Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 62 (2006) 4705–4708

Optimisation and scale-up of microwave assisted cyanation

Michael R. Pitts,* Peter McCormack and John Whittall

StylaCats Ltd, The Heath Business & Technology Park, Runcorn, Cheshire, WA7 4QX, UK

Received 2 September 2005; revised 20 November 2005; accepted 20 November 2005
Available online 24 March 2006

Abstract—A microwave enhanced palladium catalysed cyanation procedure was optimised for the final step of a production method for citalopram **2**. The method was demonstrated on multigram batch scale for the synthesis of escitalopram (*S*)-**2** and then in a stop-flow continuous process for citalopram.

1. Introduction

Microwave-assisted organic synthesis is a rapidly expanding area of research, aided, in recent years, because of the availability of commercial systems that offer safe and reproducible heating. The last decade has seen a growing number of papers and reviews appearing in the literature on the subject.[1] Microwave heating seems to be particularly compatible with transition metal catalysed processes normally associated with long reaction times (>4 h), bringing these times down to minutes and reducing the levels of by-products from (thermal) side-reactions.[2]

The substituted benzonitrile motif is present in a significant proportion of pharmaceuticals, agrochemicals and natural products.[3] The nitrile group also offers a useful functionality for subsequent manipulations to important functional groups such as acids, ketones, oximes, amines and also various heterocycles. The nitrile group can be used as a convenient starting point for short-lived radiocarbon-labelled functional groups.[4]

Although simple benzonitriles can be easily prepared by ammoxidation,[5] the most common, and direct method for the introduction of the cyano group is via cyanation of the parent aryl halide. Industrially this tends to be achieved by the Rosemund–von Braun reaction, requiring stoichiometric amounts of copper(I) cyanide.[6] The alternative Sandmeyer reaction also uses copper(I) cyanide. The selectivity and waste considerations involved in these reactions led to the use of transition metal (usually palladium) catalysed cyanations being examined by various industrial groups.[7] The relatively high catalyst loading requirements have prompted various innovative methods for stabilising the catalyst. Cyanide ions poison homogeneous palladium catalysts and thus the cyanide concentration in solution needs to be kept low. The levels of cyanide can vary significantly with even small amounts of other additives.[8] Most solutions to this problem involve slow addition of soluble cyanide sources such as TMSCN[9] or acetone cyanohydrin,[10] or the use of an insoluble cyanide source with an additive to transmetallate the cyanide. Examples of the latter utilised potassium cyanide in solvents in which it is virtually insoluble are: in toluene with TMEDA,[11] in THF with copper(I) iodide,[12] or in acetonitrile with catalytic tributyltin chloride, generate low levels of Bu_3SnCN.[13] Recently potassium hexaferricyanide has been employed as a non-toxic source of cyanide.[14] The slow release of cyanide from the complex maintains low levels in solution.[†] This procedure was further refined to obviate the needs for palladium by employing a copper catalyst.[15]

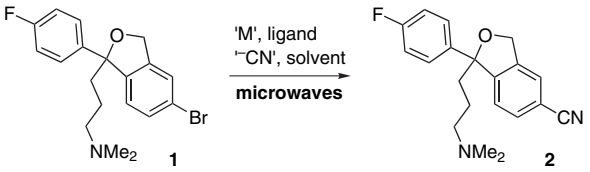
Our interest in cyanation was for the improvement of the last step in the synthesis of citalopram **2** from the parent bromide **1** (Scheme 1). The cyanation via Rosemund–von Braun conditions took 24 h, and was low yielding after exhaustive, time consuming wash cycles used to purify the material. It was our belief that a transition metal catalysed method could be employed, and enhanced with microwave-assisted heating, to provide a highly selective transformation with a good impurity profile. The work by Hallberg and Alterman[16] had shown a precedent for using microwave heating to increase the rate of cyanation of various bromides with the previously utilised palladium–tetrakistriphenylphosphine.[17] However, Maligres and co-workers at Merck Process Research had screened a range of phosphine ligands and found 1,1′-diphenylphosphinoferrocene (dppf) to be superior and

Keywords: Microwave assisted chemistry; Cyanation; Citalopram; Palladium catalysis.
* Corresponding author at present address: Reaxa Ltd, Hexagon Tower, Blackley, Manchester, M9 8ZS, UK; e-mail: michael.pitts@reaxa.co.uk

[†] During the course of this work we had tested $K_4[Fe(CN)_6]$ (see Table 2, entry 4) as a cyanide source—it seems the slow breakdown of the complex is unsuitable for the rapid microwave timescale, giving only trace amounts of product.

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.11.095

more consistent and had demonstrated the cyanation on kilo-scale.[18] A room temperature palladium catalysed cyanation has recently been reported employing *tert*-butylphosphine as the ligand.[19]



Scheme 1.

All these methods utilised zinc cyanide in DMF. Zinc cyanide is very sparingly soluble in DMF, a factor that keeps the concentration of cyanide ions at the required low level.[20] The Merck process provided the cleanest reaction with DMF and 2–5% water. Other additives used to improve the zinc cyanide/DMF/palladium system include zinc,[21] zinc with bromine[22] and zinc acetate.[23] These observations formed the starting point for our investigations.

2. Results and discussion

Initially we tested $Pd_2(dba)_3$ and dppf (1:1) at 5 mol % in DMF in the cyanation of 4-bromoacetophenone. The reaction (1.0 mmol starting material, 2 mL solvent) was heated with microwave irradiation to 120 °C and after 5 min it showed complete conversion. It was determined to keep the reaction time at a maximum of 5 min to assist eventual transfer to a continuous flow system for scale-up. With no catalyst present starting material was recovered quantitatively. Reduction of the level of palladium to 1 mol % was not detrimental to the yield. Further reduction to 0.1 mol % gave incomplete conversion at 120 °C, but was quantitative at 180 °C. Repeating the reactions with a range of nickel catalysts under similar conditions resulted in little or no conversion.[24]

Surprisingly, subjecting the bromo-precursor **1** to cyanation at 180 °C with 0.1 or 1 mol % of palladium–dppf gave no reaction. A range of additives were then investigated with the results shown in Table 1.

Although water as an additive allowed good conversion, detectable quantities of the amide, from hydrolysis of the nitrile, and debrominated material were formed. Since these impurities needed to be kept below 0.2%, exclusion of protic solvents became important. Levels of the amide, bromo-reduced material and unreacted **1** were measured by HPLC. Full conversion was critical in achieving low impurity levels.

Table 1

Entry	Additives	Conversion (%)
1	None	0
2	1% H_2O	97
3	5% Zn	90
4	5% CuI	15
5	20% TMEDA	100

All reactions with 1 mol % Pd–dppf, 1 equiv $Zn(CN)_2$, DMF, MW at 180 °C for 300 s.

Table 2

Entry	Cyanide source	Conversion (%)
1	Acetone cyanohydrin	0
2	KCN	1
3	CuCN	60
4	$KFe(CN)_6$	1
5	TMSCN	0

All reactions with 1 mol % Pd–dppf, 1 equiv cyanide source, 0.2 equiv TMEDA, DMF, MW at 180 °C for 300 s.

TMEDA as an additive provided a quantitative yield with high purity. Changes in the solvent were briefly examined; acetonitrile and THF both gave lower yields than in DMF. Addition of TMEDA also allowed the temperature to be dropped to 140 °C with no loss in conversion or purity of the crude material. At this lower temperature, discolouring of the reaction mixture was eliminated.

Further optimisation showed zinc cyanide could also be used at 0.6 equiv, consistent with previous work suggesting both cyano groups are transferred.[18] Alternative cyanide sources were tried, all giving lower yields than zinc cyanide, as shown in Table 2. Interestingly the addition of only 10 mol % of acetone cyanohydrin to the zinc cyanide reaction increased cyanide ions in solution sufficiently to poison of the catalyst and reduce the yield to 10%.

Altering the ligand had a significant effect on the yield. Triphenylphosphine or tri-2-furylphosphine in place of dppf gave no reaction. Bidentate ligands dppe and dpppe gave trace amounts of product whereas DPE-phos gave complete reaction. This prompted the test of Xantphos, which in contrast to dppf, allowed the use of 0.5 mol % Pd (1 mol % ligand) at 140 °C. These conditions are the lowest reported catalyst levels for microwave-enhanced cyanation to date (Fig. 1).[25]

Lastly, examination of reaction time revealed the cyanation to be complete after 120 s at the target temperature. The reaction takes around 100 s to achieve the target temperature (max. power 300 W) and around 1 min to cool to below 40 °C giving an overall time for the process of under 5 min.

Scale-up was achieved in the CEM Voyager SF microwave reactor.[26] The Voyager is based on the same microwave cavity as the Discover, but uses a larger (80 mL) glass vessel, with a sealed head that has inlets for a temperature probe and a tube for addition/removal of reaction mixtures. Valves seal the vessel during operation through a loop containing a pressure sensor. The addition/removal of solutions/slurries requires calibration, but can then be automated to give a stop-flow continuous process capability.

The optimised conditions were exactly reproduced at 50 mL (14 g of **1**) batch scale. The same program could be used, only by changing the increase in target temperature (160 °C), which was required for complete conversion (isolated yield 99%, >98.5% purity). The target temperature difference is presumably due to the reported discrepancy in temperature measurement between the Discover and Voyager systems (infra-red vs fibre optic).[27] With the larger vessel, but same maximum power input (300 W), the overall

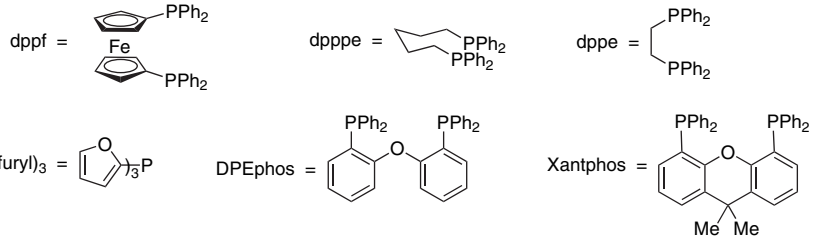


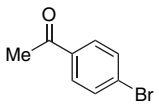
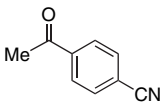
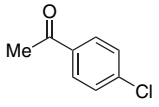
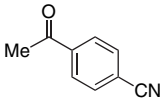
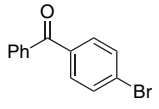
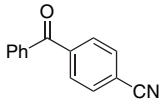
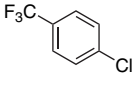
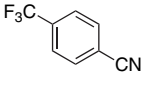
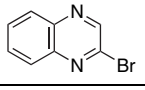
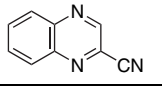
Figure 1.

heating step takes lightly longer. Target temperature is still reached in less than 2 min, but cooling takes around 3 min rather than one to reach a safe temperature. This equates to around a 7 min heating step. When the addition/removal automation time is added for stop-flow use, this gives a cycle time of around 10 min per batch, with approximately 12 g of starting material processed per batch.

Two batches of (*S*)-**1** were subjected to the procedure yielding over 20 g of escitalopram with no loss of enantiomeric purity. Racemic **1** (56 g) was run under a continuous (stop-flow) process in four cycles yielding 47 g of citalopram **2** (>98% purity) in a total run time of 40 min. A sample from each cycle was analysed by HPLC, showing a very high degree of consistency between batches. A longer run provided 150 g in 11 cycles (under 2 h). Extrapolation of this shows multikilogram quantities could be produced in a useful timeframe (days).

The system developed for citalopram was tested on a series of simple aryl halide substrates. Xantphos as ligand was demonstrated to give more active catalysts for aryl chlorides than dppf. Cyanation conditions were rapidly optimised in the microwave for a small selection of aryl halides; all giving very high yields in clean reactions (see Table 3).

Table 3

Entry	Starting material	Product	Catalyst (mol %)	Conversion (%)
1			0.1	100
2			0.5	100
3			0.2	100
4			1.0	93
5			0.5	100

All reactions with Pd–Xantphos, 0.6 equiv $Zn(CN)_2$, 0.2 equiv TMEDA, DMF, MW at 180 °C for 300 s.

3. Conclusions

We have developed a robust cyanation procedure for **1**, using the lowest catalyst loadings yet reported for microwave-enhanced cyanation. The process cuts the reaction time from 24 h to 2 min with an excellent impurity profile. These conditions have been demonstrated to be generally applicable to cyanation for a range of substrates. The cyanation was successfully run in a continuous stop-flow reactor.

4. Experimental

Microwave reactions were carried out in a commercially available monomode system (CEM Discover or Voyager). The reactor has a variable power output from 0 to 300 W. Small scale (<2 g) test reactions were carried out in the Discover with the accompanying 10 mL (5 mL working volume) tubes with septum tops. The Voyager batch reactions were performed in a thick-walled glass vessel (capacity 80 mL, maximum working volume 50 mL). The vessel is isolated from the computer controlled system for charging the reaction contents by a valve. The pressure is controlled and monitored by a load cell connected through this valve with a 300 psi release valve for safety. The temperature of the reaction mixture was monitored using a fibre-optic probe inserted into the reaction vessel in a sapphire immersion well. 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. Temperature, pressure and power profiles are recorded by the accompanying software.

4.1. Preparation of escitalopram (*S*)-2, batch method

To a solution of bromo compound (*S*)-**1** (>98% ee, 13.88 g, 36.7 mmol) in DMF (35 mL) in an 80 mL CEM Voyager microwave tube *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (1.1 mL, 7.3 mmol, 0.2 equiv), zinc cyanide (2.58 g, 22.0 mmol, 0.6 equiv), tris(dibenzylideneacetaone)dipalladium(0) (84 mg, 92 μmol, 0.5 mol %) and Xantphos (213 mg, 0.37 mmol, 1.0 mol %) were added successively. The reaction tube was sealed and heated to 160 °C under microwave irradiation with a 200 s hold time, and 300 W maximum power input. After cooling under a stream of compressed air, the reaction mixture was washed out (with dichloromethane) through a pad a Celite with a thin layer of silica in the middle.

The combined filtrates were concentrated, and then dried extensively under high vacuum to give escitalopram as a yellow

gum (~22 g). Structure confirmed by GC–MS and ^{1}H NMR; chiral purity measured by cHPLC (OD-H column, 95:5 hexane with 0.4% diethylamine to isopropanol, 0.5 mL min^{-1}, 220 nm detection) shows >98% ee.

4.2. Preparation of citalopram 2, continuous stop-flow method

The cyanation was also carried out in a continuous process for racemic citalopram.

The CEM Voyager stop-flow reactor was fed from two stirred vessels: (1) tris(dibenzylideneacetaone)dipalladium(0) (400 mg, 0.87 mmol, 0.6 mol %) and Xantphos (920 mg, 1.59 mmol, 1.1 mol %) slurried in DMF (40 mL), and (2) the bromo starting material **1** (56.0 g, 148 mmol), zinc cyanide (ground to 600 micron powder, 10.8 g, 92 mmol, 0.62 equiv) and TMEDA (4.8 mL, 32 mmol, 0.22 equiv) slurried in DMF to a total volume of 160 mL. A program cycle was calibrated to add 10 mL from vessel 1 and 40 mL from vessel 2, then heat with microwave irradiation to 160 °C (300 W max. power) for a 200 s hold time, cool to 50 °C then remove to a clean vessel. The program was repeated continuously over four cycles with a total run time of 40 min. The slurry generated was filtered through Celite and analysed by GC–MS to show >98% conversion. Chemical purity was further determined by HPLC as >98% (Zorbax SB C_{18} column, 25 cm×4.6 mm, MeCN/[NaH_2PO_4/$OctSO_3H$ aqueous buffer pH 2.8] 32:68, 1.5 mL min^{-1}, 210 nm detection).

Acknowledgements

We thank Ajit Bhobe and Nandu Chodankar of Sekhsaria for important suggestions for parts of this work and supply of **1**.

References and notes

1. (a) *Microwave Assisted Organic Synthesis*; Lidström, P., Tierney, J. P., Eds.; Blackwell: Oxford, 2004; (b) *Microwaves in Organic Synthesis*; Loupy, A., Ed.; Wiley-VCH: Weinheim, 2002; (c) *Microwave Synthesis: Chemistry at the Speed of Light*; Hayes, B. L., Ed.; CEM: Matthews, NC, 2002; (d) Kappe, C. O. *Angew Chem., Int. Ed.* **2004**, *43*, 6250–6284; (e) Lidström, P.; Tierney, J. P.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225–9283; (f) Caddick, S. *Tetrahedron* **1995**, *51*, 10403–10432.
2. (a) Leadbeater, N. E. *Chem. Commun.* **2005**, 2881–2902; (b) Stadler, A.; Yousefi, B. H.; Dallinger, D.; Walla, P.; Van der-Eycken, E.; Kaval, N.; Kappe, C. O. *Org. Process Res. Dev.* **2003**, *7*, 707–716; (c) Appukkuttan, P.; Van der Eycken, E.; Dehaen, W. *Synlett* **2003**, 1204–1206; (d) Erdélyi, M.; Gogoll, A. *J. Org. Chem.* **2001**, *66*, 4165–4169; (e) Walla, P.; Kappe, C. O. *Chem. Commun.* **2004**, 564–565.
3. Sundermeier, M.; Zapf, A.; Beller, M. *Eur. J. Inorg. Chem.* **2003**, 3513–3526; Ager, D. J.; Erickson, R. A.; Froen, D. E.; Prakash, I.; Zhi, B. *Org. Process Res. Dev.* **2004**, *8*, 62–71; U.S. Patent 6,699,993.
4. Ponchant, M.; Hinnen, F.; Demphel, S.; Crouzel, C. *Appl. Radiat. Isot.* **1997**, *48*, 755–762.
5. Lücke, B.; Narayana, K. V.; Martin, A.; Jähnisch, K. *Adv. Synth. Catal.* **2004**, *346*, 1407–1424.
6. Ellis, G. P.; Romney-Alexander, T. M. *Chem. Rev.* **1987**, *87*, 779–794.
7. Excellent review: Sundermeier, M.; Zapf, A.; Mutyala, S.; Baumann, W.; Sans, J.; Weiss, S.; Beller, M. *Chem.—Eur. J.* **2003**, *9*, 1828–1836.
8. Marcantonio, K. M.; Frey, L. F.; Liu, Y.; Chen, Y.; Strine, J.; Phenix, B.; Wallace, D. J.; Chen, C. *Org. Lett.* **2004**, *6*, 3723–3725.
9. Sundermeier, M.; Mutyala, S.; Zapf, A.; Spannenberg, A.; Beller, M. *J. Organomet. Chem.* **2003**, *684*, 50–55.
10. Sundermeier, M.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 1661–1664.
11. Sundermeier, M.; Zapf, A.; Beller, M.; Sans, J. *Tetrahedron Lett.* **2001**, *42*, 6707–6710.
12. Anderson, B. A.; Bell, E. C.; Ginah, F. O.; Harn, N. K.; Pagh, L. M.; Wepsiec, J. P. *J. Org. Chem.* **1998**, *63*, 8224–8228.
13. Yang, C.; Williams, J. M. *Org. Lett.* **2004**, *6*, 2837–2840.
14. Schareina, T.; Zapf, A.; Beller, M. *Chem. Commun.* **2004**, 1388–1389.
15. Schareina, T.; Zapf, A.; Beller, M. *Tetrahedron Lett.* **2005**, *46*, 2585–2588.
16. Alterman, M.; Hallberg, A. *J. Org. Chem.* **2000**, *65*, 7984–7989.
17. Tschaen, D. M.; Desmond, R.; King, A. O.; Fortin, M. C.; Pipik, B.; King, S.; Verhoeven, T. R. *Synth. Commun.* **1994**, *24*, 887–890.
18. Maligres, P. E.; Waters, M. S.; Fleitz, F.; Askin, D. *Tetrahedron Lett.* **1999**, *40*, 8193–8195.
19. Stazi, F.; Palmisano, G.; Turconi, M.; Santagostino, M. *Tetrahedron Lett.* **2005**, *46*, 1815–1818.
20. Zinc cyanide solubility in DMF (at 80 °C) is 1.8×10^{-4} g mL^{-1}.
21. Jin, F.; Confalone, P. N. *Tetrahedron Lett.* **2000**, *41*, 3271–3273.
22. Hatsuda, M.; Seki, M. *Tetrahedron Lett.* **2005**, *46*, 1849–1853.
23. Chidambaram, R. *Tetrahedron Lett.* **2004**, *45*, 1441–1444.
24. For cyanation with nickel catalysts: Sakakibara, Y.; Ido, Y.; Sasaki, K.; Sakai, M.; Uchino, N. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 2776–2778; Sakakibara, Y.; Okuda, F.; Shimobayashi, A.; Kirino, K.; Sakai, M.; Uchino, N.; Takagi, K. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1985–1990; Arvela, R. K.; Leadbeater, N. E. *J. Org. Chem.* **2003**, *68*, 9122–9125.
25. Zhang, A.; Neumeyer, J. L. *Org. Lett.* **2003**, *5*, 201–203.
26. For recent report using the Voyager: Arvela, R. K.; Leadbeater, N. E.; Collins, M. J. *Tetrahedron* **2005**, *61*, 9349–9355.
27. Leadbeater, N. E.; Pillsbury, S. J.; Shanahan, E.; Williams, V. A. *Tetrahedron* **2005**, *61*, 3565–3585.