



Schmidt reaction in ionic liquids: highly efficient and selective conversion of aromatic and heteroaromatic aldehydes to nitriles with [BMIM(SO₃H)][OTf] as catalyst and [BMIM][PF₆] as solvent

Ganesh C. Nandi, Kenneth K. Laali*

Department of Chemistry, University of North Florida, 1 UNF Drive, Jacksonville, FL 32224, USA

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ABSTRACT

A mild and selective method is presented for the conversion of aromatic and heteroaromatic aldehydes to nitriles via the Schmidt reaction with TMSN₃ by using [BMIM(SO₃H)][OTf] as catalyst and [BMIM][PF₆] as solvent. The method offers high yields and simple product isolation, and avoids the use of liquid superacids or corrosive Lewis acids commonly employed for this transformation. It also offers some potential for recycling/reuse of the IL solvent.

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As a highly versatile functional group that is abundantly present in natural products, pharmaceuticals, and functional materials, and can be easily transformed into other functionalities, the nitrile moiety occupies a pivotal place in organic chemistry. Synthesis of nitriles via the aldoximes is extensively studied over the years and a plethora of reagents have been employed.¹ The efficacy of the Schmidt reaction as a method to convert carbonyl compounds into amides, lactams, and oxazolines is well documented,² and the intramolecular Schmidt reaction of alkyl azides and allyl azides has been successfully implemented as a key step in a number of synthetic schemes.³ The related Brønsted acid-promoted addition of azides to activated olefins as a method to synthesize the corresponding aziridines has also been studied.⁴ By comparison, direct synthesis of nitriles from aldehydes via the classical Schmidt reaction⁵ has not received wide acceptance by the synthetic community likely due to the drawbacks associated with the use of toxic HN₃ which is generated in situ via NaN₃ and HX (typically sulfuric acid). In addition, this method requires the use of large quantities of liquid acid and presents handling, acid-neutralization, and disposal issues. Another drawback of the classical method is the formation of variable amounts of formamide byproduct depending on the amount of sulfuric acid.⁶ Formation of *gem*-diazides was reported by Nishiyama et al.⁷ by using TMSN₃, with SnCl₂ as catalyst and chloroform as solvent. Suzuki and Nakaya⁸ were able to

convert electron rich aromatic aldehydes into nitriles with NaN₃/AlCl₃ in boiling THF. Under these conditions *gem*-diazides were formed as side products with electron deficient or hindered aldehydes.

A recent study by Rokade and Prabhu⁹ showed that NaN₃/TfOH provides a superior medium for selective conversion of aromatic aldehydes to nitriles, when MeCN is used as solvent.

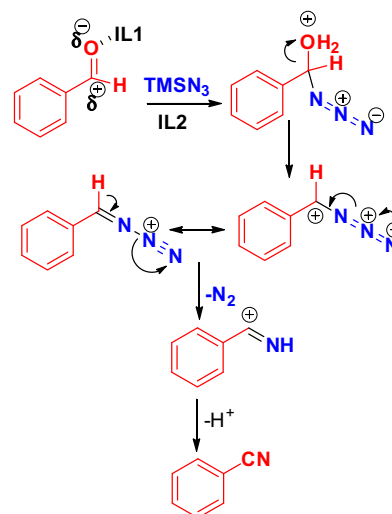
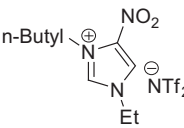


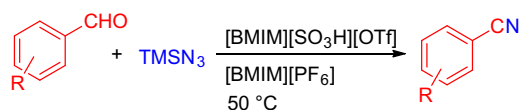
Figure 1. Mechanism of the Schmidt reaction.

* Corresponding author. Tel.: +1 904 620 1503; fax: +1 904 620 3535.

E-mail address: Kenneth.laali@UNF.edu (K.K. Laali).

Table 1Influence of IL and catalyst in the Schmidt reaction with benzaldehyde and TMSN₃ at 50 °C

Entry	Ionic liquid	Catalyst	Time (h)/yield (%)
1	EAN	—	24/—
2	[BMIM][BF ₄]	—	24/—
3		—	24/—
4	[BMIM][PF ₆]	—	24/—
5	EAN	IL2	24/—
6	[BMIM][PF ₆]	IL2	2/100

IL2 = [BMIM][SO₃H][OTf].**Figure 2.** Schmidt reaction in IL.

The Schmidt reaction requires carbonyl activation by protonation or Lewis acid complexation to generate a carboxonium ion which undergoes nucleophilic attack by azide to form the mesomeric iminodiazonium/azidocarbenium ion as a key intermediate that can form the nitrile either directly upon dediazonation/deprotonation or via the iminocarbenium ion (Fig. 1).

In continuation of our work on electrophilic chemistry in ionic liquids (ILs) as solvents and catalysts¹⁰ and in line with our ongoing interest in the development of environmentally more acceptable synthetic/preparative methods for carbocation and onium ion chemistry, we turned our attention to the Schmidt reaction of aldehydes with the goal to develop a high yielding selective method that avoids the use of liquid superacids. At the onset, several control experiments were performed by using benzaldehyde as substrate and TMSN₃ as a convenient azide source (Table 1).

Table 2Recycling and reuse of [BMIM][PF₆] using benzaldehyde as substrate

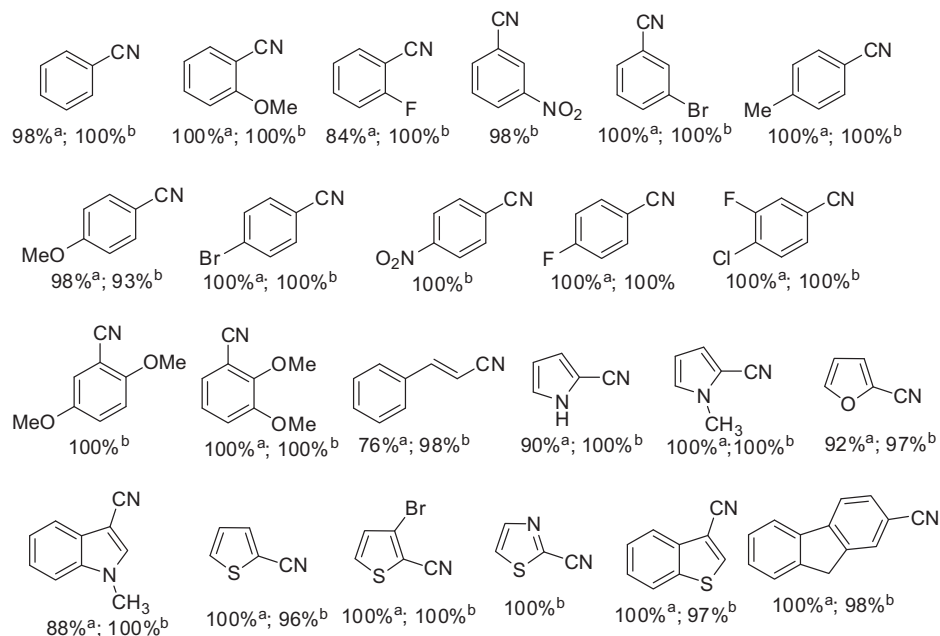
Run #	Time (h)	Yield (%)
1	6	98
2	10	95
3	24	88
4	24	57

Ethylammonium nitrate (EAN), [BMIM][BF₄], [BMIM][PF₆], and [nitro-BMIM][NTf₂] proved ineffective (entries 1–5), showing that additional protic activation is required. We therefore turned our attention to [BMIM][SO₃H][OTf] as a Brønsted acid-IL in combination with EAN or [BMIM][PF₆] as solvent. Surprisingly, where EAN/[BMIM][SO₃H][OTf] did not work, the [BMIM][PF₆]/[BMIM][SO₃H][OTf] system proved quite effective. The conversion achieved in entry 6 after 24 h at 25 °C was typically around 50%. Raising the temperature to 50 °C led to quantitative conversion after 2 h, whereas no reaction occurred at 50 °C for other entries in Table 1.

Based on this study, [BMIM][PF₆]/[BMIM][SO₃H][OTf] was selected for the investigation of the scope of this transformation (Fig. 2). Reactions were conveniently carried out at 50 °C and were completed between 30 min and 2.5 h depending on the substrate (Chart 1).^{11,12}

A variety of aromatic aldehydes bearing activating and deactivating substituents were conveniently transformed to the corresponding nitriles in high yields (close to quantitative in most cases). The method is equally applicable to heterocyclic aldehydes and to cinnamaldehyde (see Chart 1).

Having demonstrated the efficacy of the IL version of the Schmidt reaction, the prospects of recycling/re-use of the IL solvent were examined.¹³ Using benzaldehyde to benzonitrile reaction as model, the reaction was repeated by adding a fresh catalyst to the recycled [BMIM][PF₆]. The outcomes are shown in Table 2. The data indicate that under these conditions the used IL can be re-employed for at least 3 cycles but longer reaction times are needed to achieve acceptable yields. There is a significant drop in yield in the 4th cycle even after 24 h, likely due to gradual buildup

^aGC-MS Yield; ^bNMR Yield**Chart 1.** Scope of the Schmidt reaction of aldehydes.

of impurities and tar in the IL which requires additional steps for cleanup.¹⁴

In summary, we have developed a mild and selective method to convert aromatic and heteroaromatic aldehydes into nitriles in high yields with high selectivity via the Schmidt reaction with TMSN₃ by using the Brønsted acid IL [BMIM(SO₃H)][OTf] as catalysts and [BMIM][PF₆] as solvent. The method offers simple product isolation, avoids the use of liquid superacids or corrosive Lewis acids for carbonyl activation, and offers the possibility of recycling/reuse of the IL solvent. The combined attributes promise a new life for the classical Schmidt reaction as a selective and high yielding approach for the synthesis of a wide range of nitriles.

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References and notes

1. Kalkhambkar, R. G.; Bunge, S. D.; Laali, K. K. *Tetrahedron Lett.* **2011**, 52, 5184–5187. and references cited therein.
2. Hassner, A.; Namboothiri, I. *Organic Syntheses Based on Name Reactions*, 3rd ed.; Elsevier: Oxford, UK, 2012. p 420.
3. (a) Liu, R.; Gutierrez, O.; Tantillo, D. J.; Aubé, J. J. *Am. Chem. Soc.* **2012**, 134, 6528–6531; (b) Frankowski, K. J.; Golden, J. E.; Zeng, Y.; Lei, Y.; Aubé, J. J. *Am. Chem. Soc.* **2008**, 130, 6018–6024; (c) Chaudhry, P.; Schoenen, F.; Neuenswander, B.; Lushington, G. H.; Aubé, J. J. *Comb. Chem.* **2007**, 9, 473–476; (d) Iyengar, R.; Schildknecht, K.; Morton, M.; Aubé, J. J. *Org. Chem.* **2005**, 70, 10645–10652; (e) Forsee, J. E.; Aubé, J. J. *Org. Chem.* **1999**, 64, 4381–4385; (f) Gutierrez, O.; Aubé, J.; Tantillo, D. J. *Org. Chem.* **2012**, 77, 640–647.
4. Moheney, J. M.; Smith, C. R.; Johnston, J. R. *J. Am. Chem. Soc.* **2005**, 127, 1354–1355.
5. (a) Schmidt, K. F. Z. *Angew. Chem.* **1923**, 36, 511; (b) Schmidt, K. F. *Chem. Ber.* **1924**, 57, 704–706; (c) Koldobskii, G. I.; Ostrovskii, V. A.; Gidasov, B. V. *Russ. Chem. Rev.* **1978**, 47, 1084–1094.
6. McEwan, W. E.; Conrad, W. E.; Vanderwerf, C. A. *J. Am. Chem. Soc.* **1952**, 74, 1168–1171.
7. Nishiyama, K.; Oba, M.; Watanabe, A. *Tetrahedron* **1987**, 43, 693–700.
8. Suzuki, H.; Nakaya, C. *Synthesis* **1992**, 641–643.
9. Rokade, B. V.; Prabhu, K. R. *J. Org. Chem.* **2012**, 77, 5364–5370.
10. See for example (a) Kumar, G. G. K. S. N.; Laali, K. K. *Tetrahedron Lett.* **2013**, 54, 965–969; (b) Kumar, G. G. K. S. N.; Laali, K. K. *Tetrahedron Lett.* **2012**, 53, 3066–3069; (c) Kumar, G. G. K. S. N.; Laali, K. K. *Org. Biomol. Chem.* **2012**, 10, 7347–7355; (d) Aridoss, G.; Laali, K. K. *Tetrahedron Lett.* **2011**, 52, 6859–6864; (e) Aridoss, G.; Laali, K. K. *J. Org. Chem.* **2011**, 76, 8088–8094.
11. *General procedure:* [BMIM][PF₆] ionic liquid (2 ml) was charged into an oven-dried 5 ml round bottom flask. The corresponding aldehyde (1 mmol) and trimethylsilyl azide (TMSN₃) (1.5 mmol) were introduced, and finally the catalyst [BMIM][SO₃H][OTf] (20 mol%) was added under stirring at rt. The reaction mixture was sonicated to achieve homogeneity and subsequently heated at 50 °C between 30 min and 2.5 h depending on the substrate. After completion (monitored by GC–MS) the reaction mixture was extracted several times with 30% ethyl acetate in hexane and the combined organic extract was washed with aq. saturated NaHCO₃ followed by water, dried (MgSO₄), and evaporated under reduced pressure to obtain the pure product. The ArCN compounds synthesized in this study are all known compounds. They were characterized by GC–MS and NMR (¹H and ¹³C) and by comparison of the data with the literature.
12. Under the reaction conditions employed and working on small scale we have not experienced any problems with the use of TMSN₃ in the Schmidt reaction. However, necessary precautions should be taken on scaling up this chemistry.
13. *Recycling and re-use of IL:* After extraction, the ionic liquid was dried under high vacuum at 70 °C for about 5 h and re-used in successive runs (see Table 2).
14. This can be accomplished by dissolving the used IL in MeCN, filtration, removal of solvent, and vacuum drying.