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Copper-catalyzed N-arylation of carbamate-protected hydrazones with organobismuthanes

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Abstract—Efficient copper(II) acetate-catalyzed N-arylation of carbamate-protected hydrazones was achieved under mild reaction conditions with organobismuthanes.
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Carbon–nitrogen bond formation remains one of the most extensively reviewed areas in organic chemistry, with palladium,[1] nickel[2] and copper-catalyzed[3] N-arylations playing an important role in the toolbox of organic synthesis.[1] However, some of these methods have drawbacks. Palladium salts are expensive, toxic[4] and require the use of phosphines, N-heterocyclic carbenes or other ligands.[1] Nickel catalysts have been reported to show low tolerance to functional groups and to be highly toxic.[5] At the same time, copper-mediated reactions have gained popularity due to mild reaction conditions and the applicability to a variety of aryl donors.[3]

Substituted hydrazines are important in a diverse array of fields, including agrochemicals and pharmaceuticals.[6] Recently, several aspects of copper-catalyzed N-arylation of hydrazines[7] and azo compounds[8] were studied within our group. In the present study we focused on hydrazones, since they are appealing precursors to monoarylated and 1,1-disubstituted hydrazines as well as to a number of azaheterocycles, inorganic heterocycles and indoles (Fig. 1).[9] Previously, to allow the synthesis of such compounds, only palladium catalysis was employed.[10]

The hydrazones of interest were prepared by condensation of hydrazines with the corresponding aldehyde or ketone as described previously (Scheme 1).[11] In the presence of copper(II) acetate benzophenone hydrazone with a free amino moiety underwent rapid oxidation to afford the symmetric azine $Ph_2C{=}NN{=}CPh_2$ (92%), the carbamate-protected hydrazone derivatives

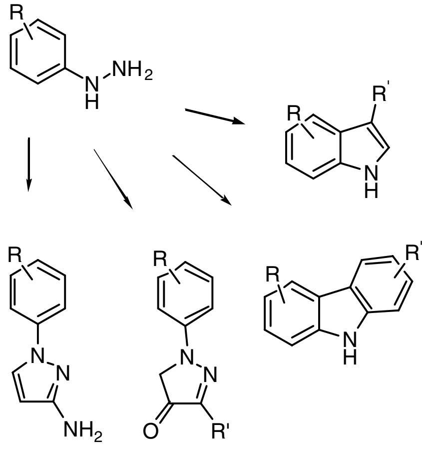
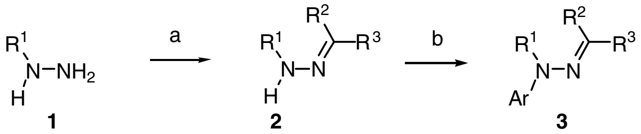


Figure 1.



Scheme 1. Preparation of arylated hydrazones. Reaction conditions: (a) ketone/aldehyde, H^+, reflux; (b) arylating agent, $Cu(OAc)_2$, Et_3N.

Keywords: N-Arylation; Hydrazines; Organobismuthanes.

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Table 1. Optimization of the N-arylation of Boc-protected acetophenone hydrazone **2a**[a]

Entry	Bi reagent	Cu salt	Solvent	Temperature	Time (d)	Yield **3aa** (%)
1	Ph_3Bi	$Cu(OAc)_2$	DCM	rt	3	92
2	Ph_3Bi	$Cu(OAc)_2$	DCE	Reflux	1	97
3	$Ph_3Bi(OAc)_2$	$Cu(OAc)_2$	DCM	rt	3	89
4	Ph_3Bi	$Cu(OAc)_2$	DCM	rt	1	72
5	Ph_3Bi	CuCl	DCM	rt	1	20
6[b]	Ph_3Bi	$Cu(OAc)_2$	MeOH	rt	1	n.r.[c]

[a] Reaction conditions: hydrazone **2a** (0.427 mmol), Bi reagent (1.5 equiv), Cu salt (1.5 equiv), Et_3N (1.5 equiv), solvent (3 mL).

[b] Without Et_3N.

[c] No product formation was detected by TLC.

Table 2. Copper(II) acetate-catalyzed N-arylation of hydrazones **2** with triarylbismuthanes[a]

Entry	R^1	R^2	R^3	Ar	2	3	Conditions	Time (d)	Yield (%)
1	Boc	Ph	Me	Ph	**2a**	**3aa**	A	1	97
2	Boc	Ph	Me	*p*-Tol	**2a**	**3ab**	B	3	90
3	Boc	Ph	Me	*o*-Tol	**2a**	**3ac**	B	3	10
4	Boc	Ph	Me	*p*-An	**2a**	**3ad**	B	3	96
5	Boc	CH=CHPh	Me	Ph	**2b**	**3ba**	B	3	72
6	Boc	Ph	H	Ph	**2c**	**3ca**	A	1	44[b]
7	Ph	Ph	Ph	*p*-Tol	**2d**	**3db**	A	1	98

[a] Reaction conditions: hydrazone (1 equiv), Ar_3Bi (1.5 equiv), $Cu(OAc)_2$ (1.5 equiv), Et_3N (1.5 equiv); condition A: DCE, heating under reflux; condition B: DCM, rt.

[b] Partially decomposed on the silica column.

were found to be stable against oxidation. However, carbamate protection increases the amidic nature of the hydrazones, which compared to amines, show a poorer reactivity towards arylation.

Primarily, optimization of the reaction with triarylbismuthane and its diacetate with Et_3N serving as a promoter[12] showed that the former reagent gave slightly improved results (Table 1).[13] When the reaction was carried out at ambient temperature in dichloromethane, the yield of **3aa** approached 70% over 24 h and 90% over three days. When the reaction mixture was heated under reflux in DCE, the starting material **2a** was consumed within 24 h. Copper(II) acetate gave superior results compared to copper(I) chloride, which is in accordance with mechanistic considerations.[1a] Previously, N-arylation using arylboronic acids as aryl donors carried out in methanol was shown to be successful even with the catalytic loadings of the copper(II) salt.[14] However, when we used organobismuthanes in methanol, no reaction was detected even upon heating under reflux.

In general, N-arylation of carbamate-protected hydrazones takes place under mild reaction conditions (Table 2), and can be employed as a convenient alternative to Buchwald–Goldberg amidation.[15] The yield of the phenylated product of Boc-protected benzaldehyde hydrazone, **3ca**, was 44% due to partial decomposition during purification on silica gel. Arylation of the aminic nitrogen in 2-phenyl benzophenone hydrazone **2d** with *p*-Tol_3Bi proceeded in 24 h to afford the corresponding product **3db** in a 98% isolated yield.

The only limitation is in the introduction of sterically hindered aryls. The reaction of **2a** with *o*-Tol_3Bi over three days gave only a 10% yield. Arylation with both 1-Np_3Bi and 1-$Np_3Bi(OAc)_2$ yielded no product. Raising the temperature and using different promoters (*t*-BuOK, Py, Et_3N, DBU, DMAP) did not lead to an increase in reactivity and only the formation of 1-NpOAc was detected by TLC. Thus, as has been previously reported, introduction of sterically congested aryl substituents with bismuth reagents is somewhat complicated.[12]

As a comparison, arylation with arylboronic acids,[16] which are less sterically hindered and more 'aryl-economic', was attempted. Reaction of hydrazone **2a** with $PhB(OH)_2$ in DCM over three days yielded 4% and 7% of the product in the presence of Et_3N and pyridine, respectively. No reaction was detected with 1-$NpB(OH)_2$. Reaction of **2a** with $PhB(OH)_2$ in methanol with heating under reflux for three days afforded only 15% of the product.

In summary, we have demonstrated the applicability of organobismuth reagents rather than arylboronic acids in the copper-catalyzed N-arylation of amidic nitrogen. The carbamate-protected hydrazones used as model substrates generally give good to excellent yields under mild reaction conditions. Taken together, this method represents a useful alternative to Buchwald–Goldberg amidation and can be successfully applied to the synthesis of trisubstituted amides and hydrazides.

Acknowledgements

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Supplementary data

Analytical data for new compounds **2b** and **3ab–db**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.12.071.

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13. *Typical procedure for tert-butyl 1-phenyl-2-(1-phenylethylidene)hydrazinecarboxylate* **3aa**: Hydrazone **2a** (0.427 mmol; 1 equiv) was dissolved in DCE (3 mL), then TEA (1.5 equiv), Cu(OAc)$_2$ (1.5 equiv), Ar$_3$Bi (1.5 equiv) were added and the reaction mixture was left to stir under reflux in DCE. The reaction was monitored by TLC, using EtOAc/hexanes 1:5 as the eluent. The product was isolated by purification on silica gel column with a Celite® pad. Firstly, EtOAc/hexanes 1:30 was used to elute most of the unpolar components. Then, elution was continued using EtOAc/hexanes 1:5. The fractions containing the arylated hydrazone were combined and the solvent was evaporated in vacuo to afford a yellow viscous oil (97%). IR (film, KBr) ν 3396, 2975, 1710, 1589, 1494, 1373, 1298, 1153 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$) δ 8.00–7.00 (m, 10H), 2.27 (s, 3H), 1.49 (s, 9H), ^{13}C NMR (50 MHz, CDCl$_3$) δ 172.1, 151.6, 142.7, 137.7, 130.5, 128.5, 128.4, 127.2, 125.2, 124.2, 81.9, 28.4, 17.1; HRESIMS *m/z* 333.1587 [M+Na]$^+$, calcd for C$_{19}$H$_{22}$N$_2$NaO$_2$ 333.1579.
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