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Organic synthesis in water: 1,3-dipolar cycloaddition reactions at ambient temperature with aqueous suspensions of solid reactants

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Abstract—Huisgen cycloaddition reactions of the insoluble yellow solid, phthalazinium dicyanomethanide occurred readily for vigorously stirred aqueous suspensions when the solid dipolarophile had solubility >ca. 10^{-3} mol L^{-1}. For a solubility of ca. 10^{-4} mol L^{-1}, liquefaction of the dipolarophile was necessary in order to achieve reactions.
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Following the work of Breslow[1–6] on the influence of water on organic reactions and the identification of the hydrophobic effect[7,8] as the pervasive common factor in rate increases and stereochemical effects in water there has been increasing interest in water as a medium for organic reactions.[9–12] Since many organic reactants appear to be insoluble in water giving suspensions, it has been suggested[9] that the term 'on water' be applied to reactions between insoluble reactants which are suspensions in water. It has been pointed out that non-polar liquids that separate from water into a clear organic phase are good candidates for these reactions and that solids can also be used provided one reactant is a liquid.[9] Herein we suggest that when one or both reactants is a liquid the reactions could readily be occurring through an interfacial oily phase penetrated by water where both reactants are present at low concentrations. The oily phase is envisaged as transient single-phase nanoemulsion regions created under vigorous stirring when one of the reactants is a liquid.

Recently, we have examined[13,15] kinetic and some synthetic effects of water for 1,3-dipolar cycloadditions of the water-insoluble ($\leqslant 5 \times 10^{-6}$ mol L^{-1}) phthalazinium-2-dicyanomethanide **1** (mp 252–254 °C). Reactions between aqueous suspensions of **1** and insoluble liquid alkene and alkyne dipolarophiles[13,15] give high yields of cycloadducts (Scheme 1) through reactions
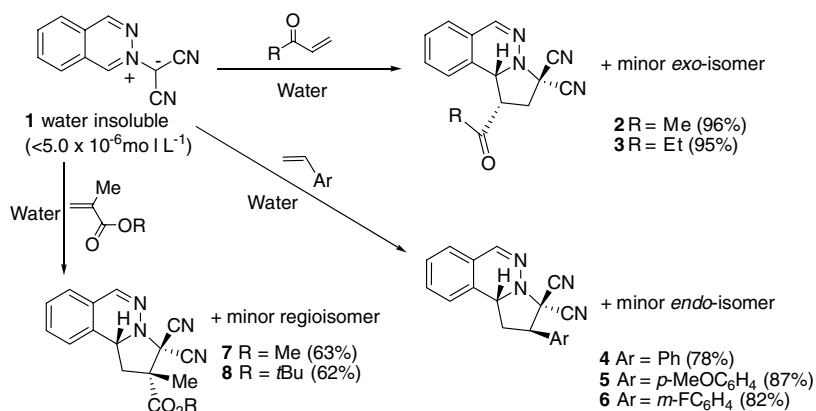
Scheme 1. Products from liquid dipolarophiles in water (Ref. 15).

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which can occur in an oily phase at the water-organic interface or the solid–liquid interface in the stirred mixture. To explore these types of reactions we have now focused on a number of cases where both reactants are water-insoluble solids. It has been pointed out that a significant challenge for organic synthesis in water will be to devise a protocol allowing the use of two solid reactants.[14]

The results of our reactions in the water environment are shown in Table 1 and Scheme 2. The products have been previously synthesised in organic solvents and fully characterised by us.[15,16] A number of solid dipolarophiles of decreasing water solubility were selected. The water solubilities of the dipolarophiles quoted are calculated values from Ref. 17 and we use the terminology 'slightly soluble' for solubility of the order 10^{-2} mol L^{-1}, 'sparingly soluble' for solubility of the order 10^{-3} mol L^{-1}, 'very sparingly soluble' for 10^{-4} mol L^{-1} or less, all of which give the appearance of insoluble suspensions in water.

Stirring[18] equimolar aqueous suspensions of the very sparingly soluble solid substrate **1** with a range of slightly or sparingly soluble solid N-substituted maleimides for 24 h at ambient temperatures (well below melting points) gave high yields of the products (Table 1, entries 1–6).

The yellow coloured suspensions changed to white as substrate **1** was consumed and replaced by product. The insoluble water-wet products stuck to the insides of the flask, but could be collected with care. When the solubility of the dipolarophile was lower by a further order of magnitude, a similar procedure with the very sparingly soluble diploarophile, *p*-chlorobenzylideneacetone gave less than 1% of product after stirring for 48 h at ambient temperatures. At 40 °C a small quantity of product was formed after stirring for 48 h, (Table 1, entries 7, 8). However, once the temperature of this reaction was raised above the mp of *p*-chlorobenzylidene-acetone (62 °C), namely, at 75 °C, the product was formed in high yield after stirring for 24 h (Table 1,

Table 1. Products from the reaction of **1** with solid dipolarophiles (1:1 mol ratio) in water (Scheme 2)

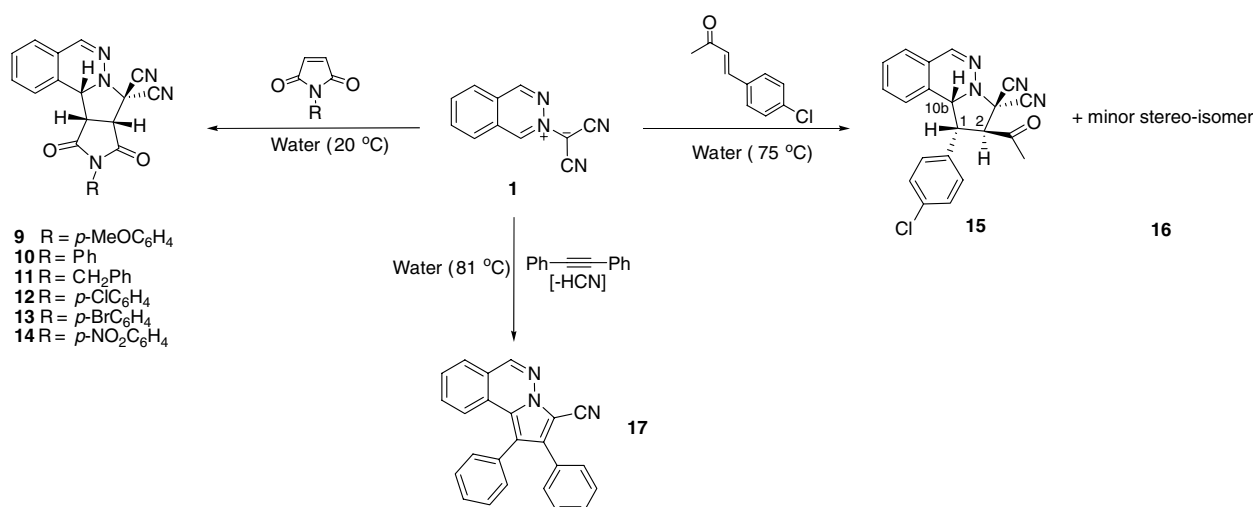| Entry	Dipolarophile	Mp (°C)	Molar solubility[a] (mol L^{-1})	Stirring time (h), T (°C)	Product	Yield (%)	Mp (°C)
1	*N-p*-MeOC$_6$H$_4$ maleimide (MI)	130–132	2.2×10^{-2}	24, 20[b]	**9**	95	215–216
2	*N*-Ph MI	89–90	1.2×10^{-2}	24, 20	**10**	96	252–253
3	*N*-CH$_2$Ph MI	70	3.2×10^{-3}	24, 20	**11**	91	205–207
4	*N-p*-ClC$_6$H$_4$ MI	95–97	2.0×10^{-3}	24, 20	**12**	94	237–238
5	*N-p*-BrC$_6$H$_4$ MI	128–130	1.7×10^{-3}	24, 20	**13**	93	235–236
6	*N-p*-NO$_2$C$_6$H$_4$ MI	168–170	1.7×10^{-3}	24, 20	**14**	95	226–227
7	*p*-Cl Benzylideneacetone	58–62	1.2×10^{-4}	48, 20	**15**	<1	—
8	*p*-Cl Benzylideneacetone	58–62	1.2×10^{-4}	48, 40	**15**	3.5[c]	162–163[d]
9	*p*-Cl Benzylideneacetone	58–62	1.2×10^{-4}	24, 75	**15**	86[c]	162–163[d]
10	Diphenylacetylene[e]	59–61	1.8×10^{-5}	24, 20	**17**	<1	—
11	Diphenylacetylene[e]	59–61	1.8×10^{-5}	24, 81	**17**	71	213–214

[a] At 25 °C from Ref. 17.
[b] Ambient temperature.
[c] Total yield including **16** (ratio **15:16**, 6.2:1).
[d] Mp of pure **15**.
[e] 10:1 mol ratio.

9 R = *p*-MeOC$_6$H$_4$
10 R = Ph
11 R = CH$_2$Ph
12 R = *p*-ClC$_6$H$_4$
13 R = *p*-BrC$_6$H$_4$
14 R = *p*-NO$_2$C$_6$H$_4$

Scheme 2. Products from solid reactants in water.

entry 9). Similar results were obtained with solid diphenylacetylene as dipolarophile (in 10 mol excess), (Table 1, entries 10 and 11). At ambient temperature no reaction occurred, but at 81 °C a high yield of product **17** (from cycloaddition and HCN elimination) was obtained. Hence, where both solid reactants are very sparingly soluble, liquefaction of one allows a reaction to occur as expected for an oily phase process. The solid substrate **1** has an intense yellow colour and even trace quantities present in a solution show a yellow colouration. These reactions, at temperatures where the dipolarophile was liquefying the oily phase, showed yellow colouration suggesting that compound **1** was passing through the solution. The solubility of the very sparingly soluble substrates may be higher at higher temperatures and this could also be a contributing factor to the dramatic effect of liquefaction of one reactant on the product formation.

The results suggest that these synthetic scale reactions with sparingly soluble diploarophiles are passing through the water at low concentrations. When the solubilities of both reactants are well below the millimolar threshold, liquefaction of one is necessary thereby allowing the reaction to pass through a water-penetrated oily phase. In both cases the reactions are likely driven by the hydrophobic effect which, (i) accelerates the reaction of sparingly soluble reactants and, (ii) immediately expels the more insoluble cycloadducts with larger organic surface areas from the medium as soon as they are formed (when they appear to stick to available surfaces).

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18. *Typical synthetic procedures*: (i) *Synthesis of endo-1,2-(dicarboxy-N-p-chlorophenylimido)-3,3-dicyano-1,2,3,10b-tetrahydropyrrolo[2,1-a]phthalazine* **12**. A suspension of compound **1** (0.30 g, 1.54 mmol) in water (20 cm^3, Millipore grade) was treated with N-(p-chlorophenyl)maleimide (0.32 g, 1.54 mmol) and stirred at ambient temperature for 24 h. During this time the suspended solids were converted to the product which was collected by filtration to give compound **12**, (0.541 g, 94%); mp 237–238 °C (ethanol). Anal. Calcd for $C_{21}H_{12}ClN_5O_2$: C, 62.7; H, 3.0; N, 17.4%. Found: C, 62.9; H, 3.1; N, 17.4%. IR (Nujol mull, cm^{-1}) 1781, 1716 (C=O); δ_H NMR (400 MHz, DMSO-d_6) 4.31 (dd, 1H, *J*, 7.8, 8.1, H-1), 4.68 (d, 1H, *J*, 7.8, H-2), 5.07 (d, 1H, *J*, 8.1 H-10b), 7.13 (d, 2H, *J*, 8.8, H-2′ of N–C_6H_4Cl), 7.41–7.57 (m, 5H, H-3′ of N–C_6H_4Cl and H-7 to H-9), 7.71 (d, 1H, *J* 7.3, H-10), 7.95 (s, 1H, H-6); δ_C NMR (100 MHz, DMSO-d_6) 45.2 (C-2), 51.2 (C-1), 59.1 (C-3), 59.8 (C-10b), 110.6, 112.2 (C≡N) 123.5 (C-10a) 127.0 (C-8), 127.6 (C-9), 129.2 (C-10), 129.3, 128.8, 133.3 (C-1′, C-2′, C-4′) of N–C_6H_4Cl, respectively. 130.2 (C-6a), 131.8 (C-7), 146.7 (C-6), 170.2, 172.4 (C=O).
(ii) *Synthesis of Compounds* **15** *and* **16**. A suspension of compound **1** (0.20 g, 1.03 mmol) and p-chlorobenzylideneacetone (0.19 g, 1.05 mmol) in water (10 cm^3, Millipore grade) was stirred vigorously at 75 °C for 24 h. During this time the suspended solids compacted into a sticky mass surrounding the stir bar and were converted to the products which were collected by filtration and scraping from the stir bar to give a mixture of compounds **15** and **16**; (0.35 g, 86% total yield); (ratio **15**:**16** determined by proton NMR, 6.2:1). Compound **15**, mp 162–163 °C (ethanol). Anal. Calcd for $C_{21}H_{15}ClN_4O$: C, 67.3; H, 4.05; N, 14.9%. Found: C, 67.0; H, 3.9; N, 15.4%. IR (Nujol mull, cm^{-1}) 761 (C–Cl), 1725 (C=O); δ_H NMR (400 MHz, CDCl$_3$) 1.87 (s, 3H, CH$_3$), 3.86 (dd, 1H, H-1), 4.26 (d, 1H, *J*, 7.8, H-2), 5.25 (d, 1H, *J*, 7.3, H-10b), 7.21 (d, 1H, *J*, 7.3, H-10), 7.34 (d, 1H, *J*, 7.3, H-7), 7.41–7.47 (m, 6H, H-8, H-9 and H-2′, H-3′), 7.63 (s, 1H, H-6); δ_C NMR (100 MHz, CDCl$_3$) 31.6 (CH$_3$), 57.2 (C-10b), 58.9, 59.4 (C-1, C-2), 65.9 (C-3), 11.2, 11.9 (C≡N), 124.3 (C-10a), 126.2 (C-10), 127.5 (C-9), 129.3 (C-1′), 129.8 (C-2′), 129.9 (C-8), 130.1 (C-3′), 130.4 (C-6a), 132.1 (C-7), 136.1 (C-4′), 144.6 (C-6), 204.5 (C=O).
Compound **16**, δ_H NMR (400 MHz, CDCl$_3$) (from mixture) key signals: 3.67 (dd, 1H, H-1), 4.19 (1H, *J*, 7.3, H-2), 4.66 (d, 1H, *J*, 8.7, H-10b). Other signals overlapped in the mixture. Regiochemistry and stereochemistry was confirmed by NOEDS.[15]