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A Mild and Efficient Method for the Deformylation of 5-Formyl Uracils and Synthesis of 4,4′-Methylidenebis(1-phenyl-3-methyl-5-pyrazolone)

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Abstract: 6-Substituted 5-formyl uracils undergo an interesting reaction with 1-phenyl-3-methyl-5-pyrazolone in the presence of base catalyst to afford deformylated uracils and 4,4′-methylidenebis(1-phenyl-3-methyl-5-pyrazolone) in excellent yields.

Key words: uracil, deformylation, pyrazolone, 4,4′-methylidenebis(1-phenyl-3-methyl-5-pyrazolone)

The importance of uracil and its derivatives is well recognized by synthetic as well as biological chemists.[1] Compounds with this ring system have diverse pharmacological activity.[2] Therefore, considerable effort has been made towards the synthetic manipulation of the uracil core.[3]

6-Hydroxy- and 6-aminouracils are two important classes of functionalized uracils.[4] 6-Hydroxyuracils constitute the basic moiety of clinically used hypnotic drugs of the barbiturates class, such as veronal, seconal, and phenobarbital. 6-Aminouracils are the key intermediates in the synthesis of purines, which constitute the basic moiety of a number of drugs, including caffeine, penciclovir, theobromine and theophylline. Moreover, 6-hydroxy- and 6-aminouracils find wide application as precursors for the synthesis of a large number of annelated uracils of biological significance.[5] The C5=C6 double bond of 6-hydroxy- and 6-aminouracils is nucleophilic in nature and electrophiles attack at the 5-position of these compounds. Thus, Michael addition takes place at the 5-position of 6-amino- or 6-hydroxyuracils.[6] However, 5-substituted derivatives of these compounds give aza- or oxa-Michael addition products.[7] Similarly, acylation of 6-aminouracils gives 5-acylated compounds, whereas the 5-substituted analogues afford N-acylated compounds.[8] Moreover, many electrophilic substitution reactions occurs at the 5-position instead of the nitrogen atoms of uracils even under basic conditions.[9] Therefore, the protection and deprotection of the 5-position of uracils is an important reaction from the synthetic point of view.

The formyl group has been widely used as an activating/protecting group during the synthesis of secondary amines from primary amines;[10] however, it has been limited from wide use due to the harsh conditions required for its removal.[11]

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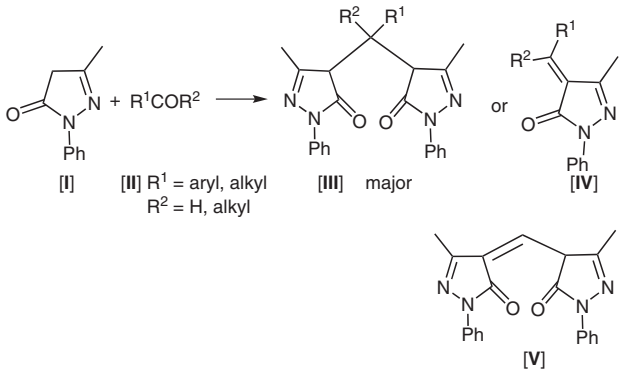
1-Phenyl-3-methyl-5-pyrazolone (**I**) reacts with ketones as well as aromatic and aliphatic aldehydes **II** to give 4-substituted pyrazolone derivatives (Scheme 1).[12] In most instances bis-pyrazolones **III** are obtained as the major product with minor amounts of Knoevenagel condensed product **IV**. However, Betti et al. and Papine et al. observed that, in the reaction of **I** and **II** (when R^1 = H), an occasional side reaction occurs to give trace amounts of an orange colored compound.[13] After characterization, it was found that the compound was 4,4′-methylidenebis(1-phenyl-3-methyl-5-pyrazolone) (**V**), which is highly useful as an antihalation dye in the photographic process.[14]

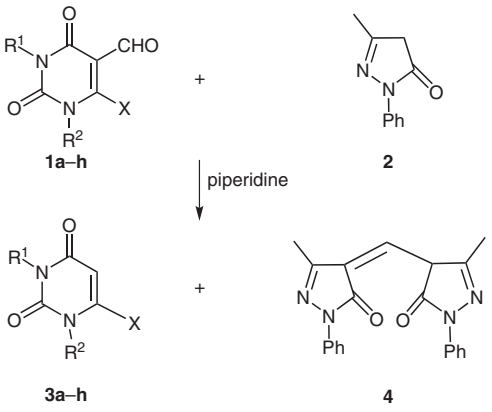


Scheme 1

Formylation at the 5-position of 6-amino- and 6-hydroxyuracils can be achieved by the action of Vilsmeier reagent.[15] However, deformylation of these compounds has not been reported so far. In a recent study, we showed that 6-substituted uracils are very good leaving groups.[16] Taking all these observations in view, and in a continuation of our work on uracils,[17] we studied the reaction of various 5-formyl-6-substituted uracils **1** with 1-phenyl-3-methyl-5-pyrazolone (**2**) and thus report herein a highly efficient method for the deformylation of various 5-formyl-6-substituted uracils that affords the deformylated compound **3** (Scheme 2). Moreover, the reaction demonstrates a suitable method for the synthesis of 4,4′-methylidenebis(1-phenyl-3-methyl-5-pyrazolone) (**4**), which is a compound of considerable industrial importance.

In our reaction strategy, utilizing one equivalent of *N*,*N*-dimethyl-5-formyl-6-hydroxyuracil (**1a**)[15a] with two equivalents of 1-phenyl-3-methyl-5-pyrazolone (**2**), in the presence of a catalytic amount of piperidine at room temperature, afforded, after work up, 80% of *N*,*N*-dimethyl-6-

hydroxyuracil **3a** (Scheme 2).[18] The structure of the compound was ascertained from the spectroscopic data and by comparison with an authentic sample.[19] Compound **4** was obtained as a dark orange solid in the reaction mixture, which could be isolated simply by filtration.



Scheme 2

Table 1 Deformylation Reaction of 6-Substituted 5-Formyluracils **1**

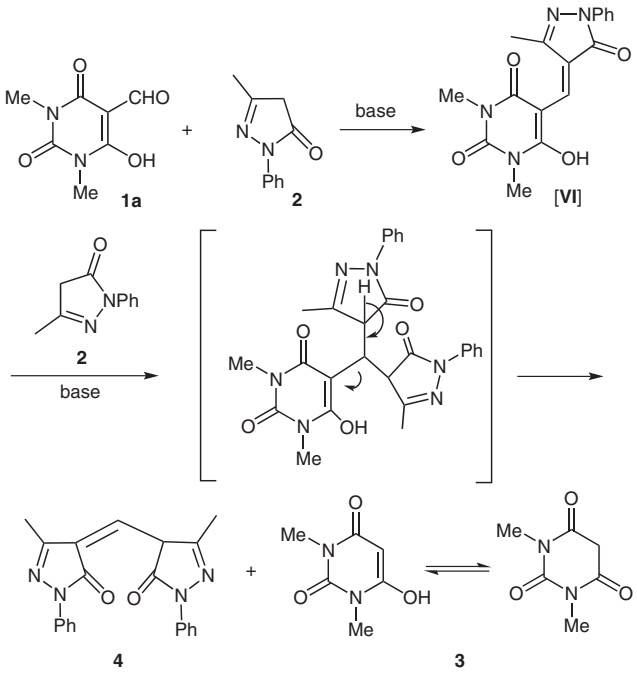
Entry	X	R^1	R^2	Product	Time (min)	Yield (%)
1	OH	Me	Me	**3a**	30	80
2	Cl	Me	Me	**3b**	30	75
3	NH_2	Me	Me	**3c**	60	60
4	N(Me)($CH_2CH{=}CH_2$)	Me	Me	**3d**	150	80[a]
5	N(Ph)($CH_2CH{=}CH_2$)	Me	Me	**3e**	40	75
6		Me	Me	**3f**	150	80[a]
7	OH	H	Me	**3g**	40	70
8	Cl	H	Me	**3h**	40	70

[a] Performed under reflux in the presence of DIPEA.

The structure of compound **4** was determined from the spectroscopic data and elemental analysis. The ^{1}H NMR spectrum showed a resonance at δ = 2.36 ppm for the two equivalent methyl groups and the aromatic protons appeared in the range δ = 7.18–7.91 ppm. The single hydrogen at the 4-position appeared much further downfield because of resonance participation with the amide carbonyl groups. The mass spectrum showed the molecular ion peak (*m/z* 357.5 $[M - H]^+$) that is quite close to the calculated value.

In order to establish the generality of the reaction, a number of 5-formyl-6-substituted uracils **1**[15] were reacted with 1-phenyl-3-methyl-5-pyrazolone (**2**) and, in all the cases, deformylated compounds **3** were obtained in excellent yields. In each case we isolated the bis-pyrazolone product **4** in 60–80% yield. Our observations are recorded in Table 1.

With suitable conditions established, the deformylation reaction was studied by utilizing other cyclic active methylene compounds e.g. *N*,*N*-dimethylbarbituric acid, Meldrum's acid, dimedone etc. in place of pyrazolone **2**. However, no satisfactory results were obtained except with dimedone, which was found to react with **1** to afford the deformylated compound **3** in comparatively low yield and only under reflux after a long period of time (4–5 hours). Therefore, 1-phenyl-3-methyl-5-pyrazolone is considered to be the most suitable reagent for the deformylation reaction. We also studied the deformylation process with other bulky heterocyclic aldehydes e.g. various 2-substituted-3-formyl-quinolines, which only gave the Knoevenagel condensed product.



Scheme 3

A suitable mechanism for the reaction is outlined in the Scheme 3. First the Knoevenagel condensation of **1** and **2** occurs to give intermediate **VI** and then a second molecule of pyrazolone **2** adds in a Michael addition to the newly formed double bond of the intermediate **VI**. The substituted uracil moiety, being a good leaving group, is eliminated to give the deformylated compound **3** and 4,4′-methylidenebis(1-phenyl-3-methyl-5-pyrazolone) (**4**). The mechanism and the formation of the product **3** are supported by the isolation and characterization of the compound **4**, which is obtained in each deformylation reaction.

In conclusion, we have reported a very mild and highly efficient method for the deformylation of various 5-formyl-6-substituted uracils. Moreover, the reaction offers a method for the synthesis of 4,4′-methylidenebis(1-phenyl-3-methyl-5-pyrazolone) (**4**), which is an industrially important compound. A suitable mechanism is put forwarded for the reaction. This reaction, which demon-

strates an important deformylation process and also the synthesis of a compound of industrial importance, is a valuable addition to the chemistry of both uracils and pyrazolones.

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(18) In a simple experimental procedure, *N*,*N*-dimethyl-5-formyl-6-hydroxyuracil (**1a**; 184 mg, 1 mmol) and 1-phenyl-3-methyl-5-pyrazolone (**2**; 348 mg, 2 mmol) were stirred in ethanol (8 mL) at r.t. in the presence of two drops of piperidine for 30 min. The dark-orange solid compound **4** that appeared was filtered, washed with cold ethanol and dried in air. Yield: 286 mg (80%); mp 182–184 °C (Lit.[13] 183–184 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.36 (s, 6 H), 7.18–7.31 (m, 3 H), 7.45 (t, *J* = 7.52 Hz, 4 H), 7.91 (d, *J* = 7.72 Hz, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.46, 110.03, 121.60, 127.08, 129.44, 138.18, 138.82, 153.27, 161.78; MS: *m*/*z* = 357.5 $[M - H]^+$. The solvent was evaporated and the residue was purified by column chromatography using CH_2Cl_2 as eluent. The yield of product **3a** = 80% (125 mg); mp 120–122 °C (Lit.[19] 121–122 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.31 (s, 6 H), 3.69 (s, 2 H); IR: 3364, 1706, 1651 cm^{-1}; MS (EI): *m*/*z* = 157 $[M + H]^+$, 155 $[M - H]^+$.

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