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***N*-Butyl-2,4-dinitro-anilinium *p*-toluenesulfonate as a highly active and selective esterification catalyst**

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Abstract

N-Butyl-2,4-dinitro-anilinium *p*-toluenesulfonate (**1**) was found to be a very active esterification catalyst that promotes condensation of equal mole amount of carboxylic acids and alcohols under mild conditions. This catalyst is also highly selective towards carboxylic acid and alcohol substrates at ambient temperature.

Keywords

esterification; catalyst; selectivity; anilinium *p*-toluenesulfonate

Highly active esterification catalysts¹ that show selectivity towards carboxylic acids and alcohols are needed for the laboratory synthesis of complicated molecules and industrial production of pharmaceuticals and their intermediates with diverse functionalities. For example, a selective esterification catalyst will allow a primary alcohol to react with a carboxylic acid—without the need to go through protection and de-protection steps for a secondary or a tertiary alcohol group copresent in the substrate. However, despite tremendous progress in uncovering esterification catalysts,^{1,2} only a few highly selective esterification catalysts have been reported so far, most of which are organic catalysts.³ As a result, research work to develop active and highly selective esterification catalysts is still required.

Rational designs to introduce steric hindrance to the catalytic center of an organic catalyst could enable the catalyst to demonstrate steric selectivity towards carboxylic acid and/or alcohol substrates. In addition, an organic catalyst can be more easily removed out of the reaction mixture than a metal catalyst during work-up, which avoids repeated recrystallization steps or multiple chromatography purifications to remove the leached metal out of a drug intermediate. Recently, we reported a group of lipid-modified pyridinium *p*-toluenesulfonate salts for promoting methylation of carboxylic acids.⁴ The hydrophobic

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Supplementary Material Experiment procedures, ¹H & ¹³C NMR, IR and MS characterizations of compounds can be found, in the online version, at <http://xxxxx>

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catalytic center drives out water byproduct and thus shifts the reaction equilibrium towards the esterification product.

Unfortunately, these catalysts do not show significant selectivity towards substrates and their activities towards a secondary or a tertiary alcohol are generally poor. In this communication paper, we would like to report our more recent study of *N*-butyl-2,4-dinitro-anilinium *p*-toluenesulfonate (**1**, Figure 1) as a very active esterification catalyst with high substrate selectivity.

Four anilinium salts were synthesized and evaluated as esterification catalysts (Figure 1). The synthetic protocols of these salts are reported in Supplementary Material. The protonated aniline serves as a Brønsted/Lewis acid while the nitro group is used to enhance its acidity. Aromatic rings as well as alkyl side chains are used to provide a hydrophobic local environment that shifts the reaction equilibrium to favor the formation of an esterification product. The condensation of 4-phenylbutyric acid (2 mmol) and 1-octanol (2 mmol) in 4 mL isooctane under reflux was employed to gauge the catalytic activities of these four anilinium salts. The amount of catalyst was 1 mol% and the reaction progress was monitored by GC analysis. Figure 1 shows the GC yields after 2 h of reaction. The acetic acid salt of aniline (**4**) only led to less than 5% formation of the ester product. This may suggest that the aromatic ring of *p*-toluenesulfonate plays an important role in the formation of a local hydrophobic catalytic center, which is in agreement with our previous observations in the study of lipid-modified pyridinium salts. Compared with **2**, the presence of two nitro groups on the anilinium ring greatly enhanced the activities of **1** and **3**. A long C11 chain of **3** is sterically demanding and it actually reduced the condensation yield of 1-octanol and 4-phenylbutyric acid to 87% yield. *N*-Butyl-2,4-dinitro-anilinium *p*-toluenesulfonate (**1**) showed the highest catalytic activity (>99%) and was subsequently selected for further investigations.

Table 1 lists catalyst **1**-promoted condensation reactions between a group of carboxylic acids and alcohols. In a typical experiment, an equal mole amount (2 mmol) of a carboxylic acid and an alcohol were mixed in isooctane with 1 mol% **1** under reflux. GC experiments were used to monitor reaction progresses and the products were isolated and purified by flash chromatography. Entries 1-8 in table 1 show condensation of 4-phenylbutyric acid with various alcohols with 1 mol% catalyst **1**. Within 2 h, catalyst **1** converted >99% 1-octanol into an ester and 92% isolation yield was obtained (entry 1). In entry 2, after 24 h, a GC yield of 91% and the isolation yield of 72% were obtained for its methyl ester. The lower yield could be due to the partial loss of methanol and the methyl ester during reaction and workup. Methanol and methyl 4-phenylbutyrate are volatile chemicals. The condensation between benzyl alcohol and 4-phenyl butyric acid (entry 3) also led to excellent GC and isolation yields. Reactions of the acid with secondary alcohols like cyclohexanol (entry 4) and 1-phenyl-1-ethanol (entry 5) all gave rise to moderate or excellent yields, respectively. Catalyst **1** also led to the formation of a number of esters of 4-phenylbutyric acid with an olefinic alcohol (entry 6), a diol (entry 7) and a phenol (entry 8) albeit with lower yields. Other carboxylic acids have also been examined for esterification reactions under 1 mol% **1**, which include bulky 1-adamantanecarboxylic acid (entries 9 & 14) and 2-ethyl-butanoic acid (entry 12), a phenol (entries 10 & 15), an allylic acid (entry 11) and a di-acid (entry 13). Many of these catalytic reactions gave rise to moderate or excellent yields under 1 mol% catalyst **1**.

The selectivity of catalyst **1** towards alcohols was examined and the results are reported in table 2. In a typical experiment, equimolar amount of two alcohols (2 mmol each) was treated with 1 mmol of 4-phenylbutyric acid in isooctane (4 mL) with 1-4 mol% catalyst **1**. The molar ratio of two ester products from each reaction was determined by GC

experiments and was further confirmed by ^1H NMR analyses after flash chromatography purification. Entries 1 & 4 show that a primary alcohol (methanol and 1-octanol) is preferred to react with the acid in the presence of a secondary alcohol (cyclohexanol). The molar selectivities are 95/5 and 85/15, respectively. A primary alcohol (1-octanol) (entry 2) is a preferred substrate over a phenol with the selectivity of 99/1. Entry 3 also suggests that a secondary alcohol reacts faster with the acid than the phenol substrate. Ambient temperature (25 °C) is required for good selectivities between a primary alcohol and a secondary alcohol (entries 1 & 4). Excellent selectivities can still be obtained even at a higher temperature under reflux (> 99 °C) when a primary alcohol or a secondary alcohol is mixed with a phenol substrate (entries 2 & 3).

The selectivity of catalyst **1** towards acids were also examined by mixing 4-phenylbutyric acid (**6**) (2 mmol), 2-ethylbutyric acid (**7**) (2 mmol) and 1-adamantanecarboxylic acid (**8**) (2 mmol) in isooctane (4 mL) with a primary alcohol of either benzyl alcohol (2 mmol) or methanol (2 mmol) under 1 mol% catalyst **1** (Table 3). In entries 1-4, catalyst **1** prefers a sterically less hindered carboxylic acid—4-phenylbutyric acid (**6**) over 2-ethylbutyric acid (**7**). Very bulky **8** led to no detectable ester products (entries 2-4) or a very low yield (2%, entry 1). The carboxylic acid selectivity also depends on the reaction temperature. At ambient temperature (25 °C) (entry 3), a high selectivity of 99/1/0 was achieved for **III/IV/V** when benzyl alcohol was used as the alcohol substrate.

Although the mechanism of selectivity is not clear at this stage, it is reasonable to hypothesize that at ambient temperature, catalyst **1**, alcohol and carboxylic acid substrates form a stable complex. The hydrophobic catalytic center of **1** promotes the esterification reaction while its bulky aromatic rings and the butyl chain prefer the adoption of a sterically less demanding substrate to the catalytic center. This size preference induces steric selectivity of **1** towards alcohol and carboxylic acid substrates. Raising the reaction temperature will enhance the catalytic activity of **1**, but could also destabilize the catalytic complex and reduce the selectivity of **1**. However, more experiments will be needed to validate our working hypothesis.

In summary, in this communication we report *N*-butyl-2,4-dinitro-anilinium *p*-toluenesulfonate (**1**) as an active organic catalyst that can promote condensation between carboxylic acids and alcohols with high selectivity. The selectivity of this catalyst is improved when the reaction temperature is lowered. Such a highly active and selective esterification catalyst can be a useful tool for synthetic organic chemists. Our study also suggests that rational designs is a good strategy that can potentially lead to novel esterification catalysts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.

Anilinium salts as esterification catalysts. The GC yields of a test reaction of 4-phenylbutyric acid and 1-octanol were shown.

Table 1Catalyst 1-promoted esterification reactions.^a

Entry	Product (R ₁ COOR ₂)		Time (h)	Yield (%) GC	Yield (%) Isolated
1		5a	2	>99	92
2		5b	24	91	72
3		5c	3.5	>99	97
4		5d	3	87	77
5		5e	19	>99	92
6		5f	24	79	54
7		5g	28	75	73
8		5h	115	67	59
9		5i	19	95	92

Entry	Product (R ₁ COOR ₂)		Time (h)	Yield (%) GC	Yield (%) Isolated
10		5j	24	98	91
11		5k	18	91	80
12		5l	22	80	54
13		5m	25	>99	93
14		5n	44	76	64
15		5o	44	56	46

^aUnless otherwise shown, the reaction was carried out with a carboxylic acid (2 mmol), an alcohol (2 mmol) and catalyst **1** (1 mol%) in isoctane (4 mL) under reflux.

Table 2Selective condensation of 4-phenylbutyric acid with various alcohols by catalyst **1**.^a

Entry	R_2OH	$R_2'OH$	Conditions	Yield (%) (I + II)	Molar ratio ^b (I / II)
1	CH ₃ OH		24 h, 25 °C, 2 mol% 1	72	95/5
2			2 h, reflux 1 mol% 1	98	99/1
3			20 h, reflux 1 mol% 1	>99	96/4
4			116 h, 25 °C, 4 mol% 1	>99	85/15

^a Unless otherwise shown, the reaction was carried out with a mixture of three carboxylic acids (2 mmol each), benzyl alcohol or methanol (2 mmol each) and catalyst **1** (1 mol%) in isooctane (4 mL) under various temperatures.

^b Determined by GC analyses. The structures of products were confirmed by ¹H NMR and MS experiments after flash chromatography purification.

Table 3

Selective condensation of benzyl alcohol and methanol with various carboxylic acids by catalyst 1.^a

Entry	R ₂ OH	Conditions	Yield (%) (III+IV+V)	Molar ratio ^b (III/IV/V)
1	PhCH ₂ OH	4h, reflux	>99	72/26/2
2	PhCH ₂ OH	19 h, 60°C	>99	58/42/0
3	PhCH ₂ OH	135 h, 25°C	96	99/1/0
4	CH ₃ OH	68 h, 25°C	76	87/13/0

^a Unless otherwise shown, the reaction was carried out with a mixture of three carboxylic acids (2 mmol each), benzyl alcohol or methanol (2 mmol each) and catalyst 1 (1 mol%) in isooctane (4 mL) under various temperatures.

^b Determined by GC analyses. The structures of products were confirmed by ¹H NMR and MS experiments after flash chromatography purification.