Tetrahedron 69 (2013) 8088–8095

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

The dual role of ionic liquid $BmimBF_4$, precursor of *N*-heterocyclic carbene and solvent, in the oxidative esterification of aldehydes

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A R T I C L E I N F O

Article history:
Received 15 March 2013
Received in revised form 23 May 2013
Accepted 3 June 2013
Available online 29 June 2013

Keywords:
Esters
N-Heterocyclic carbene
Aldehydes
Umpolung
Room temperature ionic liquid
Oxidations

A B S T R A C T

Room temperature ionic liquid $BmimBF_4$ (1-butyl-3-methylimidazolium tetrafluoroborate) has been utilized in the *N*-heterocyclic carbene-catalyzed oxidation of aldehydes to yield esters. In the presence of MnO_2 as oxidant and of DBU and caesium carbonate as bases, aromatic, heteroaromatic and aliphatic esters have been isolated in good to excellent yields. The recyclability of the used ionic liquid along with the excess of inorganic reagents has been proved. The simple and cheap $BmimBF_4$ ionic liquid played the dual role of precatalyst and solvent. This is the first time that such a reaction has been carried out with an ionic liquid as solvent.

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1. Introduction

In the last decade, an increasing demand for ecofriendly and economical strategies for organic synthesis, performed without stoichiometric reagents, has spurred an extensive study directed to the design of new organocatalysts.

Accordingly, *N*-heterocyclic carbenes (NHCs)[1] have attracted enormous interest in organocatalysis[2] as well as in organometallic chemistry.[3] These NHCs, initially regarded as laboratory curiosities,[4] are easily obtainable via deprotonation of several heteroazolium salts under mild conditions.

NHCs are able to induce the umpolung (i.e., the inversion of the polarity) in the structure of aldehydes, opening up new synthetic routes. The reaction between an NHC and an aldehyde gives rise to the formation of the 'Breslow intermediate',[5] an acylation equivalent in which a nucleophilic carbonyl carbon atom (umpolung) is present. Many synthetic procedures have been reported based on the functionalization of this acyl anion equivalent; representative examples include: the benzoin condensation, the Stetter reaction, cross-condensation of enals and aldehydes.[6]

Along with the classical synthesis of esters,[7] the oxidative esterification of aldehydes has received increasing attention during recent years, as it allows the oxidation and C—O bond formation in one-pot.[8]

Procedures based on the NHC-catalyzed oxidation of aldehydic substrates to esters have been developed recently. The syntheses are performed in solution (THF, CH_2Cl_2, CH_3CN, DMSO, DMF, etc. as solvents) containing an aldehyde in the presence of a heteroazolium salt (as precatalyst), a base (DBU or NEt_3, able to deprotonate the heteroazolium salt in the C_2 position), an oxidant (MnO_2, azobenzene, O_2, quinones, etc.) and an alcohol or an alkyl halide.[9] The NHC-catalyzed anodic oxidation of aldehydes to yield esters has been recently reported.[10] The possible utilization of suitable additives (K_2CO_3, Cs_2CO_3, $NaHCO_3$) has been reported by some authors.[11]

In the same way, functionalized aldehydes (α,β-unsaturated- or α-halo-aldehydes) have been converted to esters via internal redox reaction catalyzed by NHC in the absence of an exogenous oxidant.[12] This last methodology unfortunately limits the range of useful aldehydes to α-functionalized ones and precludes the use, for example, of benzaldehydes.

In any case, the yields of the isolated products are strongly affected by pK_b of the base, the presence of additives as well as by the nature of the solvent and the oxidant and the structure of the NHC (and of the precatalyst), the latter being the main influencing factor. In fact, it seems that each different reaction requires a particular NHC, often purposely synthesized, rendering the use of NHCs impractical in general.

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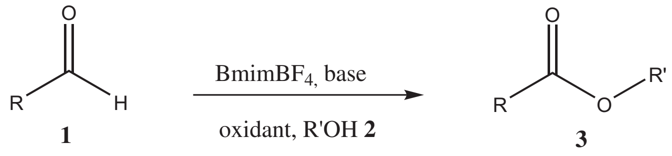
0040-4020/$ — see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2013.06.014

The systematic utilization of volatile and/or toxic organic solvents (VOCs) should be avoided and synthetic procedures, which reduce the use of VOCs should be considered a priority in modern organic synthesis.[13] The use of room temperature ionic liquids (RTILs), in place of VOCs, has been reported by many authors as an alternative.[14]

The exceptionally low vapour pressure of the ionic liquids encourage their use as solvents, which are not air-pollutant and in the majority of the cases they can be recycled in the same reaction and reused many times, thus abating their costs. Moreover, the use of ionic liquids as solvents can drastically change the outcome of a reaction due to their ionic nature, which can accelerate the rate of reactions with ionic or dipolar intermediates and retard reactions with intermediates, which do not present a charge separation. Concerning this, we have considered the easily available and cheap imidazolium room temperature ionic liquid $BmimBF_4$ (1-butyl-3-methylimidazolium tetrafluoroborate) and studied the synthesis of esters via NHC-catalyzed oxidation of aldehydes, based on the double role of $BmimBF_4$ as precatalyst (in the presence of a suitable base) and solvent (in place of VOCs). Moreover, we have evaluated the reaction medium recyclability.

2. Results and discussion

Initially, to verify the efficiency of $BmimBF_4$ in the dual role of precatalyst and solvent, we have investigated the reactivity of benzaldehyde **1a** and an alcohol, with base and either MnO_2 or azobenzene (classical oxidants, previously utilized by other authors in the procedures carried out in organic solvents, Scheme 1).[9,11]



Scheme 1. NHC-catalyzed oxidation of aldehyde **1** to ester **3**.

Accordingly, 0.5 mL of $BmimBF_4$, containing an organic base (DBU, 0.2 mmol) was added to a mixture of benzaldehyde **1a** (0.5 mmol), MnO_2 or azobenzene (2.5 mmol) and methanol (1.5 mmol). The workup of the resulting solution, stirred under a nitrogen atmosphere (25 °C, 24 h), provides methylbenzoate **3aa** (12% or 46% isolated yield utilizing azobenzene or MnO_2, respectively, Table 1, entries 1 and 2).[15]

Table 1
Optimization of the conditions for the NHC-catalyzed oxidation of benzaldehyde **1a** to methylbenzoate **3aa** in ionic liquid $BmimBF_4$ as solvent and precatalyst[a]

Entry	Oxidant (mmol)	Organic base (mmol)	Inorganic base (mmol)	Yield of **3aa**[b] (%)
1	Ph—N═N—Ph (2.5)	DBU (0.2)	—	12
2	MnO_2 (2.5)	DBU (0.2)	—	46
3	Ph—N═N—Ph (2.5)	DBU (1.0)	—	21
4	MnO_2 (2.5)	DBU (1.0)	—	70
5	MnO_2 (2.5)	DBU (2.5)	—	85
6	MnO_2 (2.5)	—	Cs_2CO_3 (1.5)	50
7	MnO_2 (2.5)	—	Cs_2CO_3 (3.0)	52
8	MnO_2 (2.5)	—	K_2CO_3 (1.5)	—
9	MnO_2 (2.5)	DBU (0.5)	Cs_2CO_3 (1.5)	89
10	MnO_2 (0.75)	DBU (1.0)	—	38
11	MnO_2 (1.5)	DBU (1.0)	—	40
12	MnO_2 (1.5)	DBU (0.5)	Cs_2CO_3 (1.5)	86
13	MnO_2 (1.0)	DBU (0.5)	Cs_2CO_3 (1.5)	68

[a] Reaction conditions: a mixture of **1a** (0.5 mmol), oxidant agent and methanol **2a** (1.5 mmol) was added to 0.5 mL of $BmimBF_4$ containing the base (T=25 °C; t=24 h).
[b] Reported yields of the isolated **3aa** are based upon the starting aldehyde **1a**.

Following these results, we evaluated the influence of the molar ratio base/aldehyde on the efficiency of the reaction. By increasing the value of this ratio, significant improvements have been observed in the yields of the ester (Table 1, entriy 3 vs 1 and entry 5 vs 2).

In order to understand the role of the base, inorganic bases (Cs_2CO_3, K_2CO_3), instead of the organic base DBU, were added to the $BmimBF_4$ solution, which showed that the efficiency of the reaction is strongly affected by the nature of the counter-ion (Cs^+ or K^+). In fact, ester **3aa** was isolated in good yields using Cs_2CO_3, but no product was formed in the presence of K_2CO_3 (Table 1, entries 6 and 7 vs 8).

When DBU and Cs_2CO_3 were used together, the efficiency of the procedure appeared better than when using only DBU (Table 1, entry 9 vs 5), showing a synergy of the two bases. The yield of isolated ester was strongly influenced by the molar ratio oxidant/aldehyde (Table 1, entries 10–13 vs 4 and 9). However, when a smaller amount of oxidant was used with both DBU and Cs_2CO_3, the reaction proceeded with an excellent yield (Table 1, entry 12).

This synthesis of esters via the oxidation of aldehydes is, in any case, related to the deprotonation of the heteroazolium cation to NHC, to the coupling of NHC with the aldehyde yielding the Breslow intermediate and, finally, to the ability of the NHC to activate the structure of the aldehyde, present in the Breslow intermediate, versus the oxidative process.[11] Moreover, the efficiency of the synthesis is affected by the competition between the reaction of the Breslow intermediate with the oxidant (yielding the ester) and with a further molecule of aldehyde (yielding benzoin) (Scheme 2).

Our preliminary results suggest that the organic base DBU is strong enough to deprotonate the ionic liquid $BminBF_4$ yielding the corresponding NHC, while the reactivity (and solubility) of the anionic inorganic base CO_3^{2-} is influenced by the counter-ion. In addition, the NHC thus generated leads to the Breslow intermediate, in which the aldehyde is activated enough to be oxidated by MnO_2. Azobenzene, under the same conditions, proved to be ineffective.

Therefore, a solution of DBU or a mixture DBU/Cs_2CO_3 (as base) and MnO_2 (as oxidant) in $BmimBF_4$ (as solvent and precatalyst) could be regarded as suitable conditions for the synthesis of esters via oxidation of aldehydes in environmental friendly conditions (i.e., in the absence of volatile and/or toxic organic solvent, except during work up/recycling).

To test the efficiency and the generality of this procedure for the synthesis of esters in $BmimBF_4$, the investigation, carried out in the optimized condition (Table 1, entry 12), has been extended to aromatic **1b**–**l**, heteroaromatic **1m**–**p** and aliphatic **1q** aldehydes with several alcohols **2a**–**e**. The procedure is successful (in addition to benzaldehyde **1a**) with aromatic aldehydes incorporating electron withdrawing or donating groups, with 1- or 2-napthaldehydes (**1h**, **i**) and it does not seem to be sensitive to steric effects (see substituted benzaldehydes **1d**–**g**, **j**–**l**). Heteroaromatic (**1m**–**p**) and aliphatic aldehydes (**1q**) gave modest results except for ethyl 3-pyridinecarboxyaldehyde (giving **3ob**, 70% yield). Among the aliphatic alcohols, ethanol **2b** gave better yields than methanol **2a** and dodecanol **2d** whereas a high yield was obtained using benzyl alcohol **2c** and diethylamino ethanol **2e** (Table 2 entries 14 and 16). In any case, esters **3** have been isolated in good to elevated yields (Table 2).

Room temperature ionic liquids, due to their remarkable physico-chemical properties, have received attention as possible recyclable solvents. The recyclability is a significant feature of this reaction medium to abate their costs. The used ionic liquid was recovered and recycled using two different methodologies. The first one was the most obvious, being the purification of the used ionic liquid carried out by flash chromatography on silica gel increasing the polarity of the mobile phase to pure acetonitrile after the

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