

Reformatsky Reaction in Water: Evidence for a Radical Chain Process

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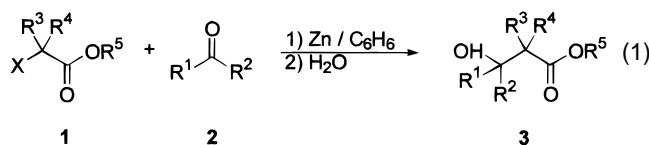
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The Reformatsky reaction of 2-bromo esters and carbonyl compounds in the presence of zinc can be carried out in concentrated aqueous salt solutions without any cosolvent. The reaction of bromoacetates is greatly enhanced by catalytic amounts of benzoyl peroxide or peracids and gives satisfactory yields with aromatic aldehydes. Preparative yields comparable to those of the traditional procedure are obtained with ethyl 2-bromoisobutyrate. This ester needs no catalyst and reacts even with saturated aldehydes and aromatic ketones, although in low yields. A radical chain mechanism, initiated by electron abstraction from the organometallic Reformatsky reagent, is proposed. Two nonchain pathways, involving radicals directly produced on the metal surface, may compete, especially in the case of secondary and tertiary halides.

Introduction

First discovered by Reformatsky in 1887,¹ the reaction of 2-halo esters **1** and carbonyl compounds **2** in the presence of zinc (eq 1) was the first example of a large number of now commonly used C–C bond forming reactions: the addition of organometallic reagents to the



carbonyl group. For nearly a century, these reactions were believed to require strictly anhydrous and oxygen free conditions. Only during the past decade have chemists witnessed numerous examples of one-step reactions between organic halides, a reactive metal, and an electrophilic substrate, commonly a carbonyl compound, which proceeded not only in “wet” solvents, but sometimes in water or salt solutions.² Many of these procedures gave addition products in preparative yields, comparable or superior to those obtained with preformed organometallic reagents under anhydrous conditions. In other cases, addition reactions became possible on polyhydroxylated substrates such as carbohydrates without any protection/deprotection process. Nevertheless, almost all of these transformations were accomplished with allylic and propargylic halides, and attempts to extend the methodology to other halogen compounds have had only limited success. For example, haloalkanes in the presence of zinc gave 1,4-addition to unsaturated carbonyl compounds,³ and bromo ketones reacted with tin, zinc or indium in the presence of benzaldehyde to produce the crossed aldol type adducts.^{2d,4} In view of the elec-

tronic analogy of 2-halo esters with the latter example it seemed obvious to try to extend the method to the Reformatsky reaction. However, a first attempt reported by Luche and co-workers in 1985,⁵ using zinc under sonication, was unsuccessful. Only in 1993, did Chan and co-workers succeed with the indium-promoted reaction between secondary and tertiary bromo carboxylates and benzaldehyde in water;^{2d} even the free acids and their sodium salts reacted under these conditions. In the same year, Li mentioned an analogous reaction using zinc or tin,^{2c} but no structural or experimental details have been published to the present date. Yields were low to moderate with all three metals. Reactions using simple haloacetates or carbonyl compounds other than benzaldehyde have yet to be described in the literature.

Results

Two years ago, without knowledge of the partially successful reports mentioned above, we started some exploratory work on the Reformatsky reaction using ethyl bromoacetate, benzaldehyde, and zinc dust in aqueous ammonium chloride. To our surprise, the first experiment performed with commercial, unpurified, and unactivated reagents produced a strongly exothermic reaction; zinc dissolved within a few seconds and NMR analysis of the crude extract of the reaction mixture unequivocally revealed a 10% yield of the Reformatsky adduct, in addition to ethyl acetate and unreacted benzaldehyde. Some improvement was achieved when the mixture of bromo ester and aldehyde was added to a vigorously stirred suspension of zinc in ammonium chloride solution. Inverse, portionwise addition or use of zinc granules was contraproductive. The influence of the composition of the aqueous solution was tested using highly hygroscopic salts of ammonium, sodium, potassium, magnesium, calcium, barium, aluminum, and zinc. This led to two solvent systems of superior yield: saturated ammonium chloride further saturated with magnesium perchlorate (solvent A) and saturated calcium chloride containing some ammonium chloride (solvent B). Use of a 3-fold excess of bromoacetate raised the yield to almost 50%; higher excess gave no further improvement. Addition of

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Table 1. Reformatsky Reaction of Carbonyl Compounds in Water at 30 °C

entry	substrate 2	halo ester 1	solvent ^a	catalyst	unchanged 2 (%) ^b	yield 3 (%) ^b
1	C ₆ H ₅ CHO	BrCH ₂ CO ₂ Et	A	–	72	8
2	C ₆ H ₅ CHO	BrCH ₂ CO ₂ Et	A	(BzO) ₂	21	52 (45 ^c)
3 ^d	C ₆ H ₅ CHO	BrCH ₂ CO ₂ Et	A	(BzO) ₂	74	11
4	C ₆ H ₅ CHO	BrCH ₂ CO ₂ Et	A	MCPBA	–	35
5	C ₆ H ₅ CHO	BrCH ₂ CO ₂ Et	A	MMPP	21	38
6	C ₆ H ₅ CHO	BrCH ₂ CO ₂ Et	B	–	63	21
7 ^d	C ₆ H ₅ CHO	BrCH ₂ CO ₂ Et	B	–	70	19
8	C ₆ H ₅ CHO	BrCH ₂ CO ₂ Et	B	(BzO) ₂	47	36
9	C ₆ H ₅ CHO	BrCH ₂ CO ₂ Et	B	MCPBA	16	49
10	C ₆ H ₅ CHO	BrCH ₂ CO ₂ Et	B	galvinoxyl ^e	51	17
11	C ₆ H ₅ CHO	BrCH ₂ CO ₂ Et	B	hydroquin ^f	46	13
12	C ₆ H ₅ CHO	ICH ₂ CO ₂ Et	A	(BzO) ₂	45	–
13	C ₆ H ₅ CHO	ICH ₂ CO ₂ Et	B	(BzO) ₂	38	23
14 ^g	C ₆ H ₅ CHO	ClCH ₂ CO ₂ Et	A	(BzO) ₂	52	–
15	C ₆ H ₅ CHO	BrCH ₂ CO ₂ Me	A	(BzO) ₂	36	30
16	C ₆ H ₅ CHO	BrCH ₂ CO ₂ tBu	B	(BzO) ₂	54	20
17	C ₆ H ₅ CHO	BrCH(CH ₃)CO ₂ Et	B	–	35	51
18 ^d	C ₆ H ₅ CHO	BrCH(CH ₃)CO ₂ Et	B	–	32	41
19	C ₆ H ₅ CHO	BrCH(CH ₃)CO ₂ Et	B	(BzO) ₂	26	53 (52 ^c)
20	C ₆ H ₅ CHO	BrC(CH ₃) ₂ CO ₂ Et	B	–	2	76
21	C ₆ H ₅ CHO	BrC(CH ₃) ₂ CO ₂ Et	B	(BzO) ₂	2	80 (82 ^c)
22	C ₆ H ₅ CHO	BrC(CH ₃) ₂ CO ₂ Et	B	galvinoxyl ^e	1	57
23	C ₆ H ₅ CHO	BrC(CH ₃) ₂ CO ₂ Et	B	hydroquin ^f	18	32
24	2-C ₁₀ H ₇ CHO	BrCH ₂ CO ₂ Et	A	(BzO) ₂	28	59
25	2-C ₄ H ₃ OCHO	BrCH ₂ CO ₂ Et	A	(BzO) ₂	13	38
26	2-C ₄ H ₃ SCHO	BrCH ₂ CO ₂ Et	A	(BzO) ₂	28	35
27	4-CH ₃ O-C ₆ H ₄ CHO	BrCH ₂ CO ₂ Et	A	(BzO) ₂	38	35
28	4-Cl-C ₆ H ₄ CHO	BrCH ₂ CO ₂ Et	A	(BzO) ₂	7	58
29	2,4-Cl ₂ -C ₆ H ₃ CHO	BrCH ₂ CO ₂ Et	A	(BzO) ₂	6	66
30	2,3-(CH ₃ O) ₂ -C ₆ H ₃ CHO	BrCH ₂ CO ₂ Et	A	(BzO) ₂	22	60
31 ^h	2-HO-C ₆ H ₄ CHO	BrCH ₂ CO ₂ Et	A	(BzO) ₂	31	36
32 ^h	2-HO-C ₆ H ₄ CHO	BrC(CH ₃) ₂ CO ₂ Et	B	(BzO) ₂	24	52
33 ^h	3-HO-C ₆ H ₄ CHO	BrCH ₂ CO ₂ Et	A	(BzO) ₂	21	36
34 ^h	3-HO-C ₆ H ₄ CHO	BrC(CH ₃) ₂ CO ₂ Et	B	(BzO) ₂	11	70
35 ^h	4-HO-C ₆ H ₄ CHO	BrCH ₂ CO ₂ Et	A	(BzO) ₂	49	18
36 ^h	4-HO-C ₆ H ₄ CHO	BrC(CH ₃) ₂ CO ₂ Et	B	(BzO) ₂	–	83
37	(CH ₃) ₂ C=CHCHO	BrCH ₂ CO ₂ Et	A	(BzO) ₂	12	15
38	(CH ₃) ₂ C=CHCHO	BrC(CH ₃) ₂ CO ₂ Et	B	–	2	86
39	C ₆ H ₅ CH=CHCHO	BrCH ₂ CO ₂ Et	A	(BzO) ₂	–	32
40	C ₆ H ₅ CH=CHCHO	BrC(CH ₃) ₂ CO ₂ Et	B	–	–	60
41	(CH ₃) ₂ CHCHO	BrCH ₂ CO ₂ Et	A	(BzO) ₂	50	–
42	(CH ₃) ₂ CHCHO	BrC(CH ₃) ₂ CO ₂ Et	B	–	37	36 (35 ^c)
43	C ₆ H ₅ CH ₂ CH ₂ CHO	BrCH ₂ CO ₂ Et	A	(BzO) ₂	62	–
44	C ₆ H ₅ CH ₂ CH ₂ CHO	BrC(CH ₃) ₂ CO ₂ Et	B	–	43	50
45	C ₆ H ₅ COCH ₃	BrCH ₂ CO ₂ Et	A	(BzO) ₂	92	–
46	C ₆ H ₅ COCH ₃	BrC(CH ₃) ₂ CO ₂ Et	B	(BzO) ₂	81	16
47	4-F-C ₆ H ₄ COCH ₃	BrC(CH ₃) ₂ CO ₂ Et	B	(BzO) ₂	75	15

^a Solvent A: saturated ammonium chloride/magnesium perchlorate; solvent B: saturated calcium chloride/ammonium chloride.

^b Determined by ¹H NMR on the crude extract. ^c Isolated yield in a 5 mmol scale. ^d Granulated zinc was used. ^e 10 mg of galvinoxyl was dissolved in the mixture of **1** and **2**. ^f 10 mg of hydroquinone each was added to the solvent and to the organic reagents. ^g The reaction was carried out at 70 °C for 1 h; 30% of **1** remained unreacted. ^h Ratio **1**:**2** = 1.5:0.1 mmol; extraction with chloroform.

any kind of cosolvent (protic, aprotic polar, unpolar) as well as any change of temperature (0 °C and 70 °C) produced lower yields.

After this preliminary optimization of the experimental conditions, we repeated the reaction with freshly distilled benzaldehyde. In solvent A, the reaction occurred instantaneously as before, but the yield dropped down to nearly an undetectable 8% (Table 1, entry 1). Solvent B gave somewhat better results (entry 6) but still far from those obtained with unpurified aldehyde. Addition of benzoic acid or anhydride, the main impurities of the crude starting material, brought no significant change. The same negative results were observed on addition of other organic and inorganic acids. Finally, we added catalytic amounts of benzoyl peroxide, and the previous good yields were obtained again (entries 2 and 8); 0.01 equiv of the catalyst was sufficient, higher amounts reduced the proportion of unreacted aldehyde but also the yield of adduct **3**. Other radical initiators such as 3-chloroperbenzoic acid and magnesium monoperoxy-

phthalate also catalyzed the reaction with somewhat lower yields (entries 4, 5 and 9), probably due to the competition of Baeyer–Villiger reaction. *tert*-Butyl hydroperoxide, azobis(isobutyronitrile), and ammonium persulfate were found to be inefficient. On the other hand, radical quenchers such as galvinoxyl or hydroquinone inhibited but did not suppress the reaction (entries 10 and 11). These findings suggest at least the partial occurrence of a radical chain process. To learn more about this surprising behavior and to evaluate the preparative scope of the procedure, a wide variety of carbonyl substrates and halo esters were tested using standard conditions in the two selected solvent systems.

Change of the halide in the ester was rather disappointing: ethyl iodoacetate in solvent A produced no hydroxy ester **3** at all (entry 12) and in solvent B the yield was much lower than for the bromide (entry 13); ethyl chloroacetate in solvent A reacted only partially, even at 70 °C, and no adduct was observed (entry 14). Variation of the ester group also resulted in lower yields

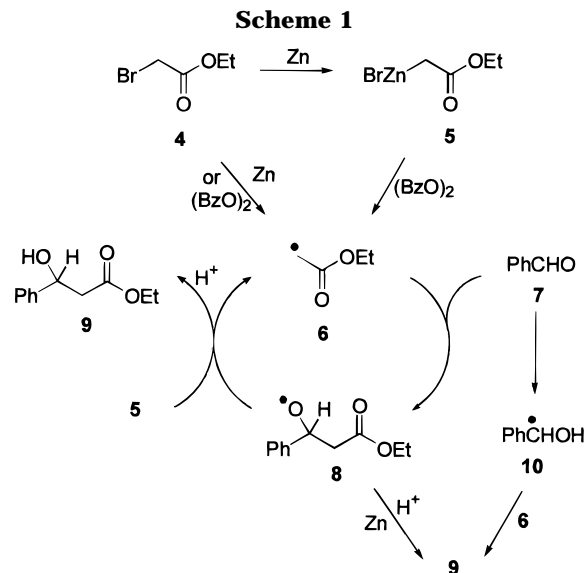
for both methyl and *tert*-butyl bromoacetate (entries 15 and 16). Ethyl 2-bromopropionate produced similar results of about 50% in the presence as well as absence of the catalyst (entries 17 and 19). Much better yields were obtained with ethyl 2-bromoisobutyrate: 76% in the absence and 80% in the presence of benzoyl peroxide (entries 20 and 21). Nevertheless, with this ester too, the addition reaction was strongly inhibited by galvinoxyl and hydroquinone (entries 22 and 23). In all of the previous examples (entries 16–23), solvent B was superior to solvent A; although less exothermic, the reaction ran its course in a few minutes. For this reason, in the following examples where the influence of the structure of the carbonyl compound was examined, solvent A was used only in the reactions with bromoacetate and solvent B with bromoisobutyrate.

In the series of other unsubstituted aromatic and heteroaromatic aldehydes, 2-naphthaldehyde gave a better yield with ethyl bromoacetate than benzaldehyde, furfural, and 2-thiophenecarbaldehyde (entries 24–26). Comparing several substituted benzaldehydes (entries 27–30), increasing yields were observed, especially with one or two electron-withdrawing groups. One of the most attractive aspects of reactions in water is the possibility of maintaining hydroxy groups unprotected. In fact, all three isomeric hydroxybenzaldehydes gave moderate yields with bromoacetate (entries 31–36); more complete transformations were obtained with bromoisobutyrate, but the low solubility of 3- and 4-hydroxybenzaldehyde made necessary a large excess of bromo ester, thus limiting its preparative interest. Unsaturated aldehydes (entries 37–40) also produced Reformatsky adducts with the tertiary bromo ester in good yields. In contrast to the findings of Luche and co-workers who used haloalkanes in similar reactions,³ no cases of 1,4-addition were observed. With saturated aldehydes and bromoacetate no more adduct was detected, but bromoisobutyrate produced still moderate yields (entries 41–44). Even in the case of acetophenone, it was possible to detect 16% of product **3** with this ester; substitution with an electronegative fluorine atom had little influence on the yield (entries 46 and 47).

Discussion

The examples given in Table 1 demonstrate that the Reformatsky reaction can be carried out in water with a wide range of carbonyl substrates, including saturated and unsaturated aldehydes and ketones where the indium-promoted reaction in water was previously reported to be ineffective.^{2d} Preparatively interesting yields, comparable to those of the classical procedure in anhydrous solvents, can be obtained from substituted benzaldehydes with ethyl bromoacetate and from aromatic and unsaturated aldehydes with ethyl 2-bromoisobutyrate. This is demonstrated by the isolated yields of selected examples in preparative scale (entries 2, 19, 21, and 42).

From the mechanistic point of view, our results raise new questions about pathways and intermediates of organometallic *in situ* reactions in general and specifically of the Reformatsky reaction. Although the inhibition by galvinoxyl and hydroquinone fits very well with the radical mechanism of two SET proposed by Chan,^{2d} the observed catalytic effect of benzoyl peroxide is completely unexpected. As a first hypothesis, we considered a hydrogen abstraction from the bromo ester as postulated in the benzoyl peroxide catalyzed addition to



olefins.⁶ When the reaction was carried out in deuterium oxide, however, no deuterium was incorporated in any position of the hydroxy ester, but exclusively in the reduction product ethyl acetate. In Scheme 1 we propose an alternative radical chain mechanism which does not involve hydrogen abstraction. It should predominate when bromoacetate **4** is reacted in solvent A where zinc is probably reactive enough to produce directly the organometallic Reformatsky reagent **5**. This will react with water to form ethyl acetate or with a benzoyl radical to form benzoate and radical **6** which adds to the aldehyde **7**, giving the oxyl radical **8**. Reduction of the intermediate **8** by another molecule of Reformatsky reagent **5** produces the final adduct **9** and a new radical **6** to continue the chain. Alternatively, the initial radical **6** may be produced by bromine abstraction from **4**, either by a phenyl radical or on the zinc surface. This chain process is probably more important in the case of bromoacetate in solvent A, because the primary carbanionic intermediate **5** is more stable than a secondary or tertiary species. In solvent B, where the reaction is slower and less dependent on a peroxide catalyst, **6** may be formed, at least in part, directly from **4** on the zinc surface. In this case, there is no need for a chain process, since **8** can be reduced to **9** by the metal. When bromoisobutyrate is used, this may be the main pathway, because a tertiary radical of type **6** is more stable than a primary one. Reactions with bromopropionate probably occupy an intermediate position where both processes are competing. In a third alternative, the aldehyde **7** may be reduced to the radical **10** and then combined with **6** to the final product **9**. The real occurrence of radical species is supported by the inhibitory effect of galvinoxyl and hydroquinone (entries 10, 11, 22, and 23). Furthermore, the intermediates **6** and **10** should be capable of dimerization; indeed, careful GC/MS analyses of the crude extracts revealed trace amounts of diethyl succinate and 1,2-diphenyl-1,2-ethanediol. Most of the intermediates discussed here are thought to react adsorbed or close to the metal surface. Specifically for the strongly exothermic and very fast reactions of bromoacetate in solvent A, a large active metal surface is crucial as demonstrated by markedly decreased yields when granulated zinc is used (entry 3); in solvent B, the particle size of the metal

is much less important (entries 7 and 18). A less effective adsorption of ketones and saturated aldehydes can also explain their lower reactivity.

Although the mechanism proposed in Scheme 1 gives a satisfactory explanation of the differences in reactivity between primary and tertiary bromo esters, it should be regarded only as a first hypothesis. Further work focusing on structural effects and attempts to identify possible intermediates will be necessary in the future.

Experimental Section

All reagents were purchased from commercial suppliers and used without further purification, except benzaldehyde which was distilled before use. ^1H NMR spectra were recorded on Varian spectrometers EM 390 (90 MHz) and Unity plus 300 (300 MHz). GC/MS analyses were performed on a Finnigan Mat GCQ instrument equipped with a 30m DB 5 capillary column.

General Procedure. Microscale. Solvent A: To 2 mL of saturated aqueous ammonium chloride solution was added 0.45 g of magnesium perchlorate. Solvent B: To 2 mL of saturated aqueous calcium chloride solution was added 0.25 g of ammonium chloride. A 2 mmol (130 mg) amount of zinc (powder or granules) was suspended in the solvent indicated

in Table 1 and vigorously stirred for 5 min. A mixture of 0.5 mmol of carbonyl compound, 1.5 mmol of halo ester, and, where indicated, 1 mg of catalyst was added at once. After 15 min, 1 mL of 2 N hydrochloric acid was added, and stirring was continued for 5 min. The mixture was extracted with 1 mL of carbon tetrachloride or chloroform (hydroxybenzaldehydes) containing 0.05 mmol of cyclohexane as an internal quantitative reference. The extracts were analyzed directly by NMR and GC/MS.

Preparative Scale. A 5 mmol amount of the carbonyl compound, 15 mmol of bromo ester, and 20 mmol of zinc were reacted in 20 mL of the described solvents, using a rt water bath to attenuate the exothermic reaction. Acid hydrolysis, extraction with ether, drying over sodium sulfate, and chromatography over a short column of silica gel produced the yields indicated in Table 1 (entries 2, 19, 21, and 42 in parentheses). All isolated compounds are known in the literature.^{1b}

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