

Electrophilic Amination of Organozinc Halides

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Abstract

The reaction of several functionalized primary, secondary and tertiary organozinc bromides, benzylzinc bromide, functionalized arylzinc halides and one heteroarylzinc bromide with *di**tert*-butyl azodicarboxylate is described. The reaction products, *N,N'*-*di**tert*-butoxycarbonylhydrazino derivatives are obtained in excellent yields for most aliphatic substrates and good yields for aromatic substrates. These compounds are direct precursors of hydrazino and amino derivatives by deprotection. The process constitutes the first synthetically useful electrophilic amination of organozinc derivatives, and takes advantage of the broad functional group tolerance of the organozinc chemistry. © 1998 Elsevier Science Ltd. All rights reserved.

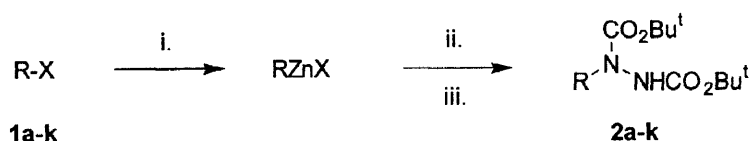
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Organozinc compounds have become an important group of reagents among all the tools now available to the synthetic organic chemist [1]. As a main group metal, endowed with moderated electronegativity, organozinc reagents are generally regarded as intermediates of low reactivity. It is after transmetalation with transition metals that the richest chemistry of these species is displayed [2]. However, a small number of synthetically useful processes involving direct reaction of organozinc reagents with electrophiles are known. These include Reformatsky-type reactions [3], enantioselective additions to aldehydes [4], conjugate additions [5,6], reaction with oxygen [7], tosyl cyanide [8] and halogens [9], among others [1].

Recent studies in our group concerning the nature of the insertion of highly reactive zinc into the carbon-bromine bond prompted us to search for reagents to react with secondary organozinc bromides in high yield [10]. The reagent of choice was *di**tert*-butyl azodicarboxylate (DTBAD). Reaction with 1eq. of 2-octylzincbromide (**1a**, Table 1) yielded the corresponding hydrazino derivative (**2a**, Table 1, 94%), which is the immediate precursor of 2-octylamine by deprotection.

The only examples of electrophilic amination [11] of organozinc compounds described in the literature correspond to the reaction of an excess of diethyl/diisopropyl zinc with several chloroamines. The reaction afforded moderate to low yields of substitution products, often as a mixture of amines [12-13]. On the other hand, electrophilic amination using dialkyl azodicarboxylates has been reported for other nucleophilic species, including lithium enolates and silyl enol ethers [14-20].

In this work, we explored the scope of this reaction with a variety of organozinc halides, easily prepared by reaction of the corresponding organic bromide or iodide with highly reactive zinc (Scheme 1) [2].



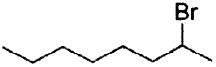
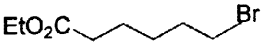
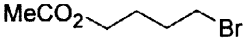
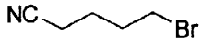
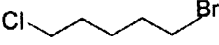

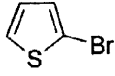
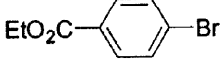
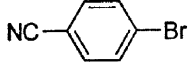
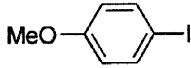
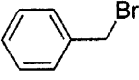
Scheme 1. i. Zn^* (1.5-3 eq.), THF. ii. DTBAD (1 eq.), 0°C. iii. Sat. NaHCO_3 . X = Br (**1a-i**, **1k**), I (**1j**).

Thus, in a representative example, 2-bromothiophene (**1g**, 1 mmol) was added to a 50 ml centrifuge tube containing active zinc (Zn^* , 1.5 eq.) in dry tetrahydrofuran under Ar atmosphere. After 30 min stirring at rt, the reaction mixture was centrifuged and cannulated to another flask at 0°C. *Ditert*-butyl azodicarboxylate (1 mmol in THF) was then added dropwise over 5 min. After stirring (1h), the reaction was quenched with sat. NaHCO_3 , extracted (Et_2O), concentrated and purified by flash chromatography (silica gel, hexanes: ethyl acetate) to afford pure **2g** as a white solid¹ (Table 1, **2g**, 80%). In the case of aromatic bromides, reflux conditions were required (Table 1, **1h-i**). An excess of active zinc was used in all cases to assure that oxidative addition went to completion within reasonable times.

Ditert-butyl hydrazinodicarboxylates (*i.e.* **2a-k**) have been reported to have largely uninterpretable ¹H-NMR spectra at room temperature [16-17, 19]. We also found that NMR procurement at either 300 MHz, 25°C in CDCl_3 or 500 MHz, 100°C in $\text{DMSO}-d_6$ proved to be unsuccessful. Line broadening and coalescence phenomena were observed throughout, as a consequence of the restricted rotation of the hydrazino and amide bonds in these biplanar hydrazino derivatives [21]. Low field NMR (200 MHz, 100°C in $\text{DMSO}-d_6$), however gave satisfactory results [22]. Complete spectroscopical characterization of the products **2** were done under these conditions.

¹ 2-(*N*, *N'*-bis-(*tert*-butoxycarbonyl)hydrazino)thiophene (**2g**): mp: 82-4°C (Et_2O); IR (cm^{-1} , neat): 3318 (NH), 1717, 1734 (C=O), 1539 (C=C), 1154 (C-O), 851, 758, 680 (=C-H); ¹H-NMR (200 MHz, $\text{DMSO}-d_6$, 100°C): 1.44 (s, 9H, $\text{C}(\text{CH}_3)_3$), 1.47 (s, 9H, $\text{C}(\text{CH}_3)_3$), 6.70 (dd, J = 3.8, 1.6 Hz, 1H, 3-thienylH), 6.82 (dd, J = 5.5, 3.8 Hz, 1H, 4-thienylH), 7.03 (dd, J = 5.5, 1.6 Hz, 1H, 5-thienylH), 9.54 (br s, 1H, NH); ¹³C-NMR (125 MHz, $\text{DMSO}-d_6$, 100°C): 27.3 (3C, $\text{C}(\text{CH}_3)_3$), 27.55 (3C, $\text{C}(\text{CH}_3)_3$), 79.65, 81.5 (C-O), 114.4, 118.7, 124.05 (thienylCH), 145.05 (thienylCN), 151.7, 153.8 (NCO_2); m/z (FAB MS): 314.1 (M^+ , 23%); Anal. Calc. for $\text{C}_{14}\text{H}_{22}\text{N}_2\text{O}_4\text{S}$: C, 53.48; H, 7.05; N, 8.91; S, 10.20. Found: C, 53.8; H, 7.0; N, 8.7; S, 10.2.

Table 1
Preparation of Compounds 2^a

	Starting Halide (RX, 1)	Conditions ^b Zn*:1; T (°C); time (h)	Product 2, NMR/Isolated yield ^c
1a		2:1; 25°; 3	2a, 94/94
1b		2:1; 25°; 3	2b, 95/90
1c		2:1; 25°; 3	2c, 90/90
1d		2:1; 25°; 1	2d, 94/90
1e		2:1; 25°; 3	2e, 90/81
1f		2:1; 25°; 0.5	2f, 73/75
1g		1.5:1; 25°; 0.5	2g, 80/80
1h		3:1; 70°; 3	2h, -/40
1i		3:1; 70°; 3	2i, 65/66
1j		3:1; 25°; 3	2j, 55/-
1k		1.5:1; 25°; 0.5	2k, 90/90

^a All products were $\geq 95\%$ pure (300 and/or 200 MHz ¹H-NMR) and were fully characterized by spectroscopic means (IR, ¹H- and ¹³C-NMR, MS).

^b Corresponding to the reaction of 1 with Zn*.

^c ¹H-NMR yield using bibenzyl as a standard added to the crude mixture. Isolated yield after flash chromatography (silica gel, hexanes:ethyl acetate). Both based on starting material 1 or DTBAD.

The reaction products are direct precursors of the corresponding hydrazino derivatives by removal of the *tert*-butoxycarbonyl groups with CF₃CO₂H [14-15, 20, 23]. Reductive cleavage of the N-N bond can be accomplished using H₂/Ni Raney to afford the amines [15-16, 23]. Other deprotective protocols are also widely described [14, 17, 20, 24-25]. In summary, the new reported reaction expands the range of uncatalyzed processes of organozinc reagents. It is the first synthetically applicable electrophilic amination of organozinc reagents. It proceeds with excellent yields for most alkyl organozinc bromides, as well as benzylic ones. Good to medium yields are obtained in the reaction with aromatic and heteroaromatic organozinc bromides or

iodides. Excellent functional group tolerance is also exhibited in the process, similar to other reactions mediated by organozinc reagents. Finally, the reaction can be considered as environmentally friendly as it does not require any transition metal catalyst.

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