Activation of Reducing Agents. Sodium Hydride Containing Complex Reducing Agents, Part 34.[1] Complete or Partial Reduction of Aromatic Nitro Compounds

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It is shown that, with some limitations, Complex Reducing Agents† (MCRA where M is a metal salt) allow selective reduction of aromatic nitro compounds. NiCRA leads to the corresponding anilines while ZnCRA and CdCRA respectively lead mainly to azoxy and azo derivatives. Yields vary from very good to excellent.

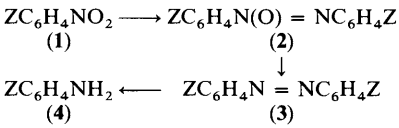
The reduction of aromatic nitro compounds may lead to azoxy or azo derivatives or to anilines. Numerous reducing agents have been devised in order to give selective reduction of these substrates.[2] However, it appears from data in the literature that selective reductions are obtained with difficulty and constitute an interesting challenge.[3]

As part of our investigations into the properties of Complex Reducing Agents (CRA)[4] we decided to undertake the study of the reduction of aromatic nitro compounds and investigate the reactivity of our reagents in this context.

Exploratory experiments performed with CRA containing Fe, Co, Ni, Zn, and Cd showed that NiCRA, ZnCRA, and CdCRA were the most efficient and Table 1 gives the results obtained with a number of representative substrates.

Interestingly it appears, as is usual with CRA's, that a simple change in the nature of the metal included in the reagent dramatically changes the reactivity and consistently the selectivity of the reductions.

Monitoring the reductions by g.l.c. showed that the classical reduction steps of aromatic nitro compounds[5] occurred (Scheme 1). Broadly speaking, NiCRA, the most powerful



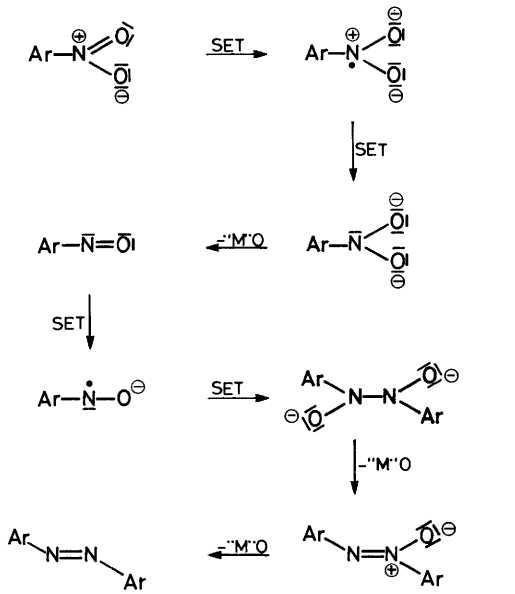
Scheme 1.

reducing agent,[6] led to anilines while with few exceptions, CdCRA and ZnCRA respectively led to the corresponding azo and azoxy derivatives.

With NiCRA the reductions may be performed in THF instead of dioxane. However, reactions were faster and yields higher in dioxane, particularly with sensitive substrates. Anilines were always obtained except with 2,2′-dinitrodiphenyl which led to benzo[*c*]cinnoline. As reported in the literature,[7] further reduction was unsuccessful.

NiCRA's were also found to be chemoselective since under appropriate conditions, they tolerated halides, and amines as well as ethers, ketals, acids, and nitriles. The chemoselectivity against halides[6a] was particularly surprising since NiCRA's easily reduce organic halides. The explanation is probably that a nitro group has a much higher electron affinity than does an halide and, therefore, is much more susceptible to reduction.

† In the present paper we have adopted the convention given in ref. 4. Thus a MCRA (metal atom specified) prepared from NaH, Pent^{t}ONa (alkoxide) and metallic salt will be abbreviated MCRA [*x*/*y*/*z*] where the molar ratio NaH/RONa/MX_n (in that order) is equal to *x*/*y*/*z*.



Scheme 2.

This observation agrees with the fact that, generally speaking in competitive reactions, CRA's chemoselectively react with the most reactive substrate.

An unexpected reaction occurred between CdCRA or ZnCRA and 4-$MeC_6H_4NO_2$. The main product isolated was 4,4′-dinitrodibenzyl from a radical coupling reaction.[8]

The formation of complex mixtures of products and tars in the reduction of 2-Me-, 2-MeO-and 2-CN-nitrobenzene with CdCRA and ZnCRA could be due to single electron transfer (SET).[9] However NiCRA's, more prone to SET than CdCRA or ZnCRA, lead to regular reduction of the same substrates. At the present time we have no clear explanation for this apparent contradiction.

The formation of 4-nitrosoaniline alone from 4-nitroaniline could be explained by the mechanism of reduction of nitrobenzene in aprotic solvents which was proposed by Kalyanaraman and George[9] (Scheme 2). Clearly an analogous mechanism must take place with our reagents. The presence of such a strong donating group as NH_2 must reduce the electron affinity of the nitroso group intermediate and impede further reduction. With these exceptions, CdCRA and ZnCRA tolerated the same functional groups as NiCRA.

Table 1. Reduction of aromatic nitro compounds by MCRA

Z or Compounds	MCRA[a]	Solvent	T/°C	t/h	% Reduced	Product Yield (%) (2)	(3)	(4)
H	A	Diox.	65	18	94	—	Trace	94
	B	THF		3	92	Trace	92	—
2-Me	C	THF		42	86	80	6	—
	A	Diox.	65	0.5	75	—	Trace	75
	B	THF			*b*	—	—	—
3-Me	C	THF			*b*	—	—	—
	A	Diox.	65	1	99	—	Trace	98
	B	THF		3	92	Trace	92	—
4-Me	C	THF		8	97	93	4	—
	A	Diox.	65	1	99	—	Trace	98
	B	THF		1	25[c]	25	Trace	—
4-Pr^i	C	THF		4	*d*	—	—	—
	A	Diox.	65	1	99	—	Trace	98
	B	THF		18	82	Trace	82	—
2-MeO	C	THF		24	86	76	10	—
	A	Diox.	65	0.25	70	—	—	70
	B	THF			*b*	—	—	—
3-MeO	C	THF			*b*	—	—	—
	A	Diox.	65	0.5	82	—	Trace	82
	B	THF		18	70	Trace	70	—
4-MeO	C	THF		8	94	86	8	—
	A	Diox.	65	1	70	—	Trace	70
	B	THF		3	70	Trace	70	—
3-NH_2	C	THF		24	94	84	10	—
	A	Diox.	65	4	85	—	—	85
	B	THF		28	85	85	—	—
4-NH_2	C	THF		42	76	76	—	—
	A	Diox.	65	18	78	—	—	78
	B	THF		66	*e*	—	—	—
3-Cl	C	THF		66	*f*	—	—	—
	A	Diox.	25	3	70	—	—	70
	B	THF	65	18	73	8	65[g]	—
4-Cl	C	THF	65	7	90	78	12	—
	A	Diox.	25	18	55	—	—	55
	B	THF	65	18	65	5	60[g]	—
4-Br	C	THF	65	4	89	88	1	—
	A	Diox.	25	18	64	—	6	58
	B	THF	65	18	74	6	68[g]	—
	C	THF	65	18	83	83	—	—
3-C(Me)OCH_2OCH_2	A	Diox.	65	0.5	84	—	—	84
	B	THF		18	74	5	69[h]	—
	C	THF		9	86	82	4	—
4-CO_2H	A	Diox.	65	42	78	—	—	78
	B	THF		42	81	81	—	—
	C	THF		66	85	85	—	—
4-CN	A	Diox.	65	4	80	—	—	80
	B	THF		—	*b*	—	—	—
	C	THF		—	*b*	—	—	—
2,2′-Dinitrobiphenyl	A	Diox.	65	0.25	86	—	86	—
	B	THF		5	82	—	82	—
	C	THF		9	92	82	10	—
1-Nitronaphthalene	A	Diox.	65	0.5	84	—	—	84
	B[i]	THF		4	72	22	50	—
	C	THF		9	74	58	16	—

[a] NiCRA: NaH, Pent^{t}ONa, $Ni(OAc)_2$ (7:1:1:1), called A; CdCRA: NaH, Pent^{t}ONa, $CdCl_2$ (7:1:1), called B; ZnCRA: NaH, Pent^{t}ONa, $ZnCl_2$, $MgBr_2$ (7:1:1:1), called C. Runs performed on a 10 mmol scale. [b] Intractable mixture of products obtained even at lower temperature. [c] 52% Of *p,p′*-dinitrodibenzyl isolated. [d] 50% Of *p,p′*-dinitrodibenzyl isolated. [e] 88% Of *p*-nitrosoaniline isolated. [f] 20% Of *p*-nitrosoaniline formed; 60% of starting material recovered. [g] 5—10% Of dehalogenated product formed. [h] Obtained as a monohydrate. [i] Reaction performed in the presence of $MgBr_2$ (10 mmol).

It must be emphasized that selective reductions by ZnCRA are possible only in the presence of $MgBr_2$. The beneficial effect of this salt had already been observed.[10]

Finally, it was of interest to know if the above reductions could be catalytic. The reactions performed with $PhNO_2$ are reported in Table 2. It appears that this reduction could be considered to some extent as catalytic. However, this result must be improved to make this reaction really catalytic.

In conclusion, it appears that CRA's are good reagents for performing selective reduction of aromatic nitro compounds, thus extending the field of application of these inexpensive and easily prepared and handled reagents.

Table 2. Catalytic reductions of nitrobenzene by MCRA[a]

MCRA[a]	Solvent	T/°C	t/h	Yield (%)[b] (2)	(3)	(4)	Yield (%)[c] (2)	(3)	(4)
NaH–Pent^{t}ONa–$Ni(OAc)_2$ 22 1 1	Dioxane	65	18	5	34	61	15	102	183
NaH–Pent^{t}ONa–$CdCl_2$ 22 1 1	THF	65	18	5	60	—	15	180	—
NaH–Pent^{t}ONa–$ZnCl_2$–$MgBr_2$ 22 1 1 1	THF	65	9	75	16	—	225	48	—

[a] Run performed on a 30 mmol scale. [b] Yield relatively to $PhNO_2$ determined by g.c. analysis. [c] Yield relatively to metal salt determined by g.c. analysis.

Experimental

Commercial nitro compounds were used (Aldrich, Fluka, or Lancaster). Dry tetrahydrofuran (THF) and dioxane were obtained by the standard method. t-Pentyl alcohol (Pent^{t}OH) was distilled over sodium. Metal salts were dried *in vacuo* at 110 °C for 16 h. M.p.s were determined with a Tottoli apparatus and were uncorrected. I.r. spectra were recorded on a 580B Perkin-Elmer spectrophotometer. ^1H N.m.r. spectra were recorded at 80 MHz on a Bruker AW80 instrument or at 400 MHz on a Bruker AM400. T.l.c. analyses were performed with hexane–ethyl acetate mixtures (100:0 to 80:20); spots were located with u.v. light or with H_2SO_4 reagent.

General Procedure.—Preparation of MCRA. A solution of Pent^{t}OH (10 mmol) in THF (10 ml) was added under nitrogen at 63 °C to a suspension of degreased NaH (80 mmol) with the appropriate solvent and anhydrous metal salt [10 mmol: $Ni(OAc)_2$, $ZnCl_2$, or $CdCl_2$] (the specific use of each salt is indicated below). After the mixture had been stirred for 2 h at 63 °C, $MgBr_2$ (10 mmol) was added when required. The nitro compounds (10 mmol) and a suitable internal standard (C_{10}—C_{12}) was added over a period of 2—3 min. The reaction was monitored by g.l.c. analysis of small aliquots by comparison with an authentic sample using a Girdel 330 chromatograph (flame ionization) equipped with a 10 ft SE 30 column.

The coupling and reduction products were identified by comparing their physical and spectral properties with those of commercially available authentic samples or those prepared by recognized procedures.

Preparation of Authentic Samples.—Azo compounds were prepared according to literature methods.[2g,2h,11,12] Azoxy compounds were prepared according to published procedures.[13,14]

Reduction of nitro compounds to azoxy compounds. MCRA was prepared from $ZnCl_2$ using THF as a solvent. For this reduction $MgBr_2$ (10 mmol) was added. After the time indicated in the Table, the suspension was cooled, quenched with water, washed with a 10% solution of HCl, and extracted with ether. The extract was evaporated under reduced pressure and the products were isolated by flash chromatography.

Reduction of nitro compounds to azo compounds. MCRA was prepared from $CdCl_2$ using THF as a solvent. The purification of the product was as described above.

Reduction of nitro compounds to amino compounds. MCRA was prepared from $Ni(OAc)_2$ using dioxane as a solvent. After the time indicated in the Table, the suspension was isolated, quenched with water, and washed with a solution of 10% HCl. The aqueous layer was made basic with $NaHCO_3$ or NH_4OH and extracted with ether or CH_2Cl_2. The extract was then dried ($MgSO_4$) and evaporated and the residue either distilled or recrystallised to give the pure amino compounds.

4,4′-Di-isopropylazoxybenzene. This was isolated by flash chromatography (5% ethyl acetate–hexane) as a yellow crystalline *solid*, m.p. 58—59 °C; δ_H(80 MHz; $CDCl_3$; Me_4Si) 7.9—8.4 (4 H, m), 7.0—7.5 (4 H, m), 2.6—3.2 (2 H, m), and 1.28 (12 H, d, *J* 7 Hz) (Found: C, 76.5; H, 7.9; N, 10.05. $C_{18}H_{22}N_2O$ requires C, 76.6; H, 7.8; N, 9.9%).

3,3′-Bis(2-methyl-1,3-dioxolan-2-yl)azoxybenzene. This was isolated by flash chromatography (15% ethyl acetate–hexane) as a yellow crystalline *solid*, m.p. 161—162 °C; δ_H(80 MHz; $CDCl_3$; Me_4Si) 7.4—9 (8 H, m), 3.6—4.25 (8 H, m), and 2.0 (6 H, s) (Found: C, 64.9; H, 5.95; N, 7.5. $C_{20}H_{22}N_2O_5$ requires C, 64.86; H, 5.90; N, 7.57%).

Benzo[c]cinnoline 5-oxide. This was isolated by flash chromatography (20% ethyl acetate–hexane) as a yellow crystalline *solid*, m.p. 139—140 °C (lit.,[7] m.p. 139 °C); δ_H(400 MHz; $CDCl_3$; Me_4Si) 7.66—7.8 (3 H, m), 7.85—7.96 (2 H, m), 8.28—8.35 (1 H, m), 8.43—8.48 (1 H, m), and 8.76—8.82 (1 H, m).

4,4′-Di-isopropylazobenzene. This was isolated by flash chromatography (5% ethyl acetate–hexane) as an orange–red crystalline *solid*, m.p. 104—105 °C; δ_H(80 MHz; $CDCl_3$;Me_4Si) 7.6—8.1 (4 H, m), 7.1—7.5 (4 H, m), 2.7—3.25 (2 H, m), and 1.3 (12 H, d, *J* 7 Hz) (Found: C, 80.95; H, 8.35; N, 10.45. $C_{18}H_{22}N$ requires C, 81.2; H, 8.27; N, 10.53%).

3,3′-Bis(2-methyl-1,3-dioxolan-2-yl)azobenzene. This was isolated by flash chromatography (15% ethyl acetate–hexane) as an orange crystalline *monohydrate*, m.p. 198—199 °C; δ_H(80 MHz; $CDCl_3$; Me_4Si) 7.1—8.15 (8 H, m), 3.6—4.25 (8 H, m), and 1.7 (6 H, s) (Found: C, 64.1; H, 6.18; N, 7.25. $C_{20}H_{22}N_2O_4.H_2O$ requires C, 64.5; H, 6.49; N, 7.50%).

Benzo[c]cinnoline. This was isolated by flash chromatography (20% ethyl acetate–hexane) as an orange–red crystalline *solid*, m.p. 156—157 C (lit.,[7] m.p. 156 °C); δ_H(400 MHz; $CDCl_3$; Me_4Si) 7.81—7.9 (4 H, m), 8.45—8.53 (2 H, m), and 8.68—8.74 (2 H, m).

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