COMMUNICATION

An alternative isoxazole route to α-alkoxycarbonyl-β-diketones

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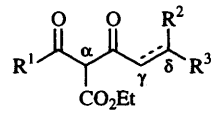
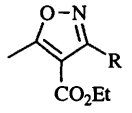
Cycloaddition of oxygen-functionalized nitrile oxides to the enamine from ethyl acetoacetate produces 4-ethoxycarbonyl-5-methylisoxazoles carrying a 3-tetrahydropyranyloxymethyl, 3-diethoxymethyl or 3-ethoxycarbonyl substituent; the 3-formylisoxazole is prepared from the former two and condensed *in situ* with phosphoranes to give 3-alkenylisoxazoles that are cleaved by hexacarbonylmolybdenum or hydrogenolysis to afford α-alkoxycarbonyl-β-diketones.

We have investigated routes to α-alkoxycarbonyl-β-diketones **1** as part of our synthetic studies of metabolites containing the 3-acyltetramic and tetronic acid, and the 3-acyl-4-hydroxypyridone and pyrone structural units[1] and have reported[2] a sequence utilizing isoxazoles as masked 1,3-dicarbonyl compounds[3] *via* an intermediate 3-phosphonomethylisoxazole **2a** that provided for nucleophilic elaboration at the C-3 substituent of a 3,5-dialkylisoxazole.[4] In order to provide a more flexible access to tricarbonyl compounds **1** we now report an alternative sequence wherein the C-3 substituent of a 3,5-dialkylisoxazole **2f** is functionalized as an electrophile for elaboration.

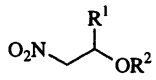
We investigated oxygenated C-3 substituents at three different oxidation levels. Thus 2-(2-nitroethoxy)tetrahydropyran **3a** was prepared from 2-nitroethanol and 3,4-dihydropyran (catalytic toluene-*p*-sulfonic acid, 20 °C; 90%).[5] Treatment of the nitro compound **3a** in chloroform with phosphorus oxychloride at 0 °C in the presence of triethylamine and the enamine **4**, prepared from ethyl acetoacetate (pyrrolidine, toluene at reflux), generated a nitrile oxide that underwent *in situ* 1,3-dipolar cycloaddition to the enamine **4** to afford 4-ethoxycarbonyl-3-(tetrahydropyran-2-yloxy)methyl-5-methylisoxazole **2b** (46%);†[6] the best results were obtained using a ten-fold excess of nitro compound over enamine. At a higher oxidation level, the acetal 2,2-diethoxynitroethane **3b** was prepared from nitromethane and triethyl orthoformate (reflux, $ZnCl_2$; 20%).[7] Cycloaddition of the nitrile oxide prepared from nitro compound **3b** with enamine **4** under the usual conditions (Et_3N, $POCl_3$, 0 °C) led to 3-diethoxymethyl-4-ethoxycarbonyl-5-methylisoxazole **2c** (31%); this yield was achieved with a five-fold excess of nitro compound and larger excesses were not helpful. Finally, at the carboxylate oxidation level, ethyl chlorohydroxyiminoacetate **5** was prepared from ethyl glycinate hydrochloride ($NaNO_2$, aq. HCl) as precursor to the nitrile oxide.[8] Treatment of the enamine **4** with chlorooxime **5** and triethylamine (each 3 equiv., diethyl ether, 25 °C) gave the cycloadduct 3,4-bis(ethoxycarbonyl)-5-methylisoxazole **2d** (60%). This compound was also available by photolytic bromination of acetal **2c** (*N*-bromosuccinimide, CH_2Cl_2; aqueous work-up; 75%).



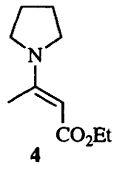
1 a; γ,δ CH=C; R^1 = Me; R^2, R^3 = H, *E*-CH=CHMe
b; γ,δ CH=C; R^1 = Me; R^2, R^3 = H, Ph
c; γ,δ CH=C; R^1 = R^2 = R^3 = Me
d; γ,δ CH_2–CH; R^1 = Me; R^2, R^3 = H, Ph



2 a; R = $CH_2P(O)(OEt)_2$
b; R = CH_2OTHP
c; R = $CH(OEt)_2$
d; R = CO_2Et
e; R = CH_2OH
f; R = CHO
g; R = CH_2OEt



3 a; R^1 = H; R^2 = THP
b; R^1 = OEt; R^2 = Et



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The isoxazoles **2b** and **2c** could each be easily converted into a suitable C-3 electrophilic building block. Thus the THP ether **2b** underwent acetal exchange (MeOH, Amberlyst-15, 25 °C; 73%) or cleavage with iodotrimethylsilane (Me_3SiCl–NaI, MeCN; 55%) to give the alcohol **2e**. Swern oxidation of alcohol **2e** [Me_2SO, $(COCl)_2$; Et_3N; 78%] afforded 4-ethoxycarbonyl-3-formyl-5-methylisoxazole **2f** which was also available from acetal **2c** by hydrolysis (TFA–H_2O) and used without further purification; treatment of acetal **2c** with iodotrimethylsilane led unexpectedly to the 3-ethoxymethylisoxazole **2g** (43%) rather than to the aldehyde.

In contrast we were unable to convert the 3-ethoxycarbonylisoxazole **2d** into the 3-formyl compound **2f** by simple reductive methods; attempts to prepare a 3-carboxyisoxazole for conversion to a more electrophilic derivative were also inconclusive. One interfering pathway was illustated during hydrolysis (aq. NaOH, reflux) of the related diester **6a** by the isolation of nitrile **7** (43%), a product of decarboxylation–fragmentation.[9] Diesters **6a** and **6b** were obtained by reaction of ethyl chlorohydroxyiminoacetate **5** with enamines **8a**‡ and **8b**[1b] under the conditions described above (Et_3N, diethyl ether, 25 °C; 43 and 34%, respectively).

Condensations of the aldehyde **2f** were carried out with a selection of Wittig-type nucleophiles to give 3-alkenylisoxazoles **9**. Thus methoxycarbonylmethylene and formylmethylene

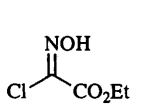
† All new compounds have spectral data (IR, UV, NMR, MS) in accord with the assigned structure, and satisfactory combustion analysis or accurate mass measurement.

‡ Enamine **8a** was prepared in quantitative yield by addition of pyrrolidine to ethyl 4-(*N*,*N*-dibenzylamino)pent-2-ynoate, itself prepared in 5 steps from alanine.

triphenylphosphoranes afforded isoxazoles **9a** and **9b**, respectively (CH_2Cl_2, reflux; 71 and 40%). Ethyltriphenylphosphonium bromide (potassium *tert*-butoxide, THF) gave the 3-(prop-1-enyl)isoxazole **9c** (33%; 1:1 *E*:*Z*) whilst but-2-enyltriphenylphosphonium bromide (butyllithium, THF, −78 °C) gave the 3-(penta-1,3-dienyl)isoxazole **9d** (36%, 1:1 1*E*,3*E*:1*Z*,3*E*); diene **9d** was also prepared from aldehyde **9b** and ethyltriphenylphosphonium bromide under the latter conditions (61%). The 3-(2-phenylethen-1-yl)isoxazole **9e** was obtained from benzyltriphenylphosphonium bromide and **2f** under these conditions (40%, 8:1 *E*:*Z*), but reaction of 2-propyltriphenylphosphonium iodide with **2f** gave only low (8%) yields of the 3-(2-methylprop-1-enyl)isoxazole **9f** even at reflux.

We have demonstrated before[2] that alkenes **9** are a masked form of the required α-alkoxycarbonyl-β-diketones **1**. Thus for example, brief treatment of **9d–f** with hexacarbonylmolybdenum (moist acetonitrile, reflux 30 min) led to the tricarbonyl compounds **1a–c** as previously reported.§[2] Unsurprisingly, hydrogenolysis of the N–O bond[3] led additionally to saturation of the alkenyl substitution,[2] illustrated by the formation of **1d** from **9d** (i, H_2–Pd, MeOH; ii, 2 M aq. NaOH; 86%); diketo ester **1d** could also be accessed by reduction of the corresponding alkene **1b** (H_2–Pd, MeOH; 83%). Alkenylisoxazoles **9a** and **9b**, containing oxygen functionality in the side chain, did not survive treatment with $Mo(CO)_6$; hydrogenation of **9a** afforded the product **10** of N–O cleavage, side-chain saturation and cyclization (H_2–Pd, MeOH; 71%).¶

The 3-formylisoxazole **2f** is thus a useful building block, and we continue to exploit this methodology.



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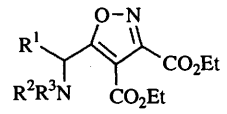
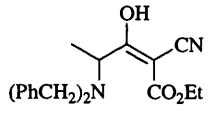


6 a; R^1 = Me; R^2 = R^3 = CH_2Ph
b; R^1 = R^2 = H; R^3 = CO_2CH_2Ph



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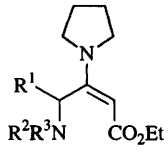
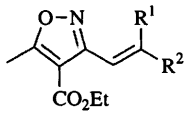
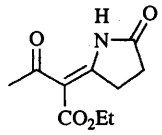


8 a; R^1 = Me; R^2 = R^3 = CH_2Ph
b; R^1 = R^2 = H; R^3 = CO_2CH_2Ph



9 a; R^1 = H; R^2 = CO_2Me
b; R^1 = H; R^2 = CHO
c; R^1, R^2 = H, Me
d; R^1, R^2 = H, *E*-CH=CHMe
e; R^1, R^2 = H, Ph
f; R^1 = R^2 = Me



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Experimental

The following are sample procedures.

3-Diethoxymethyl-4-ethoxycarbonyl-5-methylisoxazole 2c

Ethyl acetoacetate (2.6 cm^3, 0.02 mol) and pyrrolidine (1.7 cm^3, 0.02 mol) were heated together in dry toluene (50 cm^3) under reflux with a Dean–Stark trap. After 2 h water had separated and the solvent was evaporated under reduced pressure. To the residue was added triethylamine (30.4 g, 0.3 mol) and 2,2-diethoxynitroethane **3b** (17.9 g, 0.11 mol) in chloroform (100 cm^3). The solution was cooled to 0 °C and to this was added phosphorus oxychloride (16.8 g, 0.11 mol) in chloroform (50 cm^3) dropwise over 1.5 h, and the mixture stirred at 25 °C for a further 16 h. The dark mixture was poured into water (200 cm^3) and the organic phase washed successively with hydrochloric acid (6 M, 100 cm^3), aqueous sodium hydroxide (5% w/v, 100 cm^3) and saturated brine (100 cm^3). The organic phase was dried ($MgSO_4$), filtered and evaporated under reduced pressure to give a dark oil which was purified by column chromatography on silica gel, using hexane–ethyl acetate (6:1 v/v) as eluent to yield the *title compound* **2c** (1.60 g, 31%) as a yellow oil [Found: M^+ + H (FAB), 258.1351; C, 55.74; H, 7.48; N, 5.70%. $C_{12}H_{19}NO_5$ requires *M* + *H*, 258.1341; C, 56.02; H, 7.44; N, 5.44%]; $\nu_{max}(CHCl_3)/cm^{-1}$ 2978, 2931, 2900, 1721, 1607, 1105 and 1059; δ_H(250 MHz; $CDCl_3$) 1.23 (6 H, t, 2 × acetal OCH_2CH_3), 1.37 (3 H, t, ester OCH_2CH_3), 2.68 (3 H, s, 5-CH_3), 3.71 (4 H, m, 2 × acetal OCH_2), 4.35 (2 H, q, ester OCH_2) and 6.06 (1 H, s, 3-CH); δ_C(100 MHz; $CDCl_3$) 13.0, 14.0, 14.95, 60.65, 62.0, 95.6, 107.8, 160.1, 161.4 and 175.1; *m*/*z* (FAB) 258 (M^+ + H, 8.5%).

4-Ethoxycarbonyl-5-methyl-3-(2-phenylethen-1-yl)isoxazole 9e

To 3-diethoxymethyl-4-ethoxycarbonyl-5-methylisoxazole **2c** (0.2 g, 0.78 mmol) was added trifluoroacetic acid–water (9:1 v/v, 10 cm^3) and the resulting mixture stirred at 25 °C overnight. Water (20 cm^3) was then added, the aqueous mixture extracted with dichloromethane (3 × 25 cm^3), and the combined organic extracts were dried ($MgSO_4$) and filtered. To the filtrate was added anhydrous potassium carbonate and stirring continued for 30 min before the mixture was filtered and evaporated under reduced pressure to yield the aldehyde **2f** as a yellow oil (0.14 g, 96%) that was used without further purification; δ_H(250 MHz; $CDCl_3$) 10.37 (1 H, s, CHO); $\nu_{max}(CHCl_3)/cm^{-1}$ 1720. To benzyltriphenylphosphonium bromide (0.37 g, 0.85 mmol) in dry THF (20 cm^3) was added butyllithium (1.6 M solution in hexanes; 0.54 cm^3, 0.85 mmol) at −78 °C. The solution was allowed to warm to 0 °C, during which time it turned orange, before it was recooled to −78 °C and the aldehyde **2f** added. The resulting mixture was allowed to warm to 25 °C overnight, water (20 cm^3) was then added and the aqueous mixture extracted with ethyl acetate (3 × 25 cm^3). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure to afford a residue that was purified by column chromatography on silica gel, using hexane–ethyl acetate (4:1 v/v) as eluent to yield the *title compound* **9e** (80 mg, 40%) as a white solid, 8:1 *E*:*Z* isomers (Found: M^+, 257.1110. $C_{15}H_{15}NO_3$ requires *M*, 257.1052); $\nu_{max}(CHCl_3)/cm^{-1}$ 2929, 2854, 1714, 1642, 1600, 1580, 1498, 1456, 1440, 1111 and 973; δ_H(400 MHz; $CDCl_3$) for major *E* isomer 1.41 (3 H, t, OCH_2CH_3), 2.69 (3 H, s, 5-CH_3), 4.36 (2 H, q, OCH_2CH_3) and 7.2–7.6 (7 H, m, Ar-H, CH=CH) and for minor *Z* isomer 1.30 (3 H, t), 2.66 (3 H, s), 4.23 (2 H, q), 6.59 and 6.93 (each 1 H, d, *J* 12), 7.2–7.6 (5 H, m); δ_C(100 MHz; $CDCl_3$) for major *E* isomer 13.5 and 14.3 (CH_3), 60.8 (CH_2), 108.1 (C), 114.5, 127.2, 128.7, 128.9 and 136.0 (CH), 136.1, 159.5, 162.3 and 175.4 (C); *m*/*z* 257 (M^+, 42%), 256 (100).

§ Treatment of 3-propenylisoxazole **9c** with $Mo(CO)_6$ led to low recoveries of a mixture of the desired diketone **1** (R^1 = Me; R^2, R^3 = H, Me) and the dihydropyrone resulting from subsequent cyclization (ref. 2).

¶ Sample data for **10**: $\nu_{max}(CHCl_3)/cm^{-1}$ 3205, 1766, 1699, 1632 and 1558; δ_H(400 MHz; $CDCl_3$) 1.36 (3 H, t, OCH_2CH_3), 2.43 (3 H, s, CH_3CO), 2.54 and 3.30 (each 2 H, m, CH_2CH_2), 4.30 (2 H, q, OCH_2CH_3); δ_C(100 MHz; $CDCl_3$) 14.3 and 27.1 (CH_3), 28.7, 31.0 and 60.8 (CH_2), 106.4, 166.7, 167.5, 178.6 and 198.6 (C); *m*/*z* 211 (M^+, 75%).

Acknowledgements

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