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LETTERS

Diethylzinc/Cu^{II}-mediated alkylation of aromatic amines and related compounds[†]

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Abstract—A mild and efficient method for the *N*-alkylation of aromatic amines and related compounds is described. The approach developed herein utilizes, as the key step, a transmetallation between a cupric salt and the dialkylzinc species. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Organozinc compounds are useful reagents which, since their discovery in 1849, have mainly been involved in nucleophilic addition reactions[1] but also in cyclopropanation processes as carbene precursors.[2] The ability of these Zn^{II} species to interact with other metals by transmetallation expanded the scope of organozinc chemistry.[3] However, to the best of our knowledge, dialkylzinc reagents have not yet been reported to be effective for the *N*-alkylation of organic compounds. We found that, upon treatment with 3 equiv. of diethylzinc and 3 equiv. of a Cu^{II} salt in CH_2Cl_2, aromatic amines and derived substrates can be *N*-alkylated (Scheme 1).

Amongst the various copper salts tested (CuI, $CuBr_2$, $Cu(OAc)_2$, $Cu(OPiv)_2$, $Cu(OTf)_2$), cupric acetylacetonate ($Cu(acac)_2$) was found to be the most efficient in effecting *N*-alkylation. The mechanism for this transformation is probably analogous to that of the Cu^{II}/Al^{III}-mediated alkylation of amines[4] and involves, as the key step, a transmetallation[5] between diethylzinc and the copper^{II} species.[6]

$$\text{Ar-NH}_2 \quad + \quad \text{ZnEt}_2 \quad \xrightarrow[\text{CH}_2\text{Cl}_2]{\text{Cu}^{\text{II}}} \quad \text{Ar-NHEt}$$

Scheme 1.

To find out the scope and limitations of this novel reaction, the diethylzinc/$Cu(acac)_2$-mediated alkylation was attempted on various substrates (Table 1). The overall yields are in most cases satisfactory. The reaction has successfully been extended to diversely substituted anilines (entries 1–5) but also to a hydrazone (entry 7), a hydrazine (entry 8) and a hydroxylamine *O*-benzyl ether derivative (entry 6). The reaction of a bulky substrate (entry 5) and of methylated aniline (entry 4), under our conditions, led to the formation of the expected products albeit in moderate yields. The nature of the substitution of the aromatic ring has also been briefly studied, showing that electron-donating substituents induced some loss in selectivity (entry 2). While electron-withdrawing groups, on the other hand, increased the selectivity of the alkylation process (entry 3). In both cases, the alkylated aniline derivatives were obtained in comparable yields. Our attempts to alkylate aliphatic amines (e.g. benzylamine) under the aforementioned conditions were unsuccessful. This is possibly due to the formation of a strong complex between the more basic amine and copper.

In conclusion, we have shown that diethylzinc, in the presence of a copper^{II}-based promoter, selectively alkylates selected aromatic amines and related compounds.

2. Typical experimental procedure

Under Ar, to a stirred solution of $Cu(acac)_2$ (0.430 g, 3 equiv.) and aniline (0.051 mL, 0.55 mmol, 1 equiv.) in

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Keywords: alkylation; amine; copper; transmetallation; zinc.

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[†] Dedicated to the memory of Sir Derek H. R. Barton who initiated this work.

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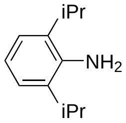
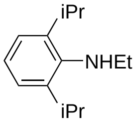
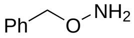
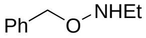
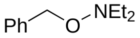
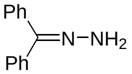
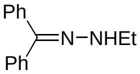
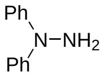
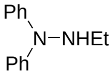
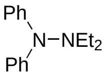
Table 1. Examples of alkylation of amines and related compounds

entry	substrate	products		ratio[a]	yield (%)[b]
1	Ph-NH_2	Ph-NHEt	Ph-NEt_2	90/10	95
2	MeO*p*-C_6H_4-NH_2	MeO*p*-C_6H_4-NHEt	MeO*p*-C_6H_4-NEt_2	65/35	83
3	O_2N*p*-C_6H_4-NH_2	O_2N*p*-C_6H_4-NHEt			85
4	Ph-NH-Me	Ph-N(Me)Et			35
5					41
6				15/85	67
7					60
8				65/35	78

[a] Determined by ^1H NMR analysis of the crude reaction mixture. [b] Isolated yields.

6 mL of anhydrous CH_2Cl_2 was added dropwise, over a period of 1 h, $ZnEt_2$ (1.7 mL of a 1 M soln in hexane, 3 equiv.). The reaction was then quenched with 10% HCl and made basic with 10% NaOH. The mixture was filtered through a sintered glass funnel and the aqueous layer was extracted three times with Et_2O. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by column chromatography over silica gel (hexane/AcOEt, 8/2).

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