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A convenient synthesis of 5-(1,2,4-oxadiazol-5-yl)pyrimidine-2,4(1*H*,3*H*)-diones

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ABSTRACT

The synthesis of 5-heteroaryl-substituted uracil derivatives is presented. The 1,3-dipolar cycloaddition reaction was applied for the construction of a heterocyclic ring. The nitrile oxides were obtained from the appropriate 4-substituted benzaldoximes using *N*-chlorosuccinimide (NCS) under basic conditions. [2+3] Cycloaddition of nitrile oxides with 5-cyanouracil as a dipolarophile gave the corresponding 5-(3-substituited-1,2,4-oxadiazol-5-yl)uracils in satisfactory yields under mild conditions. 5-Substituted uracils having an additional heterocyclic ring were obtained as a result of the [2+3] cycloaddition of 5-cyanouracil to nitrile oxides generated from thiophene-2-carbaldehyde and 5-formyluracil derivatives.

Nucleoside analogues have very well recognized activity against several types of neoplastic cells. They belong to the group of antimetabolites which are compounds applied in the anticancer therapy. The best known are floxuridine, cytarabine and gemcitabine.[1] The antiviral activity of several modified nucleosides is another area of interest. The most prominent are the drugs available for the treatment of HIV infections (AZT, ddC, d4T and others) or HBV infections.[1,2] The efficacy of nucleosides depends on their ability to mimic natural congeners. At present, significant attention has been paid to nucleoside analogues having a heterocyclic ring as a substituent.[3,4] Modifications are mainly introduced on the C5 carbon atom of the uracil ring, since substituents at this location are not involved in the complementary base-pairing of DNA. Among other modifications, the introduction of a heterocyclic system to the uracil ring gives increased anticancer activity.[5] The construction of a heterocyclic ring on the C5 carbon atom of the uracil ring was performed using different strategies. Among others, several approaches based on traditional syntheses of heterocyclic rings using 5-aminouracil as a building block were reported.[6,7] A pyrrole ring was formed by a simple condensation of 5-aminouracil with 2,5-dimethoxytetrahydrofuran.[6] In the reaction of 5-aminouracil with 1,4-dinitroimidazole, 5-(4-nitroimidazol-1-yl)uracil was obtained.[7] Here, the reaction proceeds via ANRORC (addition of the nucleophile, ring opening, ring closure) degenerate transformation of the 1,4-dinitro-imidazole ring. The introduction of a heteroaryl group onto the uracil ring can be performed using other methods. UV irradiation of persilylated 5-iodo-2′-deoxycytidine in the presence of thiophene leads to the appropriate 5-(2-thienyl)-2′-deoxycytidine in moderate yield.[8] Several 5-heteroaryl-2′-deoxyuridines were obtained by the reaction of 5-iodo-2′-deoxyuridine with heteroaryltrialkyltin derivatives catalysed by palladium complexes.[9] The palladium-catalysed Suzuki–Miyaura reaction was also applied for the synthesis of 5-heteroaryl uracils.[10,11] In recent years, many attempts based on [2+3] cycloaddition reactions for the construction of a heterocyclic system on the uracil ring have been reported.[12–16] Using nitrile oxide or *N*-methylnitrone derived from 5-formyluracil, uracil derivatives possessing isoxazoline, isoxazole or isoxazolidine rings on carbon C5 were obtained in satisfactory yields.[15] In most of the modification reactions, uridine or N-alkylated uracils were used as scaffolds for the construction of the 5-heteroaryl derivatives.

In our investigations we used as the dipolarophile commercially available 5-cyanouracil unsubstituted on both nitrogen atoms (N1 and N3). This approach retained the opportunity for further modifications of the uracil moiety including coupling with a sugar molecule. The 1,3-dipoles were obtained according to a previously described procedure.[16] Thus, 4-substituted benzaldehydes were converted into oximes **1a**–**f**, followed by chlorination using a small excess of NCS. Reactions were carried out in dry DMF at room temperature (Scheme 1).[17] The extent of the reaction was monitored by TLC (ethyl acetate/*n*-hexane, 1:1, v/v) and usually after 1 h total consumption of the starting material was observed. The oximoyl chlorides **2a**–**f** were used immediately for the next step without further purification. A solution of oximoyl chloride **2a**–**f** was mixed with 5-cyanouracil **3** and triethylamine was added dropwise while stirring. The reaction was run for 24 h at room temperature and the expected products **4a**–**f** were obtained in moderate yields (19–51%) (Table 1).[18] The presence of an electron-withdrawing nitro group decreased significantly the yield, and the expected

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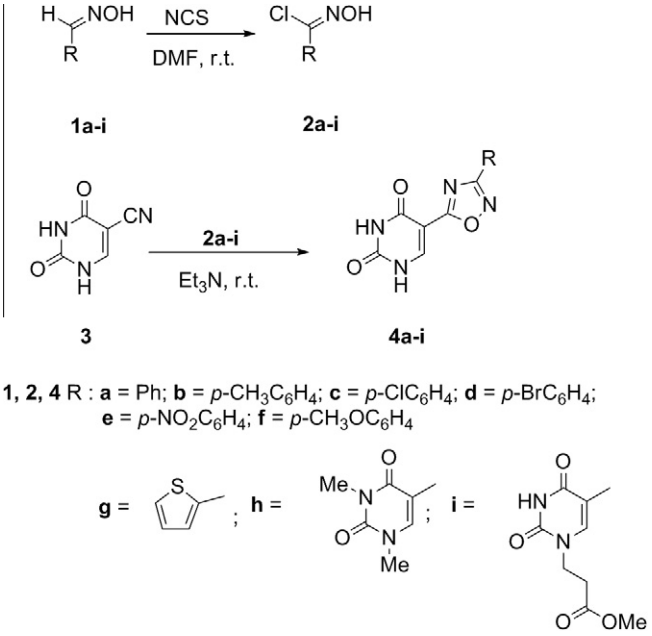
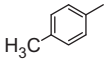
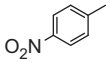
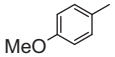
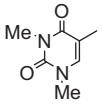
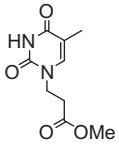


Scheme 1. The synthesis of 5-(1,2,4-oxadiazol-5-yl)pyrimidine-2,4(1*H*,3*H*)-diones.

Table 1
Synthesized 5-(1,2,4-oxadiazol-5-yl)uracils **4a–i**

Product	*R*	Yield[a] (%)	Mp (°C)
4a		40	204–206
4b		51	195–197
4c		40	170–172
4d		44	171–173
4e		19	178–179
4f		51	172–174
4g		28	>190
4h		60	207–209
4i		51	234–235

[a] Isolated yields.

cycloadduct **4e** was obtained in only 19% yield. In another trial the oxime of thiophene-2-carbaldehyde **2g** was used. Using the same procedure, the [2+3] cycloaddition product **4g** was isolated in 28% yield.[19] In two other experiments we used oximes of 1,3-dimethyl-5-formyluracil (**1h**) and methyl 3-[5-formyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl]propanoate (**1i**)[20] as the nitrile oxide precursors. These experiments were performed in order to establish the possibility of constructing 5-(1,2,4-oxadiazol-5-yl)uracils bearing an additional uracil moiety.

Using the same reaction conditions cycloadducts **4h** and **4i** were obtained in 60% and 51% yields, respectively. The performed experiments suggest that the presence of the weakly acidic N1 and N3 hydrogen atoms in unsubstituted 5-cyanouracil does not affect the dehalogenation of the oximoyl chlorides or the course of the [2+3] cycloaddition reaction. The amount of base used was equimolar with respect to the starting aldoxime (in the case of aldoxime chloride **2h** a 100% excess of triethylamine was used). It is noteworthy that we did not observe the formation of the corresponding furoxans. Perhaps the in situ prepared nitrile oxides have considerably lower stability or higher reactivity towards 5-cyanouracil in comparison with other nitrile oxides.[21,22]

In conclusion, we have developed a procedure for the easy access to 5-substituted uracil derivatives, possessing a 1,2,4-oxadiazole ring on carbon C5 of the uracil ring. The described route opens access to 5-heteroaryluracils, and may be used for the synthesis of new analogues of uridine and its congeners.

Acknowledgement

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17. *General procedure for the preparation of uracils* **4a–i**: To a solution of oxime **1a–i** (0.4 mmol) in dry DMF (3 ml), NCS (0.44 mmol, 0.059 g) was added at room temperature while stirring. Completion of the reaction was indicated by TLC (EtOAc/*n*-hexane, 1:1 v/v). The solution of generated oximoyl chloride **2a–i** was immediately used for the next step without purification. 5-Cyanouracil (**3**) (0.35 mmol, 0.048 g) was added followed by dropwise addition of Et_3N (0.4 mmol, 0.06 ml). In the case of **1h**, 0.8 mmol of Et_3N was used. The reaction mixture was stirred for 24 h at room temperature. After that time the solvent was removed under reduced pressure and the residue purified on a silica gel packed column using EtOAc/*n*-hexane (1:1) as eluent. The products **4a–i** were obtained in satisfactory yields.
18. *5-(3-Phenyl-1,2,4-oxadiazol-5-yl)pyrimidine-2,4(1H,3H)-dione* (**4a**): white crystals; yield 40%; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.53 (s, 1H, NH), 12.33 (s, 1H, NH), 8.77 (s, 1H, H-6), 7.72 (dd, 2H, arom, J = 7.8 Hz, J = 1.5 Hz), 7.54–7.39 (m, 3H, arom) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ 160.3, 153.5, 147.6, 142.8, 130.6, 130.4, 128.8 (2C), 125.6 (2C), 113.8, 89.7 ppm. Anal. Calcd for $C_{12}H_8N_4O_3$: C, 56.25; H, 3.15; N, 21.87. Found: C, 56.05; H, 2.98; N, 21.56 MS: m/z $[M+H]^+$ = 257 (100%); 258 (15.5%).
19. *5-[3-(Thien-2-yl)-1,2,4-oxadiazol-5-yl]pyrimidine-2,4(1H,3H)-dione* (**4g**): white crystals; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.37 (s, 1H, NH), 12.34 (s, 1H, NH), 8.81 (s, 1H, H-6), 7.67 (dd, 1H, arom, J = 5.1 Hz, J = 0.9 Hz), 7.50 (dd, 1H, arom, J = 3.8 Hz, J = 0.9), 7.11 (dd, 1H, arom, J = 5.1 Hz, J = 3.8 Hz) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ 160.2, 152.9, 147.3, 139.5, 133.7, 129.3, 129.1, 127.7, 113.6, 89.8 ppm. Anal. Calcd for $C_{10}H_6N_4O_3S$: C, 45.80; H, 2.31; N, 21.36. Found: C, 45.49; H, 2.08; N, 21.09. MS m/z $[M+H]^+$ = 263 (100%); 264 (14%); 265 (6%).
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