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A bifunctional approach towards the mild oxidation of organic halides: 2-dimethylamino-*N*,*N*-dimethylaniline *N*-oxide

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Abstract

The titled reagent incorporates an oxygen-centred nucleophile and a basic moiety—in a suitably mutual orientation—in the same molecule. It oxidises various primary benzylic bromides to the corresponding aromatic aldehydes under relatively mild conditions (MeCN/rt–50°C/6–24 h) in high yields (83–97%), and is thus a useful alternative to the Kornblum procedure. © 2000 Elsevier Science Ltd. All rights reserved.

The oxidation of organic halides to the corresponding aldehydes or ketones is a very useful synthetic transformation which, in many cases, affords more convenient access to the carbonyl compound than the oxidation of the corresponding alcohol.[1,2] The earliest example of the oxidation of an organic halide is apparently the Hass–Bender reaction involving a nitronate anion, which was reported in 1949. (The older Sommelet reaction, employing hexamethylenetetramine, is rather circuitous and less general.) Several new versions were reported in the ensuing decades, most notably the Kröhnke (pyridine/*p*-nitrosodimethylaniline) and the Kornblum (DMSO) reactions. Amongst the simplest of the above procedures is apparently the Kornblum reaction, in which the organic halide is refluxed in DMSO along with sodium bicarbonate; however, the high temperature involved and the fact that only activated halides are reactive apparently limit its scope. A related—and attractive—method employs various amine *N*-oxides,[1–3] but suffers from variable yields. Mechanistically, the above methods generally involve displacement of the halide by an oxygen or nitrogen centred nucleophile, followed by a base-induced dehydro-elimination via cleavage of a heteroatom–heteroatom bond—the actual oxidation step: e.g. **1** which represents the Kornblum reaction (Scheme 1).

In the present study, it was envisaged that incorporating the heteroatom centred nucleophile and the basic moiety in the same molecule would enhance reactivity, and thereby lead to a methodology workable under relatively mild conditions. The system chosen was 2-dimethylamino-*N*,*N*-dimethylaniline *N*-oxide **2**, in which the mutual orientation of the *N*-oxide and the basic

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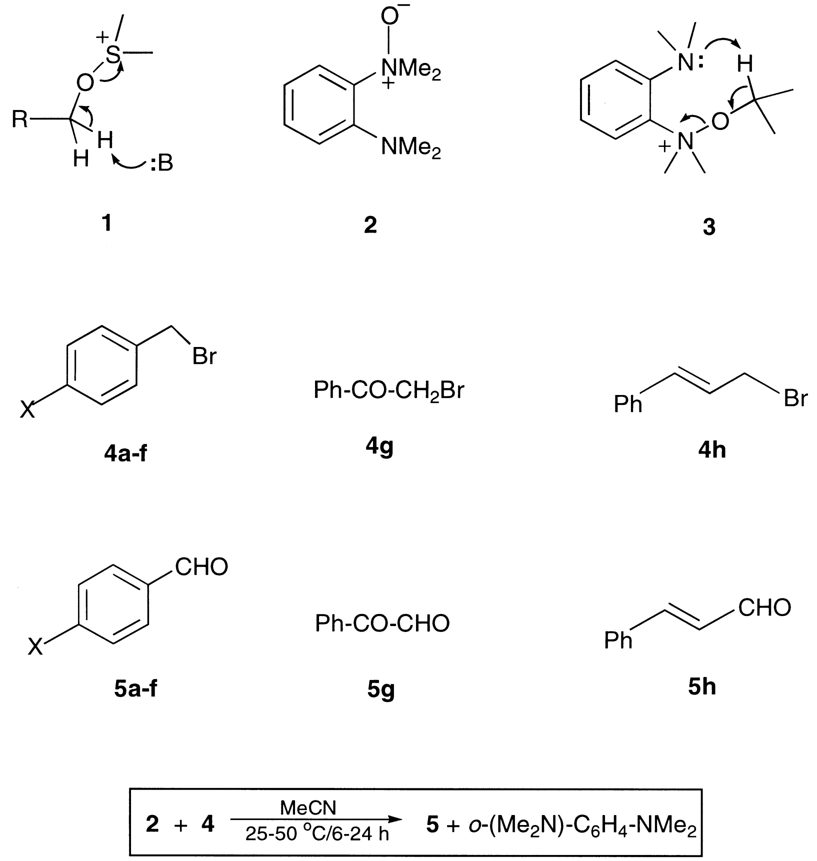

Scheme 1.

dimethylamino moieties ensures that the dehydro-elimination step occurs via the putative cyclic seven-membered transition state **3.** An important reason for the choice of the *N*-oxide **2** is the relatively hindered environment around the basic dimethylamino moiety, which prevents quaternisation with the reactant halide. (Such quaternisation was observed during initial trials with *N*,*N*,*N*′,*N*′-tetramethylethylenediamine *N*-oxide; **2** was prepared by oxidising the tetramethyl-*o*-phenylenediamine with hydrogen peroxide in 72% yield.)

It was found that the *N*-oxide **2** oxidises a variety of activated primary bromides **4**, to the corresponding aldehydes **5** in acetonitrile solution, in excellent yields (Table 1). The substrates studied include a variety of substituted benzyl bromides, apart from the cinnamyl and the phenacyl systems. The most activated systems react at room temperature, but mild heating is required for the others, with the reaction time varying between 6 and 24 h. (Benzyl chloride, 1-phenylethyl bromide, *n*-heptyl bromide and *n*-hexadecyl bromide did not react even at reflux.) In comparison, trimethylamine *N*-oxide oxidises a wider range of substrates—including unactivated aliphatic systems—but at much lower yields (generally <45% for activated systems).[3] The scope of the present method employing **2** is thus closely similar to that of the Kornblum reaction, but with the advantage of mild reaction conditions (not to mention a simpler work-up)—clearly a useful addition to existing methodology. Further work is planned to extend the above results by the design of more reactive systems—the feasibility of the bifunctional approach having been demonstrated.

Table 1
Yields and conditions for the oxidation of the halides **4** to the corresponding aldehydes **5** by the *N*-oxide **2** in MeCN solution[a]

Halide	(X in **4/5**)	Temperature (°C)	Time (h)	Aldehyde (Yield)
4a	(NO_2)	25	24	**5a** (97%)
4b	(H)	50	8	**5b** (83%)
4c	(Me)	50	8	**5c** (87%)
4d	(CO_2Et)	50	6	**5d** (92%)
4e	(Cl)	50	8	**5e** (86%)
4f	(CN)	25	24	**5f** (94%)
4g:	phenacyl bromide	25	18	**5g** (93%)
4h:	*t*-cinnamyl bromide	50	8	**5h** (91%)

[a] Preparation of the N-oxide **2.** - A solution of *N,N,N',N'*-tetramethyl-*o*-phenylenediamine (10 mmol) and 30% H_2O_2 (10.6 mmol) in methanol (25 ml) was refluxed for 24 h. Evaporation of the methanol, followed by azeotropic removal of water by employing benzene (50 ml), afforded the *N*-oxide **2** as a pale yellow solid (72%), mp 45-47 °C (benzene-hexane); IR: 2920, 1470 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): δ 2.70 (s, 6H, MeN), 3.75 (s, 6H, $MeN^+\text{-}O^-$), 7.28-7.50 (m, 3H, Ar*H*), 8.80-9.00 (m, 1H, Ar*H*); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 46.7 (N-*C*), 61.6 ($^-O\text{-}N^+\text{-}C$), 123.4-146.3 (C_{aryl}); *m/e* 180 (M^+), 164 (M^+- 16, base peak); HRMS: 180.1264 (calculated for $C_{10}H_{16}N_2O$ 180.1262). The elemental analysis indicated the formation of a trihydrate.

General oxidation procedure: A mixture of the *N*-oxide **2** (0.55 mmol) and the bromide **4** (0.50 mmol) in dry, degassed acetonitrile was stirred under the above conditions, the mixture treated with 4N HCl (5 ml) and worked up by extraction into ether. The aldehydes obtained were generally identified spectrally and by their mp's (in the case of the solids).

Acknowledgements

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