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# Anomalous Cyclization of Ethyl Acetoacetate (3,6-Dimethyl-4-oxo-3,4-dihydropyrimidin-2-yl)hydrazone

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**Abstract** — Structural modification of some (pyrimidin-2-yl)hydrazones derived from ethyl acetoacetate via methylation at the $N^3$ atom promotes anomalous cyclization to give [1,2,4]triazolo[1,5-*a*]pyrimidine derivatives. The mechanism of this transformation includes specific cleavage of the aliphatic fragment in the substrate with subsequent rearrangement of carbene-like intermediate.
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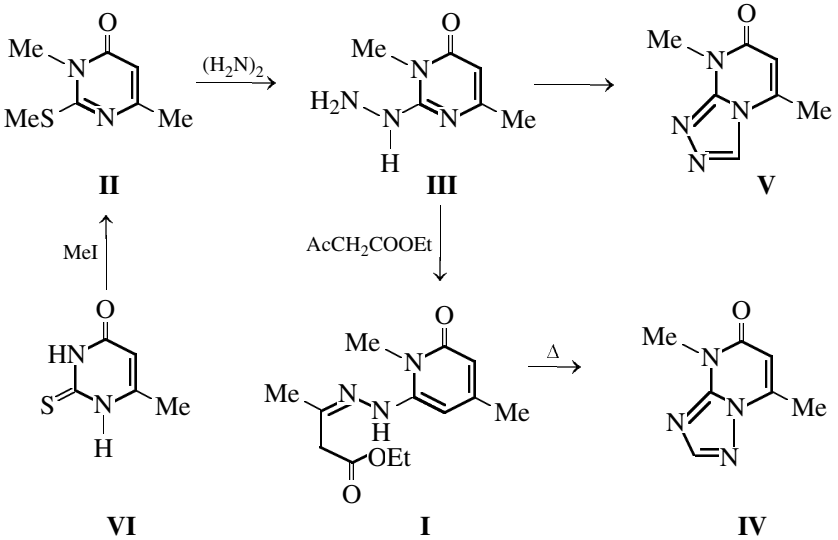
Cyclization of (pyrimidin-2-yl)hydrazones derived from ethyl alkanoylacetates is known to produce 1-(pyrimidin-2-yl)-3-alkylpyrazol-5(4*H*)-ones which are used in the synthesis of physiologically active substances [1, 2] and dyes [3, 4]. The cyclizations of ethyl 3-[(pyrimidin-2-yl)hydrazono]butanoates with removal of ethanol by azeotropic distillation [5] and via base-catalyzed ester cleavage [6] were studied most thoroughly.

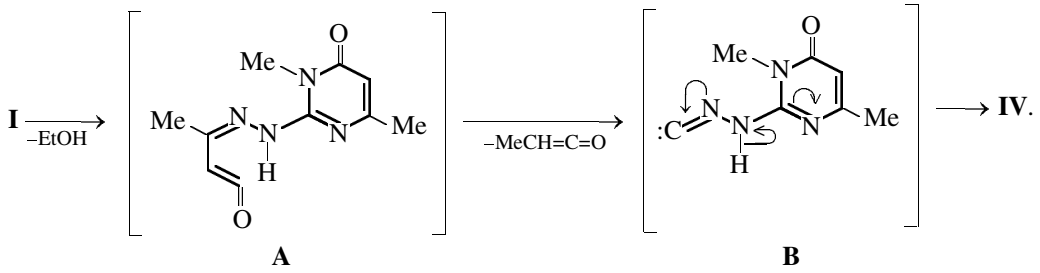
In the present work we studied the cyclization of ethyl acetoacetate (3,6-dimethyl-4-oxo-3,4-dihydropyrimidin2-yl)hydrazone (**I**) under various conditions. Initial compound **I** was prepared by treatment of 3,6-dimethyl-2-methylsulfanylpyrimidin-4(3*H*)-one (**II**) with excess hydrazine hydrate without solvent, followed by condensation of 2-hydrazino-3,6-dimethylpyrimidin-4(3*H*)-one (**III**) thus formed with ethyl acetoacetate in acetic acid. Intermediate hydrazine **III** was identified as the corresponding benzylidene derivative.

Unlike ethyl 3-[2-(6-methyl-4-oxo-3,4-dihydropyrimidin-2-yl)hydrazono]butanoate [5, 6], compound **I** remained unchanged after heating for a long time in toluene, while heating of **I** in ethanol in the presence of potassium hydroxide lead to the formation of tarry products. No pyrazole ring closure was observed even when hydrazone **I** was heated at 170–190°C: under these severe conditions, it underwent unusual cyclization to 4,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-5(4*H*)-one (**IV**). The formation and configuration of bicyclic product **IV** are confirmed by the presence of a signal at 9.35 ppm in the $^1$H NMR spectrum due



to proton in the fused triazole ring and of a characteristic [7] absorption band with its maximum at λ 267 nm (log ε 4.04) in the UV spectrum.

Taking into account the data reported in [8] on the thermolysis of methyl acetoacetate, we presumed that the mechanism of the observed transformation of compound **I** involves specific cleavage of the aliphatic fragment therein with liberation of ethanol (*M* 46) and generation of unstable ketene **A**; elimination of methylketene (*M* 56) from the latter gives bicyclic product **IV** through carbene intermediate **B**.

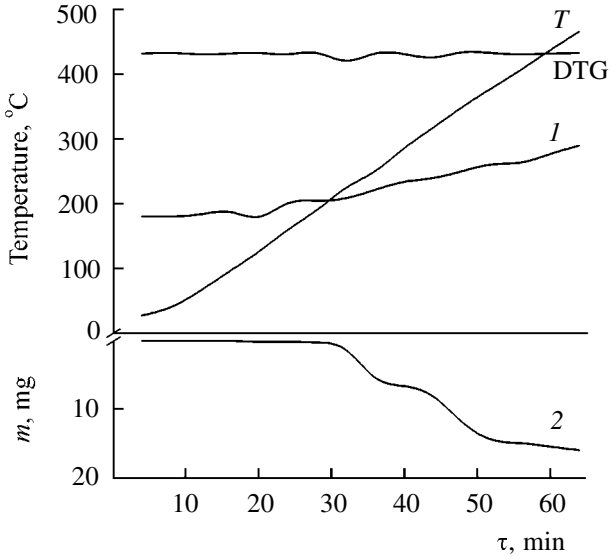



In fact, thermogravimetric analysis of hydrazone **I** showed that irreversible process at 170–190°C (see figure, curve *1*) is accompanied by weight loss by 39% (curve *2*), which is equivalent to elimination from molecule **I** of a fragment with an overall weight of 102 a.m.u. (see figure).

Elimination of methylketene from intermediate butenone **A** gives electron-deficient carbene **B** which is capable of being stabilized via cyclization to 5,8-dimethyl[1,2,4]triazolo[4,3-*a*]pyrimidin-7(8*H*)-one (**V**) or bicyclic compound **IV** with preliminary electron density redistribution and cleavage of the N–N bond. The first path can be ruled out, for no compound **V** was detected among the thermolysis products of hydrazone **I** (thermal isomerization of **V** into **IV** does not occur). When compound **V** was heated for 6 h at 170–190°C, its spectral parameters (the chemical shift of the 3-H proton at δ 8.8 ppm in the $^1$H NMR spectrum and the position of the absorption maximum at λ 249 nm in the UV spectrum [7]) did not change.

Triazolopyrimidine **V** was synthesized by condensation of hydrazine **III** with triethyl orthoformate (method *a*) under the conditions similar to those reported in [9]. This reaction gives mainly compound **V** rather than isomeric products **IV**; according to the $^1$H NMR data, the fraction of the latter in the reaction mixture does not exceed 10%. An analogous regioselectivity is inherent to reactions of hydrazine **III** with other synthetic equivalents of onecarbon fragments, such as formic acid (method *b*) and ethyl formate (method *c*).

Stabilization of carbene **B** via cyclization to the triazolo[1.5-*a*]pyrimidine system (compound **IV**) is likely to be favored by the absence of the reversible solvation effect. Assuming that the dehydration product of 3,6-dimethyl-2-(2-formylhydrazino)pyrimidin-4(3*H*)-one formed initially from hydrazine **III** and formic acid [10] is structurally similar to carbene **B**, we tried to synthesize compound **IV** by reaction of the above reagents in an inert solvent (toluene) with simultaneous removal of the liberated water by azeotropic distillation. Unlike method *b*, this procedure ensured increased concentration of isomer **IV** in the reaction mixture (by a factor of 15), but the conversion of initial hydrazine **III** was low (no more than 25%). Furthermore, we failed to separate the resulting mixture of triazolopyrimidines **IV** and **V** by fractional




Derivatogram of ethyl 3-[2-(3,6-dimethyl-4-oxo-3,4-dihydropyrimidin-2-yl)hydrazono]butanoate (**I**); the *T* and DTG curves show, respectively, change of the sample temperature with time and temperature difference between the sample and reference.

crystallization or thin-layer chromatography (both isomers have similar $R_f$ values in suitable eluent systems).

## EXPERIMENTAL

The $^1$H NMR spectra were recorded on a Bruker WM-400 spectrometer at 400.13 MHz using DMSO-$d_6$ as solvent; the chemical shifts were measured relative to the residual proton signal of the solvent. The UV spectrum was obtained on an SF-26 spectrophotometer from solutions in dilute hydrochloric acid (pH ~1, $c = 2.5 \times 10^{-5}$ M); molar absorption coefficient of 5,8-dimethyl[1,2,4]triazolo[4,3-*a*]pyrimidin-7(8*H*)-one (**V**) is not given because of its limited stability. The purity of the products was checked by TLC on Silufol UV-254 plates using the following solvent systems as eluent: acetone–hexane, 2 : 1 (A); butan-1-ol–acetic acid–water, 1 : 1 : 1 (B), acetone–hexane, 2 : 1, plus 2 drops of pyridine (C); propan-2-ol–3% aqueous ammonium chloride, 5 : 1 (D). Spots were visualized under UV light. The elemental compositions were determined on Hewlett–Packard B-185 and Leco CHNS-932 analyzers. Thermogravimetric analysis was performed on a Paulik–Paulik–Erdey derivatograph (temperature range 25 to 500°C, heating rate 5 deg min$^{-1}$, sample weight 20.2 mg). The solvents used were purified and dehydrated by standard procedures [11].

**Ethyl 3-[2-(3,6-Dimethyl-4-oxo-3,4-dihydropyrimidin-2-yl)hydrazono]butanoate (I).** A mixture of 0.50 g of hydrazine **III** and 0.46 g of ethyl acetoacetate in 10 ml of acetic acid was heated for 1 h at 100°C. The mixture was cooled and filtered, and the filtrate was evaporated under reduced pressure. The residue was treated with 10 ml of boiling benzene, the mixture was cooled, the undissolved material was filtered off, and the filtrate was evaporated to dryness. The residue was ground with diethyl ether to make it crystalline, and the precipitate was filtered off, washed with diethyl ether, and dried under reduced pressure. Yield 0.43 g (50%), mp 107°C, $R_f$ 0.62 (A). $^1$H NMR spectrum, δ, ppm: 1.22 m (3H, $OCH_2$*Me*), 2.08 m (6H, Me), 3.12 d and 3.18 d (3H, MeN), 3.37 d and 3.46 d (2H, $CH_2$), 4.09 m (2H, $OCH_2$Me), 5.20 s (1H, CH), 9.83 d and 9.90 d (1H, NH). Found, %: C 53.23; H 6.58; N 20.99. $C_{12}H_{18}N_4O_3$. Calculated, %: C 54.12; H 6.81; N 21.04.

**3,6-Dimethyl-2-methylsulfanylpyrimidin-4-(3*H*)-one (II)** was synthesized by exhaustive methylation of 6-methyl-2-thiouracil (**VI**) with methyl iodide according to the procedure described in [12].

**2-Hydrazino-3,6-dimethylpyrimidin-4(3*H*)-one (III).** A mixture of 3.06 g of compound **II** and 2.03 g of 85% hydrazine hydrate was heated for 1 h at 100°C. The mixture solidified and was twice recrystallized from ethanol; the product was dried under reduced pressure over phosphoric anhydride. Yield 1.04 g (38%), mp 198°C; published data: mp 198°C [9], 201–203°C [13]; $R_f$ 0.32 (B).

**2-(2-Benzylidenehydrazino)-3,6-dimethylpyrimidin-4(3*H*)-one** was synthesized from 0.50 g of hydrazine **III** and 0.34 g of benzaldehyde. Yield 0.38 g (48%), mp 204°C (from ethanol); published data [14]: mp 202–203°C ; $R_f$ 0.33 (A). $^1$H NMR spectrum, δ, ppm: 2.22 s (3H, Me), 3.24 s (3H, MeN), 5.27 s (1H, CH), 7.84 m (6H, $C_6H_5$, NH), 10.02 s (1H, CH=N).

**4,7-Dimethyl[1,2,4]triazolo[1,5-*a*]pyrimidin-5(4*H*)-one (IV).** Hydrazone **I**, 1.00 g, was heated at 170–190°C until gaseous products no longer evolved. The residue solidified and was recrystallized from DMF, washed with diethyl ether, and dried under reduced pressure. Yield 0.25 g (41%), mp >300°C (decomp.), $R_f$ 0.59 (B), 0.33 (C), 0.48 (D). $^1$H NMR spectrum, δ, ppm: 2.14 s (3H, Me), 3.23 s (3H, MeN), 5.18 s (1H, CH), 9.35 s (1H, CH). Found, %: C 51.27; H 5.34; N 30.29. $C_7H_8N_4O$. Calculated, %: C 51.21; H 4.91; N 34.13.

**5,8-Dimethyl[1,2,4]triazolo[4,3-*a*]pyrimidin-7(8*H*)-one (V).** *a*. A mixture of 0.50 g of hydrazine **III** and 3 ml of triethyl orthoformate was heated for 3 h at 140°C. The precipitate was filtered off, recrystallized twice from DMF, washed with diethyl ether, and dried under reduced pressure. Yield 0.36 g (64%), mp >295°C (decomp.), $R_f$ 0.59 (B), 0.33 (C), 0.48 (D). $^1$H NMR spectrum, δ, ppm: 2.49 s (3H, Me), 3.48 s (3H, MeN), 6.05 s (1H, CH), 8.82 s (1H, CH). UV spectrum: $\lambda_{max}$ 249 nm. Found, %: C 51.36; H 5.10; N 34.07. $C_7H_8N_4O$. Calculated, %: C 51.21; H 4.91; N 34.13.

*b*. A mixture of 0.50 g of hydrazine **III** and 5 ml of 85% formic acid was heated for 8 h under reflux. Excess formic acid was distilled off under reduced pressure (to dryness), and the residue was recrystallized twice from DMF, washed with diethyl ether, and dried under reduced pressure. Yield 0.28 g (52%).

*c*. A mixture of 0.25 g of hydrazine **III** and 15 ml of ethyl formate was heated for 10 h under reflux. The precipitate was filtered off, recrystallized twice from DMF, washed with diethyl ether, and dried under reduced pressure. Yield 0.14 g (52%).

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## REFERENCES

1. Jpn. Patent Appl. no. 74–43 985, 1974; *Chem. Abstr.,* 1974, vol. 81, no. P 49 699 w.
2. Jpn. Patent Appl. no. 76–16 681, 1976; *Chem. Abstr.,* 1976, vol. 82, no. P 123 961 b.
3. Jpn. Patent Appl. no. 80–155 055, 1980; *Chem. Abstr.,* 1981, vol. 94, no. P 176 695 k.
4. Roum. Patent no. 114 797, 1999; *Chem. Abstr.,* 2001, vol. 134, no. P 238 866 x.
5. Spasov, A.W., Golovinsky, E.V., and Russev, G.C., *Z. Chem.,* 1968, vol. 8, no. 11, p. 421.
6. Cristea, I. and Farcasan, V., *Rev. Chim.,* 1987, vol. 38, no. 8, p. 674.
7. Hill, M.A., Reynolds, G.A., Tinker, J.F., and Van Allan, J.A., *J. Org. Chem.,* 1961, vol. 26, no. 10, p. 3834; Beckett, A.H., Spickett, R.G.W., and Wright, S.H.B., *Tetrahedron,* 1968, vol. 24, no. 7, p. 2839.
8. Den Tonkelaar, W.A.M., Louw, R., and Kooyman, E.C., *Recl. Trav. Chim. Pays–Bas,* 1968, vol. 87, no. 11, p. 1281.
9. Allen, C.F.H., Reynolds, G.A., Tinker, J.F., and Williams, L.A., *J. Org. Chem.,* 1960, vol. 25, no. 3, p. 361.
10. Gizatullina, E.M. and Kartsev, V.G., *Khim. Geterotsikl. Soedin.,* 1993, no. 12, p. 1587.
11. Gordon, A.J. and Ford, R.A., *The Chemist's Companion,* New York: Wiley, 1972.
12. Wheeler, H.L. and McFarland, D.F., *Am. Chem. J.,* 1909, vol. 42, no. 2, p. 101.
13. Vanderhaeghe, H. and Claesen, M., *Bull. Soc. Chim. Belg.,* 1959, vol. 68, no. 3, p. 30.
14. Spickett, R.G.W. and Wright, S.H.B., *J. Chem. Soc. C,* 1967, no. 6, p. 498.