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ULTRASOUND IN ORGANIC SYNTHESES. 19. FURTHER STUDIES ON THE CONJUGATE ADDITIONS TO ELECTRON DEFICIENT OLEFINS IN AQUEOUS MEDIA.

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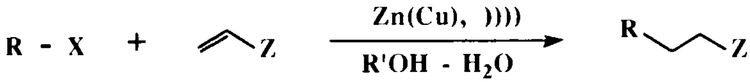
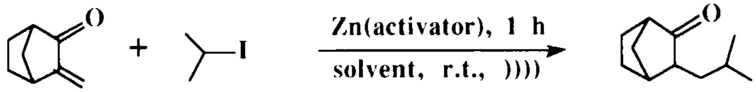
Abstract: Alkyl halides add smoothly to a variety of olefinic bonds conjugated with electron withdrawing groups, in the presence of zinc-copper couple. Sonication enhances the efficiency of the process, which takes place in aqueous media following, most probably, a radical pathway.

In previous papers we reported the possibility to effect organometallic-like reactions in the quite unusual mixture of water and an organic co-solvent, tetrahydrofuran[1] or alcohols.[2] In particular the conjugate additions, can be effected with great ease by using a zinc-copper couple under sonochemical conditions.[2-4]

This intriguing and unexpected reaction deserved further studies, some of which are reported in this paper.



Scheme 1



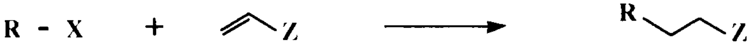
1 2 3

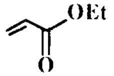
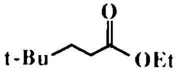
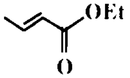
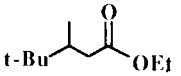
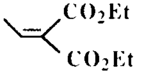
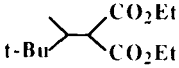
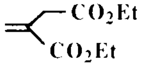
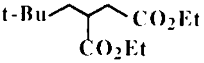
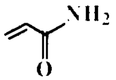
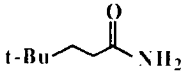
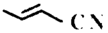
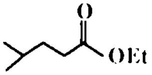
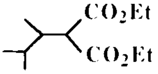
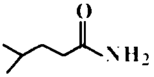
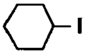
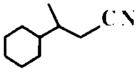
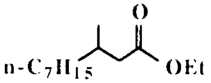
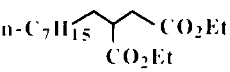
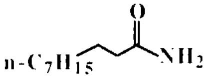
Scheme 2

The first point of interest is connected to the zinc activation. Addition shown in Scheme 2 was studied with the purpose of comparing the efficiency of several activators.

With zinc powder in ethanol-water (9:1), no reaction occurs. While the presence of sodium chloride was inefficient, addition to the mixture of 2 molar equivalents of an ammonium salt (NH_4Cl, HCO_2NH_4, n-propylamine or dimethylamine hydrochlorides) is sufficient to activate the metal, and compound 3 is produced in 50-100% yield. However, extensions to other substrates proved to be problematical and the zinc-copper couple,[5] prepared by adding to the mixture 1 molar equivalent of cuprous iodide, was chosen for the rest of the study.[6] The possibility for metallic copper to be the actual reagent was excluded : in the presence of 2 equivalents of copper iodide with respect to zinc, the resulting dark red suspension proved to be unreactive versus any alkyl iodide. The last hypothesis, that of a copper hydride, could be discarded by X ray examination of the black material,[7] and by the lack of success of the reaction attempted in the presence of copper hydride triphenylphosphine hexamer.[8]

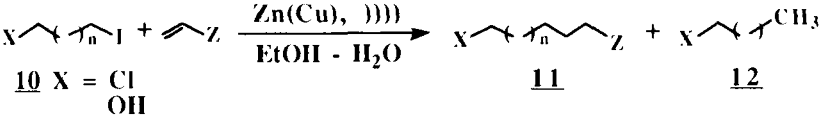
Table 1

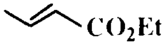
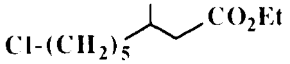
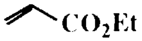
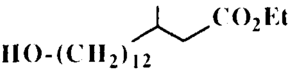
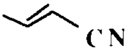
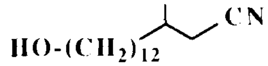


Halide	Olefin	Adduct	(%)[a]
t-BuBr	 4		88
	 5		95
	 6		73
	 7		73
	 8		66
	 9		75
i-C_3H_7I	4		70
	6		63
	8		70
	9		63
n-C_7H_{15}-I	5		74
	7		60
	8		41
	9		61

[a] Isolated yields of purified material

Table 2

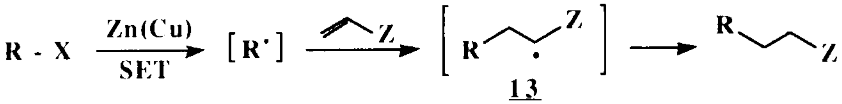


Halide	Olefin	Adduct (%)[a]
$I-(CH_2)_5-Cl$		 (69)
$I-(CH_2)_{10}-Cl$		$Cl-(CH_2)_{12}-CO_2Et$ (50)
$I-(CH_2)_{12}-OH$		 (41)
		 (28)

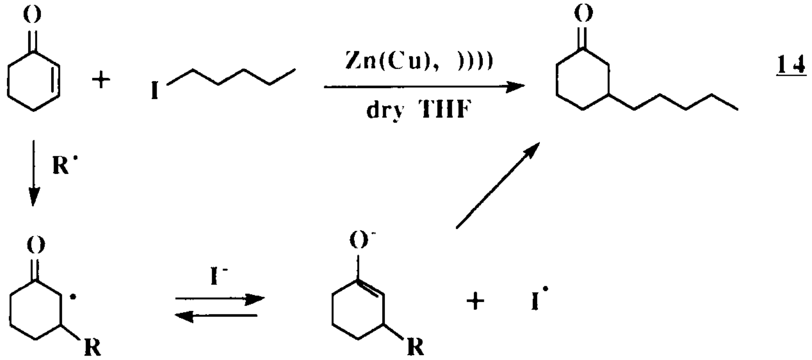
[a] Isolated yields of purified material

The second point which needed clarification was the domain of application of the method. In the first papers, the cases of α-enals and enones were described.[2] Extensions to α,β-unsaturated esters, amides and nitriles proved to be possible and gave synthetically useful yields (Table 1). From secondary and tertiary halides, satisfactory yields can be obtained with a moderate excess (2 equiv.) of the reagent. The case of primary iodides is more difficult due to the competition with the reduction to the hydrocarbon. The use of 2-propanol:water (7:3) as the solvent,[2] an excess of one of the reagents and its slow addition to the reaction mixture raise the yields to a satisfactory level. It is interesting to compare our results with the recently reported addition of an iodide to acrylonitrile (Bu_3SnH, AIBN) in 36 % yield.[9]

It proved to be of interest to perform the reaction with alkyl iodides substituted by free hydroxyl groups or less reactive halogens such as chlorine. In most cases (Table 2), the results are satisfactory.



Scheme 3

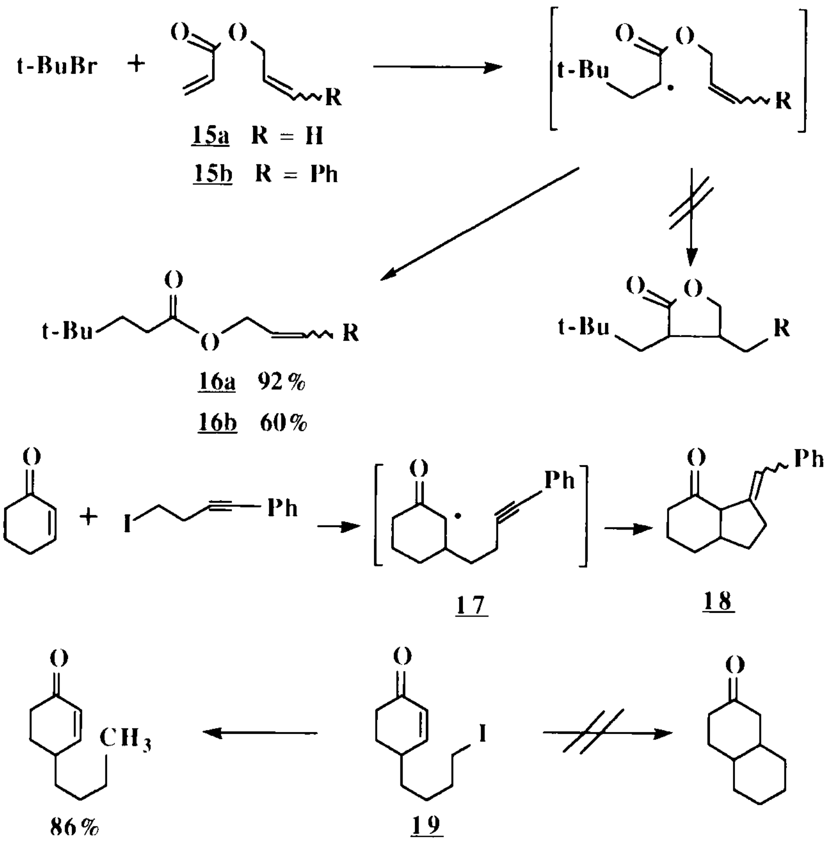


Scheme 4

Attempts to improve the yields in these particular cases met with little success, but the simplicity and ease of purification constitute important advantages even in the less favourable examples.

From the presence of a reductive process leading to compounds 12 and the reactivity sequences of the halides (3 ary > 2 ary > 1 ary and iodides > bromides >> chlorides) a strong indication of a radical pathway is obtained. Several attempts have been made to obtain evidence for the intermediate species 13 (Scheme 3).

Because of the presence of an excess of metallic zinc, the possibility of a reduction of 13 to an enolate (Z = COR') can be envisaged, rather than the direct hydrogen abstraction from the medium. However the intervention of the iodide ion, previously invoked by Russell,[10] can also account for a rapid transformation of 13 to the corresponding anion.



Scheme 5

Some experiments give substance to this interpretation (Scheme 4). With a low concentration of iodide ion,[11] the yield of 14 is only 12%, while it reaches 53% by addition of 1 equiv NaI.

Intramolecular trapping of 13 remained unconclusive as the conjugate addition of the t-butyl radical to allylic acrylates 15a or 15b gave exclusively the open chain adducts 16. On the other hand, radical 17 cyclised to 18 although in low yield (10%). The intramolecular addition expected from compound 19 failed to give any cyclised compound (Scheme 5).

As a conclusion, this study reveals several general features. Activation of zinc metal is effected generally by formation of the couple with copper. However, even if not yet conclusive, several possibilities have appeared with the activation with ammonium salts. The scope of the ultrasound promoted conjugate addition in aqueous media is extended satisfactorily to various electron deficient olefins. Several arguments favor a radical pathway, and the process described here has some similarities with the recently developped free radical methods (using tin, boron, mercury derivatives, ...).[9] Thus important differences exists as the trapping of the "second generation" radical, widely used in the case of the tin hydride method, virtually does not exist in our case. New selectivities can then be expected, and will be discussed in a next future.

Experimental

The compounds described have been purified by crystallisation or column chromatography and identified by the usual physical methods. Spectral and analytical data correspond to the proposed structures. Sonications were effected in a round bottom pyrex flask immersed in an ultrasound laboratory cleaner (Kerry Pulsatron 55 or 250, 38 kHz) filled with water thermostated to 15-18 °C by circulation of tap water in a stainless steal coil. The zinc-copper couple is prepared by sonication under argon of 500 mg (8 mmol) of zinc dust (-325 mesh, Aldrich) with 356 mg (2.4 mmol) of copper iodide in 2 mL of water. The initially grey mixture turns to a black heavy suspension in less than 3 min.

Typical procedure for secondary or tertiary halides

To the couple prepared as above there were added under sonication 2 mL of ethanol followed by 71mg (1.0 mmol) of acrylamide and 274 mg (2.0 mmol) of 2-bromo-2-methylpropane in 1 mL of ethanol over a 30 min. period. After completion of the addition, sonication was continued for 1 hr, then sat. aq. NaCl was added, and the mixture was filtered over Celite. The solid was washed with ether, and the filtrate extracted with the same solvent. The combined ethereal solutions were washed (aq. NaCl) dried ($MgSO_4$) and the solvent evaporated. The residue was recrystallised from pentane-methylene chloride to afford 81mg of 4,4-dimethyl-pentanamide. M.P. 134-135°C. IR (Nujol): 3300, 1660 cm^{-1}. NMR $(CDCl_3)^1H$: 5.8-5.6 (m, 2H), 2.20 (m, 2H), 1.55 (m, 2H), 0.91 (s, 9H) ppm. NMR $(CDCl_3)^{13}C$: 176.4, 39.2, 31.5, 29.6, 29.0 ppm.

Typical procedure for a primary iodide

In the same manner as above, 1140 mg (10 mmol) of ethyl acrylate and 316 mg (1 mmol) of 12-iodododecanol in 1 mL of 2-propanol was added slowly during 1hr. The sonication was continued for 2 hr after the addition. The usual work-up gives an oil which was purified by column chromatography (Silicagel, hexane-AcOEt). 123 mg (41%) of ethyl 15-hydroxy-3-methylpentadecanoate are obtained as a viscous oil. IR (neat): 3350, 1740 cm^{-1}. NMR $(CDCl_3)^1H$: 4.12 (q, 2H, J=7 Hz), 3.63 (t, 3H, J=6 Hz), 2.37-2.11 (2 x dd, 2H), 1.97 (m, 1H), 1.6-1.16 (m, 26H), 0.92 (d, 3H, J=6 Hz) ppm. NMR $(CDCl_3)^{13}C$: 173.4, 63.0, 60.0, 41.9, 36.7, 32.7, 30.3, 29.5, 29.4, 26.8, 25.7, 19.7, 14.2 ppm.

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Literature

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11. For this particular case, in order to lower the concentration of iodide ions, the couple was formed from zinc and cupric chloride.

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