Chemoselective reaction of spiro[oxirane-2,2′-norborn]-1′-yl triflates with nucleophiles: a new case of HSAB-principle dependence

Antonio García Martínez,[a,]* Enrique Teso Vilar,[b] Amelia García Fraile,[b]
Santiago de la Moya Cerero,[a,]* Beatriz Lora Maroto[b] and Cristina Díaz Morillo[a]

[a]*Depto. de Química Orgánica I, Fac. de C.C. Químicas, Universidad Complutense de Madrid, Ciudad Universitaria,
28040 Madrid, Spain*
[b]*Depto. de Química Orgánica y Biología, Fac. de Ciencias, UNED, Senda del Rey 9, 28040 Madrid, Spain*

Abstract—The preparation of two new spiro[oxirane-2,2′-norborn]-1′-yl triflates as well as the study on the behavior of such triflates under nucleophile treatment is reported. Three different nucleophile reagents have been chosen for this study: aqueous ethanol (a weak hard-base nucleophile), sodium hydroxide (a strong hard-base nucleophile) and lithium aluminum hydride (a strong soft-base nucleophile). It is concluded that the described norbornane-derived bridgehead triflates react chemoselectively with these nucleophiles following one of three possible reaction pathways, according to the character (strong or weak nucleophile, hard or soft base) of the reagent. For strong nucleophiles the HSAB principle is fulfilled. © 2001 Elsevier Science Ltd. All rights reserved.

Bridgehead norbornane-derived triflates are an important class of bicyclic compounds which have allowed the study on the stability and structure of corresponding interesting non-planar bridgehead carbocations.[1] Moreover, enantiopure 1-norbornyl triflates, which can be easily obtained from readily available natural camphor or fenchone, have been used by us as key intermediates for the preparation of interesting camphor-derived chiral inducers, as well as for the total synthesis of valuable natural products.[2]

On the other hand, we have recently reported on the preparation of spiro[cyclopropane-1,2′-norborn]-1′-yl triflate **1a** (Fig. 1), and the solvolytical study of such tricyclic triflate under the standard weak nuclephilic media aqueous ethanol.[3] A comparative computational DFT study showed that the corresponding bridgehead carbocation **1a**(+) (Fig. 1) resembles a sp^2-hybridized one more than the previously postulated sp^3 hybridization for this kind of norbornane carbocations.[3]

We were therefore interested in the study on the structure and stability of the spiro[oxirane-2,2′-norborn]-1′-

yl cations **2**(+) and **3**(+), which are: (a) oxa-analogous of corresponding carbocations **1**(+) and, (b) new valuable models of oxirylcarbinyl cations.[4] Nevertheless, due to the inherent possible reactivity of the rigid oxirane ring, a preliminary experimental study on the behavior of corresponding spiro-oxiranic triflates **2** and **3** with nucleophiles must be realized.
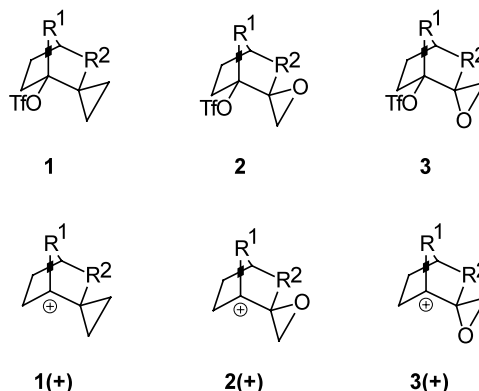
a: R1 = CMe₂, R2 = CH₂ // **b:** R1 = CH₂, R2 = CMe₂

Figure 1. Spiranic bridgehead norbornane-derived triflates and corresponding carbocations.

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* Corresponding authors.
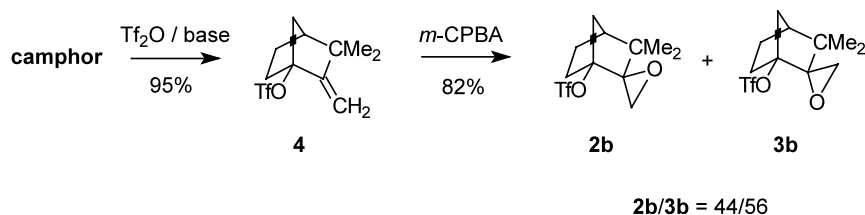
Scheme 1. Preparation of spiro[oxirane-2,2′-norborn]-1′-yl triflates **2b** and **3b**.

Accordingly, we have now prepared the epimeric triflates **2b** and **3b** and studied the reaction of such spiro-oxiranic bridgehead norbornane-derived triflates under treatment with three different nucleophiles: the weak hard-base aqueous ethanol, the strong hard-base sodium hydroxide, and the strong soft-base lithium aluminum hydride.[5]

Triflates **2b** and **3b** have been prepared by standard epoxidation of corresponding methylenenorbornane **4** with *m*-CPBA (Scheme 1).[6] On the other hand, key intermediate **4** is straightforwardly obtained from commercial camphor according to a procedure previously described by us.[7]

The reaction of triflates **2b** and **3b** with aqueous ethanol takes place with norbornane-ring contraction to yield the hydroxy ketone **5** as the only reaction product (Scheme 2).[8] Nevertheless, when triflates **2b** and **3b** are reacted with aqueous sodium hydroxide instead of aqueous ethanol, the only reaction product is 10-hydroxycamphor **6** (Scheme 2).[9]

On the other hand, the reaction of **2b** or **3b** with lithium aluminum hydride takes place with norbornane-ring contraction, as in the case of the treatment with aqueous ethanol, affording alcohol **7** (Scheme 2).[10]

These results can be explained according to three different reaction pathways, which are dependent on the weakness or strength of the nucleophile, as well as on its softness or hardness as base as defined by the 'hard and soft acids and bases principle' (HSAB principle).[5] Thus, when triflates **2b** and **3b** are reacted with aqueous ethanol, a weak nucleophile, ionization (unimolecular process) probably takes place to generate the corresponding cationic intermediates **2b**(+) or **3b**(+), which rearrange to a new cation **9** (Scheme 3).[11] Nucleophilic attack on cation **9** would give undetected ketals **10** (R = H for water attack, and R = Et for ethanol attack), which must undergo hydrolysis to obtain hydroxy ketone **5** (Scheme 3).[12]

When the nucleophile is stronger (aqueous sodium hydroxide or lithium aluminum hydride), a bimolecular nucleophilic attack, faster than the above described ionization, takes place. For the hard-base hydroxide, the nucleophile attack is directed to the harder acid center of the corresponding triflate, i.e. the sulfur atom of the triflate group according to the HSAB principle.[5] Such attack leads to the corresponding alkoxides **11** by S-O cleavage.[13] Subsequent anionic rearrangement with

synchronous oxirane-ring opening gives alkoxide **12**,[14] which is the immediate precursor of 10-hydroxycamphor **6** (Scheme 3).

On the other hand, for the strong soft-base hydride, the attack is directed to the softer acid center of corresponding triflate, i.e. the methylene group of the oxirane ring.[5] In this last case, a synchronous norbornane-ring contraction with triflate elimination takes place to generate ketone intermediate **13**,[15] whose subsequent reduction leads to alcohol **7** (Scheme 3).

In summary, interesting spiro[oxirane-2,2′-norborn]-1′-yl triflates present three different reactive centers against nucleophiles: (a) the oxiranic methylene group, (b) the sulfur atom, and (c) the C–OTf bond. These reactive centers can be chemoselected according to the character of the nucleophile. Thus, for weak nucleophiles ionization of the C–OTf bond takes place, producing a cationic norbornane-ring contraction. For strong nucleophiles the HSAB principle is rigorously fulfilled. Thus, for strong hard-base nucleophiles, the sulfur atom is the reactive center, giving place to a S-O cleavage and a subsequent anionic norbornane-ring rearrangement; whereas for strong soft-base nucleophiles, the oxiranic methylene group is selected, producing an anionic norbornane-ring contraction. We
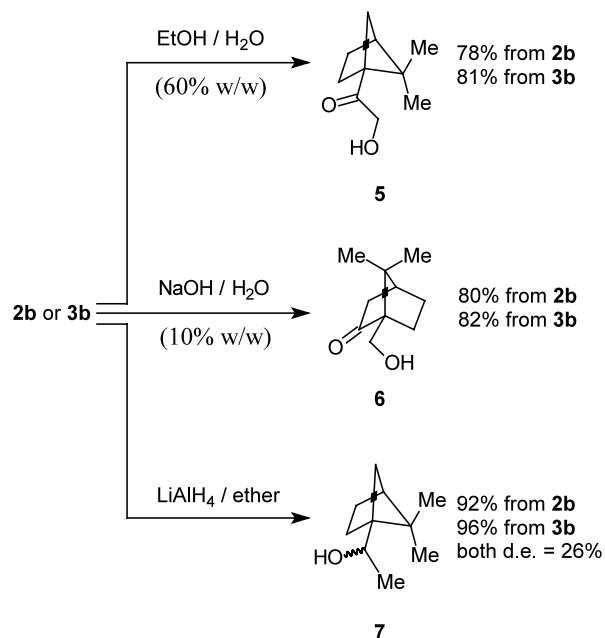
Scheme 2. Chemoselective reaction of triflates **2b** and **3b** with nucleophiles.
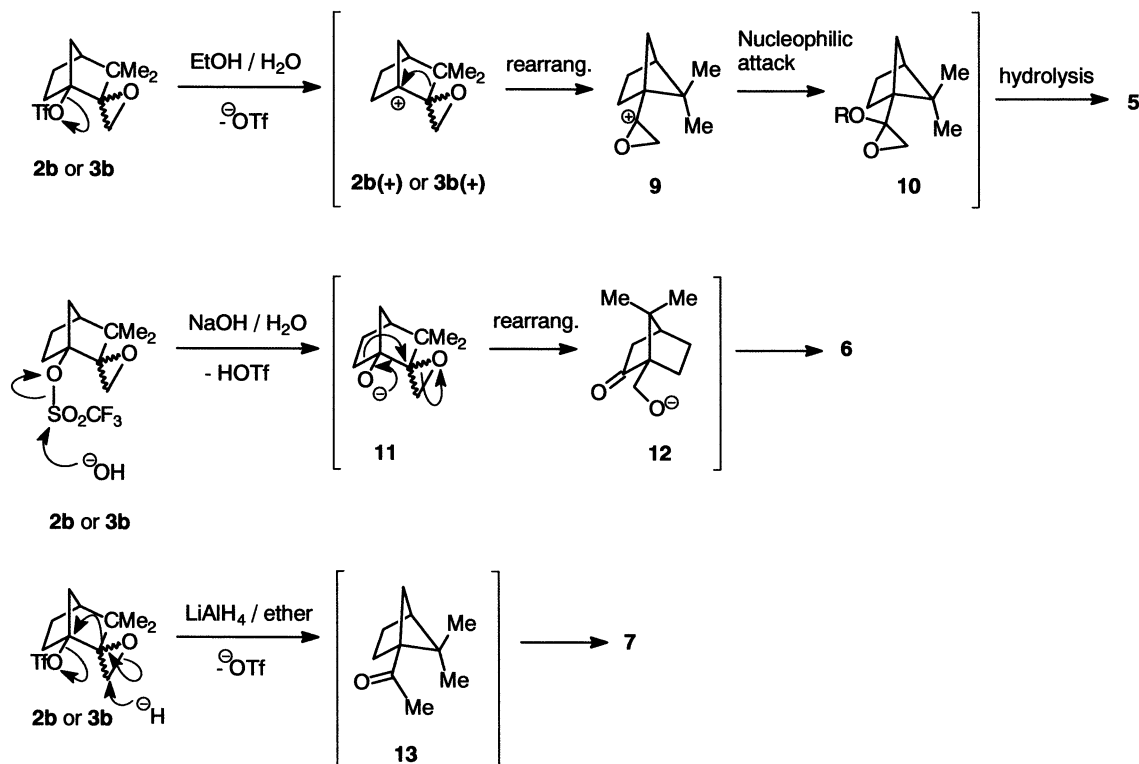
Scheme 3. Proposed reaction pathways.

continue to study the striking stability and structure of spiro[oxirane-2,2'-norborn]-1'-yl-triflate-derived carbocations,[11] by kinetic measurement of their solvolysis in aqueous ethanol.

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6. A solution of triflate **4** and 1.5 mol equiv. of *m*-CPBA (57% purity) in CH_2Cl_2 was refluxed for 20 h. After usual work up, a mixture of triflates **2b** and **3b** was obtained (d.e. = 12%). Both epimers **2b** and **3b** are easily separated

by elution chromatography (silica gel, hexane/CH$_2$Cl$_2$ 80:20): **2b** as a colorless solid (36% yield) and **3b** as a colorless liquid (46% yield). Both structures were confirmed by IR, MS and ^{1}H and ^{13}C NMR.

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8. A solution of 0.3 mmol of corresponding triflate **2b** or **3b** and 0.6 mmol of Et$_3$N (as buffer) in 6 mL of aqueous ethanol (60% w/w) was refluxed for 27 days for **2b**, or 12 days for **3b**. After usual work up, hydroxyketone **5** was obtained as a colorless oil (78% yield starting from **2b** and 81% yield starting from **3b**). IR (film) v 3460, 1710 cm^{-1}. MS m/z 137 (M$^{+\bullet}$–CH$_2$OH), 41 (100). ^{1}H NMR (200 MHz, CDCl$_3$): δ 4.28 (dd, $J=18.9$ Hz, $J=4.2$ Hz, 1H), 4.12 (dd, $J=18.9$ Hz, $J=4.4$ Hz, 1H), 3.22 (dd, $J=4.4$ Hz, $J=4.2$ Hz, 1H), 2.33 (m, 1H), 2.11–1.62 (several m, 5H), 1.19 (s, 3H), 1.15 (d, $J=7.6$ Hz, 1H), 0.95 (s, 3H) ppm. ^{13}C NMR (50 Hz, CDCl$_3$): δ 210.4, 66.8, 59.9, 50.4, 44.4, 36.8, 29.2, 25.9, 20.0, 19.4 ppm

9. A dispersion of 0.3 mmol of corresponding triflate **2b** and **3b** in 15 mL of 10% NaOH was refluxed for 24 h. After usual work up, 10-hydroxycamphor **6** was obtained as a colorless solid (80% yield starting from **2b** and 82% yield starting from **3b**). Melting point and spectroscopic data agree with the previously reported for **6** (see Ref. 2g).

10. Over a dispersion of 0.9 mmol of LiAlH$_4$ in 15 mL of dry ether, at 0°C and under argon atmosphere, a solution of 0.3 mmol of corresponding triflate **2b** or **3b** in 5 mL of dry ether was dropwise added. The reaction mixture was allowed to warm up to room temperature and stirred for 10 min. After usual work up, bicyclic alcohol **7** (d.e.= 26%) was obtained (92% yield starting from **2b** and 96% yield starting from **3b**). Both epimers can be easily separated by elution chromatography (silica gel, CH$_2$Cl$_2$). Major isomer: colorless oil, IR (film) v 3393 cm^{-1}. MS m/z 139 (M$^{+\bullet}$–15, 4), 43 (100). ^{1}H NMR (200 MHz, CDCl$_3$): δ 3.99 (c, $J=6.6$ Hz, 1H), 1.97 (s, 1H), 1.81 (m, 1H), 1.71–1.45 (several m, 5H), 1.19 (s, 3H), 1.11 (d, $J=6.6$ Hz, 3H), 0.85 (s, 3H), 0.82 (d, $J=7.1$ Hz, 1H) ppm. ^{13}C NMR (50 Hz, CDCl$_3$): δ 68.0, 57.1, 44.8, 43.3, 37.3, 25.4, 23.7, 20.6, 19.3, 18.9 ppm. Minor isomer: colorless oil, IR (film) v 3412 cm^{-1}. MS m/z 139 (M$^{+\bullet}$–15, 5), 43 (100). ^{1}H NMR (200 MHz, CDCl$_3$): δ 3.92 (c, $J=6.6$ Hz, 1H), 1.99 (s, 1H), 1.88 (m, 1H), 1.66–1.46 (several m, 5H), 1.16 (s, 3H), 1.08 (d, $J=6.6$ Hz, 3H), 0.99 (d, $J=7.1$ Hz, 1H), 0.78 (s, 3H) ppm. ^{13}C NMR (50 Hz, CDCl$_3$): δ 67.9, 57.1, 45.0, 43.6, 37.0, 25.4, 23.4, 20.6, 19.9, 19.4 ppm

11. A bimolecular mechanism analogous to the described for the reaction with lithium aluminum hydride (see Scheme 3) can be discarded in base to: (a) the weak nucleophile character of aqueous ethanol to produce oxirane-ring opening, and (b) the no-detection of corresponding ethyl ether of hydroxy ketone **5** (ethanol attack on the oxirane ring). On the other hand, since reaction products with structure retention (corresponding bridgehead alcohol and ethyl ether coming from direct nucleophilic attack on cation **2b**(+) or **3b**(+)) have not been detected, it is not possible to discard a synchronous mechanism from **2b**, or **3b**, to cation **9** (i.e. a frangomeric process). A non-classical carbocation can be also proposed instead of the classical cations **2b**(+), or **3b**(+), and **9**.

12. Cyclic ketals **10** (alkoxy- or hydroxyoxiranes) must be very unstable in the aqueous media, and undergo easy hydrolysis to hydroxy ketone **5**.

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