## A Convenient Protocol for the Synthesis of Hindered Aryl Malononitriles

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Dedicated to Prof. Richard Heck - one of the fathers of C-C coupling catalysis

**Abstract:** A technically feasible method has been developed for the synthesis of variety of aryl malononitriles in high yields (70–95%) using the palladium-catalyzed coupling reaction of malononitrile with aryl bromides and chlorides, respectively. The influence a several reaction parameters such as base, ligand, solvent or temperature were investigated in some detail.

**Key words:** arylation, aryl malononitrile, C–C coupling reaction, Pd catalysis, oxopyrazoline herbicide

2,4,6-Trialkylaryl malononitriles are key intermediates for the preparation of oxopyrazoline herbicides (see Scheme 1). One of these compounds is the ACCase inhibitor pinoxaden, the active ingredient of a family of herbicides recently introduced on the market.<sup>1</sup>



Scheme 1 Aryl malononitriles as intermediates for oxopyrazoline herbicides.

Whereas alkyl malononitriles are easily accessible by alkylation of the malononitrile anion with alkyl halides, the corresponding arylation reaction occurs only in presence of an appropriate catalyst. A review of the literature showed that good yields could be obtained with several catalytic systems but it also revealed severe restrictions concerning substrate scope and/or reaction conditions (catalyst loading, nature of solvent and base). Copperbased catalysts only work for reactions with aryl iodides and require 10-20 mol% of catalyst.<sup>2</sup> A recently described Ni system needs similar catalyst loadings but is able to activate aryl chlorides and bromides as well as iodides.<sup>3</sup> Finally, a variety of Pd complexes was described with a comparable substrate scope and giving good yields at 1-2% catalyst loading.<sup>4-6</sup> In 1984 Uno et al.<sup>4</sup> reported the reaction of aryl iodides using Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> with NaH in

SYNLETT 2006, No. 18, pp 3167–3169 Advanced online publication: 04.08.2006 DOI: 10.1055/s-2006-944215; Art ID: S03106ST © Georg Thieme Verlag Stuttgart · New York THF.<sup>5</sup> More effective protocols using PdCl<sub>2</sub>/excess PPh<sub>3</sub><sup>6</sup> and Pd(dba)<sub>2</sub>/heterocyclic carbenes<sup>7</sup> with NaH in pyridine gave very high yields with a variety of aryl bromides. Pd catalysts with more basic phosphines were shown to be highly active for the arylation of other active methylene compounds such as malonates using t-BuONa or  $K_3PO_4$ as base.<sup>8</sup> If one analyzes these results in the context of our task, i.e. the development of a technically feasible method for the synthesis of arylmalononitrile 2, there were two concerns. The first is that no 2,6-substituted, i.e. sterically hindered, aryl halide was ever used and the second that almost all protocols had a problematic component such as an unacceptable solvent, an inconvenient base or a noncommercial ligand. Here we describe a method, which allows the convenient preparation of a variety of aryl malononitriles, which satisfies all criteria for a technical application.



**Scheme 2** Catalytic preparation of sterically hindered aryl malononitriles.

We started our investigation by testing a variety of Pd complexes for the reaction of malononitrile with the sterically hindered aryl halides 1 (Scheme 2, Table 1). The screening of reaction conditions (ligands, temperature, catalyst amount) was carried out in closed Schlenk tubes using 1a, 1.1 equivalents malononitrile and 3 equivalents t-BuONa in xylene as solvent. This combination of base and solvent turned out to be the most successful one. Other bases such as  $K_3PO_4$ , MeONa, DBU or NaHCO<sub>3</sub> were ineffective. While the reaction proceeded well using NaH in DMSO at 140 °C (entry 1), mixtures of DMSO with a strong base and bromide anions are known to be very hazardous. As indicated by entry 2, oil bath temperatures of 160 °C were required for smooth reaction (due to refluxing tert-butanol, temperatures inside the tube were ca. 20 °C lower). In toluene, the reaction also proceeded to some extent, but the highest reachable temperature was too low for an efficient reaction.

 Table 1
 Effect of Various Parameters on the Reaction<sup>a</sup> of 1a with Malononitrile<sup>9</sup>

Entry	Catalytic system	Mol (%)	P/Pd ratio	Solvent	T (°C)	Yield (%) <sup>c</sup>	Comments
1	$Pd(PCy_3)_2Cl_2$	2	2	DMSO <sup>d</sup>	140	83	No reaction in THF at 80 °C
2	$Pd(PPh_3)_2Cl_2$	2	2	Xylene	160 <sup>b</sup>	100	No reaction at 140 °C (1% Pd)
3	PdCl <sub>2</sub> /PCy <sub>3</sub> <sup>e</sup>	0.1	5	Xylene	160 <sup>b</sup>	86	Yield 2% with 2 equiv t-BuONa
4	$Pd(PCyp_3)_2Cl_2$	0.2	2	Xylene	160 <sup>b</sup>	81	
5	PdCl <sub>2</sub> /PBu <sub>3</sub> <sup>e</sup>	0.1	7	Xylene	160 <sup>b</sup>	4	
6	PdCl <sub>2</sub> /P(OEt) <sub>3</sub> <sup>e</sup>	0.1	100	Xylene	160 <sup>b</sup>	49	Yield $<32\%$ when P/Pd $\leq 20$
7	PdCl <sub>2</sub> /PP <sup>e</sup>	0.1	10	Xylene	160 <sup>b</sup>	30–34	for $PP = dppf$ , f $dppp^f$ or binap
8	Pd(iprpp)Cl <sub>2</sub> <sup>f</sup>	0.1	2	Xylene	160 <sup>b</sup>	8	

<sup>a</sup> Reaction conditions: **2b** (2.5 mmol), malononitrile (2.75 mmol), *t*-BuONa (7.5 mmol), xylene (15 mL), 16 h.

 $^{\rm b}$  Oil bath temperature. Temperature inside the Schlenk tube was approximately 20  $^{\circ}{\rm C}$  lower.

<sup>c</sup> Determined by HPLC.

<sup>d</sup> With NaH as base and 2 equiv of malononitrile.

<sup>e</sup> Palladium complex was formed prior to reaction in a separate vessel.

<sup>f</sup> dppf: 1,1'-bis(diphenylphosphino)ferrocene; dppp: 1,3-bis(diphenylphosphino)propane; iprpp: 1,3-bis(diisopropylphosphino)propane.

At a relatively low catalyst loading, a variety of ligands were screened (entries 3–8). For good and reproducible results, it was necessary to use either isolated palladium– phosphine complexes or to form the complexes in xylene in a separate vessel prior the reaction. In the latter cases it was beneficial to apply a five- to seven-fold excess of ligand. The best ligands were the monodentate and bulky trialkylphosphines tricyclohexylphosphine, Cy<sub>3</sub>P, and tricyclopentylphosphine, Cyp<sub>3</sub>P, (entries 3 and 4).

Triphenylphosphine (not shown) was completely ineffective at these low loadings. Modest yields were observed with bidentate arylphosphines (entry 7), whereas the bidentate alkylphosphine (entry 8) gave very low yields. Interestingly, phosphite ligands gave also modestly active catalyst, but large excess of phosphite had to be used (entry 6). The same observation was previously made in other palladium-catalyzed reactions with this class of ligands.<sup>10</sup> For high conversion at least three equivalents of *t*-BuONa were necessary (see entry 3). One equivalent of base is needed for the neutralization of the HBr formed and a second one for the deprotonation of the formed arylmalononitrile, which is more acidic but less reactive than the malononitrile itself.

The optimized system with  $PdCl_2/tricyclohexylphosphine$ in xylene was used to demonstrate the scope of the method. The results summarized in Table 2 demonstrate that a variety of substituted arylmalononitrile can be synthesized under these conditions with good to very good yields in reasonable reaction times with 1% catalyst. As expected, the reaction proceeds at milder conditions with aryl iodides (entries 1–3). Aryl bromides with electrondonating (entries 4–7) as well as electron-withdrawing groups (entries 8 and 9) reacted equally well and the products were isolated in 70–95% yields. It is interesting to note that reactions with sterically hindered 2,6-substituted

 
 Table 2
 Scope of the Coupling Reaction<sup>a</sup> of Aryl Halides with Malononitrile<sup>10</sup>

Entry	Aryl halide	Temp (°C)	Time (h)	Yield (%)
1	PhI <sup>b</sup>	80	20	91
2	2,6-Et-4-Me-PhI <sup>b</sup>	80	20	58
3	2,4,6-Me-PhI <sup>b</sup>	80	20	86
4	4-Me-PhBr	160 <sup>c</sup>	20	94
5	2,6-Et-4-Me-PhBr	160 <sup>c</sup>	20	92
6	4- <i>t</i> -Bu-PhBr	160 <sup>c</sup>	6	95
7	4-MeO-PhBr	160 <sup>c</sup>	4	70
8	3-CF <sub>3</sub> -PhBr	160 <sup>c</sup>	3.5	83
9	4-Cl-PhBr	160 <sup>c</sup>	15	80 <sup>d</sup>
10	4-CN-PhBr	160 <sup>c</sup>	20	15
11	4-Ac-PhBr	160°	4.4	0
12	2-Bromopyridine	160 <sup>c</sup>	2.2	94
13	4-MeO-PhCl <sup>e</sup>	140 <sup>c</sup>	16	74
14	4-Me-PhCl <sup>e</sup>	140 <sup>c</sup>	16	39

<sup>a</sup> Reaction conditions: PdCl<sub>2</sub> (1%), PCy<sub>3</sub> (3%), ArX (1 equiv), malononitrile (1.1 equiv), *t*-BuONa (3 equiv), 0.13 M in xylene, isolated yields.

<sup>b</sup> With NaH as base, 2 equiv of malononitrile in THF.

 $^{\rm c}$  Oil bath temperature. Temperature inside the Schlenk tube was approximately 20  $^{\rm o}{\rm C}$  lower.

<sup>d</sup> No reaction of the Ar-Cl bond.

<sup>e</sup> With diadamantylphosphine as ligand.

aryl halides proceeded with only slightly lower yields. Problems only arose in cases where the substituents are base sensitive, e.g. with 4-bromobenzonitrile or 4-bromoacetophenone (entries 10 and 11). The procedure is also applicable for heteroaromatic bromides such as 2-bromopyridine (entry 12), while chloro arenes did not react under these conditions (see entry 9). However, with a more activating ligand such as the secondary diadamantylphosphine which was found to be very effective for various coupling reactions of aryl chlorides,<sup>11</sup> good to medium yields were obtained (entries 13 and 14), while 2chloropyridine gave only 23% yield (result not shown).

In conclusion, we have developed a convenient and general protocol, which allows the preparation of a wide variety of substituted aryl malononitriles starting from the corresponding aryl bromides or even aryl chlorides. Compared to most other methodologies, good yields are obtained at much lower catalyst loadings with reasonable reaction times. The catalyst is easy to prepare from relatively cheap palladium chloride and the readily available  $PCy_3$  ligand. The reaction using aryl bromide **1a** was carried out on a 100 kg scale, demonstrating that the method is easy to scale up for technical applications.

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## **References and Notes**

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