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Electron-transfer-induced reductive cleavage of chlorinated aryloxyalkanoic acids

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ABSTRACT

We investigated the degradation of chlorinated herbicides, with an aryloxyalkanoic acid skeleton, under reductive electron transfer reaction conditions. Although Li and Na metals proved useless, activated forms of these metals, either their soluble naphthalene radical anions or 1,2-diarylethane dianions, promoted the degradation of the starting materials to various extents. Indeed, lithium naphthalenide promoted both extensive dehalogenation and dealkylation of chlorinated aryloxyalkanoic acids, with formation of the corresponding phenols as the main reaction products. In contrast, the employment of 1,2-diphenyl-1,2-disodioethane as a reducing agent led, in most examples, to the chemoselective recovery of the corresponding dechlorinated acids.

1. Introduction

Several chlorinated aryloxyalkanoic acids are extensively used as herbicides, with 2,4-dichlorophenoxyacetic acid (2,4-D)[1] being one of the most widely used pesticide in the world. Furthermore, an approximately 1:1 mixture of 2,4-D and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), the latter in the form of its *n*-butyl ester, was extensively used as a general purpose herbicide for defoliation and crop destruction during the Vietnam War.[2] Due to their toxicity and environmental hazard, several methodologies have been proposed for their degradation, including photocatalyzed oxidation,[3] electrocatalytic reduction[4] or combustion,[5] and catalyzed hydrodechlorination.[6] Although the employment of alkali metals as Single Electron Transfer (SET) reducing agents was successfully applied to the degradation of several chlorinated persistent aromatic pollutants,[7] to the best of our knowledge no report concerns the application of such a procedure to the hydrodehalogenation of chlorinated aryloxyalkanoic acids.

We previously reported on the successful application of the reductive dehalogenation to halogenated benzoic[8] acids, using 1,2-diaryl-1,2-disodioethanes[9] in THF as highly activated forms of Na metal, functioning under homogeneous and mild reaction conditions. Following our interest in the field, we now wish to report the results of an investigation aimed to highlight the reductive degradation of chlorinated aryloxyalkanoic acids under electron transfer reaction conditions.

2. Results and discussion

We first investigated the reductive degradation of a series of chlorinated aryloxyacetic acids widely employed as herbicides. These include 4-chlorophenoxyacetic acid (4-CPA, **1a**), 2-methyl-4-chlorophenoxyacetic acid (MCPA, **1b**), 2,4-D (**1c**) and 2,4,5-T (**1d**).

Their reactivity was investigated towards different SET reducing agents, including Li and Na metals, Li naphthalenide (LiN, **2a**), Na naphthalenide (NaN, **2b**), 1,2-dilithio-1,2-diphenylethane (1,2-dilithiostilbene, DLS, **3a**), 1,2-diphenyl-1,2-disodioethane (1,2-disodiostilbene, DSS, **3b**) and 1,2-disodiostilbene-1,2,3,4-tetraphenylethane (DSTPE, **3c**). Concerning the different activated forms of the alkali metals employed in this work, it is worth noting that radical anions **2a** and **2b** are one-electron donors, whilst the *vic*-diorganometals **3a**–**c** are two-electrons donor reagents.

The reaction of one of these reducing agents with a halogenated carboxylic acid can be foreseen to give rise to deprotonation of the carboxylic moiety as well as to different reductive cleavage pathways, i.e., dehalogenation (C–Cl bond cleavage) and dealkylation (aliphatic C–O bond cleavage).[10,11] The deprotonation reaction should require a 1:1 molar ratio of acid to alkali metal (or to radical anion), whilst the same reaction should require a 1:0.5 molar ratio of acid to dianion. In contrast, reductive cleavage of a carbon–heteroatom bond could require an acid to alkali metal (or radical anion) molar ratio reaching 1:2, or an acid to *vic*-diorganometal molar ratio reaching 1:1.[8,10] Accordingly, we run most reactions with an acid to reducing agent molar ratio chosen in order to allow all the above cited reaction pathways to go to completion.

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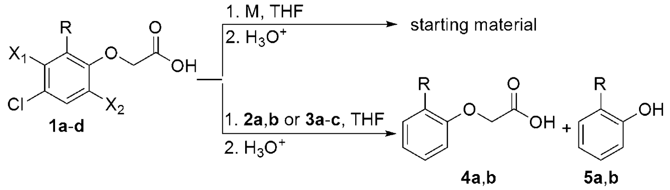
All reactions were run in dry THF under a N_2 atmosphere, by adding solutions of the different halogenated aryloxyalkanoic acids to suspensions (for Li and Na metals) or solutions (for radical anions and dianions) of the reducing agent, cooled to 0 °C. No attempt was made to determine the minimum reaction time required for the reaction to go to completion. Accordingly, reaction mixtures were stirred and allowed to warm to rt for 12 h, and quenched with H_2O. Acidic reaction products were recovered by acidifying the aqueous phase with 1 N HCl; this work-up led to a mass recovery typically $\geq$ 90%, and crude mixtures were analyzed by ^{1}H NMR spectroscopy. The results are reported in Table 1 (Scheme 1).



Scheme 1. Reaction of chlorophenoxyacetic acids, **1a**–**d**, with various SET reagents. **1a**, R=X_1=X_2=H; **1b**, R=CH_3, X_1=X_2=H; **1c**, R=X_1=H, X_2=Cl; **1d**, R=H, X_1=X_2=Cl; **4a**, **5a**, R=H; **4b**, **5b**, R=CH_3; M=Li or Na; **2** and **3**, see Table 1 and text.

Table 1
Reductions of acids **1** with various SET reagents[a]

Entry	Substrate	SET reagent	Acid/SET reagent[b]	Product distribution[c,d]		
				1 (%)	**4** (%)	**5** (%)
1	4-CPA, **1a**	Li	1:5	**1a**, >95	—	—
2	4-CPA, **1a**	Na	1:5	**1a**, >95	—	—
3	4-CPA, **1a**	LiN, **2a**	1:5	—	**4a**, 22	**5a**, 78
4	4-CPA, **1a**	LiN, **2a**	1:6.5	—	**4a**, 8	**5a**, 92
5	4-CPA, **1a**	NaN, **2b**	1:5	—	**4a**, 56	**5a**, 44
6	4-CPA, **1a**	DLS, **3a**	1:2.5	—	**4a**, 57	**5a**, 43
7	4-CPA, **1a**	DSS, **3b**	1:2.5	—	**4a**, >95	—
8	4-CPA, **1a**	DSTPE, **3c**	1:2.5	**1a**, 60	**4a**, 40	—
9	MCPA, **1b**	DSS, **3b**	1:2.5	—	**4b**, >95	—
10	2,4-D, **1c**	Li	1:7.0	**1c**, >95	—	—
11	2,4-D, **1c**	Na	1:7.0	**1c**, >95	—	—
12	2,4-D, **1c**	LiN, **2b**	1:8.0	—	**4a**, 16	**5a**, 84
13	2,4-D, **1c**	DSS, **3b**	1:3.5	—	**4a**, >95	—
14	2,4,5-T, **1d**	DSS, **3b**	1:4.5	—	**4a**, >95	—

[a] All reactions were run in dry THF, under N_2, for 12 h at rt.
[b] Molar ratio.
[c] As determined by ^{1}H NMR spectroscopic analyses of crude reaction mixtures.
[d] Formation of minor amounts (<10%) of unidentified by-products was occasionally observed.

The reactivity of **1a**, taken as a model compound, was investigated in some detail. In agreement with previous results obtained with halobenzoic acids,[8] reaction of **1a** with either Li or Na metal did not result in any cleavage reaction (Table 1, entries 1 and 2).

In contrast, and depending on the relative amount of the reducing agent, reaction of **1a** with LiN, **2a**, resulted in the quantitative cleavage of the aromatic carbon–chlorine bond, as well as in the extensive cleavage of the aliphatic carbon–oxygen bond (Table 1, entries 3 and 4). Comparable results were observed employing NaN, **2b**, as a reducing agent, although this reagent proved less effective in promoting the dealkylation reaction (Table 1, entry 5).

Similar results were obtained in the reduction of **1a** with the corresponding dianionic derivative. Indeed, the reaction of **1a** with DLS, **3a**, afforded an almost equimolar mixture of phenoxyacetic acid, **4a**, and phenol, **5a** (Table 1, entry 6), whilst a similar reaction employing its sodium analogue, **3b**, as a reducing agent, regioselectively afforded the product of cleavage of the carbon–chlorine bond (Table 1, entry 7).

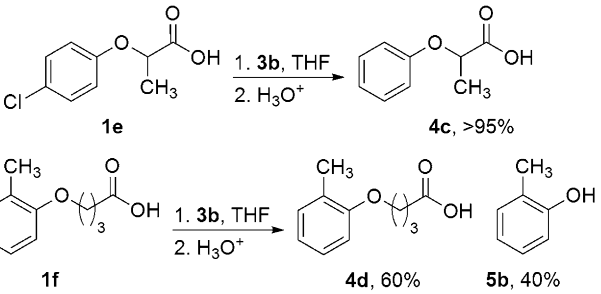
Quenching the last reduction mixture with D_2O did not lead to the incorporation of deuterium on the aromatic ring (as determined by ^{1}H NMR spectroscopic analysis of the crude mixture, not reported in Table 1), thus suggesting that some component(s) of the reaction medium behaved as proton (or hydrogen atom) donor(s) towards some reactive dechlorinated intermediate(s).[12]

Finally, and in agreement with the relatively low reducing properties of this reagent,[9] the reduction of **1a** with DSTPE afforded relatively low conversion of the starting material into the corresponding dechlorinated product, **4a** (Table 1, entry 8).

We further investigated the reduction of MCPA, **1b**, 2,4-D, **1c** and 2,4,5-T, **1d**, under similar reaction conditions. In agreement with the previous results, the employment of DSS, **3b**, as a SET reducing agent, allowed their highly regioselective conversion into the corresponding dehalogenated aryloxyacetic acids (Table 1, entries 9, 13 and 14). Moreover, the reduction of 2,4-D, **1c**, with LiN, **2a**, further highlighted the ability of the last reagent to promote both the dehalogenation and the dealkylation reaction (Table 1, entry 12). Furthermore, it is worth noting that Li and Na alone proved useless in the degradation of the dichloro-substituted acid **1c** (Table 1, entries 10 and 11).

Finally, we investigated the reductive cleavage of two chlorinated herbicides possessing a somewhat different aryloxyalkanoic skeleton, i.e., 2-[4-chlorophenoxy]propionic acid (4-CPP), **1e**, and 4-[4-chloro-2-methylphenoxy]butanonic acid (4-CPB), **1f**, employing DSS, **3b**, as a reducing agent.

Under appropriate conditions, i.e., with an acid to reducing agent molar ratio of 2:1 and within relatively short reaction time, it was possible to achieve the highly regioselective dehalogenation of the aryloxypropionic acid **1e**; at variance with this result the aryloxybutanoic acid **1f** underwent dehalogenation as well as dealkylation with particularly ease (Scheme 2).



Scheme 2. Reduction of 2-[4-chlorophenoxy]propionic acid, **1e**, and 4-[4-chloro-2-methylphenoxy]butanoic acid, **1f**, with DSS, **3b**.

3. Conclusions

The above reported results show that activation of Li or Na metal, either in the form of their soluble naphthalene radical anions or 1,2-diarylethane dianions, allows their employment in the reductive degradation of chlorinated aryloxyalkanoic acids. Some of these reagents are able to promote, besides the cleavage of aromatic carbon–chlorine bonds, the reductive dealkylation of chlorophenoxy herbicides. This observation is particularly interesting in the case of aryloxyacetic acids, due to the known stability of this kind of aliphatic carbon–oxygen bond under a variety of reaction conditions.[13]

In addition, the above reported results show that Li derivatives, either the radical anion or the dianion, are more effective as reducing agents than the corresponding Na derivatives. Furthermore, the lithium radical anion of naphthalene (LiN, **2a**) proved more effective, under the above reported set of reaction conditions, then the corresponding lithium dianion (DLS, **3a**), and the same was true for the couple NaN, **2b**, and DSS, **3b**. Accordingly, the choice of an appropriate SET reagent appears as a key step to obtain the reduction of chlorinated aryloxyalkanoic acids either into the corresponding dehalogenated carboxylic acids or phenols, thus disclosing an approach not only to the degradation but also to the reuse of this class of compounds.

4. Experimental

4.1. General

Starting materials were of the highest commercial quality and were purified by distillation or recrystallization immediately prior to use. THF was distilled from Na/K alloy under N_2 immediately prior to use. ^1H NMR spectra were recorded at 300 MHz and ^{13}C NMR spectra were recorded at 75 MHz in DMSO-d_6 (unless otherwise indicated) on a Varian VXR 300 spectrometer. IR spectra were recorded on an FT-IR Jacso 680 P. TLC analyses on Macherey-Nagel silica gel pre-coated plastic sheets (0.20 mm).

4.2. Starting materials

Aryloxyalkanoic acids **1a**–**c** are commercially available; aryloxyalkanoic acids **1d**,[14] and **1f**[15] were synthesized according to a procedure described in Ref. 16, whilst **1e**[17] was synthesized according to a procedure described in Ref. 18. Literature characterization of acid **1f** reports only its mp;[15] accordingly, we wish to report here a more complete characterization of this compound.

*4.2.1. 4-[4-Chloro-2-methylphenoxy]butanoic acid, **1f**.* White powder, mp=100–102 °C (CH_2Cl_2) (lit.[15] mp=101 °C). Anal. Found: C, 57.64; H, 5.92; $C_{11}H_{13}ClO_3$ requires: C, 57.78; H, 5.73%; IR (Nujol) 1710 cm^{-1}; ^1H NMR (DMSO) δ 1.95 (2H, m, CH_2), 2.13 (3H, s, CH_3), 2.39 (2H, t, J=7.2 Hz, CH_2), 3.97 (2H, t, J=6.4 Hz, CH_2), 6.91 (1H, d, J=8.8 Hz, ArH), 7.15–7.20 (2H, m, 2×ArH). ^{13}C NMR (DMSO): δ 15.6, 24.2, 30.3, 66.9, 112.6, 123.6, 126.4, 128.2, 129.8, 155.4, 174.1.

0.2 M solutions of radical anions **2a**[19] and **2b**,[20] as well as of dianions **3a**,[21] **3b**[21] and **3c**,[22] in dry THF were prepared as already described.

4.3. Reductive cleavage of chloronated aryloxyalkanoic acids 1a–f. General procedure

To 10 mL of a 0.2 M solution of a SET reagent **2** or **3** (2 mmol), cooled to 0 °C, was added a solution of the appropriate aryloxyalkanoic acid **1** (for the relative molar ratios, see Table 1), dissolved in dry THF (5 mL). Reactions with Li or Na metal were run under closely related reaction conditions, by adding solutions of the appropriate aryloxyalkanoic acid **1** to suspension of the freshly cut metal in dry THF.

Each mixture was vigorously stirred and allowed to reach rt for 12 h, after which time it was quenched by slow dropwise addition of H_2O (15 mL). The organic solvent was evaporated in vacuo and the resulting mixture was extracted with CH_2Cl_2 (3×10 mL). The aqueous phase was acidified with 1 N HCl, extracted with CH_2Cl_2 (3×10 mL), and the organic phases were collected, washed with H_2O (1×10 mL), brine (10 mL) and dried (Na_2SO_4). After evaporation of the solvent, the resulting mixture was analyzed by ^1H NMR spectroscopy.

Reaction products **4a**–**c**, **5a** and **5b** were characterized by comparison with commercially available samples; aryloxybutanoic acid **4d**[23] was characterized by comparison with literature data.[23]

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Appendix. Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2011.03.057. These data include MOL files and InChIKeys of the most important compounds described in this article.

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