Tetrahedron Letters,Vol.23,No.33,pp 3361-3364,1982 0040-4039/82/333361-04$03.00/0
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ULTRASOUNDS IN ORGANIC SYNTHESIS 3[1]. A SIMPLE, HIGH YIELD MODIFICATION OF THE BOUVEAULT REACTION

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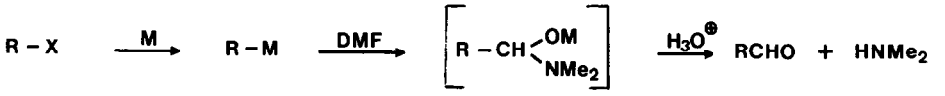
Summary. Aldehydes are readily obtained in high yield by ultrasonic irradiation of various alkyl and aryl halides in the presence of lithium and DMF.

Since our first report on the effects of ultrasounds in organometallic chemistry[3], new applications of ultrasonic irradiation in various synthetic transformations have been published. The formation and in situ reaction of organozinc derivatives have been described[4] and we have shown that organocopper species can also be generated by this method[1].

These findings demonstrate that ultrasonic irradiation of heterogeneous reaction mixtures can offer some important advantages, such as improved yields and selectivity, reduced reaction times and temperatures, and the possibility of using reduced amounts of reagents[5].

We wish now to report a significant improvement in the Bouveault reaction achieved through the use of ultrasonic irradiation. The Bouveault reaction[6] involves the formylation of an alkyl or aryl halide to the homologous aldehyde by transformation to the corresponding organometallic (usually lithium or magnesium) then addition to dimethylformamide (DMF).



This transformation for a long time suffered from numerous side-reactions[7]. Several modifications have recently been reported, employing various formic acid derivatives[8] designed for the purpose of stabilizing the intermediate aminoalkoxide, but in some cases an expensive reagent is required.

We have found that sonication of a mixture of lithium, an alkyl or aryl halide, and DMF in dry THF substantially improves this reaction. High yields of the expected aldehydes are

obtained under exceedingly simple experimental conditions. Typically, 1 mmol of the alkyl halide, 1 mmol dry DMF, and 50 mg (2 1 mg-atoms, i.e. approximately the stoichiometric amount) of lithium sand in mineral oil[9] in 4 ml dry THF are sonicated in an ultrasound cleaner (96 W/1, 40 kHz). The reaction is usually complete at 10-20°C in less than 15 min. After work-up (addition of ether and washing with dil HCl and sat NaCl, drying over sodium sulfate and removal of solvent) the crude aldehyde, uncontaminated with starting material, is obtained as a colorless oil in reasonable purity, as shown by VPC, TLC, IR, and NMR. Filtration over silica gel affords a pure product, identified by the usual spectral techniques and, when possible, through comparison with an authentic sample Isolated yields are given in Table I.

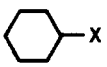
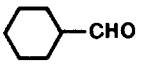
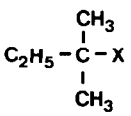
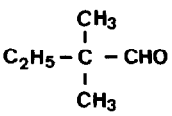
As can be seen, the reaction works well with primary, secondary, and tertiary aliphatic bromides as well as with aromatic bromides. This result contrasts with the unsuccessful condensation of secondary Grignard reagents with formic acid[8c]. In addition, lithiation of chlorides, which has not previously been reported[3], and subsequent in situ formylation can also be effected quite satisfactorily somewhat longer irradiation times are sometimes required

As shown in the Table, this method is also useful for the bis-homologation of dibromo compounds. To the best of our knowledge, the Bouveault reaction has seldom been used for the preparation of dialdehydes[8c]

It has previously been established that this reaction also takes place in the absence of ultrasounds, but the rate and yields are significantly lower[10]. In our hands, under conditions similar to the aforementioned with rapid stirring in lieu of irradiation, n-butyl bromide, DMF and lithium gave only a very low yield of the expected aldehyde (<10%) after 10 min. The effect of the ultrasonic waves thus appears to be more complex than a mere agitation effect. Cavitation[11,12], known to effect the erosion of metallic surfaces[13], can be accompanied and greatly amplified by a stationary waves phenomenon[14]. These phenomena, which can act synergistically, may be responsible for the observed effects. Additional applications of the ultrasonic irradiation on organic reactions are currently under study

Acknowledgements. The authors wish to thank Dr. A E Greene for stimulating comments, and M Bosso for mass spectra measurements

Table

Halide	Aldehyde	Irradiation Time (min)	t°C	Yield[a]
nC_4H_9-X	nC_4H_9-CHO			
X = Cl		5	20	78[b]
X = Br		5	10	88[b]
$nC_7H_{15}-Br$	$nC_7H_{15}-CHO$	5	20	83
$Br-(CH_2)_n-Br$	$OCH-(CH_2)_n-CHO$			
n = 4	n = 4	10	20	64
n = 7	n = 7	5	10	84
n = 10	n = 10	10	20	83
				
X = Cl		10	10	70
X = Br		5	10	76
tC_4H_9-Br	tC_4H_9-CHO	5	10	(67)[c]
				
X = Cl		15	20	84[b]
X = Br		5	20	80[b]
$C_6H_5CH_2-Br$	$C_6H_5CH_2-CHO$	5	10	85
C_6H_5-X	C_6H_5-CHO			
X = Cl		5	15	78
X = Br		5	10	86

[a] Isolated yield unless specified [b] VPC yield with internal standard [c] THF (Eb = 65°) and pivalaldenyde (Eb = 71°) were not satisfactorily separated The yield is estimated by VPC after reduction ($NaBH_4$) of the crude mixture to neopentyl alcohol

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(Received in France 5 June 1982)