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Palladium-catalysed direct arylations of heteroaromatics bearing dicyanovinyls at C2

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ABSTRACT

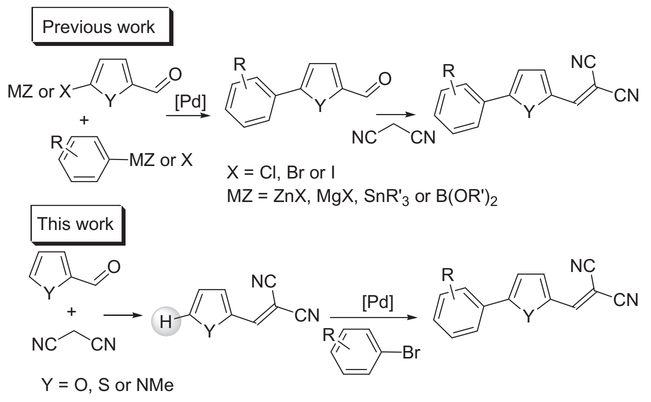
The palladium-catalysed direct 5-arylation of heteroaromatics bearing dicyanovinyls at C2 with aryl bromides via C–H bond functionalisation allows the synthesis of a variety of new conjugated systems in only one step. The nature of the solvent was found to be crucial to perform such arylations. In DMAc, complete decomposition of the dicyanovinyl derivatives was observed, whereas they were found to be stable in cyclopentyl methyl ether.

Mixed bi(hetero)aryl derivatives display a set of bioactive or physical properties and their preparation constitutes an active field of research in organic chemistry. Among them, some bi(hetero)aryls bearing dicyanovinyls on the heteroaromatic moiety have been found to display useful optical properties.[1] In most cases the bi(hetero)aryl motif was prepared by palladium-catalysed cross-coupling reactions between aryl halides and heteroarene derivatives such as a 5-formylthiophene-2-boronic acid. Then, the Knoevenagel condensation of malononitrile with the appropriate aldehyde produces the dicyanovinyl derivatives (Scheme 1, top).[1–3]

An example of the synthesis of organic semiconductors via Stille coupling of 5-bromo-2-dicyanovinylthiophene with 2,7-di(tributyltin)-9,9-bis-*n*-hexylfluorene has also been described by Lui and co-workers.[4]

However, these methods are not very convenient for three reasons; (i) organometallic derivatives have to be prepared for the cross-coupling reactions; (ii) these reactions are not environmentally attractive as they provide an organometallic or a salt (MX) as the by-product; (iii) as the malononitrile is generally introduced after the cross-coupling reaction, the introduction of various functional groups on the aryl requires two steps. Therefore, to overcome these limitations, a straightforward functionalisation of heteroaromatics bearing dicyanovinyls is highly desirable.

In recent years, several interesting results for the palladium-catalysed coupling of aryl halides with heteroaromatic derivatives via C–H bond functionalisation have been reported and provide attractive procedures for the preparation of arylated heteroaromatics.[5–9] These coupling reactions provide only HX associated to a base as the by-product and therefore are very interesting both in terms of atom-economy and inert wastes. However, if the palladium-catalysed direct arylation of heteroaromatics bearing acetyl, formyl, nitrile, silyl, ester, methylalcohol, amide or even amino as the functional groups has been described,[7–10] on the other hand,



Scheme 1.

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0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
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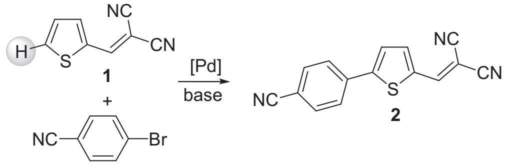
the use of vinyl substituents has attracted much less attention.[11,12] This might be due to the possible competitive Heck reaction and also to the moderate stability of some vinyl derivatives.[13] To our knowledge, only a few examples of the intermolecular direct arylations of such heteroaromatics have been reported. Trisubstituted alkenes [2-(2,2-diarylvinyl)-thiophenes] have been employed by Mori and co-workers to prepare 5-arylthiophene derivatives.[11] We have also recently reported the palladium-catalysed C5 arylation of furans or thiophenes bearing enal, enone or acrylate functions at carbon C2.[14]

To our knowledge, the intermolecular direct arylation of thiophenes, pyrroles or furans bearing dicyanovinyl function has not been described, although it would allow a more simple access to such arylated heteroaromatics (Scheme 1, bottom). Therefore, the discovery of effective conditions, for the direct coupling of such heteroarenes with aryl halides, would be a considerable advantage. Here, we wish to report on the palladium-catalysed reaction of some heteroaromatics bearing dicyanovinyl function at C2 with a set of aryl bromides.

For this study, we initially employed 0.5 mol % of $Pd(OAc)_2$ as the catalyst, KOAc as the base and DMAc as the solvent at 110 °C for the coupling of 2-thiophen-2-ylmethylenemalononitrile **1** with 4-bromobenzonitrile, as we previously observed that these conditions are generally effective for the direct arylation of several heteroaromatics.[14,15] However, the use of these conditions resulted in the decomposition of the dicyanovinyl derivative **1** and no trace of the target product **2** was detected (Table 1, entry 1). Similar results were obtained at 70 °C using 0.5 mol % $PdCl(C_3H_5)(dppb)$ as the catalyst (Table 1, entry 3). On the other hand, the use of cyclopentyl methyl ether (CPME) as the solvent for this reaction, using 1 mol % $PdCl(C_3H_5)(dppb)$ as the palladium source at 125 °C, afforded selectively the desired C5 arylated product **2** in 70% conversion and 57% yield (Table 1, entry 5). No formation of other regioisomers or diarylated thiophenes was detected. This selectivity is consistent with a 'concerted metallation deprotonation' mechanism.[16] We had previously observed that the use of CPME as the solvent allows the palladium-catalysed direct arylations with some quite unstable heteroaromatic derivatives, including dithienylperfluorocyclopentenes, in high yields.[17] It should be noted that this solvent presents several advantageous features such as limited miscibility in water and low formation of peroxides. Moreover CPME can be manufactured by the addition of MeOH to cyclopentene. This process produces no apparent waste.[18] We also performed reactions in CPME or xylene using 1 mol % $Pd(OAc)_2$ as the catalyst; however, low yields in **2** were obtained (Table 1, entries 6 and 7) (see Scheme 2).

Then, we examined the coupling of 2-thiophen-2-ylmethylenemalononitrile **1** with a variety of aryl bromides (Table 2). The highest yields were obtained with 4-bromoacetophenone or 3-bromobenzonitrile. With these two reactants, **4** and **7** were isolated in 68% and 61% yields, respectively (Table 2, entries 2 and 5). Lower yields were obtained in the presence of 3- or 4-(trifluoromethyl)bromobenzenes and also from ethyl 4-bromobenzoate due to moderate conversions of these aryl bromides (Table 2, entries 1, 3 and 4). It should be noted that in the presence of the electron-rich aryl bromide, 4-bromoanisole, no formation of the desired coupling product was detected and the aryl bromide was recovered unreacted.



Scheme 2. Arylation of 4-bromobenzonitrile with 2-thiophen-2-ylmethylenemalononitrile **1.**

Table 1

Influence of the reaction conditions for palladium-catalysed direct arylation of 4-bromobenzonitrile with 2-thiophen-2-ylmethylenemalononitrile **1** (Scheme 2)[19,20]

Entry	Catalyst (mol %)	Solvent	Base	Temp. (°C)	Yield in **2** (%)
1	$Pd(OAc)_2$ (0.5)	DMAc	KOAc	110	0
2	$Pd(OAc)_2$ (0.5)	DMAc	K_2CO_3	70	0
3	$PdCl(C_3H_5)(dppb)$ (0.5)	DMAc	KOAc	70	0
4	$PdCl(C_3H_5)(dppb)$ (1)	CPME	KOAc	125	30
5	$PdCl(C_3H_5)(dppb)$ (1)	CPME	KOAc	125	70 (57)[a]
6	$Pd(OAc)_2$ (1)	CPME	KOAc	125	20[b]
7	$Pd(OAc)_2$ (1)	Xylene	KOAc	100	6[b]

Conditions: 4-bromobenzonitrile (1 equiv), 2-thiophen-2-ylmethylenemalononitrile **1** (2 equiv), base (2 equiv) under argon, 12 h.

[a] 36 h.

[b] 20 h.

Next, we studied the reactivity of 2-furan-2-ylmethylenemalononitrile **8** (Table 3). Quite similar results than with **1** were obtained. Again a regioselective arylation at C5 was observed. However, the best yields were obtained in the presence of 4-(trifluoromethyl)bromobenzenes and from ethyl 4-bromobenzoate. With these two reactants, **10** and **11** were obtained in 70 and 72% yields, respectively (Table 3, entries 2 and 3). Even the more congested aryl bromide, 2-bromobenzonitrile gave the desired coupling product **14** in good yield (Table 3, entry 6).

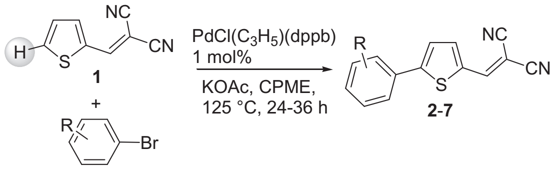
Finally, we explored the reactivity of 2-(1-methylpyrrol-2-ylmethylene)-malononitrile **15** (Table 4). To our knowledge, so far no examples of preparation of 2-(1-methylpyrrol-2-ylmethylene)-malononitrile substituted at C5 by aryls have been described in the literature. Only one example of such motif bearing a 2-thienyl substituent has been reported.[21] From malononitrile and a 2-formylthienylpyrrole the condensation product was obtained by Raposo and co-workers. Then, its properties as non linear optical chromophore were studied.

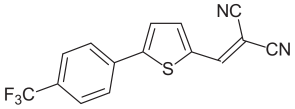
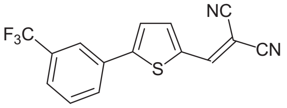
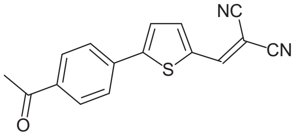
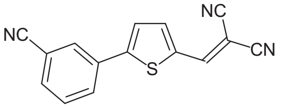
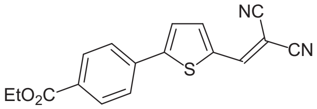
Again, we observed a regioselective arylation at C5 of the pyrrole derivative. However, lower yields than with **1** or **8** were obtained due again to partial conversions of the aryl bromides. From 4-(trifluoromethyl)bromobenzene, **16** was isolated in 50% yield (Table 4, entry 1). On the other hand, 2-(trifluoromethyl)bromobenzene, 3,5-bis(trifluoromethyl)bromobenzene or 3- or 4-bromobenzonitriles gave **17**–**20** in moderate yields due to partial conversions of the aryl bromides (Table 4, entries 2–5). With this heteroarene, the best yield of 58% was obtained from 3-(trifluoromethyl)-4-nitrobromobenzene (Table 4, entry 6).

In summary, we report here that a range of heteroaromatics bearing a dicyanovinyl at C2 undergoes palladium-catalysed coupling via C–H bond activation/functionalisation reaction at C5 with electron-deficient aryl bromides. It should be noted that this protocol, which employs a moderate loading of an air stable catalyst and a cheap base, is compatible to a range of functions, including reactive ones, such as acetyl, ester, nitrile or nitro on the aryl bromide. Such functional group tolerance allows the modification of the electronic structure of such derivatives. For all these reactions, CPME 99+%, which can be considered as a 'greener' solvents than DMAc or DMF, which are generally employed for palladium-catalysed direct arylations, was used without any purification. The major by-products of these couplings are KBr/AcOH instead of metallic salts with more classical coupling procedures. For these reasons, this process should give a more economically viable and environmentally attractive access to these products.

Table 2

Palladium-catalysed 5-arylation of aryl bromides with 2-thiophen-2-ylmethylenemalononitrile **1**[19,20]

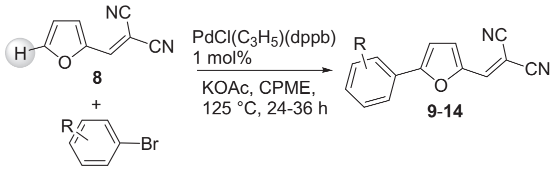


Entry	Product	Entry	Product
1	 **3** 53%	4	 **6** 48%
2	 **4** 68%	5	 **7** 61%
3	 **5** 55%		

Conditions: PdCl(C_3H_5)(dppb) (0.01 mmol), aryl bromide (1 mmol), 2-thiophen-2-ylmethylenemalononitrile **1** (2 mmol), KOAc (2 mmol), CPME (6 mL), 24–36 h, 125 °C, isolated yields.

Table 3

Palladium-catalysed 5-arylation of aryl bromides with 2-furan-2-ylmethylenemalononitrile **8**[19,20]



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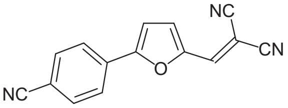
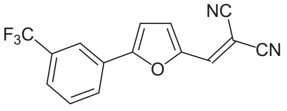
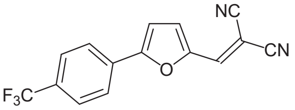
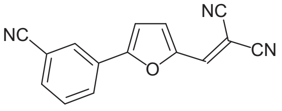
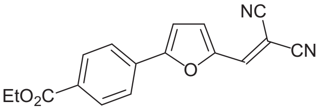
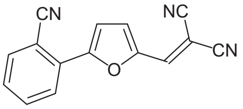
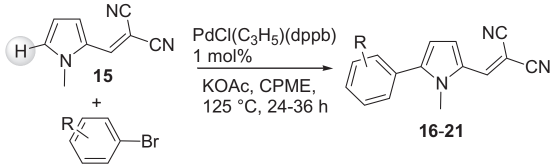
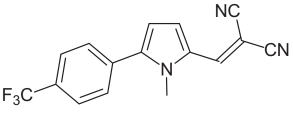
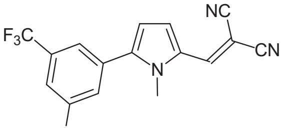
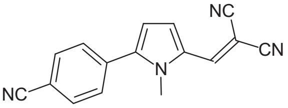
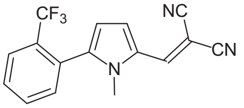
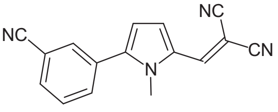
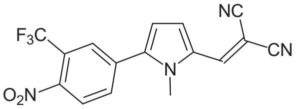
1	 **9** 45%	4	 **12** 66%
2	 **10** 70%	5	 **13** 42%
3	 **11** 72%	6	 **14** 59%

Conditions: PdCl(C_3H_5)(dppb) (0.01 mmol), aryl bromide (1 mmol), 2-furan-2-ylmethylenemalononitrile **8** (2 mmol), KOAc (2 mmol), CPME (6 mL), 24–36 h, 125 °C, isolated yields.

Table 4

Palladium-catalysed 5-arylation of aryl bromides with 2-(1-methylpyrrol-2-ylmethylene)-malononitrile **15**[19,20]



Entry	Product	Entry	Product
1	 **16** 50%	4	 **19** 41%
2	 **17** 37%	5	 **20** 40%
3	 **18** 33%	6	 **21** 58%

Conditions: PdCl(C_3H_5)(dppb) (0.01 mmol), aryl bromide (1 mmol), 2-(1-methylpyrrol-2-ylmethylene)-malononitrile **15** (2 mmol), KOAc (2 mmol), CPME (6 mL), 24–36 h, 125 °C, isolated yields.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.10.008.

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19. General procedure for the direct arylation of 2-(thiophen-2-ylmethylene)malononitrile **1**, 2-(furan-2-ylmethylene)malononitrile **8** and 2-((1-methylpyrrol-2-yl)methylene)malononitrile **15**: In a typical experiment, the aryl bromide (1 mmol), heteroaromatic **1**, **8** or **15** (2 mmol), KOAc (0.196 g, 2 mmol) and $PdCl(C_3H_5)(dppb)$[22] (0.006 g, 0.01 mmol) were dissolved in CPME (6 mL) under an argon atmosphere. The reaction mixture was stirred at 125 °C for 24-36 h. Then, the solvent was evaporated and the product was purified by silica gel column chromatography.
20. All compounds gave satisfactory ^1H, ^{13}C and elementary analysis. **2**: ^1H NMR (400 MHz, $CDCl_3$): δ 7.86 (s, 1H), 7.82 (d, $J = 8.5$ Hz, 2H), 7.79 (d, $J = 4.3$ Hz, 1H), 7.77 (d, $J = 8.5$ Hz, 2H), 7.55 (d, $J = 4.3$ Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.7, 150.3, 139.6, 136.3, 135.9, 133.1, 127.0, 126.2, 118.1, 113.6, 113.4, 112.9, 78.9. Electronic Supplementary data available: procedures and NMR data.
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