

A General and Convenient Catalytic Synthesis of Nitriles from Amides and Silanes

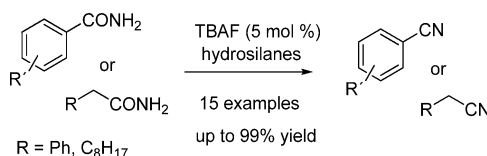
Shaolin Zhou, Kathrin Junge, Daniele Addis, Shoubhik Das, and Matthias Beller*

Leibniz-Institut für Katalyse e.V. an der Universität Rostock, Albert-Einstein-Strasse 29a,
18059 Rostock, Germany

matthias.beller@catalysis.de

Received April 4, 2009

ABSTRACT



A new and convenient protocol for the catalytic dehydration of aromatic and aliphatic amides using silanes in the presence of catalytic amounts of fluoride is presented. The synthesis of aliphatic and aromatic nitriles proceeds with high selectivity under mild conditions. Notably, a wide substrate range is converted in good to excellent yields.

Nitriles are important intermediates in the production of polyamides, pharmaceuticals, agrochemicals, dyes, pigments, and various fine chemicals.¹ In addition, the nitrile group also serves as an important intermediate in organic synthesis for various transformations into other functional groups, such as benzylamines, benzaldehydes, heterocycles, etc.

Obviously, nitriles can be prepared in numerous ways. For more than a century, stoichiometric methods prevailed in laboratory and industry. For aromatic nitriles especially the Rosenmund–von Braun reaction of aryl halides² and the diazotization of anilines with subsequent Sandmeyer reaction have been applied.³ However, due to (over) stoichiometric amounts of metal waste such processes do not meet the

criteria of today's sustainable synthesis. In industry, bulk scale ammoxidation is the method of choice,⁴ whereby the corresponding arene or alkene is reacted with oxygen and ammonia at 300–550 °C in the presence of heterogeneous fixed-bed catalysts.⁵ However, lack of functional group tolerance and harsh reaction conditions make this method less suitable for functionalized nitriles.

During the last decades, several novel catalytic methods have been established for the synthesis of benzonitriles, especially palladium-catalyzed cyanations aryl halides.⁶ Nevertheless, the development of new and improved ways to aromatic and aliphatic nitriles continues to be a challenging goal.

Among the different known methods, the dehydration of amides to the corresponding nitriles is a well-documented process in the literature.⁷ In general, dehydration of amides requires the use of highly reactive reagents, such as thionyl chloride,⁸ phosphorus pentoxide,⁹ phosphorus oxychloride,¹⁰ titanium tetrachloride,¹¹ or sodium borohydride.¹² More recently, dehydrating reagents which can be used under

(1) (a) Larock, R. C. *Comprehensive Organic Transformations*; VCH: New York, 1989; p 819. (b) Grundmann, C. In *Houben-Weyl: Methoden der organischen Chemie*, 4th ed.; Falbe, J., Ed.; Georg Thieme Verlag: Stuttgart, 1985; Vol. E5, p 1313.

(2) Lindley, J. *Tetrahedron* **1984**, *40*, 1433.

(3) For a catalytic variant of the Sandmeyer reaction, see: Beletskaya, I. P.; Sigeev, A. S.; Peregudov, A. S.; Petrovskii, P. V. *J. Organomet. Chem.* **2004**, *689*, 3810.

(4) For recent examples, see: (a) Martin, A.; Kalevaru, V.; Lücke, B.; Sans, J. *Green Chem.* **2002**, *4*, 481. (b) Liu, Y.; Zhong, M.; Yu, W.; Ma, Y. L. *Synth. Commun.* **2005**, *35*, 2951. (c) Rombi, E.; Ferino, I.; Monaci, R.; Picciau, C.; Solinas, V.; Buzzoni, R. *Appl. Catal. A: Gen.* **2004**, *266*, 73. (d) Lücke, B.; Narayana, K. V.; Martin, A.; Jähnisch, K. *Adv. Synth. Catal.* **2004**, *346*, 1407.

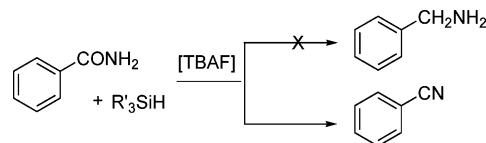
(5) (a) Hagedorn, F.; Gelbke, H.-P. In *Ullmanns Encyklopädie der technischen Chemie*, 4th ed.; Bartholomé, E., Biekert, E., Hellmann, H., Ley, H., Weigert, W. M., Weise, E., Eds.; 4th Ed., Verlag Chemie, Weinheim, 1979; Vol. 17, pp 333–338. (b) Ellis, G. P.; Romney-Alexander, T. M. *Chem. Rev.* **1987**, *87*, 779.

milder conditions have been also reported, such as pivaloyl chloride,¹³ EtOP(O)Cl₂,¹⁴ benzenesulfonyl chloride,¹⁵ and trichloroacetyl chloride.¹⁶ Unfortunately, the use of these chlorides causes severe storage and handling problems as well as significant waste generation.¹⁷ Therefore, there exists considerable interest in finding ready available, easily handling, and environmentally benign dehydration reagents.¹⁸

Recently, we became interested in the development of new methods for reduction of carboxylic acid derivatives in order to avoid stoichiometric amounts of metal hydrides.¹⁹ Based on this work, we started to explore different catalysts for the hydrosilylation of amides to amines. In addition to well-known metal catalysts, we also investigated the use of

tetrabutylammonium fluoride (TBAF)²⁰ catalyzed hydrosilylation of primary amides to amines with methyl-diethoxy-silane. Initially, benzamide was chosen as the model substrate to identify and optimize critical reaction parameters. To our surprise, exclusive formation toward benzonitrile took place and no benzylamine was observed (Scheme 1).

Scheme 1. Reactions of Benzamide with Hydrosilanes



(6) For reviews, see: (a) Sundermeier, M.; Zapf, A.; Beller, M. *Eur. J. Inorg. Chem.* **2003**, 3513. (b) Schareina, T.; Zapf, A.; Cotté, A.; Müller, M. B. *Synthesis* **2008**, 3351–3355. (c) M. Sundermeier, A.; Zapf, N.; Beller, M.; Sans, J. *Tetrahedron Lett.* **2001**, 42, 6707. (d) Ramnauth, J.; Bhardwaj, N.; Renton, P.; Rakhit, S.; Maddaford, S. P. *Synlett* **2003**, 2237. (e) Sundermeier, M.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2003**, 42, 1661. (f) Sundermeier, M.; Mutyala, S.; Zapf, A.; Spannenberg, A.; Beller, M. *J. Organomet. Chem.* **2003**, 684, 50. (g) Sundermeier, M.; Zapf, A.; Sateesh, M.; Beller, M. *Chem.—Eur. J.* **2003**, 9, 1828. (h) Chobanian, H. R.; Fors, B. P.; Lin, L. S. *Tetrahedron Lett.* **2006**, 47, 3303. (i) Jensen, R. S.; Gajare, A. S.; Toyota, K.; Yoshifuji, M.; Ozawa, F. *Tetrahedron Lett.* **2005**, 46, 8645. (j) Veauthier, J. M.; Carlson, C. N.; Collis, G. E.; Kiplinger, J. L.; John, K. D. *Synthesis* **2005**, 2683. (k) Cristau, H. J.; Ouali, A.; Spindler, J. F.; Taillefer, M. *Chem.—Eur. J.* **2005**, 11, 2483. (l) Tylleman, B.; Gomez-Aspe, R.; Gbabode, G.; Geerts, Y. H.; Sergeev, S. *Tetrahedron* **2008**, 64, 4155. (m) Ryberg, P. *Org. Proc. Res. Dev.* **2008**, 12, 540. (n) Iqbal, Z.; Lyubimtsev, A.; Hanack, M. *Synlett* **2008**, 2287. (o) Challenger, S.; Dessi, Y.; Fox, D. E.; Hesmondhalgh, L. C.; Pascal, P.; Pettman, A. J.; Smith, J. D. *Org. Proc. Res. Dev.* **2008**, 12, 575. (p) Wang, X.; Zhi, B.; Baum, J.; Chen, Y.; Crockett, R.; Huang, L.; Eisenberg, S.; Ng, J.; Larsen, R.; Martinelli, M.; Reider, P. *J. Org. Chem.* **2006**, 71, 4021. (q) Martin, M. T.; Liu, B.; Cooley, B. E.; Eaddy, J. F. *Tetrahedron Lett.* **2007**, 48, 2555. (r) Schareina, T.; Zapf, A.; Beller, M. *Chem. Commun.* **2004**, 1388–1389. (s) Schareina, T.; Zapf, A.; Beller, M. *J. Organomet. Chem.* **2004**, 689, 4576. (t) Schareina, T.; Zapf, A.; Mägerlein, W.; Müller, N.; Beller, M. *Chem.—Eur. J.* **2007**, 13, 6249. (u) Schareina, T.; Zapf, A.; Mägerlein, W.; Müller, N.; Beller, M. *Synlett* **2007**, 555. (v) Schareina, T.; Zapf, A.; Beller, M. *Tetrahedron Lett.* **2005**, 46, 2585. (w) Schareina, T.; Zapf, A.; Mägerlein, W.; Müller, N.; Beller, M. *Tetrahedron Lett.* **2007**, 48, 1087. (x) Littke, A.; Soumeillant, M.; Kaltenbach, R. F.; Cherney, R. J.; Tarby, C. M.; Kiau, S. *Org. Lett.* **2007**, 9, 1711.

(7) (a) Kent, R. E.; McElvain, S. M. *Org. Synth.* **1945**, 25. (b) Mowry, D. T. *Chem. Rev.* **1948**, 42, 189.

(8) Krynskiy, J. A.; Carhart, H. W. *Org. Synth.* **1963**, IV, 436–438.

(9) Reiser, D. B.; Horning, E. C. *Org. Synth.* **1963**, IV, 144–145.

(10) Rickborn, B.; Jensen, F. R. *J. Org. Chem.* **1962**, 27, 4608.

(11) Lehnert, W. *Tetrahedron Lett.* **1971**, 19, 1501.

(12) Ellzey, S. E.; Mack, C. H.; Connick, W. J. *J. Org. Chem.* **1967**, 32, 846.

(13) Narsaiah, A. V.; Nagaiah, K. *Adv. Synth. Catal.* **2004**, 346, 1271.

(14) Kuo, C. W.; Zhu, J. L.; Wu, J. D.; Chu, C. M.; Yao, C. F.; Shia, K. J. *Chem. Commun.* **2007**, 3, 301.

(15) Stephens, C. R.; Bianco, E. J.; Pigrim, F. J. *J. Am. Chem. Soc.* **1955**, 77, 1701.

(16) Mander, L. N.; McLachlan, M. M. *J. Am. Chem. Soc.* **2003**, 125, 2400.

(17) Caddick, S.; Wilden, J. D.; Wadman, S. J.; Bush, H. D.; Judd, D. B. *Org. Lett.* **2002**, 4, 2549.

(18) Recent examples of dehydration of amides: (a) Campbell, J. A.; McDouglad, G.; McNab, H.; Rees, L. V. C.; Tyas, R. G. *Synthesis* **2007**, 3179. (b) Vaccari, D.; Davoli, P.; Bucciarelli, M.; Spaggiari, A.; Prati, F. *Lett. Org. Chem.* **2007**, 4, 319. (c) Vaccari, D.; Davoli, P.; Ori, C.; Spaggiari, A.; Prati, F. *Synlett* **2008**, 1317.

(19) (a) Enthaler, S.; Junge, K.; Beller, M. *Angew. Chem.* **2008**, 120, 3363; *Angew. Chem., Int. Ed.* **2008**, 47, 3317. (b) Shaikh, N. S.; Enthaler, S.; Junge, K.; Beller, M. *Angew. Chem.* **2008**, 120, 2531; *Angew. Chem., Int. Ed.* **2008**, 47, 2497. (c) Enthaler, S.; Spilker, B.; Erre, G.; Tse, M. K.; Junge, K.; Beller, M. *Tetrahedron* **2008**, 64, 3867. (d) Shaikh, N. S.; Junge, K.; Beller, M. *Org. Lett.* **2007**, 9, 5429. (e) Enthaler, S.; Erre, G.; Tse, M. K.; Junge, K.; Beller, M. *Tetrahedron Lett.* **2006**, 47, 8095. (f) Enthaler, S.; Hagemann, B.; Erre, G.; Junge, K.; Beller, M. *Chem. Asian J.* **2006**, 1, 598.

To the best of our knowledge, this unique transformation has only been described once before, where a triruthenium carbonyl cluster and a bifunctional organosilane were used for the dehydration of amides to nitriles.²¹ Hence, we studied this reaction in more detail. Herein, we report for the first time a general procedure for the fluoride-catalyzed dehydration of amides to nitriles.

As shown in Table 1, various base and standard copper hydrosilylation catalysts were tested using (EtO)₂MeSiH (3.0

Table 1. Dehydration of Benzamide with (EtO)₂MeSiH in the Presence of Various Catalysts^a

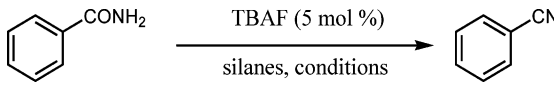
entry	catalyst (mol %)	time (h)	yield ^b (%)
1	none	24	0
2	Bu ₄ NF (5)	0.5	99
3	Bu ₄ NBr (5)	21	0
4	KF (5)	24	41
5	KOBu ^t (5)	19	44
6	CuCl (5)	24	2
7	CuBr (5)	24	3
8	CuI (5)	24	0
9	CuCl ₂ (5)	24	3

^a Reaction conditions: **1a** (1.0 mmol), catalyst (5 mol %), (EtO)₂MeSiH (3.0 equiv), toluene (2 mL), 100 °C, argon atmosphere. ^b Determined by GC.

equiv) as the dehydrating reagent (Table 1, entries 2–9). Notably, the reaction did not occur in the presence of the silane alone (Table 1, entry 1). Remarkably, studies revealed

(20) For selected papers on fluoride-catalyzed hydrosilylation of ketones, aldehydes, and esters, see: (a) Fujita, M.; Hiyama, T. *J. Org. Chem.* **1988**, 53, 5405. (b) Drew, M. D.; Lawrence, N. J. *Tetrahedron Lett.* **1997**, 38, 5857. (c) Kobayashi, Y.; Takahisa, E.; Nakano, M.; Watatani, K. *Tetrahedron Lett.* **1997**, 53, 1627. (d) Drew, M. D.; Lawrence, N. J.; Fontaine, D. L.; Sehki, *Synlett* **1997**, 8, 989.

(21) Hanada, S.; Motoyama, Y.; Nagashima, H. *Eur. J. Org. Chem.* **2008**, 24, 4097.

Table 2. TBAF-Catalyzed Dehydration of Benzamide with Different Silanes^a


entry	hydrosilane (equiv)	solvent	time (h)	T (°C)	yield ^b (%)
1	(EtO) ₂ MeSiH (3)	toluene	0.5	100	99
2	Et ₂ SiH ₂ (3)	toluene	0.5	100	74
3	PMHS (3)	toluene	0.5	100	42
4	Ph ₂ SiH ₂ (3)	toluene	0.5	100	92
5	Et ₂ MeSiH (3)	toluene	0.5	100	22
6	TMSOSiMeH (3)	toluene	0.5	100	47
7	Me ₂ SiHSiHMe ₂ (3)	toluene	0.5	100	82
8	PhSiH ₃ (1)	toluene	0.5	100	85
9	PhSiH ₃ (1)	toluene	0.5	50	83
10	(EtO) ₂ MeSiH (3)	toluene	24	80	0
11	PhSiH ₃ (1)	toluene	24	40	67
12	PhSiH ₃ (1.2)	toluene	0.5	50	79
13	PhSiH ₃ (1)	THF	0.5	50	25

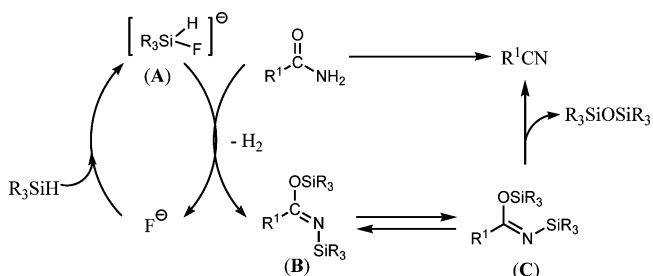
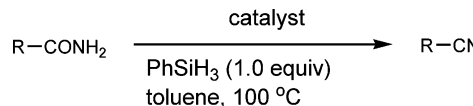
^a Reaction conditions: **1a** (1.0 mmol), silanes (1.0–3.0 equiv), toluene (2 mL), TBAF (0.05 mmol), argon atmosphere. ^b Determined by GC.

that simple tetrabutylammonium fluoride (TBAF) is the most efficient catalyst for the desired transformation. Here, >99% yield within 30 min is achieved (Table 1, entry 2)! The effect of the fluoride anion is demonstrated by comparison of TBAF with tetrabutylammonium bromide (TBAB), where no reaction took place (Table 1, entry 3). KF and KOBu^t were significantly less effective than TBAF (Table 1, entries 4 and 5). In addition, the different copper salts showed no or only very low conversion (Table 1, entries 6–9).

Next, we investigated the influence of different solvents and silanes on the nitrile formation. Selected results from this study are shown in Table 2.

Among the different solvents investigated, toluene gave the best results (Table 2, entries 9 and 13). In this solvent, PhSiH₃ showed the highest reactivity. Here, the dehydration of benzamide occurred smoothly even with 1.0 equiv of PhSiH₃ at 50 °C (Table 2, entry 9).

A plausible mechanism of our novel catalytic transformation is shown in Scheme 2: Coordination of the silane by fluoride leads to an activated silyl species **A**,²⁰ which allows for dehydrogenative silylation of the primary amide to

Scheme 2. Proposed Reaction Mechanism**Table 3.** TBAF-Catalyzed Dehydration of Aromatic and Aliphatic Amides to Nitriles^a


entry	amide	product	yield (%) ^b
1			85
2			85
3			74
4			87
5			86
6			73
7 ^c			71
8			80
9			80
10			93
11			75
12			55
13			87
14			94

^a Reaction conditions: amide (1.0 mmol), TBAF (5 mol %), PhSiH₃ (1.0 equiv), toluene (2 mL), 100 °C, argon atmosphere, 30 min. ^b Isolated yield. ^c 10 mol % of TBAF was used.

produce a mixture of the bis(silyl)imidates **B** and **C**. Thermodynamic attractive elimination of the siloxane forms the corresponding nitriles.²¹ Notably, dehydrogenation of the silane is observed, too. For example, when primary amides are treated with PhSiH₃ in the presence of TBAF at room temperature, hydrogen gas evolved immediately.

After the optimization of the reaction conditions, we explored the scope and limitation of the TBAF-catalyzed

nitrile formation with PhSiH_3 as dehydrating reagent. For this purpose, various aromatic, heteroaromatic, and aliphatic primary amides were examined (Table 3). Using uncomplicated methyl-, methoxy-, and *tert*-butyl-substituted benzamides, the corresponding nitriles were obtained in 74–87% yield (Table 3, entries 1–5). For chloride- and bromide-substituted benzamides, 71% and 73% yields were achieved, respectively (Table 3, entries 6 and 7). Notably, no dehydrohalogenation was observed. Both 1- and 2-naphthalenecarboxamide gave the corresponding nitriles in 80% yield. Interestingly, 4-aminobenzamide **1k** led to the corresponding nitrile **2k** in excellent yield (93%) without side reactions (Table 3, entry 10). Notably, substrate **1l**, containing both a secondary and primary amido groups, afforded 4-acetamidobenzonitrile **2l** in good yield, and no reduction of the other amido group was observed (Table 3, entry 11). Dehydration of heterocyclic substrates such as benzo[*b*]thiophene-2-carboxamide (Table 3, entry 12) gave the corresponding nitrile **2m** in 55% yield. Finally, the system was also adapted to araliphatic and aliphatic amides (Table 3, entries 13 and 14). For example, benzyl cyanide and decanonitrile are obtained in 87% and 94% yields, respectively.

In summary, we presented the first fluoride-catalyzed dehydration reaction of primary amides to the corresponding nitriles. The procedure makes use of a convenient cheap catalyst and commercially available, easily handling hydrosilanes as dehydrating reagents. The general applicability of the method and functional group tolerance of the presented catalyst system is shown in the dehydration of 15 different aromatic, heteroaromatic, and aliphatic amides. Further studies on the reaction mechanism and to extend the synthetic utility of this system are in progress in our laboratory.

Acknowledgment. We thank Dr. W. Baumann, Dr. C. Fischer, S. Buchholz, S. Schareina, A. Kammer, A. Koch, and S. Rossmeisl (all Leibniz-Institut für Katalyse e.V.) for analytical and technical support. Financial support from the BMBF, the DFG (“Leibniz-price”), and the state Mecklenburg-Vorpommern are gratefully acknowledged.

Supporting Information Available: Experimental procedures and full spectroscopic data for all products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL900716Q