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ALUM CATALYZED EFFICIENT ONE POT SYNTHESIS OF α-AMINO NITRILES

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ABSTRACT

α-Amino nitriles are prepared in a one pot three component coupling of aldehydes, amines and trimethylsilyl cyanide employing catalytic amount of Alum at room temperature.

Keywords: Alum, α-Amino nitriles, aldehydes, amines, trimethylsilyl cyanide.

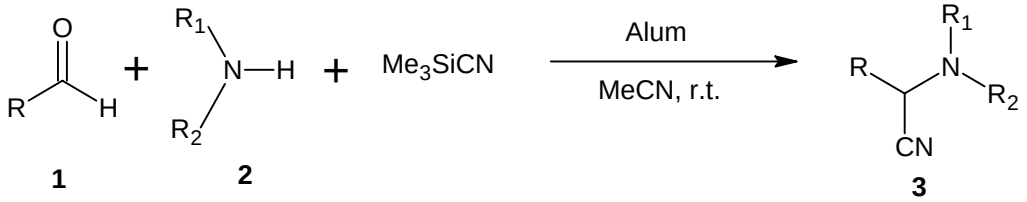
INTRODUCTION

Addition of cyanide to C=N bond is common strategy to prepare α-amino nitriles, which serve as important synthons in organic chemistry for preparation of a variety of heterocycles. As a historical fact this strecker reaction seems to be the first MCR reported by Strecker using aldehydes, amines and sodium cyanide/potassium cyanide[1] to afford α-amino nitriles. These nitriles can be conveniently converted into a variety of amino acids[2] and several nitrogen heterocycles like thiadiazoles[3], imidazoles[4] and other biologically significant compounds such as saframycin A[5]. Over and above all these applications in heterocycles preparations, discovery of Bruylants reaction[6] placed α-amino nitriles at very prestigious position as they serve as intermediates for the production of a variety of short-acting opioid analgetics[7]. A Barbier version of Bruylants type reaction using zinc is reported recently[8]. Due to their wide range of applications these compounds have received a great deal of attention in recent years in connection with their synthesis. As alkali cyanides are well known poisons and also they produce highly alkaline reaction conditions which are not tolerant in many cases particularly when conjugated aldehydes are used[9], clearly some improvements were necessary. Because of poisonous nature and alkaline conditions created by alkali cyanides several alternatives were explored like diethyl phosphorocyanidate[10], α-trimethylsiloxy nitriles[11], acetone cyanohydrin[12] and trimethylsilyl cyanide[13]. Out of these non-alkali metal cyanide variants trimethylsilyl cyanide has found safer and more effective cyanide source for nucleophilic addition to carbon-oxygen or carbon-nitrogen double bonds. It is worth mentioning here in aprotic solvents, it almost produces neutral conditions. Invariably on mixing aldehyde and amine, Schiff's bases are produced which are used in situ and TMSCN addition occurs. Evidently this process requires polarization of C=N bond to facilitate nucleophilic attack of cyanide from TMSCN and is achieved by using suitable Lewis acid and other additives[14]. Several of these already reported methods suffer form drawbacks like long reaction time, harsh reaction conditions low product yield etc. Moreover, the use of strong acids such as H_2SO_4 etc frequently leads to the formation of undesirable side products, which in turn decrease the yield of product. Therefore, there is still need to search a mild, inexpensive and eco-friendly catalyst for the synthesis of α-amino nitriles. Recently alum ($KAl(SO_4)_2.12H_2O$), which is relatively nontoxic and inexpensive catalyst, has emerged as an efficient alternative catalyst for a variety of prominent organic reactions such as Biginelli[15], Pechmann reaction[16] and also used for the synthesis of isoquinolonic acids[17], 2,3-dihydroquinazolin-4(1H)-ones[18], 1,3,4-oxadiazoles[19-21] and very recently alum is used for the synthesis of 1,5-benzodiazepines[22]. In continuation of our own interest herein we report

efficient process for the production of strecker nitriles using in expensive non-toxic non-hazardous catalyst Alum ($KAl(SO_4)_2.12H_2O$).

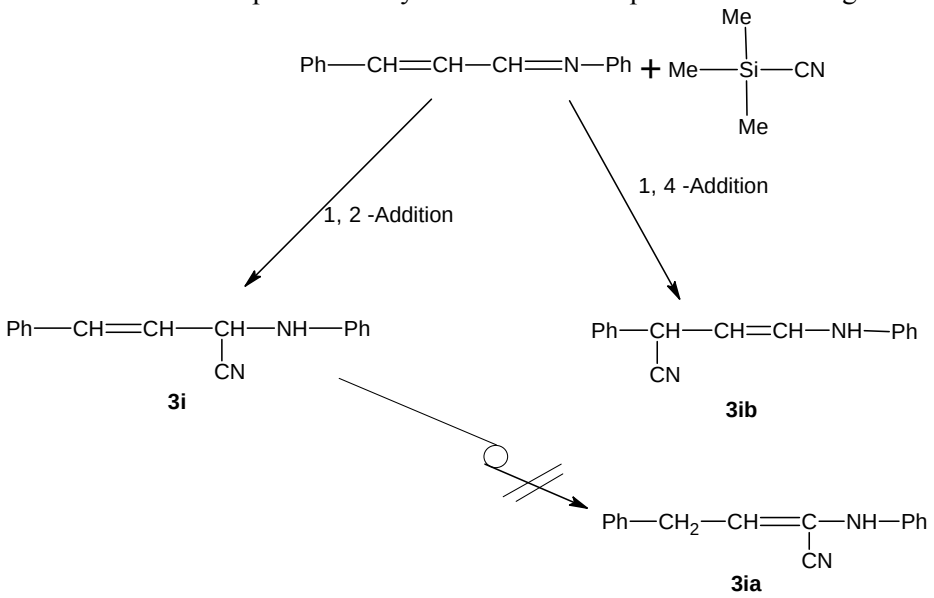
RESULTS AND DISCUSSION

Herein, we report the catalytic use of mild Lewis acid Alum in one pot coupling of aldehydes, amines and trimethylsilyl cyanide at room temperature leading for synthesis of α-amino nitriles (Scheme 1). In a typical case, benzaldehyde (2 mmol), aniline (2 mmol) trimethylsilyl cyanide (2 mmol) and Alum (0.2 mmol, 10 mol %) were stirred in acetonitrile (15 mL) at room temperature for 45 minutes to afford α-amino nitrile in 94 % yield. Similarly, other aldehydes and amines were reacted with trimethylsilyl cyanide at room temperature using catalytic amount of Alum to obtain corresponding α-amino nitriles in 78-94 % yields.



Scheme- 1

A variety of aromatic, conjugated and heterocyclic aldehydes have been reacted with amines and TMSCN at room temperature to obtain α-amino nitriles (Table 1). Secondary amines such as morpholine, piperidine, pyrrolidine have also been employed along with aromatic amines. The reaction completes within 45-80 minutes and 10 mol % of catalyst is enough to facilitate the reaction to completion. The use of large amount of catalyst did not improve the yields or reduce the reaction time. It is worth mentioning here we did not observe the formation of any ring ruptured dyes as is observed in the past rather nitriles are obtained in good yields. As the furan ring is very much sensitive to acids as well as bases, certainly, during Schiff's base formation the present catalyst Alum did not rupture the furan ring[23].



Scheme -2

Further utility and superiority of present protocol is demonstrated using conjugated aldehydes, where no double bond migration **3ia** is observed (4) rather normal nitriles **3i,m,n** are obtained (Scheme 2). These results are in contrast to previous reports where double bond migrates to conjugate with cyanide[24]. It is worth mentioning here that in conjugated systems double bond migrates, if nitriles are heated for few minutes or allowed to stand at room temperature in solution for a long time. Not only this selectivity we also did not observed the formation of 1,4-addition products **3ib**[25].

Table-1*:* Alum mediated synthesis of α-amino nitriles.

Compd[a]	Aldehyde	Amine	Time (min.)	Yield (%)[b]
3a	Benzaldehyde	Aniline	45	94
3b	4-Methylbenzaldehyde	Aniline	55	92
3c	4-Methylbenzaldehyde	Benzyl amine	50	89
3d	Benzaldehyde	4-chloroaniline	45	86
3e	Benzaldehyde	4-Anisidine	60	92
3f	Benzaldehyde	Benzyl amine	65	93
3g	4-Methylbenzaldehyde	4-chloroaniline	50	85
3h	4-Methoxybenzaldehyde	Aniline	55	84
3i	Cinnamaldehyde	Aniline	75	87
3j	Furfural	Benzyl amine	80	82
3k	Benzaldehyde	Pyrrolidine	70	79
3l	Benzaldehyde	Morpholine	65	86
3m	Cinnamaldehyde	Piperidine	75	83
3n	Cinnamaldehyde	Morpholine	80	78

[a] The products were characterized by comparison of their melting points and spectral (IR, ^{1}H NMR) data with those of authentic samples.
[b] Isolated yields after recrystallization.

CONCLUSION

In conclusion, the present protocol employing catalytic amount of Alum, is an efficient, mild and one pot strategy for the preparation of α-amino nitriles. The time required is less and products are obtained in excellent yields. The present procedure is fairly general as, a number of aromatic, conjugated and heterocyclic aldehydes are coupled with primary, secondary and aromatic amines and trimethylsilyl cyanide at room temperature.

REFERENCES

1. A. Strecker, *Ann. Chem. Pharm.*, **75**, 27 (1850).
2. (a.)J. March, *Advanced Organic Chemistry*, 4th ed. Wiley, New York, pp.965 (1995);(b)Y.M. Shafran, V.S. Bakulev and V.S. Mokrushin, *Russ. Chem. Rev.*, **58**, 148 (1989).
3. L.M. Weinstock, P. Davis, B. Handelsman and R. Tull, *J. Org. Chem.*, **32**, 2823 (1967).
4. W.L. Mantier, D.A. Owens, W.T. Comer, D. Deitchman, H.C. Ferguson, R.J. Seidehamel and J.R. Young, *J. Med. Chem.*, **16**, 901 (1973).
5. R.O. Duthaler, *Tetrahedron*, **50**, 1539 (1994).
6. P. Bruylants, *Bull. Chem. Soc. Belg.*, **33**, 467 (1924).
7. P.L. Feldman, M.K. James, M.F. Brackeen, J.M. Bilotta, S.V. Schuster, A.P. Lahey, M.W. Lutz, M.R. Johnson and H.J. Leighton, *J.Med.Chem.*, **34**, 2202 (1991).
8. L. Barnardi, B.F. Bonini, E. Capito, G. Dessole, M. Fochi, M. Comes-Franchini and A. Ricci, *Synlett*, 1778 (2003).
9. N. Singh and J.S. Sandhu, *Chem. Industry*, 1415 (1966).
10. S. Harusaya, Y. Hamada and T. Shioiri, *Tetrahedron Lett*., **20**, 4663 (1979).
11. (a)M. Takamura, Y. Hamashima, D. Usuda, M. Kanai and M. Shibasaki, *Angew. Chem. Int. Ed.*, **39**, 1650 (2000);(b)M.S. Sigman and E.N. Jacobsen, *J. Am. Chem.Soc.*, **120**, 5315 (1998).
12. A.S. Paraskar and A. Sudalai, *Tetrahedron Lett*., **47**, 5759 (2006).
13. A. Shaabani and A. Maleki, *App. Catal. A: General*, **331**, 149 (2007).
14. (a)W.-Y. Chen and J. Lu, *Synlett*, 2293 (2005); (b)A. Heydari, S. Khaksar, M. Pourayoubi and A.R. Mahjoub, *Tetrahedron Lett*., **48**, 4059 (2007);(c)J. Mulzer, A. Meier, J. Buschmann and P. Luger, *Synthesis*, 123 (1996); (d)S.K. De, *Synth. Commun.*, **35**, 653 (2005);(e)S.K. De, *Synth. Commun.*, **35**,

1577 (2005);(f)M. Narasimhulu, T.S. Reddy, K.C. Mahesh, S.M. Reddy, A.V. Reddy and Y. Venkateswarlu, *J. Mol. Catal. A: Chemical*, **264**, 288 (2007).

15. J. Azizian, A.A. Mohammadi, A.R. Karimi and M.R. Mohammadizadeh, *Applied Catal A: General*, **300**, 85 (2006).

16. M. Dabiri, M. Baghbanzadeh, S. Kiani and Y. Vakilzadeh, *Monatsh Chem*., **138**, 997 (2007).

17. J. Azizian, A.A. Mohammadi, A.R. Karimi and M.R. Mohammadizadeh, *J. Org. Chem*., **71**, 350 (2006).

18. M. Dabiri, P. Salehi, S. Otokesh, M. Baghbanzadeh, G. Kozehgary and A.A. Mohammadi, *Tetrahedron Lett*., **46**, 6123 (2005).

19. M. Dabiri, P. Salehi, S. Otokesh, M. Baghbanzadeh and M. Bahramnejad, *Monatsh Chem.*, **138**, 1253 (2007).

20. J. Azizian, A.A. Mohammadi, A.R. Karimi and M.R. Mohammadizadeh, *J. Chem,. Res (S)*, **6**, 424 (2004).

21. J. Azizian, A.A. Mohammadi, A.R. Karimi, M.R. Mohammadizadeh and M. Koohshari, *Heterocycles*, **63**, 2013 (2004).

22. D. Mahajan, T. Naqvi, R.L. Sharma and K.K. Kapoor, *Australian J. Chem.*, **61**, 159 (2008).

23. K.G. Lewis and C.E. Mulquiney, *Tetrahedron*, **33**, 463 (1977).

24. L.A. Yanovskya, C. Shachidayatov and V.E. Kutcherav, *Tetrahedron*, **23,** 1311 (1967).

25. (a)A.-A.S.El-Ahl, *Synth. Commun.*, **33**, 989 (2003);(b)J.S. Sandhu, S. Mohan and P.S. Sethi, *Chem. Ind.*, **52**, 1658 (1970);(c)J.S. Walia and D.H. Rao, *Indian J. Chem.*, **3**, 327 (1965).

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