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Chemoselective Reductive Coupling of Nitroarenes with Magnesium in Methanol via Single Electron Transfer

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A chemoselective reductive coupling of nitroarenes using magnesium in methanol has been reported at ambient temperature. While the cyano, formyl, methoxycarbonyl, methyl, methoxy, phenyl, amino, and chloro groups are unaffected, iodo and bromo groups undergo dehalogenation but in a slower reaction than the coupling of nitro group. The coupling is believed to be proceeding via SET from Mg to nitroarenes.

The importance of nitroarenes in organic synthesis is based on the possibility of their modification and removal by a variety of reagents. Reduction of nitro compounds can be carried out by heterogeneous as well as homogeneous catalysts. Aromatic nitro compounds are reduced to amines using a variety of reagents.[1] The partial reduction of nitroarenes to azoxyarenes had been reported with reagents like sodium arsenite,[2a] NaOEt,[2a] lead,[2b] NaTeH,[2c] $NaBH_4$–$CoCl_2$,[2d] Zn–$BiCl_3$,[2e] glucose,[2f] triphenylphosphite, triphenylphosphine,[2g] trialkylstibene,[2h] and Mg–methanol.[2i] Cross coupling of amines with nitroso derivatives to give azoxy compounds in the presence of hypervalent iodine has also been reported.[2j] The coupling of nitroarenes to azoarenes has been observed with reagents like LAH[1], Zn and alkali,[3a] $NaBH_4$,[3b] $HOCH_2CH_2ONa$,[3c] and $TiCl_2Cp_2$.[3d] Sodium arenetellurolate[3e] and complex reducing agents containing Zn and Cd[3f] have also been reported in the selective conversion of nitro aromatics to azoxy or azo compounds.

Recently magnesium in methanol has evoked considerable interest as an inexpensive and efficient reagent e.g., chemoselective reduction of α,β-unsaturated esters,[4a] nitriles,[4b] amides,[4c] and vinyl furans conjugated to a carbonyl,[4d] deoxygenation of *N*-oxides,[4e] reduction of azides,[4f] and diphenylethylenes.[4g] Acetonides, cyclic carbonates or cyclic sulfides of γ,δ-dihydro (*E*)-α,β-unsaturated esters[4h] and C–O/C–N bonds conjugated to the γ-position of α,β-unsaturated esters[4i] have been reported to undergo reductive cleavage with Mg–MeOH. Synthesis of chiral 5-substituted 2-pyrrolidinone[4i] and reduction of alkyl and allyl halides with magnesium in methanol has been reported.[4k] We have also been investigating the scope and limitations of magnesium in methanol.

Results and Discussion

In this paper, we report the chemoselective reductive coupling of nitroarenes with Mg in methanol. The reactions of nitroarenes have been observed to be complete in reasonable periods of time using 1 : 10 molar ratio of nitroarenes to magnesium at ambient temperature as monitored by the disappearance of the starting material on thin-layer chromatography (TLC). The products are invariably a mixture of azoarenes and hydrazoarenes initially but when the reactions were carried out for longer periods, azoarenes were obtained as the predominant product as hydrazoarenes are known to undergo rapid aerial oxidation to azoarenes. Our results can be generalized as in Eq. 1.

$$p\text{-}C_6H_4NO_2 \xrightarrow[\text{r.t.}]{\text{Mg, MgOH}} p\text{-}RC_6H_4N{=}NC_6H_4\text{-}p \rightleftharpoons p\text{-}RC_6H_4NHNHC_6H_4\text{-}p \qquad (1)$$

The reductive coupling of nitrobenzene with magnesium was not observed when methanol was replaced by ethanol (Run 5), isopropyl alcohol (Run 6) or tetrahydrofuran (Run 7). These results are listed in Table 1.

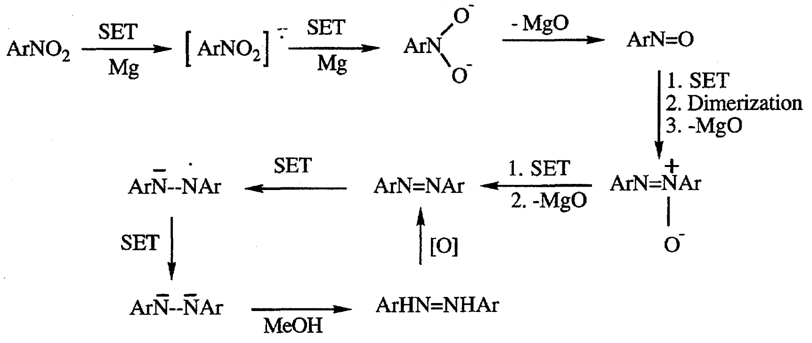
The chemoselective reductive coupling of nitro group in the presence of methoxy (Run 12), methoxycarbonyl (Run 13), formyl (Run 14), phenyl (Run 15), and cyano (Run 16) group is noteworthy because of exclusive formation of azoarenes. This could be due to extended conjugation provided by the functional groups. In the reactions of *p*-halonitroarenes, chloro substituent remained unaffected (Run 18) unlike complete deiodination in the reaction of *p*-iodonitrobenzene (Run 21). However, partial debromination was observed in the reaction of *p*-bromonitrobenzene (Run 19) and complete debromination could be achieved by using excess of reagent (Run 20). This suggests that reductive coupling of nitroarenes is faster than dehalogenations.

The possibility of magnesium methoxide [$Mg(OMe)_2$], formed in situ, acting as a reducing/coupling agent was eliminated by a reaction of nitrobenzene with preformed $Mg(OMe)_2$ in methanol when nitrobenzene was recovered unchanged after 24 h. It is likely that anilines are formed initially and undergo subsequent coupling with nitroarenes or nitrosoarenes (obtained from nitroarenes) in the presence of magnesium methoxide to give coupled products, namely azoarenes and/or hydrozoarenes. The absence of any cou-

Table 1. Reactions of Nitroarenes with Magnesium in Methanol

Run No.	Substrate	Molar ratio	Time h	Products Azo(%)[a]	mp (lit, mp)	Hydrazo (%)
1.	$ØNO_2$	1 : 10	1	65.4	67 (68)	34.5
2.	$ØNO_2$	1 : 5	1	43	67 (68)	56
3.	$ØNO_2$	1 : 3[b]	5	32	68 (68)	38
4.	$ØNO_2$	1 : 5[c]	3	78	68 (68)	22
5.	$ØNO_2$	1 : 5[d]	24	—	—	—
6.	$ØNO_2$	1 : 5[e]	28	—	—	—
7.	$ØNO_2$	1 : 5[f]	48	—	—	—
8.	$ØNO_2$	1 : 5[g]	24	—	—	—
9.	$ØNO_2+ØNH_2$	1 : 10[h]	24	—	—	—
10.	p-$CH_3ØNO_2$	1 : 5	1.5	51	143 (144—5)	47.5
11.	p-$CH_3ØNO_2$	1 : 3[i]	5	40.7	144 (144—5)	27.6
12.	p-$CH_3OØNO_2$	1 : 10	5	66	165 (165)	36
13.	p-$CH_3OCOØNO_2$	1 : 10	2	93	240 (242)	—
14.	p-$HCOØNO_2$	1 : 10	3.5	97	238 (238)	—
15.	p-$ØØNO_2$	1 : 10	24	90	248 (249—250)	—
16.	p-$NCØNO_2$	1 : 10	2	70	—	—
17.	p-$NH_2ØNO_2$	1 : 10	1	50	240 (242)	49
18.	p-$ClØNO_2$	1 : 5	2	51	189 (189)	48.7
19.	p-$BrØNO_2$	1 : 10	2	31[j]	205 (205)	17[k]
20.	p-$BrØNO_2$	1 : 40	2	14[l]	—	9[m]
21.	p-$IØNO_2$	1 : 10	48	70.27[n]	—	28.72[o]
22.	$(CH_3)_2NØNO_2$	1 : 10	1	99	261 (265)	—
23.	$(C_2H_5)_2NØNO$	1 : 10[p]	2	40	—	30
24.	$(C_2H_5)_2NØNO+ØNH_2$	1 : 10[q]	2	22	—	10
25.	$Ø\text{-}N{=}\underset{\overset{\mid}{O}}{N}\text{-}Ø$	1 : 10	1	95	67 (68)	—

a) Yields in Runs 1—12 are GLC ratios, yields in Runs 13—25 are HPLC ratios. b) The reaction was incomplete. Nitrobenzene (25.4%) was detected. c) Oxygen bubbled through the solution. Induction time increased from 7 min to 30 min. d) The reaction was done in dry ethanol. e) The reaction was done in dry isopropyl alcohol. f) The reaction was carried out in dry THF at room temperature (24 h) and under reflux (4 h). g) The reaction was carried out with preformed magnesium methoxide. h) The reaction was carried out with preformed magnesium methoxide. Nitrobenzene and aniline were recovered unchanged. i) The reaction was incomplete. *p*-Nitrotoluene (25.7%) was also detected. j) Azobenzene (9.5%) was also detected. k) Hydrazobenzene (34%) was also detected. l) Azobenzene (5.43%) was also detected. m) Hydrazobenzene (70.49%) was also detected. n) No *p*-iodoazobenzene was detected. o) No *p*-iodohydrazobenzene was detected. p) Two more unidentified peaks were observed. q) Aniline (51%) was also detected besides a couple of small unidentified peaks.



Scheme 1.

pled product in the reaction of nitrobenzene and aniline with $Mg(OMe)_2$ in methanol as well as the absence of any cross-coupled product in the reaction of *N*,*N*-diethyl *p*-nitrosoaniline and aniline (Run 23) in presence of $Mg(OMe)_2$ rules out any such possibility.

We believe that the reductive coupling of nitroarenes proceeds by single electron transfer (SET) from magnesium to nitroarenes as shown in Scheme 1. The role of magnesium as a single electron donor[5] and of nitroarenes as a single electron acceptor[6] is an established fact. The rapid reduction of azoxybenzene (a proposed intermediate) to azobenzene with Mg in MeOH (Run 25) is in agreement with the above proposal. The involvement of nitrosobenzene as another intermediate in the above pathway can also be deduced from its

Table 2. Composition of the Reaction Mixture of Nitrobenzene with Magnesium in Methanol against Time

Time		Nitrobenzene	Azobenzene	Hydrazobenzene
Min	hr	%	%	%
10		92	7.8	—
20		48	46	—
30		22	70.5	—
40		12	86	—
50		—	77.6	19
60	1	—	26	72
70		—	15.4	83
80		—	9	88.6
90	1.5	—	4.5	91.2
115		—	11	86
120	2	—	11.8	85
	3	—	12.3	85.4
	4	—	7.7	80.9
	5	—	12.84	87.15
	6	—	1.07	79
	7	—	29.8	65
	24	—	46.78	53

reaction of *N*,*N*-diethyl *p*-nitrosoaniline (Run 23). Another reaction of *N*,*N*-dimethyl *p*-nitroaniline (Run 22) was carried out to observe the change in the characteristic colors [*N*,*N*-dimethyl *p*-nitroaniline is yellow, *N*,*N*-dimethyl *p*-nitrosoaniline is green, and 4,4′-bis(dimethylamino)azobenzene is red in color]. A distinct color change was observed from yellow to green to red when the reaction was carried out under dilution. Bubbling of oxygen through the reaction mixture increased the induction time of reaction from 7 min in Run 1 to 30 min in Run 4 and the reaction time from 1 to 3 h as expected of radical reactions. Our results are in agreement with the reported dehalogenation of haloarenes with Mg–MeOH by Hutchins et al.4k) The order of reactivity I>Br>Cl is also in conformity with known order of reactivity in electron-transfer reactions.7)

A reaction of nitrobenzene with Mg–methanol was carried out to study the composition of the reaction mixture at small intervals of time. Our results have been listed in Table 2 and represented in Figs. 1 and 2. It is evident from the plot of the graphs that (a) starting material reacts within first ten min of the reaction, (b) the rate of disappearance of the starting material is first order with respect to the nitrobenzene and (c) aerial oxidation of hydrazobenzene competes with the reduction of azobenzene. The oxidation of hydrazoarenes is known to proceed with a variety of mild oxidizing agents including aerial oxidation.8)

We conclude that nitroarenes undergo reductive coupling with magnesium in methanol to give azoarenes and hydrazoarenes. These couplings are chemoselective as cyano, formyl, methoxycarbonyl, methoxy, phenyl, amino, and chloro groups are unaffected whereas iodo and bromo undergo dehalogenation but at a slower rate than the coupling of the nitro group. This is an inexpensive and convenient method for the preparation of a variety of azoarenes.

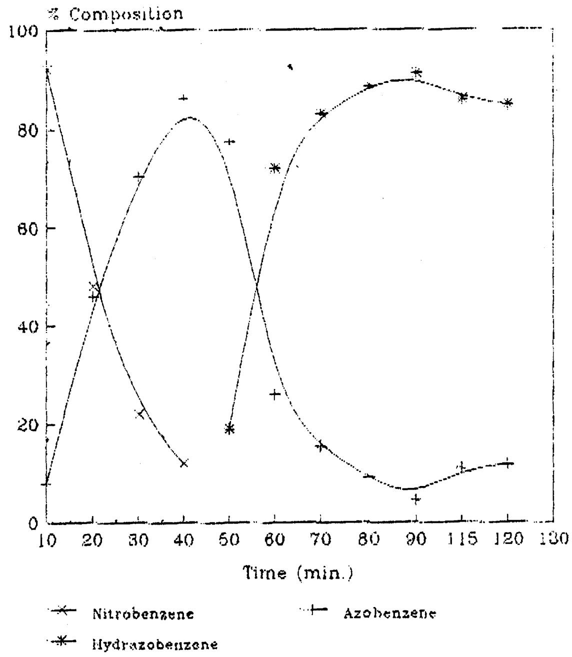


Fig. 1. Composition of reaction mixture vs. time.

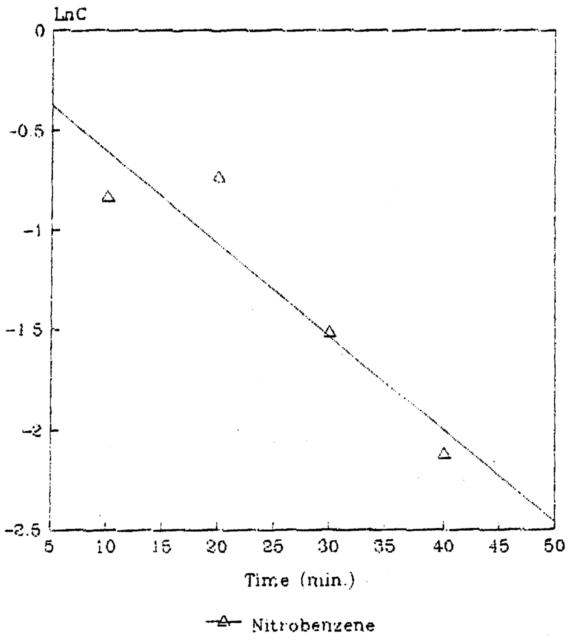


Fig. 2. Plot of LnC against time for nitrobenzene.

Experimental

All the melting points were recorded on Tropical Labequip apparatus and are uncorrected. The PMR spectra were recorded on Perkin–Elmer model R-32 (90 MHz) and Hitachi FT-NMR (60 MHz) using TMS as the internal reference. GLC analyses were done on a 3 meter-long SE-30 column using nitrogen as carrier gas on a Shimadzu GC-9A model. HPLC analyses were done using ODS-18 (Zorbax, 150 mm × 4.6 mm) column using methanol as eluent on Shimadzu Model LC-4A.

Magnesium turnings (E. Merck) were used after washing with 1% HCl, ethanol and ether. Methanol, ethanol, tetrahydrofuran, and isopropyl alcohol were dried by known procedures.[9a] Nitrobenzene (Ranbaxy), *p*-nitrotoluene (Sisco-Chem), *p*-nitrobenzaldehyde (Sisco-Chem), and *p*-Chloronitrobenzene (E. Merck) were distilled/recrystallized before use. Methyl *p*-nitrobenzoate,[9b] *p*-bromonitrobenzene,[9c] *p*-iodonitrobenzene,[9d] azoxybenzene,[9e] *N*,*N*-dimethyl *p*-nitroaniline,[9f] *p*-cyanonitrobenzene,[10] *p*-methoxynitrobenzene,[11] and *N*,*N*-diethyl *p*-nitrosoaniline[12] were prepared by known procedures.

Reactions of Nitroarenes with Magnesium–Methanol. Nitroarene (1 g, *x* mol), magnesium turning (*nx* mol), and dry methanol (30 mL) were placed in a 100 mL round-bottom flask mounted over a magnetic stirrer. The contents were stirred at ambient temperature with a crystal of iodine. After induction the reaction was allowed to continue by constant stirring and monitored by tlc using petroleum ether (60—80 °C): benzene (90 : 10 v/v) as eluent. The reaction was continued till complete disappearance of the starting material. The reaction mixture was worked up with distilled water (150 mL) and acidified till just acidic by hydrochloric acid. The solution was then neutralized with aqueous $NaHCO_3$. It was extracted with dichloromethane (3 × 10 mL) and the combined extract was dried over anhyd. K_2CO_3. The product(s) were analyzed by HPLC by comparison with authentic samples. The azoarenes were recrystallized and further authenticated by mp, mixed mp, and NMR.

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