Tetrahedron Letters 56 (2015) 4934–4937

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Noncovalent catalysis of glucose-containing imidazolium salt in solvent-free one-pot synthesis of *Ortho*-aminocarbonitriles

Li-zhuo Zhang [a], Yu Wan [b,*], Xiao-xiao Zhang [a], Hao Cui [a], Huan Zou [a], Qiu-ju Zhou [a], Hui Wu [a,b,*]

[a] School of Chemistry and Chemical Engineering, Jiangsu Normal University, Xuzhou 221116, PR China
[b] State Key Laboratory Cultivation Construction Base of Biotechnology on Med-edible Plant of Jiangsu Province, Jiangsu Normal University, Xuzhou 221116, PR China

ARTICLE INFO

Article history:
Received 6 May 2015
Revised 22 June 2015
Accepted 29 June 2015
Available online 2 July 2015

Keywords:
Glucose-containing imidazolium salt
Noncovalent organocatalyst
Ortho-aminocarbonitriles

ABSTRACT

A glucose-containing imidazolium salt β-1-imidazole-2,3,4,6-tetraacetyl-D-glucopyranosyl bromide was firstly used as efficient noncovalent organocatalyst to promote the solvent-free preparation of *ortho*-aminocarbonitriles via a four-component condensation of aromatic aldehyde, cyclohexanone, and 2 equiv of malononitrile at room temperature. Seven bonds were cleaved while four new bonds were formed and a six-membered ring was constructed in one-pot.

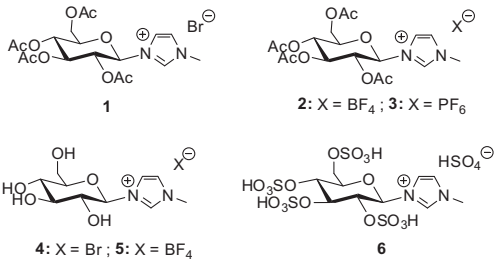
Introduction

Compared with colvant catalysts, noncolvant catalysts have many advantages such as the lower kinetic barriers, less directional and less distance dependent,[1,2] especially, unnecessary additive and rigorous conditions, and easier removing of catalyst.[3–5] The main reason is that the formation of intermediate from the substrate and the noncovalent catalyst is easier than the covalent one due to the low orbital overlap between the substrate and the noncovalent catalyst.[4,6]

Glucose is an important nature product bearing five hydroxyl groups. It is envisioned that the poly-hydroxyl glucose-containing H-bond donor would be the efficient noncovalent catalyst.[7,8] Based on this idea, the catalytic activity of a series of glucose-containing imidazolium salt catalysts **1**–**6** (Scheme 1) was investigated in this Letter.

Ortho-aminocarbonitriles, an important intermediate in organic synthesis,[9] is widely used in the preparation of various heterocyclic compounds.[10,11] Therefore, their synthesis attracted the attention of organic chemists.[12–16] However, most methods have their limitations. Specific conditions such as organic solvents (MeOH, HOAc),[13,14] strong basic catalyst (1,2-diamine,[14] Et_3N,[15] morpholine,[16] etc), complex substrate,[13–16] and tedious post-processing were necessary.

To obtain these potential units efficiently and environment-friendly, and to expand the application of glucose-containing imidazolium salt in organic synthesis, we herein report an efficient, solvent-free one-pot method to successfully synthesize a series of 2-amino-4a,5,6,7-tetrahydronaphthalene-1,3,3(4*H*)-tricarbonitriles *via* four-component reaction of 1 equiv of aromatic aldehyde, cyclohexanone, and 2 equiv of malononitrile catalyzed by a new glucose functionalized noncolvant catalyst β-1-imidazol-2,3,4,6-tetraacetyl-D-glucopyranosyl bromide ($[Bmim\text{-}G]^+[Br]^-$) at room temperature (Scheme 2).



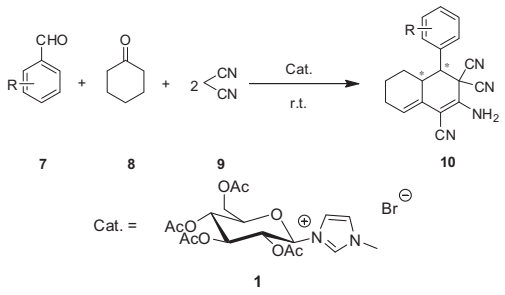
Scheme 1. Catalysts been tested.

Results and discussion

Malononitrile is one of the most versatile reagents to be used in MCRs because of the high reactivity of both the methylene and the cyano groups.[17] Traditionally, it is a very useful molecule to prepare heterocyclic compounds which have medical and industrial utility.[18]

* Corresponding authors. Tel./fax: +86 051683536977 (H.W.).
E-mail address: wuhui72@aliyun.com (H. Wu).

http://dx.doi.org/10.1016/j.tetlet.2015.06.094
0040-4039/



Scheme 2. The synthesis of *ortho*-aminocarbonitriles.

Table 1
Synthesis of **10a** under different conditions[a]

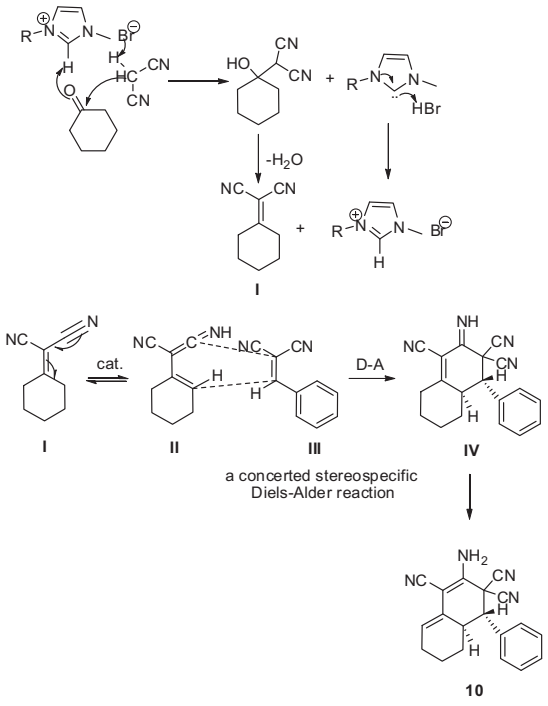
Entry	Cat.	X/mol %	Time/h	Temp./°C	Yield/%[b]
1	–	–	8	r.t.	Nr[c]
2	*N*-Methylimidazole	20	8	r.t.	23
3	[Bmim]Br	20	8	r.t.	70
4	**1** (pH = 4.63) [19]	20	8	r.t.	85
5	**2** (pH = 3.67) [19]	20	8	r.t.	NP[d]
6	**3** (pH = 4.10) [19]	20	8	r.t.	NP[d]
7	**4** (pH = 10.09) [19]	20	8	r.t.	70
8	**5** (pH = 9.12) [19]	20	8	r.t.	NP[d]
9	**6** (pH = 1.44) [19]	20	8	r.t.	NP[d]
10	Sodium bromide	20	8	r.t.	NP[d]
11	**1**	20	4	r.t.	83
12	**1**	20	12	r.t.	86
13	**1**	5	4	r.t.	22
14	**1**	10	4	r.t.	83
15	**1**	30	4	r.t.	75
16	**1**	10	4	0	25
17	**1**	10	4	50	84

[a] Reactions were performed in 1:1:2 (benzaldehyde:cyclohexanone:malononitrile) in different conditions.
[b] Isolated yields.
[c] No reaction.
[d] No product **4a**.

In the solvent-free synthesis of **10a**, reaction conditions such as the type and amount of catalysts (Scheme 2), reaction temperature, and reaction time were tested firstly to explore the optimum (Table 1). Catalysts illustrated in Scheme 1 synthesized in our lab (Experimental section) were tested firstly. It was found that the reaction could not run smoothly without catalyst (Table 1, Entry **1**). N-methylimidazole and 1-butyl-3-methylimidazolium bromide ([Bmim]$^+$Br$^-$) could promote this reaction but with lower yield (Table 1, Entries **2**–**3**). Interestingly, in the catalysts mentioned above, only **1** and **4** which contain bromide ion could promote the reaction and **1** gave the best yield (Table 1, Entries **4**–**9**). It seems that the counteranion of Br$^-$ plays more determinative role in controlling the overall reaction. However, inorganic bromide ion from sodium bromide could not improve the reaction (Table 1, Entry **10**). It means the catalytic activity of **1** is the result of synergistic effect of all parts of the catalyst which was supposed in the mechanism (Scheme 3).

As shown in Table 1, the suitable reaction time was 4 h and the appreciable amount of catalyst **1** was 10 mol %. But the increasing of catalytic loading could not enhance the yield of the product (Table 1, Entry **14**). Finally, the results in Table 1 indicated the optimal temperature was room temperature. Therefore, 10 mol % of **1** as the catalyst under solvent-free condition and at room temperature for 4 h were the optimal reaction condition.

To explore the application of this method, the scope of the substrates was evaluated with a variety of aromatic aldehydes under the optimal condition (Table 2). The electro effect and steric



Scheme 3. A supposed mechanism.

Table 2
Synthesis of **10** under optimum conditions

Entry	R	Product	Time/h	Yield/%
1	H	**10a**	4	83
2	4-F	**10b**	4	85
3	4-Cl	**10c**	4	89
4	4-Br	**10d**	4	87
5	4-I	**10e**	4	91
6	4-CN	**10f**	4	92
7	4-OH	**10g**	5	84
8	2-Cl	**10h**	5	89
9	2-Br	**10i**	5	87
10	3-F	**10j**	5	82
11	3-NO_2	**10k**	4	88
12	2,4-Cl_2	**10l**	5	84
13	4-CH_3	**10m**	5	90
14	2-CH_3O	**10n**	5	89
15	2,3-$(CH_3O)_2$	**10o**	5	86
16	3,4-$(CH_3O)_2$	**10p**	5	85
17	3,4,5-$(CH_3O)_3$	**10q**	4	83

hindrance of group in aromatic aldehydes had no obvious and regular influence on the yield. Both electro-withdrawing and electro-donating in aromatic aldehydes could afford high yield.

The catalyst recyclability has been investigated for the synthesis of **10f** (Table 3). The catalyst was recovered by extraction with CH_2Cl_2 (3 × 15 mL) from the aqueous phase. After removing the water under vacuum, the organic phase was dried in infrared drying oven and reused for subsequent runs. It was observed that the catalyst can be used for 2 times with minimal loss of activity.

The possible mechanism is proposed in Scheme 3. We supposed that the catalyst had two functions: (1) to provide a nucleophilic bromide ion to start the nucleophilic addition of malononitrile with cyclohexylene via capturing a proton of malononitrile; (2) to provide an electrophilic imidazolium cation meanwhile to accept the transferred electron to complete the reaction cycle. 2-Cyclohexylene malononitrile **I** was then formed through the dehydration of the condensation product of cyclohexanone and