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Preparation of oxetanes by 4-*endo trig* electrophilic cyclisations of cinnamic alcohols

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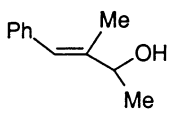
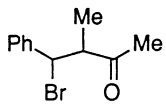
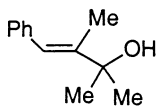
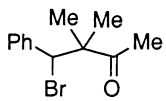
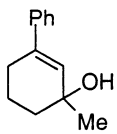
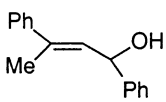
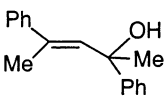
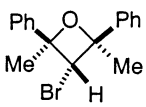
Abstract—The reaction of substituted cinnamic alcohols with bis(*sym*-collidine)bromine(I) hexafluorophosphate was examined. In general no oxetane was obtained when a substituent was fixed on the carbon–carbon double bond. However, oxetanes were formed in high yields when two substituents were present in α of the alcohol function.

We have recently reported that oxetanes could be obtained by cyclisation of cinnamyl alcohols using bis-(collidine)bromine(I) hexafluorophosphate as electrophile.[1] However, only the alcohol possessing a *gem*-dimethyl group in α of the alcohol function led to the oxetane in a satisfactory yield (Scheme 1).[1] These

Table 1. Reaction of α- and β-substituted cinnamyl alcohols with bis(collidine)bromine(I) hexafluorophosphate

Entry	Alcohol **1**	Product **2**, (Yield, %)
a		 (15)
b		 (76)
c		a
d		a
e		 (55)

[a]Degradation of the alcohol.

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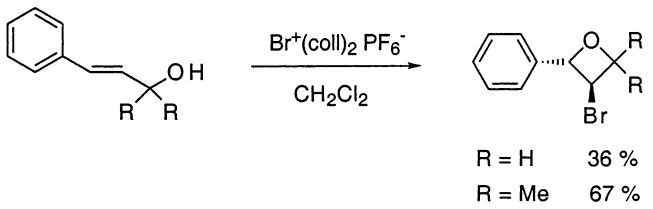
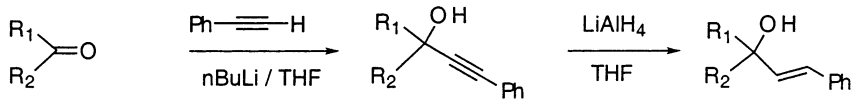


Scheme 1.

cyclisations occurred via a carbocationic intermediate.

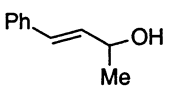
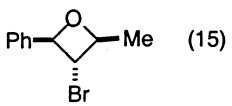
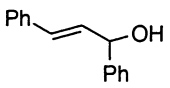
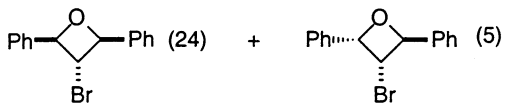
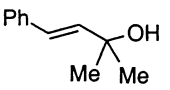
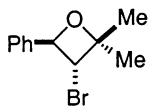
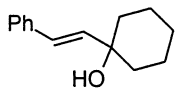
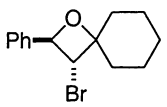
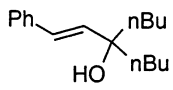
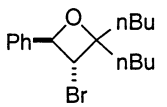
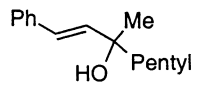
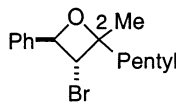
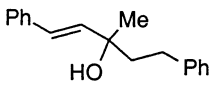
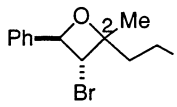
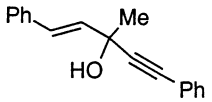
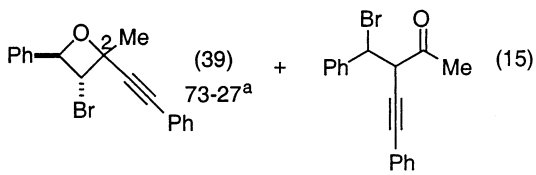
Interest in oxetanes has increased rapidly, mainly in organic synthesis and in industry (for example for the formation of polymers);[2] thus, we decided to investigate the scope of this electrophilic cyclisation. In a first study, we examined the influence of a substituent fixed on the carbon–carbon double bond. The substrates were prepared by conventional procedures. The cyclisations were carried out by addition of a methylene chloride solution of bis(collidine)bromine(I) hexafluorophosphate to the alcohols.[3] Our results are reported in Table 1.

No oxetane was obtained with α-substituted cinnamic alcohols (entries a and b). Ketones formed by migration of a hydrogen (entry a) or a methyl (entry b) were isolated. This kind of rearrangement of allylic alcohols induced by an electrophile has some precedents in the literature.[4] Only the β-substituted cinnamic alcohol **1e** led to the oxetane **2e** in moderate yield (entry e). Its

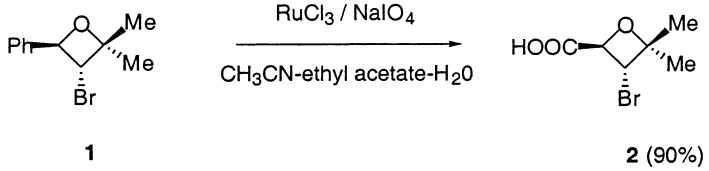


Scheme 2.

Table 2. Reaction of cinnamyl alcohols with bis(collidine)bromine(I) hexafluorophosphate

Entry	Alcohol	Product(s), (Yield, %)
a		 (15)
b		 (24) + (5)
c		 (78)
d		 (72)
e		 (87)
f		 (88) 73-27[a]
g		 (48) 63-37[a]
h		 (39) 73-27[a] + (15)

[a] ratio of diastereomers (carbon 2).



1 **2** (90%)

Scheme 3.

stereochemistry was easily deduced from its NMR spectra,[5] and by a NOESY experiment.

Since the presence of a substituent on the carbon–carbon double bond was detrimental to the formation of oxetanes, we decided to examine the cyclisation of compounds only substituted in α of the alcohol function. These alcohols were obtained in two steps by addition of phenylacetylide lithium to carbonyl compounds, followed by reduction of the carbon–carbon triple bond (Scheme 2).

The subsequent reactions with bis(collidine)bromine(I) hexafluorophosphate were conducted as reported above.[3] Our results are reported in Table 2. The structures of the products were established from their spectral data,[5] and their stereochemistries were established by NOESY experiments. Secondary alcohols (entries a and b) led mainly to degradation; oxetanes were only obtained in low yields. Only the tertiary alcohols (entries c–f) led to oxetanes in good to high yields. When the two substituents in α of the alcohol function were different (entries f–h) a mixture of two diastereomers was obtained. With the acetylenic alcohol (entry h) we observed a competition between the cyclisation and migration of the phenylethynyl group.

We also examined the oxidative cleavage of the phenyl groups. For example, reaction of 3-bromo-2,2-dimethyl-4-phenyl oxetane **1** with $NaIO_4$ in the presence of a catalytic amount of ruthenium(III) chloride led to the desired acid **2** in excellent yield (Scheme 3). These results allow the preparation of oxetin derivatives. Oxetin (oxetan-2-carboxylic acid) was reported to be a natural product possessing antibiotic activities.[6]

In conclusion we report that oxetanes can be obtained in good yields from cinnamyl alcohols using bis(collidine)bromine(I) hexafluorophosphate as electrophile. Their transformation into oxetin derivatives is under investigation.

References

1. Homsi, F.; Rousseau, G. *J. Org. Chem.* **1999**, *64*, 81–85.
2. See for example: Searles, S. In *Comprehensive Heterocyclic Chemistry*; Katrisky, A. R.; Rees, C. W., Eds.; Pergamon Press: New York, 1984; Vol. 7 pp. 363–402.
3. General procedure: To a solution of alcohol (2 mmol) in methylene chloride (20 mL) was added over 6 h at rt a methylene chloride solution (60 mL) of bis(collidine)bromine(I) hexafluorophosphate (2.6 mmol).[7] After stirring for 30 min, the solvent was removed and the residue purified by chromatography over silica gel (hexane/ether).
4. (a) Brueckner, K.; Irmschen, K.; Werder, F. V.; Bork, K.-H.; Metz, H. *Chem. Ber.* **1961**, *94*, 2897–2909; (b) Bodrikov, I. V.; Kartashov, V. R.; Temnikova, T. I. *J. Org. Chem. (USSR) Engl. Trans.* **1968**, *4*, 1286–1293; (c) Thompson, H. W.; Muccino, R. R.; Trubelhorn, M. T. *J. Org. Chem.* **1972**, *37*, 3531–3536; (d) Schneider, G.; Wolfling, J.; Mesko, E.; Dombi, G. *Steroids* **1988**, *51*, 317–328.
5. Selected data: *(2S*,3S*,4R*)-3-Bromo-2,4-dimethyl-2,4-diphenyloxetane*: ^{1}H NMR (200 MHz, $CDCl_3$); 2.24 (s, 6H); 4.50 (s, 1H); 7.20–7.59 (m, 10H). ^{13}C NMR 19.6; 66.6; 105.4; 125.9; 127.8; 128.8; 141.4. *(2S*,3S*,4R*)-3-Bromo-2-methyl-4-phenyloxetane*: ^{1}H NMR 1.53 (d, $J=6$ Hz, 3H); 4.17 (t, $J=7$ Hz, 1H); 5.03 (q, $J=6$ Hz, 1H); 5.70 (d, $J=7$ Hz, 1H); 7.28–7.57 (m, 5H). ^{13}C NMR 21.2; 49.1; 83.5; 87.3; 125.4; 128.7; 128.8; 134.0. *(2S*,3S*,4R*)-3-Bromo-2,4-diphenyloxetane*. ^{1}H NMR 4.47 (t, $J=8$ Hz, 1H); 5.35 (d, $J=8$ Hz, 2H); 7.40–7.67 (m, 10H). ^{13}C NMR 50.0; 87.0; 125.6; 128.7; 128.9; 139.1. *(2R*,3S*,4R*)-3-Bromo-2,4-diphenyloxetane*. ^{1}H NMR 5.05 (dd, $J=6$ and 7 Hz, 1H); 5.95 (d, $J=6$ Hz, 1H); 6.06 (d, $J=7$ Hz, 1H); 7.30–7.70 (m, 10H). ^{13}C NMR 50.5; 82.9; 89.9; 127.6; 128.0; 128.2; 128.3; 128.4; 128.8; 138.4; 139.7. *(2S*,3S*)-3-Bromo-2-phenyl-1-oxaspiro[3.5]nonane:* ^{1}H NMR 1.24–2.25 (m, 10H); 4.32 (d, $J=7$ Hz, 1H); 5.62 (d, $J=7$ Hz, 1H); 7.22–7.50 (m, 5H). ^{13}C NMR 21.9; 22.1; 25.0; 34.2; 38.9; 54.7; 85.3; 85.5; 125.3; 128.5; 128.6; 140.1. *(2S*,3S*)-3-Bromo-2,2-di-butyl-4-phenyloxetane:* ^{1}H NMR 0.80–2.20 (m, 18H); 4.42 (d, $J=7$ Hz, 1H); 5.59 (d, $J=7$ Hz, 1H); 7.10–7.50 (m, 5H). ^{13}C NMR 13.9; 14.1; 23.0; 23.1; 24.8; 25.0; 34.3; 38.9; 54.0; 85.3; 87.9; 125.2; 128.5; 128.7; 139.9. *(2S*,3S*)-3-Bromo-2-methyl-2-pentyl-4-phenyloxetane*. Major diastereomer: ^{1}H NMR 1.25–1.95 (m, 14H); 4.39 (d, $J=7$ Hz, 1H); 5.61 (d, $J=7$ Hz, 1H); 7.20–7.55 (m, 5H). ^{13}C NMR 13.9; 22.5; 22.6; 22.7; 31.9; 37.4; 53.2; 85.0; 86.5; 125.2; 128.5; 128.5; 139.8. Minor diastereomer: ^{1}H NMR 1.25–1.95 (m, 14H); 4.41 (d, $J=7$ Hz, 1H); 5.58 (d, $J=7$ Hz, 1H); 7.20–7.55 (m, 5H). ^{13}C NMR 13.9; 22.6; 22.9; 26.3; 32.1; 37.4; 55.3; 85.0; 85.7; 125.2; 128.3; 128.4; 139.8. *(2S*,3S*)-3-Bromo-2-methyl-4-phenyl-2-phenylethynyloxetane*. Minor diastereomer: ^{1}H NMR 1.98 (s, 3H); 4.90 (d, $J=8$ Hz, 1H); 5.61 (d, $J=8$ Hz, 1H); 7.10–7.41 (m, 10H). Major diastereomer: ^{1}H NMR 1.90 (s, 3H); 4.52 (d, $J=8$ Hz, 1H); 5.81 (d, $J=8$ Hz, 1H); 7.28–7.65 (m, 10H). ^{13}C NMR 28.6; 53.3; 81.0; 86.3; 87.5; 90.3; 122.2; 125.5; 128.3; 128.7; 128.8; 128.9; 132.0; 138.9. *3-(Bromophenylmethyl)-5-phenyl-pent-4-yn-2-one*: ^{1}H NMR 2.49 (s, 3H); 3.35 (d, $J=9.5$ Hz, 1H); 4.46 (d, $J=9.5$ Hz, 1H); 7.25–7.50 (m, 10H). ^{13}C NMR 26.6; 41.5; 56.7; 86.2; 86.6; 122.7; 128.0; 128.2; 128.5; 128.6; 128.6; 137.2; 200.2.
6. Bach, T.; Schröder, J. *Liebigs Ann./Recueil* **1997**, 2265–2267.
7. Homsi, F.; Robin, S.; Rousseau, G. *Org. Synth.* **2000**, *77*, 206–211.