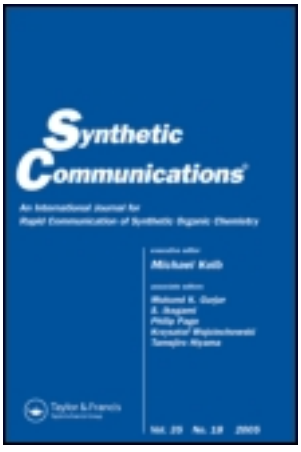


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Microwave-Assisted Selenium Dioxide Oxidation of Camphor Derivatives to α-Dicarbonyl Compounds and Oxoimines

Sarah Belsey [a b], Timothy N. Danks [a c] & Gabriele Wagner [a]

[a] Chemistry Division, SBMS, University of Surrey, Guildford, Surrey, United Kingdom

[b] Prior's Field School, Godalming, Surrey, United Kingdom

[c] Oratory School, Woodcote, Reading, Berkshire, United Kingdom

Version of record first published: 16 Aug 2006.

To cite this article: Sarah Belsey, Timothy N. Danks & Gabriele Wagner (2006): Microwave-Assisted Selenium Dioxide Oxidation of Camphor Derivatives to α-Dicarbonyl Compounds and Oxoimines, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 36:8, 1019-1024

To link to this article: http://dx.doi.org/10.1080/00397910500501557

Synthetic Communications®, 36: 1019–1024, 2006

ISSN 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910500501557

Microwave-Assisted Selenium Dioxide Oxidation of Camphor Derivatives to α-Dicarbonyl Compounds and Oxoimines

Sarah Belsey
Chemistry Division, SBMS, University of Surrey, Guildford, Surrey, United Kingdom and Prior's Field School, Godalming, Surrey, United Kingdom

Timothy N. Danks
Chemistry Division, SBMS, University of Surrey, Guildford, Surrey, United Kingdom and Oratory School, Woodcote, Reading, Berkshire, United Kingdom

Gabriele Wagner
Chemistry Division, SBMS, University of Surrey, Guildford, Surrey, United Kingdom

Abstract: Camphor-derived α-dicarbonyl compounds and 3-oxo-camphorsulfonylimine have been synthesized from the corresponding ketones or sulfonylimine by microwave-assisted oxidation with selenium dioxide. Compared to the classical reaction conditions, good yields were obtained in much shorter reaction times. Additionally, the selenium precipitation is more quantitative, and its removal from the reaction mixture is easier.

Keywords: Diketones, microwave irradiation, oxoimines, selenium dioxide

Camphor-derived α-dicarbonyl compounds do not only play an important role as chiral building blocks or auxiliaries in organic synthesis but have also

Received in the U.K. April 9, 2005
Address correspondence to Gabriele Wagner, Chemistry Division, SBMS, University of Surrey, Guildford, Surrey, GU2 7XH, United Kingdom. Tel.: +44 (0) 1483 686831; Fax: +44 (0) 1483 686851; E-mail: g.wagner@surrey.ac.uk

received interest in biomolecular sciences in recent years. Thus, 3-oxo-camphorsulfonic acid was found to act an arginine-specific reagent in the functional characterization of enzymes.[1] Camphor-derived α-dicarbonyl compounds have also been proposed as anticancer agents because of their ability to deactivate prenylating enzymes.[2] Such enzymes modify oncoproteins with the effect that cell growth becomes uncontrolled.

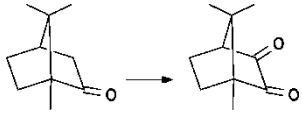
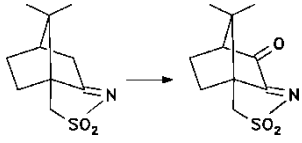
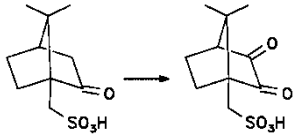
Generally, α-dicarbonyl compounds can be synthesized by SeO_2 oxidation of α-methylene ketones.[3] Methods of more limited range use reagents such as $CuBr_2/KI/DMSO$, $tBuOCH(NMe_2)_2/O_2/hv$, HNO_3, $KMnO_4$, DDQ, or PCC.[4] Alternatively, 1,2-diketones can be prepared by oxidation of alkynes,[5] vicinal diols,[6] or α-hydroxidations.[7]

SeO_2 oxidations are typically performed in refluxing dioxane, ethanol, or acetic acid, and reactions with easily enolizable substrates are complete within approximately 4 h.[8] Poorly enolizing substrates such as camphor derivatives, however, are less prone to SeO_2 oxidations. Reaction of camphor takes 15 h, in acetic anhydride,[9] and camphorsulfonylimine takes 20 h, in acid[10a] and 14 days in dioxane.[10b] The oxidation of camphorsulfonic acid with selenous acid in dioxane has been reported to be complete within 72 h; reaction of camphorsulfonylnorleucine requires 90 h.[11] The use of microwave irradiation is anticipated to accelerate these reactions in a similar way to other organic transformations,[12] in particular the microwave-assisted SeO_2 oxidation of allylic[13] and heteroaromatic[14] methyl groups to aldehydes and the dehydrogenation of 4,5-dihydropyridazin-3(2H)-ones with SeO_2.[15] In the present work, the effect of microwave irradiation on the reactions shown in Table 1 was studied. For all reactions, the optimum reaction time was determined by ^1H NMR monitoring. A 20% excess of SeO_2 was used to achieve complete conversion.

Under focused monomode microwave irradiation, camphor, camphorsulfonylimine, and camphorsulfonic acid oxidized to the respective 3-oxo compounds within 75 min at 150°C, with the further advantage of an almost quantitative precipitation of black selenium, which is easy to remove by filtration. Camphor and camphorsulfonylimine were reacted in ethanol or acetic acid as solvents without noticeable difference. If camphorsulfonic acid is oxidized in EtOH at 150°C under microwave irradiation, 3-oxo-camphorsulfonic acid is formed as the major product in 60% yield, together with two uncharacterized camphor-derived compounds in approx. 10 and 15%. However, the sulfonic acid catalyzes the condensation of ethanol to diethyl ether under these conditions,[16] causing an undue rise of pressure in the reaction vessel to up to 16 bar. To avoid this side reaction, the reaction was run in water under otherwise the same conditions to provide a similar product distribution as in ethanol.

When the oxidation of camphor was attempted in water, no reaction occurred because the camphor sublimed into the cold upper parts of the tube. Camphorsulfonylimine (**1**) was oxidized to the 3-oxo compound (2) in water; however, the reaction is accompanied by hydrolysis to provide the sulfonamides (**3**) and (**4**) and sulfonic acids (**5**) and (**6**) together with a minor

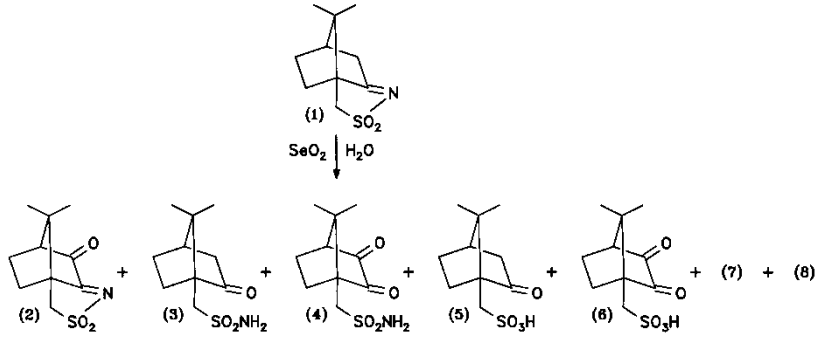
Table 1. SeO_2 oxidation of camphor derivatives

Entry	Reaction	Solvent	T (°C)	Time (min)	Yield (%)
1		HOAc	150	75	90
		EtOH	150	75	92
		H_2O	150	75	0
2		HOAc	150	75	88
		EtOH	150	75	85
		H_2O	150	75	29[a]
3		EtOH	150	75	60[b]
		H_2O	150	75	56[b]

[a]Oxidation is accompanied by hydrolysis of the sulfonamide (see Scheme 1).
[b]Two by-products of unknown structure are formed in approx. 10% and 15%.

quantity of two uncharacterized compounds (**7**) and (**8**) (Scheme 1). Compounds (**7**) and (**8**) were also detected in the oxidation of camphorsulfonic acid. Compounds (**2**), (**3**), and (**4**) were extracted with dichloromethane, and (**4**) was isolated by chromatography. Compounds (**5**) and (**6**) were identified in the aqueous phase. Samples irradiated with microwaves for 75 min at a set temperature of 150°C showed the following composition: (**1**) 5.7%, (**2**) 28.5%, (**3**) 1.5%, (**4**) 14.3%, (**5**) 11.7%, (**6**) 26.6% (**7**) 4.7%, and (**8**) 7.0%.

In conclusion, the use of focused monomode microwave irradiation for the SeO_2 oxidation of camphor derivatives to α-dicarbonyl compounds and oxoimines provides several advantages over traditional thermal heating: (a)



Scheme 1. SeO_2 oxidation of camphorsulfonylimine in water.

the reactions complete within significantly shorter times, (b) work in sealed vessels allows use of higher temperatures and moderate pressure, (c) work in a closed system is also safer because volatile selenium-containing by-products produced during the reaction are not released into the environment in an uncontrolled way, as it would be the case in an open reflux system, and (d) the workup procedure is simplified because the selenium forming during the reaction precipitates almost quantitatively in its black modification, which is easy to filter. Thermal reactions, in contrast, often require repeated reflux–filtration cycles to achieve complete selenium removal.

EXPERIMENTAL

In a typical procedure, a Pyrex cylindrical reaction tube adapted to the SmithCreator^{TM} microwave (Personal Chemistry/Biotage) was charged with the corresponding substrate (5 mmol), SeO_2 (6 mmol, 665 mg), 3 ml of the solvent (see Table 1), and a magnetic stirrer bar. The septum-sealed tube was irradiated with microwaves at the set temperature, which was measured by IR detection and maintained constant by modulated irradiation of 100 W to 15 W. The cooled reaction mixture was subjected to individual workup procedures. (a) Reactions in EtOH: the black selenium was filtered off, and the filtrate was evaporated to dryness to produce TLC- and NMR-pure products whose analytical data correspond to those given in the literature. (b) Reactions in HOAc: the solvent was evaporated under reduced pressure, and the solid residue extracted with dichloromethane (3 × 10 ml). After evaporation of the solvent, TLC- and NMR-pure products were obtained. (c) Reactions in water: the reaction mixture was filtered to remove the black selenium, and the filtrate was extracted with dichloromethane (3 × 10 ml). Organic and aqueous phases were evaporated to dryness in separate flasks, and the residues were analyzed by ^{1}H and ^{13}CNMR.

7,7-dimethyl-2,3-dioxo-bicyclo[2.2.1]heptane-methanesulfonamide (4): Method (c), after chromatography of the CH_2Cl_2 soluble fraction (SiO_2, CH_2Cl_2/Et_2O 9:l). Elemental analysis calculated for $C_{10}H_{15}SO_4N$: C, 48.96; H, 6.16; N, 5.71; S, 13.07; found: C, 48.19; H, 6.34; N, 5.93; S, 12.88. CI-MS: (M = 245.30) 246 $[M + H]^+$, 228 $[M - H_2O]^+$, 164 $[M - H_2O - SO_2]^+$. IR (selected bands), cm^{-1}: 3336 and 3270 s ν(NH), 1760 and 1775 s ν(C═O), 1323 and 1165 s v (SO_2). ^{1}H NMR in $CDCl_3$, δ (ppm): 1.01 (s, 3H, H-9) 1.14 (s, 3H, H-10), 1.75 (m, 1H, H-5 endo), 2.22 (m, 1H, H-6 endo), 2.25 (m, 1H, H-5 exo), 2.44 (m, 1H, H-6 exo), 2.71 (d, 5.0 Hz, 1H, H-4), 3.31 (d, 15.0 Hz, 1H, H-8), 3.67 (d, 15.0 Hz, 1H, H-8), 5.36 (s, br., 2H, NH_2). ^{13}C NMR in $CDCl_3$, δ (ppm): 18.0 (CH_3, C-10), 2.14 (CH_3, C-9), 22.3 (CH_2, C-5), 26.9 (CH_2, C-6), 44.6 (C_q, C-7), 52.9 (CH_2, C-8), 57.6 (CH, C-4), 59.6 (C_q, C-1), 200.1, 202.1 (C_q, C-2, C-3).

7,7-dimethyl-2,3-dioxo-bicyclo[2.2.1]heptane-methanesulfonic acid (6): Method (c), after crystallization from a minimum amount of H_2O. Elemental analysis calculated for $C_{10}H_{14}SO_5$: C, 48.77; H, 5.73; S, 13.02; found: C, 49.22; H, 5.96; S, 12.76. CI-MS: (M = 246.28) 247 $[M + H]^+$, 165 $[M - SO_3H]^+$. IR (selected bands), cm^{-1}: 3131 s ν(OH), 1752 and 1771 s ν(C═O), 1400, 1191, and 1051 s $\nu(SO_3)$. ^1H NMR in $CDCl_3$, δ (ppm): 0.93 (s, 3H, H-9), 1.17 (s, 3H, H-l0), 1.66 (m, 1H, H-5 endo), 1.95 (m, 1H, H-6 endo), 2.24 (m, 1H, H-5 exo), 2.65 (d, 5.2 Hz, 1H, H-4), 2.71 (m, 1H, H-6 exo), 3.00 (d, 14.8 Hz, 1H, H-8), 3.37 (d, 14.8 Hz, 1H, H-8). ^{13}C NMR in $CDCl_3$, δ (ppm): 17.9 (CH_3, C-10), 21.1 (CH_3, C-9), 22.1 (CH_2, C-5), 25.1 (CH_2, C-6), 44.0 (C_q, C-7), 46.7 (CH_2, C-8), 57.7 (CH, C-4), 59.0 (C_q, C-1), 202.0, 202.1 (C_q, C-2, C-3).

ACKNOWLEDGMENT

The authors are grateful to Personal Chemistry/Biotage for the provision of a Smith Creator™ microwave reactor and to the Nuffield Foundation for a science bursary.

REFERENCES

1. (a) Schasteen, C. S.; Reed, D. J. *Biochim. Biophys. Acta* **1983**, *742*, 412–425; (b) Meves, H.; Rubly, N.; Stampfli, R. *Biochim. Biophys. Acta* **1988**, *943*, 1–12; (c) Pearson, R. B.; Kemp, B. E. *Biochim. Biophys. Acta* **1986**, *870*, 312–319.
2. (a) Okolotowicz, K. J.; Lee, W.-J.; Hartmann, R. F.; Kim, A. Y.; Ottersberg, S. R.; Robinson, D. E., Jr.; Lefler, S. R.; Rose, S. D. *Arch Pharm.* **2001**, *334*, 194–202; (b) Rose, S. D.; Ottersberg, S. R.; Okolotowicz, K. J.; Robinson, D. E.; Hartmann, R. M. F.; Lefler, S. R. PCT Int. Appl. WO 00 33,826, 2000. *Chem. Abstr.* 133, P38221a.
3. Rabjohn, N. *Org. Rxs.* **1976**, *24*, 261–415.
4. (a) Bauer, D. P.; Macomber, R. S. *J. Org. Chem.* **1975**, *40*, 1990–1992; (b) Wasserman, H. H.; Ives, J. L. *J. Org. Chem.* **1985**, *50*, 3573–3580; (c) Jiang, Q.; Joshi, B. S.; Pelletier, S. W. *Tetrahedron Lett.* **1991**, *32*, 5283–5286.
5. Adam, G.; Zibuck, R.; Seebach, D. *J. Am. Chem. Soc.* **1987**, *109*, 6176–6177.
6. Iwahama, T.; Sakaguchi, S.; Nishiyama, Y.; Ishii, Y. *Tetrahedron Lett.* **1995**, *36*, 1523–1526.
7. Klein, B. *J. Am. Chem. Soc.* **1941**, *63*, 1474–1475.
8. Riley, H. L.; Morley, J. F.; Friend, N. A. C. *J. Chem. Soc.* **1932**, 1875–1883.
9. Dallacker, F.; Erkens, M.; Knops, C. *Chem. Ber.* **1978**, *111*, 3183–3190.
10. (a) Davis, F. A.; Kumar, A.; Chen, B. C. *J. Org. Chem.* **1991**, *56*, 1143–1145; (b) Glahsl, G.; Herrmann, R. *J. Chem. Soc., Perkin. Trans.* **1988**, *1*, 1753–1757.
11. Pande, C. S.; Pelzig, M.; Glass, J. D. *Proc. Natl. Acad. Sci. USA.* **1980**, *77*, 895–899.
12. (a) Tierney, J.; Lidström, P. (Eds.); *Microwave Assisted Organic Synthesis*; Blackwell: Oxford, UK, 2004; (b) Loupy, A (Ed.), *Microwaves in Organic*

Synthesis, Wiley/VCH: Weinheim, Germany, 2002; (c) Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225–9283.
13. Kad, G. L.; Khurana, A.; Singh, V.; Singh, J. *J. Chem. Res. Synop.* **1999**, 164–165.
14. Goswami, S.; Adak, A. K. *Synth. Commun.* **2003**, *33*, 475–480.
15. Meenakshi, C.; Ramamoorthy, V.; Muthusubramanian, S.; Sivasubramanian, S. *Synth. Commun.* **2001**, *31*, 645–651.
16. (a) For examples using TsOH see; Murdyk, B.; Cohen, T. *J. Org. Chem.* **1989**, *54*, 5657–5659; (b) Paquette, L. A.; Negri, J. T. *J. Am. Chem. Soc.* **1991**, *113*, 5072–5073.