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Amidation Reaction of Carboxylic Acid with Formamide Derivative Using SO_3•pyridine

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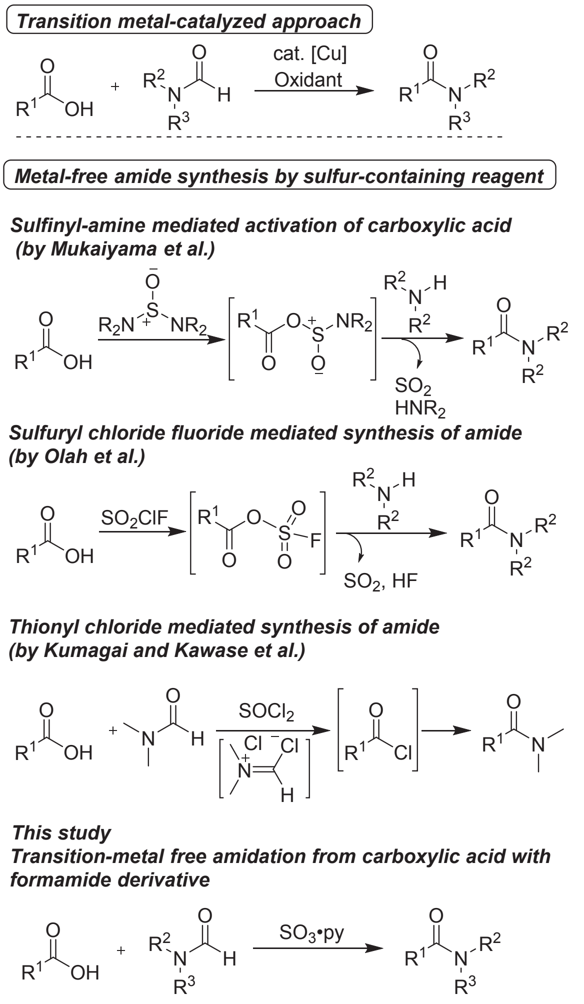
The amidation reaction of carboxylic acid derivatives was developed using sulfur trioxide pyridine complex (SO_3•py) as a commercially available and easily handled oxidant. This method could be applied to the reaction of various aromatic and aliphatic carboxylic acids, including optically active ones, with formamide derivatives to afford the corresponding amides in good to high yields.

Keywords: Amidation | Sulfur oxide | Metal-free synthesis

Amides widely exist in various natural products, useful pharmaceuticals, as well as in important synthetic building blocks. Due to their importance and broad applications, a variety of methodologies for their synthesis have been developed.[1] However, traditional synthetic routes to amides usually require multiple steps, and toxic or expensive reagents. For these reasons, considerable effort has been made for developing efficient and economically friendly methods, which are still highly desirable.

A carboxylic acid is one of the most ideal substrates of amide synthesis. Recently, the Cu-catalyzed amidation reaction using carboxylic acid derivatives with formamide derivatives was reported by several research groups (Scheme 1).[2] As a seminal work, Reddy's group reported the Cu-catalyzed amidation reaction of various carboxylic acids with *N*,*N*-dialkyl formamide derivatives using *tert*-butyl hydroperoxide (TBHP) as a re-oxidant.[2a] After this report, although the Cu-catalyzed oxidative coupling was frequently used,[2b–2d] the development of other methods was not fully achieved.[2e] In particular, there is concern over metal contamination for the transition metal catalyzed methodologies. Thus, the development of alternative approaches toward amides is highly desirable, and in this context, transition-metal-free protocols appear particularly more attractive.

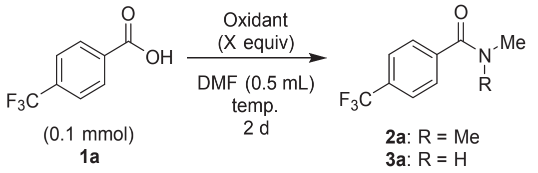
A carboxylic acid could be generally activated either by transformation into more reactive derivatives or by the use of condensation reagent under transition-metal-free conditions.[3] Among several works for the metal-free synthesis of amides using a carboxylic acid as the starting material, the use of a sulfur-containing reagent that mediated the in situ activation of carboxylic acids is one of the representative approaches (Scheme 1). Mukaiyama et al. reported sulfinyl amine mediated amidation reaction of carboxylic acids with secondary amines.[4] However, the generality of this method was not fully investigated, and it was needed to prepare the sulfinyl amine. Although Olah's group also reported SO_2ClF-mediated method,[5] and Kumagai and Kawase more recently developed $SOCl_2$-mediated conversion of carboxylic acid to amides,[6] these sulfur oxide derivatives are toxic and moisture sensitive. Among sulfur oxide derivatives,[7] sulfur trioxide pyridine complex (SO_3•py) is a solid substance and could be easily available from commercial sources and handled on the bench. Although the formation of an acylated sulfuric acid as an intermediate in the reaction with an aliphatic carboxylic acid with SO_3 is known, the application of this intermediate to convert to an amide has not been reported.[8] We now wish to report SO_3•py mediated amide synthesis using carboxylic acid as the starting material. A wide substrate scope was confirmed for the synthesis of aromatic, aliphatic, and optically active amides.



Scheme 1. Related studies for the synthesis of an amide from a carboxylic acid and this study.

We initially selected 4-(trifluoromethyl)benzoic acid **1a** as the model substrate and treated it with $(NH_4)_2S_2O_8$ in DMF.[9] At first, we examined the effect of the reaction temperature. When this reaction was carried out at 120 °C, no reaction was observed (Table 1, Entry 1). When this reaction was done at 140 °C, the corresponding amide **2a** was obtained in 42% and **1a** was recovered in 56% yield (Entry 2). Although a higher temperature was employed for this reaction to improve the conversion of

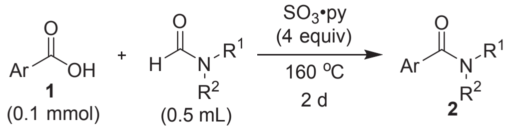
Table 1. Examination of reaction conditions

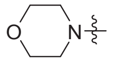


Entry	Oxidant	X /equiv	Temp /°C	Yield of **2a** /%[a]	Yield of **3a** /%[a]	RSM /%[a]
1	$(NH_4)_2S_2O_8$	2	120	No reaction		
2	$(NH_4)_2S_2O_8$	2	140	42	0	56
3	$(NH_4)_2S_2O_8$	2	160	30	6	18
4	$(NH_4)_2S_2O_8$	4	160	56	13	8
5	$K_2S_2O_8$	4	160	47	23	24
6	H_2SO_4	4	160	81	0	4
7	SO_3•py	4	160	96[b]	0	0
8[c]	SO_3•py	4	160	95[b]	0	0
9	none	—	160	15	4	80

[a]NMR yields. [b]Isolated yields. [c]1,2-Dichlorobenzene (DCB) was used as co-solvent (DCB:DMF = 3:2, 0.5 mL).

Table 2. Generality of amidation of aromatic carboxylic acids



Entry	Ar	R^1	R^2	**2**	Yield[a]
1	4-$CF_3C_6H_4$	Me	Me	**2a**	96
2	4-$NO_2C_6H_4$	Me	Me	**2b**	quant
3[b]	4-MeC_6H_4	Me	Me	**2c**	87
4[b]	4-$MeOC_6H_4$	Me	Me	**2d**	82
5[b]	4-PhC_6H_4	Me	Me	**2e**	87
6[b]	1-Naphthyl	Me	Me	**2f**	83
7	2-IC_6H_4	Me	Me	**2g**	quant
8	2-MeC_6H_4	Me	Me	**2h**	97
9[b]	3-HOC_6H_4	Me	Me	**2i**	63
10	4-$CF_3C_6H_4$	Et	Et	**2j**	74
11	4-$CF_3C_6H_4$			**2k**	84
12[b,c]	4-$NO_2C_6H_4$	Me	Bn	**2l**	79

[a]Isolated yields. [b]1,2-Dichlorobenzene (DCB) was used as a co-solvent (DCB:formamides = 3:2, 0.5 mL). [c]150 °C.

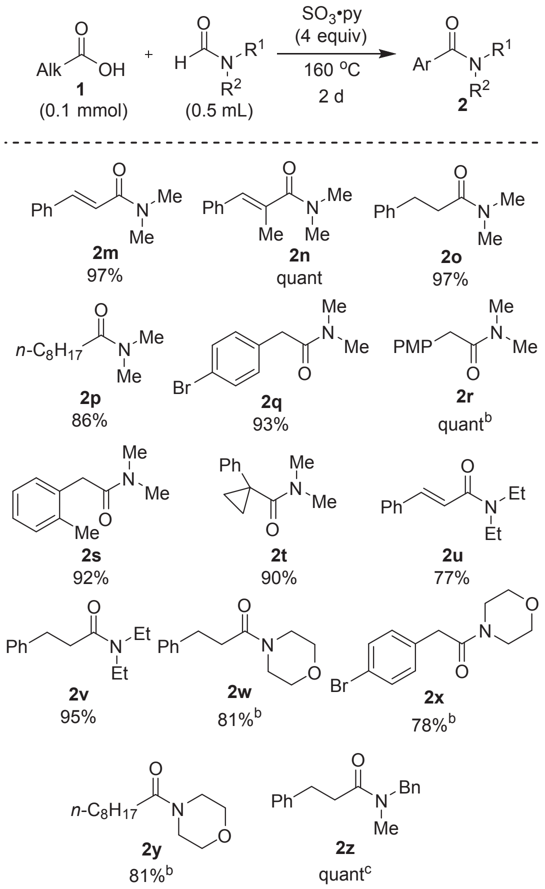


Figure 1. Generality of amidation of conjugated and aliphatic carboxylic acids. [a]Isolated yields. [b]DCB:formamides = 3:2 (0.5 mL) was used. [c]*N*-Benzyl-*N*-methylformamide (0.3 mL) was used. PMP = 4-methoxyphenyl.

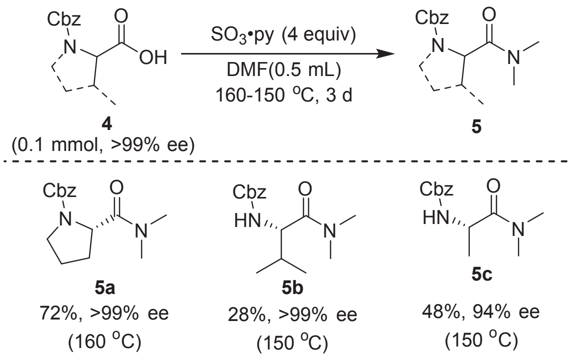


Figure 2. Amidation of amino acids.

the starting material, the yield of **1a** decreased, involving the formation of the side-product **3a** (Entry 3). The use of 4 equivalents of $(NH_4)_2S_2O_8$ resulted in the improvement of the yield of **2a** and the conversion of **1a**, however, the production of **3a** increased (Entry 4). Next, we investigated the effect of sulfur oxides. Although the significant formation of **3a** was observed in the case of $K_2S_2O_8$ (Entry 5), the use of H_2SO_4 and SO_3•py dramatically improved the efficiency of this amidation reaction to furnish **2a** in 81% and 96% yields, respectively (Entries 6 and 7).[10–12] As another available conditions, we discovered that 1,2-dichlorobenzene could be used as a co-solvent for this reaction and the amount of DMF could be reduced by approximately half (Entry 8).[13] We studied the thermally-induced background reaction in the absence of the sulfur oxide, revealing that the reaction was highly accelerated by the addition of the sulfur oxide (Entry 9). Finally, we concluded that Entries 7 and 8 were the optimal conditions.

With the optimized reaction conditions in hand, the scope of the aromatic carboxylic acid in SO_3•py mediated amidation reaction was next examined using various formamide derivatives (Table 2). The reaction of an aromatic carboxylic acid bearing an electron-withdrawing group **1b** smoothly provided **2b** quantitatively. Electron-donating group substituted aromatic carboxylic acids were also applicable to give the corresponding amides **2c** and **2d** in good yields under similar reaction conditions. Substitution of a phenyl group and fused aromatic ring, such as the 1-naphthyl structure, did not affect the efficiency of this amidation. Substrates **2g** and **2h** bearing an ortho-substituted aromatic ring also displayed high reactivities. 3-Hydroxybenzoic acid **1i** could be directly transformed into **2i** without the protection of the hydroxy group. *N*,*N*-Diethylformamide, 4-formylmorpholine and *N*-benzyl-*N*-methylformamide were also applicable for this reaction as an amidation reagent to give the corresponding amides **2j–2l** in good yields.

Next, we investigated the scope of the amidation reaction using various conjugated and aliphatic carboxylic acids (Figure 1). Cinnamic acid and its derivative were successfully converted to the corresponding amides **2m** and **2n** in high yields. Substrates **1o** and **1p** bearing simple alkyl groups, such as phenethyl and *n*-octyl, were also applicable. Benzyl amide derivatives containing various functional groups and the substrate bearing a quaternary carbon center at the α-position were tolerant to the conditions, furnishing **2q–2s** in high yields. These substrates could be applied to the amidation reactions with other amidation reagents to give **2t–2z** in good yields.

A further substrate scope was explored by using amino acid derivatives (Figure 2). When *N*-Cbz-L-proline was employed for this reaction, the corresponding amide **5a** was obtained in good yields without any loss of the enantiomeric excess.[14,15] Although *N*-CBz-L-valine and *N*-CBz-L-alanine were not efficiently converted to amides, the ees of the starting materials were highly retained under the optimized conditions.

In summary, we have established SO_3•py based conditions for the amidation of aromatic and aliphatic carboxylic acid with various formamide derivatives. Using this protocol, the corresponding amides were obtained in good to high yields. Elucidation of the detailed reaction mechanism and exploration of further application of this method are currently underway in our laboratory.

Supporting Information is available on http://dx.doi.org/10.1246/cl.171216.

This communication is dedicated to Professor Teruaki Mukaiyama in celebration of his 90th birthday.

References and Notes

1. For selected reviews of amide synthesis, see: a) E. Valeur, M. Bradley, *Chem. Soc. Rev.* **2009**, *38*, 606. b) V. R. Pattabiraman, J. W. Bode, *Nature* **2011**, *480*, 471. c) R. M. Lanigan, T. D. Sheppard, *Eur. J. Org. Chem.* **2013**, 7453.
2. a) P. S. Kumar, G. S. Kumar, R. A. Kumar, N. V. Reddy, K. R. Reddy, *Eur. J. Org. Chem.* **2013**, 1218. b) Y.-X. Xie, R.-J. Song, X.-H. Yang, J.-N. Xiang, J.-H. Li, *Eur. J. Org. Chem.* **2013**, 5737. c) H. Li, C. Pan, Y. Cheng, C. Zhu, *Tetrahedron Lett.* **2013**, *54*, 6679. d) S. Priyadarshini, P. J. A. Joseph, M. L. Kantam, *RSC Adv.* **2013**, *3*, 18283. Silver-catalyzed amidation reaction of α-keto acids, see: e) X. Zhang, W. Yang, L. Wang, *Org. Biomol. Chem.* **2013**, *11*, 3649.
3. Representative examples, see: a) J. C. Sheehan, G. P. Hess, *J. Am. Chem. Soc.* **1955**, *77*, 1067. b) J. D. Wilson, C. F. Hobbs, H. Weingarten, *J. Org. Chem.* **1970**, *35*, 1542. c) T. Yasuhara, Y. Nagaoka, K. Tomioka, *J. Chem. Soc., Perkin Trans. 1* **2000**, 2901. d) C. Burnell-Curty, E. J. Roskamp, *Tetrahedron Lett.* **1993**, *34*, 5193. e) P. Frøyen, *Synth. Commun.* **1995**, *25*, 959. f) D. O. Jang, D. J. Park, J. Kim, *Tetrahedron Lett.* **1999**, *40*, 5323. g) K. Ishihara, S. Ohara, H. Yamamoto, *J. Org. Chem.* **1996**, *61*, 4196. h) M. Thorsen, T. P. Andersen, U. Pedersen, B. Yde, S.-O. Lawesson, H. F. Hansen, *Tetrahedron* **1985**, *41*, 5633. i) Y. Basel, A. Hassner, *Tetrahedron Lett.* **2002**, *43*, 2529. j) R. Sanchez, G. Vest, L. Despres, *Synth. Commun.* **1989**, *19*, 2909. k) K. S. Keshavamurthy, Y. D. Vankar, D. N. Dhar, *Synthesis (Mass.)* **1982**, 506. l) M. A. Bailén, R. Chinchilla, D. J. Dodsworth, C. Nájera, *Tetrahedron Lett.* **2000**, *41*, 9809. m) K. Ishihara, Y. Lu, *Chem. Sci.* **2016**, *7*, 1276. n) H. Noda, M. Furutachi, Y. Asada, M. Shibasaki, N. Kumagai, *Nat. Chem.* **2017**, *9*, 571.
4. T. Mukaiyama, H. Takei, H. Shimizu, *Bull. Chem. Soc. Jpn.* **1967**, *40*, 939.
5. G. A. Olah, S. C. Narang, A. Garcia-Luna, *Synthesis (Mass.)* **1980**, 661.
6. T. Kumagai, T. Anki, T. Ebi, A. Konishi, K. Matsumoto, H. Kurata, T. Kubo, K. Katsumoto, C. Kitamura, T. Kawase, *Tetrahedron* **2010**, *66*, 8968.
7. Other examples using sulfur-containing reagents, see: a) A. Khalafi-Nezhad, A. Parhami, M. N. S. Rad, A. Zarea, *Tetrahedron Lett.* **2005**, *46*, 6879. b) C. O. Kangani, D. E. Kelley, *Tetrahedron Lett.* **2005**, *46*, 8917.
8. a) W. E. Truce, C. E. Olson, *J. Am. Chem. Soc.* **1953**, *75*, 1651. b) H. Yamaguchi, S. Akieda, *Nippon Kagaku Kaishi* **1980**, 285.
9. Examination of amidation reaction using dialkyl amine as amine source resulted in failure. Therefore, DMF was used as dimethyl amine source.
10. Although H_2SO_4 is one of the most ideal sulfur oxides and we extensively examined the reaction conditions using H_2SO_4, side products **3** (*N*-methyl amides) were significantly observed in the reactions of aromatic carboxylic acids bearing an electron-donating group such as **1c** and **1d**.
11. We also investigated on the effect of the addition of H_2O (10 equivalents) under the condition based on Entry 7 in Table 1, in which the yield of **2a** dramatically decreased.
12. According to previous reports,[8] the reaction of sulfur trioxide with a carboxylic acid proceeds to afford the corresponding acylated sulfuric acid intermediate. The intermediate would react with DMF under high temperature, involving the release of carbon monoxide and sulfuric acid, to furnish the amide.
13. It was found that DCB was the best for this reaction after co-solvent screening. However, the effect of DCB is not clear.
14. When L-proline was employed for this reaction, no reaction was observed. Therefore, we used *N*-protected amino acids as the substrates.
15. After several examinations of the reaction temperature and time using an amino acid derivative as a substrate, it turned out that the yield tends to be improved by performing the reaction at a slightly lower temperature (150 °C) and longer reaction time (3 d) in some cases. The enantiomeric excess did not change below 160 °C.