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Rapid Microwave Induced Palladium Catalyzed Amination of Aryl Bromides

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Summary. The palladium-catalyzed coupling reaction of aryl bromides with various amines under microwave irradiation was studied using $PdCl_2$ $[P(o\text{-tolyl})_3]_2$ which gave various aryl amines in good yields. The reactions were carried out under normal atmospheric conditions.

Keywords. Amination; Palladium; Microwave; Coupling reaction; Arylamines.

Introduction

Owing to the many important applications of aniline derivatives, a considerable amount of effort has been recently devoted to the development of new and more general methods for their preparation [1]. Procedures for the synthesis of aniline derivatives involve nitration, reduction, or substitution. Some of these procedures are incompatible with many functional groups and often involve protection and deprotection steps [2]. Palladium- and nickel-catalyzed amination of aromatic halides and triflates, pioneered by *Buchwald* [1a, 1c] and *Hartwig* [1b, 3], provide an efficient, safer, and mild route for the synthesis of substituted anilines. This important discovery opens up a new route for the preparation of many interesting organic molecules that are otherwise difficult to prepare [4].

Microwave irradiation is known to accelerate some organic reactions in polar solvents [5], and microwave assisted palladium-catalyzed reactions have been recently reported [6]. We here present the microwave assisted facile amination of aryl bromides with secondary or tertiary amines using $PdCl_2$ $[P(o\text{-tolyl})_3]_2$ in toluene under normal atmosphere.

Results and Discussion

The results of the amination reactions are summarized in Table 1. The data indicate that coupling between a variety of aryl bromides and secondary or primary amines readily occurs under microwave irradiation.

The cross-coupling of 2-bromonaphthalene with dibenzylamine was selected for optimization of the reaction conditions. No reaction occurred in the absence of

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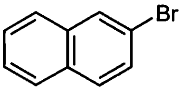
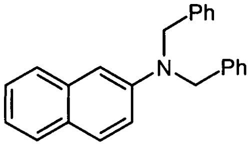
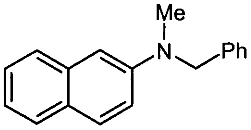
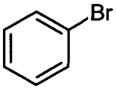
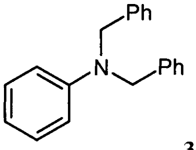
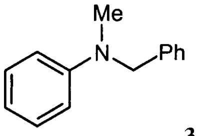
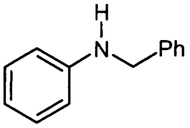
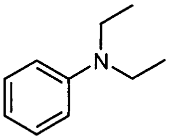
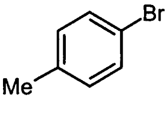
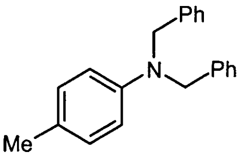
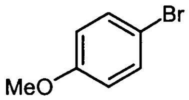
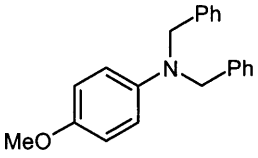
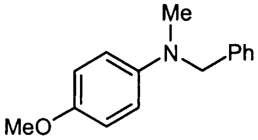
Table 1. Palladium-catalyzed amination of aryl bromides under microwave irradiation

$$\underset{\mathbf{1a\text{-}d}}{\text{Ar-Br}} \quad + \quad \underset{\mathbf{2a\text{-}d}}{RR'\text{NH}} \xrightarrow[\text{microwaves, toluene}]{\text{Pd catalyst, NaOCMe}_3} \underset{\mathbf{3a\text{-}h}}{\text{Ar-N}RR'}$$

Entry	Ar–Br	Catalyst[a]	Product	t/min	Yield/%[b]
1	 **1a**	$PdCl_2/2PPh_3$	 **3a**	15	trace
2	**1a**	$PdCl_2(PhCN)_2$	**3a**	15	trace
3	**1a**	$Pd(PPh_3)_4$	**3a**	15	25
4	**1a**	$PdCl_2(PPh_3)_2$	**3a**	15	45
5	**1a**	$PdCl_2$ [P(*o*-tolyl)$_3$]	**3a**	4	86
6	**1a**	[c]	 **3b**	7	70
7	 **1b**	[c]	 **3c**	6	85
8	**1b**	[c]	 **3d**	7	50
9	**1b**	[c]	 **3e**	6	48
10	**1b**	[c]	 **3f**	6	32
11	 **1c**	[c]	 **3g**	5	83

(*continued*)

Table 1 (*continued*)

Entry	Ar–Br	Catalyst[a]	Product	t/min	Yield/%[b]
12	 **1d**	[c]	 **3h**	6	51
13	**1d**	[c]	 **3i**	6	42

[a] Condition: 1 equiv. arylbromide, 1.5 equiv. amine, 1.5 equiv. sodium *tert*-butoxide, 0.02 equiv. Pd

catalyst. $PdCl_2/2PPh_3$ and $PdCl_2(PhCN)_2$ also did not serve as an effective palladium source for the above reaction (Table 1, entries 1–2). However, a 45% yield of amination product was obtained when the reaction was performed in the presence of $Pd(PPh_3)_4$ (entry 4). With $PdCl_2$ $[P(o\text{-tolyl})_3]_2$ the yield was improved to 86% (entry 5). We also examined the same amination reaction with other aryl bromides. Bromobenzene (**1b**, entry 7) or 4-methylbromobenzene (**1c**, entry 11) gave very good yields. However, when 4-methoxybromobenzene (**1d**) was treated with dibenzylamine under the same conditions, aryl amine **3h** was obtained with a lower yield (entry 12). The results indicate that an electron donating group on the aromatic ring leads to moderate yields (*ca.* 40–50%). Table 1 also shows the cross-coupling results obtained with bromobenzene and a diverse selection of amines (entries 7–10). The coupling of diethylamine with aryl bromides gives low yields of the corresponding aniline derivatives, obviously due to the volatility of the amine (entry 10).

In summary, a reliable, rapid, and practical procedure for the synthesis of arylamines *via* a palladium-catalyzed coupling reaction under microwave irradiation was developed. A particularly noteworthy feature of this method is the dramatically shortened reaction time (from hours to a few minutes) without the need to employ inert conditions.

Experimental

All reactions were carried out in a domestic microwave oven (Moulinex Microchef, 900 W) at 2450 MHz. All reported yields refer to isolated products.

General procedure for the palladium catalyzed amination of aryl bromides under microwave irradiation

A mixture of aryl bromide (1 mmol), amine (1.5 mmol), sodium *tert*-butoxide (1.5 mmol), and palladium catalyst (0.02 mmol) in toluene (3 cm^3) in a 25 cm^3 beaker was irradiated in a microwave oven for 4–15 min. After cooling to room temperature, the reaction mixture was washed with water, dried over sodium sulfate, and the solvent was evaporated using a rotavapor. The residue was purified with a short silica gel column (eluent: light petroleum ether:ethyl acetate = 20:1). The structures of the products were ascertained by comparison of their physical and spectroscopic data with those given in the literature.

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