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Guanidine hydrochloride: An active and simple catalyst for Strecker type reaction

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Dedicated to Mohammad E. Zolfaghari for his contribution in Iranian pharmaceutical industry.

Abstract

Commercially available guanidine hydrochloride (GuHCl) has been found to be a highly efficient catalyst for the Strecker reaction. A wide variety of aldehydes can be easily transformed into the corresponding α-aminonitriles using 3 mol% GuHCl within 1 h at 40 °C in methanol.

Keywords: Multicomponent reaction; Strecker reaction; Guanidine hydrochloride; α-Aminonitrile

1. Introduction

One-pot three-component condensation reactions are interesting and important, not only because two bonds are formed in one-pot, but also because the methodology is useful for making a broad variety of compounds in a minimum number of steps. However, it is difficult to extend the Lewis acids-catalyzed three-component condensation to the synthesis of amine derivatives, because the strong affinity of many Lewis acids for amino groups does not allow the regeneration of the Lewis acids in the reaction [1]. In addition, the Lewis acids can be decomposed by the amine and water which are present at the stage of amine derivative formation [2].

The Strecker reaction, the three-component coupling of an amine, a carbonyl compound (generally an aldehyde) and either alkaline metal cyanides or hydrogen cyanide, discovered in 1850, [3] has been recognized as the oldest multicomponent reaction [4]. In addition, the reaction represents one of the simplest and most economical methods for the preparation of α-aminonitriles [5], an important intermediate for the synthesis of α-aminoacids on laboratory, as well as on an industrial scale. The classical Strecker reaction is usually carried out in aqueous solution which has some limitations and the work-up procedure is too tedious leading to generation of large amount of toxic waste. In order to partially avoid these inconveniences, several modifiations of the Strecker reaction have been reported using a variety of cyanating agents, such as diethyl phosphorocyanidate [6], α-trimethylsiloxy nitrile [7], tri-*n*-butyltin cyanide [8], diethylaluminum cyanide [9], and trimethylsilyl cyanide (TMSCN) [10] under various conditions [11]. TMSCN has been used as a safer and more effective cyanide anion source compared to some of the above cyanide reagents [12]. Its addition to imines, affords α-aminonitriles which are useful intermediates for an indirect route in the synthesis of natural and unnatural α-amino acids and various nitrogen-containing heterocycles [13]. The reaction is well known, yet its course is very dependent on the catalyst used. Many catalysts have been used to promote the Strecker reaction for example: lithium perchlorate [14], scandium triflamide [15], vanadyl triflate [16], nickel(II) chloride [17], zinc halides [18], ruthenium(III) chloride [19], ytterbium triflate [20], bismuth(III) chloride [21], and montmorillonite KSF [22]. In some cases, the protocols involves the use of strong and expensive Lewis acids, harsh conditions and tedious aqueous work-up leading to the generation of large amount of waste. Moreover, some of the Lewis acids used are like their hydrolysis products toxic. Therefore, there is a further scope to explore milder, safer and more efficient protocols for this reaction.

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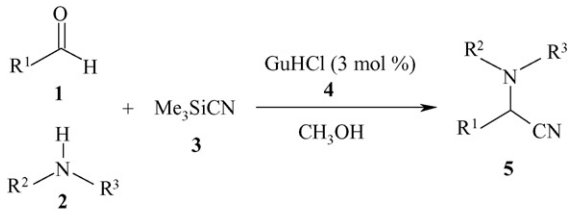

	R1	R2	R3	5%
a	*tert*-Butyl	H	Phenyl	89
b	Benzyl	H	Phenyl	84
c	*n*-Pentyl	H	Phenyl	97
d	Phenyl	H	Phenyl	94
e	4-Cl-Phenyl	H	Phenyl	98
f	2-Furyl	H	Phenyl	82
g	4-Pyridyl	H	Phenyl	95
h	Cinnamyl	H	Phenyl	90
i	*i*-Propyl	Ethyl	Ethyl	88
j	*n*-Pentyl	Ethyl	Ethyl	91
k	Phenyl	Ethyl	Ethyl	94
l	4-Cl-Phenyl	Ethyl	Ethyl	94
m	2-Furyl	Ethyl	Ethyl	84
n	4-Pyridyl	Ethyl	Ethyl	88
o	4-MeO-Phenyl	Ethyl	Ethyl	90
p	Phenyl	Benzyl	Benzyl	96
q	*i*-Propyl	Benzyl	Benzyl	96

Scheme 1.

2. Results and discussion

Guanidine hydrochloride ($H_2NC{=}NHNH_2{\cdot}HCl$, GuHCl) is a dry, nonvolatile, odorless and white crystalline solid with outstanding physical property and stability. The crystals can be kept in the laboratory for many years without change. It is commercially available and is a very cheap. Recently, we found that GuHCl was stable in water and realized Brønsted acid catalysis in aqueous solution. We also demonstrated that GuHCl efficiently activated aldehydes [23]. Bearing in mind the usefulness and efficiency of one-pot procedures, we decided to explore the GuHCl as a catalyst for the Strecker type α-aminonitrile synthesis.

In the presence of 3 mol% of GuHCl, the three component coupling reaction involving 4-chlorobenzaldehyde, aniline and trimethylsilyl cyanide successively proceeded smoothly in methanol at 40 °C to afford the corresponding α-aminonitrile derivative in 98% yield. The new methodology allowed us to prepare the α-aminonitriles shown in Scheme 1. This one-pot process, can be defined as Strecker reaction between imines or iminium ions and TMSCN. Aliphatic, aromatic, heterocyclic and conjugated aldehydes [24] afforded the desired products in high yields. The method worked very well for acid sensitive aldehydes, such as furfural and also for enolizable aldehyde (entry c). Finally, it should be mentioned that the best results were obtained using both primary and secondary amines. In all cases, no undesired side products, such as cyanohydrins are obtained under these conditions. We believe that this is mainly due to the rapid formation and activation of the imines catalyzed by GuHCl. Although the amount of catalyst has been optimized to 3 mol%, lesser amounts (0.5 mol%) also worked with longer reaction times.

3. Experimental

All products are known and were identified by comparison of their spectra data and physical properties with those of authentic samples. All yields refer to isolated products.

3.1. General procedure: preparation of α-aminonitriles derivatives

Guanidine hydrochloride (6 mg, 0.06 mmol) was added to a mixture of aldehyde (2 mmol) and amine (2.2 mmol) in methanol (4 mL) at r.t. The mixture was stirred at 40 °C for 15 min and then trimethylsilyl cyanide (2.2 mmol) was added. After completion of the reaction (1 h), as indicated by TLC, the reaction mixture was quenched with aq. sat. $NaHCO_3$ followed by brine solution and then extracted with CH_2Cl_2, dried over Na_2SO_4, concentrated under vacuum and the crude mixture was purified by column chromatography on silica gel (hexane:ethylacetate, 2:1) to affored pure products. Spectral data for selected products, **5a**: ^{1}H NMR (90 MHz, $CDCl_3$)—δ = 1.1 (s, 9H), 4.0 (s, 1H), 3.8 (bs, NH), 6.8 (t, 1H), 7.2–7.5 (m, 4H); **5c**: ^{1}H NMR (90 MHz, $CDCl_3$)—δ = 0.7–1.6 (m, 9H), 1.9 (m, 2H), 3.4 (bs, NH), 4.3 (t, 1H), 6.6–7.3 (m, 5H); **5d**: ^{1}H NMR (90 MHz, $CDCl_3$)—δ = 4.1 (bs, NH), 5.4 (s, 1H), 6.5–6.8 (m, 5H), 7.1–7.8 (m, 5H); **5e**: ^{1}H NMR (90 MHz, $CDCl_3$)—δ = 4.1 (bs, NH), 5.4 (s, 1H), 6.5–6.8 (m, 5H), 7.1–7.8 (m, 4H); **5f**: ^{1}H NMR (90 MHz, $CDCl_3$)—δ = 4.1 (bs, NH), 5.1 (s, 1H), 6.3 (d, 1H), 6.5 (t, 1H), 7.1–7.8 (m, 6H); **5g**: ^{1}H NMR (90 MHz, $CDCl_3$)—δ = 4.5 (bs, NH), 5.6 (s, 1H), 6.5–6.8 (m, 5H), 7.6 (d, 2H), 8.7 (d, 2H); **5h**: ^{1}H NMR (90 MHz, $CDCl_3$)—δ = 3.9 (bs, NH), 5.1 (m, 1H), 6.3 (m, 1H), 6.9 (t, 1H), 7.1–7.8 (m, 10H); **5j**: ^{1}H NMR (90 MHz, $CDCl_3$)—δ = 1.0–1.9 (m, 15H), 2.4–2.7 (m, 6H), 3.7 (t, 1H); **5k**: ^{1}H NMR (90 MHz, $CDCl_3$)—δ = 1.1 (t, 6H), 2.5 (q, 4H), 5(s, 1H), 7.1–7.8 (m, 5H); **5l**: ^{1}H NMR (90 MHz, $CDCl_3$)—δ = 1.1 (t, 6H), 2.5 (q, 4H), 5.0 (s, 1H), 7.1–7.8 (m, 4H); **5m**: ^{1}H NMR (90 MHz, $CDCl_3$)—δ = 1.1 (t, 6H), 2.5 (q, 4H), 5.0 (s, 1H), 6.2–6.4 (dd, 2H), 7.5 (d, 1H); **5n**: ^{1}H NMR (90 MHz, $CDCl_3$)—δ = 1.1 (t, 6H), 2.5 (q, 4H), 5.0 (s, 1H), 7.6 (d, 2H), 8.7(d, 2H); **5o**: ^{1}H NMR (90 MHz, $CDCl_3$)—δ = 1.0–1.4 (t, 6H), 2.2–2.8 (m, 4H), 3.9 (s, 1H), 5.0 (s, 1H), 6.8–7.8 (m, 4H); **5q**: ^{1}H NMR (90 MHz, $CDCl_3$)—δ = 0.9–1.2 (t, 6H), 2.0 (m, 1H), 3.0 (d, 1H), 3.2–4.2 (dd, 4H), 7.0–8.0 (m, 10H).

4. Conclusion

In summary, this new protocol represents a safer, simpler and more environmentally friendly alternative to the usual classical Strecker conditions, avoiding the use of expensive and/or toxic Lewis acids and therefore permitting the use of substrates sensitive to Lewis acid conditions. The purification of products after the usual work-up was in some cases unnecessary.

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