Tetrahedron Letters 49 (2008) 4693–4694

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Palladium-catalyzed cyanation of aryl halides using $K_4[Fe(CN)_6]$ as cyanide source, water as solvent, and microwave heating

Sivan Velmathi [a,b], Nicholas E. Leadbeater [b,*]

[a] Department of Chemistry, National Institute of Technology, Tiruchirappalli 620 015, India
[b] Department of Chemistry, University of Connecticut, 55 North Eagleville Road, Storrs, CT 06269-3060, USA

ARTICLE INFO

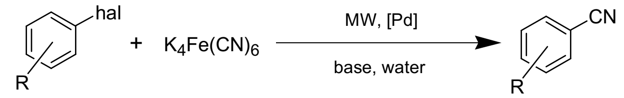
Article history:
Received 7 May 2008
Revised 22 May 2008
Accepted 28 May 2008
Available online 2 June 2008

ABSTRACT

A methodology for the cyanation of aryl iodides and activated aryl bromides is reported using water as the solvent and $K_4[Fe(CN)_6]$ as the cyanide source. Reactions are complete within 20 min.

Aryl nitriles represent an important class of compounds since the motif is found in a range of pharmaceuticals, dyes, agrochemicals, and natural products.[1,2] They are also valuable intermediates in organic synthesis and can be easily transformed to a range of heterocycles. A number of synthetic methods for the preparation of aryl nitriles have been developed including the direct cyanation of aryl halides by copper(I) cyanide, known as Rosenmund–von Braun reaction.[3] The classical Rosenmund–von Braun procedure can require harsh conditions,[4] making it incompatible with sensitive substrates. While modifications to this procedure have been made[5] palladium-, copper-, or nickel-catalyzed aryl cyanation approaches show more promise.[6] A downside with these protocols was that toxic inorganic or organic cyanide sources such as alkali-metal cyanides trimethylsilyl cyanide[7] or acetone cyanohydrin[8] are often required. However, this has been overcome by the discovery that cheap, non-toxic potassium hexacyanoferrate(II), $K_4[Fe(CN)_6]$ can be used as a cyanide source.[9] Based around this discovery, a number of methodologies have been developed[10] including some procedures using ligand-free palladium sources.[11,12]

Research in our laboratory has been focused around the application of microwave heating as a tool for preparative chemistry, particularly in conjunction with the use of water as a solvent.[13] Microwave heating has found use as a tool for performing the reaction.[14] Sparked by a number of recent reports of cyanation of aryl halides facilitated using microwave heating,[15,16] in addition to our previous interest in this transformation,[17,18] we turned our attention to developing a methodology based around the use of water as a solvent in conjunction with microwave heating and $K_4[Fe(CN)_6]$ as a cyanide source (Scheme 1). We report our results here.



Scheme 1. Cyanation of aryl halides using water as a solvent in conjunction with microwave heating, and $K_4[Fe(CN)_6]$ as a cyanide source.

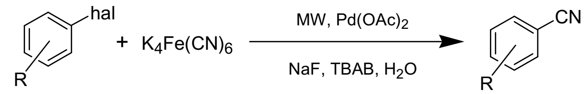
To initiate the work, we decided to screen 4-bromoacetophenone as a test substrate on the 1 mmol scale and start by using reaction conditions similar to those we had developed previously for Suzuki and Heck couplings: water as a solvent, sodium carbonate as base, and tetrabutylammonium bromide (TBAB) as a phase transfer agent, heating at 150–170 °C. We used 5 mol % palladium acetate as catalyst and a 1:1 molar equiv of 4-bromoacetophenone to $K_4[Fe(CN)_6]$. Performing the reaction for 20 min at 150 °C led to a 15% yield of the desired nitrile product. A study of the literature suggested that sodium carbonate, while efficient as a base for the reaction in organic solvents, may not be optimal for use in water. We screened a number of mineral bases and found that sodium fluoride gave by far the best results. Keeping all other conditions the same, using NaF (1 equiv) as base gave an 80% yield of 4-acetylbenzonitrile. We next turned our attention to reducing the quantity of $K_4[Fe(CN)_6]$. One molar equivalent corresponds to a sixfold excess. We therefore tried reducing the quantity used to a stoichiometric equivalent. This was possible but product yield dropped. Increasing the ratio of $K_4[Fe(CN)_6]$ to aryl halide very slightly to 0.2:1 allowed us to retain an 80% product yield. We then tried reducing the reaction time but found that this was not possible without sacrificing product yield. The same was true when we tried to reduce the catalyst loading. We tried eliminating the TBAB from the reaction or replacing it with ethanol as a co-solvent but both of these modifications resulted in no conversion to product. We screened a range of palladium complexes as potential catalysts for the reaction including $Pd_2(dba)_3$ and Pd/C but found that palladium acetate gave the best results. Thus, our optimal reaction conditions were: aryl halide (1 mmol), $K_4[Fe(CN)_6]$ (0.22 mmol),

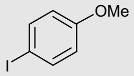
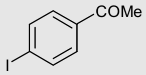
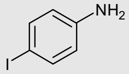
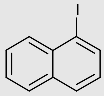
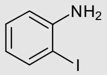
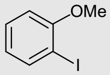
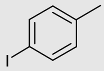
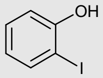
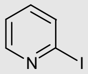
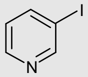
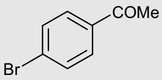
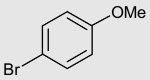
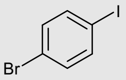
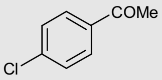
---

[*] Corresponding author. Tel.: +1 860 486 5076; fax: +1 860 486 2981.
E-mail address: nicholas.leadbeater@uconn.edu (N. E. Leadbeater).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.05.124

Table 1
Cyanation of aryl halides using $K_4[Fe(CN)_6]$ as a cyanide source[a]



Entry	Aryl halide	Product yield (%)
1		86
2		81
3		94
4		86[b]
5		88
6		78
7		0
8		(80)[c] 40
9		0
10		0
11		80
12		40
13		90[d]
14		0

[a] Sealed tube, using 1.0 mmol aryl halide, 0.22 mmol $K_4[Fe(CN)_6$, 1.0 mmol NaF, 1.0 mmol TBAB, 5 mol % $Pd(OAc)_2$, 2.0 mL water. Initial microwave irradiation of 150 W, temperature ramped from rt to 150 °C where it was then held until a total time of 20 min had elapsed.

[b] Reaction run for 40 min.

[c] Conversion to product.

[d] 4-Bromobenzonitrile.

NaF (1 mmol), TBAB (1 mmol), $Pd(OAc)_2$ (5 mol %), water (2 mL), heat to 150 °C, and hold until a total time of 20 min had elapsed.

We next screened a range of aryl halides in the reaction, the results are shown in Table 1.[19] A number of aryl iodides can be converted to the corresponding nitriles in good yields (Table 1, entries 1–9). Interestingly however, those substrates bearing an alkyl group could not be effectively cyanated (Table 1, entry 7). In the case of 2-iodophenol, although a high conversion to the desired nitrile was observed, product purification was difficult and so the isolated yield was only modest (Table 1, entry 8). Attempts to use iodopyridines as substrates were not successful, significant decomposition being observed (Table 1, entries 9 and 10). The scope of aryl bromides is limited to those bearing electron-withdrawing groups (Table 1, entries 11 and 12). Using 1-bromo-4-iodobenzene, we observe a chemoselective cyanation to yield 4-bromobenzonitrile (Table 1, entry 13). Aryl chlorides are unreactive under the conditions used (Table 1, entry 14).

In summary, we have developed a methodology for the cyanation of aryl iodides and activated aryl bromides using water as the solvent and $K_4[Fe(CN)_6]$ as the cyanide source. Reactions are complete within 20 min microwave heating at 150 °C.

Acknowledgments

The Technical Education Quality Improvement Programme (TEQIP) of the Government of India is thanked for a scholarship (S.V.). Equipment support from CEM Corp. is acknowledged.

References and notes

1. Kleemann, A.; Engel, J.; Kutscher, B.; Reichert, D. *Pharmaceutical Substances: Syntheses, Patents, Applications*, 4th ed.; Georg Thieme: Stuttgart, 2001.
2. Collier, S. J.; Langer, P. *Sci. Synth.* **2004**, *19*, 403.
3. (a) Rosenmund, K. W.; Struck, E. *Ber. Dtsch. Chem. Ges.* **1919**, *2*, 1749; (b) Lindley, J. *Tetrahedron* **1984**, *40*, 1433.
4. For a review see Ellis, G. P.; Romney-Alexander, T. M. *Chem. Rev.* **1987**, *87*, 779.
5. Wang, D. P.; Kuang, L. P.; Li, Z. W.; Ding, K. *Synlett* **2008**, 69.
6. For a review see Sundermeier, M.; Zapf, A.; Mutyala, S.; Baumann, W.; Sans, J.; Weiss, S.; Beller, M. *Chem. Eur. J.* **2003**, *9*, 1828.
7. Sundermeier, M.; Mutyala, S.; Zapf, A.; Spannenberg, A.; Beller, M. *J. Organomet. Chem.* **2003**, *684*, 50.
8. Sundermeier, M.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 1661.
9. Schareina, T.; Zapf, A.; Beller, M. *Chem. Commun.* **2004**, 1388.
10. See for example (a) Cheng, Y. N.; Duan, Z.; Yu, L. J.; Li, Z. X.; Zhu, Y.; Wu, Y. J. *Org. Lett.* **2008**, *10*, 901; (b) Schareina, T.; Zapf, A.; Beller, M. *Tetrahedron Lett.* **2005**, *46*, 2585.
11. Weissman, S. A.; Zewge, D.; Chen, C. *J. Org. Chem.* **2005**, *70*, 1502.
12. (a) Zhu, Y. Z.; Cai, C. *Eur. J. Org. Chem.* **2007**, *15*, 2401; (b) Zhu, Y. Z.; Cai, C. *Synth. Commun.* **2007**, *37*, 3359.
13. Leadbeater, N. E. *Chem. Commun.* **2005**, 2881.
14. A number of books on microwave-promoted synthesis have been published recently. For a recent example see: *Microwaves in Organic Synthesis*; Loupy, A., Ed., 2nd ed.; Wiley-VCH: Weinheim, 2006.
15. For the first report see: Alterman, M.; Hallberg, A. *J. Org. Chem.* **2000**, *65*, 7984.
16. (a) Srivastava, R. R.; Zych, A. J.; Jenkins, D. M.; Wang, H. J.; Chen, Z. J.; Fairfax, D. J. *Synth. Commun.* **2007**, *37*, 431; (b) Chobanian, H. R.; Fors, B. P.; Lin, L. S. *Tetrahedron Lett.* **2006**, *47*, 3303; (c) Pitts, M. R.; McCormack, P.; Whittall, J. *Tetrahedron* **2006**, *62*, 4705; (d) Cai, L. Z.; Liu, X.; Tao, X. C.; Shen, D. *Synth. Commun.* **2004**, *34*, 1215; (e) Zhang, A.; Neumeyer, J. L. *Org. Lett.* **2003**, *5*, 201.
17. Arvela, R. K.; Leadbeater, N. E.; Torenius, H. M.; Tye, H. *Org. Biomol. Chem.* **2003**, *1*, 1119.
18. Arvela, R. K.; Leadbeater, N. E. J. *Org. Chem.* **2003**, *68*, 9122.
19. *Typical procedure for the cyanation of aryl halides with $K_4[Fe(CN)_6]$*: In a 10 mL glass tube was placed 4-iodoanisole (243 mg, 1.0 mmol), potassium hexacyanoferrate(II) (93 mg, 0.22 mmol), sodium fluoride (40 mg, 1.0 mmol), tetrabutylammonium bromide (323 mg, 1 mmol), and $Pd(OAc)_2$ (10 mg, 5 mol %). After adding water (2 mL), the vessel was sealed with a septum and placed into the microwave cavity (CEM Discover®). Initial microwave irradiation of 150 W was used, the temperature being ramped from rt to the desired temperature of 150 °C (measured using the built-in IR temperature device). Once this was reached, the reaction mixture was held at this temperature until a total time of 20 min had elapsed. During this time, the power was modulated automatically to hold the reaction mixture at 150 °C. The mixture was stirred continuously during the reaction. After allowing the mixture to cool to room temperature, the reaction vessel was opened and the contents poured into a separating funnel. Water (30 mL) and diethyl ether (30 mL) were added, and the organic material extracted and removed. After further extraction of the aqueous layer, combining the organic washings and drying them over $MgSO_4$, the ethyl acetate was removed in vacuo leaving the crude product. That product was then isolated and characterized by comparison of NMR data with that in the literature.