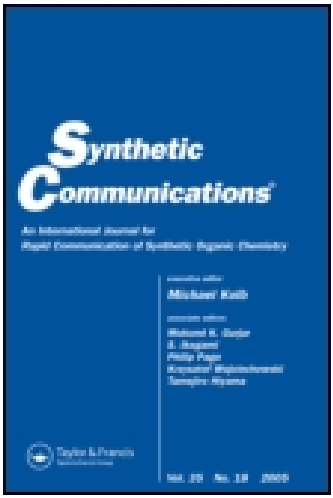

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A Study on the Ring Transformation of Dihydroisoxazolopyrimidine

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A STUDY ON THE RING TRANSFORMATION OF DIHYDROISOXAZOLOPYRIMIDINE

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Abstract : Dihydroisoxazolopyrimidine derivatives could be cleaved to form either pyrimidine ring or isoxazole ring derivatives depending upon the reaction conditions employed.

The reactions of uracil nucleosides and nitrile oxides have been studied in our group.[1-2] Fundamentally, [3+2] cycloaddition reaction between the 5,6-double bond of the pyrimidine ring and nitrile oxide has been observed. However, the initially formed dihydroisoxazolopyrimidine derivatives are unstable toward various reaction conditions such as acid, base, and even polar solvents such as *N, N*-dimethylformamide or dimethyl sulfoxide, and the dihydroisoxazolopyrimidine nucleoside derivatives can not be isolated.[1] Instead, the ring-opened *Z*-oxime derivatives were obtained.

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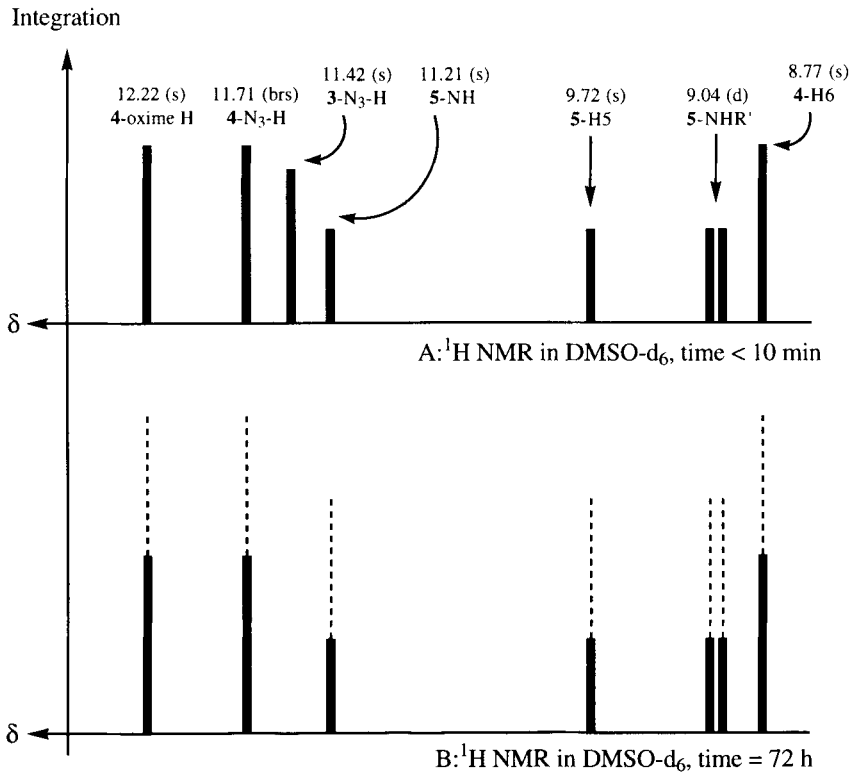
Thus, we reasoned that under reaction conditions in which acid, base, and polar solvent could be avoided we could prepare the dihydroisoxazolopyrimidine nucleoside derivatives and this proved to be the case with 1,3-dimethyluracil as a simple model substrate. 3-(2,6-Dichlorophenyl)-5,7-dimethyl-8,9-dihydroisoxazolo[5,4-d]pyrimidine-4,6(5H, 7H)-dione was obtained in 45% yield from the reaction of 1,3-dimethyluracil and 2,6-dichlorobenzonitrile oxide in dry toluene.[1] However, the reaction of 2', 3', 5'-tri-*O*-benzoyluridine (**1**)[3] with 2,6-dichlorobenzohydroximoyl chloride (**2**)[4] in dry toluene afforded the desired dihydroisoxazolopyrimidine derivative **3** in about 35% yield as determined by ^{1}H NMR, together with some side products. The compound could not be isolated from the reaction mixture due to the inseparable side products **4** and **5** and the instability of **3**. From the study of ^{1}H NMR and the related reports[5] the two major side products were considered to be the ring-opened oxime product **4** and the isoxazole derivative **5**. Scrutiny of the ^{1}H NMR spectra in the range of δ = 8.5 - 13.0 showed the presence of the reported oxime derivative **4** (δ = 8.77, 11.71, and 12.22) in about 40% as determined by the integration of the corresponding peaks (**Figure 1**). Dihydroisoxazolopyrimidine derivative **3** showed peak of NH at 11.42 ppm in about 35% ratio. The characteristic peaks of **3** at the ring fusion site appeared at δ = 4.88 and 6.54 ppm as doublets (J = 9.5 Hz), respectively.[6] The remaining peaks in this range (δ = 9.04, 9.72, and 11.21) might correspond to the isoxazole derivative **5** (25% integration). All of the peaks in the range of δ = 8.5 - 13.0 are singlets except that of δ = 9.04 ppm. The NHR' proton peak of **5** is split as a doublet (J = 8.4 Hz) by the anomeric proton of the 2', 3', 5'-tri-*O*-benzoylribosyl moiety.[5] This compound was formed by the cleavage of the C-N bond of the initially formed **3**. Further evidence is the complete disappearence of the peak at δ = 11.42 in DMSO-d_6 within 72 h. Finally, the ratio of **4** to **5** reached about 55 : 45. The formation of oxime derivative **4** was expected from our early study,[1] however, isoxazole derivative **5** was an unexpected compound.



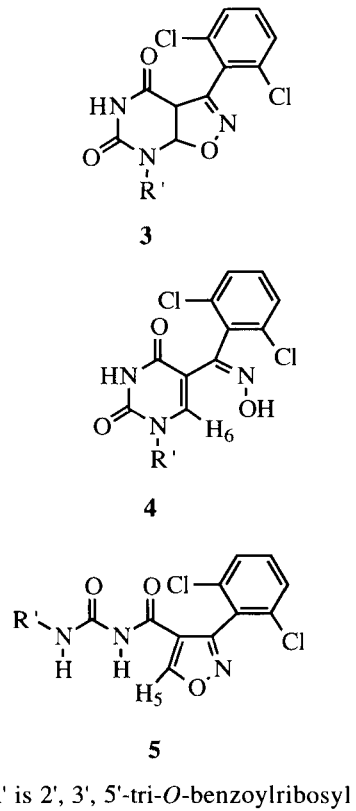
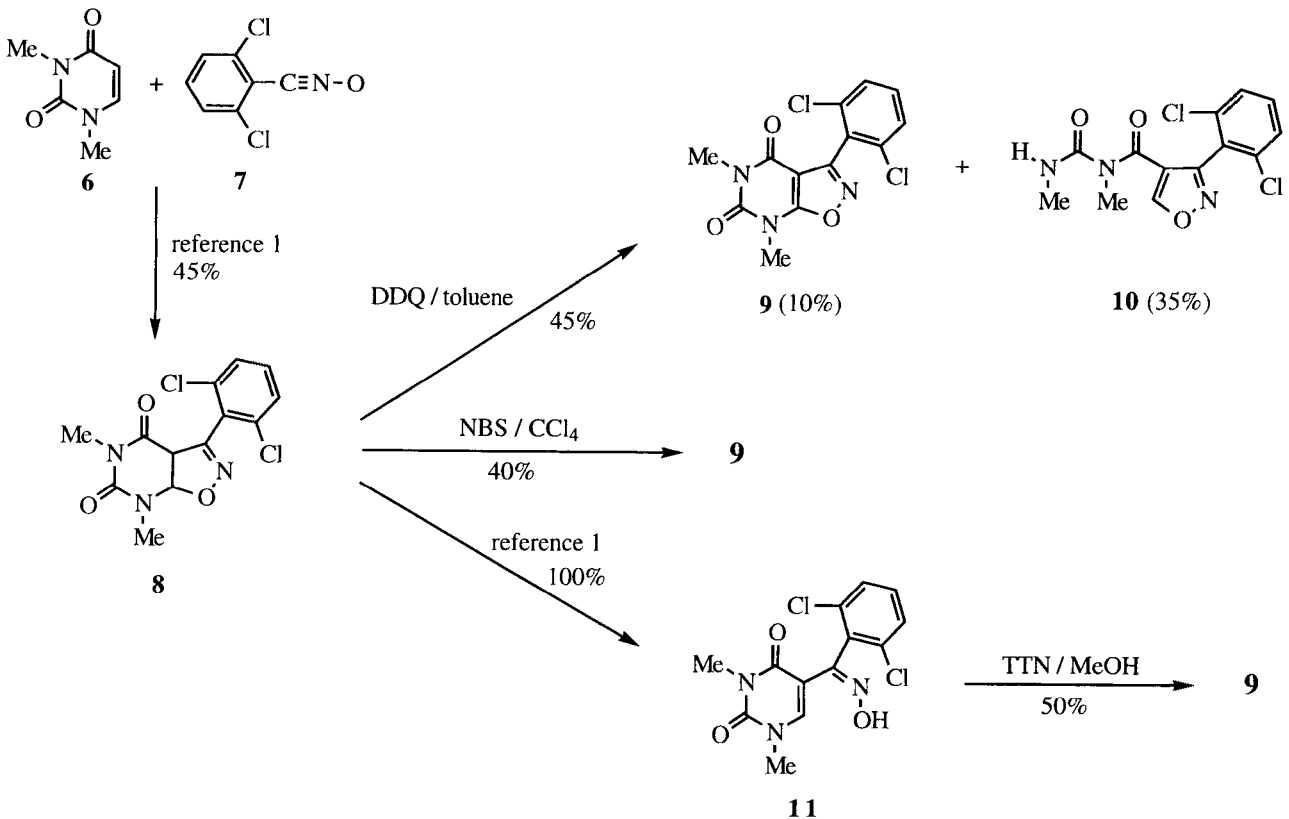


Figure 1. Partial ^{1}H NMR spectra of the mixture 3 + 4 + 5 in DMSO-d$_6$.



Scheme 1. Transformation of 8 in various reaction conditions.

Thus, we examined the decomposition of the dihydroisoxazolopyrimidine derivative under various conditions. The results are represented in **Scheme 1**. As shown in **Scheme 1**, isoxazolopyrimidine derivative **9** was obtained in 40% yield by oxidation of **8** with NBS.[7] Moreover, the oxime derivative **11** was transformed unexpectedly by TTN (thallium nitrate trihydrate) in 50% yield to produce **9**. Oxidative cyclization of **11** occurred instead of the normally expected deoximation reaction.[8] The oxidation of **8** with DDQ[5] produced the expected **9** in 10% yield together with unexpected ring-opened isoxazole derivative **10** in 35% isolated yield. The H-5 proton of **10** appeared in 8.72 ppm. Thus, we tentatively concluded that the dihydroisoxazolopyrimidine derivatives could be ring-opened either to the formation of pyrimidine (route a) or isoxazole (route b) depending upon the reaction conditions as shown in **Figure 2**. The steric and electronic effects of R^1 and R^2 on the ring cleavage are currently under study.

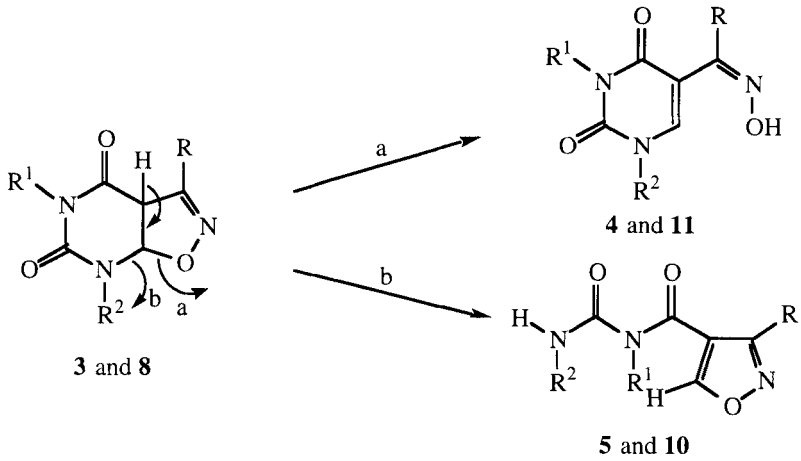


Figure 2. Ring opening mode of dihydroisoxazolopyrimidines.

EXPERIMENTAL

The reaction of 2', 3', 5'-tri-*O*-benzoyluridine (1) and 2,6-dichlorobenzohydroxymoyl chloride (2).

The reaction mixture of **1** (1115 mg, 2.0 mmol) and **2** (430 mg, 2.3 mmol) in dry toluene (60 mL) was heated to 70-80 °C under gentle stream of dry nitrogen gas for 3 days. After toluene was removed and the reaction mixture was purified by flash chromatograpy (hexane / ether, 4 / 6) to afford a white solid (1.0 g, 68%). The white solid contained three inseparable components **3**, **4**, and **5** (roughly in a ratio of 40 : 25 : 35) as described in the text. ^{1}H NMR (DMSO-d_6, time < 10 min) δ 4.50-4.80 (m, 3H), 4.88 (d, *J* = 9.5 Hz, 0.35H), 5.77-6.31 (m, 3H), 6.54 (d, *J* = 9.5 Hz, 0.35H), 7.30-8.12 (m, 18H), 8.77 (s, 0.4 H), 9.04 (d, *J* = 8.4 Hz, 0.25 H), 9.72 (s, 0.25 H), 11.21 (s, 0.25 H), 11.42 (s, 0.35 H), 11.71 (brs, 0.4 H), 12.22 (s, 0.4 H). ^{1}H NMR (DMSO-d_6, time = 72 h) δ 4.50-4.80 (m, 3H), 5.77-6.30 (m, 3H), 7.30-8.05 (m, 18H), 8.77 (s, 0.55 H), 9.04 (d, *J* = 8.4 Hz, 0.45 H), 9.72 (s, 0. 45 H), 11.21 (s, 0.45 H), 11.71 (brs, 0.55 H), 12.22 (s, 0.55 H).

3-(2,6-Dichlorophenyl)-5,7-dimethyl-8,9-dihydroisoxazolo[5,4-d]pyrimidine-4,6-dione (8) and 1,3-dimethyl-5-(2,6-dichlorophenyl)uracil oxime (11) were prepared according to the reported procedure.[1]

The reaction of 8 with DDQ.

The reaction mixture of **8** (1.32 g, 4 mmol) and DDQ (0.96 g, 4.2 mmol) in dry toluene (100 mL) was heated to reflux during 20 h. Toluene was removed under reduced pressure and the residue was purified by column chromatograpy (20% hexane in ether) to afford **9** (130 mg, 10%) and **10** (460 mg, 35%).

9; white solid (mp = 199 - 201 °C); MS (20 eV) m/z (rel intensity) 261 (12), 268 (15), 290 (100), 292 (42), 325 (M+, 19), 327 (M++2, 14); ^{1}H NMR (chloroform-

d_3) δ 3.36 (s, 3H), 3.68 (s, 3H), 7.35-7.60 (m, 3H).

10; white solid (mp = 208-210 °C); MS (20 eV) m/z (rel intensity) 173 (100), 175 (70), 327 (M^+, 55), 329 (M^++2, 36); ^{1}H NMR (chloroform-d_3) δ 3,35 (s, 3H), 3.48 (s, 3H), 7.20-7.50 (m, 3H), 8.27 (brs, 1H), 8.72 (s, 1H).

Oxidation of 8 with NBS.

The reaction mixture of **8** (820 mg, 2.5 mmol), NBS (450 mg, 2.5 mmol), and AIBN (70 mg) in carbon tetrachloride (50 mL) was heated to reflux for 2 h. After the reaction mixture was cooled to room temperature sodium acetate (2.0 g) and acetic acid (0.7 mL) was added, and heated to reflux for 30 min. This was poured into cold 0.5 *N* aqueous sodium hydroxide solution, and extracted with ethyl acetate (2 x 50 mL). The organic layer was dried, filtered, evaporated, and purified by column chromatograpy to give **9** as a white solid, 330 mg (40%).

Conversion of 11 to 9 by TTN.

11 (985 mg, 3 mmol) was dissolved in benzene (50 mL) and methanol (50 mL). Thallium nitrate trihydrate (1.85 g, 4.1 mmol) solution in methanol (10 mL) was added dropwise during 10 min and the reaction mixture was stirred for 2 h at 30 - 40 °C. After removal of solvent the residue was partitioned between ether and dilute aqueous sulfuric acid. The organic layer was seperated and washed with water, dried ($MgSO_4$), evaporated, and separated by column chromatograpy (hexane followed by methylene chloride) to afford desired product as a white solid, 490 mg (50%). The obtained product was identical to **9** in all respects.

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