

Communications to the Editor

Ultrasounds in Organic Syntheses. 1. Effect on the Formation of Lithium Organometallic Reagents

Sir:

Ultrasounds have rarely been employed by organic chemists. Recently, they have been reported to accelerate the hydrolysis of carboxylic esters,¹ to induce the cleavage of carbon-halogen bonds of various halides,² and to assist in the mercury reduction of α, α' -dibromo ketones.³ Several other processes, most of them destructive, have also been described,⁴ but to our knowledge no finding to date in this domain has enjoyed any significant application in synthetic organic chemistry.

We chose to study the formation of organometallics under the influence of ultrasounds, particularly the lithium and magnesium reagents, due to their extreme popularity in many fields of chemistry. Typical preparations of these reagents require dry diethyl ether or tetrahydrofuran, and, preferably, an inert atmosphere, especially with lithium.⁵ An induction period, during which no reaction between the organic halide and the metal occurs, constitutes a problem which can be serious in large-scale experiments. Various activating agents (I_2 , CH_3I) are often used to shorten the induction time; however, in many cases initiation of the reaction can nevertheless be difficult, irreproducible, and strongly dependent on the skill of the operator.

We have found that ultrasonic irradiation affords a significant amelioration in the preparation of lithium and magnesium organometallics. A flask containing a 0.1 M ethereal solution of an alkyl or aryl halide in the presence of lithium wire or Li-2% Na sand (4 equiv) is irradiated in the water bath of an ultrasound laboratory cleaner (60 W, 50 kHz). A strong agitation of the mixture results from the cavitation phenomenon⁶ and the metal is attacked almost immediately without the aid of any initiator. The resulting turbid white solution is standardized by the usual techniques or condensed with various keto compounds.⁷ *N*-Propyl-, *n*-butyl-, and phenyllithium were thus prepared from the bromides in 90, 61, and 95% yield, respectively, but isopropyl and *tert*-butyl bromides required rather long irradiation times (>1 h) so that the advantages of ultrasound irradiation appear not to be general for this particular procedure.

Contrastingly, the superiority of the ultrasound irradiation method is strikingly evidenced in the Barbier reaction. This one-step coupling of an organic halide with a carbonyl compound is usually achieved with magnesium,⁹ but lithium has recently been

Table I. Modified Barbier Reaction with Ultrasonic Irradiation

R-X	Carbonyl compound	Product	Reaction time (min)	Yield ^a
CH_3I			10	100 (92)
$n-C_3H_7Br$	C_6H_5-CHO		10	100
$s-C_3H_7Br$			15	100 (96)
$n-C_4H_9Br$	$(n-C_4H_9)_2C=O$	$(n-C_4H_9)_2C-OH$	15	100 (90)
			30	80 (88)
$n-C_4H_9Br$			15	100 (80)
$n-C_4H_9Br$			15	84
$t-C_4H_9Br$			30	76
C_6H_5Br			30	100 (95)
$C_6H_5CH_2Br$	$C_6H_5-COCH_3$		10	95
C_6H_5Br	$C_6H_5-COCH_3$		30	92 (83)
$CH_2=CH-CH_2Br$			15	76 (60) ^b
$CH_2=C(CH_3)Br$	$C_6H_{11}-CHO$		40	96 (71)
$CH_3-CH=CH-Br$	$C_6H_{11}-CHO$	$C_6H_{11}-CHOH-CH=CH-CH_3$	40	95 (78)

^a The yields are calculated with respect to the initial carbonyl compound from VPC measurements (Fractovap Carlo-Erba, Carbowax 20M, flame ionization detector). Figures in parentheses are isolated yields. ^b 7:3 equatorial-axial mixture of epimeric alcohols.

found to improve the yields significantly.¹⁰ We have found that ultrasonic irradiation allows this reaction to be performed in wet technical grade tetrahydrofuran. The formation of the organolithium intermediate and its subsequent reaction proceed readily and in high yield, as shown in Table I. The progress of the reaction is monitored by TLC. In all cases the reaction is complete in less than 1 h and often in only 10-15 minutes. Normally observed side reactions such as reduction and enolization are minimized. It has been noted previously¹⁰ that primary, secondary, and tertiary bromides give excellent results in the Barbier reaction. Our results agree with these findings. In contrast, the present conditions allow the direct in situ formation of benzyl lithium from benzyl bromide and Li-2% Na sand. Condensation with acetophenone yields the expected compound, while Wurtz coupling normally predominates with benzyl halides.^{5,10} Allylic and vinylic bromides also undergo clean and high-yield reactions under the ultrasound Barbier conditions, although their transformations to the corresponding lithio derivative are usually difficult. Thus, it is worth mentioning that the sonication procedure might be used to obtain easily and rapidly various types of organolithium reagents. Use of wet solvents, at room temperature, could be of interest for large-scale industrial operations. A twofold excess of the halide, with respect to the carbonyl compound, has to be used in order to obtain a maximum yield. Most probably, a partial hydrolysis of the reagent occurs due to the solvent moisture.

(10) Pearce, P. J.; Richards, D. H.; Scilly, N. F. *J. Chem. Soc., Perkin Trans. 1* 1972, 1655.

(1) Sung Moon; Duchin, L.; Cooney, J. V. *Tetrahedron Lett.* 1979, 3917.

(2) Prakash, S.; Pandey, J. D. *Tetrahedron* 1965, 21, 903.

(3) Fry, A. J.; Ginsburg, G. S.; Parente, R. A. *J. Chem. Soc., Chem. Commun.* 1978, 1040.

(4) See, for example: Staas, W. H.; Spurlock, L. A. *J. Chem. Soc., Perkin Trans. 1* 1975, 1675. Reifsnider, S. B.; Spurlock, L. A. *J. Am. Chem. Soc.* 1973, 95, 299.

(5) Inter alia: Wakefield, B. J. "The Chemistry of Organolithium Compounds"; Pergamon Press: Oxford, 1974. March, J. "Advanced Organic Chemistry"; McGraw-Hill Kogakusha: Tokyo, 1977; pp 836 sqq and the numerous references cited.

(6) Cavitation is the production by ultrasounds of microscopic gas bubbles in the solution. Their formation and then implosion liberates considerable energy.

(7) With magnesium, initiation occurs almost instantaneously in all the cases tested. The solutions of the organomagnesium reagent also contain an abundant white precipitate, probably magnesium hydroxide. It is important to mention that this reaction can be performed in commercial grade quality diethyl ether,⁸ not dried prior to use. Under the normal, nonultrasound, conditions, this drying is necessary.

(8) Normapur Quality (Prolabo) contains normally ca. 1000 ppm H_2O and 500 ppm ethanol.

(9) For a recent review see: Blomberg, C.; Hartog, F. A. *Synthesis* 1977, 18.

Excellent yields are obtained when dry THF is used, and in this case 1.2 equiv of the halide is sufficient for optimal reaction. For instance, the reaction of 2-bromopropene with hexanal gives the expected allylic alcohol in 91% isolated yield.

It is not yet possible to interpret the effect of ultrasounds on the formation of organometallic reagents. However, the mechanical effects can produce some alterations at the metal surface: it has recently been shown that lattice defects such as dislocations are important factors in the initiation of the Grignard reaction.¹¹ It can also be supposed that ultrasound energy keeps the metal surface free from the derived species (organolithium, lithium halides, or hydroxide) in such a way that it remains highly activated. Further work concerning the extension of this reaction to various substrates and metals is currently under way.

Acknowledgment. Useful discussions with Dr. A. E. Greene are warmly acknowledged.

(11) Hill, C. L.; Van der Sande, J. B.; Whitesides, G. M., *J. Org. Chem.* 1980, 45, 1020.

[†] Deceased June 8, 1980.

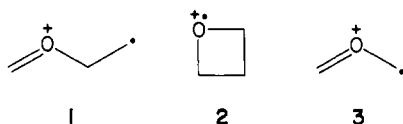
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Experimental Proof for the Gas-Phase Existence of the C...C Ring-Opened Trimethylene Oxide Cation: A New Stable C₃H₆O⁺ Isomer

Sir:

In a recent paper,¹ we presented ab initio theoretical predictions of the structures and stabilities of 17 possible C₃H₆O⁺ (*m/z* 58) isomers. In addition to those that had been well established by experimental techniques,² we identified a number of low-energy, potentially observable structures. One of these, the C...C ring-opened isomer **1** of the trimethylene oxide radical cation **2**, was shown to lie slightly lower in energy than **2** and represents a higher homologue of the stable C...C ring-opened ethylene oxide ion **3**.³



By analogy with ion **3**, which transfers CH₂⁺ to a variety of neutral substrates,³ ion **1** would be expected to show a C₂H₄⁺ transfer to similar substrates. Indeed, both the *m/z* 58 ion generated by ionization of trimethylene oxide and the *m/z* 58 ion formed from ionized 1,4-dioxane by loss of formaldehyde showed a transfer of C₂H₄⁺ to neutral acetonitrile when mixtures of these compounds were investigated by ICR spectrometry.¹ This observation did not in itself, however, rule out the possibility that C₂H₄⁺ transfer could occur from ion **2**. From collisional activation studies, McLafferty^{2a} had proposed that the C₃H₆O⁺ ions from trimethylene oxide and 1,4-dioxane were identical and possessed the closed-ring structure **2**. We therefore set out to determine whether the *m/z* 58 ion from 1,4-dioxane, which showed C₂H₄⁺ transfer to acetonitrile in the ICR spectrometer, had the open-ring structure **1** or the closed-ring structure **2**.

(1) Bouma, W. J.; MacLeod, J. K.; Radom, L. *J. Am. Chem. Soc.* 1980, 102, 2246-52.

(2) (a) Van de Sande, C. C.; McLafferty, F. W. *J. Am. Chem. Soc.* 1975, 97, 4617-20. (b) For other relevant papers, see ref 1.

(3) Bouma, W. J.; MacLeod, J. K.; Radom, L. *J. Chem. Soc., Chem. Commun.* 1978, 724-5. *J. Am. Chem. Soc.* 1979, 101, 5540-5. *Adv. Mass Spectrom.*, in press.

Scheme I

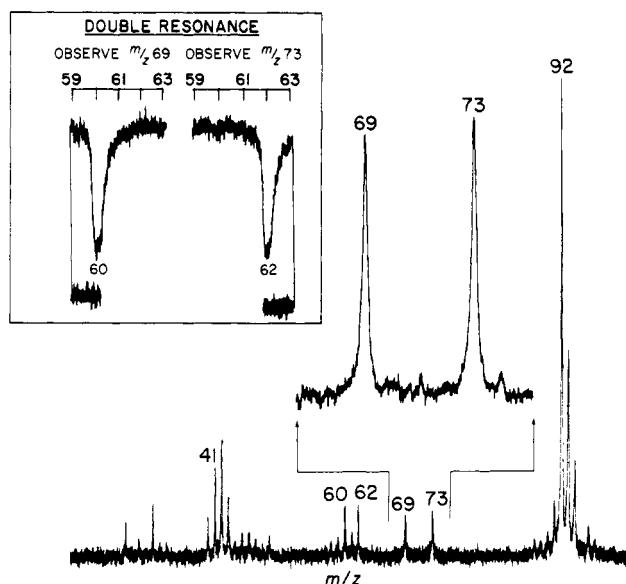
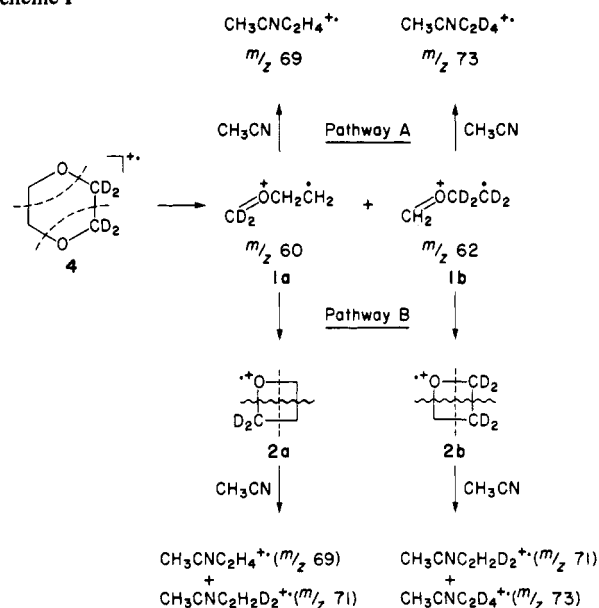


Figure 1. ICR spectrum of a mixture of 2,2,3,3-[²H₄]-1,4-dioxane and acetonitrile.

2,2,3,3-[²H₄]-1,4-Dioxane (92% d₄, 5% d₈, 3% d₀) was synthesized by the method of Jensen and Neese.⁴ In the ICR spectrometer⁵ its molecular ion **4** showed about equal losses of CH₂O and CD₂O to give ions at *m/z* 62 and 60, respectively (Scheme I). If, in reactions of these ions with acetonitrile, transfer of the ethylene radical cation proceeds without prior cyclization of **1a** and **1b** and without H/D scrambling, then pathway A would be followed and two product ions observed at *m/z* 69 and 73. Alternatively cyclization of **1a** and **1b** to **2a** and **2b**, respectively (pathway B), renders one CH₂ and one CD₂ group equivalent in each case and therefore in the absence of H/D scrambling would be expected to lead to product ions at *m/z* 69, 71, and 73 in a ratio of ~1:2:1 (Scheme I).⁶

The ICR spectrum of a mixture of 2,2,3,3-[²H₄]-1,4-dioxane (M⁺ *m/z* 92, 1 × 10⁻⁵ torr) and acetonitrile (5 × 10⁻⁶ torr) is shown in Figure 1. Product ions at *m/z* 69 and 73 only are observed and double resonance establishes that their sole precursor

(4) Jensen, F. R.; Neese, R. A. *J. Org. Chem.* 1972, 37, 3037-8.

(5) For general experimental conditions, see ref 1.

(6) If H/D scrambling in **2a** and **2b** were to occur, an even larger number of product ions would be observed for the reaction with acetonitrile, namely, *m/z* 69, 70, and 71 from **2a** and *m/z* 71, 72, and 73 from **2b**.