Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 8811–8813
Tetrahedron Letters

A convenient synthesis of substituted 3-bromotetrahydrofurans from homoallylic alcohols

Marina V. Chirskaya,[a] Andrei A. Vasil'ev,[b,*] Natalia L. Sergovskaya,[a] Sergey V. Shorshnev[a] and Sergey I. Sviridov[a]

[a]*ChemBridge Corporation Ltd, Box 424, 119048 Moscow, Russian Federation*
[b]*N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Leninsky pr. 47, 119991 Moscow, Russian Federation*

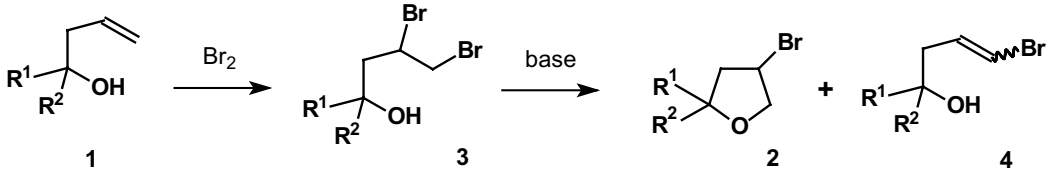
Received 2 August 2004; revised 22 September 2004; accepted 1 October 2004

Abstract—Substituted 3-bromotetrahydrofurans were prepared from homoallylic alcohols via bromination and cyclization in methanol in the presence of potassium carbonate.

The tetrahydrofuran fragment is not uncommon among biologically active and natural compounds. Oxidative cyclization of homoallylic alcohols is a traditional strategy to access tetrahydrofurans with functional groups in position 3.[1] However, such a transformation under electrophilic conditions, in particular in the case of allylcarbinols **1**, is kinetically unfavorable and therefore has to be performed indirectly, for example, via preliminary oxidative functionalization of the double bond. Some progress in the preparation of 3-hydroxytetrahydrofurans has been reported recently. For example, the reaction of homoallylic alcohols **1** with the $NaIO_4$/$NaHSO_3$ system allows a direct synthesis of 3-hydroxytetrahydrofurans in moderate yields.[2] Epoxidation of **1** followed by treatment with $MgBr_2$ or MgI_2 provides 3-hydroxytetrahydrofurans in satisfactory yields and sometimes very good diastereoselectivity.[3] Iodoetherification leading to 3-iodotetrahydrofurans has been thoroughly investigated and is restricted to chemotypes of crotyl (and homologous higher alk-2-enyl) carbinols with 1,2-disubstituted double bonds, the reaction being driven via a secondary carbocation.[4] Analogous iodoetherification of allylcarbinols such as **1** with bis(*sym*-collidine)iodine(I) perchlorate leads to four-membered 2-(iodomethyl)oxetanes.[5]

The equivalent 3-bromotetrahydrofurans **2** represent a challenge for their straightforward preparation from **1** via bromination followed by cyclization of dibromoalcohols **3** by the action of appropriate bases.[6–9] However, KOH in ether, reported previously for this purpose,[6] showed very moderate chemoselectivity in our experiments, and the cyclization was accompanied by formation of a significant fraction of vinylic bromides **4**, especially in the cases of tertiary alcohols (R^1 and $R^2 \neq H$). Other procedures involving pyridine,[7] quinoline[8] and *n*-BuLi[9] are not convenient for large scale preparations.

In the present work, we have tested a broad variety of base systems and discovered that bases of moderate strength in protic solvents are expedient to achieve a favorable ratio between bromotetrahydrofurans **2** and vinylic bromides **4** (Table 1). Alkali carbonates in



1 3 2 4

Keywords: Tetrahydrofurans; Bromination; Homoallylic alcohols; Cyclization.
* Corresponding author. Fax: +7 095 1355328; e-mail: vasiliev@ioc.ac.ru

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.10.013

Table 1. Cyclization of 1-(2,3-dibromopropyl)cyclohexanol [**3a**, $R^1 + R^2 = (CH_2)_5$] into 3-bromo-1-oxaspiro[4.5]decane **2a** using various bases

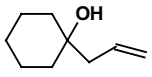
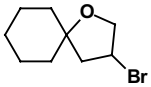
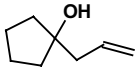
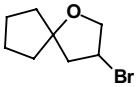
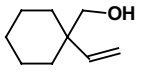
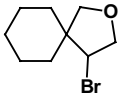
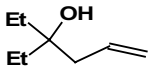
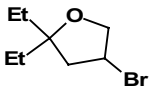
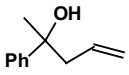
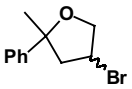
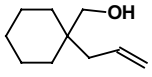
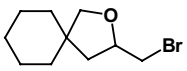
Entry	Reagent system[a]	Temperature, °C	Time, h	Conversion,[b] %	**2/4** ratio[b]
1	Li_2CO_3/MeOH	20–60	6	~0	—
2	Na_2CO_3/MeOH	20	24	6	—
		60	18	99	92/8
3	K_2CO_3/MeOH	20	6–24	100	90/10
4	Rb_2CO_3/MeOH	20	6	100	89/11
5	Cs_2CO_3/MeOH	20	6	100	85/15
6	K_3PO_4/MeOH	20	6	100	90/10
7	MeONa/MeOH	20	0.5	100	90/10
8	EtONa/EtOH	20	0.5	100	82/18
9	K_2CO_3/EtOH	20	6	47	88/12
		60	12	100	87/13
10	DBU/THF	60	2	100	54/46
11	KOH/Et_2O	20	12	80	34/66
12	K_2CO_3/DMSO	50	6	100	21/79
13	K_2CO_3/acetone	50	12	86	12/88
14	K_2CO_3/MeCN	50	18	100	10/90
15	K_2CO_3/[bmim]BF_4	20	6	100	6/94
16	*t*-BuOK/THF	20	0.1	100	15/85

[a] 5 equiv carbonates or 1.2–1.3 equiv of other bases, 0.22 M concentration of **3a**.
[b] GC and/or NMR data.

methanol, except for Li_2CO_3, which failed to give any product, provided >85% chemoselectivity (entries 1–5), an equally good result was observed with K_3PO_4 (entry 6). The use of sodium methoxide (entry 7) was also successful, but its application required careful attention to stoichiometry to prevent further HBr elimination from **2**. Ethanol as a solvent provided similar but somewhat poorer yields (entries 8 and 9). All other base systems in aprotic media tended to give mainly vinylic bromides **4** (entries 10–16). The best selectivity (94%) for bromo olefin **4** was achieved in the case of K_2CO_3 in the ionic liquid [bmim]BF_4 (entry 15); similar results were observed in entries 12–16. These reagent systems can be recommended for the preparation of vinylic bromides **4**, mainly as (*E*)-isomers. Another possible regioisomer of vinylic bromide, possessing a C(Br)=CH_2 fragment, was not usually formed (sometimes it was detected in negligible amounts).

To evaluate the scope and limitations of our two-step protocol, we have tested several homoallylic alcohols (Table 2).[10] Clean bromination of starting alcohols **1** was found to be crucial: cyclization should be carried out with the crude material, since dibromo alcohols **3** would decompose during attempted purification by vacuum distillation or column chromatography. Homoallylic alcohols **1a**–**e** were brominated relatively cleanly in CH_2Cl_2 at −30 °C, and after the cyclization, the target

Table 2. Preparative syntheses of 3-bromotetrahydrofurans (for details, see Ref. 10)

Starting olefinic alcohol		Product		**2/4** ratio	Yield of **2**,[a] %
	**1a**		**2a**	90/10	80
	**1b**		**2b**	93/7	78
	**1c**		**2c**	~100/0	82
	**1d**		**2d**	84/16	72
	**1e**		**2e**[b]	80/20	68
	**5**		**6**	—	~90

[a] Isolated yields after two steps.
[b] 9/10 diastereomeric mixture.

bromotetrahydrofurans **2** were separated from alcohols **4** by column chromatography.[11] The amount of vinyl bromide side products **4** is to some extent substrate dependent (Table 2).

The attempted synthesis of analogous 3-bromotetrahydropyran derivatives in the same manner was unsuccessful. Homologous olefinic alcohol **5** afforded directly 2-bromomethyltetrahydrofuran derivative **6** during the bromination step (with less than 10% of other components), which was not unexpected.[1,12]

To conclude, we have developed a practical protocol for the conversion of homoallylic alcohols into 3-bromotetrahydrofurans that allows good access to various 3-derivatized tetrahydrofurans. All the steps are easy to perform, do not require expensive reagents and may tolerate certain sets of functional groups.

Acknowledgements

A.A.V. acknowledges greatly financial support from the Russian Science Support Foundation and ChemBridge Corporation.

References and notes

1. Larock, R. C. *Comprehensive Organic Transformations. A Guide to Functional Group Preparations*; VCH: NY, 1989.
2. Okimoto, Y.; Kikuchi, D.; Sakaguchi, S.; Ishii, Y. *Tetrahedron Lett.* **2000**, *41*, 10223–10227.
3. Karikomi, M.; Watanabe, S.; Kimura, Y.; Uyehara, T. *Tetrahedron Lett.* **2002**, *43*, 1495–1498.
4. (a) Lipshutz, B. H.; Barton, J. C. *J. Am. Chem. Soc.* **1992**, *114*, 1084–1086; (b) Mihelech, E. D.; Hite, G. A. *J. Am. Chem. Soc.* **1992**, *114*, 7318–7319; (c) Bedford, S. B.; Bell, K. E.; Fenton, G.; Hayes, C. J.; Knight, D. W.; Shaw, D. *Tetrahedron Lett.* **1992**, *33*, 6511–6514; (d) Barks, J. M.; Knight, D. W. *Tetrahedron Lett.* **1994**, *35*, 7259–7262.
5. Evans, R. D.; Magee, J. W.; Schauble, J. H. *Synthesis* **1988**, 862–868.
6. (a) Yur'ev, Yu. K.; Voronkov, M. G.; Gragerov, I. P.; Kondrat'eva, G. Ya. *Zh. Obsch. Khim.* **1948**, *18*, 1804–1810; (b) Ou, K.-H. *Ann. Chim.* **1940**, *13*, 175–241.
7. Normant, H. *Compt. Rend.* **1948**, *226*, 1734–1736.
8. Huet, J. *Bull. Soc. Chim. Fr.* **1964**, 2677–2680.
9. Prostakov, N. S.; Varlamov, A. V.; Kozm, K.; Aliev, A. E.; Fomichev, A. A. *Khim. Geterotsikl. Soedin.* **1989**, *5*, 670–696, [*Chem. Heterocycl. Compd. (Engl. Transl.)*, **1989**, *5*, 581–585].
10. *Representative procedure*. A solution of bromine (1.15–1.25 mL, 22–24 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a stirred solution of 1-allylcyclohexanol **1a** (2.80 g, 20 mmol) in CH_2Cl_2 (20 mL) at ca. −30 °C under an argon atmosphere. The addition of bromine was stopped when its color persist. The mixture was then treated with $Na_2S_2O_3$–$NaHCO_3$ (aq), the organic layer was separated, dried ($MgSO_4$) and concentrated in vacuo. The crude dibromoalcohol **3a** was dissolved in MeOH (50 mL), freshly powdered K_2CO_3 (8.3 g) was added, and the mixture stirred for 4–24 h at ambient temperature until the consumption of dibromide **3a** was complete (TLC, GC or NMR control). Most of volatiles were distilled off, the residue treated with water, and the organic components extracted with ether. The extracts were dried ($CaCl_2$) and concentrated in vacuo. The residue was subjected to column chromatography (gradient 0 → 3% EtOAc in hexane) to afford 3.5 g (80%) of 3-bromo-1-oxaspiro-[4.5]decane **2a**. Further elution to 5% EtOAc in hexane gave 0.175 g (4%) of (*E*)-1-(3-bromoprop-2-en-1-yl)cyclohexanol **4a**. Compound **2a**, bp 123–5 °C (20 Torr), α_D^{20} 1.5092. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.28–1.46 (m, 5H, CH_2), 1.50 (m, 1H, H from CH_2), 1.58–1.78 (m, 4H, CH_2), 2.07 (dd, 1H, J = 13.7, 5.9 Hz, 1H, H from 4-CH_2), 2.30 (dd, 1H, J = 13.7, 7.6 Hz, H from 4-CH_2), 3.92 (dd, 1H, J = 9.8 and 5.9 Hz, H from 2-CH_2), 4.13 (dd, 1H, J = 9.8, 5.6 Hz, H from 2-CH_2), 4.32 (m, 1H, CHBr). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 23.5, 23.6, 25.3, 37.4 and 37.7 (CH_2 from cyclohexane), 45.1 (CH_2CHBr), 47.3 (CHBr), 74.0 (OCH_2), 83.3 (OC). Compound **4a**, bp 96 °C (1 Torr), α_D^{20} 1.5237. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.16–1.63 (several peaks, 11H, CH_2 and OH), 2.15 (dd, 1H, J = 8.0, 1.1 Hz, allylic CH_2), 6.05 (dt, 1H, J = 13.6, 1.1 Hz, =CHBr), 6.24 (dt, 1H, J = 13.6, 8.0 Hz, =CH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.9 (3- and 5-CH_2 of cyclohexane), 25.5 (4-CH_2 of cyclohexane), 37.2 (2- and 6-CH_2 of cyclohexane), 45.5 (allylic CH_2), 70.9 (C-OH), 106.5 (=CHBr), 133.4 (=CH). Anal. Calcd for $C_9H_{15}BrO$ (219.12) (%): C, 49.33; H, 6.90; Br, 36.47. Found(%): C, 49.80; H, 7.04; Br, 36.20. The structures of other products **2b–e** were confirmed by spectral data. CAS registry numbers: **2a** 1195-85-3; **2d** 1920-14-5.
11. Branched 1-(1-methylprop-2-en-1-yl)cyclohexanol, 1-(1-phenylprop-2-en-1-yl)cyclohexanol as well as homologous 1-allylcycloheptanol and in particular 1-allylcyclooctanol were found to form large amounts of side products during bromination, and, therefore, the corresponding final materials **2** were heavily contaminated even after double purification (chromatography + distillation). We have found, however, that the material thus obtained can be safely used in nucleophilic substitution reactions of bromine, for the impurities remain unchanged. The yields of products in these cases are at the 50% level.
12. An authentic sample of compound **6** was prepared cleanly by treatment of **5** with *N*-bromosuccinimide in CH_2Cl_2.