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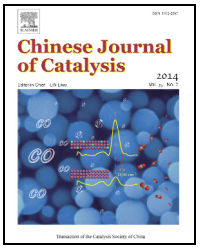

Article

Tribromo melamine as novel and versatile catalyst for the formylation and acetylation of alcohols

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ABSTRACT

Tribromo melamine has been found to be an efficient and green organocatalyst for the acetylation and formylation reactions of alcohols with acetic anhydride and ethyl formate at room temperature and under mild reaction conditions.

1. Introduction

During the multistep synthesis of natural products, the efficiency of the synthetic protocol employed often depends largely on protection and deprotection of the functional groups. To this end, protecting groups have played a crucial role in the synthesis of complex natural products [1]. Acetylation and formylation of hydroxy groups are the most widely used transformations in organic synthesis [2–4].

Amongst protecting groups for alcohols, esters are the most important with acetate being the simplest and easiest to use. Acetylation is usually performed with reagents such as acetic anhydride or acetyl chloride in the presence of variety of acidic or basic catalysts [5].

Formylation is also a very important process in organic chemistry. *O*-Formylation is the method of choice for protecting an alcoholic group in a complex synthetic sequence because deformylation can be affected selectively in the presence of acetate or other ester protecting groups [6–8].

Several acetylation and formylation procedures for alcohols have been reported over the years [9–14], but these methods suffer from some disadvantages, such as heavy metal contamination, high temperature, formation of undesirable or toxic byproducts, expensive reagents, or long reaction times [15–18]. These issues stimulated us to research a simple, efficient, and safe catalyst for the acetylation and formylation of alcohols. In this regard, a group of compounds entitled *N*-halo reagents is widely used in fine organic synthesis [19].

2. Experimental

Chemicals were purchased from Fluka, Merck, and Aldrich. The formylated and acetylated products were characterized by comparison of their spectral (IR, ^{1}H NMR, and ^{13}C NMR) and physical data with those of authentic samples.

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2.1. Formylation of 4-tert-butylbenzyl alcohol

To the stirred mixture of 4-*tert*-butyl benzyl alcohol (1 mmol, 0.164 g) and ethyl formate (2 mL), tribromo melamine (0.1 mmol) was added without additional solvents. The resulting mixture was stirred at room temperature for 30 min. The reaction was monitored by TLC. On completion of reaction, the product was extracted with CH_2Cl_2 (5 mL × 4). The organic layer was separated, dried over anhydrous Na_2SO_4 (1.5 g), and concentrated under reduced pressure. Finally, the organic solvents were evaporated, and 4-*tert*-butylbenzyl formate was obtained in 92% yield. The identity of the product was confirmed by comparing the physical and spectral data with those of the known compound.

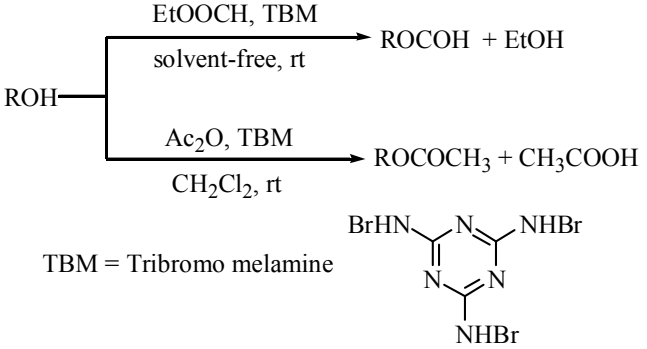
2.2. Acetylation of 3-fluorobenzyl alcohol

Tribromo melamine (0.1 mmol) was added to a solution of 3-fluorobenzyl alcohol (0.126 g, 1 mmol) and acetic anhydride (0.204 g, 2 mmol) in dichloromethane (5 mL), and the reaction mixture was stirred at room temperature for 1 h (the progress of the reaction was monitored by TLC). On completion of the reaction, water (5 mL) and then 5% $NaHCO_3$ (5 mL) was added to the mixture with stirring, and the product was extracted with CH_2Cl_2 (5 mL × 4). The organic layer was dried over anhydrous Na_2SO_4 (1.5 g). Finally, the organic solvents were evaporated, and 3-fluorobenzyl acetate was obtained in 86% yield.

3. Results and discussion

Following our previous work in developing new methods for the protection of the hydroxy group [20–23], an effective procedure for the acetylation and formylation of alcohols with acetic anhydride and ethyl formate in the presence of catalytic amounts of tribromo melamine at room temperature (Scheme 1) has been developed.

To find the optimal conditions for the formylation of alcohols by this method, we selected 4-bromobenzyl alcohol as a model substrate and treated it with ethyl formate in the presence of different amounts of tribromo melamine at room temperature. We found that 0.05 equivalents of tribromo melamine gave the highest yield of the respective alkyl formate after 60 min at room temperature (Table 1, entry 5). The results clearly show that the tribromo melamine is effective for this transformation, whereas, in its absence, the reaction fails to initiate even after 24 h (Table 1, entry 6). Additionally, 4-bromobenzyl alcohol was used as a model substrate for acetylation (Table 1, entries 7–12). The reaction was monitored with different amounts of catalyst. Increasing the loading of tribromo melamine from 0.01 mmol to 0.05 mmol resulted in a considerable improvement of the yield from 22% to 95% (Table 1, entries 7 and 11). The acetylation reaction was also carried out in the absence of catalyst. Again, the reaction had not initiated after 24 h (Table 1, entry 12).



Scheme 1. Formylation and acetylation of alcohols.

Table 1
Optimization of the amount of tribromo melamine in the reaction of 4-bromobenzyl alcohol with ethyl formate or acetic anhydride.

Entry	Catalyst amount (mmol)	Yield [a] (%)
1	0.01	13
2	0.02	40
3	0.03	41
4	0.04	56
5	0.05	99
6	No catalyst	Trace
7	0.01	22
8	0.02	28
9	0.03	30
10	0.04	57
11	0.05	95
12	No catalyst	Trace

Reaction conditions: 4-bromobenzyl alcohol 1 mmol, ethyl formate 2 mL or acetic anhydride 2 mmol, room temperature.
[a] Yields refer to isolated pure products.

To find the best solvent for the formylation, the model reaction was performed in a number of solvents, and moderate to poor yields of the corresponding alkyl formates were obtained (Table 2, entry 2–6). A far higher yield was obtained under solvent-free conditions (Table 2, entry 1).

The acetylation reaction was also investigated in various solvents; the model reaction consisted of 1 mmol of 4-bromobenzyl alcohol with acetic anhydride (2 mmol) using 0.05 mmol of tribromo melamine as the catalyst (Table 2, entry

Table 2
Effect of solvent on the conversion of 4-bromobenzyl alcohol to the corresponding formate or acetate.

Entry	Solvent	Time (min)	Yield [a] (%)
1	Solvent-free	1 h	99
2	Acetone	24 h	40
3	Dichloromethane	24 h	54
4	Acetonitrile	24 h	9
5	Ethyl acetate	24 h	58
6	Chloroform	24 h	23
7	Solvent-free	240	96
8	Acetone	180	95
9	Dichloromethane	20	95
10	Acetonitrile	165	83
11	Ethyl acetate	202	99
12	Chloroform	106	97

Reaction conditions: substrate:ethyl formate/acetic anhydride = 1 mmol/2 mmol, catalyst 0.05 mmol, solvent 5 mL.
[a] Yields refer to isolated pure products.