Tetrahedron Letters 54 (2013) 262–266

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

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

Formylation of amines catalysed by protic ionic liquids under solvent-free condition

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ARTICLE INFO

Article history:
Received 23 August 2012
Revised 1 November 2012
Accepted 3 November 2012
Available online xxxx

Keywords:
Amine
Protic ionic liquid
N-formylation
Formamides
Catalysis
Formic acid

ABSTRACT

A fast, efficient and simple route for the N-formylation of amines has been developed by treating amines with 85% formic acid at 70 °C in the presence of 5 mol % of protic ionic liquid as catalyst under solvent-free condition. This method provides a green and much improved protocol over the existing methods.

Formyl group is the one of the most useful and versatile protecting group for the protection of amine functionality in organic molecules.[1] Formamides are important intermediates in the preparation of amine derivatives and have been widely used in the synthesis of many fine chemicals and pharmaceutically valuable compounds.[2] They are also important precursors for isocyanide preparation,[3,4] formamidine synthesis,[5] catalyst for allylation and hydrosilylation[6] of carbonyls. In addition, formyl group is used for the protection of the amino group during peptide synthesis.[7] In view of these potential applications of *N*-formyl derivative of amines, a large number of formylating methods have been reported which include chloral,[8] formic acid with activating agents such as DCC[3] or EDCI,[9] activated formic esters,[10] ethyl formate,[11] ammonium formate,[12] acetic formic anhydride,[13] formic acid with activated zinc[14] or ZnO,[15] $[TMG]^+$,[16] solid supported reagents[17] and recently by formic acid under azeotropic removal of water with toluene.[18] Polyethylene glycol has also been reported as a medium for formylation of aniline derivatives with formic acid.[19] Very recently the formylation using $ZnCl_2$, $FeCl_3$, $AlCl_3$ and $NiCl_2$ has been reported.[20] Direct formylations using formic acid in sealed tube without any additional solvent and catalyst have also been reported.[21] Despite the usefulness of these methods, many of them suffer from serious drawbacks such as a longer reaction time, use of high temperature, moisture sensitive, expensive and toxic reagents and generation of hazardous bi-products. Thus pursuit of more convenient, mild, high yielding, inexpensive catalysts which have no or minimal harmful effect on our environment still remains an active area of research. In this context, much attention has been focused on organic reactions promoted by room temperature ionic liquids as a useful alternative to conventional organic solvents or catalysts due to their particular properties, such as negligible vapour pressure, chemical stability, excellent solvation and coordination power for organic and inorganic compounds.[22] Formylation of *N*-methyl aniline by formic acid was first reported by Fieser in 1955.[23] Recently, other research groups have re-examined this method using formic acid/toluene with Dean–Stark trap under reflux conditions[18] and heated under closed (sealed) conditions.[21] As a part of our ongoing research programme towards the development of new synthetic methodology, we have extended this method as a solvent-less general procedure promoted by imidazolium based protic ionic liquid which adopted operational simplicity.

Protic ionic liquids (pILs) are a class of ionic liquids that are formed by mixing strictly equimolar amounts (1:1) of Brønsted acids and bases. The strength of the acid/base combination determines the degree to which the acidic proton is transferred to the proton activity. This tuneable parameter has been used previously to probe the suitability of pILs to carry out organic transformations.[24] Amongst the various protic ionic liquids, we were particularly interested in N-substituted imidazolium trifluoroacetate based ionic liquids because of their easy accessibility, stability and low viscosity. Thus, five structurally related imidazolium and

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http://dx.doi.org/10.1016/j.tetlet.2012.11.017

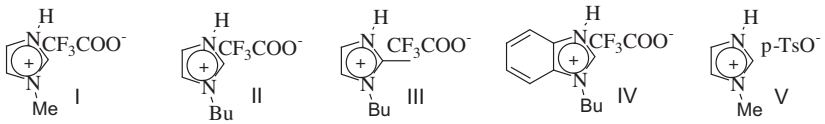
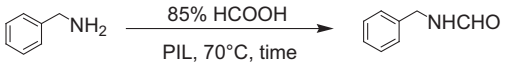


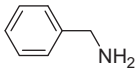
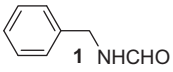
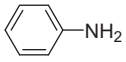
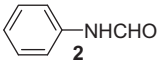
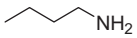
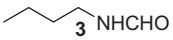
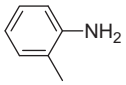
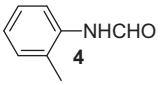
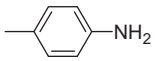
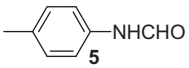
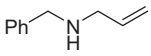
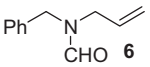
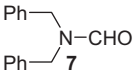
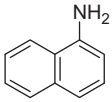
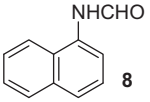
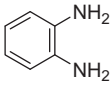
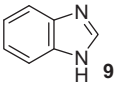
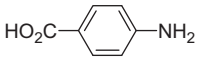
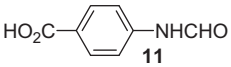
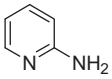
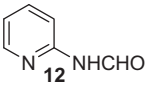
Figure 1. Structurally related imidazolium based protic ionic liquids.

Table 1
Optimization of reaction conditions for the N-formylation of benzyl amine catalysed by protic ionic liquid under solvent free condition



Entry	Benzyl amine (mmol)	HCOOH (equiv)	Ionic liquid	Time (min)	Yield (%)
1	10	1.4	**I**, 10 mmol	20	92
2	10	7.0	**I**, 10 mmol	90	76
3	10	14	**I**, 10 mmol	360	52
4	10	1.4	**I**, 10 mol %	60	89
5	10	1.4	**I**, 5 mol %	60	92
6	10	1.4	**II**, 5 mol %	60	93
7	10	1.4	**III**, 5 mol %	60	95
8	10	1.4	**IV**, 5 mol %	60	94
9	1.0	1.4	**V**, 5 mol %	120	56
10	100	1.4	**III**, 5 mol %	60	96

Table 2
Solvent less formylation of amines with 85% formic acid in the presence of 5 mol % of protic ionic liquid **III**

Entry	Substrate	Time (h)	Product	Yield (%) Ref.
1		1	 **1**	96[19]
2		1	 **2**	97[19]
3		2	 **3**	92[20]
4		2	 **4**	96[19]
5		2	 **5**	97[19]
6		2	 **6**	96[34]
7		1.5	 **7**	93[27]
8		2	 **8**	98[28]
9		1	 **9**	92[29]
10		2.5	 **10**	50[16]
11		3	 **11**	80[30]
12		2	 **12**	84[31]

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