A New and Efficient Method for the Chemoselective Reduction of Azidoarenes and Aroylazides: Use of Zinc-Cobalt Chloride

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Reduction of azidoarenes and aroylazides to the parent primary amines or amides respectively occurs in excellent yields upon treatment with a novel reduction system consisting of Zn-$CoCl_2.6H_2O$-THF.

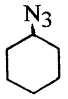
Reduction of azides to amines is an important reaction in organic synthesis.[1] There are many methods on this conversion describing the use of, for example, lithium aluminium hydride,[2] triethyl phosphate,[3] zinc borohydride,[4] samarium iodide,[5] (BER)-nickel acetate,[6] lithium aminoborohydride,[7] sodium borohydride,[8] benzyltriethylammonium tetrathiomolybdate,[9] etc. for this purpose have been reported recently. But most of them have some disadvantages in relation to their general applicability, selectivity, ready availability, operational convenience or toxicity. For instance, $LiAlH_4$ is not tolerable to many functionalities such as CO_2R, NO_2 etc., and now on the other hand, catalytic hydrogenation and diborane reduction have limitations for being applied to unsaturated compounds containing a double or a triple bond. As a result, there is always considerable interest in finding more selective methods. Herein we report a novel reduction system consisting of zinc-cobalt chloride hexahydrate in tetrahydrofuran for the chemoselective reduction of various azidoarenes and aroylazides. The reductions generally proceeded with high yields at room temperature and showed selectivity over other labile substituents.

$$\underset{\mathbf{1}}{R\text{-}N_3} \xrightarrow{Zn\text{-}CoCl_2.6H_2O\text{-}THF} \underset{\mathbf{2}}{R\text{-}NH_2}$$

R = Aryl, Aroyl, Arylsulfonyl and Alkyl

In a typical procedure, to a solution of phenyl azide (3 mmol) in anhydrous tetrahydrofuran (10 ml), was added a mixture of zinc powder (15 mmol) and cobalt chloride hexahydrate[10] (18 mmol) under nitrogen atmosphere. An exothermic reaction takes place immediately which is controlled by keeping the reaction in an ice bath. After about 45 minutes when TLC of the reaction mixture showed disappearance of the starting material, the reaction mixture is diluted with THF (50 ml) and filtered. Evaporation of the filtrate gave the corresponding crude aniline in virtually quantitative yield. Purification of the crude through silica gel column furnished the pure amine in 95% yield. Similar treatment of other aryl or aroyl azides gave the corresponding amines or amides respectively in 80-95% yields (Table). This reduction system in combination with DMF and water i.e. Zn-$CoCl_2$-DMF-H_2O[11] has earlier been used for the reduction of nitroaromatics to arenamines[12] at room temperature.

Table 1: Reduction of Azides with Zn-$CoCl_2 6H_2O$-THF System

Entry	Azides[a]	Reaction time (min)	Yield[b] %
1	$C_6H_5N_3$	45	95
2	2-NO_2-$C_6H_4N_3$	30	80
3	3-$ClC_6H_4N_3$	45	85
4	4-$ClC_6H_4N_3$	45	82
5	4-$MeCOC_6H_4N_3$	30	80
6	4-MeO-$C_6H_4N_3$	55	90
7	4-$MeC_6H_4CON_3$	45	86
8	4-$BrC_6H_4N_3$	50	83
9	$C_6H_5SO_2N_3$	30	82
10	$C_6H_5CON_3$	60	80
11	$C_6H_5CH{=}CHCON_3$	55	80
12	4-$MeC_6H_4SO_2N_3$	40	85
13	$CH_3(CH_2)_5N_3$	30[c]	66
14		35	70

[a]All products are known compounds and gave satisfactory m.p., IR and ^1H NMR spectra. [b]All the yields refer to isolated chromatographycally pure compounds. [c]The reduction was performed under nitrogen in THF. Further increasing the reaction time gave no significant improvement in yields but rather decomposition occurred.

The excellent yields of the reduction products demonstrate the efficiency of this new method. Table1 summarizes our results on the reduction of a number of aryl, aroyl and arylsulfonyl azides. In all the reactions, the cleavage takes place between the N-N bond, rather than the C-N or S-N bond. At the same time, azides are selectively reduced in the presence of a double bond (entry 11) or an aromatic methoxy group (entry 6). In case of nitro substituted aromatic azides, the corresponding nitro aniline was selectively obtained without any further reduction of nitro group (entry 2). Furthermore, haloaromatic azides showed remarkable selectivity to give the amine without any dehalogenation (entry3,4&8). Also the amides are not reduced further to the corresponding amines. In addition it was worth commenting that 4-acetylphenylazide was converted to the 4-aminoacetophenone and the sensitive carbonyl group remains intact. On the other hand, 4-azidophenol affords only little amount of 4-aminophenol and instead leads to a rather complex mixture of unidentified products. Similar to arylazides, toluene-4-sulfonyl azide also undergoes fast and clean reduction with this novel reduction system. This method requires atleast 6 mol of $CoCl_2$ per mole of the azide. The use of a lesser amount of the reagent normally results in significant recovery of the starting azide. To include an example of aliphatic azide we have carried out the reduction of 1-hexyl azide under same conditions and the corresponding 1-hexyl amine was obtained in 66% yield. The use of magnesium in combination with cobalt chloride hexahydrate in tetrahydrofuran is equally effective in these reactions and the corresponding primary amines or amides were obtained in almost comparable yields.

In conclusion, the present results demonstrate the novelty of zinc-cobalt chloride hexahydrate combination system which shows unique selectivity and constitute a useful alternative to the commonly accepted procedure[11] for the synthesis of various primary amines or amides. Moreover, this simple and easily reproducible technique affords various adducts in excellent yields without involvement of toxic or expensive material and without the formation of any undesirable side products than the classical methods.

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References and Notes

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