An Approach to Amino Ester Subunits of Tamiflu

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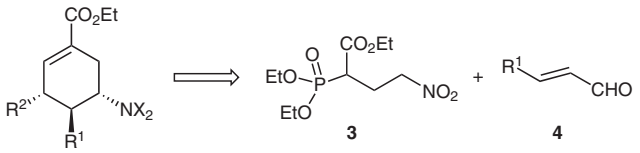
Abstract: A two-step synthesis of amino cyclohexene carboxylic acid esters has been achieved in good overall yield from nitro phosphonate and unsaturated aldehydes.

Key words: Tamiflu, Michael addition, ring closure

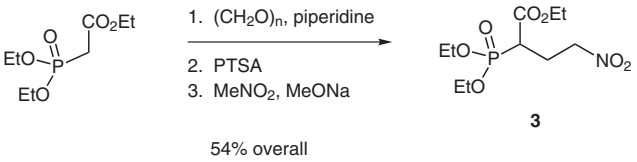
The emergence of virulent strains of avian influenza, combined with the concern that one of these strains could evolve and trigger a human health emergency, has prompted considerable research into new antiviral agents.[1] Antiviral agents typically used to manage influenza, such as the M2 ion channel blockers amantidine and rimantadine, inhibit viral replication. Unfortunately, drug-resistant variants have developed rapidly.[2] Tamiflu (**1**) is a neuraminidase inhibitor and prevents the release of the virus from cells.[3] Tamiflu treatment must be started within two days of the onset of flu symptoms. Recently, two routes to Tamiflu have been reported.[4]



1: R^1 = NHAc, R^2 = $OCHEt_2$, X = H
2: R^1 = Me, R^2 = H, X = O

Scheme 1

As part of a program to develop useful antiviral agents,[5] we devised a [3+3] ring-forming strategy using the phosphonate **3** and an unsaturated aldehyde **4** (Scheme 1). Phosphonate **3** was prepared in three steps as shown in Scheme 2. Base-catalyzed hydroxymethylation followed by *p*-toluenesulfonic acid (PTSA)-mediated dehydration[6] and Michael addition of nitromethane, afforded nitro phosphonate **3** in 54% overall yield.

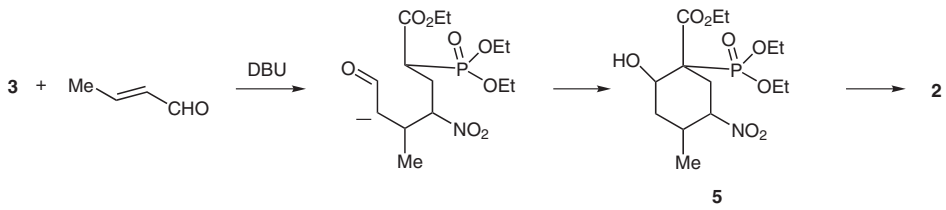


Scheme 2

Initially, we studied the reaction of the dianion of **3**, generated using two equivalents of potassium *tert*-butoxide in tetrahydrofuran, with crotonaldehyde. These conditions led to destruction of the aldehyde. The use of one equivalent of sodium methoxide produced a low yield of product derived from Michael addition of the nitroalkane moiety to the unsaturated aldehyde. Fortunately, with two equivalents of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dichloromethane from ambient temperature to reflux, nitro ester **2** was produced in 74% isolated yield. Interestingly, if the reaction was quenched before completion, the hydroxyphosphonate ester **5** was co-produced with **2** (Scheme 3). Intermediates such as **5** are rarely isolated.[7]

In order to understand the scope and limitations of this annulation, we reacted nitro phosphonate **3** with a number of unsaturated aldehydes and ketones. The results of this study are summarized in Table 1.

Compounds **2**, **6**, **7**, **8** and **9** were formed as predominantly single diastereomers (80–85%). Proton NMR data supported a *trans*-diequatorial relationship between the nitro group and R^1. In the case of compound **2**, the NMR multiplet (δ = 4.41 ppm), corresponding to the methine proton alpha to the nitro group, was a doublet of triplets with coupling constants of J = 5.6 and 10 Hz. In the case of bicyclic



Scheme 3

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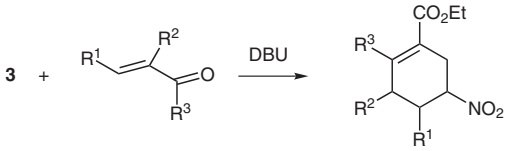
Table 1 Reaction of **3** with Aldehydes and Ketones



R^1	R^2	R^3	Temp (°C)	Yield[a] (%)	Product
Me	H	H	40	74	**2**
Ph	H	H	40	59	**6**
Ph	H	Me	80[b]	26	**7**
2-furyl	H	H	25	60	**8**
C_7H_{16}	H	H	40	64	**9**
$-CH_2CH_2CH_2-$		H	40	45	**10**
$-CH_2SCH_2-$		H	25	36	**11**

[a] Isolated yield.
[b] Reaction performed in MeCN.

products **10** and **11**, the nitro group appears to be on the *exo*-face of the fused bicyclic ring system. In nitro ester **11** the ratio of *exo*- to *endo*-nitro group was 4:1.

We could not find any literature precedent for the selective reduction of an aliphatic nitro group in the presence of an unsaturated ester. The most promising reducing agents appeared to be Raney nickel or tin and hydrochloric acid.[8] However, the latter reductive system also reduced α,β-unsaturated ketones to saturated ketones.[9] Fortunately, when the reduction was carried out in ethanol, amino esters **12**, **13** and **14** from nitro esters **2**, **10** and **6** were cleanly provided in 67%, 86% and 72% yields, respectively (Figure 1).

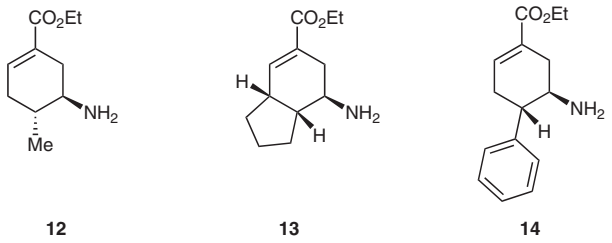


Figure 1

The development of a two-step synthesis of amino esters from nitro phosphonate **3** constitutes a flexible synthetic pathway to these little-studied compounds. With suitably modified unsaturated aldehydes, this chemistry is expected to readily provide promising new candidates for viral assays.

THF was distilled from sodium benzophenone ketyl. CH_2Cl_2, toluene and HMPA were distilled over CaH_2. All experiments were performed under argon atmosphere. Organic extracts were dried over anhydrous Na_2SO_4. IR spectra were obtained on a Perkin-Elmer model 1320 spectrophotometer. NMR experiments were performed with either a Varian 300 MHz or a Bruker 400 MHz instrument. HRMS were recorded on a Kratos model MS-50 spectrometer and LRMS were performed with a Finnegan 4023 mass spectrometer. Standard grade silica gel (60 Å) was used for flash column chromatography.

Synthesis of Phosphonate 3

To a solution of MeONa (1.2 M, 17.6 mL, 21.2 mmol) at 0 °C under argon, was added a solution of nitromethane (2.6 g, 42.6 mmol) in MeOH (3 mL). The reaction mixture was stirred for 1 h and allowed to warm to r.t. After cooling to 0 °C for 10 min, a solution of ethyl diethylphosphonoacetate (5 g, 21.2 mmol) in MeOH (5 mL) was added to the reaction flask dropwise. The reaction mixture was slowly warmed to r.t. and stirred for 3–4 h. The reaction mixture was filtered to remove the precipitate that formed during the course of the reaction, neutralized to pH 7 with AcOH and evaporated. A brown solid was obtained which was dissolved in EtOAc (25 mL). The resulting mixture was filtered, and the filtrate was evaporated to give a brown oil. Column chromatography on silica gel (EtOAc–hexanes, 50%) gave pure **3**.

Yield: 3.4 g (54%); yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.13–1.23 (9 H, m), 2.36–2.50 (2 H, m), 2.90–3.08 (1 H, m), 3.97–4.11 (6 H, m), 4.30–4.50 (2 H, m).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 16.4, 41.5, 42.8, 62.1, 63.2, 73.0, 167.9.

HRMS: *m/z* calcd for $C_{10}H_{20}NO_7P$: 297.0977; found: 297.0982.

Synthesis of Nitro Esters; General Procedure

To a solution of unsaturated aldehyde (0.34 mmol) in CH_2Cl_2 (1 mL) was added DBU (0.64 mmol). The reaction mixture was cooled to 0 °C and, after 10 min, a solution of **3** (0.34 mmol) in CH_2Cl_2 (1 mL) was added dropwise to the reaction mixture, which was then allowed to warm to r.t. over 2 h. The reaction mixture was then heated as indicated in Table 1. After cooling to r.t., HCl (2 M, 1 mL) was added and the organic layer was taken and again washed with HCl (2 M, 5 mL) and brine (2 × 10 mL), dried (Mg_2SO_4) and evaporated to give an oil. Column chromatography on silica gel yielded pure product. For the ketone example leading to product **7**, the solvent was MeCN.

2

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.04 (3 H, d, *J* = 6.3 Hz), 1.27 (3 H, t, *J* = 6.9 Hz), 1.60–2.10 (1 H, m), 2.28–2.42 (1 H, m), 2.48–2.60 (1 H, m), 2.85–2.92 (1 H, m), 2.94–3.24 (1 H, m), 4.17 (2 H, q, *J* = 7.2 Hz), 4.35–4.45 (1 H, dt, *J* = 5.6, 10 Hz), 6.90 (1 H, br s).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.3, 17.8, 29.1, 32.6, 61.1, 88.2, 127.1, 137.6, 166.0.

HRMS: *m/z* calcd for $C_{10}H_{15}NO_4$: 213.1001; found: 213.1005.

6

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (3 H, t, *J* = 7.2 Hz), 2.47–2.60 (1 H, m), 2.68–2.82 (1 H, m), 2.94–3.02 (1 H, m), 3.08–3.18 (1 H, m), 3.38–3.49 (1 H, m), 4.21 (2 H, q, *J* = 7.2 Hz), 4.90–5.00 (1 H, m), 7.05–7.09 (1 H, m), 7.21–7.33 (5 H, m).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.5, 30.0, 33.2, 43.5, 61.2, 87.0, 127.3, 127.5, 128.2, 129.2, 137.8, 139.3, 165.8.

HRMS: *m/z* calcd for $C_{15}H_{17}NO_4$: 275.1158; found: 275.1161.

7

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.29 (3 H, t, *J* = 7.2 Hz), 2.11 (3 H, s), 2.50–2.65 (2 H, m), 2.92–3.02 (1 H, m), 3.10–3.2 (1 H, m), 3.40–3.48 (1 H, m), 4.20 (2 H, q, *J* = 7.2 Hz), 4.88–4.96 (1 H, m), 7.20–7.33 (5 H, m).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.5, 21.4, 32.1, 41.4, 44.0, 60.8, 87.0, 120.6, 127.4, 128.1, 129.2, 139.3, 146.3, 166.9.

HRMS: *m*/*z* calcd for $C_{16}H_{19}NO_4$: 289.1314; found: 289.1317.

8

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.30 (3 H, t, *J* = 6.9 Hz), 2.68–2.74 (2 H, m), 2.98–3.20 (2 H, m), 3.62–3.70 (1 H, m), 4.21 (2 H, q, *J* = 7.2 Hz), 4.90–4.98 (1 H, m), 6.15 (1 H, d, *J* = 3.2 Hz), 6.29–6.35 (1 H, m), 7.02–7.06 (1 H, m), 7.35–7.36 (1 H, m).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.5, 28.9, 29.4, 36.6, 61.2, 84.9, 107.6, 110.6, 126.9, 136.8, 142.7, 152.0, 165.7.

HRMS: *m*/*z* calcd for $C_{13}H_{15}NO_5$: 265.0956; found: 265.0961.

9

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86 (3 H, t, *J* = 7.2 Hz), 1.27–1.33 (14 H, m), 1.38–1.44 (1 H, m), 1.96–2.10 (1 H, m), 2.20–2.34 (1 H, m), 2.50–2.62 (1 H, m), 2.89–2.93 (2 H, m), 4.19 (2 H, q, *J* = 7.2 Hz), 4.47–4.6 (1 H, m), 6.93–6.98 (1 H, m).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.3, 14.5, 22.8, 26.3, 28.7, 29.3, 29.6, 29.7, 32.0, 36.2, 61.1, 86.8, 126.9, 137.5, 166.0.

HRMS: *m*/*z* calcd for $C_{16}H_{27}NO_4$: 297.1940; found: 297.1944.

10

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (3 H, t, *J* = 6.9 Hz), 1.38–1.48 (2 H, m), 1.80–1.90 (3 H, m), 1.98–2.10 (2 H, m), 2.16–2.28 (1 H, m), 2.88–2.94 (1 H, m), 3.08–3.16 (1 H, m), 4.18 (2 H, q, *J* = 7.2 Hz), 4.60–4.68 (1 H, m), 7.07–7.09 (1 H, m).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.5, 22.2, 27.0, 28.4, 31.5, 44.6, 46.7, 61.1, 86.8, 128.5, 140.6, 166.1.

HRMS: *m*/*z* calcd for $C_{12}H_{17}NO_4$: 239.1158; found: 239.1160.

11

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.29 (3 H, t, *J* = 7.2 Hz), 2.36–2.48 (1 H, m), 2.70–2.82 (2 H, m), 2.98–3.02 (2 H, m), 3.12–3.25 (3 H, m), 4.21 (2 H, q, *J* = 7.2 Hz), 4.66–4.78 (1 H, m), 7.00 (1 H, br s).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.5, 31.4, 32.2, 33.3, 46.9, 48.1, 61.5, 86.1, 129.2, 137.4, 165.6.

HRMS: *m*/*z* calcd for $C_{11}H_{15}NO_4S$: 257.0756; found: 257.0722.

Reduction of Nitro Esters; General Procedure

To a solution of the nitro ester (1 equiv) in EtOH (2 mL) was added tin shot (5.3 equiv). The reaction was heated to 70 °C and HCl (12 M, 54 equiv) was added. The reaction was boiled for 20 min and cooled to r.t. The solution was made weakly basic (pH 8) with NaOH (2 M) and the aqueous layer was extracted with EtOAc (2 × 25 mL). The combined organic layers were washed once with brine (25 mL), dried (Mg_2SO_4) and evaporated to give a yellow oil. Flash silica gel column chromatography yielded the pure product.

12

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.01 (3 H, d, *J* = 7 Hz), 1.26 (3 H, t, *J* = 6.9 Hz), 1.46–1.57 (1 H, m), 1.82–1.98 (2 H, m), 1.99–2.08 (1 H, m), 2.22–2.48 (2 H, m), 2.57–2.70 (2 H, m), 4.14 (2 H, q, *J* = 7.2 Hz), 6.88 (1 H, br s).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.5, 18.2, 33.4, 33.5, 35.1, 52.3, 60.6, 129.0, 138.3, 167.3.

HRMS: *m*/*z* calcd for $C_{10}H_{17}NO_2$: 183.1259; found: 183.1262.

13

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.27 (3 H, t, *J* = 6.9 Hz), 1.33–1.38 (1 H, m), 1.38–1.44 (1 H, m), 1.50–1.62 (1 H, m), 1.73–1.83 (2 H, m), 1.88–2.02 (2 H, m), 2.03–2.17 (2 H, m), 2.80–2.84 (1 H, br s), 2.84–2.89 (1 H, br s), 2.94–3.03 (1 H, m), 3.04–3.14 (1 H, m), 4.16 (2 H, q, *J* = 7.2 Hz), 7.05 (1 H, br s).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.5, 22.5, 27.2, 28.3, 31.3, 45.4, 46.0, 52.4, 60.7, 130.1, 141.2, 167.3.

HRMS: *m*/*z* calcd for $C_{12}H_{19}NO_2$: 209.1416; found: 209.1419.

14

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.27 (3 H, t, *J* = 7.2 Hz), 2.17–2.28 (1 H, m), 2.32–2.48 (2 H, m), 2.52–2.62 (1 H, m), 2.63–2.72 (1 H, m), 2.82 (1 H, br s), 2.86 (1 H, br s), 3.18–3.26 (1 H, m), 4.17 (2 H, q, *J* = 7.2 Hz), 7.00 (1 H, br s), 7.21–7.27 (3 H, m), 7.29–7.35 (2 H, m).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.5, 33.0, 34.3, 47.6, 51.4, 60.8, 127.3, 127.9, 128.1, 129.2, 138.5, 142.4, 167.0.

HRMS: *m*/*z* calcd for $C_{15}H_{19}NO_2$: 245.1416; found: 245.1420.

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