Accepted Manuscript

p-TsOH mediated solvent and metal catalyst free Synthesis of Nitriles from Aldehydes via Schmidt Reaction

Bijeta Mitra, Gyan Chandra Pariyar, Rabindranath Singha, Pranab Ghosh

PII:	\$0040-4039(17)30563-4
DOI:	http://dx.doi.org/10.1016/j.tetlet.2017.04.100
Reference:	TETL 48892
To appear in:	Tetrahedron Letters
Received Date:	30 March 2017
Revised Date:	22 April 2017
Accepted Date:	29 April 2017



Please cite this article as: Mitra, B., Pariyar, G.C., Singha, R., Ghosh, P., *p*-TsOH mediated solvent and metal catalyst free Synthesis of Nitriles from Aldehydes via Schmidt Reaction, *Tetrahedron Letters* (2017), doi: http://dx.doi.org/10.1016/j.tetlet.2017.04.100

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

ACCEPTED MANUSCRIPT

Graphical Abstract

To create your abstract, type over the instructions in the template box below. Fonts or abstract dimensions should not be changed or altered.





Tetrahedron Letters

journal homepage: www.elsevier.com

p-TsOH mediated solvent and metal catalyst free Synthesis of Nitriles from Aldehydes via Schmidt Reaction

Bijeta Mitra, Gyan Chandra Pariyar, Rabindranath Singha, Pranab Ghosh*

Department of Chemistry, University of North Bengal, Dt. Darjeeling, West Bengal, India. Tel.: +91 (0353) 2776381; fax: +91 (0353) 2699001. E-mail address: pizy12@yahoo.com (P. Ghosh).

ARTICLE INFO

Received in revised form

p-toluene sulphonic acid

Article history: Received

Available online

Accepted

Keywords:

Aldehyde Nitrile Sodium azide

Silica

ABSTRACT

A new and efficient protocol for the conversion of aldehyde into nitriles by modified Schmidt reaction. The reaction is carried out under solvent free condition using sodium azide as a source of nitrogen and catalysed by p-toluene sulphonic acid in presence of silica surface with no side product. This transformation gives good to excellent yield for numerous aromatic, aliphatic and heterocyclic nitriles using very simple reagent. This method has avoided the use of transition metal catalyst, toxic cyanide, hazardous solvent and offers a greener, simple and environment friendly procedure.

2017 Elsevier Ltd. All rights reserved.

Introduction

Organonitrile derivatives have diverse utility as bioactive molecules¹ (figure.1). They act as a precursor and intermediate for pharmaceuticals, agrochemicals, polymers, dye² etc. In addition its usefulness has been widely recognized as a functional group in organic synthesis. Several preparations like alcohol, amine, ester, amide³ including many heterocyclic compounds such as 1,2-diarylimidazol, thiazole, tetrazole etc can be carried out using suitable nitrile precursors.

Classical method for nitrile synthesis are Sandmeyer reaction⁴, ammoxidation of aldehydes⁵, Kolbe nitrile synthesis⁶, hydrocyanation of alkenes⁷ and Rosenmund-von Braun⁸ reaction. Nitrile can be prepared from alcohol⁹, amines,¹⁰ amides,¹¹ azides¹² and carbonyls¹³ this include oxidative rearrangement of alkene,¹⁴ methyl arenes¹⁵ and benzyl or allyl halides,¹⁶ but these methods result in the corresponding higher homologs. Literature survey also reveals that aldehydes get converted into nitrile by using hydroxyl amine hydrochloride in presence of Fecl₃¹⁷ or also in presence of Fe₃O₄-CTAB NPs¹⁸. It was also prepared from oxime by using FeCl₃ in silica surface¹⁹

$$R-CHO \xrightarrow{HN_3} R-NHCHO + R-CN$$

Scheme 1. Schmidt reaction

The well known Schmidt reaction²⁰has been used as a synthetic tool to convert ketone and carboxylic acid to their corresponding amide²¹ and amine²² respectively whereas aldehydes are converted to a mixture of formanilides and nitrile (Scheme 1)²³. Schmidt reactions of aldehydes have limitations due to the formation of mixture although it is great for ketones and acids. In this reaction, the amounts of the two products depend on the amount of the sulphuric acid used²³. So, selectivity of Schmidt reaction of aldehydes to one of the two possible products is very important.²⁴ Preparation of nitrile from aldehyde by this method has also been reported previously by using triflic acid.²⁵



Fig 1. potent bioactive organonitrile derivative

^{*} Corresponding author. Tel.: +91(0353) 2776381; fax: +91(0353) 2699001; e-mail: pizy12@yahoo.com (P. Ghosh).

2

ACCEPTED MANUSCRIPT

Tetrahedron Letters

One pot synthesis promises numerous advantages in economical and environment aspects as in one pot synthesis²⁶ there is no need of separating intermediate which help to reduce the energy consumption, solvent waste and reaction time. Although, as per literature survey, a large number of protocol has been reported, it is evident that most of the one pot synthesis suffer from use of metal catalyst, harsh reaction conditions, longer reaction time, low yield, work-up difficulties and waste of toxic metal salt or solvents.

In most of the protocol metal salts are used as a catalyst^{17,18,19} which gives toxic metal at the end of the reaction and sometimes it leads to metal contamination which may not be desired. We have thus concentrated our investigation in generating a metal free protocol for this purpose. The use of silica is often considered as a green approach. In recent years, silica is used as a reaction medium in many organic reactions to avoid hazardous solvent which may cause chemical pollution. In other words, silica gel is non-toxic and has a high thermal and chemical stability.

$$R-CHO \xrightarrow{\text{NaN}_3, p-\text{TsOH}}_{\text{silica, 120}^0\text{C}} R-CN$$

R= aryl, aliphatic, napthyl, heterocyclic

Scheme 2. p-TsOH catalysed nitrile synthesis from aldehyde

Therefore, we have developed a metal catalyst free and solvent free solid supported method to prepare nitrile from aldehyde devoid of side product and moreover it is cost efficient, environment friendly and has high functional group tolerance (Scheme 2).

Result and Discussion

For the reaction protocol, o-vanillin was taken as the starting material. The model reaction comprising of o-vanillin (1 mmol), sodium azide (2 mmol) in silica (1g) at room temperature gave no product both in absence and presence of the acid even after 24h (entry 1, 2 table 1). The same reaction when carried out in presence of 3 mmol p-TsOH, increased the yield upto 42% (entry 3, table 1). Finally we optimized the reaction temperature to obtain 88% of the product in 3h at 120°C and when the same reaction was carried out in absence of acid, no product was

Table 1.

^a Optimisation	of	temperature
Optimisation	U1	temperature

Entry	Temperature(⁰ C)	Time(h)	p-TsOH(mmol)	^b Yield(%)
1	RT	24	Nil	-
2	RT	24	3	-
3	50	9	3	42
4	90	5	3	68
5	120	3	3	88
6	120	10	Nil	-

^aReaction of aldehyde (1 mmol), NaN_3 (2 mmol) in presence of *p*-TsOH as well as in absence of the acid and silica gel 60-120 mesh (1g) on magnetic stirrer

^bIsolated yield

formed even after 10h. So, the reaction is catalysed by p-toluene sulphonic acid which is shown in table 2. Further, it was

observed that with increasing the amount of acid, the yield of the products get increased. When the reaction was performed with 1 mmol of acid the yield was only 31%, but when the reaction was proceeded with 3 mmol of p-TsOH yield of product was 88% (entry 3, table 2). So, the sharp increase in the yield of nitrile with increase in the amount of p-TsOH indicated that the reaction was acid catalysed.

Table 2.

^a Optimisation of <i>p</i> -TsOH at 120 ⁰ C			
Entry	p-TsOH(mmol)	Time(h)	^b Yield(%)
1	1	3	31
2	2	3	48
3	3	3	88

^aReaction of aldehyde (1 mmol), NaN_3 (2 mmol), *p*-TsOH (1-3 mmol) in silica gel 60-120 mesh (1g) on magnetic stirrer.

^bIsolated yield

Table 3.

^a*p*-TsOH catalysed synthesis of nitrile

Entry	Aldehyde	Time (h)	Product	^b Yield(%)
1	СНО	3.5	CN	86
	но		HO	
	OMe		OWe	
2	CHO	4	CN	74
, Ť	O ₂ N		O ₂ N	
3	СНО	3	CN	90
4	СНО	3.5	CN CN	77
	ų.		$\mathbf{\nabla}$	
	NO ₂		NO ₂	
5	OH	3	OH	88
	СНО		CN	
	ÓМе		ÓMe	
6	CHO	3	CN	83
	HO		но	
7	CHO	3.5	CN	85
	СН		СН	
8	СНО	3	CN	81
0	Me ₂ N ~ CHO	2		70
9		L		19
	MeO		MeO	
10	CHO	2		81
	\square			
11	СНО	1.5	CN	85
12		2		79
	_0CH0		O CN	
13	СНО	4	CN CN	69
14		3		76
17	и и и и и и и и и и и и и и и и и и и	5	/ ~ ~ `CN	10
15	COCH ₃	5	No reaction	-
16	COCH3	5	No reaction	-
	но			

^aReaction condition: Aldehyde (1 mmol), NaN₃ (2 mmol), *p*-TsOH (3 mmol) and silica gel 60-120 mesh (1g) on a magnetic stirrer at 120^{0} C at different time interval.

ACCEPTED MANUSCRIPT

^bIsolated yield

Finally the optimised reactant ratio and condition showed that aldehyde (1 mmol), sodium azide (2 mmol), p-TsOH (3 mmol) and silica gel mesh 60-120 (1g) at 120°C to be the best combination to furnish maximum yield of the desired product (90%) in 3 h (entry 4, Table 3). No side product was obtained in our protocol. Since both sodium azide and *p*-toluenesulphonic acid are soluble in water, product separation is much easier. For the generalisation of our scheme, aldehyde 1-14 was successfully converted to their corresponding nitriles under the optimised reaction condition. Aldehydes such as heterocyclic aldehydes (entry 12, table 3), aliphatic aldehydes (entry 14, table 3), aldehyde with napthyl moiety both 1 and 2 position (entry 10,11, table 3) furnished good yield. Aromatic aldehyde having both electron withdrawing (entry 4, table 3) and electron donating group (entry 8, table 3) give good yield. But when same reaction was carried out with acetophenone (entry 15, table 3) and its derivative no nitrile was obtained. Therefore, it can be concluded that the reaction is highly selective for aldehyde.

Plausible mechanism for *p*-TsOH catalysed one pot synthesis of nitrile from aldehyde was shown in scheme 3. At first *p*-TsOH reacts with NaN₃ and produces HN₃, then *p*-TsOH activate the carbonyl carbon, afterwards nucleophilic attack done by HN₃. Then expulsion of water molecule followed by N_2 gives the desired product.



Scheme 3. Plausible mechanism for the fomation of nitrile from aldehyde

Conclusion

In conclusion, we have developed a solvent free and metal catalyst free method to prepare nitrile from aldehyde, sodium azide, *p*-TsOH in silica medium using the Schmidt reaction protocol. Advantages of the protocol include cost efficiency, use of no transition metal, no toxic cyanide, functional group tolerance, environment friendly, simple work up process and no side product.

Acknowledgments

One of the authors (BM) is thankful to CSIR, New Delhi, for financial support.

Supplementary Data

Supplementary data associated with this article can be found, in the online version, at

References and notes

- (a) Fleming, F. F.; Yao, L.; Ravikumar, P. C.; Funk, L.; Shook, B. C. J. Med. Chem. 2010, 53, 7902–7917; (b) Sweeney, A. M.; Grosche, P.; Ellis, D.; Combrink, K.;Erbel, P.; Hughes, N.; Sirockin, F.; Melkko, S.; Bernardi, A.; Ramage, P.; Jarousse,N.; Altmann, E. ACS Med. Chem. Lett. 2014, 5, 937–941; (c) Frizler, M.; Lohr, F.;Furtmann, N.; Kläs, J.; Gutschow, M. J. Med. Chem. 2011, 54, 396–400; (d) Chuck,C.-P.; Chen, C.; Ke, Z.; Wan, D. C.; Chow, H.-F.; Wong, K.-B. Eur. J. Med. Chem. 2013, 59, 1–6.
- (a) Larock, R. C. Comprehensive Organic Transformations; VCH: New York, 1989; p 819; (b) Houben-Weyl, C. Grundmann, Methodender Organischen Chemie InIn Falbe, J., Ed.; Georg Thieme Verlag: Stuttgart, 1985; E5, p 1313.
- 3. (a) Munoz, J. M.; Alcazar, J.; Hoz, A.; Diaz-Ortiz, A. *Tetrahedron Lett.* 2011, 52, 6058–6060;
- (b) Caddick, S.; Haynes, A. K. K.; Judd, D. B.; Williams, M. R. V. *Tetrahedron Lett.* 2000, 41, 3513–3516; (c) Heller, B.; Sundermann, B.; Buschmann, H.; Drexler, H.-J.; You, J.; Holzgrabe,U.; Heller, E.; Oehme, G. *J. Org. Chem.* 2002, 67, 4414–4422; (d) Bosch, L.; Vilarrasa, J. *Angew. Chem., Int. Ed.* 2007, 46, 3926–3930; (e) Aureggi, V.; Sedelmeier, G. *Angew. Chem., Int. Ed.* 2007, 46, 8440–8444 (f) Aldhoun, M.; Massi, A.; Dondoni, A. *J. Org. Chem.* 2008, 73, 9565–9575; (g) Bokach, N. A.; Kuznetsov, M. L.; Haukka, M.; Ovcharenko, V. I.; Tretyakov, E. V.; Kukushkin, V. Y. *Organometallics* 2009, 28, 1406–1413; (h) Cohen, M. A.; Sawden, J.; Turner, N. J. *Tetrahedron Lett.* 1990, 31, 7223–7226
- Beletskaya, I. P.; Sigeev, A. S.; Peregudov, A. S.; Petrovskii, P. V. J. Org. Chem. 2004, 689, 3810–3812.
- 6. Ellis, G. P.; Romney-Alexander, T. M. Chem. Rev. 1987, 87, 779–794.
- 7. Friedman, L.; Shechter, H. J. Org. Chem. 1960, 25, 877-879.
- Bini, L.; Muller, C.; Wilting, J.; Chrzanowski, L.; Spek, A. L.; Vogt, D. J. Am. Chem. Soc. 2007, 129, 12622–12623.
- 9. Lindley, J. Tetrahedron. 1984, 40, 1433–1456.
- (a) Rad, M. N. S.; Khalafi-Nezhad, A.; Behrouz, S.; Faghihi, M. A. *Tetrahedron Lett.* 2007, 48,6779–6784; (b) Chen, F.-E.; Li, Y.-Y.; Xu, M.; Jia, H.-Q. *Synthesis.* 2002, 1804–1806.
- (a) Yamaguchi, K.; Mizuno, N. Angew. Chem., Int. Ed. 2003, 42, 1480–1483; (b) Ghorbani-Vaghei, R.; Veisi, H. Synthesis. 2009, 945–950.
- 12. Zhou, S.; Junge, K.; Addis, D.; Das, S.; Beller, M. Org. Lett. 2009, 11, 2461–2464.
- (a) Lamani, M.; Prabhu, K. R. Angew. Chem. Int. Ed. 2010, 49, 6622–6625; (b) He, J.; Yamaguchi, K.; Mizuno, N. J. Org. Chem. 2011, 76, 4606–4610.
- (a) Shargi, H.; Sarvari, M. H. Synthesis 2003, 243–246; (b) Zhu, J.-L.; Lee, F.-Y.; Wu, J.-D.; Kuo, C.-W.; Shia, K.-S. Synlett 2007, 1317–1319; (c) Augustine, J. K.; Atta, R. N.; Ramappa, B. K.; Boodappa, C. Synlett. 2009, 3378–3382 (d) Sridhar, M.; Reddy, M. K. K.; Sairam, V. V.; Raveendra, J.; Godala, K. R.; Narsaiah, C.; Ramanaiah, B. C.; Reddy, C. S. Tetrahedron Lett. 2012, 53, 3421–3424; (e) Cos_kun, N.; Arikan, N. Tetrahedron. 1999, 55, 11943–11948; (f) Erman, M. B.; Snow, J. W.; Williams, M. J. Tetrahedron Lett. 2000, 41, 6749–6752; (g) Carmeli, M.; Shefer, N.; Rozen, S. Tetrahedron Lett. 2006, 47, 8969–8972; (h) Telvekar, V. N.; Patel, K. N.; Kundaikar, H. S.; Chaudhari, H. K. Tetrahedron Lett. 2008, 49, 2213–2215; (i) Sharghi, H.; Sarvari, M. H. Tetrahedron. 2002, 58, 10323–10328; (j) Reddy, K. R.; Maheswari, C. U.; Venkateshwar, M.; Prashanthi, S.; Kantam, M. L. Tetrahedron Lett. 2009, 50, 2050–2053.
- 15. Qin, C.; Jiao, N. J. Am. Chem. Soc. 2010, 132, 15893-15895.
- Zhou, W.; Zhang, L.; Jiao, N. Angew. Chem., Int. Ed. 2009, 48, 7094–7097.
- 17. Zhou, W.; Xu, J.; Zhang, L.; Jiao, N. Org. Lett. 2010, 12, 2888–2891.
- 18. Ghosh, P.; Subba, R. Tetrahedron Lett. 2013, 54, 4885-4887
- Ghosh, P.; Saha, B, ; Pariyar C.G. ; Tamang, A, ; Subba, R. Tetrahedron Lett. 2016, 57,3618–3621
- Ghosh, P.; Pariyar, C.G.; Saha, B.; Subba, R. Synlett. 2016, 46,685-691
- (a) Schmidt, K. F. Z. Angew. Chem. 1923, 36, 511. (b) Schmidt,
 K. F. Chem. Ber. 1924, 57, 704. (c) Koldobskii, G. I.; Ostrovskii,
 V. A.; Gidaspov, B. V. Russ. Chem. Rev. 1978, 47, 1084.

СЕРТЕО М ISCRIPT

Tetrahedron Letters

Smith, P. A. S.; Horwitz, J. P. J. Am. Chem. Soc. 1950, 72, 3718 22. 23. Datta, S. K.; Grundmann, C.; Bhattacharyya, N. K. J. Chem. Soc. C 1970, 2058. McEwen, W. E.; Conrad, W. E.; Vanderwerf, C. A. J. Am. Chem. Soc. 1952, 74, 1168

4

- 24. (a) Pavlov, P. A. Chem. Heterocycl. Compd. 2001, 37, 1199 and references cited therein. (b) Suzuki, H.; Nakaya, C. Synthesis 1992, 641. (c) Suzuki, H.; Hwang, Y. S.; Nakaya, C.; Matano, Y. Synthesis. 1993, 1218. (d) Nishiyama, K.; Watanabe, A. Chem. Lett. 1984, 13,773. (e) Nishiyama, K.; Oba, M.; Watanabe, A. Tetrahedron. 1987, 43, 693.
- 25 Rokade, V. B ; Prabhu, R. K. J. Org. Chem. 2012, 77, 5364-5370.
- (a) An, X.-D.; Yu, S. Org. Lett. 2015, 17, 5064-5067. (b) Shargi, 26. H.; Sarvari, M. H. Synthesis. 2003, 243-246. (c) Zhu, J.-L.; Lee, F.-Y.; Wu, J.-D.; Kuo, C.-W.; Shia, K.-S. Synlett 2007, 1317-1319. (d) Augustine, J. K.; Atta, R. N.; Ramappa, B. K.;Boodappa, C. Synlett. 2009, 3378–3382. (e) Sridhar, M.; Reddy, M. K. K.; Sairam, V. V.; Raveendra, J.; Godala, K. R.; Narsaiah, C.; Ramanaiah, B. C.; Reddy, C. S. Tetrahedron Lett. 2012, 53, 3421-3424. (f) Cos_kun, N.; Arikan, N. Tetrahedron. 1999, 55, 11943-11948. (g) Erman, M. B. J.; Snow, W.; Williams, M. J. Tetrahedron Lett. 2000, 41, 6749-6752. (h) Carmeli, M.; Shefer, N.; Rozen, S. Tetrahedron Lett. 2006, 47, 8969-8972. (i) Telvekar, V. N.; Patel, K. N.; Kundaikar, H. S.; Chaudhari, H. K. Tetrahedron Lett. 2008, 49, 2213-2215. (j) Sharghi, H.; Sarvari, M. H. Tetrahedron. 2002, 58, 10323-10328. (k) Reddy, K. R.; Maheswari, C. U.; Venkateshwar, M.; Prashanthi, S.; Kantam, M. L. Tetrahedron Lett. 2009, 50, 2050-2053.
- General procedure for synthesis of nitrile from aldehyde: 27. Aldehyde (1 mmol), sodium azide (2 mmol) and p-toluene sulphonicacid (3 mmol) were finely mixed with silica gel 60-120

mesh (1g) in mortar and pestle. The resultant solid mixture was poured into a round-bottom flask (50 ml) and allowed to stir on magnetic stirrer at 120° for an appropriate time. The progress of the reaction was monitored by thin-layer chromatography (TLC). After completion of the reaction, the reaction mixture was extracted with ethyl acetate (4×15 ml) and washed several times with water. The combined organic mixture dried over anhydrous Na₂SO₄, concentrated and purified by column chromatography on silica gel 60-120 mesh using petroleum ether/ethyl acetate as an eluent to afford pure nitrile. The desired isolated product was characterised by IR, ¹H NMR and ¹³C NMR spectroscopy,

ACCEPTED MANUSCRIPT

p-TsOH mediated solvent and metal catalyst free Synthesis of Nitriles from Aldehydes via Schmidt Reaction

Bijeta Mitra, Gyan Chandra Pariyar, Rabindranath Singha, Pranab Ghosh*

Department of Chemistry, University of North

Bengal, Dt. Darjeeling, West Bengal, India.

Tel.: +91 (0353) 2776381; fax: +91 (0353)

2699001.

E-mail address: pizy12@yahoo.com (P. Ghosh).

HIGHLIGHTS OF THE WORK

- 1. Safe and mild reaction condition for a wide variety of substrates.
- 2. Solvent and metal catalyst free
- 3. Simple and easy workup procedure.
- 4. Cost and time effective.
- 5. Environmental friendly.