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REFORMATSKY INTERMEDIATE. A C-METALLATED SPECIES.

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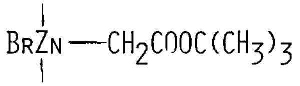
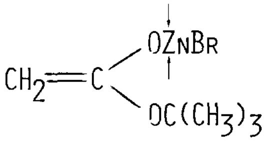
Abstract ^{13}C-NMR and ^{1}H-NMR spectra of the Reformatsky reagent from t-butylbromoacetate, evidence a C-metallated species: within the limits of detectability of the methods, no O-metallated species can be detected in solution.

The reaction between an α-haloester, zinc metal and carbonyl compounds was formulated by Reformatsky in 1887 and its utility in carbon-carbon bond formation is widely recognised as a powerful synthetic tool for organic chemists. In spite of it the mechanism of this fundamental reaction still remain unclear. Even more unsettled is the question of the nature of the zinc intermediate which may be formulated as an analog of the classical Grignard reagent, with a zinc-carbon bond (I) or as the bromozinc enolate of an ester, with a zinc-oxygen bond (II).

I



$BrZn-CH_2COOC(CH_3)_3$



II

The huge amount of papers published on this subject are mostly dealing with the structure and stereochemistry[1] of the reaction products and would support an enolate anion. On the other hand only few Authors[2] reported the infrared and ^{1}H-NMR data for some Reformatsky reagent as a direct proof of their structure: these results, more supporting a C-metallated form, are, however, contradictory and misleading.

Up to now it is only known for certain that the solvent systhem may be of great importance in realizing a good yield of the Reformatsky reagent and in determining the real structure of the intermediate itself.

To obtain definitive evidence on the structure of the intermediate it is necessary to isolate a real, pure Reformatsky intermediate, uncontaminated by any side products. Previous experiments had shown that using ethyl bromoacetate and ethyl-methyl-, t-butyl-α-bromopropionate, in several solvents and at different temperature, results in very rapid production of "condensed ester" and, in smaller amount, in its bromoderivative[3]. In fact with methyl-α-bromopropionate in benzene at 40°C, after acidic hydrolysis, we obtained methyl propionyl propanoate as main product [detected by GC-MS analysis (10% Carbowax C 20 M; column temperature=60-80°C; injector temperature=150°C; carrier gas pressure=1 5 Kg/cm^2) m/z 144 (M^+), 115,113, 112, 88, 57, 56] , a small amount of methyl propanoate (gas chromatographically identical with an authentic sample) and traces of γ-bromopropionyl propanoate m/z 143 (M^+-Br), 142,115,114,88,57,56). Raising the tem perature of the reaction (refluxing benzene) or changing the solvent from benzene to benzene-ether 1:1 or ether did not improve significantly the results as well as using ethyl-α-bromopropionate in benzene or t-butyl-α-bromopropionate in THF at room temperature.

Also with ethyl bromoacetate in THF we were not able to isolate the Reformatsky intermediate which was contaminated by ethyl acetoacetate (gaschromatographycally identified by comparison with an authentic sample). The presence of these side products infirms the assignments in the ^{13}C- and ^{1}H-NMR spectra.

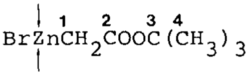
We were indeed successful with t-butylbromoacetate: from a 2 M solution of t-butylbromoacetate in tetrahydrofurane (in presence of an equimolecolar amount of zinc wool) we have obtained (in 80 % yield) a colorless microcrystalline product which can be decanted, washed and dried. It behaves as expected for the so called Reformatsky t-butyl reagent: by work up with diluted hydrochloric acid it affords quantitatively t-butylacetate (identical in all respects with an authentic sample) and on treatment with benzaldeyde gives t-butyl,3-hydroxy,3-phenylpropionate exclusively (bp=98-100° C at 0.05 mm; ^{1}H-NMR ($CDCl_3$)δ 7.39 (bs, 5H), 5.1 (t,1H,J=7Hz), 4.03 (bs,1H, disappears with D_2O), 2.66 (d,2H,J=7Hz), 1.45 (s,9H); MS m/z 222 (M^+),166,165,149,147,107,106,105. Anal.:calcd. ($C_{13}H_{18}O_3$) C,H: 70.27,8 11; found C,H: 70.31, 8.19

As the first goal we aimed at the elucidation of the structure of the reagent (I or II) as a function of the solvent: this has been successfully achieved with ^{13}C-NMR and ^{1}H-NMR spectroscopies.

Structural elucidation of the reagent is more interesting in solution than in the solid state as the Reformatsky reaction is, as a matter of fact, carried out in solution. To this purpose we have examinated solvents of different basicity as HMPT, DMSO, Py and THF.[4]

Spectroscopic data are collected in Table I and II and deserve some comments.

TABLE I - ^{13}C-NMR DATA

		C_1	C_2	C_3	C_4	J_{C-H}
$\overset{1}{C}H_3\overset{2}{C}OO\overset{3}{C}(\overset{4}{C}H_3)_3$	DMSO	22.2	169.5	79.4	27.1	128.8
	Py	22.2	169.5	79.5	28.1	128.8
	HMPT	23.1	170.2	80.4	28.9	
	THF	21.3	168.8	79.6	27.4	128.8
 $BrZn\overset{1}{C}H_2\overset{2}{C}OO\overset{3}{C}(\overset{4}{C}H_3)_3$	DMSO	20 8	177.4	75.5	28.6	128.6
	Py	20.4	179.5	76.7	29.1	130.0
	HMPT	22 1	179.0	75.2	29.8	
	THF	22.7	186.2	80.4	27.6	132.0

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 XL 100 Varian spectrometer (25.18 MHz):spectral width 6000 Hz, acquisition 0.6 sec., pulse delay 0.5 sec.; 45° pulse width.

From the little upfield shift observed (δ=-1 to -1.8 ppm) for the C-1 carbon in DMSO, Py, HMPT and the little downfield shift in THF compared with the chemical shift of the same carbon in t-butylacetate, it emerges that there is no significant change in the electron distribution replacing a carbon-hydrogen bond by a zinc-carbon bond in a sp^3 hybridization[5].

Concerning a possible zinc enolate, the C-1 carbon, in passing from a sp^3 to sp^2 hybridization, should resonate in the range observed for the scarcely electropositive-metal enolates as, for instance, magnesium enolates[6], that is in the range 80-110 ppm. The signals observed at 75-81 ppm are singlets: they can not be therefore mistaken for the sp^2 carbon of an enolate form and are unequivocally attributed to the quaternary carbon of the ester moiety.

In all spectra we also observed the presence of the carbonyl carbon, downfield respect to t-butylacetate.

The ^{1}H-NMR spectra in DMSO, Py and THF complete the ^{13}C-NMR results. In no cases vinylic protons can be detected.

TABLE II - ^{1}H-NMR DATA

$\overset{1}{C}H_3\overset{2}{C}OO\overset{3}{C}(\overset{4}{C}H_3)_3$	DMSO	1.84(s,3H)	1.36(s,9H)
	Py	1.93(s,3H)	1.43(s,9H)
	THF	1.85(s,3H)	1.40(s,9H)
$Br\underset{\vert}{\overset{\vert}{Zn}}\overset{1}{C}H_2\overset{2}{C}OO\overset{3}{C}(\overset{4}{C}H_3)_3$	DMSO	1.04(s,2H)	1.30(s,9H)
	Py	2.00(s,2H)	1.46(s,9H)
	THF	1.88(s,2H)	1.40(s,9H)

The value of the chemical shift are given in ppm (δ) with TMS as internal standard.

In all three solvents a two-proton singlet due to $-ZnCH_2-$ is observed. at 1.04 in DMSO, at 2.00 δ in Py and at 1.88 δ in THF. The assignments were confirmed by single frequency decoupling experiments.

By irradiation of the signal at 1.04 in the proton spectrum in DMSO, the methylene resonance at δ_C 20.8 collapses to a singlet.

In a similar manner the resonances at δ_H 2.00 and at δ_C 20.4 in Py were correlated and the resonances at δ_H 1.88 and at δ_C 22.7 in THF.

That we are dealing with a real organometallic species (I) is once more confirmed by the invariance of the coupling constant J_{C-H}, characteristic of a sp^3 hybridized carbon[7].

In addition the ^{13}C-NMR and ^{1}H-NMR data let us do some preliminary observations on the zinc coordinating sites.

In all solvents the carbonyl carbon resonates in the range -10 to -20 ppm downfield in the comparison with the corresponding carbon atom in the related t-butylacetate. These results indicate that the carboxylic group is involved in the coordination to the zinc atom, decreasing the electron density on the carbonyl carbon. When the solvent is the less coordinating THF, the interaction of the carboxylic group with the zinc atom is quite important and causes the highest downfield effect (-20 ppm).

Infrared spectra are also in agreement with the above mentioned results. In THF the intermediate shows a strong absorption at 1580 cm^{-1}, while in DMSO it shifts to 1660 cm^{-1}.

A more detailed investigation on zinc coordination is in progress, using ^{17}O NMR with particular tecniques.

From Tables I and II it is also clear that the coordination of the carboxylic group with the zinc atom influence as well the C-1 chemical shift and coupling constant.

Concerning the stability of the intermediate, it is still present mostly unchanged in the solvents used even after 4 - 6 days, unlike starting t-butylbromoacetate which in Py immediately gives a pyridinium salt as indicated from the chemical shift of the $-CH_2Br$ which resonates at 61 7 δ (in THF and DMSO the same carbon resonates at 26.7 and 28.3 δ respectively).A slow nydrolysis to t-butylacetate and a gradual elimination of zinc t-butoxybromide was, however, observed· the latter verified by addition of t-butyl alcohol to the Reformatsky intermediate itself

In conclusion, ^{13}C-NMR spectra of the Reformatsky reagent from t-butylbromoacetate, supported by infrared and ^{1}H-NMR data, do indicate unambigously the absence of any O-metallated species in solution, within the limits of detectability of the methods.

References and Notes.

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(4) Relatively high concentrations (0 8-1.4 M) of the reagent in DMSO, Py, HMPT were used in order to obtain satisfactory natural abundance ^{13}C-NMR spectra in a reasonable period of time.Due to the less solubility of the reagent in THF (about 0.4 M at room temperature) spectra in THF were run at 54° C. The Reformatsky intermediate was always prepared in THF solution, isolated and dissolved in the selected solvent to avoid possible side reactions due to the interaction of the starting t-butylbromoacetate with the solvent.

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(8) To this purpose, ^{13}C-NMR spectra were recorded every 24 hours.

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