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# 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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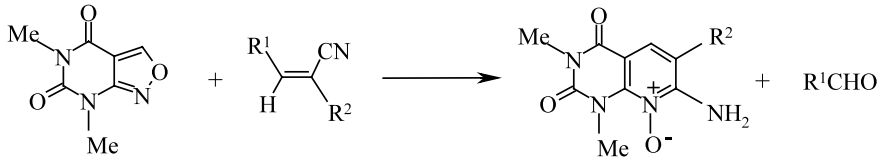
**Abstract**—The reaction of isoxazolo[3,4-*d*]pyrimidine **1** and cyanoolefins **2** in the presence of triethylamine ($Et_3N$) as a catalyst afforded an unprecedented one-pot synthesis of biologically important pyrido[2,3-*d*]pyrimidine oxides **3** in excellent yields. 

The importance of uracil and its annelated derivatives is well recognised by synthetic[1] as well as biological[2] 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 uracils[5] 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 uracils[6] 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 $Et_3N$ (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-aminopyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione-8-oxide **3a**[7a] from spectroscopic data and elemental analysis. Its IR spectrum exhibited sharp bands



**1** + **2a** $R^1 = C_6H_5$-, $R^2$ = CN; **b** $R^1 = CH_3OC_6H_4$-, $R^2$ = CN; **c** $R^1$ = *p*-Cl-$C_6H_4$-, $R^2$ = CN; **d** $R^1 = C_6H_5$-, $R^2 = COOC_2H_5$; **e** $R^1 = CH_3OC_6H_4$, $R^2 = COOC_2H_5$; **f** $R^1$ = *p*-Cl-$C_6H_4$, $R^2 = COOC_2H_5$; **g** $R^1 = C_6H_4$, $R^2 = CONH_2$; **h** $R^1 = CH_3OC_6H_4$, $R^2 = CONH_2$ → **3a** $R^2$ = CN; **b** $R^2 = COOC_2H_5$; **c** $R^2 = CONH_2$ + **4** $R^1CHO$

**Scheme 1.**

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

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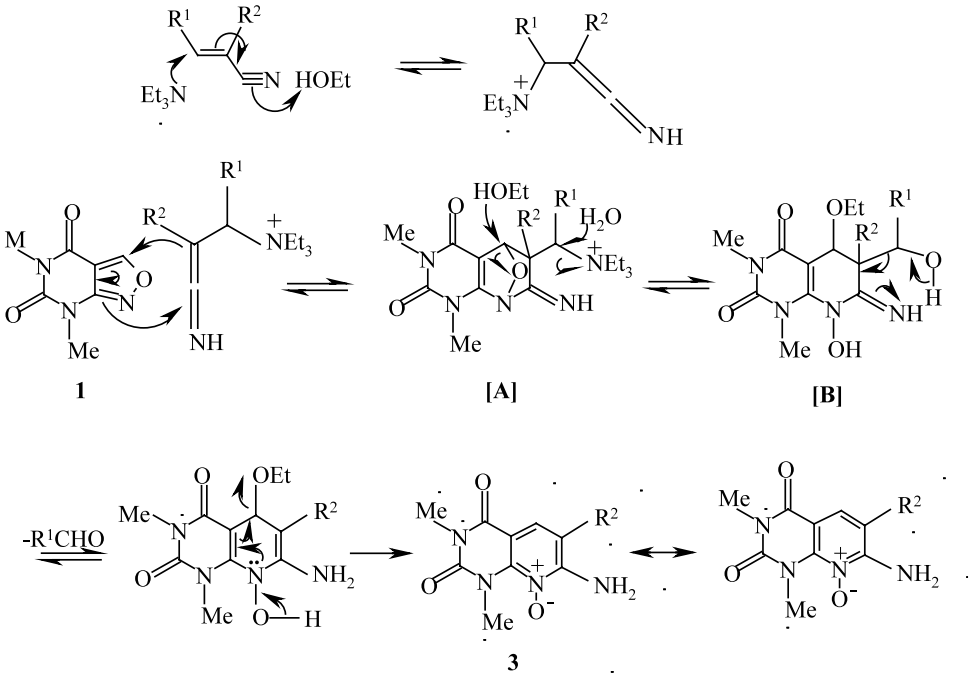

**Scheme 2.**

at 3250 $cm^{-1}$ ($NH_2$), 2220 (CN) and at 1625 ($N^+$–$O^-$). The $^1H$ 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** ($R^1 = p$-$CH_3OC_6H_4$, $p$-$ClC_6H_4$) 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 α-cyanocinamates **2d–f** and α-cyanocinamides **2g–h** under identical conditions. As expected the same product **3b**[7b] was obtained from the reaction of the substituted cinamates **2d–f** with **1**. The aldehydes **4** eliminated were detected in each case. Similarly the α-cyanocinamides **2g–h** gave the same product **3c**[7c] 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.

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7. (a) Compound **3a**. ($C_{10}H_9N_5O_3$) mp 218°C. $^1$H NMR 90 MHz ($CDCl_3$+TFA) $\delta$ 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**. ($C_{12}H_{11}N_4O_5$) mp 205°C. $^1$H NMR 90 MHz ($CDCl_3$+TFA) $\delta$ 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**. ($C_{10}H_{11}N_5O_4$) mp 212°C. $^1$H NMR 90 MHz ($CDCl_3$+TFA) $\delta$ 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%.