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A mild and efficient reaction for conversion of carboxylic acids into acid bromides with ethyl tribromoacetate/triphenylphosphine under acid-free conditions

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Abstract—Acid bromides were prepared efficiently from carboxylic acids with readily available ethyl tribromoacetate and triphenylphosphine at room temperature under neutral conditions. The present process is applicable to the preparation of various acid bromides from aromatic and aliphatic carboxylic acids. Aromatic carboxylic acids were found to be more reactive than aliphatic carboxylic acids under reaction conditions.
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Acid halides have been playing an important role as intermediates for the synthesis of esters, amides, and other carboxylic acid derivatives.[1] A variety of coupling reagents have also been used for the formation of these compounds directly from carboxylic acids.[2] However, the coupling reagents failed in forming the desired compounds such as amides with carboxylic acids and amines with low nucleophilicity or steric hindrance.[3] Hence, there is still a need to utilize acid halides for preparing various carboxylic acid derivatives. Compared with acid chlorides,[1] acid bromides are less commonly employed for the purpose even though they have higher reactivity than the corresponding acid chlorides because relatively few methods have been reported on preparing acid bromides, and the brominating agents are not readily available.[4] Herein, we report on a method of preparing acid bromides from carboxylic acids with readily available triphenylphosphine (PPh₃) and ethyl tribromoacetate (Br₃CCO₂Et) under mild and neutral conditions.

Based on the previous studies,[5] we presumed that the reaction of Br_3CCO_2Et with PPh_3 readily formed an acyloxyphosphonium bromide intermediate, which would react readily with carboxylic acids. As expected, the treatment of benzoic acid with 1.1 equiv of Br_3CCO_2Et and 1.1 equiv of Ph_3P in CH_2Cl_2 at room temperature for 3 h gave cyclohexyl benzamide in 66% yield along with the unreacted benzoic acid (Table 1, entry 1). The benzoic acid treatment was followed by conversion of the produced acid bromide into the amide with 1.0 equiv of cyclohexylamine in the presence of 3.0 equiv of Et_3N. The reaction proceeded completely within 3 h with 2.0 equiv of Br_3CCO_2Et and 2.0 equiv of Ph_3P affording 92% yield of amide (entry 2). When the reaction was carried out in the presence of cyclohexylamine and Et_3N at the first step, the yield of amide decreased slightly (entry 3). Next, we examined the reactivity of other reagents as the brominating reagents of carboxylic acids. Tribromoacetic amide afforded a relatively high yield of amide (entry 5), whereas tribromoacetic acid gave a poor yield (entry 4). We expected that the combination of Br_3CNO_2 and Ph_3P may afford a highly reactive species for the synthesis of acid bromides because Br_3CNO_2 may be more reactive in a halophilic process. However, the reaction of benzoic acid with Br_3CNO_2/Ph_3P afforded a moderate yield of amide (entry 6). An increase in the amount of Br_3CNO_2 was
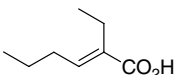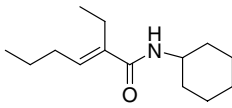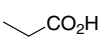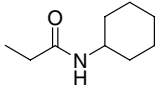
Table 1. Synthesis of *N*-cyclohexyl benzamide by the reaction of benzoic acid with Br_3CO_2Et/PPh_3
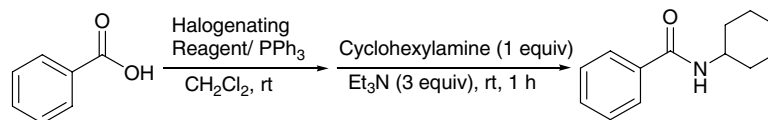
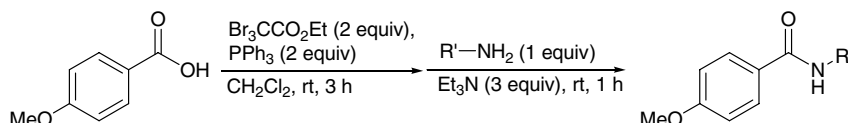| Entry	Halogenating reagents (equiv)	Ph$_3$P (equiv)	Time (h)	Yield (%)
1	Br$_3$CCO$_2$Et (1.1)	1.1	3	66
2	Br$_3$CCO$_2$Et (2.0)	2.0	3	92
3	Br$_3$CCO$_2$Et (2.0)	2.0	3	51[a]
4	Br$_3$CCO$_2$H (2.0)	2.0	1	43
5	Br$_3$CCONEt$_2$ (2.0)	2.0	1	72
6	Br$_3$CNO$_2$ (1.0)	1.0	3	40
7	Br$_3$CNO$_2$ (2.0)	2.0	3	51
8	Br$_3$CNO$_2$ (2.0)	2.0	4	47[b]
9	Br$_3$CNO$_2$ (10)	2.0	3	36

[a] The reaction was carried out in one pot.
[b] The reaction was performed at −10 °C.

Table 2. Synthesis of amides from various carboxylic acids and cyclohexylamine with Br_3CCO_2Et/PPh_3[a]
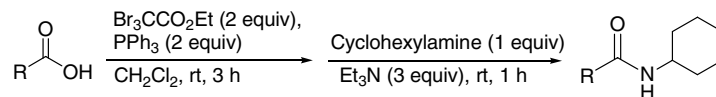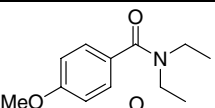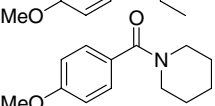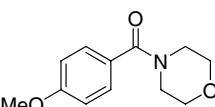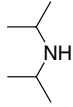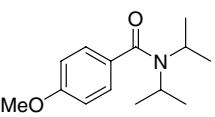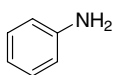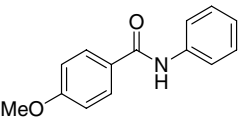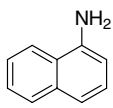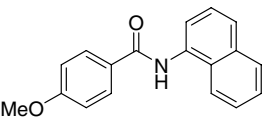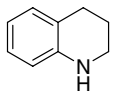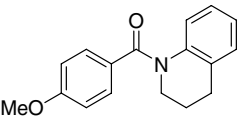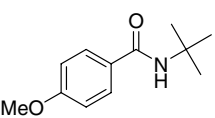

Entry	Carboxylic acid	Product	Isolated yield (%)
1			91
2			90
3			92
4			75
5			73
6			72
7			85
8			89
9			72
10			46

Table 2 (*continued*)

Entry	Carboxylic acid	Product	Isolated yield (%)
11			32
12			61

[a] Identification of the products was ascertained by ^{1}H NMR and mass spectroscopy and by comparison with available physical and spectroscopic data.

Table 3. Synthesis of amides from *p*-methoxy benzoic acid and various amines with Br_3CCO_2Et/PPh_3[a]

Entry	Amine	Product	Isolated yield (%)
1			96
2			97
3			81
4			90
5			93
6			77
7			85
8			98

[a] Identification of the products was ascertained by ^{1}H NMR and mass spectroscopy and by comparison with available physical and spectroscopic data.

not effective and afforded a poor yield (entries 7–9). Therefore, Br_3CCO_2Et was our choice of the halogenating reagent for the preparation of carboxylic acid bromides.

With optimal reaction conditions in hand, various aromatic and aliphatic carboxylic acids were brought in to react with Br_3CCO_2Et/PPh_3 to examine the scope and limitations of the present process. The results are

98%
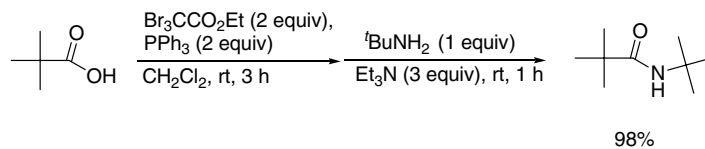
Scheme 1.

summarized in Table 2. The reaction of aromatic carboxylic acids with electron-donating groups such as *p-tert*-butylbenzoic acid and *p*-methoxybenzoic acid at room temperature afforded the corresponding amide in 91% and 90% yield, respectively (entries 1 and 2). The reaction also proceeded efficiently with a slightly deactivated aromatic carboxylic acid such as *p*-chlorobenzoic acid (entry 3). However, the yields of amide decreased with aromatic carboxylic acids that have electron-withdrawing groups, indicating that the key step for the process is the reaction of carboxylic acid with the phosphonium bromide intermediate (entries 4–6). Heteroaromatic carboxylic acids such as furan-2-carboxylic acid and thiophene-2-carboxylic acid produced amides in high yields (entries 7 and 8). α,β-Unsaturated carboxylic acids were not good substrates under the reaction conditions and afforded poor yields of amide (entries 10 and 11), although a moderate yield of amide was obtained with *trans*-cinnamic acid (entry 9). Aliphatic carboxylic acids were also found to be less reactive than aromatic carboxylic acids under the reaction conditions (entry 12).

We next investigated the generality of our process by varying the structure of amines at the second step. The results are summarized in Table 3. The reaction of *p*-methoxybenzoic acid with secondary amines under the reaction conditions afforded high yields of the corresponding amides (entries 1–4). And the amides were obtained in high yields when weakly nucleophilic amines such as aniline, 1-naphthylamine, and 1,2,3,4-tetrahydroquinoline were used as nucleophiles (entries 5–7). Moreover, the reaction with sterically hindered amines was also achieved. When the reaction was performed with ^{t}BuNH$_2$, a high yield of the amide was obtained (entry 8).

We also carried out the reaction of sterically hindered carboxylic acid, pivalic acid, with sterically hindered amine, ^{t}BuNH$_2$, under the present conditions to give 98% yield of the corresponding amide (Scheme 1).

In conclusion, we developed a method of preparing acid bromides from carboxylic acids with readily available Br$_3$CCO$_2$Et and PPh$_3$ under mild and neutral conditions. The present process is not only easy to perform but also has other advantages such as neutral reaction conditions and low toxicity of the reagents.

A typical experimental procedure is as follows: Benzoic acid (122 mg, 1.0 mmol) was added to a mixture of Br$_3$CCO$_2$Et (650 mg, 2.0 mmol) and PPh$_3$ (524 mg, 2.0 mmol) in CH$_2$Cl$_2$ (2 mL). The mixture was stirred at room temperature for 3 h. Et$_3$N (0.42 mL, 3.0 mmol) and cyclohexylamine (0.12 mL, 1.0 mmol) were added subsequently, and after stirring for 1 h at room temperature, the mixture was diluted with CH$_2$Cl$_2$, washed with water and dried over anhydrous MgSO$_4$. After evaporation, the residue was purified by column chromatography on silica gel eluting with hexane:EtOAc (8:2) to give *N*-cyclohexyl benzamide (204 mg, 90%): mp 148–149 °C (lit.[6] 147 °C); IR (KBr) 3315, 2936, 2852, 1627, 1535, 1489, 1446, 1330 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.12–2.03 (m, 10H), 3.88–4.02 (m, 1H), 6.03 (br, 1H), 7.24–7.75 (m, 5H); MS *m/z* (relative intensity) 203 (M$^+$, 51), 122 (77), 105 (100), 77 (42).

References and notes

1. (a) *The Chemistry of Acyl Halides*; Patai, S., Ed.; Interscience: New York, 1972; (b) Larock, R. C. *Comprehensive Organic Transformations*; VCH: New York, 1989.
2. Benz, G. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 6, pp 381–418.
3. (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.
4. (a) Coulson, E. A. *J. Chem. Soc.* **1934**, 1406; (b) Burton, T. M.; Degering, E. F. *J. Am. Chem. Soc.* **1940**, *62*, 227; (c) Devos, A.; Remion, J.; Frisque-Hesbain, A.-M.; Colens, A.; Ghosez, L. *J. Chem. Soc., Chem. Commun.* **1979**, 1180; (d) Aizpurua, J. M.; Palomo, C. *Synthesis* **1982**, 684; (e) Bains, S.; Green, J.; Tan, L. C.; Pagni, R. M.; Kabalka, G. W. *Tetrahedron Lett.* **1992**, *33*, 7475; (f) Fryeyen, P. *Phosphorus, Sulfur Silicon Relat. Elem.* **1995**, *102*, 253; (g) Matveeva, E. D.; Podrugina, T. A.; Sandakova, N. G.; Zefirov, N. S. *Russ. J. Org. Chem.* **2004**, *40*, 1469.
5. (a) Jang, D. O.; Park, D. J.; Kim, J. *Terahedron 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.
6. Cannon, G. W.; Grebber, K. K.; Hsu, Y. *J. Org. Chem.* **1953**, *18*, 516.