Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Version of record first published: 10 Dec 2007.

To cite this article: M. Monzur Morshed, Qinwei Wang, Shahidul Islam & M. Mahmun Hossain (2007): Convenient Synthesis of 5-Aryl Uracils, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 37:23, 4173-4181

To link to this article: http://dx.doi.org/10.1080/00397910701575319

Synthetic Communications®, 37: 4173–4181, 2007

ISSN 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910701575319

Convenient Synthesis of 5-Aryl Uracils

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Abstract: A convenient one-step synthesis of 5-aryl uracils has been developed. The procedure involves heating ethyl 3-hydroxy-2-arylpropenate with urea at 130°C, followed by base-catalyzed cyclization. The method is simple and high yielding.

Keywords: arylpropenate, uracil, urea

5-Aryl uracils are key precursors in the synthesis of pyrimidine nucleosides[1,2] (cytidine analogs, Fig. 1), which when substituted at the 5-position represent an important class of biologically active compounds. Tegafur-uracil, for example, is a well-known chemotherapy drug in cancer treatment.[3] Some 5-aryl derivatives have also been shown to possess potential antiviral activity against the human immunodeficiency virus (HIV) and other viral diseases.[4,5]

There are several ways to synthesize 5-aryl uracils,[5–8] but many of these routes are restricted to producing only a particular type of 5-aryl uracil. Most of these methods require the preparation of specific reagents and are not high in overall yield. One of the most successful methods developed to date is based on the Suzuki Pd(0)-catalyzed coupling between 2,4-di-*t*-butoxy-5-pyrimidineboronic acid and an appropriate aryl bromide (Scheme 1).[9] Unfortunately, this coupling route is low in yield and involves the tedious synthesis

Received in the USA May 9, 2007
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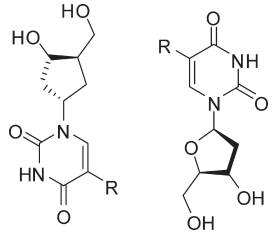
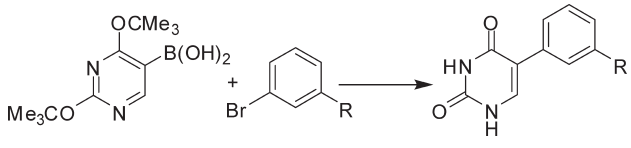


Figure 1. Cytidine analogs.

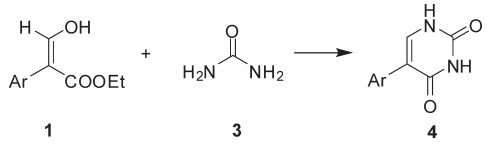
of boronic acid. Therefore, there is a need to develop an efficient synthetic route for uracils.

Our group has already developed an efficient method for the synthesis of ethyl 3-hydroxy-2-arylpropenate, **1**, from the corresponding benzaldehydes, ethyl diazo acetate (EDA), and the catalyst $[(\eta^5\text{-}C_5H_5)(CO)_2Fe(THF)]^+[BF_4]^-$, **2**, and/or HBF_4.[10] This method can be further extended to the direct synthesis of 5-aryl uracils (Scheme 2), which is essentially the condensation of urea (**3**) with the ester **1**.

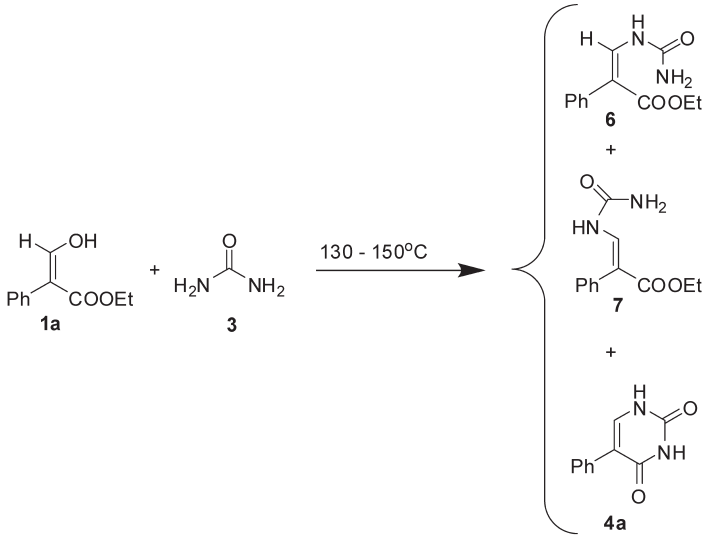
To test the feasibility of this new approach, various reaction conditions were explored, and it was found that directly heating the ethyl 3-hydroxy-2-phenylpropenate (**1a**) and urea in the absence of solvent for 2 h at 130 to 150°C provided the uracil **4a** in small amounts (see Scheme 3). The resulting reaction mixture mostly contained *Z*- and *E*-amido esters, **6** and **7**, with a total yield of about 60%. The amido esters were separated by column chromatography and were fully characterized by ^{1}H NMR,^{13}C NMR, and high-resolution mass spectroscopy.



Scheme 1.



Scheme 2.



Scheme 3.

The stereochemistry of the intermediates was confirmed using NOE spectra (Fig. 2). The nuclear overhauser effect (NOE) of the *Z*-isomer (a) shows the correlation of the H^3 (7.60 ppm) with the *ortho*-aromatic proton (7.32 ppm), when there is no correlation between N-H proton (10.04 ppm) and the *ortho*-aromatic proton. On the other hand, the NOE of the *E*-isomer (b) shows no correlation between H^3 (8.28 ppm) and *ortho*-aromatic proton (7.24 ppm), when there is correlation between N-H proton (7.88 ppm) and the *ortho*-aromatic proton.

Although the product mixture contained a small amount of uracil, it could not be made into a major product with prolonged heating or at elevated temperatures. At temperatures greater than 170°C, some unidentified by-products were found. Attempts were then made to convert isolated **6** and **7** to **4a**. The cyclization of amido ester **6** could be initiated easily by dissolving it in ethanol with 1 equiv. of sodium and refluxing for 1–2 h. After simple workup using dilute HCI (aq), **4a** was obtained in almost quantitative yield. The isolated amido ester **7** was also converted quantitatively to **4a** using the same procedure. Consequently, the synthesis of uracil (**4a**) was performed in one pot by heating the propenate (**1a**) and urea followed by cyclization with sodium in ethanol. In addition, to improve the yield of uracil, the esters and urea were heated in a sealed or closed flask under vacuum.

During heating at 130°C under nitrogen, urea was found to partially sublime and affect the yield of the intermediate.

The base-catalyzed amonolysis of *Z*-amido ester **6** to form **4a** is a straightforward reaction. Although the mechanistic details of conversion of *E*-amido ester **7** to uracil **4a** were not studied, we propose a plausible mechanism

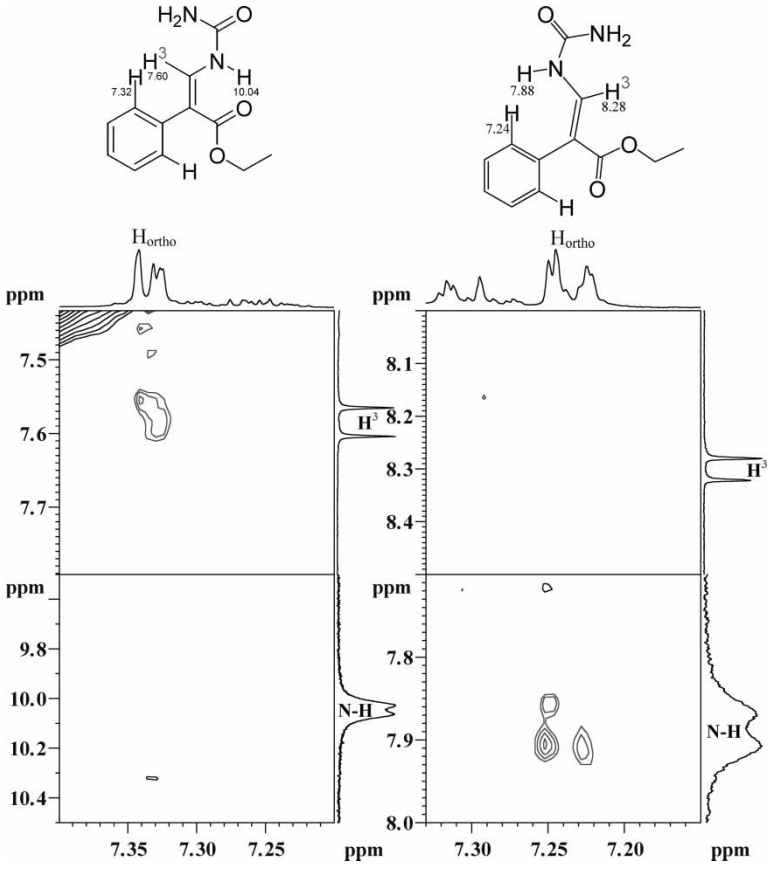
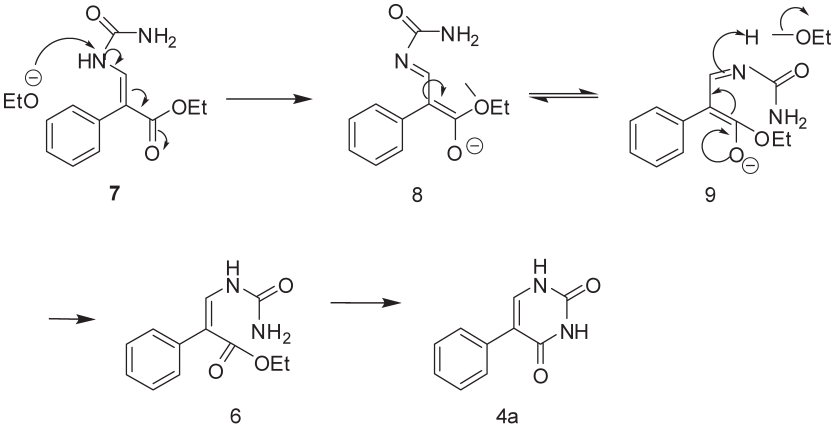


Figure 2. NOE for the *Z*- and *E*-isomer of the intermediate.



Scheme 4.

outlined in Scheme 4. First, we believe the base deprotonates **7** to form an enolate **8**, which undergoes rotation about C2–C3 carbon bond to form the enolate **9**. Later, the enolate **9** is protonated by ethanol to form *Z*-amido ester **6**, which cyclizes to form the uracil **4a**.

The general scope of the reaction was investigated using substituted ethyl 3-hydroxy-2-arylpropenates, which were prepared according to the method developed by our group.[10–13] The various esters were successfully treated with urea, giving the desired uracil products in excellent isolated yield. Results are summarized in Table 1.

In conclusion, a high-yielding, convenient, and general method has been developed for the synthesis of 5-aryl uracil. Currently, we are using this method in the preparation of biologically important uracil compounds.

EXPERIMENTAL SECTION

General Procedure

One equivalent of ethyl-3-hydroxy-2-arylpropenate was mixed with 2 to 3 equiv. of urea in a glass tube. The tube was sealed under vacuum and heated in a silicon oil bath overnight at 130°C. After cooling, the yellow solid was dissolved in EtOH (50–100 mL) in a round-bottomed flask, and 2–3 equiv. of sodium were added. After refluxing the reaction mixture at 80°C for 4 to 5 h, dilute HCl was added to bring the pH of the solution to 5 to 6, and a white precipitate of 5-aryl uracil was formed. The compound was collected by filtration and dried in a drying pistol using P_2O_5 as the drying agent.

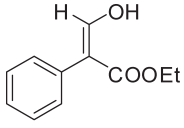
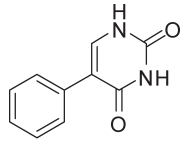
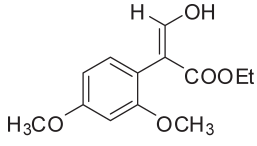
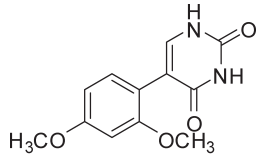
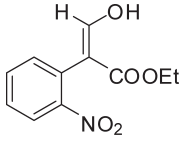
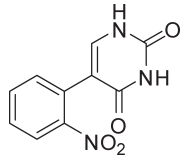
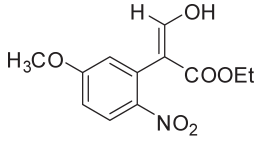
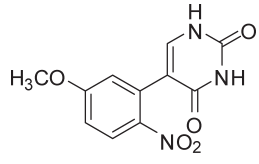
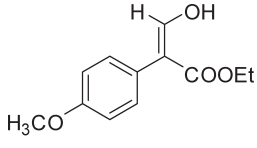
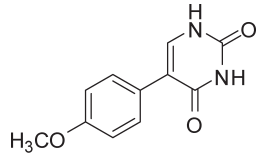
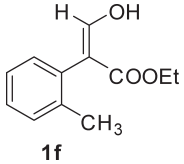
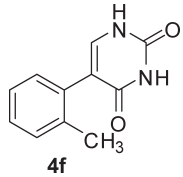
Synthesis of 5-Phenyl Uracil (4a)[14]

Using the general procedure, 5-phenyl uracil (**4a**) was isolated in 95% yield from 0.51 g (2.65 mmol) of ethyl-3-hydroxy-2-phenylpropenate (**1a**) and 0.24 g (4.0 mmol) of urea. The uracil **4a** was identified by comparing its spectra to the reported literature values.[13] ^{1}H NMR (DMSO, 300 MHz) δ: 11.23 (s, 1H, NH), 11.12 (s, 1H, broad, NH), 7.58 (d, $J = 5.8$ Hz, 1H, CH), 7.50 (d, $J = 7.1$ Hz, 2H, Ph), 7.34 (t, $J = 6.9$, 2H, Ph), 7.26 (t, $J = 7.1$ Hz, 1H, Ph).

Synthesis of 5-(2,4-Dimethoxyphenyl) Uracil (4b)

Using the general procedure, 5-(2,4-dimethoxyphenyl) uracil (**4b**) was isolated in 98% yield from 0.43 g (1.71 mmol) of ethyl-3-hydroxy-2-(2,4-dimethoxyphenyl) propenate (**1b**)[13] and 0.11 g (1.83 mmol) of urea. ^{1}H NMR (DMSO, 300 MHz) δ: 11.06 (s, 1H, NH), 10.88 (d, $J = 4.9$ Hz, 1H, NH), 7.29 (d, $J = 5.9$ Hz, 1H,

Table l. Isolated yield of 5-aryl uracils

Entry	2-Aryl-3-hydroxy-propenoic acid ester	Uracil	Uracil yield (%)
1	 **1a**	 **4a**	95
2	 **1b**	 **4b**	98
3	 **1c**	 **4c**	85
4	 **1d**	 **4d**	96
5	 **1e**	 **4e**	96
6	 **1f**	 **4f**	97

CH), 7.10 (d, $J = 8.3$ Hz, 1H, Ph), 6.57 (s, 1H, Ph), 6.51 (d, $J = 8.4$ Hz, 1H, Ph), 3.77 (s, CH_3), 3.71 (s, CH_3); ^{13}C NMR (DMSO, 75.4 MHz) δ: 163.5, 160.5, 158.5, 151.5, 140.4, 132.2, 114.8, 110.0, 104.9, 98.9, 55.9, 55.6. HRMS (m/z): calculated for $C_{12}H_{12}N_2O_4$, 248.0797; found 248.0803.

Synthesis of 5-(2-Nitrophenyl) Uracil (4c)

Using the general procedure, 5-(2-nitrophenyl) uracil (**4c**) was isolated in 85% yield from 0.39 g (1.64 mmol) of ethyl-3-hydroxy-2-(2-nitrophenyl) propenate (**1c**)[13] and 0.28 g (4.67 mmol) of urea. ^{1}H NMR (DMSO, 300 MHz) δ: 11.34 (s, 1H, NH), 10.32 (s, 1H, NH), 7.97 (d, $J = 8.1$ Hz, 1H), 7.73 (m, 2H, Ph), 7.50 (d, $J = 7.6$ Hz, 1H), 6.59 (t, $J = 7.7$ Hz, 1H, Ph). ^{13}C NMR (DMSO, 75.4 MHz) δ: 162.7, 151.4, 149.2, 140.2, 133.8, 132.5, 129.3, 128.0, 124.5, 111.6. HRMS (m/z): calculated for $C_{10}H_7N_3O_4$, 233.0437; found 233.0437.

Synthesis of 5-(2-Nitro-5-methoxyphenyl) Uracil (4d)

Using the general procedure, 5-(2-nitro-5-methoxyphenyl) uracil (**4d**) was isolated in 96% yield from 0.34 g (1.27 mmol) of ethyl-3-hydroxy-2-(2-nitro-5-methoxyphenyl) propenate (**1d**)[13] and 0.23 g (3.83 mmol) of urea. ^{1}H NMR (DMSO, 300 MHz) δ: 11.31 (s, 1H, NH), 11.25 (d, $J = 6.04$, 1H, NH), 8.01 (d, $J = 9.15$ Hz, 1H), 7.72 (d, $J = 6.04$ Hz, 1H), 7.08 (d, $J = 2.74$ Hz, 1H), 7.00 (d, $J = 2.74$ Hz, 1H), 3.88 (s, 3H). ^{13}C NMR (DMSO, 75.4 MHz) δ: 162.99, 162.57, 151.46, 142.34, 139.92, 127.06, 117.45, 113.99, 112.19, 56.53. Anal. calculated for $C_{13}H_{15}O_6N_3$: C, 50.20; N, 15.96, H, 3.45. Found: C, 50.20, N, 14.86; H, 3.66.

Synthesis of 5-(4-Methoxyphenyl) Uracil (4e)[14]

Using the general procedure, 5-(4-methoxyphenyl) uracil (**4e**)[14] was isolated in 96% yield from 0.33 g (1.486 mmol) of ethyl-3-hydroxy-2-(4-methoxyphenyl) propenate (**1e**)[10] and 0.27 g (4.5 mmol) of urea. The uracil **4e** was identified by comparing its spectra to the reported literature values.[14] ^{1}H NMR (DMSO, 300 MHz) δ: 11.34 (s, 1H, NH), 11.10 (s, 1H, NH), 7.58 (s, 1H), 7.46 (d, $J = 8.75$ Hz, 2H), 6.92 (d, $J = 8.75$, 2H), 3.75 (s, 3H).

Synthesis of 5-(2-Methylphenyl) Uracil (4f)

Using the general procedure, 5-(2-methylphenyl) uracil (**4f**) was isolated in 97% yield from 0.63 g (3.06 mmol) of ethyl-3-hydroxy-2-(2-methylphenyl) propenate (**1f**)[11] and 0.55 g (9.18 mmol) of urea. ^{1}H NMR (DMSO, 300 MHz) δ: 11.50 (s, 1H, NH), 11.00 (d, $J = 4.57$, 1H, NH), 7.36 (d, $J = 5.85$ Hz, 1H), 7.24–7.06 (m, 4H), 2.15 (s, 3H). ^{13}C NMR (DMSO, 75.4 MHz) δ: 163.29, 151.70, 140.57, 137.80, 130.99, 129.98, 128.07, 125.83, 113.70, 20.03. HRMS (m/z): calculated for $C_{10}H_7N_3O_4$, 202.0742; found 202.0736.

Synthesis of 6 and 7

A sample of ethyl 3-hydroxy-2-phenylpropenate **1a** (0.380 g, 1.97 mmol) was mixed with urea (0.145 g, 2.41 mmol) and heated at 130°C overnight; the crude products were separated using a silica column. The 40% *Z*-intermediate (**6**), 20% *E*-intermediate (**7**), and a small amount of 5-phenyl uracil (**4a**) were isolated by column chromatography using pentane/ethyl acetate solvent.

Z-Intermediate (**6**)

^{1}H NMR (DMSO, 300 MHz) δ: 9.98 (d, $J = 11.9$ Hz, 1H, NH), 6.70 (d, $J = 11.9$ Hz, 1H, CH), 7.32 (m, 5H, Ph), 7.04 (s, broad, NH_2), 4.18 (q, $J = 7.1$ Hz, 2H, CH_2), 1.18 (t, $J = 7.1$ Hz, 3H, CH_3). ^{13}C NMR (DMSO, 75.4 MHz) δ: 167.8 (COOEt), 154.5 (CO), 141.0 (CH), 137.7 (C, Ph), 129.5 (2 CH, Ph), 128.3 (2 CH, Ph), 126.6 (CH, Ph), 105.7 (C_α), 60.2 (OCH_2), 14.5 (CH_3). HRMS (m/z): calculated for $C_{12}H_{14}N_2O_3$, 234.1004. Found 234.1018.

E-Intermediate (**7**)

^{1}H NMR (DMSO, 300 MHz) δ: 8.30 (d, $J = 12.7$ Hz, 1H, NH), 8.10 (d, $J = 12.4$ Hz, 1H, CH), 7.35 (m, 3H, Ph), 7.19 (d, $J = 7.3$ Hz, 2H, Ph), 6.58 (s, broad, NH_2), 4.08 (q, $J = 7.1$ Hz, 2H, CH_2), 1.18 (t, $J = 7.1$ Hz, 3H, CH_3). ^{13}C NMR (DMSO, 75.4 MHz) δ: 167.3, 154.4, 136.8, 134.1, 130.6, 129.5, 128.8, 128.3, 127.5, 107.7, 60.1, 14.7. HRMS (m/z): calculated for $C_{12}H_{14}N_2O_3$, 234.1004. Found 234.1017.

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