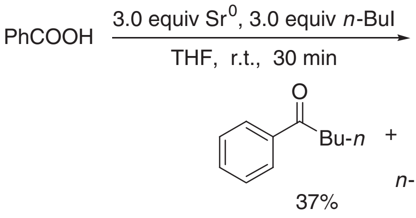
A New Synthetic Method for Para Alkylation of Benzoic Acids Using Metallic Strontium and Alkyl Iodide

Norikazu Miyoshi,*[1] Tsuyoshi Matsuo,[1] Mariko Mori,[1] Aki Matsui,[1] Makoto Kikuchi,[1]
Makoto Wada,[1] and Masahiko Hayashi[2]
[1]*Department of Chemistry, Faculty of Integrated Arts and Sciences, The University of Tokushima,*
1-1 Minamijosanjima, Tokushima 770-8502
[2]*Department of Chemistry, Graduate School of Science, Kobe University, Kobe 657-8501*

(Received August 6, 2009; CL-090733; E-mail: miyoshi@ias.tokushima-u.ac.jp)

Aromatic carboxylic acids reacted with metallic strontium and alkyl iodides to give para alkylated products preferentially in moderate to good yields.

Few studies of the preparation and reactivity of organostrontium compounds have been found in the literature[1–3] until the current decade. We have been investigating synthetic reactions using strontium compounds, and we have reported that the alkylation of aldehydes or imines with alkyl iodides,[4] and dialkylation of esters with alkyl iodides[5] proceeds smoothly using metallic strontium to afford the corresponding adducts in good yields. When we recently extended our investigation to include the addition reaction of carboxylic acids, we found that carboxylic acids reacted with metallic strontium and alkyl iodides to give monoalkylated ketones preferentially in moderate to good yields.[6] In the reaction of benzoic acid with *n*-butyl iodide, the monoalkylated ketone was obtained in 37% yield and the unexpected 4-*n*-butylbenzoic acid was detected in a trace amount (eq 1).



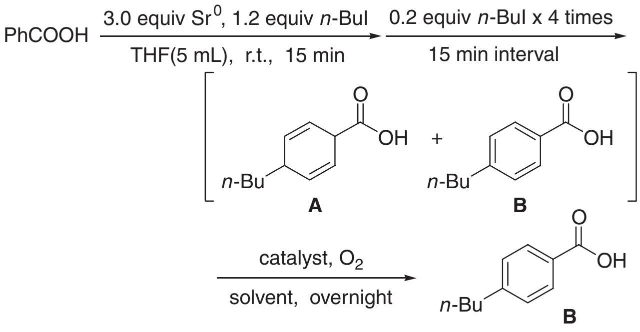
(1)

In this reaction, alkylation of the carboxyl group of benzoic acid and at the para position of the aromatic ring of benzoic acid occurred competitively. We were interested in the para alkylated product because this alkylation reaction is unusual under these conditions. The selective functionalization of an aromatic nucleus has become increasingly important in synthetic organic chemistry. There are only a few reports of the ortho or para alkylation of nucleophilic addition to an aromatic nucleus with simple carbonyl and carboxyl functionalities. Tomioka and Koga reported ortho alkylation by using the conjugate addition of organolithiums to sterically hindered 2,6-di-*tert*-butyl-4-methoxyphenyl naphthalenecarboxylate.[7] Hattori and Miyano reported that the para alkylation of benzoate with butyllithium proceeded using also a particularly sterically bulky ester of benzoic acid.[8] Yamamoto and Maruoka reported that the para alkylation of benzaldehyde with butyllithium took place using a special sterically bulky aluminum catalyst.[9] On the other hand, we have already reported that the reaction of ethyl benzoate with *tert*-butyl iodide and metallic strontium proceeded smoothly at −20 °C for 36 h to afford ethyl 4-*tert*-butylbenzoate as the sole product in 55% yield.[4] The yield was still moderate, but this reaction has the advantages over other methodology in that the selective para alkylation proceeded by simple operation and without preparing sterically hindered esters or using a special sterically bulky catalyst. However, in this case, the reaction allowed only to using *tert*-butyl iodide or isopropyl iodide. Here we wish report the selective para alkylation of aromatic carboxylic acids by using several alkyl iodides and metallic strontium.

Initially, we examined the reaction using benzoic acid and *n*-butyl iodide under various conditions. It was found that best result was obtained using 3.0 equivalents of metallic strontium and 2.0 equivalents of *n*-butyl iodide to benzoic acid. It was noted that higher yield was achieved by a unique addition sequence of *n*-butyl iodide as follows; first, 1.2 equivalents of *n*-butyl iodide were added, then 0.8 (0.2 × 4) equivalents of *n*-butyl iodide were added in four aliquots at 15 min intervals, successively. A mixture of the 1,6-adduct **A** and the oxidative aromatization product, para alkylated compound **B**, were obtained in moderate to good yield, although it was difficult to separate the reaction mixtures. In order to purify the crude products, the mixture was successively oxidized using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to afford 4-*n*-butylbenzoic acid **B** in moderate good yield. Moreover, we examined other oxidants instead of DDQ, because the 1,6-adduct **A** was unstable and gradually decomposed and was not always converted using DDQ into the para alkylated adduct **B** completely. As shown in Table 1, the oxidation with palladium–carbon proceeded smoothly to give the para alkylated adduct **B**, but the decomposition of 1,6-adduct **A** also occurred slightly. The use of activated carbon, Darco® KB (Aldrich Inc.) as an oxidant,[10] gave the improvement in the yield (67%) (Entry 5). However, the yields are less satisfactory for synthetic methods. It was suggested that Darco® KB absorbed products slightly to decrease the yield. We tried to use another activated carbon (Tokyo Chemical Industry Co., Ltd.),[10] which was less absorbent than Darco® KB. Using TCI activated carbon, the oxidation proceeded smoothly to increase the yields (75%) (Entry 7).

Next we investigated several alkyl iodides using benzoic acid, which are summarized in Table 2. As described above, we have already reported that the reaction of ethyl benzoate with *tert*-butyl iodide proceeds smoothly to afford ethyl 4-*tert*-butylbenzoate.[4] However, in that case, the reaction only proceeds using *tert*-butyl iodide or isopropyl iodide, which seems to produce the stable nucleophilic radicals.[2] In this reaction, not only *tert*- or *sec*-alkyl iodide but also primary alkyl iodide reacted to give the corresponding products in moderate to good yields. Especially, isobutylation is significant (Entry 2), because isobutyllithium is not commercial available and it is difficult to prepare isobutylating agent, as β-hydride elimination occurs. Moreover, the reaction has the advantages of using unmodified benzoic acid without special protection or activation as reported before.

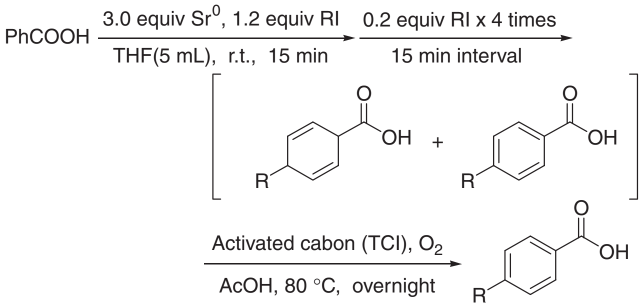
Table 1. Investigation of reaction conditions



Entry	Catalyst	Solvent	Temp/°C	Yield/%[a]
1	5% Pd/C	AcOH	55	45
2	5% Pd/C	AcOH	80	57
3	Darco® KB	AcOH	55	—[b]
4	Darco® KB	Toluene	80	58
5	Darco® KB	AcOH	80	67
6	Darco® KB	AcOH	100	64
7	TCI-AC[c]	AcOH	80	75

[a]Yields were determined by ^{1}H NMR spectra. [b]Not completely oxidized. [c]As TCI-AC (TCI activated carbon), see Ref. 10.

Table 2. Investigation of several alkyl iodides



Entry	R-	Yield/%[a]
1	*n*-Bu	75
2	*i*-Bu	74
3	*i*-Pr	80[b]
4	*s*-Bu	83[b]
5	*t*-Bu	68

[a]Isolated yields. As reaction conditions in detail, see Ref. 11.
[b]Alkyl iodide was added in 5 aliquots (total 2.5 equiv to acid).

In summary, a new alkylation method at the para position of the aromatic ring of benzoic acid was demonstrated. Aromatic carboxylic acids reacted with metallic strontium and alkyl iodides to give para alkylated products predominantly in moderate to good yields. The para alkylation of benzoic acid is a unique characteristic in organostrontium chemistry. We found dialkylation of esters[5] and monoalkylation of carboxylic acid.[6] In this time, we found that only the change of additional procedure inhibited 1,2-addition at carbonyl group of benzoic acid to proceed 1,6-addition (para alkylation) of benzoic acid predominantly. Further applications are now progress.

This work was supported by Grant-in-Aid for Scientific Research on Priority Areas “Advance Molecular Transformation of Carbon Resources” from MEXT, Japan.

References and Notes

1 a) N. A. Bell, *Beryllium*, and W. E. Lindsell, *Magnesium, Calcium, Strontium and Barium* in *Comprehensive Organometallic Chemistry*, ed. by G. Wilkinson, F. G. A. Stone, E. W. Abel, Pergamon Press, Oxford, **1982**, Vol. 1, Chap. 3 and 4, p. 121 and p. 155, respectively. b) W. E. Lindsell, in *Comprehensive Organometallic Chemistry II*, ed. by E. W. Abel, F. G. A. Stone, G. Wilkinson, Pergamon Press, Oxford, **1995**, Vol. 1, Chap. 3, p. 57, and references cited therein. c) N. Miyoshi, *Product Class 8: Strontium Compounds* in *Houben-Weyl: Methods of Molecular Transformation, Science of Synthesis*, ed. by H. Yamamoto, Thieme, Stuttgart, **2004**, Vol. 7, p. 685.

2 Lindsell et al. reported that alkylstrontium halides reacted with carbonyl compounds to afford the corresponding products in low yields, with the exception of the reaction with benzophenone. a) B. G. Gowenlock, W. E. Lindsell, B. Singh, *J. Organomet. Chem.* **1975**, *101*, C37. b) B. G. Gowenlock, W. E. Lindsell, B. Singh, *J. Chem. Soc., Dalton Trans.* **1978**, 657.

3 a) M. S. Sell, R. D. Rieke, *Synth. Commun.* **1995**, *25*, 4107. b) L. N. Cherkasov, V. I. Panov, V. N. Cherkasov, *Russ. J. Org. Chem.* **1993**, *29*, 411. c) L. N. Cherkasov, S. I. Radchenko, *Russ. J. Org. Chem.* **1994**, *30*, 456. d) L. N. Cherkasov, V. N. Cherkasov, *Russ. J. Org. Chem.* **1995**, *31*, 267.

4 a) N. Miyoshi, K. Kamiura, H. Oka, A. Kita, R. Kuwata, D. Ikehara, M. Wada, *Bull. Chem. Soc. Jpn.* **2004**, *77*, 341. b) N. Miyoshi, D. Ikehara, T. Kohno, A. Matsui, M. Wada, *Chem. Lett.* **2005**, *34*, 760.

5 N. Miyoshi, T. Matsuo, M. Wada, *Eur. J. Org. Chem.* **2005**, 4253.

6 N. Miyoshi, T. Matsuo, M. Asaoka, A. Matsui, M. Wada, *Chem. Lett.* **2007**, *36*, 28.

7 K. Tomioka, M. Shindo, K. Koga, *Tetrahedron Lett.* **1990**, *31*, 1739.

8 T. Hattori, N. Koite, T. Satoh, S. Miyano, *Tetrahedron Lett.* **1995**, *36*, 4821.

9 K. Maruoka, M. Ito, H. Yamamoto, *J. Am. Chem. Soc.* **1995**, *117*, 9091.

10 a) Y. Kawashita, N. Nakamichi, H. Kawabata, M. Hayashi, *Org. Lett.* **2003**, *5*, 3713. b) N. Nakamichi, H. Kawabata, M. Hayashi, *J. Org. Chem.* **2003**, *68*, 8272. TCI activated carbon is commercial available from Tokyo Chemical Industry Co., Ltd (TCI C2194).

11 A typical reaction procedure is as follows: Under an argon atmosphere, benzoic acid (122 mg, 1.00 mmol) and THF (5 mL) were added to a vessel with small pieces of metallic strontium (269 mg, 3.09 mmol) cut with a chisel, and *n*-butyl iodide (213 mg, 1.16 mmol) and additional *n*-butyl iodide (142 mg, 0.77 mmol) in four portions at 15 min intervals were added successively to the reaction mixture at room temperature. After stirring 15 min, the reaction mixture was quenched with 1 M HCl aq (20 mL) (1 M $=$ 1 mol dm^{-3}). The organic materials were extracted with diethyl ether (15 mL × 3), and the combined organic layers were washed successively with 5% $NaHSO_3$ aq and brine. The organic layer was washed with 2 M NaOH (15 mL × 3) aq. The combined aqueous extracts were acidified with 3 M HCl aq. The resulting cloudy suspension was extracted with diethyl ether (15 mL × 3). These organic extracts were combined and dried over anhydrous Na_2SO_4. After evaporation of the solvent, acetic acid (5 mL) and TCI activated carbon (ca. 80 mg) was added to the residue, and the reaction mixture was allowed to stand at 80 °C for 14 h under an oxygen atmosphere and then filtered through a short pad of Celite. The Celite was washed with diethyl ether and the solvent was removed on a rotary evaporator. The residue was dissolved in ether, and the organic layer was washed with 2 M NaOH aq (15 mL × 3). The combined aqueous extracts were acidified with 3 M HCl aq. The resulting cloudy suspension was extracted with diethyl ether (15 mL × 3). These organic extracts were combined and dried over anhydrous Na_2SO_4. After evaporation of the solvent, 4-*n*-butylbenzoic acid (134 mg, 75%) was obtained as a white crystal.

Published on the web (Advance View) September 19, 2009; doi:10.1246/cl.2009.996