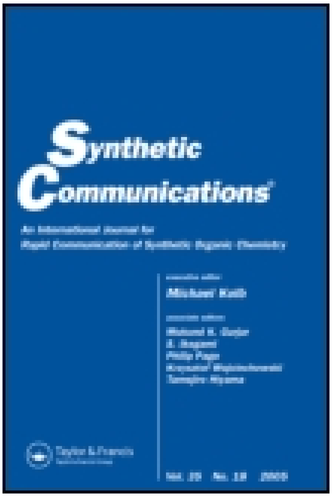

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Temperature and Ultrasound Rate Enhancement in the Baylis-Hillman Reaction

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To cite this article: Gregory H. P. Roos & Pradish Rampersadh (1993) Temperature and Ultrasound Rate Enhancement in the Baylis-Hillman Reaction, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 23:9, 1261-1266, DOI: 10.1080/00397919308011212

To link to this article: http://dx.doi.org/10.1080/00397919308011212

SYNTHETIC COMMUNICATIONS, 23(9), 1261-1266 (1993)

TEMPERATURE AND ULTRASOUND RATE ENHANCEMENT IN THE BAYLIS-HILLMAN REACTION

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ABSTRACT: Synthetically useful increases in reaction rate are achieved in the DABCO (1,4-diazabicyclo [2.2.2] octane) catalysed coupling of aldehydes with methyl acrylate by the application of ultrasound.

The Baylis-Hillman[1] coupling of activated vinyl moieties with suitable sp^2 electrophiles (mostly aldehydes) continues to attract attention in the literature.[2] The major drawback of this approach is the relative slowness (typically 3-7 days or longer) of reaction unless particularly reactive components are chosen.[2c] In the cases of sterically hindered or electronically deactivated components, this reaction time may stretch to a number of weeks.[2d] Examples which

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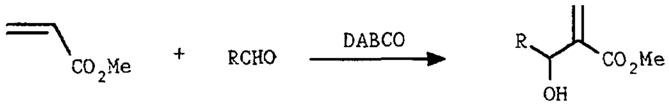
deal with solid vinyl and/or electrophilic coupling partners are particularly troublesome since a solvent/cosolvent is required, and leads to a further retardation of reaction rate.[3]

To date, this rate problem has largely been ignored or addressed largely via chemical solutions. Thus, the use of reactive vinyl,[1] reactive electrophile,[1,2c] alternative catalyst,[1] and increased catalyst quantities (up to 100 mole %)[2b] have all been reported. The only attempt to use physical means has been the remarkable reports of pressure induced (typically 5-9 kbar) rate acceleration by the Isaacs group.[2a] In the absence of the equipment to achieve these pressures, we sought a practical, routine alternative in the application of ultrasound. We would here like to report the findings of our simple preliminary study (**TABLE**).

For ease of comparison, only the aldehyde component and catalyst ratio were varied, with methyl acrylate serving as the standard vinylic reagent. Because of the warming effect of ultrasound, simultaneous control reactions were run in all cases in a thermostatically controlled bath. In selected cases, additional reactions were monitored at room temperature in order to estimate any rate changes due to temperature effects. From the **TABLE** it is clear that, whilst the sonicated reactions show small to moderate increases in reaction rate over the thermostatted controls, a more

TABLE Results of the Baylis-Hillman reaction rate study



R	DABCO%	$t_{1/2}$ (22°C) (min)[a]	$t_{1/2}$ (43°C) (min)[a]	$t_{1/2}$ (U/S) (min)[a]	U/S rate %[b] (Temp rate %)[b]
Me	5	3000[c]	88	50	43 (97)
Et	5	2760[c]	2600	1900	27 (6)
Et	10	2600	2100	1700	19 (19)
Et	20	—	1570	1110	30
^{i}Pr	20	—	6850	5800	15
Ph	2	—	6000	5350	11
Ph	10	3100	1900	1300	32 (39)
Ph	20	—	900	750	17
C_6H_{11}	20	14600	9900	9500	4 (32)

a. Mean value obtained from repetitive experiments

b. Describes rate % increase obtained from [$t_{1/2}$ (control) - $t_{1/2}$ x 100] / $t_{1/2}$ (control)

c. Values reported in ref. 5

marked rate increase is achieved by gentle warming. Whilst the rate factor increases may not appear all that remarkable, even a 10-20% enhancement on a 14 day reaction is a significant improvement in efficiency. It was surprising to note that to date no report of temperature effects in the Baylis-Hillman reaction have appeared. Isolated attempts in our laboratories to conduct these couplings under conditions of reflux (with and without co-solvents) have led to the formation of side products and/or polymeric materials. In this study, presumably because of the gentle nature of the heating, no deterioration relative to the room temperature reactions was observed. We have, whilst this work was underway, regularly used sonication on particularly slow (2-3 months) reactions involving solid acrylates with considerable success.[3] Although these runs were not quantitated, the improved observed rates prompt us to reccomend that this become a standard part of Baylis-Hillman protocol where necessary.

EXPERIMENTAL:

Methyl acrylate and all aldehydes were freshly distilled prior to use. DABCO (Fluka) was used as supplied. A Bandelin Sonorex TK52® ultrasonic cleaner (50-60 Hz) was used.

Kinetic measurements: All reactions were conducted neat (molar ratios of aldehyde : acrylate : DABCO were 1 : 1 : 0.05-0.20) in NMR tubes either at room temperature (22°C) or under ultrasonic or thermostatted bath (43°C) conditions. Reaction progress was followed by ^{1}H NMR via integral monitoring of the consumption of starting materials and appearance of products. All known[4] product hydroxyalkenoate esters gave spectral characterisation consistent with reported values.[1]

ACKNOWLEDGEMENTS:

The authors thank the FRD and the University of Natal for financial support, and Mr P Mason for product characterisation.

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3. Jensen, K.N. and Roos, G.H.P., S.Afr.J.Chem., 1992, in press.

4. Methyl α-methylene-β-cyclohexyl-β-hydroxy propanoate is unreported: m/e:198.3 (M^+); $C_{11}H_{18}O_3$ requires: C, 66.64; H, 9.09 % ; Found: C, 65.60; H, 8.88 %; δ_H (200 MHz; $CDCl_3$) 0.93-1.31 (m, 5H), 1.49-1.79 (m, 5H), 1.87-1.94 (m, 1H), 3.23 (br s, 1H), 3.76 (s, 3H), 4.13 (d, 1H, J=6.6 Hz), 5.76 (t, J=1.2 and 1.1 Hz), 6.25 (d, 1H, J=1.4 Hz); δ_C (50 MHz; $CDCl_3$) 26.03, 26.20, 26.44, 28.08, 29.94, 42.47, 51.83, 76.49, 126.04, 141.44, 167.18.

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(Received in UK 24 November 1992)