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Palladium-Catalyzed *N*-Arylation of *N,N*-Dialkylhydrazines with Aryl Chlorides

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Abstract: *N,N*-Dialkyl-*N'*-arylhydrazines have been prepared usually in high to excellent yields via the reaction of *N,N*-dialkylhydrazines with aryl chlorides in the presence of $Pd_2(dba)_3$, Xphos and NaO-*t*-Bu in dioxane at 120 °C. With *ortho*-substituted aryl chlorides best results have been obtained by using 2-(2′,6′-dimethoxybiphenyl)dicyclohexylphosphine (ligand **d)** as the ligand.

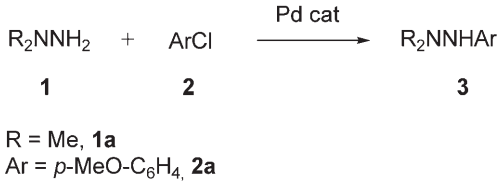
Keywords: aryl chlorides; carbon-nitrogen bond forming reaction; hydrazines; palladium

Introduction

Because of their biological activities, *N,N*-dialkyl-*N'*-arylhydrazines represent an important synthetic target. Most of them act as inhibitors of ileal bile acid transport,[1] herbicides,[2] interleukin-8 receptor antagonists,[3] antibacterial agents,[4] inhibitors of the coagulation cascade.[5] *N,N*-Dialkyl-*N'*-arylhydrazines are also useful synthetic intermediates.[6] One of the most obvious and straightforward approaches to their synthesis would be the palladium-catalyzed *N*-arylation of *N,N*-dialkylhydrazines. Indeed, because of the lack in the literature of an efficient procedure based on such a C–N bond forming reaction,[7] we recently explored this chemistry and found that the palladium-catalyzed reaction of aryl bromides with *N,N*-dialkylhydrazine/2 LiCl adducts affords the desired *N,N*-dialkyl-*N'*-arylhydrazines usually in good yields.[8] The procedure, however, suffers from some limitations such as the moderate yields obtained with electron-rich aryl bromides and the reluctance of *ortho*-substituted aryl bromides to give the desired products. Our interest in *N,N*-dialkyl-*N'*-arylhydrazines prompted us to investigate further this synthetic approach in an attempt to overcome these drawbacks and to extend the procedure to the attractive class of aryl chlorides. Herein we report the result of this study.

Results and Discussion

Initial studies were directed toward finding a general set of reaction conditions that could be applied to a wide range of aryl chlorides and *N,N*-dialkylhydrazines. Since reactions such as that of *p*-chloroanisole **2a** with *N,N*-dimethylhydrazine **1a** were likely to prove among the most difficult, we decided to optimize that particular process (Scheme 1). On the basis of our previous work, which showed that *N,N*-dialkylhydrazine/2 LiCl adducts give significantly higher yields than the corresponding free hydrazines, the *N,N*-dimethylhydrazine/2 LiCl adduct was used in the first reaction examined. The reaction was carried out under the following conditions: 0.025 equivs. of $Pd_2(dba)_3$, 0.1 equiv. of Xphos [2-(2′,4′,6′-triisopropylbiphenyl)dicyclohexylphosphine] – recently developed by Buchwald et al.[9] and shown to produce catalyst systems with a greater degree of activity in the oxidative addition of aryl chlorides to Pd(0) species than other commonly used ligands – 1.4 equivs. of NaO-*t*-Bu in toluene at 120 °C. After 24 h, the arylated *N,N*-dimethylhydrazine **3a** was isolated in 45% yield. Surprisingly, when we repeated the same reaction using free *N,N*-dimethylhydrazine as the nitrogen partner, compound **3a** was isolated in 65% yield. Therefore, we turned our attention to optimizing the reaction of



Scheme 1.

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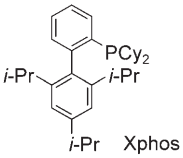
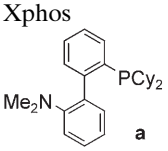
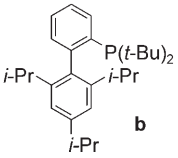
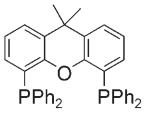
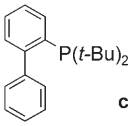
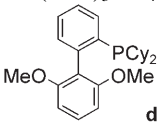
Table 1. Ligands, bases, and solvents in the palladium-catalyzed reaction of *N,N*-dimethylhydrazine **1a** with *p*-chloroanisole **2a**.[a]

Entry	Ligand	Base	Solvent	Reaction time [h]	Yield [%] of **3a**[b]
1	 Xphos	NaO-*t*-Bu	toluene	24	65
2	Xphos	NaO-*t*-Bu	dioxane	24	81
3	Xphos	NaO-*t*-Bu	dioxane	24	70[c]
4	Xphos	K_3PO_4	dioxane	24	72
5	Xphos	Cs_2CO_3	dioxane	24	23
6	Xphos	NaO-*t*-Bu	dioxane	6	80[d]
7	Xphos	NaO-*t*-Bu	dioxane	5	70[e]
8	Xphos	NaO-*t*-Bu	DMF	6	21
9	Xphos	NaOH	dioxane	8	60
10	Xphos	NaOH	dioxane/H_2O	24	30[f]
11	 **a**	NaO-*t*-Bu	dioxane	24	65
12	 **b**	NaO-*t*-Bu	dioxane	24	75
13	 Xantphos	NaO-*t*-Bu	dioxane	24	7 [g]
14	 **c**	NaO-*t*-Bu	dioxane	24	74
15	$HP(t\text{-}Bu)_3{\cdot}BF_4$	NaO-*t*-Bu	dioxane	24	39 [h]
16	 **d**	NaO-*t*-Bu	dioxane	5	62[i]

[a] Unless otherwise stated, reactions were carried out on a 0.563 mmol scale at 120 °C in 2 mL of solvent using 1 equiv. of *p*-chloroanisole, 2 equivs. of *N,N*-dimethylhydrazine, 0.025 equivs. of $Pd_2(dba)_3$, 0.1 equiv. of the phosphine ligand, and 1.4 equivs. of base.
[b] Yields are given for isolated products.
[c] In the presence of 0.0125 equivs. of $Pd_2(dba)_3$ and 0.05 equivs. of Xphos.
[d] In the presence of 0.05 equivs. of Xphos.
[e] With 1.5 equivs. of *N,N*-dimethylhydrazine.
[f] In 1.8 mL of dioxane and 0.2 mL of H_2O.
[g] In the presence of 0.05 equivs. of Xantphos.
[h] Anisole, derived from a reduction process, was obtained in 7% yield and the starting *p*-chloroanisole was recovered in 50% yield.
[i] In the presence of 0.05 equivs. of the phosphine ligand.

p-chloroanisole with *N,N*-dimethylhydrazine. Part of our optimization work using different ligands, bases and solvents is shown in Table 1.

Conducting our model reaction in dioxane led to a significant increase of the yield (Table 1, entry 2) whereas the use of DMF afforded **3a** in 21% yield

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(Table 1, entry 8). The reaction was subsequently carried out using other bases, but the desired *N*-aryl derivative was obtained in lower yield with K_3PO_4 (Table 1, entry 4) and NaOH (Table 1, entries 9 and 10). With Cs_2CO_3 **3a** was isolated only in 23% yield (Table 1, entry 5). A variety of Buchwald dialkylmonophosphine ligands was also screened along with P(*t*-Bu)$_3$ (added to the reaction mixture as the tetrafluoroborate salt)[10] and bidentate Xantphos.[11] In general, monophosphine ligands **a**, **b**, **c**, and **d** all gave satisfactory results (Table 1, entries 11, 12, 14, and 16, respectively), always significantly better than P(*t*-Bu)$_3$ or Xantphos. P(*t*Bu)$_3$ led to a 50% conversion producing 39% of **3a** and 7% of anisole, derived from reduction of *p*-chloroanisole (Table 1, entry 15). With Xantphos, which afforded *N*-aryl derivatives in good yields with a variety of aryl bromides and *N,N*-dialkylhydrazine/2 LiCl adducts,[8] the reaction was particularly unsatisfactory, compound **3a** being isolated only in 7% yield (Table 1, entry 13). The best result in terms of yield and reaction time was obtained when the reaction was carried using 0.025 equivs. of $Pd_2(dba)_3$ and 0.05 equivs. of Xphos in the presence of 1.4 equivs. of NaO-*t*-Bu in dioxane at 120 °C (Table 1, entry 6). The higher efficiency in some palladium-catalyzed reactions of catalyst systems based on bulky electron-rich monophosphine ligands and palladium in a 1:1 ratio has been already observed.[12] This has been attributed to the propensity of bulky ligands to form monoligated LPd(0) species,[13] with beneficial effects on the catalytic cycle.

Using the "optimal" conditions found, we next examined the reaction using various aryl chlorides and *N,N*-dialkylhydrazines in order to determine the scope and limitations of this process. The results are listed in Table 2.

Usually, under these conditions the reaction gave *N,N*-dialkyl-*N'*-arylhydrazines in high to excellent

Table 2. Preparation of *N,N*-dialkyl-*N'*-arylhydrazines **3** *via* palladium-catalyzed reaction of *N,N*-dialkylhydrazines **1** with aryl chlorides **2**.[a]

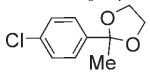
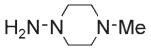
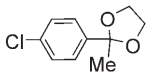
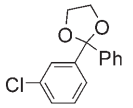
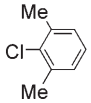
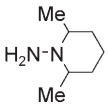
Entry	*N,N*-Dialkylhydrazine **1**	Aryl chloride **2**	Reaction time [h]	Yield [%] of **3**[b]	
1	H_2NNMe_2	*p*-MeO-C_6H_4-Cl	6	80	**3a**
2		*m*-MeO-C_6H_4-Cl	24	85[c]	**3b**
3		*m*-MeO-C_6H_4-Cl	5	81	**3b**
4		*o*-Me-C_6H_4-Cl	8	43	**3c**
5		*o*-Me-C_6H_4-Cl	4	78[d]	**3c**
6			7	76	**3d**
7		PhCl	7.5	78[e]	**3e**
8			2.5	78	**3f**
9		*m*-CF_3-C_6H_4-Cl	5	75	**3g**
10			5	85	**3h**
11		*p*-MeO-C_6H_4-Cl	5.5	87	**3i**
12			2.5	90	**3j**
13			2.7	85	**3k**
14		PhCl	5	88	**3l**
15			5.5	90[d]	**3m**
16		*p*-MeO-C_6H_4-Cl	3.5	81	**3n**
17		*o*-Me-C_6H_4-Cl	5	85[d]	**3o**
18		PhCl	5	85	**3p**
19		*m*-CF_3-C_6H_4-Cl	5	80	**3q**

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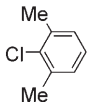
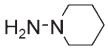
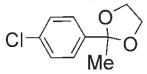
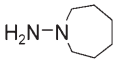
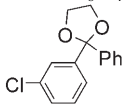
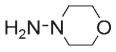
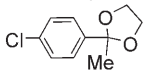
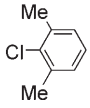
Table 2. (Continued)

Entry	*N,N*-Dialkylhydrazine **1**	Aryl chloride **2**	Reaction time [h]	Yield [%] of **3**[b]	
20			3.5	90[d]	**3r**
21		*p*-MeO-C_6H_4-Cl	7	85	**3s**
22		*m*-MeO-C_6H_4-Cl	3	87	**3t**
23		*o*-Me-C_6H_4-Cl	3	87[d]	**3u**
24			3.5	83	**3v**
25		PhCl	3.5	87	**3w**
26			2.5	82	**3y**
27		*m*-CF_3-C_6H_4-Cl	3	85	**3z**
28			3	80	**3za**
29		*p*-MeO-C_6H_4-Cl	4.5	67 (97)[e]	**3zb**
30		*o*-Me-C_6H_4-Cl	5	85[d]	**3zc**
31			6	85	**3zd**
32		PhCl	5	87	**3ze**
33		*m*-CF_3-C_6H_4-Cl	4.5	86	**3zf**
34		*p*-MeO-C_6H_4-Cl	3	83	**3zg**
35		*m*-MeO-C_6H_4-Cl	4	79	**3zh**
36		*m*-MeO-C_6H_4-Cl	24	82[c]	**3zh**
37		*o*-Me-C_6H_4-Cl	3	87[d]	**3zi**
38			3.5	83	**3zj**
39		PhCl	3	88	**3zk**
40			3.5	93	**3zl**
41		*m*-CF_3-C_6H_4-Cl	3	91	**3zm**
42			3	84	**3zn**
43			7	90[d]	**3zo**

[a] Unless otherwise stated, reactions were carried out on a 0.563 mmol scale at 120 °C in 2 mL of dioxane using 1 equiv. of aryl chloride, 2 equivs. of *N,N*-dialkylhydrazine, 0.025 equivs. of $Pd_2(dba)_3$, 0.05 equivs. of Xphos, and 1.4 equivs. of KO-*t*-Bu.
[b] Yields are given for isolated products.
[c] In toluene.
[d] In the presence of ligand **d**.
[e] Yield calculated by HPLC analysis.

yields with a variety of aryl chlorides. Only with *o*-chlorotoluene was a moderate yield obtained (Table 2, entry 4). To our delight, on simply replacing Xphos with the bulky electron-rich monodentate dialkylphosphinobiaryl ligand **d**,[14] a 78% yield of **3c** was isolated (Table 2, entry 5). This ligand was also successfully used in a number of reactions of *o*-chlorotoluene with other *N,N*-dialkylhydrazines (Table 2, entries 17, 23, 30, 37). Even the sterically encumbered 2-chloro-*m*-xylene gave excellent yields of the desired

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product under these modified conditions (Table 2, entries 15, 20, 43).

Conclusions

We have developed a straightforward route for the preparation of *N,N*-dialkyl-*N'*-arylhydrazines from *N,N*-dialkylhydrazines and aryl chlorides in the presence of $Pd_2(dba)_3$ as the palladium source, Xphos [or 2-(2′,6′-dimethoxybiphenyl)dicyclohexylphosphine, ligand **d**, with *ortho*-substituted aryl chlorides] as the ligand, dioxane as the solvent, and NaO-*t*-Bu as the base. The usually high to excellent yields and the simplicity of the experimental procedure make this method particularly convenient for the preparation of this class of compounds.

Experimental Section

Melting points were determined with a Büchi B-545 apparatus and are uncorrected. All of the reagents, catalysts, and solvents are commercially available and were used as purchased, without further purification. Reaction products were purified on axially compressed columns, packed with SiO_2 25–40 μm (Macherey–Nagel), connected to a Jasco RI-031 Plus solvent delivery system and to a Jasco PU-2087 Plus refractive index detector, and eluting with *n*-hexane/ethyl acetate mixtures. ^{1}H NMR (400 MHz), ^{13}C NMR (100.6 MHz) and ^{19}F NMR (376.5 MHz) spectra were recorded with a Bruker Avance 400 spectrometer. Splitting patterns are designed as s (singlet), d (doublet), t (triplet), q (quartet), qp (quintuplet), m (multiplet), or bs (broad singlet). IR spectra were recorded with a Jasco FT/IR-430 spectrometer. Mass spectra were recorded with a Shimadzu GCMS-QP2010S.

Typical Procedure for the Synthesis of *N,N*-Dialkyl-*N'*-arylhydrazines (3) from *N,N*-Dialkylhydrazines (1) and Aryl Chlorides (2); Preparation of (3a)

In a Carousel Tube Reactor (Radley Discovery), $Pd_2(dba)_3$ (0.0129 g, 0.014 mmol) and Xphos (0.0134, 0.028 mmol) were stirred at room temperature under argon in 1.0 mL of dioxane for ten minutes. Then 4-chloroanisole (0.080 g, 0.563 mmol), *N,N*-dimethylhydrazine (0.086 mL, 1.126 mmol), 1 mL of dioxane and NaO-*t*-Bu (0.0757 g, 0.788 mmol) were added. The reaction mixture was stirred at 120 °C under argon for 6 h. After cooling, the reaction mixture was diluted with ethyl acetate, washed with $NaHCO_3$, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by chromatography (silica gel, 35 g; *n*-hexane/ethyl acetate, 80/20 v/v) to give **3a**; yield: 0.083 g (71 %); IR (neat): $\nu = 3218$, 2978 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 6.89$–6.80 (m, 4H), 4.01 (bs, 1H), 3.78 (s, 3H), 2.53 (s, 6H); ^{13}C NMR ($CDCl_3$): $\delta =$ 153.6, 141.7, 115.5, 114.7, 55.8, 47.9; MS: calculated for $C_9H_{14}N_2O = 166.22$; MS (*m/z*) (relative intensity) = 166 (M^+, 35), 122 (100), 151 (14), 42 (57).155.3, 154.1, 142.6, 139.9, 133.9, 131.9, 128.9, 128.9, 127.9, 127.5, 127.1, 126.9, 124.1, 118.9, 117.3, 115.0.

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