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AN EXAMPLE OF A DOMINO REACTION IN THE SYNTHESIS OF PYRAZOLO[1,5-*a*]PYRIMIDINE DERIVATIVE

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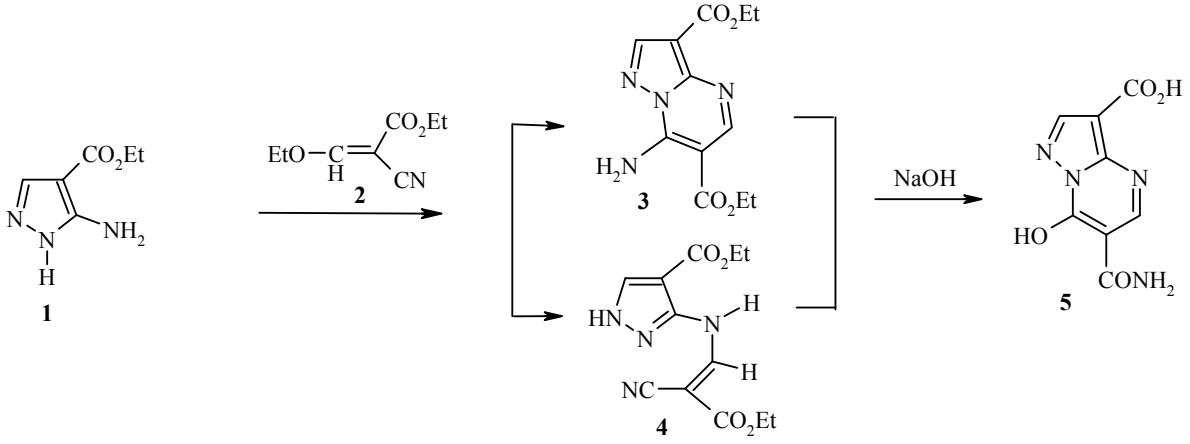
Condensation of ethyl 3-aminopyrazole-4-carboxylate (**1**) with ethyl ethoxymethylenecyanoacetate (**2**) was carried out with the aim of preparing diethyl 7-aminopyrazolo[1,5-*a*]pyrimidine-3,6-dicarboxylate (**3**) and subsequent study of its C–C recyclization [1] to the isomeric 6-carbamoyl-7-hydroxypyrazolopyrimidine but the reaction did not go to completion. From ^{1}H NMR spectra (including experiments using the NOESY method) it was clear that a mixture of compounds including both the cyclization product **3** and the uncyclized condensation adduct ethyl 3-[(2-cyano-3-ethoxy-3-oxoprop-1-en-1-yl)amino]-1H-pyrazole-4-carboxylate (**4**) had been obtained. However, in basic medium both the condensed pyrazolopyrimidine **3** and the cyano derivative **4** were readily converted in high yield to the 6-carbamoyl-7-hydroxypyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (**5**).



Bearing in mind that the starting 3-aminopyrazole **1** is synthesized by reaction of hydrazine with the same ethoxymethylenecyanoacetate ester **2** [2] we believed that compound **5** could be prepared directly by

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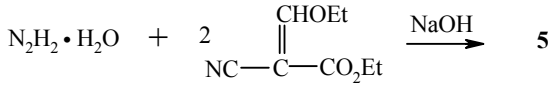
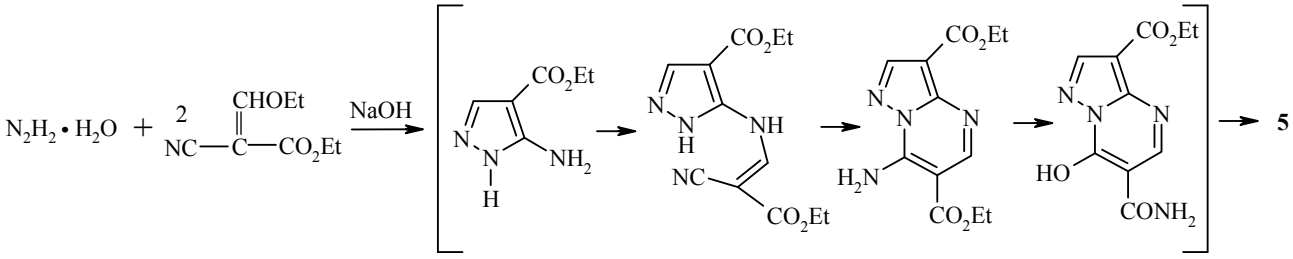
condensation of an excess of the ethoxymethylenecyanoacetate with hydrazine. We were able to achieve this unusual reaction to yield the previously stated compound **5** by refluxing the reagents with alkali.



It should be noted that the intermediates, in fact pyrazole **1**, the noncyclized adduct **4**, the 7-amino-pyrazolo[1,5-*a*]pyrimidine **3**, and 6-carbamoyl-3-ethoxycarbonyl-7-hydroxypyrazolopyrimidine formed due to C–C recyclization of pyrazolopyrimidine **3** [3] were also individually separated and characterized in the intermediate steps of the reaction or with less prolonged refluxing.

The realization of this chain of transformations leads us to assign it as a "domino" process of consecutive reactions [4-6].

The overall scheme of the reactions is presented below.



IR spectra were recorded on a UR-20 instrument. ^{1}H NMR spectra were taken on a Varian Mercury 300 (300 MHz) spectrometer using DMSO-d_6 and with TMS as internal standard. Mass spectra were obtained on an MK-1321 spectrometer with direct introduction into the ion source (EI, 70 eV).

6-Carbamoyl-7-hydroxypyrazolo[1,5-*a*]pyrimidine-3-carboxylic Acid (5). A mixture of 60% hydrazine hydrate solution (4.1 g, 5 mmol), ethyl ethoxymethylenecyanoacetate (2.1 g, 12.5 mmol) and sodium hydroxide (0.8 g, 20 mmol) was refluxed in ethanol (30 ml) for 18-20 h. The ethanol was evaporated and the residue was dissolved in water and acidified using dilute hydrochloric acid to pH 6. The precipitate formed was filtered off, washed with hexane, and dried. Yield of compound **5** 0.7 g (63%) with mp 265-267ºC and R_f 0.2 (acetone, Silufol UV-254). IR spectrum (vaseline oil), ν, cm^{-1}: 1515, 1560, 1620 (C=N), 1650 ($CONH_2$); 1680 (COOH), 3060-3180 ($CONH_2$), 3235 (OH). ^{1}H NMR spectrum, δ, ppm: 8.41 (1H, s, H-2); 8.67 (1H, br. s, NH); 8.76 (1H, br. s, NH); 8.78 (1H, s, H-5); 10.5-12.0 (1H, br. s, COOH). Mass spectrum, *m/z* (I_{rel}, %): 222 $[M]^+$ (21), 179 $[M^+-CONH]$ (89), 178 $[M^+-CO_2]$ (10), 161 (37), 135 (56), 94 (25), 53 (13), 52 (21), 44 (100). Found, %: C 43.53; H 2.99; N 25.05. $C_8H_6N_4O_4$. Calculated, %: C 43.25; H 2.71; N 25.23.

REFERENCES

1. R. S. Vardanyan, V. J. Hruby, G. G. Danagulyan, and A. D. Mkrtchyan, *J. Heterocycl. Chem.*, **42**, 557 (2005).
2. P. Schmidt and J. Druey, *Helv. Chim. Acta*, **39**, 986 (1956).
3. G. G. Danagulyan, A. D. Mkrtchyan, and G. A. Panosyan, *Khim. Geterotsikl. Soedin.*, 569 (2005). [*Chem. Heterocycl. Comp.*, **41**, 485 (2005)].
4. L. Tietze, *Chem. Rev.*, **96**, 115 (1996).
5. K. C. Nicolaou, D. J. Edmonds, and P. G. Bulger, *Angew. Chem., Int. Ed.*, **45**, 7134 (2006).
6. A. P. Kadina, M. S. Novikov, A. F. Khlebnikov, and I. Magull, *Khim. Geterotsikl. Soedin.*, 730 (2008). [*Chem. Heterocycl. Comp.*, **44**, 576 (2008)].