Pergamon

Tetrahedron Letters, Vol. 36, No. 23, pp. 3997-4000, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)00697-4

Organic Reducing Agents. Reduction of Electron Deficient Bromides by 1,2,2,6,6-Pentamethylpiperidine (PMP)/Mercaptoethanol[1]

Maryam Amoli, Mark S. Workentin and Danial D. M. Wayner*

Steacie Institute for Molecular Sciences, National Research Council of Canada
Ottawa, Ontario K1A 0R6 CANADA

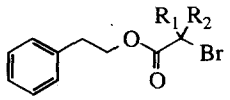
Abstract: 1,2,2,6,6 - pentamethylpiperidine (PMP) is shown to be an effective reducing agent for the radical chain conversion of primary bromoesters to the corresponding esters. The problem of inefficient reduction of tertiary bromoesters in these reactions has been overcome by the addition of an alkyl thiol which mediates the hydrogen atom transfer between the two hindered alkyl centers.

Recently, we reported the radical induced chain reduction of α-bromoesters by ketyl and dioxolanyl radicals.[2-4] Chain propagation involves the reaction of an electron rich alkyl radical with the bromide to generate an electron deficient carboalkoxyl radical (eq. 1) and subsequent hydrogen atom abstraction from an alcohol (eq. 2) or dioxolane to obtain the reduction product and regenerate the reducing radical. The efficiency with which the chain reactions proceed for primary and secondary bromoesters make these non-toxic reagents attractive alternatives to the more usual radical chain reducing agents such as tin and silicon hydrides. However, a major disadvantage of alcohols or dioxolanes is that the chain reactions are inefficient with tertiary bromides. Since the radical mediated reduction of secondary and tertiary bromoesters has some synthetic application,[4-7] the development of methodology suitable for these systems is of value.

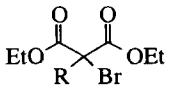
$$R_2\dot{C}OH + BrCR'_2C(O)OEt \rightarrow R_2C{=}O + HBr + EtOC(O)CR'^{\bullet}_2 \quad (1)$$

$$EtOC(O)CR'^{\bullet}_2 + R_2CHOH \rightarrow EtOC(O)CR'_2H + R_2\dot{C}OH \quad (2)$$

Although it has been known for some time that α-aminoalkyl radicals can react with organic substrates by electron transfer,[8-10] the use of amines in the radical chain reduction of halides has not been exploited to a great extent. Amines have the same attributes which make alcohols and dioxolanes useful as radical chain reducing agents;[2] weak R_2NCH_2-H bonds (ca. 85-90 kcal mol^{-1})[11] and low oxidation potentials (<-1 V versus SCE).[12] On the other hand, amines tend to be nucleophilic and substitution (i.e. alkylation of the amine) might be expected to compete with a radical chain process. With these advantages and limitations in mind, reactions of a number of bromoesters (**1a**, $R^1 = R^2 = H$; **1b**, $R^1 = H$; $R^2 = Me$; **1c**, $R^1 = H$; $R^2 = CHMe_2$; **1d**, $R^1 = R^2 = Me$), 2-bromodiethyl malonate (**2a**, R = H) and 2-bromo-2-methyldiethyl malonate (**2b**, R = Me) with 1,2,2,6,6-pentamethylpiperidine (PMP) in acetonitrile solution have been studied.



1



2

Results and Discussion

The radical chain reactions were initiated by the thermal decomposition of a small amount (5 mol percent) of di-*tert*-butylhyponitrite which generates *tert*-butoxyl radicals (eq. 3) and subsequently abstracts hydrogen atom from the PMP (eq.4). Chain propagation proceeds by the reaction of the aminoalkyl radical with the bromide (eq. 5) followed by hydrogen atom abstraction from PMP by the resulting alkyl radical (eq. 6). For less hindered amines (e.g. N-methylpiperidine or di-isopropylethylamine), nucleophilic substitution (eq. 7) was shown to compete effectively with the chain reaction. The data from alkoxyl radical initiated reactions of PMP with **1** and **2** are shown in the Table. The reaction of the primary bromide, **1a**, proceeds quantitatively under these conditions. Comparison of two secondary bromides, **1b** and **1c**, indicates a significant steric effect on at least one of the chain propagating reactions (eqs. 3,4). The steric effect is even more pronounced in the reaction of **1d** which is completely stable under the reaction conditions. In addition, with the exception of the reaction of **1a** the overall selectivity (i.e. the fraction of reacted bromide that is reduced to the corresponding ester) is poor. The reactions of **2a** and **2b** are more facile, however, the selectivities remain low.

$$\text{t-BuONNOBu-t} \rightarrow 2\text{t-BuO}^{\bullet} + N_2 \quad (3)$$

$$\text{t-BuO}^{\bullet} + R_2NCH_3 \rightarrow \text{t-BuOH} + R_2NCH_2^{\bullet} \quad (4)$$

$$R_2NCH_2^{\bullet} + R'Br \rightarrow R_2\overset{+}{N}{=}CH_2 + R''^{\bullet} + Br^- \quad (5)$$

$$R''^{\bullet} + R_2NCH_3 \rightarrow R_2NCH_2^{\bullet} + R'H \quad (6)$$

$$R'Br + R_2NCH_3 \rightarrow R_2\overset{+}{N}R'CH_3Br^- \quad (7)$$

There are two potential sources of the steric effect that lead to low conversions in the reactions of the tertiary bromides (**1d** and **2b**). Of the two propagation reactions, reaction 5 should have a small steric effect since it is likely an electron transfer reaction.[12] On the other hand, reaction 6, a hydrogen atom transfer, is expected to have a significant steric demand. One approach to overcome this difficulty is to use another reagent to mediate the hydrogen atom transfer. Recent work by Roberts and coworkers[13,14] has shown that hydrogen atom transfer to carbon centered radicals from alkyl thiols is a synthetically useful process. In those cases, thiols were used to mediate the radical chain reduction of alkyl halides by silanes taking advantage of the relatively weak S-H bond (about 92 kcal mol^{-1})[15] compared to alkyl C-H bonds. The subsequent hydrogen atom transfer from the silane to the thiyl radical is essentially thermoneutral but has a low intrinsic barrier. In this present study, a similar thermochemical situation exists, however, the thiol would mediate the hydrogen atom transfer between two carbon centers (eqs. 8,9).

$$R''^{\bullet} + R''SH \rightarrow R'H + R''S^{\bullet} \quad (8)$$

$$R''S^{\bullet} + R_2NCH_3 \rightarrow R''SH + R_2NCH_2^{\bullet} \quad (9)$$

Table. Radical Chain Reduction of Bromoesters by PMP[a]

Bromoester	$[HOCH_2CH_2SH]$ (eq)	percent conversion[b]	percent selectivity[c]
1a	0	100	100
1b	0	13	11
1c	0	16	16
1d	0	0	0
2a	0	100	46
2b	0	78	50
1a	2.5	100	0
1b	2.5	100	0
1c	2.5	100	45
1d	2.5	98	66
2a	2.5	100[d]	100
2b	2.5	100[d]	71
2b	15	100[d]	80

[a]Reactions were carried out in acetonitrile containing 2 equivalents of the amine and 5 mol percent of di-*tert*-butyl hyponitrite (initiator) at 60°C for 5 h. [b]Percent of consumed bromide = 100 x $[RBr]_{final}/[RBr]_{initial}$ [c]Percent of the consumed bromide reduced to the corresponding ester = 100 x $[RH]_{final}/\{[RBr]_{initial} - [RBr]_{final}\}$. [d]Conversion after only 10 minutes at room temperature.

The result of the thiol mediated reduction (using mercaptoethanol as the mediator) are also shown in the Table. For the primary and secondary bromides **1a-b** a thermal reaction (substitution) between the thiol and the halide precluded the use of a thiol in these systems. However, for the more hindered bromides (**1c**, **d** and **2a**, **b**) significant improvements in both the conversion and the selectivities were observed. In fact, for **2a** and **2b**, the reaction was complete after only 10 minutes at room temperature (no reaction occurred in the absence of the initiator) indicating that the chain reactions induced by a small amount of thermal and/or light induced decomposition of the initiator were extremely efficient (chain lengths >> 1000).

In summary, primary bromoesters are efficiently reduced by hindered amines in a radical chain process analogous to previously reported reductions using alcohols or dioxolanes.[2] The chain propagating reactions involve the electron transfer reduction of the bromide by an α-aminoalkyl radical followed by hydrogen atom transfer to the alkyl radical from the amine. The problem of inefficient reduction of tertiary bromoesters in these reactions has been overcome by the addition of an alkyl thiol. The role of the thiol is to mediate the hydrogen atom transfer between the two hindered alkyl centers which appears to be the rate limiting step. The thiol mediated reduction of malonyl bromides proceeds with very long chain lengths and opens the possibility of using this methodology in more synthetically useful reactions involving addition or cyclization reactions of the intermediate radicals.[7]

Experimental

The amines and mercaptoethanol were commercially available (Aldrich®) and were used as received. The bromides **1a-d** were prepared by the reactions of 2-phenethyl alcohol with the appropriate acid bromide: bromoacetyl bromide, 2-bromopropionyl bromide, 2-bromoisobutyryl bromide, and 2-bromo-3-methylbutyric acid respectively. The corresponding reduced ester derivatives were prepared in the same way from the acid bromides. All products were colorless or pale yellow liquids after purification, and were identified by GC/MS and ^{1}H NMR which agreed with those reported in the literature.[2] The diethyl bromomalonate (**2a**) and diethyl 2-bromo-2-methylmalonate (**2b**) and the corresponding reduced products were obtained from Aldrich and used without further purification.

The reductions were carried out in acetonitrile (2 mL) solutions containing the bromide (0.25 M) using di-*tert*-butylhyponitrite (prepared by the method of Mendenhall *et al*[16]) as initiator (5 mol percent based on the bromide), the amine (2 eq. based on the bromide) and when applicable mercaptoethanol (2.5 eq. based on the bromide). The reaction mixtures were oxygen purged with a stream of dry argon for 15 min. and then placed in a constant temperature bath at 60±0.5°C for 5 h (*ca.* 5 half-lives of the initiator). The reaction mixture was analyzed by gas chromatography (HP Model 5890 equipped with an HP Model 7673A automatic injector). The yields of unreacted starting material and the reduced ester products were quantified using tridecane as an internal standard and appropriate calibration curves.

References

(1) Issued as NRCC publication number 37316.

(2) Fontana, F.; Kolt, R. J.; Huang, Y.; Wayner, D. D. M. *J. Org. Chem.* **1994**, *59*, 4671-4676.

(3) Kolt, R. J.; Wayner, D. D. M.; Griller, D. *J. Org. Chem.* **1989**, *54*, 4259-4260.

(4) Kolt, R. J.; Griller, D.; Wayner, D. D. M. *Tetrahedron Lett.* **1990**, *31*, 7539-7540.

(5) Guindon, Y.; Yoakim, C.; Lemieux, R.; Boisvert, L.; Delorme, D.; Lavallée, J.-F. *Tetrahedron Lett.* **1990**, *31*, 2845-2848.

(6) Guindon, Y.; Lavallée, J.-F.; Boisvert, L.; Chabot, C.; Delorme, D.; Yoakim, C.; Hall, D.; Lemieux, R.; Simoneau, B. *Tetrahedron Lett.* **1991**, *32*, 27-30.

(7) Curran, D. P. *Synthesis* **1988**, 417-439 and references cited therein.

(8) DeLawe, P. J.; Lee, J. T.; Sprintschnik, H. W.; Abruna, H.; Meyer, T. J.; Whitten, D. G. *J. Am. Chem. Soc.* **1977**, *99*, 7094-7097.

(9) Chandrasekaran, K.; Whitten, D. G. *J. Am. Chem. Soc.* **1980**, *102*, 5119-5120.

(10) Bhattacharyya, K.; Das, P. K. *J. Phys. Chem.* **1986**, *90*, 3987-3993.

(11) Clark, K. B.; Wayner, D. D. M.; Demirdji, S. H.; Koch, T. H. *J. Am. Chem. Soc.* **1993**, *115*, 2447-2453.

(12) Wayner, D. D. M.; Dannenberg, J. J.; Griller, D. *Chem. Phys. Lett.* **1986**, *131*, 189-191.

(13) Cole, S. J.; Kirwan, J. N.; Roberts, B. P.; Willis, C. R. *J. Chem. Soc. Perkin Trans. 1* **1991**, 103-112.

(14) Allen, R. P.; Roberts, B. P.; Willis, C. R. *J. Chem. Soc. Chem. Commun.* **1989**, 1387-1388.

(15) McMillen, D. F.; Golden, D. M. *Ann. Rev. Phys. Chem.* **1982**, *33*, 493-532.

(16) Mendenhall, G. D. *Tetrahedron Lett.* **1985**, *24*, 451-452.

(*Received in USA* 17 *February* 1995; *revised* 6 *April* 1995; *accepted* 11 *April* 1995)