Reductive alkylation of nitrobenzene promoted by zinc and tin in protic solvents

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Abstract

Barbier-type organometallic reactions of nitrobenzene with organic halides in protic solvents produce directly *N,N*-dialkylanilines. With allyl bromide, best yields are obtained using zinc in an aqueous monobasic sodium phosphate solution in the presence of cuprous iodide or tin in methanol. The latter procedure is also successful in the case of benzyl bromide and primary alkyl iodides. Control experiments exclude a mechanism of reduction followed by nucleophilic alkylation and show that the reaction is initiated by a nucleophilic attack of the organometallic species on the nitro group. Similar reactions with Grignard reagents under anhydrous conditions are reported to have a completely different outcome. © 2000 Elsevier Science Ltd. All rights reserved.
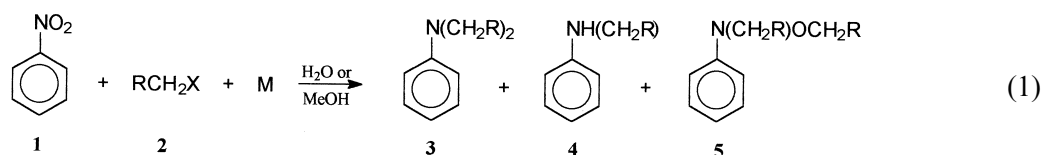
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In recent years, the in situ addition of organic halides to carbonyl compounds promoted by various metals in aqueous medium has found increasing applications even for the synthesis of complex molecules.[1] Initially restricted to allylic halides, the methodology has now been extended to α-bromo ketones[2] and esters,[3] to propargylic,[4] benzylic,[5] and even saturated halides.[6] In sharp contrast to this great variability of the organometallic component of the reaction, the electrophiles used in most cases have been aldehydes and ketones; a few reports deal with carboxylic derivatives[7,8] and with electron deficient alkenes.[9] Some nitrogen containing substrates can also react in special cases, for example, sulfonimines,[10] immonium ions[11] and oximes.[12] In order to evaluate the synthetic potential of such simple and environmentally clean reactions, we directed our interest to unconventional, non-carbon electrophiles. Organic nitro compounds possess a formal positive charge on the nitrogen and therefore should be highly reactive towards nucleophiles. However, with few exceptions, their synthetic use remains restricted to reductions leading to hydroxylamines, amines or several other dimeric intermediates.[13]

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$$\underset{\mathbf{1}}{\overset{NO_2}{\text{(◯)}}} + RCH_2X + M \xrightarrow[\text{MeOH}]{H_2O \text{ or}} \underset{\mathbf{3}}{\overset{N(CH_2R)_2}{\text{(◯)}}} + \underset{\mathbf{4}}{\overset{NH(CH_2R)}{\text{(◯)}}} + \underset{\mathbf{5}}{\overset{N(CH_2R)OCH_2R}{\text{(◯)}}} \qquad (1)$$

In our first attempts, we reacted nitrobenzene (**1**) with allyl bromide (**2a**) and zinc dust at room temperature in a concentrated aqueous solution of monobasic sodium phosphate producing diallyl aniline (**3a**) as the main product together with considerable amounts of monoallyl aniline (**4a**) and *N,O*-diallyl-*N*-phenylhydroxylamine (**5a**) (Eq. (1), Table 1, entry 1); a trace of aniline was also detected. Investigating the influence of different metal salts on the reaction, we found that the addition of cuprous iodide improved the yield of **3a** and reduced the relative amounts of **4a** and **5a** significantly (entry 2). Still better yields of **3a** were produced with tin powder in water:methanol, 3:1 (entry 3); this reaction was much slower, but no **5a** at all was formed. Finally, the best results were obtained with tin in pure, undried methanol: **3a** was produced in 90% yield with 6% of the monoalkylated **4a** as the only side product (entry 4). More importantly, the same procedure was also successful with benzyl bromide and, in moderate yields, even with methyl and ethyl iodide (entries 5 to 7). The possibility of reduction of **1** prior to alkylation could be excluded on the basis of the following control experiments:

(i) Nitrobenzene alone was readily reduced to aniline by zinc in monobasic phosphate solution, but was nearly unreactive in the presence of tin in methanol; only traces of aniline were detected after 20 h.

(ii) The possible reduced intermediates nitrosobenzene, phenylhydroxylamine, azoxy-benzene and aniline produced only a few percent of both **3** and **4** with zinc and only traces with tin under standard conditions.

(iii) Similar trace amounts of allylated anilines were observed, when allyl bromide was reacted first with tin in water (20 h) and then nitrobenzene or aniline was added; a second amount of halide **2a**, added at this stage, which would enable S_N-type alkylations, had no effect.

Table 1
Reductive alkylation of nitrobenzene[a]

| Entry	Halide **2**	Solvent	Metal (mmol)	Yields(%)[b]		
				3	**4**	**5**
1	allyl bromide (**2a**)	NaH_2PO_4/H_2O	Zn (4)	35	14	12
2	allyl bromide (**2a**)	NaH_2PO_4/H_2O	Zn (4)/CuI (0.5)[c]	44	9	10
3	allyl bromide (**2a**)	$H_2O/MeOH$ 3:1	Sn (2)	56	8	-
4	allyl bromide (**2a**)	MeOH	Sn (2)	90(72)	6	-
5	benzyl bromide (**2b**)	MeOH	Sn (2)	82(69)	8	-[d]
6	methyl iodide (**2c**)	MeOH	Sn (2)	28	5	-
7	ethyl iodide (**2d**)	MeOH	Sn (2)	30	7	-

[a] General procedure: To a vigorously stirred mixture of 2 mL of the indicated solvent, 0.5 mmol of nitrobenzene and 2 mmol of halide **2** the metal was added portionwise during 15 min at r.t. (30°); after 1 h (Zn) or 20 h (Sn) 10 ml of aqueous NaOH 10% were added and the mixture was extracted with 1 mL of CCl_4 containing 0.05 mmol of cyclohexane; the crude extracts were analyzed by ^{1}H NMR and GC/MS.
[b] Determined by ^{1}H NMR or GC in the crude extract; isolated yields in a 5 mmol scale in parentheses.
[c] A mixture of zinc dust (4 mmol) and cuprous iodide (0.5 mmol) was added portionwise.
[d] 37% of benzyl methyl ether and 17% of bibenzyl were also detected (yields based on **2b**).

Based on these results, we conclude that the reduction/alkylation process can account only for a small part of **3** and **4** and the main reaction seems to proceed via nucleophilic additions of organometallic intermediates to the highly electron deficient nitrogen. A possible mechanism is proposed in Scheme 1.
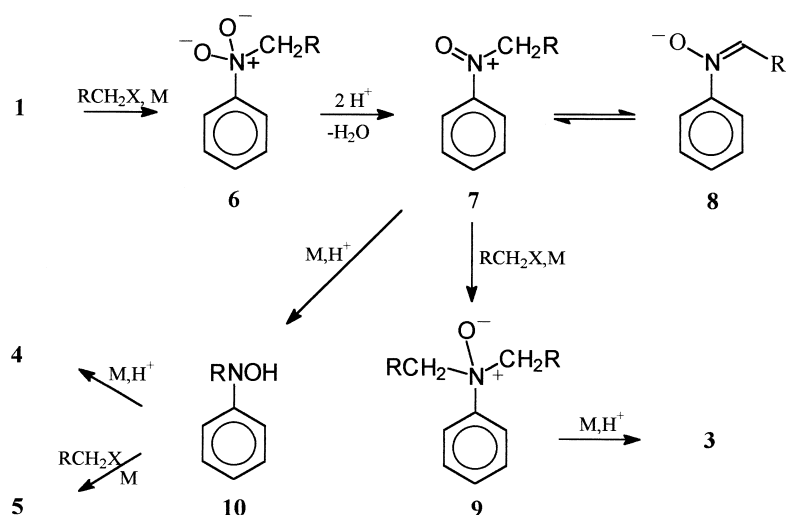
Scheme 1. Proposed mechanism for reductive alkylation of nitrobenzene

In the first step, an organometallic species formed in situ attacks the nitro group and produces the intermediate **6** already postulated by Bartoli for the analogous reaction under anhydrous conditions.[14,15] In protic solvent, **6** can eliminate water to the oxoammonium ion **7**. Oxoammonium salts are highly electrophilic and some stable representatives have been used as oxidizing reagents.[16] In protic medium, they are expected to exist in equilibrium with the corresponding nitrones **8**.[17] In fact, compounds of type **8** have been isolated in good yield after aqueous work-up, when nitroarenes were reacted with crotyl magnesium chloride in THF.[15] Under our conditions, a second attack of organometallic reagent on **7** leads to the *N*-oxide **9** which is readily reduced to the final product **3**.[18] The formation of the intermediates **7** and **9** must be very fast to explain the high yield of **3**. A concurrent reduction, however, may lead to some hydroxylamine **10** and then to the monoalkyl aniline **4**; the latter two products have been isolated on reductive work-up of the anhydrous reaction.[14] Alternatively, **10** can be alkylated on the oxygen atom by excess of halide **2** to produce **5**. Indeed, when we reacted phenylhydroxylamine with allyl bromide in the presence of Zn^{2+} ions, but in the absence of metallic zinc, we isolated high yields of **5** even in monobasic phosphate solution (pH ~4). Furthermore, an analoguous reaction has been observed on electrolysis of **1** in the presence of *n*-butyl iodide in DMF.[19]

We obtained further support for the intermediates **7** and **8** by the reaction of the easily accessible nitrone **8b** (R = Ph)[17] with benzyl bromide and tin under the conditions of entry 5 (Table 1) 25% yield of **3** was produced as the main product. As the heterogeneous reaction of the halide **2b** with tin is rather slow, several side products due to solvolysis or reduction were also observed (benzaldehyde, its dimethyl acetal, azobenzene, benzyl and benzylidene aniline).

In conclusion, the mechanism presented here corresponds in the first steps to that proposed by Bartoli for the reaction of allylic Grignard reagents in THF.[14,15] On the other hand, the same author observed a completely different behaviour with benzylic and primary alkylic Grignard

reagents; in these cases, the main reaction was a conjugate addition to the ring in *ortho*- or *para*-position leading to ring-substituted nitrosobenzenes after work-up.[20] Similarly, organometallic additions to nitrones in aprotic solvents are known to occur on the carbon atom under aprotic conditions.[15,17] On the basis of our observations, we can conclude that the protic medium not only changes the relative electrophilicity of different positions in the substrate **1** towards the first attack of certain organometallic reagents, but also enables the following reaction sequence: transformation to the even more reactive oxoammonium ion **7**, second addition of the nucleophile and final reduction to **3**. In contrast to the allylation of benzaldehyde, where allyltin(II) bromide or diallyltin dibromide react under aqueous conditions,[21] these preformed reagents produced only trace amounts of allylated products in the case of **1** and can be excluded as the reactive intermediates. For this reason, radicals or radical anions have to be considered.

The described transformations represent the first example of Barbier-type reactions with non-carbon electrophiles in protic media. They provide direct access to *N*,*N*-dialkyl anilines starting from nitrobenzene. Although monoalkylation or introduction of two different substituents is not yet possible, this procedure may be useful for the preparation of benzyl- or allyl-protected anilines. More detailed studies on mechanism and scope of this reaction are in progress.

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