Tetrahedron Letters,Vol.29,No.45,pp 5789-5792,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

ENOLATE ALKYLATION OF BICYCLO(2.2.2)OCT-5-EN-2-ONE AND RADICAL CYCLISATION - A POTENTIAL APPROACH FOR THE CONSTRUCTION OF TRICYCLIC CARBOCYCLES

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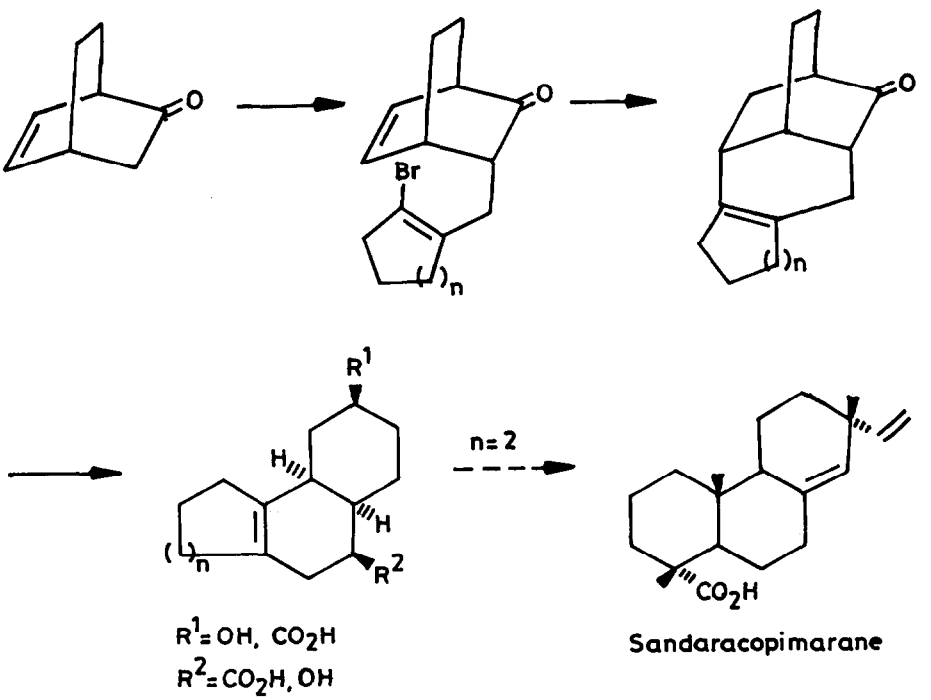
Abstract: The alkylation of bicyclo(2.2.2)oct-5-en-2-one (1) and intramolecular radical cyclisation towards the synthesis of functionalised tricyclic carbocycles - is reported.

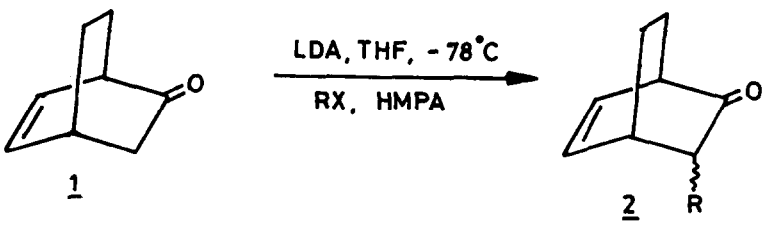
The alkylation of bicyclo(2.2.2)oct-5-en-2-one (1)[1] and its synthetic potential has hardly been explored. Only methylation[2,3] of this ketone has been reported in this ketone till today. As part of one of our synthetic projects aimed at developing a general approach for the construction of functionalised tricyclic ring systems present in diterpenoids such as primaranes, we became interested in the enolate alkylation of bicyclo(2.2.2)oct-5-en-2-one (1). The recent report of Clive et al.,[4] on the application

Scheme I



of radical cyclisation to the synthesis of cyclopentanones, has prompted us to communicate our preliminary findings. In this publication, we describe the alkylation of 1, successful radical cyclisation of the alkylated products 2d, 2e and 2f to 3, 4, 5 and application of this methodology for the synthesis of angularly fused tricyclohexyl lactone 6a/6b. Slow addition of the ketone 1 (1 equivalent) to LDA (1.5 equivalents) in THF at -78°C and stirring at that temperature for 1h afforded the enolate of 1. Quenching the enolate with a solution of the alkyl halide in HMPA at -78°C and leaving the reaction mixture at room temperature overnight, furnished the alkylated enones in good yields. A high preference for endo alkylation was noticed in all the cases studied. While selectivity dropped somewhat in the case of alkylation of other alkylhalides (Table-1), in the case of methylation 100% endo selectivity was observed. This is in contrast to the literature observation[2] that on methylation of 1 with NaH in diglyme at 55°C for 3h, a mixture of three products (consisting of 74.7% endo isomer, 10% of dimethylated enone and 3.7% of exo

Table 1



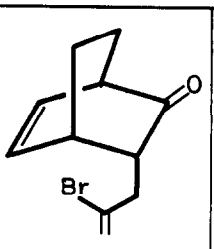
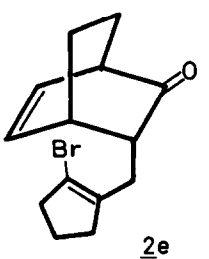
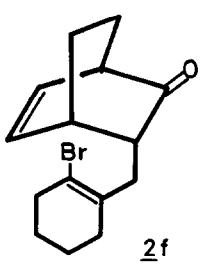
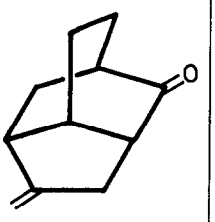
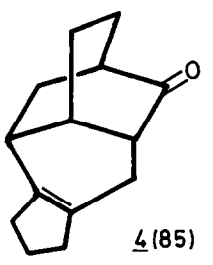
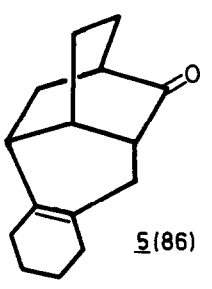
1 2

R	$-CH_3$ 2a	$\rightarrow CH_2-$ 2b	CH_2- 2c	Br CH_2- 2d	Br CH_2- 2e	Br CH_2- 2f
Yield %	85	72	70	85	80	88
endo:exo[8]	100 : 0	84:16	87:13	83:17	92:8	95:5

methylated product) along with the 11.6% of the starting material was obtained. The authors observed that longer reaction duration lead to isomerisation with the formation of endo and exo isomers in the ratio of 64.6:35.4. In our experiments the reactions were clean and free from complications such as formation of oligomers and polymers by the aldol condensation which is reported in the case of norbornenone[5]. The endo stereochemistry of alkylated products was clearly revealed by the facile intramolecular cyclisation undergone 2d to 2f on treatment with nBu_3SnH. When 2d was refluxed in benzene (0.02M) with nBu_3SnH in the presence of AIBN for 6h, it underwent a smooth cyclisation and afforded the cyclised product 3 in 75% yield. Likewise, compounds 2e and 2f were also cyclised in high yields to the respective products 4 and 5 (Table-II)[7]. The preference for the 5-exo-trig cyclisation over 6-exo-trig in a similar bicyclo(2.2.2)derivative has

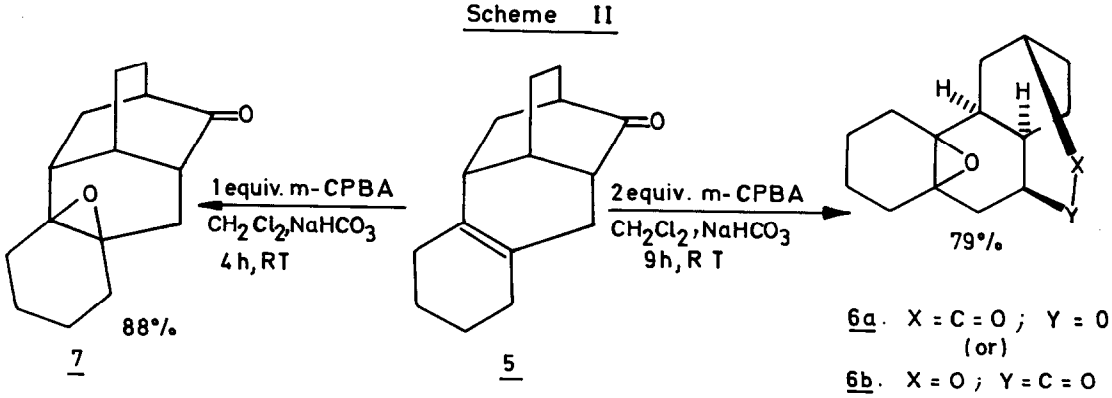
recently been reported by Clive et al.,[4].

Table II

Substrate	 2d	 2e	 2f
Product (Yield %)	 3(75)	 4(85)	 5(86)

Unlocking of the enone 5 by Baeyer-Villiger oxidation[6] with 2 equiv. of m-chloroperbenzoic acid in CH_2Cl_2 in the presence of $NaHCO_3$ afforded the epoxylatone as a liquid in 79% yield, whereas reaction of 5 with lequiv of peracid yielded the epoxide 7 as a solid (m.p. 82-83°C) in 88% yield. The epoxylactone has been found to consist of

Scheme II

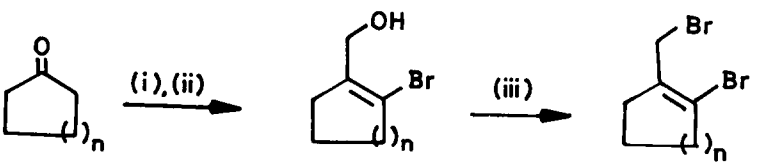


6a. X = C = O ; Y = O
(or)
6b. X = O ; Y = C = O

only one isomer as evinced by ^{13}C nmr and tlc which can be either 6a or 6b. With the available spectral data, the exact structure cannot be assigned at this stage. As the epoxylactone is a highly functionalised tricyclic cyclohexyl ring system with defined stereochemistry, further elaboration of this compound towards the synthesis of speicific natural products will be explored.

It may be mentioned here that none of the 1-bromo-2-bromomethylcycloalkenes used in the present study is described in the literature. They have been prepared as shown in the scheme-III.

Scheme III



(i) DMF, PBr_3, $CHCl_3$, 60°C (n=1, 75% ; n=2, 76%)

(ii) $NaBH_4$, MeOH (n=1, 85 % ; n=2 , 91 %)

(iii) PBr_3 , Py, CH_2Cl_2 (n=1, 90 % ; n=2, 92 %)

Acknowledgements: One of us (TR) acknowledges the CSIR for financial support and our thanks are due to Professor Dr. G. Schroder and Dr. H. Rottele, University of Karlsruhe, West Germany for high resolution ^1H nmr and for ^{13}C nmr, and Professor B. Gross, University of Nancy, France for a gift of tri-n-butyltin chloride.

References:

1. P.K. Freeman, D.M. Balls, and D.J. Brown J. Org. Chem., 33, 2211 (1968).
2. M.R. Willcott, III, R.E. Davis, and R.W. Holder, J. Org. Chem., 40, 1952 (1975).
3. M.C. Lasne, J.L. Ripoll Tetrahedron Letters 1980, 21, 463.
4. D.L.J. Clive, and D.R. Cheshira, J. Chem. Soc., Chem. Commun. 1520 (1987).
5. J.H. Horner, M. Vera, and J.B. Grutzner, J.Org. Chem., 51, 4212, (1986).
6. J. Meinwald and E. Frauenglass, J. Am. Chem. Soc., 82, 5235 (1960).
7. Spectral data of representative compounds 2f and 5.
   2f: ir (CCL_4) 3020cm^{-1}, 2930cm^{-1}, 1710cm^{-1} 700cm^{-1}
   ^1H nmr($CDCl_3$/TMS) δ:6.5(m,1H), 6.1(m,1H) 3.2(m,1H), 2.9(m,1H), 1.5-2.5 (multiplets, 15H).
   ^{13}C nmr($CDCl_3$/TMS) PPM: 213.6(s), 137.2(d), 133.9(s), 126.8(d), 121.2(s), 48.3(d), 47.6(d) 38.97(t), 36.9(t), 35.7(d), 30.8(t), 24.9(t), 24.8(t), 22.6(t), 22.2(t).
   MS: m/s 215(M-Br)$^+$, 80(base peak, ion due to retro Diels-Alder Fragmentation).
   5: ir (CCl_4) 2910cm^{-1}, 1715cm^{-1}.
   ^1H nmr($CDCl_3$/TMS δ:0.9-2.4 (multiplets for 20H).
   ^{13}C nmr($CDCl_3$/TMS) PPM: 221.9(s), 132.8(s), 125.8(s), 46.05(d), 41.9(d), 36.6(d), 33.01(d), 32.7(t), 29.6(t), 28.7(t), 23.3(t), 22.95(4t).
   MS: m/z 216(M^+), 188(M-CO)$^+$, 145, 136(base peak), 91.
8) The endo:exo ratios were determined from the HPLC analysis (the HPLC analysis was performed using Schimadzu LC-5A, Column-Zorbax, ODS 4.6mmx15cm, with 100% MeOH as the eluant) and also from the high resolution ^1H nmr spectrum of the alkylated product in the case of 2a.

(Received in UK 20 September 1988)