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C-METALLATED REFORMATSKY INTERMEDIATES. STRUCTURE AND REACTIVITY.

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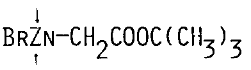
Abstract. - ^{13}C-NMR analysis of the Reformatsky intermediates from t-butyl-α-bromo acetate, t-butyl-α-bromo isobutyrate and t-butyl-α-bromo propionate have evidenced C-metallated species. Their ability to act as nucleophilic reagents under mild conditions and their selectivity towards halogen- and oxygen containing electrophiles is reported.

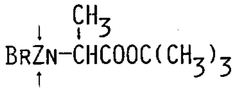
In a previous paper[1] we demonstrated the C-metallated structure of the Reformatsky reagent from t-butyl-α-bromo acetate (1) in solution.
13C-NMR spectroscopy proved to be, by far, the best spectroscopic tool for the elucidation of the nature of the zinc intermediate which "a priori" could be formulated as an analog of the classical Grignard reagent, with a Zn-C bond (C-metallated species) or as the bromo zinc enolate of an ester, with a Zn-O bond (O-metallated species).
Later other authors[2] prepared (1) according to the procedure developed in our laboratory and analyzed it by X-ray diffraction: in the solid state (1) has a dimeric structure with a eight-membered ring held toghether by coordination Zn-O bonds.



$$\overset{\downarrow}{\underset{\uparrow}{\mathrm{BrZn}}}\text{-}CH_2COOC(CH_3)_3 \qquad (1)$$

In this paper we report the extension of the investigation to the Reformatsky intermediates from t-butyl-α-bromo propionate and t-butyl-α-bromo isobutyrate.
From a 2.8 M solution of t-butyl-α-bromo propionate in tetrahydrofurane (in presence of an equimolecolar amount of zinc wool) we obtained in 85% yields a colorless microcrystalline compound which behaves as expected for the Reformatsky intermediate. In fact by treatment with diluted hydrochloric acid in ethereal solution it quantitatively affords t-butyl propionate (gaschromatographically compared with an authentic sample).
t-Butyl-α-bromo isobutyrate, treated as described above, gave no crystalline compounds (only an opalescence occurred at the very beginning of the reaction when the concentration of the intermediate was very high). However removal of the solvent at reduced pressure afforded a foamy colorless compound which almost quantitatively gave t-butyl isobutyrate on acidic treatment.
^{13}C-NMR data for both intermediates (2)

and (3) in different solvents are reported in Table 1 and 2 and deserve some

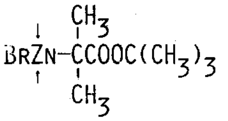


$$\overset{\downarrow}{\underset{\uparrow}{\mathrm{BrZn}}}\mathrm{-}\overset{\overset{\displaystyle \mathrm{CH_3}}{|}}{\mathrm{C}}\mathrm{HCOOC(CH_3)_3} \qquad (2)$$

comments.

In both cases the C-2 chemical shift is slightly upfield shifted in dimethylsulfoxide and pyridine compared with the C-2 chemical shift in t-butyl propionate and t-butyl isobutyrate respectively.

This trend is the same observed for the Reformatsky intermediate from t-butyl-α-bromo acetate (1), as pointed out in Table 3: the differences between chemical shifts in δ(ppm) for the zinc in



$$\overset{\downarrow}{\underset{\uparrow}{\mathrm{BrZn}}}\mathrm{-}\overset{\overset{\displaystyle \mathrm{CH_3}}{|}}{\underset{\underset{\displaystyle \mathrm{CH_3}}{|}}{\mathrm{C}}}\mathrm{COOC(CH_3)_3} \qquad (3)$$

termediates (1), (2) and (3) respect to t-butyl acetate, t-butyl propionate and t-butyl isobutyrate are reported. The spectroscopic data are therefore in agreement with the presence of a zinc-carbon bond, that is with a C-metallated species either for (2) or for (3). The organometallic nature of (2) is once more confirmed by the values

TABLE 1 ^{13}C-NMR data for $CH_3\underset{\mid}{C}HCOOC(CH_3)_3$ ZnBr

		C_1	C_2	C_3	C_4	C_5	J_{C-H}
$\overset{3}{C}H_3\overset{2}{C}H_2\overset{1}{C}OO\overset{4}{C}(\overset{5}{C}H_3)_3$	DMSO	172.9	28.6	9.3	79.3	28.1	
	Py	173.1	28.8	9.3	79.4	28.1	
	THF	174.1	29.2	9.6	80.5	28.4	
$CH_3\underset{\mid}{C}HCOOC(CH_3)_3$ ZnBr	DMSO	180.1	27.0	13.4	75.5	28.8	125
	Py	181.2	26.3	14.4	75.9	28.5	125
	THF	187.4	33.3	12.8	81.8	29.1	128

The values of the chemical shifts are given in ppm (δ) with TMS as internal standard. The ^{13}C-NMR spectra were determined on a Brucker CXP-300; spectral width 20.000 Hz; acquisition time 0.8192 sec.; pulse width 15 μs(45°)

TABLE 2 - ^{13}C-NMR data for $(CH_3)_2\underset{\mid}{C}COOC(CH_3)_3$ ZnBr

		C_1	C_2	C_3	C_4	C_5
$(\overset{3}{C}H_3)_2\overset{2}{C}H\overset{1}{C}OO\overset{4}{C}(\overset{5}{C}H_3)_3$	DMSO	176.1	34.1	18.7	78.7	27.6
	Py	175.8	34.9	19.1	79.2	28.0
	THF	175.9	35.3	19.3	79.5	28.2
$(CH_3)_2\underset{\mid}{C}COOC(CH_3)_3$ ZnBr	DMSO	180.6	33.6	23.5	75.7	29.1
	Py	181.9	32.9	24.0	76.2	28.3
	THF	185.8	38.2	22.8	80.7	29.0

The values of the chemical shifts are given in ppm (δ) with TMS as internal standard. The ^{13}C-NMR spectra were determined on a Brucker CXP-300; spectral width 20.000 Hz; acquisition time 0.8192 sec.; pulse width 15μs(45°)

TABLE 3.

	C_1	C_2	C_4	C_5
DMSO				
$\underset{ZnBr}{\overset{2}{C}H_2}\overset{1}{C}OO\overset{4}{C}(\overset{5}{CH_3})_3$	+7.9	-1.4	-3.9	+1.5
$\overset{2}{CH_3}\underset{ZnBr}{\overset{1}{C}H}COO\overset{4}{C}(\overset{5}{CH_3})_3$	+7.2	-1.6	-3.8	+0.7
$\overset{2}{(CH_3)_2}\underset{ZnBr}{\overset{1}{C}}COO\overset{4}{C}(\overset{5}{CH_3})_3$	+4.5	-0.5	-3.0	+1.5
PY				
$\underset{ZnBr}{CH_2}COOC(CH_3)_3$	+10.0	-1.8	-2.8	+1.0
$CH_3\underset{ZnBr}{CH}COOC(CH_3)_3$	+8.1	-2.5	-3.5	+0.4
$(CH_3)_2\underset{ZnBr}{C}COOC(CH_3)_3$	+6.1	-2.0	-3.0	+0.3
THF				
$\underset{ZnBr}{CH_2}COOC(CH_3)_3$	+17.4	+1.4	+0.8	+0.2
$CH_3\underset{ZnBr}{CH}COOC(CH_3)_3$	+13.3	+4.1	+1.3	+0.7
$(CH_3)_2\underset{ZnBr}{C}COOC(CH_3)_3$	+9.9	+2.9	+1.2	+0.8

The differences between the chemical shifts in ppm (δ) for the zinc intermediates 1,2 and 3 respect to t-butylacetate, t-butylpropionate and t-butylisobutyrate are reported.

of the coupling constant J_{C-H}, characteristic of a sp^3 hybridized carbon[1,3]. The stability as well as the solubility of the intermediates decreases in the order (1), (2) and (3). While (1) is still present mostly unchanged in the solvents used after few days, (2) and (3) are stable in tetrahydrofurane for few hours and in pyridine and dimethylsulfoxide for about ten, fifteen minutes. After this time, both in pyridine and dimethylsulfoxide an abundant precipitate of $(CH_3)_3COZnBr$ occurs[1,4]: in solution a mixture of several unidentified products remains.

Most likely the solubility as well as the stability of (1), (2) and (3) depends on the possibility, in solution, of a stable dimeric structure as the one verified for (1) in the solid state. Substitution of one or both hydrogen atoms at C-2 in (1) with methyl groups (intermediates (2) and (3)) results in an increased steric hyndrance which destabilizes the eight-membered ring of the dimer, loosening the highly stabilizing Zn-O coordination bonds.

When the solvent is a strongly coordinating one as pyridine or dimethylsulfoxide an external destabilizing factor joins in definitively breaking the Zn-O coordination bonds with rapid destruction of the dimer.

The decreased stability of the dimeric structure is also reflected by the chemical shift of the carbonyl carbon.

To this purpose two observations are worth. Firstly, in all the solvents tested, as already observed for (1), the carbonyl carbon resonates downfield respect to the corresponding carbon atom in t-butyl propionate and t-butyl isobutyrate, indicating that the carboxylic group is involved in the coordination to the zinc atom: this downfield effect is always maximum in tetrahydrofurane. However the magnitude of the shift decreases, in all the solvents, with increasing substitution at the α carbon.

We can therefore relate the magnitude of the downfield shift of the carbonyl carbon to the degree of association of the zinc atom with the carboxylic group.

The organometallic nature of (1), (2) and (3) has found further evidence in their reactivity. The ability of (1) to act as nucleophilic reagent has been reported in hexamethylphosphoric triamide towards several halogen-containing electrophiles as allylic bromides, α-bromoesters, γ-bromo-α,β-unsaturated esters.[5]

(2) and (3) react smoothly in tetrahydrofurane solution with allyl iodide, while are inert towards epoxides: their reactivity, in tetrahydrofurane solution, therefore parallels the reactivity of (1) in hexamethylphosphoric triamide.

To attain a complete analysis of the reactivity of (1), (2) and (3) as nucleophilic reagents and to settle their selectivity, we have extended our investigation to other halogen- and oxygen-containing electrophiles.

For more convenience we have choosen (1) as model compound.

The results are reported in the Tables 4 and 5 and deserve some comments.

As far as the examples reported are concerned, there is a striking differences in the behaviour of a bromo- and the corresponding chloro compound.

In fact whereas benzyl bromide and allyl bromide react smoothly with (1) to afford the expected coupling products in high yields (90 and 75 % respectively), benzyl chloride gives t-butyl hydrocinnamate in only 38 % yields.

Displacement of the chlorine atom from allyl chloride and 3-chloro-1-butene is slower and proceeds in lower yields different reaction temperature (from room temperature to 40-50° C), reaction times (from 24 hours up to three days) and (1)/ chlorocompound ratio (from 1.0 to 4.0 molar equivalents) were tested without appreciable results.

Using 3-chloro-1-butene the only isolated product (15%) arises from a SN_2' displacement.

Also benzhydryl chloride failed to react and it was recovered in 88% yields after prolonged reaction times (three days).

Attempts to increase the nucleophilicity of (1) by adding N,N,N',N'-tetramethylethylenediamine in various amounts (from 1/1 up to 4/1 respect to (1)) to the reaction medium was unsuccessful.

Allylic and benzylic chlorides, however, react smootly with (1) previous in situ conversion to the corresponding iodides.

The facility of allyl iodides to react with (1) prompted us to test alkyl iodides.*

To this purpose methyl-, ethyl-, pen

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*Alkylbromides fail to react with (1)[1].

TABLE 4. $BrZnCH_2COOC(CH_3)_3$ + Electrophiles

	Electrophile	Products	Yields(%)[a]
1.	Benzyl chloride	t-Butyl hydrocinnamate[b]	38[c] 90[d]
2.	Allyl chloride	t-Butylpent-4-enoate[b]	15-18[c,e] 75[d]
3.	3-Chlorobut-1-ene	t-Butylhex-4-enoate[b,f]	15[c] 70[d]
4.	Benzydryl chloride	no products[g]	
5.	(Chloromethyl)-cyclopropane	t-Butyl-3-(cyclopropyl)-propanoate	traces[c] 29[d,h]

a. Yields of isolated and bulb-to-bulb distilled products.

b. F.Orsini, F.Pelizzoni, *Synthetic Commun.*, in press.

c. Reactions performed in absence of KI.

d. Reactions performed in presence of KI(NaI).

e. Yields reported for reactions performed at 25°C, with a (1)/Electrophile molar ratio from 1.2/1 to 4/1 for 24-72 hours. Performing the reactions at 50°C for 3 hours with 2 molar excess of (1), the yields rose to about 30%(gaschromatographically determined).

f. E/Z mixture

g. Starting benzydryl chloride was recovered in 88% yields.

h. 38% of starting (chloromethyl)cyclopropane and 15% of(iodomethyl)cyclopropane were recovered.

TABLE 5. $BrZnCH_2COOC(CH_3)_3$ + Iodoalkanes

	Iodoalkane	Products	Yields(%)[a]	Time(hours)
1.	Iodomethane	t-Butylpropanoate[b]	75	2
2.	Iodoethane	t-Butylbutanoate	55	15
3.	Iodopentane	t-Butylheptanoate[c]	45	24
4.	Iodododecane	t-Butyldodecanoate[d]	39	48
5.	Cyclohexyliodide	no reactions[e]		

a. Yields of isolated and bulb-to-bulb distilled products.

b. F.Orsini, G.Ricca, *Org. Magnetic Resonance*, in press.

c. 43% of iodopentane was recovered.

d. 40% of iodododecane was recovered.

e. 95% of starting cyclohexyl iodide was recovered.

tyl- and decyl iodides were reacted with (1) and gave the expected substitution products with yields depending on the lengh of the alkylic chain (Table 5).

These results indicates that selective substitution of alkyl iodides in presence of alkyl bromides and of activated bromides in presence of activated chlorides can be achieved.

Furthermore, it is also possible to differentiate activated chlorides (allyl-, benzyl-) from acetates and epoxides as these compounds are inert to (1) even in the presence of KI.

In conclusion, the Reformatsky reagents (1), (2) and (3) are real organometallic species which act as selective nucleophilic reagents and allow a simple and mild procedure for two-carbons homologation.

EXPERIMENTAL

Materials. - HMPT (from Fluka) was distilled from CaH_2 under nitrogen and at reduced pressure (112° C at 20 mmHg) and kept over conditioned 13 X molecular sieves (4 hours at 0.3 mmHg and at 250 °C). THF (RPE from C. Erba) was passed through a Al_2O_3 column, refluxed for two days over KOH pellets and distilled. It was then refluxed for few hours over $LiAlH_4$ and distilled immediately before use.

Allyl and benzyl chloride, 3-chloro-1-butene, (chloromethyl)cyclopropane, benzydryl chloride were supplied by Aldrich and distilled before use. Alkyl iodides were obtained from Fluka and directly used. Zinc wool was activated as described in the literature.[5]

All b.p. are uncorrected. IR refer to films (if not otherwise stated) and were determined on a Perkin Elmer 681 spectrometer. Mass spectra were recorded on a Varian Mat 112 spectrometer. ^{1}H-NMR spectra were recorded in $CDCl_3$ at 60 MHZ on a Hitachi-Perkin Elmer R 24 or at 80 MHZ on a Brucker WP 80 spectrometer. Chemical shifts are expressed in δ (ppm) relative to TMS as internal standart and coupling constant are expressed in Hz. GCL analysis were performed on a Carlo Erba Fractovap 2350 using a 3% OV 1 column.

Preparation of the Reformatsky reagents. To 0.335 g (5 mmols) of zinc wool about 0.2 mL of pure t-butyl-α-bromoacetate were added under vigorous stirring and in a nitrogen atmosphere. The remaining bromo acetate was diluted with 1.8 mL of dry THF and added dropwise. The addition was carefully controlled in order to mantain the temperature at about 25-30° C. At the end of the addition a colorless precipitate occurred which was filtered under nitrogen and washed twice with 0.4 mL of dry THF. Removal of the residual solvent under high vacuum afforded (2),coordinated with one mole of THF, in 85 % yields.

When t-butyl-α-bromo isobutyrate was used, after total consumption of the zinc wool, the solvent was removed under vacuum and the foamy colorless residue was directly used.

Typical procedure for substitution reactions in THF.

1.3 g (3.78 mmols) of (2) were suspended in 4 mL of dry THF and additioned of 0.3 mL of allyl iodide. The reaction mixture was stirred for half an hour at 50°C and then overnight at room temperature. It was then diluted with ether, treated with diluted (1/4) hydrochloric acid and extracted three times with ether. The combined organic extracts were washed with water, dried and the solvent removed at atmospheric pressure. The residue was bulb-to-bulb distilled to afford t-butyl-2-methyl-pent-4-enoate in 66 % yields.

Typical procedure for substitution reactions in HMPT.

a) in absence of KI (NaI). - 3.5 mmols of benzyl chloride were added to a stirred solution of (1) (5 mmols) in dry HMPT (4 mL). Stirring was continued for 15 hours, then the reaction mixture was diluted with ether and filtered. The filtrate was treated with diluted hydrochloric acid and worked up as described above. The residue was bulb-to-bulb distilled and afforded t-butyl hydrocinnamate in 38% yields.

b) in presence of KI (NaI). - 3.3 mmols of benzyl chloride were added to a suspension of KI (0.55 g, 3.3 mmols) in dry HMPT (1 mL). The mixture was vigorously stirred for fifteen minutes at 30-35° C. 5 mmols of (1) were added and the stirring continued for 6 hours. The reaction mixture was then diluted with ether and worked up as described in a.

t-Butyl-3-(cyclopropyl)-propanoate. - bp=78-81°C (20 mmHg); IR (CHCl$_3$) $\lambda_{max.}$ 1720 cm^{-1}; ^{1}H-NMR 2.25 (2H,m), 1.50 (2H, m), 1.45 (9H, s), 0.65 (1H, m), 0.45 (2H, m), 0.1 (2H, m); ^{13}C-NMR 172.5 (s), 79.5 (s), 35.6 (t), 30.3 (t), 28.1 (q), 10.5 (d), 4.43 (t), 4.42 (t); Ms m/z: 155 (M$^+$-CH$_3$).

t-Butyl butanoate. - bp=114-115°C ; IR $\lambda_{max.}$ 1730 cm^{-1}; ^{1}H-NMR 2.20 (2H, t, J=7), 1.60 (2H, tq, J=7), 1.45 (9H, s), 0.92 (3H, t, J=7); MS m/z: 144 (M$^+$).

t-Butyl eptanoate. - bp=110-113°C (35 mmHg); IR $\lambda_{max.}$ 1730 cm^{-1}; ^{1}H-NMR 2.15 (2H, m), 1.40 (9H, s), 1.5-1.15 (8H), 0.95 (3H, t, J=7); MS m/z: 186 (M$^+$).

t-Butyl dodecanoate. - bp=110-114° C (0.3 mmHg);IR $\lambda_{max.}$ 1730 cm^{-1}; ^{1}H-NMR 2.10 (2H, m), 1.45 (9H, s), 1.5-1.1 (18H), 0.9 (3H, t, J=7); MS m/z: 200 $\left[M^+- CH_2{=}C(CH_3)_2\right]$.

t-Butyl-2-methyl-pent-4-enoate. - bp=62-65° C (20 mmHg); IR $\lambda_{max.}$ 1720, 1640 cm^{-1}; ^{1}H-NMR 5.75 (1H, m), 5.12 (1H, d, J=16), 5.08 (1H, d, J=10), 2.5-2.2 (3H), 1.39 (9H, s), 1.10 (3H, d, J=7); MS m/z: 155 (M$^+$- CH$_3$).

t-butyl-2,2-dimethyl-pent-4enoate. - bp=92-95° C (20 mmHg); IR $\lambda_{max.}$ 1720, 1640 cm^{-1}; ^{1}H-NMR 5.65 (1H, m), 5.10 (1H, d, J=16), 5.05 (1H, d, J=10), 2.14 (2H, d, J=7.5), 1.35 (9H, s), 1.05 (6H, s); MS m/z: 184 (M$^+$).

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