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LETTERS

N-Phenylation of Azole Derivatives by Triphenylbismuth Derivatives / Cupric Acetate

Alexey Yu. Fedorov 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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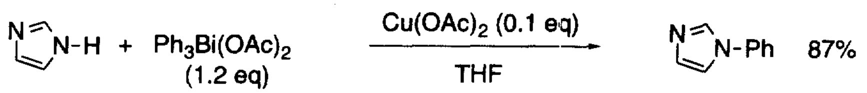
Abstract: Triphenylbismuth diacetate reacts with various N-H containing heteroarenes in the presence of a catalytic amount of copper diacetate to afford moderate to good yields of the N-phenylheteroarenes.

Formation of carbon-carbon or carbon-heteroatom bonds by reaction of an organoheteroatomic compound, acting as a carbocation synthetic equivalent, with a nucleophile is now well documented.[1] Aryl/heteroaryl C-N bond cross-coupling reactions are not common.[2-4] However, such a methodology is highly desirable for the synthesis of biologically active *N*-arylated heterocycles. The direct *N*-arylation of N-H containing heteroarenes has been obtained by three methods : (*a*) catalytic cupric acetate / *p*-tolyllead triacetate[2] (*b*) catalytic cupric trifluoroacetate / triphenylbismuth bistrifluoroacetate[3] (*c*) stoichiometric cupric acetate / arylboronic acid / pyridine / 4Å molecular sieves.[4] The first method involves toxic organolead reagents and the third method requires an excess of copper diacetate (1.5 mol equiv. in general). In the case of the second method, as only reactions of organobismuth derivatives with indole compounds had been originally reported,[3] it was recently suggested that this method is limited to indole-like heteroarenes.[4]

In this letter, we report that triphenylbismuth diacetate[5] reacts with other types of heteroarenes, in the presence of only a catalytic amount of copper diacetate under rather mild conditions in the air with protection from moisture. The use of the more reactive but more unstable triphenylbismuth bistrifluoroacetate is not necessary as in the indole case. Indeed, in a typical experiment, a mixture of imidazole, triphenylbismuth diacetate (1.2 mol equiv.) and copper diacetate (0.1 mol equiv.) in freshly distilled THF was stirred at 50°C for 6 h. After completion of the reaction, distillation of the solvent under reduced pressure followed by purification of the residue by preparative plate chromatography afforded *N*-phenylimidazole in 87% yield.



The *N*-phenyl derivatives of other N-H containing heteroarenes were similarly isolated in generally good yields (Table 1). In the case of the less nucleophilic heterocyclic substrates, moderate to good yields were obtained upon addition of 2 molar equivalents of TMG (*N*,*N*,*N'*,*N'*-tetramethylguanidine). All the *N*-arylation reactions involving copper diacetate catalysis are considered to take place by a two-step process.[6] In the first step, a [heteroarene-copper-aryl] complex is formed. Then ligand coupling takes place on this copper(III) species to lead to the products.[6a] This mechanism is supported by our recent observation that aryl radical species are not involved in any step of the sequence.[7] As bismuth is considered to be one of the less toxic heavy metals[8] and in view of the range of triarylbismuth diacetate which are now easily prepared,[9] this method appears as an environmentally friendly attractive alternative for the preparation of *N*-phenyl and

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

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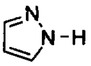
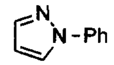
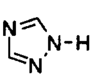
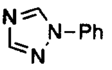
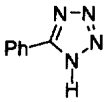
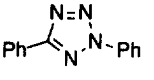
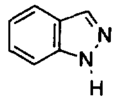
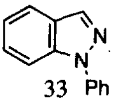
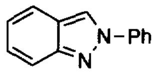
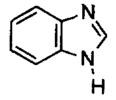
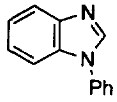
presumably other *N*-aryl heteroarenes which should be interesting for the generation of heterocycles libraries. Moreover, in some instances, this method proved superior in terms of yield to the arylboronic-stoichiometric copper diacetate reaction.[4]

Table 1: Phenylation of N-H containing heteroarenes with $Ph_3Bi(OAc)_2$ - catalytic copper diacetate

Substrate	Reaction conditions*	Products, yields (%)
	$Ph_3Bi(OAc)_2$ (1.1 eq), $Cu(OAc)_2$ (0.1 eq), 17 h	 44
	*i)* $Ph_3Bi(OAc)_2$ (1.1 eq), $Cu(OAc)_2$ (0.2 eq), TMG (2 eq), 24 h *ii)* $Ph_3Bi(OAc)_2$ (1.1 eq), $Cu(OAc)_2$ (0.2 eq), 48 h	 60
	*i)* $Ph_3Bi(OAc)_2$ (1.2 eq), $Cu(OAc)_2$ (0.2 eq), TMG (2 eq), 17 h *ii)* $Ph_3Bi(OAc)_2$ (0.8 eq), $Cu(OAc)_2$ (0.2 eq), 18 h	 87
	$Ph_3Bi(OAc)_2$ (1.1 eq), $Cu(OAc)_2$ (0.2 eq), TMG (2 eq), 7 h	 +  33 35
	$Ph_3Bi(OAc)_2$ (1.1 eq), $Cu(OAc)_2$ (0.1 eq), TMG (3 eq), 17 h	 93

* All reactions were carried out in THF at 50°C in the air with protection from moisture

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