# A Facile Synthesis of Fluorophores Based on 5-Phenylethynyluracils

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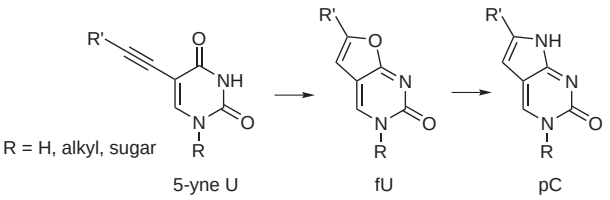
**Abstract:** Compact, fluorescent uracil aglycones and derivatives suitable for incorporation into the oligonucleotide mimic peptide nucleic acid (PNA) have been prepared by Sonogashira/Castro–Stephens coupling to monosubstituted phenylacetylenes. Cyclic 6-(phenyl)furo[2,3-d]pyrimidin-2(3*H*)-ones were accessed by the $Ag^+$-catalyzed cyclization of the 5-alkynyluracil precursors. Although this reaction was sluggish, it gave quantitative chemical yields. Electron-rich alkynes, such as *p*-methoxyphenylethyne, cyclize much more rapidly than electron-deficient alkynes. Adjustment of the reaction conditions permitted the synthesis of *p*-nitrophenylfuranouracil in excellent yield.

**Key words:** annulations, silver(I)-catalyzed cyclization, furanouracils, 5-phenylethynyluracil, nucleobases

There exists a great variety of pyrimidine heterocycles and pyrimidine nucleosides bearing substitution at the 5-position, many of which have found some practical application. Our particular interest has been in 5-alkynyluracils (5-yne U) and their use as an intermediate towards the fluorescent furo[2,3-*d*]pyrimidin-2(3*H*)-ones (furanouracil, fU; Scheme 1), which may also serve as a precursor to pyrrolocytosine (pC).[1]




**Scheme 1**

N1-Unsubstituted 5-ethynyluracils (R = H, Scheme 1) have been a synthetic target for some time and have been approached by the Corey–Fuchs reaction with 5-formyluracil,[2] or by metal-catalyzed coupling reactions with 5-iodouracil.[3] More recent work, especially with the nucleoside, has shown the utility and reliability of the Sonogashira/Castro–Stephens reaction.[4,5] However, this reaction has given more variable results with 5-iodouracil as a substrate. In this letter, we report the synthesis of N1-unsubstituted and N1-alkylated 5-phenylethynyluracils and their efficient Ag(I)-catalyzed cyclization to furanouracils. We have found that simple 5-phenylethynyluracils are fluorescent and are expected to maintain their base-pairing capacity for adenine, unlike furanouracil as illustrated in Figure 1.[6]

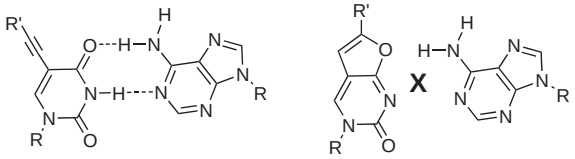
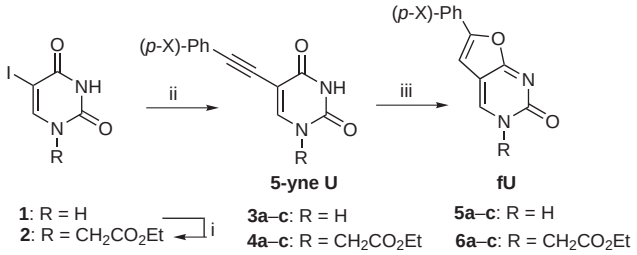



**Figure 1** Base-pairing ability of 5-yne U (left) but not fU (right).

Furthermore, the 5-phenylethynyluracils are intrinsically luminescent – neither the phenylacetylene nor the heterocycle possess any appreciable fluorescence, but once coupled together the molecule is fluorescent.[3,7,8] N1-Unsubstituted uracils have potential use as selective small molecule probes for adenine[9] or may be substrates for glycosylation reactions to prepare unusual nucleosides,[2,10] whereas the N1-alkylated uracils are suitable for use in PNA synthesis.[11]

The 5-phenylethynyluracils and furanouracils were prepared according to Scheme 2. Uracil was iodinated to yield 5-iodouracil (**1**) as previously reported.[12,13] Compound **1** was then cross-coupled to various *para*-substituted phenylacetylenes using standard Sonogashira-based conditions[5] to yield the 5-phenylethynyluracils **3a**–**c** that are unsubstituted at the N1-position.[14] Alternatively, **1** can be alkylated using ethyl bromoacetate yielding **2**,[15] which underwent analogous cross-coupling with the same phenylacetylenes to yield the N1-substituted 5-phenylethynyluracils **4a**–**c**.




**Scheme 2** *Reagents and conditons*: i) $BrCH_2CO_2Et$, DMF, $K_2CO_3$; ii) alkyne, $Pd(PPh_3)_4$, CuI, $Et_3N$, DMF; iii) $AgNO_3$, acetone or $Ag_2SO_4$, 1:1 dioxane–$H_2O$ (**5c**).

The cross-coupled products were achieved in very good yields after purification as reported in Table 1.

The few existing examples of the synthesis of 5-alkynyl N1-unsubstituted uracils in the literature indicate the reaction may be unreliable.[3] In this work, it is clear that

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**Table 1** Cross-Coupling of *p*-Substituted Phenylacetylenes

| Compound | R | *p*-X | Yield (%) |
|---|---|---|---|
| **3a** | H | H | 88 |
| **3b** | H | $OCH_3$ | 91 |
| **3c** | H | $NO_2$ | 86 |
| **4a** | $CH_2CO_2Et$ | H | 83 |
| **4b** | $CH_2CO_2Et$ | $OCH_3$ | 87 |
| **4c** | $CH_2CO_2Et$ | $NO_2$ | 78 |

phenylacetylenes react cleanly to give the cross-coupled products free from contamination of the cyclized product, under gentle thermal conditions.[3b] The N1-alkylated uracils behave well in the cross-coupling reaction as expected by analogy to the wealth of examples done on the nucleoside. For both substrate classes, the cross-coupling is completed within 16 hours.

With the 5-phenylethynyluracils in hand, we wished to synthesize the corresponding furanouracils by promoting a 5-*endo*-dig cyclization reaction (Scheme 2, *iii*). While previous authors have reported the one-step cyclization of halouracils to furanouracils,[4a,16] and while we have observed this in our own research with derivatives of cytosine,[17] we have experienced much more difficulty with uracil-based substrates. The higher temperatures required for this reaction appeared to facilitate undesirable side reactions, which often led to the formation of an intractable solid that resisted characterization. Therefore, we chose to use a two-step process: first cross-coupling; followed by the use of the cyclization conditions recently reported by Agrofoglio.[18] This procedure was found to be very successful in the case of the N1-substituted 5-phenylethynyluracils (**4a**–**c**) giving the furanouracils (**6a**–**c**) in very good yield (Table 2).[19]

For cyclization of the N1-unsubstituted compounds (**3a**–**c** → **5a**–**c**), while the reaction itself is quantitative as judged by examining the $^1H$ NMR spectrum or by TLC analysis of the crude sample,[20,21] the difficulty in purifying these compounds is reflected in the recovered yield (Table 2). The primary challenge to their purification is the water-solubility of these compounds, which complicates catalyst removal. Although various procedures have been attempted in order to remedy this problem, we have not yet discovered an optimal method of isolation/purification for the relatively water-soluble compounds. The small amount of silver catalyst only needs to be rigorously removed if it will interfere with subsequent chemistry, which was found to be the case for the saponification of compounds **6a**,**b**.

**Table 2** $AgNO_3$-Catalyzed Cyclization of 5-Alkynyluracils

| Compound | R | *p*-X | Yield (%) |
|---|---|---|---|
| **5a** | H | H | 37[a] |
| **5b** | H | $OCH_3$ | 42[a] |
| **5c** | H | $NO_2$ | 88 |
| **6a** | $CH_2CO_2Et$ | H | 80 |
| **6b** | $CH_2CO_2Et$ | $OCH_3$ | 84 |
| **6c** | $CH_2CO_2Et$ | $NO_2$ | 85 |

[a] These compounds have better solubility in water compared to the N1-substituted heterocycles (**6a**–**c**) and the *p*-nitrophenylethynyluracil (**5c**) and losses during aqueous–organic extractive work-up contributed, in part, to the diminished yields.

Under the conditions employed, for all compounds, the cyclization is much slower than the cross-coupling reaction. The N1-alkylated compounds (**4a**–**c**) tend to react more quickly than their unsubstituted analogues (**3a**–**c**), while electron-rich compounds such as **6b** (48 h, r.t.) react more quickly than electron-poor compounds (**5c**, >14 d, reflux), which is probably related to the donicity of the alkyne towards the Lewis acid. However, in all cases the cyclization is very clean, and with patience, will proceed to complete consumption of the starting material. The *p*-nitrophenylethynyl-substituted uracils reacted the most slowly and were unsatisfactory substrates under the standard reaction conditions as reported by Agrofoglio.[18] Under refluxing acetone conditions the cyclization was 80% complete after 14 days. Clearly this is not a very practical reaction, and it was found that quantitative cyclization could be achieved in 1:1 water–1,4-dioxane using a stoichiometric amount of $Ag_2SO_4$ at 50 °C in six days. The pure product was conveniently isolated by dilution of the reaction mixture with water, which caused precipitation of the product that led to an excellent recovered yield of the final product.

Both the 5-phenylethynyluracils **3a**–**c**, **4a**–**c** and cyclized furanouracils **5a**–**c**, **6a**–**c** exhibited substitution-dependent fluorescent properties as reported in Table 3.[22] In general, the trends are similar to the spectral properties observed for pyrrolocytosines,[6,17] yet with some subtle differences. N1-Substitution benefits the intensity of fluorescence as does annulation to furanouracil from the 5-alkynyluracil such that N1-substituted > N1-unsubstituted and cross-coupled vs. cyclized (fU > 5-yne U). The nature of the *para* substituent also affects the fluorescence such that a greater red shift through the series $NO_2$ >> $OCH_3$ > H was observed. However, there was no consistent trend for the effect of these substituents on the fluorescence intensity. In addition, although the nitro-substituted compounds were visibly fluorescent in solution or when deposited on silica, emitting orange light when illuminated at 360 nm, their emission spectra showed a very broad low-intensity band. The weakness of the fluorescence for these particular compounds may be limiting in their potential as a reporter group.

In this report, we have described the synthesis of simple, 5-phenylethynyluracils that exhibit substituent-dependent fluorescence and their conversion to phenyl-substituted bicyclic furanouracils by treatment with silver(I) ion.[18] Notably, the latter reaction may be done in an aqueous–

**Table 3** Spectral Properties of 5-Yne Us and fUs

| Compound | ε[a] (260 nm) | $\lambda_{excitation}$ (nm) | $\lambda_{emission}$ (nm) | Relative intensity[b] |
|---|---|---|---|---|
| **3a** | 1650 | 330 | 410 | 1.5 |
| **3b** | 2840 | 332 | 432 | 2.7 |
| **3c** | 3050 | 435 | 520 | NA[c] |
| **4a** | 6040 | 349 | 425 | 1.0 |
| **4b** | 4310 | 325 | 436 | 4.6 |
| **4c** | 4920 | 400 | 525 | NA[c] |
| **5a** | 1610 | 342 | 420 | 23 |
| **5b** | 1960 | 350 | 460 | 15 |
| **5c** | 3320 | 420 | 530 | NA[c] |
| **6a** | 6310 | 352 | 427 | 67 |
| **6b** | 4890 | 360 | 449 | 118 |
| **6c** | 1790 | 452 | 520 | NA[c] |

[a] Molar absorptivity values (l $mol^{-1}$ $cm^{-1}$) measured at the standard wavelength for nucleobases.
[b] Determined by the ratio of arbitrary fluorescence intensity (counts per second) in degassed MeOH measured at the emission maxima.
[c] NA = not available. A relative comparison cannot be made reliably because of the large difference in excitation wavelength and concentration of compound required.

organic solvent mixture which permits greater loading of the Lewis acid promoter and shorter reaction times for water-soluble substrates.

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## References and Notes

(1) (a) Woo, J.; Meyer, R. B. Jr.; Gamper, H. B. *Nucleic Acids Res.* **1996**, *24*, 2470. (b) Berry, D. A.; Jung, K.-Y.; Wise, D. S.; Sercel, A. D.; Pearson, W. H.; Mackie, H.; Randolph, J. B.; Somers, R. L. *Tetrahedron Lett.* **2004**, *45*, 2457.
(2) Synthesis of 5-ethynyluracil was achieved in 36% yield: Perman, J.; Sharma, R. A.; Bobek, M. *Tetrahedron Lett.* **1976**, *28*, 2427.
(3) (a) One example: 5-(*o*-aminophenylethynyl)uracil, 90%. See: Arcadi, A.; Cacchi, S.; Marinelli, F. *Tetrahedron Lett.* **1989**, *30*, 2581. (b) One example: 5-(phenylethynyl)uracil, 61%. See: Farina, V.; Hauck, S. I. *Synlett* **1991**, 157. (c) Two examples, failed thermal reaction but 65% of 5-(phenylethynyl)uracil under microwave irradiation. See: Petricci, E.; Radi, M.; Corelli, F.; Botta, M. *Tetrahedron Lett.* **2003**, *44*, 9181.
(4) (a) Robins, M. J.; Barr, P. J. *Tetrahedron Lett.* **1981**, *22*, 421. (b) Hudson, R. H. E.; Li, G.; Tse, J. *Tetrahedron Lett.* **2002**, *43*, 1381.
(5) (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467. (b) Stephens, R. D.; Castro, C. E. *J. Org. Chem.* **1963**, *28*, 3313.
(6) A preliminary report has appeared in conference proceedings: Hudson, R. H. E.; Dambenieks, A. K.; Moszynski, J. M. *Proc. SPIE – Int. Soc. Optical Eng.* **2005**, 103.
(7) Although 5-phenylethynyluracils (ref. 3), 5-phenylethynyluridine and 5-phenylethynyl-2′-dexoyuridine have been previously synthesized no description of their luminescent properties has appeared: (a) Rai, D.; Johar, M.; Manning, T.; Agrawal, B.; Kunimoto, D. Y.; Kumar, R. *J. Med. Chem.* **2005**, *48*, 7012. (b) Angell, A.; McGuigan, C.; Garcia Sevillano, L.; Snoeck, R.; Andrei, G.; De Clercq, E.; Balzarini, J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2397. (c) Aucagne, V.; Berteina-Raboin, S.; Guenot, P.; Agrofoglio, L. A. *J. Comb. Chem.* **2004**, *6*, 717. (d) The fluorescence of 5-tolylethynyl-2′-dexoyuridine has been recognized: Esho, N.; Davies, B.; Lee, J.; Dembinski, R. *Chem. Commun.* **2002**, 332.
(8) Intrinsically fluorescent uracils have been noted for substantially larger ethynyl-linked aromatic chromophores: (a) Hurley, D. J.; Seaman, S. E.; Mazura, J. C.; Tor, Y. *Org. Lett.* **2002**, *4*, 2305. (b) Thoresen, L. H.; Jiao, G.-S.; Haaland, W. C.; Metzker, M. L.; Burgess, K. *Chem. Eur. J.* **2003**, *9*, 4603.
(9) Yoshimoto, K.; Xu, C.-Y.; Nishizawa, S.; Haga, T.; Satake, H.; Teramae, N. *Chem. Commun.* **2003**, 2960.
(10) (a) Barr, P. J.; Jones, S.; Serafinowski, P.; Walker, R. T. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1263. (b) Valdivia, V.; Hernandez, A.; Rivera, A.; Sartillo, F.; Loukaci, A.; Fourrey, J.-L.; Quintero, L. *Tetrahedron Lett.* **2005**, *46*, 6511.
(11) Dueholm, K. L.; Egholm, M.; Behrens, C.; Christensen, L.; Hansen, H. F.; Vulpius, T.; Petersen, K. H.; Berg, R. H.; Nielsen, P. E.; Buchardt, O. *J. Org. Chem.* **1994**, *59*, 5767.
(12) Asakura, J.-I.; Robins, M. J. *J. Org. Chem.* **1990**, *55*, 4928.
(13) Compound **1**: uracil (134 mmol, 15.0 g) was suspended in 800 mL of MeOH. Then, $I_2$ (81 mmol, 20.4 g) and CAN (67 mmol, 36.7 g) were added. The reaction was refluxed for 16 h, cooled, and a white precipitate was collected by filtration. The filtrate was evaporated, and then co-evaporated with 2:1 EtOH–$H_2O$ to remove iodine (2 × 90 mL). Both product fractions were then combined and recrystallized from 1:1 EtOH–$H_2O$ to obtain 30.6 g (89% yield) of **2**. Translucent needles; mp >280 °C (dec.). HRMS (EI): *m/z* calcd for $C_4H_3IN_2O_2$: 237.9239; found: 237.9246. $^1$H NMR (DMSO-$d_6$): 11.41 (s, 1 H), 11.17 (s, 1 H), 7.88 (s, 1 H).
(14) **General Procedure for Cross-Coupling.**
5-Iodouracil compound **1** or **2** (1 mmol) was stirred in anhydrous DMF (3 mL). Then, CuI (0.2 mmol) was added and the solvent was deoxygenated. $Pd(PPh_3)_4$ (0.1 mmol), $Et_3N$ (2 mmol) and alkyne (1.5–3 mmol) were added sequentially. The reaction mixture was then stirred overnight at r.t. The completed reaction was extracted with a sat. EDTA solution against $CH_2Cl_2$, evaporated, and dried under vacuum. The residue was then suspended in a minimum amount of $CH_2Cl_2$ and precipitated with $Et_2O$. Silica gel chromatography using gradient elution with MeOH–$CH_2Cl_2$ mixtures was used to purify the 5-alkynyluracils **3a**–**c** and **4a**–**c**. All $^1$H NMR spectra were recorded at 400.09 MHz in DMSO-$d_6$.
Compound **3a**: white solid; elution at 8% MeOH–$CH_2Cl_2$; mp >280 °C (dec.). HRMS (EI): *m/z* calcd for $C_{12}H_8N_2O_2$: 212.0586; found: 212.0594. $^1$H NMR: δ = 11.41 (br s, 1 H) overlapping with 11.36 (br s, 1 H), 7.88 (s, 1 H), 7.43–7.47 (m, 2 H), 7.37–7.41 (m, 3 H).

Compound **3b**: white solid; elution at 15% MeOH; mp >270 °C (dec.). HRMS (EI): *m/z* calcd for $C_{13}H_{10}N_2O_3$: 242.0691; found: 242.0695. $^1$H NMR: δ = 11.40 (s, 1 H), 11.31 (br s, 1 H), 7.84 (s, 1 H), 7.37 (d, 2 H, *J* = 8.8 Hz), 6.96 (d, 2 H, *J* = 8.9 Hz), 3.77 (s, 3 H).
Compound **3c**: light orange solid; elution from 15–30% MeOH; mp 282–286 °C (dec.). HRMS (EI): *m/z* calcd for $C_{12}H_7N_3O_4$: 257.0437; found: 257.0440. $^1$H NMR: δ = 11.54 (br s, 1 H), 11.51 (s, 1 H), 8.24 (d, 2 H, *J* = 9.1 Hz), 8.03 (s, 1 H), 7.68 (d, 2 H, *J* = 8.9 Hz).
Compound **4a**: white crystals; elution from silica at 2% MeOH; mp 193–196 °C. HRMS (EI): *m/z* calcd for $C_{16}H_{14}N_2O_4$: 298.0954; found: 298.0498. $^1$H NMR: δ = 11.85 (s, 1 H), 8.55 (s, 1 H), 7.45–7.48 (m, 2 H), 7.40–7.43 (m, 3 H), 4.55 (s, 2 H), 4.17 (q, 2 H, *J* = 7.0 Hz), 1.21 (t, 3 H, *J* = 7.0 Hz).
Compound **4b**: white solid; elution at 2.5% MeOH–$CH_2Cl_2$; mp 196–197 °C. HRMS (EI): *m/z* calcd for $C_{17}H_{16}N_2O_5$: 328.1059; found: 328.1068. $^1$H NMR: δ = 11.82 (s, 1 H), 8.14 (s, 1 H), 7.40 (d, 2 H, *J* = 8.8 Hz), 6.96 (d, 2 H, *J* = 8.6 Hz), 4.54 (s, 2 H), 4.15 (q, 2 H, *J* = 7.1 Hz), 3.77 (s, 3 H), 1.20 (t, 3 H, *J* = 7.2 Hz).
Compound **4c**: pale yellow solid; elution at 3% MeOH–$CH_2Cl_2$; mp >245 °C (dec.). HRMS (EI): *m/z* calcd for $C_{16}H_{13}N_3O_6$: 343.0804; found: 343.0810. $^1$H NMR: δ = 11.95 (s, 1 H), 8.32 (s, 1 H), 8.25 (d, 2 H, *J* = 8.9 Hz), 7.71 (d, 2 H, *J* = 8.8 Hz), 4.57 (s, 2 H), 4.17 (q, 2 H, *J* = 7.0 Hz), 1.21 (t, 3 H, *J* = 7.1 Hz).

(15) Compound **2**: **1** (63.3 mmol, 15 g) was suspended in 100 mL DMF, to which anhyd $K_2CO_3$ (63.0 mmol, 8.7 g) was added. Then, $BrCH_2CO_2Et$ (63.1 mmol, 7.0 mL) was added dropwise under $N_2$. The reaction was stirred for 16 h, filtered to remove salts and then the solvent was evaporated. The residue was then cooled in an ice bath and acidified with 4 M HCl (65 mL). The resulting precipitate was then filtered, washed with $Et_2O$ and dried. The crude product was recrystallized from 1:1 EtOH–$H_2O$ to produce 10.6 g (85% yield) of pure product. White crystals; mp 170–172 °C. HRMS (EI): *m/z* calcd for $C_8H_9IN_2O_4$: 323.9607; found: 323.9724. $^1$H NMR: δ = 11.82 (s, 1 H), 8.20 (s, 1 H), 4.49 (s, 2 H), 4.13 (q, 2 H, *J* = 7.1 Hz), 1.19 (t, 3 H, *J* = 7.1 Hz).

(16) Robins, M. J.; Barr, P. J. *J. Org. Chem.* **1983**, *48*, 1854.

(17) Hudson, R. H. E.; Dambenieks, A. K.; Viirre, R. D. *Synlett* **2004**, 1400.

(18) Aucagne, V.; Amblard, F.; Agrofoglio, L. A. *Synlett* **2004**, 2406.

(19) **General Procedure for Annulation.**
The 5-alkynyluracil was suspended in deoxygenated acetone, and 5 mol% $AgNO_3$ was added. While the original procedure called for 0.047 mmol of alkyne and 0.009 mmol catalyst; scale-up was found to be effective up to 2 mmol of starting alkynyl-uracil. The reaction mixture was stirred in the dark for >24 h and monitored by TLC (5–15% MeOH–$CH_2Cl_2$) until completion reaction. The completed reaction was washed with $H_2O$ against $CH_2Cl_2$, evaporated and dried under vacuum to provide the phenylfuranouracils **5a**–**c** and **6a**–**c**. As the N1-unsubstituted furanouracils **5a**–**c** are quite water-soluble, silver nitrate removal caused a significant loss of product for these cases, accounting for the lower yields. All $^1$H NMR spectra were recorded at 400.09 MHz in DMSO-$d_6$.
Compound **5a**: $AgNO_3$ (5 mol%), r.t., 96 h; white solid; mp >350 °C (dec.). HRMS (EI): *m/z* calcd for $C_{12}H_8N_2O_2$: 212.0586; found: 212.0574. $^1$H NMR: δ = 8.34 (s, 1 H), 7.82 (m, 2 H), 7.51–7.40 (m, 3 H), 7.22 (s, 1 H).
Compound **5b**: $AgNO_3$ (5 mol%), 82 h. Reaction is quantitative as measured by $^1$H NMR, however, significant losses were encountered during the work-up and purification. Chromatography on an elemental sulfur column or through a plug of EDTA·2Na$^+$ was performed, but neither adsorbed the catalyst. In situ generation of $Cl^-$ by addition of chlorotrimethylsilane, or addition of brine was unsuccessful for removal of silver ion. The reaction mixture was subsequently purified by silica gel chromatography (elution at 30–40% MeOH), with some of the very polar compound remaining on the column, thereby reducing the yield. Pale yellow solid; mp >285 °C (dec.). HRMS (EI): *m/z* calcd for $C_{13}H_{10}N_2O_3$: 242.0691; found: 242.0693. $^1$H NMR: δ = 8.28 (s, 1 H), 7.75 (d, 2 H, *J* = 8.9 Hz), 7.05 (d, 2 H, *J* = 9.1 Hz), 7.04 (s, 1 H), 3.81 (s, 3 H).
Compound **5c**: $AgNO_3$ (15 mol%), reflux(acetone), 14 d, 80% yield. Alternatively, $Ag_2SO_4$ (1 equiv), 1:1 dioxane–water, 50 °C, 6 d, isolated by precipitation caused by the addition of one volume of $H_2O$: 88% yield. Yellow-orange solid; mp >320 °C (dec.). $^1$H NMR: δ = 8.52 (s, 1 H), 8.32 (d, 2 H, *J* = 9.1 Hz), 8.07 (d, 2 H, *J* = 9.4 Hz), 7.57 (s, 1 H). Note, the exchangeable proton was not observed. HRMS (EI): *m/z* calcd for $C_{17}H_{16}N_2O_5$: 257.0437; found: 257.0445.
Compound **6a**: $AgNO_3$ (5 mol%), 60 h. $^1$H NMR: δ = 8.65 (s, 1 H), 7.84 (d, 2 H, *J* = 7.1 Hz), 7.51 (t, 2 H, *J* = 7.1 Hz), 7.44 (t, 1 H, *J* = 7.3 Hz), 7.37 (s, 1 H), 4.79 (s, 2 H), 4.16 (q, 2 H, *J* = 7.1 Hz), 1.21 (t, 3 H, *J* = 7.1 Hz). White solid; mp >310 °C (dec.). HRMS (EI): *m/z* calcd for $C_{16}H_{14}N_2O_4$: 298.0954; found: 298.1023.
Compound **6b**: $AgNO_3$ (5 mol%), 48 h. Off-white powder; mp >300 °C (dec.). HRMS (EI): *m/z* calcd for $C_{17}H_{16}N_2O_5$: 328.1059; found: 328.1069. $^1$H NMR: δ = 8.56 (s, 1 H), 7.76 (d, 2 H, *J* = 8.6 Hz), 7.17 (s, 1 H), 7.05 (d, 2 H, *J* = 8.6 Hz), 4.77 (s, 2 H), 4.17 (q, 2 H, *J* = 7.0 Hz), 3.81 (s, 3 H), 1.21 (t, 3 H, *J* = 7.0 Hz).
Compound **6c**: $AgNO_3$ (10 mol%), 8 d. Orange powder; mp 310–314 °C (dec.). HRMS (EI): *m/z* calcd for $C_{16}H_{13}N_3O_6$: 343.0804; found: 343.0799. $^1$H NMR: δ = 8.79 (s, 1 H), 8.34 (d, 2 H, *J* = 9.1 Hz), 8.08 (d, 2 H, *J* = 8.9 Hz), 7.69 (s, 1 H), 4.81 (s, 2 H), 4.17 (q, 2 H, *J* = 7.1 Hz), 1.22 (t, 3 H, *J* = 7.1 Hz).

(20) The conversion of **3a**–**c** → **4a**–**c** was conveniently monitored in the $^1$H NMR spectra by observation of the appearance of the characteristic signal for the proton on the furan ring [δ(ppm) in DMSO-$d_6$: **5a**: 7.22; **5b**: 7.04; **5c**: 7.57; **6a**: 7.37; **6b**: 7.17; **6c**: 7.69], disappearance of the resonance corresponding to the N3-imino proton (ca. 11.4–11.8 ppm) and a uniform downfield shift for the resonances associated with the phenyl ring and H6 of the uracil ring.

(21) McGuigan, C.; Brancale, A.; Barucki, H.; Srinivasan, S.; Jones, G.; Pathirana, R.; Carangio, A.; Blewett, S.; Luoni, G.; Bidet, O.; Jukes, A.; Jarvis, C.; Andrei, G.; Snoeck, R.; De Clercq, E.; Balzarini, J. *Antiviral Chem. Chemother.* **2001**, *12*, 77.

(22) Fluorescence and UV measurements for N1-substituted compounds (**4a**,**b**, **6a**,**b**) were done in MeOH that had been degassed by bubbling with $N_2$ for 5 min and at a concentration of 2.5 μM. Although the N1-unsubstituted compounds (**3a**,**b**, **5a**,**b**) are soluble in water, these were also examined in degassed MeOH at 2.5 μM for comparison purposes and the difficulty with fully deoxygenating the water. Fluorescence excitation and emission spectra were determined with at least 3 replicates with a 1 min rest between scans. For comparison of intensities, excitation was done at λ = 350 nm, and emission data from the maxima were used. At this time, we have no evidence for the occurrence of photochemistry during the course of these measurements. Extinction coefficients were determined for the wavelength of interest using at least three data points.