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Synthesis of *N,N*-Dialkyl-*N*′-arylhydrazines via Palladium-Catalyzed N-Arylation by Using *N,N*-Dialkylhydrazines/2LiCl Adducts

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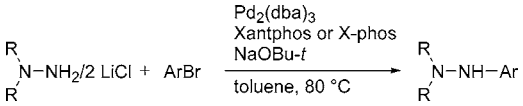
ABSTRACT



The reaction of *N,N*-dialkylhydrazine/2LiCl adducts with aryl bromides in the presence of $Pd_2(dba)_3$ as the palladium source, Xantphos or X-phos as the ligands, toluene as the solvent, and NaOBu-*t* as the base provides an efficient route to *N,N*-dialkyl-*N*′-arylhydrazines. Best results were obtained by using *N,N*-dialkylhydrazine/2LiCl adducts prepared in situ, omitting their isolation.

The development of the palladium-catalyzed N-arylation process by Buchwald[1] and Hartwig[2] has provided a powerful tool for the functionalization of a wide range of nitrogen-containing derivatives from readily available aryl halides and triflates. However, despite the huge amount of work done in this area,[3] the utilization of this procedure for the N-arylation of hydrazines has received little attention. To the best of our knowledge, hydrazines have been subjected to palladium-catalyzed N-arylation processes in intramolecular cyclizations to give 2-aryl-2*H*-indazoles,[4] 1-aryl-1*H*-indazoles,[5] and indole[1,2-*b*]indazoles.[6] An intermolecular N-arylation of N-substituted and N,N-disubstituted hydrazines has also been reported.[7] However, whereas the reaction of aryl halides with *N*-aryl and *N,N*-diarylhydrazines has usually been found to give arylation products in good to high yields, unsatisfactory results were obtained with *N,N*-dialkylhydrazines. For example, bromobenzene and *N,N*-dimethylhydrazine gave the desired *N,N*-dimethyl-*N*′-phenylhydrazine in only 24% yield.[7] Other work involving

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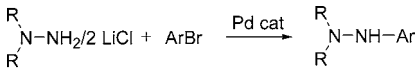
hydrazine derivatives that could be used to prepare *N*,*N*-dialkyl-*N*′-arylhydrazines has been described,[8] but in those cases, two or more steps would be needed. On the other hand, *N*,*N*-dialkyl-*N*′-arylhydrazines are useful synthetic intermediates,[9] and most of them exhibit important biological activities, acting as inhibitors of ileal bile acid transport,[10] herbicides,[11] interleukine-8 receptor antagonists,[12] antibacterial agents,[13] and inhibitors of the coagulation cascade.[14]

Thus, the development of a simple and general procedure for the direct preparation of this class of compounds would be greatly desirable. Hereafter, we report just such a process, involving the palladium-catalyzed reaction of aryl bromides **2** with *N*,*N*-dialkylhydrazine/2LiCl adducts **1** (Scheme 1).

Scheme 1



1 **2** **3**

Initial studies were directed toward finding a general set of reaction conditions that could be applied to a variety of *N*,*N*-dialkylhydrazines and aryl bromides. *N*,*N*-Dimethylhydrazine and *p*-(phenyl)bromobenzene were selected as the model system, and the influence of ligands, bases, and LiCl was examined. Some results from that study are summarized in Table 1.

Table 1. Ligands, Bases, and LiCl in the Palladium-Catalyzed Synthesis of *N*,*N*-Dimethyl-*N*′-(*p*-phenylphenyl)hydrazine **3a**[a]

entry	ligand	base	hydrazine (equiv)	time (h)	% yield[b] of **3a**
1	dppf	NaOBu-*t*	Me_2NNH_2 (1.2)	24	c
2	BINAP	NaOBu-*t*	Me_2NNH_2 (1.2)	7	50[d]
3	MOP	NaOBu-*t*	Me_2NNH_2 (1.2)	8	11
4	Xantphos	NaOBu-*t*	Me_2NNH_2 (1.2)	4	55[e]
5	Xantphos	Cs_2CO_3	Me_2NNH_2 (1.2)	24	traces
6	Xantphos	KOBu-*t*	Me_2NNH_2 (1.2)	12	32
7	Xantphos	NaOBu-*t*	Me_2NNH_2 (2)	24	40
8	Xantphos	NaOBu-*t*	Me_2NNH_2/2LiCl (2)	6.5	75[f]
9	BINAP	NaOBu-*t*	Me_2NNH_2/2LiCl (2)	7	54[g]

[a] Unless otherwise stated, reactions were carried out on a 0.563 mmol scale in 2 mL of toluene at 80 °C under argon using 1 equiv of *p*-(phenyl)bromobenzene, *N*,*N*-dimethylhydrazine (as shown in table), 0.025 equiv of $Pd_2(dba)_3$, 0.05 equiv of bidentate ligand, and 1.4 equiv of base. [b] Yields are given for isolated products. [c] $Pd(OAc)_2$ (0.05 equiv) was used. [d] Starting bromide was recovered in 16% yield. [e] Biphenyl was isolated in 30% yield. [f] Biphenyl was isolated in 4% yield. [g] Starting bromide was recovered in 42% yield.

The reaction of *N*,*N*-dimethylhydrazine with *p*-(phenyl)-bromobenzene in the presence of $Pd_2(dba)_3$, NaOBu-*t*, and BINAP or Xantphos[15] (Figure 1) in toluene at 80 °C afforded similar results (Table 1, entries 2 and 4). NaOBu-*t* proved

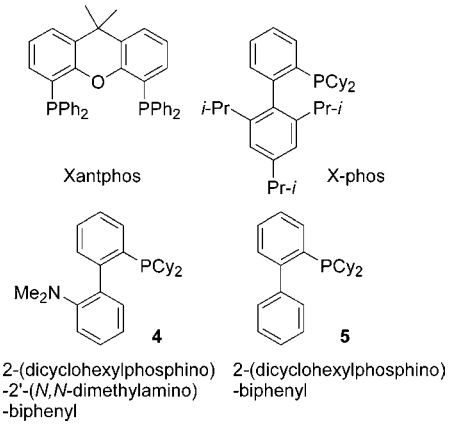


Figure 1.

to be clearly superior to Cs_2CO_3 (Table 1, compare entry 4 with entry 5) and to give higher yields than KOBu-*t* (Table 1, compare entry 4 with entry 6). However, even under the best conditions, the desired hydrazine derivative was isolated in moderate yields, one of the main side reactions being the formation of biphenyl, derived from the reduction of *p*-(phenyl)bromobenzene. Though further studies are needed to provide a detailed mechanism for this reduction reaction, on the basis of previous studies on the formation of arenes in palladium-catalyzed amination of aryl bromides[16] and the reduction of σ-alkylpalladium intermediates by tertiary amines,[17] we surmised that the main reaction pathway for the formation of reduction byproducts might involve coordination of the disubstituted nitrogen atom to the σ-arylpalladium intermediate formed in situ. According to this

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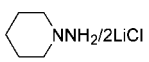
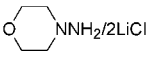
working hypothesis, preventing this coordination could minimize the observed side reaction.

Therefore, on the basis of the results obtained by some of us in the reaction of hydrazine/2LiCl adducts with tungsten and chromium Fischer-type carbene complexes,[18] wherein it was shown that the reduced nucleophilic character of the β-nitrogen of dialkylhydrazines has a beneficial effect on the hydrazinolysis of Fischer-type oxacarbenes, we decided to investigate the use of *N*,*N*-dimethylhydrazine/2LiCl adduct. This adduct was prepared according to the previously described protocol,[18] adding 1 equiv of *N*,*N*-dimethylhydrazine to an anhydrous THF solution of LiCl (2 equiv) at room temperature. The resulting white solid was subjected to N-arylation conditions. We were pleased to find that, with Xantphos as the ligand, compound **3a** could be isolated in 75% yield (Table 1, entry 8). Biphenyl was isolated only in 4% yield (30% yield under the same conditions using *N*,*N*-dimethylhydrazine; Table 1, entry 4). Interestingly, in contrast to reactions carried out with *N*,*N*-dimethylhydrazine (Table 1, entries 2 and 4), with the *N*,*N*-dimethylhydrazine/2LiCl adduct BINAP gave results significantly different from Xantphos. In fact, the use of BINAP afforded the desired product in a yield similar to that obtained with *N*,*N*-dimethylhydrazine (Table 1, compare entry 2 with entry 9).

Other hydrazine/2LiCl adducts and aryl bromides were subjected to the best conditions found (Table 1, entry 8), and the results obtained are shown in Table 2. Entries 7 and 8 (see also Table 1 footnotes c and d) highlight further the efficiency of the protocol based on the use of *N*,*N*-dialkylhydrazine/2LiCl adducts, which, most probably, are involved in the reaction as reactive species. The efficiency of *N*,*N*-dialkylhydrazine/2LiCl adducts, however, was found to decrease on standing, very likely because of the hygroscopic nature of the adducts. For example, when the reaction reported in entry 7 (Table 2) was repeated after 3 days using the same batch of 1-aminopiperidine/2LiCl adduct, compound **3g** was isolated only in 37% yield.

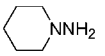
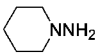
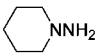
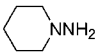
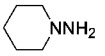
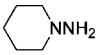
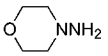
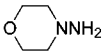
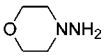
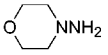
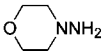
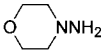
Consequently, we turned our attention to exploring the use of *N*,*N*-dialkylhydrazine/2LiCl adducts generated in situ,

Table 2. Palladium-Catalyzed Synthesis of *N*,*N*-Dialkyl-*N*′-arylhydrazines **3** from Aryl Bromides **2** and *N*,*N*-Dialkylhydrazine/2LiCl Adducts **1**[a]

entry	hydrazine/2LiCl adduct **1**	aryl bromide **2**	time (h)	yield %[b] of **3**	
1	Me_2NNH_2/2LiCl	*p*-Ph-C_6H_4-Br	7	75	**3a**
2	Me_2NNH_2/2LiCl	*p*-CN-C_6H_4-Br	24	51	**3b**
3	Me_2NNH_2/2LiCl	*p*-MeO-C_6H_4-Br	30	59	**3c**
4	Me_2NNH_2/2LiCl	*m*-MeO-C_6H_4-Br	30	56	**3d**
5	Me_2NNH_2/2LiCl	1-Br-naphthalene	24	38	**3e**
6	Me_2NNH_2/2LiCl	2-Br-naphthalene	24	39	**3f**
7		*p*-Ph-C_6H_4-Br	20	61[c]	**3g**
8		*p*-Ph-C_6H_4-Br	7	72[d]	**3h**

[a] Reactions were carried out on a 0.563 mmol scale in 2 mL of toluene at 80 °C under argon using 1 equiv of aryl bromide, 2 equiv of hydrazine/2LiCl adduct, 0.025 equiv of $Pd_2(dba)_3$, 0.05 equiv of Xantphos, and 1.4 equiv of NaOBu-*t*. [b] Yields are given for isolated products. [c] When the reaction was carried out with 1-aminopiperidine, **3g** was isolated in 41% yield after 28 h. [d] When the reaction was carried out with 4-aminomorpholine, **3h** was isolated in 51% yield after 24 h.

Table 3. Palladium-Catalyzed Synthesis of *N*,*N*-Dialkyl-*N*′-arylhydrazines **3** Omitting the Isolation of *N*,*N*-Dialkylhydrazine/2LiCl Adducts **1**[a]

entry	hydrazine	aryl bromide **2**	time (h)	yield %[b] of **3**	
1	Me_2NNH_2	*p*-CN-C_6H_4-Br	24	56[c]	**3b**
2	Me_2NNH_2	*p*-MeO-C_6H_4-Br	30	50	**3c**
3	Me_2NNH_2	*m*-MeO-C_6H_4-Br	24	71[c]	**3d**
4	Me_2NNH_2	2-Br-naphthalene	24	35	**3f**
5	Me_2NNH_2	2-Br-naphthalene	24	72[e]	**3f**
6	Me_2NNH_2	2-Br-naphthalene	24	49[d]	**3f**
7	Me_2NNH_2	2-Br-naphthalene	24	60[e]	**3f**
8		*p*-Ph-C_6H_4-Br	2	92	**3g**
9		*p*-CN-C_6H_4-Br	3	57[f]	**3i**
10		1-Br-naphthalene	24	75	**3j**
11		*p*-MeO-C_6H_4-Br	40	70	**3k**
12		*m*-MeO-C_6H_4-Br	21	83	**3l**
13		2-Br-naphthalene	3	82	**3m**
14		*p*-Ph-C_6H_4-Br	6	84	**3h**
15		*p*-CN-C_6H_4-Br	24	66	**3n**
16		1-Br-naphthalene	21	66	**3o**
17		2-Br-naphthalene	24	60[g]	**3p**
18		*p*-MeO-C_6H_4-Br	44	59	**3q**
19		*m*-MeO-C_6H_4-Br	3	71[h]	**3r**

[a] Unless otherwise stated, reactions were carried out on a 0.563 mmol scale as follows: 1 equiv of *N*,*N*-dialkylhydrazine and 2 equiv of LiCl in 3 mL of anhydrous THF for 1 h at room temperature, and then 2 mL of toluene, 1 equiv of aryl bromide, 0.025 equiv of $Pd_2(dba)_3$, 0.05 equiv of Xantphos, and 1.4 equiv of NaOBu-*t* were added under argon and the temperature was raised to 80 °C. [b] Yields are given for isolated products. [c] With 0.1 equiv of X-phos. [d] With 0.1 equiv of **4**. [e] With 0.1 equiv of **5**. [f] Corresponding *N*,*N*-diarylaminopiperidine was isolated in 40% yield. [g] Corresponding *N*,*N*-diarylaminomorpholine was isolated in 15% yield. [h] In the absence of LiCl, the yield was 51%.

omitting their isolation. *N*,*N*-Dialkylhydrazine/2LiCl adducts were prepared as usual. After evaporation of THF, toluene, the aryl bromide, the catalyst system, and the base were immediately added to the resulting white solid, and the reaction mixture was warmed to 80 °C.

Under these conditions, aryl bromides reacted efficiently with adducts derived from 1-aminopiperidine and 1-aminomorpholine. As shown in Table 3, the corresponding *N*,*N*-dialkyl-*N*′-arylhydrazines were usually isolated in good to high yields. The reaction proceeds efficiently with aryl bromides containing both electron-donating and electron-withdrawing substituents. Notably, the one-pot protocol affords higher yields than the stepwise protocol (compare entries 8 and 14 of Table 3 with entries 7 and 8 of Table 2, respectively). In some cases, *N*,*N*-dialkyl-*N*′,*N*′-diaryl derivatives were isolated in significant yield (Table 3, entries 9 and 17). With the *N*,*N*-dimethylhydrazine/2LiCl adduct, compounds **3** were isolated in yields similar to those achieved in the stepwise protocol (compare entries 2 and 4 of Table 3 with entries 3 and 6 of Table 2, respectively). We then went back and examined the influence of additional ligands on the reaction outcome. Particularly, we briefly explored the use of some commercially available Buchwald biaryl phosphines (Figure 1) and observed that the air stable X-phos can provide higher yields than ligands **4**, **5**, and Xantphos (Table 3, compare entry 5 with entries 4, 6, and 7; compare also entry 4 of Table 2 with entry 3 of Table 3). Clearly, there is room for optimization, and this further experimentation showed that an appropriate choice of the stabilizing ligand for a particular case of importance may lead to a significant increase of the yields.

In summary, we have demonstrated that the reaction of *N*,*N*-dialkylhydrazine/2LiCl adducts with aryl bromides in the presence of $Pd_2(dba)_3$ as the palladium source, Xantphos or X-phos as the ligands, toluene as the solvent, and NaOBu-*t* as the base provides an efficient route to *N*,*N*-dialkyl-*N*′-arylhydrazines. The method merits attention because of the good to high yields usually observed, the use of simple and readily available starting materials, and the simplicity of the experimental procedure.

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Supporting Information Available: Complete description of experimental details and product characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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