Selective *N*-Arylation of Aminobenzanilides under Mild Conditions Using Triarylbismuthanes

Roderick J. Sorenson

Department of Medicinal Chemistry, Pfizer Global Research and Development, Ann Arbor Laboratories, Ann Arbor, Michigan 48105

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Diarylamines are prepared selectively in good yields under mild conditions by treatment of aminobenzanilides with triarylbismuthanes in the presence of copper(II) acetate and triethylamine. Arylation under these conditions occurs preferentially at the amino- rather than the amide-nitrogen of the benzanilide. Thus, heating an aminobenzanilide in dichloromethane under reflux in the presence of 1 equiv each of a triarylbismuthane, triethylamine, and copper(II) acetate affords the diarylamine in good yields. This method thereby provides a mild and expeditious route to functionalized diarylamines.

Introduction

Diarylamines are of considerable importance as synthetic intermediates and as potential therapeutic agents.[1] Because anilines are widely available as precursors to this class of compounds, a number of methods have been developed for the arylation of aromatic amino groups. Classical methods for this transformation, typified by the Ullmann−Goldberg condensation,[2] often require high temperatures, long reaction times, or other harsh or stringent conditions incompatible with many functional groups. Accordingly, novel protocols have been developed to address these limitations. The research groups of Buchwald[3] and Hartwig[4] utilized palladium to catalyze the amination of aryl halides. Barton and co-workers introduced triarylbismuthanes[5] and organolead derivatives[6] for the *N*-arylation of anilines. Chan and co-workers subsequently demonstrated the use of organobismuth(III) reagents for the *N*-arylation of amides and amide-like moieties.[7] Finet and Combes[8] have continued to exploit the reactivity of triarylbismuth(V) reagents for arylation reactions. We have previously described a method for the *N*-phenylation of anilines bearing a wide variety of functional groups utilizing triphenylbismuthane under very mild conditions.[9] We herein report an extension of this approach in which the amino nitrogen of a benzanilide is selectively arylated while the amide functionality is preserved unchanged.

Results and Discussion

Confronted with a need for the expedient preparation of a series of diarylamines, and drawing upon previous research in this area, we were prompted to explore the reaction of organobismuth(III) reagents with functionalized aminobenzanilides. In the presence of a basic promoter, arylation was observed to occur exclusively at the amino nitrogen rather than the amide nitrogen of the substrates, thus providing a novel route to the desired class of compounds. This result is surprising in that Chan et al.[7] had originally developed this modification of the Barton procedure expressly for the purpose of arylating amide nitrogens. Even so, in most cases throughout our investigation no evidence was found for the production of any bis- or tris-adducts. Accordingly, a large number of diarylamines were prepared using this procedure. Representative examples are shown in Table 1. Both electron-withdrawing and electron-donating groups were tolerated in either the substrate or the triarylbismuthane. In some examples small amounts of unidentified byproducts were observed. These were easily removed by recrystallization or column chromatography.

The required triarylbismuthanes were readily obtained via a simple procedure in which the corresponding Grignard or aryllithium reagents were allowed to react with bismuth(III) halide.[10] These reagents are usually crystalline, easy to purify, and exhibit low reactivity toward moisture and oxygen so that multigram quantities can be prepared and stored for prolonged periods.

The anilines were either commercially available or readily synthesized using standard methods. 3-Amino-4-fluoro-*N*-(3,4-difluorophenyl)benzamide (Table 1, entry

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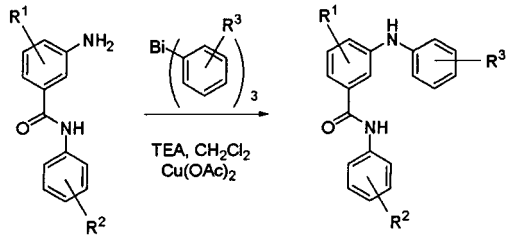
Table 1. Selective *N*-Arylation of 3-Aminobenzanilides[a,b]



1-13

entry	R^1	R^2	R^3	compd	isolated yield (%)
1	H	H	H	**1**	94
2	4-OMe	H	H	**2**	74
3	4-OMe	H	H	**2**	0[c]
4	4-OMe	2-OMe	H	**3**	85
5	4-OMe	3,4-di-F	3-OBn	**4**	81
6	4-OMe	H	2-OMe	**5**	81
7	4-OMe	H	3-Cl	**6**	82
8	4-OMe	H	3,5-di-Me	**7**	51
9	4-F	3,4-di-F	3-CF_3	**8**	74
10	4-Cl	H	H	**9**	77
11	2-F	H	3-CF_3	**10**	90
12	4-SMe	H	3-CF_3	**11**	46
13	4-OCF_3	4-F	3-CF_3	**12**	48
14	4-OMe	4-CO_2Me	3-CF_3	**13**	90

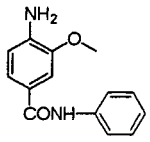
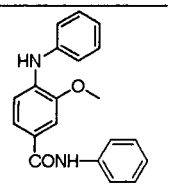
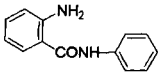
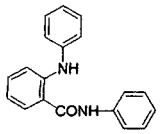
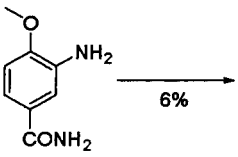
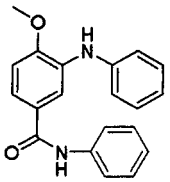
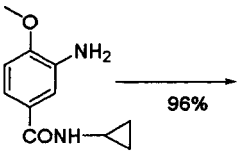
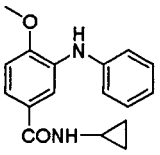
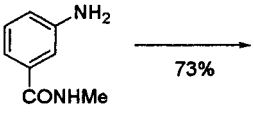
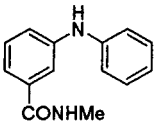
[a] Satisfactory ^{1}H NMR, CIMS, and microanalyses were obtained for all substrates and products. [b] 1.0 equiv of substrate, 1.05 equiv each of Ar_3Bi, $Cu(OAc)_2$, TEA in CH_2Cl_2; reflux; 3−20 h. [c]No TEA added.

9), for example, was prepared from 3-nitro-4-fluorobenzoic acid by formation of the acid chloride, reaction with 3,4-difluoroaniline, and subsequent catalytic reduction of the nitro group.[11]

This method is remarkable for the mild conditions required. Many of the arylations proceeded readily at room temperature, though the time required to attain completion was considerably shortened by heating under reflux in dichloromethane. Tetrahydrofuran is also a suitable solvent for the reaction, but in some experiments its use resulted in a small amount of bis-arylation. Palladium-catalyzed methodologies developed for the amination of aryl halides,[12] even when performed at room temperature, often require the use a strong base that may not be compatible with sensitive substrates. In contrast, the method described here utilizes only triethylamine as a promoter. Barton et al.[5] were able to achieve the formation of diarylamines without a promoter, but in a control experiment in which triethylamine was omitted (Table 1, entry 3) we were unable to push the chemoselective reaction to completion, despite prolonged heating under reflux.

An inert atmosphere was not required during the reaction: protection from atmospheric moisture was sufficient. An experiment in which 1 equiv of water was deliberately introduced to the reaction mixture resulted in consumption of the organobismuth reagent without concomitant appearance of product, even after another

Table 2. *N*-Arylation of Aminobenzamides[a,b]

Entry	Substrate	Yield	Product
1	 **14**	47%	 **15**
2	 **16**	93%	 **17**[c]
3	 **18**	6%	 **2**
4	 **19**	96%	 **20**
5	 **21**	73%	 **22**

[a] Satisfactory ^{1}H NMR, CIMS, and microanalyses were obtained for all substrates and products. [b] 1.0 equiv of substrate, 1.05 equiv each of Ar_3Bi, $Cu(OAc)_2$, TEA in CH_2Cl_2; room temp; 20 h. [c] See ref 13.

1 equiv of the bismuth reagent was added. When an inert atmosphere was maintained, it was in some cases necessary to add a small additional amount of copper(II) acetate after several hours to obtain full conversion of the starting material. The effect of oxygen on the reaction has been previously described.[5]

Table 2 illustrates the generalization of this method to a broader array of substrates, including those in which the relationship of the substituents is less favorable, as in entries 1 and 2. Chemoselectivity is realized even when the amino group of the benzanilide is part of a vinylogous amide.

A limitation was encountered when a primary amide was selected as the substrate, as shown in entry 3. In this case a complex mixture of products was obtained, from which previously characterized benzanilide **2** (6% yield) was the only product isolated. This limitation was not attributable to the selectivity being specific to *N*-arylbenzamides, however, as *N*-cyclopropyl and *N*-methyl analogues **20** and **22** were the only detectable products of the arylation reaction shown in entries 4 and 5.

A minor drawback to this method is that only one of the aryl groups of the bismuth reagent is transferred to

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the substrate, and this may be a disadvantage in the case of more elaborate aryl groups. Another consideration is that the copper salt is required in stoichiometric amounts, and its disposal may become a concern as the scale of the reaction is increased. Since arylations using bismuth(V) reagents are known to be catalytic in copper,[5] we are currently investigating the selectivity of these conditions.

In summary, we have developed a practical and versatile method for the selective *N*-arylation of amino groups in functionalized aminobenzanilides that proceeds under mild conditions using readily available, easily handled reagents.

Experimental Section

General Methods. Melting points are uncorrected. The ^{1}H NMR spectra were recorded at 400 MHz in DMSO-d_6. Chemical shifts are reported in ppm (δ) and referenced to the residual proton signal for DMSO-d_6 (2.49 ppm). The coupling constants (J) are reported in hertz. Elemental analyses were performed by Quantitative Technologies Inc. and were within 0.4% of theory. Reagents were obtained from commercial sources and used without additional purification. Reaction progress was monitored using EM Science precoated silica gel 60 F_{254} thin-layer chromatography plates, eluting with $CHCl_3$/EtOAc 9:1. Biotage prepacked silica gel columns were used for chromatographic purifications.

Materials. Substrates for Table 1, entries 1−3, 6−8, 10, and Table 2, entries 1 and 2, were obtained from Apin Chemicals Ltd. Benzamide **18** was obtained from Pfaltz & Bauer, Inc. Substrates for Table 1, entries 5, 11, 12, and 13 were prepared according to published procedures.[11] Substrates for Table 1, entries 4 and 14 were prepared analogously to that for Table 1, entry 8 (see Supporting Information for data). Triphenylbismuthane was obtained from Alfa Aesar. The preparation of tris(3-chlorophenyl)bismuthane and tris(3-trifluoromethylphenyl)bismuthane is described in the literature.[10] Tris(3,5-dimethylphenyl)bismuthane and tris(3-benzyloxy-phenyl)bismuthane were obtained similarly (see Supporting Information, compounds **23** and **24**). Tris(2-methoxyphenyl)-bismuthane is commercially available from Aldrich Chemical Co. Solvents were used without prior drying.

Representative Procedure for the Arylation Reaction. (3-(3-Chlorophenylamino)-4-methoxy-*N*-phenylbenzamide (6). Copper(II) acetate (1.16 g, 6.4 mmol) was added to a stirred mixture of 3-amino-4-methoxy-*N*-phenylbenzamide (1.5 g, 6.2 mmol), tris(3-chlorophenyl)bismuthane (3.5 g, 6.4 mmol), and triethylamine (0.65 g, 6.4 mmol) in dichloromethane (120 mL), and the mixture was heated to reflux. After 4 h, heating was discontinued and the mixture diluted with additional dichloromethane (150 mL) and stirred into 2 N hydrochloric acid (200 mL). After 2 h, the layers were separated, and the organic phase was washed successively with 2 N HCl, water, 0.5 M aqueous potassium carbonate, water, and saturated aqueous sodium chloride and then dried over $MgSO_4$. The solution was filtered and then stripped of solvent under reduced pressure. The residue was chromatographed on a column of silica gel in chloroform/ethyl acetate (99:1) to afford the product (1.8 g, 82% yield): mp 163−165 °C. A sample was recrystallized from ethanol to give pure **6** as glittering white scales: mp 168−170 °C; IR (KBr, cm^{-1}) 3395, 3322, 1647, 1589, 1519, 1245, 758; ^{1}H NMR (DMSO) δ 10.02 (s, 1H), 7.80 (d, J = 8.8 Hz, 2H), 7.68 (d, J = 7.6 Hz, 2H), 7.62 (d, J = 8.5 Hz, 1H), 7.27 (dd, J = 7.9 Hz, 2H), 7.13 (m, 2H), 7.02 (t, J = 7.3 Hz, 1H), 6.94 (m, 2H), 6.75 (d, J = 7.8 Hz, 1H), 3.84 (s, 3H); MS (APCI), m/z 353.0, 355.0 ($M^+ + 1$). Anal. Calcd for $C_{20}H_{17}ClN_2O_2$: C, 68.09; H, 4.86; N, 7.94. Found: C, 67.91; H, 4.71; N, 7.80.

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Supporting Information Available: ^{1}H NMR for all substrates, triarylbismuthanes, and products; microanalyses and melting points for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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