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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.

Highly active esterification catalysts[1] 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 co-present 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 centre 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 catalytic centre drives out water byproduct and thus shifts the reaction equilibrium towards the esterification product.

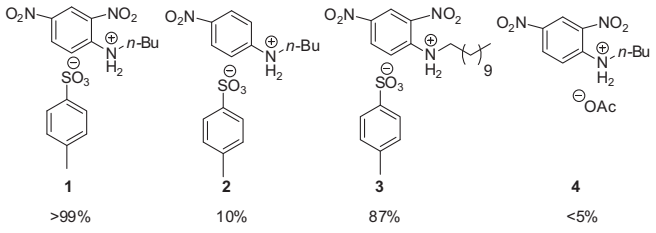

Figure 1. Anilinium salts as esterification catalysts. The GC yields of a test reaction of 4-phenylbuturic acid and 1-octanol are shown.

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 Letter, we would like to report our more recent study of *N*-butyl-2,4-dinitro-anilinium *p*-toluenesulfonate (**1**, Fig. 1) as a very active esterification catalyst with high substrate selectivity.

Four anilinium salts were synthesized and evaluated as esterification catalysts (Fig. 1). The synthetic protocols of these salts are reported in Supplementary data. 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 to provide a hydrophobic local environment that shifts the reaction equilibrium to favour the formation of an esterification product. The condensation of 4-phenylbutyric acid (2 mmol) and 1-octanol (2 mmol) in 4 mL of 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

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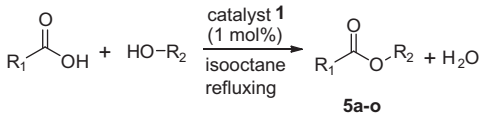
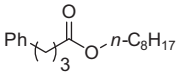
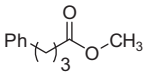
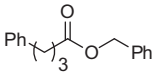
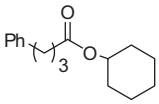
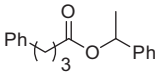
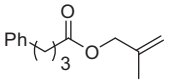
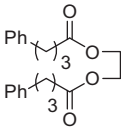
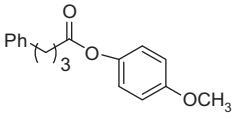
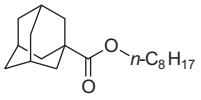
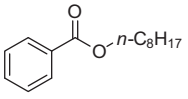
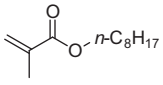
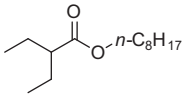
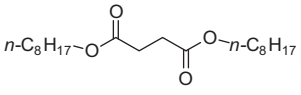
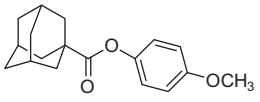
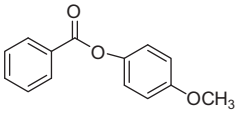
Table 1
Catalyst **1**-promoted esterification reactions[a]



5a-o

Entry	Product (R_1COOR_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
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

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