Trimethylsulfonium and trimethylsulfoxonium as versatile epoxidation reagents. A comparative study

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(received 05 Jan 00; accepted 25 Apr 00; published on the web 03 May 00)

DOI: http://dx.doi.org/10.3998/ark.5550190.0001.205

Abstract

The formation of 1-aryl-2,3,4,5-tetrahydro-1*H*-3-benzazepine can be carried out by condensation between a phenethylamine and aryl and/or hetaryl-oxiranes, followed by cyclisation of the formed alcohol. Several classical methods allow the preparation of aryl oxiranes but when applied to benzo-fused heterocycles, the results are dramatically different clearly showing the lack of comparative studies on this topic. The versatility of the use of trimethylsulfonium chloride, under basic conditions, for the formation of aryl and/or hetaryl-oxiranes has been clearly demonstrated in this work.

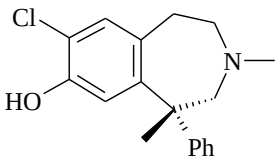
Keywords: Epoxidation, trimethylsulfonium, trimethylsulfoxonium, tetrahydro-1*H*-3-benzazepines

Introduction

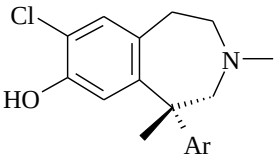
Dopamine receptors have been implicated in neuropsychiatric disorders and it has been established[1] that SCH-23390 and related benzazepine derivatives are highly selective D1 dopamine antagonists.

We decided to prepare such benzazepines bearing a heterocycle, instead of a phenyl group, in order that they could be labeled in a final step for in vivo imaging experiments: specifically, benzo[*b*]furan and thiophene rings, linked to the benzazepine at the seven-membered ring, were chosen.

One of the well documented synthetic methods[1–3] used for the preparation of these 1-aryl- 2,3,4,5-tetrahydro-1*H*-3-benzazepines 1 is based on the condensation of the appropriate phenethylamine with an aryl oxirane 2.



SCH-23390



We followed the same strategy and investigated particularly the methods of preparation of oxiranyl-benzo[*b*]furans and thiophenes 2a−f, since the synthesis of the 3-chloro-4-methoxy-phenethylamine is well known and fully described[4].

Several synthetic preparations of aryl-oxiranes are given in the literature and can be classified in two main groups :

- the oxidation of a vinyl aromatic compound, and
- the methylene addition to an aromatic aldehyde or ketone.

We investigated both procedures and report herein our results.

Results and Discussion

All our attempts to obtain a vinyl substituent from a formyl group using methyltriphenylphosphonium bromide under various basic conditions have been unsuccesful, the starting aldehyde remained unchanged.

The few examples in the literature[5,6] concerning the formation of 2 describe the use of various sulfonium salts under basic conditions, which, however, is not really a classical method. Furthermore, the products obtained have been generally poorly described, since their unambiguous identification and/or the preparation method of the starting aldehydes has not been mentioned.

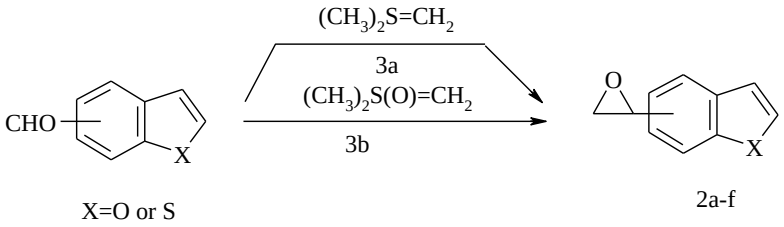
The most generally described method for the formation of aryl oxiranes consists of reacting an aldehyde or a ketone with Corey's reagent 3a formed from a trimethylsulfoxonium salt, or its equivalent 3b (Corey−Chaykovsky's reagent), which was prepared from a trimethylsulfoxonium salt. These two reagents have been used interchangeably with no comment concerning the reason why the authors chose one or the other.

The only comparative study of these two reagents was published by Corey and Chaykovsky[7] in 1965.

Several facts have been clearly established:

- sulfonium salts lead to more nucleophilic and generally more reactive species,
- they react more specifically and avoid tedious purification steps, and
- the absolute configuration of the obtained products can be different.

All these points are verified in our cases and also the difference of reactivity described[7] can be dramatically greater than expected. Indeed, all of our attempts to obtain the oxiranes 2 from the corresponding aldehydes using Corey reagent 3a have been unsuccessful, the starting material remain unchanged during the reaction time even though the same reaction with 3b led to the expected compounds with good to very good yields under basic conditions.



Scheme 1

Moreover, differently substituted benzo[*b*]thiophene and furan carbaldehydes have been prepared showing clearly the versatility of this method. The results obtained for the preparation of the oxiranes are listed below.

Table 1. Formation of aryl substituted oxiranes 2 with trimethylsulfonium chloride under basic conditions

Starting material	Reaction product	Yield
2-benzo[*b*] thiophene carbaldehyde	2-oxiranyl-benzo[*b*] thiophene 2a	88%
4-benzo[*b*] thiophene carbaldehyde	4-oxiranyl-benzo[*b*] thiophene 2b	77%
7-benzo[*b*] thiophene carbaldehyde	7-oxiranyl-benzo[*b*] thiophene 2c	60%
5-benzo[*b*] furan carbaldehyde	5-oxiranyl-benzo[*b*] furan 2d	67%
6-benzo[*b*] furan carbaldehyde	6-oxiranyl-benzo[*b*] furan 2e	61%
7-benzo[*b*] furan carbaldehyde	7-oxiranyl-benzo[*b*] furan 2f	88%

In conclusion, we have demonstrated that although they have similar structure and application, trimethylsulfonium and trimethylsulfoxonium salts lead, under basic conditions, to different reagents and it is better not to recommend one over the other for the formation of oxiranes from aromatic aldehydes.

Obviously, this first study should be extended to many other aromatic systems in order to determine all the parameters that could help the bench chemist to choose one of these two reagents.

Experimental section

All the solvents and chemicals were commercial and used as received. The starting aldehydes have been prepared in our laboratory following already known procedures.[8] ^{1}H NMR were recorded at 250 MHz.

General procedure for the synthesis of aryl and/or hetaryl oxiranes. To a solution of an aldehyde (2.2 mmol) and tetrabutylammonium iodide (27 µmol, 1.5 mol%) in a 1/1 mixture of dichloromethane and aqueous sodium hydroxyde (50%, 10 mL) was added trimethylsulfonium iodide (3.4 mmol). The mixture was stirred and heated under reflux for 3 days and allowed to reach 25 °C. The organic layer was extracted and washed with brine, dried over sodium sulfate and

evaporated to yield 2, which has been shown to be spectroscopically pure.
All the NMR data concerning the oxiranes 2 are listed in Table 2.

Table 2. NMR data for the oxiranes obtained from benzo[*b*]thiophene or furan carbaldehydes and trimethylsufonium iodide under basic conditions

Cpd	H_2	H_3	H_4	H_5	H_6	H_7	H'_1	H'_2
2a	–	7.4 s	–	–	–	–	4.19 dd (4.0, 2.6)	3.24 dd (5.4, 4.0) 3.05 dd (5.4, 2.6)
2b	7.59 d (5.6)	7.53 d (5.6)	–	7.84 d (7.6)	7.33 dd (7.6, 6.8)	7.29 d (6.8)	4.33 dd (4.3, 2.5)	3.24 dd (5.6, 4.3) 2.91 dd (5.6, 2.5)
2c	7.48 d (5.4)	7.37 d (5.4)	7.29 d (7.2)	7.4 dd (7.6, 7.2)	7.79 d (7.6)	–	4.21 dd (4.3, 2.4)	3.25 dd (5.4, 4.3) 3.05 dd (5.4, 2.4)
2d	7.63 d (2.1)	6.75 d (2.1)	7.53 d (1.4)	–	7.2 dd (8.5, 1.4)	7.48 d (8.5)	3.97 dd (4.2, 2.6)	3.18 dd (5.3, 4.2) 2.85 dd (5.3, 2.6)
2e	7.62 d (2.2)	6.76 d (2.2)	7.57 d (8.0)	7.18 dd (8.0, 1.1)	–	7.44 d (1.1)	3.98 dd (4.2, 2.6)	3.19 dd (5.5, 4.2) 2.85 dd (5.5, 2.6)
2f	7.64 d (1.9)	6.78 d (1.9)	7.16 d (6.9)	7.2 dd (7.3, 6.9)	7.53 d (7.3)	–	4.4 dd (4.2, 2.4)	3.24 dd (5.9, 4.2) 3.10 dd (5.9, 2.4)

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