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Highly selective arylation of disubstituted hydrazines by pentavalent organobismuth reagents

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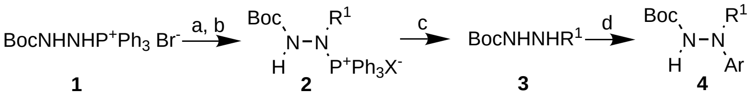
Abstract—The scope of a set of recently reported hydrazine reagents has been explored with respect to arylation. Compounds of type $R^1NHNHCOR^2$ can be selectively arylated under very mild conditions using triarylbismuth diacetates. © 2002 Published by Elsevier Science Ltd.

The intensive development within the hydrazine field has stimulated, during the last few years, the design of several triprotected reagents for the stepwise synthesis of multisubstituted derivatives.[1,2] Recently we also reported a very convenient diprotected hydrazine reagent **1** and demonstrated that various alkyl and acyl substituents could be introduced selectively.[3] The arylation of nitrogen compounds is nowadays of great significance. Two main pathways are known to fulfil this, namely halides under palladium catalysis as developed by the groups of Buchwald and Hartwig[4] and organobismuth compounds as applied by Barton and Finet.[5] In this context arylation of hydrazines has also recently attracted attention in the literature.[6] Triarylbismuthanes were successfully used in our group to arylate triprotected hydrazine precursors.[7] Up to now there are no reports on the selective arylation of disubstituted hydrazines with similar reagents which induced us to investigate compounds derived from **1** from this perspective.

A number of compounds **3**, required as starting materials in the arylation experiments below, were obtained as outlined in Scheme 1.[3] Step c afforded an equimolar mixture of **3** and Ph_3PO, which was reacted without prior separation. Initial arylation attempts using trivalent bismuth compounds and stoichiometric $Cu(OAc)_2$ catalysis were carried out, but instead of arylation we observed slow oxidation to hydrazones BocNHN=CHR. Therefore, the effect of the promoter Et_3N was examined as previously described by Chan.[8] Under these conditions both the oxidation and the *N*-arylation of the resulting hydrazone were significantly accelerated. Thus after 1 h, 55% of the hydrazone and 27% of its arylated product, Boc(Ph)NN=CHCOOEt, were formed ($R^1=CH_2COOEt$, 1.5 equiv. of Ph_3Bi, 2 equiv. of Et_3N, rt) as shown by NMR. Analogous products were detected with two other substrates ($R^1=PhCH_2$ and $CH_2=CHCH_2$) as well.

The utilization of pentavalent bismuth compounds instead of triarylbismuthanes furnished a route to the successful arylation of **3** and similar substrates. With $Ar_3Bi(OAc)_2$[9] in the presence of 5% $Cu(OAc)_2$ for a range of compounds the reactions turned out to be remarkably fast and were complete in 5–10 min at room temperature, giving the desired compounds **4** in good to high yields over the two steps starting from the phosphonium salts **2** (Table 1, compounds **4a–e**).[10] In



Scheme 1. *Reagents and conditions*: (a) BuLi, THF; (b) R^1X; (c) 1 M $NaOH/CH_2Cl_2$; (d) arylation with organobismuth compounds.

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Table 1. Synthesis of compounds $R^1ArNNHCOR^2$ by arylation of $R^1NHNHCOR^2$

Compd	R^1	R^2CO	Ar	Yield%	Mp (°C)/hexane	^1H NMR spectra
4a[12]	$PhCH_2$	Boc	Ph	95	92.5–93.5 (94–95[12])	1.44 (s, 9H, Boc), 4.71 (br s, 2H, CH_2), 6.41 (br s, 1H, NH), 6.8–7.3 (m, 10H, Ph)
4b	*n*-Bu	Boc	Ph	86	39–40	0.96 (t, 3H, CH_3, $^3J_{HH}=7.2$), 1.3–1.7 (m, 13H, $3\times CH_3$, $2\times CH_2$), 3.4–3.6 (br m, 2H, NCH_2), 6.38/6.20 (two br s, together 1H, NH), 6.8–7.3 (m, 5H, Ph)
4c[a]	CH_3	Boc	1-Naphthyl	87	85–86	1.44 (s, 9H, Boc), 3.16 (s, 3H, CH_3), 6.26 (s, 1H, NH), 7.2–8.4 (m, 7H, 1-naphthyl)
4d	$HC{\equiv}CCH_2$	Boc	$4\text{-}CH_3C_6H_4$	93	80.5–82	Ref. 10
4e[b]	$EtOCOCH_2$	Boc	$4\text{-}CH_3C_6H_4$	74	102–103.5	1.25 (t, 3H, $C\underline{H}_3CH_2$, $^3J_{HH}=7.2$), 1.50 (s, 9H, Boc), 2.25 (s, 3H, $C\underline{H}_3C_6H_4$), 4.18 (q, 2H, $CH_3C\underline{H}_2$, $^3J_{HH}=7.2$), 4.28 (br s, 2H, NCH_2), 6.7–7.1 (m, 5H, NH, C_6H_4)
5	CH_3	Cbz	$4\text{-}CH_3C_6H_4$	82	112.5–113	2.24 (s, 3H, $CH_3C_6H_4$), 3.10 (s, 3H, NCH_3), 5.14 (s, 2H, CH_2), 6.6–7.4 (m, 10H, Ar, NH)
6	CH_3	CH_3CO	1-Naphthyl	80	116–117	2.15/1.84 (two s, together 3H, CH_3CO), 3.08/3.16 (two s, together 3H, NCH_3), 7.2–8.3 (m, 7H, 1-naphthyl), 8.68 (s, NH)
7	Boc	Boc	Ph	86	106–107 (110–111[7])	Consistent with Ref. 7

[a] Additional purification by chromatography was required.

[b] Subsequent purification by crystallization from hexane/$CHCl_3$ mixture was required.

addition, regioselective substitution was possible using 1 equiv. of the pentavalent bismuth compound. Phenylation of $Ph_2C{=}NNH_2$ with this type of reagent was first reported by Barton et al.,[11] but to the best of our knowledge this is the first time such reagents have been exploited to arylate substituted hydrazines.

It is worth noting that arylation can be accomplished even without a copper catalyst. In this case the reaction occasionally requires longer time or a larger excess of $Ar_3Bi(OAc)_2$ to go to completion in the presence of air. Nevertheless, 93% of **4a** was obtained as a result of the reaction with 1.3 equiv. of the pentavalent bismuth reagent, after 10 min, under an inert gas atmosphere. With $R^1=n\text{-}Bu$ and $HC{\equiv}CCH_2$ the corresponding products **4b** and **4d** were also formed.

In order to study the scope of the reaction and to verify the selectivity, we tested a few other hydrazines under these arylation conditions (Table 1, compounds **5**–**7**). Initially $CbzNHNHCH_3$ was synthesized by analogy with Scheme 1 and arylation furnished **5**, which could subsequently be benzylated smoothly under standard PTC conditions[2a] to give $(4\text{-}CH_3C_6H_4)CH_3N\text{-}N(CH_2Ph)Cbz$ in 95% yield. The NMR spectrum was identical with recently published data,[7] which indicates a similar selectivity in the arylation step as that for the Boc-derivatives in Scheme 1. For comparison of alkoxycarbonyl and acyl moieties, an acetylated hydrazine derivative was also included. Arylation of 1-acetyl-2-methylhydrazine, prepared by Condon's method,[13] proceeded similarly to give **6**. Thus it can be stated that on reaction with 1 equiv. of these pentavalent organobismuth reagents all the monoacylated, 1,2-disubstituted hydrazines studied undergo highly selective arylation of their non-acylated nitrogens.

Finally, as an example of a diacylated hydrazine, the arylation of 1,2-di-Boc-hydrazine with $Ar_3Bi(OAc)_2$ was studied both in the presence and absence of $Cu(OAc)_2$ as catalyst. In the first case (Et_3N was used as a promoter) monoarylation required 4 h to go to completion. Obviously the increased reaction time needed in comparison with that for the monoacylated hydrazines investigated above accounts for the observed regioselectivity and explains why we did not detect any side-products due to arylation at the carbamate nitrogens. In the absence of $Cu(OAc)_2$ the only product detected was BocN=NBoc which could be isolated after reaction of 1,2-di-Boc-hydrazine for 48 h. Its identity was proved by comparison (NMR and TLC) with an authentic sample, prepared by oxidation of BocNHNHBoc with the Br_2/Py complex according to the described protocol.[14] The formation of oxidation products in the reaction of some hydrazines with Ph_3BiCO_3 has been reported earlier[15] and obviously occurs here as well due to the dual nature of the pentavalent bismuth compounds, behaving as arylation agents or oxidants. In the syntheses in Table 1 the first process dominates to the extent that only traces of hydrazones could be detected by TLC. Their formation can be explained in terms of a well-known rapid isomerization[16] of azo compounds, which arise primarily from oxidation of $BocNHNHR^1$ by the bismuth reagents.

In conclusion, a convenient protocol for the arylation of hydrazines is described. In contrast to triarylbismuthanes, pentavalent bismuth compounds can be readily used for the smooth and selective arylation of hydrazines bearing electron-donating or electron-withdrawing substituents on either nitrogen.

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10. Typical procedure: To a solution of 0.579 mmol of $HC{\equiv}CCH_2NHNHBoc/Ph_3PO$ mixture in dichloromethane (2 mL) 0.05 equiv. of $Cu(OAc)_2$ was added, followed by 1.1 equiv. of $Tol_3Bi(OAc)_2$. The reaction was monitored by TLC (EtOAc–light petroleum 1:4). After completion (10 min) silica (~0.8 g) was added, whereupon the solvent was evaporated under reduced pressure. The remaining material was placed on top of a short silica column and eluted first with EtOAc–hexane 1:30 to remove nonpolar components, then with EtOAc–light petroleum 1:4 to isolate the product **4d**. An analytical sample was prepared by crystallization from hexane. ^1H NMR ($CDCl_3$): δ 1.49 (s, 9H, Boc), 2.22 (t, 1H, $HC{\equiv}C$, $^4J_{HH}=2.6$), 2.27 (s, 3H, CH_3), 4.22 (br s, 2H, NCH_2), 6.48 (br s, 1H, BocNH), 6.8–7.2 (m, 4H, C_6H_4); ^{13}C NMR ($CDCl_3$): δ 20.4 (CH_3), 28.3 (Boc), 43.3 (NCH_2), 73.4 ($H\underline{C}{\equiv}C$), 78.1 ($HC{\equiv}\underline{C}$), 81.0 (C_q, Boc), 114.6, 129.6, 130.3, 145.8 (C_6H_4), 155.1 (CO, Boc). Anal. calcd for **4d** $C_{15}H_{20}N_2O_2$ (260.34): C, 69.20; H, 7.74; N, 10.76. Found: C, 69.2; H, 7.8; N, 10.8%.
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