Tetrahedron Letters,Vol.27,No.27,pp 3149-3152,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

CONJUGATE ADDITIONS TO α,β-UNSATURATED CARBONYL COMPOUNDS IN AQUEOUS MEDIA

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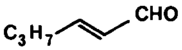
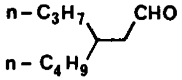
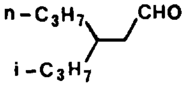
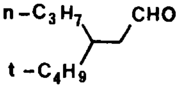
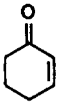
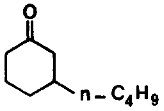
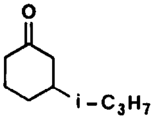
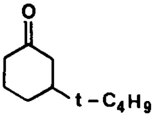
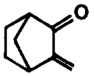
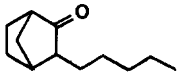
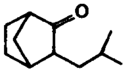
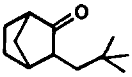
Summary Alkyl halides in the presence of zinc copper couple add smoothly to α-enones and α-enals in aqueous solvents. Sonication enhances the efficiency of the process, which leads to the conjugate adducts in high yields. The reaction follows most probably a radical pathway, and can be used for the addition of functionalized groups.

We recently described a "Grignard-like" reaction with carbonyl compounds promoted by metallic zinc or tin [1,2], which proceeds efficiently in aqueous media. This unexpected reaction was, however, limited to the addition of allylic groups and various attempts to use saturated alkyl halides left the reactants including the metal unchanged. We reasoned that in the case of zinc the lack of reactivity could possibly be overcome by the classical method of alloying it with copper[3]. As this element is known to promote conjugate additions to unsaturated carbonyl compounds[4], we envisaged the possibility of effecting this highly useful synthetic reaction in aqueous media. The initial results are reported in this note.

It was observed that sonication[5] of zinc powder and cuprous iodide in any of several aqueous solvents (THF : water,4 : 1 ; pyridine : water,1 : 4 ; ethanol : water,9 : 1) under an argon atmosphere leads instantaneously to a black suspension. In an exploratory experiment, isopropyl iodide and 3-methylene-2-norbornanone were added to this metallic suspension and the resulting reaction mixture was then sonicated for 45 min at 15-18°C. Work-up of the mixture gave an oil that consisted of the conjugate adduct, contamined only by 10-15% of unreacted enone and traces of the 1-2 addition and reduction products, i.e., the secondary allylic alcohol and the saturated alcohol and ketone (VPC analysis). This excellent selectivity led us to investigate some possible extensions of this reaction.

Experiments were conducted with a cisoid enone (3-methylene-2-norbornanone), a transoid enone (2-cyclohexenone), and an enal (2-trans-hexenal) in combination with a variety of organic halides[6]. From the results given in the Table, it appears that among the halides tested the reactivity follows the order tertiary > secondary >> primary and iodide > bromide (chlorides do not react). The preferred solvent system was aqueous ethanol which gave generally higher yields than the other systems tested.

Table

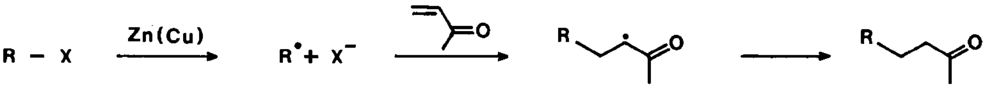
Carbonyl Compound	Halide	1- 4 Adduct	%[a]
	n - C_4H_9 - Br		trace
	n - C_4H_9 - I	—	45
	i - C_3H_7 - Br		42
	i - C_3H_7 - I	—	70
	t - C_4H_9 - Br		76
	n - C_4H_9 - I		85[b]
	i - C_3H_7 - Br		94[b]
	t - Bu - Br		78
	n - C_4H_9 - I		72
	i - C_3H_7 - I		75
	—	—	82[c]
	—	—	100[d]
	—	—	100[e]
	t - C_4H_9 - Br		80

Notes to the table.

a) All the results were obtained in EtOH : H_2O (9:1) - The yields are of isolated purified material, unless otherwise stated- **b)** VPC yields - **c)** CuI replaced by ammonium formate (1 mmol)- **d)** CuI replaced by ammonium chloride (1 mmol) - **e)** in pure water.

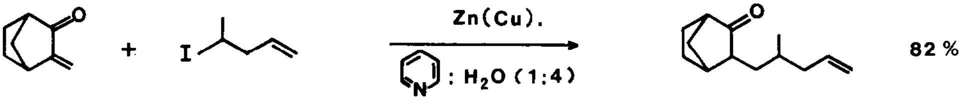
Reactions run in anhydrous solvents gave poor results, while an experiment effected in water without organic solvent produced a nearly quantitative yield of the adduct (see Table). Among several activators of zinc, CuI and $CuCl_2$ proved to be the most satisfactory, although useful results were obtained by activation with ammonium salts. The 3 unsaturated substrates gave similar results. Of particular interest is the case of trans-hexenal, as it is known that conjugate addition with the usual organometallic reagents to α-enals frequently requires indirect procedures for success, e.g., via the silyl enol ether[7].

That the reaction does occur in several aqueous media makes a free organometallic species highly improbable and, thus, we feel a radical pathway seems most likely. This assumption is substantiated by the complete inhibition of the addition in the presence of cumene. Furthermore the relative reactivities of the halides follow a parallel with the relative ease of halogen abstraction from the same compounds by trialkyl tin radicals[8].



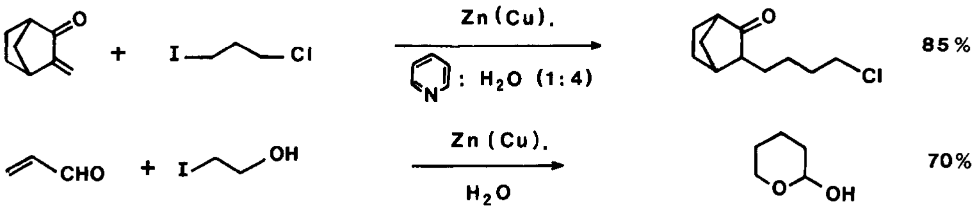
Scheme 1

The reaction should then proceed via a single electron transfert from the metal to the halide followed by an addition to the unsaturated system, as in the processes described by Brown et al[9], and by Giese[10]. The evolution of the "α-keto" radical is presently unclear. Addition of a second electron from the metal would give an enolate which could not yet be evidenced. In particular, formation of an enolate followed by its in situ protonation should increase the pH of the reaction mixture, while it was observed to be slightly acidic (ca.6). Attempts to trap the α-keto radical by an intramolecular reaction remained unconclusive (Scheme 2)



Scheme 2

The zinc-copper mediated reaction in aqueous solvents under ultrasonic irradiation offers several advantages over previously described methods for conjugate additions : besides its great ease and rapidity, only a slight excess of halide is needed. More importantly, the process is compatible with several functional groups, that would not be tolerated in other methods. Results obtained from functional primary iodides i.e., the most difficult case, gave encouraging results (Scheme 2 and 3, non-optimized yields).



Scheme 3

After optimization, the method should be useful for the introduction of halogenated or hydroxylated residues in a one step and easily effected process. Further work in connection with the fundamental aspects of this novel "organometallic" reaction in unusual media and synthetic applications are presently under development.

Acknowledgments : Financial support by the CNRS (UA 332, ATP Chimie Fine) and useful comments by DR. A.E. Greene are gratefully acknowledged.

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2. Petrier,C. ; Einhorn,J. ; Luche,J.L. Tetrahedron Lett. 1985 26 1449-1452.

3. For instance, see : Fieser,L.F. ; Fieser,M."Reagents for Organic Synthesis", Vol.1 J. Wiley, New-York 1967 p.1292.

4. Posner,G.H."An introduction to Synthesis using Organocopper Reagents", J. Wiley, New-York 1980.

5. A Sonoclean^R bath (50 kHz, 240 W) thermostated by running tap water through stainless steel coils was used.

6. In a standard procedure, 150mg (2.4 mmol) of zinc powder and 90mg (0.5 mmol) of cuprous iodide in 4mL of the solvent were sonicated for 1-3 min, and then 1.5 mmol of the halide and 1 mmol of the enone or enal in 1mL of the same solvent were added. Sonication was continued for 40 min (for the most reactive halides) to 2-3 h (for primary iodides). Sat. aqueous NaCl was then added to the mixture, which was followed by ether extraction. The usual work-up, evaporation, and purification by column chromatography gave the adduct. Spectral and analytical data are consistent with the expected structures. Replacing sonication by stirring resulted in most cases in much longer reaction times and lower yields.

7. For a review, see : Alexakis,A. ; Chuit,C. ; Commerçon-Bourgain,M ; Foulon,J.P. ; Jabri,N. ; Mangeney,P. Normant,J.F. Pure Appl. Chem. 1984 56 91-98.

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(Received in France 6 May 1986)