Unexpected Bromine-Assisted Beckmann Fragmentation of a C1-Electron-Acceptor Substituted 7-Bromonorbornan-2-one Upon Hydroxylamine Treatment

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

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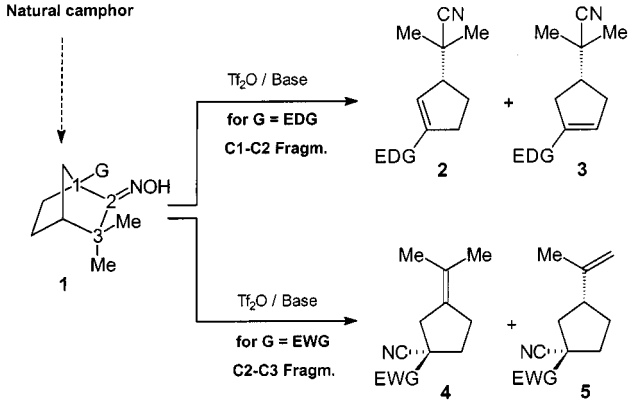
Enantiopure 7-*anti*-bromo-3,3-dimethyl-2-oxonorbornan-1-carboxamide, which is easily obtained from commercially available 3-*endo*-bromocamphor, undergoes an unexpected stereocontrolled Beckmann fragmentation in situ upon treatment with hydroxylamine. This reaction constitutes the first example in which a C1-electron-acceptor substituted 3,3-dimethylnorbornan-2-one undergoes: a) an in situ Beckmann fragmentation upon reaction with hydroxylamine, and b) a Beckmann fragmentation of the C1–C2 norbornane bond instead of the C2–C3 bond. Both facts can be attributed to the effect exerted by the bromine substituent located at the C7-norbornane position. Since the described stereocontrolled bromine-promoted fragmentation leads to an enantiopure 1,3-disubstituted five-membered carbocycle, it could constitute a model procedure for the synthesis of other interesting enantiopure cyclopentanoids.

Introduction

The Beckmann fragmentation of enantiopure 2-norbornanoximes has been widely used as a convenient synthetic strategy for the enantiospecific preparation of valuable carbocyclic nitrile intermediates.[1,2] In this sense, we have previously reported that the Beckmann fragmentation of several camphor-derived C1-electron-donor substituted 2-norbornanoximes **1** (see Scheme 1, G = electron donating group, EDG) upon treatment with triflic anhydride (Tf_2O), takes place with fragmentation of the C1−C2 norbornane bond to yield a mixture of the corresponding enantiopure 3-cyanomethylcyclopentene intermediates **2** and **3** (Scheme 1).[2] Unfortunately, when the starting camphor-derived 2-norbornanoximes **1** are C1-electron-acceptor substituted (see Scheme 1, G = electron withdrawing group, EWG) the Tf_2O-promoted Beckmann fragmentation takes place at the C2−C3 norbornane bond instead of the desired C1−C2 one, yielding a mixture of the corresponding cyclopentane nitriles **4** and **5** (Scheme 1).[2a] In both cases, formation of mixtures, which are due to a nonregioselective proton elimination after fragmentation, cannot be avoided.[2a]



Scheme 1

The present communication reports the first example of a bromine-assisted in situ Beckmann fragmentation of a C1-electron-acceptor substituted (carboxamide) 3,3-dimethylnorbornan-2-one. The substituent effect (bromine effect) at the C7-*anti*-norbornane position could be used as a synthetic strategy for the easy C1−C2 cleavage of other C1-electron-acceptor substituted 2-norbornanones and norbornan-2-oximes, allowing the stereocontrolled preparation of valuable 1,3-disubstituted cyclopentanoids.[1,2]

Results and Discussion

During the course of our research into the reactivity and synthetic applications of C1-substituted norbornanes,[2,3]

[a] Departamento de Química Orgánica, Facultad de Ciencias Químicas, Universidad Complutense de Madrid,
Ciudad Universitaria s/n, 28040 Madrid, Spain
Fax: (internat.) + 34-91/394-4236
E-mail: santmoya@eucmax.sim.ucm.es
[b] Departamento de Química Orgánica y Biología, Facultad de Ciencias, UNED,
Senda del Rey 9, Madrid, Spain
Fax: (internat.) + 34-91/398-6697
E-mail: eteso@ccia.uned.es

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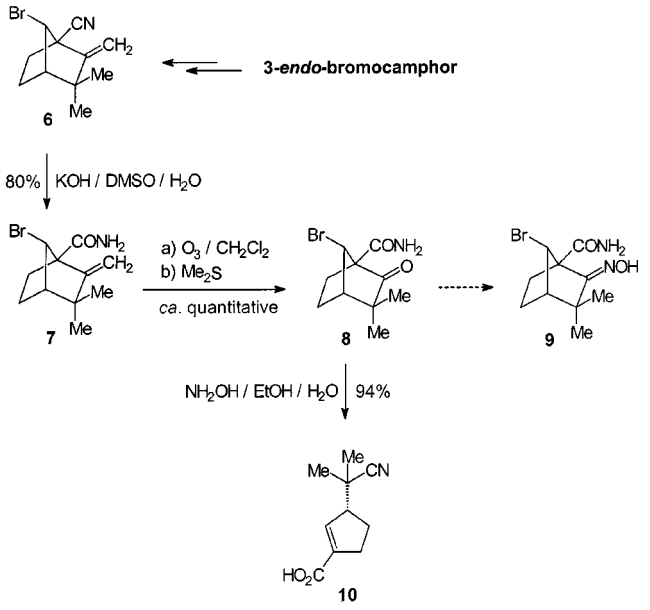
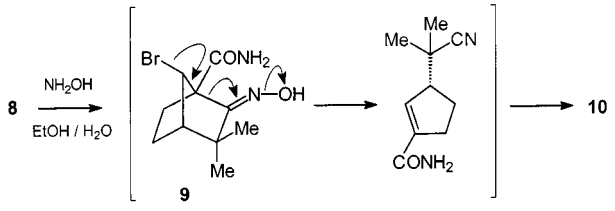
we became interested in the oximation of 2-oxonorbornan-1-carboxamide **8**, an interesting enantiopure polyfunctionalized 2-norbornanone, which is easily obtained from commercially available 3-*endo*-bromocamphor via intermediate **7** (Scheme 2).[4] Unexpectedly, the reaction of the norbornanone **8** with hydroxylamine did not lead to the desired oxime **9** (the expected product for a C1-electron-acceptor substituted 3,3-dimethylnorbornan-2-one, see Scheme 1), but instead gave the enantiopure 1,3-disusbstituted cyclopentene **10** as the only reaction product in high yield (Scheme 2).[5]



Scheme 2

The formation of the cyclopentene carboxylic acid **10** can be easily explained by an in situ Beckmann fragmentation of nonisolated norbornan-2-oxime **9**, i.e. a tandem oxime formation−stereocontrolled Beckmann fragmentation. This extremely favoured Beckmann fragmentation must be promoted by the presence of the bromine atom attached at the C7-*anti*-norbornane position (Scheme 3),[6] which also explains the fact that the cleavage takes place at the C1−C2-norbornane bond instead of the C2−C3 bond (the expected cleavage site for the Beckmann fragmentation of a C1-electron-acceptor substituted 2-norbornanone, see Scheme 1).



Scheme 3

Conclusion

In summary, the first example of a bromine-assisted stereocontrolled in situ Beckmann fragmentation of C1-electron-acceptor substituted 7-*anti*-bromonorbornan-2-ones upon treatment with hydroxylamine is described. The reaction takes place easily leading to an interesting C1-substituted 3-cyanomethylcyclopent-1-ene in high yield. The described procedure constitutes a novel 3-*endo*-bromocamphor-based model route for the stereocontrolled preparation of other 1,3-disubstituted cyclopentanoids (e.g. key natural-product intermediates or novel chiral ω-amino acids with a carbocyclic moiety).[7] We are continuing to investigate the effect that the bridgehead substituent effect exerts on the scope of this fragmentation.

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[1] [1a] R. V. Stevens, F. C. A. Gaeta, *J. Am. Chem. Soc.* **1977**, *99*, 6105−6106. [1b] R. V. Stevens, F. C. A. Gaeta, D. S. Lawrence, *J. Am. Chem. Soc.* **1983**, *105*, 7713−7719. [1c] R. V. Stevens, J. H. Chang, R. Lapalme, S. Schow, M. G. Schlageter, R. Shapiro, H. N. Weller, *J. Am. Chem. Soc.* **1983**, *105*, 7719−7729. [1d] A. S. Narula, S. P. Sethi, *Tetrahedron Lett.* **1984**, *25*, 685−688. [1e] H. Suginome, K. Furukawa, K. Orito, *J. Chem. Soc., Chem. Commun.* **1987**, 1004−1005. [1f] R. E. Gawley, *Org. React.* **1988**, *35*, 1−420.

[2] [2a] A. García Martínez, E. Teso Vilar, A. García Fraile, S. de la Moya Cerero, C. Maichle, L. R. Subramanian, *Tetrahedron: Asymmetry* **1994**, *5*, 949−954. [2b] A. García Martínez, E. Teso Vilar, A. García Fraile, S. de la Moya Cerero, P. Martínez Ruiz, L. R. Subramanian, *Tetrahedron: Asymmetry* **1996**, *7*, 2177−2180.

[3] Some recent examples are: [3a] B. Lora Maroto, S. de la Moya Cerero, A. García Martínez, A. García Fraile, E. Teso Vilar, *Tetrahedron: Asymmetry* **2000**, *11*, 3059−3062. [3b] A. García Martínez, E. Teso Vilar, S. de la Moya Cerero, B. Lora Maroto, *Tetrahedron: Asymmetry* **2000**, *11*, 4437−4440. [3c] A. García Martínez, E. Teso Vilar, A. García Fraile, S. de la Moya Cerero, B. Lora Maroto, *Tetrahedron: Asymmetry* **2001**, *12*, 189−191. [3d] A. García Martínez, E. Teso Vilar, A. García Fraile, S. de la Moya Cerero, B. Lora Maroto, *Tetrahedron Lett.* **2001**, *42*, 5017−5019. [3e] A. García Martínez, E. Teso Vilar, A. García Fraile, S. de la Moya Cerero, B. Lora Maroto, *Tetrahedron Lett.* **2001**, *42*, 6539−6541.

[4] Starting enantiopure **6** is prepared from 3-*endo*-bromocamphor in two straightforward steps with an overall yield of 85% according to ref.[3c] Compounds **7** and **8** were prepared according to well-known standard functionalization procedures. The structures of **7** and **8** were confirmed by MS, IR and NMR spectroscopy.

[5] A dispersion of 2-norbornanone **8** and excess of $NH_2OH{\cdot}HCl$/pyridine (3:3) in aqueous ethanol was refluxed for 12 h. After usual workup, **10** was obtained as a white solid, m.p. 97.6−98.1 °C. $[\alpha]_D^{20} = +92.4$ (0.47, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 2980, 2235, 1695, 1637 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 11.13 (br. s, 1 H), 6.84 (m, 1 H), 3.01 (m, 1 H), 2.74−2.58 (m, 2 H), 2.73

(m, 1 H), 1.93 (m, 1 H), 1.40 (s, 3 H), 1.36 (s, 3 H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 169.9, 143.2, 139.2, 124.0, 55.3, 35.8, 30.9, 26.1, 24.7, 24.6.

[6] A related in situ Beckmann fragmentation has been described for some strongly activated C1-electron-donor substituted 2-norbornanones, but not for C1-electron-acceptor substituted ones (see ref.[2a]). Since fragmentation of **8** to **10** also occurs in the presence of an excess of base or acid, $NH_2OH{\cdot}HCl$/pyridine (3:4) or (4:3), the described Beckmann fragmentation of **8** could be both acid-activated (protonation of the hydroxy group by hydroxylamine hydrochloride) and base-activated (nucleophilic attack of pyridine, or free hydroxylamine, at the bromine atom). A synchronous mechanism for the Beckmann fragmentation of analogously activated α-amino- and α-hydroxyketoximes has previously been demonstrated by: [6a] H. P. Fischer, C. A. Grob, *Helv. Chim. Acta* **1963**, *41*, 936−943. [6b] G. A. Olah, Y. D. Vankar, A. L. Berrier, *Synthesis* **1980**, 45−46.

[7] Enantiopure cyclopentene nitriles and cyclopentene carboxylic acids are important intermediates in the preparation of interesting natural products; see for example: [7a] B. M. Trost, D. M. T. Chan, *J. Am. Chem. Soc.* **1983**, *105*, 2315−2325 and references therein, as well as refs.[2,3c] ω-Amino acids are finding interesting applications in the design of peptidomimetics: [7b] I. L. Karle, A. Pramanik, A. Banerjee, S. Bhattacharjya, P. Balaram, *J. Am. Chem. Soc.* **1997**, *119*, 9087−9095 and references therein. For an example of ω-amino acids with a carbocyclic moiety see: [7c] M. Tichý, J. Holanova, J. Závada, *Tetrahedron: Asymmetry* **1998**, *9*, 3497−3504.

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