Hetero Diels-Alder Reaction of Thebaine with Perfluoroaldehydes and Chemical Transformation of Their Adducts

In Howa Jeong*, Young Sup Kim, Kwang Yun Cho, and Keun Jae Kim†

Korea Research Institute of Chemical Technology, Taejeon 305-606
†*Department of Chemistry, Hannam University, Taejeon 300-791*

Received January 23, 1991

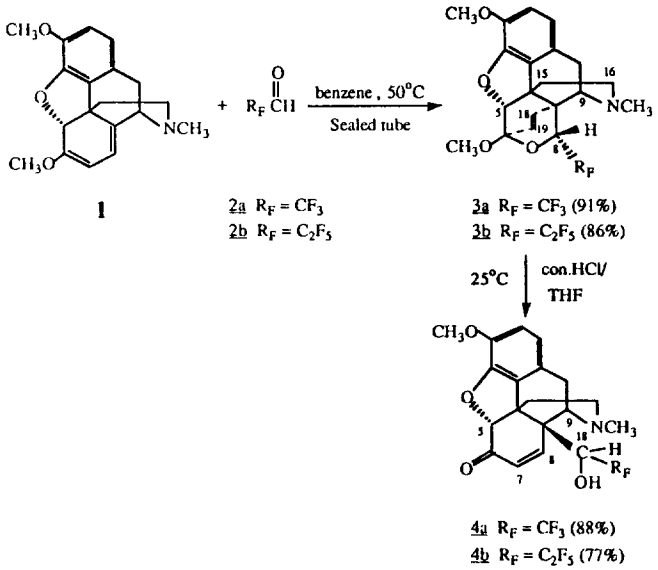
The Diels-Alder reactions of thebaine **1** with various dienophiles have been received considerable attention because of high analgesic activities of many compounds obtained *via* chemical transformation of Diels-Alder adducts.[1,2] However, less attention has been paid to utilize hetero Diels-Alder reaction in the search for more potent analgesics.[3] The heterogeneous dienophiles which are not easily accessible account for the lack of study on the hetero Diels-Alder reaction of **1**. Nevertheless, the fact that 14-aminocodeinone derivatives[3f] derived from hetero Diels-Alder adduct prepared from the reaction of **1** with nitrosobenzene possess analgesic properties stimulated the study on hetero Diels-Alder reaction of **1**.

Recently, we found that reaction of **1** with 2-fluoroacrolein afforded an unexpected hetero Diels-Alder adduct as a minor product, along with Diels-Alder adducts.[4] This prompted us to investigate the reaction of **1** with α-fluorinated aldehydes. In this communication, we wish to describe hetero Diels-Alder reaction of **1** with perfluoroaldehydes and chemical transformation of their adducts.

When **1** was allowed to react with trifluoroacetaldehyde **2a**[5] in benzene at 50℃ for 24 hours in a sealed tube, hetero Diels-Alder adduct **3a**, mp. 114℃, was obtained in 91% yield. Although **3a** itself is stable in air at room temperature, heating of **3a** in benzene at 50℃ resulted in the regeneration of **1** and finally these two compounds were equilibrated in a sealed tube (**1** : **3a** = 58 : 42). This result indicates that **2a** can be reversibly intercepted by **1** *via* hetero Diels-Alder reaction. The similar result was observed in the reaction of **1** with nitrosoimine.[3d] Thus, the use of large excess (~10 eq. excess) of **2q** is necessary to complete this interesting reaction.

The structure of **3a** was determined on the basis of spectroscopic data. The mass spectrum showed an intense molecular ion peak at m/e 409 and ^{1}H-NMR ($CDCl_3$) spectrum showed characteristic signals of H-5 proton at δ 4.57 (s), two vinyl protons at δ 5.60 (d, J=8.8 Hz, H-18) and 6.15(d, J=8.8 Hz, H-19), H-8 proton at δ 5.23 (q, J=7.7 Hz) and H-9 proton at δ 3.60 (d, J=6.7 Hz). The down-field shift of H-8 proton (δ 5.23), which is due to deshielding effect of the tertiary amine[6], indicates that a proton on C-8 of **3a** should be oriented in β-position. The ^{19}F-NMR ($CHCl_3$, standard CF_3COOH) spectrum showed one doublet signal (J=7.7 Hz) at δ −7.09, which is due to the coupling between CF_3 group and H-8 proton. The signal of ^{19}F-NMR spectrum also indicates that a proton on C-8 of **3a** should be oriented in β-position, because orientation of CF_3 group on C-8 in β-position should provide multiple signal in ^{19}F-NMR spectrum due to space coupling between CF_3 group and protons on C-16. The stereospecific orientation of CF_3 group on C-8 in α-position is probably due to the less steric effect between CF_3 group and bridged group (C-15 and C-16). Similarly, the reaction of **1** with **2b** also provided adduct **3b** as an oil in 86% yield.

When **3a** was treated with conc. HCl-tetrahydrofuran (1 : 10) at 25℃ for 7 hours, **4a** was obtained in 88% yield: mp. 162-163℃; MS, m/e 395 (M^+); IR (KBr) 3460 (s, OH), 1685 cm^{-1} (s, C=O); ^{1}H-NMR ($CDCl_3$) δ 2.37 (s, N-CH_3), 2.98 (s, OH), 3.46 (d, J=5.4 Hz, H-9), 3.83 (s, OCH_3), 4.89 (s, H-5), 5.71 (q, J=7.7 Hz, H-18), 6.11 (d, J=10.2 Hz, H-7), 6.54 (dq, J=10.2, 3.0 Hz, H-8); ^{19}F-NMR ($CHCl_3$, standard CF_3COOH) δ 6.79 (d, J=7.7 Hz). The enone structure of **4a** was confirmed by strong absorption at 1685 cm^{-1} for C=O group in IR spectrum and down-field shift of H-8 proton (δ 6.54) in ^{1}H-NMR spectrum. Hydroxy group could be easily determined by strong absorption at 3460 cm^{-1} in IR spectrum and a broad singlet at δ 2.98 ppm in ^{1}H-NMR spectrum. The reaction of **3b** with conc. HCl-tetrahydrofuran (1 : 10) at 25℃ for 7 hours also provided **4b**, mp. 158℃, in 77% yield in a similar manner.



1

2a $R_F = CF_3$
2b $R_F = C_2F_5$

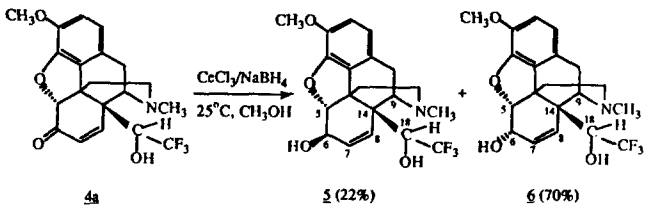
3a $R_F = CF_3$ (91%)
3b $R_F = C_2F_5$ (86%)

4a $R_F = CF_3$ (88%)
4b $R_F = C_2F_5$ (77%)

Selective reduction of ketone group in **4a** with cerium chloride/sodium borohydride resulted in the formation of two stereoisomers, **5** and **6**, which were separable by column chromatography. *Trans* isomer **5** was isolated in 22% yield: mp. 172℃; MS, m/e 397 (M^+); ^{1}H-NMR ($CDCl_3$) δ 1.64(s, OH), 2.36(s, N-CH_3), 3.04(s, OH), 3.28(d, J=4.9 Hz, H-9), 3.84 (s, OCH_3), 4.32(d, J=5.6 Hz, H-6), 4.93(s, H-5), 5.54-5.67(m, H-8 and H-18), 6.05(dd, J=10.0, 5.6 Hz, H-7); ^{19}F NMR ($CHCl_3$, standard CF_3COOH) δ 6.29(d, J=6.0 Hz). *Cis* isomer **6** was isolated in 70% yield: mp. 184-185℃; MS, m/e 397 (M^+); ^{1}H-NMR ($CDCl_3$) δ 1.60(s, OH), 2.34(s, N-CH_3), 2.98(d, J=7.5 Hz, OH), 3.26(d, J=5.0 Hz, H-9), 3.84(s, OCH_3), 4.59(t, J=7.5 Hz, H-6), 5.08(d, J=7.5 Hz, H-5), 5.35(dm, J=10.3 Hz, H-8), 5.57(q, J=8.1 Hz), 5.88(d, J=10.3 Hz, H-7); ^{19}F-NMR ($CHCl_3$, standard CF_3COOH) δ 6.29(d, J=6.0 Hz). Stereochemistry of these two compounds **5** and **6** can be confirmed by the coupling constant between H-5 and H-6 protons. Large

coupling constant (J=7.5 Hz) of H-5 proton is probably due to coupling with axial H-6 proton of **6**. Axial H-6 proton also coupled with proton of OH group attached to C-18 to give coupling constant (J=7.5 Hz). In contrast to axial H-6 proton of **6**, equatorial H-6 proton of **5** does not couple with H-5 proton because of dihedral angle between H-5 and H-6 protons, which is near 90°.

The stereoselectivity of reduction reaction of **4a** can be explained by sterical difference between approach of hydride ion from top side and one from bottom side. Less steric effect for the approach of hydride ion from top side accounts for the predominance of *cis* isomer **6**.



In conclusiom, this is the first report for the use of perfluoroaldehyde as a dienophile in Diels-Alder reaction of thebaine and this methodology provides a new and an efficient route to codeinones substituted with perfluoroalkylcarbinol at C-14, which may possess analgesic properties.

Acknowledgement. We thank the Ministry of Science and Technology for financial support, and Dr. S. K. Choi (KAIST) for recording the ^{19}F NMR spectra.

References

1. K. W. Bentley, *"The Alkaloids"*, R. H. F. Manske, Ed., Academic press, Vol 13, Chapter 1, New York (1971).
2. (a) C. W. Hutchins, G. K. Cooper, S. Purro, and H. Rapoport, *J. Med. Chem.*, **24**, 773 (1981); (b) L. L. Knipmeyer and H. Rapoport, *J. Med. Chem.*, **28**, 461 (1985); (c) P. J. Maurer and H. Rapoport, *J. Med. Chem.*, **30**, 2016 (1987).
3. (a) K. W. Bentley, P. Horsewood, G. W. Kirby, and S. Singh, *J. Chem. Soc. D*, 1411 (1969); (b) P. Horsewood and, G. W. Kirby, *J. Chem. Soc. D*, 1139 (1971); (c) G. W. Kirby, and J. G. Sweeny, *J. Chem. Soc., Chem. Commun.*, 704 (1973); (d) T. L. Gilchrist, M. E. Peek, and C. W. Rees, *J. Chem. Soc., Chem. Commun.*, 913 (1975); (e) G. W. Kirby, J. W. M. Mackinnon, and R. P. Sharma, *Tetrahedron Lett.*, 215 (1977); (f) L. S. Schwab, *J. Med. Chem.*, **23**, 698 (1980).
4. I. H. Jeong, Y. S. Kim, K. Y. Cho, and K. J. Kim, *Bull. Korea Chem. Soc.*, **11**, 178 (1990).
5. O. R. Pierce and T. G. Kane, *J. Am. Chem. Soc.*, **76**, 300 (1954).
6. J. B. Lambert, H. F. Shurvell, L. Verbit, R. G. Cooks, and G. H. Stout, *"Organic Structural Analysis"*, Macmillan, New York (1976).