Synthesis of arylacetonitrile derivatives: Ni-catalyzed reaction of benzyl chlorides with trimethylsilyl cyanide under base-free conditions†

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We developed a simple strategy for the synthesis of arylacetonitriles from benzyl chlorides and trimethylsilyl cyanide using a $Ni(cod)_2/PPh_3$ catalyst.

Arylacetonitriles are very important units for synthesizing carboxylic acids, amides, aldehydes, and azaheterocyclic compounds.[1] Additionally, these compounds are key structures in many natural products and biologically active substances,[2] including verapamil, anastrozole, cilomilast, and piritramide (Fig. 1). Furthermore, transformation of arylacetonitriles using transition-metal catalysts has been investigated,[3–5] such as cycloaddition of alkynes and nitriles,[3] carbocyanation of alkynes,[4] and synthesis of 3,4-disubstituted 2-amino-napthalenes and 1,3-benzoxazines by the Pd-catalyzed annulation of alkynes using (2-iodophenyl)acetonitriles.[5] Arylacetonitriles have attracted considerable attention from synthetic chemists for use in various reaction conditions.[6]

A strategy for preparing arylacetonitriles from aryl halides using transition-metal catalysts has been reported.[7] For example, cyanomethylation of aryl halides by the Pd-catalyzed reaction with 4-isoxazolyl boronate,[7a] cyanoacetate salts,[7b] cyanoesters,[7c] or trimethylsilylacetonitrile[7d] used as the cyanomethyl source has been reported. Recently, Wang reported the cyanation of the benzylic position by the Cu-catalyzed reaction of benzyl chlorides with $K_4[Fe(CN)_6]$ as the cyanating reagent.[8] This cyanation reaction is attractive in terms of using a non-toxic cyanating reagent. However, 4-methoxybenzyl chloride and 1-phenylethyl chloride give the corresponding cyanation products in low yield (33% and 8%, respectively).

Alternatively, trimethylsilyl cyanide (TMSCN) has been widely used as a cyanating reagent.[9] Many reactions have been reported using TMSCN in the presence of transition-metal catalysts, such as trimethylsilylcyantion of aldhydes,[9a]

ketones,[9a] and hydrazones,[9b] conjugated addition of cyanide to enones,[9c] aminocyanation of alkenes,[9d] and hydrocyanative cyclization of allene-ynes and bis-allenes.[9e]

However, to our knowledge, transition-metal-catalyzed cyanation of benzyl halides with TMSCN has not been reported. The reaction of benzyl halides with TMSCN in the presence of a stoichiometric amount of tetrabutylammonium fluoride (F^- source) to give benzyl cyanides *via* hypervalent silicate intermediates was reported by Deshong.[10] However, this reaction requires a stoichiometric amount of strong base and some organic transformations are triggered by bases. Additionally, F^- also sets off various reactions involving Hiyama coupling[11] and desilylation.[12]

In light of previous methods of cyanation, we have developed a reaction scheme for the cyanation of benzyl chlorides without base and F^-. We herein describe a convenient synthetic method for producing arylacetonitriles by the reaction of benzyl chlorides with TMSCN catalyzed by a Ni complex under base-free and mild conditions. Additionally, the reactants, catalysts, and ligands used are all commercially available compounds.

Initially, benzyl chloride (1a) and TMSCN (2) were used as model reactants for the optimization of the cyanation reaction conditions, and the results are shown in Table 1. When 1a
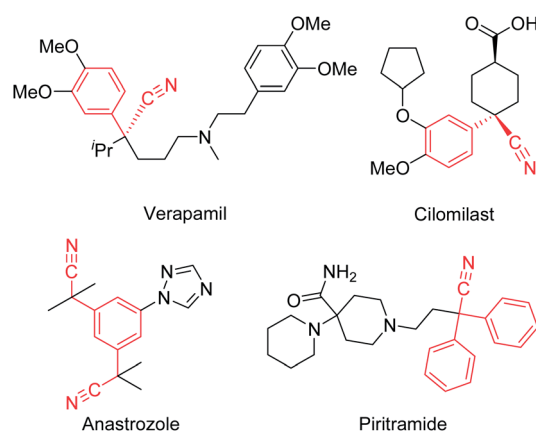
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Fig. 1 Biologically active compounds containing arylacetonitriles.

(1 mmol) was reacted with **2** (2 mmol) in the presence of Ni(cod)$_2$ (0.1 mmol, 10 mol%) (cod: 1,5-cyclooctadiene) in toluene (1 mL) at 60 °C for 16 h, the reaction produced benzyl cyanide (**3a**) in 29% yield (Table 1, entry 1). We next examined using Ni(cod)$_2$/PPh$_3$ as a catalyst and found that the reaction proceeded to give **3a** in 93% yield, as well as 1,2-diphenylethane in 6% yield (Table 1, entry 2). The results of the investigation of various ligands, such as phosphine ligands (PPh$_3$, PCy$_3$, PCy$_2$Ph, dppe (ethylenebis(diphenylphosphine)), and dppf (1,1′-ferrocenebis(diphenylphosphine), (Table 1, entries 2–6), the 2,2-bipyridyl ligand (Table 1, entry 7), and the NHC ligand (IMes, Table 1, entry 8), showed that the best ligand is PPh$_3$. It also should be noted that **3a** was not obtained without catalyst and ligand (Table 1, entry 9).

We next examined Ni(0) precursors not containing Ni(cod)$_2$ for the reaction (Table 1, entries 10 and 11). When NiCl$_2$(PPh$_3$)$_2$/Zn (ref. 13) and NiBr$_2$(DME)/Zn (ref. 14) were used as the Ni(0) precursor in the reaction, benzyl cyanide (**3a**) was not obtained. When Pd(dba)$_2$ was used as the catalyst, the cyanation product **3a** was not formed (entry 12). In these reactions, benzyl chloride (**1a**) was observed by GC. Therefore, we selected Ni(cod)$_2$ as a model catalyst for the reaction.

Additionally, we found that the optimized reaction ratio of **1a** : **2** was 1 : 4, with which **3a** was obtained in 97% yield with excellent chemoselectivity (Table 1, entry 13).

Under the optimized reaction conditions (Table 1, entry 13), we investigated the scope of the Ni-catalyzed cyanation reaction using various substituted benzyl chlorides (Table 2). Various electron-withdrawing and -donating groups at the *para* position of the benzyl chlorides were investigated (Table 2, entries 1–5).
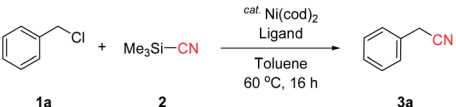
4-Methylbenzyl chloride (**1b**), 4-(chloromethyl)anisole (**1c**), 4-fluorobenzyl chloride (**1d**), and methyl 4-(chloromethyl)-benzoate (**1e**) were used in the reaction and the corresponding benzyl cyanide derivatives (**3b–3e**) were obtained in 85–96% yield (Table 2, entries 2–5).

The reaction was successful using benzyl chloride with an alkoxysilane substituent. When 4-(chloromethyl)phenyl-trimethoxysilane (**3f**) was used, the desired cyanation product (**3f**), which can be used in the Hiyama-coupling reaction, was obtained in 84% yield (Table 2, entry 6). It is noteworthy that the desilylation products were not all observed by gas chromatography because this reaction does not use base or acid.

The position of the methyl substituent on the phenyl ring had an effect on the yield (Table 2, entries 2 and 7–9). When 4-methylbenzyl chloride (**1b**) and 3-methylbenzyl chloride (**1g**) were used in place of benzyl chloride in this reaction, **1b** and **1g** smoothly converted to the desired benzyl cyanide derivatives. Benzyl chloride with *ortho*-Me substituents, such as 2-methyl-benzyl chloride (**1h**) and 2,4,6-trimethylbenzyl chloride (**1i**), were applied to the reaction. 2-Methylbenzyl cyanide (**3h**) and 2,4,6-trimethylbenzyl cyanide (**3i**), were not obtained in high yield (72% and 76%, respectively) because of steric hindrance on the phenyl ring.

Additionally, 2-(chloromethyl)naphthalene (**1j**) was applied to the reaction, and the corresponding product (**3j**) was

Table 1 Optimization of model reaction[a]

Entry	Catalyst	Ligand (*x* mmol)	Yield[b] (%), **3a**
1	Ni(cod)$_2$	—	29
2[c]	Ni(cod)$_2$	PPh$_3$ (0.2)	93
3	Ni(cod)$_2$	PCy$_3$ (0.2)	85
4[d]	Ni(cod)$_2$	PCy$_2$Ph (0.2)	89
5	Ni(cod)$_2$	dppe (0.1)	77
6	Ni(cod)$_2$	dppf (0.1)	55
7	Ni(cod)$_2$	2,2-Bipyridyl (0.1)	59
8	Ni(cod)$_2$	IMes (0.1)	78
9	—	—	n.d.[g]
10[e]	NiCl$_2$(PPh$_3$)$_2$/Zn	PPh$_3$ (0.2)	n.d.[g]
11[e]	NiBr$_2$(DME)/Zn	PPh$_3$ (0.2)	n.d.[g]
12	Pd(dba)$_2$	PPh$_3$ (0.2)	n.d.[g]
13[f]	Ni(cod)$_2$	PPh$_3$ (0.2)	97(83)

[a] Reaction conditions: **1a** (1 mmol), **2** (2 mmol), catalyst (0.1 mmol) and ligand (*x* mmol) in toluene (1 mL) at 60 °C for 16 h under Ar. [b] Yields were determined by gas chromatography on the basis of the quantity of **1a** used. The number in parentheses shows the isolated yield. [c] In addition to **3a**, 1,2-diphenylethane (6%) was formed. [d] The reaction was performed at 100 °C. [e] Zn (0.2 mmol) was used. [f] **2** (4 mmol) was used. dppe = ethylenebis(diphenylphosphine), dppf = 1,1′-ferrocenebis(diphenylphosphine), IMes = 1,3-dimesitylimidazol-2-ylidene. [g] Not detected by GC.

Table 2 Scope of the reaction of **1** with **2**[a]

Products (**3**) yield[b]
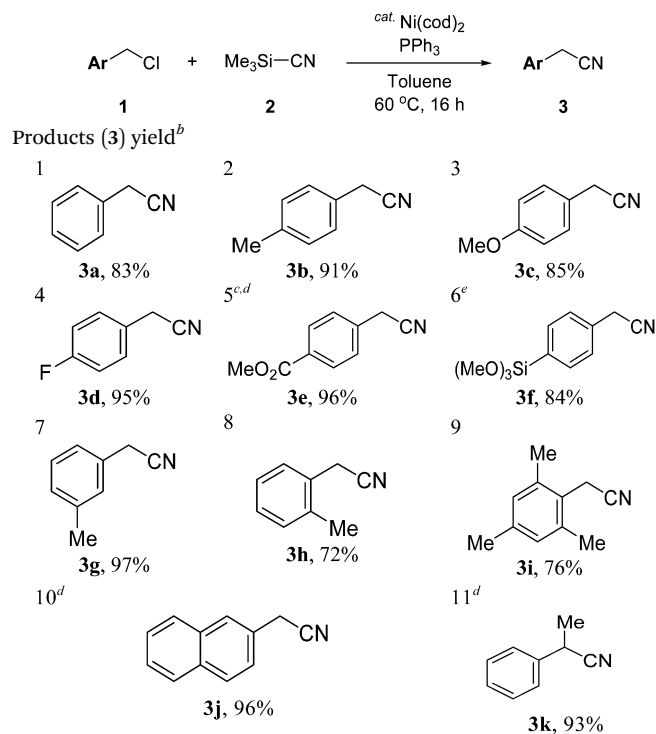
[a] For reaction conditions, see optimized conditions (Table 1, entry 13). [b] Isolated yields. [c] Dioxane (2 mL) was used as solvent. [d] The reaction was performed at 100 °C. [e] **2** (2 mmol) was used.

obtained in 96% yield (Table 2, entry 10). Furthermore, we found that 2-phenypropanenitrile (**3k**) was obtained in 93% yield with excellent chemoselectivity (Table 2, entry 11).

Previously, Jamison reported that Ni-catalyzed Heck-type reactions of benzyl chlorides with simple olefins gave functionalized allylbenzenes.[15] This reaction initiates oxidative addition of benzyl chlorides to Ni(0) and forms the Ni(η^3-CH$_2$Ph)(PCy$_2$Ph)Cl complex. Our developed cyanation method using benzyl chlorides might proceed in the same way.

Therefore, we performed the reaction of Ni(η^3-CH$_2$Ph)(PCy$_2$Ph)Cl (**6**) (0.4 mmol) with TMSCN (**2**) (1.6 mmol) in toluene (3 mL) at 100 °C for 40 h to determine the reaction mechanism (Scheme 1). This reaction gave benzyl cyanide (**3**) in substantial yield (29%). The result of this experiment indicates that **6** is the intermediate of the cyanation reaction.

Based on these experiments, we propose the cyanation mechanism shown in Scheme 2. The reaction is initiated by oxidative addition of the NiP$_2$(0) complex to benzyl chloride (**1a**) to form the Ni(η^3-CH$_2$Ph)(dicyclohexylphosphine)Cl complex (**A**) and the Ni(η^1-CH$_2$Ph)bis(dicyclohexylphosphine)Cl complex (**B**). In this case, **A** is more stable than **B**. Then, complex (**A**) rapidly reacts with trimethylsilyl cyanide (**2**), and the cross-coupling product (**3a**) is obtained *via* **C**. Furthermore, the reaction proceeds without base despite the existence of halogenated starting materials. We might expect that Me$_3$SiCl[16,17] is generated from the reaction of complex (**A**) with TMSCN (**2**).

In conclusion, we have discovered a practical, general, and efficient method for the synthesis of arylacetonitrile derivatives. This synthetic method is Ni(cod)$_2$/PPh$_3$-catalyzed cyanation of aryl chlorides with TMSCN under base- and F$^-$

source-free condition to give arylacetonitriles with high chemoselectivity.

Acknowledgements

Notes and references

1 K. Friedrich and K. Wallenfels, *The Chemistry of the Cyano Group*, Wiley-Interscience, New York, 1970.

2 (*a*) F. F. Fleming, *J. Med. Chem.*, 2010, **53**, 7902.

3 Reviews for the systhesis of pyridines from transition-metals-catalyzed [2 + 2 + 2] cycloaddition reaction: (*a*) K. P. C. Vollhardt, *Angew. Chem.*, 1984, **96**, 525; *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 539; (*b*) H. Bönnemann, *Angew. Chem.*, 1985, **97**, 264; *Angew. Chem., Int. Ed. Engl.*, 1985, **24**, 248; (*c*) J. A. Varela and C. Saá, *Chem. Rev.*, 2003, **103**, 3787; (*d*) P. R. Chopade and J. Louie, *Adv. Synth. Catal.*, 2006, **348**, 2307; (*e*) G. Domínguez and J. Pérez-Castells, *Chem. Soc. Rev.*, 2011, **40**, 3430.

4 (*a*) A. Yada, T. Yukawa, Y. Nakao and T. Hiyama, *Chem. Commun.*, 2009, 3931; (*b*) A. Yada, T. Yukawa, H. Idei, Y. Nakao and T. Hiyama, *Bull. Chem. Soc. Jpn.*, 2010, **83**, 619.

5 (*a*) Q. Tian, A. A. Pletnev and R. C. Larock, *J. Org. Chem.*, 2003, **68**, 339.

6 (*a*) R. Annunziata, M. Benaglia, M. Cinquini, F. Cozzi and G. Tocco, *Org. Lett.*, 2000, **2**, 1737; (*b*) V. N. Telvekar and R. A. Rane, *Tetrahedron Lett.*, 2007, **48**, 6051; (*c*) C. O. Kangani, B. W. Day and D. E. Kelley, *Tetrahedron Lett.*, 2008, **49**, 914; (*d*) G. Chen, Z. Wang, J. Wu and K. Ding, *Org. Lett.*, 2008, **10**, 4573.

7 (*a*) J. Velcicky, A. Soicke, R. Steiner and H.-G. Schmalz, *J. Am. Chem. Soc.*, 2011, **133**, 6948; (*b*) R. Shang, D.-S. Ji, L. Chu, Y. Fu and L. Liu, *Angew. Chem., Int. Ed.*, 2011, **50**, 4470; (*c*) N. A. Beare and J. F. Hartwig, *J. Org. Chem.*, 2002, **67**, 541; (*d*) L. Wu and J. F. Hartwig, *J. Am. Chem. Soc.*, 2005, **127**, 15824.

8 Y. Ren, C. Dong, S. Zhao, Y. Sun, J. Wang, J. Ma and C. Hou, *Tetrahedron Lett.*, 2012, **53**, 2825.

9 (*a*) J.-M. Brunel and J. P. Holmes, *Angew. Chem., Int. Ed.*, 2004, **43**, 2752; (*b*) J. M. Keith and E. N. Jacobsen, *Org. Lett.*, 2004, **6**, 153; (*c*) Y. Tanaka, M. Kanai and M. Shibasaki, *J. Am. Chem. Soc.*, 2008, **130**, 6072; (*d*) H. Zhang, W. Pu, T. Xiong, Y. Li, X. Zhou, K. Hun, Q. Liu and Q. Zhang, *Angew. Chem., Int. Ed.*, 2013, **52**, 2529; (*e*) J. Shimokawa, T. Harada, S. Yokoshima and T. Fukuyama, *J. Am. Chem. Soc.*, 2011, **133**, 17634.

10 E. D. Soli, A. S. Manoso, M. C. Patterson and P. Deshong, *J. Org. Chem.*, 1999, **64**, 3171.

11 (*a*) T. Hiyama and E. Shirakawa, *Top. Curr. Chem.*, 2002, **219**, 61; (*b*) S. E. Denmark and R. F. Sweis, in *Metal-Catalyzed Cross-Coupling Reactions*, ed. A. de Meijere and
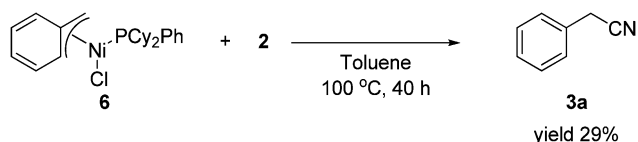
Scheme 1   Reaction of Ni−allyl complex (**6**) with **2**.
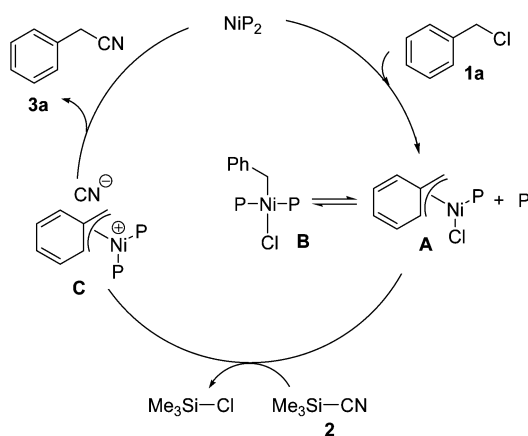
Scheme 2   Plausible reaction mechanism for the reaction of **1a** with **2**.

F. Diederich, 2nd edn, Wiley-VCH, Weinheim, Germany, 2004, pp. 163–216.

12 (*a*) T. D. Nelson and R. D. Crouch, *Synthesis*, 1996, 1031; (*b*) G. Satori, R. Ballini, F. Bigi, G. Bosica, R. Maggi and P. Righi, *Chem. Rev.*, 2004, **104**, 199.

13 D. K. Rayabarapu, C.-F. Chiou and C.-H. Cheng, *Org. Lett.*, 2002, **4**, 1679.

14 J.-C. Hsieh, Y.-C. Chen, A.-Y. Cheng and H.-C. Tseng, *Org. Lett.*, 2012, **14**, 1282.

15 (*a*) R. Matsubara, A. T. Gutierrez and T. F. Jamison, *J. Am. Chem. Soc.*, 2011, **133**, 19020; (*b*) E. A. Standley and T. M. Jamison, *J. Am. Chem. Soc.*, 2013, **135**, 1585.

16 Me_3SiCl was analyzed by using the ^{29}Si NMR (DEPT) analysis. After the model reaction (Table 1, entry 13), ^{29}Si NMR (DEPT) analysis of Me_3SiCl shows a peak at 27.1 ppm.[17]

17 J. Schraml, V. Chvalovsky, M. Magi and E. Lippmaa, *Collect. Czech. Chem. Commun.*, 1979, **44**, 854.