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Nickel-mediated amination chemistry. Part 2: Selective *N*-arylation or *N*,*N*′-diarylation of piperazine

Eric Brenner, Raphaël Schneider and Yves Fort *

Synthèse Organique et Réactivité, UMR CNRS-UHP 7565, Université Henri Poincaré, Nancy I, Faculté des Sciences, BP 239, 54506 Vandoeuvre les Nancy Cedex, France

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Abstract

The 2,2′-bipyridine liganded Ni catalyst has revealed a good selectivity in the mono arylation of piperazine starting from aryl chlorides allowing a selective and efficient synthesis of *N*-arylpiperazines using stoichiometric amounts of reagents. The preparation of *N*,*N*′-diaryl substituted piperazines is also described. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: nickel; arylamination; *N*-arylpiperazine; *N*,*N*′-diarylpiperazine.

N-Aryl and *N*,*N*′-diarylpiperazines are key structural elements of many compounds possessing broad biological activities such as ligands of serotonin (5-HT) receptors,[1] antifungals,[2] antivirals[3] or cholesterol ester transfer protein inhibitors.[4] During the last decade, numerous procedures have been reported for the preparation of these compounds including S_NAr reactions in liquid phase[5] or on solid support,[6] S_NAr reactions on tricarbonyl chromium complexes,[7] displacement of a chlorine atom in arene–iron complexes,[8] reaction of aniline derivatives with bis(2-bromoethyl) *N*-substituted amines on basic alumina[9] or, more recently, palladium catalysed aminations of aryl halides (generally bromides).[10] The latter reactions, extensively developed during recent years,[11] have only scarcely been used with piperazine itself due to the competitive bis-arylation reaction. Indeed, four equivalents of piperazine are needed to obtain *N*-arylpiperazines in moderate yields, ranging from 10 to 50%, using the Pd/P(*o*-tol)$_3$ system.[10a] A large excess of amine (up to six equivalents) associated to the Pd/P(*t*-Bu)$_3$ catalyst was used to improve the selectivity and the yields.[10c] Alternatively, the preparation of *N*-arylpiperazines in a multistep protocol starting from *N*-protected piperazines had also been described and did not afford better results.[12]

Herein, we wish to report that our recently described 2,2′-bipyridine liganded nickel catalyst[13] is effective for the synthesis of *N*-arylpiperazines **1** using only 1.1 equivalents of the starting amine relative to the aryl chloride (Scheme 1).[14]

All the results obtained using this methodology are reported in Table 1. For example, the amination of chlorobenzene using 1.1 equivalents of piperazine in the presence of 10 mol% 2,2′-bipyridine

* Corresponding author. E-mail: yves.fort@sor.uhp-nancy.fr (Y. Fort)

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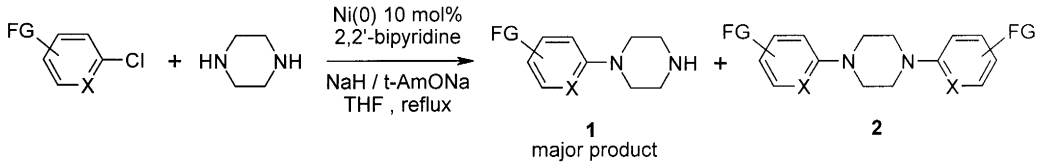
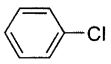
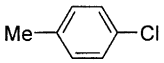
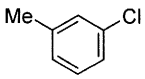
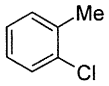
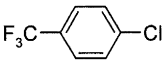
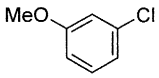
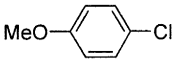
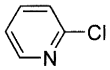


Scheme 1.

liganded Ni in refluxing THF gave after workup and purification a mixture of *N*-phenyl **1a** and *N*,*N*′-diphenylpiperazine **2a** in, respectively, 61 and 16% isolated yields (Table 1, entry a, reaction conditions A).

Table 1
Nickel-catalysed synthesis of *N*-arylpiperazines **1** from aryl chlorides

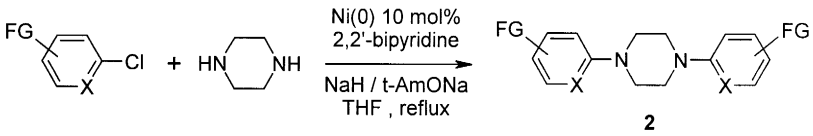
Entry	Aryl chloride	*Reaction Conditions A*[a]			*Reaction Conditions B*[b]	
		Reaction time (h)[c]	Isolated yield of **1** (%)[d]	Isolated yield of **2** (%)	Reaction time (h)[c]	Isolated yield of **1** (%)[d]
a		8.5	61	16	6	86
b		9.5	56	15	6.5	81
c		9	57	15	6	82
d		12	29	2	8	42
e		8	62	10	6	87
f		9.5	52	11	6	87
g		12	23	1	8	41
h		8	63	12	7	78

[a] Reactions were carried out with 25 mmol aryl chloride, 27.5 mmol piperazine, 2.5 mmol $Ni(OAc)_2$, 7.5 mmol 2,2'-bipyridine, 5 mmol *t*-AmOH, 30 mmol NaH and 5 mmol styrene in 40 ml THF. [b] Reactions were carried out with 25 mmol aryl chloride, 50.0 mmol piperazine, 2.5 mmol $Ni(OAc)_2$, 7.5 mmol 2,2'-bipyridine, 5 mmol *t*-AmOH, 30 mmol NaH and 5 mmol styrene in 40 ml THF. [c] Determined by GC analysis. [d] Products were isolated by chromatography on silica gel. All yields reported are isolated yields of compounds estimated to be > 97% pure by NMR and GC analysis. All compounds were characterised by NMR (^1H, ^{13}C), IR, MS or combustion analysis.

N-Arylpiperazines can be prepared from various aryl chlorides substituted either by electron-withdrawing or electron-donating groups. For all reactions described in Table 1, side products arising from reduction and homocoupling were obtained in less than 2% yield. Note that reduction was considerably decreased by addition of a catalytic amount of styrene in the reaction medium.[13a] The amination reaction was found to be sensitive to the steric hindrance of the aryl chloride. 2-Chlorotoluene gave *N*-(2-methylphenyl)piperazine **1d** in 29% yield. Electron-poor aryl chlorides gave the corresponding

arylpiperazines **1** in good yields (entries e, f and h) while lower yields were obtained with electron-rich aryl chlorides (entry g). It must be underlined that amounts of bis-arylation products increased with electron-poor aryl chlorides due to their higher reactivity. We have also examined the influence of piperazine/aryl chloride ratio on the selectivity. Increasing the initial amount of piperazine to 2 equivalents (reaction conditions B) led to **1** as the sole reaction product. These results are similar to those obtained in Pd-catalysed amination reactions using a large excess (4–6 equiv.) of piperazine. However, reaction conditions A (1.1 equiv. of piperazine) allowed for easy access to *N*-arylpiperazines especially when the starting materials are of high cost.

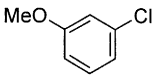
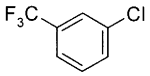
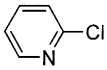
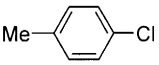
In order to extend the scope of the 2,2′-bipyridine liganded Ni catalyst, we next studied bis-arylation reactions of piperazine (Scheme 2).



Scheme 2.

GC analysis of the reaction mixture indicated that the initial coupling is more facile than the second one. Conversion into the desired products may be effected by extending the reaction time or by the use of an excess aryl chloride (4 equiv.). Under these conditions, symmetrically *N*,*N*′-biaryl substituted piperazines **2** were obtained in good yields (Table 2). Note that compound **1** and biaryl were obtained as by-products in, respectively, less than 5 and 10% isolated yields. Except 2-chloropyridine which afforded **2** in a moderate 55% yield (entry d), aryl chlorides bearing electron withdrawing substituents were more reactive in bis-arylation reactions and gave higher yields of **2** (compare entries b and c with entry e).

Table 2
Nickel-catalysed synthesis of *N*,*N*′-diarylpiperazines **2**[a]

Entry	Aryl chloride	Reaction Time (h)[b]	Isolated yield of **2** (%)[c]
a		8	70
b		7	79
c		7	82
d		10	55
e		12	54

[a] Reactions were carried out with 25.0 mmol piperazine, 100 mmol aryl chloride, 5.0 mmol $Ni(OAc)_2$, 15.0 mmol 2,2'-bipyridine, 10 mmol *t*-AmOH, 60 mmol NaH and 10 mmol styrene in 40 ml THF. [b] Determined by GC analysis. [c] Products were isolated by chromatography on silica gel. All yields reported are isolated yields of compounds estimated to be > 97% pure by NMR and GC analysis. All compounds were characterised by NMR (^1H, ^{13}C), IR, MS or combustion analysis.

We consider the mechanism of these amination reactions to proceed as follows: (i) generation of Ni(0) by reduction of $Ni(OAc)_2$ with alkoxide activated NaH followed by amine coordination to Ni; (ii) oxidative addition of the aryl chloride; (iii) reductive elimination of the arylamine and regeneration of the Ni catalyst.

In conclusion, novel syntheses of *N*-aryl and *N*,*N*′-diaryl substituted piperazines have been achieved using nickel-catalysed amination reactions. The main advantage of our method lies in the fact that monoarylations could be performed using stoichiometric amounts of the starting materials. Further extensions of these reactions with aryl polychlorides are under investigation.

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14. Representative procedure for reaction conditions A: *N*-phenylpiperazine (**1a**): A solution of *t*-AmOH (5 mmol) in THF (5 mL) was added to a suspension of NaH (30 mmol) in THF (30 mL) and the mixture was heated to 63°C. Piperazine (27.5 mmol) was added followed by dried $Ni(OAc)_2$ (2.5 mmol) and 2,2′-bipyridine (7.5 mmol) and the reflux was maintained for 2 h. To the dark suspension of 2,2′-bipyridine liganded Ni(0) thus obtained was added chlorobenzene (25 mmol) and styrene (5 mmol) in THF (5 mL) and the mixture was heated for 6 h. After cooling to room temperature, hydrolysis with water (1 mL) and dilution with CH_2Cl_2, the mixture was filtered, dried over $MgSO_4$ and concentrated. The crude material was purified by chromatography on silica gel using MeOH/AcOEt (40/60) to give *N*-phenylpiperazine **1a**[15] in 61% yield. ^{1}H NMR ($CDCl_3$, 400 MHz): 7.23 (dd, $^3J=^3J'$=8.0 Hz, 2H); 6.88 (d, ^3J=8.0 Hz, 2H); 6.83 (dd, $^3J=^3J'$=8.0 Hz, 1H); 3.12–3.04 (m, 4H); 2.98–2.90 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): 152.20, 129.48, 120.10, 116.48, 50.71, 46.48. IR (ν, cm^{-1}): 3292 (NH).
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