ORGANIC LETTERS

2008
Vol. 10, No. 5
803−805

C–H Bond Oxidation Initiated Pummerer- and Knoevenagel-Type Reactions of Benzyl Sulfide and 1,3-Dicarbonyl Compounds

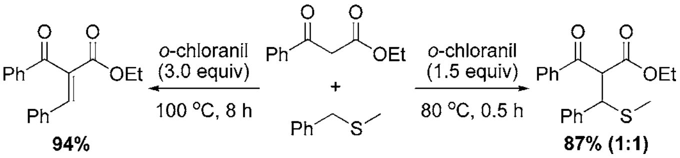
Zhiping Li,* Haijun Li, Xingwei Guo, Lin Cao, Rong Yu, Huanrong Li, and Shiguang Pan

Department of Chemistry, Renmin University of China, Beijing 100872, China

zhipingli@ruc.edu.cn

Received December 6, 2007

ABSTRACT



A novel Pummerer-type reaction was developed via *o*-chloranil-mediated C–H bond oxidation. The reaction provides a simple and efficient method to construct sulfide derivatives. A Knoevenagel-type reaction was also achieved via multiple C–H bonds activation under neutral reaction conditions.

Selective and efficient activation of C−H bonds to generate functional molecules with minimal energy, cost, and environment impacts is one of the challenging research areas in synthetic chemistry.[1,2] Among the C−H functionalizations, activation of the C−H bond adjacent to a heteroatom (such as N or O) has been widely investigated because the success of such a method could lead to future efficient synthesis of natural products and pharmaceuticals with heteroatoms imbedded.[3] However, all reported methods in this line have their limitations. For example, usually one or two transition metal catalysts have to be used in these transformations. In addition, the heteroatoms in the substrates are restricted to oxygen and nitrogen atoms. Therefore, developing metal-free activation of a C−H bond adjacent to a heteroatom ranging from oxygen[4] and nitrogen to sulfur and other atoms would advance the state of the art of today's C−H bond functionalization.

The Pummerer reaction is one elegant synthetic method to functionalize a C−H bond adjacent to a sulfur atom and has been widely applied in the synthesis of natural products and biologically active compounds.[5] However, in the classical Pummerer reactions, sulfoxide starting materials and harsh acidic initiators have to be used (Scheme 1). Therefore, to expand the scope of the Pummerer reaction, efforts focused on novel ways to generate thionium intermediates from sulfides have been undertaken.[6,7] The most challenging part in this regard resides in developing a novel way that can generate thionium intermediates or their equivalents from

---

[1] (a) Bergman, R. G. *Nature* **2007**, *446*, 391. (b) Godula, K.; Sames, D. *Science* **2006**, *312*, 67. (c) *Handbook of C-H Transformations*; Dyker, D., Ed.; Wiley-VCH: Weinheim, 2005.

[2] For representative reviews, see: (a) Crabtree, R. H. *J. Organomet. Chem.* **2004**, *689*, 4083. (b) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731. (c) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633. (d) Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1698. (e) Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.* **1997**, *97*, 2879.

[3] (a) Li, Z.; Bohle, D. S.; Li, C.-J. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 8928. (b) Zhang, Y.; Li, C.-J. *Angew. Chem., Int. Ed.* **2006**, *45*, 1949. (c) Wan, X.; Xing, D.; Fang, Z.; Li, B.; Zhao, F.; Zhang, K.; Yang, L.; Shi, Z. *J. Am. Chem. Soc.* **2006**, *128*, 12046. (d) Maruyama, T.; Suga, S.; Yoshida, J.-I. *J. Am. Chem. Soc.* **2005**, *127*, 7324. (e) DeBoef, B.; Pastine, S. J.; Sames, D. *J. Am. Chem. Soc.* **2004**, *126*, 6556. (f) Murahashi, S.-I.; Komiya, N.; Terai, H.; Nakae, T. *J. Am. Chem. Soc.* **2003**, *125*, 15312. (g) Chatani, N.; Asaumi, T.; Yorimitsu, S.; Ikeda, T.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **2001**, *123*, 10935. (h) Yoshida, J.-I.; Suga, S.; Suzuki, S.; Kinomura, N.; Yamamoto, A.; Fujiwara, K. *J. Am. Chem. Soc.* **1999**, *121*, 9546.

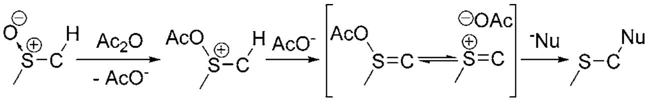
[4] DDQ-mediated C−H bond activation was reported: Zhang, Y.; Li, C.-J. *J. Am. Chem. Soc.* **2006**, *128*, 4242.

[5] (a) Feldman, K. S. *Tetrahedron* **2006**, *62*, 5003. (b) Bur, S. K.; Padwa, A. *Chem. Rev.* **2004**, *104*, 2401.

[6] Feldman, K. S.; Violulova, D. B. *Tetrahedron Lett.* **2004**, *45*, 5035.

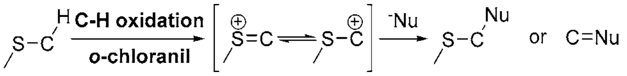
10.1021/ol702934k CCC: $40.75

Scheme 1. Classic Pummerer Reaction



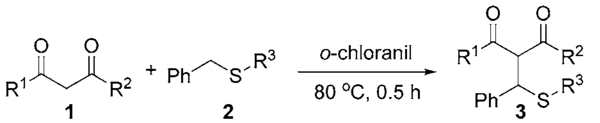
sulfides under mild and neutral reaction conditions, which are also compatible with nucleophilic addition reaction at the same time. Herein, we wish to report our endeavor to develop a metal-free activation of a C−H bond adjacent to sulfur that can efficiently generate Pummerer-type products when *o*-chloranil (tetrachloro-*o*-benzoquinone) was used as the oxidant (Scheme 2).

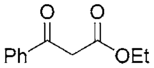
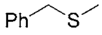
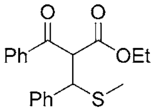
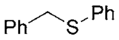
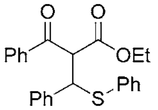
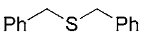
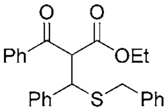
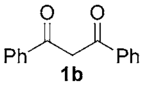
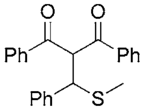
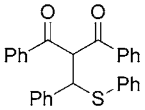
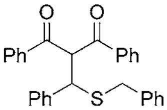
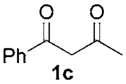
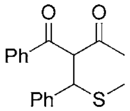
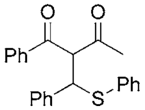
Scheme 2. *o*-Chloranil-Mediated Pummerer- or Knoevenagel-Type Reactions



To begin our study, ethyl 3-oxo-3-phenylpropanoate **1a** and benzyl methyl sulfide **2a** were chosen as the standard substrates to search for suitable reaction conditions. After many failures, we found that the desired product **3a** was obtained in 87% isolated yield in 30 min by using 1.5 equiv of *o*-chloranil as an oxidant at 80 °C (Table 1, entry 1).[8] Subsequently, various substrates were tested under the optimized conditions, and some representative results are shown in Table 1. When benzyl phenyl sulfide **2b** and dibenzyl sulfide **2c** were used, **3b** and **3c** were obtained in 87% and 70%, respectively (Table 1, entries 2 and 3). It should be noted that monoalkylation product **3c** was the only isolated product. The desired products were also obtained with good isolated yields when 1, 3-diketones **1b** and **1c** reacted with sulfides (Table 1, entries 4−8). Interestingly, **4a**, a Knoevenagel-type condensation product, was formed in 12% yield together with the oxidative product **3g** obtained in 77% yield (Table 1, entry 7).

Table 1. *o*-Chloranil-Mediated Pummerer-Type Reactions[a]



entry	1	2	3[b]
1	 **1a**	 **2a**	 **3a** 87% (1:1)
2	**1a**	 **2b**	 **3b** 87% (1:1)
3	**1a**	 **2c**	 **3c** 70% (1:1)
4	 **1b**	**2a**	 **3d** 73%
5	**1b**	**2b**	 **3e** 82%
6	**1b**	**2c**	 **3f** 73%
7[c]	 **1c**	**2a**	 **3g** 77% (1:1)
8	**1c**	**2b**	 **3h** 80% (2:1)

[a] **1** (0.25 mmol), **2** (1.5 mmol), and *o*-chloranil (0.38 mmol) were used. [b] Isolated yields are reported, and the ratios of two diastereomers are reported in the parentheses. [c] **4a** was obtained in 12%.

Subsequently, we optimized the reaction conditions aiming to obtain the Knoevenagel-type condensation products selectively. Studies showed that the yield of **4a** was increased up to 81% together with 19% yield of **3g** in the presence of 3.0 equiv of *o*-chloranil, at 100 °C (Table 2, entry 1). When **2b** and **2c** were used, **4a** was exclusively obtained in 97% and 93% yields and no Pummerer-type oxidative coupling products **3** were observed (Table 2, entries 2 and 3). When **1a** was used, **4b** was obtained in excellent yields (Table 2, entries 4−6). The desired products **4** were also obtained with good to excellent yields when cyclic substrate **1d** and *β*-ketoimide **1e** were used (Table 2, entries 7−10). 2,4-Pentadione **1g** reacted with **2b** and **2c** to give Knoevenagel-type product **4f** in 62% and 80% yields, respectively (Table 2, entries 12 and 13). However, the corresponding Pummerer product **3i** was also obtained in 28% when **2b** was used (Table 2, entry 12). In all entries in Table 2, products **4** were obtained as single regioisomer when unsymmetrical dicarbonyl compounds were used.

A tentative mechanism of the *o*-chloranil-mediated Pummerer-type and Knoevenagel-type reactions is shown in Scheme 3. C−H oxidation of **2** by *o*-chloranil gives a thionium intermediate, **5a**,[9] which could also exist as a neutral species, **5b**, in which a possible weak C−O bond is formed between the two charged moieties in **5a**. Nucleophilic addition of **5a** to **1** then generates the coupling product **3**.[10] If excess *o*-chloranil is used, compound **3** is transformed to product **4** via the C−S bond cleavage.[11]

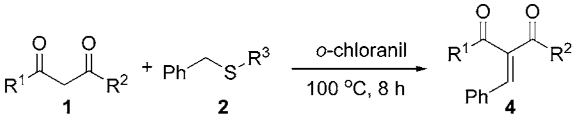
---

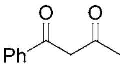
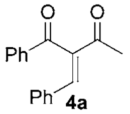
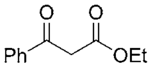
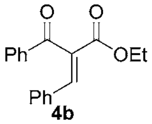
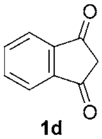
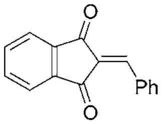
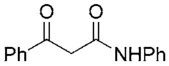
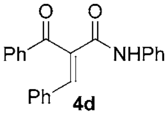
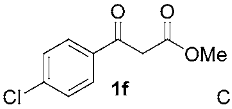
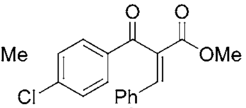
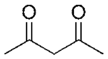
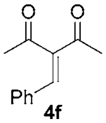
(7) An alternative method for generation of the thionium precursor, hemithioacetal, is based on the addition of thiols to glyoxamide; see: McAllister, L. A.; McCormick, R. A.; Brand, S.; Procter, D. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 452.

(8) No desired product was obtained when *p*-fluoranil, *p*-chloranil, and *p*-bromanil were used as oxidants under the same reaction conditions.

(9) One of possibilities of C−H bond oxidation is initiated by single electron transfer from sulfur to quinone; see: Gorner, H. *Photochem. Photobiol.* **2006**, *82*, 71.

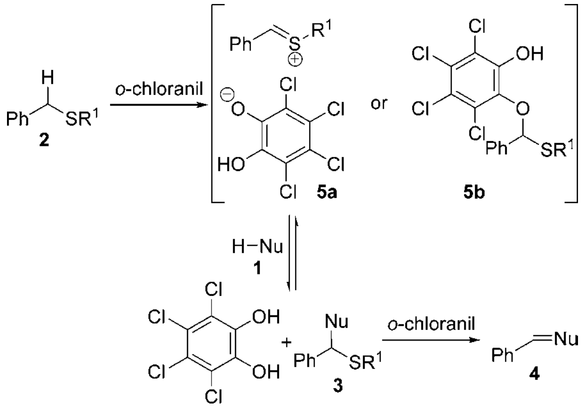
Table 2. *o*-Chloranil-Mediated Knoevenagel-Type Reactions[a]



entry	1	4^b	
1^c	 **1c**	 **4a**	81% (R^3 = Me)
2^d			97% (R^3 = Ph)
3			93% (R^3 = Bn)
4	 **1a**	 **4b**	94% (R^3 = Me)
5			97% (R^3 = Ph)
6			99% (R^3 = Bn)
7^e	 **1d**	 **4c**	90% (R^3 = Me)
8^e			73% (R^3 = Ph)
9^e			84% (R^3 = Bn)
10	 **1e**	 **4d**	63% (R^3 = Me)
11	 **1f**	 **4e**	91% (R^3 = Ph)
12^f	 **1g**	 **4f**	62% (R^3 = Ph)
13			80% (R^3 = Bn)

[a] Compounds **1** (0.25 mmol) and **2** (1.5 mmol) and *o*-chloranil (0.75 mmol) were used unless otherwise noted. [b] Isolated yields are reported.[c] 2 equiv of *o*-chloranil was used; 3 g was obtained in 19%. [d] 2 equiv of *o*-chloranil was used; 120 °C. [e] 2 equiv of o-chloranil was used. [f] Compound **3i** was obtained in 28%.

Scheme 3. Tentative Mechanism for the *o*-Chloranil-Mediated C−H Bond Oxidation Initiated C−C Bond and C═C Formation



In summary, a novel Pummerer-type reaction and a Knoevenagel-type reaction have been developed via a metal-free C−H bond oxidation strategy. The high selectivity of the reactions is achieved by controlled reaction conditions. The metal-free, neutral, and mild reaction conditions make these attractive reactions for potential applications. The scope, mechanism, and synthetic application of these reactions are under investigation.

Acknowledgment. We are grateful to the Scientific Research Starting Foundation of Renmin University of China (to Z.L.) and the National Natural Science Foundation of China (no. 20602038). We also thank Prof. Zhenfeng Xi and Prof. Zhi-Xiang Yu, Peking University, for helpful discussions.

Supporting Information Available: Representative experimental procedure, characterization of all new compounds and ^{1}H NMR and ^{13}C NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL702934K

---

(10) This step is reversible. Compound **3e** was obtained as a major product by the reaction of **3d** and **2b**. Oxidative cleavage benzylic C−C bonds assisted by heteroatoms: Wang, L.; Seiders, J. R., II; Floreancig, P. E. *J. Am. Chem. Soc.* **2004**, *126*, 12596.

(11) Compound **3a** was transformed into **4b** in 93% isolated yield at 100 °C for 8 h in the presence of 2 equiv of *o*-chloranil. For related examples of C−S bond cleavage, see: (a) Baciocchi, E.; Del, Giacco, T.; Giombolini, P.; Lanzalunga, O. *Tetrahedron* **2006**, *62*, 6566. (b) Mukaiyama, T.; Narasaka, K.; Hokonok, H. *J. Am. Chem. Soc.* **1969**, *91*, 4315.