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Tetrahedron Letters 45 (2004) 1457–1459
Tetrahedron Letters

Tandem Diels–Alder reaction/radical cyclizations for the rapid construction of bridged ring systems

George A. Kraus* and Junwon Kim

Department of Chemistry, Iowa State University, 2759 Gilman Hall, Ames, IA 50011, USA

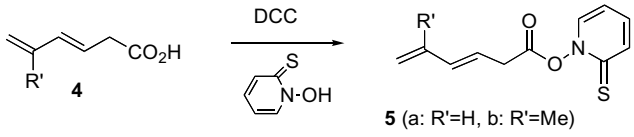
Received 8 October 2003; revised 8 December 2003; accepted 9 December 2003

Abstract—Bridged tricyclic ring systems can be prepared in a one-pot reaction using a tandem Diels–Alder reaction/radical cyclization strategy. The regiochemistry of the radical addition is unexpected.

Tandem reaction chemistry has been frequently utilized in the synthesis of polycyclic molecules. While there are many applications of tandem reactions to fused systems,[1] there are few applications of tandem reactions to bridged ring systems. Except for examples using a furan as the diene, the use of a Diels–Alder reaction in tandem with a radical cyclization has not been reported.[2] We describe herein a novel tandem Diels–Alder reaction/radical cyclization strategy for the construction of bridged tricyclic ring systems.

The general plan is to react a suitable diene with an activated quinone[3–5] to produce intermediate **1**. The group G in the resulting *endo*-Diels–Alder adduct could then give rise to a radical, which could cyclize to form tricyclic system **2** or **3** (Fig. 1).

Although the dienes with G = Br or OC(S)SMe were easily prepared from the corresponding alcohol,[6] they afforded poor yields in the Diels–Alder step. Fortunately, the dienes **5a** and **5b**, wherein G was a Barton thiopyridyl ester,[7] were stable enough to undergo successful cycloadditions at ambient temperature.



Cycloaddition followed by irradiation of the adduct using a 275 W sunlamp at 0 °C generated the tricyclic diketone **6**.[8,9] The reactions of dienes **5a** and **5b** with various quinones are listed below (Schemes 1 and 2).

The cycloaddition proceedes well with quinones bearing an electron withdrawing substituent. Desulfurization of the adduct using Raney nickel in ethanol[10] produced the product in modest yield. However, reduction of **6a** with tributyltin hydride[11] afforded product **7** in 88% yield.

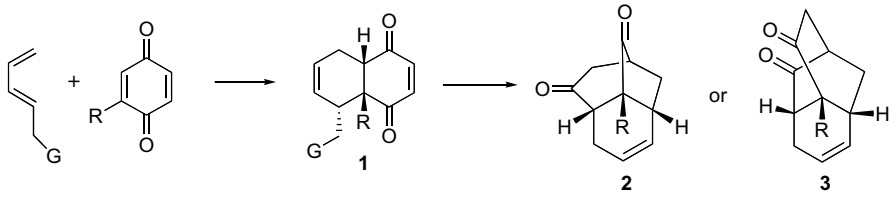


Figure 1.

* Corresponding author. Tel.: +1-515-2947794; fax: +1-515-2940105; e-mail: gakraus@iastate.edu

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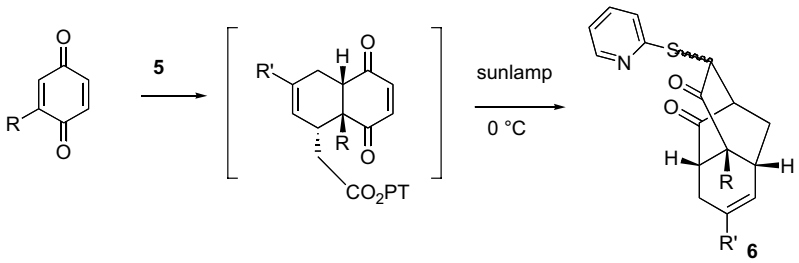
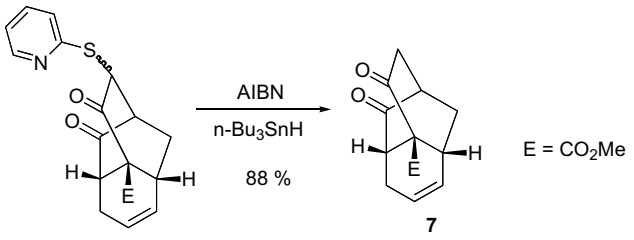
doi:10.1016/j.tetlet.2003.12.039



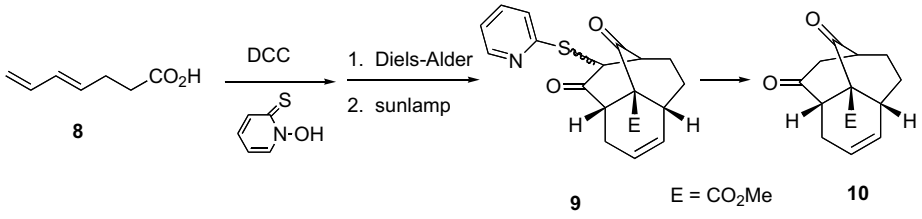
Scheme 1. Reagents and conditions: (a) R = CO_2Me, R′ = H 73%; (b) R = CO_2Me, R′ = Me 57%; (c) R = COMe, R′ = H 55%; (d) R = COMe, R′ = Me 75%.



Scheme 2.

The regiochemistry of **7** was confirmed by an X-ray structure determination. The regiochemistry of radical attack by a 6-*endo*-trig pathway is unexpected and may reflect a reversible radical addition.

In view of the unexpected results with dienes **5a** and **5b**, we also synthesized known diene **8**[12] and reacted its thiopyridyl ester with carbomethoxybenzoquinone at ambient temperature followed by irradiation with a sunlamp at 0 °C. Tricyclic diketone **9** was produced in 61% yield. The regiochemistry of **9** was confirmed by an X-ray structure determination of the desulfurized product **10**.[13] Interestingly, this radical preferred the opposite regioselectivity.



The reaction of dienes with quinones provides a convenient entry to bridged bicyclic systems from readily available starting materials.

Acknowledgements

We thank NIH grant ES12020 for partial support of this research.

References and notes

1. Winkler, J. D. *Chem. Rev.* **1996**, *96*, 167–176.
2. Finch, H.; Harwood, L. M.; Robertson, G. M.; Sewell, R. C. *Tetrahedron Lett.* **1989**, *30*, 2585–2588; Ghosh, T.; Hart, H. *J. Org. Chem.* **1989**, *54*, 5073–5085.
3. Kraus, G. A.; Taschner, M. J. *J. Org. Chem.* **1980**, *45*, 1174; Kraus, G. A.; Yue, S.; Sy, J. *J. Org. Chem.* **1985**, *50*, 283; Kraus, G. A.; Woo, S. H. *J. Org. Chem.* **1986**, *51*, 114; Kraus, G. A.; Zhao, G. *Synlett* **1995**, 541.
4. Brimble, M. A.; Elliott, R. J. R. *Tetrahedron* **1997**, *53*, 7715–7730.
5. Evans, D. A.; Wu, J. *J. Am. Chem. Soc.* **2003**, *125*, 10162–10163; Heckrodt, T. J.; Mulzer, J. *J. Am. Chem. Soc.* **2003**, *125*, 4680–4681; White, J. D.; Choi, Y. *Helv. Chim. Acta* **2002**, *85*, 4306–4327; Carlini, R.; Higgs, K.; Older, C.; Randhawa, S.; Rodrigo, R. *J. Org. Chem.* **1997**, *6*, 2330–2331; Jarvo, E. R.; Boothroyd, S. R.; Kerr, M. A. *Synlett* **1996**, 897–899.
6. Mori, K. *Tetrahedron* **1974**, *30*, 3807.
7. Ling, T.; Poupon, E.; Rueden, E. J.; Theodorakis, E. A. *Org. Lett.* **2002**, *4*, 819–822; Barton, D. H. R.; Sas, W. *Tetrahedron* **1990**, *46*, 3419–3430; Barton, D. H. R.; Bridon, D.; Zard, S. Z. *Tetrahedron* **1987**, *43*, 5307–5314.
8. General procedure: A solution of 3,5-hexadienoic acid (222 mg, 1.98 mmol) in dry CH_2Cl_2 (4 mL) was added dropwise to a stirred solution of 2-mercaptopyridine *N*-oxide (252 mg, 1.98 mmol) and DCC (417 mg, 2.02 mmol) in dry CH_2Cl_2 (5 mL) at 0 °C in the dark (Al foil) under an argon atmosphere. After 4 h at 0 °C, the resultant orange suspension was filtered through a short pad (ca. 4 cm) of silica gel (prepacked with CH_2Cl_2) to remove dicyclohexylurea and washed with CH_2Cl_2 (300 mL). The filtrate was concentrated at 25 °C to give the diene **5** (440 mg, 99%) as a red oil. A solution of diene **5** (474 mg, 2.14 mmol) and 2-(methoxycarbonyl)-1,4-benzoquinone (391 mg, 2.35 mmol) in dry CH_2Cl_2 (10 mL) was placed in a flask protected from the light with aluminum foil at rt. After 24 h at rt, the solution was diluted with CH_2Cl_2 (10 mL) and degassed with Ar for 10 min. The reaction was exposed to light using 275 W sunlamp from a

distance of 15 cm, while maintaining the temperature at 0 °C. After 2 h at 0 °C, the reaction mixture was concentrated and purified using sgc (hexane/Et_2O = 10:1 to 1:1) to give tricyclic diketone **6a** (538 mg, 73%) as a yellow foam.

9. Spectra for **7**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86–5.82 (m, 1H), 5.59 (dd, 1H, $J = 9.6$, 2 Hz), 3.79 (s, 3H), 3.24 (t, 1H, $J = 9.2$ Hz), 3.04 (d, 1H, $J = 6$ Hz), 2.82 (br s, 1H), 2.68–2.54 (m, 3H), 2.35 (br d, 1H, $J = 18.8$ Hz), 2.14 (t, 1H, $J = 12.8$ Hz), 1.88 (br d, 1H, $J = 13.2$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.8, 207.2, 169.4, 129.7, 124.5, 61.4, 52.7, 44.1, 43.5, 40.9, 30.3; 30.4; 25.3; R_f (hexane/EtOAc 2:1) = 0.36; HRMS m/e (EI) for $C_{13}H_{14}O_4$ $(M)^+$ calcd 234.0892, measured 234.0897. Spectra for **10**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81–5.76 (m, 1H), 5.60 (dt, 1H, $J = 10$, 3.6 Hz), 3.79 (s, 3H), 3.43 (d, 1H, $J = 7.6$ Hz), 3.19–3.14 (m, 1H), 3.07–3.05, 3.02–3.01 (m, 1H), 2.97–2.91 (m, 2H), 2.76 (dd, 1H, $J = 18.8$, 3.6 Hz), 2.17–2.14, 2.12–2.10 (m, 1H), 2.06–2.02 (m, 2H), 1.98–1.91 (m, 1H), 1.51–1.39 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.5, 205.9, 170.4, 128.9, 124.9, 61.8, 52.9, 48.9, 46.4, 45.9, 40.3, 32.7, 26.1, 21.7; R_f (hexane/EtOAc 2:1) = 0.43; HRMS m/e (EI) for $C_{14}H_{16}O_4$ $(M)^+$ calcd 248.1049, measured 248.1051.
10. Takahashi, T.; Iyobe, A.; Arai, Y.; Koizumi, T. *Synthesis* **1989**, 189–191.
11. Barton, D. H. R.; Camara, J.; Cheng, X.; Gero, S. D.; Jaszberenyi, J. C.; Quiclet-Sire, B. *Tetrahedron* **1992**, *48*, 9261–9276.
12. Baillie, L. C.; Batsanov, A.; Bearder, J. R.; Whiting, D. A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3471–3478.
13. We have submitted the X-ray data for both compounds to the Cambridge Database.