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Reformatsky-type aldol reactions of 4-bromo-4,4-difluoroacetoacetate with aldehydes and ketones

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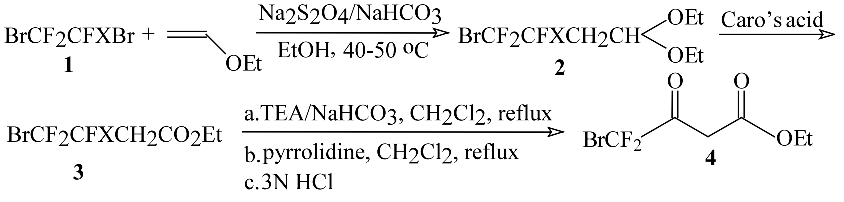
Abstract—In the presence of zinc and a catalytic amount of copper(I) chloride, 4-bromo-4,4-difluoroacetoacetate **4** reacted with a series of aromatic aldehydes and aryl alkyl ketones to give the corresponding δ-hydroxyl-γ,γ-difluoro-β-ketoesters **6** in good to excellent yields under mild conditions. © 2001 Published by Elsevier Science Ltd.

The selective introduction of fluorine into organic compounds has been receiving increasing attention in research on biological chemistry and in the development of medicines due to fluorine's unique biological and physical properties.[1] Particularly, the *gem*-difluoromethylene group, with the CF_2-carbon at both the sp^3 and sp^2 hybridization level is a key structural unit in many fluorinated compounds of biological and pharmaceutical significance.[2] α,α-Difluorination of ketones imparts increased electrophilicity to the carbonyl and contributes to the formation of stable hydrates and hemiketals which are purported to mimic the tetrahedral transition states involved in the hydrolytic action of proteases and estereases, and enzyme inhibition can occur when the nucleophilic hydroxyl is part of the active site.[3] In addition, since difluoromethylene-containing compounds often exhibit biological stability, the difluoromethylene functionality may prove particularly significant as a replacement for a CH_2 or CHOH linkage at a biochemically labile position.[4]

The preparation of *gem*-difluoromethylene substituted molecules falls broadly into two classes. The first involves direct *gem*-difluorination,[5] and the second draws from the construction of molecules derived from CF_2-synthons. The Reformatsky reaction of halodifluoroacetates and halodifluoroketones is by far the most common of all the CF_2-synthon approaches.[6] Its products are versatile intermediates which have found significant use in the synthesis of peptidase inhibitors designed around α,α-difluoro ketones,[7] difluoromethylene analogues of carbohydrates,[8] nucleosides,[9] and natural products.[10] However, the Reformatsky reaction of 4-bromo-4,4-difluoroacetoacetate with aldehydes and ketones has not been examined. In this work, we report the preparation of a series of δ-hydroxy-γ,γ-difluoro-β-ketoesters by zinc-mediated Reformatsky-type aldol reactions of 4-bromo-4,4-difluoroacetoacetate **4** with a series of aromatic aldehydes and aryl alkyl ketones. The resulting aldol-addition products are anticipated to contribute to the construction of fluorinated intermediates by further transformation.



X = Br(a), Cl(b).

Scheme 1.

Keywords: Reformatsky reaction; zinc; *gem*-difluoromethylen; aldehydes; ketones.

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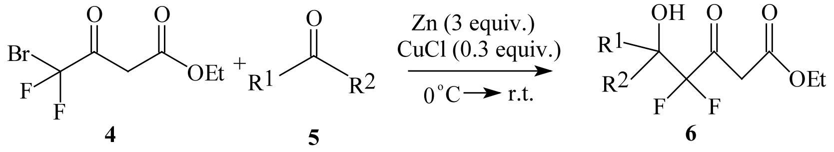
4-Bromo-4,4-difluoroacetoacetate **4** was prepared in four steps in about 50% yield as shown in Scheme 1.[11] In the first step, fluorohaloalkanes reacted with ethyl vinyl ether in absolute ethanol initiated by sodium dithionite and sodium bicarbonate to give the fluorohaloalkyl diethyl acetals **2**, which were oxidized with Caro's acid to give the corresponding esters **3** in a 75% yield over two steps.[12] Dehydrohalogenation of the ester **3**, followed by substitution of fluorine with pyrrolidine and hydrolysis gave the 4-bromo-4,4-difluoroacetoacetate **4**.[13]

We conducted the reaction of 4-bromo-4,4-difluoroacetoacetate **4** with zinc dust and benzaldehyde in refluxing THF, as recommended for Reformatsky reactions using bromodifluoroacetates,[6a] but no reaction occurred. We then noticed that literature Reformatsky reactions of chlorodifluoromethyl ketones with aldehydes and ketones in the presence of 3 equiv. of zinc dust activated in situ by 0.3 equiv. of copper(I) chloride in refluxing THF gave α,α-difluoro-β-ketones in good to excellent yields[6f] (Scheme 2). Accordingly, the aldol-addition product **6a** ($R^1 = Ph$, $R^2 = H$) was obtained in good yield when **4** was reacted with benzaldehyde under these conditions. In order to establish the optimal conditions for this reaction, we screened various reaction conditions. Some typical reaction conditions and the results obtained are summarized in Table 1. We found that both copper(I) halides and silver acetate could activate the reaction, and that diethyl ether was the best solvent.

With the optimized conditions (Table 1, entry 7) in hand, we next carried out the Reformatsky reaction of **4** with a variety of aromatic aldehydes. Thus, the reactions of **4** with a variety of aromatic aldehydes in the presence of both acid-washed zinc dust (3 equiv.) and a catalytic amount of copper(I) chloride (0.3 equiv.) in ether from 0°C to ambient temperature occurred smoothly and were completed within 2 h, affording the aldol products **6** in good to excellent yields (Table 2, entry 1). Various substituents on the phenyl ring, either electron-withdrawing or electron-donating, such as methyl, chloro, bromo, and methoxy, could be tolerated and had little effect on the yields except for *p*-nitrobenzaldehyde which gave no aldol-addition product under various conditions.[14] The aldol-addition reaction also proceeded with alkyl and heteroaromatic aldehydes giving moderate and good yields, respectively, under similar conditions (Table 2, entry 7, 8). However, the zinc-mediated addition of **4** to α,β-unsaturated aldehydes, such as acrylaldehyde and cinnamaldehyde did not occur at all. Although the products **6** could be obtained through trimethylsilyl protection of the Reformatsky adducts of ethyl bromodifluoroacetate with aldehydes followed by condensation with lithio ethylacetate,[15] we provide here a more direct and convenient method for this transformation.

Aromatic ketones also proved to be efficacious substrates, little or no qualitative difference being observed amongst the reactions of **4** with aldehydes and ketones. Ketones containing electron-withdrawing groups gave higher yields of addition products, presumably due to the enhanced electrophility of the carbonyl carbon (Table 2, entry 10). Unfortunately, the reaction of 2-butanone with **4** under the Zn-CuCl conditions failed. The reaction system became complex as shown by ^{19}F NMR and only a trace of Reformatsky product was detected which could not be isolated from the other unidentified materials. All products exhibited satisfactory spectroscopic data in accord with the assigned structures.[16]



Scheme 2.

Table 1. Optimized conditions for the Reformatsky reaction using benzaldehyde

Entry[a]	MX /0.3 equiv.	Solvent	*T* (°C)	Time (h)	Yield (%)[b]
1	CuCl	THF	−78	20	–
2	CuCl	THF	−20	8	–
3	CuCl	THF	0→rt	2	90[c]
4	CuBr	THF	0→rt	2	86[c]
5	CuI	THF	0→rt	2	85[c]
6	AgOAc	THF	0→rt	6	50
7	CuCl	Ether	0→rt	2	92
8	CuCl	DMF	0→rt	2	80
9	CuCl	CH_3CN	0→rt	2	–[d]

[a] The reaction was conducted on a scale of 0.3 mmol **4** with 0.33 mmol benzaldehyde and 0.9 mmol zinc dust in 0.6 mL solvent.

[b] Yield determined by ^{19}F NMR.

[c] 5–10 mol% of $HCF_2COCH_2CO_2Et$ was detected by ^{19}F NMR.

[d] The reaction mixture became a gel.

Table 2. The Reformatsky reactions of 4-bromo-4,4-difluoroacetoacetate **4** with aldehydes and ketones.

Carbonyl compounds				Solvent	Product **6**	Yield[a] (%)
Entry	**5**	R^1	R^2			
1	**5a**	Ph	H	Ether	**6a**	90
2	**5b**	2-ClC_6H_4	H	Ether	**6b**	83
3	**5c**	2-BrC_6H_4	H	Ether	**6c**	80
4	**5d**	4-MeC_6H_4	H	Ether	**6d**	85
5	**5e**	4-$MeOC_6H_4$	H	Ether	**6e**	91
6	**5f**	4-$NO_2C_6H_4$	H	Ether	**6f**	–
7	**5g**	$(CH_3)_2CHCH_2$	H	THF	**6g**	30[b]
8	**5h**	2-furyl	H	Ether	**6h**	80
9	**5i**	Ph	CH_3	THF	**6i**	50[b]
10	**5j**	4-BrC_6H_4	CH_3	THF	**6j**	45[b]
11	**5k**	4-$CH_3OC_6H_4$	CH_3	THF	**6k**	30[b]
12	**5l**	Ph	C_2H_5	THF	**6l**	36[b]

[a] Isolated yields of pure compounds based on **4**.

[b] 30–40 mol% $HCF_2COCH_2CO_2Et$ was detected by ^{19}F NMR.

In summary, we have described the successful Reformatsky-type reactions of **4** with a diversity of aromatic aldehydes, alkyl aldehydes, heteroaromatic aldehydes and aryl alkyl ketones in the presence of zinc dust activated in situ by catalytic amounts of copper(I) chloride to produce δ-hydroxy-γ,γ-difluoro-β-keto-esters. Further transformations of these products, such as reduction to 1,3-diol derivatives, intramolecular cyclization to δ-lactones, and diazotization of the active methylene, are now in progress.

Acknowledgements

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12. With magnetic stirring, a mixture of sodium dithionite (75 mmol, 13.1 g) and sodium bicarbonate (150 mmol, 12.6 g) was added to a solution of dibromotetrafluoroethane (75 mmol, 19.5 g) and ethyl vinyl ether (75 mmol, 8 mL) in absolute ethanol (300 mL). The mixture was stirred at 50°C for 15 h (3 h for **1b**) and was then diluted with water (300 mL) and extracted with ether (150 mL×3). The organic layer was concentrated under vacuum to afford diacetal **2a** as a yellowish liquid. Then the Caro's acid prepared from 85% sulfuric acid (765 mmol, 47.3 mL) and ammonium persulfate (37.5 mmol, 85.5 g) was added to a vigorously stirred solution of diacetal in absolute ethanol (150 mL). After being stirred for 24 h at rt, the mixture was diluted with cold water (300 mL) and extracted with ether (150 mL×4). The organic layer was washed with brine and dried over sodium sulfate. Concentration under vacuum and distillation afforded ester **3a** in a 75% 2-step yield (68–70°C/20 mmHg).
13. To a well-stirred solution of **3a** (20 mmol, 5.3 g) in dichloromethane (40 ml) was added triethylamine (30 mmol, 4.2 mL) and sodium bicarbonate (30 mmol, 2.5 g) at 0°C. The mixture was refluxed for 1 h, then pyrrolidine (20 mmol, 1.65 mL) was added to the mixture. After further reflux for 2 h, the mixture was hydrolyzed with 3N hydrochloric acid (40 mL), neutralized with saturated sodium carbonate, and extracted with dichloromethane (30 mL×3). The organic layer was washed with water and then with brine. After drying over sodium sulfate and concentration in vacuum, the residue was distilled to give 4-bromo-4,4-difluoroacetoacetate **4** as a colourless liquid. (78–82°C/10 mmHg)
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16. Representative general procedure for the Reformatsky-type aldol reactions of **4** with aldehydes and ketones: A solution of 4-methylbenzaldehyde (0.132 g, 1.1 mmol) and **4** (0.245 g, 1 mmol) in diethyl ether (1 mL) was added dropwise to a heterogeneous solution of acid-washed zinc dust (0.196 g, 3.0 mmol) and copper(I) chloride (0.030 g, 0.3 mmol) in diethyl ether (2 mL), which had been stirred at rt for 0.5 h. After the addition was completed, the reaction mixture was warmed to rt and stirred for another 1.5 h. Then saturated ammonium chloride (5 mL) was added. Excess zinc was removed by suction filtration and washed with ethyl acetate (10 mL). The organic layer was separated. The aqueous layer was extracted with ethyl acetate (10 mL×3), and the organic layers were combined and washed with water and brine and then dried over sodium sulfate. After evaporation of the solvents, the residue was chromatographed on silica gel eluting with petroleum ether–ethyl acetate (3:1/v:v) to give **6d** (0.243 g) in 85% yield. For **6d**: ^{1}H NMR (CDCl$_3$, 300 MHz): δ 1.29 (t, 3H, $J=7.1$ Hz), 2.36 (s, 3H), 2.72 (s, 0.46H), 2.93 (s, 0.54H), 3.65 (s, 1.2H), 4.19 (q, 2H, $J=7.1$ Hz), 5.05 (m, 1H), 5.48 (s, 0.4H), 7.17–7.35 (m, 4H), 12.10 (s, 0.4H). ^{19}F NMR (CDCl$_3$, 300 MHz): δ −111.6 (dd, 0.56F, $J=265$ Hz, $J=6.2$ Hz), −114.8 (dd, 0.44F, $J=260$ Hz, $J=8.7$ Hz), −121.2 (dd, 0.44F, $J=260$ Hz, $J=8.7$ Hz), −123.6 (dd, 0.56F, $J=265$ Hz, $J=6.2$ Hz).