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RAPID CRYSTALLISATION USING ULTRASONIC IRRADIATION - SONOCRYSTALLISATION

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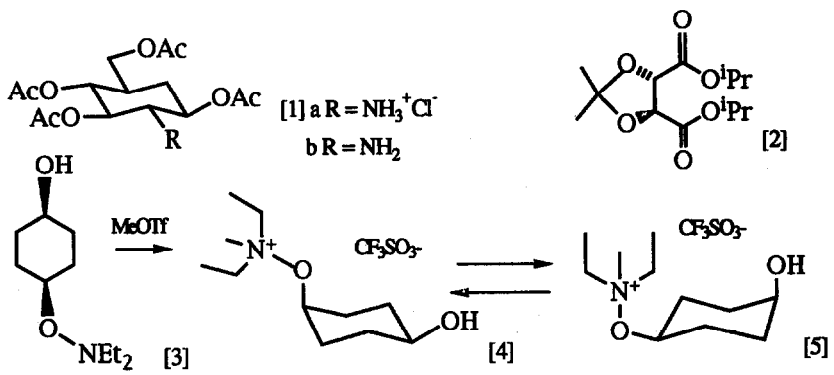
Abstract Ultrasonic irradiation induces rapid crystallisation of materials which normally only crystallise with difficulty.

The induction of crystallisation is more of an "art than a science"[1] and has become the subject of a considerable body of folklore. We find that many saturated solutions can be crystallised quickly, easily and reproducibly by ultrasonic irradiation[2] in a high power cleaning bath. In this letter we describe three examples which demonstrate the generality and effectiveness of this methodology.



The hydrochloride **[1a]** was treated with sodium acetate to give the unstable amine **[1b]**[3]. After an aqueous workup a chloroform solution of crude material showed 3 spots by TLC. Addition of ether effected crystallisation overnight, but when the same solution was sonicated, clean, well formed white crystals were produced in 5 minutes (mpt. 141, lit. 143°C; 60-70% yield).

(L)-(+)-Di-isopropyl tartrate was dissolved in acetone to which was added zinc chloride. After 48 hours the solution was filtered, added to water, extracted with ether, dried over magnesium sulfate, filtered, concentrated and columned over silica gel to give a viscous oil. Ultrasonic irradiation in in ether and petrol, yielded clear rhomboidal crystals of the isopropylidene adduct **[2]** (mpt. 43-45, lit. 42-42.7°C[4]; 88% yield).

The hydroxy aminoether **[3]** was treated with an excess of methyl trifluoromethyl sulphonate in methylene chloride for one hour. The reaction mixture was concentrated to a yellow waxy solid which could not be induced to crystallise.

Addition of ether yielded a clear gum with a yellow supernatant. Ultrasonic irradiation of this mixture, precipitated a white solid from the supernatant and the gradual dissolution of the gum. Alternatively if a small amount of 2-propanol is added crystals are formed from homogenous solution. Recrystallisation from acetone and ether gave white crystals (mpt. 87-88°C; yield 40% or 47%). An X-ray structure determination[5] of this material indicated that unusually the ammonium ether group was in the axial position [4], however in solution the chemical shift of the protons of the hydroxyl group indicates that it is in the axial position **[5]**[6].

Ultrasonic irradiation has been used previously for enhancing the rate of crystallisation of metals, inorganic salts[7] and procaine penicillin[8] , however we are not aware of an example where it has been used in organic synthesis. Two factors seem to be in operation. On one hand nucleation is enhanced by the shear forces that are produced when the bubbles produced by cavitation collapse. Secondly the rate of crystallisation is enhanced by the fragmentation of the seed crystals[9] and this is consistent with the observation that smaller crystals are produced from irradiated than from silent crystallisations.

EXPERIMENTAL

Sonocrystallisations were performed in sealed round bottom flasks or under a reflux condensor in a 200W Ultrawave Ltd. bath (1 Oxford St., Cardiff, CF2 1YY), operating at a nominal frequency of 40 KHz (32-34 KHz actual), containing 500mls of water, in an efficient fume cupboard. **Caution:** heating occurs during the sonication and so pressure in the flask must be released periodically. The flow of air through the fume cupboard causes some cooling, but despite this, the bath temperature increases from 18.5-28°C in 12 minutes and after 30 minutes stabilises at 45°C.

REFERENCES

1 Mullins, J. W. *Crystallisation*, Butterworths, London, 1966; Gilman, J. J. *The Art and Science of Growing Crystals*, Wiley, New York, 1963.

2 Reviews; Einhorn, C.; Einhorn, J.; Luche, J. L., *Synthesis*, **1989**, 787. Suslick, S., (ed.) Ultrasound : Its Chemical, Physical and Biological Effects, VCH, New York, 1988; Mason, T. J.; Lorimer, J. P., *Sonochemistry, Theory, Applications and Uses of Ultrasound in Chemistry*, Ellis-Horwood, Chichester, 1989; Giguere, R. J., in *Organic Synthesis: Theory and Applications*, Hudlicky, T., (ed.), Jai Press, Greenwich, CT, 1989; Gol'berg, Y.; Sturkovich, R.; Lukevics, E., *Heterocycles*, **1989**, *29*, 597; Mason, T. J., *Critical Reports on Applied Chemistry*, **28**, *Chemistry with Ultrasound*, Elsevier, Barking, 1990.

3 Bergmann, M.; Zervas, L.; *Ber*, **1931**, *64*, 975.

4 Seebach, D; Hungerbuhler, E; Naef, R; Schnurrenberger, P.; Weidmann, B.; Zuger, M., *Synthesis*, **1982**, 138.

5 This determination was made by M. B. Hursthouse of this department. Full details will be published elsewhere.

6 δ ($CDCl_3$) 4.87 (1H, m, H^1), 3.96(1H, m, H^4, expected values for equatorial and axial hydroxyl groups 3.89 and 3.38 respectively)), δ (DMSO) 4.5 (1H, br, OH, expected values for equatorial and axial hydroxyl groups 4.0-4.5 and 3.8-4.2). Pretsch, E.; Seibl, J.; Clerc, T.; Simon, W., *Tables of Spectroscopic Data for Structure Determination of Organic Compounds*, 2nd edition, Springer-Verlag, Berlin, 1989. Assignments were confirmed by nOe measurements.

7 Sirota, N. N.; Gorskii, F. K.; Varikash, V. M., *Crystallisation Processes*, Consultants Bureau (Plenum Press), New York, 1966; Kmamski, E. V., *Crystallization from Solutions*, Consultants Bureau (Plenum Press), New York, 1969; Van Hook, A., *Crystallisation*, ACS monograph 152, Reinhold Publishing Corporation, New York, 1961, p206.

8 Umbdenstock, R. R., *US Patent*, 2,727,892, 1955.

9 For an example involving fragmentation of the crystals by the stirrer see Kondepudi, D. K.; Kaufman, R. J.; Singh, N., *Science*, **1990**, *259*, 975; McBride, J. M.; Carter, R. L., *Angew. Chem. Int. Ed. Engl.*, **1991**, *30*, 293.

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