High-intensity ultrasound-promoted Reformatsky reactions of pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8,11-dione

Nathan A. Ross,[a] Richard A. Bartsch,*[a] and Alan P. Marchand*[b]

[a] Department of Chemistry and Biochemistry, Texas Tech University, Lubbock, Texas 79409-1061 U. S. A. and [b]Department of Chemistry, University of North Texas,
Denton, Texas 76203-5070
E-mail: richard.bartsch@ttu.edu , marchand@unt.edu

Dedicated to Professor Henry J. Shine on the occasion of his 80th birthday

(received 23 May 03; accepted 06 June 03; published on the web 13 June 03)

Abstract
Reformatsky reactions of pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8,11-dione (1) with ethyl bromoacetate and ethyl difluorobromoacetate have been performed in the presence zinc dust and iodine in dioxane under irradiation by high-intensity ultrasound (HIU). In each case, addition of one equivalent of the organozinc reagents occurs with concomitant intramolecular hemiacetal formation, thereby affording 3a (75% yield) and 3b (89% yield), respectively.

Keywords: Pentacyclic cage diketone, Reformatsky reaction, high-intensity ultrasound

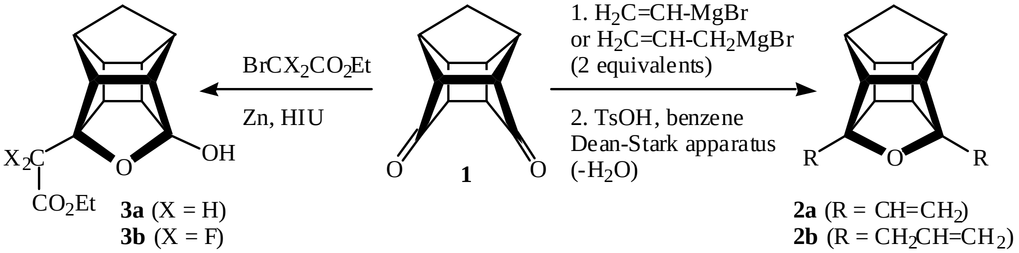
---

Introduction

Our respective research groups have held a long-standing interest in the design and construction of novel macrocyclic host systems.[1,2] In this connection, the University of North Texas research team has utilized Grignard reactions of pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8,11-dione (1)[3] to prepare precursors to cage-annulated podands (e.g., systems of the type 2, Scheme 1) that have been used extensively to construct a wide variety of cage-annulated macrocycles.[2.4]

Efforts currently are underway to develop new approaches to sodium hydroxide extraction that utilize proton-ionizable fluorinated alcohols to effect pseudo-hydroxide extraction.[5] Thus, it was of interest to develop a method by which a fluorinated alcohol moiety might be introduced into cage-annulated podands of the type 2 (Scheme 1).

We elected to use an approach based upon the familiar Reformatsky reaction for this purpose.[6] Recently, the Texas Tech University research team has demonstrated that high-energy ultrasound (HIU)-promoted Reformatsky reactions offer several advantages over conventional thermal methods.[7,8] Herein, we report the results of HIU-promoted Reformatsky reactions of 1 with ethyl bromoacetate and also with ethyl difluoroacetate.



Scheme 1

Results and Discussion

Reformatsky reactions of pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8,11-dione (1) with ethyl bromoacetate and ethyl difluorobromoacetate were performed in the presence zinc dust and iodine in dioxane under irradiation by high-intensity ultrasound (HIU).[7,8] In each case, addition of one equivalent of the organozinc reagents occurs with concomitant intramolecular hemiacetal formation, thereby affording 3a (75% yield) and 3b (89% yield), respectively (Scheme 1).

Cage dione 1 was first prepared by Cookson and coworkers in 1958.[9] Since that time, the chemistry of this interesting and unusual cage diketone has been studied extensively.[10] Transannular interactions occur commonly in this system; thus, reversible hemiacetal formation at the C(11) carbonyl group frequently accompanies reactions that involve nucleophilic attack at the C(8) carbonyl group.[11]

Although addition of two equivalents of Grignard reagents to the C(8) and C(11) carbonyl groups in 1 has been achieved,[2,4] in the present study we were not able to develop conditions whereby 1 could be induced to reaction with a second equivalent of organozinc reagent. Indeed, all efforts to promote addition of a second equivalent of the bromoester to 3a and 3b, respectively, were not successful.

Experimental Section

Melting points are uncorrected.

General procedure for Reformatsky reactions of pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}] undecane-8,11-dione (1) conducted under irradiation by high intensity ultrasound (HIU). The apparatus for generating HIU irradiation, the sonochemical reaction flask, and sources of reagents were the same as described previously.[7,8] A 25-mL, four-armed sonochemical reaction flask capped with rubber septa was flushed with nitrogen for several minutes. Zinc dust (1.18 g, 18 mmol, 3.6 equiv) and iodine (0.50 g, 2 mmol, 0.4 equiv) were added, followed by dioxane (7.5 mL). Compound 1 (870 mg, 5.0 mmol) and the appropriate ethyl ester (15 mmol, 3.0 equiv) were added, followed by dioxane (7.5 mL). The flask was attached to the ultrasonic probe, and the lower portion was immersed in a 1:1 ethylene glycol-water constant temperature bath maintained at 20 °C. The reaction mixture was sonicated for 5 minutes in a 6-sec pulse mode. The flask was detached from the probe, and the reaction mixture was poured into a beaker that contained distilled water-ice (200 mL). The resulting mixture was transferred to a 1 L separatory funnel. The beaker was rinsed with 2% aqueous HCl (100 mL), and the rinsings were added to the separatory funnel. The sonochemical flask was rinsed with CH_2Cl_2, and these rinsings also were added to the separatory funnel. The mixture in the separatory funnel was extracted with CH_2Cl_2 (2 × 200 mL). The combined CH_2Cl_2 layers were dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. The residue was dried *in vacuo*, and the crude product was purified by column chromatography.

Reformatsky reaction of 1 with ethyl bromoacetate. Chromatography of the crude reaction product on silica gel by eluting with 20% EtOAc-hexane afforded pure 3a (980 mg, 75%) as a colorless oil; IR (film) 3446 (br, OH), 1756 (C=O) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.26 (t, 3 H, J = 7 Hz), 1.54 (AB, 1 H, J_{AB} = 10.5 Hz), 1.88 (AB, 1 H, J_{AB} = 10.5 Hz), 2.43-2.47 (m, 2 H), 2.58-2.67 (m, 4 H), 2.72-2.87 (m, 3 H), 4.14 (q, 2 H, J = 7 Hz), 4.52 (s, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 38.4, 41.8, 41.9, 43.2, 43l7, 45.0, 47.4, 48.1, 57.6, 58.4, 60.5, 66.9, 88.8, 118.2, 170.2. Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.89; H, 6.73.

Reformatsky reaction of 1 with ethyl difluorobromoacetate. Chromatography of the crude reaction product on silica gel by eluting with 20% EtOAc-hexane afforded pure 3a (1.33 g, 89%) as a colorless oil; IR (film) 3405 (br, OH), 1768 (C=O) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.36 (t, 3 H, J =7 Hz), 1.58 (AB, 1 H, J_{AB} = 10.5 Hz), 1.93 (AB, 1 H, J_{AB} = 10.5 Hz), 2.52-2.58 (br t, 1 H), 2.61-2.76 (m, 3 H), 2.76-2.83 (m, 1 H), 3.09 (m, 1 H), 3.18-3.24 (m, 1 H), 4.34 (q, 2 H, J = 7 Hz), 4.48 (s, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 13.6, 13.8, 25.4, 41.8, 53.1, 43.3, 44.9, 45.5, 54.9, 63.0, 64.2, 67.8, 90.5, 119.9, 159.3. Anal. Calcd for $C_{15}H_{16}F_2O_4$: C, 60.40; H, 5.41. Found: C, 60.15; H, 5.53.

Acknowledgments

We thank The Robert A. Welch Foundation [Grants D-0775 (R. A. B.) and B-0963 (A. P. M.)] and the Division of Chemical Sciences, Office of Basic Energy Sciences of the U. S. Department of Energy [DE-FG07-98ER14936 (A. P. M.)] for financial support of the study reported herein.

References

1. (a) Aguilar, J. C.; Miguel, E. R. d. S.; de Gyves, J.; Bartsch, R. A.; Kim, M. *Talanta* **2001**, *54*, 1195. (b) Tong, A.-J.; Song, Y.-S.; Li, L.-D.; Hayashita, T.; Teramae, N.; Park, C.; Bartsch, R. A. *Analytica Chim. Acta* **2000**, *420*, 57. (c) Batinic-Haberle, I.; Spasojevic, I.; Jang, Y.; Bartsch, R. A.; Crumbliss, A. L. *Inorg. Chem.* **1998**, *37*, 1438.
2. Marchand, A. P.; Kumar, K. A.; McKim, A. S.; Alihodzic, S.; Chong, H.-S.; Krishnudu, K.; Takhi, M.; Mlinaric-Majerski, K.; Kragol, G.; Sumanovac, T. *Kem. Ind.* **2001**, *50*, 129.
3. (a) Marchand, A. P. In *Advances in Theoretically Interesting Molecules*; Thummel, R. P., Ed.; JAI: Greenwich, CT, Vol. 1, 1989, pp 357-399. (b) Marchand, A. P.; Allen, R. W. *J. Org. Chem.* **1974**, *39*, 1596.
4. (a) Marchand, A. P.; Cal, D.; Mlinaric-Majerski, K.; Ejsmont, K.; Watson, W. H. *J. Chem. Crystallogr.* **2002**, *32*, 447. (b) Hayashita, T.; Higuchi, T.; Sawano, H.; Marchand, A. P.; Kumar, K. A.; Bott, S. G.; Mlinaric-Majerski, K.; Sumanovac, T.; Elkarim, N. S.; Hwang, H.-S.; Talanova, G.; Bartsch, R. A. *Talanta* **2000**, *52*, 385. (c) Marchand, A. P.; Kumar, K. A.; McKim, A. S.; Mlinaric-Majerski, K.; Kragol, G. *Tetrahedron* **1997**, *53*, 3467.
5. (a) Levistskaia, T. G.; Moyer, B. A.; Bonnesen, P. V.; Marchand, A. P.; Krishnudu, K.; Chen, Z.; Huang, Z.; Kruger, H. G.; McKim, A. S. *J. Am. Chem. Soc*. **2001**, *123*, 12099. (b) Moyer, B. A.; Bonnesen, P. V.; Chambliss, C. K.; Haverlock, T. J.; Marchand, A. P.; Chong, H.-S.; McKim, A. S.; Krishnudu, K.; Ravikumar, K. S.; Kumar, V. S.; Takhi, M. In: Eller, P. G.; Heineman, W. R., Eds., *Nuclear Site Remediation: First Accomplishments of the Environmental Science Program*, ACS Symposium Series, Vol. 778, American Chemical Society: Washington, DC, 2001, pp 114-132.
6. For a review of the Reformatsky reaction, see: Rathke, M. W. In *Organic Reactions*, Dauben, W. G., Ed.; Wiley: New York, 1975; Vol. 22, pp 423-458.
7. N. A. Ross and R. A. Bartsch, *J. Heterocyclic Chem.* **2001**, *38*, 1255.
8. N. A. Ross and R. A. Bartsch, *J. Org. Chem.* **2003**, *68*, 360.
9. Cookson, R. C.; Crundwell, E.; Hudec, J. *Chem. Ind. (London)* **1958**, 1003.
10. (a) Cookson, R. C.; Crundwell, E.; Hill, R. R.; Hudec, J. *J. Chem. Soc.* **1964**, 3062. (b) Marchand, A. P. In *Advances in Theoretically Interesting Molecules*; Thummel, R. P., Ed.; JAI: Greenwich, CT, 1989; Vol. 1, pp 357-399. (c) Mehta, G.; Srikrishna, A.; Reddy, A. Veera; Nair, Mangalam S. *Tetrahedron* **1981**, *37*, 4543.
11. Marchand, A. P.; Keith, J. M.; Alihodzic, S.; Ganguly, B.; Somers, A. W.; Hariprakasha, H. K.; Power, T. D.; Watson, W. H.; Bodige, S. G. *Struct. Chem*. **2001**, *12*, 313-322.