JOURNAL OF CHEMICAL RESEARCH 2004 FEBRUARY, 139–140 **RESEARCH PAPER** 139

Reductive coupling of benzylic and allylic halides with sodium dithionite in DMF or HMPA

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Reductive coupling of secondary benzylic halides is reported with sodium dithionite in dry DMF or HMPA at 155-160°C under N_2 atmosphere. Primary benzylic and allylic halides gave the reductively coupled dimers and/or sulfones. The formation of the products is proposed by SET from sulfur dioxide radical-anion.

Keywords: sodium dithionite, secondary benzylic halides, DMF, HMPA

Sodium dithionite is reported to be a powerful reducing agent. It is inexpensive and conveniently employed in aqueous media, often in the presence of an excess of sodium bicarbonate in order to keep the reaction mixture basic. It can also be used with organic solvents like dimethylformamide, methanol, ethanol and dioxane. It is a versatile reagent for the reduction of variety of functional groups.[1] The reagent is known to dehalogenate α-haloketones[2] *via* corresponding pyridinium salts. Viologen-mediated dehalogenation of α-haloketones with sodium dithionite has also been reported.[3] Khurana *et al.*[4] have reported the chemoselective and stereoselective debromination of *vicinal*-dibromides with sodium dithionite in DMF at ambient temperature. The reduction of pyridinium salts and debromination of *vicinal*-dihalides are reported to be proceeding by single electron transfer (SET) from sodium dithionite. In the light of these reports, we believed that it would be possible to bring about reductive coupling and/or reduction of benzylic halides with sodium dithionite under appropriate reaction conditions.

In this paper we report the reductive coupling of secondary benzylic halides to the corresponding reductively coupled dimers in high yields with sodium dithionite in N, N-dimethylformamide (DMF) or hexamethylphosphoramide (HMPA) at 155–160°C under a nitrogen atmosphere (eqn. (1)). The primary benzylic and allylic halides, on the other hand, gave the reductively coupled dimers and/or corresponding sulfones (eqn. (2)) under these conditions. Reactions of primary, secondary and allylic halides were invariably complete in 5–30 min using 1:0.5 molar ratio of substrate to sodium dithionite. All the results are listed in Table 1.

$$\mathrm{Ar_2CHX} \xrightarrow[\text{DMF/HMPA, N}_2]{\mathrm{Na_2S_2O_4}\text{, 155-160°}} \mathrm{Ar_2CHCHAr_2} \qquad (1)$$

Ar = Aryl ; X = Br, Cl

$$\mathrm{ArCH_2X} \xrightarrow[\text{DMF/HMPA, N}_2]{\mathrm{Na_2S_2O_4}\text{, 155-160°}} \mathrm{ArCH_2CH_2Ar}\text{ and/or }\mathrm{ArCH_2SO_2CH_2Ar} \qquad (2)$$

Ar = Benzylic, Allylic; X = Br, Cl

No reaction was observed when the halides and the sodium dithionite were stirred in DMF or HMPA at room temperature even after 5 h, unlike the quantitative debromination in the reactions of *vicinal*-dihalides.[4] Starting halides were also recovered unchanged when reactions were carried out with

Table 1 Reactions of benzylic/allylic halides with sodium dithionite in DMF/HMPA at 155–160°C under N_2 atmosphere

Run no.	Substrate(S)	Solvent[a]	Molar ratio $S:Na_2S_2O_4$	Reaction time (min)	Isolation method	% Isolated yield	
						Dimer	sulfone
1.	9-Bromofluorene	HMPA	1:0.5	30	A	85	–
2.	9-Bromofluorene	DMF	1:0.5	10	A	82	–
3.	Bromodiphenylmethane	HMPA	1:0.5	5	B	68	–
4.	Bromodiphenylmethane	HMPA	1:2	5	B	73	–
5.	Bromodiphenylmethane	DMF	1:0.5	5	B	66	–
6.	Chlorodiphenylmethane	HMPA	1:0.5	5	B	63	–
7.	Chlorodiphenylmethane	HMPA	1:2	5	B	79	–
8.	Chlorodiphenylmethane	DMF	1:0.5	5	B	65	–
9.	9-Chlorofluorene	HMPA	1:1	20	C	40[b]	–
10.	9-Chlorofluorene	DMF	1:1	30	C	51[c]	–
11.	α-Bromomethylnaphthalene	HMPA	1:0.5	5	C	32	38
12.	α-Bromomethylnaphthalene	DMF	1:0.5	10	C	24	44
13.	β-Bromomethylnaphthalene	HMPA	1:0.5	15	C	16	51
14.	β-Bromomethylnaphthalene	DMF	1:0.5	15	C	26	50
15.	α-Chloromethylnaphthalene	HMPA	1:0.5	30	B	–	70
16.	α-Chloromethylnaphthalene	DMF	1:0.5	30	B	–	68
17.	Cinnamyl bromide	HMPA	1:0.5	15	C	55	–
18.	Cinnamyl bromide	DMF	1:0.5	15	C	56	8
19.	Cinnamyl chloride	HMPA	1:0.5	15	C	10	47
20.	Cinnamyl chloride	DMF	1:0.5	30	C	11	51
21.	9-Bromofluorene	HMPA	1:0.5	15	C	51[d]	–
22.	β-Bromostyrene	HMPA	1:0.5	180	–	–[e]	–

[a] 25 ml of the solvent was used/g of the substrate.
[b] Fluorene (26%) was also isolated.
[c] 16% fluorene was also isolated.
[d] Reaction was carried out in presence of 20 molar excess of cumene. 17% fluorene was also isolated.
[e] Starting material was recovered unchanged.

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sodium dithionite in dry tetrahydrofuran, acetonitrile, dioxane or chloroform at reflux temperatures under a nitrogen atmosphere. Therefore, DMF and HMPA are the solvents of choice for reductive coupling of benzylic and allylic halides with sodium dithionite. Since no reductively coupled or reduced product was obtained when the reactions of halides were carried out in the absence of sodium dithionite under otherwise identical conditions, this confirms the involvement of dithionite anions. Unlike reactions of secondary benzylic halides with sodium dithionite which yielded dimers, reactions of primary benzylic and allylic halides gave mixture of dimers and corresponding sulfones in varying yields irrespective of whether DMF or HMPA was used.

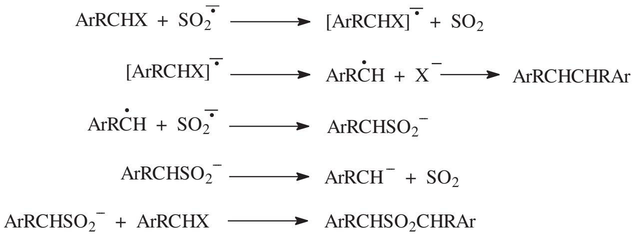
It has been reported that the dithionite anion exists in equilibrium with the sulfur dioxide radical-anion ($SO_2^{\bar{\bullet}}$) even at room temperature.[5] Thus it is likely that at elevated temperatures employed by us, the reagent largely exists as $SO_2^{\bar{\bullet}}$ which is reported to act as a source of SET. Therefore, in the reactions under discussion, the $SO_2^{\bar{\bullet}}$ species can transfer an electron to the benzylic halide to give a radical anion which breaks apart to give a benzylic radical and a halide ion. A proposed pathway for the reactions of benzylic halides with sodium dithionite is outlined in Scheme 1. The formation of carbanions by two successive electron transfers has been ruled out.[5d-e]

The absence of any sulfone in the reactions of secondary benzylic halides could be due to greater stabilisation of secondary benzylic radicals which undergo preferential coupling and also due to stabilised carbanions formed by loss of sulfur dioxide from sulfinate anion, compared to primary benzylic halides in which the nucleophilic attack by $ArCH_2SO_2^-$ on benzylic halides competes with the loss of sulfur dioxide. The primary halides are known to undergo preferred S_N2 attack unlike secondary halides.[7] Coupling by nucleophilic attack of carbanion on a benzylic halide is also likely. The fact that we did not isolate any sulfinic acids makes nucleophilic attack by sodium dithionite unlikely. This is supported by the fact that undissociated sodium dithionite anion is incapable of existence under our reaction conditions, owing to its fragmentation[8] into sulfur dioxide radical anions.

The isolation of fluorene (17%) in the reaction of 9-bromofluorene with sodium dithionite in the presence of 20 molar excess of cumene, is in agreement with the proposed mechanism involving radicals since the benzylic radical, once formed, can abstract a hydrogen atom from cumene. β-Bromostyrene, a vinylic bromide, did not undergo any reaction with $Na_2S_2O_4$ probably due to the greater difficulty of forming a vinyl radical as opposed to the stabilised allylic or benzylic radicals formed from these halides. The formation of mixture of products in case of alkyl halides could be due to other reactions like disproportionation competing with dimerisation and sulfone formation.

Experimental

All the melting points were recorded on a Tropical Labequip apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT-IR SPECTRUM-2000. NMR spectra were recorded on a FT-NMR model R-600 Hitachi (60 MHz) spectrometer in $CDCl_3$ with TMS as the internal standard. Mass spectra were recorded on a Jeol JMS D300 spectrometer using electron ionization (70 eV). The products were identified by co-TLC, melting point, mixed melting point (wherever applicable), IR, NMR and mass spectra. All the starting materials were prepared by known methods. Sodium dithionite (E. Merck, 82%) was used in all the reactions. DMF and HMPA were dried by allowing to stand over CaO for 24 h, followed by filtration and distillation.



$$\mathrm{ArRCHX} + \mathrm{SO_2}^{\bar{\bullet}} \longrightarrow [\mathrm{ArRCHX}]^{\bar{\bullet}} + \mathrm{SO_2}$$

$$[\mathrm{ArRCHX}]^{\bar{\bullet}} \longrightarrow \mathrm{ArR\dot{C}H} + \mathrm{X}^- \longrightarrow \mathrm{ArRCHCHRAr}$$

$$\mathrm{ArR\dot{C}H} + \mathrm{SO_2}^{\bar{\bullet}} \longrightarrow \mathrm{ArRCHSO_2}^-$$

$$\mathrm{ArRCHSO_2}^- \longrightarrow \mathrm{ArRCH}^- + \mathrm{SO_2}$$

$$\mathrm{ArRCHSO_2}^- + \mathrm{ArRCHX} \longrightarrow \mathrm{ArRCHSO_2CHRAr}$$

Scheme 1

General procedure: In a 50 ml two-necked round-bottomed flask, equipped with a reflux condenser, a mercury trap and a nitrogen inlet tube, was placed a mixture of 0.2g (*n* mmol) of halide, 0.5n mmol of sodium dithionite and 5 ml of dry DMF or HMPA. The reaction mixture was stirred at room temperature and flushed with dry nitrogen gas for 20 min. The R.B. flask was then placed in a preheated oil-bath maintained at 155–160°C. The reaction was monitored by TLC using petroleum ether as eluent until the reaction was complete. After complete disappearance of the starting material, the reaction mixture was cooled to room temperature and water (~ 50 ml) was added to quench the reaction. Further work up was done by one of the methods listed below and the products were identified by melting point and spectral methods.

Method A: The product was extracted with diethyl ether (3 × 10 ml). The combined organic layer was washed with water (3 × 5 ml) to remove traces of DMF or HMPA and the organic layer was then dried over anhydrous $MgSO_4$. The solvent was distilled off on a Buchi rotavapor. The isolated white solid was washed with petroleum ether and filtered. The product was identified after drying and recrystallisation.

Method B: The solid separated, after addition of water, was filtered at pump under vacuum and dried. TLC showed the presence of only one product which was identified after recrystallisation.

Method C: The products were extracted with diethyl ether (3 × 10 ml). The combined organic layer was washed with water (3 × 5 ml) to remove traces of DMF or HMPA and dried over anhydrous $MgSO_4$. Combined ether layer was filtered and evaporated over a Buchi rotavapor. The product mixture was subjected to column chromatography over silica gel (100–200 mesh) and eluted with petroleum ether. The isolated products were identified.

G.B. and P.K.S. are grateful to CSIR, New Delhi, India for providing Junior and Senior Research Fellowships.

Received 12 November 2003; accepted 12 January 2004
Paper 03/2207

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