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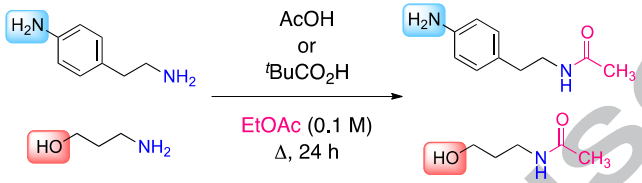

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Chemoselective *N*-acetylation of primary aliphatic amines promoted by pivalic or acetic acid using ethyl acetate as an acetyl donor

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ABSTRACT

The combination of pivalic or acetic acid as a promoter and EtOAc as a solvent and acetyl donor proved to be efficient for the chemoselective *N*-acetylation of primary aliphatic amines to afford the corresponding acetamides. We developed a simple and convenient approach, which requires mild reaction conditions. Competitive inter- and intramolecular reactions between aliphatic amines, alcohols, and aromatic amines were examined, and chemoselectivity was achieved by adjusting the conditions of the reaction.

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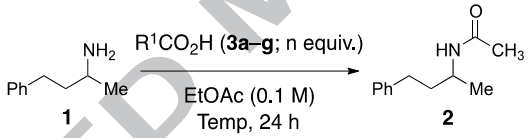
Amidation reactions, including peptide bond-forming reactions, are one of the most fundamental transformations in organic chemistry.[1] Among them, *N*-acetylation of amines is a frequently used protecting group strategy[2,3] in organic synthesis, and a useful isolation and identification technique in natural product chemistry; moreover, acetamide is a ubiquitous functional group in organic molecules. Thus, many methods for the synthesis of acetamides have been developed to date; among these, the direct acetylation of amines with acetyl chloride[4] or acetic anhydride[5] as acetyl donors is considered to be the simplest approach. However, these reagents generally require the use of excess base, such as triethylamine, pyridine, and imidazole, resulting in the production of significant amounts of salts at the end of the reaction. Moreover, because of their high reactivity, they are not capable of selective *N*-acetylation in the presence of other functional groups. On the other hand, the direct amidation of esters has attracted significant attention in recent years as a promising amide-forming reaction. In a pioneering study, Yamamoto and co-workers have achieved a metal-templated intramolecular ester–amide exchange reaction of triamino and tetraamino esters.[6] Since then, several other direct amidation reactions of esters have been developed based on the use of metal Lewis acids,[7] bases,[8] *N*-heterocyclic carbenes,[9] and enzymes.[10] However, to the best of our knowledge, a practical Brønsted acid-promoted direct amidation of esters has not been reported until very recently.[11] Herein, we describe a simple and efficient chemoselective *N*-acetylation of primary aliphatic amines promoted by pivalic or acetic acid using EtOAc as a solvent and acetyl donor, under mild reaction conditions.

To optimize the reaction conditions, we chose the *N*-acetylation of primary aliphatic amine **1** with a branched alkyl chain as a model reaction (Table 1). At first, a variety of aliphatic and aromatic carboxylic acids with increasing *p*Ka values were examined for the *N*-acetylation of **1** in EtOAc at 70 °C for 24 h (entries 1–7). The reaction using the strong acid CF_3CO_2H (**3a**, *p*Ka = 0.23[12]) gave no product (entry 1). When CH_3CO_2H (**3b**) or $CH_3CH_2CO_2H$ (**3c**) with similar *p*Ka values (4.76[12] and 4.87[13]) were used, acetamide **2** was obtained in 74% yield (entries 2 and 3). When the reaction was carried out using $^tBuCO_2H$ (**3d**, *p*Ka = 5.05[14]), which has the highest *p*Ka among the tested acids, starting material **1** was almost completely consumed to afford acetamide **2** in 91% yield (entry 4). The same tendency was observed using aromatic carboxylic acids (**3e**, *p*Ka = 3.99;[15] **3f**, *p*Ka = 4.21;[15] and **3g**, *p*Ka = 4.47[15]): the yield of **2** increased with increasing *p*Ka values (entries 5–7). In order to achieve complete consumption of **1**, the reaction was performed at reflux (90 °C) in an oil bath in the presence of an equimolar amount of **3b** or **3d**, and both reactions proceeded smoothly to afford **2** in high yield (entries 8 and 9). The same reaction was carried out by increasing or decreasing the amount of **3d**, and high yields were obtained by using double or half amount of **3d** (entries 10 and 11). However, the use of 0.1 equivalents of **3d** was not sufficient to complete the reaction (entry 12). A control experiment performed in the absence of a carboxylic acid in EtOAc at 70 °C for 24 h revealed that there was no appreciable background reaction (entry 13).

Table 1 Optimization of reaction conditions for the *N*-acetylation of primary amine **1** with branched alkyl chains



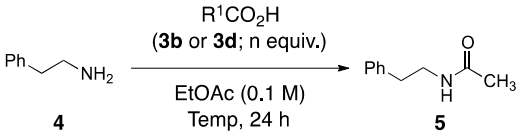
Entry	R^1CO_2H	*p*Ka	n (equiv)	Temp (°C)	Yield of **2**[a] (%)
1	CF_3CO_2H (**3a**)	0.23	1.0	70	NR[b]
2	CH_3CO_2H (**3b**)	4.76	1.0	70	74
3	$CH_3CH_2CO_2H$ (**3c**)	4.87	1.0	70	74
4	$^tBuCO_2H$ (**3d**)	5.05	1.0	70	91
5	*p*-$ClC_6H_4CO_2H$ (**3e**)	3.99	1.0	70	37
6	$PhCO_2H$ (**3f**)	4.21	1.0	70	56
7	*p*-$MeOC_6H_4CO_2H$ (**3g**)	4.47	1.0	70	64
8[c]	CH_3CO_2H (**3b**)	4.76	1.0	reflux	97
9[d]	$^tBuCO_2H$ (**3d**)	5.05	1.0	reflux	98
10	$^tBuCO_2H$ (**3d**)	5.05	2.0	reflux	99
11[c]	$^tBuCO_2H$ (**3d**)	5.05	0.5	reflux	96
12	$^tBuCO_2H$ (**3d**)	5.05	0.1	reflux	52
13	None	–	–	70	NR[b]

[a] Isolated yield.
[b] No reaction.
[c] Average of two runs.
[d] Average of three runs.

Next, we optimized the reaction conditions using amine **4** with a linear chain structure instead of branched amine **1** (Table 2). The *N*-acetylation of amine **4** in the presence of an equimolar amount of acetic acid (**3b**) as a promoter proceeded completely at both 70 °C and 50 °C to afford acetamide **5** in high yield (entries 1 and 2). On the other hand, a low yield of **5** was obtained at room temperature (entry 3). The reaction was then conducted at 70 °C using lower amounts of **3b**: a high yield was obtained in the presence of 0.5 equivalents of **3b** (entry 4), whereas using 0.1 equivalents of **3b** gave the product in moderate yield (entry 5). When pivalic acid (**3d**) was used as a promoter, the same tendency was observed (entries 6–10). In the presence of an equimolar amount of **3d**, high yields of **5** were obtained at 70 °C or 50 °C (entries 6 and 7), whereas performing the reaction at room temperature gave a very low yield (entry 8). Excellent yields of **5** were obtained at 70 °C even with catalytic amounts of

3d (entry 9). However, moderate yield was obtained at 50 °C in the presence of 0.1 equivalents of **3d** (entry 10). A comparison of the activity of carboxylic acids **3b** and **3d** for the *N*-acetylation reaction revealed that **3d** was more efficient. It should be noted that, in this case, a slight background reaction occurred in the absence of a carboxylic acid, which afforded **5** in 4% yield (entry 11).

Table 2 Optimization of reaction conditions for the *N*-acetylation of primary amine **4** with linear alkyl chains



4 **5**

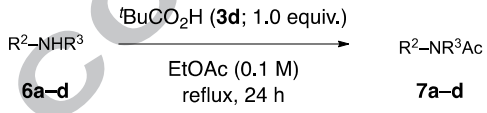
Entry	R^1CO_2H	n (equiv)	Temp (°C)	Yield of **5**[a] (%)
1	**3b**	1.0	70	99
2	**3b**	1.0	50	97
3	**3b**	1.0	RT	22
4	**3b**	0.5	70	quant
5	**3b**	0.1	70	74
6	**3d**	1.0	70	93
7	**3d**	1.0	50	98
8	**3d**	1.0	RT	19
9	**3d**	0.1	70	95
10	**3d**	0.1	50	65
11	None	–	70	4[b]

[a] Isolated yield.

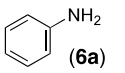
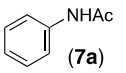
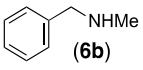
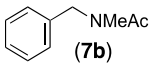
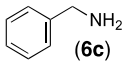
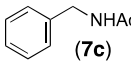
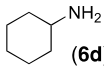
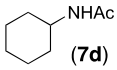
[a] NMR yield.

With the optimized conditions in hand, we next explored the scope and limitations of the reaction using several amines (Table 3). In the presence of an equimolar amount of **3d** in EtOAc at reflux for 24 h, the reaction of aromatic amine **6a** gave a low yield of the desired product **7a** (entry 1), and a moderate yield was obtained from the reaction of secondary amine **6b** (entry 3). On the other hand, the reactions of aliphatic primary amines **6c** and **6d** gave high yields of the corresponding products (entries 5 and 6). When the reactions of **6a** and **6b** were performed under milder conditions (0.10 equivalents of ^{t}BuCO$_2$H (**3d**) at 70 °C), only traces of acetamide **7a** and small amounts of **7b** were obtained, respectively (entries 2 and 4). This result indicates that chemoselectivity between aromatic and aliphatic amines in the *N*-acetylation reaction is achieved under the above reaction conditions.

Table 3 *N*-Acetylation of several kinds of amines



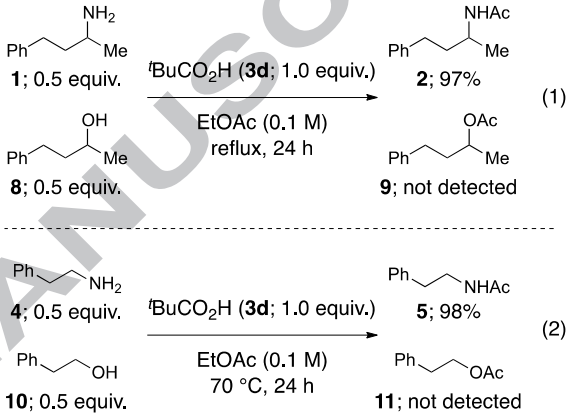
6a–d **7a–d**

Entry	6	7	Yield of **7**[a] (%)
1	 (**6a**)	 (**7a**)	16
2[b]			trace
3	 (**6b**)	 (**7b**)	77
4[b]			8
5	 (**6c**)	 (**7c**)	quant
6	 (**6d**)	 (**7d**)	99

[a] Isolated yield.

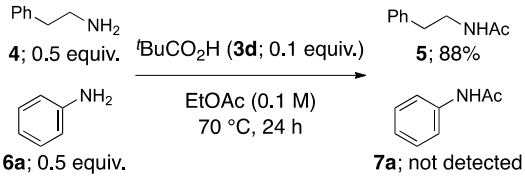
[b] The reaction was carried out using 0.10 equiv of ^{t}BuCO$_2$H (**3d**) at 70 °C.

To demonstrate the utility of this approach, the intermolecular competitive acetylation between amines and alcohols was examined, as shown in Scheme 1. When equimolar amounts of amine **1** and alcohol **8** with the same branched alkyl substituents were subjected to the reaction in the presence of an equivalent amount of ^{t}BuCO$_2$H (**3d**) in EtOAc at reflux for 24 h, acetamide **2** was obtained in 97% yield and acetate **9** was not detected (eq. 1). In the reaction of equimolar amounts of amine **4** and alcohol **10** with the same linear alkyl structure, only acetamide **5** was obtained in high yield at a lower reaction temperature of 70 °C (eq. 2).



Scheme 1 Competitive acetylation of amine *versus* alcohol.

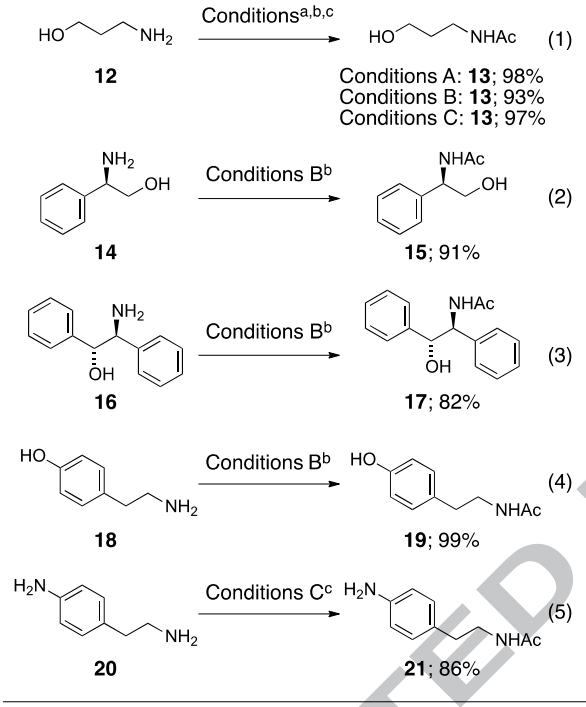
We further examined the intermolecular competitive acetylation between aliphatic amine **4** and aromatic amine **6a**, as shown in Scheme 2. Based on the results in Table 2 (entry 9) and Table 3 (entry 2), the selective acetylation of amine **4** was expected to be achieved using a catalytic amount of ^{t}BuCO$_2$H (**3d**) in EtOAc at 70 °C for 24 h. As a result, selective acetylation of **4** occurred to afford the corresponding acetamide **5** in 88% yield; acetate **7a** was not detected by ^{1}H NMR.



Scheme 2 Competitive acetylation of aliphatic primary amine *versus* aromatic amine.

Next, we examined the intramolecular competitive acetylation of aminoalcohols **12**, **14**, **16**, and **18**, and diamine **20**, with aromatic and/or aliphatic substituents, under conditions A, B, or C (Scheme 3). The reaction of aliphatic aminoalcohol **12** with linear chain structure was carried out using 1.0 equivalent of AcOH (**3b**) in EtOAc at 70 °C for 24 h (conditions A) to afford acetamide **13** in 98% yield without acetylation of the alcohol moiety (eq. (1), upper result). The same reaction was performed under conditions B (^{t}BuCO$_2$H (**3d**; 1.0 equivalent), EtOAc (0.1 M), reflux, 24 h), and C (^{t}BuCO$_2$H (**3d**; 0.1 equivalents), EtOAc (0.1 M), 70 °C, 24 h), which afforded **13** in 93% and 97% yield,

respectively (eq. (1), middle and lower results). The reactions of primary benzylic amines **14** and **16** with a branched structure and neighboring primary and secondary alcohol groups, respectively, were examined under conditions B (eqs. (2) and (3)). Whereas the reaction of **14** gave the corresponding product in high yield (eq. (2)), the reaction of **16** was not complete presumably because of steric hindrance (eq. (3)). Moreover, the reaction of linear amine **18** containing a phenol group proceeded smoothly under conditions B to afford acetamide **19** in 99% yield (eq. (4)). In the case of linear amine **20** containing an aniline moiety, reaction conditions C were adopted on the basis of the results in Scheme 2. In the event, the desired acetamide **21** was obtained in high yield (eq. (5)). These findings reveal that all reactions are highly chemoselective.

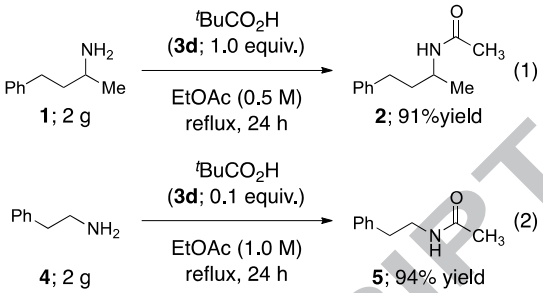


[a] Conditions A; AcOH (**3b**; 1.0 eq.), EtOAc (0.1 M), 70 °C, 24 h.

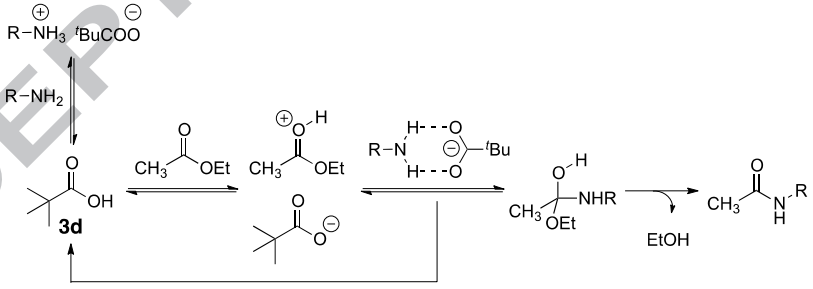
[b] Conditions B; ^{t}BuCO$_2$H (**3d**; 1.0 eq.), EtOAc (0.1 M), reflux, 24 h.

[c] Conditions C; ^{t}BuCO$_2$H (**3d**; 0.1 eq.), EtOAc (0.1 M), 70 °C, 24 h.

Scheme 3 Chemoselective *N*-acetylation of primary aliphatic amines.



Scheme 4 Gram scale synthesis of acetamides **2** and **5**.



Scheme 5 Proposed reaction pathway.

To demonstrate the practicality of this approach, the gram-scale synthesis of acetamides **2** and **5** was performed, as shown in Scheme 4. The reaction of amine **1** with a branched alkyl chain was carried out under conditions B, but a higher concentration (0.5 M) was used. As a result, the reaction proceeded smoothly, and acetamide **2** was obtained in 91% yield (eq. (1)). Similarly, the reaction of amine **4** with a linear alkyl chain was performed with a lower amount of **3d** (0.1 equivalents) and at a higher concentration (1.0 M), to afford acetamide **5** in 94% yield (eq. (2)). These results demonstrate the potential utility of the present method for the synthesis of acetamides.

A plausible reaction pathway is proposed in Scheme 5. It is considered that free amine and pivalic acid (**3d**) are in equilibrium with the corresponding salt, and EtOAc is activated by protonation by free **3d**. This is supported by the fact that when a strong acid such as CF_3CO_2H (**3a**) was used, no reaction occurred because the equilibrium is shifted toward salt formation. Next, the formed pivalate anion activates the amine, which reacts with the oxonium cation derived from EtOAc to produce the desired acetamide upon release of EtOH.

In summary, we have developed an efficient chemoselective *N*-acetylation of primary aliphatic amines, which react preferentially over alcohols and aromatic amines. The reaction is

promoted by pivalic or acetic acid using EtOAc as an acetyl donor, and the conditions were optimized by adjusting the catalyst loading and the reaction temperature. Further studies are currently in progress in our laboratory to expand the scope of this transformation.

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Supplementary Material

Supplementary data associated with this article can be found, in the online version, at

Highlights

1. A chemoselective *N*-acetylation of primary aliphatic amines was achieved.
2. Ethyl acetate was used as an acetyl donor.
3. This method is very simple and convenient for the preparation of acetamides.