Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

An Improved Synthesis of Camphorquinone-3-Oxime

Brian E. Love [a] & Edward G. Jones [a]

[a] Department of Chemistry, East Carolina University, Greenville, NC, 27858

Published online: 25 Sep 2007.

To cite this article: Brian E. Love & Edward G. Jones (1999) An Improved Synthesis of Camphorquinone-3-Oxime, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 29:16, 2831-2840, DOI: 10.1080/00397919908086451

To link to this article: http://dx.doi.org/10.1080/00397919908086451

SYNTHETIC COMMUNICATIONS, 29(16), 2831-2840 (1999)

AN IMPROVED SYNTHESIS OF CAMPHORQUINONE-3-OXIME

Brian E. Love* and Edward G. Jones

Department of Chemistry
East Carolina University, Greenville, NC 27858

Abstract: Camphorquinone 3-oxime is prepared in 77% yield in one step from camphor. The synthesis avoids the use of toxic selenium reagents, and provides the *syn* compound as the major stereoisomer.

Camphorquinone-3-oxime (**1**) has proven to be a useful intermediate in organic synthesis, particularly in the preparation of chiral auxiliaries. A few representative auxiliaries synthesized via this oxime are shown on the next page (Figure 1). Oxime (**1**) has not only been used as a common precursor for the formation of a number of stereoisomeric 2-aminoalcohols,[1,2] but has also been used as a ligand itself in complexes with nickel and zinc.[3]

---

* To whom correspondence should be addressed.

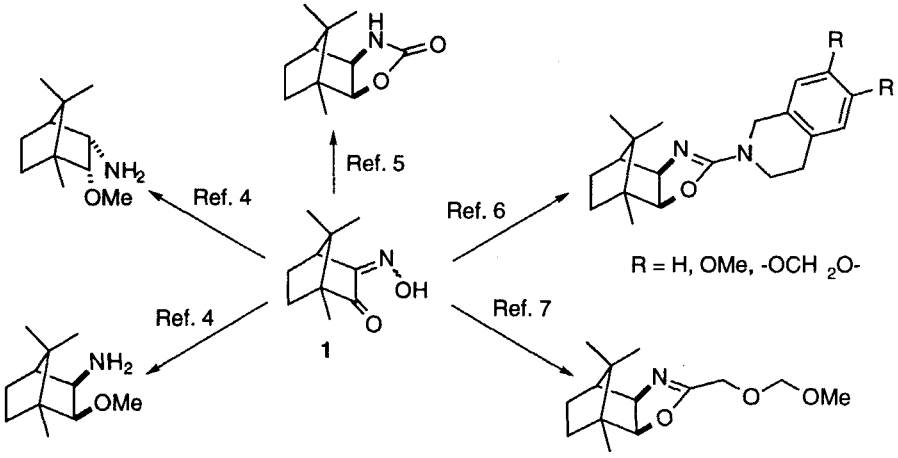
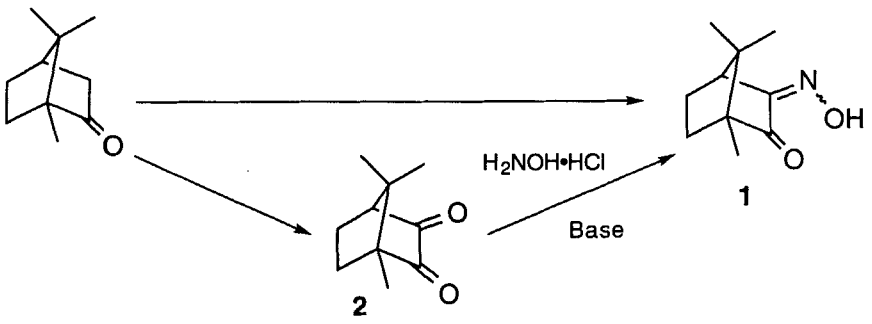


FIG. 1

Chiral Auxiliaries Derived from Camphorquinone-3-oxime

Preparation of (**1**) directly from camphor has been reported,[8] however it is more commonly prepared by treatment of camphorquinone (**2**) with hydroxylamine (see below). Though two synthetic steps are required, the overall yield for the conversion of camphor to camphorquinone followed by oximation has traditionally been higher than that of the direct conversion of camphor into (**1**).[9]



Camphorquinone itself has been prepared by a number of methods, including oxidation of camphor with benzeneseleninic anhydride,[10] reaction of camphor enolate with MoO5•py•HMPA (MoOPH),[11] and treatment of 3-bromo-camphor with NaI in DMSO.[12] By far the most common method of preparing (**1**) from camphor, however, is treatment with selenium dioxide.[13] Though this reaction proceeds in high yield,[14] selenium dioxide is a potent skin irritant, and the toxicity of this reagent (and to a certain extent, the selenium metal which is a by-product of the reaction) diminishes the attractiveness of this approach.[15] We report herein a high yield synthesis of camphorquinone 3-oxime (**1**) in one step from camphor which avoids the use of toxic selenium compounds.

Though reaction of the sodium enolate of camphor with alkyl nitrites leads directly to (**1**), yields reported for this reaction have been fairly low in both the early references (32%),[16] as well as a more recent example (31%).[17] After the work described herein was completed, a paper appeared which reported the use of potassium *tert*-butoxide as base allows preparation of (**1**) in 85% yield exclusively as the *anti* isomer.[18]

Since *N*-nitrosodiphenylamine (**3a**) has been shown to be a useful nitrosating agent for indole[19] as well as other carbon based[20] and non-carbon based nucleophiles,[21] we chose to investigate the use of this reagent for the nitrosation of camphor under basic conditions. We found reaction of camphor

with LDA followed by treatment with *N*-nitrosodiphenylamine produced camphorquinone 3-oxime in 77% yield as a mixture of *syn* and *anti* isomers (Figure 2).[22]

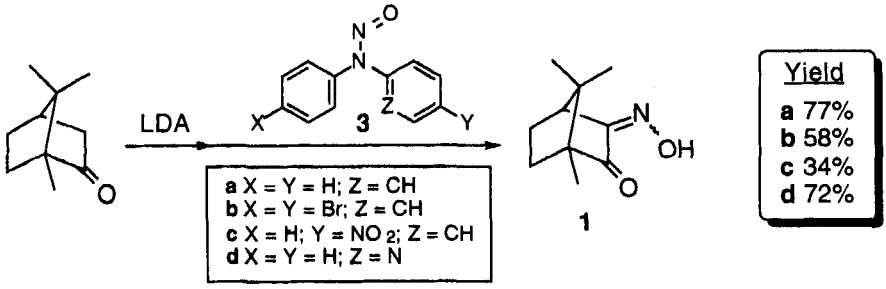


FIG. 2

Synthesis of Camphorquinone-3-oxime via Nitrosamines

Separation of the camphorquinone-3-oxime from the diphenylamine by-product and unreacted camphor was easily accomplished by means of a base extraction. It was interesting to note that the major product in this reaction was the *syn* isomer, by a factor of approximately 10:1 over the thermodynamically more stable[23] *anti* isomer. (The *anti* isomer is the major product obtained by treatment of (**2**) with hydroxylamine).[1,5] An explanation for the *syn* selectivity of this reaction, or the differing stereoselectivities of analogous reactions (see below) is currently lacking.

We then sought to improve the yield of this reaction by replacing (**3a**) with *N*-nitrosodiphenylamines substituted with

electron-withdrawing groups (**3b-d**) in an effort to increase the reactivity of the nitrosating agent. Diphenylamine was brominated in quantitative yield by treatment with NBS, then nitrosated by reaction with sodium nitrite in acetic acid to produce (**3b**) in 94% yield. Reaction of the enolate of camphor with (**3b**), however, failed to improve the yield of (**1**) compared to that obtained with (**3a**). Furthermore, the *syn/anti* ratio was found to be only approximately 2:1. *N*-nitrosodiphenylamine (**3a**) could be nitrated according to the procedure of Curtis,[24] but once again reaction of camphor enolate with (**3c**) gave a disappointingly low yield of (**1**). In this case the *anti* isomer was the major product of the reaction. Pyridine-based nitrosamine (**3d**) was prepared from 2-anilinopyridine, and while the yield was comparable to that obtained with (**1a**), the much greater expense of 2-anilino-pyridine relative to diphenylamine favors the use of (**3a**). As was observed in the reaction with (**3b**), the *syn/anti* ratio using (**3d**) was approximately 2:1

Though camphorquinone (**2**) is often a precursor in the synthesis of camphorquinone-3-oxime (**1**), the conversion of (**1**) into (**2**) was also investigated, as this would provide a means (albeit in two steps) of preparing (**2**) from camphor without need for selenium reagents. Of the numerous reagents tried, a solution of formaldehyde in aqueous hydrochloric acid heated at reflux was the most effective, providing (**2**) in 98% yield from (**1**).[25]

In summary, a one step, high yielding method has been developed which allows the preparation of the useful intermediate camphorquinone-3-oxime directly from camphor. This method avoids the use of selenium-based reagents (and the associated toxicity),[26] and produces the *syn* isomer as the major product. Further transformations of camphorquinone-3-oxime which benefit from the predominantly *syn* stereochemistry of (**1**) obtained by this method are currently under investigation.

EXPERIMENTAL PROCEDURES

***N*-nitrosodiphenylamine** (**3a**):[24] A 20.42g sample (120.8 mmol) of diphenylamine was dissolved in 150 mL glacial HOAc and stirred while 50 mL of 5M $NaNO_2$ were added dropwise over 15 min. The solution was stirred at room temperature for 90 min, then poured into 150 mL H_2O. The solid which formed was collected by filtration and washed with H_2O. The solid was then dissolved in 200 mL CH_2Cl_2 and washed with 100 mL sat'd $NaHCO_3$. The organic layer was dried ($MgSO_4$) and solvent removed under reduced pressure to give 22.19g of (**3a**) (93%). mp 64-66 °C (lit.[24] 66 °C) ^1H NMR ($CDCl_3$) δ 7.3-7.7 (m, 8H), 7.10 (dd, J = 8.1, 2.0 Hz, 2H).

Camphorquinone-3-oxime (**1**): A 0.26g sample (2.6 mmol) of diisopropylamine was dissolved in 5 mL freshly distilled THF and cooled in an ice bath under nitrogen. 1.6 mL of 1.7M

n-BuLi (2.7 mmol) were added slowly via syringe, and the solution was stirred in the bath for 30 min, followed by the addition of 0.34g (2.2 mmol) of camphor, dissolved in 10 mL THF. The solution was removed from the ice bath and allowed to come to room temperature over 1 hour. The solution was cooled once again in an ice bath, then 0.60g (3.0 mmol) of *N*-nitrosodiphenylamine (**3a**) dissolved in 10 mL of THF were added. The solution was allowed to come to room temperature overnight, diluted with 50 mL ether, and washed with 25 mL each H_2O and 6M NaOH. The aqueous extracts were cooled in an ice bath and carefully neutralized with 6M HCl, then extracted with CH_2Cl_2 (50, 25, 25 mL). The combined organic extracts were dried ($MgSO_4$) and solvent removed under reduced pressure to give 0.31g of (**1**) (77%) as a 10:1 mixture of *syn*:*anti* isomers. mp: 108-110 °C (lit.[23] 116-117 °C for pure *syn*; 154-155 °C for pure *anti*) ^1H NMR ($CDCl_3$)
δ 2.73 (d, J = 4.3 Hz, 1H), 2.0-2.3 (m, 1H), 1.5-1.9 (m, 3H), 1.04 (s, 3H), 1.02 (s, 3H), 0.94 (s, 3H).

REFERENCES

1. Chittenden, R. A.; Cooper, G. H. *J. Chem. Soc. (C)* **1970**, 49.

2. Deseke, E.; Hoyer, W.; Winterfeldt, E. *Tetrahedron* **1996**, *52*, 14,577.

3. Ma, M. S.; Angelici, R. J. *Inorg. Chem.* **1980**, *19*, 924.

4. Ikota, N.; Sakai, H.; Shibata, H.; Koga, K. *Chem. Pharm. Bull.* **1986**, *34*, 1050.

5. Bonner, M. P.; Thornton, E. R. *J. Am. Chem. Soc.* **1991**, *113*, 1299.

6. Gawley, R. E.; Zhang, P. *J. Org. Chem.* **1996**, *61*, 8103.

7. Kelly, T. R.; Arvanitis, A. *Tetrahedron Lett.* **1984**, *25*, 39.

8. Claisen, L.; Manasse, O. *Liebigs Ann. Chem.* **1893**, *274*, 71.

9. Yields for the conversion of (**2**) to (**1**) have been reported ranging from 38%[27] to 86%.[5]

10. Barton, D. H. R.; Hui, R. A. H. F.; Lester, D. J.; Ley, S. V. *Tetrahedron Lett.* **1979**, 3331.

11. Vedejs, E.; Engler, D. A.; Telschow, J. E. *J. Org. Chem.* **1978**, *43*, 188.

12. Hattori, K.; Yoshida, T.; Rikuta, K.; Miyakoshi, T. *Chem. Lett.* **1994**, 1885.

13. Original report: Evans, W. C.; Ridgion, J. M.; Simonsen, J. L. *J. Chem. Soc.* **1934**, 137. Some recent examples and/or improvements: (a) Burgstahler, A. W.; Boger, D. L.; Naik, N. C. *Tetrahedron* **1976**, *32*, 309; (b) Herzog, H.; Scharf, H.-D. *Synthesis* **1986**, 788; (c) Ellis, M. K.; Golding, B. T.; Maude, A. B.; Watson, W. P. *J. Chem. Soc., Perkin Trans. 1* **1991**, 747; (d) Pouilhes, A.; Uriarte, E.; Kouklovsky, C.; Langlois, N.; Langlois, Y.; Chiaroni, A.; Riche, C. *Tetrahedron Lett.* **1989**, *30*, 1395; (e) Oppolzer, W.; Chapuis, C.; Dupuis, D.; Guo, M. *Helv. Chim. Acta* **1985**, *68*, 2100.

14. Yields reported in reference 13 range from 74% to 96%. We have observed that significant reductions in yield result if greater amounts of acetic anhydride solvent are used than specified in the original reference.

15. (a) Luxon, S. G., Ed. *Hazards in the Chemical Laboratory, 5th Ed.*, Royal Society of Chemistry: Cambridge, 1992; p. 567; (b) Zingaro, R. A.; Cooper, W. C., Eds. *Selenium*, Van Nostrand Reinhold Co.: New York, 1974, pp. 664-667.

16. Forster, M. O.; Rao, K. A. N. *J. Chem. Soc.* **1926**, 2670. (The earlier report of this transformation by Claisen and Manasse,[8] reported the yield as approximately 40% based on consumed camphor).

17. Liu, J.-H. *Angew. Makromol. Chem.* **1987**, *155*, 83.

18. Roy, S.; Chakraborti, A. K. *Tetrahedron Lett.*, **1998**, *39*, 6355.

19. Cardellini, L.; Greci, L.; Stipa, P. *Synth. Commun.* **1994**, *24*, 677.

20. Schmidt, C. H. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 101.

21. Challis, B. C.; Osborne, M. R. *J. Chem. Soc., Perkin Trans. 2* **1973**, 1526; (b) Thompson, J. T.; Williams, D. L. H. *J. Chem. Soc., Perkin Trans. 2* **1977**, 1932.

22. As work on this project was concluding, an earlier report came to our attention regarding the nitrosation of camphor using *N*-nitrosodiphenylamine by simply heating the two reagents in ethanol.[28] We have been unable to reproduce these results using the conditions stated, however, and have not found any citations of this paper that suggest it has been successfully used by others to prepare (**1**).

23. Cherry, P. C.; Cottrell, W. R. T.; Meakins, G. D.; Richards, E. E. *J. Chem. Soc. (C)* **1968**, 459.

24. Curtis, N. J. *Propellants, Explosives, Pyrotechnics* **1990**, *15*, 222. (*Chem. Abstr.* **1991**, *114*, 65308y).

25. Cava, M. P.; Little, R. L.; Napier, D. R. *J. Am. Chem. Soc.* **1958**, *80*, 2257.

26. *N*-Nitrosodiphenylamine itself is not without potential hazard. While the presence of an α-hydrogen on nitrosamines is generally required for potent carcinogenicity,[29] (**3a**) has been shown to be carcinogenic to rodents.[30] Other animal studies, however, have indicated (**3a**) is not carcinogenic.[31]

27. Vaidya, S. P. *Indian J. Chem., Sect. B* **1986**, *25B*, 36.

28. Parihar, D. B.; Sharma, S. P. *Chem. Ind.* **1966**, 1227.

29. Loeppky, R. N.; Michejda, C. J., Eds. *Nitrosamines and Related N-Nitroso Compounds*; ACS Symposium Series 553; American Chemical Society: Washington, D. C., 1994, Chapter 1.

30. (a) Benigni, R. *Mutat. Res.* **1990**, *244*, 79; (b) Ashby, J.; Tennant, W. *Mutat. Res.* **1988**, *204*, 17.

31. See reference 29, Chapter 40, and references therein.

(Received in the USA 02 February 1999)