An Isoxazole Route to Unsaturated α-Alkoxycarbonyl-β-diketones

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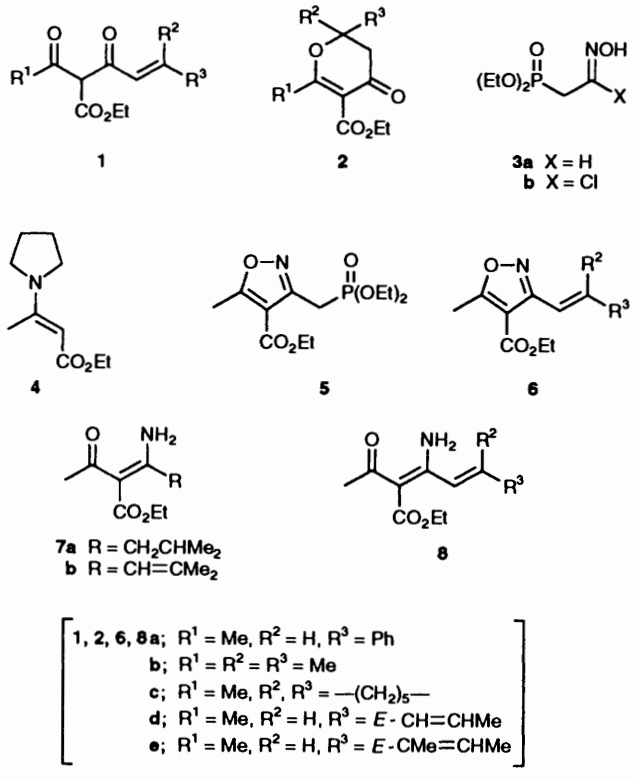
Cycloaddition of diethylphosphonomethyl nitrile oxide to the enamine from ethyl acetoacetate produces 4-ethoxycarbonyl-3-diethoxyphosphonylmethyl-5-methylisoxazole; condensation of the phosphonate with aldehydes and ketones gives 3-alkenylisoxazoles that are cleaved by hexacarbonylmolybdenum to afford unsaturated α-alkoxycarbonyl-β-diketones.

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] we required access to unsaturated α-alkoxycarbonyl-β-diketones **1**. Preparation of these molecules can be envisaged from *C*-acylation of β-keto esters with α,β-unsaturated acid chlorides. Such acylations have indeed been reported *via* the ethoxymagnesium enolates of the β-keto esters,[2] but the intermediates **1** cyclise spontaneously under the acylation conditions to produce 5-alkoxycarbonyl-2,3-dihydro-4-oxopyrans **2** which have proved valuable in heterocyclic[3a] and natural product synthesis.[3b] We report now an alternative sequence utilising isoxazoles as masked 1,3-dicarbonyl compounds,[4] that provides β,β′-tricarbonyl compounds **1** or pyrones **2** according to the exact conditions. The scheme also includes an intermediate that provides for nucleophilic elaboration at the C-3 substituent of a 3,5-dialkylisoxazole rather than at the C-5 substituent as is normal.[5]



Scheme 1

Thus, the oxime **3a** was prepared from bromoacetaldehyde diethyl acetal by Arbusov reaction with triethyl phosphite at reflux (57%), followed by successive treatments of the phosphonate acetal with hydrochloric acid (2% w/v; 96%) and hydroxylamine hydrochloride (69%),[6] and then converted quantitatively (as confirmed by ^{1}H NMR spectroscopy) into the chloro oxime **3b** by reaction with chlorine gas (CH_2Cl_2, −60 °C, 5 min).† Treatment of the chloro oxime **3b** with triethylamine at 0 °C in the presence of the enamine **4**, prepared from ethyl acetoacetate (pyrrolidine, reflux), generated a nitrile oxide; *in situ* 1,3-dipolar cycloaddition to the enamine **4** afforded 3-diethylphosphonomethyl-4-ethoxycarbonyl-5-methylisoxazole **5** (40%).[7]‡ Condensation of this phosphonate under basic conditions ($LiNPr^i_2$, −78 °C) with a variety of aldehydes and ketones [benzaldehyde, propanone, cyclohexanone, but-2-enal and (*E*)-2-methylbut-2-enal] afforded the 3-alkenylisoxazoles **6a–e**, respectively, in very high yields (95, 94, 91, 98 and 99%) and, in the case of aldehydes, with the *E*-geometry of the new carbon–carbon double bond.

These alkenes are a masked form of the required unsaturated α-alkoxycarbonyl-β-keto esters **1**. Our first attempts at revealing the tricarbonyl functionality confirmed that hydrogenolysis of the N–O bond could be achieved,[4] but at the cost of saturation of the alkenyl substituent, shown for example by the formation of **7a** from **6b** (H_2–Pd, EtOH). Samarium diiodide was examined as an alternative[8] but at best we achieved only a 50% conversion of **6b** into the enamino ketone **7b**, and the reaction proved somewhat capricious. Eventually we found that brief treatment of **6b–e** with hexacarbonylmolybdenum in moist acetonitrile (30 min, reflux)[9] gave efficient access to the required tricarbonyl compounds **1b–e** (98, 93, 95 and 97%, respectively) with retention of the unsaturation, presumably *via* the enamino ketones **8** and hydrolysis by the water present. The dihydropyrones **2** could be obtained using longer reaction times (4 h; **2a** from **6b**, 90%; **2b** from **6c**, 85%) and the acyclic materials were observed to undergo slow cyclisation with time.§

The phosphonomethylisoxazole **5** is thus a useful building block, and we continue to exploit this methodology.

Experimental

Typical Procedure (*for* **6b** *and* **7b**).—Butyllithium (1.6 mol dm^{-3} solution in hexanes; 2.5 cm^3, 3.96 mmol) was added dropwise to a stirred solution of diisopropylamine (0.56 cm^3, 3.96 mmol) in dry tetrahydrofuran (30 cm^3) at 0 °C under nitrogen. The resultant solution was stirred for 20 min and

† Alternatives for chloro oxime generation, including *N*-bromosuccinimide (ref. 6), or sodium hypochlorite in a two-phase system, were unsuccessful. There was evidence for chlorination of the active methylene group in some instances.

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

§ Attempts to reverse the cyclisation, for example by treatment of the pyrones with aqueous base, aqueous acid, or $LiNPr^i_2$ and Bu^tMe_2SiCl, proved fruitless, in accord with earlier observations (ref. 2).

cooled to −78 °C before the addition of 3-diethylphosphonomethyl-4-ethoxycarbonyl-5-methylisoxazole **5** (1.1 g, 3.6 mmol). After the purple solution had been stirred for a further 2 h, propanone (0.3 cm^3, 3.96 mmol) was added to it and the mixture allowed to warm to room temperature over 10 h. The mixture was then poured into water (75 cm^3) and extracted with chloroform (3 × 50 cm^3). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated to afford **6b** (0.71 g, 94%) as a pale yellow oil (Found: M^+, 209.1046. $C_{11}H_{15}NO_3$ requires *M*, 209.1052); λ_{max}(EtOH)/nm 217 (ε/dm^3 mol^{-1} cm^{-1} 16 300); ν_{max}($CHCl_3$)/cm^{-1} 2979, 2933, 1720, 1654, 1602, 1455, 1430 and 1110; δ_H($CDCl_3$) 1.4 (3 H, t, *J* 7, OCH_2CH_3), 1.95 and 2.05 (each 3 H, s, CH_3), 2.60 (3 H, s, 5-CH_3), 4.70 (2 H, q, *J* 7, OCH_2CH_3) and 6.5 (1 H, s, CH); δ_C($CDCl_3$) 174.2, 162.3, 159.1, 145.1 (all quaternary C), 111.6 (CH), 108.2 (C), 59.5 (CH_2), 26.7, 20.9, 14.2 and 13.3 (all CH_3); *m*/*z* 209 (M^+), 194, 163, 122 and 43 (100%). The isoxazole **6b** (0.3 g, 1.43 mmol) and hexacarbonylmolybdenum (0.4 g, 1.43 mmol) in acetonitrile (30 cm^3) containing water (20 mg) were heated together at reflux for 30 min. The dark mixture was filtered through Kieselguhr and the solvent evaporated under reduced pressure to leave a brown solid purified by column chromatography on silica gel, eluting with hexane–ethyl acetate (2:1, v/v), to afford **7b** (297 mg, 98%) as a pale yellow oil (Found: M^+, 212.1054. $C_{14}H_{16}O_4$ requires *M*, 212.1049); ν_{max}($CHCl_3$)/cm^{-1} 3480, 3155, 1694, 1614, 1573, 1462, 1123 and 899; δ_H($CDCl_3$) 1.25 (3 H, t, *J* 7, OCH_2CH_3), 1.77 and 1.81 (each 3 H, s, $=CCH_3$), 2.25 (3 H, s, CH_3CO), 4.15 (2 H, q, *J* 7, OCH_2CH_3) and 6.05 (1 H, s, CH); δ_C($CDCl_3$) 197.2, 169.3, 164.3, 140.2 (all quaternary C), 122.2 (CH), 103.0 (C), 59.7 (CH_2), 29.8, 25.4, 19.6 and 14.0 (all CH_3); *m*/*z* 212 (M^+), 196, 150 and 43 (100%).

Acknowledgements

We thank SERC for a studentship (G. B.) and Shell Research for financial support.

References

1 For leading references, see: R. C. F. Jones and M. Tankard, *J. Chem. Soc., Perkin Trans. 1*, 1991, 240; R. C. F. Jones, M. J. Begley, G. E. Peterson and S. Sumaria, *J. Chem. Soc., Perkin Trans. 1*, 1990, 1959.
2 S. Gelin and R. Gelin, *Bull. Soc. Chim. Fr.*, 1968, 288; 1969, 1383.
3 (*a*) B. Chantegrel, A. Nadi and S. Gelin, *J. Heterocycl. Chem.*, 1984, **21**, 13; B. Chantegrel, A. Nadi and S. Gelin, *Synthesis*, 1983, 948; S. Gelin, C. Deshayes and M. Chabannet, *J. Heterocycl. Chem.*, 1979, **16**, 1117; C. Deshayes and S. Gelin, *J. Heterocycl. Chem.*, 1979, **16**, 657; S. Gelin and C. Deshayes, *Synthesis*, 1978, 900; (*b*) M. Blouin, M. C. Bélard and P. Brassard, *J. Org. Chem.*, 1990, **55**, 1466; D. L. Boring and R. D. Sindelar, *J. Org. Chem.*, 1988, **53**, 3617; T. Sakai, K. Miyata, M. Ishikawa and A. Takeda, *Tetrahedron Lett.*, 1985, **26**, 4727; K. Sato, S. Inoue and M. Ohashi, *Bull. Chem. Soc. Jpn.*, 1973, **46**, 1288.
4 For a discussion of the strategy of isoxazoles as masked functionality, see: K. B. G. Torssell, *Nitrile Oxides, Nitrone and Nitronates in Organic Synthesis*, VCH Publishers, Weinheim, 1988.
5 N. R. Natale, J. I. McKenna, C.-S. Niou and M. Borth, *J. Org. Chem.*, 1985, **50**, 5660; R. G. Micetich, *Can. J. Chem.*, 1970, **48**, 2006; E. W. Collington, J. G. Knight, C. J. Wallis and S. G. Warren, *Tetrahedron Lett.*, 1989, **30**, 877.
6 O. Tsuge, S. Kanemasa, H. Suga and N. Nakagawa, *Bull. Chem. Soc. Jpn.*, 1987, **60**, 2463.
7 G. Stork and J. E. McMurry, *J. Am. Chem. Soc.*, 1967, **89**, 5463.
8 N. R. Natale, *Tetrahedron Lett.*, 1982, **48**, 5009.
9 M. Nitta and T. Kobayashi, *J. Chem. Soc., Chem. Commun.*, 1982, 877.

Paper 3/02949B
Received 24*th May* 1993
Accepted 6*th June* 1993