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Triarylbismuthane - Iodobenzene Diacetate: One-pot System for Copper-Catalysed N-Arylation under Neutral Conditions

Sébastien Combes and Jean-Pierre Finet*

Laboratoire "Chimie, Biologie et Radicaux Libres" UMR 6517 CNRS-Universités d'Aix-Marseille 1 et 3 Faculté des Sciences Saint-Jérôme, 13397 Marseille Cedex 20 France

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Abstract: Triarylbismuthanes react with iodobenzene diacetate in dichloromethane under mild, neutral conditions to afford triarylbismuth diacetates, which can be isolated in good yields. The reagents can also be directly used in a one-pot copper-catalysed N-arylation of anilines to give near quantitative yields of the corresponding diarylamines, except in the case of the 2-methoxyphenylbismuth derivative. N-arylation with tris(2-methoxyphenyl)bismuth diacetate was quantitative only when the reaction was performed with the pure isolated reagent. © 1998 Elsevier Science Ltd. All rights reserved.

Bismuth is considered to be one of the less toxic heavy metals.¹ Some bismuth compounds are even used as internal medicines for intestinal disorders. Its organic derivatives are now becoming more frequently used synthetic tools.² Among them, pentavalent arylbismuth derivatives are mild and selective arylating reagents for a wide range of functional groups.³ Their utility in medicinal chemistry has been recently highlighted by the selective arylation of immunosuppressive macrolides.^{4,5} Selective *N*-arylation of amines (aliphatic, heterocyclic amines or anilines) and *O*-arylation of phenols and glycols can be easily realized under very mild conditions by copper-catalysed arylation with triarylbismuth diacetates.⁶⁻⁸ Various methods are available for the synthesis of triarylbismuth diacetates from triarylbismuthanes. Multistep sequences are involved in the reaction of triarylbismuth dichloride with silver acetate,⁹ or in the reaction of triarylbismuth diacetate can be performed with lead tetraacetate in acetic acid,^{11,12} with *tert*-butylhydroperoxide in acetic acid,¹³ with peracetic acid in acetic acid,^{5,14} or with sodium perborate in acetic acid.¹⁵ However, they are performed in an acidic medium, and this can be detrimental to acid-sensitive triarylbismuthane derivatives.

We therefore decided to look for a cheap, non-toxic and easily handled combination of reagents which would lead to good to high yields of triarylbismuth diacetates under neutral conditions. We considered that iodobenzene diacetate should be well-suited for this purpose. We now report that variously substituted triarylbismuthanes can be easily oxidized to their diacetates simply by treatment with iodobenzene diacetate in dichloromethane at room temperature. In this way, a variety of derivatives (10) - (18) were prepared, in which the aryl group is substituted by electron-donating or electron-attracting groups (Table 1). The evolution

^{*} Fax : 33 4 91 98 85 12; E-mail : finet@srepir1.univ-mrs.fr

of the reaction was monitored by t.l.c. until the trivalent organobismuth had completely disappeared, and the average reaction time was 7 hours. Good yields of pure compounds were generally obtained for all substituted phenyl derivatives. In the case of the 2-methoxyphenyl derivative, a significant amount of the unreacted triarylbismuthane (4) remained always present, even after a longer reaction time (9 hours). The pentavalent triarylbismuth diacetate (13) was nevertheless isolated in a good yield (65%). In the case of the 3-trifluoro-methylphenyl and the naphthyl compounds, crystallization of the triarylbismuth diacetate derivatives (17) and (18), which are low-melting solids, was unsuccessful.

Table 1: Synthesis of triarylbismuth diacetates by reaction of triarylbismuthane with iodobenzene diacetatea

A D:		I(OAc) ₂	CH ₂ Cl ₂	OAc Ar Pi
Аг ₃ ві (1) - (9)	+	\bigcirc	7-9 h / r.t.	Ar-Bi I Ar OAc
(-) (*)				(10) - (18)

Ar3Bi	Ar	R'n time (h) ^b	Ar ₃ Bi(OAc) ₂	Yield (%) ^c	mp (°C)	mp (°C) [lit]
(1)	C ₆ H ₅	7	(10)	80	189	189 [16]
(2)	2-MeC ₆ H ₄	7	(11)	78	129	-
(3)	4-MeC ₆ H ₄	7.	(12)	65	172	162 [16]
(4)	2-MeOC ₆ H ₄	9	(13)	65	147	147 [15]
(5)	4-MeOC ₆ H ₄	7	(14)	65	170-173	170-173 [15]
(6)	4-ClC ₆ H ₄	7	(15)	67	154-156	158-162 [17]
(7)	4-FC ₆ H ₄	7	(16)	68	162	>193 [17]
(8)	3-CF3-C6H4	7	(17)	d	-	89-92 [17]
(9)	1-Naphthyl	7	(18)	d	-	95 (dec.) [15]

a) for general reaction conditions, see experimental part

b) reaction time until complete disappearance of the triarylbismuthane

c) yield of recrystallized product

d) the product could not be isolated pure

As the oxidation of triarylbismuthanes took place under mild conditions to afford the diacetate derivatives as the only detectable compounds, we then attempted to use the *in situ* generated reagent for the *N*-arylation of an aniline substrate. Iodobenzene, the by-product of the oxidation step, should not interfere with the copper-catalysed amine *N*-arylation under the reaction conditions which are used. In preliminary experiments, a slight excess of iodobenzene diacetate compared to the bismuthane substrate was used, as in the synthesis of the triarylbismuth diacetates. After addition of the aniline and a catalytic amount of copper (II) diacetate, the reaction led to a coloured mixture of products. The expected diarylamine was detected, but numerous other polar products were also present. Under these conditions, the excess of iodobenzene diacetate is likely to react with the aniline to form various oxidized products. The conditions were therefore slightly modified. A small excess of triarylbismuthane relative to iodobenzene diacetate was used, and the reaction was left to run overnight to consume all the oxidizing iodine reagent. After addition of the aniline and catalytic copper diacetate, the reaction eventually afforded the diarylamine in practically quantitative yields for all the reagents except the 2-methoxyphenyl derivative. When the reaction was performed with the

solution of the 3-trifluoromethylphenyl or the 1-naphthyl reagents (17) and (18) which could not be isolated pure, high yields of the derived diarylamines (26) and (27) were also obtained (93% for both reagents).

1) Ar ₃ Bi ` (1.2 equiv.) 2 (1) - (9)) PhI(OAc) ₂ (1 eq CH ₂ Cl ₂ / r.t. / 1') 3,4-Me ₂ C ₆ H ₃ NI Cu(OAc) ₂ (0.1 e	uiv.) 7h H ₂ (0.95 equiv. equiv.) / r.t. / 2h)) Me-	NH-Ar e (19) - (27)
Diarylamine	Ar	Yield (%)	mp (°C)	mp (°C) [lit]
(19)	C ₆ H ₅	86	55	56-57 [18]
(20)	2-MeC ₆ H ₄	92	oil	-
(21)	4-MeC ₆ H ₄	98	54	-
(22)	2-MeOC ₆ H ₄	23-25	oil	-
(23)	4-MeOC ₆ H ₄	96	85	-
(24)	4-ClC ₆ H ₄	97	74	-
(25)	4-FC ₆ H ₄	95	65	-
(26)	3-CF ₃ -C ₆ H ₄	93	oil	-
(27)	1-Naphthyl	93	oil	oil [19]

Table 2: Arylation of 3,4-dimethylaniline with in situ generated triarylbismuth diacetates

In the case of the ortho-substituted 2-methoxyphenyl reagent (13), the reaction appeared troublesome. When arylation of the aniline was performed with the in situ generated reagent, a poor yield (23-25%) of the diarylamine (22) was usually observed. As only meta- and para-substituted phenylbismuth derivatives had been previously tested in O- and N-arylation, this poor yield could have been explained by the specific reactivity of tris-ortho-methoxyphenylbismuth derivatives.²⁰ An alternative possibility would be a lowered reactivity of this diacetate (13) due to the steric hindrance of the ortho-substituents. However, the reaction of the tris(ortho-methylphenyl)bismuth diacetate (11) led to a good yield (92%) of the diarylamine (20). Moreover, the copper-catalysed arylation reaction with pure isolated tris(2-methoxyphenyl)bismuth diacetate (13) afforded a nearly quantitative yield (93%) of the diarylamine (22). When the evolution of the oxidation of tris(2-methoxyphenyl)bismuthane (4) by iodobenzene diacetate in deuterochloroform was monitored by ¹H NMR, the amount of the diacetate (13) appeared to increase regularly up to a maximum of 60-65%. Prolonged monitoring failed to show any further increase. For example, after 27 hours, the amount of (13) remained close to 60%. Moreover, when tris(2-methoxyphenyl)bismuthane was treated with iodobenzene diacetate for 17 hours, the diacetate (13) was isolated after work-up in a 60% yield. When the aniline and the catalytic copper diacetate were added to the a mixture containing 65% (¹H NMR estimation) of (13) [prepared by oxidation of tris(2-methoxyphenyl)bismuthane (4) with iodobenzene diacetate for 17 hours], ¹H NMR of the resulting mixture after 2 hours indicated the formation of only 25% of the diarylamine (22) and the complete disappearance of the pentavalent bismuth diacetate (13). Thus, it appears that the in situ generation conditions are not appropriate for the 2-methoxyphenyl derivative. This was supported by the study of the stability of the reagent. When a solution of the diacetate (13) in deuterochloroform was kept at room temperature, the ¹H NMR spectrum revealed the presence of two degradation products: anisole and tris(2-methoxyphenyl)bismuthane (4). When a solution of the diacetate (13) in dichloromethane was heated under reflux for 2 hours, a new product was formed. Its ¹H NMR spectrum was in favour of a structure such as an oxide of tris(2-methoxyphenyl)bismuth or a polymeric form thereof. However, it decomposed in solution to yield anisole and tris(2-methoxyphenyl)bismuthane (4). Therefore, it appears that tris(2-methoxyphenyl)bismuth diacetate (13) is moderately stable in solution. Its decomposition is accelerated under the *in situ* generation conditions. But the formation of 2-methoxyphenyl acetate as a dogradation product was not observed in contrast with triphenylbismuth diacetate, for which the decomposition into phenyl acetate is accelerated by the presence of a copper catalyst.²¹

In summary, the reaction of iodobenzene diacetate with various substituted triarylbismuthanes leads to the corresponding triarylbismuth diacetates, which can be isolated in good yields or used directly for the *in* situ N-arylation reaction. In the case of the presence of an ortho-methoxy substituent, the *in situ* generated reagent is prone to rapid decomposition under the N-arylation reaction conditions. However, a good yield of the N-arylation product can be obtained with the aniline substrate when the reaction is performed with the pure isolated pentavalent triarylbismuth diacetate.

Experimental

Melting points were taken on a Büchi capillary apparatus and are uncorrected. ¹H-NMR spectra were obtained on Bruker AC200 spectrometer. Chemical shifts (δ) are reported in ppm for solution of the compounds in CDCl3 with internal Me4Si and J values in Hertz.

General Procedure for the Oxidation of Triarylbismuthane to Triarylbismuth Diacetate: A mixture of triarylbismuthane (2 mmol) and iodobenzene diacetate (2.2 mmol) in dichloromethane (20 cm³) was stirred at room temperature for 7 hours. The solvent was concentrated under reduced pressure to a small volume. A mixture of diethyl ether-pentane was added and the solution kept overnight at -15°C. The solid was filtered and recrystallized from a mixture of dichloromethane and pentane. Yields and m.p.s are reported in Table 1.

Bis(acetato) tris(2-methylphenyl)bismuth (11): Crystallized from ether, recrystallized as colourless plates from dichloromethane-pentane (1:1), m.p. 129°C; $\delta_{\rm H}$ 1.71 (6H, s, CH₃CO), 2.59 (9H, s, CH₃), 7.35-7.48 (9H, m, 3-H, 4-H and 5-H) and 8.26 (3H, dd, $J_{\rm H5-H6}$ 7.6 and $J_{\rm H4-H6}$ 1.8, 6-H) (Found: C, 50.00; H, 4.46. C₂₅H₂₇BiO₄ requires C, 49.99; H, 4.53 %).

General Procedure for the Arylation of 3,4-Dimethylaniline: A mixture of triarylbismuthane (1.2 mmol) and iodobenzene diacetate (1 mmol) in dichloromethane (10 cm^3) was stirred at room temperature for 17 hours. Then, copper diacetate (0.1 mmol) and the amine (0.95 mmol) were added and the resulting mixture was stirred for 2 hours. The solvent was distilled and the residue was purified by flash column chromatography on silica gel (pentane-ethyl acetate). When solid, the diarylamine was recrystallized from pentane.

Phenyl(3,4-dimethylphenyl)amine (19): white needles, m.p. 55°C (lit.¹⁸ m.p. 56-57°C); IR (V_{NH}) 3396 cm⁻¹; δ_H 2.21 (6H, s, CH₃), 5.56 (1H, s, NH), 6.83-6.91 (3H, m, 2-H, 6-H and 10-H), 7.01 (2H, d, J 7.9, 8-H and 12-H), 7.04 (1H, d, J 6.6, 5-H) and 7.24 (2H, t, J 7.9, 9-H and 11-H) (Found: C, 85.19; H, 7.59; N, 7.07. C₁₄H₁₅N requires C, 85.24; H, 7.66; N, 7.10 %).

(2-Methylphenyl)(3,4-dimethylphenyl)amine (20): yellow oil; IR (V_{NH}) 3410 cm⁻¹; δ_H 2.20 (6H, s, CH₃), 2.23 (3H, s, 8-CH₃), 5.25 (1H, s, NH), 6.75 (1H, dd, J_{H5-H6} 8.0 and J_{H2-H6} 2.3, 6-H), 6.81 (1H, d, J 2.3, 2-H), 6.87 (1H, dd, $J_{H11-H12}$ 7.1 and $J_{H10-H12}$ 1.8, 12-H), 7.01(1H, d, J8.0, 5-H) and 7.05-7.22 (3H, m, 9-H, 10-H and 11-H) (Found: C, 85.21; H, 8.12; N, 6.54. C₁₅H₁₇N requires: C, 85.26; H, 8.11; N, 6.63 %).

(4-Methylphenyl)(3,4-dimethylphenyl)amine (21): colourless plates, m.p. 54°C; IR (V_{NH}) 3412 cm⁻¹; δ_H 2.24 (6H, s, CH₃), 2.33 (3H, s, 10-CH₃), 5.49 (1H, s, NH), 6.82-6.87 (2H, m, 2-H and 6-H), 6.97 (2H, d, J 8.4, 8-H and 12-H), 7.05 (1H, d, J 7.6, 5-H) and 7.10 (2H, d, J 8.4, 9-H and 11-H) (Found: C, 85.23; H, 8.08; N, 6.57. C₁₅H₁₇N requires: C, 85.26; H, 8.11; N, 6.63 %).

(2-Methoxyphenyl)(3,4-dimethylphenyl)amine (22): yellow oil; IR (v_{NH}) 3413 cm⁻¹; δ_{H} 2.21 (3H, s, CH₃), 2.23 (3H, s, CH₃), 3.88 (3H, s, CH₃O), 6.04 (1H, s, NH), 6.75-6.94 (5H, m, 2-H, 6-H, 9-H, 10-H and 11-H), 7.03 (1H, d, *J* 7.8, 5-H) and 7.21 (1H, dd, *J*_{H11-H12} 7.5, *J*_{H10-H12} 1.9, 12-H) (Found: C, 79.25; H, 7.54; N, 6.13. C₁₅H₁₇NO requires C, 79.26; H, 7.54; N, 6.16 %).

(4-Methoxyphenyl)(3,4-dimethylphenyl)amine (23): colourless plates, m.p. 85° C; IR (v_{NH}) 3365 cm⁻¹; δ_H 2.17 (3H, s, CH₃), 2.18 (3H, s, CH₃), 3.78 (3H, s, CH₃O), 5.34 (1H, s, NH), 6.68 (1H, dd, J_{H5-H6} 7.6 and J_{H2-H6} 2.4, 6-H), 6.73 (1H, d, J 2.4, 2-H), 6.84 (2H, d, J 9.0, 8-H and 12-H), 6.98 (1H, d, J 7.6, 5-H) and 7.02 (2H, d, J 9.0, 9-H and 11-H) (Found: C, 79.27; H, 7.51; N, 6.15. C₁₅H₁₇NO requires C, 79.26; H, 7.54; N, 6.16 %).

(4-Chlorophenyl)(3,4-dimethylphenyl)amine (24): colourless plates, m.p. 74°C; IR (ν_{NH}) 3412 cm⁻¹; δ_{H} 2.21 (6H, s, CH₃), 5.53 (1H, s, NH), 6.81 (1H, dd, J_{H5-H6} 7.9 and J_{H2-H6} 2.3, 6-H), 6.85 (1H, d, J 2.3, 2-H), 6.90 (2H, d, J 8.9, 8-H and 12-H), 7.03 (1H, d, J 7.9, 5-H) and 7.16 (2H, d, J 8.9, 9-H and 11-H) (Found: C, 72.40; H, 6.09; N, 6.03. C₁₄H₁₄ClN requires: C, 72.57; H, 6.09; N, 6.04 %).

(4-Fluorophenyl)(3,4-dimethylphenyl)amine (25): colourless plates, m.p. 65°C; IR (V_{NH}) 3379 cm⁻¹; δ_H 2.21 (6H, s, CH₃), 5.43 (1H, s, NH), 6.76 (1H, dd, J_{H5-H6} 7.9 and J_{H2-H6} 2.4, 6-H), 6.81 (1H, d, J 2.4, 2-H), 6.88-6.97 (4H, m, 8-H, 9-H, 11-H and 12-H), and 7.02 (1H, d, J 7.9, 5-H) (Found: C, 78.15; H, 6.63; N, 6.50. C₁₄H₁₄FN requires: C, 78.11; H, 6.56; N, 6.51 %).

(3-Trifluorophenyl)(3,4-dimethylphenyl)amine (26): light yellow oil; IR (v_{NH}) 3399 cm⁻¹; δ_H 2.22 (6H, s, CH₃), 5.68 (1H, s, NH), 6.86-6.89 (2H, m, 2-H and 6-H), 7.05-7.11 (3H, m, 5-H, 10-H and 12-H), 7.17 (1H, s, 8-H) and 7.29 (1H, t, *J* 7.8, 11-H) (Found: C, 67.94; H, 5.36; N, 5.26. C₁₅H₁₄F₃N requires: C, 67.92; H, 5.32; N, 5.28 %).

(3,4-Dimethylphenyl)(1-naphthyl)amine (27): red oil; IR (V_{NH}) 3394 cm⁻¹; δ_H 2.21 (6H, s, CH₃), 5.85 (1H, s, NH), 6.79 (1H, dd, J_{H5-H6} 7.9 and J_{H2-H6} 2.6, 6-H), 6.86 (1H, d, J 2.6, 2-H), 7.03 (1H, d, J 7.9, 5-H), 7.28 (1H, dd, J_{H8-H9} 7.5 and J_{H8-H10} 1.1, 8-H), 7.35 (1H, t, J 7.5, 9-H), 7.43-7.50 and 7.82-8.01 (5H, m, 10-H, 11-H, 12-H, 13-H and 14-H) (Found: C, 87.43; H, 6.92; N, 5.65. C₁₈H₁₇N requires: C, 87.41; H, 6.93; N, 5.66 %).

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