Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 8183–8185
Tetrahedron Letters

Sequential Birch reduction–allylation and Cope rearrangement of *o*-anisic acid derivatives

William P. Malachowski* and Marisha Banerji

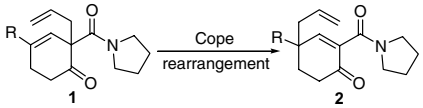
Department of Chemistry, Bryn Mawr College, Bryn Mawr, PA 19010-2899, USA

Received 6 August 2004; revised 2 September 2004; accepted 3 September 2004
Available online 21 September 2004

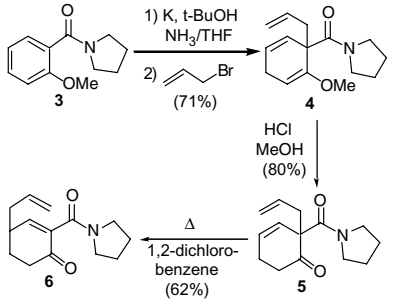
Abstract—A new method for the construction of quaternary centers on cycloalkane rings is reported. The Cope rearrangement of 4-methyl-2-allyl-2-(*N*-pyrrolidinyl)-carboxamide-3-cyclohexenone yields 4-methyl-4-allyl-2-(*N*-pyrrolidinyl)-carboxamide-2-cyclohexenone in high yield. The rearrangement substrates are easily generated from Birch reduction–allylation of *o*-anisic acid derivatives.

The synthesis of carbocyclic quaternary centers remains the focus of considerable effort in the synthetic chemistry community due to the considerable challenge presented by their construction.[1] We were intrigued by the possibility that a quaternary center could be formed via the Cope rearrangement[2] of a cycloalkenone such as compound **1** (Scheme 1). We anticipated that the thermal equilibration of the rearrangement reaction would favor the conjugated dicarbonyl system. Surprisingly, there are no reports of Cope rearrangement in simple cyclohexenone systems and there are only two previous examples[3] of quaternary carbon construction on a monocycloalkane.

The requisite 2-acyl-3-cyclohexenone derivatives are easily synthesized via Birch reduction–allylation of *o*-anisic acid derivatives.[4] Therefore, the first test of the proposition was undertaken with the *o*-anisic acid derivative,



Scheme 1. Quaternary center synthesis on a cycloalkenone via Cope rearrangement.



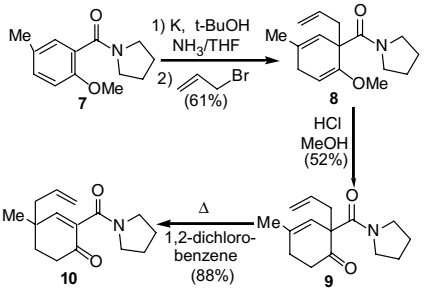
Scheme 2. Birch reduction–allylation and Cope rearrangement of *N*-pyrrolidinyl 2-methoxybenzamide.

N-pyrrolidinyl 2-methoxybenzamide[5] (**3**, Scheme 2). Birch reduction of **3** with potassium in the presence of *tert*-butanol, followed by the addition of allyl bromide afforded **4**. The enol ether was hydrolyzed to generate the 3-cyclohexenone **5**,[6,7] which has one 1,5-diene system. After exploring a variety of thermal conditions, we found that heating at reflux in 1,2-dichlorobenzene lead to good yields of 2-cyclohexenone product **6**.[8]

To test the potential of the current methodology to generate a quaternary center on a cyclohexenone skeleton, *N*-pyrrolidinyl 2-methoxy-5-methylbenzamide **7**[9] was similarly subjected to Birch reduction–allylation (Scheme 3). Reduction with potassium in the presence of *tert*-butanol, followed by reaction with allyl bromide provided **8**. Hydrolysis afforded the β-ketoamide **9**,[10] which was subjected to the identical thermal conditions

Keywords: Cope rearrangement; [3,3]-Sigmatropic rearrangement; Birch reduction–allylation; Quaternary carbon synthesis.
* Corresponding author. Tel.: +1 610 526 5016; fax: +1 610 526 5086; e-mail: wmalacho@brynmawr.edu

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.09.025



Scheme 3. Birch reduction–allylation and Cope rearrangement of *N*-pyrrolidinyl 2-methoxy-5-methylbenzamide.

as used for **3** to afford an excellent yield of the rearranged product **10**.[11]

It is apparent that Birch reduction–allylation can be combined with Cope rearrangement to create a powerful tool for the construction of substituted 2-cyclohexenones, a potentially versatile synthetic intermediate.[12] Most notably, the Cope rearrangement of **9** afforded a new quaternary center in **10** in excellent yield. This represents the first example of quaternary carbon synthesis on a cycloalkenone ring by a Cope rearrangement process. When combined with the reported stereocontrol of the Birch reduction–alkylation reaction of *o*-anisic acid derivatives,[13] the Cope rearrangement will also result in 1,3-chirality transfer and access to enantiomerically pure products.

Representative experimental procedure for the thermal Cope rearrangement: Diene **9** (105 mg) was dissolved in 1,2-dichlorobenzene (3 mL) and heated to reflux temperature overnight. Upon cooling, the solvent was removed in vacuo and the residue purified by silica gel column chromatography (eluted with 1:1 hexanes/EtOAc) to provide the white crystalline product, **10**[11] (92 mg, 88%).

Acknowledgements

The authors are grateful for the financial support of Bryn Mawr College. Manuscript review and helpful discussions with Prof. Douglass F. Taber of the University of Delaware are also acknowledged.

References and notes

1. For a few recent examples see: (a) Wolckenhauer, S. A.; Rychnovsky, S. D. *Org. Lett.* **2004**, *6*, 2745; (b) Kerr, M. S.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 8876; For recent reviews see: (c) Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105; (d) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591; (e) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388; (f) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037.
2. (a) Cope, A. C.; Hardy, E. M. *J. Am. Chem. Soc.* **1940**, *62*, 441; For reviews of the Cope rearrangement, see: (b) Nubbemeyer, U. *Synthesis* **2003**, *7*, 961; (c) Hill, R. K. Cope, Oxy-Cope and Anionic Oxy-Cope Rearrangements In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford; Vol. 5, Chapter 7.1; (d) Rhoads, S. J.; Raulins, N. R. *Org. React.* **1975**, *22*, 1.
3. One example involves cyclohexadienone rearrangement: (a) Miller, B. *J. Am. Chem. Soc.* **1965**, *87*, 5115; (b) Miller, B. *J. Am. Chem. Soc.* **1970**, *92*, 6246; (c) Miller, B. *J. Org. Chem.* **1970**, *35*, 4262; The second example involves the rearrangement of methylenecyclooctene: (d) Buchanan, G. L.; McKillop, A.; Raphael, R. A. *J. Chem. Soc.* **1965**, 833.
4. For reviews of Birch reduction–alkylation chemistry see: (a) Rabideau, P. W.; Marcinow, Z. *Org. React.* **1992**, *42*, 1; (b) Mander, L. N. Partial Reduction of Aromatic Rings by Dissolving Metals and by Other Methods. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 8, Chapter 3.4.
5. *N*-Pyrrolidinyl 2-methoxybenzamide, **3**, was synthesized from *o*-anisic acid by conversion to the acid chloride and reaction with pyrrolidine. The product matched the spectroscopic data previously reported in: Katrizky, A. R.; He, H.-Y.; Suzuki, K. *J. Org. Chem.* **2000**, *65*, 8210.
6. Compound **5**: ^{1}H NMR ($CDCl_3$): δ 5.99 (d, 1H, $J = 10$ Hz), 5.88–5.76 (m, 1H), 5.64 (d, 1H, $J = 10$ Hz), 5.04 (s, 1H), 4.99 (d, 1H, $J = 7$ Hz), 3.47 (br s, 2H), 3.26 (br s, 1H), 3.03 (br s, 1H), 2.74–2.59 (m, 2H), 2.58–2.45 (m, 4H), 1.78 (br s, 4H) ppm. ^{13}C NMR ($CDCl_3$): δ 207.9, 168.1, 134.1, 128.8, 127.3, 118.0, 61.4, 47.3, 46.0, 41.7, 37.2, 26.4, 25.8, 23.4 ppm. IR ($CDCl_3$): 2980, 1710, 1619, 1420 cm^{-1}. Mp = 50.5–52.5 °C. EIMS *m/z* (relative intensity) 233 (M+, 13), 177 (26), 164 (14), 98 (100). GC retention time: 15.74 min.[7]
7. All new compounds were pure as determined by a combination of NMR, GC, and, where applicable, melting point. GC analyses were performed on an Agilent 6890 gas chromatograph with an EIMS detector fitted with a 30 m × 0.25 mm column filled with crosslinked 5% PH ME siloxane (0.25 μm film thickness); gas pressure: 7.63 psi He. The method for analysis of all samples involved heating from 50 to 150 °C (10 °C/min), then from 150 to 260 °C (5 °C/min) and finally holding at 260 °C for 2 min.
8. Compound **6**: ^{1}H NMR ($CDCl_3$): δ 7.02 (s, 1H), 5.84–5.73 (m, 1H), 5.15 (s, 1H), 5.11–5.09 (m, 1H), 3.54 (t, 1H, $J = 6$ Hz), 3.31–3.18 (m, 2H), 2.64–2.53 (m, 2H), 2.49–2.37 (m, 1H), 2.27 (t, 2H, $J = 7$ Hz), 2.18–2.09 (m, 1H), 1.93–1.86 (m, 4H), 1.84–1.69 (m, 1H) ppm. ^{13}C NMR ($CDCl_3$): δ 195.3, 165.6, 152.6, 138.9, 134.7, 117.8, 47.6, 45.5, 38.5, 37.0, 35.7, 28.2, 25.8, 24.3 ppm. IR ($CDCl_3$) 2980, 1682, 1618, 1469, 1382 cm^{-1}. EIMS *m/z* (relative intensity) 233 (M+, 15), 191 (10), 123 (12), 98 (17), 70 (100). GC retention time: 18.57 min.[7]
9. *N*-Pyrrolidinyl 2-methoxy-5-methylbenzamide, **7**, was synthesized from 5-methylsalicylate by dimethylation and saponification to make 2-methoxy-5-methyl-benzoic acid. Conversion of the acid to the acid chloride and reaction with pyrrolidine afforded **5**, which matched the previously reported spectroscopic data in: Hart, D. J.; Havas, F. *C. R. Acad. Sci., Ser. IIc: Chim.* **2001**, *4*, 591.
10. Compound **9**: ^{1}H NMR ($CDCl_3$): δ 5.87–5.73 (m, 1H), 5.34 (s, 1H), 5.02 (s, 1H), 4.98 (d, 1H, $J = 6$ Hz), 3.47 (br s, 2H), 3.22 (br s, 1H), 3.03 (br s, 1H), 2.71–2.58 (m, 2H), 2.58–2.48 (m, 2H), 2.46–2.40 (m, 2H), 1.80 (s, 7H) ppm. ^{13}C NMR ($CDCl_3$): δ 208.3, 168.6, 135.5, 134.4, 123.2, 117.8, 60.9, 47.3, 45.9, 41.8, 37.0, 30.4, 26.4, 23.3, 22.9 ppm. IR ($CDCl_3$) 2979, 1709, 1619, 1417 cm^{-1}. Mp = 33.5–34.5 °C. EIMS *m/z* (relative intensity) 247 (M+, 10), 191 (57), 178 (13), 98 (100). GC retention time: 16.44 min.[7]
11. Compound **10**: ^{1}H NMR ($CDCl_3$): δ 6.75 (s, 1H), 5.80–5.68 (m, 1H), 5.12–5.04 (m, 1H), 3.48 (t, 2H, $J = 7$ Hz), 3.17 (t, 2H, $J = 5.5$ Hz), 2.48 (t, 2H, $J = 6.5$ Hz), 2.20 (d,

2H, $J = 7.5$ Hz), 2.07–1.90 (m, 1H), 1.88–1.82 (m, 4H), 1.81–1.72 (m, 1H), 1.15 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ 195.1, 165.4, 156.3, 137.1, 132.8, 119.0, 47.5, 45.4, 44.9, 35.7, 34.0, 33.1, 25.7, 24.3, 24.2 ppm. IR ($CDCl_3$) 2978, 1682, 1620, 1444 cm^{-1}. Mp = 71–73 °C. EIMS *m/z* (relative intensity) 247 (M+, 10), 206 (16), 178 (37), 165 (44), 137 (23), 70 (100). GC retention time: 18.76 min.[7]

12. For an example of conjugate addition to a similar 2-cyclohexenone system, see: (a) Schultz, A. G.; Lee, H. *Tetrahedron Lett.* **1992**, *33*, 4397; (b) Schultz, A. G.; Harrington, R. E. *J. Am. Chem. Soc.* **1991**, *113*, 4926.
13. (a) Schultz, A. G. *Chem. Commun.* **1999**, 1263; (b) Schultz, A. G. *Acc. Chem. Res.* **1990**, *23*, 207; (c) Schultz, A. G.; Macielag, M.; Sundararaman, P.; Taveras, A. G.; Welch, M. *J. Am. Chem. Soc.* **1988**, *110*, 7828.