JOC*Note*

Rapid, Easy Cyanation of Aryl Bromides and Chlorides Using Nickel Salts in Conjunction with Microwave Promotion

Riina K. Arvela and Nicholas E. Leadbeater*

Department of Chemistry, King's College London,
Strand, London WC2R 2LS, United Kingdom

nicholas.leadbeater@kcl.ac.uk

Received July 22, 2003

Abstract: We report here a fast, easy, and efficient method for the preparation of aryl nitriles from aryl bromides and chlorides. The methodology for aryl bromides involves the use of either $Ni(CN)_2$ or NaCN and $NiBr_2$. With aryl chlorides, a mix of NaCN and $NiBr_2$ is used and the reaction proceeds via the in situ formation of the corresponding aryl bromide. The reaction can be performed in air and is complete within 10 min.

Aryl nitriles form integral parts of a range of dyes, herbicides, natural products, and pharmaceuticals. They are also useful intermediates in synthesis. As a result, their preparation has attracted considerable attention. In particular, a number of routes to aryl nitriles from aryl halides have been developed.[1,2] There are a number of methodologies for this. One is the direct reaction between aryl halides and copper cyanide (the Rosenmund von Braun reaction) which has been known for over 80 years. The reaction is usually carried out for prolonged times at high temperatures (150−250 °C) using solvents such as nitrobenzene. More recently, a number of transition-metal-mediated processes have been developed allowing inexpensive cyanide salts to be used. Many of these use nickel or palladium complexes as catalysts.[3−10]

A theme running through many of the methods for preparation of aryl nitriles from halides is the use of high temperatures in order to effect the transformation. In our laboratories, we have an interest in the microwave promotion of organic reactions. Microwave-promoted synthesis is an area of increasing research interest as evidenced by the number of papers and recent reviews appearing in the literature.[11,12] As well as being energy efficient, microwaves can also enhance the rate of reactions and in many cases improve product yields. It is possible to obtain high temperatures very easily and, by using current state-of-the-art scientific laboratory microwave apparatus, this can be done in a very safe manner as compared to conventional heating. Alterman and Hallberg have shown that it is possible to use microwave irradiation to effect the palladium-mediated coupling of aryl halides with zinc cyanide, these reactions being performed in DMF.[13] Reaction times of between 2 and 2.5 min are reported with product yields comparable to longer conventional heating methods being obtained. We have recently reported two methodologies for the synthesis of a range of aryl nitriles from halides using microwave promotion without the need for palladium catalysts and the anaerobic conditions or expensive ligands often required. We performed the Rosenmund von Braun reaction in an ionic liquid, which offers a route into nitriles from aryl bromides.[14,15] However, isolated yields are low because of problems isolating the nitrile. We then looked at using water as a solvent for cyanation reactions.[16] Using either CuCN or CuI/NaCN (to generate CuCN in situ from the cheaper NaCN), it is possible to convert aryl iodides to nitriles rapidly and in good yields. This, however, does not work for aryl bromides. In this paper, we present a methodology for the clean and easy cyanation of aryl bromides and chlorides using microwave promotion, again without the need for a palladium catalyst.

We have recently reported that it is possible to use cheap, readily available nickel halide salts as sources of halide ions for the interconversion of aryl halides.[17] The methodology can be used for conversion of aryl chlorides to bromides, aryl iodides to bromides and chlorides, and aryl bromides to chlorides. We believe that the nickel plays a key role in the reaction. It occurred to us that it may be possible to effect the cyanation of aryl halides using nickel cyanide as a source of the cyanide ion, again with the potential advantage of the use of nickel as a promoter of the reaction and hence no need for an additional catalyst or promoter. Although $Ni(CN)_2$ has been used as a catalyst for a number of transformations,[18] we believe that this is the first use of this as a cyanation reagent. As a starting point for the development of our methodology we chose to study the reaction of 4-bromo-

---

(1) For a review of cyano-dehalogenation, see: Ellis, G. P.; Romney-Alexander, T. M. *Chem. Rev.* **1987**, *87*, 779.

(2) Grushin, V. V.; Alper, H. *Chem. Rev.* **1994**, *94*, 1047.

(3) For nickel-catalyzed cyanations, see: (a) Cassar, L. *J. Organomet. Chem.* **1973**, *54*, C57. (b) Sakakibara, Y.; Ido, Y.; Sasaki, K.; Sakai, M.; Uchino, N. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 2776. (c) Percec, V.; Bae, J.-Y.; Hill, D. H. *J. Org. Chem.* **1995**, *60*, 6895.

(4) Sundermeier, M.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 1661.

(5) Sundermeier, M.; Zapf, A.; Mutyala, S.; Baumann, W.; Sans, J.; Weiss, S.; Beller, M. *Chem. Eur. J.* **2003**, *9*, 1828.

(6) Sundermeier, M.; Zapf, A.; Beller, M.; Sans, J. *Tetrahedron Lett.* **2001**, *42*, 6707.

(7) Jin, F.; Confalone, P. N. *Tetrahedron Lett.* **2000**, *41*, 3271.

(8) Kubota, H.; Rice, K. C. *Tetrahedron Lett.* **1998**, *39*, 2907.

(9) Maligres, P. E.; Waters, M. S.; Fleitz, F.; Askin, D. *Tetrahedron Lett.* **1999**, *40*, 8193.

(10) Sakamoto, T.; Ohsawa, K. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2323.

(11) For recent reviews on the area, see: (a) Larhed, M.; Moberg, C.; Hallberg, A. *Acc. Chem. Res.* **2002**, *35*, 717. (b) Lew, A.; Krutzik, P. O.; Hart, M. E.; Chamberlin, A. R. *J. Comb. Chem.* **2002**, *4*, 95. (c) Lindström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225.

(12) For a review on the concepts see: Gabriel, C.; Gabriel, S.; Grant, E. H.; Halstead, B. S.; Mingos, D. M. P. Chem. *Soc. Rev.* **1998**, *27*, 213.

(13) Alterman, M.; Hallberg, A. *J. Org. Chem.* **2000**, *65*, 7984.

(14) Leadbeater, N. E.; Torenius, H. M.; Tye, H. *Tetrahedron* **2003**, *59*, 2253.

(15) Using conventional heating only aryl iodides have been cyanated (Ren, R. X.; Wu, J. X. *Tetrahedron Lett.* **2002**, 43, 387).

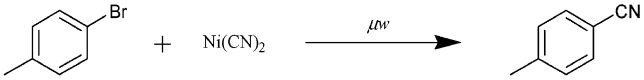
(16) Arvela, R. K.; Leadbeater, N. E.; Torenius, H. M.; Tye, H. *Org. Biomol. Chem.* **2003**, *1*, 1119.

(17) Arvela, R. K.; Leadbeater, N. E. *Synlett* **2003**, 1145.

(18) See, for example: (a) McGuire, M. A.; Sorenson, E.; Klein, D. N.; Baine, N. H. *Synth. Commun.* **1998**, *28*, 1611. (b) Zhou, Z. X.; Alper, H. *Organometallics* **1996**, *15*, 3282. (c) RosoLevi, G.; Amer, I. *J. Mol. Catal. A* **1996**, *106*, 51.

10.1021/jo0350561 CCC: $25.00

TABLE 1. Screening of Conditions for the Direct Cyanation of 4-Bromotoluene with Ni(CN)$_2$[a]



entry	reaction conditions[b]	yield (%)
1	2 equiv of Ni(CN)$_2$, 0.5 mL of DMF, T = 170 °C, hold time 5 min	0[c]
2	**1 equiv of Ni(CN)$_2$**, 0.5 mL of DMF, **0.25 equiv of TBAB**, T = 170 °C, hold time 5 min	27
3	**1 equiv of Ni(CN)$_2$**, 0.5 mL of DMF, **0.25 equiv of TBAB, T = 200 °C**, hold time 5 min	99
4	**1 equiv of Ni(CN)$_2$, 1 mL of NMP, T = 200 °C, hold time 10 min**	99
5	**0.6 equiv of Ni(CN)$_2$, 1.0 mL of NMP, T = 200 °C, hold time 10 min**	99
6	**0.5 equiv of Ni(CN)$_2$, 1.0 mL of NMP, T = 200 °C, hold time 10 min**	95

[a] Reactions were run using 1 mmol of aryl halide, a microwave power of 100 W for reactions using DMF or 120 W for those using NMP, and a pressure threshold of 200 psi. The temperature was ramped to that stated and held there for the allotted time. [b] Conditions changed from entry 1 are highlighted in bold. [c] Only reaches 150 °C.

toluene with Ni(CN)$_2$, our optimization data being shown in Table 1.

Using the same reaction conditions as for the halogen interconversion, namely 1 mmol of aryl halide, 2 mmol of Ni(CN)$_2$, 0.5 mL of DMF, a microwave power of 100 W, a temperature of 170 °C, and a reaction time of 5 min we obtained no 4-methylbenzonitrile (Table 1, entry 1), we believe primarily due to the fact that the reaction mixture only reaches around 150 °C.[19] We thought that this could be remedied by adding a small quantity of tetrabutylammonium bromide (TBAB), which we know allows us to heat mixtures to high temperatures rapidly.[20,21] Using 0.25 equiv of TBAB, we can heat the reaction mixture to the desired 170 °C and obtain a 27% yield of the desired 4-methylbenzonitrile (Table 1, entry 2). We then tried increasing the temperature to 200 °C and found that this resulted in excellent yields of the nitrile product (Table 1, entry 3). However, the use of the TBAB as an additive is not ideal, and its removal at the end of the reaction is not easy. As a result, we screened a range of solvents that would allow us to perform the reaction at higher temperatures and without the TBAB and found that 1-methyl-2-pyrrolidinone (NMP) was the best solvent, reaching 200 °C easily.[22] Longer reaction times (10 min instead of 5 min) were required to take the reaction to completion and a slightly higher microwave power (120 W instead of 100 W) was optimum; these modifications gave us a 99% yield of the nitrile (Table 1, entry 4). We next wanted to decrease the quantity of Ni(CN)$_2$ used in the reaction. We found that it was possible to reduce this to 0.6 equiv, corresponding to 1.2 equiv of cyanide ion (Table 1, entry 5). The quantity of Ni(CN)$_2$ used can be further reduced to 0.5 equiv (ie to 1.0 equiv of cyanide ion) with only a slight decrease in product yield (Table 1, entry 6).

With our optimized reaction conditions in hand, we screened a representative range of aryl bromides in the reaction, choosing examples from across the spectrum of those bearing electron-donating and electron-withdrawing substituents. All the reactions were performed in air and without degassing the solvent prior to use. The results are presented in Table 2 and show that the methodology is applicable to a range of substrates with good yields being obtained (Table 2, entries 1−9). The exceptions to this are 1-bromo-4-nitrobenzene and heteroaromatic aryl bromides where only a moderate to low yield of product is obtained and significant decomposition is observed (Table 2, entries 10−12). This is a problem that has been reported previously using other methods for cyanation of heteroaromatic halides.

We were keen to see if it was possible to adapt the procedure for use of cheaper sodium cyanide rather than nickel cyanide. We find that if NaCN is used in conjunction with NiBr$_2$ it is possible to obtain the nitrile product via an in situ transmetalation (Table 2, entries 13−15). We find that it is necessary to use a 1:1:2 ratio of aryl iodide/NiBr$_2$/NaCN in order to obtain good yields of the nitriles. If catalytic quantities of NiBr$_2$ are used the product yields drop considerably.

We then wanted to see if the methodology could be adapted for conventional heating. Using an oil bath, we screened the reaction of bromotoluene with NaCN + NiBr$_2$ to form 4-methylbenzonitrile. We kept the quantities of reagents exactly the same as in the microwave-assisted reaction and performed the reaction in a sealed 10 mL microwave tube. We dipped the tube into an oil bath preheated to 170 °C and held it there for 10 min before removing it and cooling the reaction mixture.[23] A yield of 4-methylbenzonitrile of 19% was obtained. We decided to run the reactions at 170 °C rather than the 200 °C used in the microwave-promoted reactions simply from a safety viewpoint since oil at elevated temperatures poses a fire risk and also since the vessel is not held within a safety cavity there is a risk from explosion due to high pressures generated during the reaction. Extending the reaction time to 30 min leads to an increased yield of 33%, but even if this is further extended to 4 h, the product yield does not improve (Table 2, entries 16 and 17). To make a direct comparison between these results and those obtained using microwave heating, we performed the reaction in the microwave at 170 °C rather than 200 °C and obtained a 44% yield of nitrile within 10 min (Table 2, entry 18). Clearly, the microwave methodology has the advantages of being faster and easier and leads to significantly higher yields of product. We should state that we believe that the microwave simply provides an efficient heating method rather than there being any specific microwave effect.

---

(19) **CAUTION:** All necessary precautions should be taken when performing such experiments. Vessels designed to withhold elevated pressures must be used. The microwave apparatus used here incorporates a protective metal cage around the microwave vessel in case of explosion. After completion of an experiment, the vessel must be allowed to cool to room temperature before removal from the microwave cavity and opening to the atmosphere.

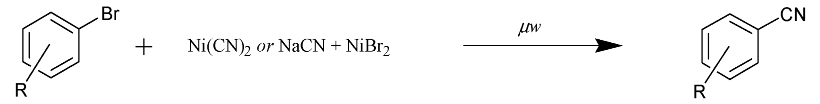
(20) Deshayes, S.; Liagre, M.; Loupy, A.; Luche, J. L.; Petit, A. *Tetrahedron* **1999**, *55*, 10851.

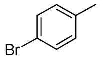
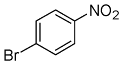
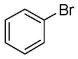
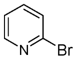
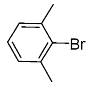
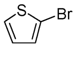
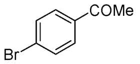
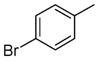
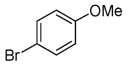
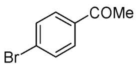
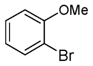
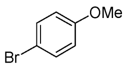
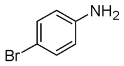
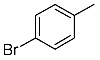
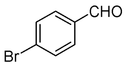
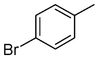
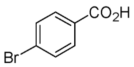
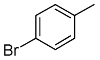
(21) Leadbeater, N. E.; Marco, M. *Org. Lett.* **2002**, *4*, 2973.

(22) Yields for the transformation with other solvents: water, 0%; DME, 0%; no solvent, 0%.

(23) **CAUTION**: A blast shield should be in place and vessels designed to withhold elevated pressures must be used. After completion of an experiment, the vessel must be allowed to cool before opening to the atmosphere.

TABLE 2. Microwave-Promoted Cyanation of Aryl Bromides[a]



Entry	Aryl halide	Yield (%)	Entry	Aryl halide	Yield (%)
1		99	10		48[b]
2		99	11		33[b]
3		99	12		60[b]
4		99	13		93[c]
5		86	14		98[c]
6		91	15		53[c]
7		95	16		19[c,d]
8		96	17		33[c,e]
9		98	18		44[c,f]

[a] Reactions were run using 1 mmol of aryl halide, 0.6 mmol of Ni(CN)$_2$, and 1 mL of NMP. Reactions were run using a microwave power of 120 W and a pressure threshold of 200 psi. The temperature was ramped to 200 °C and held there for 10 min. [b] Significant decomposition observed. [c] Using 2 mmol of NaCN and 1 mmol of NiBr$_2$. [d] After 10 min in an oil bath preheated to 170 °C. [e] After 30 min in an oil bath preheated to 170 °C. [f] Performed in the microwave but using a temperature threshold of 170 °C.

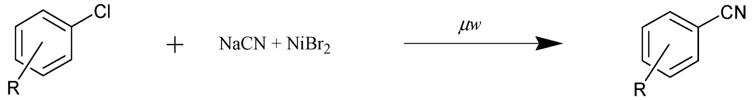
Having shown that the methodology works well for aryl bromides, we were keen to extend it for use with aryl chlorides. The cyanation of aryl chlorides has been the focus of a number of recent reports.[4−7] The most general procedures involve the use of phosphine-ligated palladium catalysts, elevated temperatures for prolonged times, and the use additives such as tetramethylethylenediamine (TMEDA) or some other amine. Even then, yields can be variable depending on the susbtituents on the aryl chloride. An obvious extension to our methodology was to see whether it could be used with aryl chlorides. Using 1-chloro-4-methoxybenzene, we attempted to prepare the corresponding nitrile using our conditions developed for use with the aryl bromides. However, using nickel cyanide only a 9% yield of product is observed after 10 min microwave heating at 200 °C. We then decided to attempt an in-situ halogen exchange/cyanation reaction. The aim was to use our halogen exchange methodology to convert the aryl chloride to the corresponding bromide and then effect a sequential cyanation reaction. We thought that simply using NiBr$_2$ and NaCN both these steps would be feasible, and indeed, this is the case. Using a stoichiometric ratio of 4-chloroanisole/NiBr$_2$/NaCN of 1:1:2, a 61% yield of the desired nitrile was prepared in 10 min microwave heating at 200 °C. With these conditions in hand, we screened a representative range of aryl chlorides, the results being shown in Table 3. Good yields of the desired nitriles are formed in every case except for chlorobenzaldehyde. Interestingly, Buchwald and co-workers have very recently reported the use of their copper-catalyzed aryl Finkelstein reaction in conjunction with a copper-catalyzed cyanation reaction to take aryl bromides to aryl nitriles via the intermediate formation of the aryl iodide.[24]

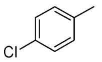
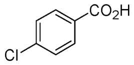
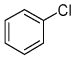
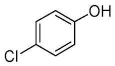
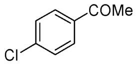
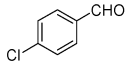
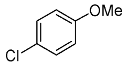
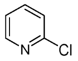
In summary, we report here a fast, easy, and efficient method for the preparation of aryl nitriles from aryl bromides and chlorides. The methodology for aryl bromides involves either the use of Ni(CN)$_2$ or NiCN and NiBr$_2$, the latter forming Ni(CN)$_2$ in situ. With aryl chlorides, a mix of NiCN and NiBr$_2$ is used and the reaction proceeds via the in situ formation of the corresponding aryl bromide. Although the reaction does involve the use of significant quantities of nickel salts

---

(24) Zanon, J.; Klapars, A.; Buchwald, S. J. *J. Am. Chem. Soc.* **2003**, *125*, 2890.

TABLE 3. Microwave-Promoted Cyanation of Aryl Chlorides[a]



Entry	Aryl halide	Yield (%)	Entry	Aryl halide	Yield (%)
1		85	5		99
2		80	6		99[b]
3		78	7		0[c]
4		61	8		24

[a] Reactions were run using 1 mmol of aryl halide, 2 mmol of NaCN, 1 mmol of $NiBr_2$, and 1 mL of NMP. Reactions were run using a microwave power of 120 W and a pressure threshold of 200 psi. The temperature was ramped to 200 °C and held there for 10 min. [b] After 20 min of heating (reaction had not reached completion within 10 min). [c] Significant decomposition observed.

(i.e., not catalytic), there are some distinct advantages of this over other palladium-mediated methodologies. The reaction can be performed in air, does not require expensive palladium salts or ligands, and does not suffer from the problems of catalyst deactivation and reliability observed in many palladium-mediated examples. Purification of the product at the end of the reaction is easy since all the cyanating reagents are water soluble and the reactions are very clean, giving either product and unreacted starting material (together with some aryl bromide in the case of the aryl chlorides).

Acknowledgment. The Royal Society is thanked for a University Research Fellowship (N.E.L.). Funding from King's College London is acknowledged.

Supporting Information Available: Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0350561