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Zwitterionic Salts as Mild Organocatalysts for Transesterification

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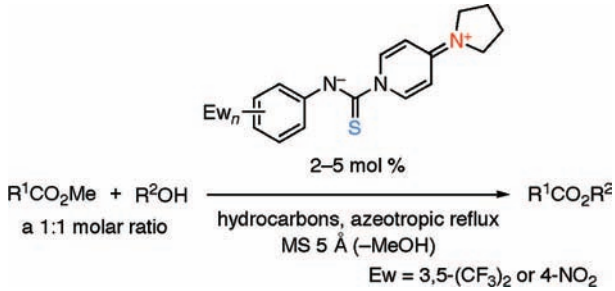
ABSTRACT



The exothermic reaction of 3,5-bis(trifluoromethyl)phenyl or 4-nitrophenyl isothiocyanate with 4-pyrrolidinopyridine (PPY) gave the corresponding arylaminothiocarbonylpyridinium salts in quantitative yields. These novel zwitterionic salts were effective as organocatalysts for the transesterification reaction of an equimolar mixture of methyl carboxylates and alcohols in hydrocarbons such as heptane and octane under azeotropic reflux conditions with the removal of methanol. In sharp contrast, PPY was inert as a catalyst under the same reaction conditions.

The transesterification reaction is one of the most popular methods for synthesizing carboxylic esters. Although several procedures catalyzed by a variety of protic and Lewis acids, organic and inorganic bases, enzymes, and antibodies have been developed,[1,2] a more efficient and more generally applicable transesterification procedure involving simple preparations and a nontoxic catalyst is still needed. We report here that [3,5-bis(trifluoromethyl)phenyl]aminothiocarbonylpyridinium salt (**1**) and (4-nitrophenyl)aminothiocarbonylpyridinium salt (**2**) are mild organocatalysts for the transesterification reaction of an equimolar mixture of methyl carboxylates and alcohols.

Initially, we envisaged the possibility of dual activation of the transesterification reaction based on acid−base combination chemistry.[3,4] *N*,*N*′-[3,5-Bis(trifluoromethyl)phenyl]thiourea (**3**)[5] and 4-pyrroridinopyridine (PPY)[6] were examined as a Brønsted acid catalyst and a nucleophilic base catalyst, respectively, for the dual activation of methyl phenylacetate for transesterification between methyl phenylacetate and benzyl alcohol. As shown in entries 1 and 2 of Table 1, transesterification in heptane under azeotropic reflux conditions with the removal of methanol proceeded smoothly in the presence of 2 mol % each of **3** and PPY. Methanol

(1) For reviews of (trans)esterifications, see: (a) Otera, J. *Chem. Rev.* **1993**, *93*, 1449–1470. (b) Otera, J. *Esterification*; Wiley-VCH Verlag GmbH: Weinheim, Germany, 2003. (c) Otera, J. *Acc. Chem. Res.* **2004**, *37*, 288–296. (d) Grasa, G. A.; Singh, R.; Nolan, S. P. *Synthesis* **2004**, *971*, 985. (e) Hoydonckx, H. E.; De Vos, D. E.; Chavan, S. A.; Jacobs, P. A. *Top. Catal.* **2004**, *27*, 83–06. (f) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606–5655.

(2) For recent contributions regarding catalytic transesterifications, see: (a) de Sairre, M. I.; Bronze-Uhle, E. S.; Donate, P. M. *Tetrahedron Lett.* **2005**, *46*, 2705–2708. (b) Jiang, P.; Zhang, D.; Li, Q.; Lu, Y. *Catal. Lett.* **2006**, *110*, 101–106. (c) Remme, N.; Koschek, K.; Schneider, C. *Synlett* **2007**, *491*, 493. (d) Kondaiah, G. C. M.; Reddy, L. A.; Babu, K. S.; Gurav, V. M.; Huge, K. G.; Bandichhor, R.; Reddy, P. P.; Bhattacharya, A.; Anand, R. V. *Tetrahedron Lett.* **2008**, *49*, 106–109. (e) Ohshima, T.; Iwasaki, T.; Maegawa, Y.; Yoshiyama, A.; Mashima, K. *J. Am. Chem. Soc.* **2008**, *130*, 2944–2945. (f) Inahashi, N.; Fujiwara, T.; Sato, T. *Synlett* **2008**, 605–607.

(3) For our account article, see: Ishihara, K.; Sakakura, A.; Hatano, M. *Synlett* **2007**, *686*, 703.

(4) For a recent review of bifunctional acid−base catalysts, see: Kanai, M.; Kato, N.; Ichikawa, E.; Shibasaki, M. *Synlett* **2005**, *1491*, 1508.

(5) (a) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289–296. (b) Wittkopp, A.; Schreiner, P. R. *Chem. Eur. J.* **2003**, *9*, 407–414.

(6) (a) Hassner, A.; Krepski, L. R.; Alexanilan, V. *Tetrahedron* **1978**, *34*, 2069–2076. (b) Held, I.; Xu, S.; Zipse, H. *Synthesis* **2007**, 1185–1196, and references cited therein.

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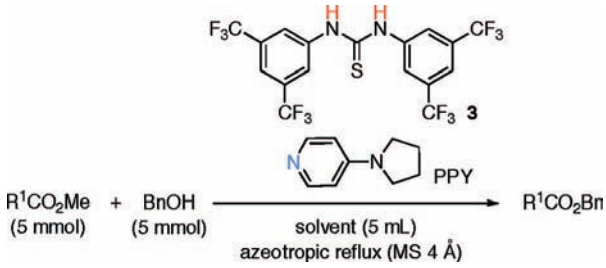
Table 1. Transesterification of Methyl Carboxylates with Benzyl Alcohol[a]



entry	R^1CO_2Me	**3** (mol %)	PPY (mol %)	solvent (bp, °C)	time (h)	yield (%)
1	$PhCH_2CO_2Me$	2	2	heptane (98)	24	96
2	$PhCH_2CO_2Me$	1	1	heptane (98)	22.5	66
3	$PhCH_2CO_2Me$	1[b]	1	heptane (98)	22.5	4
4	$PhCH_2CO_2Me$	2	0	heptane (98)	24	0
5	$PhCH_2CO_2Me$	0	2	heptane (98)	24	7
6	n-$C_9H_{19}CO_2Me$	2	2	heptane (98)	24	96
7	c-$C_6H_{11}CO_2Me$	2	2	heptane (98)	24	37
8	c-$C_6H_{11}CO_2Me$	2	2	octane (126)	6	99
9	$PhCO_2Me$	2	2	heptane (98)	24	72
10	$PhCO_2Me$	2	2	octane (126)	24	100

[a] 3 g of molecular sieves 4 Å was used. [b] **4** was used instead of **3**.

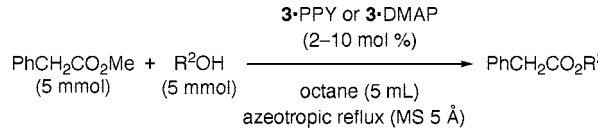
was removed through a pressure-equalized addition funnel containing a cotton plug and 4 Å molecular sieves (pellets), which served as a Soxhlet extractor. When *N*,*N*′-bis[3,5-bis(trifluoromethyl)phenyl]urea (**4**) was used instead of **3**, transesterification almost did not occur (entry 2 versus entry 3). Interestingly, **3** and PPY each had no catalytic activity (entries 4 and 5). Methyl decanoate was also transesterified to give the corresponding benzyl ester in high yield under the same conditions as in entry 1 (entry 6). Sterically demanding carboxylic acids such as methyl cyclohexanecarboxylate and methyl benzoate were quantitatively transesterified under azeotropic reflux conditions in octane instead of heptane (entries 7−10).

As a result of the optimization of the above transesterification, we found that the reaction proceeded more smoothly with the use of moleculer sieves 5 Å instead of 4 Å (entry 1 of Table 2). The reactivity was decreased with the use of 4-(*N*,*N*-dimethylamino)pyridine (DMAP)[7] instead of PPY (entry 2). As shown in Table 2, other primary alcohols such as (*E*)-cinnamyl alcohol and *n*-dodecanol and cyclohexanemethanol also quantitatively reacted with methyl phenylacetate in the presence of 5 mol % of **3**·PPY (entries 3−5). However, the transesterification of a secondary alcohol such as cyclododecanol was quite slow (entry 6).

In the course of the present study, we observed some strange but significant phenomena. During transesterification, **3** gradually decomposed under these reaction conditions, but the transeterification reaction proceeded even after **3** had completely disappeared. In addition, trace amounts of 3,5-

(7) Sakakura, A.; Kawajiri, K.; Takuro Ohkubo, T.; Kosugi, Y.; Ishihara, K. *J. Am. Chem. Soc.* **2007**, *129*, 14775–14779, and references cited therein.

Table 2. Transesterification of Methyl Phenylacetate with Alcohols[a]

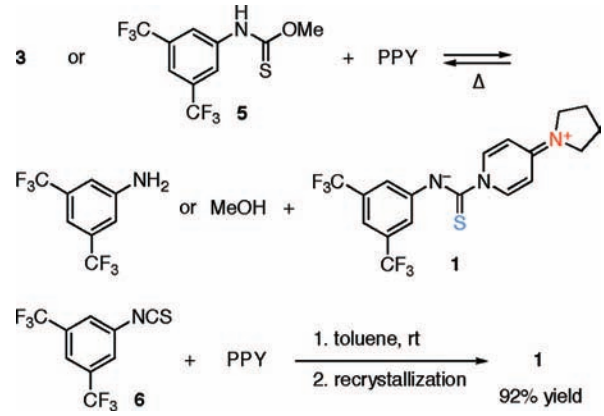


entry	R^2OH	catalysts (mol %)	time (h)	yield (%)
1	BnOH	**3**·PPY, 2	6	98
2	BnOH	**3**·DMAP, 2	6	64
3	(*E*)-$PhCH{=}CHCH_2OH$	**3**·PPY, 10	24	90
4	n-$C_{11}H_{23}OH$	**3**·PPY, 10	24	97
5	c-$C_6H_{11}CH_2OH$	**3**·PPY, 10	24	98
6	c-$C_{12}H_{23}OH$	**3**·PPY, 10	24	65

[a] 3 g of molecular sieves 5 Å was used.

bis(trifluoromethyl)aniline and *N*-[3,5-bis(trifluoromethyl)phenyl]carboxamides derived from methyl carboxylates were detected in the reaction mixture. Based on these phenomena, we supposed that 3,5-bis(trifluoromethyl)phenylaminothiocarbonylpyridinium salt **1** might be the actual catalytic species for the transesterification reaction. In fact, we confirmed that **1** was generated from **3** or *O*-methyl 3,5-bis(trifluoromethyl)phenylcarbamothioate (**5**) and PPY under heating in toluene (Scheme 1). These reactions were revers-

Scheme 1. Preparation of **1**



ible. Synthetically, **1** was prepared as yellow crystals in 92% yield by the exothermic reaction of 3,5-bis(trifluoromethyl)phenyl isothiocyanate (**6**) with PPY and subsequent recrystallization from its hot solution in toluene (Scheme 1). Surprisingly, compound **1** was insoluble and stable in most protic organic solvents and water at ambient temperature but was soluble in acetonitrile.

The molecular structure of zwitterionic salt **1** was ascertained by an X-ray diffraction analysis, as depicted in Figure 1. To the best of our knowledge, this is the first example of the isolation of zwitterionic salts of isothiocyanates with

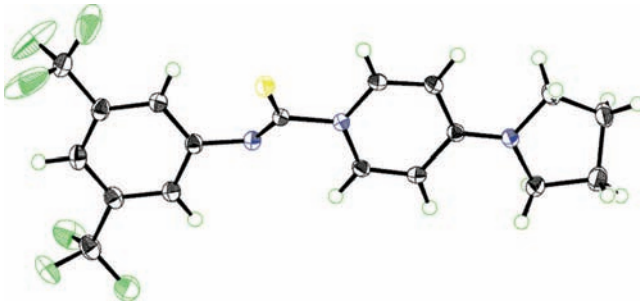
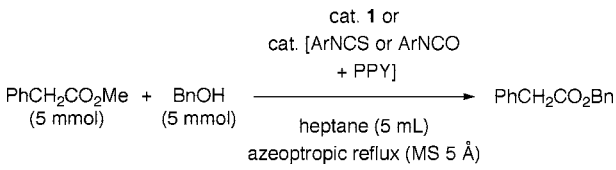


Figure 1. X-ray structure of **1**.

nucleophilic bases. In general, zwitterionic salts of isothiocyanates or isocyanates with pyridine derivatives are not kinetically stable under rapid equilibration.[8] Therefore, it is difficult to isolate them in high yield. Nevertheless, novel zwitterionic salt **1** was much more stable due to the slow decomposition of **1** to highly electrphilic **3** and highly nucleophilic PPY.

Thus, the transesterification reaction of methyl phenylacetate with benzyl alcohol was examined in the presence of 2 mol % of **1**, which was isolated. As expected, the reaction proceeded homogeneously and smoothly under azeotropic reflux conditions in heptane (entry 1 of Table 3). In contrast,

Table 3. Transesterification of Methyl Phenylacetate with Alcohols[a]



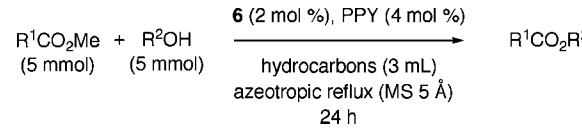
entry	catalysts (mol %)	conversion (%) after 5 h	conversion (%) after 19 h
1	**1**,[b] 2		89
2[c]	**1**,[b] 2		trace
3	**6**, 2 + PPY, 2	53	93
4	**6, 2 + PPY, 4**	**75**	**95**
5	**6**, 4 + PPY, 2	66	98
6	4-$NO_2C_6H_4NCS$ (**7**), 2 + PPY, 2	49	96
7	C_6H_5NCS, 2 + PPY, 2	16	
8	3,5-$(CF_3)_2C_6H_3NCO$, 2 + PPY, 2	trace	22
9	4-$NO_2C_6H_4NCO$, 2 + PPY, 2	trace	30

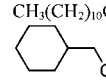
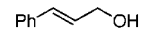
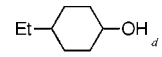
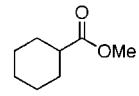
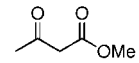
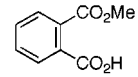
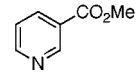
[a] 3 g of molecular sieves 5 Å was used. [b] Isolated **1** was used. [c] EtCN was used as a solvent.

1 was inert in propionitrile, which dissolved **1** at ambient temperature (entry 2). The transesterification reaction proceeded quantitatively in the coexistence of 2 mol % each of **6** and PPY as well as **1** (entry 3). This result is comparable to that using **3** and PPY (entry 1 in Table 1). The transesterification reaction proceeded more rapidly with a 1:2 molar ratio of **6** and PPY than a 1:1 or 2:1 molar ratio (entries 3−5). These results may be ascribed to the kinetic stabilization of **1** with the addition of excess PPY per **6**. 4-Nitrophenyl isothiocyanate (**7**) was also suitable instead of **6** (entry 6 versus entry 3). Both **6** and **7** are commercially available, but **6** is three times more expensive than **7**. In contrast, phenyl isothiocyanate and aryl isocyanates bearing electron-withdrawing groups were much less active than **6** and **7** (entries 7−9).

Under the optimal conditions shown in entry 4 of Table 3, several methyl carboxylates[9] and alcohols were examined as substrates for the transesterification reaction. Representative results are summarized in Table 4. Both aliphatic and aromatic carboxylates were transesterified with primary or secondary alcohols to give the corresponding esters in good to excellent yields. In particular, the present catalytic system was effective for the transesterification reaction of cinnamyl alcohol and 1-phenylethanol, which were acid-sensitive, and

Table 4. Transesterification of Methyl Carboxylates with Alcohols[a]



entry	R^1CO_2Me	R^2OH	solvent	conversion (%)
1	$PhCO_2Me$	BnOH	heptane	96
2	$C_9H_{19}CO_2Me$	BnOH	heptane	93
3	$PhCH_2CO_2Me$	$CH_3(CH_2)_{10}OH$	octane	>99 (99)[b]
4 5	$PhCH_2CO_2Me$		octane	>99
6[c]	$PhCH_2CO_2Me$		octane	90
7[c]	$PhCH_2CO_2Me$	PhMeCHOH	octane	98
8[c]	$PhCH_2CO_2Me$		octane	82[d]
9[c]	$PhCH_2CO_2Me$	$CH_3(CH_2)_{13}MeCHOH$	octane	73 (70)[b]
10		BnOH	octane	99
11		BnOH	heptane	82
12		BnOH	heptane	(87)[b]
13		BnOH	heptane	93

[a] 3 g of molecular sieves 5 Å was used. [b] Isolated yields are shown in parentheses. [c] **6** (5 mol %) and PPY (10 mol %) were used. [d] trans/cis = 72:28.

(8) Sheinkman, A. K.; Fedash, E. V.; Vovk, M. V.; Chmilenko, T. S.; Vysotskii; Yu, B.; Chernyshev, A. I.; Grigor'ev, A. A. *Z. Org. Khim.* **1991**, *27*, 1198–1205.

(9) Ethyl carboxylates were less reactive than the corresponding methyl carboxylates.

methyl acetoacetate, which was acid/base-sensitive[2d] (entries 6, 7, and 11). The transesterification reaction of monomethyl ester of phthalic acid with benzyl alcohol chemoselectively gave 2-(benzyloxycarbonyl)benzoic acid in 87% yield (entry 12). An alkalic ester such as methyl nictinate was also transesterified to the benzyl ester in high yield (entry 13).

The catalytic activities of **1** and **2** observed for the transesterification reaction may be understood on the basis of their conjugated anionic and highly nucleophilic natures (Figure 2). The nucleophilic substitution of **1** and **2** to methyl carboxylates may lead to an active thiocarboxylic intermediate **8**, which may subsequently react with alcohols through acyclic transition-state assembly **9** or cyclic transition-state assembly **10** to give the corresponding esters and methanol. Thus, **1** and **2** may be regenerated as catalysts.

In summary, we have developed new types of nucleophilic organocatalysts **1** and **2** for the transesterification of methyl carboxylates with alcohols without using excess amounts of either substrate. Very interestingly, zwitterionic salts such as **1** and **2**, which should be much less basic than PPY, were far superior to PPY as transesterification catalysts. The further application of zwitterionic salts as nucleophilic catalysts is being studied in our laboratories.

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Supporting Information Available: Experimental procedures and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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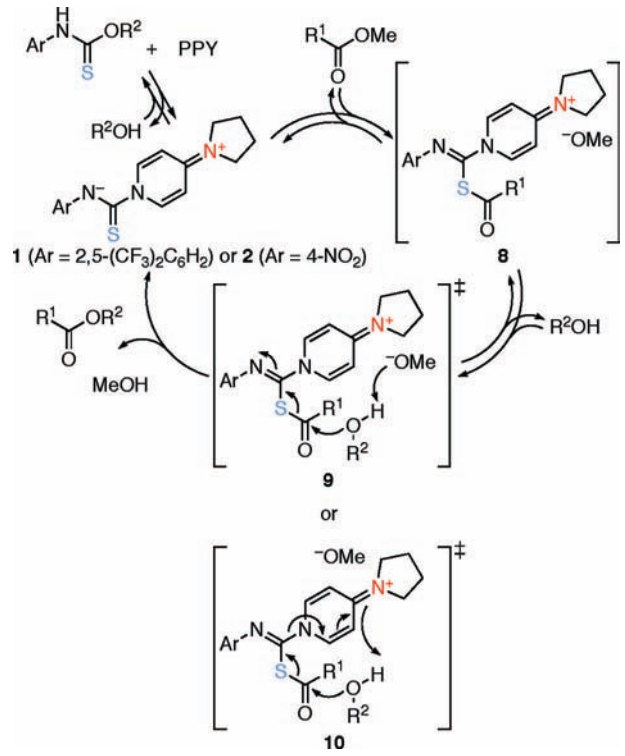

Figure 2. Proposed catalytic cycle. Ar = 3,5-$(CF_3)_2C_6H_3$ or 4-$NO_2C_6H_4$.