Pergamon

Tetrahedron Letters 41 (2000) 1287–1290

TETRAHEDRON LETTERS

The anionic route to tricyclanes

Kamyar Afarinkia * and Farzana Mahmood

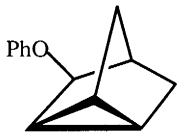
Department of Chemistry, King's College, The Strand, London WC2R 2LS, UK

Received 29 October 1999; accepted 7 December 1999

Abstract

A very mild anion induced intramolecular ring closure route to tricyclanes is reported.

The extensive development of the chemistry of the tricyclane (tricyclo[2.2.1.0^{2,6}]heptane) ring system over the past three decades owes much to its role in unravelling mechanistic aspects of Wagner–Meerwein rearrangements and the concept of non-classical carbocations. Interestingly, tricyclanes have even found a biological role as phenoxytricyclane **1** is reported to have as equal a potency as an insecticide as DDT.[1]



(1)

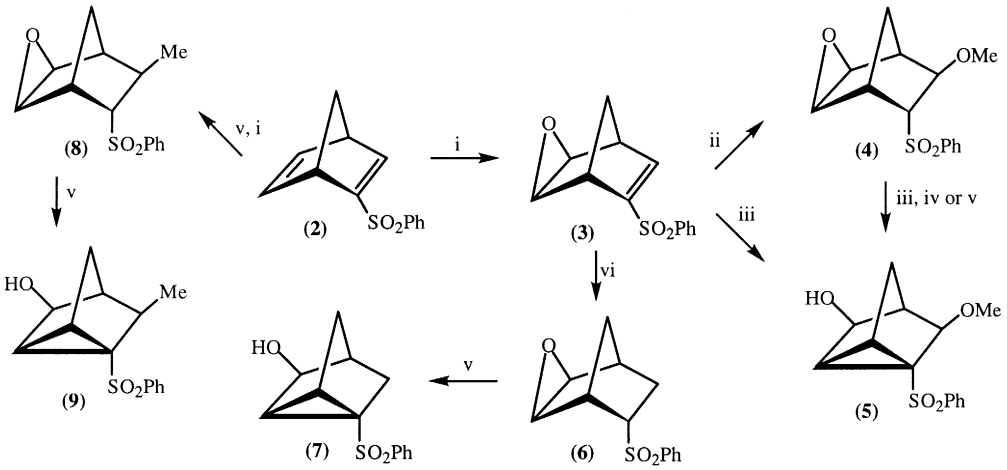
Carbene insertion in norbornanes,[2] and both radical[3] and cationic[4] ring closures in norbornenes have been widely employed for the synthesis of tricyclanes. However, there are very few examples of the analogous anion-induced ring closure in the literature.[5] Here, we report a series of observations which suggest that the anionic route is a significantly more versatile route to tricyclanes than previously believed.

Compound **2** was prepared by cycloaddition of *cis*-1,2-phenylsulfonylethene and cyclopentadiene followed by base-induced elimination of phenylsulfinic acid. Epoxidation (mCPBA/CH_2Cl_2 or H_2O_2/*t*-BuOK in THF) afforded *exo* epoxide **3** in quantitative yield under both reaction conditions. Upon treatment with lithium methoxide in methanol at room temperature, an addition product was obtained which on the basis of NMR spectra was assigned structure **4**. However, when this reaction was carried out at reflux, compound **4** was not the isolated product. Instead, tricyclane **5** was isolated in 81% yield (Scheme 1). X-Ray structure determination confirmed the formation of tricyclane and that the nucleophilic methoxide had attacked from the less hindered *exo* face.[6] Compound **4** could be transformed

* Corresponding author. E-mail: kamyar.afarinkia@kcl.ac.uk (K. Afarinkia)

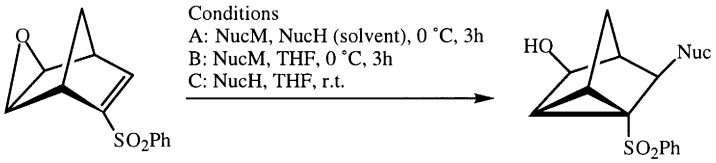
0040-4039/00/$ - see front matter
PII: S0040-4039(99)02270-4

to **5** by treatment with a variety of bases in good yield (Scheme 1). A related observation was recently made confirming that such anionic ring closure of tricyclanes are facile.[5c]



Scheme 1. Reagents and conditions: (i) mCPBA, CH_2Cl_2, 100%; (ii) MeOLi, MeOH, rt, 3 h, 100%; (iii) MeOLi, MeOH, reflux, 5 days, 81%; (iv) *t*-BuOK, DMSO, 70°C, 5 days, 90%; (v) MeLi, THF, 0°C, 3 h, 100%; (vi) 10% Pd/C, hydrogen, EtOAc, rt, 100%

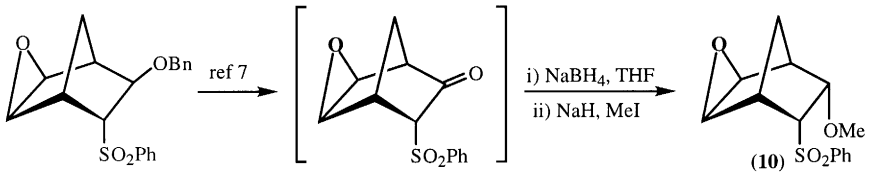
Further investigation revealed that nucleophilic addition/epoxide ring opening is a general reaction of compound **3**. Additions of a number of other nucleophiles afforded the corresponding tricyclanes in a similar manner (Scheme 2). Reactions can be carried out under a range of conditions and even treatment with nucleophiles in organic solvents at room temperature afforded tricyclane, albeit in moderate yields. Presumably, these reactions proceed in two steps. The first is a slow and reversible conjugate addition of the nucleophile to the vinylsulfone which is then followed by a fast and irreversible intramolecular nucleophilic attack of the sulfonyl-stabilised carbanion on the epoxide, leading to ring opening of the epoxide. However, when we prepared **6** and **8**, which lack the methoxy group, and studied the tricyclane formation under basic conditions we made an unexpected observation. Under conditions previously employed (MeOLi, MeOH, reflux, 5 days) the rates of cyclisation of compounds **6** and **8** are relatively slow compared to that observed for **4**. Following the progress of the reaction by NMR revealed that compound **4** was half transformed to compound **5** in 85 h. Under similar conditions, compound **8** was half transformed to compound **9** in 215 h. Furthermore, compound **6** afforded none or only trace quantities of cyclised tricyclane upon treatment with reagents that gave near quantitative yields of cyclisation with **3** (e.g. 0.1 M aqueous KOH in THF at room temperature) or **4** (e.g. potassium *t*-butoxide in DMSO at 70°C). Indeed, good yields of tricyclane **7** could only be obtained when a strong organometallic base (methyllithium in THF) was used.



Scheme 2. Nuc=OMe (A, 100%, M=Li); OCH_2Ph (A, 100%, M=Li); OH (A, 100%, M=K); Me (B, 100%, M=Li); Ph (B, 82%, M=Li or 100%, M=MgBr); PhS (C, 42%); $PhNCH_3$ (C, 35%); NH_2 (C, 28%, dioxane as solvent)

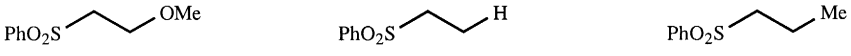
The contrast between the relatively mild basic conditions used for formation of tricyclanes from **4** and the more strongly basic condition required for formation of tricyclane from **6** and **8** is striking. The only

feature of compound **4** which distinguishes it from **6** and **8** is the methoxy substituent at the position β to the sulfonyl rather than hydrogen (for compound **6**) or methyl (for compound **8**). To gauge if the effect is related to the stereochemistry of the methoxy substituent in compound **4**, we also prepared its epimer containing the β-methoxy substituent at the *endo* position (Scheme 3).[7] In a competition experiment, the half life of cyclisation of **10** when treated with lithium methoxide at reflux was 130 h compared to 85 h for that of **4**.



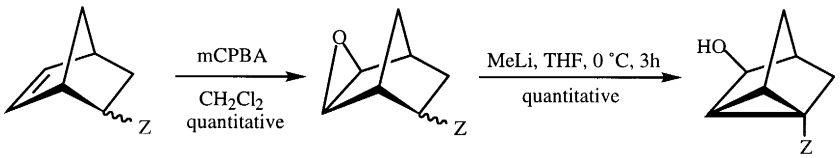
Scheme 3.

The role of the β-methoxy substituent in the more facile cyclisation of **4**, compared to that of **6** or **8**, may be attributed to easier deprotonation at the position α to the sulfonyl group. Stirling has previously reported that loss of an α proton from methoxyethylphenylsulfone **11** is faster than that observed from propyl- and ethylphenylsulfone **12** and **13**.[8] Although, as proposed by Stirling, the influence of the methoxy substituent can be attributed to the polar effect of the methoxy substituent, that will not explain the slight, though observable, differences in the rates of cyclisation between **4** and its epimer **10**.



(**11**) (**12**) (**13**)

The anionic cyclisation is a general and high yielding route to tricyclanes and other norbornene and norbornane epoxides undergo a similar reaction (Scheme 4). There were no observable differences in the facility of the reaction between the *endo* and *exo* isomers. Interestingly, the use of two molar equivalents of MeLi in the reaction of **17** affords the corresponding acetyl derivative **20**, which is obtained via formal addition of a methyl anion to a nitrile followed by hydrolysis; however, in general, MeLi acts as a base and not a nucleophile. Our results also showed that the effect of a β-methoxy substituent is significantly less pronounced, but never-the-less observable, for groups such as carbomethoxy.



Z = CO_2Me (**14**) (**18**)
Z = $PO(OEt)_2$ (**15**) (**19**)
Z = COMe (**16**) (**20**)
Z = CN (**17**) (**20**)

Scheme 4.

In conclusion, we have shown a new, facile and general anionic route for synthesis of tricyclanes. The tricyclanes obtained by this method are functionally rich. We are currently further investigating the factors that influence the facility of the cyclisation and also the use of these functionalised tricyclane templates in peptide design.

Acknowledgements

We would like to thank Prof. W. B. Motherwell for useful discussions, and the Commonwealth Scholarship Commission for a studentship to F.M. We are indebted to the University of London Intercollegiate Research Services (ULIRS) at King's College and EPSRC's Chemical Database Service at Daresbury Laboratories for the use of their facilities. This work was made possible by a grant from the University of London Central Research Fund (Stern Trust).

References

1. Stepanov, D. E.; Kron, E. M.; Sedigkh, A. S.; Kalabina, A. B. *Izv. Vyssh. Ucheb. Zaved., Khim. Khim. Tekhnol.* **1967**, *10*, 778 (CA 69: 2558m).
2. For recent examples, see: (a) Kirmse, W.; Meinert, T. *Chem. Commun.* **1994**, 1065. (b) Bartsch, R. A.; Lee, J. G. *J. Org. Chem.*, **1990**, *55*, 5247. (c) Fermann, M.; Herpers, E.; Kirmse, W.; Neubauer, R. *Chem. Ber.* **1989**, *122*, 975. (d) Creary, X.; Wang, Y. X. *Tetrahedron Lett.* **1989**, *30*, 2493.
3. For an example, see: Ziman, S. D.; Trost, B. M. *J. Org. Chem.*, **1973**, *38*, 649.
4. For a recent example, see: Subramanian, R. S.; Balasubramanian, K. K. *Tetrahedron Lett.* **1990**, *31*, 2201.
5. (a) Campbell, M. M.; Kaye, A. D.; Sainsbury, M.; Yavarzadeh, R. *Tetrahedron Lett.* **1984**, *25*, 162. (b) Campbell, M. M.; Kaye, A. D.; Sainsbury, M.; Yavarzadeh, R. *Tetrahedron* **1984**, *40*, 2461. (c) Merchand, A. P.; Dong, E. Z.; Bott, S. G. *Tetrahedron* **1998**, *54*, 4459. (d) Thomas, A. F.; Rey, F. *J. Org. Chem.* **1989**, *54*, 3504. (e) There is one example of anion induced synthesis of quadricyclane (quadricyclo[2.2.1.$0^{2,6}$.$0^{3,5}$]heptane) ring in literature: Cristol, S. J.; Harrington, J. K.; Singer, M. S. *J. Am. Chem. Soc.* **1966**, *88*, 1529.
6. X-Ray crystallography was performed with a κ_{CCD} diffractometer. Crystal data: Monoclinic, *P21/n*, *a*=8.0759(4) Å, *b*=29.6140(2) Å, *c*=11.8972(4) Å. *Z*=2 molecules per cell. D_c=1.376 Mgm^{-3}. Full crystallographic details are deposited in the Cambridge Organic Crystal database.
7. Olah, G.; Gupta, B. G.; Fung, A. P. *Synthesis* **1980**, 897.
8. (a) Thomas, P. J.; Stirling, C. J. M. J. Chem. Soc., *Chem. Commun.* **1976**, 829. (b) Thomas, P. J.; Stirling, C. J. M. *J. Chem. Soc., Perkin Trans. 2* **1977**, 1909.