Direct Arylation of Pyrrole Derivatives in Superbasic Media

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Received 29 April 2011; revised 10 June 2011

Abstract: Direct arylation of *N*-alkyl- and *N*-arylpyrroles with aryl iodides can be performed in superbasic media, without external addition of a transition-metal catalyst. Lithium hydroxide in dimethyl sulfoxide promotes this reaction in a regioselective manner, leading to the expected 2-arylated products in good yield.

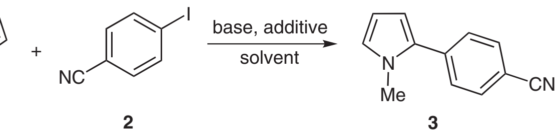
Key words: pyrrole, heterocycles, C–C coupling, C–H activation, aryl halides

Direct arylation of aromatic heterocycles continues to attract the attention of synthetic chemists as a more convenient alternative to classical methods for the construction of biaryl linkages.[1] Most published protocols are catalyzed by transition-metal salts; however, recently, a number of metal-free protocols have been reported.[2]

Although the use of pyrroles and their derivatives in cross-coupling reactions is relatively rare in comparison to indole[3] and thiophene,[4] these compounds are very valuable building blocks for the synthesis of more complex compounds with important properties.[5] In spite of the remarkable progress achieved in direct arylation, research focused on the exploration of new, inexpensive, and efficient methods for the formation of arylated products is still necessary. Over the past few years, several research groups have investigated the formation of pyrrole–aryl linkages.[6] Recently, we reported that catalysts containing transition metals are not necessary to perform direct arylation of electron-rich heterocycles with aryl iodides and bromides.[7] Lithium *tert*-butoxide in *N*,*N*-dimethylformamide promotes this reaction for variety of *N*-alkyl- and *N*-arylpyrroles, as well as for benzofuran and some other electron-rich aromatic compounds, and provides the desired products at moderate to high yields.

Intriguingly, we found that the reaction outcome strongly depended on the use of a pre-prepared solution of lithium *tert*-butoxide in *N*,*N*-dimethylformamide. Lithium cations have a well-known tendency to associate with chelating or chiral diamines, as well as organic solvents (DMF, DMSO),[8] and such donor-acceptor systems are of interest in modern organic chemistry. For example, the successful use of alkali metal hydroxide–dimethyl sulfoxide,[9] together with other super bases,[10] has been reported. Solvate-separated ion pairs, with active anions, dominate in such systems.

Thus, we wondered if known superbasic media can promote a reaction between *N*-methylpyrrole (**1**) and 4-iodobenzonitrile (**2**), leading to the formation of a heteroarylated product **3** (Scheme 1). Initially, our focus was aimed on the use of simple inorganic bases, such as lithium hydroxide, sodium hydroxide, and potassium hydroxide in *N*,*N*-dimethylformamide (in analogy to *t*-BuOLi in DMF). Among the screened bases, lithium hydroxide showed the highest efficiency (Table 1, entries 1–3).



Scheme 1

Interestingly, DMSO is also known to form complexes with lithium hydroxide,[8a,c] and use of dimethyl sulfoxide as a reaction medium resulted in increase in the yield of product **3** to 73% (Table 1, entry 4). Surprisingly, in contrast to lithium *tert*-butoxide,[7] it was noticed that in the case of lithium hydroxide there was no need to prepare a base solution prior to use (Table 1, entry 5). The reactivity of hydroxide anions may also depend on the number of associated water molecules in the media, and based on our experimental data, the presence of increasing amounts of water in the reaction mixture results in decreasing yields of product **3** (Table 1, entries 6–8).

Pyrroles bearing electron-donating groups on their nitrogen are relatively sensitive to the presence of oxidants, which could cause oxidation of the pyrrole core.[11] Because of this, we were interested in determining if the presence of dissolved oxygen in dimethyl sulfoxide inhibits the formation of the desired arylated product. When dimethyl sulfoxide was first degassed under a stream of argon for 10 minutes before use, compound **3** was obtained in 83% yield (Table 1, entry 9). Subsequently the effect of the amount of base was analyzed (Table 1, entries 10 and 11). The apparent need for excess lithium hydroxide may be explained by its incomplete solubility in organic solvent.

Recently, an efficient, organocatalyzed protocol for the direct arylation of benzene was described.[12] Inspired by

SYNTHESIS 2011, No. 17, pp 2833–2837
Advanced online publication: 20.07.2011
DOI: 10.1055/s-0030-1260128; Art ID: Z46011SS

Table 1 Influence of the Reaction Conditions on the Coupling of *N*-Methylpyrrole (**1**) with 4-Iodobenzonitrile (**2**)[a]

Entry[a]	Base	Solvent	Yield (%) of **3**
1	KOH	DMF	27
2	NaOH	DMF	36
3	LiOH	DMF	65
4	LiOH	DMSO	73
5	LiOH	DMSO (fresh soln)	74
6	LiOH	DMSO (wet)	34
7	$LiOH·H_2O$	DMSO	67
8[b]	LiOH	DMSO	65–71
9	LiOH	DMSO (degassed)	83
10	LiOH (1 equiv)	DMSO	49
11	LiOH (4 equiv)	DMSO	82
12[c]	LiOH	DMSO	44
13[d]	LiOH	DMSO	70
14[e]	LiOH	DMSO	61
15[f]	LiOH	DMSO	14
16[g]	LiOH	DMSO	43
17[h]	LiOH	DMSO	37
18[i]	LiOH	DMSO	75

[a] Unless otherwise noted, reactions were performed under the following conditions: 4-iodobenzonitrile (1 equiv), *N*-methylpyrrole (15 equiv), base (2 equiv), 145 °C, overnight; yields were determined by HPLC.

[b] Reactions were performed with the addition of increasing amounts of H_2O (1–5 equiv).

[c] Reaction was performed with the addition of 20 mol% L-proline.

[d] Reaction was performed with the addition of 20 mol% DMEDA.

[e] Reaction was performed with the addition of 20 mol% TMEDA.

[f] For 5 equiv of *N*-methylpyrrole.

[g] For 10 equiv of *N*-methylpyrrole.

[h] Reaction was performed at 100 °C.

[i] Yield was recorded after 5 h.

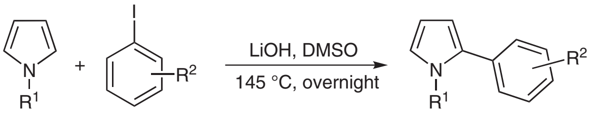
these results, we decided to investigate the effect of L-proline, *N*,*N*′-dimethylethane-1,2-diamine (DMEDA), and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) on the formation of compound **3**. As can be seen (Table 1, entries 12–14), these bases system do not appear to participate in the lithium hydroxide–dimethyl sulfoxide promoted transformation reaction.

In agreement with our observations of lithium *tert*-butoxide promoted arylation, decreasing the ratio of *N*-methylpyrrole to 4-iodobenzonitrile led to a sharp decrease in the yield of compound **3** (Table 1, entries 15 and 16). The influence of other factors, such as time and temperature, were also investigated. While lowering the reaction temperature to 100 °C resulted in decreased yield (Table 1, entry 17), reactions conducted at 145 °C were complete after only five hours (Table 1, entry 18).

Optimum reaction conditions were chosen based on the above results. A fresh solution of lithium hydroxide in degassed dimethyl sulfoxide was found to be the most efficient combination among all of the tested reaction systems, giving 83% of the expected product **3**. These optimal reaction conditions were also confirmed in preparative reactions conducted on a 1 mmol scale.

Using these new conditions as a starting point, the scope and limitations of the reaction were investigated. *N*-Methylpyrrole, together with *N*-phenyl- and *N*-benzylpyrrole, were reacted with a range of aryl iodides bearing electron-withdrawing groups, giving corresponding products in good yields (50–86%). 1-Iodo-4-methoxybenzene (**11**) showed lower reactivity, resulting in the formation of the corresponding *N*-methyl-2-(4-methoxyphenyl)pyrrole (**17**) in only 26% yield (Table 2).

Table 2 Scope of the Optimized Conditions for the Arylation of Pyrrole Derivatives[a]



Pyrrole	R^1	Aryl iodide	R^2	Product	Yield (%)[b]
1	Me	**2**	4-CN	**3**	78
1	Me	**6**	$4-NO_2$	**12**	69
1	Me	**7**	3-CN	**13**	72
1	Me	**8**	$3-NO_2$	**14**	77
1	Me	**9**	2-CN	**15**	86
1	Me	**10**	$2-NO_2$	**16**	72
1	Me	**11**	4-MeO	**17**	26
4	Ph	**2**	4-CN	**18**	54
5	Bn	**2**	4-CN	**19**	50

[a] Reactions were performed under the following conditions: aryl iodide (1 equiv), N-substituted pyrroles (15 equiv), LiOH (4 equiv), DMSO.

[b] Yields of isolated products after column chromatography.

In contrast with the lithium *tert*-butoxide promoted system,[7] under the current protocol, bromides display lower reactivity than iodides. For example, in the reaction between 4-bromobenzonitrile (**20**), and *N*-methylpyrrole (**1**), the desired product **3** was obtained in only 49% yield. Similarly, as expected, 4-chlorobenzonitrile (**21**) gave only 20% of the corresponding product.

Unfortunately, pyrrole itself, as well as *N*-TIPS-pyrrole and *N*-benzoylpyrrole, could not be transformed into their corresponding products under these reaction conditions.

In order to further clarify the reaction mechanism, *N*-substituted pyrrole was reacted with iodoarene in the presence of a radical scavenger. Reaction between *N*-phenylpyrrole and 4-iodobenzonitrile was completely inhibited in the presence of TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl).

We could not exclude the possibility that trace amounts of transition metal salts in lithium hydroxide are responsible for catalyzing the above described transformation.[13] The presence of impurities in lithium hydroxide was examined by inductively coupled plasma-atomic emission spectrometry (ICP-AES, see Table in SI). These results clearly show that the concentrations of most of transition metals (Pd, Fe, Cu, Rh, and Ru) were in the range of 0.1–0.2 ppm. Among metals, which are known to be able to catalyze such coupling reactions, only nickel was present at a level of 7 ppm; furthermore, experiments testing the addition of nickel, palladium, copper, or iron salts to the model reaction did not improve the yield of product **3**. In addition, no difference was observed when the model reaction was performed in brand-new glassware. Still, in view of the fundamental study by Leadbeater, which demonstrated that Suzuki coupling is catalyzed by palladium present in sodium carbonate at only 50 ppb,[13b] we cannot definitively conclude that the process studied here is metal-free. However, ever to minimize the likelihood of contamination, all reaction glassware were exhaustively cleaned prior to use.

In summary, we have demonstrated that direct arylation of pyrrole derivatives bearing *N*-alkyl and *N*-aryl substituents with aryl iodides can be promoted using a lithium hydroxide–dimethyl sulfoxide system, which is known for its superbasic properties. The corresponding 2-arylated products were prepared in good yields, and with high regioselectivity. Based on our results, we propose that the reaction proceeds via a radical type mechanism. Taking into consideration the absence of a transition-metal catalyst, the applied base, and substrate availability, the above described methodology may be useful for the synthesis of aromatic compounds.

All reagents and solvents were purchased from commercial sources and were used as received, unless otherwise noted. Flash chromatography was performed on silica gel (200–400 mesh). ^{1}H and ^{13}C NMR spectra were measured on a Bruker AV 400 or a Bruker AV 500 spectrometer. All chemical shifts are reported in ppm. Mass spectra were obtained via EI-MS or ESI-MS. The optimization study was performed by HPLC (samples were prefiltered through a silica pad).

'Aged' Solution of LiOH in DMSO

LiOH (240 mg, 10 mmol) was dissolved in anhyd DMSO (6.25 mL) and the resulting mixture was stirred at 80 °C overnight. Subsequently, the mixture was cooled down and used for the final coupling reactions. The resulting base solution was stored for 12 h before use.

Arylation of Pyrrole Derivatives; General Procedure

Aryl iodide (0.6 mmol, 1 equiv), LiOH (2.4 mmol, 4 equiv), pyrrole (9 mmol, 15 equiv), and DMSO (250 μL) were placed in a glass tube, and flushed with argon. The resulting reaction mixture was stirred at 145 °C overnight, and subsequently evaporated under reduced pressure. Finally, reaction products were purified by column chromatography (Table 2).

N-Methyl-2-(4-cyanophenyl)pyrrole (3)

Reaction of *N*-methylpyrrole (**1**; 800 μL, 9 mmol) with 4-iodobenzonitrile (**2**; 137 mg, 0.6 mmol) was performed following the above general procedure. The product was further purified by column chromatography (silica gel, Et_2O–hexanes, 1:9); fine white crystals; yield: 85 mg (78%); mp 102 °C (Et_2O–pentane) (Lit.[7] mp 102–103 °C).

Spectral properties concur with the published data.[7]

N-Methyl-2-(4-nitrophenyl)pyrrole (12)

Reaction of *N*-methylpyrrole (**1**; 800 μL, 9 mmol) with 1-iodo-4-nitrobenzene (**6**; 149.4 mg, 0.6 mmol) was performed following the above general procedure. The product was further purified by column chromatography (silica gel, Et_2O–hexanes, 1:9); fine yellow crystals; yield: 84 mg (69%); mp 115–116 °C (CH_2Cl_2) (Lit.[7] mp 114–115 °C).

Spectral properties concur with the published data.[7]

N-Methyl-2-(3-cyanophenyl)pyrrole (13)

Reaction of *N*-methylpyrrole (**1**; 800 μL, 9 mmol) with 3-iodobenzonitrile (**7**; 137 mg, 0.6 mmol) was performed following the above general procedure. The product was further purified by column chromatography (silica gel, Et_2O–hexanes, 1:9); fine white crystals; yield: 79 mg (72%); mp 113 °C (Et_2O–pentane) (Lit.[7] mp 112–113 °C).

Spectral properties concur with the published data.[7]

N-Methyl-2-(3-nitrophenyl)pyrrole (14)

Reaction of *N*-methylpyrrole (**1**; 800 μL, 9 mmol) with 1-iodo-3-nitrobenzene (**8**; 149.4 mg, 0.6 mmol) was performed following the above general procedure. The product was further purified by column chromatography (silica gel, Et_2O–hexanes, 1:9); fine yellow crystals; yield: 93 mg (77%); mp 118–109 °C (CH_2Cl_2–hexanes) (Lit.[7] mp 118.5–119.5 °C).

Spectral properties concur with the published data.[7]

N-Methyl-2-(2-cyanophenyl)pyrrole (15)

Reaction of *N*-methylpyrrole (**1**; 800 μL, 9 mmol) with 2-iodobenzonitrile (**9**; 137 mg, 0.6 mmol) was performed following the above general procedure. The product was further purified by column chromatography (silica gel, Et_2O–hexanes, 1:9); fine white crystals; yield: 94 mg (86%); mp 83 °C (Et_2O–pentane) (Lit.[7] mp 83–84 °C).

Spectral properties concur with published data.[7]

N-Methyl-2-(2-nitrophenyl)pyrrole (16)

Reaction of *N*-methylpyrrole (**1**; 800 μL, 9 mmol) with 1-iodo-2-nitrobenzene (**10**; 149.4 mg, 0.6 mmol) was performed following the above general procedure. The product was further purified by column chromatography (silica gel, Et_2O–hexanes, 1:9); fine yellow crystals; yield: 87 mg (72%); mp 62–63 °C (CH_2Cl_2–hexanes) (Lit.[7] mp 62–63 °C).

Spectral properties concur with the published data.[7]

N-Methyl-2-(4-methoxyphenyl)pyrrole (17)

Reaction of *N*-methylpyrrole (**1**; 800 μL, 9 mmol) with 1-iodo-4-methoxybenzene (**11**; 140.4 mg, 0.6 mmol) was performed following the above general procedure. The product was further purified by column chromatography (silica gel, Et_2O–hexanes, 5:95), fine white crystals; yield: 29 mg (26%); mp 58 °C (Et_2O–pentane) (Lit.[7] mp 59–60 °C).

Spectral properties concur with published data.[7]

N-Phenyl-2-(4-cyanophenyl)pyrrole (18)

Reaction of *N*-phenylpyrrole (**4**; 1.29 g, 9 mmol) with 4-iodobenzonitrile (**2**; 137 mg, 0.6 mmol) was performed following the above general procedure. The product was further purified by column chromatography (silica gel, Et_2O–hexanes, 5:95); fine crystals; yield: 82 mg (82%); mp 125–126 °C (Et_2O–pentane) (Lit.[7] mp 124–125 °C).

Spectral properties concur with the published data.[7]

N-Benzyl-2-(4-cyanophenyl)pyrrole (19)

Reaction of *N*-benzylpyrrole (**5**; 1.40 mL, 9 mmol) with 4-iodobenzonitrile (**2**; 137 mg, 0.6 mmol) was performed following the above general procedure. The product was further purified by column chromatography (silica gel, Et_2O–hexanes, 5:95); yellowish oil; yield: 77.6 mg (50%).

Supporting Information for this article is available online at: http://www.thieme-connect.com/ejournals/toc/synthesis.

Acknowledgment

This study was financed by the European Community [RTN Network (R) Evolutionary Catalysis MRTN-CT-2006-035866].

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