Addition of Ethyl Bromodifluoroacetate to Lactones: Reactivity and Stereoselectivity

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Abstract: Reformatsky-type additions, under various metal-mediated activation, of ethyl bromodifluoroacetate toward a series of unactivated lactones and various sugar lactones proceeded with medium to good yields and in a completely diastereoselective manner.

Key words: addition reactions, fluorine, lactones, carbohydrates, stereoselectivity

Organofluorine compounds have received considerable interest in recent years due to their growing importance in life sciences, especially for drug development and crop protection.[1] Modification of the physiological activity of bioactive compounds by introducing fluorine into the molecules frequently leads to the discovery of novel and potent biochemical tools and medicinal agents.

Among them, *gem*-difluoromethylene group has a singular importance and techniques to meet the particular demands of its deployment have proliferated.[2] However, the use of special fluorinating agents (DAST, SF_4, CF_3OF, HF, Selectfluor and others)[3] is limited to specific compounds because of the high reactivity of these reagents. In addition, many of these reagents are expensive, toxic and hazardous. Consequently, with the increasing accessibility of fluorinated building blocks, the CF_2-synthon approach has blossomed. Reformatsky reaction of halodifluoroacetates[4] and halodifluoroketones is by far the most common of all these approaches.

In our laboratory, we have focused our attention to explore the preparation of this kind of 'flustrate'[5] via Reformatsky-type addition of ethyldifluoroacetate. In this way, we have reported previously the preparation of difluoroderivatives of chiral 1,3-oxazolidines.[6] As continuation of our work in this topic, we have considered the addition reaction of ethyldifluoroacetate to unactivated carbonyl lactones. The preparation of such type of compounds, to our knowledge, has not been previously reported. In contrast, the applications of different metal-promoted Reformatsky reactions using non-fluorinated reagents, with unactivated lactones as well as the sugar lactones, were reported by various authors.[7]

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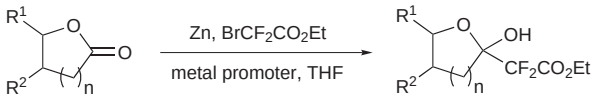
We wanted to report herein a study on the reactivity of a series of unactivated lactones towards the classical Reformatsky reaction and three metal-promoted Reformatsky-type additions of ethyl bromodifluoroacetate under 'one-pot', mild and easy conditions. We have extended this study to the addition of various sugar lactones. These substrates could be an entry to fluorinated CF_2-glycosides that are of considerable interest in carbohydrate chemistry, as well as in organic synthesis, because of the stability of the C-glycosidic linkage toward glycosidases. A study of the stereoselectivity outcome of the reaction when the non-racemic lactones were used as substrates was also reported.

Addition to the Non-Sugar Lactones

Zn(0)-mediated classical Reformatsky[8,9] addition of ethyl bromodifluoroacetate[10] to the simple γ-lactone **1** and dihydrocoumarin (**3**, Scheme 1) occurs giving the addition products in moderate yield (Table 1, entries 1 and 7). In contrast, when the same conditions were used for the addition to the δ-valerolactone (**2**), only degradation of the starting material was observed.

In order to circumvent this problem, we tried modified Reformatsky-type reaction that have been reported in the literature.[11] Indeed, Zn/Cp_2TiCl_2-promoted[12] 'one-pot' addition of ethyl bromodifluoroacetate to lactones **1**–**3** was found to occur under mild conditions at room temperature (Table 1, entries 2, 5 and 8). The number of equivalents of Zn and any additive was optimized in each case, and only selected results are presented (see Table 1).



1: R^1, R^2 = H; n = 1
2: R^1, R^2 = H; n = 2
3: R^1, R^2 = $-C_4H_4-$; n = 2

4: R^1, R^2 = H; n = 1
5: R^1, R^2 = H; n = 2
6: R^1, R^2 = $-C_4H_4-$; n = 2

Scheme 1 Addition of ethyl bromodifluoroacetate on lactone

We also decided to try organocerium derivatives. Indeed, recent years have seen the development of synthetic procedures involving lanthanide metals, especially cerium, in organometallic reactions. One of the most important examples is the conversion of organolithium compounds

Table 1 Reformatsky-Type Reaction between Simple Lactones and Ethyl Bromodifluoroacetate[13]

Entry	Lactone	Reaction conditions[a]	$BrCF_2CO_2Et$ (equiv)	Product	Yield (%)
1	**1**	A	3	**4**	16
2	**1**	B	2	**4**	34
3	**1**	C	1.5	**4**	40
4	**2**	A	3	**5**	–
5	**2**	B	1.1	**5**	60
6	**2**	C	1.5	**5**	40
7	**3**	A	3	**6**	42
8	**3**	B	5	**6**	45
9	**3**	C	1.5	**6**	50

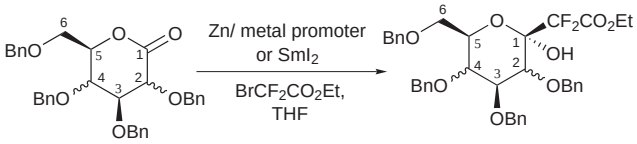
[a] Method A: Zn (7 equiv), THF reflux. Method B: Zn (7 equiv)/Cp_2TiCl_2 (0.05 equiv), THF, r.t.. Method C: Zn (3.5 equiv)/$CeCl_3$ (0.04 equiv), THF, r.t.

to organocerium derivatives by $CeCl_3$. It is well-known that this salt exerts a strong activation of carbonyl compounds toward addition of organometallics,[14] giving in this way higher conversion of addition products.

Inspired by Shen and Qi's use of cerium methodology for the fluoro-Reformatsky reaction,[10b,15] we carried out the addition of ethyl bromodifluoroacetate with the carbonyl derivatives **1**, **2** and **3** in the presence of 0.04 equivalent of $CeCl_3 \cdot 7H_2O$. The addition occurs in all cases but the yields of the expected fluorinated lactols were only slightly improved (Table 1, entries 3, 6 and 9).

Addition to the Sugar Lactones

To attain one of our objectives and continue to explore the reactivity of the lactones towards ethyl bromodifluoroacetate, we decided to extend our studies to sugar lactone derivatives. For this purpose, we have selected three pyranoid aldonolactones **7**, **8** and **9** (Scheme 2).



7: glucono lactone (2*R*,4*R*) **10** (2*R*,4*R*)
8: galacto lactone (2*R*,4*S*) **11** (2*R*,4*S*)
9: mannoso lactone(2*S*,4*R*) **12** (2*S*,4*R*)

Scheme 2 Addition of ethyl bromodifluoroacetate on sugar lactone

When additions were carried out using the 2,3,4,6-tetra-*O*-benzyl-D-glucono-1,5-lactone (**7**) under classical Reformatsky conditions, we observed nearly a quantitative conversion, although compound **10** can only be isolated in 73% yield. Nevertheless, the addition was completely stereoselective giving a single diastereoisomer (Table 2, entry 1). With titanium or cerium reagents at room temperature, the additions to the glucono lactone were also completely stereoselective (Table 2, entries 2 and 3).

Table 2 Reformatsky-Type Reaction between Sugar Lactones and Ethyl Bromodifluoroacetate[13]

Entry	Sugar lactone	Reaction conditions[a]	$BrCF_2CO_2Et$ (equiv)	Product	Yield	dr
1	**7**	A	3	**10**	73	99:1
2	**7**	B	5	**10**	65	99:1
3	**7**	C	1.5	**10**	70	99:1
4	**7**	D	3	**10**	71	98:2
5	**8**	A	3	**11**	72	88:12
6	**8**	B	5	**11**	70	99:1
7	**8**	C	1.5	**11**	65	99:1
8	**8**	D	3	**11**	71	92:8
9	**9**	A	3	**12**	70	99:1
10	**9**	B	5	**12**	72	99:1
11	**9**	C	1.5	**12**	55	95:5
12	**9**	D	3	**12**	71	99:1

[a] Method A: Zn (7 equiv), THF, reflux. Method B: Zn (7 equiv)/Cp_2TiCl_2 (0.05 equiv), THF, r.t. Method C: Zn (3.5 equiv)/$CeCl_3$ (0.04 equiv), THF, r.t. Method D: SmI_2 (8.4 equiv), THF, r.t.

As a new activator, we then decided to try organosamarium intermediates. Indeed, both non-asymmetric and asymmetric versions of SmI_2-mediated Reformatsky-type reaction with aldehydes and ketones have been described.[16] On our substrate **7**, the mild and rapid SmI_2-promoted addition occurred, yielding the fluorinated lactol **10** in 71% yield and with excellent stereoselectivity (Table 2, entry 4).

Systematically, we applied the same four methodologies to the 2,3,4,6-tetra-*O*-benzyl-D-mannoso-1,5-lactone (**8**). In this case, the addition of the bromodifluoro compound required only the presence of Zn(0) to achieve a 72% yield of expected product, but we also observed a slight loss of stereoselectivity, 88:12. When titanium, cerium or samarium were used as reaction promoters, the yields were equivalent, but with better diastereoselectivities (Table 2, entries 6–8).

With the 2,3,4,6-tetra-*O*-benzyl-D-galacto-1,5-lactone (**9**), the addition proceeded with good yield and complete diastereoselectivity when the reaction was performed using Zn(0) alone, or in combination with Ti or Sm promoters (Table 2, entries 9, 10 and 12). However, when cerium promotion was tested with the lactone derived from galactose **9**, both yield and diastereoselectivity slightly decreased (Table 2, entry 11). The assignment of the relative configuration at C-1 of compound **10**, **11**, **12** was carried out by NMR spectroscopy with ^1H–^{19}F HOESY experiments (for example see Figure 1).

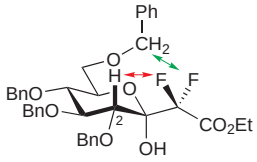


Figure 1 Correlation observed on the 600 MHz ^1H–^{19}F HOESY spectrum of compound **10** recorded with a mixing time of 200 ms at 288 K in $CDCl_3$[17]

We were able to verify that the 1*R* diastereoisomer was obtained in all cases, even the mannose derivative one. As the most stable conformation is the $^4C_1$, placing the C-2, C-3, C-4 and C-5 groups in equatorial positions (confirmed by NMR), the C-1 hydroxyl group of the major diastereoisomers of **10**, **11**, **12** was always axial, probably due to the anomeric effect which stabilizes the axial OH by orbital interaction.[18] Thus, the predominant diastereomer obtained is the more stable stereoisomer according to the calculations. Unfortunately, we could not determine if the mechanism proceeded through a kinetically controlled attack of the organozinc species onto the less hindered face of the lactone, followed by a rapid anomerization leading to the thermodynamically more stable *R* isomer or a thermodynamically controlled attack of the organozinc species.

In conclusion, we have developed Reformatsky-type additions of ethyl bromodifluoroacetate to a series of lactones under mild and experimentally single 'one-pot' conditions. Different reaction conditions were investigated: Zn at THF reflux, Zn with catalytic amount of Cp_2TiCl_2 or $CeCl_3$ at room temperature, and SmI_2 at room temperature. On our substrates, the three last conditions gave good results, with the titanocene-promoted reactions being slightly advantageous. The additions proceeded with medium to good yields and in a completely diastereoselective manner. The major isomers always had the ethyldifluoroacetate group in an equatorial position, irrespective of the starting sugar lactone, even with an axial protected hydroxyl group at C-2 position (compound **12**). The sugar adducts could provide an entry to fluorinated CF_2-glycosides that are of considerable interest in carbohydrate chemistry.

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(13) **Method A.**
To a suspension of zinc[19] (7 equiv, 15.7 mmol) in anhyd THF (31 mL) warmed to reflux temperature were added ethyl bromodifluoroacetate (3 equiv, 6.7 mmol) and the desired lactone (1 equiv, 2.24 mmol) in anhyd THF (31 mL). The reaction was stirred at the same temperature under inert atmosphere during a variable period between 2.30–4 h depending of the substrate. The resulting mixture was then diluted with 1 N aq HCl and stirred for 10 min before extraction with CH_2Cl_2. The extracts were dried over anhyd $MgSO_4$. After removal of the solvent under reduced pressure, the crude mixture thus obtained was subjected to flash silica gel chromatography.
Method B.
To a suspension of zinc (7 equiv, 7 mmol) in anhyd THF (12 mL) was added Cp_2TiCl_2 (0.05 equiv, 0.05 mmol) at r.t. The initial reddish color was turned to easily identifiable green color after 2–3 min, the corresponding lactone (1 equiv, 1 mmol) was then added in anhyd THF (12 mL). Finally ethyl bromodifluoroacetate (5 equiv, 5 mmol) in anhyd THF (6 mL) was added. The reaction was stirred at the same temperature under inert atmosphere for 12 h. The resulting mixture was then diluted with 1 N aq HCl and stirred for 10 min before extraction with CH_2Cl_2. The extracts were dried over anhyd $MgSO_4$. After removal of the solvent under reduced pressure, the crude material thus obtained was subjected to flash silica gel chromatography.
Method C.
To a mixture of (3.5 equiv, 1.33 mmol) of Zn and $CeCl_3$ (0.06 equiv, 0.023 mmol) in anhyd THF (3 mL) was added a solution of the required lactone (1 equiv, 0.38 mmol) in anhyd THF (6 mL) at r.t. Ethyl bromodifluoroacetate (3 equiv, 1.8 mmol) was added. The reaction mixture was stirred at the same temperature under inert atmosphere for 2–3 h. The resulting mixture was then diluted with 1 N aq HCl and stirred for 10 min before extraction with CH_2Cl_2. The extracts were dried over anhyd $MgSO_4$. After removal of the solvent under reduced pressure, the crude material thus obtained was subjected to flash silica gel chromatography.
Method D.
To a solution of the required lactone (0.22 mmol, 1 equiv) in anhyd and degassed THF (20 mL) was added, at r.t. and under argon, ethyl bromodifluoroacetate (0.66 mmol, 3 equiv). At this moment, a 0.037 M solution of SmI_2 (50 mL, 8.40 equiv) was added, at r.t., until the blue color persisted. The reaction was stirred at the same temperature until the blue color disappeared and the mixture turned yellow. The resulting mixture was poured into a solution of $NaHCO_3$ (30 mL) and stirred for 10 min before extraction with CH_2Cl_2. The extracts were dried over anhyd $MgSO_4$. After removal of the solvent under reduced pressure, the crude material thus obtained was subjected to flash silica gel chromatography.

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(17) **Ethyl 2-{(2*R*,3*R*,4*S*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-6-[(benzyloxy)methyl]-tetrahydro-2-hydroxy-2*H*-pyran-2-yl}-2,2-difluoroacetate (10).**
Procedure A: column chromatography (cyclohexane–EtOAc = 25:1) of the crude product gave a colorless syrup (73%); $[\alpha]_D^{20}$ +49.8 (*c* 0.616, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.23–7.17 (m, 18 H), 7.12–7.09 (m, 2 H), 4.80 (s, 1 H), 4.73 (m, 4 H), 4.55–4.37 (m, 3 H), 4.15 (q, 2 H, *J* = 7.17 Hz), 4.10 (m, 1 H), 3.95–3.90 (m, 3 H), 3.68–3.51 (m, 3 H), 1.16 (t, 3 H, *J* = 7.17 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.82 (t, $^2J_{CF}$ = 30.8 Hz), 138.26, 138.16, 137.90, 137.45, 128.29, 127.82, 127.60, 127.52, 112.30 (dd, J_{CF} = 263.6 Hz, J_{CF} = 259.6 Hz), 96.08 (dd, J_{CF} = 28.17 Hz, J_{CF} = 26.4 Hz), 83.28, 78.12, 77.33, 75.88, 75.17, 74.97, 73.31, 72.54, 68.16, 63.21, 13.78. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –119.94 (d, 1 F, J_{FF} = 256.5 Hz), –117.63 (d, 1 F, J_{FF} = 256.5 Hz). MS (EI): 685.3 [M + Na]. Anal. Calcd for $C_{38}H_{40}F_2O_8$: C, 68.87; H, 6.08. Found: C, 68.56; H, 5.79.

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