Tetrahedron Letters 49 (2008) 7311–7314

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Free radical ring expansion and spirocyclization of 1,3-diketone derivatives

Wei Xu [a], Jian-Ping Zou [a,*], Xue-Jun Mu [a], Wei Zhang [b,*]

[a] Key Laboratory of Organic Synthesis of Jiangsu Province, College of Chemistry and Chemical Engineering, Suzhou University, 199 Renai Street, Suzhou, Jiangsu 215123, China
[b] Department of Chemistry, University of Massachusetts Boston,100 Morrissey Boulevard, Boston, MA 02125, USA

ARTICLE INFO

Article history:
Received 20 September 2008
Accepted 8 October 2008
Available online 14 October 2008

ABSTRACT

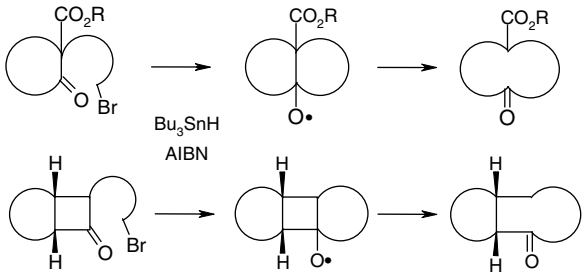
Free radical-promoted three-carbon ring expansions of 1,3-diketones to form corresponding nine-membered 1,6-diketones and associated spirocyclization reactions are described.

1. Introduction

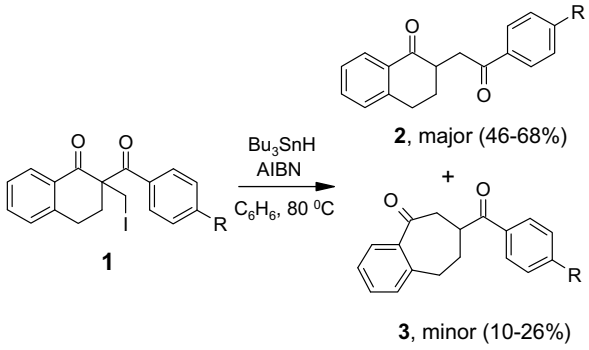
Free radical cyclizations to form five- and six-membered cyclic compounds are important synthetic methods for the preparation of biologically active natural products and pharmaceutical chemicals.[1] Free radical ring expansions[2] of five- and six-membered rings further extend the utility of radical chemistry to access medium and large cyclic compounds. The Dowd-Beckwith reaction of cyclic β-ketoesters[3] and ring expansion of fused-cyclobutanones[4,5] are two well-known systems, which are both good for one- and three-carbon ring expansions (Scheme 1).[6] The ring expansions are accomplished through the β-scission of an alkoxy radical[7] generated by carbon radical addition to the carbonyl. The ester group and the strained ring are critical for the ring expansion of these two systems.[8]

Recently, we designed a unique 1,3-diketone system **1** which has neither ester group nor strained ring, but contains a cyclic keto group and an acyclic keto group. This system can be used to test the competitive ring expansion versus chain extension reactions. Our previous work shows that for the reactions of single-carbon radicals, chain extension compounds **2** were the major products, and the ring expansion compounds **3** were the minor ones (Scheme 2).[9] Reported in this Letter are the new results obtained from a similar system but involving reactions of three-carbon chain radicals.

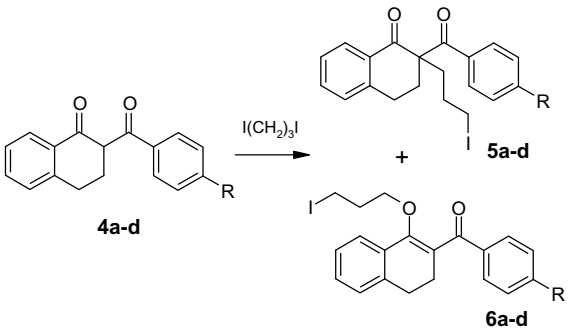
The synthesis of radical precursors is shown in Scheme 3. Readily prepared 2-benzoyl-3,4-dihydro-2*H*-naphthalen-1-ones **4** were



Scheme 1.



Scheme 2.



Scheme 3.

* Corresponding authors. Tel./fax: +86 512 65112371 (J.-P.Z.); tel.: +1 617 287 6147; fax: +1 617 287 6030 (W.Z.).
E-mail addresses: wuyanhong@pub.sz.jsinfo.net (J.-P. Zou), wei2.zhang@umb.edu (W. Zhang).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.10.038

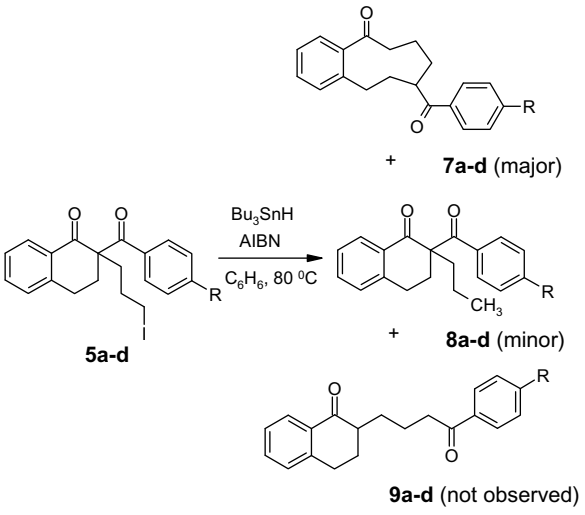
used for alkylations with 1,3-diiodopropane to form 2-benzoyl-2-(3-iodopropyl)-3,4-dihydro-2*H*-naphthalen-1-ones **5**. We found that in addition to the desired C-alkylation products **5**, the O-alkylated compounds **6** were generated as the major products (Table 1). Since the cyclic keto is preferred to exist in enol form that leads to O-alkylation as the major product. We were able to separate the reaction mixtures and got enough C-alkylated compounds to study ring expansion versus chain extension reactions.

Free radical reaction of **5a** was carried out under general free radical reaction conditions using tri-*n*-butyltin hydride, a catalytic amount of AIBN, and reflux benzene as a solvent. From the reaction mixture, two compounds were isolated and characterized to be 2-benzoyl-2-propyl-3,4-dihydro-2*H*-naphthalen-1-one **8a** and three-carbon ring expansion product **7a**, respectively. Compound **8a** was a direct reduction product and in a minor amount. The ring-expansion product **7a** was the major product and in 68% yield (Scheme 4, Table 2, entry 1). It was surprised to find that no chain extension product **9a** in reaction mixture. We then carried out similar reactions on other substrates **5b–d** with the variation of R substitution. Similar ring expansion products **7b–d** were obtained in 69–72% yields together with a small amount of direct reduction products **8b–d** (Table 2, entries 2–4).

Table 1
C- and O-alkylations of 1,3-diketones **4a–d**

Entry	Product (yield %)[a,b]	R	Total yield[b] (%)
1	**5a**(21) + **6a**(40)	H	61
2	**5b**(28) + **6b**(48)	CH_3	76
3	**5c**(16) + **6c**(52)	OCH_3	68
4	**5d**(15) + **6d**(59)	Cl	74

[a] All products were characterized by ^1H NMR, ^{13}C NMR and HRMS.
[b] Isolated yield.

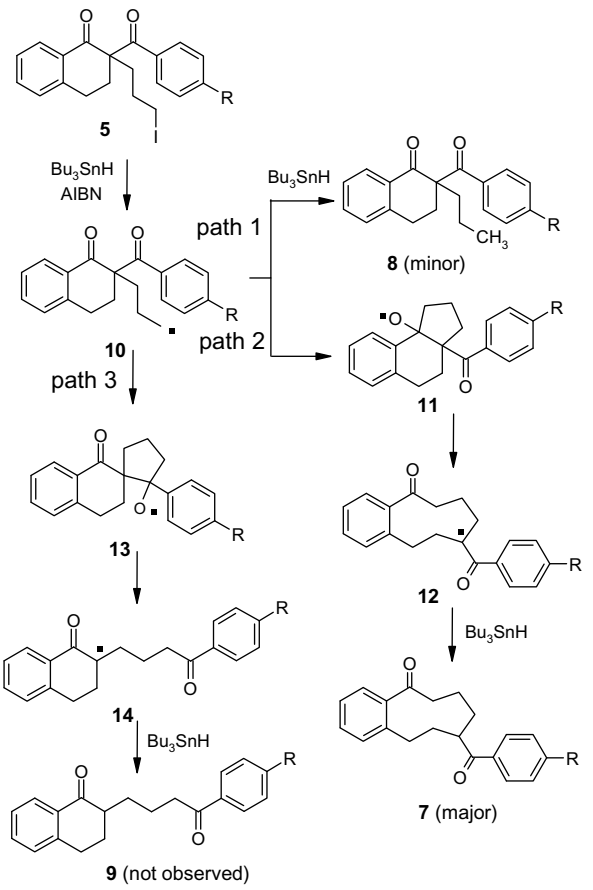


Scheme 4.

Table 2
Reaction of 2-aroyl-2-(3-iodopropyl)-3,4-dihydro-2*H*-naphthalen-1-ones **5a–d**

Entry	Product (yield %)[a]	R	Total yield[b] (%)
1	**7a**(68) + **8a**(8)	H	76
2	**7b**(69) + **8b**(8)	CH_3	77
3	**7c**(72) + **8c**(12)	OCH_3	84
4	**7d**(70) + **8d**(15)	Cl	85

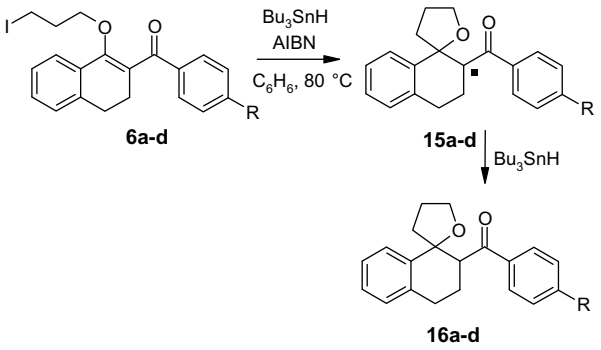
[a] All products were characterized by ^1H NMR, ^{13}C NMR, and HRMS.
[b] Isolated yield.



Scheme 5.

Based on the results described above, radical transformation mechanisms for the reaction of **5** were proposed (Scheme 5). Alkyl radical **10** is generated by the reaction of **5** with tri-*n*-butyltin hydride and AIBN. This radical has following three potential pathways: (1) formation of **8** via direct reduction; (2) three-carbon ring expansion via radicals **11** and **12** to form product **7**; and (3) chain-extension via radicals **13** and **14** to form compound **9**. Since only compounds **7** and **8** were isolated from the reaction mixtures, the third pathway seems to be not so competitive to the first two pathways. The formation of a new nine-membered ring as the major product makes it to be a synthetically useful ring-expansion reaction. This result is different from that obtained from the reaction of one-carbon chain radical shown in Scheme 2, where the chain extension product was the major one. Different results suggest that for one-carbon ring expansion, carbon radical attacking of the rigid cyclic keto has more steric hindrance than attacking the acyclic keto, and leads to chain extension product as the major one. In the case of three-carbon ring expansion, the long chain is kinetically more favorable to attack the cyclic keto than the flexible acyclic keto, and leads to ring expansion product as the major one.

For the purpose of study on ring-expansion reactions, the yields of C-alkylation reaction for compounds **5** should be optimized. But on the other hand, the O-alkylated compounds **6** may be synthetically useful for formation of tetrahydrofuran which is spiro to the naphthalen-1-one skeleton. Indeed, under the general free radical reaction conditions using tri-*n*-butyltin hydride and AIBN, compounds **6** led to the formation of tetrahydrofuran through the conjugate addition to the α,β-unsaturated ketone group. The spiro products **16** were the only compounds isolated from the reaction mixture (Scheme 6, Table 3), no direct reduction products were observed.



Scheme 6.

Table 3
Cyclization of O-alkylated compounds **6**

Entry	Product (yield %)[a,b]	R	Total yield[b] (%)
1	**16a**	H	55
2	**16b**	CH_3	64
3	**16c**	OCH_3	75
4	**16d**	Cl	64

[a] All products were characterized by ^1H NMR, ^{13}C NMR and HRMS.
[b] Isolated yield.

In conclusion, six-membered 2-aroylbenzocyclohexanones **5** can be converted to nine-membered 5-aroylbenzocyclononanones **7** in 68–72% yields via the three-carbon ring expansion process. On the other hand, using O-alkylated compounds **6** as radical precursors, tetrahydrofuran spiro-benzocyclohexanones **16** can be synthesized in 55–75% yields.

2. Typical procedure for alkylation

Preparation of C-alkylated product **5a** and O-alkylated product **6a**. 2-Benzoyl-3,4-dihydro-2*H*-naphthalen-1-one **4a** (1.25 g, 5 mmol), anhydrous potassium carbonate (1.38 g, 10 mmol), tetrabutylammonium bromide (0.64 g, 2 mmol), and dry toluene (15 mL) were added to a 50 mL three-necked flask, and the mixture was refluxed for 1 h under the nitrogen atmosphere.[7] Then, the mixture was cooled to 40 °C, 1,3-diiodopropane (1.47 g, 5.5 mmol) was added, stirred at 40 °C for 2 h and refluxed for another 2 h. After the reaction was completed (monitored by TLC), the resultant was cooled to room temperature, filtered, and washed with diethyl ether. The filtrate was concentrated, and the residue was purified by chromatography on silica gel eluted with petroleum ether/ethyl acetate (20:1) to afford **5a** in 21% and **6a** in 40% yields, respectively.[7] *Compound* **5a**: ^1H NMR ($CDCl_3$, 400 MHz): δ 1.80–1.96 (m, 2H, CH_2), 2.05–2.17 (m, 2H, CH_2), 2.21–2.29 (m, 1H), 2.82–2.89 (m, 1H), 3.05–3.08 (m, 2H, CH_2), 3.16–3.23 (m, 2H, CH_2), 7.22–8.01 (m, 9H, C_6H_4, C_6H_5). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 198.5, 198.4, 143.1, 136.3, 134.3, 132.9, 132.5, 129.4, 129.3, 128.7, 128.5, 127.4, 62.1, 35.1, 31.9, 29.0, 25.9, 7.1. *Compound* **6a**: ^1H NMR ($CDCl_3$, 400 MHz): δ 1.77–1.84 (m, 2H, CH_2), 2.65–2.69 (m, 2H, CH_2), 2.87–2.91 (m, 4H, $2 \times CH_2$), 3.67–3.70 (m, 2H, CH_2), 7.22–7.89 (m, 9H, C_6H_4, C_6H_5). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 198.0, 155.4, 139.1, 138.8, 132.9, 131.0, 129.7, 129.5, 128.6, 128.1, 127.0, 123.9, 121.6, 73.3, 33.9, 28.3, 25.6, 2.4.

3. Typical procedure for free radical three-carbon ring expansion

Preparation of **7a**. Compound **5a** (83 mg, 0.20 mmol), AIBN (10 mg, 0.06 mmol), tri-*n*-butyltin hydride (116 mg, 0.40 mmol), and dry benzene (22 mL) were added to a 50 mL three-necked flask. The mixture was refluxed for 0.5 h under the nitrogen atmosphere.[7] After the reaction was completed (monitored by TLC), the solvent was removed, and the residue was dissolved in dichloromethane (25 mL), washed with 10% aqueous potassium fluoride, dried over $MgSO_4$, and concentrated. The residue was then dissolved in acetonitrile (25 mL), washed with petroleum ether, and concentrated to afford the crude product, which was purified by silica gel chromatography eluted with petroleum ether/ethyl acetate (15:1) to afford major three-carbon ring expansion product **7a** in 68% yield, and minor reduced product **8a** in 10% yield.

Compound **7a**: ^1H NMR ($CDCl_3$, 400 MHz): δ 1.63–1.68 (m, 1H), 1.83–1.89 (m, 1H), 1.91–2.00 (m, 2H, CH_2), 2.03–2.11 (m, 1H), 2.29–2.36 (m, 1H), 2.52–2.59 (m, 1H), 3.05–3.10 (m, 4H, $2CH_2$), 7.26–8.06 (m, 9H, C_6H_5, C_6H_4). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 200.6, 200.5, 144.4, 137.4, 133.6, 133.4, 132.9, 129.1, 129.0, 128.4, 127.8, 127.0, 47.9, 39.1, 29.5, 28.9, 28.6, 22.1. HRMS: *m/z* calcd for $C_{20}H_{20}O_2$ 292.1463; found 292.1460 (M^+). *Compound* **8a**: ^1H NMR ($CDCl_3$, 400 MHz): δ 0.92–0.95 (t, 3H, CH_3, $J = 7.2$ Hz), 1.32–1.44 (m, 1H), 1.94–2.01 (m, 1H), 2.04–2.11 (m, 1H), 2.15–2.22 (m, 1H), 2.83–2.89 (m, 1H), 2.97–3.04 (m, 1H), 3.07–3.31 (m, 1H), 7.20–7.90 (m, 9H, C_6H_4, C_6H_5). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 199.8, 198.9, 143.3, 136.9, 134.0, 132.9, 132.6, 129.5, 129.2, 128.6, 128.4, 127.2, 62.8, 36.5, 31.7, 26.1, 18.3, 15.0. HRMS: *m/z* calcd for $C_{20}H_{20}O_2$ 292.1463; found 292.1460(M^+).

4. Typical procedure for preparation of 16a

Compound **6a** (83 mg, 0.20 mmol), AIBN (10 mg, 0.06 mmol), tri-*n*-butyltin hydride (116 mg, 0.40 mmol), and dry benzene (22 mL) were added to a 50 mL three-necked flask, and the mixture was refluxed for 0.5 h under the nitrogen atmosphere. After the reaction was completed (monitored by TLC), the solvent was removed, the residue was dissolved in dichloromethane (25 mL), washed with 10% aqueous potassium fluoride, dried over $MgSO_4$, and concentrated. The residue was then dissolved in acetonitrile (25 mL), washed with petroleum ether, and concentrated to afford the crude product, which was purified by silica gel chromatography eluted with petroleum ether/ethyl acetate (15:1) to give **16a** in 55% yield. *Compound* **16a**: ^1H NMR ($CDCl_3$, 400 MHz): δ 2.05–1.63 (m, 4H, $2CH_2$), 2.73–2.22 (m, 2H, CH_2), 2.93–2.91 (m, 2H, CH_2), 3.98–3.43 (dd, 1H, CH, $J_1 = 14.4$ Hz, $J_2 = 7.2$ Hz), 4.05–4.00 (m, 2H, CH_2), 8.13–7.08 (m, 9H, C_6H_4, C_6H_5). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 204.3, 145.4, 138.3, 135.5, 133.3, 129.6, 128.8, 128.7, 127.3, 126.7, 125.7, 86.7, 70.2, 51.0, 36.3, 28.5, 26.6, 24.9. HRMS: *m/z* calcd for $C_{20}H_{20}O_2$ 292.1463; found 292.1472 (M^+).

Acknowledgment

J.P.Z. thanks the financial support from National Natural Science Foundation of China (No. 20772088).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.10.038.

References and notes

1. Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237.
2. Reviews on free radical ring expansion reactions: (a) Zhang, W.. In *Radical in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; 2, pp 234–245; (b) Dowd, P.; Zhang, W. *Chem. Rev.* **1993**, *93*, 209; (c) Larry, Y. *Tetrahedron* **1999**, *55*, 9350.
3. (a) Dowd, P.; Choi, S.-C. *J. Am. Chem. Soc.* **1987**, *109*, 3493; (b) Dowd, P.; Choi, S.-C. *Tetrahedron* **1989**, *45*, 77; (c) Beckwith, A. L. J.; Shea, D. M.; Westwood, S. W. *J. Am. Chem. Soc.* **1988**, *110*, 2565; (d) Baldwin, J. E.; Adlington, R. M.; Robertson,

J. *Tetrahedron* **1989**, *45*, 909; (e) Bowman, W. R.; Westlake, P. J. *Tetrahedron* **1992**, *48*, 4027.
4. (a) Zhang, W. *Curr. Org. Chem.* **2002**, *6*, 1015; (b) Dowd, P.; Zhang, W. *J. Am. Chem. Soc.* **1991**, *113*, 9875; (c) Dowd, P.; Zhang, W. *J. Org. Chem.* **1992**, *57*, 7163; (d) Zhang, W.; Hua, Y.; Geib, S. J.; Hoge, G.; Dowd, P. *Tetrahedron* **1994**, *50*, 12579; (e) Zhang, W.; Dowd, P. *Tetrahedron Lett.* **1992**, *33*, 3285; (f) Zhang, W.; Collins, M.; Mahmood, K.; Dowd, P. *Tetrahedron Lett.* **1995**, *36*, 2729; (g) Zhang, W.; Dowd, P. *Tetrahedron Lett.* **1992**, *33*, 7307.
5. (a) Oh, H.-S.; Cha, J. K. *Tetrahedron: Asymmetry* **2003**, *14*, 2911; (b) Oh, H.-S.; Lee, H. I.; Cha, J. K. *Org. Lett.* **2002**, *4*, 3707.
6. Diego, A.; Tomas, L. S. *J. Org. Chem.* **2005**, *70*, 9417.
7. (a) Bietti, M.; Lanzalunga, O.; Salamone, M. *J. Org. Chem.* **2005**, *70*, 1417; (b) Bietti, M.; Gente, G.; Salamone, M. *J. Org. Chem.* **2005**, *70*, 6820; (c) Ueng, S.-H.; Chen, M.-J.; Chu, S.-F.; Shao, Y.-F.; Fan, G.-T.; Chang, S.-Y.; Tsai, Y.-M. *J. Org. Chem.* **2006**, *71*, 1502; (d) Tang, K.-H.; Liao, F.-Y.; Tsai, Y.-M. *Tetrahedron* **2005**, *61*, 2037.
8. (a) Wilsey, S.; Dowd, P.; Houk, K. N. *J. Org. Chem.* **1999**, *64*, 8801; (b) Ardura, D.; Sordo, T. L. *Tetrahedron Lett.* **2004**, *45*, 8691.
9. Mu, X.-J.; Zou, J.-P.; Wang, Z.-T.; Zhang, W. *Tetrahedron Lett.* **2005**, *46*, 4727.