

## Radical mediated-direct conversion of aldehydes into acid bromides

Dong Ho Kang,<sup>a</sup> Tae Young Joo,<sup>a</sup> Warinthorn Chavasiri<sup>c</sup> and Doo Ok Jang<sup>a,b,\*</sup>

<sup>a</sup>Department of Chemistry, Yonsei University, Wonju 220-710, Republic of Korea

<sup>b</sup>Center for Bioactive Molecular Hybrids, Yonsei University, Seoul 120-749, Republic of Korea

<sup>c</sup>Department of Chemistry, Faculty of Science, Chulalongkorn University, 10330, Thailand

Received 7 October 2006; revised 28 October 2006; accepted 2 November 2006

Available online 27 November 2006

**Abstract**—A method of preparing acid bromides directly from aldehydes with  $\text{Br}_3\text{CCO}_2\text{Et}$  under radical conditions was developed. Aromatic aldehydes with electron-donating group were found to be more reactive than aromatic aldehydes with electron-withdrawing group and aliphatic aldehydes under reaction conditions.

© 2006 Elsevier Ltd. All rights reserved.

Acid halides have been utilized as important intermediates for the synthesis of esters, amides, and other carboxylic acid derivatives.<sup>1</sup> Although a variety of coupling reagents have also been reported for the formation of these compounds directly from carboxylic acids,<sup>2</sup> there is still a need to utilize acid halides for preparing various carboxylic acid derivatives because the coupling reagents failed in forming the desired compounds such as amides with carboxylic acids and amines with low nucleophilicity or steric hindrance.<sup>3</sup> Accordingly, many procedures for the preparation of acid halides have been developed. The general synthetic methods are mainly the transformation of carboxylic acids into acid halides.<sup>3,4</sup> However, the examples of direct conversion of aldehydes into acid halides were very rare. Chlorine,<sup>5</sup> cesium fluoroxysulfate,<sup>6</sup> and 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)<sup>7</sup> were used for the direct transformation of aldehyde into acid halides under ionic reaction conditions. Sulfuryl chloride,<sup>8</sup> *t*-butyl hypochlorite,<sup>9</sup> carbon tetrachloride,<sup>10</sup> and NBS<sup>11</sup> were utilized for the purpose under radical reaction conditions.<sup>12</sup> However, these methods suffered from disadvantages including the use of corrosive reagents, strong acidic conditions, or the limitations on substituents of substrates such as olefinic functions. Accordingly, development of a new and convenient method for direct conversion of aldehydes into acid halides is

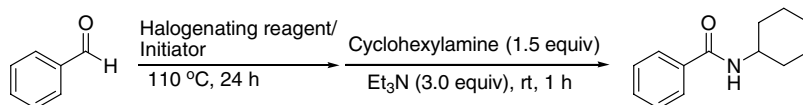
invaluable in organic synthesis. Herein, we report on a simple procedure of preparing acid bromides from aldehydes with ethyl tribromoacetate ( $\text{Br}_3\text{CCO}_2\text{Et}$ ) under radical reaction conditions.

The procedure of the transformation of aldehydes into acid bromides is quite simple. A mixture of benzaldehyde,  $\text{Br}_3\text{CCO}_2\text{Et}$  (2.0 equiv), and benzoyl peroxide (BPO) in chlorobenzene was heated to 110 °C for 24 h. Because of moisture sensitivity of acid halide, the produced acid bromide was converted into the amide derivative by treatment with cyclohexylamine in the presence of  $\text{Et}_3\text{N}$  affording cyclohexyl benzamide in 72% yield (Table 1, entry 2). A small increase of the amide was attained with 3.0 equiv of  $\text{Br}_3\text{CCO}_2\text{Et}$  (entry 3). The same reaction was carried out with lauroyl peroxide or  $\text{Et}_3\text{B}$  instead of benzoyl peroxide as radical initiator giving low to moderate yields of the amide (entries 4 and 5). We presumed that  $\text{Br}_3\text{CNO}_2$  is more reactive than  $\text{Br}_3\text{CCO}_2\text{Et}$  since a radical intermediate from  $\text{Br}_3\text{CNO}_2$  might be more stable and then readily generated. When the reaction was performed with  $\text{Br}_3\text{CNO}_2$ , 61% of the amide was obtained (entry 6). The reactivity of  $\text{CCl}_3\text{CN}$  as a radical halogenating reagent was also examined to give a moderate yield of the amide (entries 7 and 8). Among the radical halogenating reagents we have examined,  $\text{Br}_3\text{CCO}_2\text{Et}$  afforded the highest yield of acid bromide from aldehyde under the present conditions.

To examine the scope and limitations of the present process, we then carried out the reaction with various aromatic and aliphatic aldehydes using  $\text{Br}_3\text{CCO}_2\text{Et}$ /BPO, which was the most effective condition. These

**Keywords:** Acid bromide; Aldehyde; Radical; Ethyl tribromoacetate; Amide.

\* Corresponding author. Tel.: +82 337602261; fax: +82 337602208; e-mail: [dojang@yonsei.ac.kr](mailto:dojang@yonsei.ac.kr)

**Table 1.** Conversion of benzaldehyde into *N*-cyclohexylbenzamide via benzoic acid bromide under various radical reaction conditions<sup>a</sup>

| Entry | Halogenating agent (equiv)                | Initiator <sup>b</sup> | Solvent        | Isolated yield (%) |
|-------|---|------------------------|----------------|--------------------|
| 1     | Br <sub>3</sub> CCO <sub>2</sub> Et (2.0) | — <sup>c</sup>         | Chlorobenzene  | 0                  |
| 2     | Br <sub>3</sub> CCO <sub>2</sub> Et (2.0) | BPO                    | Chlorobenzene  | 72                 |
| 3     | Br <sub>3</sub> CCO <sub>2</sub> Et (3.0) | BPO                    | Chlorobenzene  | 77                 |
| 4     | Br <sub>3</sub> CCO <sub>2</sub> Et (2.0) | LPO                    | Chlorobenzene  | 55                 |
| 5     | Br <sub>3</sub> CCO <sub>2</sub> Et (2.0) | Et <sub>3</sub> B      | Benzene        | 32 <sup>d</sup>    |
| 6     | Br <sub>3</sub> CNO <sub>2</sub> (2.0)    | BPO                    | Chlorobenzene  | 61                 |
| 7     | Cl <sub>3</sub> CCN (2.0)                 | BPO                    | Chlorobenzene  | 41 <sup>d</sup>    |
| 8     | Cl <sub>3</sub> CCN (8.0)                 | AIBN                   | — <sup>e</sup> | 48 <sup>d</sup>    |

<sup>a</sup> The initiator was added portionwise (0.2 equiv).

<sup>b</sup> BPO = benzoyl peroxide, LPO = lauroyl peroxide, AIBN = 2,2'-azobisisobutyronitrile.

<sup>c</sup> Without initiator.

<sup>d</sup> The reaction was carried out at 80 °C.

<sup>e</sup> The reaction was performed at 80 °C without solvent.

results are presented in Table 2. Under these reaction conditions, aromatic aldehydes with electron-donating groups such as 3,4-dimethoxybenzaldehyde, *p*-methoxybenzaldehyde, and *p*-*tert*-butylbenzaldehyde reacted and produced the corresponding amides in high yields (entries 1–3). The treatment of slightly deactivated aromatic aldehydes such as *p*-chlorobenzaldehyde and *m*-bromobenzaldehyde under the same conditions gave the corresponding amides in moderate yields (entries 4

and 5). On the other hand, the yields of amide decreased with aromatic aldehydes that have electron-withdrawing groups (entries 6 and 7). Similarly, we examined the reactivity of aliphatic aldehydes under these conditions. When heptanal and stearaldehyde were brought in to react under these conditions, the corresponding amides were obtained in moderate yields (entries 8 and 9). The above results implied that the rate-determining step for the reaction was very sensitive to the electronic effect

**Table 2.** Preparation of amides from various aldehydes

| Entry | Aldehyde   | Product <sup>b</sup> | Yield (%) <sup>a</sup> |
|-------|--|----------------------|------------------------|
| 1     |  |                      | 75                     |
| 2     |  |                      | 72                     |
| 3     |  |                      | 69                     |
| 4     |  |                      | 69                     |
| 5     |  |                      | 61                     |
| 6     |  |                      | 51                     |
| 7     |  |                      | 55                     |
| 8     | CH <sub>3</sub> (CH <sub>2</sub> ) <sub>5</sub> CHO  |                      | 52                     |
| 9     | CH <sub>3</sub> (CH <sub>2</sub> ) <sub>16</sub> CHO |                      | 58                     |

<sup>a</sup> Isolated yield.

<sup>b</sup> Identification of the products was confirmed by comparison with available physical and spectroscopic data of authentic compounds.


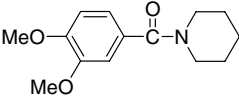

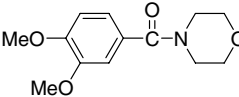

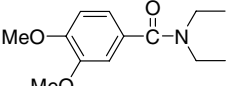

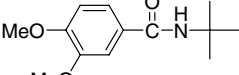
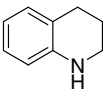
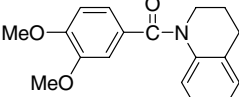
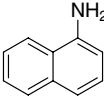
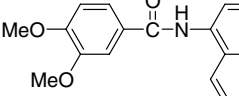
although the intermediate of the reaction was presumed to be a radical.

Next, we examined the generality of the present process by varying the amines at the second step. The results are presented in Table 3. The reaction of 3,4-dimethoxybenzaldehyde with secondary amines under the present reaction conditions gave high yields of the corresponding amides (entries 1–3), while the reaction with a sterically hindered amine, *t*-BuNH<sub>2</sub>, or weakly nucleophilic amines such as 1-naphthylamine and 1,2,3,4-tetrahydroquinoline gave moderate yields of the corresponding amides.

In conclusion, we developed a method of preparing acid bromides directly from aldehydes with readily available Br<sub>3</sub>CCO<sub>2</sub>Et under radical conditions. The present process is easy to perform, and could be applied to the preparation of various acid bromides. In addition, the present method afforded several advantages including neutral reaction conditions and low toxicity of the reagents.

A typical experimental procedure is as follows. A mixture of *p*-methoxybenzaldehyde (62 μL, 0.5 mmol) and Br<sub>3</sub>CCO<sub>2</sub>Et (487 mg, 1.5 mmol) in chlorobenzene (4 mL) under argon was heated to 110 °C for 24 h. During the reflux, benzoyl peroxide (121 mg, 0.5 mmol) was added portionwise to the mixture four times. The

**Table 3.** Preparation of various amides from 3,4-dimethoxybenzaldehyde

| Entry | Amine   | Product <sup>a</sup>  | Isolated yield (%) |
|-------|---|---|--------------------|
| 1     |  |  | 72                 |
| 2     |  |  | 70                 |
| 3     |  |  | 73                 |
| 4     |  |  | 65                 |
| 5     |  |  | 62                 |
| 6     |  |  | 51                 |

<sup>a</sup> Identification of the products was ascertained by <sup>1</sup>H NMR and mass spectroscopy and by comparison with available physical and spectroscopic data.

mixture was cooled to room temperature, and Et<sub>3</sub>N (210 μL, 1.5 mmol) and cyclohexylamine (73 μL, 0.75 mmol) were added subsequently. The mixture was stirred at room temperature for 1 h, and the mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub>, washed with water, and dried over anhydrous MgSO<sub>4</sub>. After evaporation, the residue was purified by column chromatography on silica gel eluting with hexane/EtOAc (8:2) to give *p*-methoxy-*N*-cyclohexyl benzamide (84 mg, 72%); mp 159–162 °C (lit.<sup>13</sup> 159–162 °C); IR (KBr) 3331, 2936, 2853, 1626, 1608, 1335, 1253, 1029 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.64–2.07 (m, 10H), 3.87 (s, 3H), 3.95–4.00 (m, 1H), 5.91 (br, 1H), 6.94 (d, *J* = 8.8 Hz, 2H), 7.74 (d, *J* = 8.8 Hz, 2H); MS *m/z* (relative intensity) 233 (M<sup>+</sup>, 26), 151 (39), 135 (100), 92 (8), 77 (11).

### Acknowledgments

This work was supported by joint research project under the KOSEF-NRCT cooperative program (F01-2004-000-10252-0) and CBMH.

### References and notes

- (a) *The Chemistry of Acyl Halides*; Patai, S., Ed.; Interscience: New York, 1972; (b) Larock, R. C. *Comprehensive Organic Transformations*; VCH: New York, 1989.
- Benz, G. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 6, pp 381–418.
- (a) Villeneuve, G. B.; Chan, T. H. *Tetrahedron Lett.* **1997**, 38, 6489; (b) Azumaya, I.; Okamoto, T.; Imabeppu, F.; Takayanagi, H. *Tetrahedron* **2003**, 59, 2325.
- (a) Jang, D. O.; Park, D. J.; Kim, J. *Tetrahedron Lett.* **1999**, 40, 5323; (b) Girard, C.; Tranchant, I.; Nioré, P.-A.; Herscovici, J. *Synlett* **2000**, 1577; (c) Vágó, I.; Greiner, I. *Tetrahedron Lett.* **2002**, 43, 6039; (d) Kang, D. H.; Joo, T. Y.; Lee, E. H.; Chaysripongkul, S.; Chavasiri, W.; Jang, D. O. *Tetrahedron Lett.* **2006**, 47, 5693.
- Clarke, H. T.; Taylor, E. R. *Org. Syn. Coll.* **1941**, 1, 155.
- (a) Stavber, S.; Planinsek, Z.; Zupan, M. *Tetrahedron Lett.* **1989**, 30, 6095; (b) Stavber, S.; Planinsek, Z.; Zupan, M. *J. Org. Chem.* **1992**, 57, 5334.
- Banks, R. E.; Lawrence, N. J.; Popplewell, A. L. *Synlett* **1994**, 831.
- Lee, K. H. *Tetrahedron* **1969**, 25, 4363.
- (a) Ginsburg, D. *J. Am. Chem. Soc.* **1951**, 73, 702; (b) Wilson, S. R.; Tofigh, S.; Misra, R. N. *J. Org. Chem.* **1982**, 47, 1360.
- (a) Seubold, F. H., Jr. *J. Am. Chem. Soc.* **1947**, 69, 2916; (b) Ol'dekop, Y. A.; Kalinina, A. M. *Zh. Obshch. Khim.* **1964**, 34, 3473.
- (a) Cheung, Y.-F. *Tetrahedron Lett.* **1979**, 3809; (b) Markó, I. E.; Mekhalfia, A. *Tetrahedron Lett.* **1990**, 31, 3809.
- Some recent reports on the synthesis of thioesters from aldehydes under radical conditions: (a) Nambu, H.; Hata, K.; Matsugi, M.; Kita, Y. *Chem. Eur. J.* **2005**, 11, 719; (b) Nambu, H.; Hata, K.; Matsugi, M.; Kita, Y. *Chem. Commun.* **2002**, 1082; (c) Takagi, M.; Goto, S.; Tazaki, M.; Matsuda, T. *Bull. Chem. Soc. Jpn.* **1980**, 53, 1982.
- Cannon, G. W.; Grebber, K. K.; Hsu, Y. *J. Org. Chem.* **1953**, 18, 516.