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Unexpected reactivity of 1-amine-2-methylenenorbornane hydrochlorides with *m*-CPBA

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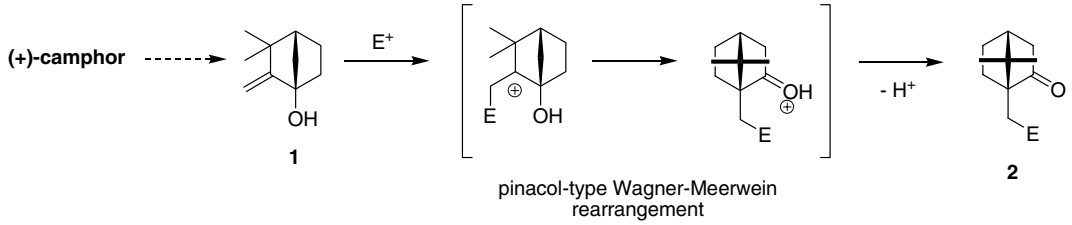
Abstract—Two different 1-amino-3,3-dimethyl-2-methylenenorbornane hydrochlorides, a primary ammonium chloride and a tertiary one, react unexpectedly with *m*-CPBA (*meta*-chloroperbenzoic acid) according to two different paths. The primary ammonium chloride gives place to a diastereomeric mixture of the corresponding spiranic 1-nitronorbornane-based epoxides, whereas the tertiary derivative undergoes a skeleton rearrangement giving 10-chlorocamphor. The results are interpreted in terms of competitive reaction pathways controlled by the nitrogenated group located at the C1 norbornane position.

During the past years we have studied the reactivity of camphor-derived 3,3-dimethyl-2-methylenenorbornan-1-ol **1** with electrophiles, as well as its application in the preparation of valuable enantiopure C10-substituted camphors of type **2** (Scheme 1).[1] This reactivity can be extended to other 2-methylenenorbornan-1-ols[1,2] and its utility as a synthetic tool has been pointed out by different authors.[3]

The enantiospecific process takes place by a regio- and stereocontrolled tandem electrophilic carbon–carbon double-bond addition—pinacol-type Wagner–Meerwein rearrangement, which is promoted by the presence of the electron-donating hydroxyl group at the initial C1 norbornane position.[1] In this sense, other O-and N-based electron-donating groups (e.g., alcoxyl, acyloxyl, amino, etc.) could also activate this process.[4]

On the other hand, electron-withdrawing groups disrupt this process, by deactivating the pinacol-type Wagner–Meerwein rearrangement.[1,5]

During our ongoing research on the preparation of enantiopure N/O chiral ligands based on bridgehead-substituted norbornanes,[6] we were also interested in the preparation of diastereomeric norbornanic aminoepoxide intermediates **3**(**R**) (R = H and Et). To reach this objective, we proposed a simple epoxidation of



Scheme 1. Electrophilic reactivity of camphor-derived 2-methylenenorbornan-1-ol **1**. Synthesis of C10-substituted camphors **2**.

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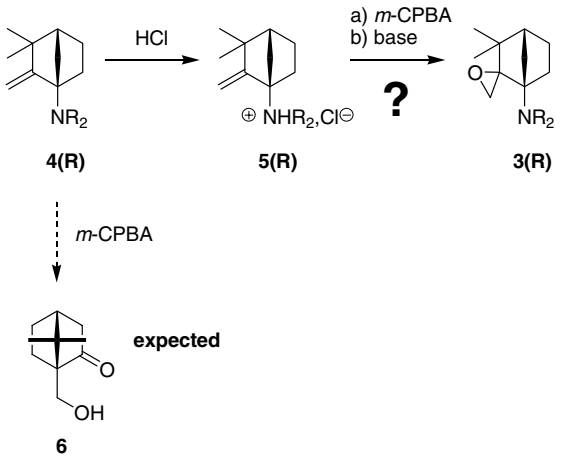
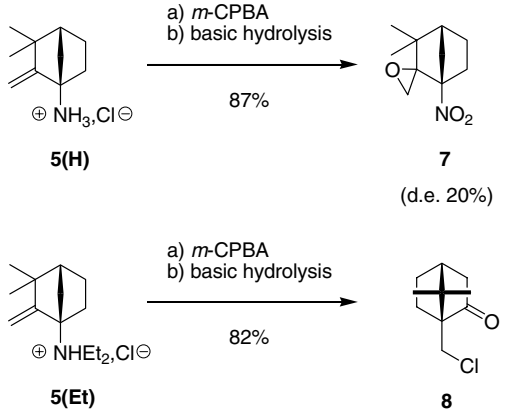


Scheme 2. Proposed route to aminoepoxides **3**(**R**) from camphor-derived aminoolefines **4**(**R**).

amino-olefine precursors **4**(**R**) with *m*-CPBA. However, due to the mentioned reactivity of C1-substituted 2-methylenenorbornanes with electrophiles, we thought that we should transform the electron-donating amino group of **4**(**R**) into an electron-withdrawing ammonium one, previous to the reaction with *m*-CPBA. This way we would avoid an undesired pinacol-type (amino promoted) Wagner–Meerwein rearrangement to 10-hydroxycamphor **6** (Scheme 2).

Starting amine **4**(**H**) was prepared from (+)-camphor according to procedures previously described by us.[6a] Amine **4**(**Et**) was prepared by standard N,N-diethylation of **4**(**H**) with ethyl iodide.[7] Amine hydrochlorides **5**(**H**) and **5**(**Et**) were prepared from corresponding amines **4**(**H**) and **4**(**Et**) by reaction with dry hydrogen chloride.[8]

Unexpectedly, standard treatment of hydrochlorides **5**(**H**) and **5**(**Et**) with *m*-CPBA[5,9] did not yield the expected norbornane-based spiranic aminoepoxides **3**(**H**) and **3**(**Et**). Diastereomeric nitroepoxides **7**[10] [in the case of **5**(**H**)] and enantiopure 10-chlorocamphor **8**[11] [in the case of **5**(**Et**)] were obtained instead (Scheme 3).

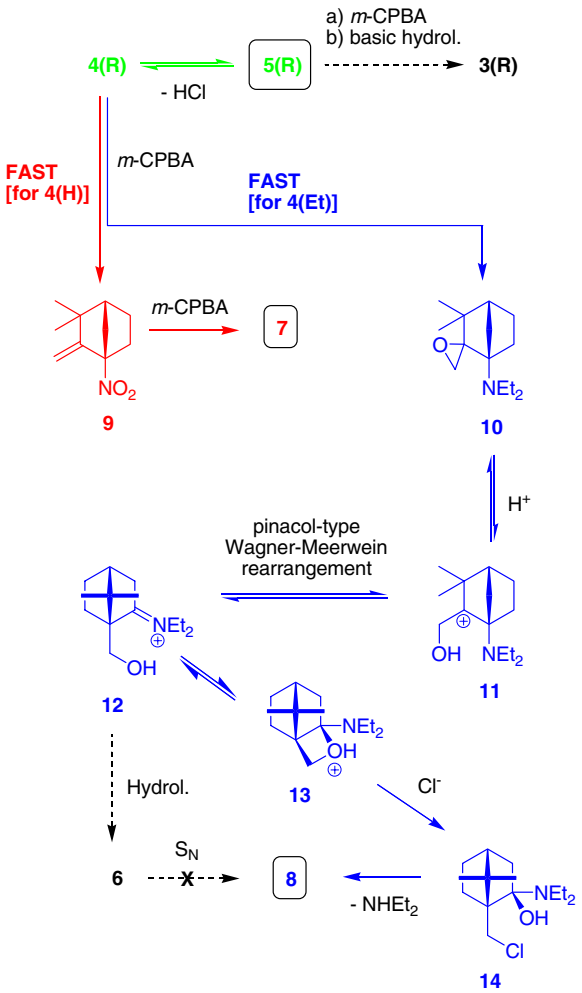


Scheme 3. Unexpected reaction of amine hydrochlorides **5**(**H**) and **5**(**Et**) with *m*-CPBA in refluxing CH_2Cl_2.

Formation of epoxides **7** and chloride **8** from respective amine hydrochlorides **5**(**H**) and **5**(**Et**) can be explained by the presence of free amine **4**(**R**), in equilibrium with the hydrochloride **5**(**R**) in the reaction medium (commercial non-dry *m*-CPBA was used).[9] Thus, in the case of **5**(**H**), fast oxidation of the corresponding primary free amine **4**(**H**) is expected to give nitro compound **9**,[12,13] which then undergoes a carbon–carbon double-bond epoxidation giving place to **7** (green-and-red pathway in Scheme 4). In the case of **5**(**Et**), a fast tandem epoxidation—pinacol-type Wagner–Meerwein rearrangement of the corresponding tertiary free amine **4**(**Et**) is expected to give alcohol **6**,[1] after hydrolysis of intermediate **12** (green-and-blue pathway in Scheme 4).

In theory, formation of chloride **8** could arise from an acid-catalyzed substitution of hydroxyl group in **6**. Nevertheless, treatment of alcohol **6**[1] with ammonium chloride in the same reaction conditions (excess of wet *m*-CPBA with refluxing CH_2Cl_2) left **6** unchanged.[14]

The hypothetic formation of chloride **8** from intermediate **12** could be explained by formation of the strained protonated 2-oxetanamine **13**,[15] which must react easily



Scheme 4. Possible reaction pathways of **5**(**H**) and **5**(**Et**) upon *m*-CPBA treatment.

with chloride anion onto its less hindered methylene group,[16] yielding aminal **14**. The latter liberates detected **8** upon aqueous work-up.[17]

In summary, 1-amino-2-methylenenorbornane hydrochlorides react with *m*-CPBA via the corresponding free amine, which is more reactive than the starting amine hydrochloride. On the one hand, primary amine undergoes tandem amino-to-nitro oxidation—carbon–carbon double-bond epoxidation to corresponding 1-nitronorbornane-based spiranic epoxides. On the other hand, tertiary amine undergoes a cascade process initialized by epoxidation and subsequent amino-promoted pinacol-type Wagner–Meerwein rearrangement, to yield chlorocamphor **8**. Therefore, a simple non-substituted amino group (i.e., a primary amine) is an efficient autoprotective group in the reaction conditions to avoid the undesired Wagner–Meerwein rearrangement of 1-amino-2-methylenenorbornanes, making possible the O-functionalization of the methylene group in 1-amino-2-methylenenorbornanes, with preservation of the N-substitution at the bridgehead position.

Acknowledgments

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3. For example, see: (a) Kurti, L.; Czako, B. *Strategies Applications of Named Reactions in Organic Synthesis*; Elsevier: Amsterdam, 2005; (b) Li, J. J. *Name Reactions: A Collection of Detailed Reaction Mechanisms*; Springer: Berlin, 2003; Also see: (c) Pellisier, H. *Tetrahedron* **2006**, *62*, 1619.
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6. For instance, see: (a) García Martínez, A.; Teso Vilar, E.; García Fraile, A.; de la Moya Cerero, S.; Martínez Ruiz, P.; Subramanian, L. R. *Tetrahedron: Asymmetry* **1996**, *7*, 1257; (b) García Martínez, A.; Teso Vilar, E.; García Fraile, A.; de la Moya Cerero, S.; Martínez Ruiz, P. *Tetrahedron: Asymmetry* **2002**, *13*, 1457; (c) García Martínez, A.; Teso Vilar, E.; García Fraile, A.; de la Moya Cerero, S.; Martínez Ruiz, P.; Chicharro Vilas, P. *Tetrahedron: Asymmetry* **2002**, *13*, 1; (d) García Martínez, A.; Teso Vilar, E.; García Fraile, A.; de la Moya Cerero, S.; Lora Maroto, B. *Tetrahedron* **2005**, *61*, 3055.
7. Amine **4**(**H**) was reacted with EtI/K_2CO_3 (10 mol equiv) in refluxing absolute ethanol for 8 h. After usual work-up, amine, **4**(**Et**) (84% yield) was obtained pure as a colorless oil. ^1H and ^{13}C NMR, IR, MS, and HRMS agree with the structure.
8. A hydrogen chloride steam was bubbled through a cooled (0 °C) solution of the corresponding amine **4**(**R**) in dry ether. Insoluble **5**(**R**) was filtered and purified by recrystallization (MeOH/Et_2O). Amine hydrochlorides **5**(**H**) and **5**(**Et**) were obtained as white crystals in ca quantitative yield.
9. A dispersion of hydrochloride amine **5**(**R**) in CH_2Cl_2 was treated with 1.5 mol equiv of commercial *m*-CPBA (57% purity) and the resulting reaction mixture refluxed overnight.
10. Relative configurations at C2 (*exo-O* vs *endo-O*) were determined unambiguously on the basis of ^1H–^{13}C HMQC and selective 1D NOESY NMR experiments realized on the purified (elution chromatography, silica gel, hexane–CH_2Cl_2 6:4) mixture of epimers **7**. Both epimers were inseparable in such chromatographic conditions. After mixture configuration assignments, e.d. was determined by ^1H NMR on the reaction crude (e.d. 20%, the major epimer being the C2-*exo-O* one). A pure sample of the major C2-*exo-O* epimer was obtained after three consecutive recrystallizations from hexane: $[\alpha]_D^{20}$ +3.1 (0.93, CH_2Cl_2); mp 110–111 °C; elemental analysis, found (calcd for $C_{10}H_{15}NO_3$), C: 60.11 (60.90), H: 7.41 (7.67), N: 7.00 (7.10). ^1H and ^{13}C NMR, IR, and MS agree with the structures.
11. Data agree with the previously reported ones (see Ref. 1).
12. C1-electron-withdrawing-substituted 2-methylenenorbornanes undergo slow epoxidation with *m*-CPBA (heating is usually necessary, see Ref. 5).
13. Primary 1-norbornyl amines, such as **4**(**H**), undergo easily oxidation to the corresponding nitro compounds under *m*-CPBA treatment: García Martínez, A.; Teso Vilar, E.; García Fraile, A.; de la Moya Cerero, S.; Martínez Ruiz, P.; Subramanian, L. R. *Tetrahedron: Asymmetry* **1996**, *7*, 2177.
14. Note the impossibility for an acid-promoted water elimination in primary alcohol **6**, due to its neopentylic-like character. On the other hand, the low capacity of related derivatives to undergo cationic rearrangement is known: García Martínez, A.; Teso Vilar, E.; García Fraile, A.; de la Moya Cerero, S.; Díaz Morillo, C. *Tetrahedron* **2005**, *61*, 599.
15. Note the energetically-favored oxetane's cis-fusion, compared to the trans one.
16. Acid-catalyzed oxetane ring opening can be promoted by aqueous HCl (inclusive at room temperature). For instance see: Patterson, I.; Delgando, O. *Tetrahedron Lett.* **2003**, *44*, 8877.
17. Process **12**-to-**14** constitutes a nice example of intramolecular activation for the nucleophilic substitution of primary alcohols by iminium salts.