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THE APPLICATION OF ULTRASOUND TO THE STRECKER SYNTHESIS ON 9,10-DIMETHOXY-1,3,4,6,7,11b-HEXAHYDROBENZO[a]QUINOLIZIN-2-ONE

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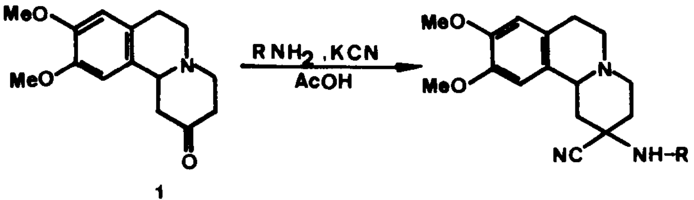
Summary: Irradiation with ultrasound in acetic acid solution was found to facilitate the aminocyanation of 9,10-dimethoxy-1,3,4,6,7,11b-hexahydrobenzo[a]quinolizin-2-one.

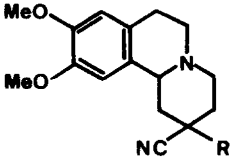
A growing list of successful applications of ultrasound to organic reactions has developed during the last seven years[1,2]. Sonication has proved to be of value in organometallic chemistry, improving the Grignard[3], Bouveault[4], Barbier[5], and Reformatskii[6] reactions, among others. Additional examples of the benefitial application of ultrasound in N-alkylation of amines[7], synthesis of thioamides[8], hydrolysis of carboxylic esters[9], etc. have been given. We want now to report that ultrasound facilitates the Strecker synthesis[10] on 9,10-dimethoxy-1,3,4,6,7,11b-hexahydrobenzo[a]quinolizin-2-one (Scheme 1), allowing a reduction of the reaction time and increasing the yield of the α-aminonitriles obtained.



SCHEME 1

The employment of the usual Strecker conditions, such as treatment of aminoketone 1 with the suitable amine or an ammonium salt and potassium cyanide in water or aqueous ethanol gave rise only to the isolation of the cyanohydrin 2, which had been previously described by us [11]. When the reaction was carried out in an homogenoeus glacial acetic acid solution, the target aminonitriles were obtained, but the reaction was incomplete, even when vigorous stirring was prolonged for a period up to 13 days. Similar results were obtained when the reaction was heated at 40°C for 30-40 h[12].

When ultrasound was applied to the aminocyanation, high yields of the aminonitriles 3 could be obtained using shorter reaction times. The results are summarized in the table[13,14].



2 R = OH

3 R = R^1-NH

Compound nr.	R^1	Mp/°C (rec.)	Yield/%		Reaction time	
			A	B	A/h	B/days
3a	H	111-113 (water)[a] 170-172 (2-propanol)[b]	100.0	62.1	25	12
3b	nC_4H_9	135-138 (2-propanol)[b]	87.5	60.3	25	12
3c	C_6H_5	138-140 (ethanol)[a]	99.7	73.2	35	13
3d	$(4\text{-Me})C_6H_5$	149-151 (ethanol)[a]	97.1	69.3	35	13
3e	$CH_2\text{-}C_6H_5$	116-117 (2-propanol)[a] 128-130 (2-propanol)[b]	99.4	78.9	20	12
3f	$CH_2\text{-}CH_2\text{-}C_6H_5$	123-125 (2-propanol)[a]	99.8	68.5	20	12

[a] Free base [b] Hydrochloride

The reactions were monitored by ir in order to obtain the optimal conditions. Due to the sonication process, the temperature of the reaction increased gradually over a period of 3 h, getting stabilized at about 40°C. Yields were virtually unaffected when the reaction was cooled to room temperature during sonication. In the cases in which ultrasound was applied for 10-15 h following a prolonged stirring, the results were similar to those obtained for sonication alone.

Although most of the literature on organic sonochemistry deals with two-phase reactions, a number of papers have been published which describe ultrasound-induced enhancements of reaction rates for homogeneous reactions[15-18]. Such improvements have usually been ascribed to cavitation[19] - the formation of cavities inside the homogeneous liquid phase and their subsequent collapse - , a consequence of which is the appearance of high temperatures (10^4 - 10^6 K) and pressures up to several thousand atmospheres[17] in the centre of the microbubbles.

Studies on ultrasound-aided Strecker reaction are in progress for other carbonyl compounds.

Preliminary results for 4-piperidone derivatives seem to show that ultrasound has also in this case a positive effect on the yields of aminocyanation procedures.

EXPERIMENTAL

A laboratory ultrasonic cleaner (150 W, 50-55 kHz) manufactured by Branson Co. was employed.

Ilustrative Procedure

To an ice-cooled mixture of aminoketone 1 hydrochloride (5.04 mmole), potassium cyanide (12.6 mmole) in water (5 ml), and the suitable amine (7.56 mmole) or ammonium acetate or chloride (7.56 mmole) were added dropwise 30 ml of glacial acetic acid. The reaction mixture was irradiated with ultrasound for 20-35 h (method A) or stirred at room temperature for 12-13 days (method B). The solution was then poured onto 20 g of ice, basified to pH 8 with ammonium hydroxide or aqueous sodium carbonate while externally cooled. In the cases in which a solid was formed, it was filtered off and recrystallized from an appropriate solvent. Otherwise, the basified reaction was extracted with chloroform (5 x 75 ml) and the combined organic layers were dried over sodium sulphate and evaporated under reduced pressure. The residue was crystallized from an appropriate solvent or dissolved in a dry mixture of ether and dichloromethane (3:1) and treated with dry, gaseous hydrogen chloride. The solid formed was filtered off and recrystallized.

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12. Temperatures higher than 40°C gave rise to partial condensation between the amines and the acetic acid employed as solvent.
13. Some alkyl and dialkylaminonitriles (3, R = CH_3, $CH(CH_3)_2$, $(CH_2)_5$), which seem to be

highly reactive, could not be isolated, since they gave rise either to the N-unsubstituted aminonitrile 3 (R = H) or to the cyanohydrin 2 when the reaction was neutralized with ammonium hydroxide or with aqueous sodium hydroxide or carbonate, respectively. The products obtained from these reactions were identified by their spectral data.

14. All compounds showed analytical and spectral data consistent with their structures. Salient spectral data for new compounds follow :

3a : ir^a : 3320, 3260 (NH_2), 2205 ($C\equiv N$). ^{1}H-nmr^b : 6.70, 6.65 (2 s, 2H, 11-H and 8-H), 3.85 (s, 6H, 2 OMe), 2.00 (s, 2H, NH_2, exch.). Ms^c : 287 (M^+, 20.6), 286 (19.7), 272 (16.8), 271 (67.8), 270 (36.8), 260 (30.7), 259 (57.7), 218 (69.3), 205 (57.0), 204 (16.4), 191 (100.0), 190 (74.3), 177 (15.8), 176 (57.5), 146 (17.7), 133 (20.6), 105 (19.3), 42 (28.2), 41 (32.0).

3b : ir : 3350 (NH), 2205 ($C\equiv N$). ^{1}H-nmr : 6.75, 6.65 (2 s, 2H, 11-H and 8-H), 3.90 (s, 6H, 2 OMe), 3.00-1.20 (m, 20H), 2.50 (s, 1H, NH, exch.).

3c : ir : 3350 (NH), 2210 ($C\equiv N$). ^{1}H-nmr : 7.30-7.00 (m, 5H, C_6H_5), 6.70, 6.60 (2 s, 2H, 11-H and 8-H), 3.80 (s, 6H, 2 OMe), 2.90 (s, 1H, NH, exch.).

3d : ir : 3340 (NH), 2205 ($C\equiv N$). ^{1}H-nmr : 7.40-6.50 (m, 4H, 4-Me(C_6H_4)), 6.70 (s, 2H, 11-H and 8-H), 3.85 (s, 6H, 2 OMe), 3.45 (s, 1H, NH, exch.), 2.35 (s, 3H, 4-Me (C_6H_4)).

3e : ir : 3300 (NH), 2210 ($C\equiv N$). ^{1}H-nmr : 7.30 (s, 5H, CH_2-C_6H_5), 6.60 (s, 2H, 11-H and 8-H), 4.05 (s, 2H, CH_2-C_6H_5), 3.85 (s, 6H, 2 OMe), 3.60 (s, 1H, NH, exch.). Ms : 377 (M^+, 0.1), 376 (0.1), 351 (4.5), 350 (18.1), 260 (3.5), 259 (20.4), 218 (25.5), 206 (15.3), 205 (100.0), 192 (13.9), 191 (20.5), 190 (39.0), 176 (15.5), 159 (7.4), 158 (8.5), 91 (67.9), 77 (10.6), 65 (19.0), 42 (5.4), 41 (4.1).

3f : ir : 3380 (NH), 2205 ($C\equiv N$). ^{1}H-nmr : 7.25 (s, 5H, CH_2-CH_2-C_6H_5), 6.65, 6.60 (2 s, 2H, 11-H and 8-H), 3.80 (s, 6H, 2 OMe), 3.00-2.50 (m, 4H, CH_2-CH_2-C_6H_5), 1.90 (s, 1H, NH, exch.)

Notes : [a] Frequencies in cm^{-1}. Samples were compressed into KBr pellets.
[b] In δ units relative to TMS. Solvent $CDCl_3$. A 60 MHz spectrometer was used.
[c] Ionization was carried out by electron impact. Samples were introduced directly.

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