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METHYL 3-OXOBICYCLO[2,2,1]HEPTANE- AND 3-OXOBICYCLO[2,2,2]OCTANE-2-CARBOXYLATES: PREPARATION AND PROPERTIES

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Recent publications have described the synthesis of cyclic and bicyclic β-keto esters by a Diels-Alder reaction using a carboalkoxyketene equivalent as a dienophile. Reaction of methylthiomaleic anhydride with dienes followed by oxidative decarboxylation of the adduct yields the keto ester in protected form[1]. A route to C-nucleosides involves Diels-Alder reaction of furan and 1,3-diethoxycarbonylallene followed by ozonolysis[2]. This prompts us to report that bicyclic keto esters may be prepared using methyl 3-bromopropiolate[3,4] (1) as a carbomethoxyketene equivalent. (1) is a reactive dienophile and the adduct may be converted either to the keto ester or to a keto-protected form in one further step. We also describe how some of the characteristic properties of β-keto esters are modified by a bicyclic ring system.

The route is summarised in the scheme.

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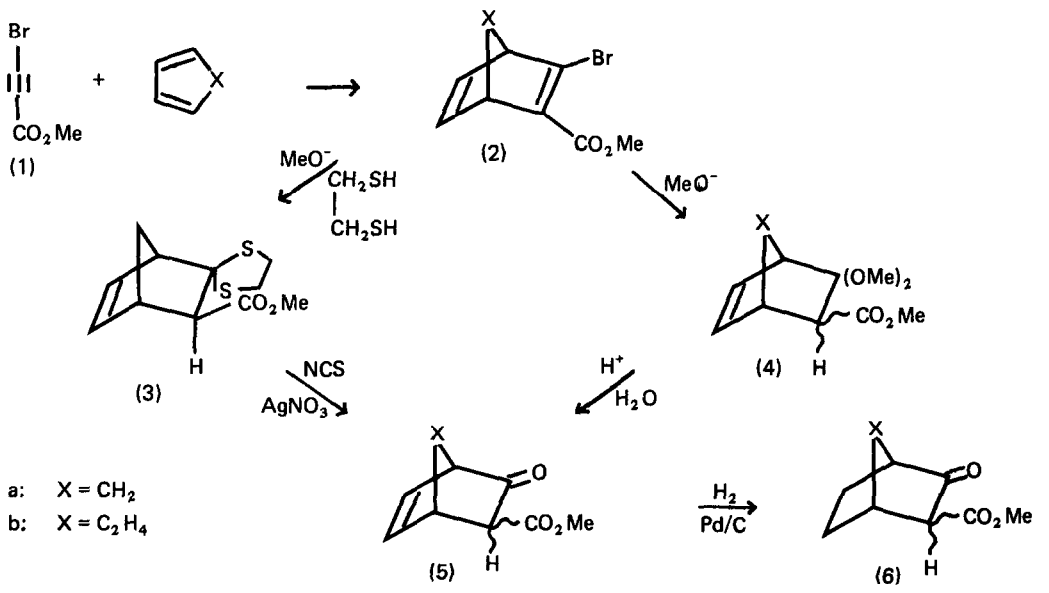
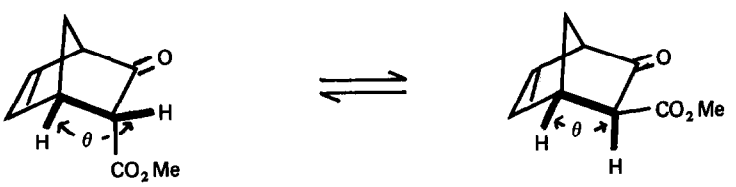


Reaction of (1) and cyclopentadiene (3 hr. reflux in benzene) afforded (2a) (89% yield)[5]. Addition of sodium methoxide (1.1 mol.) to a stirred solution of (2a) and ethanedithiol (1 mol.) under nitrogen gave the dithioketal (3a) in 72% yield, predominantly as a single epimer. (3a) was assigned the exo configuration since Raney nickel desulphurisation took place with concomitant hydrogenation, yielding methyl exo-norbornane-2-carboxylate. Keto ester (5a) was obtained in 70% yield after removal of the thioketal protecting group with N-chlorosuccinimide in presence of silver nitrate[6].

Alternatively (2a) was converted to the ketal ester (4a) by heating with 1M sodium methoxide (1.1 mol.). (4a) was isolated by work up under neutral conditions. However, addition of dilute aqueous hydrochloric acid to the reaction mixture afforded (5a) directly from (2a) (76% yield) in a "one pot" reaction. Hydrogenation of (5a) (Pd/C,EtOH) produced (6a) in 86% yield.

Similarly, (1) and cyclohexadiene gave the adduct (2b) (24 hr. reflux in benzene; 77% yield). Reaction of (2b) with sodium methoxide followed by aqueous acid as above afforded (5b) in 70% yield and this in turn was readily hydrogenated to give (6b) (84% yield).

I.R.[7] and N.M.R. indicated that keto esters (5a), (5b) and (6a) occur almost exclusively in the keto form[8]. Distillation of (5a) gave an opproximately 40:60 mixture of the keto esters epimeric at C2, separable by column chromatography on silica gel. The structures of the epimers follow from their N.M.R. spectra (60MHz,$CDCl_3$) minor epimer: δ2.4 (2H,m,H7), 2.9 (1H,d,J=4Hz,H2), 3.2 (2H,m,allyl), 3.75 (3H,s,$\underline{CH_3}O$-), 6.3 (1H,m,vinyl), 6.6 (1H,m,vinyl): major epimer δ2.2 (2H,m,H7), 3.2 (1H,bs,H2), 3.3 (2H,m,allyl), 3.70 (3H,s, $\underline{CH_3}O$-), 6.2 (1H,m,vinyl), 6.8 (1H,m,vinyl). The coupling constants for the C2 proton in the minor and major epimers indicate by the Karplus equation that the dihedral angles between the protons at C1 and C2 approximate to the measured angles of the endo and exo epimers respectively[9]:-



40% (5a endo) $\theta \approx 45°$ 60% (5a exo) $\theta \approx 80°$

Support for the assignment was provided by the hydrolysis of exo thioketal (3a). The initial product was the major, exo keto ester which epimerised slowly under the reaction conditions.

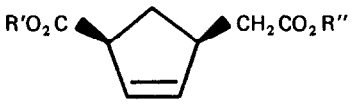
The two epimers of (5a) did not equilibrate at 0°. In CD_3OD, each epimer underwent slow equilibration with exchange of the C2 proton, complete equilibration requiring one week at room temperature. However, the epimers equilibrated on distillation and were inseparable by gas chromatography on a variety of columns. Chromatography on Kieselgel G also led to equilibration[10].

In contrast to (5a), compounds (5b), (6a) and (6b) enolise more readily, undergoing complete exchange of the C2 proton in 0.5 - 3 hr. at room temperature in CD_3OD. The NMR spectra suggest that (5b) is a single epimer [δ3.70 (3H,s,$\underline{CH_3}O$-)] while (6a) is a mixture of epimers [δ3.68 (s, $\underline{CH_3}O$-) and δ3.73 (s,$\underline{CH_3}O$-)].

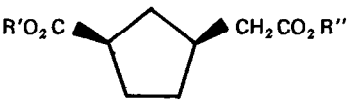
Presumably (5a) is reluctant to enolise since the process involves the introduction of a second double bond into a norbornene system, which has been shown both theoretically[11] and experimentally[12] to increase the associated strain energy.

(5a) is extremely sensitive to ring cleavage by base. Thus, cis diester (7a) was formed in quantitative yield on reaction of (5a) with a catalytic quantity (0.1 mol.) of sodium methoxide (10 min. at R.T.). Reaction of (5a) with cold, dilute aqueous sodium hydroxide (1 mol.) afforded monoacid ester (7c), while diacid (7b) was obtained on reaction with two equivalents of alkali (m.p. 112 - 113°, 82% yield). (7b) was also obtained by alkaline hydrolysis of (7a) or (7c).

(6a) is less reactive, but was readily converted to cis diester (8a) by sodium methoxide in 80% yield, while aqueous alkali afforded the diacid (8b) (m.p. 133 - 134°). Hydrogenation (Pd/C, EtOH) of (7b) afforded (8b).



(7) (a) R' = R' = Me
(b) R' = R''= H
(c) R' = H, R'' = Me



(8) (a) R' = R'' = Me
(b) R' = R'' = H

In contrast (5b) and (6b) were both recovered unchanged after standing overnight in 1M sodium methoxide solution. Dilute aqueous alkali cleanly hydrolysed the ester without ring opening. Decarboxylation of the keto acids yielded bicyclo[2,2,2]oct-5-en-2-one and bicyclo[2,2,2]octan-2-one respectively.

Acknowledgements

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References and Notes

1. B.M. Trost and G. Lunn, J. Amer. Chem. Soc. 99, 7079, (1977)
2. A.P. Kozikowski, W.C. Floyd and M.P. Kuniak, J. Chem. Soc. Chem. Commun. 582 (1977).
3. F. Strauss, L. Kollek and W. Heyn, Berichte 63B, 1868 (1930).
4. C.D. Heaton and C.R. Noller, J. Amer. Chem. Soc. 71, 2948 (1949).
5. Alkaline hydrolysis of (2a) yielded the acid: K. Alder, R. Hartman and W. Roth, Annalen 613, 6 (1958).
6. E.J. Corey and D. Crouse, J. Org. Chem. 33, 298 (1968).
7. e.g. (5a). IR (neat) 1720, 1750 cm^{-1}.
8. For a discussion of keto-enol tautomerism in β-keto esters see S.J. Rhoads, J.C. Gilbert, A.W. Decora, T.R. Garland, R.J. Spangler and M.J. Urbigkit, Tetrahedron. 19, 1625 (1963).
9. The H3-H4 coupling constants in norbornan-2-one are: H3 exo, 4·76Hz; H3 endo, 0.0Hz. J.L. Marshall and S.R. Walter, J. Amer. Chem. Soc. 96, 6358 (1974).
10. The exo : endo equilibrium in the methyl norborn-5-ene-2-carboxylates is 50:50. A.C. Cope, E. Ciganek and N.A. LeBel, J. Amer. Chem. Soc. 81, 2799 (1959). J.A. Berson & D.A. Ben-Efraim J. Amer. Chem. Soc. 81, 4083 (1959).
11. N.L. Allinger and T.J. Sprague, J. Amer. Chem. Soc. 94, 5734 (1972).
12. R.B. Turner, W.R. Maedor and R.E. Winkler, J. Amer. Chem. Soc. 79, 4116 (1957).

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