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Guanidine-catalyzed Henry reaction and Knoevenagel condensation

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ABSTRACT

A method for direct Henry reaction and Knoevenagel condensation promoted by guanidine organocatalyst has been developed. The relationship of the structure and amount catalyst has been investigated.

Organocatalyst has been drawn great attention in recent years, and the reactions promoted by organocatalyst have become an intensively study area in organic chemistry [1]. Compared with organometallic catalysts, most of the organocatalysts are easier to prepared and handled, cheaper, more stable and more environmental friendly. Knoevenagel condensation and Henry Reaction, both of them are an active carbon anion compound with an aldehyde reaction in organic synthesis. Their products are all important intermediates for synthesis complexes natural products.

Guanidines are structurally novel molecules reported to exhibit remarkable biological and pharmacological activities, which are affected by the guanidine functionality. As strong base, guanidines have been used as strong basic catalysts in organic synthesis [2], and the organocatalystic guanidines have been applied in Henry reaction [3] and Knoevenagel condensation [4]. However, the relationship between the structure and activity of the guanidines has not been reported. As part of our ongoing efforts directed toward their utility as strong base catalysts for synthetic purposes, we explored, herein, the influence of guanidine structure on the catalytic activity of guanidine towards the Knoevenagel condensation and Henry Reaction (Scheme 1).

Guanidines **1**–**5** have been prepared via two steps protocols from 1,3-dimethylimidazolidin-2-one [5]. Benzaldehyde was chosen as test substrate, the two reactions were investigated (Tables 1 and 2).

As shown in Table 1, the yields decreased when the longer alkyl substituents chain was connected to the guanidines in Henry reaction, and the best result was achieved when guanidine **5** was used as catalyst, which contains a hydroxyl group on the alkyl substituent, indicating that hydroxyl group was playing a role in the reaction. Besides the nitrogen atoms on guanidines, it was conjectured that the hydroxyl group can also activate the carbonyl group and nitromethane by hydrogen bond [6] (Scheme 2).

Especially, the guanidine **5** offers advantages over TMG in Henry reaction. And in the Knoevenagel condensation the yields are enhanced along with alkyl chain from $-C_4H_9$ (guanidine **1**) to $-C_{12}H_{25}$ (guanidine **3**), but further increasing the alkyl chain to $-C_{16}H_{33}$ (guanidine **4**), that has brought lower yield, indicating that the catalytic activity of guanidine was affected by the alkyl chain on the guanidine. However, guanidine **5**, with hydroxyl group on the alkyl chain ($-CH_2CH_2OH$) can improve the yields in comparison with unfunctionalized alkyl such as $-(CH_2)_3CH_3$.

With the optimal conditions in hand, the different aldehydes were examined in the presence of a catalytic amount of guanidine **5** in Henry reaction (Table 3) [7] and guanidine **3** in Knoevenagel condensation (Table 4)

As shown in Table 3, the reactions are suitable for both aromatic aldehydes and aliphatic aldehydes with an easy isolation of the desired adducts in satisfactory yields. Aromatic aldedydes carrying electron-donating substitutents gave products in high yields, while with withdrawing group gave the products in long time and moderate yields.

Knoevenagel condensation of different aldehydes and methylene compounds with guanidine **3** as catalyst were investigated, and the results were summarized In Table 4. Knoevenagel condensation of benzaldehyde and malononitrile or ethyl cyanoacetate was examined in the presence of a catalytic amount of guanidine **3**; better yield was achieved with 0.1 eq guanidine as catalyst at room temperature in dichloromethane. Then several aromatic aldehydes were used as substrates, and the results showed that it needed longer reaction time to achieve high yield when aromatic

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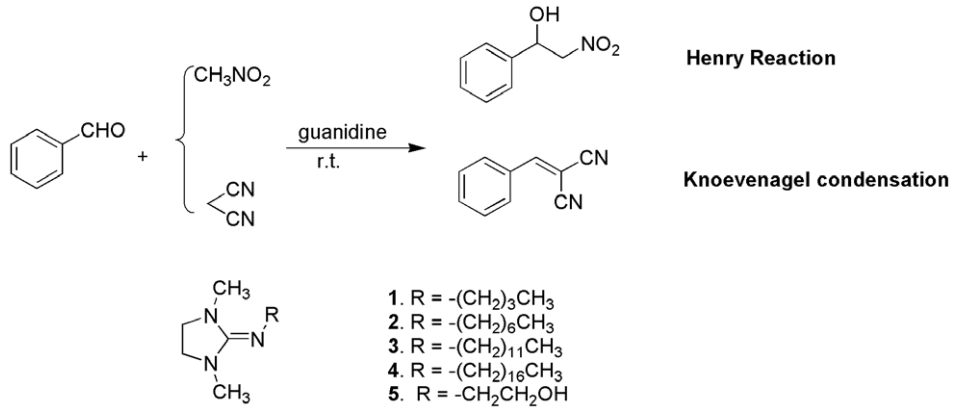


Scheme 1.

Table 1
Henry reaction of benzaldehyde with nitromethane

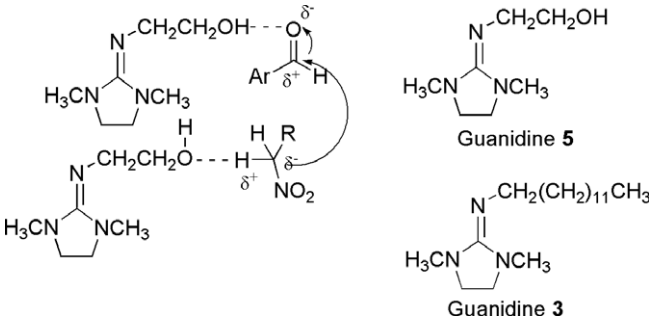
Guanidine	1	2	3	3[a]	4	5[b]	TMG[b]
Yield (%)	83	49	47	84	64	83	73

All of the reaction were carried out with 1 mmol benzaldehyde using 20% catalyst and 1 ml nitromethane in 1 h.
[a] Reaction time 24 h.
[b] 10% catalyst.

Table 2
Knoevenagel condensation of benzaldehyde with malononitrile

Guanidine	1	2	3	4	5
Yield (%)	70.8	78.3	91.9	83.4	90.2

Reaction conditions: benzaldehyde 1 mmol, malononitrile 1 mmol, guanidine 0.1 mmol, dichloromethane 2 mL, room temperature, 2 h.



Scheme 2.

aldehyde carrying electron-donating substituents such as –OCH_3. While the aromatic aldehyde carrying electron-drawing substituents reacted very well and gave excellent yields under the same conditions. Therefore, it indicated that electron-donating substituents in aromatic ring appear to retard the rate of reaction due to inactivation of aldehyde group.

In summary, we have developed a new bifunctional organocatalyst that possesses a guanidine moiety and hydroxyl group. The catalyst is easily accessible and shown to be highly efficient for Henry reaction and Knoevenagel condensation. Especially in terms of milder reaction conditions (at room temperature) and that anhydrous solvents or reagents and inert atmosphere conditions are not required. Further effects toward the applications for variety

Table 3
Synthesis of 2-nitroalkanols using guanidine **5** as catalyst

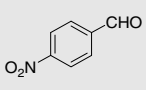
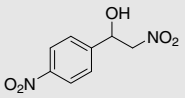
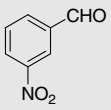
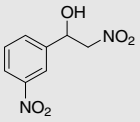
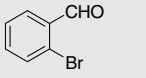
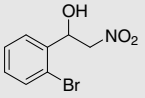
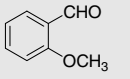
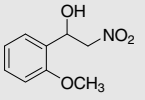
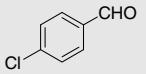
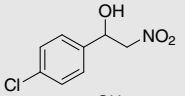
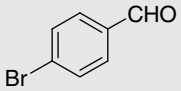
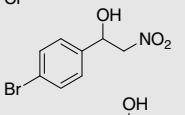
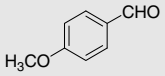
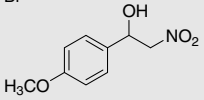
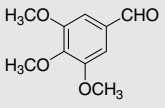
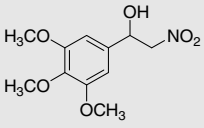
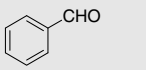
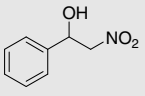
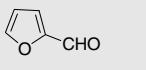
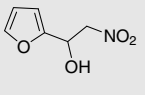
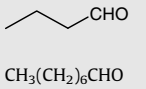
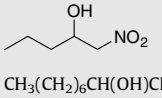
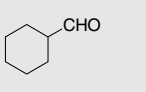
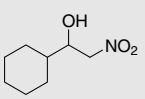
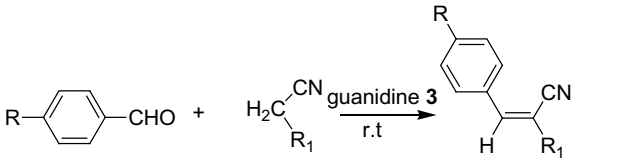
Entry	Aldehyde	Time (h)	Product	Yield (%)
1		5 min		89
2		5 min		98
3		2		91
4		2		80
5		15		87
6		15		96
7		24		74
8		24		60
9		1		83
10		1		88
11		4		72
12	$CH_3(CH_2)_6CHO$	2	$CH_3(CH_2)_6CH(OH)CH_2NO_2$	73
13		2		85

Table 4
Knoevenagel condensation catalyzed with guanidine **3** in dichloromethane



Entry	R	R_1	Guanidine **3** (eq)	Time (h)	Yield (%)
1	H	CN	0.05	4	89.8
2	H	CN	0.1	2	91.9
3	OCH_3	CN	0.1	10	87.0
4	Cl	CN	0.1	6	97.3
5	Br	CN	0.1	4	93.6
6	NO_2	CN	0.1	2	96.5
7	H	$CO_2CH_2CH_3$	0.05	2	90.7
8	H	$CO_2CH_2CH_3$	0.1	2	90.8

types of reactions with guanidines including chiral guanidines as catalysts are in progress.

Acknowledgements

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(c) K. Iwona, R. Jerzy, U. Zofia, J. Janusz, Tetrahedron 60 (2004) 4807.
[4] (a) S. Jaenicke, G.K. Chuah, X.H. Lin, X.C. Hu, Micropor. Mesopor. Mater. 143 (2000) 35;
(b) S.G. Wang, Catal. Commun. 4 (2003) 469.
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[6] X. Xu, Y. Li, M. Zhou, Chin. J. Org. Chem. 24 (2004) 1523. in Chinese.
[7] Typically experimental procedure for Henry reaction: The aldehyde (1 mmol) and nitromethane (1 ml) were mixed together in the presence of a catalytic amount of the guanidine base, which stirring at room temperature. At the end of the reaction workup, the pure product was obtained by flash chromatography. The product was analyzed by ^{1}H NMR and ^{13}C NMR.