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K_2PdCl_4 catalyzed efficient multicomponent synthesis of α-aminonitriles in aqueous media

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ABSTRACT

An efficient, mild and environmentally friendly method has been developed for the Strecker reaction to synthesize α-aminonitriles in the presence of K_2PdCl_4 as a catalyst. The three-component one-pot condensation of an aldehyde, amine and trimethylsilyl cyanide proceeded smoothly in water to afford the corresponding product in high yield with short reaction times.

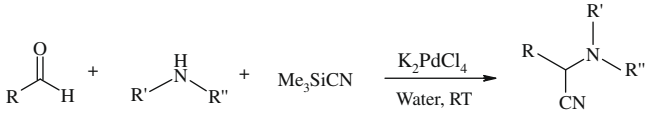
1. Introduction

In recent times organic reactions in aqueous media have received high priority in view of green methodology.[1] The use of water is also preferred due to its abundance, being economical and also due to its highly polar nature. Sometimes it shows higher reactivity and selectivity compared to other conventional organic solvents due to its strong hydrogen bonding ability.[2] The use of water in multicomponent organic reactions is also of great interest. The Strecker reaction[3] is one of the most important multicomponent reactions in organic chemistry for the one-pot synthesis of α-aminonitriles. They serve as efficient precursors for the synthesis of natural and unnatural α-amino acids and different nitrogen containing heterocycles.[4] They are also very effective intermediates for the preparation of different diamines, amides and pharmaceuticals.[5] The α-amino acids have gained immense importance due to their significant biological activities.

The Strecker reaction provides an important method for the synthesis of these α-amino acids and their analogues. One of the popular methods involves the nucleophilic addition of cyanide anions to imines.[3] A number of cyanating agents have been utilized in this process, viz., alkaline cyanides,[6] Et_2AlCN,[7] Bu_3SnCN,[8] $(EtO)_2POCN$[9] and acetone cyanohydrin.[10] However, most of them are found to be hazardous and special caution has to be taken during their use. It has been observed that the use of Me_3SiCN could overcome all those problems as it is safe to handle and is an effective cyanide source.[11] Many of the catalysts used as a promoter in this reaction are either moisture sensitive or take longer reaction time, involve tedious work-up and generate toxic byproducts.[12] In continuation of our studies in developing simple methodologies following green protocol,[13] we report herein the use of K_2PdCl_4 for one-pot three-component condensation of amine, aldehyde and trimethylsilyl cyanide in water for the expeditious synthesis of α-aminonitriles (Scheme 1). The synthetic use of K_2PdCl_4 in multicomponent organic reactions has not been very common. This has prompted us to apply this catalyst in the Strecker synthesis. The reactions were observed to be completed within several minutes with high yield of α-aminonitriles.

2. Results and discussion

A very simple methodology has been followed in our protocol. In this synthesis, a mixture of aryl aldehyde, aryl or aliphatic amine and TMSCN was stirred in water in the presence of K_2PdCl_4. The progress of the reaction was checked by TLC and after work-up the corresponding α-aminonitriles were obtained in excellent yields. The reaction between benzaldehyde, aniline and TMSCN



Scheme 1. Strecker synthesis of α-aminonitriles.

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Table 1
Standardization of the catalytic conditions in Strecker reaction[a]

Entry	K_2PdCl_4 (mol %)	Time (h)	Yield[b] (%)
1	0	12	<5
2	5	8	84
3	10	0.5	95
4	20	15 min	97
5	30	15 min	98

[a] Reaction condition: 1.0 mmol benzaldehyde, 1.0 mmol aniline, 1.3 mmol TMSCN, room temperature stirring in water.
[b] Isolated yield.

was chosen as a probe to evaluate the catalytic activity of K_2PdCl_4 (Table 1). An increase in the quantity of the catalyst up to 30 mol % not only increased the yield but also reduced the reaction time. Considerably, our studies clearly indicate that even 10 mol % of K_2PdCl_4 was sufficient to catalyze the reaction efficiently to produce high yield (95%) within very short reaction time. Therefore, the catalyst loading was optimized to 10 mol % for further reactions. It seems noteworthy to mention that the reaction was not successful in the absence of the catalyst. A screening of the solvents was also carried out under similar reaction conditions. Solvents such as dichloromethane, toluene, THF, acetonitrile, ethanol and water were used to study the reaction. The results have been summarized in Table 2. The yields of the reactions in ethanol and acetonitrile were comparable to that in water but in an aqueous medium the reaction was much faster. This could be due to the high polarizability and amphoteric nature of water.[14]

On establishing optimum conditions, a series of α-aminonitriles were synthesized by using different aldehydes and amines using TMSCN in the presence of K_2PdCl_4 in water in order to prove the scope and generality of our method.[16] Most of the aldehydes reacted efficiently with aniline and TMSCN in water in the presence of the catalyst to furnish the corresponding product in good to excellent yield (73–95%). The results are summarized in Table 3. A variety of substituted aromatic aldehydes were used and all of them furnished good results. Acid sensitive heterocycles like furfural and pyridine-2-carboxaldehyde and unsaturated aldehyde like cinnamaldehyde also produced excellent yields without affecting any other functionality.

Encouraged by the above-mentioned results we continued our exploration of the Strecker synthesis by treating various amines with benzaldehyde and TMSCN under similar reaction conditions. Different aromatic and aliphatic amines were used in the reaction and they underwent efficient coupling with benzaldehyde and TMSCN as shown in Table 4. We observed that the reaction rates were comparable for both aromatic and aliphatic amines. Cyclic amines like pyrrolidine and piperidine also produced high yields in short time.

The protocol devised by us did not require any other additives to promote the reaction. The reactions were carried out at ambient condition in open atmosphere. K_2PdCl_4 acts as efficient Lewis acid to furnish the formation of imines by condensation of aldehyde and amine. The activated imine reacts with TMSCN to generate the desired product. No silylated cyanohydrins were observed to be formed. So, this methodology could be regarded as one of the better methods for Strecker reaction in a single step.

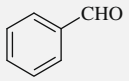
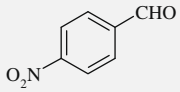
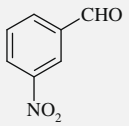
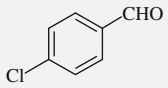
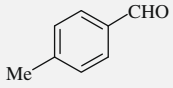
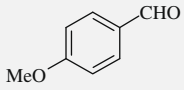
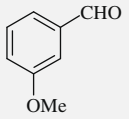
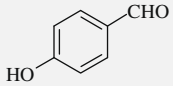
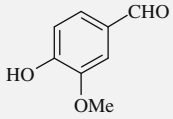
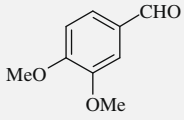
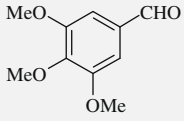
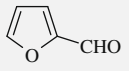
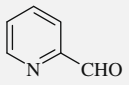
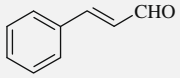
Table 2
Screening of solvents using 10 mol % K_2PdCl_4[a]

Entry	Solvent	Time (h)	Yield[b] (%)
1	Dichloromethane	8	68
2	Toluene	12	52
3	THF	8	47
4	Acetonitrile	2	88
5	Ethanol	2	91
6	Water	0.5	95

[a] Reaction condition: 1.0 mmol benzaldehyde, 1.0 mmol aniline, 1.3 mmol TMSCN, room temperature stirring.
[b] Isolated yield.

Table 3
One-pot synthesis of α-aminonitriles with various aromatic aldehydes in water[a]

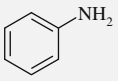
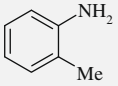
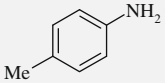
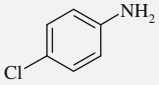
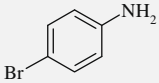
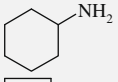
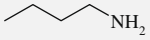
1a-n **2a** **3a-n**

Entry	Aldehyde	Product	Time (h)	Yield[b] (%)
1		**3a**	0.2	95
2		**3b**	0.5	92
3		**3c**	0.5	86
4		**3d**	0.5	91
5		**3e**	1.0	88
6		**3f**	0.7	89
7		**3g**	1.0	86
8		**3h**	1.0	83
9		**3i**	1.5	75
10		**3j**	0.7	89
11		**3k**	0.5	90
12		**3l**	0.5	96
13		**3m**	1.0	88
14		**3n**	1.0	80

[a] Reaction condition: 1.0 mmol aldehyde, 1.0 mmol aniline, 1.3 mmol TMSCN, 10 mol % K_2PdCl_4, room temperature stirring.
[b] Isolated yield.

Table 4
One-pot synthesis of α-aminonitriles with various amines in water[a]

1a **2a-i** **4a-i**

Entry	Amines	Product	Time (h)	Yield[b] (%)
1		**4a**	0.5	95
2		**4b**	0.5	84
3		**4c**	0.5	89
4		**4d**	1.0	90
5		**4e**	1.0	88
6		**4f**	1.2	80
7		**4g**	1.0	85
8		**4h**	1.0	88
9		**4i**	0.75	78

[a] Reaction condition: 1.0 mmol benzaldehyde, 1.0 mmol amine, 1.3 mmol TMSCN, 10 mol % K_2PdCl_4, room temperature stirring.
[b] Isolated yield.

3. Conclusion

In summary, we have developed an efficient and clean protocol employing catalytic amount of K_2PdCl_4 for the one-pot synthesis of α-aminonitriles. The reaction is completed within a very short time with excellent yields of the product. This methodology does not involve the use of hazardous chemicals and it is carried out in an aqueous medium satisfying the green chemistry criteria.

Acknowledgements

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References and notes

1. (a) Li, C.-J. *Chem. Rev.* **2005**, *105*, 3095; (b) Li, C.-J.; Chan, T.-H. *Organic Reactions in Aqueous Media*; Wiley: NewYork, 1997.
2. Ranu, B. C.; Banerjee, S. *Tetrahedron Lett.* **2007**, *48*, 141.
3. Strecker, A. *Ann. Chem. Pharm.* **1850**, *75*, 27; Shafran, Y. M.; Bakulev, V. A.; Mokrushin, V. S. *Russ. Chem. Rev.* **1989**, *58*, 148.
4. Weinstock, L. M.; Davis, P.; Handelsman, B.; Tull, R. *J. Org. Chem.* **1967**, *32*, 2823; Mantier, W. L.; Owens, D. A.; Comer, W. T.; Deitchman, D.; Ferguson, H. C.; Seidehamel, R. J.; Young, J. R. *J. Med. Chem.* **1973**, *16*, 901.
5. Enders, D.; Shilvock, J. P. *Chem. Soc. Rev.* **2000**, *29*, 359. and references cited therein.
6. Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069.
7. Nakamura, S.; Sato, N.; Sugimoto, M.; Toru, T. *Tetrahedron: Asymmetry* **2004**, *15*, 1513.
8. Ishitani, H.; Komiyama, S.; Hasegawa, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 762.
9. Harusawa, S.; Hamada, Y.; Shioiri, T. *Tetrahedron Lett.* **1979**, *20*, 4663.
10. Paraskar, A. S.; Sudalai, A. *Tetrahedron Lett.* **2006**, *47*, 5759.
11. Shaabani, A.; Maleki, A. *Appl. Catal. A: Gen.* **2007**, *331*, 149.
12. (a) Heydari, A.; Fatemi, P.; Alizadeh, A.-A. *Tetrahedron Lett.* **1998**, *39*, 3049; (b) Kobayashi, S.; Nagayama, S.; Busujima, T. *Tetrahedron Lett.* **1996**, *37*, 9221; (c) De, S. K.; Gibbs, R. A. *J. Mol. Catal. A: Chem.* **2005**, *232*, 123; (d) De, S. K. *J. Mol. Catal. A: Chem.* **2005**, *225*, 169; (e) De, S. K.; Gibbs, R. A. *Tetrahedron Lett.* **2004**, *45*, 7407; (f) De, S. K. *Synth. Commun.* **2005**, *35*, 653; (g) Kobayashi, S.; Ishitani, H.; Ueno, M. *Synlett* **1997**, 115; (h) Sakurai, R.; Suzuki, S.; Hashimoto, J.; Baba, M.; Itoh, O.; Uchida, A.; Hattori, T.; Miyano, S.; Yamaura, M. *Org. Lett.* **2004**, *6*, 2241; (i) Majhi, A.; Kim, S. S.; Kadam, S. T. *Tetrahedron* **2008**, *64*, 5509.
13. (a) Karmakar, B.; Nayak, A.; Chowdhury, B.; Banerji, J. *Arkivoc* **2009**, *XII*, 209; (b) Postole, G.; Chowdhury, B.; Karmakar, B.; Pinki, K.; Banerji, J.; Auroux, A. *J. Catal.* **2010**, *269*, 110; (c) Karmakar, B.; Chowdhury, B.; Banerji, J. *Catal. Commun.* **2010**, *11*, 601.
14. (a) Harrerias, C. I.; Yao, X.; Li, Z.; Li, C.-J. *Chem. Rev.* **2007**, *107*, 2546; (b) Dallinger, D.; Kappe, C. O. *Chem. Rev.* **2007**, *107*, 2563; (c) Babu, G.; Perumal, P. T. *Aldrichim. Acta* **2000**, *33*, 16.
15. (a) Shen, Z.-L.; Ji, S.-J.; Loh, T.-P. *Tetrahedron* **2008**, *64*, 8159; (b) Karimi, B.; Safari, A. A. *J. Orgmet. Chem.* **2008**, *693*, 2967; (c) Shaabani, A.; Maleki, A.; Soudi, M. R.; Mofakham, H. *Catal. Commun.* **2009**, *10*, 945; (d) Kumar, M. A.; Babu, M. F. S.; Srinivasulu, K.; Kiran, Y. B.; Reddy, C. S. *J. Mol. Catal. A: Chem.* **2007**, *265*, 268.
16. *Representative experimental procedure*: A mixture of aldehyde (1.0 mmol), amine (1.0 mmol), and trimethylsilylcyanide (1.3 mmol) was stirred at room temperature in water (5 mL) in the presence of 10 mol % of K_2PdCl_4 for certain period as indicated in Tables 3 and 4. After completion of the reaction as indicated by TLC (after elusion the silica gel precoated aluminium plates were visualized under UV light and dipping into ethanolic-ninhydrin solution and charring), the reaction mixture was extracted with ethyl acetate (3 × 10 mL). The extract was concentrated under reduced pressure and purified by column chromatography using 60–120 mesh silica gel with ethyl acetate/hexane as eluant. However, in some cases solid product appeared in the reaction flask which were filtered and crystallized from hot ethanol to get the pure products. The isolated compounds were characterized by mp, IR, ^{1}H NMR, ^{13}C NMR and elemental analysis (C, H and N) and the data of known compounds were found to be identical with the literature.[15] The spectral data of some representative new products are provided below.
2-(N-Anilino)-2-(4-hydroxyphenyl)acetonitrile (**3h**): Yield 152 mg; grey solid, mp 120–122 °C; IR (KBr): 3341, 3022, 2232, 1602, 1271, 1156, 751 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.58 (br s, 1H), 5.28 (s, 1H), 6.70–6.85 (m, 5H), 7.17 (t, *J* = 7.0 Hz, 2H), 7.32 (d, *J* = 8.5 Hz, 2H), 9.74 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 49.19, 113.69, 115.85, 118.54, 119.21, 124.36, 128.25, 129.03, 144.9, 157.99. Anal. Calcd for $C_{14}H_{12}N_2O$: C, 75.0; H, 5.36; N, 12.5. Found: C, 75.11; H, 5.41; N, 12.38.
2-(N-Anilino)-2-(4-hydroxy-3-methoxyphenyl)acetonitrile (**3i**): Yield 125 mg; yellow solid, mp 106–108 °C; IR (KBr): 3377, 3021, 2237, 1604, 1509, 1253, 1208, 1028, 758, 691 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.93 (br s, 1H), 3.93 (s, 3H), 5.35 (s, 1H), 5.76 (br s, 1H), 6.78 (d, *J* = 8.5 Hz, 2H), 6.88–6.98 (m, 3H), 7.06 (d, *J* = 2.0 Hz, 1H), 7.3 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 50.08, 56.11, 109.6, 114.13, 114.9, 118.37, 120.26, 120.49, 125.69, 144.72, 146.67, 147.05. Anal. Calcd for $C_{15}H_{14}N_2O_2$: C, 70.87; H, 5.51; N, 11.02. Found: C, 70.84; H, 5.56; N, 11.0.
2-(N-Anilino)-2-(3,4-dimethoxyphenyl)acetonitrile (**3j**): Yield 144 mg; pale yellow solid, mp 134–136 °C; IR (KBr): 3337, 2933, 2230, 1601, 1512, 1287, 1239, 1141, 1024, 761 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.83 (s, 3H), 3.84 (s, 3H), 3.9 (s, 1H), 5.31 (s, 1H), 6.72 (d, *J* = 8.5 Hz, 2H), 6.83 (t, *J* = 8.7 Hz, 2H), 6.99 (d, *J* = 2.1 Hz, 1H), 7.1 (d, *J* = 9.3 Hz, 1H), 7.2 (t, *J* = 7.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 50.05, 56.0, 56.02, 110.22, 111.37, 114.27, 118.28, 119.73, 120.37, 126.17, 129.54, 144.57, 149.6, 149.95. Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.64; H, 5.97; N, 10.45. Found: C, 71.60; H, 5.99; N, 10.41.
2-(N-Anilino)-2-(3,4,5-trimethoxyphenyl)acetonitrile (**3k**): Yield 137 mg; pale yellow solid, mp 130–132 °C; IR (KBr): 3350, 2974, 2942, 2220, 1599, 1505, 1238, 1129, 1001, 760, 701 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.7 (s, 3H), 3.72 (s, 3H), 3.73 (s, 3H), 3.9 (s, 1H), 5.21 (s, 1H), 6.64 (d, *J* = 9.7 Hz, 2H), 6.66 (s, 2H), 6.76 (t, *J* = 7.3 Hz, 1H), 7.14 (t, *J* = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 50.05, 56.28, 60.86, 104.35, 112.3, 117.17, 120.38, 129.31, 129.57, 139.31, 144.64, 153.8. Anal. Calcd for $C_{17}H_{18}N_2O_3$: C, 68.46; H, 6.04; N, 9.40. Found: C, 68.51; H, 6.01; N, 9.44.