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New methodology for 2-alkylation of 3-furoic acids: application to the synthesis of tethered UC-781/d4T bifunctional HIV reverse-transcriptase inhibitors

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Abstract—New methodology for 2-alkylation of 3-furoic acids is presented involving Wittig reactions of the 3-methoxycarbonyl-2-furanylmethylphosphonium salt. The methodology has been used to prepare a tethered 2-alkylated-UC-781/d4T conjugate as a potentially new type of HIV reverse-transcriptase inhibitor.

2,3-Disubstituted furans constitute a widely encountered sub-unit in a range of natural and synthetic products. 2-Alkylation of 3-furoic acids has been a commonly employed strategy for entry[1] into this sub-unit with two carbanionic methodologies standing out as versatile options. Knight was the first person to demonstrate[2] that treatment of 3-furoic acid with 2 equiv of LDA (THF/ −78 °C) regioselectively furnishes the dianion **1** (Fig. 1), which can be alkylated with a range of reactive electrophiles. However, with less reactive electrophiles, for example, ethyl iodide, yields were low. Keay and co-workers subsequently[3] demonstrated that 2-methyl-3-furoic acid reacts with 2 equiv of *n*-BuLi at −20 °C to furnish the 2-lithiomethyl dianion **2** which is more stable than **1**, giving higher yields with less reactive electrophiles. Development of **2** followed pioneering work by Tada et al.[4] on use of the 2-dianion of 2,4-dimethyl-3-furoic acid **3** in natural product synthesis (Fig. 1).

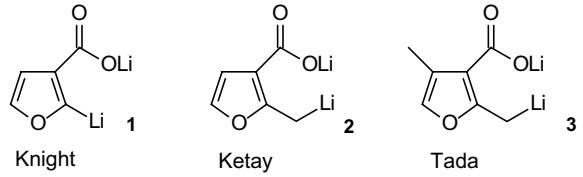

Figure 1.

As part of a programme to synthesise novel, bifunctional HIV reverse-transcriptase inhibitors, we needed access to quantities of 2-alkylated-3-furoates in conjunction with incorporation of the non-nucleoside inhibitor UC-781[5] into a bifunctional inhibitor. In view of the unattractive prospect of using large quantities of *n*-BuLi, we embarked on a study to identify an alternative, which we successfully report in this communication. It occurred to us that Wittig methodology based on the 3-methoxycarbonyl-2-furanylmethylphosphonium salt might provide the answer in view of the option of using a mild base to generate the stabilised ylide. Although 2-furanylmethylphosphonium salts[6] have been known and used in synthesis for some time, the corresponding 3-furoates are hitherto unknown. To this end, radical bromination of commercially available methyl 2-methyl-furoate using conditions recently reported by Khatuya[7] furnished methyl 2-bromomethyl furoate in high yield, which, following evaporation of the solvent and addition of triphenylphosphine in toluene furnished (rt, overnight) the desired and novel triphenylphosphonium salt **4** by filtration. Isolation of product involved no chromatography, with a single crystallisation from methanol returning analytically pure material in 80% overall yield.

Pleasingly, reaction of **4** in methanol with sodium methoxide as base (5 M in MeOH; 1.1 equiv) at rt followed by addition of hexanal (1.2 equiv) as a model aldehyde

Keywords: Furan alkylation; Wittig reaction of 2-furanylphosphonium salt; Alkylated-UC-781; Bifunctional HIV reverse-transcriptase inhibitors.
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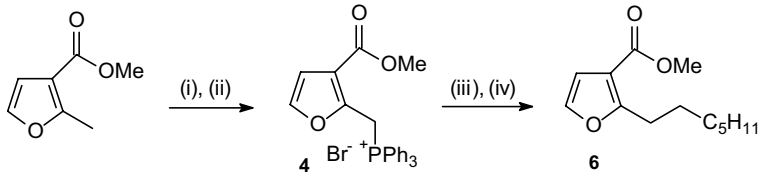


Scheme 1. Reagents and conditions: (i) NBS, $(BzO)_2$ (cat), CCl_4, Δ; (ii) PPh_3, toluene, rt (80% over two steps); (iii) NaOMe (1.1 equiv), MeOH, $C_5H_{11}CHO$ (92%); (iv) H_2, Pd–C, EtOH (80%).

Table 1. Wittig olefination and hydrogenation of **4** with various aldehydes

R of RCHO	% Yield of **5**	% Yield of **6**
(a) H	92	80
(b) CH_3	90	61
(c) C_5H_{11}	92	80
(d) C_4H_9OBn	91	84

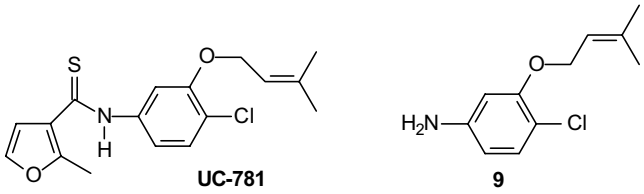


Figure 2.

resulted in rapid transformation to the Wittig product **5** in high yield as a mixture (~1:1) of *E*/*Z* stereoisomers. Carrying the reaction out in THF using sodium hydride as base gave a significantly lower yield (~50%) of the Wittig product in a higher *E*/*Z* ratio. Subsequent hydrogenation (H_2/Pd–C) gave the anticipated 2-alkylated product **6** in high yield (80%). A small percentage (~10%) of the 4,5-dihydro-2-alkylated product[8] was also obtained, which could be minimised by varying the reaction conditions, but not completely eliminated (Scheme 1).

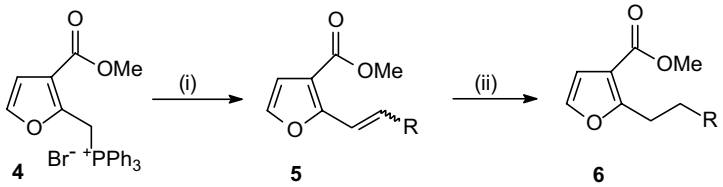
A range of aldehydes appropriate to producing alkylated side chains were subjected to the olefination/hydrogenation sequence and the results are presented in Table 1. Yields cited are relevant to reactions carried out in 1–10 mmol range. Reactions involving formaldehyde, ethanal and 5-benzyloxypentanal[9] all underwent smooth Wittig reactions in high yield as with the model reaction and, where appropriate, similarly to products with about an equal *E*/*Z* isomer ratio. Subsequent hydrogenation of each one gave a small percentage of the 4,5-dihydro derivative as in the hexanal case, which could be separated from the desired alkylated product by careful silica-gel column chromatography. Hydrogenation of alkene **5d** resulted in concomitant hydrogenolysis of the benzyl ether (Scheme 2).

As part of a programme on the synthesis of new HIV reverse-transcriptase inhibitors, we were able to demonstrate applicability of the methodology to two new C-2 variants of the potent thiocarboxanilide non-nucleoside HIV reverse-transcriptase inhibitor, UC-781[5] (Fig. 2).

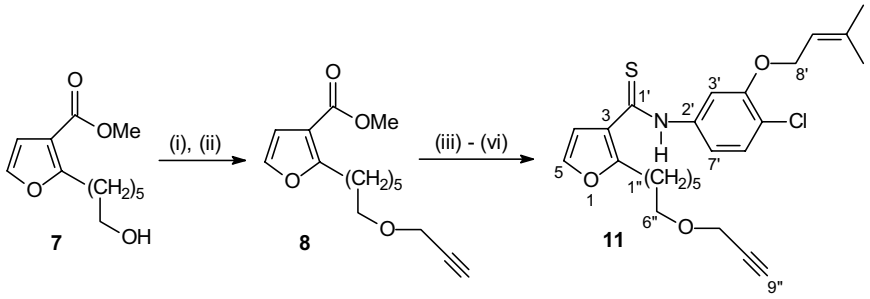
To this end, hydrogenolysis of **6d** to alcohol **7** followed by tosylation and substitution with propargyloxy anion furnished the propynyl ether **8**. Interestingly, the substitution proceeded more cleanly this way round, that is, was superior than propargylation of the alkoxide of **7** with propargyl bromide. Subsequent base-mediated ester hydrolysis, conversion to the acid chloride with thionyl chloride followed by substitution with substituted aniline **9**[10] (Fig. 2) furnished amide **10** in high overall yield from the acid. Finally, thiation of amide **10** with Lawesson's reagent[11] produced the C-2 elongated UC-781 derivative **11**[12] for biological probing[13] of substituent effects in the HIV reverse-transcriptase pocket (Scheme 3).

Alkyne **10** was also subjected to a Sonogashira[14] reaction with the nucleoside reverse-transcriptase inhibitor derivative, 5′-*O*-benzoyl-5-iodo-d4T,[15] to afford conjugate **12**[16] following benzoyl group deprotection. Conjugate **12** involves a combination of the two antiretroviral drugs d4T and UC-781, albeit with the amide of UC-781 unthiated. Significant interest has been shown recently in conjugates[17] of this type, in view of the fact that the nucleotide substrate binding-site is proximal to the non-nucleoside binding pocket. Compound **12** is the first example of a UC-781-derived conjugate (unthiated) as a result of developing this methodology. Further work on thiation is in progress to produce UC-781 analogues (Scheme 4).

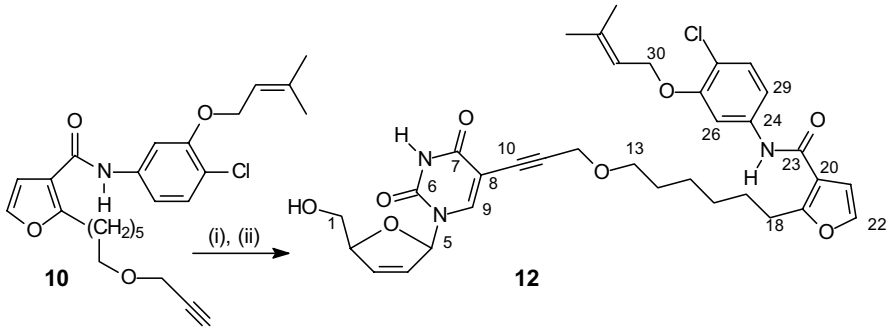
In summary, new methodology applicable to medium to large-scale work has been developed for C-2 alkylation



Scheme 2. Reagents: (i) NaOMe, MeOH, RCHO; (ii) H_2, Pd–C, EtOH.



Scheme 3. Reagents and conditions: (i) *p*-TsCl, NEt_3, CH_2Cl_2, DMAP (cat) (97%); (ii) propargyl alcohol (10 equiv), NaH (10 equiv), THF, Δ; (iii) KOH, EtOH, (85%, two steps); (iv) $SOCl_2$, Δ; (v) RNH_2, Py, (99%, two steps to give amide **10**); (vi) Lawesson's reagent, $NaHCO_3$, toluene, Δ (70%).



Scheme 4. Reagents and conditions: (i) 5′-benzoyl-5-iodo-d4T, $Pd(PPh_3)_4$ (10%), CuI (50%), NEt_3 (2 equiv), DMF–THF (1:2), rt (65%); (ii) NaOMe, MeOH, rt (52%).

of 3-furoates of interest to both natural product synthesis and medicinal chemistry.

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9. Prepared from 1,5-pentanediol via the sequence: (a) NaH, BnBr, THF, Δ (63%); (ii) Swern oxidation (99%).
10. Prepared from 2-amino-5-nitrophenol via the following sequence: (i) (a) aq $NaNO_2$, HCl, NH_2SO_3H (cat); (b) CuCl (69%); (ii) K_2CO_3, 4-bromo-2-methyl-2-butene, 2-butanone, rt (94%); (iii) Fe, HCl, EtOH, Δ (82%).
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12. Data for compound **11** (see numbering in Scheme 3): ν_{max}/cm^{-1} ($CHCl_3$): 3234m (N–H, thioamide), 2858s (C–H, aliphatic), 2270s (C≡C, alkyne), 1618s (C=C, aromatic), 1389s+1162s (C=S stretches); ^1H NMR (400 MHz, C_6D_6): δ_H 1.24–1.46 (8H, m, H-2″, 3″, 4″, 5″), 1.45+1.51 (6H, 2 × s, H-10′, 11′), 2.02 (1H, t, *J* 2.4 Hz, H-9″), 3.00 (2H, t, *J* 7.6 Hz, H-1″), 3.28 (2H, t, *J* 6.4 Hz, H-6″), 3.83 (2H, d, *J* 2.4 Hz, H-7″), 4.41 (2H, d, *J* 6.1 Hz, H-8′), 5.47 (1H, tt, *J* 6.1, 1.4 Hz, H-9′), 6.13 (1H, d, *J* 1.2 Hz, H-4), 6.38 (1H, d, *J* 7.3 Hz, H-7′), 6.82 (1H, d, *J* 7.6 Hz, H-6′), 7.15 (1H, d, *J* 1.2 Hz, H-5), 7.98 (1H, s, NH), 8.17 (1H, s, H-3′); ^{13}C NMR (75 MHz, C_6D_6): δ_C 17.9 (*C*H_3), 25.5 (*C*H_2), 25.9 (*C*H_3), 27.9 (C-1″+*C*H_2), 29.1+29.5 (*C*H_2′s), 57.8 (C-7″), 66.1 (C-8′), 69.8 (C-6″), 73.9 (C-9″), 80.5 (C-8″), 106.1 (C-3′), 108.1 (C-4), 109.4 (C-7′), 115.7 (C-3), 119.7 (C-5′), 120.6 (C-9′), 130.1 (C-5+C-6′), 138.2 (C-2′), 138.7 (C-12′), 141.1 (C-2), 154.8 (C-4′), 160.0 (C-1′); HRMS: *m/z* (rel int.) 459.16343 [M^+] (9). Calculated for $C_{25}H_{30}O_3NSCl$: 459.16349 [M^+].
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16. Data for compound **12** (see numbering in Scheme 4): $[\alpha]_D$ −15.7 (*c* 1.03, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$): 3592br (O–H, free), 2932s (C–H, aliphatic), 2254s (C═C, alkyne), 1720s (C═O, ester), 1693s (C═O, amide), 1599s (N–H and C–N stretching), 1514s+1492s (C═C, aromatic); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.24–1.33 (8H, m, H-14, 15, 16, 17), 1.73–1.79 (6H, 2 × s, H-33, 34), 2.70 (1H, s, –OH), 3.03 (2H, t, *J* 7.6 Hz, H-18), 3.46 (2H, t, *J* 6.8 Hz, H-13), 3.78 (1H, d, *J* 12.4 Hz, H-1), 3.88 (1H, d, *J* 12.4 Hz, H-1), 4.21 (2H, s, H-12), 4.59 (2H, d, *J* 6.7 Hz, H-30), 4.91 (1H, s, H-2), 5.51 (1H, tt, *J* 6.7, 1.4 Hz, H-31), 5.83 (1H, dt, *J* 5.9, 1.9 Hz, H-3), 6.32 (1H, dt, *J* 5.9, 1.6 Hz, H-4), 6.56 (1H, d, J_{AB} 2.2 Hz, H-21), 6.96 (2H, m, H-5,29), 7.26 (1H, m, H-28), 7.30 (1H, d, J_{AB} 2.2 Hz, H-22), 7.53 (1H, s, H-9), 7.74 (1H, s, NH), 8.05 (1H, s, H-25), 8.23 (1H, s, H-6); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 18.3, 25.6, 25.8, 27.2, 27.7, 28.7, 29.2, 58.7, 63.0, 66.2, 70.2, 76.8 × 2, 87.6, 89.9, 90.3, 99.5, 106.4, 108.2, 112.7, 115.6, 119.1, 125.9, 129.9, 134.9, 137.7, 138.6, 140.6, 144.4, 149.7, 149.7, 154.5, 161.8, 162.2.
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