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Mild, powerful, and robust methods for esterification, amide formation, and thioesterification between acid chlorides and alcohols, amines, thiols, respectively

Hidefumi Nakatsuji, Mami Morimoto, Tomonori Misaki and Yoo Tanabe*

Department of Chemistry, School of Science and Technology, Kwansei Gakuin University, 2-1 Gakuen, Sanda, Hyogo 669-1337, Japan

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Abstract—We developed two efficient practical methods for esterification, amide formation, and thioesterification between acid chlorides and alcohols, amines, thiols, respectively. The present mild and robust reaction was performed by two separate methods both by combining cheap and readily available amines, *N*-methylimidazole, and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA). Method A uses catalytic *N*-methylimidazole and TMEDA with an equimolar amount of K_2CO_3, whereas Method B uses equimolar amounts of *N*-methylimidazole and TMEDA. The salient features are as follows. (i) With regard to reactivity, Method B was superior to Method A for esterification and thioesterification, whereas cost-effective Method A was superior to Method B for amide formation. (ii) Amide formation proceeded smoothly between acid chlorides and less nucleophilic and stereocongested amines such as 2,6-dichloroaniline. (iii) This protocol was applied to the successful synthesis of two agrochemicals, bromobutide and carpropamid.

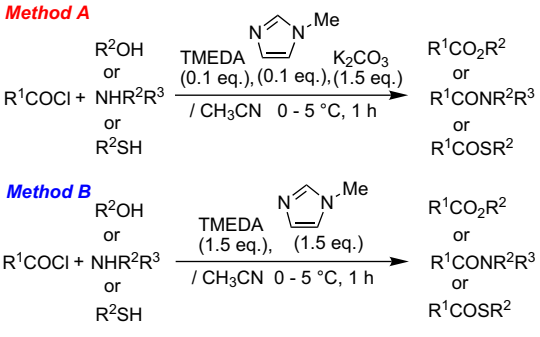
1. Introduction

Esterification, amide formation, and thioesterification are important unit processes frequently used for a wide range of organic syntheses.[1] These reactions between carboxylic acid chlorides (the most popular activated acid derivative) and alcohols, amines, and thiols are among the most general and conventional synthetic methods available. These methods generally require stoichiometric or excess amounts of tertiary amines such as pyridine and Et_3N as HCl scavengers. These wasted organic amine reagent requires a large quantity of biological and chemical oxygen demands (BOD and COD) and is not suitable in terms of recent trends in process chemistry.

In our continuing studies toward the development of mild, practical, and cost-effective esterifications, amide formations, and thioesterification, we found that *N*-methylimidazole efficiently activates carboxylic acid derivatives.[2] Recently, a water solvent Schotten–Baumann-type method for esterification and amide formation between acid chlorides and alcohols or amines was developed.[3] This protocol is cost-effective and environmentally benign for esterification and amide formation from a green chemical standpoint, however, it requires tedious procedures for many synthetic chemists, because it has to handle both pH controller and microfeeder apparatuses to strictly maintain a pH of around 11.5. Moreover, the reactivity is generally poor probably due to the use of water media.

2. Results and discussion

To solve these critical problems, we devised two mild, powerful, and robust methods for esterification, amide formation, and thioesterification between acid chlorides and alcohols, amines, and thiols, respectively, in conventional CH_3CN or 1,2-dichlorobenzene solvent without using any special techniques and apparatuses (Scheme 1).



Scheme 1. Mild and powerful esterification, amide formation, and thioesterification by Methods A and B.

* Corresponding author. E-mail: tanabe@kwansei.ac.jp

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The present reaction involves two methods; (i) Method A uses K_2CO_3 functioning as the main base and a combination of catalytic bases, *N*-methylimidazole and TMEDA, and (ii) Method B uses a combination of equimolar amounts of bases, *N*-methylimidazole and TMEDA (Scheme 1).

2.1. Esterification using Methods A and B: *B is superior to A*

The initial attempt was guided by more cost-effective Method A for the reaction between $PhCH_2CH_2COCl$ and 3-octanol utilizing K_2CO_3 as the main base with representative and available amine catalysts (Et_3N, Me_3N, $BnNMe_2$, $BuNMe_2$, DMAP, TMEDA, and *N*-methylimidazole) (Table 1).

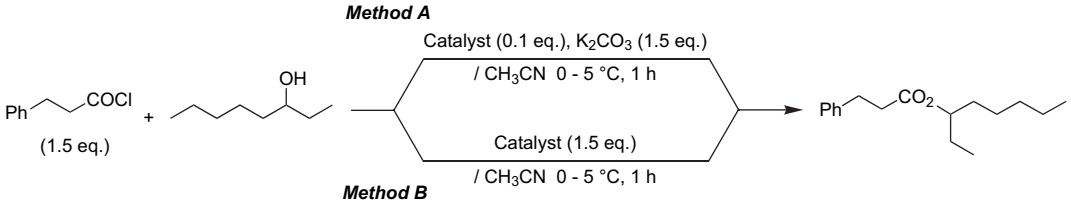
No reaction occurred without the catalyst (entry 1). The use of simple trialkylamines, such as Et_3N (the most familiar tertiary amine), Me_3N (a sterically uncrowded and effective sulfonylation reagent),[4] and $BuNMe_2$ had a small effect (entries 2–5). Low to moderate yields were obtained when DMAP (a super acylation catalyst),[1] TMEDA (an effective diamine for benzoylation),[5] and *N*-methylimidazole (a new acylation agent)[2] were used (entries 6–8). The combined use of different amine catalysts, however, exhibited synergistic activity (entries 9–13). The increasing order of yield for all six possible combinations was as follows. Method A: (i) Et_3N and TMEDA, (ii) DMAP and TMEDA, (iii) Et_3N and DMAP, (iv) Et_3N and *N*-methylimidazole, (v) DMAP and *N*-methylimidazole, and (vi) TMEDA and *N*-methylimidazole (entry 14). Method B: (i), (iv), (ii), (iii), (v), and (vi). The order was not necessarily the same between Methods A and B, however, the best synergy effect in both methods (joint action of amines) was obtained using TMEDA and *N*-methylimidazole [entry 14, case (vi)]. This result shows good agreement with the reported water solvent method (see also Table 4).[3] Eventually, we chose the combined base catalysts, TMEDA and *N*-methylimidazole, for the standard protocols.

Table 2 lists the successful results of esterifications between various acid chlorides and alcohols. From cost-effective and process chemical standpoints, Method A should precede Method B: when Method A produced disappointing results, we switched to Method B. The salient features are as follows. (i) The procedures are much simpler and more robust than the water solvent method and the yields are good to excellent.[3] The reaction conditions are mild and practical (0–5 °C, 1 h; an additional 20–25 °C, 1 h in some cases). (ii) Several primary alcohols and less reactive phenols underwent smooth esterification using $PhCH_2CH_2COCl$ and 10-dodecenoyl chloride in Method A (entries 1–10). (iii) Although Method A was somewhat less efficient for secondary alcohols such as L-menthol and 3-octanol, Method B was more successful (entries 10, 12, 13, 16, 18, 20, 24, 26). (iv) *t*-BuOH did not undergo the reaction (entry 14). (v) Stereocongested *t*-BuCOCl underwent a smooth reaction using Method B (entry 26). (vi) A double bond, α-phenoxy and α-chlorocarbonyl cyclopropane carbonyl groups, was tolerated. (vii) Two useful synthetic pyrethroids, chlovaporthrin and permethrin,[6] were successfully synthesized (entries 27 and 28). (viii) *N*-Benzyloxycarbonylproline chloride was smoothly esterified with MeOH without any racemization (entries 29 and 30).

2.2. Amide formation using Methods A and B: *A is superior to B*

The present protocol was applied to amide formation. Table 3 lists the successful results. The salient features are as follows. (i) In all cases examined, the reaction proceeded successfully to give the desired amides in excellent yields under mild and practical conditions (0–5 °C, 1 h). (ii) Surprisingly, *Method A was superior to Method B*, with respect to the yield, especially for amide formation between $PhCH_2CH_2COCl$ and piperidine or Weinreb amine (entries 2 and 4). This tendency is in clear contrast to the esterification mentioned above. (iii) The reaction using important Weinreb amine, a water-soluble amine, and stereocongested *t*-butylamine also proceeded smoothly (entries 4–6). (iv) Using Method A, several types of acid chlorides produced successful results (entries 7–16).

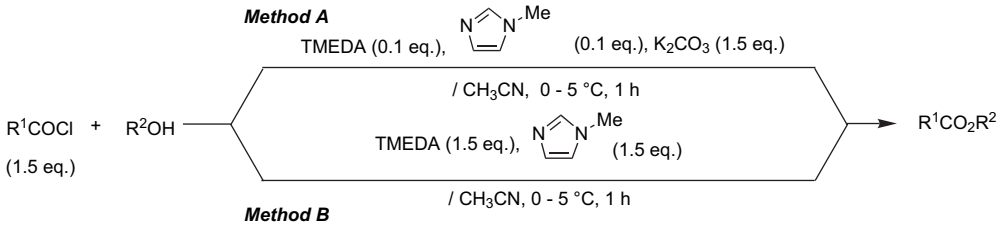
Table 1. Screening of amine catalysts during the esterification between $PhCH_2CH_2COCl$ and 3-octanol using Methods A and B

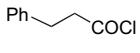
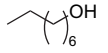
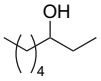
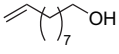
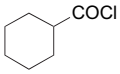
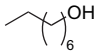
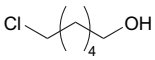
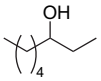
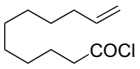
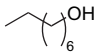
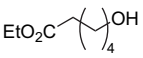
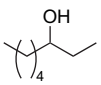
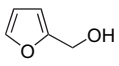
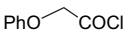
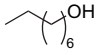
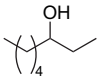
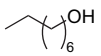
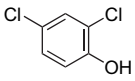
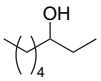
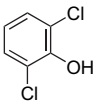
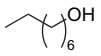
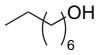
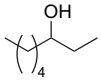
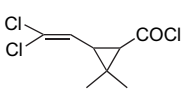
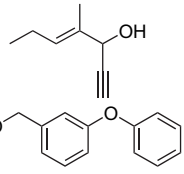
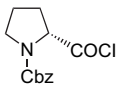


Entry	Catalyst	Yield[a]/%		Entry	Catalyst	Yield[a]/%	
		Method A	Method B			Method A	Method B
1	None	NR	—	8	*N*-Methylimidazole	49 (54[b])	48
2	Et_3N	37	38	9	Et_3N, DMAP	58	81
3	Me_3N	16	19	10	Et_3N, TMEDA	27	57
4	$BnNMe_2$	15	40	11	Et_3N, *N*-methylimidazole	68	67
5	$BuNMe_2$	23	45	12	DMAP, TMEDA	53	79
6	DMAP	54	43	13	DMAP, *N*-methylimidazole	68	82
7	TMEDA	34 (45[b])	49	14	*N*-methylimidazole, TMEDA	77[c]	85[c]

[a] Determined by ^1H NMR.
[b] Catalyst of 0.2 equiv was used.
[c] Isolated.

Table 2. Esterification of various substrates using Methods A and B



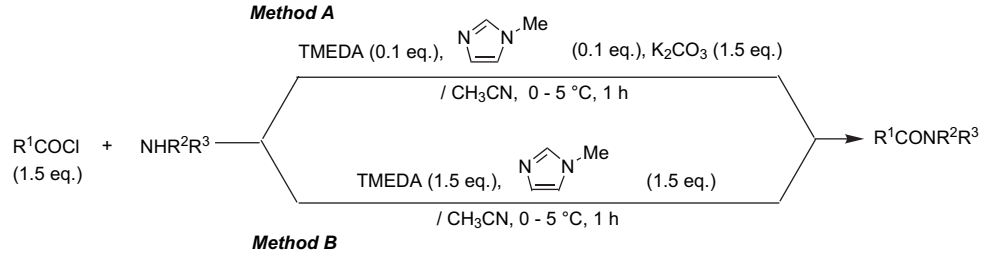
Entry	R^1COCl	R^2OH	Yield/% Method A (B)	Entry	R^1COCl	R^2OH	Yield/% Method A (B)
1			95	16			46[a] (89[a])
2			98	17			99
3			90	18			62[a] (94[a])
4			95	19			98
5			82	20			71[a] (98[a])
6			99	21			94
7		PhOH	85	22			76[a] (71[a])[a]
8			93 (96)	23			89
9			99 (98)	24			80[a] (97[a])
10			69 (98)	25			84
11			91	26			50[a] (95[a])
12			77 (86)	27			94[a]
13		(−)-Menthol	74 (95[a])	28			92[a]
14		*t*-BuOH	Trace	29		MeOH	89[b]
15	BzCl		85	30		$PhCH_2OH$	82[b]

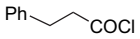
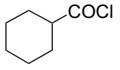
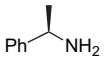
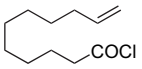
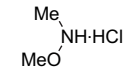
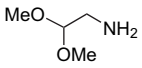
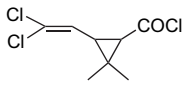
[a] Reaction conditions: 0–5 °C for 1 h and 20–25 °C for 1 h.
[b] Without loss of optical purity.

2.3. Amide formation for weakly nucleophilic anilines using Methods A and B, and an application to the synthesis of two agrochemicals: *A is far superior to B*

We next focused our attention on the amide formation of *weakly nucleophilic* arylamines such as nitroanilines and chloroanilines, because there has been much demand for this reaction from pharmaceutical and agrochemical industries. Nonetheless, it generally requires harsh reaction conditions[7] (high temperatures, excess amounts of acid chlorides, or a use of specific $TiCl_4$–AgOTf catalyst).[7c] Thus, we evaluated the ability of the present amide formation using

Table 3. Amide formation of various substrates using Methods A and B

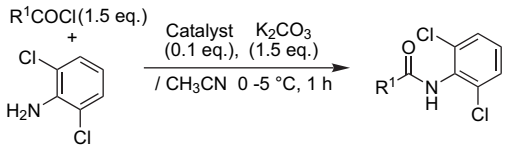


Entry	R^1COCl	NHR^2R^3	Yield/%		Entry	R^1COCl	NHR^2R^3	Yield/%
			Method A	Method B				Method A
1		$PhNH_2$	98	96	7	PhCOCl	$PhNH_2$	97
					8		Piperidine	99
2		Piperidine	97	17[a]	9		$PhNH_2$	97
					10		Piperidine	99
3			99	77	11		$PhNH_2$	99
					12		Piperidine	99
4			99[b]	27[a,c]	13		$PhNH_2$	99
5			86	84	14		$PhNH_2$	99
6		$^tBuNH_2$	99[d]	88[d]	15		Piperidine	89
					16		$PhNH_2$	99

[a] Determined by ^1H NMR.
[b] K_2CO_3 (2.5 equiv) was used.
[c] TMEDA (2.5 equiv) was used.
[d] Reaction conditions: 0–5 °C for 1 h and 20–25 °C for 1 h.

such less nucleophilic anilines. All six possible combinations for both Methods A and B using different amine catalysts were re-checked by the amide formation between $PhCH_2CH_2COCl$ or *c*-HexCOCl and very weakly nucleophilic 2,6-dichloroaniline (Table 4). The best synergy effect was obtained using TMEDA and *N*-methylimidazole (entry 6). Note that *N*-methylimidazole is superior to DMAP in a couple of comparable cases (entries 1 and 3, 5 and 6).

Table 4. Comparable experiments of amine catalysts during the amide formation between $PhCH_2CH_2COCl$ or cyclohexanoyl chloride and 2,6-dichloroaniline



Entry	Catalyst	Yield[a]/%	
		R^1=$PhCH_2CH_2$	R^1=*c*-Hex
1	Et_3N, DMAP	62	27←
2	Et_3N, TMEDA	57	20
3	Et_3N, *N*-methylimidazole	64	34←
4	DMAP, TMEDA	50	33⇐
5	DMAP, *N*-methylimidazole	60	29
6	*N*-methylimidazole, TMEDA	82	57⇐

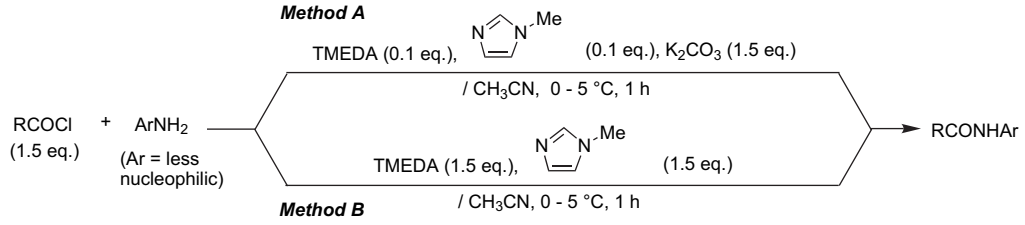
[a] Determined by ^1H NMR.

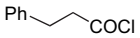
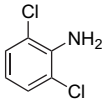
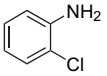
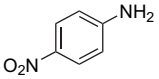
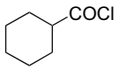
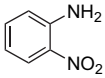
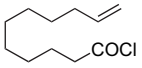
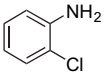
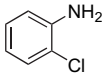
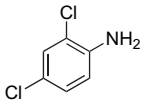
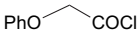
Table 5 lists the successful results of amide formation using weakly nucleophilic anilines using Method A. It should be noted that *Method A was far superior to Method B* in every case examined. In general, systems using a main inorganic base such as K_2CO_3, KOH, etc.,—and catalytic amine bases are cost-effective, but inferior to conventional systems using main amine bases with regard to reaction speed and yield.[4a,b]

We propose a plausible mechanism to account for this unique relationship reversal of amide formation that Method A is superior to Method B (Scheme 2).

Method A. Two different roles of *N*-methylimidazole and TMEDA are assumed. An *N*-methylimidazole catalyst captures an acid chloride (R^1COCl) to form a highly reactive acylimidazolium chloride intermediate **A**, which in turn condenses with an amine (R^1R^2NH) to produce the desired amide ($R^1CONR^2R^3$), while releasing TMEDA·HCl **B**. In **B**, TMEDA might chelate with a proton through bidentate hydrogen bonds. K_2CO_3 immediately neutralizes **B** to reform TMEDA while releasing $KHCO_3$ and KCl for completing the catalytic cycle. Note that (i) HCl is eventually

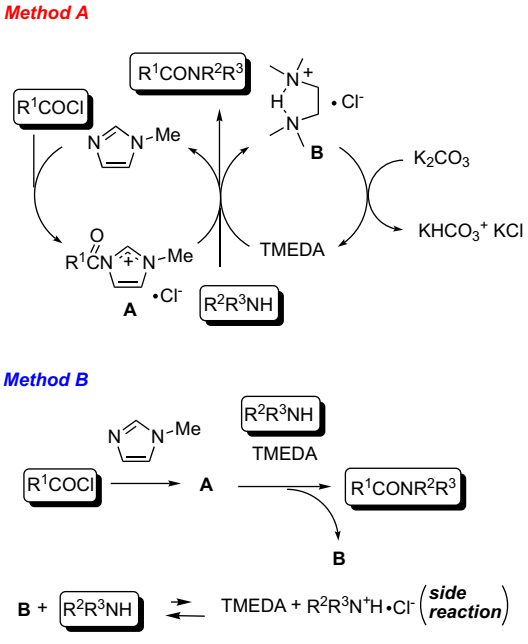
Table 5. Amide formation between several acid chlorides and weakly nucleophilic anilines using Methods A and B



Entry	R^1COCl	$ArNH_2$	Yield/%		Entry	R^1COCl	R^2NH_2	Yield/%
			Method A	Method B				Method A
1			82	Trace	6	PhCOCl		99
2			95	26[a]	7			89[b]
3			92	14[a]	8			94
4			91	39[a]	9			94
5			99	12[a]	10			93

[a] Determined by ^1H NMR.
[b] Reaction conditions: 0–5 °C for 1 h and 20–25 °C for 1 h.

transformed to inert inorganic salts, $KHCO_3$ and KCl, by the action of K_2CO_3 and (ii) the two amines have different roles: *N*-methylimidazole activates acyl chloride, whereas TMEDA acts as an HCl scavenger. A previous report of the water solvent method describes the ^1H NMR characterization for the formation of intermediate **A**.[3]



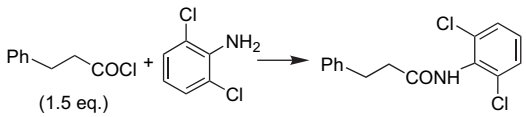
Scheme 2. Proposed mechanism for Methods A and B.

Method B. The formation of **A** and **B** is similar to Method A. The most crucial feature is that **B** is progressively accumulated in the system and reacts with R^2R^3NH by the equilibrium to form less reactive $R^2R^3NH\cdot HCl$. This side reaction significantly retards the desired amide formation.

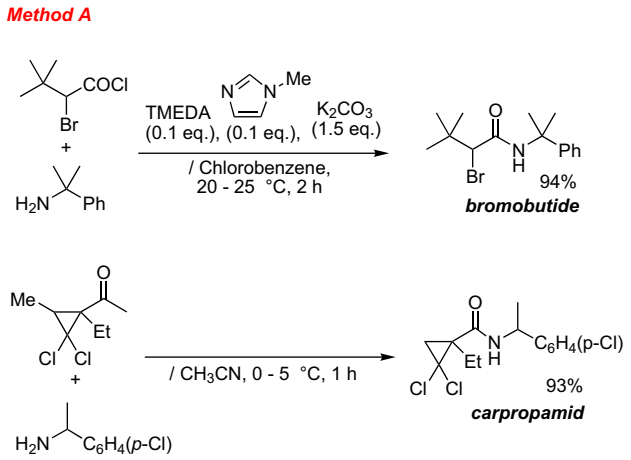
We next compare the performance of the present method with the water solvent method.[3] Clear contrast is shown in Table 6; the present method using 2,6-dichloroaniline was much more powerful than the water solvent method with or without amine catalysts.

The present amide formation of Method A is demonstrated by the synthesis of couple of commercial agrochemicals, bromobutide (herbicide)[8] and carpropamid (fungicide),[9] as shown in Scheme 3. The desired reactions using bulky substrates, between 2-bromo-3,3-dimethylbutanoyl chloride

Table 6. Comparison of Method A with the water solvent method



Entry	Conditions	Yield/%
1	K_2CO_3 (1.5 equiv)/H_2O (pH ~11.5), 20 °C, 1 h	Trace
2	TMEDA (0.1 equiv), *N*-methylimidazole/H_2O (pH ~11.5), 20 °C, 1 h	Trace
3	TMEDA (0.1 equiv), *N*-methylimidazole, K_2CO_3 (1.5 equiv)/CH_3CN, 0–5 °C, 1 h	82



Scheme 3. Synthesis of bromobutide and carpropamid.

and α,α-dimethylbenzylamine, between 1-ethyl-2,2-dichloro-3-methylcyclopropanecarbonyl chloride and 1-(4-chlorophenyl)ethylamine, proceeded smoothly under much milder conditions to give bromobutide and carpropamid, respectively, in both excellent yields.

2.4. Thioesterification using Methods A and B: *B is superior to A*

Finally, the present protocol was applied to thioesterification. Table 7 lists the successful results. The salient features are as follows. (i) In every case examined, the desired reaction proceeded smoothly using several aromatic and aliphatic thiols, and acid chlorides under mild and practical conditions (0–5 °C, 1 h and 20–25 °C, 1 h) (entries 1–12). (ii) Method B produced slightly better results with regard to yield compared to Method A. This tendency resembles the esterification described in Table 1. Similar to esterification, functionalized or stereocongested acid chlorides produced satisfactory results using Method B (entries 7–10).

3. Conclusions

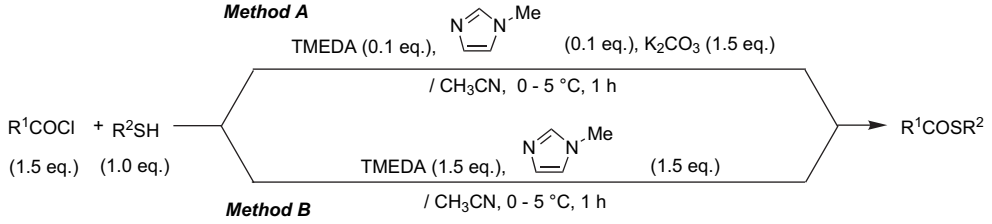
We presented two mild, powerful, and robust methods, Method A (cat. *N*-methylimidazole and TMEDA–K_2CO_3) and Method B (*N*-methylimidazole and TMEDA) for esterification, amide formation, and thioesterification. Method B produced higher yields than Method A for esterification and thioesterification, whereas the more cost-effective Method A showed considerably higher yield for amide formation including the use of important but less nucleophilic anilines. This amide formation was applied to an efficient synthesis of two agrochemicals, bromobutide and carpropamid. Because of the high efficiency and generality, the present protocol, particularly amide formation, will provide a new avenue for practical, cost-effective, and environmentally benign process chemistry for such acylation reactions.

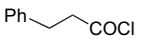
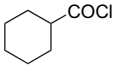
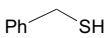
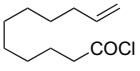
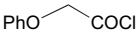
4. Experimental and references

4.1. General

Melting points were determined on a hot stage microscope apparatus (Yanagimoto) and were uncorrected. NMR spectra were recorded on a JEOL DELTA300 spectrometer, operating at 300 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR. Chemical shift (δ ppm) were reported downfield from tetramethylsilane (0 ppm) for ^{1}H NMR and were reported in the scale relative to $CDCl_3$ (77.00 ppm) for ^{13}C NMR. IR spectra were recorded on JASCO FT/IR-8000 and/or FT/IR-5300 spectrophotometer. Mass spectra were measured on a JEOL JMS-T100LC spectrometer.

Table 7. Thioesterification of several substrates using Methods A and B



Entry	R^1COCl	R^2SH	Yield/% Method A (B)	Entry	R^1COCl	R^2SH	Yield/% Method A (B)
1			89	6			87
2			98	7			83
3		PhSH	92	8			86
4			81 (94)	9			95
5	BzCl		88	10			67 (99)

The following esters and amides obtained in this paper are known compounds: 1-octyl 3-phenylpropanoate,[10] 9-decene-1-yl 3-phenylpropanoate,[11] 6-chlorohexyl 3-phenylpropanoate,[11] 2-hexyn-1-yl 3-phenylpropanoate,[11] ethyl 6-(3-phenylpropanoyloxy)hexanoate,[11] furfuryl 3-phenylpropanoate,[3] phenyl 3-phenylpropanoate,[12] 1-octyl 2-chlorobenzoate (commercially available: AKos Screening Library), 1-octyl 2,4-dichlorobenzoate (commercially available: AKos Screening Library), 1-phenylethyl 3-phenylpropanoate,[13] 3-octyl 3-phenylpropanoate,[3] 1-menthyl 3-phenylpropanoate,[11] *tert*-butyl 3-phenylpropionate,[14] 1-octyl benzoate,[11] 3-octyl benzoate,[15] 1-octyl cyclohexanecarboxylate,[10] 3-octyl cyclohexanecarboxylate,[3] 1-octyl 10-undecenoate,[16] 1-octyl phenoxyacetoate,[17] 1-octyl 2-chloropropanoate,[18] 1-octyl methacrylate,[19] 1-octyl 2,2-dimethylpropanoate,[11] 1-ethynyl-2-methyl-2-pentenyl 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate (chlovaporthrin: vaporthrin analog),[20] *m*-phenoxybenzyl 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate,[21] *N*-carbobenzoxy-L-proline methyl ester,[22] *N*-carbobenzoxy-L-proline phenylmethyl ester,[23] *N*-phenyl-3-phenylpropiaonamide,[24] *N*-(2,6-dichlorophenyl)-3-phenylpropanamide (commercially available: Aurora Screening Library), *N*-(2,6-dichlorophenyl)cyclohexamide (commercially available: Aurora Screening Library), *N*-(3-phenylpropanoyl)-piperidine,[11] *N*-[(*S*)-1-phenylethyl]-3-phenylpropanamide,[11] *N*-methoxy-*N*-methyl-3-phenylpropanamide,[25] *N*-(2,2-dimethoxyethyl)-3-phenylpropanamide,[26] *N*-(1,1-dimethylethyl)-3-phenylpropanamide,[11] *N*-phenylbenzamide,[27] *N*-benzoylpiperidine,[11] *N*-phenylcyclohexamide,[28] *N*-cyclohexanecarbonyl piperidine,[11] *N*-phenyl-10-undecenoylamide,[29] 10-undecenecarbonylpiperidine,[30] *N*-phenyl phenoxyacetyl amide,[31] *N*-phenyl-2-chloropropanoylamide,[32] 2-chloropropanoylpiperidine,[33] *N*-phenyl-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanamide,[34] *N*-(4-nitrophenyl)-3-phenylpropanamide,[35] *N*-(2-nitrophenyl)-3-phenylpropanamide (commercially available: Aurora Screening Library), *N*-(2-chlorophenyl)-3-phenylpropanamide,[36] *N*-(2,4-dichloro)-3-phenylpropanamide (commercially available: Aurora Screening Library), *N*-(2-chlorophenyl)benzamide,[37] *N*-(2-chlorophenyl)cyclohexamide,[38] *N*-(2-chlorophenyl)-10-undecenoyl amide,[39] *N*-(2-chlorophenyl)phenoxyacetyl amide,[40] *N*-(2-chlorophenyl)-2-chloropropanoyl amide,[41] *S*-1-octyl 3-phenylpropanthioate,[2] *S*-benzyl 3-phenylpropanthioate,[2] *S*-phenyl 3-phenylpropanthioate,[2] *S*-cyclohexyl 3-phenylpropanthioate,[2] *S*-1-octyl cyclohexanthioate,[2] *S*-1-octyl 2,2-dimethylpropanthioate.[42]

4.2. A typical procedure of esterification (Method A) (Table 2, entry 1)

$PhCH_2CH_2COCl$ (252 mg, 1.5 mmol) was added to a stirred suspension of 1-octanol (130 mg, 1 mmol), *N*-methylimidazole (8 mg, 0.1 mmol), TMEDA (12 mg, 0.1 mmol), and K_2CO_3 (207 mg, 1.5 mmol) in CH_3CN (1 mL) at 0–5 °C under an Ar atmosphere, and the mixture was stirred at the same temperature for 1 h. Water was added to the stirred mixture, which was extracted with EtOAc. The organic phase was washed with water and brine, dried (Na_2SO_4), and concentrated. The obtained crude product was purified by silica gel column chromatography (hexane/EtOAc=25:1) to give 1-octyl 3-phenylpropanonate (248 mg, 95%).

4.3. A typical procedure of esterification (Method B) (Table 2, entry 12)

$PhCH_2CH_2COCl$ (252 mg, 1.5 mmol) was added to a stirred suspension of 3-octanol (130 mg, 1 mmol), *N*-methylimidazole (123 mg, 1.5 mmol), and TMEDA (174 mg, 1.5 mmol) in CH_3CN (1 mL) at 0–5 °C under an Ar atmosphere, and the mixture was stirred at the same temperature for 1 h. Water was added to the stirred mixture, which was extracted with EtOAc. The organic phase was washed with water and brine, dried (Na_2SO_4), and concentrated. The obtained crude product was purified by silica gel column chromatography (hexane/EtOAc=25:1) to give 1-octyl 3-phenylpropanonate (224 mg, 86%).

4.3.1. 1-Octyl 2,6-chlorobenzoate (Table 2, entry 10). Colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 2.96–3.05 (2H, m), 3.09–3.17 (2H, m), 7.07–7.16 (1H, m), 7.19–7.38 (8H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.7, 35.1, 126.4, 127.1, 128.3, 128.6, 128.9, 139.8, 144.0, 169.2; IR (neat) 3030, 2957, 2184, 1773, 1564, 1451, 1354, 1284 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{20}Cl_2O_2$ ($M+Na^+$) 317.0112, found 317.0112.

4.3.2. 3-Octyl 10-undecenoate (Table 2, entry 20). Colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 0.80–0.92 (6H, m), 1.19–1.69 (22H, m), 1.97–2.08 (2H, m), 2.29 (2H, t, J=7.6 Hz), 4.82 (1H, quin, J=6.2 Hz), 4.87–5.06 (2H, m), 5.81 (1H, ddt, J=6.9, 10.0, 17.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.6, 14.0, 22.5, 25.0, 25.1, 26.9, 28.9, 29.0, 29.2, 29.3, 31.7, 33.6, 33.7, 34.7, 75.1, 114.1, 139.1, 173.7; IR (neat) 3073, 2930, 2857, 1734, 1644, 1462, 1370, 1242 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{36}O_2$ ($M+Na^+$) 319.2613, found 319.2613.

4.3.3. 3-Octyl phenoxyacetoate (Table 2, entry 22). Colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 0.78–0.96 (6H, m), 1.15–1.39 (6H, m), 1.46–1.67 (4H, m), 4.62 (2H, s), 4.95 (1H, quin, J=6.5 Hz), 6.85–7.03 (3H, m), 7.21–7.34 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.6, 14.1, 22.6, 25.0, 27.0, 31.7, 33.6, 65.4, 77.6, 114.6, 121.7, 129.6, 158.0, 169.0; IR (neat) 2934, 2863, 1759, 1732, 1601, 1497, 1460, 1383, 1285 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{24}O_3$ ($M+Na^+$) 287.1623, found 287.1623.

4.3.4. 3-Octyl 2-chloropropanoate (Table 2, entry 24). Colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 0.79–0.97 (6H, m), 1.19–1.41 (6H, m), 1.48–1.69 (4H, m), 1.74 (3H, d, J=6.9 Hz), 4.40 (1H, q, J=6.9 Hz), 4.88 (1H, quin, J=6.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.5, 14.0, 21.5, 22.5, 24.8, 24.9, 26.9, 31.6, 33.4, 52.9, 77.5, 169.9, 191.3; IR (neat) 2934, 2863, 1742, 1460, 1379, 1335, 1275, 1246 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{21}Cl_1O_2$ ($M+Na^+$) 243.2231, found 243.1128.

4.4. A typical procedure of amide formation (Method A) (Table 3, entry 1)

$PhCH_2CH_2COCl$ (252 mg, 1.5 mmol) was added to a stirred suspension of aniline (93 mg, 1 mmol), *N*-methylimidazole (8 mg, 0.1 mmol), TMEDA (12 mg, 0.1 mmol), and K_2CO_3 (207 mg, 1.5 mmol) in CH_3CN (1 mL) at 0–5 °C under an Ar atmosphere, and the mixture was stirred at the same

temperature for 1 h. Water was added to the stirred mixture, which was extracted with EtOAc. The organic phase was washed with water and brine, dried (Na_2SO_4), and concentrated. The obtained crude product was purified by silica gel column chromatography (hexane/EtOAc=25:1) to give *N*-phenyl 3-phenylpropanamide (220 mg, 98%).

4.5. A typical procedure of amide formation (Method B) (Table 3, entry 1)

$PhCH_2CH_2COCl$ (252 mg, 1.5 mmol) was added to a stirred suspension of aniline (93 mg, 1 mmol), *N*-methylimidazole (123 mg, 1.5 mmol), and TMEDA (174 mg, 1.5 mmol) in CH_3CN (1 mL) at 0–5 °C under an Ar atmosphere, and the mixture was stirred at the same temperature for 1 h. Water was added to the stirred mixture, which was extracted with EtOAc. The organic phase was washed with water and brine, dried (Na_2SO_4), and concentrated. The obtained crude product was purified by silica gel column chromatography (hexane/EtOAc=25:1) to give *N*-phenyl 3-phenylpropiaonamide (216 mg, 96%).

4.6. A typical procedure of amide formation using a weakly nucleophilic aniline (Method A) (Table 5, entry 1)

$PhCH_2CH_2COCl$ (252 mg, 1.5 mmol) was added to a stirred suspension of 2,6-dichloroaniline (162 mg, 1 mmol), *N*-methylimidazole (8 mg, 0.1 mmol), TMEDA (12 mg, 0.1 mmol), and K_2CO_3 (207 mg, 1.5 mmol) in CH_3CN (1 mL) at 0–5 °C under an Ar atmosphere, and the mixture was stirred at the same temperature for 1 h, and at 20–25 °C for 1 h. Water was added to the stirred mixture, which was extracted with EtOAc. The organic phase was washed with water and brine, dried (Na_2SO_4), and concentrated. The obtained crude product was purified by silica gel column chromatography (hexane/EtOAc=5:1) to give *N*-(2,6-dichlorophenyl) 3-phenylpropanamide (242 mg, 82%).

4.6.1. Synthesis of bromobutide[8] using Method A (Scheme 3). 3,3-Dimethyl-2-bromobutanoyl chloride (320 mg, 1.5 mmol) was added to a stirred suspension of α,α-dimethylbenzylamine (135 mg, 1 mmol), *N*-methylimidazole (8 mg, 0.1 mmol), TMEDA (12 mg, 0.1 mmol), and K_2CO_3 (207 mg, 1.5 mmol) in chlorobenzene (1 mL) at 0–5 °C under an Ar atmosphere, and the mixture was stirred at 20–25 °C for 2 h. Water was added to the stirred mixture, which was extracted with EtOAc. The organic phase was washed with water and brine, dried (Na_2SO_4), and concentrated to give the crude product. The obtained crude product was washed with hexane (ca. 5 mL) to give bromobutide (294 mg, 94%).

Colorless crystals; mp 176.0–176.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50 (9H, s), 1.69 (3H, s), 1.74 (3H, s), 4.03 (1H, s), 6.32 (1H, br), 7.30–7.45 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.9, 27.6, 28.1, 29.2, 35.1, 56.3, 64.7, 124.6, 126.8, 128.4, 146.3, 166.7; IR (KBr) 3319, 3059, 2968, 1820, 1678, 1541, 1367, 1199 cm^{-1}.

4.6.2. Synthesis of carpropamid[9] using Method A (Scheme 3). 2,2-Dichloro-1-ethyl-3-methylcyclopropanecarbonyl chloride (321 mg, 1.5 mmol) was added to a stirred suspension of 1-(4-chlorophenyl)ethylamine (156 mg, 1 mmol), *N*-methylimidazole (8 mg, 0.1 mmol), TMEDA (12 mg, 0.1 mmol), and K_2CO_3 (207 mg, 1.5 mmol) in CH_3CN (1 mL) at 0–5 °C under an Ar atmosphere, and the mixture was stirred at the same temperature for 1 h. Water was added to the stirred mixture, which was extracted with EtOAc. The organic phase was washed with water and brine, dried (Na_2SO_4), and concentrated to give the crude product. The obtained crude product was washed with hexane (ca. 5 mL) to give bromobutide (311 mg, 93%).

Colorless crystals; mp 169.0–169.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (3H×2/3, t, J=7.6 Hz), 0.99 (3H×1/3, t, J=7.6 Hz), 1.17–1.22 (3H, m), 1.49–1.59 (4H, m), 1.83–2.01 (1H, m), 2.21 (1H, q, J=6.5 Hz), 5.17 (1H, quin, J=7.2 Hz), 5.85 (1H, br), 7.28–7.34 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.6, 10.8, 10.9, 21.2, 21.3, 22.0, 29.6, 43.2, 48.7, 66.6, 127.6, 127.9, 128.7, 128.8, 133.2, 141.0, 141.4, 167.2, 167.4; IR (KBr) 3270, 3057, 2878, 1644, 1530, 1493, 1456, 1414 cm^{-1}.

4.7. A typical procedure of thioesterification (Method A) (Table 7, entry 1)

$PhCH_2CH_2COCl$ (252 mg, 1.5 mmol) was added to a stirred suspension of 1-octanthiol (146 mg, 1 mmol), *N*-methylimidazole (8 mg, 0.1 mmol), TMEDA (12 mg, 0.1 mmol), and K_2CO_3 (207 mg, 1.5 mmol) in CH_3CN (1 mL) at 0–5 °C under an Ar atmosphere, and the mixture was stirred at the same temperature for 1 h, and at 20–25 °C for 1 h. Water was added to the stirred mixture, which was extracted with EtOAc. The organic phase was washed with water and brine, dried (Na_2SO_4), and concentrated. The obtained crude product was purified by silica gel column chromatography (hexane/EtOAc=25:1) to give *S*-1-octyl 3-phenylpropanthioate (247 mg, 89%).

4.8. A typical procedure of thioesterification (Method B) (Table 7, entry 10)

t-BuCOCl (252 mg, 1.5 mmol) was added to a stirred suspension of 1-octanthiol (146 mg, 1 mmol), *N*-methylimidazole (123 mg, 1.5 mmol), and TMEDA (174 mg, 1.5 mmol) in CH_3CN (1 mL) at 0–5 °C under an Ar atmosphere, and the mixture was stirred at the same temperature for 1 h, and at 20–25 °C for 1 h. Water was added to the stirred mixture, which was extracted with EtOAc. The organic phase was washed with water and brine, dried (Na_2SO_4), and concentrated. The obtained crude product was purified by silica gel column chromatography (hexane/EtOAc=25:1) to give *S*-1-octyl 2,2-dimethylpropanthioate (230 mg, 99%).

4.8.1. *S*-1-Octyl 10-undecenthioate (Table 7, entry 7). Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, t, J=6.9 Hz), 1.16–1.41 (20H, m), 1.48–1.71 (4H, m), 2.02 (2H, q, J=6.9 Hz), 2.53 (2H, t, J=7.6 Hz), 2.86 (2H, t, J=7.6 Hz), 4.88–5.04 (1H, m), 5.81 (1H, ddt, J=6.6, 10.3, 17.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.6, 25.7, 28.8, 28.9, 28.9, 29.0, 29.1, 29.1, 29.2, 29.2, 29.6, 31.8, 33.8, 44.1, 114.1, 139.1, 199.8; IR (neat) 2926, 2855, 1744, 1694, 1642, 1462, 1414, 1238 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{36}O_1S_1$ (M+Na^+) 335.2385, found 335.2383.

4.8.2. *S*-1-Octyl phenoxyacetothioate (Table 7, entry 8). Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, t, J=7.2 Hz), 1.18–1.42 (10H, m), 1.51–1.65 (2H, m), 2.93 (2H, t, J=7.2 Hz), 4.68 (2H, s), 6.88–7.05 (3H, m), 7.23–7.35 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 22.5, 28.0, 28.7, 29.0, 29.0, 29.2, 31.7, 72.8, 114.7, 121.9, 129.5, 157.7, 198.2; IR (neat) 2928, 2855, 1682, 1599, 1495, 1458, 1435, 1302, 1244 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{24}O_1S_1$ (M+Na$^+$) 275.1446, found 275.1446.

4.8.3. *S*-1-Octyl 2-chloropropanthioate (Table 7, entry 9). Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.88 (3H, t, J=6.9 Hz), 1.19–1.43 (10H, m), 1.51–1.65 (2H, m), 1.71 (3H, d, J=6.9 Hz), 2.91 (2H, t, J=7.2 Hz), 4.47 (1H, q, J=6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 22.1, 22.6, 28.8, 29.0, 29.1, 29.5, 31.7, 59.8, 197.8; IR (neat) 2928, 2857, 1674, 1451, 1412, 1375, 1275, 1235 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{21}O_1S_1$ (M+Na$^+$) 259.0899, found 259.0895.

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