Facile Synthesis of 5-(Substituted vinyl)-uracil Derivatives through Knoevenagel and Stobbe type Condensations of 5-Formyluracils

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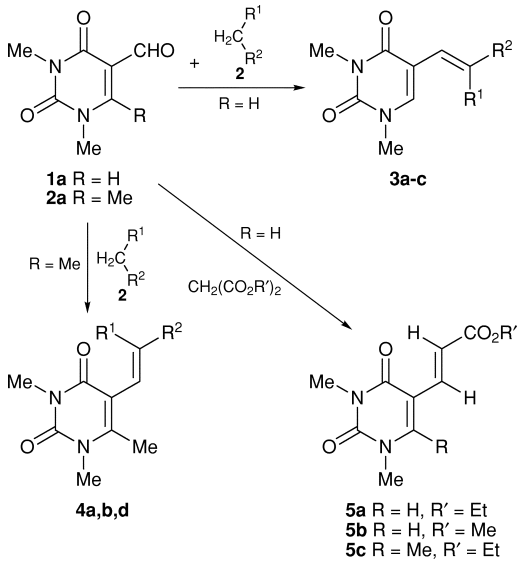
5-Formyl-1,3-dimethyl/1,3,6-trimethyl uracils (**1**) react with malononitrile, ethyl cyanoacetate, phenyl acetonitrile/acetyl acetone in Knoevenagel and with diethyl/dimethyl malonates in Stobbe modes to provide respective 5-(ethoxy/methoxy carbonyl)vinyluracils.

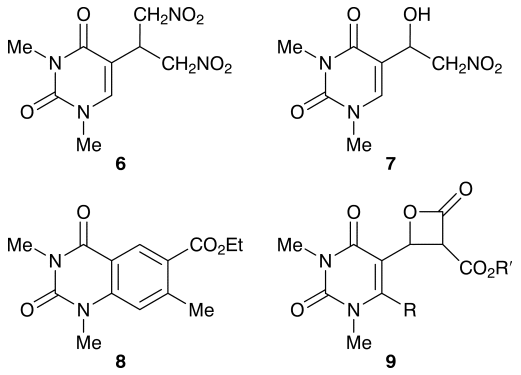
The presence of 5-vinyl substituents in uracils due to enhancement of conjugative and Michael acceptor abilities could trigger other than C-6 attack of the thiol group of the enzyme thymidylate synthase. Thus by inhibiting the enzyme functions such systems would acquire antitumor properties.[1] Amongst these, halo- or acyl-vinyluracils are available through arduous methodologies, and studies with such substrates having strong electron withdrawing group(s) on the vinyl moiety, which should further enhance their Michael acceptor properties, have not been possible because of their non-availability. Here, we report that heating of 5-formyluracils with active methylene compounds, without solvent, provides a simple methodology for the synthesis of 5-(substituted alkenyl)uracils (Scheme 1).



Scheme 1 For **2**, **3** and **4**: **a** $R^1 = R^2 = CN$; **b** $R^1 = CN$, $R^2 = CO_2Et$; **c** $R^1 = CN$, $R^2 = Ph$; **d** $R^1 = R^2 = COMe$

A homogeneous mixture of **1a** and **2a** on heating at 115 ± 5 °C (without solvent) gives **3a** (85%). From the appearance of two singlets at δ 7.97 (6-H) and 8.75 (vinyl H) in the ^{1}H NMR spectrum and an absorption band at 2250 cm^{-1} in the IR spectrum and other spectral data, this compound can be assigned structure **3a**. Similarly, **1a** reacts with **2b** (115 ± 5 °C) and **2c** [115 ± 5 °C in the presence of triethylamine (0.05 equiv.)] to provide 5-vinyluracils **3b** (70%), mp 200–205 °C and **3c** (70%), mp 225–230 °C, respectively. Therefore, for weaker carbon acids, the use of higher temperatures and base becomes essential. For the reaction of **1a** with nitromethane [115 ± 5 °C, triethylamine (0.05 equiv.)], compounds **6** (30%), mp 115 °C and **7** (20%), mp 135 °C are formed. The reactions of ketone based active methylene compounds, ethyl acetoacetate and acetylacetone with **1a** give a multitude of products, which could not be separated.

All these reactions proceed by the attack of active methylene compounds **2** and nitromethane on formyl carbon followed by elimination of a water molecule. For the reaction with nitromethane, **7** undergoes slow elimination of water but once water is eliminated, the respective 5-nitrovinyluracil undergoes subsequent addition of a further molecule of nitromethane to form **6**.



5-Formyl-1,3,6-trimethyluracil (**1b**) is known to show somewhat different reaction modes with nucleophiles. Under basic conditions, an anion is generated at the 6-Me carbon which reacts at any electrophilic site present on the nucleophilic reactant.[12] Here, under neutral reaction conditions, a homogeneous mixture of **1b** and malononitrile on heating at 115 ± 5 °C for 10 h gives **4a** (60%), mp 230–235 °C, M^+ m/z 230. Similarly, **1a** on heating with ethyl cyanoacetate for 48 h gives **4b** (62%), mp 108–110 °C but phenyl acetonitrile, even in the presence of triethylamine, fails to react. **1b** on heating with acetylacetone (72 h, 115 ± 5 °C) provides **4d** along with traces of 6-acetyl-1,3,7-trimethylquinazoline-2,4(1*H*,3*H*)-dione, mp 210 °C (lit.,[10] 210–211 °C) but with ethyl acetoacetate only quinazoline derivative **8** is formed. Therefore, reactions of **1b** with active methylene compounds require higher temperature or longer reaction time in comparison with reactions of **1a**. Probably, the steric hinderance of the 6-Me unit slows down the attack of active methylene compound on the 5-formyl carbon.

These reactions constitute cases of Knoevenagel type condensations which when performed under the usual basic conditions are plagued by base catalyzed ring transformations at the intermediate stage and the respective 5-vinyluracils are not formed.[10,13]

Uracils **1a** and **1b** on heating with diethyl malonate provide 5-vinyluracil derivatives **5a** (65%), mp 138–140 °C and **5c** (65%), mp 135 °C, respectively. **1a** reacts with dimethyl malonate to form **5b**. The formation of **5** could be rationalised through the formation of a β-lactone inter-

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mediate (**9**) followed by loss of carbon dioxide. The formation of such intermediates is quite similar to Stobbe condensation[15] reactions of carbonyl compounds with succinate and glutarate esters where intermediate γ- and δ-lactones are hydrolysed to half esters. However, in the present case, the transient less stable β-lactone ring undergoes decarboxylative collapse to generate the vinyl group. To the best of our knowledge, the formation of compounds **5** constitutes unprecedented cases of Stobbe type condensations with malonate esters and this mode of reaction provides a simple and practicable synthesis of carboxyvinyluracils, the key intermediate in the synthesis of 5-bromovinyluracils.[16]

Thus, 5-formyluracils on heating with active methylene compounds undergo facile Knoevenagel and Stobbe type condensations to provide the respective 5-vinyluracil derivatives.

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Techniques used: ^{1}H and ^{13}C NMR, mass spectrometry and IR

Figures: 1

Schemes: 3

References: 16

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