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Direct Coupling between β-Functionalized Organolithium Compounds and Aryl and Vinyl Halides

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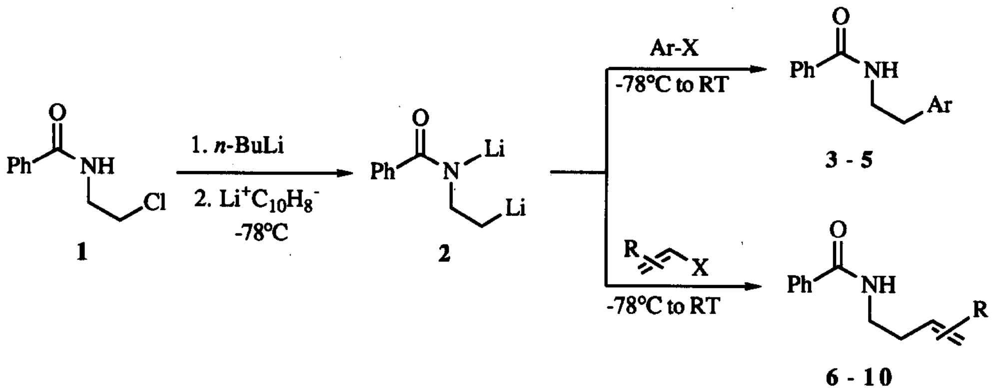
Abstract: Treatment of *N*-lithio-*N*-(2-lithioethyl)benzamide with different aromatic and vinylic halides affords directly the corresponding substitution products: functionalized benzamides **3** - **10**.

The reaction of organometallic reagents with organic halides represents one of the most straightforward methods of carbon-carbon sigma bond formation, but unfortunately not any type of this coupling reaction occurs directly.[1] In this sense, the difficulty of selective cross-coupling reaction between alkyllithiums compounds and aryl and vinyl halides has been overcome by using transition metal complexes or salts as catalysts, mainly copper,[2] palladium[3] and nickel[4] derivatives. Nevertheless, in the literature there are some examples of this uncatalyzed direct coupling. As far as we know, methyllithium reacts readily with iodobenzene and 1-iodonaphthalene;[5] *n*-butyllithium and ethyllithium gave the cross-coupled products with different aryl halides;[6] and the reaction of octyllithium with 1-bromocyclopentene leads to 1-octylcyclopentene.[7] Presumably, these coupling reactions proceed through halogen-metal exchange followed by nucleophilic substitution.

On the other hand, we have previously described the preparation of β-nitrogen-functionalized organolithium compounds and their reaction with different electrophiles.[8] As part of our continuing studies to more fully examine the synthetic applications of these dianionic intermediates, we report herein our preliminary results on the direct coupling reaction between *N*-lithio-*N*-(2-lithioethyl)benzamide and aromatic and vinylic halides, which demonstrate that this uncatalyzed one pot coupling reaction could be more general and synthetically applicable than it has been recognized so far.

As shown in the Scheme 1 *N*-lithio-*N*-(2-lithioethyl)benzamide (**2**) was generated from *N*-(2-chloroethyl)benzamide (**1**) by successive treatment with *n*-butyllithium and lithium naphthalenide at -78°C.[8,9] The *in situ* reaction of this dianion **2** with different aromatic and vinylic halides between -78°C and room temperature affords directly the corresponding coupling products **3** - **10**.

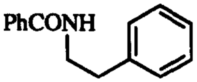
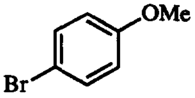
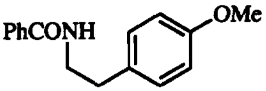
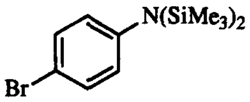
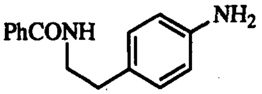
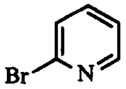
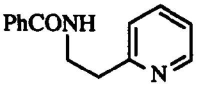
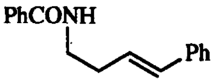
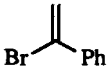
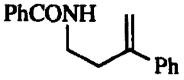
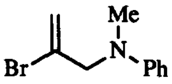
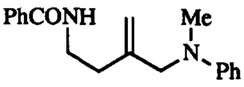
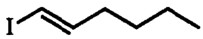
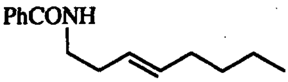


Scheme 1

The unoptimized results are summarized in the Table 1. Thus, the coupling reaction works better with iodide and bromide derivatives than with chloride compounds, as evidenced by the lower yield obtained with chlorobenzene (entry 3) compared with iodobenzene (entry 1) and bromobenzene (entry 2). Substituted aryl bromides (entries 4, 5), 2-bromopyridine (entry 6), and different vinyl bromides and iodides (entries 7 - 10) also coupled smoothly in good yields. When *E*-β-bromostyrene (entry 7) and *E*-1-iodohexene (entry 10) were used, the coupling reaction proceeded with retention of configuration at the double bond as evidenced by ^{1}H- and ^{13}C-NMR. 4-Bromo-*N*,*N*-bis(trimethylsilyl)aniline,[10] *N*-methyl-*N*-phenyl-2-bromo-2-propenylamine[11] and *E*-1-iodohexane[12] were prepared following literature procedures. From a mechanistic viewpoint the reaction probably involves halogen-metal exchange, which seems to take place at -78°C, followed by alkylation upon warming to room temperature. Work on this subject is currently in progress in our laboratory.

A **typical procedure** is as follows. To a solution of *N*-(2-chloroethyl)benzamide (3 mmol) in THF (30 ml) under nitrogen at -78°C was added a solution of *n*-butyllithium in hexane (3.15 mmol) and stirring was continued for 30 min at the same temperature. To the resulting mixture was added a solution of lithium naphthalenide (6.15 mmol) in THF and it was stirred for 7h at -78°C. Then a solution of the corresponding aryl or vinyl halide (3mmol) in THF (20 ml) was added and the mixture was stirred at -78°C for 3h and then allowed to rise to room temperature overnight. The resulting mixture was hydrolyzed with water and extracted with ether, and the organic layer was dried over anhydrous sodium sulphate and concentrated *in vacuo* (15 mmHg). Naphthalene was removed by sublimation (0.01 mmHg, 40-50°C bath temperature) and the residue was purified by flash column chromatography (silica gel; dichloromethane / diethyl ether).

Table 1. Coupling Reaction of Organolithium **2** with Aryl and Vinyl Halides

Entry	Aryl or vinyl halide	Products[a] **3 - 10**		Yields[b,c](%)
1	Ph-I		**3**	95 (75)
2	Ph-Br	"	**3**	95 (75)
3	Ph-Cl	"	**3**	23[d]
4			**4**	91 (65)
5			**5**	-[e] (53)[f]
6			**6**	85 (58)
7			**7**	70 (55)
8			**8**	98 (75)
9			**9**	95 (78)
10			**10**	95 (79)

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[a] All compounds gave correct spectroscopic data (IR, ^1H-, ^{13}C-NMR, and MS spectra). [b] Isolated yields based on starting material **1**. [c] Numbers between brackets refer to yields after chromatographic purification. [d] *N*-Ethylbenzamide (70%) was also formed. [e] Not calculated; the product obtained after usual work up was the *bis*-trimethylsilylated amine derivative of **5**. [f] Isolated by acid-base extraction (1N HCl, 1N NaOH).

In summary, we have shown that different *N*-substituted benzamides can be efficiently prepared by direct coupling reaction of aryl and vinyl halides with *N*-lithio-*N*-(2-lithioethyl)benzamide.

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