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Preliminary Communication

Regioselective *ortho*-alkylation of *N,N*-diethylbenzamides *via* lithiation and copper transmetalation

Dario Pini, Stefano Superchi and Piero Salvadori

Centro Studi C.N.R. per le Macromolecole Stereordinate ed Otticamente Attive, Dipartimento di Chimica e Chimica Industriale, Università di Pisa, via Risorgimento, 35, 56126 Pisa (Italy)

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Abstract

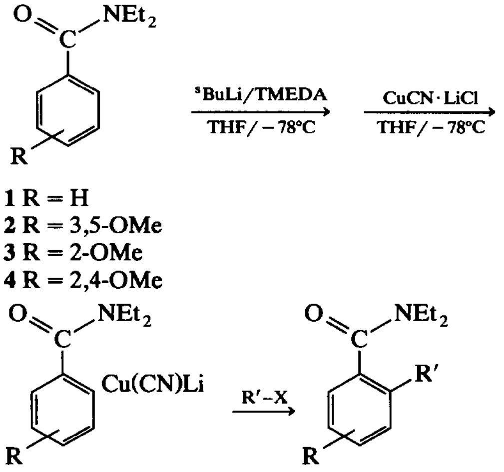
One-pot *ortho*-lithiation and copper transmetalation with CuCN · LiCl of *N,N*-diethylbenzamides afford the corresponding aryl cyanocuprate, which gives coupling with some aliphatic halides in fair to good yields.

The alkyllithium-induced regiospecific deprotonation *ortho* to a directed metalation group (aromatic directed metalation) is an important synthetic tool for the synthesis of polysubstituted aromatic compounds which are difficult to prepare *via* conventional electrophilic substitution [1]. One of the most effective and useful *ortho*-metalation director groups is *N,N*-diethylbenzamide. Indeed *o*-lithio-*N,N*-diethylbenzamides react with a large variety of electrophiles producing good intermediates for the synthesis of substituted aromatic compounds, including natural products [2].

Unfortunately, simple *o*-lithiated benzamides do not allow the direct regioselective introduction of long and branched alkyl chains onto the aromatic ring, because these organometallics do not couple with aliphatic halides, with the only exception of methyl and ethyl iodides [3].

We overcame this limitation to the synthetic versatility of directed aromatic metalation by modifying the original organometallic species. We thought that the conversion of the lithioamide into another organometallic species with less basic and more nucleophilic properties would permit the coupling reaction with halides, avoiding unwanted elimination side reactions. Some examples of coupled *ortho*-lithiation and transmetalation have been already described. Organomagnesium derivatives have been prepared by transmetalation from the lithiated benzamides [4] and copper derivatives have been obtained from *ortho*-lithiated oxazolines [5]. Nevertheless these organometallic compounds react only with allyl bromide and this does not constitute a general method for the alkylation of aromatic substrates.

We investigated the reactivity of copper compounds, since copper organometallics are good nucleophilic reagents [6] and possess low basicity. Here we report our results on the synthesis of aryl cyanocuprate [7*] derivatives from the *ortho*-lithiated amides and their reactivity with aliphatic halides and analogous electrophiles.



1 R = H
2 R = 3,5-OMe
3 R = 2-OMe
4 R = 2,4-OMe

Ortho-lithiation [3] (1.1 eq. ^{s}BuLi/TMEDA, −78°C, THF, 45 min) of amides **1**, **2**, **3**, and **4** resulted in a yellow solution, to which was added successively by syringe a colourless solution of CuCN · LiCl 1 : 1 complex [8] (1 eq., 0.4 M in THF, −78°C) giving a white clear solution of the amide cyanocuprates [9*]. Halides and other electrophiles (3 eq.) were added to the cuprates at −78°C, the solution was allowed to warm overnight to room temperature and then stirred for some hours. Whereas allyl and benzyl bromide reacted in a short time (30–90 min) and at low temperature,

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Correspondence to: Professor P. Salvadori.

* Reference number with asterisk indicates a note in the list of references.

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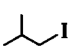
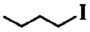
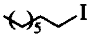
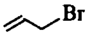
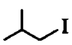
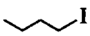
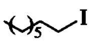
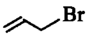
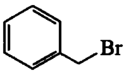
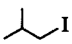
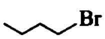
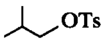
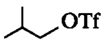
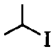
TABLE 1. Coupling reactions of *N*,*N*-diethylbenzamides

Entry	Amide	Electrophile	Coupling product [a]	Yield (%) [b]
1	1		**1a**	85
2	1		**1b**	30
3	1		**1c**	62
4	1		**1d**	72
5	2		**2a**	92
6	2		**2b**	35
7	3		**3c**	58
8	3		**3d**	65
9	4		**4a**	98
10	4		**4e**	85
11	4		**4b**	60
12	4		**4c**	30
13	4		**4b**	0
14	4		**4b**	0
15	4		**4f**	10

[a] All products were isolated and fully characterized by NMR and MS spectra. [b] Yields were determined from NMR and GLC of crude.

the less reactive alkyl halides needed several hours (12–24 h) at room temperature. After workup liquid chromatography [10*] we obtained the corresponding alkylated amides.

The results in Table 1 show that coupling reactions with allyl and benzyl bromides are almost quantitative, while reactions with alkyl halides give fair yields. The coupling with benzyl bromides and alkyl halides is noteworthy because these substrates do not react both with *o*-lithio and with *o*-bromomagnesium benzamides [4]. These results suggest that these cyanocuprates may be reactive towards other substrates not reactive with usual *o*-lithiated amides. Concerning the leaving groups on the alkyl halides, the iodides are better than bromides, and there was no reaction with the analogous tosylates and triflates. Moreover we noted a strong steric hindrance in the coupling of secondary halides (entry 15). In some cases (entries 2 and 6) we found unexpected lower yields of alkylated products together with by-products of self-condensation of the organometallic compound. Probably side reactions are faster than coupling with isobutyl iodide with amides **1** and **2**, lacking methoxy group in the *ortho*-position.

In conclusion, these new cyanocuprate derivatives of *N*,*N*-diethylbenzamides have interesting reactivity and synthetic utility, giving coupling reactions with substrates such as alkyl and benzyl halides that do not react with organometallics obtained by aromatic directed metalation [4]. The transmetalation of *ortho*-lithiated benzamides into cyanocuprates allows the direct regiospecific introduction of allyl, benzyl, and alkyl moieties, widely extending the utility of the benzamide-directed metalation strategy.

References

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7 Preliminary results showed the greater reactivity of cyanocuprate derivatives compared to the corresponding organocopper compounds obtained from lithiated amides and CuI.

8 B. H. Lipshutz, C. Ung, T. R. Elworthy and D. C. Reuter, *Tetrahedron Lett.*, *31* (1990) 4539.

9 This organometallic species is reactive up to room temperature, even if warming of the mixture causes progressive darkening, and at −10°C the solution turns to a black-green suspension.

10 Standard workup: THF was evaporated from the mixture, and the residue was dissolved in CH_2Cl_2, washed with saturated NH_4Cl and water, and dried over Na_2SO_4.