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Acceleration in water of the Baylis-Hillman reaction

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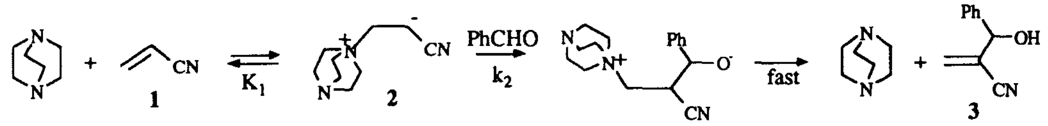
Abstract: DABCO-catalyzed coupling reaction of benzaldehyde with acrylonitrile was greatly accelerated in water compared to usual organic solvents. The reaction was even more accelerated by adding lithium or sodium iodide in the aqueous medium. Other structured solvents also enhanced the reaction, but to a smaller extent.

The tertiary amine catalyzed coupling reaction of acrylic derivatives with aldehydes, first reported by Baylis and Hillman is a general method to afford 3-hydroxy-2-methylenealkanoic acid derivatives,[1] but the reaction suffers from being inconveniently slow. Thus, the reaction of acrylonitrile with benzaldehyde in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) requires 3 days for completion. The reaction may be accelerated, (i) by substituting 3-hydroxyquinuclidine for DABCO,[2] (ii) by complexing the arene to the electrophilic $Cr(CO)_3$ group,[3] (iii) by high pressure,[4] (iv) under ultrasound,[5] or (v) by microwave irradiation.[6] Although the use of an aqueous solution was recently recommended in a special case,[7] no general studies were undertaken with water as the solvent. We have shown the new potentialities of the aqueous medium, especially when the activation volume was negative.[8] As a matter of fact, the Baylis Hillman reaction displays a very large and negative volume of activation (- 70 $cm^3.mol^{-1}$).[9] The rate of the formation of the adduct 3 may be expressed according the equation $v = k_{obs}$ [1] [PhCHO] [DABCO] where $k_{obs} = k_2K_1$ is a third-order rate constant or, assuming the concentration of DABCO to be constant, pseudo second-order constant.[10]



This letter deals with the influence of differents solvents on the rate of the reaction. The influence of some additives in aqueous medium was investigated as well. As a model, the reaction of acrylonitrile with benzaldehyde in the presence of 0.15 equivalent of DABCO was studied.[11] The reaction could be carried out to 90-98% yield at r.t. in 7-8 h in water, formamide or ethylene glycol, in 34 h in methanol and in 48 h in N-methylacetamide ; in DMSO, DMF, or neat, 3-5 d were required to achieve similar results and in THF or toluene, even after one week, only 15-30% were obtained. Structured liquids, such as water, formamide or ethylene glycol accelerate the reaction. A closer examination reveals that this similitude is only apparent. Whereas benzaldehyde and acrylonitrile are totally soluble in formamide or ethylene glycol, they are soluble to 60 and 110 mM, respectively, in water. The acceleration in water is therefore due to a large increase of the rate constant k_2 and/or the equilibrium constant K_1 in water *versus* organic solvents. The first step is probably even more rapid in water than in organic solvents, as in the Menschutkin reaction,[12] but this effect cannot have any influence on the overall rate of the reaction, since the second step is the rate-determining one.[9,10] Much more influent is the increase of the equilibrium constant K_1 in polar solvents, such as water ($\varepsilon = 78.5$), formamide ($\varepsilon = 109$), or N-methylacetamide ($\varepsilon = 183$). Moreover water or, to a smaller extent, ethylene glycol and methanol, could stabilize the zwitterionic form **2** through hydrogen bonds.[13] Since the volume of activation of the second step is negative ($\Delta V_2^{\neq} = -25$ cm^3.mol^{-1}),[9] this reaction could be accelerated via a process in which the hydrophobic effect could be involved.[8] This type of acceleration is largely dependent upon salting-in/ salting-out effects.[14] Such dichotomous effects were not observed clearly in our case. Paired with iodide anion, the cations can be ranked $Li^+ > Na^+ > K^+ > Cs^+$ in order of decreasing rate. The reaction could be carried out to 92-93% yield in only 2-3 h with a 4 M solution of LiI and NaI, respectively ; KI as an additive had no influence on the rate, but CsI slowed down the reaction (11 h, 92% yield). Paired with chloride anion, the cations do not follow this series. Unexpectively, lithium chloride slowed down the reaction (24 h, 82% yield), in contrast with many results where the hydrophobic effects could be invoked.[8]

Preliminary kinetic measurements were carried out in water and some organic solvents. In water one plot of x *versus* t (where x corresponds to the concentration of product **3** at time t) gave a straight line with slope equal to 7.4×10^{-5} M.s^{-1}, which is consistent with a zero-order reaction. This is probably due to the insolubility of the reactants, so that we can consider their concentrations to remain constant during the reaction. In formamide, ethylene glycol and N-methylacetamide, plots of ln(a-x)/(b-x) *versus* t (where a = 2.2 and b = 2 correspond to the initial concentrations of acrylonitrile and benzaldehyde, respectively) gave straight lines with slopes equal to 10.74×10^{-5}, 9.2×10^{-5}, and 3.86×10^{-5} M^{-1}.s^{-1}, respectively, which is consistent with pseudo second-order reactions.

An acceleration in water was also observed with other aldehydes, such as acetaldehyde, butyraldehyde, or furaldehyde. In the latter case, the reaction took place within 2 h at 0°C in water.

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