7 | 7.1-7.3 (5H, m) | 5.67 (1H, t, $J$ = 4.8) | 2.86 (1H, dd, $J_{AB}$ = -16.8); 3.45 (1H, dd) | 2.45 |
| **7b** | 11.6 | 6.9-7.1 (4H, dd, $J$ = 8.8) | 5.58 (1H, t, $J$ = 4.4) | 2.88 (1H, dd, $J_{AB}$ = -16.0); 3.31 (1H, dd) | 2.45, 3.70 ($OCH_3$) |
| **7c** | 11.5 | 7.1-7.2 (4H, m) | 5.67 (1H, dd, $J_{AX}$ = 7.0, $J_{BX}$ = 5.8) | 2.84 (1H, dd, $J_{AB}$ = -16.0); 3.34 (1H, dd) | 2.43 |
| **7d** | 11.7 | 6.9-7.5 (3H, m) | 5.89 (1H, dd, $J_{AX}$ = 7.4, $J_{BX}$ = 6.0) | 2.86 (1H, dd, $J_{AB}$ = -16.6); 3.38 (1H, dd) | 2.45 |
| **7e** | 11.7 | 7.4-8.2 (4H, dd, $J$ = 8.6) | 5.83 (1H, dd, $J_{AX}$ = 7.0, $J_{BX}$ = 5.6) | 2.96 (1H, dd, $J_{AB}$ = -16.7); 3.40 (1H, dd) | —*[2] |
| **8a** | 8.9 | 7.3-7.6 (5H, m) | 4.99 (1H, t, $J$ = 7.8) | 3.04 (2H, d, $J_{A2}$ = -16.2) | 2.42 |
| **8b** | 8.8 | 7.0-7.3 (4H, dd, $J$ = 8.4) | 4.92 (1H, t, $J$ = 7.6) | 2.97 (2H, d, $J_{A2}$ = -14.4) | 2.43, 3.74 ($OCH_3$) |
| **8c** | 8.9 | 7.3-7.4 (4H, m) | 5.00 (1H, t, $J$ = 7.4) | 3.03 (2H, m) | 2.38 |
| **8d** | 8.8 | 7.4-7.7 (3H, m) | 5.34 (1H, t, 7.8) | 2.99 (2H, d, $J_{A2}$ = -14.2) | 2.42 |
| **8e** | 9.0 | 7.7-8.3 (4H, dd, $J$ = 8.8) | 5.18 (1H, t, $J$ = 7.6) | 3.07 (2H, d. $J_{A2}$ = -15.4) | 2.44 |

* $^{1}$H NMR spectra recorded in DMSO-$d_6$.

*[2] Obscured by DMSO signals.

## EXPERIMENTAL

IR spectra were recorded on a Specord M-82 spectrometer and $^1$H NMR spectra on a Varian-200 (200 MHz) instrument for solutions in DMSO-$d_6$ and using TMS as internal standard. Monitoring of the composition of the reaction mixtures and the purity of the compounds obtained was carried out using TLC on Silufol UV-254 plates with chloroform–methanol–dioxane (3:3:4) as eluent.

**2-Methylthio-7-phenyl-4,5,6,7-tetrahydro-1,2,4-triazolo[1,5-*a*]pyrimidin-5-one (7a).** A. A solution of the amine **1** (0.26 g, 2 mmol) and methyl cinnamate **2a** (0.32 g, 2 mmol) in DMF (1 ml) was refluxed for 5 h, cooled, mixed with 2-propanol (5 ml), and filtered to give compound **7a** (0.15 g).

Compounds **7b,c** were prepared similarly from amine **1** and the corresponding esters **2b,c**.

B. A mixture of amine **1** (0.26 g, 2 mmol), benzaldehyde **3a** (0.21 g, 2 mmol), and 2,2-dimethyl-1,3-dioxane-4,6-dione **4** (0.29 g, 2 mmol) in DMF (0.5 ml) was refluxed for 20-25 min and cooled. 2-Propanol (5-7 ml) was added and the product was filtered to give compound **7a** (0.14 g).

Compounds **7b-e** were prepared similarly.

C. A mixture of amine **1** (0.26 g, 2 mmol) and the arylidene derivative **5a** (0.46 g, 2 mmol) in DMF (0.5 ml) was refluxed for 20 min and cooled. 2-Propanol (5-7 ml) was added and the product was filtered to give compound **7a** (0.17 g).

Compounds **7b-e** were prepared similarly.

D. A mixture of amine **1** (0.26 g, 2 mmol) and the Michael adduct **6a** [9] (0.76 g, 2 mmol) in DMF (1 ml) was refluxed for 15-20 min. 2-Propanol (10-12 ml) was added and the product was filtered to give compound **7a** (0.17 g).

Compounds **7b-e** were prepared similarly.

**Cyclocondensation of Amine 1 with Benzaldehydes and Compound 4 in Ethyl Acetate–Pyridine.** A solution of compound **4** (0.43 g, 3 mmol) and the benzaldehyde **3a** (0.318 g, 3 mmol) in ethyl acetate (1.5 ml) in the presence of catalytic amounts of pyridine was stirred at room temperature for 2 h. Amine **1** (0.39 g, 3 mmol) was added and the product was refluxed for 30 min. After cooling, the precipitate formed was filtered to give a mixture of 2-methylthio-5-phenyl-4,5,6,7-tetrahydro-1,2,4-triazolo[1,5-*a*]pyrimidin-7-one **8a** and 2-methylthio-7-phenyl-4,5,6,7-tetrahydro-1,2,4-triazolo[1,5-*a*]pyrimidin-5-one **7a** in the ratio 3:1 (according to $^1$H NMR data). TLC: **8a** $R_f$ = 0.28, **7a** $R_f$ = 0.21. The mixture was separated by repeated crystallization from methanol.

Compounds **8b-e** were prepared similarly.

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