Zn(OAc)₂·2H₂O-Catalyzed One-Pot Efficient Synthesis of α-Amino Nitriles

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A mild, efficient one-pot three component strecker reaction involving electronically and structurally divergent aldehydes, amines and trimethly silyl cyanide in chloroform as solvent at room temperature was accomplished in moderate to excellent yields using an inexpensive and readily available catalyst, Zn(OAc)₂.2H₂O.

Keywords: Strecker reaction, α-Amino nitriles, Zn(OAc)₂.2H₂O, Multicomponet reaction.

INTRODUCTION

The synthesis of α-amino nitriles *via* addition of cyanides to imines (the strecker reaction) has been subjected to considerable interest, as these molecules are useful intermediates towards preparation of α-amino acids[1] and various nitrogen containing heterocycle like imidazoles or thiazoles[2,3]. α-Amino nitriles are useful intermediates in drugs and other pharmaceutical products[4-6].

The classical strecker reaction is usually carried out with alkaline cyanides in aqueous solution and the workup procedure is also tedious. α-Amino nitriles are prepared using imines or one pot synthesis using carbonyl compounds, amines, various catalysts and cyanide source substrate such as KCN[7], HCN, trimethly silyl nitriles[9], diethyl phosphoro-cyanidate $(EtO)_2$-P(O)CN[10], Bu_3SnCN[11], Et_2AlCN[12]. Among these, trimethyl silyl cyanide is a safe and more effective cyanide anion source for the nucleophilic addition reactions of imines under mild conditions[13]. Substantial progress has been made towards the development of efficient methods for the preparation of these compounds, using various catalysts like $Sc(OTf)_3$[14], $InCl_3$[15], $BiCl_3$[16], $RuCl_3$[17], $NiCl_2$[18], $Cu(OTf)_2$[19], $Fe(Cp)_2PF_6$[20], $La(NO_3)_3.6H_2O$ or $GdCl_3.6H_2O$[21], molecular iodine[22], montmorillonite KSF clay[23], heteropoly acids[24], guanidine hydrochloride[25], lithium perchlorate[26], using ionic liquids such as 1-butyl-3-methylimidazolium tetrafluoroborate [bmim]BF₄ and other catalysts[27]. However, many of these reagents are not easily accessible due to their high cost and extended reaction times and involve the use of expensive reagents, harsh conditions

and also require tedious workup leading to the generation of a large amount of toxic waste.

Thus, there is a continued need for a simpler, straight forward and cost effective method for the syntheses of these useful compounds. Earlier, we explored the utility of $Zn(OAc)_2.2H_2O$[28] in the one-pot synthesis of propargylamines from aldehydes, amines and phenyl acetylene *via* three component coupling reaction. In continuation of our interest in exploring novel strategies for C-C, C-hetero bond formations[29], herein we, describe the establishment of reaction conditions that enable the use of readily available, bench stable $Zn(OAc)_2.2H_2O$ as inexpensive, high yielding catalyst for the synthesis of α-amino nitriles.

EXPERIMENTAL

All melting points were determined on an Electrothermal Gallenkamp apparatus. ¹H and ¹³C NMR spectra were recorded on a Varian Gemini Spectrometer 300 and 400 MHz respectively. IR spectra were recorded on Nicolet Fourier Transform spectrometer. Mass spectra were obtained on a 7070H or VG Autospec Mass spectrometer using LSIMS technique. Thin-layer chromatography (TLC) was performed on GF-25U (Anal. Tech) plates and silica gel glass-backed plates. Routine column chromatography was conducted using silica gel 100-200 mesh.

Typical procedure: A mixture of the amine (1 mmol), $Zn(OAc)_2.2H_2O$ (5 mol %) trimethylsilyl cyanide (1.1 mmol) and the aldehyde (1 mmol) in chloroform (3 mL) was stirred at ambient temperature for an appropriate time (Tables 1-3).

Then, the reaction was quenched by addition of a saturated solution of NH_4Cl (5 mL) and the mixture was extracted with ethyl acetate (10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvents were removed under reduced pressure to give in many cases the pure α-aminonitrile. In some cases, the aforementioned residues had to be subjected to chromatography using silica gel and mixtures of hexane/ethyl acetate of increasing polarity in order to obtain the pure α-aminonitrile products.

2-Phenyl-2-piperidinoacetonitrile (Entry 4, Table-2): Viscous oil, ^{1}H NMR (200 MHz, CDCl₃): δ (ppm) 1.47-1.59 (m, 6H), 2.49 (m, 4H), 4.75 (s, 1H), 7.29-7.32 (m, 3H), 7.49-7.52 (m, 2H); MS (ESI): *m/z* 201 (M + 1).

2-Phenyl-2-(1,4-thiazinan-4-yl) acetonitrile (Entry 6, Table-2): Pale yellow solid, m.p.: 65-66 °C; ^{1}H NMR (200 MHz, CDCl₃): δ (ppm) 2.67 (m, 4H), 2.83 (m, 4H), 4.71 (s, 1H), 7.33-7.41(m, 3H), 7.49-7.52 (m, 2H); MS (ESI): *m/z* 219 (M + 1).

(4-Benzylpiperazino)phenyl methyl cyanide (Entry 7, Table-2): Solid, m.p.: 117-119 °C; ^{1}H NMR (200 MHz, CDCl₃): δ (ppm) 2.51 (brs, 4H), 2.62 (brs, 4H), 3.51 (s, 2H), 4.8 (s, 1H), 7.22-7.43 (m, 10H); MS (ESI): *m/z* 292 (M + 1).

2-Phenyl-2-piperazinoacetonitrile (Entry 8, Table-2): Solid, m.p.: 94-96 °C; ^{1}H NMR (200 MHz, CDCl₃): δ (ppm) 1.24 (brs, 4H), 2.63 (brs, 4H), 4.85- (s, 1H), 7.33-7.52 (m, 5H); MS (ESI): *m/z* 202 (M + 1).

(4-Chlorophenyl) (4-toluidino) methyl cyanide (Entry 8, Table-3): Colourless Solid, m.p.: 85-88 °C; ^{1}H NMR (200 MHz, CDCl₃): δ (ppm) 2.27 (s, 3H), 3.85 (d, *J* = 8.0 Hz, 1H), 5.28 (d, *J* = 8.0 Hz, 1H), 6.58 (d, *J* = 8.0 Hz, 2H), 7.0 (d, *J* = 7.3 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.49 (d, *J* = 7.3 Hz, 2H), MS (ESI): *m/z* 257 (M + 1).

RESULTS AND DISCUSSION

Initially, a variety of zinc catalysts were tested (5 mol % as standard) in chloroform for the effective A[3] coupling of benzaldehyde, morpholine and trimethylsilyl cyanide at ambient temperature (**Scheme-I**).

Scheme-I
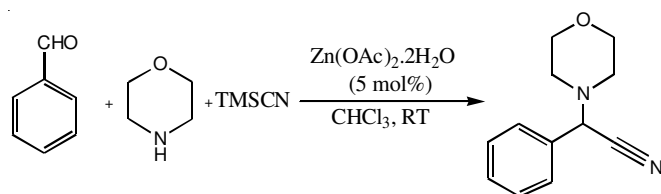
Among the catalysts screened, [ZnCl₂ (6.5 h, 45 %), zinc dust (12 h, 0 %), Zn(OAc)₂. 2H₂O (3.5 h, 92 %), ZnCO₃ (5.5 h, 53 %), zinc granules (5.5 h, 60 %), Zn(OTf)₂ (4.5 h, 80 %), Zn(NO₃)₂ (5 h, 48 %) and Zn(CN)₂ (5 h, 52 %)], Zn(OAc)₂.2H₂O found to be effective catalyst both in terms of isolated yield and reaction time. Among the solvents tested, chloroform proved to be effective (Table-1). We further carried out our studies in order to optimize the catalyst ratio with respect to aldehyde. Using 10 mol %, 0.5 equiv. and 1equiv. of catalyst, no significant improvement in the yield was observed. 5 mol% of catalyst was found to be sufficient for maximum yield.

TABLE-1
SOLVENT STUDIES UNDER DIFFERENT PARAMETERS FOR THE MODEL REACTION CATALYZED BY Zn(OAc)₂·2H₂O

Entry	Solvent	Time (h)	Conversion (%)[a]
1	MeOH	4.5	79
2	1,4-dioxane	5.0	72
3	H₂O	8.0	0
4	Toluene	4.0	72
5	THF	6.0	46
6	DMF	5.5	56
7	CH₃CN	3.5	85
8	DCM	2.5	78
9	DMSO	4.5	65
10	CHCl₃	3.5	92

[a]Isolated yield
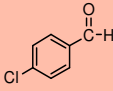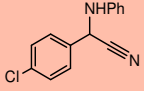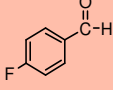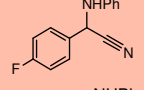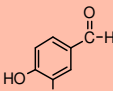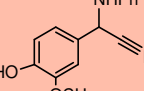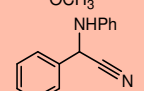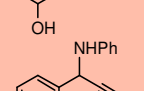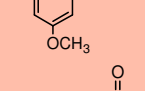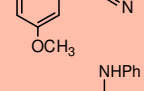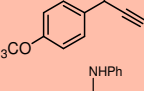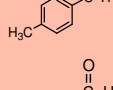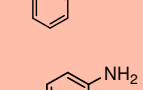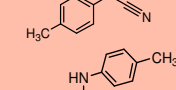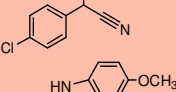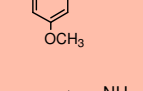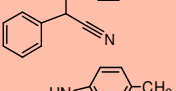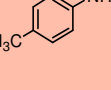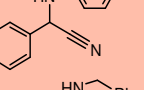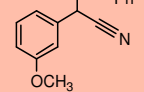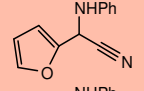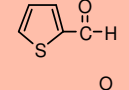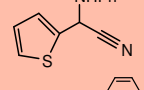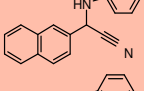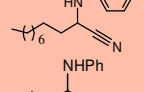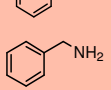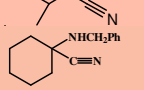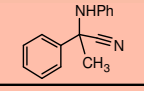
TABLE-2
CYANATION REACTION CATALYZED BY Zn(OAc)₂.2H₂O

Entry	Amine	Aldehyde	Product	Time	Yield (%)[a]
1		A		2.5	85[30]
2		A		4.5	76[30]
3		A		5.0	68[31]
4		A		4.0	85
5		A		3.5	92[31]
6		A		4.5	76
7		A		4.5	78
8		A		5.5	80
9		A		5.0	82[31]
10		A		5.5	62[31]

[a]Isolated yield A = Benzaldehyde

Intrigued by these results, we proceeded to apply the catalytic system (5 mol %, chloroform at ambient temperature) for the

TABLE-3
CYANATION REACTION CATALYZED BY Zn(OAc)₂.2H₂O

Entry	Aldehyde	Amine	Product	Time	Yield (%)[a]
1	4-Cl-C₆H₄-CHO	aniline	α-amino nitrile	2.5	85[30]
2	4-F-C₆H₄-CHO	aniline	α-amino nitrile	3.5	76[11]
3	4-HO-3-OCH₃-C₆H₃-CHO	aniline	α-amino nitrile	4.5	71[32]
4	3-OH-C₆H₄-CHO	aniline	α-amino nitrile	3.5	52[32]
5	3-OCH₃-C₆H₄-CHO	aniline	α-amino nitrile	5.0	86[31]
6	4-OCH₃-C₆H₄-CHO	aniline	α-amino nitrile	3.0	81[30]
7	4-CH₃-C₆H₄-CHO	aniline	α-amino nitrile	3.0	81[30]
8	4-Cl-C₆H₄-CHO	4-CH₃-aniline	α-amino nitrile	3.0	83
9	C₆H₅-CHO	3-OCH₃-aniline	α-amino nitrile	5.0	82[30]
10	C₆H₅-CHO	4-CH₃-aniline	α-amino nitrile	4.5	85
11	3-OCH₃-C₆H₄-CHO	benzylamine	α-amino nitrile	5.5	72[31]
12	furfural	aniline	α-amino nitrile	4.0	82[30]
13	2-thiophene-CHO	aniline	α-amino nitrile	4.5	78[11]
14	2-naphthaldehyde	aniline	α-amino nitrile	5.5	72[32]
15	alkyl-CHO	aniline	α-amino nitrile	5.5	77[30]
16	isobutyraldehyde	aniline	α-amino nitrile	5.0	75[31]
17	cyclohexanone	benzylamine	α-amino nitrile	3.0	62[31]
18	acetophenone	aniline	α-amino nitrile	8.0	0

[a]Yield refer to the isolated pure products after column chrome orgraphy

reaction of structurally and electronically divergent amines, benzaldehyde and trimethyl silyl cyanide as shown in Table-2 (entries 1-10, Table-2). Aliphatic, aromatic primary amines and 20 amines such as morpholine, diverse functionalized piperazines were also well tolerated to give the corresponding products in moderate to excellent isolated yields (52-92 %).

The longer reaction times for aliphatic amines can be attributed due to the stability of the intermediate imines. Satisfied by these results, we extended our methodology to produce divergent α-aminonitriles using electronically and structurally divergent aldehydes and aromatic amines with trimethyl silyl cyanide in shorter reaction times (entries 1-18, Table-3).

Acid sensitive heteroaromatic aldehydes such as furfural (entry 12, Table-3) and thiophene 2-carboxaldehyde (entry 13, Table-3) gave corresponding products in good yields. No undesired side product (such as cyanohydrins trimethylsilyl ether, an adduct between the aldehyde and trimethylsilyl cyanide) was observed because of the rapid formation and activation of the imine intermediate. The reactions are clean and highly selective affording exclusively α-aminonitriles in high yields in a short reaction time. Enolizable aldehydes such as decanal and isobutanal (entries 15 and 16, Table-3) also produced the corresponding α-aminonitriles in good yields.

Interestingly, cyclohexanone gave addition product with benzyl amine and trimethyl silyl cyanide (entry 17, Table-3) in moderate yield. As expected, tricomponent cyanation of aromatic ketone with aniline and trimethyl silyl cyanide did not give the addition product (entry 18, Table-3).

The possible mechanism of the reaction might be involving no trimethylsilylether formation; instead, corresponding imines are formed initially due to greater nucleophilicity of amines compared to trimethyl silyl cyanide. The *in situ* generated imine was polarized by the catalyst making the imine carbon susceptible to the attack by cyanide producing the trimethylsilyl-derivative of a-aminonitrile, which was readily hydrolyzed with water to give the product a-aminonitrile.

Conclusion

The present methodology using $Zn(OAc)_2 \cdot 2H_2O$ provides an efficient synthesis of a-aminonitriles by a one-pot three component coupling of aldehydes, amines and trimethyl silyl cyanide in moderate to excellent yields with the following notable features: use of a readily available and inexpensive catalyst; tolerability of various functional groups and clean reaction conditions.

REFERENCES

1. (a) Y.M. Shafran, V.A. Bakulev and V.S. Mokrushin, *Russ. Chem. Rev.*, **58**, 148 (1989); (b) A. Strecker, *Ann. Chem. Pharm.*, **75**, 27 (1850); (c) R.O. Duthaler, *Tetrahedron*, **50**, 1539 (1994); (d) R.M. Williams and J.A. Hendrix, *Chem. Rev.*, **92**, 889 (1992).
2. L.M. Weinstock, P. Davis, B. Handelsman and R. Tull, *J. Org. Chem.*, **32**, 2823 (1967).
3. W.L. Matier, D.A. Owens, W.T. Comer, D. Deitchman, H.C. Ferguson, R.J. Seidehamel and J.R. Young, *J. Med. Chem.*, **16**, 901 (1973).
4. C. Schultz, H. Groger, C. Dinkel, K. Drauz and H. Waldmann, in eds,: B. Cornils and W. A. Herrmann, In Applied Homogeneous Catalysis with Organometallic Compounds, VCH Wiley: Weinheim, edn. 2, Vol. 2, Chapter 3.2.1 (2002).
5. (a) G.R. Heintzelman, I.R. Meigh, Y.R. Mahajan and S.M. Weinreb, *Org. React.*, **65**, 141 (2005); (b) J.E. Tarver Jr., K.M. Terranova and M. Joullie´, *Tetrahedron*, **60**, 10277 (2004); (c) I.A. Motorina, F.W. Fowler and D.S. Grierson, *J. Org. Chem.*, **62**, 2098 (1997); (d) N.J. Sisti, I.A. Motorina, M.-E. Tran Huu Dau, C. Riche, F.W. Fowler and D.S. Grierson, *J. Org. Chem.*, **61**, 3715 (1996).
6. (a) K.M. Maloney and R.L. Danheiser, *Org. Lett.*, **7**, 3115 (2005); (b) D.T. Amos, A.R. Renslo and R.L. Danheiser, *J. Am. Chem. Soc.*, **125**, 4970 (2003); (c) W.J. Middleton and C.G. Krepsan, *J. Org. Chem.*, **33**, 3625 (1968).
7. S.K. De and R.A. Gibbs, *Tetrahedron Lett.*, **45**, 7407 (2004).
8. M. North, *Angew. Chem. Int. Ed.*, **43**, 4126 (2004).
9. S.I. Murahashi, N. Komiya, H. Terai and T. Nakae, *J. Am. Chem. Soc.*, **125**, 15312 (2003).
10. S. Paraskar and A. Sudalai, *Tetrahedron Lett.*, **47**, 5759 (2006).
11. N.-U.H. Khan, S. Agrawal, R.I. Kureshy, S.H.R. Abdi, S. Singh, E. Suresh and R.V. Jasra, *Tetrahedron Lett.*, **49**, 640 (2008).
12. M. Narasimhulu, T.S. Reddy, K.C. Mahesh, S.M. Reddy, A.V. Reddy and Y. Venkateswarlu, *J. Mol. Catal. Chem.*, **264**, 288 (2007).
13. L. Royer, S.K. De and R.A. Gibbs, *Tetrahedron Lett.*, **46**, 4595 (2005).
14. J.S. Yadav, B.V.S. Reddy, B. Eeshwaraiah and M. Srinivas, *Tetrahedron*, **60**, 1767 (2004).
15. B.M. Fetterly, N.K. Jana and J.G. Verkade, *Tetrahedron*, **62**, 440 (2006).
16. A. Heydari, A. Arefi, S. Khaksar and R.K. Shiroodi, *J. Mol. Catal. Chem.*, **271**, 142 (2007).
17. A. Heydari, P. Fatemi and A.-A. Alizadeh, *Tetrahedron Lett.*, **39**, 3049 (1998).
18. J. Jarusiewicz, Y. Choe, K.S. Yoo, C.P. Park and K.W. Jung, *J. Org. Chem.*, **74**, 2873 (2009).
19. S. Kobayashi and H. Ishitani, *Chem. Rev.*, **99**, 1069 (1999).
20. (a) H. Groger, *Chem. Rev.*, **103**, 2795 (2003); (b) C. Spino, *Angew. Chem. Int. Ed.*, **43**, 1764 (2004).
21. B.A.B. Prasad, A. Bisai and V.K. Singh, *Tetrahedron Lett.*, **45**, 9565 (2004).
22. S. Harusawa, Y. Hamada and T. Shioiri, *Tetrahedron Lett.*, **20**, 4663 (1979).
23. P. Vachal and E.N. Jacobsen, *J. Am. Chem. Soc.*, **124**, 10012 (2002).
24. S. Nakamura, N. Sato, M. Sugimoto and T. Toru, *Tetrahedron Asymm.*, **15**, 1513 (2004).
26. S. Kobayashi, T. Busujima and S. Nagayama, *Chem. Commun.*, 981 (1998).
27. B.C. Ranu, S.S. Dey and A. Hajra, *Tetrahedron*, **58**, 2529 (2002).
28. E. Ramu, R. Varala, N. Sreelatha and S.R. Adapa, *Tetrahedron Lett.*, **48**, 7184 (2007).
29. (a) V.R. Narayana, Z. Pudukulathan and R. Varala, *Org. Commun.*, **6**, 110 (2013); (b) A. Kasa, R. Varala, P.M. Swami and P.K. Zubaidha, *Chemistry J.*, **3**, 66 (2013); (c) P.S. Kulkarni, D.D. Kondhare, R. Varala and P.K. Zubaidha, *J. Serb. Chem. Soc.*, **78**, 909 (2013); (d) V.R. Narayana, P.K. Zubaidha and R. Varala, *Int. J. Org. Chem.*, **2**, 287 (2012); (e) V.B.C. Figueira, A.G. Esqué, R. Varala, C. González-Bello, S. Prabhakar and A.M. Lobo, *Tetrahedron Lett.*, **51**, 2029 (2010).
30. S.K. De, *J. Mol. Catal. Chem.*, **225**, 169 (2005).
31. B.C. Ranu, S.S. Dey and A. Hajra, *Tetrahedron*, **58**, 2529 (2002).
32. B. Das, R.A. Kumar and P. Thirupathi, *Helv. Chim. Acta*, **90**, 1206 (2007).