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$Pd(OAc)_2$/DPPF-catalysed microwave-assisted cyanide-free synthesis of aryl nitriles

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Abstract. This study reports microwave-assisted cyanide-free synthesis of aryl nitriles from aryl halides using palladium acetate/1,1-bis(diphenylphosphino)ferrocene as a new catalyst system. Reported protocol is a rapid, cyanide-free, single step reaction, wherein formamide acts as a solvent as well as a source of cyanide. The use of microwave increases the rate of reaction substantially and it was observed that aryl nitriles can be synthesised in 50 min of microwave irradiation compared to conventional thermal heating protocol which requires 48 h.

Keywords. Cyanation; benzonitrile; palladium; cyanide-free; C-C coupling; 1,3-diketones; amines; ionic liquids.

1. Introduction

Aryl nitriles are an important class of intermediates in pharmaceuticals, dyes, agrochemicals, and natural products,[1] since they can be easily transformed to different functional groups and heterocycles.[2] On the other hand, various derivatives of aryl nitriles are themselves used as drugs or intermediates in a range of pharmaceutically important molecules (figure 1).[3]

Numerous methods are reported in the literature for the synthesis of aryl nitriles using various reagents. Traditionally, nitriles were prepared from aryl halides by Rosenmund–von Braun[4] and Sandmeyer reaction[5] and both methods require stoichiometric amounts of Copper (I) cyanides, tedious work-up procedure and harsh reaction conditions.[6] While on the industrial scale, ammoxidation of toluene derivatives at 300–350°C is a method of choice for nitrile synthesis,[7] ammoxidation is applicable only to a limited number of substituted toluene derivatives and it also requires high temperature and high pressure besides the use of excess ammonia restricts its application.

Recent developments in transition metal-catalysed reactions made it possible to synthesize aryl nitriles via catalytic route under mild reaction conditions.[8] In 1973, Takagi *et al.* were the first to report palladium-catalysed protocol for cyanation of aryl halides using potassium cyanide as a cyanating agent.[9] Since then, there have been rapid developments in the transition metal-catalysed methodologies for aryl nitrile synthesis.[10] It can be seen that most of these reported protocols require hazardous metal cyanide sources such as NaCN, KCN, $Zn(CN)_2$, CuCN, trimethylsilyl cyanide and acetone cyanohydrins, restricting the application of developed protocols.[11] In 2004, Beller and co-workers were the first to report, a non-toxic potassium ferrocyanide as a cyanide source.[12] After this report, many other protocols were developed using $K_4[Fe(CN)_6]$ and $K_3[Fe(CN)_6]$ as a non-toxic cyanide source.[13] Recently, an extensive research on alternative cyanide sources for nitrile synthesis has been conducted. Beller and co-workers reported electrophilic cyanation of aryl halides using *N*-cyano-benzimidazole as a new cyanide source.[14] Same group also reports *N*-cyano-*N*-phenyl-p-methylbenzenesulphonamide as a new cyanation reagent.[15] Very recently, Yang *et al.* further explored *N*-cyano-*N*-phenyl-p-methylbenzenesulphonamide for cyanation of indole by C–H activation.[16] In recent years, development of new cyanide-free protocols for aryl nitrile synthesis by direct cyanation of arene C–H bond has attracted much attention.[17–21] It can be seen that there are only few types of cyanide-free protocols for synthesis of aryl nitriles from aryl halides. In this regard, Ushijima and Togo reported one-pot conversion of aryl halides to aryl nitriles via reaction of aryl halide with n-butyl lithium and subsequent reaction with DMF, followed by treatment with molecular iodine in aqueous ammonia.[20] However, the protocol

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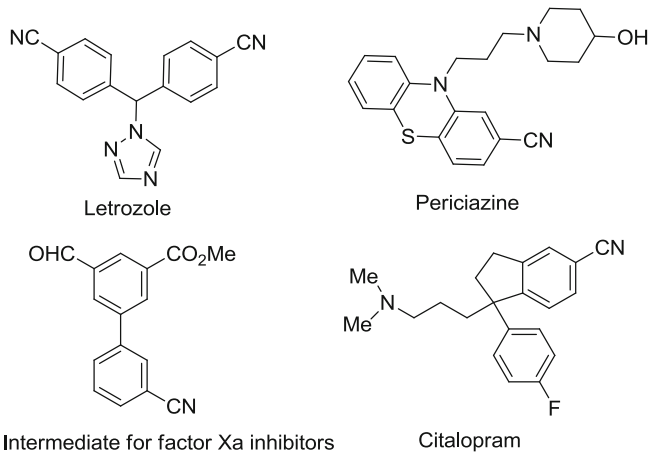
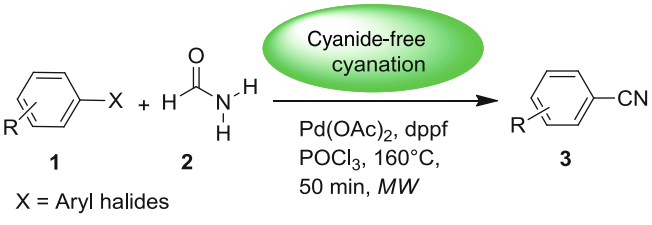


Figure 1. Biologically active benzonitrile derivatives.

requires harsh reaction conditions and reagents restricting its application.[22] Zhang *et al.* reported copper-mediated cyanation of aryl halides with the combination of DMF and NH_4HCO_3 as safe cyanide source; but requirement of stoichiometric amount of copper salt, high temperature and longer reaction time limits its application.[23] Recently, we have reported cyanide-free protocol for cyanation using formamide as nitrile source for the first time. However, our reported protocol requires longer reaction time 48 h.[24] After first report in 2000 by Alterman and Hallberg[25] on cyanation using microwave heating, many protocols for aryl nitriles synthesis were reported using microwave techniques an various metal cyanide source.[26,27] However, till date, applicability of cyanide-free protocols for aryl nitriles synthesis have not been explored under microwave conditions (scheme 1). Herein, we report for the first time a rapid microwave-promoted, simple, solvent-free, cyanide-free protocol for the synthesis of aryl nitriles using $Pd(OAc)_2$/dppf as a new catalytic system, which requires very short reaction time (50 min).

2. Materials and methods

A microwave tube (10 mL) was dried and charged with degassed formamide (2 ml), $Pd(OAc)_2$ (5 mol%), and L2 (20 mol%), iodobenzene (0.5 mmol) and $POCl_3$ (2 mmol) under nitrogen atmosphere. The vessel was then sealed with a septum under nitrogen atmosphere and placed into the microwave cavity of standard microwave system at 160°C which was reached within 30 s and reaction mixture was pre-stirred for 2 min; then reaction was performed for 50 min under microwave irradiation. After completion, the reaction mixture was cooled to room temperature and sealed tube was opened (caution). The reaction mixture was poured into a saturated solution of $NaHCO_3$ (50 mL). The product was extracted with ethyl acetate (4 × 20 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to afford the crude product which was purified by column chromatography on silica gel (petroleum ether/ethyl acetate combination) to afford the pure product. The product was confirmed by GC, IR and GCMS analysis.



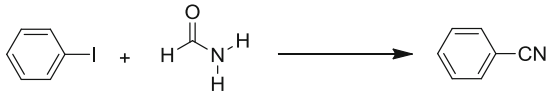
Scheme 1. Microwave-assisted cyanide-free synthesis of aryl nitriles.

3. Results and discussion

Reaction of iodobenzene and formamide with $POCl_3$ as an additive with palladium/Xantphos (**L1**) catalyst system was chosen as a model reaction (table 1, entry 1). Reactions were performed in specially designed sealed microwave tubes of 10 mL capacity using standard microwave system at 150°C which was reached within 30 s and reaction was performed for 20 min under microwave irradiation. After work-up with $NaHCO_3$ and subsequent extraction with ethyl acetate; the product benzonitrile (41%) was obtained along with traces of benzamide as side product (table 1, entry 1). CAUTION![28]

Encouraged by this result, various phosphine ligands were screened (table 1, entries 1–5) (figure 2). It was observed that dppf also provided comparable yield up to 39% as dppf is more economical than Xantphos, a selected ligand of choice for further optimization (table 1, entry 2). In order to increase yield of product, role of various palladium-precursors were checked. Only $Pd(OAc)_2$ was found to provide higher yield with only traces of benzamide as side product (table 1, entry 2). However, use of $PdCl_2$ provided benzamide as well as benzonitrile as product and pressure developed was more than 7 bar (table 1, entry 6). $Pd(tmhd)_2$ which was also screened resulted in rapid increase in pressure in microwave tube up to more than 10 bar (table 1 entry 7). Next, we checked effect of catalyst loading which showed that decreasing catalyst loading and metal to ligand ratio leads to decrease in yield of product (table 1, entries 8–12). Hence, it can be seen that 5 mol% of $Pd(OAc)_2$ and 20 mol%

Table 1. Optimization of reaction parameters for microwave-promoted nitrile synthesis.[a]



1a 2a 3a

Entry	Ligand	Pd catalyst	Temp (°C)	Time (min)	Yield (%)[b]
Effect of ligand					
1	**L1** (10)	$Pd(OAC)_2$(5)	150	20	41
2	**L2** (10)	$Pd(OAC)_2$(5)	150	20	39
3	**L3** (10)	$Pd(OAC)_2$(5)	150	20	30
4	**L4** (10)	$Pd(OAC)_2$(5)	150	20	0
5	**L5** (10)	$Pd(OAC)_2$(5)	150	20	7
Effect of metal precursor					
6	**L2** (10)	$PdCl_2$(5)	150	20	23 (15)[c]
7	**L2** (10)	$Pd(tmhd)_2$(5)	150	20	4[d]
Effect of catalyst loading					
8	**L2** (5)	$Pd(OAC)_2$(5)	150	20	29
9	**L2** (15)	$Pd(OAC)_2$(5)	150	20	46
10	**L2** (20)	$Pd(OAC)_2$(5)	150	20	52
11	**L2** (12)	$Pd(OAC)_2$(3)	150	20	32
12	**L2** (22)	$Pd(OAC)_2$(6)	150	20	53
Effect of temprature					
13	**L2** (20)	$Pd(OAC)_2$(5)	140	20	31
14	**L2** (20)	$Pd(OAC)_2$(5)	160	20	58
15	**L2** (20)	$Pd(OAC)_2$(5)	170	10	59[d]
16	**L2** (20)	$Pd(OAC)_2$(5)	180	10	28[d]
Effect of time					
17	**L2** (20)	$Pd(OAC)_2$(5)	160	15	38
18	**L2** (20)	$Pd(OAC)_2$(5)	160	30	57
19	**L2** (20)	$Pd(OAC)_2$(5)	160	40	65
20	**L2** (20)	$Pd(OAC)_2$(5)	160	50	80
21	**L2** (20)	$Pd(OAC)_2$(5)	160	60	81
22	**L2** (20)	$Pd(OAC)_2$(5)	160	60	12[e]

[a]Reaction conditions: Iodobenzene (0.5 mmol), formamide (2 mL), Pd precursor, ligand, $POCl_3$ (2.0 mmol), under nitrogen
[b]GC yield
[c]Benzamide as side product
[d]Pressure developed rapidly to more than 10 bar
[e]Reaction by conventional heating

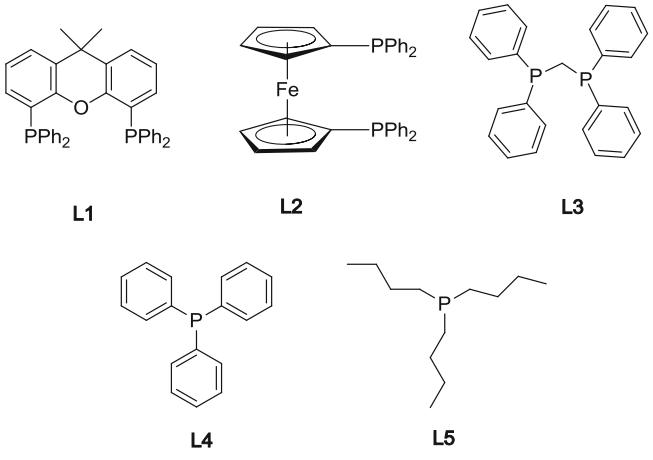


Figure 2. Structure of ligands from **L1**–**L5**.

Table 2. Influence of Lewis acids.[a]

No.	Lewis acids (mmol)	Yield **3a** (%)[b]
1	$POCl_3$ (1)	42
2	$POCl_3$ (1.5)	64
3	$POCl_3$(2)	80
4	$POCl_3$ (2.5)	81
5	PCl_3 (2)	26
6	BF_3:OEt_2 (2)	0
7	$SOCl_2$ (2)	0[c]
8	$FeCl_3$ (2)	0

[a]Reaction conditions: Iodobenzene (0.5 mmol), formamide (2 mL), $Pd(OAc)_2$ (5 mol%), **L2** (20 mol%), $POCl_3$, 160°C, 50 min, under nitrogen
[b]GC yield
[c]Reaction stoped in 10 min as pressure developed rapidly more than 10 bar within 10 min

Table 3. Influence of formamide concentration on cyanide-free cyanation.[a]

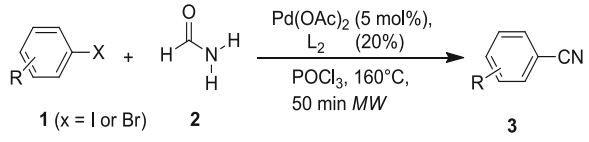
No.	Formamide (mL)	Yield of **3a** (%)[b]
1	1	54
2	2	80
3	3	79
4	4	74

[a]Reaction conditions: Iodobenzene (0.5 mmol), formamide, $Pd(OAc)_2$ (5 mol%), **L2** (20 mol%), $POCl_3$ (2.0 mmol), 160°C, 50 min under nitrogen atm
[b]GC yield

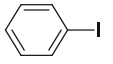
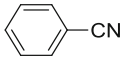
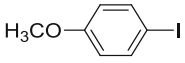
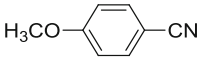
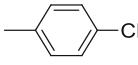
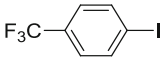
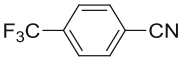
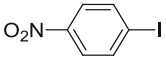
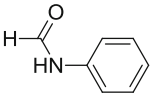
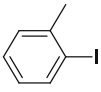
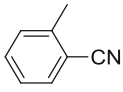
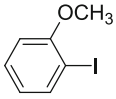
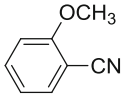
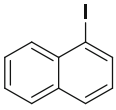
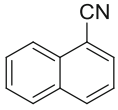
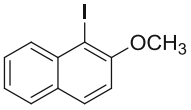
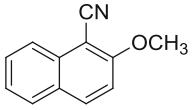
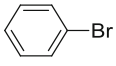
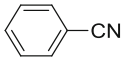
of **L2** was essential for higher yields (table 1, entry 10). As time and temperature are key factors in microwave conditions, we found that 160°C is the optimized reaction temperature; and at this temperature, indigenous pressure of 4 bar was developed. Increase in temperature above 160°C leads to rapid increase pressure in microwave tube, while decrease in temperature resulted in lower conversion (table 1, entries 13–16). Study of reaction time reveals that 50 min are essential for maximum conversion of product (table 1, entry 20) and further increase in reaction time does not lead to increase in the product yield (table 1, entries 17–21). Direct comparison between microwave and conventional heating was studied and for this we performed the same reaction in an oil bath using same microwave tube which gave only 12% yield (table 1, entry 22). This clearly shows the advantage of microwave methodology of being rapid, easier and leads to comparatively higher yields of product than conventional heating.

As $POCl_3$ is a key component of the reaction, we checked the effect of $POCl_3$ concentration, which

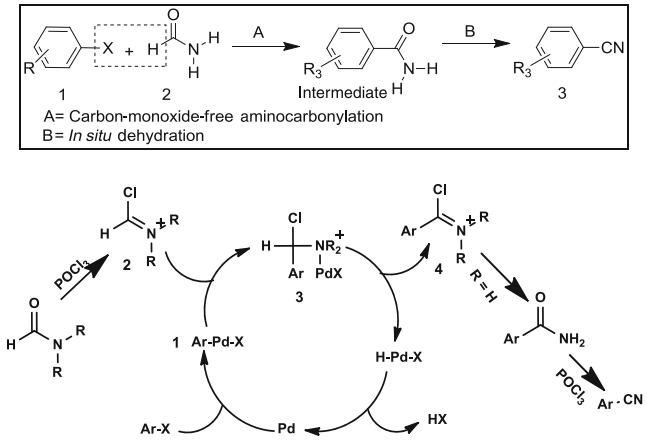
Table 4. Scope of microwave-assisted cyanide-free cyanation of aryl halides.[a]



1 (x = I or Br) **2** **3**

Entry	Aryl halide	Product		Yield (%)[b]
1			**3a**	75
2			**3b**	78
3			**3c**	72
4			**3d**	69
5			**4**	89
6			**3e**	74
7			**3f**	71
8			**3g**	73
9			**3h**	52
10			**a3**	9

[a]Reaction conditions: **1** (0.5 mmol), formamide (2 mL), $Pd(OAc)_2$ (5 mol%), **L2** (20 mol%), $POCl_3$ (2.0 mmol), 160°C, 50 min under nitrogen atm
[b]Isolated of yield



Scheme 2. Proposed mechanism for cyanation.

reveals that 2 equivalents of $POCl_3$ is essential for maximum conversion (table 2, entries 1–4). Use of other Lewis acids was futile (table 2, entries 5–8).

Effect of formamide concentration was also checked; it was found that 2 mL of formamide is sufficient for maximum conversion (table 3).

The optimized reaction conditions were found to be iodobenzene (0.5 mmol), formamide (2 mL), $POCl_3$ (2 mmol), $Pd(OAc)_2$ (5 mol%), **L2** (20 mol%) at 160°C for 50 min microwave irradiation under nitrogen atmosphere.

To check the wider applicability of the present protocol, various aryl halides were reacted with formamide and they gave moderate yields of product (table 4). It was observed that various electron-donating *para* substituents on aryl halides such as Me-, MeO- are well-tolerated giving good yields of corresponding product (table 4, entries 1–3). However, electron-withdrawing substituent such as CF_3 is also well-tolerated (table 4, entry 4). Attempts to use *para*-nitro substituent failed, significantly dehalogenated and reductive formylated product of nitro-derivative was obtained as major product (table 4, entry 5). Stearically hindered *ortho*-substituted aryl iodides were also well-tolerated providing moderate yield of product (table 4, entries 6 and 7). Similarly, 1-iodonapthalene also exhibited a good yield of desired product, while 2-methoxy substituent of 1-iodonapthalene resulted in slightly lower yield of corresponding product (table 4, entries 8 and 9). Use of aryl bromides as a substrate provided only traces of corresponding product (table 4, entry 10). It is noteworthy to mention that no *N*-arylated product was observed in any case.

3.1 *Mechanism*

From our previous report on carbon-monoxide-free aminocarbonylation,[29,30] cyanide-free cyanation,[24] and the results obtained, we predict that nitrile synthesis involves oxidative insertion of Pd into the C–X bond which produces an aryl palladium halide intermediate 1 (scheme 2). Thereafter, imminium salt (Vilsmeier type reagent) undergoes nucleophilic addition of the aryl palladium halide to form 3, which then undergoes β-hydride elimination forming intermediate 4, which is a key intermediate of the reaction. Then formamide, intermediate 4 undergoes aminocarbonylation followed by dehydration to give nitriles. During optimization and substrate screening studies, small amount of benzamide derivatives was obtained which also supports the hypothesis. Therefore, $POCl_3$ plays a dual role of reagent for formation of Vilsmeier type reagent and dehydrating agent. It should be noted that the development of 'one-pot combination' of a Pd-catalysed aminocarbonylation and subsequent dehydration with $POCl_3$ for direct synthesis of aryl nitriles is not as easy as often thought.

4. Conclusion

In summary, we have developed a new catalytic system based on palladium acetate and 1,1-bis (diphenylphosphino)ferrocene and for the first time employed microwave irradiation for cyanide-free nitrile synthesis. Reported protocol does not require any toxic cyanide source; the process is a one-step reaction, wherein no extra solvent is required as formamide plays a dual role of solvent as well as source of cyanide. We believe that this method will attract attention because of its shorter reaction time.

Supplementary information

The electronic Supplementary information can be seen at www.ias.ac.in/chemsci.

Acknowledgements

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28. Precautions should be taken when performing microwave experiments. Specially design microwave tubes 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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