BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 47(4), 1037—1038 (1974)

Synthesis of Alkoxycyclopropane Derivatives, Intermediates in the Synthesis of Hirsutic Acid[1]

Fujio SAKAN, Emiko SUGIURA, Takeshi MATSUMOTO,* Haruhisa SHIRAHAMA,* and Hisanobu HASHIMOTO*

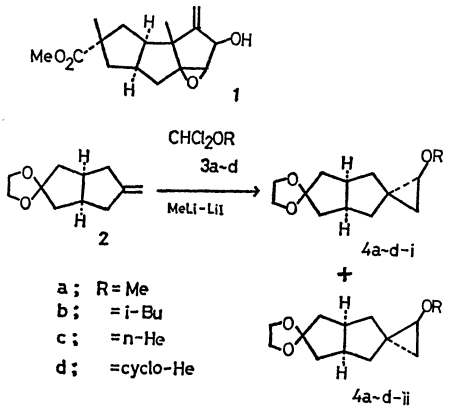
Chemical Laboratory, Faculty of Education, Fukui University, Fukui 910

**Department of Chemistry, Faculty of Science, Hokkaido University, Sapporo 060*

(Received November 1, 1973)

Synopsis. The addition of several alkoxycarbenes on *cis*-bicyclo[3,3,0]octane derivative (**2**) was tried. The bulkier reagent gave the better stereoselectivity and *exo* adducts were obtained more predominantly.

Recently we achieved the total synthesis of methyl hirsutate (**1**),[2] a sesquiterpene derived from a biogenetic intermediate, protoilludane.[3] A carboxylic function correctly oriented was constructed with a certain stereoselectivity by the predominant *exo* attack of methoxycarbene on *cis*-bicyclo[3,3,0]octane derivative (**2**). This paper describes the procedure of the addition of several alkoxycarbenes on *exo* methylene compound **2** and shows how the ratio of *exo* to *endo* adduct varies with alkyl group of alkoxycarbene.



Compound **2** was obtained from known *cis*-bicyclo[3,3,0]octadione.[2a] Addition of alkoxycarbenes, prepared from dichloromethyl alkyl ethers (**3a**—**3d**) and methyllithium–lithium iodide in ether at −20——15 °C,[4] to **2** afforded epimeric mixtures of alkoxycyclopropane derivatives (**4**). The reaction was carried out with four different sizes of alkoxycarbene. Yields and ratios of *exo* to *endo* adduct are listed in Table 1. In the NMR spectra of **4**, signals due to three cyclopropyl protons appeared as typical ABX systems.[5] The configurations were assigned by taking account of the steric course of the reaction.[2b,6]

TABLE 1. RESULTS OF THE ADDITION OF ALKOXYCARBENES ON **2**

Products	Yields (%)[a]	Ratios of *exo* (**i**) to *endo* adduct (**ii**)[b]
4a (R=methyl)	75	2.2
4b (R=isobutyl)	83	2.5
4c (R=*n*-hexyl)	77	2.2
4d (R=cyclohexyl)	73	2.9

a) Isolated yield, not optimized. b) Determined by glc (see Expeeimental).

The results obtained show that the bulkier reagent clearly gave the better stereoselectivity. However, the steric course of the reaction was not so markedly effected by the bulkiness of alkoxycarbene, since the bulky alkyl group might not be close enough to the attacking point of the reagent.

Experimental

NMR spectra were measured at 100 MHz on a JEOL Co. Model PS-100 spectrometer using TMS as an internal standard. IR spectra were taken on a Hitachi Model EPI-G3 with NaCl optics. Glc were carried out on a Yanaco G8-TEP and an Aerograph Autoprep 700.

3,3-Methoxyethano-7,7-ethylenedioxy-cis-*bicyclo[3,3,0]octane (**4a**)* A typical procedure for carbene addition. To a solution of **2** (200 mg) and dichloromethyl methyl ether **3a**[7] (1 g) in dry ether (10 ml) was added 0.8 N ether solution of methyllithium–lithium iodide (30 ml) under stirring in an ice-salt bath (−20——15 °C). Addition was completed in 1 hr and the mixture was stirred at −20——15 °C for further 1 hr. Water was added to the resulting mixture and products were taken up with ether. The extracts were washed with brine, dried and evaporated to leave crude material which on chromatography (silica gel, 10% ethyl acetate-*n*-hexane elution) gave a mixture of methoxycyclopropane derivatives (**4a-i**) and (**4a-ii**) (188 mg, 75% yield, *exo* adduct **4a-i**/*endo* adduct **4a-ii**=2.2 by glc). Further purification by preparative glc (5% DC-550 column at 150 °C) gave pure **4a-i** and **4a-ii** as colorless oils. **4a-i**: IR (neat) 3060 cm^{-1}; NMR δ (CCl_4) 0.44, 0.55 and 2.78 (each 1H, ABX with J_{AB}=5.6, J_{AX}=6.1 and J_{BX}=3.8 Hz, CH_2 and CH–O on cyclopropane), 3.22 (3H, s., CH_2–O) and 3.77 (4H, s, O–CH_2CH_2–O); Found: C, 69.42; H, 8.85%. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99%. **4a-ii**: IR (neat) 3060 cm^{-1}; NMR δ (CCl_4) 0.27, 0.44 and 2.95 (each 1H, ABX with J_{AB}=5.8, J_{AX}=6.0 and J_{BX}=3.4 Hz, CH_2 and CH–O on cyclopropane), 3.28 (3H, s, CH_3O) and 3.77 (4H, s, O–CH_2CH_2–O); Found: C, 69.71; H, 8.93%. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99%.

3,3 - Isobutoxyethano - 7,7 - ethylenedioxy - cis - *bicyclo[3,3,0]octane (**4b**).* Crude product from **2** (200 mg), dichloromethyl isobutyl ether **3b**[7] (1.4 g) and 0.8 N methyllithium-lithium iodide ether solution (30 ml) gave a mixture of isobutoxy cyclo derivatives (**4b-i**) and (**4b-ii**) (245 mg, 83% yield, *exo* adduct **4b-i**/*endo* adduct **4b-ii**=2.5 by glc) on chromatography. Preparative glc (5% QF-1 column at 165 °C) afforded pure **4b-i** and **4b-ii** as colorless oils. *Exo* adduct **4b-i**: IR (neat) 3054 cm^{-1}; NMR δ (CCl_4) 0.46, 0.58 and 2.81 (each 1H, ABX with J_{AB}=5.7, J_{Ax}=6.5 and J_{Bx}=3.4 Hz, CH_2 and CH–O on cyclopropane), 0.86 (6H, d with J=6.0 Hz, $CH(C\underline{H}_3)_2$), 3.10 (2H, AB part of ABX,

O-CH$_2$CH) and 3.78 (4H, s, O-CH$_2$CH$_2$-O); Found: C, 72.43; H, 9.57%. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84%. *Endo* adduct **4b-ii**: IR (neat) 3040 cm^{-1}; NMR $\delta(CCl_4)$ 0.28, 0.42 and 2.96 (each 1H, ABX with J_{AB}= 5.3, J_{AX}=6.2 and J_{BX}=3.1 Hz CH_2 and CH-O on cyclopropane), 0.87 (6H, d with J=6.0 Hz, CH(CH$_3$)$_2$), 3.16 (2H, AB part of ABX, O-CH$_2$CH) and 3.72 (4H, s, O-CH$_2$CH$_2$-O); Found: C, 72.38; H, 9.86%. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84%.

*3,3 - n -Hexoxylthano - 7,7-ethylenedioxy - cis - bicyclo[3,3,0]octane (**4c**).* Epimeric mixture of *n*-hexoxycyclopropane derivatives (**4c-i**) and (**4c-ii**) (248 mg, 77% yield, *exo* adduct **4c-i**/*endo* adduct **4c-ii**=2.2 by glc) was obtained from the reaction of **2** (200 mg), dichloromethyl *n*-hexyl ether **3c**[7] (1.6 g) and 0.8 N methyllithium-lithium iodide ether solution (30 ml). Preparative glc (5% QF-1 column at 180 °C) gave pure **4c-i** and **4c-ii** as colorless oils. *Exo* adduct **4c-i**: IR (neat) 3047 cm^{-1}; NMR $\delta(CCl_4)$ 0.46, 0.58 and 2.82 (each 1H, ABX with J_{AB}=5.7, J_{AX}=6.3 and J_{BX}=3.5 Hz, CH_2 and CH-O on cyclopropane), 0.89 (3H, destorted t., CH$_2$CH$_3$), 3.33 (2H, destorted t, O-CH$_2$CH$_2$) and 3.78 (4H, s, O-CH$_2$CH$_2$-O); Found: C, 73.55; H, 10.37%. Calcd for $C_{18}H_{30}O_3$: C, 73.43; H, 10.27%. *Endo* adduct **4c-ii**: IR (neat) 3042 cm^{-1}; NMR $\delta(CCl_4)$ 0.30, 0.44 and 2.96 (each 1H, ABX with J_{AB}=5.3, J_{AX}=6.9 and J_{BX}=2.7 Hz, CH_2 and O-CH on cyclopropane), 0.87 (3H, destorted t, CH$_2$CH$_3$), 3.38 (2H, m, O-CH$_2$CH$_2$) and 3.74 (4H, s, O-CH$_2$CH$_2$-O); Found: C, 73.17; H, 10.49%. Calcd for $C_{18}H_{30}O_3$: C, 73.43; H, 10.27%.

*3,3 - Cyclohexoxyethano - 7,7-ethylenedioxy - cis - bicyclo[3,3,0]octane (**4d**).* **2** (150 mg) and dichloromethyl cyclohexyl ether **3d**[7] (1g), was treated with 0.8 N methyllithium-lithium iodide ether solution (30 ml), gave an epimeric mixture of cyclohexoxycyclopropane derivatives (**4d-i**) and (**4d-ii**) (175 mg, 73% yield, *exo* adduct **4d-i**/*endo* adduct **4d-ii**=2.9 by glc). Pure **4d-i** and **4d-ii** were obtained from this mixture by preparative glc (5% DC-550 at 200 °C) as colorless oils. *Exo* adduct **4d-i**: IR (neat) 3045 cm^{-1}; NMR $\delta(CCl_4)$ 0.46, 0.58 and 2.92 (each 1H, ABX with J_{AB}= 5.4, J_{AX}=5.7 and J_{BX}=4.1, CH_2 and CH-O on cyclopropane), 3.20 (1H, m, O-CH(CH$_2$-)$_2$) and 3.75 (4H, s, O-CH$_2$CH$_2$-O); Found: C, 73.91; H, 9.63%. Calcd for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65%. *Endo* adduct **4d-ii**: IR (neat) 3045 cm^{-1}; NMR δ (CCl_4) 0.32, 0.44 and 3.06 (each 1H, ABX with J_{AB}=5.3, J_{Ax}=6.1 and J_{Bx}=3.4 Hz, CH_2 and CH-O on cyclopropane), 3.32 (1H, m, O-CH(CH$_2$-)$_2$) and 3.72 (4H, s, O-CH$_2$CH$_2$-O); Found: C, 73.75; H, 9.61%. Calcd for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65%.

References and Notes

1) Most of this work appeared in: E. Sugiura, Graduation Thesis, Fukui Univ., 1972.

2) a) H. Hashimoto, F. Sakan, K. Tsuzuki, H. Shirahama, and T. Matsumoto, 17th Symposium on the Chemistry of Natural Products, Tokyo, Oct. 17—19, 1973, Symposium Papers, p. 33. b) Synthesis of Skeleton; F. Sakan, H. Hashimoto, A. Ichihara, H. Shirahama, and T. Matsumoto, *Tetrahedron Lett.*, **1971**, 3703.

3) We completed the total synthesis of the following three sesquiterpenes of the protoilludane family: illudin M; T. Matsumoto, H. Shirahama, A. Ichihara, H. Shin, S. Kagawa, F. Sakan, S. Matsumoto, and S. Nishida, *J. Am. Chem. Soc.*, **90**, 3286 (1968), illudin S; T. Matsumoto, H. Shirahama, A. Ichihara, H. Shin. S. Kagawa, F. Sakan, and K. Miyano, *Tetrahedron Lett.*, **1971**, 2049, illudol; T. Matsumoto, K. Miyano, S. Kagawa, S. Yö, J. Ogawa, and A. Ichihara, *Tetrahedron Lett.*, **1971**, 3521.

4) U. Schöllkopf and J. Paust, *Angew. Chem.*, **75** 670 (1963).

5) U. Schöllkopf, A. Lerch, and J. Paust, *Chem. Ber.*, **96**, 2266 (1963).

6) Completion of the synthesis of methyl hirsutate shows these configurational assignments to be correct.

7) H. Gross, A. Rieche, and E. Höft, *Chem. Ber.*, **94**, 544 (1961).