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

Mohit L. Deb, Swarup Majumder, Pulak J. Bhuyan*

Medicinal Chemistry Division, North East Institute of Science & Technology, Jorhat 785006, Assam, India
Fax +91(376)2370011; E-mail: pulak_jyoti@yahoo.com
Received 17 February 2009

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. Compounds with this ring system have diverse pharmacological activity. Therefore, considerable effort has been made towards the synthetic manipulation of the uracil core.

6-Hydroxy- and 6-aminouracils are two important classes of functionalized uracils. 6-Hydroxyuracils constitute the basic moiety of clinically used hypnotic drugs of the barbiturate 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. 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. However, 5-substituted derivatives of these compounds give aza- or oxa-Michael addition products. Similarly, acylation of 6-aminouracils gives 5-acylated compounds, whereas the 5-substituted analogues afford N-acylated compounds. Moreover, many electrophilic substitution reactions occurs at the 5-position instead of the nitrogen atoms of uracils even under basic conditions. 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, however, it has been limited from wide use due to the harsh conditions required for its removal.

1-Phenyl-3-methyl-5-pyrazolone (I) reacts with ketones as well as aromatic and aliphatic aldehydes to give 4-substituted pyrazolone derivatives (Scheme 1). 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 R¹ = H), an occasional side reaction occurs to give trace amounts of an orange colored compound. 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.

Formylation at the 5-position of 6-amino- and 6-hydroxyuracils can be achieved by the action of Vilsmeier reagent. 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. Taking all these observations in view, and in a continuation of our work on uracils, 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) 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). The structure of the compound was ascertained from the spectroscopic data and by comparison with an authentic sample. Compound 4 was obtained as a dark orange solid in the reaction mixture, which could be isolated simply by filtration.

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.

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′-methylidenedi(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′-methylidenedi(1-phenyl-3-methyl-5-pyrazolone) (4), which is an industrially important compound. A suitable mechanism is put forward for the reaction. This reaction, which demon-

The structure of compound 4 was determined from the spectroscopic data and elemental analysis. The 1H 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 hydroxy group 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 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.

### Table 1. Deformylation Reaction of 6-Substituted 5-Formyluracils 1

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>R¹</th>
<th>R²</th>
<th>Product</th>
<th>Time (min)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OH</td>
<td>Me</td>
<td>Me</td>
<td>3a</td>
<td>30</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>Cl</td>
<td>Me</td>
<td>Me</td>
<td>3b</td>
<td>30</td>
<td>75</td>
</tr>
<tr>
<td>3</td>
<td>NH₂</td>
<td>Me</td>
<td>Me</td>
<td>3c</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>N(Me)(CH₂CH=CH₂)</td>
<td>Me</td>
<td>Me</td>
<td>3d</td>
<td>150</td>
<td>80⁺</td>
</tr>
<tr>
<td>5</td>
<td>N(Ph)(CH₂CH=CH₂)</td>
<td>Me</td>
<td>Me</td>
<td>3e</td>
<td>40</td>
<td>75</td>
</tr>
<tr>
<td>6</td>
<td>N(Ph)</td>
<td>Me</td>
<td>Me</td>
<td>3f</td>
<td>150</td>
<td>80⁺</td>
</tr>
<tr>
<td>7</td>
<td>OH</td>
<td>H</td>
<td>Me</td>
<td>3g</td>
<td>40</td>
<td>70</td>
</tr>
<tr>
<td>8</td>
<td>Cl</td>
<td>H</td>
<td>Me</td>
<td>3h</td>
<td>40</td>
<td>70</td>
</tr>
</tbody>
</table>

* Performed under reflux in the presence of DIPEA.
strates an important deamination process and also the synthesis of a compound of industrial importance, is a valuable addition to the chemistry of both uracils and pyrazolones.

Acknowledgment

We thank the DST, New Delhi, for financial support. M.L.D. and S.M. thank the CSIR (India) for the award of Research Fellowships.

References and Notes


(9) Cline, R. E.; Fink, R. M.; Fink, K. J. Am. Chem. Soc. 1959, 81, 2521.


(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;14 182 °C;15 186–188 °C;16 185–187 °C;17 186–187 °C); 1H NMR (300 MHz, CDCl3); δ = 2.36 (s, 6 H), 7.18–7.31 (m, 3 H), 7.45 (t, J = 7.52 Hz, 0.5 H), 7.91 (d, J = 7.72 Hz, 4 H); 13C NMR (75 MHz, CDCl3); δ = 13.46, 110.03, 121.60, 127.08, 129.48, 131.18, 138.22, 153.27, 161.78; MS: m/z = 357.5 [M–H]+. The solvent was evaporated and the residue was purified by column chromatography using CH2Cl2 as eluent. The yield of product 3a = 80% (125 mg); mp 120–122 °C (Lit.14 121–122 °C);15 120–122 °C;16 182 °C;17 186–187 °C;18 185–187 °C;19 186–187 °C;20 186–187 °C). The yield of product 3a = 80% (125 mg); mp 120–122 °C (Lit.14 121–122 °C;15 120–122 °C;16 182 °C;17 186–187 °C;18 185–187 °C;19 186–187 °C;20 186–187 °C).