Tetrahedron Letters,Vol.29,No.42,pp 5369-5372,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

ULTRASOUND IN ORGANIC SYNTHESIS 16[1].
OPTIMISATION OF THE CONJUGATE ADDITIONS TO α,β-UNSATURATED CARBONYL COMPOUNDS IN AQUEOUS MEDIA.

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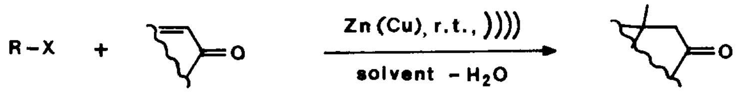
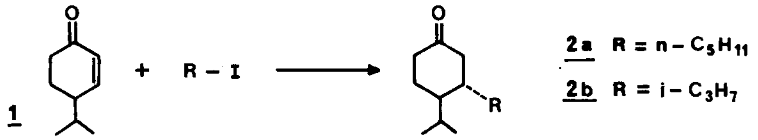
Abstract : Optimisation of the conjugate addition of alkyl groups to α-enones under sonochemical conditions can be effected, especially by a proper choice of the solvent, most probably because of its structural properties.

We recently described a new procedure for the conjugate additions of alkyl groups to α,β-unsaturated carbonyl compounds, under sonochemical aqueous conditions[2]. This method combines several advantages such as simplicity, ease of use and compatibility with the presence of functionnalities which usually cannot coexist with organometallic derivatives :



In this note, new progress in the knowledge of the experimental conditions is described, with the proposal of an optimisation procedure of the reaction. Most of the experimentation was run with 4-isopropyl cyclohex-2-enone 1, 1-iodopentane, and 2-iodopropane.



Under the conditions described in our first note[2], adduct **2b** was formed in 36 % yield under sonication, and 22 % with stirring only. In each case, **2a** was obtained in low yields, less than 10 %. Both products 2 contain a single diastereoisomer, prepared almost exclusively by addition to 1 of the corresponding organocuprate reagent ; in analogy with related cases[3], the relative configuration of the substituents in 2a and 2b should be trans.

A Zn-Cu couple with optimal reactivity is prepared by sonication, at room temperature, of zinc dust with 0.3 molar equ. of CuI in the appropriate solvent (see below). Although both reagents are insoluble, a black, heavy suspension is formed in less than 3 min. and can be used immediately, as further sonication affords no advantage (same yield in **2b**). Practically, best results are obtained with a horn sonicator operated at its maximum power (75 W). A couple with lower but frequently sufficient reactivity can be prepared in an ordinary cleaning bath[4].

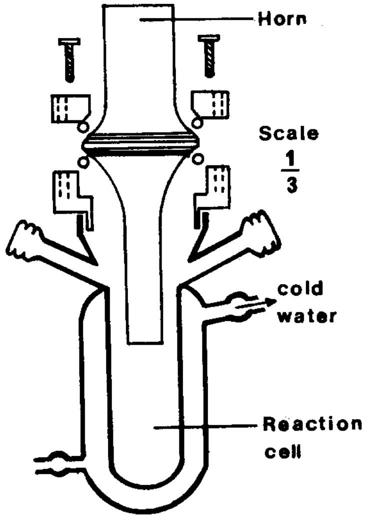
After much experimentation and a systematic exploration of the factors considered as important (temperature, time, solvent etc...) optimal conditions are exemplified as follows: a couple is prepared under argon from 4.6 mmol of zinc and 1.4 mmol of CuI in 12 ml of $EtOH-H_2O$ (65-35). 2 mmol of 1 are then introduced, and 3 mmol of $i-C_3H_7-I$ in 2 ml of EtOH are added over a 75 min period under sonication using the highest ultrasound intensity compatible with an efficient energy transmission[5]. Irradiation is effected at room temperature using the experimental system shown in the scheme. After work-up, 3,4-diisopropylcyclohexanone 2b is obtained in 70 % isolated yield. Using 7 mmol of the couple and 6 mmol (3 equiv.) of the iodide increases the yield to 95 %. In this last case, an interesting 83 % yield is obtained by sonication in a cleaning bath, despite the low energy density.

The parameter of highest importance is the solvent composition. Of the aqueous mixtures tested (H_2O + THF, acetone, DMF etc) alcohols are the more satisfactory organic cosolvents. When using secondary and tertiary halides[2], ethanol-water (65-35 in vol.) is the medium of choice. In the case of a primary iodide such as n-pentyl iodide, the optimal conditions defined above gave a poor 12 % yield. Most of the parameters can be varied without important yield modification, except the solvent. Both the nature of the organic component and the water content exhibit a strong influence, as summarized in Table 1.

Table 1 : yield of **2a** according to the solvent mixture

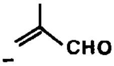
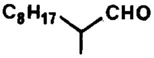
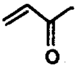
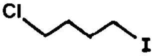
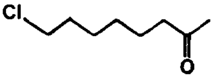
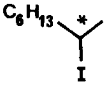
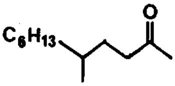
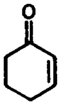
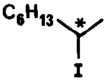
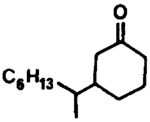
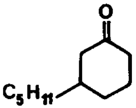
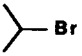
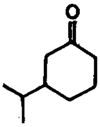
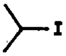
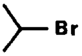
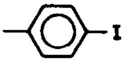
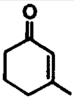
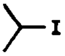
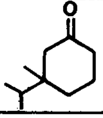
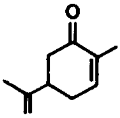
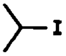
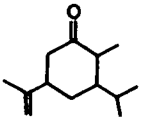
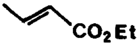
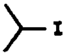
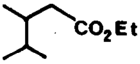
Solvent % vol		alcohol molar fraction	2a % (VPC)
$EtOH-H_2O$	65-35	0.35	12
$i-PrOH-H_2O$	90-10	0.68	30
	80-20	0.48	32
	50-50	0.2	28
	35-65	0.11	21
$n-PrOH-H_2O$	65-35	0.3	36
	40-60	0.13	37
	25-75	0.07	40

Scheme : Reaction vessel

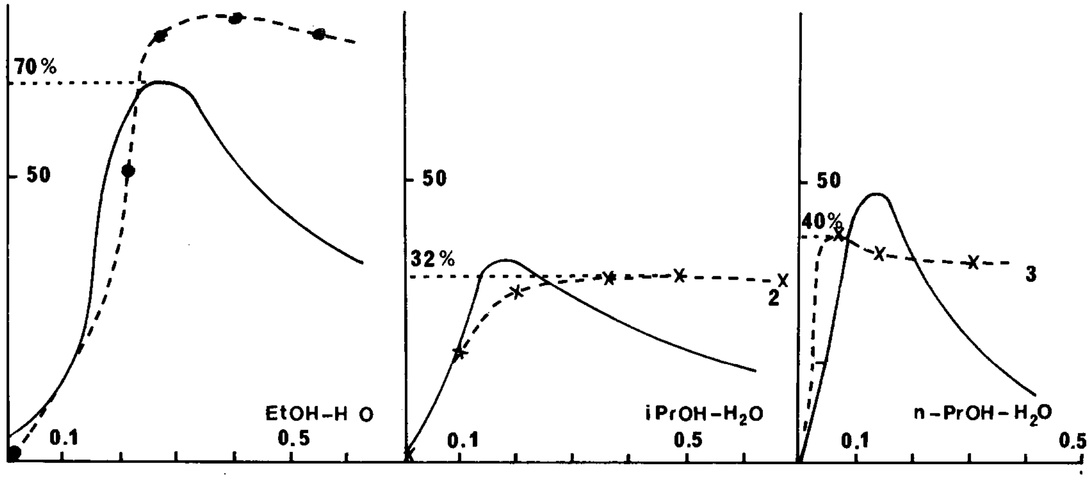


When plotted against the alcohol molar fraction, the yield of **2a** or **2b** exhibits a dependence more or less similar to that of sound absorption (Curves 1-3).

Table 2 : New synthetically useful examples

Carbonyl compound	Halide	Adduct (%)[a]	
	n-C_7H_{15}-I		(71)
			(49)[b]
			(80)[c]
			(90)[c]
	n-C_5H_{11}-I		(77)
			(50)
			(95)
	 + NaI		(75)
		trace of reaction	
			(10)
	n-C_5H_{11}-I	trace of reaction	
			(76)[d]
			(73)[e]

[a] Reactions were run optimal conditions. Isolated yields unless specified otherwise. All the compounds isolated gave satisfactory analytical data. [b] Non-optimized conditions. [c] Racemic adduct. [d] Mixture of 4 stereoisomers. [e] VPC yield.



Abcissas : molar fraction of alcohol in water

Ordinates : solid curve sound absorption (arbitrary units)

dotted line ,curve 1 : yield of 2b.dotted line, curve 2 and 3 : yield of 2a

These sound absorptions have been measured at ultrasound frequencies ca. 5 MHz[6], much higher than the frequency used in our experiments (30 kHz). However, the existence of absorption maxima indicates a maximum 3-dimensional structure organisation of the liquid[6]. That such an optimal organisation parallels a maximum in the reaction yield, most probably indicates a strong solvent participation in a determining step[7]. The optimisation procedure given in this note proved to be useful and examples of conjugate additions are displayed in Table 2.

References

1- Previous paper : C. Einhorn, C. Allavena, J.L. Luche J.C.S. Chem. Commun. 1988, 333.
2- C. Pétrier, C. Dupuy, J.L. Luche Tetrahedron Lett. 1986, 27, 3149. For applications, see : L. Castedo, J.L. Mascareñas, A. Mouriño, L.A. Sandareses Tetrahedron Lett. 1988, 29, 1203. M. Ohno, K. Ishizaki, S. Eguchi J. Org. Chem. 1988, 53, 1285. K.M. Petrusewicz, M. Zablocka Tetrahedron Lett. 1988, 29, 937.
3- H. Rivière, J. Tostain Bull. Soc. Chim. Fr. 1969, 568
4- In the reaction of isopropyl iodide with 3-methylene-2-norbornanone, an almost quantitative yield is obtained when zinc is activated with ammonium chloride or formate. This excellent result could not be reproduced with cryptone **1**. Cuprous bromide or cupric chloride activation always give lower yields than cuprous iodide.
5- Increasing the sound intensity beyond a limiting value gives rise to a very important cavitation, producing bubbles in large amounts. These bubbles absorb or disperse the energy, leading to a rate (or yield) decrease of the sonochemical reaction. For an illustration of this phenomenon see : J.C. de Souza Barboza, C. Petrier, J.L. Luche J. Org. Chem. 1988, 53, 1212.
6- J.C. Burton J. Acoust. Soc. Am. 1948, 20, 186. For the definition of sound absorption see also : J.P. Lorimer, T.J. Mason Chem. Soc. Rev. 1987, 16, 239.
7- For a related example see : T.J. Mason, J.P. Lorimer, B.P. Mistry. Ultrasonics 1987, 25, 23, and Tetrahedron 1985, 26, 5201.

(Received in France 25 June 1988)