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Novel and efficient method for esterification, amidation between carboxylic acids and equimolar amounts of alcohols, and amines utilizing Me_2NSO_2Cl and *N*,*N*-dimethylamines; its application to the synthesis of coumaperine, a natural chemopreventive dieneamide

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Abstract—Various carboxylic esters or amides were prepared in good to excellent yield between carboxylic acids and equimolar amounts of alcohols or amines under very mild conditions (0–45°C; within 3 h) using dimethylsulfamoyl chloride (Me_2NSO_2Cl; **1**) combined with *N*,*N*-dimethylamines (Me_2NR: **2a**; R=Me, **2b**; R=Bu). The choice of the sulfamoyl chloride and the amine is crucial for the reaction; that is, sterically uncrowded amines accelerated the present esterification and amidation. This agent had some advantages over methanesulfonyl chloride (**3**)/amines as for the atom-economy, avoidance of side reactions, and had very high chemoselectivity toward the carboxyl group vs the hydroxyl group; the experiment was performed by the addition of **1** to the mixture of carboxylic acids and alcohols. Application of this method to the synthesis of coumaperine, a chemopreventive natural product, was performed using the present amidation as a key step.

1. Introduction

From the standpoint of elaborated complex natural product synthesis and process chemistry, mild and effective esterification or amidation between equimolar amounts of carboxylic acids and alcohols or amines is one of the most frequently used unit reactions due to its broad utility.[1] Several efficient methods have been exploited for the esterification and/or amidation using specific dehydrating reagents under mild liquid-phase conditions; 1,3-dicyclohexylcarbodiimide (DCC),[2] halopyridinium salts,[3] 2,4,6-trichlorobenzoyl chloride,[4] $(Im)_2CO$ (*N*,*N*-carbonyldiimidazole),[5] bis(2-oxo-3-oxazoilodinyl)phosphinic chloride (BOP-Cl),[6] di-2-pyridyl carbonate (DPC),[7] di-2-pyridyl thiocarbonate (DPTC),[8] 2-methyl-6-nitrobenzoic anhydride (MNBA)[9] and other condensation agents.[10]

In view of green chemistry, there still remains a strong need for simpler, more convenient, inexpensive, and atom-economical agents. The mixed anhydride method using different counter acids is recognized as a rational process. The method using counter sulfonyl mixed anhydrides with carboxylic acids is a promising candidate due to its simplicity, availability, and economy.

Consistent with our interests in green chemical esterifications,[11] sulfonylations,[12] and silylations,[13] we have reported some methods for smooth sulfonylations of alcohols using sulfonyl chlorides promoted by the sterically unhindered amines such as Me_3N and $Me_2N(CH_2)nNMe_2$, wherein these amines significantly activate sulfonyl chlorides with formation of the reactive sulfonylammonium chloride intermediates. We describe the full details[14] of a novel efficient condensation agent for esterification and amidation, dimethylsulfamoyl chloride (Me_2NSO_2Cl; **1**) together with sterically unhindered *N*,*N*-dimethylamines (Me_2NR: **2a**; R=Me, **2b**; R=Bu) (Scheme 1), and its application to the synthesis of coumaperine, a naturally occurring bioactive compound, using the present amidation method as a key step.

Keywords: esterification; amidation; sulfamoyl chloride; tertiary amine; coumaperine.

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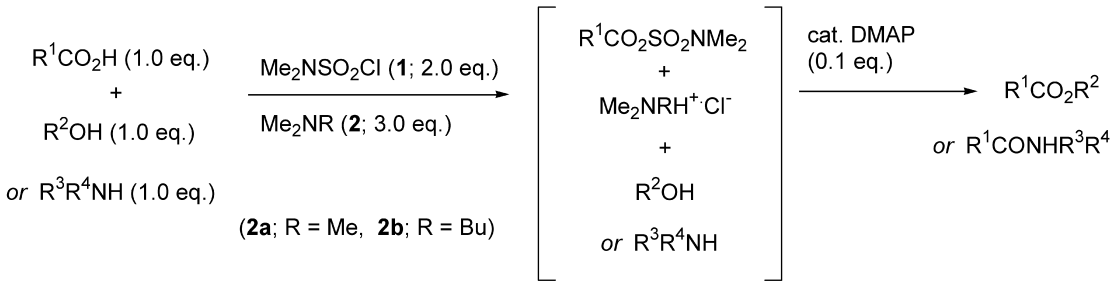


Scheme 1.

2. Results and discussion

We focused on the mixed anhydride formation between carboxylic acids and sulfonyl chlorides, because some sulfonyl chlorides are more inexpensive and atom-economic than acid chlorides such as 2,4,6-trichlorobenzoyl chloride.[4] Thus, use of commercially available sulfonyl chlorides and tertiary amines was initially examined.

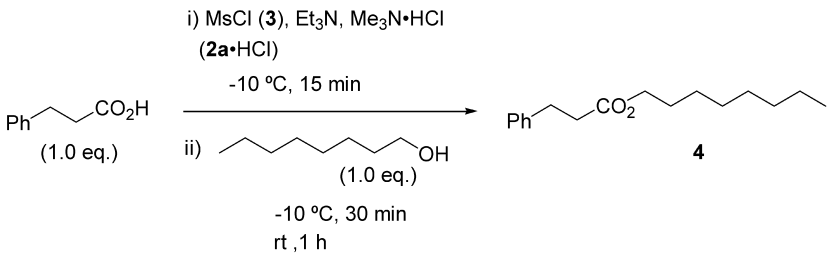
Methanesulfonyl chloride (MsCl; **3**) is the most obvious candidate, and a study using **3** together with Et_3N has been reported.[10g] As shown in Table 1, reexamination of this method in our hands revealed that the high yields previously reported were not reproducible; excess amounts of **3** (2.0 equiv.) and Et_3N (4.0 equiv.) were required for esterification (reported account; 1 equiv. of **3** and 2 equiv. of Et_3N at −10°C in THF solvent). Thus, we assumed that the first step of the mixed-anhydride formation does not proceed smoothly, i.e. considerable concomitant loss of **3** occurs due to undesirable side sulfene-dimerization.[15] The addition of Me_3N·HCl to more basic Et_3N for in situ generation of Me_3N (**2a**; bp 2.9°C) and the use of 1.0 equiv. of *N*,*N*-dimethylaminopyridine (DMAP) significantly improved the yield, wherein **2a** enhanced the reactivity of **3** and DMAP accelerated the acylation step.

Although this reaction necessitated somewhat excess amounts of the condensation reagents, application of the conditions in Table 1 resulted in successful esterifications in good to high yields (Table 2).

The method using MsCl (**3**), however, was not chemoselective, that is, not applicable to the case of co-existence of acids and alcohols; methanesulfonate **10** was produced as a major by-product as exemplified in Eq. 1 of Scheme 2. Moreover, in the case of amidation using 3-phenylpropanoic acid with 1-phenethylamine produced not only the desired amide **11** but also sulfonamide **12**, which was apparently derived from the sulfene-dimerization,[15] even following the standard procedure shown in Tables 1 and 2 (Eq. 2).

To overcome these problems, we planned the use of Me_2NSO_2Cl (**1**) instead of MsCl (**3**), because **1** lacks α-hydrogens, which cause the undesirable sulfene-dimerization. The initial trial of esterification of 3-phenylpropanoic acid with an equimolar amount of 1-octanol resulted in 34% yield using Et_3N (3.0 equiv.) in MeCN at 0–5°C—room temperature (Table 3). The use of Me_3N·HCl (**2a**·HCl) also affected the present esterification, and the yield markedly increased up to 86%. The addition of DMAP (0.1 and 1.0 equiv.) enhanced the second acylation step up to 93 and

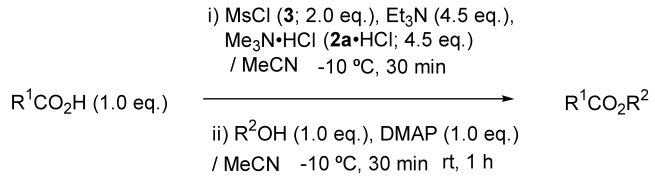
Table 1. Esterification between 3-phenylpropanoic acid and equimolar amounts of 1-octanol using MsCl (**3**)/amines

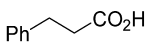
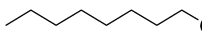
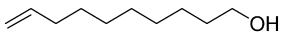
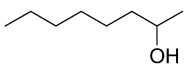
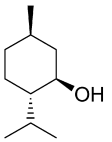
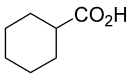
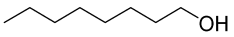


MsCl (**3**) (equiv.)	Et_3N (equiv.)	Me_3N·HCl (**2a**·HCl) (equiv.)	Solvent	Yield (%)
1.2	3.6	None	Toluene	Trace
1.2	3.6	None	THF	Trace
1.2	3.6	None	MeCN	20
1.2	3.6	1.2	MeCN	48
1.2	3.6	3.6	MeCN	60
2.0	4.5	4.5	MeCN	80
2.0	4.5	4.5	MeCN	83* [a]
2.0	4.5	4.5	MeCN	92* [b]

[a] DMAP (0.1 equiv.) was used in the second step.
[b] DMAP (1.0 equiv.) was used in the second step.

Table 2. Esterification between carboxylic acids and equimolar amounts of alcohols using MsCl (**3**)/amines

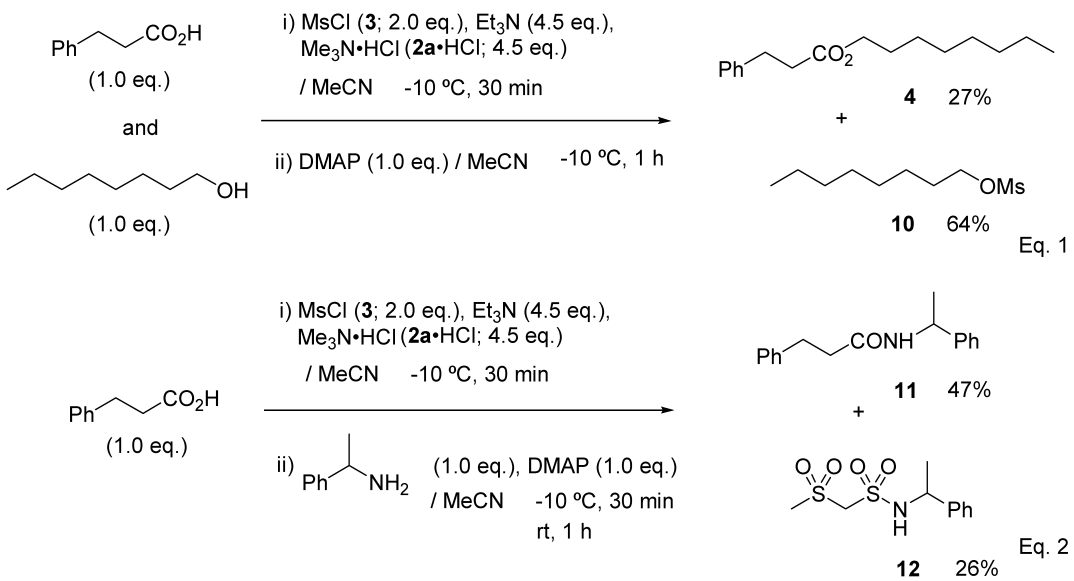


R^1CO_2H	R^2OH	Product	Yield (%)
		**4**	92 (80)* [a]
		**5**	93
		**6**	91
		**7**	89
		**8**	94
		**9**	93

[a] Without DMAP.

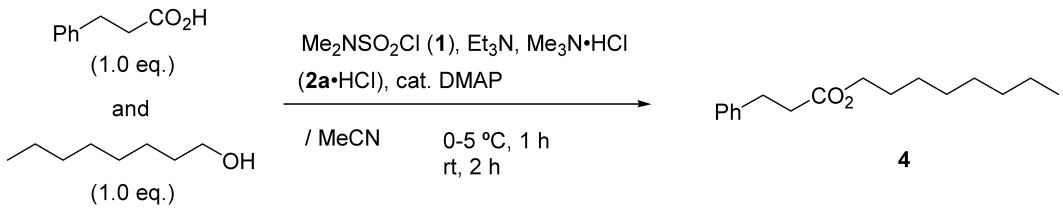
97%, respectively. (Note: After finishing this work, we have recently found that DMAP was replaced by more inexpensive and less toxic 1-methylimidazole for the acylation step. See Table 3 and Experimental Section 3.5.) The only amine used, *N*,*N*-dimethylbutylamine ($BuNMe_2$, **2b**) in the place of Et_3N and **2a**·HCl, also promoted esterification at 40–45 °C (92%). Results of the screening of other amines with DMAP (0.1 equiv.) under identical conditions were as follows; DABCO[16] (82%), TMEDA (63%), DBU (42%), and $PhCH_2NMe_2$ (31%). MeCN was a better solvent than toluene or THF.

Based on these results, esterifications between several carboxylic acids and alcohols were successfully performed (Table 4). The esters of primary and secondary alcohols were prepared in good to excellent yields under the two unified conditions. Several functionalities on alcohols such as a double and a triple bond, a halogen, and an ester were tolerated. Higher yields were generally obtained compared with those reported using the halopyridinium salts method.[3a] This reaction is so mild that *E*-crotonic acid, a base-sensitive substrate (leading to easy isomerization) underwent esterification and maintained good stereochemistry. Unfortunately,



Scheme 2.

Table 3. Esterification between 3-phenylpropanoic acid and equimolar amounts of 1-octanol using Me_2NSO_2Cl (**1**)/amines



Me_2NSO_2Cl (equiv.)	Et_3N (equiv.)	Me_3N·HCl (equiv.)	DMAP (equiv.)	Yield (%)
2.0	3.0	–	–	34
2.0	3.0	2.0	–	86
2.0	3.0	2.0	0.1	93
2.0	3.0	2.0	1.0	97
1.5	2.5	1.5	1.0	88
2.0	3.0	2.0	1.0* [a]	92
2.0	3.0 ($BnNMe_2$)	–	–	31
2.0	3.0 ($BuNMe_2$)	–	0.1	79
2.0	3.0 ($BuNMe_2$)	–	0.1	92* [b]

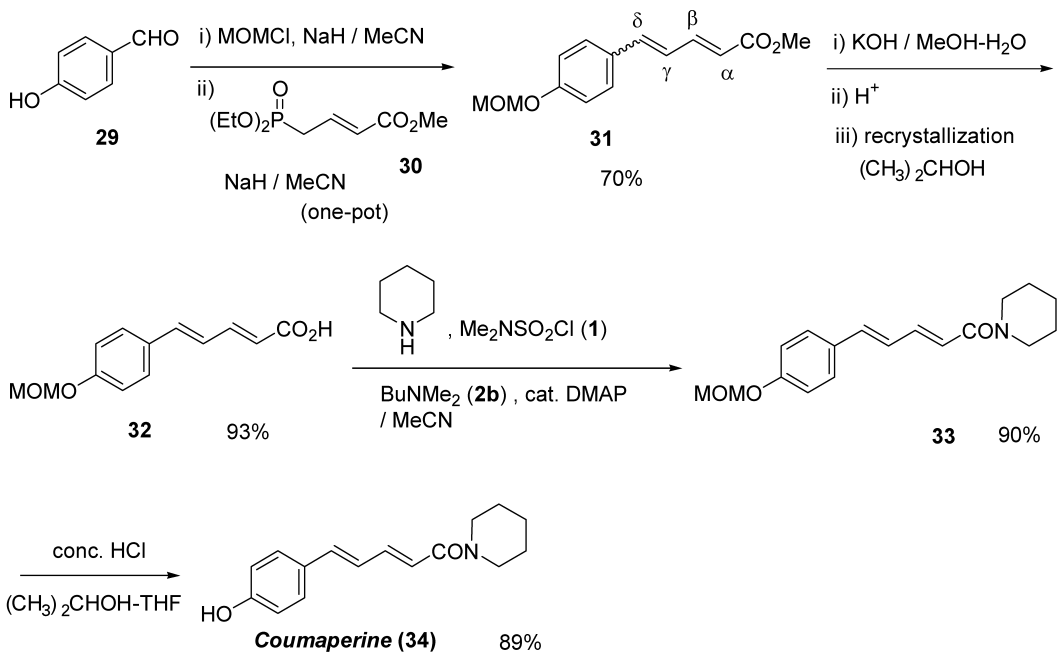
[a] Use of 1-methylimidazole instead of DMAP.
[b] Reaction temperature; 45–50°C.

sterically crowded substrates such as pivalic acid and *t*-butyl alcohol did not produce high yields. The yields were 40% between pivalic acid and 1-octanol and only trace amounts between 3-phenylpropanoic acid and *t*-butyl alcohols.

The salient features are as follows: (i) Me_2NSO_2Cl (**1**) and the amines used are relatively inexpensive and commercially available, structurally simple, and atom-economical, and **1** is slightly less hygroscopic among sulfonyl chlorides. (ii) The *N*,*N*-dimethyl structure in **2a** and **2b** is crucial, except for the case of DABCO,[16] because our previous studies of green chemical sulfonylations suggest that such less-hindered amines significantly activate the sulfonyl chlorides during the first mixed-anhydride formation.[12] (iii) This agent had very high chemoselectivity toward the carboxyl group vs the hydroxyl group, namely, the experiment could be performed with the addition of **1** into the mixture of carboxylic acids and alcohols. This chemoselectivity is rarely observed using other sulfonyl chloride reagents. Thus, the experimental procedure is simple and convenient, and would ensures the lactonization reaction of ω-hydroxyl carboxylic acids.

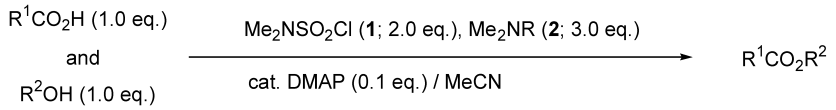
This protocol could also be extended to an amidation reaction between carboxylic acids and equimolar amounts of primary or secondary amines (Table 5). The present reaction proceeded with good to excellent yield in every case examined. It should be noted that no substantial isomerization occurred when using *E*-crotonic acid.

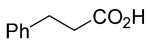
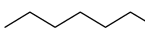
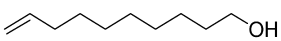
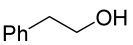
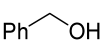
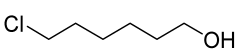
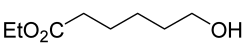
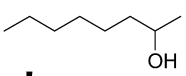
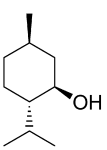
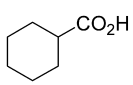
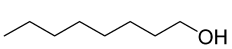
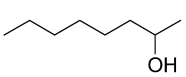
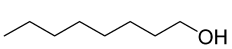
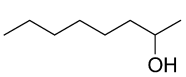
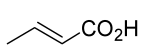
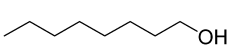
Finally, we describe an application to natural product synthesis. Coumaperine (**34**) is a dieneamide isolated from



Scheme 3.

Table 4. Esterification between various carboxylic acids and equimolar amounts of alcohols using Me_2NSO_2Cl (**1**)/amines (**2a** or **2b**)



R^1CO_2H	R^2OH	Method* [a]	Product	Yield (%)
		A B	**4**	93 92
		A B	**5**	95 92
		A B	**6**	91 93
		A B	**13**	90 94
		A B	**14**	86 (69)* [b] 86
	PhOH	A B	**15**	80 (61)* [b] 80
		A B	**16**	91 90
		A B	**17**	90 88
		A B	**7**	95* [c] 94* [c]
		A B	**8**	96* [c] 94* [c]
		A B	**9**	93 92
		A B	**18**	90* [c] 94* [c]
$PhCO_2H$		A B	**19**	92 92
		A B	**20**	91* [c] 92* [c]
		A B	**21**	73* [d] 71* [e]

[a] A: use of Me_3N·HCl (**29**·Hcl)/Et_3N, 0–5°C, 3 h. B: use of $BuNMe_2$ (**2b**), 40–45°C, 1 h.
[b] Parantheses indicate the reported data using 2-chloro-1-methylpyridinium iodide.
[c] DMAP (1.0 equiv.) was used.
[d] *E*/*Z*=10:1.
[e] *E*/*Z*=7:1.

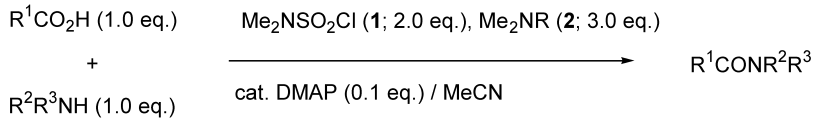
Piper nigrum L. (white pepper), and is present at a concentration of approximately 6 ppm in dry fruit.[17] There was notable antioxidative activity of **34** against linoleic acid oxidation.[17b] A recent study indicates that **34** has significant chemopreventive activity in rats carcinogenesis.[18] These informations prompted us to synthesize coumaperine (**34**) using the present amidation as a key step (Scheme 3).

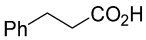
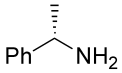
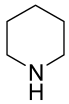
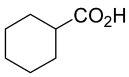
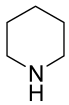
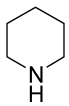
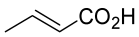
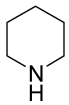
Methoxymethyl (MOM) protection of 4-hydroxybenzaldehyde (**29**) followed by the Wadsworth–Horner–Emmons reaction using methyl 4-phosphono-2-butenoate (**30**) afforded the α,β-*E*, γ,δ-*E* rich diene ester **31** in a one-pot procedure. Hydrolysis of methyl ester **31** gave α,β-*E*, γ,δ-*E* rich carboxylic acid **32**, which was recrystallized from 2-propanol to give pure α,β-*E*, γ,δ-*E* acid **32**.

The present essentially neutral amidation of **32** with piperidine proceeded successfully in 90% yield (compared to 76% with small amounts of polymer by the method using 2-chloro-1-methylpyridinium iodide under standard conditions[3a]). Finally, the deprotection of MOM with conc. HCl gave coumaperine (**34**) (purity; 99.8% by HPLC analysis) in 52% overall yield.

In conclusion, practical esterification and amidation were achieved using the combined reagents, Me_2NSO_2Cl (**1**) and Me_2NR (**2a**; R=Me, **2b**; R=Bu). This method has the

Table 5. Amidation between various carboxylic acids and equimolar amounts of primary or secondary amines using Me_2NSO_2Cl (**1**)/amines (**2a** or **2b**)



R^1CO_2H	R^2R^3NH	Method* [a]	Product	Yield (%)
		A	**22**	95
		B		96
	$^tBuNH^2$	A	**23**	96
		B		97
		A	**24**	92
		B		93
		A	**25**	92
		B		92
$PhCO_2H$		A	**26**	90
		B		94
	$^tBuNH^2$	A	**27**	88* [b,c]
		B		92* [b,c]
		A	**28**	90* [c]
		B		93* [c]

[a] A: use of Me_3N·HCl (**2a**·HCl)/Et_3N, 0–5°C, 3 h. B: use of $BuNMe_2$ (**2b**), 40–45°C, 1 h.
[b] DMAP (1.0 equiv.) was used.
[c] *E* only.

advantages of being the mild conditions (0–45°C; within 3 h), chemoselective, operationally simple, reagent economical, and has good reactivity. These characteristics rival those reported for related condensation agents.

3. Experimental

3.1. General

Melting points were determined on a hot-stage microscope apparatus (Yanagimoto) and are uncorrected. NMR spectra were recorded on a JEOL ALPHA 400 or DELTA 300 spectrometer, operating at 400 or 300 MHz for ^1H NMR and 100 MHz for ^{13}C NMR. Chemical shifts (δ ppm) in $CDCl_3$ were reported downfield from TMS (=0) for ^1H NMR. For ^{13}C NMR, chemical shifts were reported in the scale relative to $CDCl_3$ (77.00 ppm) as an internal reference. IR Spectra were recorded on a JASCO FT/IR-8000 spectrophotometer. Optical rotations were measured on a JASCO DIP-370 (Δ 589 nm).

Attention. It is important to dry up Me_3N·HCl (**2a**·HCl) under reduced pressure before use.

The following obtain esters and amides are known compounds: 1-octyl 3-phenylpropanoate (**4**);[11d] 2-octyl 3-phenylpropanoate (**7**);[19] 1-octyl cyclohexanecarboxylate (**9**);[20] 2-phenylethyl 3-phenylpropanoate (**13**);[21] benzyl 3-phenylpropanoate (**14**);[22] phenyl 3-phenylpropanoate (**15**);[23] 1-octyl benzoate (**19**);[24] 2-octyl benzoate (**20**);[25] *N*-[(*S*)-1-phenylethyl]-3-phenylpropionamide (**22**);[26] *N*-(1,1-dimethylethyl)-3-phenylpropionamide (**23**);[27] *N*-(3-phenylpropionoyl)piperidine (**24**);[28] *N*-(cyclohexanecarbonyl)piperidine (**25**);[29] *N*-(benzoyl)piperidine (**26**);[30] *N*-(2*E*-butenoyl)piperidine (**28**).[31]

3.2. General procedure of esterification using $MeSO_2Cl$ (3), Et_3N, and Me_3N·HCl (2a·HCl)

Me_3N·HCl (**2a**·HCl; 4.50 mmol) was added to a stirred solution of a carboxylic acid (1.00 mmol) and Et_3N (4.50 mmol) in MeCN (1.0 ml) at 0–5°C under an Ar atmosphere, and the mixture was stirred for 10 min. MsCl (**3**; 2.00 mmol) in MeCN (1.0 ml) was added to the mixture at −15–−10°C, and the mixture was stirred at that temperature for 30 min. An alcohol (1.00 mmol) and DMAP (1.00 mmol) in MeCN (1.0 ml) was successively added to the mixture at −15–−10°C. Then the mixture was stirred at that temperature for 1 h and at 20–25°C for 1 h. Water was added to the mixture, which was extracted with ether. The organic phase was washed with water, brine,

dried (Na_2SO_4), and concentrated. The obtained crude product was purified by silica-gel column chromatography (hexane/ether=40:1–10:1) to give the desired ester.

3.3. General procedure of esterification using Me_2NSO_2Cl (1), Et_3N, Me_3N·HCl (2a·HCl), and cat. DMAP ⟨method A⟩

Me_3N·HCl (**2a**·HCl; 2.00 mmol) was added to a stirred solution of a carboxylic acid (1.00 mmol), an alcohol (1.00 mmol), Et_3N (3.00 mmol), and DMAP (0.10 mmol) in MeCN (1.0 ml) at 0–5°C under an Ar atmosphere, and the mixture was stirred for 10 min. Me_2NSO_2Cl (**1**; 2.00 mmol) in MeCN (1.0 ml) was added to the mixture at 0–5°C, and the mixture was stirred at that temperature for 3 h. Water was added to the mixture, which was extracted with ether. The organic phase was washed with water, brine, dried (Na_2SO_4), and concentrated. The obtained crude product was purified by silica-gel column chromatography (hexane/ether=40:1–10:1) to gave the desired ester.

3.4. General procedure of esterification using Me_2NSO_2Cl (1), $BuNMe_2$ (2b), and cat. DMAP ⟨method B⟩

Me_2NSO_2Cl (**1**; 2.00 mmol) in MeCN (1.0 ml) was added to a stirred solution of a carboxylic acid (1.00 mmol), an alcohol (1.00 mmol), $BuNMe_2$ (3.00 mmol), and DMAP (0.10 mmol) in MeCN (1.0 ml) at 40–45°C under an Ar atmosphere, and the mixture was stirred at that temperature for 1 h. A similar work up procedure as described above (the method A) gave the desired ester.

3.5. Typical procedure of esterification of 3-phenylpropanoic acid with 1-octanol using Me_2NSO_2Cl (1), Et_3N, Me_3N·HCl (2a·HCl) and cat. 1-imidazole (in the place of cat. DMAP)

In a similar manner as for the general procedure of ⟨method A⟩ the reaction proceeded in 92% yield.

3.5.1. 9-Decene-1-yl 3-phenylpropaonate (5). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24–1.42 (10H, m), 1.54–1.64 (2H, m), 1.99–2.09 (2H, m), 2.62 (2H, t, J=7.8 Hz), 2.95 (2H, t, J=7.8 Hz), 4.05 (2H, t, J=6.7 Hz), 4.89–5.05 (2H, m), 5.74–5.89 (1H, m), 7.16–7.32 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.86, 28.59, 28.80, 29.01, 29.17, 29.32, 31.00, 33.76, 35.93, 64.62, 114.15, 126.21, 128.27, 128.46, 139.14, 140.57, 172.99; IR (neat) 3028, 2928, 2855, 1736, 1456, 1161 cm^{-1}. Anal. found: C, 79.2; H, 9.7%. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.78%.

3.5.2. 2-Hexyn-1-yl 3-phenylpropaonate (6). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (3H, t, J=7.3 Hz), 1.48–1.58 (2H, m), 2.14–2.24 (2H, m), 2.66 (2H, t, J=7.8 Hz), 2.96 (2H, t, J=7.8 Hz), 4.67 (2H, s), 7.17–7.31 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.43, 20.72, 21.84, 30.81, 35.68, 52.85, 74.03, 87.56, 126.27, 128.29, 128.49, 140.35, 172.21; IR (neat) 2965, 2240, 1742, 1454, 1381, 1152, 1032 cm^{-1}. Anal. found: C, 78.1; H, 7.6%. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88.

3.5.3. *N*-1-Phenylethyl(methylsulfonyl)methanesulfonamide (12). Colorless crystals; mp 120.0–121.0°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.60 (3H, d, J=7.1 Hz), 3.12 (3H, s), 3.55 (1H, d, J=15.1 Hz), 4.16 (1H, d, J=15.1 Hz), 4.62–4.72 (1H, m), 5.60 (1H, d, J=8.1 Hz), 7.16–7.46 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.04, 42.18, 55.03, 68.90, 126.71, 128.53, 129.19, 140.52; IR (KBr) 3308, 2980, 1426, 1339, 1321, 1167, 1138 cm^{-1}. Anal. found: C, 43.21; H, 5.43; N, 4.92%. Calcd for $C_{10}H_{15}NO_4S_2$: C, 43.30; H, 5.45; N, 5.05%.

3.5.4. 6-Chlorohexyl 3-phenylpropanoate (16). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27–1.37 (2H, m), 1.29–1.39 (2H, m), 1.56–1.66 (2H, m), 1.71–1.81 (2H, m), 2.63 (2H, t, J=7.6 Hz), 2.95 (2H, t, J=7.6 Hz), 3.52 (2H, t, J=6.7 Hz), 4.06 (2H, t, J=6.6 Hz), 7.17–7.31 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.22, 26.47, 28.44, 30.97, 32.41, 35.86, 44.89, 64.31, 126.22, 128.26, 128.45, 140.51, 172.93; IR (neat) 2938, 2863, 1734, 1454, 1258, 1163, 700 cm^{-1}. Anal. found: C, 66.8; H, 7.7%. Calcd for $C_{15}H_{21}ClO_2$: C, 67.03; H, 7.88%.

3.5.5. Ethyl 6-(3-phenylpropanoyloxy)hexanoate (17). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (3H, t, J=7.3 Hz), 1.29–1.39 (2H, m), 1.56–1.68 (4H, m), 2.28 (2H, t, J=7.5 Hz), 2.62 (2H, t, J=7.8 Hz), 2.95 (2H, t, J=7.8 Hz), 4.06 (2H, t, J=6.6 Hz), 4.07–4.17 (2H, m), 7.16–7.32 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.21, 24.53, 25.45, 28.28, 30.95, 34.13, 35.86, 60.21, 64.22, 126.20, 128.24, 128.44, 140.50, 172.90, 173.48; IR (neat) 2941, 2866, 1734, 1454, 1238, 1163 cm^{-1}. Anal. found: C, 69.9; H, 8.3%. Calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27.

3.5.6. 2-Octyl cyclohexanecarboxylate (18). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, t, J=7.0 Hz), 1.18 (3H, d, J=6.1 Hz), 1.21–1.36 (12H, m), 1.40–1.50 (2H, m), 1.55–1.65 (2H, m), 1.70–1.80 (2H, m), 1.84–1.94 (2H, m), 2.21–2.29 (1H, m), 4.81–4.89 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.04, 20.01, 22.56, 25.34, 25.44, 25.49, 25.81, 28.98, 29.10, 29.12, 31.74, 35.97, 43.48, 70.39, 175.78; IR (neat) 2932, 2857, 1730, 1453, 1377, 1248, 1173 cm^{-1}. Anal. found: C, 75.1; H, 11.6%. Calcd for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74%.

3.5.7. 1-Octyl 2-butenoate (*E*/*Z*=10:1) (21). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80–0.96 (3H, m), 1.21–1.41 (10H, m), 1.59–1.69 (2H, m), 1.80–1.96 (3H, m), 4.09 (2H×1/11, t, J=6.8 Hz), 4.11 (2H×10/11, t, J=6.8 Hz), 5.81–5.89 (1H, m), 6.92–7.00 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.05, 17.91, 22.62, 25.87, 25.95, 28.58, 28.69, 29.17, 29.22, 31.78, 39.21, 64.33, 64.87, 118.37, 122.85, 130.43, 144.30, 166.67; IR (neat) 2928, 2857, 1726, 1447, 1312, 1181, 1103 cm^{-1}. Anal. found: C, 72.5; H, 11.3%. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18.

3.6. General procedure of amidation using Me_2NSO_2Cl (1), Et_3N, Me_3N·HCl (2a·HCl), and cat. DMAP ⟨method A⟩

An amine (1.00 mmol), Et_3N (3.00 mmol), and DMAP (0.10 mmol) in MeCN (1.0 ml) was added to a stirred solution of a carboxylic acid (1.00 mmol), Me_3N·HCl (**2a**·HCl; 2.00 mmol), and Me_2NSO_2Cl (**1**; 2.00 mmol) in MeCN (1.0 ml) at 0–5°C under an Ar atmosphere, and the mixture was stirred at that temperature for 3 h. Water was

added to the mixture, which was extracted with EtOAc. The organic phase was washed with water, brine, dried (Na_2SO_4), and concentrated. The obtained crude product was purified by silica-gel column chromatography (hexane/EtOAc=3:1–1:1) to give the desired amide.

3.7. General procedure of amidation using Me_2NSO_2Cl (1), $BuNMe_2$ (2b), and cat. DMAP ⟨method B⟩

An amine (1.00 mmol), $BuNMe_2$ (3.00 mmol) and DMAP (0.10 mmol) in MeCN (1.0 ml) was added to the stirred solution of a carboxylic acid (1.00 mmol) and Me_2NSO_2Cl (**1**; 2.00 mmol) in MeCN (1.0 ml) at 40–45°C under an Ar atmosphere, and the mixture was stirred at that temperature for 1 h. A similar work-up procedure as described above (method A) gave the desired amide.

3.7.1. *N*-(1,1-Dimethylethyl)-2*E*-butenamide (27). Colorless crystals; mp 102.5–103.5°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (9H, s), 1.82 (3H, dd, J=1.7, 6.8 Hz), 5.25 (1H, brs), 5.72 (1H, dq, J=1.7, 15.1 Hz), 6.75 (1H, dq, J=6.8, 15.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.47, 28.82, 51.09, 126.21, 138.72, 165.28; IR (neat) 3264, 1626, 1458, 1354, 1227, 980 cm^{-1}. Anal. found: C, 67.8; H, 10.6; N, 9.88%. Calcd for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92.

3.7.2. Methyl 5-(4-methoxymethoxyphenyl)-2*E*,4-butadienoate (31). A mixture of chloromethyl methyl ether (874 mg, 10.9 mmol) and 4-hydroxybenzaldehyde (**29**; 1.11 g, 9.05 mmol) in MeCN (10.0 ml) was added to a stirred suspension of NaH (0.94 g, 23.5 mmol) in MeCN (10.0 ml) at 0–5°C under an Ar atmosphere and the mixture was stirred the same temperature for 1 h. Methyl 4-phosphono-2-butenoate (**30**; 2.14 g, 9.05 mmol) in MeCN (10.0 ml) was added to that stirred suspension at 0–5°C and the mixture was stirred the same temperature for 1 h. Water was added to the mixture, which was extracted with EtOAc. The organic phase was washed with water, brine, dried (Na_2SO_4), and concentrated. The obtained crude product was purified by silica-gel column chromatography (hexane/EtOAc=7:1) to give the desired product **31** (2.28 g, 70%; 2-(α,β)-*E*,4-(γ,δ)-*E*/2-(α,β)-*E*,4-(γ,δ)-*Z*=>95:5).

Colorless crystals; mp 52.0–54.0°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.47 (3H, s), 3.76 (3H, s), 5.19 (2H, s), 5.95 (1H, d, J=15.4 Hz), 6.75 (1H, dd, J=10.5, 15.4 Hz), 6.85 (1H, d, J=15.6 Hz), 7.01–7.03 (2H, m), 7.35–7.45 (2H, m), 7.43 (1H, dd, J=10.5, 15.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.28, 55.87, 94.09, 116.31, 119.67, 124.38, 128.45, 129.73, 139.96, 144.97, 157.88, 167.36; IR (KBr) 3383, 2951, 1714, 1626, 1599, 1510, 1437, 1246, 1153, 995, 847 cm^{-1}. Anal. found: C, 67.55; H, 6.39%. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50%.

3.7.3. 5-(4-Methoxymethoxyphenyl)-2*E*,4*E*-butadienoic acid (32). KOH (1.76 g, 31.4 mmol) in water (6.0 ml) was added to a stirred solution of methyl 5-(4-methoxymethoxyphenyl)-2*E*,4-butadienoate (**31**; 1.56 g, 6.29 mmol) in MeOH (12 ml) at room temperature. The mixture was stirred at 80°C for 15 h. After cool down, the reaction mixture was concentrated under reduced pressure. 6 M-HCl aqueous solution was added to the mixture, which was extracted with EtOAc. The organic phase was washed with water and brine, dried (Na_2SO_4) and concentrated to give 5-(4-methoxymethoxyphenyl)-2*E*,4-butadienoic acid (1.37 g, 93%). Recrystallization from 2-propanol gave pure 2*E*,4*E*-acid (**32**).

Colorless crystals; mp 149.5–151.0°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.48 (3H, s), 5.20 (2H, s), 5.95 (1H, d J=15.1 Hz), 6.79 (1H, dd, J=10.7, 15.1 Hz), 6.90 (1H, d, J=15.1 Hz), 7.02–7.04 (2H, m), 7.41–7.43 (2H, m), 7.53 (1H, dd, J=10.7, 15.1 Hz), 10.64 (1H, brs); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.09, 94.23, 116.48, 119.27, 124.31, 128.78, 129.72, 141.22, 147.29, 158.18, 173.57; IR (KBr) 2905, 2536, 1676, 1597, 1315, 1277, 1236, 1151, 1074, 1003, 920 cm^{-1}. Anal. found: C, 66.8; H, 6.0%. Calcd for $C_{13}H_{14}O_4$: C, 66.66; H, 6.02%.

3.7.4. *N*-5-(4-Methoxymethoxyphenyl)-2*E*,4*E*-butadienoyl piperidine (33). Piperidine (85 mg, 1.00 mmol), $BuNMe_2$ (303 mg, 3.00 mmol), and DMAP (12 mg, 0.10 mmol) in MeCN (1.0 ml) was added to a stirred solution of 5-(4-methoxymethoxyphenyl)-2*E*,4*E*-butadienoic acid (**32**; 234 mg, 1.00 mmol) and Me_2NSO_2Cl (**1**; 287 mg, 2.00 mmol) in MeCN (1.0 ml) at 40–45°C under an Ar atmosphere, and the mixture was stirred at that temperature for 1 h. Water was added to the mixture, which was extracted with EtOAc. The organic phase was washed with water, brine, dried (Na_2SO_4), and concentrated. The obtained crude product was purified by silica-gel column chromatography (hexane/EtOAc=3:2) to give *N*-5-(4-methoxymethoxyphenyl)-2*E*,4*E*-butadienoyl piperidine (**33**; 271 mg, 90%).

Colorless crystals; mp 70.0–71.5°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.53–1.72 (6H, m), 3.49 (3H, s), 3.49–3.59 (2H, m), 3.60–3.70 (2H, m), 5.21 (2H, s), 6.47 (1H, d, J=14.7 Hz), 6.76–6.86 (2H, m), 6.97–7.07 (2H, m), 7.34–7.44 (2H, m), 7.40–7.50 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.57, 25.55, 26.66, 43.14, 46.83, 56.06, 94.04, 116.22, 119.72, 125.23, 128.19, 130.16, 138.02, 142.66, 157.37, 165.32; IR (KBr) 3450, 2934, 2855, 1638, 1588, 1510, 1449, 1242, 1010, 839 cm^{-1}. Anal. found: C, 71.7; H, 7.6%. Calcd for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69; N, 4.65%.

3.7.5. *N*-5-(4-hydroxyphenyl)-2*E*,4*E*-pentadienoyl piperidine (*Coumaperine*) (34).[17] Conc. HCl (0.89 g) was added to a stirred solution of *N*-5-(4-Methoxymethoxyphenyl)-2*E*,4*E*-butadienoyl piperidine (**33**; 532 mg, 1.77 mmol) in THF–2-propanol (3.5 ml, v/v=1) at 0–5°C. The mixture was stirred at room temperature for 15 h. Water was added to the mixture, which was extracted with EtOAc. The organic phase was washed with water, brine, dried (Na_2SO_4), and concentrated. The obtained crude product was purified by silica-gel column chromatography (hexane/EtOAc=2:3) to give coumaperine (**34**; 404 mg, 89%).

Colorless crystals (MeOH); mp 209.5–211.0°C; ^{1}H NMR (300 MHz, Acetone-d_6) δ 1.38–1.69 (6H m), 3.55 (4H, s), 6.64 (1H, d, J=14.4 Hz), 6.82–6.96 (4H, m), 7.28–7.42 (3H, m), 8.84 (1H, s, OH); IR (KBr) 3200, 1634, 1603, 1572, 1510, 1460, 1440, 1277, 1256, 1007, 841 cm^{-1}. HPLC analysis; 99.8% purity [SHIMADZU HPLC system (SLC-10A, DGU-4A, LC-10AD, SIL-10A, CTO-10A, and

detector SPD-10AV, measured at 254 nm; column LiChrosorb® Si-60; 10 μ, 4 mm i.d.×30 cm); flow rate 1.0 ml/min, solvent: hexane/2-propanol=95:5] t_R=17.56 min.

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