ORGANIC LETTERS

2010
Vol. 12, No. 8
1824−1826

A Novel Synthesis of Oxabicyclo[3.3.1]nonanone via (3,5)-Oxonium−Ene Reaction

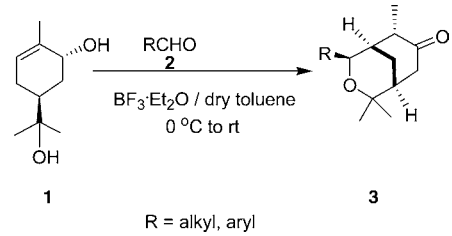
Pipas Saha, U. C. Reddy, S. Bondalapati, and Anil K. Saikia*

Department of Chemistry, Indian Institute of Technology Guwahati, Guwahati 781039, India

asaikia@iitg.ernet.in

Received February 22, 2010

ABSTRACT



Oxabicyclo[3.3.1]nonanone can conveniently be prepared by the reaction of *trans-p*-menth-6-ene-2,8-diol and aldehyde or epoxide mediated by boron trifluoride etherate in good yields. The reaction proceeds via (3,5)-oxonium−ene-type reaction.

Oxonium−ene reactions are powerful tool for construction of various cyclic ethers.[1] Mikami and co-workers have made a thorough study on oxonium−ene cyclization reactions.[2] There are three different types of oxonium−ene cyclization reactions, namely, (1,5), (2,5), and (3,5).[1e,2d] Although (1,5)[1a−c] and (2,5)[2a−c] oxonium−ene-type cyclizations have been well studied, the (3,5)-oxonium−ene cyclization has not been investigated extensively.[1e,2d] Loh and co-workers[1e] and others[3] have reported the synthesis of some cyclic ethers by using the (3,5)-oxonium−ene reaction. Several cyclic ethers[4] and oxabicyclic compounds possess biological properties. Oxabicyclo[3.3.1]nonene and its derivatives are known as estrogen receptor ligands.[5] In continuation of our interest in oxygen heterocycles,[6] we were in search of an efficient methodology for the synthesis of oxabicyclic compounds. Naturally occurring terpenoids are precursors of biologically active compounds[7] and intermediates in asymmetric synthesis.[8] Il'ina and co-workers have reported the synthesis of oxabicyclo[3.3.1]nonanone from verbenone epoxide in acidic

(1) (a) Blumenkopf, T. A.; Look, G. C.; Overman, L. E. *J. Am. Chem. Soc.* **1990**, *112*, 4399–4403. (b) Overman, L. E. *Acc. Chem. Res.* **1992**, *25*, 352–359. (c) Overman, L. E.; Thompson, A. S. *J. Am. Chem. Soc.* **1988**, *110*, 2248–2256. (d) Sonawane, H. R.; Maji, D. K.; Jana, G. H.; Pandey, G. *Chem. Commun.* **1998**, 1773–1774. (e) Loh, T.-P.; Hu, Q.-Y.; Tan, K.-T.; Cheng, H.-S. *Org. Lett.* **2001**, *3*, 2669–2672. (f) Loh, T.-P.; Yang, J.-Y.; Feng, L.-C.; Zhou, Y. *Tetrahedron Lett.* **2002**, *43*, 7193–7196.

(2) (a) Ohmura, H.; Smyth, G. D.; Mikami, K. *J. Org. Chem.* **1999**, *64*, 6056–6059. (b) Mikami, K.; Ohmura, H.; Yamanaka, M. *J. Org. Chem.* **2003**, *68*, 1081–1088. (c) Ohmura, H; Mikami, K. *Tetrahedron Lett.* **2001**, *42*, 6859–6863. (d) Mikami, K.; Shimizu, M. *Chem. Rev.* **1992**, *92*, 1021–1050.

(3) Nussbaumer, C.; Frater, G. *J. Org. Chem.* **1987**, *52*, 2096–2098.

(4) (a) Clarke, P. A.; Santos, S. *Eur. J. Org. Chem.* **2006**, *204*, 5–2053. (b) Class, Y. J.; DeShong, P. *Chem. Rev.* **1995**, *95*, 1843–1857. (c) Kopecky, D. J.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2001**, *123*, 8420–8421. (d) Wang, Y.; Janjic, J.; Kozmin, S. A. *J. Am. Chem. Soc.* **2002**, *124*, 13670–13671. (e) Aubele, D. L.; Wan, S.; Floreancig, P. E. *Angew. Chem., Int. Ed.* **2005**, *44*, 3485–3488. (f) Bahnck, K. B.; Rychnovsky, S. D. *Chem. Commun.* **2006**, 2388–2390. (g) Tian, X. T.; Jaber, J. J.; Rychnovsky, S. D. *J. Org. Chem.* **2006**, *71*, 3176–3183.

(5) (a) Sibley, R.; Hatoum-Mokdad, H.; Schoenleber, R.; Musza, L.; Stirtan, W.; Marrero, D.; Carley, W.; Xiao, H.; Dumas, J. *Biorg. Med. Chem. Lett.* **2005**, *15*, 1463–1466. (b) Hamann, L. G.; Meyer, J. H.; Ruppar, D. A.; Marschke, K. B.; Lopez, F. J.; Allegretto, E. A.; Karanewsky, D. S. *Biorg. Med. Chem. Lett.* **2005**, *15*, 1463–1466. (c) Nakamura, M.; Niiyama, K.; Yamakawa, T. *Tetrahedron Lett.* **2009**, *50*, 6462–6465.

(6) (a) Reddy, U. C.; Bondalapati, S.; Saikia, A. K. *Eur. J. Org. Chem.* **2009**, *162*, 5–1630. (b) Reddy, U. C.; Bondalapati, S.; Saikia, A. K. *J. Org. Chem.* **2009**, *74*, 1625–1630. (c) Reddy, U. C.; Raju, B. R.; Kumar, E. K. P.; Saikia, A. K. *J. Org. Chem.* **2008**, *73*, 1625–1630.

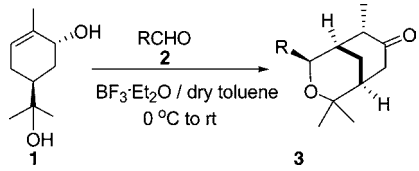
(7) Mora, P. C.; Ranise, A. U.S. Pat. 6649658.

(8) Masui, M.; Shioiri, T. *Tetrahedron* **1995**, *51*, 8363–8370.

10.1021/ol1004092
Published on Web 03/18/2010

medium. The yield of the products was very low due to the formation of side products.[9] *trans-p*-Menth-6-ene-2,8-diol has long been used as a starting material for many organic transformations.[10] Here we wish to disclose a methodology for the synthesis of oxabicyclo[3.3.1]nonanone via (3,5)-oxonium−ene reaction from the reaction of aldehydes or epoxides with commercially available *trans-p*-menth-6-ene-2,8-diol, mediated by boron trifluoride etherate. We envisioned that treatment of *trans-p*-menth-6-ene-2,8-diol with boron trifluoride etherate would provide carbocation at the side chain, which after nucleophilic attack by aldehyde and subsequent (3,5)-oxonium−ene cyclization will give bicyclic product. Thus, the treatment of *trans-p*-menth-6-ene-2,8-diol with benzaldehyde and boron trifluoride etherate in dry toluene gave 2,2,6-trimethyl-4-phenylbicyclo[3.3.1]nonan-7-one in 80% yield. The reaction can be generalized as shown in Table 1.

Table 1. Synthesis of Oxabicyclo[3.3.1]nonanone



entry	RCHO **2**	time (h)	product **3**	yield[a] (%)
1	C_6H_5CHO, **2a**	8	**3a**	80
2	*p*-Cl-C_6H_4CHO, **2b**	10	**3b**	50
3	*p*-Br-C_6H_4CHO, **2c**	10	**3c**	51
4	*p*-F-C_6H_4CHO, **2d**	10	**3d**	62
5	*p*-MeO_2C-C_6H_4CHO, **2e**	12	**3e**	52
6	*p*-NO_2-C_6H_4CHO, **2f**	12	**3f**	50
7	*p*-Me-C_6H_4CHO, **2g**	10	**3g**	68
8	*p*-MeO-C_6H_4CHO, **2h**	10	**3h**	56
9	C_6H_5-CH=CHCHO, **2i**	12	**3i**	57
10	*p*-NO_2-C_6H_4-CH=CHCHO, **2j**	12	**3j**	62
11	C_6H_5-CH_2CHO, **2k**	4	**3k**	50
12	$C_6H_{11}CHO$, **2l**	5	**3l**	90
13	$C_6H_{13}CHO$, **2m**	5	**3m**	80
14	$(CH_3)_2CHCH_2CHO$, **2n**	6	**3n**	82
15	C_3H_7CHO, **2o**	6	**3o**	98
16	C_2H_5CHO, **2p**	5	**3p**	98

[a] Yields refer to isolated yield. The compounds are characterized by IR, ^1H, ^{13}C, and ^{19}F NMR, and mass spectroscopy.

The scope of the reaction is investigated by using different types of aliphatic and aromatic aldehydes (Table 1). It was observed that the aromatic aldehydes, except benzaldehyde, gave lower yield, irrespective of electron-withdrawing or -donating groups on the ring, than the aliphatic aldehydes. The reason might be due to the formation of some highly nonpolar side products, which were unable to be characterized by spectroscopic methods. The reaction was diastereoselective, and in all cases, the substituents at 4 and 6 are in the *trans* position. The structure of the compound was determined by NOE experiment and X-ray crystallographic analysis (Figure 1).[11]

The mechanism of the reaction can be explained as follows. The reaction of compound **1** with Lewis acid generates carbocation **4**, which after nucleophilic attack by aldehyde provides oxocarbenium ion **5**, which forms a stable six-membered transition state. The oxocarbenium ion **5** undergoes (3,5)-oxonium−ene cyclization reaction to give enol **6**, which after tautomerization gives **3** (Scheme 1).

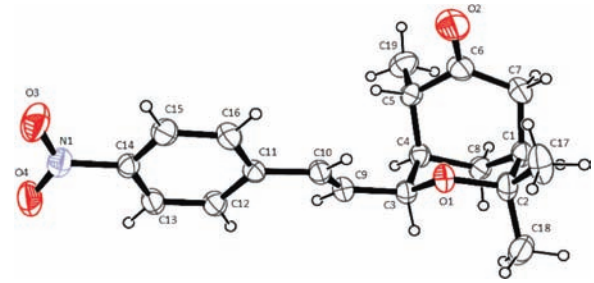
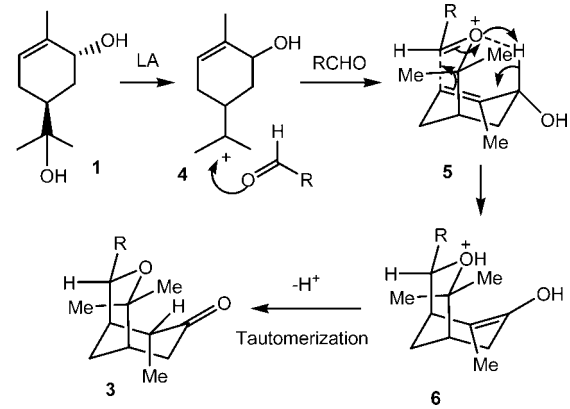


Figure 1. ORTEP diagram of 2,2,6-trimethyl-4-[2-(4-nitrophenylvinyl)]-3-oxabicyclo[3.3.1]nonan-7-one **3j**.

Scheme 1. Proposed Mechanism of the Reaction



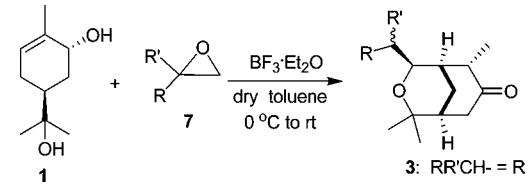
The same oxabicyclic compounds can also be prepared by using epoxide as the aldehyde equivalent as shown in Table 2. It was observed that monosubstituted terminal epoxides are nonreactive, whereas the 2,2-disubstituted and styrene oxides are reactive and give good to moderate yields. This is attributed to the lower stability of the carbocation **8**, obtained from monosubstituted epoxides, compared to 2,2-

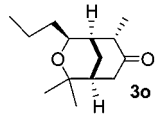
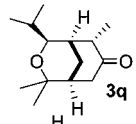
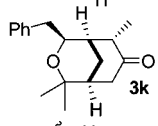
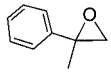
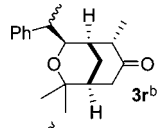
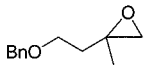
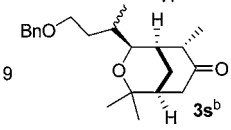
(9) (a) Il'ina, I. V.; Korchagina, D. V.; Salakhutdinov, N. F.; Barkhash, V. A. *Russ. J. Org. Chem.* **2000**, *36*, 1446–1454. (b) Il'na, I. V.; Volcho, K. P.; Korchagina, D. V.; Barkhash, V. A.; Salakhutdinov, N. F. *Helv. Chim. Acta* **2006**, *89*, 507–514.

(10) (a) Wustrow, D. J.; Smith, W. J., III; Wise, L. D. *Tetrahedron Lett.* **1994**, *35*, 61–64. (b) Popova, L. A.; Biba, V. I.; Prishchepenko, V. M.; Shavyrin, S. V.; Kozlov, N. G. *Zh. Obsh. Khim.* **1992**, *62*, 1639–1645. (c) Bhaumik, A.; Tatsumi, T. *J. Catal.* **1999**, *182*, 349–356. (d) Kozlov, N. G.; Popova, L. A.; Valimae, T.; Shavyrin, S. V. *Zh. Org. Khim.* **1989**, *25*, 1188–1194. (e) Cocker, W.; Grayson, D. H. *J. Chem. Soc., Perkin Trans. 1* **1978**, 155–159.

(11) The crystallographic data for compound **3j** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 760090.

Table 2. Reaction of *trans-p*-Menth-6-ene-2,8-diol with Epoxides



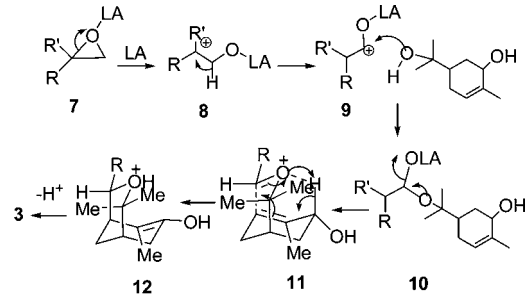
entry	epoxide **7**	time/h	product **3**	yield(%)[a]
1		24	 **3o**	0
2		9	 **3q**	78
3		10	 **3k**	45
4		10	 **3r**[b]	44
5		9	 **3s**[b]	75

[a] Yields refer to isolated yield. Compounds are characterized by IR, NMR, and mass spectroscopy. [b] Mixture of two isomers with a ratio of 1:1.

disubstituted epoxides and styrene oxides, where carbocation **8** is better stabilized due to tertiary and benzylic centers, respectively.[12a] However, the low yield obtained in the case of styrene epoxides is also due to the formation of similar types of nonpolar side products. Epoxide **4** gave two separable isomers, whereas **5** gave two inseparable isomers.

The mechanism of the reaction with epoxide can be explained by considering the already reported fact that epoxide after ring-opening with Lewis acid rearranges to aldehyde.[12] Here, the intermediate **9** is attacked by alcohol to give acetal **10**, which after (3,5)-oxonium−ene cyclization gives enol **12** (Scheme 2). The enol **12** tautomerizes to give oxabicyclic compound **3**.

Scheme 2. Mechanism of the Reaction with Epoxide



In conclusion, we have demonstrated an efficient methodology for the synthesis of oxabicyclo[3.3.1]nonanone in moderate to good yields. The bicyclic unit can further be transformed by manipulating carbonyl functionalities and, therefore, can be used as a precursor for the synthesis of complex molecules. The scope and synthetic application of this novel reaction are under investigation in our laboratory.

Acknowledgment. Authors are grateful to the Department of Science and Technology (DST), New Delhi, for financial support (Grant No. SR/S1/OC-33/2007).

Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL1004092

(12) (a) Ranu, B. C.; Jana, U. *J. Org. Chem.* **1998**, *63*, 8212–8216. (b) Li, J.; Li, C.-J. *Tetrahedron Lett.* **2001**, *42*, 793–796.