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Graphical Abstract

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Noncovalent Catalysis of Glucose-containing Imidazolium Salt in Solvent-free One-pot Synthesis of *Ortho*-aminocarbonitriles

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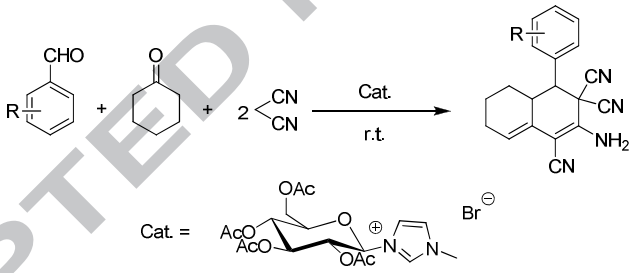
A glucose-containing imidazolium salt β-1-imidazole-2,3,4,6-tetraacetyl-D-gluco-pyranosyl bromide was firstly used as efficient noncovalent organocatalyst to promote the solvent-free preparation of *ortho*-aminocarbonitriles via a four-component condensation of aromatic aldehyde, cyclohexanone and two equivalents 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.



Scheme 1. The synthesis of *ortho*-aminocarbonitriles.

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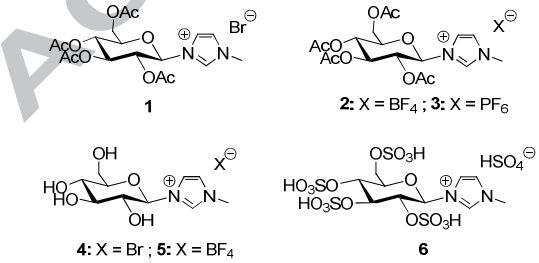
ABSTRACT

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 two equivalents 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.

1. Introduction

Compared with colvant catalysts, noncolvant catalysts has 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 interdiate from the substrate and the noncovalent cataltyst is easier than the covalent one due to the low orbital overlap between the substrate and the noncovalent cataltyst.[4,6]

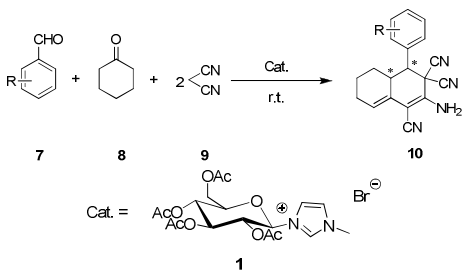
Glucose is an important nature product bearing five hydroxyl groups. It is envisioned that the poly-hydroxyl glucose-containing H-bond donor would be the efficient noncovalent catalyst.[7-8] Based on this idea, the catalystic activity of a series of glucose-containing imidazolium salt catalysts **1**-**6**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



Scheme 1 Catalysts been tested

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 one equivalents of aromatic aldehyde, cyclohexanone and two equivalents 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 2 The synthesis of *ortho*-aminocarbonitriles

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2. 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]

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 containing bromide ion could promoted 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**).

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** (*p*H=4.63)[19]	20	8	r.t.	85
5	**2** (*p*H=3.67)[19]	20	8	r.t.	NP[d]
6	**3** (*p*H=4.10)[19]	20	8	r.t.	NP[d]
7	**4** (*p*H=10.09)[19]	20	8	r.t.	70
8	**5** (*p*H=9.12)[19]	20	8	r.t.	NP[d]
9	**6** (*p*H=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**.

As shown in Table **1**, the suitable reaction time was 4h 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 effict and steric hindrance of group in aromatic aldehydes had no obvious and regular influence on the yield. Both electro-withdrawing and electro-dondring in aromatic aldehydes could afford high yield.

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

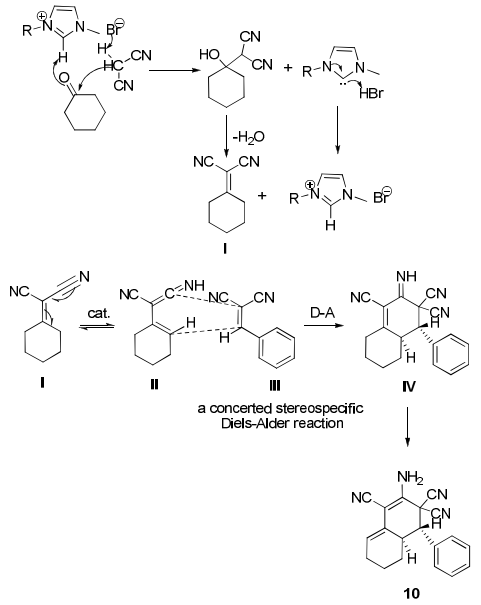
Entry	R	Product	Time / h	Yield / %
1	H	**10a**	4	83
2	4-F	**10b**	4	85
3	4-Cl	**10c**	4	89
4	4-Br	**10d**	4	87
5	4-I	**10e**	4	91
6	4-CN	**10f**	4	92
7	4-OH	**10g**	5	84
8	2-Cl	**10h**	5	89
9	2-Br	**10i**	5	87
10	3-F	**10j**	5	82
11	3-NO_2	**10k**	4	88
12	2,4-Cl_2	**10l**	5	84
13	4-CH_3	**10m**	5	90
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

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 removed 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 five times with minimal loss of activity.

Table 3 Recyclability of catalyst for the synthesis of **10f**

Number of times the catalyst was reused	Isolated yield / %
1	92
2	86
3	84
4	79
5	70
6	55

The possible mechanism was 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 transfered electron to complete the reaction cycle. 2-Cyclohexylene malononitrile **I** was then formed through the dehydration of the condensation product of cyclohexanone and malononitrile. After that, **I** transformed to **II** promoted by the catalyst. The concerted stereospecific Diels-Alder reaction of **II** and **III** which was formed from the condensation of malononitrile and aromatic aldrhyde promoted by the catalyst similarly afforded intermediate **IV.** The isomerization of **IV** gave the final product **10**. The sugar part may provide the solubility overall polarity pH etc.



Scheme 3 A supposed mechanism

Theoretically, *trans-* is the more stable configuration of product **10** (Figure **1**). The X-ray singal crystal structure of **10h** (Figure **2**, **3**) confirmed it. However, the enantioselectivity of chiral product was not detected. A possible reason is that the chiral centre on sugar ring of **1** is wraped up by outside groups, which prevented it from binding with reactants very well. It is necessary to modify the structure of **1** if we want to use it and its derivatives as chiral catalyst in asymmetric synthesis. There is still a long way to go.

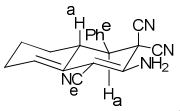


Figure 1 The stable configuration of compound **10**

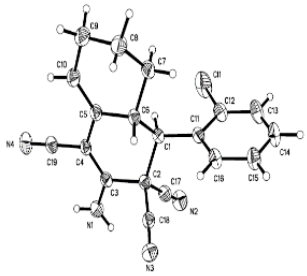


Figure 2 The crystal structure of **10h**

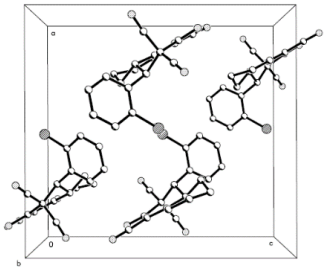


Figure 3 Crystal packing diagram of **10h**

3. Conclusion

In summary, we reported a high yield one-pot solvent-free synthesis of trans-2-amino-4a,5,6,7-tetrahydronaphthalene-1,3,3(4*H*)-tricarbo nitriles from readily available aromatic aldehyde, cyclohexanone and malononitrile catalyzed by β-1-imidazole-2,3,4,6-tetraacetyl-D-glucopyranosyl bromide ($[Bmim\text{-}G]^+[Br]^-$). In the one-pot process, four new bonds formed while seven bonds breakaged to built a new six-membered ring. The role of catalyst in this reaction was supposed. It is expected to expand this kind of new and effective sugar-containing organocatalysts, providing valuable supplement for organic catalytic reaction.

4. Experimental section

4.1. General remarks

IR spectra were recorded with a Varian FTIR-Tensor-27 spectrophotometer using KBr optics. ^{1}H NMR spectra were recorded at 400 MHz on a Bruker DPX 400 spectrometer using TMS as an internal standard and DMSO-d_6 as solvent. Mass was determined by using a Bruker TOF-MS high resolution mass spectrometer.

4.2. General procedure for the preparation of $[Bmim\text{-}G]^+[Br]^-$.

1-Bromo-2,3,4,6-tetraacetyl-glucopyranose (10 mmol) and N-methyl-imidazole (20 mmol) were placed in 50 mL round bottom flask and then acetonitrile (1 mL) was added. The reactants were stirred for 2 h at room temperature to give the white viscous solid, which was washed with acetone and filtered to give a white solid **1** ($[Bmim\text{-}G]^+[Br]^-$).

*4.3. General procedure for the preparation of 2-amino-4a,5,6,7-tetrahydronaphthalene-1,3,3(4H)-tricarbonitriles **10**.*

A mixture of aromatic aldehyde **7** (1 mmol), cyclohexanone **8** (1 mmol), malononitrile **9** (2 mmol), and $[Bmim\text{-}G]^+[Br]^-$ (10 mol%) were stirred at room temperature. After completion of the reaction (monitored by TLC), distilled water (20 mL) was added, the organic layer was extracted with dichloromethane. Removed dichloromethane of organic phase under vacuum, recrystallized the residue with 95% EtOH/DMF (1/4, v/v) to provide the pure product **10**.

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Supplementary Material

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