Studies on uracils: synthesis of novel pyrido[2,3-d]pyrimidine oxides via ring transformation of isoxazolo[3,4-d]pyrimidine

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Abstract—The reaction of isoxazolo[3,4-d]pyrimidine 1 and cyanoolefins 2 in the presence of triethylamine (Et₃N) as a catalyst afforded an unprecedented one-pot synthesis of biologically important pyrido[2,3-d]pyrimidine oxides 3 in excellent yields. © 2003 Elsevier Science Ltd. All rights reserved.

The importance of uracil and its annelated derivatives is well recognised by synthetic¹ as well as biological² chemists. Organic N-oxides are an important class of compounds that possess a wide range of biological activities.³ Readily available cyanoolefins are versatile reagents having diverse uses in organic synthesis.⁴ Utilizing these organic synthons, we studied their reactivity with 6-amino and 6-hydrazino uracils⁵ which involved electrophilic attack of the cyanoolefins on the amino and hydrazino uracils leading to the formation of pyrido[3,4-d]pyrimidines and pyrazolo[2,3-d]pyrimidines, respectively. In continuation of our studies on uracils⁶ we describe in this communication the results of reactions between isoxazolo[3,4-d]pyrimidine and cyanoolefins in the presence of triethylamine as a catalyst which affords an unprecedented one-pot synthesis of pyrido[2,3-d]pyrimidine oxides of biological importance in excellent yields (Scheme 1).

In our reaction, equimolar amounts of isoxazolo[3,4-d]pyrimidine 1 (0.175 g, 1 mmol) and cyanoolefin 2a (0.154 g, 1 mmol) in the presence of a catalytic amount of Et₃N (0.01 g) were refluxed in ethanol for 1 h. The solvent was removed under reduced pressure. The residue was chromatographed over silica gel using chloroform–ethyl acetate (50:50) as eluent. An 80% yield of the product (0.197 g) was obtained and identified as 6-cyano-7-amino pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione-8-oxide 3a from spectroscopic data and elemental analysis. Its IR spectrum exhibited sharp bands

Scheme 1.

Keywords: uracil; cyanoolefins; pyrido[2,3-d]pyrimidines.

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at 3250 cm$^{-1}$ (NH$_2$), 2220 (CN) and at 1625 (N=O$^-$).

The $^1$H NMR spectrum showed singlets at $\delta$ 8.20 for the aromatic protons. Similarly compound 1 was reacted with 2b–c. When substituted cyanoolefins 2b–c (R$^1$=p-CH$_3$OC$_6$H$_4$, p-ClC$_6$H$_4$) were employed, the same product 3a was obtained. The corresponding aldehydes 4 were detected (by TLC) as byproducts in the reaction mixtures. The reaction was generalised by reacting the isoxazolo[3,4-d]pyrimidine 1 with a number of $\alpha$-cyanocinamates 2d–f and $\alpha$-cyanocinamides 2g–h under identical conditions. As expected the same product 3b was obtained from the reaction of the substituted cinamates 2d–f with 1. The aldehydes 4 eliminated were detected in each case. Similarly the $\alpha$-cyanocinamides 2g–h gave the same product 3c when reacted with 1.

A possible mechanism of the reaction is outlined in Scheme 2. The reaction occurs via initial keteneimine formation from the cyanoolefin in the presence of triethylamine. The keteneimine undergoes [4+2] cycloaddition with the isoxazolo[3,4-d]pyrimidine to give the adduct [A]. This is then attacked by ethanol and water molecules resulting in the rupture of the C–O bond to give the hydroxy intermediate [B], which eliminates an arylaldehyde and rearranges to afford the product 3.

Further study of this effective reaction is in progress. In conclusion, our results have demonstrated a very simple and effective ring transformation process leading to an important class of annulated uracils of biological significance.

References


4. For reviews and synthetic development, see: (a) Campeigne, E.; Schneller, S. W. Synthesis 1976, 705; (b) Freeman, F. Chem. Rev. 1980, 80, 324; (c) Freeman, F. Synthesis 1981, 925.


7. (a) Compound 3a. (C_{10}H_{12}N_{5}O_{3}) mp 218°C. 1H NMR 90 MHz (CDCl₃+TFA) δ 3.30 (s, 3H), 3.48 (s, 3H), 8.20 (s, 1H). IR 3250, 2200, 1700, 1625 cm⁻¹. MS 247 M⁺. CHN analyses calcd: C, 48.58; H, 3.64; N, 28.34; found: C, 48.45; H, 3.61; N, 28.23%. (b) Compound 3b. (C_{11}H_{13}N_{4}O_{5}) mp 205°C. 1H NMR 90 MHz (CDCl₃+TFA) δ 1.41 (t, 3H), 3.35 (s, 3H), 3.66 (s, 3H), 4.3 (q, 2H), 8.10 (s, 1H). IR 3250, 1710, 1695, 1620 cm⁻¹. MS 294 M⁺. CHN analyses calcd: C, 48.98; H, 4.76; N, 19.05; found: C, 48.79; H, 4.72; N, 18.75%. (c) Compound 3c. (C_{10}H_{11}N_{5}O_{4}) mp 212°C. 1H NMR 90 MHz (CDCl₃+TFA) δ 3.10 (s, 3H), 3.44 (s, 3H), 8.00 (s, 1H). IR 3250, 1700, 1675, 1615 cm⁻¹. MS 265 M⁺. CHN analyses calcd: C, 45.28; H, 4.15; N, 26.41; found: C, 45.12; H, 4.11; N, 26.20%.