Tetrahedron 69 (2013) 607–612

Contents lists available at SciVerse ScienceDirect

Tetrahedron

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

N-Heterocyclic carbene mediated Reformatsky reaction of aldehydes with α-trimethylsilylcarbonyl compounds

Xiao-Lei Zou [a], Guang-Fen Du [a,*], Wan-Fu Sun [b], Lin He [a,*], Xiao-Wei Ma [a], Cheng-Zhi Gu [a], Bin Dai [a,*]

[a] *Key Laboratory for Green Processing of Chemical Engineering of Xinjiang Bingtuan, School of Chemistry and Chemical Engineering, Shihezi University, Xinjiang 832003, PR China*
[b] *Center for Physical and Chemical analysis, Xinjiang University, Urumqi, Xinjiang 830046, PR China*

ARTICLE INFO

Article history:
Received 16 June 2012
Received in revised form 14 October 2012
Accepted 2 November 2012
Available online 9 November 2012

Keywords:
N-Heterocyclic carbenes
Aldehydes
α-Trimethylsilylethylacetate
Reformatsky reaction
β-Hydroxyesters

ABSTRACT

N-Heterocyclic carbenes have been employed as highly efficient organocatalysts to mediate silyl-Reformatsky type reaction. In the presence of only 0.5 mol % nucleophilic carbene **1**, various aldehydes coupled with α-trimethylsilylethylacetate very smoothly in DMF at room temperature to provide the corresponding β-hydroxyesters in moderate to high yields. α-Trimethylsilylketone and α-trimethylsilylamide can also undergo the addition reaction to give β-hydroxyketone and β-hydroxyamide in moderate yields.

1. Introduction

The reaction of α-halogenated esters, zinc dust, and carbonyl compounds, named Reformatsky reaction,[1] is one of the most fundamental organic transformations, which provides a convenient synthesis of β-hydroxyesters and their derivatives.[2] Over the past half-century, great efforts have been made to develop these reactions, mainly involving heterogeneous reaction with activated zinc reagents or other metals,[3] homogeneous reaction with dialkylzincs[4] as well as catalytic enantioselective Reformatsky reaction.[5] However, some drawbacks, such as using stoichiomeric amounts of metals, unselective dehydration of the desired products, low yield, and poor stereoselectivity restrain the application of this classical reaction. Therefore, the development of efficiently catalytic method for Reformatsky-type reaction is extremely desirable.

As an important type of organocatalyst, *N*-heterocyclic carbenes (NHCs) have been applied widely in the formation of C–C bond via umpolung strategy.[6] Recently, we and other groups have demonstrated the remarkable ability of NHCs to activate organo-silicon reagents in some important reaction, such as Mukaiyama aldol reaction,[7] Cyanation reaction,[8] Pudovik reaction,[9] Cyanomethylation reaction,[10] and other transformation.[11] Herein, we would like to disclose our preliminary results of NHCs catalyzed silyl-Reformatsky reaction of α-silylester with aldehydes. This type of reaction mainly mediated by several fluorides[12] or organophosphines,[13] giving β-hydroxyesters in moderate to high yields.

2. Results and discussion

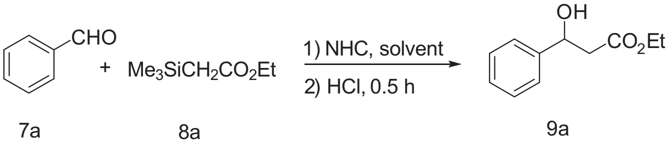
Initially, we have selected the coupling of benzaldehyde with α-trimethylsilylethylacetate as a model reaction for the optimization of various reaction parameters. The results are summarized in Table 1. It was observed that 1,3-bis (2,6-diisopropylphenyl)imidated-2-ylidene (IPr)[14] can initiate the reaction in DMF, giving β-hydroxyester **9a** in 68% yield (Table 1, entry 1). Encouraged by this result, several different types of NHC generated in situ from the corresponding precursor and a base were screened. It was found that NHC derived from imidazolium salt **2** and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in situ can catalyze the reaction efficiently (Table 1, entry 2). Whereas NHC generated from saturated imidazolinium salt **3** only promote the reaction with low efficiency (Table 1, entry 6). To our surprise, NHCs derived from thiazolium salts **4**, **5**, and triazolium salt **6** cannot initiate the reaction at the same conditions (Table 1, entries 7–9). Other media, such as toluene, THF, dichloromethane,

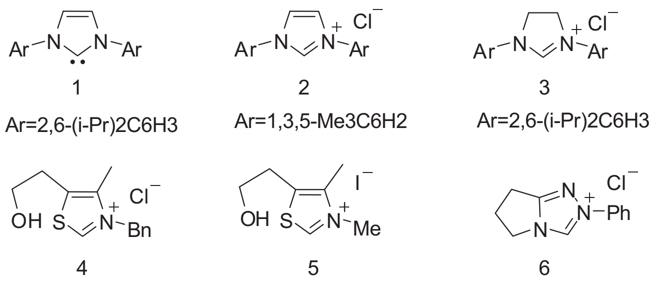
---

* Corresponding authors. E-mail addresses: duguangfen@shzu.edu.cn (G.-F. Du), helin@shzu.edu.cn (L. He), db_tea@shzu.edu.cn (B. Dai).

0040-4020/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2012.11.015

Table 1
Evaluation of NHCs and conditions for silyl-Reformatsky reaction[a]





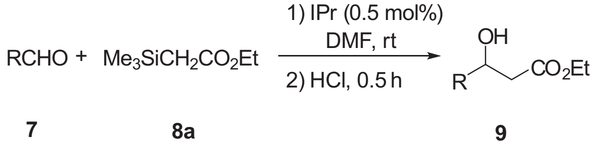
Entry	NHC	Solvent	Time (h)	Yield[b] (%)
1	**1**, (10 mol %)	DMF	24	68
2[c]	**2**, DBU (10 mol %)	DMF	24	54
3[c]	**2**, KO-^{t}Bu(10 mol %)	DMF	24	29
4[c]	**2**, Cs_2CO_3(10 mol %)	DMF	24	41
5[c]	**2**, DIPEA(10 mol %)	DMF	24	24
6[c]	**3**, DBU (10 mol %)	DMF	24	17
7[c]	**4**, DBU (10 mol %)	DMF	24	NR
8[c]	**5**, DBU (10 mol %)	DMF	24	NR
9[c]	**6**, DBU (10 mol %)	DMF	24	NR
10	**1**, (10 mol %)	toluene	24	38
11	**1**, (10 mol %)	DCM	24	51
12	**1**, (10 mol %)	Et_2O	24	36
13	**1**, (10 mol %)	THF	24	17
14	**1**, (10 mol %)	CH_3CN	24	41
15	**1**, (5 mol %)	DMF	24	71
16	**1**, (0.5 mol %)	DMF	24	72
17	**1**, (0.1 mol %)	DMF DMF	24	52
18	No catalyst		36	—

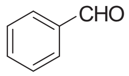
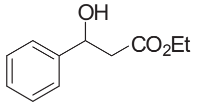
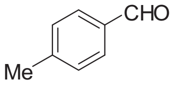
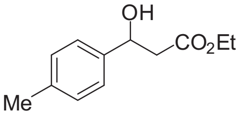
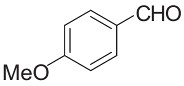
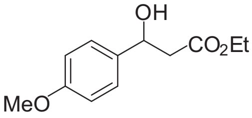
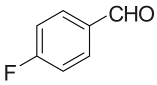
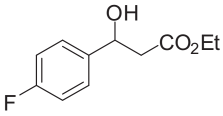
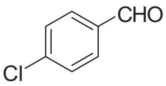
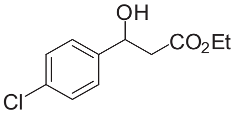
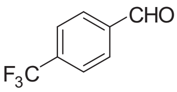
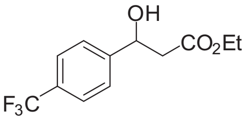
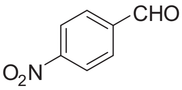
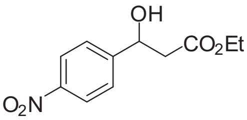
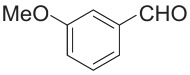
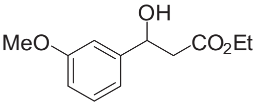
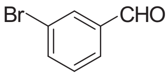
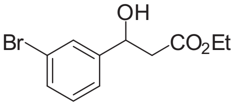
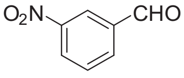
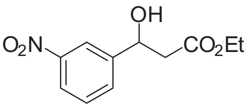
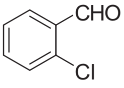
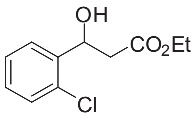
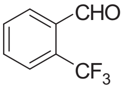
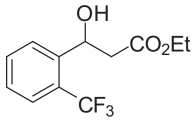
[a] **8a** (1.5 equiv), **7a** (1.0 equiv), solvent: 1.0 mL rt.
[b] Isolated yields.
[c] Using 12 mol % NHC-precursors and 10 mol % base.

ether, and acetonitrile were also evaluated and the results indicated that DMF was the best choice with respect to yield (Table 1, entries 10–14). Lowered catalyst loading to 5 mol %, no obvious effect to the yield was found (Table 1, entry 15). Further decreased the NHC to 0.5 mol %, good yield was maintained (Table 1, entry 16). However, lowering the NHC loading to 0.1 mol %, led a dramatic decrease in the yield (Table 1, entry 17). Finally, a control experiment confirmed that the reaction did not occur in the absence of NHC (Table 1, entry 18).

The optimized reaction conditions (0.5 mol % IPr, DMF) were then applied to a variety of aldehydes to investigate the generality of the reaction. As indicated in Table 2, aryl aldehydes bearing both electron-donating and electron-withdrawing groups worked well to give the corresponding β-hydroxyesters in high yield (Table 2, entries 1–7), while the position of the substituents had no obvious impact on the yield (Table 2, entries 8–14). Interestingly, β-naphthaldehyde, heliotrapine as well as heteroaromatic aldehyde, such as furfural were also proved to be good candidates for the coupling, gave β-hydroxyesters in high yield (Table 2, entries 15–17). Gratifyingly, cinnamaldehyde was also good reactant for the addition, offered **9t** in 80% yield (Table 2, entry 18). It is noteworthy to mention that aliphatic aldehydes, such as phenylpropionaldehyde and cyclohexanecarboxaldehyde can also react with α-trimethylsilylethylacetate, but only provided the alkyl-substituted β-hydroxyester in 32% and 31% yield, respectively (Table 2, entries 19 and 20).

Table 2
Survey of aldehydes in NHC-catalyzed silyl-Reformatsky reaction[a]



Entry	Aldehydes	Time (h)	Product	Yield[b] (%)
1		24		72
2		24		76
3		23		84
4		24		83
5		24		89
6		24		82
7[c]		22		76
8		23		90
9		24		80
10		21		87
11		21		82
12		24		93