ELSEVIER

Available online at www.sciencedirect.com

SCIENCE DIRECT®

Tetrahedron Letters 46 (2005) 39–41

Tetrahedron Letters

Microwave assisted synthesis of the fragrant compound Calone 1951®

Britta Drevermann, Anthony Lingham, Helmut Hügel* and Philip Marriott

Department of Applied Chemistry, RMIT University GPO Box 2476V Melbourne, Victoria 3001, Australia

Received 28 May 2004; revised 3 November 2004; accepted 8 November 2004

Abstract—Calone 1951®, 7-methyl-benzo[*b*][1,4]dioxepin-3-one, possesses a strong marine, ozone note with floral nuances and is synthesised via a three-step procedure using microwave irradiation. High yields were obtained, and reaction times reduced to a few minutes, allowing for an efficient and inexpensive synthesis of Calone 1951®.

Calone 1951® was discovered by Beereboom, Cameron and Stephens at Pfizer, and is a member of a family of benzodioxepinones, which share similarities in odour. Furthermore it is the only one of this group to have been commercially exploited (C.A.L. SA, Grasse, France) in perfumery.[1] An efficient synthesis of Calone 1951® was required by our group for further research into structure–odour–activity-relationships of fragrance compounds.

The utilisation of microwave irradiation in organic syntheses is becoming increasingly popular.[2] In many cases product purity and reaction times are improved when compared to conventional methods, with improvements often being attributed to reduction in latent heating times, superheating of solvents and more recently, implementation of microwave specific effects.[3,4] Current microwave protocol involves either pressure sealed vessels[5] or irradiation in open vessels under a reflux condenser, generally at atmospheric pressure. The latter method has been used for the current work.[6]

In this study, a known route has been significantly improved by utilising microwave irradiation, to provide a relatively fast and high yielding path to 7-methyl-benzo[*b*][1,4]dioxepin-3-one (**4**) from 4-methyl catechol (**1**) (Scheme 1).

We have found that microwave assisted Williamson ether synthesis of phenols,[7–9] is also applicable to catechols (**1** → **2**). Short reaction times gave impressive yields of the dietherified product (90–97%).[†,10] With conventional heating,[11] it was found that the lengthy time required at an elevated temperature favours the formation of by-products due to the facile oxidation of **1**. Alkylation using phase-transfer catalysis showed little success under both classical heating and microwave irradiation. Solvent-free conditions were also unsuccessful.[12,13] Favourable conditions for the dialkylation of **1** involved K_2CO_3 (3 equiv) in a dipolar aprotic solvent and an excess of the alkylating agent added portionwise prior to irradiation periods (2 × 2 min). DMF and DMSO both gave similar results (89–97%) on a small

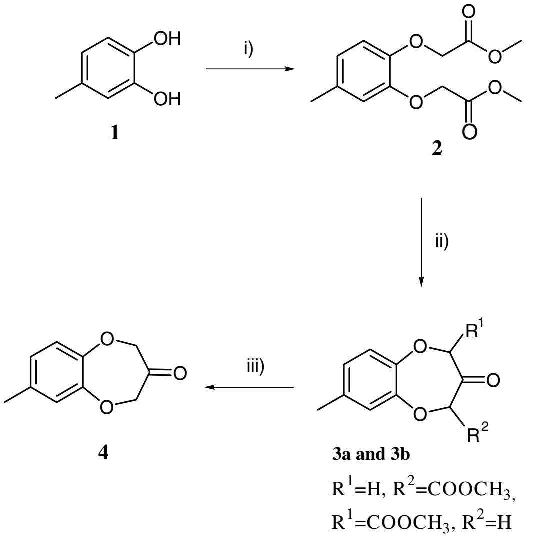
---

Keywords: Calone 1951®; Fragrant compound; Microwave irradiation.

* Corresponding author. Tel.: +61 3 9925 2626; fax: +61 3 9639 1321; e-mail: helmut.hugel@rmit.edu.au

[†] Synthesis of (2-methoxycarbonylmethoxy-4-methyl-phenoxy)-acetic acid methyl ester (**2**): Ground, oven-dried K_2CO_3 (9.0 g, 65.22 mmol) and methyl bromoacetate (6.0 mL, 64.71 mmol) were added sequentially to a solution of **1** (2.0 g, 16.13 mmol) in anhydrous DMF (100 mL). The solution was irradiated under nitrogen (2 min, 200 W) with vigorous stirring. After ambient cooling (15 min), methyl bromoacetate (2.0 mL) was added and the solution irradiated a final time (2 min, 200 W). Upon cooling (15 min), the solution was added to H_2O (200 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The organic portion was washed with 5% aqueous NaOH (2 × 50 mL) followed by distilled water (2 × 50 mL). Drying over $MgSO_4$ and concentration in vacuo resulted in a yellow oil (3.80 g), consisting of 89% **2** according to NMR and GC–MS data. The crude material was purified by vacuum column chromatography through a short silica gel column, initially washed with pentane then eluted with ethyl acetate/pentane using a 1:9–3:7 gradient. Evaporation followed by Kugelrohr distillation, (210 °C/1.0 mmHg) gave **2** as a low melting pale yellow solid (3.60 g, 83%).

0040-4039/$ - see front matter © 2004 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2004.11.045



Scheme 1. Reagents and conditions: (i) methyl bromoacetate (5 equiv), K_2CO_3 (3 equiv), DMF, 89–97%; (ii) KO^{t}Bu (2 equiv), anhydrous THF, 94–100%; (iii) 10% ethanolic/6 M HCl, 92–95%.

scale ($\geqslant$2.0 g), however DMSO proved superior to DMF upon scale-up (10 g). The results of the scale-up gave **2** in 75% and 50% yields for DMSO and DMF, respectively. These solvents are known to heat efficiently by dipole interactions under microwave irradiation, with small additional ionic heating contributed by the K_2CO_3. An excess of methyl bromoacetate was necessary, and an efficient condenser was required to prevent loss of the alkylating agent. After irradiation, cooling times exceeding 15 min encouraged decomposition, which was more prominent in DMSO than DMF. Residual DMF and alkylating agent were easily removed by flushing with pentane through a short silica column prior to bulb-to-bulb distillation. The column may not be required if the DMF and alkylating agent can be removed under sufficient reduced pressure. Compound **5** was found to be the major impurity (2–10%) (Fig. 1), with by-products **6** and **7** also present in trace amounts.

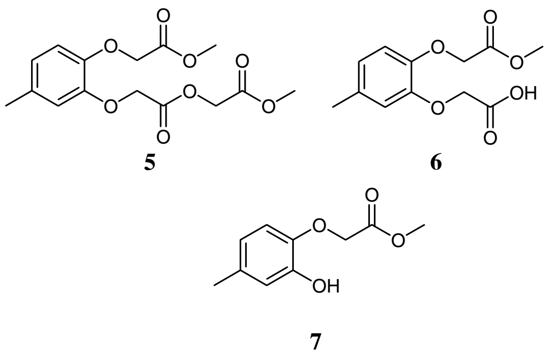
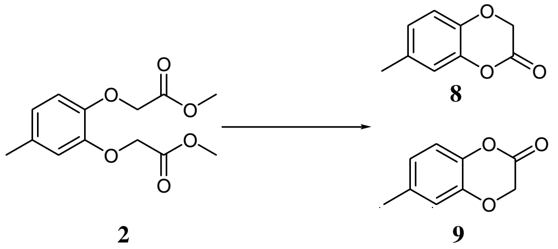


Figure 1. (2-Methoxycarbonylmethoxycarbonylmethoxy-4-methyl-phenoxy)-acetic acid methyl ester (**5**), (2-methoxycarbonylmethoxy-5-methyl-phenoxy)-acetic acid (**6**), (2-hydroxy-4-methyl-phenoxy)-acetic acid methyl ester (**7**).



Scheme 2. 6/7-Methyl-benzo[1,4]dioxin-2-one (**8** and **9**).

Dieckmann cyclisation (**2** → **3**) using conventional methods[14] proved superior to microwave heating, giving the desired product in 94% and 68% yields, respectively,[‡,15] which were obtained as a mixture of regioisomers (**3a** and **3b**) in approximately 1:1 proportions. Successful protocol involved the use of KO^{t}Bu in THF under dry conditions, with sodamide giving comparable yields. Temperatures above 70 °C encouraged the formation of by-products **8** and **9** (Scheme 2), indicated by the development of a deep red colour. These were also isolated as a 1:1 mixture of regioisomers and had a tendency to polymerise.

Hydrolysis of **3** in LiCl/H_2O/DMSO[16] followed by decarboxylation under acidic conditions provided **4** in low yield. The hydrolysis and decarboxylation were performed in a one-pot microwave reaction in ethanolic HCl, affording **4** in 93% yield.[§,17] The decarboxylation was performed promptly following work-up, or directly following purification by column chromatography or distillation, as **3** undergoes decomposition upon storage. Comparable yields were obtained by conventional heating, although reaction times were significantly longer.

In conclusion, the promising synthetic methodology proposed for the fragrant compound Calone 1951® has been achieved by performing a microwave assisted reaction sequence, improving reaction times and yields.

[‡] Synthesis of 7-methyl-3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepine-2/4-carboxylic acid methyl esters (**3a** and **3b**): Under an inert atmosphere, a solution of **2** (3.72 g, 13.88 mmol) in anhydrous THF (35 mL) was added over 5 min to KO^{t}Bu (3.11 g, 27.76 mmol) in anhydrous THF (35 mL) cooled in an ice/H_2O bath. The reaction flask was transferred to an oil bath at 70 °C for 30 min, after which time the caramel coloured solution was poured into HCl/ice (200 mL, pH 2.0) and extracted with CH_2Cl_2 (3 × 100 mL). Concentration in vacuo gave a viscous light brown oil (3.00 g), consisting of 94% **3a** and **3b** according to NMR and GC–MS data. When required, further purification involved column chromatography on silica gel (hexane/ethyl acetate, 1:1).

[§] Synthesis of 7-methyl-benzo[*b*][1,4]dioxepin-3-one (**4**): Immediately following work-up or purification of the cyclised mixture, **3** (1.00 g, 4.24 mmol) was dissolved in EtOH (10 mL). 6 M HCl (100 mL) was added and the solution irradiated with stirring (4 min, 200 W). The reaction mixture was quenched with ice/H_2O (100 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The product was dried over $MgSO_4$ and concentrated in vacuo to give a yellow resin (0.73 g) exhibiting an intense marine odour. NMR and GC–MS analysis confirmed yields of **4** ranging from 92% to 95%. The product was purified further (97–98%) by elution with Et_2O using dry column vacuum chromatography.

Acknowledgements

Financial support (B.D.) from the Faculty of Applied Science, RMIT University, is acknowledged. We also thank Michael Malcmann (Warlock Engineering) and Raymond Lingham for technical assistance and provision of microwave apparatus.

References and notes

1. Gaudin, J. U.S. Patent 5, 990, 076, Nov 23, 1999; *Chem. Abstr*. **1999**, *130*, 227560.
2. (a) Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225–9283; (b) Strauss, C. R.; Trainor, R. W. *Aust. J. Chem.* **1995**, *48*, 1665–1692.
3. Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *44*, 9199–9223.
4. Thanh, G. V.; Loupy, A. *Tetrahedron Lett.* **2003**, *44*, 9091–9094.
5. Raner, K. D.; Strauss, C. R.; Trainor, R. W.; Thorn, J. S. *J. Org. Chem.* **1995**, *60*, 2456–2460.
6. Microwave experiments were performed in a prototype microwave applicator 'MDV2.4' and 0–700 W variable power microwave source (2m172) provided on trial by Warlock Engineering: www.warlock.com.au/chemreactor.htm.
7. Bogdal, D.; Pielichowski, J.; Jascot, K. *Org. Prep. Proced. Int.* **1998**, *30*, 427–432.
8. Bogdal, D.; Pielichowski, J.; Boron, A. *First International Electronic Conference on Synthetic Organic Chemistry (ECSOC-1)* September 1–30, **1997**.
9. Li, F.; Wang, Q.; Ding, Z.; Tao, F. *Org. Lett.* **2003**, *5*, 2169–2171.
10. The structure of each compound was confirmed by ^{1}H, ^{13}C, DEPT135, COSY and HMQC NMR data.
    Spectroscopic data: **2** pale yellow solid mp 39–41 °C; ^{1}H NMR (200 MHz, CDCl$_3$): δ (in ppm): 6.82–6.67 (m, 3H), 4.71 (s, 2H), 4.69 (s, 2H), 3.80 (s, 3H), 3.78 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (50 MHz, CDCl$_3$): δ (in ppm): 169.4, 169.2, 147.5, 145.5, 132.2, 122.5, 116.0, 115.5, 66.6, 66.2, 51.8, 51.8, 20.6; EIMS parent ion 268 *m*/*z*.
11. Loupy, A.; Monteux, D.; Petit, A.; Aizpurua, J. M.; Dominguez, E.; Palomo, C. *Tetrahedron Lett.* **1996**, *37*, 8177–8180.
12. Rechsteiner, B.; Texier-Boullet, F.; Hamelin, J. *Tetrahedron Lett.* **1993**, *34*, 5071–5074.
13. Varma, R. S.; Kumar, D. *Org. Lett.* **1999**, *1*, 697–700.
14. Beereboom, J. J.; Lyme, O.; Cameron, D. P.; Stephens, C. R. U.S. Patent 3, 517, 031, June 23, 1970; *Chem. Abstr*. **1970**, *73*, 56143.
15. A regioselective outcome was not required since subsequent decarboxylation of both isomers led to **4**. Hence, separation of regioisomers **3a** and **3b** was not pursued. Assignment of methylene protons was achieved through COSY and HMQC correlations.
    Spectroscopic data: **3a** and **3b** (isomeric mixture) viscous light brown oil; ^{1}H NMR (200 MHz, CDCl$_3$): δ (in ppm): 7.00–6.69 (m, 3H), 7.00–6.69 (m, 3H), 5.32 (s, 1H), 5.31 (s, 1H), [**3a**: 4.77–4.71 (d, $J = 16.7$ Hz, 1H), 4.54–4.49 (d, $J = 16.6$ Hz, 1H)], [**3b**: 4.74–4.68 (d, $J = 16.9$ Hz, 1H), 4.52–4.47 (d, $J = 17.0$ Hz, 1H)], 3.84 (s, 3H), 3.84 (s, 3H), 2.27 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (50 MHz, CDCl$_3$): δ (in ppm): 199.7, 199.6, 165.5, 165.5, 147.0, 146.6, 145.0, 144.8, 135.1, 133.7, 125.6, 124.2, 121.7, 121.2, 120.7, 120.3, 82.1, 81.8, 77.0, 76.6, 52.9, 52.9, 20.7, 20.6; EIMS parent ion 236 *m*/*z*.
16. Paquette, L. A.; Wang, H. *J. Org. Chem.* **1996**, *61*, 5352–5356.
17. Spectroscopic data: **4** yellow resin; ^{1}H NMR (200 MHz, CDCl$_3$): δ (in ppm): 6.93–6.71 (m, 3H), 4.72 (s, 2H), 4.67 (s, 2H), 2.29 (s, 3H); ^{13}C NMR (50 MHz, CDCl$_3$): (in ppm): 204.9, 147.9, 145.9, 133.7, 124.3, 121.1, 120.6, 75.7, 75.4, 20.5; EIMS parent ion 178 *m*/*z*.