Studies on Uracils: A Facile One-pot Synthesis of Pyrazolo[3,4-*d*]pyrimidines

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The reaction of 6-hydrazino uracils **1** and nitrones **2** result in an efficient one-pot synthesis of pyrazolo[3,4-*d*]pyrimidines **3** in excellent yields. The isolation of the by-product aniline from the reaction mixture supported the plausible mechanism for the formation of pyrazolo[3,4-*d*]pyrimidines.

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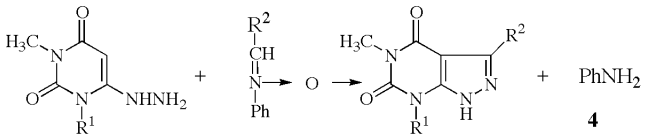
The importance of uracil and its annelated substrate is well recognised by synthetic [1] as well as biological [2] chemists. Pyrazolo[3,4-*d*]pyrimidines are a class of annulated uracils of special interest in medicinal chemistry [3], which have been studied extensively as antitumor agents [4]. 4-(*n*-Propylamino)-pyrazolo[3,4-*d*]pyrimidine has been examined in clinical studies against disseminated tumors and human leukemia [5]. Interestingly, the literature survey revealed only few reports for the synthesis of pyrazolo[3,4-*d*]pyrimidines the majority of which require drastic conditions and complex synthetic pathways. As a part of our research programme on uracils [6] we report here a very simple, mild and efficient method for the synthesis of Pyrazolo[3,4-*d*]pyrimidines by exploring the nucleophilic double bond of uracils.

A previous synthesis for pyrazolo[3,4-*d*]pyrimidine reported by Yoneda *et al*. [7] involved the cycloaddition of azahexatriene obtained from the reaction of arylaldehyde and 6-uracil hydrazone. One disadvantage of this approach is the concomitant alkylation of the pyrazolo moiety. Another synthesis reported by Maki *et al*. [8] required the cycloaddition of arylhydrazones with 6-chloro-5-nitro uracils involving several steps. Kanazawa *et al.* [9] synthesised pyrazolo[3,4-*d*]pyrimidines by the reaction of 6-arylidinehydrazinouracils with *N*-bromosuccinimide (NBS) in acetic acid under refluxing conditions, which yield triazino and pyridazinouracils in addition to the pyrazolo[3,4-*d*]pyrimidines.

Our synthetic strategy utilising 6-hydrazinouracils **1** with nitrones **2** at room temperature afforded an unprecedented one pot synthesis of pyrazolo[3,4-*d*]-pyrimidines **3** in excellent yields.

In a very simple experimental procedure equimolar amount of 6-hydrazino uracil **1** and nitrone **2a** were stirred at room temperature for 12 hours (Scheme 1). The product appeared as a thick precipitate which was filtered, washed with a small amount of ethanol and dried. The compound, obtained in 95% yield, was recrystallised from ethanol. The structure was fully characterised as **3a** through spectral and elemental analyses and found to be comparable in all respect to the authentic sample. The eliminated by-product aniline **4** was isolated from the filtrate by evaporating the solvent and passing the residue through a silica gel column using chloroform-ethylacetate (4:1) as eluent. The structure was confirmed from spectroscopic data and by comparing with the authentic compound. The formation of the by-product can be explained by the mechanism shown. Similarly compounds **3b-f** were synthesised and structures confirmed from spectroscopic data and elemental analyses. Melting points and mixed melting points of compounds **3b-c** are comparable with authentic compounds. The reaction was extended to conjugated nitrones and found to proceed smoothly in the presence of the carbon carbon double bond, which remains intact

Scheme 1



1a, $R^1 = CH_3$ **2a**, $R^2 = C_6H_5$ **3a**, $R^1 = CH_3$, $R^2 = C_6H_5$
b, $R^1 = H$ **b**, $R^2 = 4\text{-OMe-}C_6H_4$ **b**, $R^1 = CH_3$, $R^2 = 4\text{-OMe-}C_6H_4$
c, $R^2 = 4\text{-Cl-}C_6H_4$ **c**, $R^1 = CH_3$, $R^2 = 4\text{-Cl-}C_6H_4$
d, $R^2 =$ Furyl **d**, $R^1 = CH_3$, $R^2 =$ Furyl
e, $R^2 = C_6H_5CH{:}CH$ **e**, $R^1 = H$, $R^2 = C_6H_5$
f, $R^1 = H$, $R^2 =$ Furyl
g, $R^1 = CH_3$, $R^2 = C_6H_5CH{:}CH$
h, $R^1 = H$, $R^2 = C_6H_5CH{:}CH$

Scheme 2

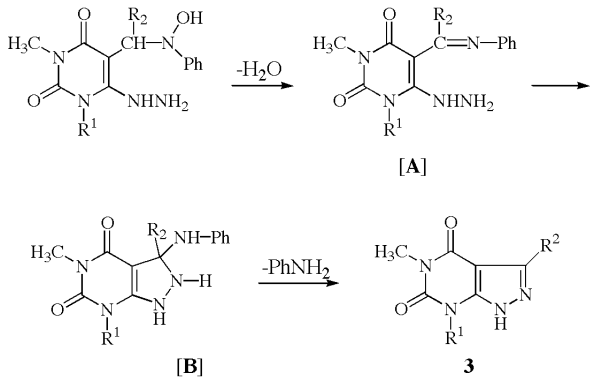


Table 1

Compound No.	Molecular Formula	Analytical Data: Calcd./Found C	H	N
3a	$C_{13}H_{12}N_4O_2$	60.93/60.85	4.72/4.65	21.86/21.75
3b	$C_{14}H_{14}N_4O_3$	58.73/58.70	4.93/4.98	19.57/19.40
3c	$C_{13}H_{11}N_4O_2Cl$	57.79/57.70	3.79/3.75	19.31/19.25
3d	$C_{11}H_{10}N_4O_3$	53.66/53.80	4.09/4.05	22.75/22.63
3e	$C_{12}H_{10}N_4O_2$	59.50/59.41	4.16/4.22	23.13/23.02
3f	$C_{10}H_8N_4O_3$	51.73/51.79	3.47/3.39	24.13/24.08
3g	$C_{15}H_{14}N_4O_2$	63.82/63.75	4.96/4.90	19.85/19.90
3h	$C_{14}H_{12}N_4O_2$	62.68/62.60	4.47/4.40	20.89/20.85

in the products. Thus the reaction of **1** and **2e** yielded **3g** and **3h** in excellent yield. In each case the by-product aniline was isolated as usual from the reaction mixture.

A reasonable mechanism for the formation of **3** can be explained by an initial nucleophilic addition of **1** to **2** with a proton shift followed by the formation of the imine [**A**], which subsequently undergoes a nucleophilic attack by the 6-hydrazino group to give the intermediate dihydropyrazolo[2,3-*d*]pyrimidine [**B**]. Elimination of an aniline molecule affords the fully aromatised compound **3** (Scheme 2). The mechanism is consistent with the observation that aniline **4**, which was isolated from the reaction mixture and fully characterised, is a by-product.

In conclusion, we have demonstrated a very simple, mild and efficient method for the synthesis of pyrazolo-[3,4-*d*]pyrimidines of biological importance in excellent yields. Heteroannulation on the nucleophilic double bond of uracils, which is an important field in view of great variety of potential products [10], usually requires either forcing conditions [7,11] or relatively longer and complex synthetic pathways [8,12]. Our results delineated above have demonstrated that heteroannulation on the double bond of uracils is possible under mild condition using suitable organic synthones such as nitrones.

EXPERIMENTAL

Melting points were determined in open capillary tubes on a Buchi apparatus and are uncorrected. The 90 MHz NMR spectra were recorded on a JEOL EX 90A spectrometer with deuteriochloroform ($CDCl_3$) or $CDCl_3$ + trifluoroacetic acid (TFA) as solvent and tetramethylsilane (TMS) as the internal standard. Chemical shift values are recorded in δ units (ppm). The IR spectra were recorded on a Perkin-Elmer 237B spectrometer as KBr discs. Mass spectra were recorded on a INCOS-50 GC-MS instrument. Elemental analyses were performed on a Hitachi 026 CHN analyser.

General Procedure for the Synthesis of Pyrazolo[3,4-*d*]pyrimidines **3**.

A mixture of 0.170 g (1 mmol) of 6-hydrazino uracil **1a** and 0.197 g (1 mmol) of nitrone **2a** in 10 ml ethanol was stirred at room temperature for 12 hours. The thick precipitate formed was filtered, washed with a small amount of ethanol and dried. The filtrate was evaporated under reduced pressure and the residue was chromatographed in a silica gel column using chloroform-ethylacetate (4:1) as eluent. The product isolated was identified as aniline from the physicochemical data and by comparing with authentic sample. Similarly, compound **3b-h** were prepared and the structures confirmed from spectroscopic data and elemental analysis (Tables 1).

5,7-Dimethyl-3-phenyl-1,7-dihydropyrazolo[3,4-*d*]pyrimidine-4,6-dione (**3a**)

The product **3a** was obtained in 95% yield (0.243 g) and recrystallised from ethanol mp. 257 °C (lit. mp. 256-257 °C [9]). Mixed mp. 257 °C. ^{1}H NMR (deuteriochloroform + trifluoroacetic acid): δ 2.95 (s, 3H), 3.30 (s, 3H), 6.75-7.20 (m, 5H). IR 3220, 1700 cm^{-1}. MS 256 (M^+).

3-(4-Methoxyphenyl)-5,7-dimethyl-1,7-dihydropyrazolo[3,4-*d*]-pyrimidine-4,6-dione (**3b**).

Compound **3b** was obtained in 95% yield, mp. 271 °C [9]; ^{1}H NMR (deuteriochloroform + trifluoroacetic acid): δ 2.95 (s, 3H), 3.30 (s, 3H), 3.80 (s, 3H), 6.75-7.20 (m, 4H). IR 3225, 1700 cm^{-1}; MS 286 (M^+).

3-(4-Chlorophenyl)-5,7-dimethyl-1,7-dihydropyrazolo[3,4-*d*]-pyrimidine-4,6-dione (**3c**).

Compound **3c** was obtained in 94% yield, mp. >300 °C [9]; ^{1}H NMR (deuteriochloroform + trifluoroacetic acid): δ 2.95 (s, 3H), 3.30 (s, 3H), 6.75-7.20 (m, 4H). IR 3220, 1700 Cm-1, MS 290 (M+).

3-(Furyl)-5,7-dimethyl-1,7-dihydropyrazolo[3,4-*d*]pyrimidine-4,6-dione (**3d**).

Compound **3d** was obtained in 85% yield, mp. 236 °C, ^{1}H NMR (deuteriochloroform + trifluoroacetic acid): δ 3.00 (s, 3H), 3.45 (s, 3H), 6.35-6.65 (m, 2H), 7.25 (d, 1H, J=2.6). IR 3225, 1705 cm^{-1}, MS 246 (M^+).

5-Methyl-3-phenyl-1,7-dihydropyrazolo[3,4-*d*]pyrimidine-4,6-dione (**3e**).

Compound **3e** was obtained in 96% yield, mp. 257 °C, ^{1}H NMR (deuteriochloroform + trifluoroacetic acid): δ 2.95 (s, 3H), 6.80-7.25 (m, 5H), IR 3250, 3125 cm^{-1}, MS 242 (M^+).

3-Furyl-5-methyl-1,7-dihydropyrazolo[3,4-*d*]pyrimidine-4,6-dione (**3f**).

Compound **3f** was obtained in 85% yield, mp. 243 °C; ^{1}H NMR (deuteriochloroform + trifluoroacetic acid): δ 3.00 (s, 3H), 6.30-6.45 (m, 2H), 7.10 (d, 1H, J = 2.6). IR 3245, 3120, 1695 cm^{-1}, MS 232 (M^+).

cis-5,7-Dimethyl-3-(2-phenylethenyl)-1,7-dihydropyrazolo-[3,4-*d*]pyrimidine-4,6-dione (**3g**).

Compound **3g** was obtained in 90% yield, mp. 251 °C; ^{1}H NMR (deuteriochloroform + trifluoroacetic acid): δ 3.00 (s, 3H), 3.45 (s, 3H), 6.30 (d, 1H, J = 10.4), 6.75-7.20 (m, 5H), 7.85 (d, 1H, J = 12.4). IR 3225, 1705 cm^{-1}, MS 282 (M^+).

cis-5-Methyl-3-(2-phenylethenyl)-1,7-dihydropyrazolo-[3,4-*d*]pyrimidine-4,6-dione (**3h**).

Compound **3h** was obtained in 90% yield, mp. 265 °C; ^{1}H NMR (deuteriochloroform + trifluoroacetic acid): δ 3.00 (s, 3H), 6.30 (d, 1H, J = 12.6), 6.75-7.20 (m, 5H), 7.85 (d, 1H, J = 10.6). IR 3225, 1705 cm^{-1}, MS 268 (M^+).

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