



Original article

N-Heterocyclic carbene-catalyzed synthesis of acetyltributylcitrate via a transesterification reaction

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ABSTRACT

A new methodology for the synthesis of a green plasticizer acetyltributylcitrate through a transesterification reaction was developed. Under the catalysis of alkyl-substituted imidazol-type N-heterocyclic carbenes, tributyl citrate can react with vinyl acetate smoothly to give ATBC in high yield.

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1. Introduction

N-Heterocyclic carbenes (NHCs) have attracted considerable attention in the past decade, which have been utilized successfully in both transition-metal-catalyzed reactions [1] and organocatalyzed reactions [2]. As versatile nucleophilic organocatalysts, NHCs can catalyze a variety of important transformations such as benzoin reaction [3], Stetter reaction [4], homoenolate reactions [5] via polarity reversal of carbonyl compounds. We and others have also demonstrated that NHCs can be used as the catalyst for redox reactions [6], the cyanation reaction [7], the aldol reaction [8] and several other reactions [9]. Aside from these applications, NHCs have been used as highly efficient organocatalysts for acyl transfer reactions. More than ten years ago, the group of Nolan [10] and Hedrick [11] reported the first two examples of NHC-catalyzed transesterification reaction independently. Following these seminal findings, great effort has been devoted to the NHC-promoted transesterifications, including their application in polymerization reactions [12].

Acetyltributylcitrate (ATBC) is an ester derived from citric acid, which can be used to replace phthalate esters as a green and nontoxic plasticizer in many plastic products such as toys, child care articles, food packages, medicinal instruments and so on. To date, this environmentally friendly plasticizer is mainly prepared by two methods (Scheme 1), namely, the direct esterification of

tributyl citrate with HOAc [13] and the acetylation of tributyl citrate with Ac₂O [14]. In line with our continuing interest in NHCs catalysis [15], we found that NHCs can catalyze the transesterification reaction between vinyl acetate and tributyl citrate to afford ATBC in high yield (Scheme 2), which might be used as the third method for the preparation of this green plasticizer. Herein, we would like to disclose our preliminary results.

2. Experimental

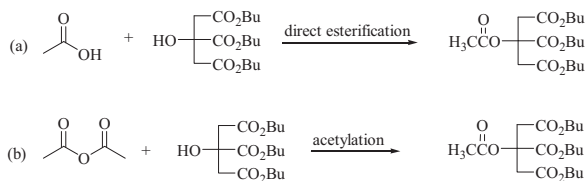
To a solution of **10** (60 mg, 0.3 mmol) in 0.5 mL THF was added tBuOK (34 mg, 0.3 mmol) under N₂. After the mixture was stirred for 30 min at rt, tributyl citrate (720 mg, 2.0 mmol) was added followed by vinyl acetate (1.0 mL). The reaction mixture was then stirred at 70 °C for 12 h. The solution was filtered through a short silica pad and concentrated. The crude products were purified using silica-gel chromatography (ethyl acetate/petroleum ether) to afford ATBC as a colorless oil. Yield: 81%; R_f = 0.25 (petroleum ether–EtOAc, 15:1); IR (KBr, cm⁻¹): 3498, 2962, 2874, 1740, 1466, 1188; ¹H NMR (400 MHz, CDCl₃): δ 4.21 (t, 2H, J = 6.7 Hz), 4.09 (m, 4H, J = 6.7 Hz), 2.84 (q, 4H, J = 38.8, 15.5 Hz), 2.05 (s, 3H), 1.71–1.55 (m, 6H), 1.45–1.30 (m, 6H), 0.97–0.88 (m, 9H); GC–MS (EI): m/z 402 (M⁺).

3. Results and discussion

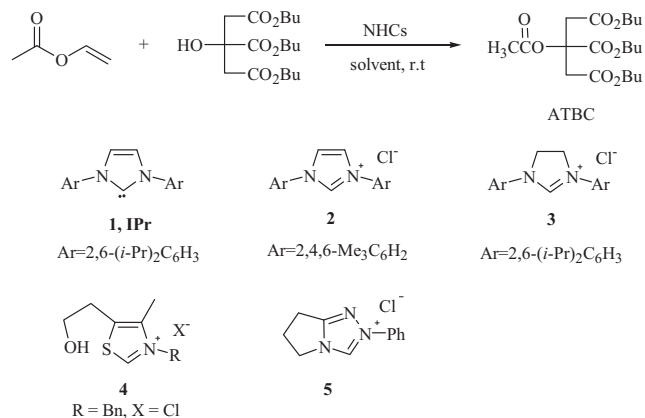
Our investigation commenced with the transesterification between vinyl acetate and tributyl citrate in the presence of a

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Scheme 1. The synthetic method of ATBC.



Scheme 2. NHCs-catalyzed synthesis of ATBC.

catalytic amount of 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene (IPr, a stable NHC) [16]. To our delight, under the catalysis of 20 mol% IPr, the reaction proceeded smoothly in THF at room temperature, giving 21% conversion of ATBC (Table 1, entry 1). Encouraged by this result, a range of simple NHC precursors such as imidazolium **2**, imidazolium **3**, thiazolium **4** and triazolium **5** were tested for the reaction. The results indicated that NHCs generated from **2** or **3** can promote the reaction with low efficiency (Table 1, entries 2 and 3), whereas NHCs generated from **4** and **5** cannot catalyze the transesterification (Table 1, entries 4 and 5). ^tKOBu, DBU, Et₃N and Cs₂CO₃ all can react with the azolium salts to produce the corresponding NHC catalyst *in situ*, but no obvious differences were observed (Table 1, entries 6–8). Other reaction

Table 1
Evaluation of conditions for transesterification reaction.^a

Entry	NHC	Solvent	Time (h)	ATBC conversion ^b (%)
1	1 , IPr (20 mol%)	THF	12	21
2	2 , ^t BuOK (20 mol%)	THF	12	24
3	3 , ^t BuOK (20 mol%)	THF	12	12
4	4 , ^t BuOK (20 mol%)	THF	24	/
5	5 , ^t BuOK (20 mol%)	THF	24	/
6	2 , DBU (20 mol%)	THF	24	23
7	2 , Et ₃ N (20 mol%)	THF	12	22
8	2 , Cs ₂ CO ₃ (20 mol%)	THF	12	24
9	2 , ^t BuOK (20 mol%)	Toluene	12	21
10	2 , ^t BuOK (20 mol%)	Et ₂ O	12	22
11	2 , ^t BuOK (20 mol%)	CH ₂ Cl ₂	12	23
12	2 , ^t BuOK (20 mol%)	Vinyl acetate	12	29
13 ^c	2 , ^t BuOK (20 mol%)	Vinyl acetate	12	32
14 ^d	2 , ^t BuOK (20 mol%)	Vinyl acetate	12	41
15 ^{d,e}	2 , ^t BuOK (15 mol%)	Vinyl acetate	12	43
16 ^{d,f}	2 , ^t BuOK (10 mol%)	Vinyl acetate	12	9

^a Reaction conditions: tributyl citrate (2.0 mmol), vinyl acetate (2.0 mL), 20 mol% precatalyst, 20 mol% ^tBuOK, room temperature.

^b Determined by GC–MS analysis.

^c Performed the reaction at 40 °C.

^d Performed at 70 °C.

^e Using 15 mol% catalyst.

^f Using 10 mol% catalyst.

Table 2
NHC-Catalyzed transesterification reaction of vinyl acetate with tributyl citrate.^a

Entry	Imidazolium salt	Time (h)	ATBC conversion ^b (%)
1		12	73
2		12	71
3		24	36
4		12	76
5		12	81
6		12	78
7		12	74
8		12	52

^a Reaction conditions: tributyl citrate (2.0 mmol), vinyl acetate (2.0 mL), 15 mol% imidazolium salt, 15 mol% ^tBuOK, 70 °C.

^b Determined by GC–MS analysis.

media, such as toluene, diethyl ether, DCM were also surveyed briefly and the results showed that vinyl acetate was the best choice with respect to the conversion of ATBC (Table 1, entry 9–12). When the reaction temperature was elevated to 40 °C and 70 °C, the conversion of ATBC can be increased to 32% and 41% respectively (Table 1, entries 13 and 14). Lowering the catalyst loading to 15 mol% had no obvious effects on the reaction (Table 1, entry 15). However, further reduction of NHC to 10 mol% led to a dramatic decrease of the conversion of ATBC (Table 1, entry 16). Therefore, the optimized conditions were determined as follows: 15 mol% imidazolium salt as precatalyst and 15 mol% ^tKOBu as base to generate NHC *in situ* in vinyl acetate at 70 °C for a given period of time.

Since the steric and electronic properties of the *N*-substituents in NHCs had an obvious effect on their nucleophilicity, a series of imidazolium salts with different *N*-substituents were then investigated for the transesterification reaction under the optimal reaction conditions as mentioned above. Using more nucleophilic alkyl-substituted NHC **6** or **7** as catalyst precursors instead of IMes-HCl, the catalytic efficiency of NHC increased significantly, giving >70% conversion of ATBC (Table 2, entries 1 and 2). The stable NHC IAd, owing to the large bulky adamantyl group, only catalyzed the reaction with moderate efficiency with 36% conversion of ATBC (Table 2, entry 3). Several alkyl-substituted ionic liquids such as **9**, **10**, **11** and **12** were also evaluated for the reaction (Table 2, entries 4–7). In the presence of ^tKOBu, the ionic liquid converted to the corresponding NHC *in situ*, which can promote the transesterification efficiently. Benzimidazolium salt

13 was also tested for the reaction as a precatalyst, which can give 52% conversion of the desired product (Table 2, entry 8).

4. Conclusion

In conclusion, we have developed a NHC-promoted transesterification reaction between tributyl citrate and vinyl acetate. The mild conditions and simple procedures provide a new approach for the synthesis of ATBC. Further studies on the scale-up and applications of this methodology are ongoing in our laboratory.

Acknowledgments

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