CHEMISTRY LETTERS, pp. 593-596, 1989.

1,3-Dipolar Cycloaddition of 1-Methyl-3-oxidopyridinium and Sulfonylethenes. A Synthesis of 2-Tropanols and Monofluorinated 2-Tropanol

Tamiko TAKAHASHI, Toru HAGI, Kazuyoshi KITANO, Yoshio TAKEUCHI, and Toru KOIZUMI*

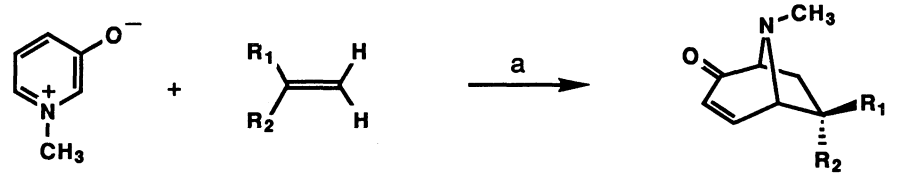
Faculty of Pharmaceutical Sciences, Toyama Medical & Pharmaceutical University, Sugitani 2630, Toyama 930-01

2α- and 2β-Tropanols were synthesized by 1,3-dipolar cycloaddition of phenyl vinyl sulfone and 1-methyl-3-oxidopyridinium regio- and stereoselectively. The method was extended to a preparation of 6α-fluoro-2β-tropanol from 1-(benzenesulfonyl)-1-fluoroethene.

In the last decade, 1,3-dipolar cycloaddition provided one of the most powerful tools for the synthesis of complex skeletons of biologically active natural products because of the high level of regio- and stereochemical control.[1] For example, Katritzky and his co-worker have reported a construction of a tropane ring system by dipolar cycloaddition of 1-methyl-3-oxidopyridinium (1) with acrylonitrile (2) and related compounds.[2] This method seems to be as useful as well-known Robinson-Schopf's[3] and Noyori's.[4] However, generalization of the method to naturally occurring tropane alkaloids has not been accomplished yet, probably owing to the problems in removing nitrile or carboxyl group at 6-position of the cycloadducts. To resolve this problem and to develop a general method for the synthesis of biologically important tropane alkaloids, we decided to investigate the 1,3-dipolar cycloaddition of sulfur-functionallized ethenes, such as phenyl vinyl sulfone (3) with 1. The advantages of this new approach are as follows: 1) the sulfur functionality is expected to be removed quite easily from the cycloadducts by reductive desulfurization, 2) the use of 1-(benzenesulfonyl)-1-fluoroethene (5), which was currently introduced by us as an effective monofluorinated building block,[5] will provide a new entry to the synthesis of monofluorinated tropane alkaloids which are attractive candidates for new medicines, 3) chiral synthesis of both natural and unnatural enantiomers of tropanes is possible in this cycloaddition by using optically active sulfinylethenes, such as $(R)_S$-p-tolyl vinyl sulfoxide $(R)_S$-(4). In this paper, we thus describe our recent studies along this line which comprises the highly regio- and stereoselective cycloaddition of 1 with the sulfonylethenes, 3 and 5, and the first successful preparation of 2-tropanols (12 and 13) and monofluorinated 2-tropanol (18). Our next paper will be concerned with an enantioselective synthesis of (1S)-(-)-2α-tropanol (-)-12 using $(R)_S$-4.[6]

Cycloaddition reaction of the pyridinium 1 with the sulfone 3 proceeded at 90 °C for 13 h regio- and stereoselectively to give a single product (7)[7] (mp 124-

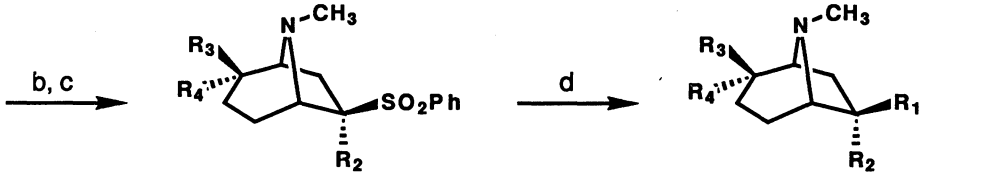
127 °C) in 84% yield. The structure of 7 was determined by the NMR spectrum comparing with that of the cycloadduct (6).[2] Reduction of 7 with sodium borohydride followed by catalytic hydrogenation in the presence of palladium-black afforded the 2α-alcohol (10) (mp 173-175 °C) and the 2β-alcohol (11) (mp 139-141 °C) in 31% and 62% yield, respectively. Desulfonylation of 10 proceeded successfully under a reaction condition of Bouveault-Blanc[8] to give 2α-tropanol 12 (mp 35-40 °C, lit.[9] mp 38-41 °C, lit.[10] mp 45-48 °C). The spectral data of 12 were



1

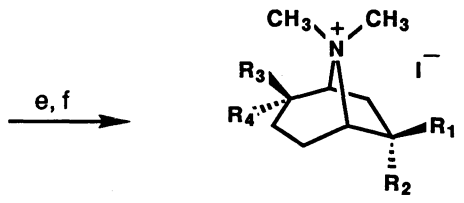
2 : R_1=CN, R_2=H
3 : R_1=SO_2Ph, R_2=H
4 : R_1=SOTol, R_2=H
5 : R_1=SO_2Ph, R_2=F

6 : R_1=CN, R_2=H
7 : R_1=SO_2Ph, R_2=H
8 : R_1=SOTol, R_2=H
9 : R_1=SO_2Ph, R_2=F



10 : R_2=R_3=H, R_4=OH
11 : R_2=R_4=H, R_3=OH
16 : R_2=F, R_3=H, R_4=OH
17 : R_2=F, R_3=OH, R_4=H

12 : R_1=R_2=R_3=H, R_4=OH
13 : R_1=R_2=R_4=H, R_3=OH
18 : R_1=R_4=H, R_2=F, R_3=OH



14 : R_1=R_2=R_3=H, R_4=OAc
15 : R_1=R_2=R_4=H, R_3=OAc
19 : R_1=R_4=H, R_2=F, R_3=OAc

Reagents and conditions: (a) THF, 90 °C; (b) $NaBH_4$, EtOH, rt; (c) H_2/Pd-C, MeOH, 3 atm; (d) Na, EtOH/THF, 0 °C; (e) Ac_2O, reflux; (f) MeI, CH_3CN, 50-70 °C.

consistent with those of (1R)-(+)-2α-tropanol.[11] 2α-Tropanol 12 was converted to the acetate methiodide 14 (mp 265-267 °C, lit.[12] mp 263-265 °C) in 16% yield from 10. Under these reaction conditions, desulfonylation of 11 gave 2β-tropanol 13, of which the NMR spectrum was consistent with that of 13 reported previously.[13] Then 2β-tropanol 13 was transformed to the acetate methiodide (15) (mp 202-203 °C) in 36% yield from 11.

Monofluorinated derivatives of biologically active compounds have recently attracted considerable attention from synthetic and medicinal points of view.[14] (1R)-2β-Tropanyl acetate methiodide (1R)-15, which is derived from natural cocaine, has been shown to exhibit parasympatholytic activity.[12] Replacement of a hydrogen atom in 15 by a fluorine atom is expected to cause an enhancement or an alteration of the inherent biological activity. We thus examined further the synthesis of 6α-fluoro-2β-tropanol 18 and the acetate methiodide 19 according to a similar method as described above. Cycloaddition of 1 with fluorovinyl sulfone 5 was time-consuming (7 days), but also gave a sole product (9) (mp 118-121 °C) in 97% yield. Endo configuration of fluorine substituent in 9 was determined by the NMR spectrum of 9 comparing with that of 7. Reduction of the enone moiety of 9 gave 2α-alcohol (16) and 2β-alcohol (17) (mp 138-141 °C) in 32% and 63% yield, respectively. Desulfonylation of 17 afforded 6α-fluoro-2β-tropanol 18, which was transformed to the acetate methiodide 19 (mp 212-214 °C) in 30% yield from 17. The biological and medicinal roles of this compound 19 are now under investigation.

We are grateful to Drs. M. R. Bell and R. L. Clarke of the Sterling-Winthrop Research Institute, Rensseler, New York, 12144, for supply of (1R)-2α-tropanyl benzilate hydrochloride. This work was supported in part by grants from the Sankyo Foundation of Life Science and the Ministry of Education, Science and Culture of Japan (No. 62570934 and 63570985).

References

1) "Advances in Cycloaddition," ed by D. P. Curran, JAI Press, Inc., London (1988), Vol. 1.
2) A. R. Katritzky and Y. Takeuchi, J. Chem. Soc., C, 1971, 874.
3) R. Robinson, J. Chem. Soc., 111, 762 (1917); C. Schopf, Angew. Chem., 50, 779 (1937).
4) R. Noyori, Y. Baba, and Y. Hayakawa, J. Am. Chem. Soc., 96, 3336 (1974).
5) T. Koizumi, T. Hagi, Y. Horie, and Y. Takeuchi, Chem. Pharm. Bull., 35, 3959 (1987).
6) T. Takahashi, K. Kitano, T. Hagi, H. Nihonmatsu, and T. Koizumi, Chem. Lett., accompanying paper in this issue.
7) All new compounds reported here gave satisfactory spectroscopic and analytical data. Some of the spectral data are listed below.
7: IR(KBr), 1675(C=O) and 1290 cm^{-1}(SO_2); NMR($CDCl_3$), δ 1.92(1H, dd, J=9, 14 Hz, endo 7-H), 2.38(3H, s), 2.77(1H, ddd, J=4, 8, 14 Hz, exo 7-H), 3.54(1H, br d, J=8 Hz, 1-H), 3.57(1H, dd, J=4, 9 Hz, endo 6-H), 4.23(1H, br d, J=5 Hz, 5-H), 6.06(1H, dd, J=2, 10 Hz, 3-H), 6.93(1H, dd, J=5, 10 Hz, 4-H).
10: IR(KBr), 3400(OH) and 1290 cm^{-1}(SO_2); NMR($CDCl_3$), δ 2.05(1H, dd, J=9, 14

Hz, endo 7-H), 2.31(1H, ddd, J=7, 7, 14 Hz, exo 7-H), 2.52(3H, s), 3.22(1H, br dd, J=4, 6 Hz, 1-H), 3.39(1H, dd, J=7, 9 Hz, 6-H), 3.74(1H, br s, 5-H), 3.92 (1H, m, 2-H).

11: IR(KBr), 3390(OH) and 1290 cm^{-1}(SO_2); NMR($CDCl_3$), δ 1.72(1H, dd, J=9, 14 Hz, endo 7-H), 2.51(1H, m, exo 7-H), 2.52(3H, s), 3.26(1H, br d, J=7 Hz, 2-H), 3.49(2H, m, 1-H and 6-H), 3.76(1H, br s, 5-H).

12: IR($CHCl_3$), 3625 and 3350 cm^{-1}(OH); NMR($CDCl_3$), δ 2.28(3H, s), 3.08(2H, m, 1-H and 5-H), 3.88(1H, ddd, J=3.5, 5, 10 Hz, 2-H).

13: NMR($CDCl_3$), δ 2.19(3H, s), 3.00(2H, m, 1-H and 5-H), 3.47(2H, br, 2-H and OH).

14: IR(KBr), 1745 cm^{-1}(C=O); NMR(CD_3OD), δ 2.07(3H, s), 3.17(3H, s), 3.31 (3H, s), 3.89-3.97(2H, m, 1-H and 5-H), 5.42(1H, ddd, J=3, 6, 10 Hz, 2-H).

15: IR(KBr), 1735 cm^{-1}(C=O); NMR(CD_3OD), δ 3.13(3H, s), 3.42(3H, s), 3.99 (2H, br s, 1-H and 5-H), 5.07(1H, br d, J=5 Hz, 2-H).

9: IR(KBr), 1685(C=O) and 1325 cm^{-1}(SO_2); NMR($CDCl_3$), δ 1.84(1H, dd, J=15, 24 Hz, endo 7-H), 2.50(3H, s), 3.21(1H, ddd, J=8, 15, 15 Hz, exo 7-H), 3.60(1H, br d, J=8 Hz, 1-H), 4.43(1H, br d, J=5 Hz, 5-H), 6.26(1H, dt, J=1.5, 10 Hz, 3-H), 6.74(1H, ddd, J=1.5, 5, 10 Hz, 4-H).

16: IR(neat), 3500, 3400(OH) and 1320 cm^{-1}(SO_2); NMR($CDCl_3$), δ 2.57(3H, s), 2.78(1H, ddd, J=7, 16, 18 Hz, exo 7-H), 3.26(1H, br s, 1-H), 3.65(1H, br s, 5-H), 4.12(1H, m, 2-H).

17: IR(KBr), 3500(OH) and 1310 cm^{-1}(SO_2); NMR($CDCl_3$), δ 2.61(3H, s), 2.98 (1H, ddd, J=8, 12, 15 Hz, exo 7-H), 3.18(1H, br s, 1-H), 3.38(1H, d, J=11 Hz, OH), 3.62(1H, br d, J=11 Hz, 2-H), 3.71(1H, br s, 5-H).

19: IR(KBr) 1740 cm^{-1}(C=O); NMR(CD_3OD), δ 2.14(3H, s), 3.12(3H, s), 3.45(3H, s), 4.07(1H, br d, J=7 Hz, 1-H), 4.19(1H, br s, 5-H), 5.22(1H, br s, 2-H), 5.71(1H, dddd, J=3, 7, 9, 54 Hz, exo 6-H).

8) K. Ogura, T. Noguchi, S. Mitamura, and G. Tsuchihashi, The 7th Symposium on Organic Sulfur and Phosphorus Chemistry, Kyoto (1979), Abstracts p.76.

9) W. A. M. Davies, A. R. Pinder, and I. G. Morris, Tetrahedron, 18, 405 (1962).

10) S. Sarel and E. Dykman, Heterocycles, 15, 719 (1981).

11) An authentic sample of (1R)-(+)-2α-tropanol was obtained by reduction (lithium aluminum hydride) of (1R)-2α-tropanyl benzilate hydrochloride [E. R. Atkinson, D. D. McRitchie, L. F. Shoer, L. S. Harris, S. Archer, M. D. Aceto, J. Pearl, and F. P. Luduena, J. Med. Chem., 20, 1612 (1977)], which was kindly provided by Drs. M. R. Bell and R. L. Clarke.

12) S. Archer, A. M. Lands, and T. R. Lewis, J. Med. Pharm. Chem., 5, 423 (1962).

13) J. W. Bastable, I. R. Dunkin, and J. D. Hobson, J. Chem. Soc., Perkin Trans. 1, 1981, 1346.

14) "Biomedical Aspects of Fluorine Chemistry," ed by R. Filler and Y. Kobayashi, Kodansha Ltd., Tokyo (1982).

(Received January 17, 1989)