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Rapid cyanation of aryl iodides in water using microwave promotion

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Received 26th November 2002, Accepted 30th January 2003
First published as an Advance Article on the web 4th March 2003

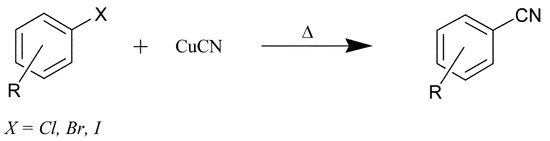
We show that using water in conjunction with microwave heating it is possible to prepare aryl nitriles from the corresponding aryl iodides rapidly and in high yield without the need for a palladium catalyst.

Introduction

Microwave-mediated synthesis is a fast growing area of research interest as evidenced by the increasing numbers of papers and patents published in the area.[1,2] This is because it is often possible to reduce reaction times from many hours to a few minutes and also it opens up avenues for new chemistry.[3] With its high relative permittivity water is a very useful solvent for microwave-mediated synthesis. Water, being cheap, readily available, non-toxic and non-flammable has clear advantages as a solvent for use in chemistry.[4,5] There are however problems such as solubility of substrates but these problems have to some extent been overcome by the use of phase-transfer catalysts or using water–organic solvent mixtures. The dipole moments of these solvents means that they can be heated very rapidly using microwave irradiation.

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,[6] many using palladium complexes as catalysts and a range of metal cyanides as the source of cyanide.[7–9] Alterman and Hallberg have shown that it is possible to use microwave irradiation to effect that palladium-mediated coupling of aryl halides with zinc cyanide, these reactions being performed in DMF. Reaction times of between 2 and 2.5 min are reported with product yields comparable to longer conventional heating methods being obtained.[10]

One of the most direct ways to prepare aryl nitriles is the Rosenmund–von Braun reaction (direct reaction between aryl halides and copper cyanide to give aryl nitriles) which has been known for over 80 years.[6]



The reaction is usually carried out at high temperatures (150–250 °C) using solvents such as nitrobenzene; however recently there has been a report of the use of ionic liquids as solvents.[11] When using 1,3-dialkylimidazolium halide-based ionic liquids it is possible to obtain nitriles from aryl iodides when performing the reaction using 2 or 3 equivalents of CuCN and heating at around 90–130 °C for 24 h. However isolated yields are low because of problems isolating the nitrile. We have recently shown that the reaction can be accelerated by the use of microwave heating.[12] Although this method offers a more rapid route to aryl nitriles and also opens up the scope of the reaction to aryl bromides, there is still the problem of product isolation. We were therefore keen to investigate other solvents for the the direct cyanation of aryl halides with CuCN using microwave promotion. In this paper we present our results when using water as a solvent. We show that it is possible to prepare aryl nitriles from aryl halides rapidly and in high yield using CuCN. We also show that it is possible to perform the reaction using inexpensive NaCN as the cyanide source in the presence of CuI (this forming CuCN *in situ*).

Results and discussion

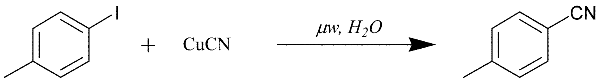
As a starting point for the development of our methodology we chose to study the reaction of 4-iodotoluene with copper(I) cyanide in water (Table 1). Reactions were run in sealed 10 mL capacity glass tubes using a focused microwave system. **CAUTION!**[13]

We find that using a molar ratio of iodide : CuCN of 1 : 2, one equivalent of tetrabutylammonium bromide (TBAB) as a phase transfer agent and 0.5 ml water it was possible to obtain an isolated yield of 80% of 4-methylbenzonitrile after 3 min microwave irradiation. Using a microwave power of 100 W we ramped the temperature from rt to 170 °C, this taking approximately 30 s, and then held at this temperature for 3 min. The addition of a phase-transfer catalyst to the reaction mixture is essential to the success of the cyanation. Without this, the reaction does not occur. Reduction of the quantity of TBAB from 1 equiv to 0.5 equiv relative to the 4-iodotoluene has a significant detrimental effect on the product yield. We find that with 4-iodotoluene the optimum reaction time is 3 min. If longer times are used, product decomposition is observed. The optimum reaction temperature is 170 °C. It is necessary to use 2 equiv of CuCN in order to obtain good yields of product because the addition of cyanide to aryl halides in the reaction is known to be reversible so a high concentration of cyanide is key to drive the reaction towards completion. With 1 equiv. a product yield of only 39% is obtained.

Since the start of the development of microwave-promoted synthesis, debate into the nature of the microwave heating of reactions has been sparked.[14] The acceleration of reactions could simply be an effect of the thermal energy generated by the microwaves interacting with the substrates or could be an effect specific to microwave heating. In most cases the observed differences between microwave and conventional heating can be attributed to simple thermal effects. We wanted to determine whether our reaction could be equally well performed using conventional heating. Keeping the quantities of reagents, TBAB and water exactly the same as in the microwave-promoted reaction we performed the reaction in an oil bath. We dipped a sealed 10 mL microwave tube containing the reactants into oil pre-heated to 170 °C and held it there for 3 min before removing it and cooling. No product was obtained. We attrib-

DOI: 10.1039/b211612j

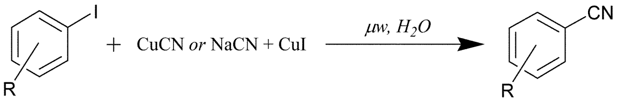
Table 1 Screening of conditions for the cyanation of 4-iodotoluene with CuCN[a]

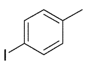
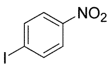
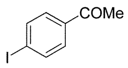
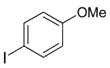
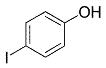
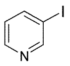


Entry	Reaction conditions[b]	Yield (%)[c]
1	2 equiv. CuCN, T = 170 °C, hold time 3 min (no solvent)	0
2	2 equiv. CuCN, **0.5 mL water**, T = 125 °C, hold time 3 min[d]	0
3	2 equiv. CuCN, **1.0 equiv. TBAB**, **0.5 mL water**, T = 170 °C, hold time 3 min	80
4	2 equiv. CuCN, **0.5 equiv. TBAB**, **0.5 mL water**, T = 170 °C, hold time 3 min	68
5	2 equiv. CuCN, **1.0 equiv. TBAB**, **0.5 mL water**, T = 170 °C, **hold time 5 min**	61
6	**1 equiv. CuCN**, **1.0 equiv. TBAB**, **0.5 mL water**, T = 170 °C, hold time 3 min	39
7	2 equiv. CuCN, **1.0 equiv. TBAB**, **0.5 mL water**, T = 170 °C, **oil bath**, hold time 3 min	0

[a] Reactions were run using 1 mmol aryl halide and 0.5 mL water. Reactions were run using a power of 100 W 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] Isolated yields. [d] Reaction mixture only reached 125 °C.

Table 2 Microwave-promoted cyanation of aryl halides in water[a]



Entry	Aryl halide	Yield (%)[bc] using CuCN	Yield (%)[cd] using NaCN + CuI
1		80	72
2		81	63
3		99	99
4		81	64
5		99[e]	90[e]
6		47	34

[a] Reactions were run using 1 mmol aryl halide, 1 mmol TBAB. Reactions were run using a power of 100 W, a temperature threshold of 170 °C and a pressure threshold of 200 psi. The temperature was ramped to 170 °C and held there for 3 min unless stated otherwise. [b] Using 2 mmol CuCN. [c] Isolated yield. [d] Using 2 mmol NaCN and 1 mmol CuI. [e] Hold time of 5 min.

ute this difference to the fact that, with microwave promotion, efficient heating of the sample is possible whereas transfer of heat through reaction vessel walls is necessary with conventionally heated systems, *e.g.* oil baths. This internal heat transfer results in minimised wall effects (no thermal boundary layer) and reaction mixtures can be heated to high temperatures rapidly.

With our optimized conditions in hand, we screened a range of aryl iodides bearing electron withdrawing and donating groups in the microwave-promoted reaction. The results are shown in Table 2. With the exception of 3-iodopyridine, excellent yields of product can be obtained showing the applicability of the methodology. The isolated yields of product obtained from these reactions is significantly higher than that when using ionic liquids as solvents, primarily because the work-up procedure is much easier when using water as the reaction medium. Unfortunately unlike when using ionic liquids as solvents, we find that it is not possible to expand the substrate scope to aryl bromides when using water, no product being obtained even when using activated bromides.

We were next keen to develop the procedure using the cheaper sodium cyanide rather than copper cyanide. We found that the direct reaction of NaCN and aryl iodides in water with TBAB does not yield any product. This is not unexpected since it is known that alkali metal cyanides do not react directly with aryl halides, even activated ones. However if NaCN is used in conjunction with copper(I) iodide it is possible to obtain the nitrile products *via* an *in situ* transmetallation (Table 2). We find that it is necessary to use a 1 : 1 : 2 ratio of aryl iodide : CuI : NaCN in order to obtain good yields of the nitriles. If catalytic quantities of copper iodide are used the product yields drop considerably.

Conclusions

We have shown here that is is possible to prepare aryl nitriles from aryl iodides using either CuCN or NaCN as the cyanide sources, the latter requiring CuI as an additive. The reactions are performed in water and tetrabutylammonium bromide is used as a phase transfer catalyst. The reactions are promoted by microwave irradiation with reaction times of 3–5 min.

Experimental

General experimental

Microwave experiments were conducted using a focused microwave system. The machine consists of a continuous focused microwave power delivery system with operator selectable power output from 0–300 W. Reactions were performed in glass vessels (capacity 10 mL) sealed with a septum. The pressure is controlled by a load cell connected to the vessel *via* a 14-gauge needle which penetrates just below the septum surface. The temperature of the contents of the vessel was monitored using a calibrated infrared temperature control mounted under the reaction vessel. All experiments were performed using a stirring option whereby the contents of the vessel are stirred by means of a rotating magnetic plate located below the floor of the microwave cavity and a Teflon-coated magnetic stir bar in the vessel. In the reactions presented here, a target temperature was set together with a maximum microwave power. This maximum power is then used to heat the reaction mixture to the target temperature and, once there, the microwave power is varied as to hold the mixture at this temperature. This is defined as the 'hold time'. A maximum pressure of 200 psi is set, this being a safety precaution since the tubes hold, at a maximum, a pressure of 250 psi. At the end of a reaction, the tube and contents are cooled rapidly using a stream of compressed air.

All chemicals used in the reactions were reagent grade and used as purchased. NMR spectra were recorded at 250 MHz and 293 K, run in $CDCl_3$ and referenced to $SiMe_4$. Chemical shifts are expressed in δ (ppm) and coupling constants (J) in hertz.

General procedure for the synthesis of aryl nitriles from aryl iodides using copper(I) cyanide

Aryl halide (1 mmol) was placed together with TBAB (1 mmol, 0.322 g) and copper(I) cyanide (2 mmol, 0.179 g) into a 10 mL glass tube equipped with a Teflon coated stirrer bar. Water (0.5 mL) was added and the tube sealed with a septum. Reactions were run using a maximum microwave power of 100 W, a temperature threshold of 170 °C and a pressure threshold of 200 psi. Once the temperature threshold was reached, the reaction mixture was held there for the requisite time. After the reaction mixture was cooled, the tube was opened and more water (2–3 mL) was added. The water layer was removed and washed with diethyl ether, the ether extract being kept. The remaining mixture in the microwave tube was dissolved in acetonitrile, the solution filtered and the filtrate combined with the ether extract. The combined organics were dried using $MgSO_4$. After filtration the solvents were removed *in vacuo* leaving the product. Reaction products were characterised by comparison of ^1H- and ^{13}C-NMR data with those in the literature.

4-Methylbenzonitrile

^1H NMR: δ 7.44 (d, 2H, J 8.1), 7.18 (d, 2H, J 8.1), 2.33 (s, 3H); ^{13}C NMR: δ 144, 131, 130, 119, 109, 21.

4-Nitrobenzonitrile

^1H NMR: δ 8.20 (d, 2H, J 8.9), 7.82 (d, 2H, J 8.9); ^{13}C NMR: δ 150, 133, 124, 118, 117.

4-Cyanoacetophenone

^1H NMR: δ 7.96 (d, 2H, J 8.2), 7.68 (d, 2H, J 8.2), 2.53 (s, 3H); ^{13}C NMR: δ 197, 140, 133, 129, 118, 27.

4-Methoxybenzonitrile

^1H NMR: δ 7.48 (d, 2H, J 7.9), 6.87 (d, 2H, J 7.9), 3.76 (s, 3H); ^{13}C NMR: δ 163, 134, 120, 115, 104, 56.

4-Cyanophenol

^1H NMR: δ 7.40 (d, 2H, J 8.7), 7.00 (d, 2H, J 8.7); ^{13}C NMR: δ 162, 134, 120, 116, 102.

3-Cyanopyridine

^1H NMR: δ 9.03 (m, 1H), 9.00 (m, 1H), 8.01 (d, 1H), 7.54 (t, 1H); ^{13}C NMR: δ 154, 153, 140, 125, 117, 111.

General procedure for the synthesis of aryl nitriles from aryl iodides using sodium cyanide

Aryl halide (1 mmol) was placed together with TBAB (1 mmol, 0.322 g), sodium cyanide (2 mmol, 0.098 g) and copper(I) iodide (1 mmol, 0.190 g) into a 10 mL glass tube equipped with a Teflon coated stirrer bar. Water (0.5 mL) was added and the tube sealed with a septum. Reactions were run using a maximum microwave power of 100 W, a temperature threshold of 170 °C and a pressure threshold of 200 psi. Once the temperature threshold was reached, the reaction mixture was held there for the requisite time. The products were isolated and characterised in an identical manner to the reactions run using copper cyanide.

Acknowledgements

The Royal Society is thanked for a University Research Fellowship (NEL) and King's College London for a PhD studentship (HMT). EvotecOAI are thanked for a CASE award (HMT). Financial support from King's College London and EvotecOAI is acknowledged.

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13 **CAUTION**: The water is heated well above its boiling point so 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 a temperature below the boiling point before removal from the microwave cavity and opening to the atmosphere.

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