Uncommon aqueous media for nitrilimine cycloadditions. I. Synthetic and mechanistic aspects in the formation of 1-aryl-5-substituted-4,5-dihydropyrazoles

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A number of 1-aryl-5-substituted-4,5-dihydropyrazoles **4** have been synthesised by 1,3-dipolar cycloaddition of variously substituted nitrilimines **2** onto the appropriate alkenyl dipolarophiles **3** in aqueous media and in the presence of a surfactant. Under these conditions, uncommon for the large majority of [3 + 2] cycloadditions, the electronic features of both the cycloaddends strongly dictate the reaction outcome. Clean and fast cycloadditions were observed between electron-rich nitrilimines and electron-poor dipolarophiles, while the reversal of the electronic features of the reactants gave poor results. Changes in surfactant concentration leads to some novel mechanistic insights.

Introduction

As a very general rule, the large majority of organic reactions are carried out in non-aqueous media, since a number of synthetic valuable methodologies are currently developed in anhydrous solvents and/or under an inert atmosphere. As a consequence of the strict exclusion of water from reaction mixtures, organic transformations carried out in water or in aqueous media were often regarded as chemical curiosities and their synthetic utility was almost neglected for a long time. In recent years, however, there has been a rediscovery of water-promoted organic reactions, as is testified by a number of reviews.[1,2] This trend reflects the fact that water itself displays a number of desirable features: (*i*) the pH of the reaction medium can be easily controlled, (*ii*) reaction rates can be significantly increased, (*iii*) product separation can often be achieved by simple filtration of the crude reaction mixture, and (*iv*) environmentally-friendly procedures can be successfully elaborated. Among the organic transformations which appear to benefit from aqueous media, Diels–Alder and 1,3-dipolar cycloadditions occupy a prominent place. These processes, which were long regarded as solvent-insensitive, "no mechanism" reactions,[3] exhibit strong rate accelerations in water.[4] As a consequence, the Diels–Alder reaction has been extensively studied in aqueous solutions[5] as well as a number of 1,3-dipolar species including nitrile oxides,[6] azides,[7] and azomethine ylides.[8] Very recently, we exploited the first study on the feasibility of nitrilimine 1,3-dipolar cycloadditions to alkenyl dipolarophiles in aqueous medium.[9] The main products of such reactions, namely 1-aryl-5-substituted-4,5-dihydropyrazoles, represent an attractive target in view of their versatile biological activity.[10–13] In this work, we undertook the first systematic investigation on the behaviour of variously substituted nitrilimines **2** onto alkenyl dipolarophiles **3** in aqueous media (Fig. 1) according to the electronic features of both the cycloaddends.

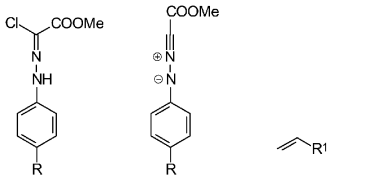

Fig. 1

Results

It is well known that the *in situ* generation of nitrilimines from the corresponding hydrazonoyl chlorides occurs in homogeneous phase by base treatment of the latter.[14] In our previous paper,[9] we described that dipolar cycloadditions between nitrilimines and dipolarophilic alkenes were best performed by shaking a heterogeneous mixture of the reactants in aqueous 0.1 M sodium hydroxide as the base and in the presence of tetrahexylammonium chloride (THAC) as the catalyst. However, since sizeable amounts of tetrazine by-product **5** (Scheme 1) were obtained in some cases, the first stage of the present work was concerned with the refinement of the above mentioned method. The search for the suitable basic agent, catalyst and catalyst concentration was achieved through the standard reactions depicted in Tables 1 and 2, respectively. Since the best results were obtained by mechanical shaking of a heterogeneous mixture of the reactants with sodium carbonate in the presence of THAC (8 mM) at room temperature, we decided to investigate the reactions of nitrilimines **2** with alkenyl dipolarophiles **3** in such conditions. Reaction times, products

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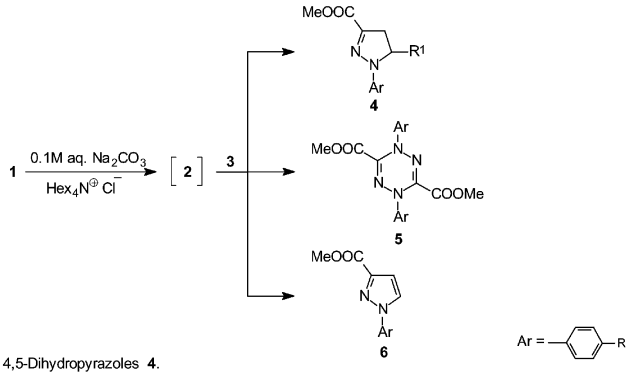


4,5-Dihydropyrazoles **4**.

Entry	aa	ab	ac	ba	bb	bc	bd	ca	cb	cc	cd	da	db	dd	ea	ed
R	H	H	H	Me	Me	Me	Me	MeO	MeO	MeO	MeO	Br	Br	Br	NO_2	NO_2
R^1	COOEt	CN	*n*-Bu	COOEt	CN	*n*-Bu	OBu	COOEt	CN	*n*-Bu	OBu	COOEt	CN	OBu	COOEt	OBu

Tetrazines **5** and pyrazoles **6**.

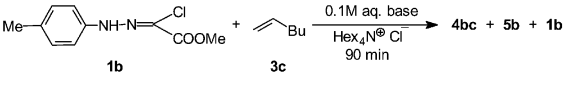
Entry	a	b	c	d	e
R	H	Me	MeO	Br	NO_2

Scheme 1

and yields are collected in Table 3. 1-Aryl-5-substituted-4,5-dihydropyrazoles **4**, which were formed as the only regioisomers, 1,2,4,5-tetrazines **5** and pyrazoles **6** were fully characterised by analytical and spectroscopic methods. The ^{1}H NMR spectra of cycloadducts **4** are in full agreement with those reported in the literature for similar 1-aryl-3-alkoxycarbonyl-5-substituted-4,5-dihydropyrazoles.[15] In particular, the hydrogens bonded to the C-4 and C-5 positions of the 4,5-dihydropyrazole ring appear as the ABX set of signals typical of these compounds, thus accounting for the depicted regiochemistry of the cycloaddition. It can be added that pyrazoles **6** arise from the corresponding 5-butoxy substituted 4,5-dihydropyrazoles. The driving force responsible for this oxidation/elimination is probably related to the extrusion of the stable butanol molecule; this behaviour has been reported for similar 5-ethoxy-4,5-dihydropyrazoles.[15a]

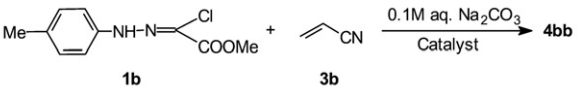
As can be inferred from Table 3, the extent of the cycloaddition was strongly dependent on the electronic features of both nitrilimines **2** and alkenyl dipolarophiles **3**. For a given nitrilimine, the cycloaddition outcome was usually satisfactory with electron-poor dipolarophiles. For example, very short reaction times and nearly quantitative yields of 4,5-dihydropyrazoles **4aa**, **4ba** and **4ca** were achieved from the cycloaddition between nitrilimines **2a**–**c** and ethyl acrylate **3a** (Table 3, entries 1, 5, 9). Conversely, in the presence of electron-rich alkenes longer reaction times were required, lower cycloadduct

Table 1 Reaction between hydrazonoyl chloride **1b** and 1-hexene **3c** in aqueous media



Entry	Base	Products and yields (%) 1b	4bc	5b
1	Na_2CO_3	9	31	25
2	K_2CO_3	10	30	25
3	Li_2CO_3	27	18	29
4	Cs_2CO_3	11	20	50
5	$NaHCO_3$	20	22	14
6	NaOH	—	—	92

Table 2 Reaction between hydrazonoyl chloride **1b** and acrylonitrile **3b** in aqueous media



Entry	Catalyst	Catalyst concentration/ mM	Time/ min	Products and Yields (%) 1b	4bb
1	*n*-Bu_4N^+ Cl^-	8	360	17	70
2	Et_3BnN^+ Cl^-	8	420	—	81
3	Cetyl $(Me)_2(Bn)N^+$ Cl^-	8	450	15	71
4	Cetyl (*n*-$Bu)_3P^+$ Cl^-	8	240	—	86
5	*n*-$C_{12}H_{25}OSO_3^-$ Na^+	2	420	—	75
6	*n*-$C_{12}H_{25}OSO_3^-$ Na^+	5	420	—	76
7	*n*-$C_{12}H_{25}OSO_3^-$ Na^+	8	420	—	80
8	*n*-$C_{12}H_{25}OSO_3^-$ Na^+	10	420	—	84
9	*n*-$C_{12}H_{25}OSO_3^-$ Na^+	12	420	—	87
10	*n*-$C_{12}H_{25}OSO_3^-$ Na^+	14	420	—	88
11	Hex_4N^+ Cl^-	1	120	12	62
12	Hex_4N^+ Cl^-	5	120	10	65
13	Hex_4N^+ Cl^-	8	120	—	78
14	Hex_4N^+ Cl^-	10	120	—	81
15	Hex_4N^+ Cl^-	14	120	—	92
16	Hex_4N^+ Cl^-	17	120	—	94

yields were observed and some tetrazine by-product and/or unreacted hydrazonoyl chloride **1** were recovered. 1-Hexene **3c** (Table 3, entries 3, 7, 11) and butyl vinyl ether **3d** (Table 3, entries 4, 8, 12) well illustrate this behaviour towards nitrilimines **2a**–**c**. Although acrylonitrile **3b** belongs to the class of electron-poor dipolarophiles, it shows an intermediate behaviour (Table 3, entries 2, 6, 10). The cycloaddition extent was less satisfactory with electron-poor nitrilimines **2d**,**e**. In particular, the presence of the strong electron-withdrawing nitro group of **2e** precluded the cycloaddition process, irrespective of the dipolarophile R^1 (Table 3, entries 17–20). To complete this picture, it can be added that in the absence of catalyst no reaction occurred between hydrazonoyl chloride **1b** and

Table 3 Reaction between hydrazonoyl chlorides **1** and dipolarophiles **3** in aqueous medium

Entry	R	R^1	Time/ min	Products and yields (%)[a] 1	4	5	6
1	H	COOEt	10	—	95	—	—
2	H	CN	70	10	56	26	—
3	H	*n*-Bu	90	5	17	42	—
4	H	OBu	150	—	—	—	15
5	Me	COOEt	10	—	95	—	—
6	Me	CN	60	—	78	—	—
7	Me	*n*-Bu	90	9	31	25	—
8	Me	OBu	105	—	24	21	15
9	MeO	COOEt	10	—	93	—	—
10	MeO	CN	45	—	80	—	—
11	MeO	*n*-Bu	120	—	52	33	—
12	MeO	OBu	180	—	27	15	28
13	Br	COOEt	70	—	68	17	—
14	Br	CN	105	8	30	43	—
15	Br	*n*-Bu	105	—	—	67	—
16	Br	OBu	90	—	25	27	29
17	NO_2	COOEt	100	—	3	—	—
18	NO_2	CN	180	—	—	—	—
19	NO_2	*n*-Bu	360	12	—	—	—
20	NO_2	OBu	360	—	10	—	10

[a] Isolation yields.

ethyl acrylate, since starting materials were recovered unchanged (see Experimental section).

Discussion

Some of the nitrilimine-alkene cycloadditions carried out in aqueous media are subjected to abnormal rate acceleration in comparison with similar water-free cycloadditions. The best results were obtained with electron-poor dipolarophiles and electron-rich nitrilimines, and reflects the usual HOMO-dipole (LUMO-dipolarophile) controlled nature of nitrilimine cycloadditions, as demonstrated from early reports.[16] On the other hand, literature calculations are generally performed *in vacuo* and/or at low level of theory. It is not surprising that such calculations are not well suited to account for reactive processes which occur in water. In order to provide an adequate level of theory for the cycloadditions under investigation, we undertake a computational effort (HF/IPCM and DFT/B3LYP/IPCM) also taking into account explicit water molecules. Full discussion of these calculations appears in the paper which immediately follows the present one in this issue. Our calculations generally predict rate accelerations for both electron-rich and electron-poor dipolarophiles, but the extent of the predicted enhancements is much smaller than that experimentally observed. It may be that, due to the very low solubility of both reactants **1** and **3** in water and to the presence of a catalyst, cycloadditions could be driven through pathways whose full evaluation escapes theoretical models. As a work hypothesis we suggested, in our previous paper, that the role played by THAC should be related to some kind of micellar catalysis.[9] To gain better insights about this point, let us examine closer the data summarised in Table 2 for the reaction between hydrazonoyl chloride **1b** and acrylonitrile in aqueous 0.1 M sodium carbonate. The concentrations of two catalysts, namely sodium dodecyl sulfate (SDS) and THAC, were varied in the range between 2–14 mM (entries 5–10) and 1–17 mM (entries 11–16), respectively. It is apparent that, for a fixed reaction time, the conversion degree of **1b** is roughly the same irrespective of the catalyst concentration. To this point, it is helpful to recall that: (*i*) the definition of the critical micellar concentration (CMC) states that "it is the concentration above which molecular aggregates, or micelles, are formed in solution";[17] and (*ii*) the CMC value for SDS is known to be 8.2 mM.[6f] On the basis of the latter datum, the findings outlined in Table 2 are in contrast with the picture of micellar catalysis, since the cycloaddition between **1b** and **3b** works well even far below the CMC value for SDS. Unfortunately, the CMC value for THAC is not known but, from the qualitative point of view, the results obtained with the latter catalyst are quite similar to those obtained with SDS. It is reasonable to think that the hydrophobic effect causes the close association of organic reactants, and the catalyst acts as a genuine phase transfer catalyst driving the basic agent from the bulk aqueous medium into the organic aggregate. The generation of the labile nitrilimine intermediate would then occur into the organic aggregate, which is characterised by a high local concentration of the dipolarophile. This kind of mechanism can justify the abnormal rate acceleration found for some nitrilimine-alkene cycloadditions carried out in aqueous media compared with similar water-free cycloadditions.

Experimental

Melting points were determined with a Büchi apparatus in open tubes and are uncorrected. IR spectra were recorded with a Perkin-Elmer 1725 X spectrophotometer. Mass spectra were determined with a VG-70EQ apparatus. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were taken with a Bruker AC 300 or a Bruker AMX 300 instrument (in $CDCl_3$ solutions at room temperature). Chemical shifts are given as ppm from tetramethylsilane and J values are given in Hz.

Hydrazonoyl chlorides **1** were synthesised according to literature procedures.[18]

Reaction between hydrazonoyl chlorides 1 and alkenyl dipolarophiles 3 in aqueous medium

A mixture of **1** (2.0 mmol), **3** (8.0 mmol), *n*-$Hex_4N^+Cl^-$ (75 mg, 0.2 mmol) and aqueous 0.1 M Na_2CO_3 (25 cm^3), was mechanically shaken at room temperature for the time indicated in Table 3.

In the case of entries 1, 5, 9, 10 and 15, the mixture was filtered; the solid material was washed with water (70 cm^3) and dried giving pure **4aa**, **4ba**, **4ca**, **4cb**, or **5d**, respectively.

1-Phenyl-3-methoxycarbonyl-5-ethoxycarbonyl-4,5-dihydropyrazole **4aa** (0.52 g, 95%) was a pale yellow solid, mp 90 °C (Found: C, 60.90; H, 5.83; N, 10.22. $C_{14}H_{16}N_2O_4$ requires C, 60.86; H, 5.84; N, 10.14%); ν_{max} (Nujol)/cm^{-1} 1730, 1720; δ_H ($CDCl_3$) 1.20 (3H, t, $J = 7.2$), 3.30 (1H, dd, $J = 18.1$, 6.9), 3.52 (1H, dd, $J = 18.1$, 13.4), 3.88 (3H, s), 4.20 (2H, q, $J = 7.2$), 4.94 (1H, dd, $J = 13.4$, 6.9), 6.90–7.20 (5H, m); δ_C ($CDCl_3$) 23.36 (q), 34.96 (t), 52.16 (q), 55.66 (t), 66.30 (d), 113.70 (d), 130.45 (d), 133.11 (d), 134.33 (s), 140.54 (s), 169.16 (s), 169.62 (s); m/z (EI) 276 (M^+).

1-(4-Methylphenyl)-3-methoxycarbonyl-5-ethoxycarbonyl-4,5-dihydropyrazole **4ba**[9] (0.55 g, 95%).

1-(4-Methoxyphenyl)-3-methoxycarbonyl-5-ethoxycarbonyl-4,5-dihydropyrazole **4ca** (0.57 g, 93%) was a yellow solid, mp 78 °C (Found: C, 58.86; H, 5.96; N, 9.21. $C_{15}H_{18}N_2O_4$ requires C, 58.82; H, 5.92; N, 9.15%); ν_{max} IR (Nujol)/cm^{-1} 1735, 1720; δ_H ($CDCl_3$) 1.19 (3H, t, $J = 7.0$), 3.30 (1H, dd, $J = 18.0$, 7.2), 3.51 (1H, dd, $J = 18.0$, 13.4), 3.76 (3H, s), 3.88 (3H, s), 4.18 (2H, q, $J = 7.0$), 4.90 (1H, dd, $J = 13.4$, 7.2), 6.80–7.10 (4H, m); δ_C ($CDCl_3$) 23.80 (q), 35.11 (t), 51.78 (q), 53.28 (q), 55.66 (t), 66.19 (d), 113.90 (d), 128.85–129.12, 133.30 (s), 134.33 (s), 139.40 (s), 169.23 (s), 169.67 (s); m/z (EI) 306 (M^+).

1-(4-Methoxyphenyl)-3-methoxycarbonyl-5-cyano-4,5-dihydropyrazole **4cb** (0.41 g, 80%) was a white solid, mp 122 °C (Found: C, 60.29; H, 5.01; N, 16.18 $C_{13}H_{13}N_3O_3$ requires C, 60.23; H, 5.05; N, 16.21%); ν_{max} (Nujol)/cm^{-1} 1720; δ_H ($CDCl_3$) 3.52 (1H, dd, $J = 18.1$, 8.6), 3.59 (1H, dd, $J = 18.1$, 8.6), 3.80 (3H, s), 3.89 (3H, s), 5.04 (1H, t, $J = 8.6$), 6.90–7.20 (4H, m); δ_C ($CDCl_3$) 34.80 (t), 52.78 (q), 55.36 (q), 65.13 (d), 114.89 (d), 125.39 (s), 130.16–130.95, 131.68 (s), 134.65 (s), 139.46 (s), 168.55 (s); m/z (EI) 259 (M^+).

1,4-Bis(4-bromophenyl)-3,6-bis(methoxycarbonyl)-1,4-dihydro-1,2,4,5-tetrazine **5d** (0.34 g, 67%) was a dark red solid, mp 163 °C (Found: C, 42.42; H, 2.80; N, 11.03. $C_{18}H_{14}Br_2N_4O_4$ requires C, 42.38; H, 2.77; N, 10.98%); ν_{max} (Nujol)/cm^{-1} 1740; δ_H ($CDCl_3$) 3.74 (6H, s), 7.10–7.50 (8H, m); δ_C ($CDCl_3$) 55.45 (q), 114.25 (d), 121.01 (d), 124.13 (s), 156.16 (s), 169.32 (s); m/z (EI) 510 (M^+).

In the case of entries 6, 11 and 13 the mixture was filtered; the solid material was washed with water (75 cm^3) and dried. Crystallisation from iPrOH gave pure **4bb**, **4cc**, or **4da**, respectively. Evaporation of the mother liquor and subsequent crystallisation from hexane–benzene gave tetrazines **5c** and **5d**, respectively.

1-(4-Methylphenyl)-3-methoxycarbonyl-5-cyano-4,5-dihydropyrazole **4bb**[9] (0.36 g, 74%).

1-(4-Methoxyphenyl)-3-methoxycarbonyl-5-butyl-4,5-dihydropyrazole **4cc** (0.38 g, 52%) was a white solid, mp 62 °C (Found: C, 66.12; H, 7.68; N, 9.70. $C_{16}H_{22}N_2O_3$ requires C, 66.18; H, 7.64; N, 9.65); ν_{max} (Nujol)/cm^{-1} 1730; δ_H ($CDCl_3$) 0.86 (3H, t, $J = 6.1$), 1.20–1.60 (6H, m), 2.86 (1H, dd, $J = 17.9$, 6.6), 3.23 (1H, dd, $J = 17.9$, 12.5), 3.74 (3H, s),

3.83 (3H, s), 4.48 (1H, dddd, J = 12.5, 6.6, 5.8, 5.2), 6.80–7.10 (4H, m); δ_C ($CDCl_3$) 13.88 (q), 22.36 (t), 26.50 (t), 31.46 (t), 35.38 (t), 52.13 (q), 55.40 (q), 66.27 (d), 113.90–115.10, 130.70 (s), 137.31 (s), 139.65 (s), 168.53 (s); m/z (EI) 290 (M^+).

1-(4-Bromophenyl)-3-methoxycarbonyl-5-ethoxycarbonyl-4,5-dihydropyrazole **4da** (0.48 g, 68%) was a yellow solid, mp 89 °C (Found: C, 47.40; H, 4.22; N, 7.94 $C_{14}H_{15}BrN_2O_4$ requires C, 47.34; H, 4.26; N, 7.89%); ν_{max} (Nujol)/cm^{-1} 1735, 1720; δ_H ($CDCl_3$) 1.16 (3H, t, J = 7.1), 3.26 (1H, dd, J = 18.0, 6.7), 3.45 (1H, dd, J = 18.0, 13.5), 3.81 (3H, s), 4.18 (2H, q, J = 7.1), 4.91 (1H, dd, J = 13.5, 6.7), 7.00–7.35 (4H, m); δ_C ($CDCl_3$) 35.22 (t), 52.80 (q), 53.19 (q), 54.78 (t), 66.37 (d), 115.70 (d), 128.45–130.16, 133.43 (s), 134.70 (s), 140.10 (s), 169.11 (s), 169.80 (s); m/z (EI) 355 (M^+).

1,4-Bis(4-methoxyphenyl)-3,6-bis(methoxycarbonyl)-1,4-dihydro-1,2,4,5-tetrazine **5c** (0.14 g, 33%) was a dark red solid, mp 160 °C (Found: C, 58.28; H, 4.92; N, 13.63 $C_{20}H_{20}N_4O_6$ requires C, 58.25; H, 4.89; N, 13.59%); ν_H (Nujol)/cm^{-1} 1740; δ_H ($CDCl_3$) 3.64 (6H, s), 3.78 (6H, s), 6.85–7.20 (8H, m); δ_C ($CDCl_3$) 53.28 (q), 55.45 (q), 114.25 (d), 121.10 (d), 125.03 (s), 155.92 (s), 168.90 (s); m/z (EI) 412 (M^+).

In the case of entries 2, 3, 7 and 14 the mixture was taken up with CH_2Cl_2 (75 cm^3). The organic layer was washed with water (100 cm^3), dried over Na_2SO_4 and evaporated. The residue was chromatographed on a silica gel column with AcOEt–Hexane 3:1. Unreacted **1a**, **1b** or **1d** was eluted first, followed by the corresponding tetrazine **5**.[19]

Further elution gave **4ab**, **4ac**, **4bc** and **4db**, respectively.

1-Phenyl-3-methoxycarbonyl-5-cyano-4,5-dihydropyrazole **4ab** (0.26 g, 56%) was a pale yellow solid, mp 109 °C (from iPrOH/iPr_2O) (Found: C, 62.93; H, 4.81; N, 18.28. $C_{12}H_{11}N_3O_2$ requires C, 62.87; H, 4.84; N, 18.33%); ν_{max} (Nujol)/cm^{-1} 1725; δ_H ($CDCl_3$) 3.54 (1H, dd, J = 18.0, 8.8), 3.59 (1H, dd, J = 18.0, 8.8), 3.92 (3H, s), 5.06 (1H, t, J = 8.8), 7.05–7.30 (5H, m); δ_C ($CDCl_3$) 34.88 (t), 52.56 (q), 65.16 (d), 115.12 (d), 125.17 (s), 128.38–130.63, 131.20 (s), 140.31 (s), 169.16 (s); m/z (EI) 229 (M^+).

1-Phenyl-3-methoxycarbonyl-5-butyl-4,5-dihydropyrazole **4ac** (88 mg, 17%) was a white solid, mp 59 °C (from iPr_2O) (Found: C, 69.24; H, 7.68; N, 10.82. $C_{15}H_{20}N_2O_2$ requires C, 69.20; H, 7.74; N, 10.76%); ν_{max} (Nujol)/cm^{-1} 1730; δ_H ($CDCl_3$) 0.85 (3H, t, J = 6.3), 1.20–1.56 (6H, m), 2.85 (1H, dd, J = 17.8, 6.5), 3.25 (1H, dd, J = 17.8, 12.4), 3.76 (3H, s), 4.52 (1H, dddd, J = 12.4, 6.6, 6.5, 5.8), 6.90–7.10 (5H, m); δ_C ($CDCl_3$) 13.85 (q), 22.34 (t), 26.49 (t), 30.90 (t), 34.85 (t), 52.38 (q), 66.54 (d), 113.60–116.40, 131.20 (s), 139.93 (s), 168.19 (s); m/z (EI) 260 (M^+).

1-(4-Methylphenyl)-3-methoxycarbonyl-5-butyl-4,5-dihydropyrazole **4bc** (0.16 g, 30%) was a dark yellow oil (Found: C, 70.10; H, 8.05; N, 10.29. $C_{16}H_{22}N_2O_2$ requires C, 70.04; H, 8.08; N, 10.21%); ν_{max} (Nujol)/cm^{-1} 1730; δ_H ($CDCl_3$) 0.86 (3H, t, J = 5.9), 1.20–1.80 (6H, m), 2.29 (3H, s), 2.86 (1H, dd, J = 17.6, 6.4), 3.23 (1H, dd, J = 17.6, 12.3), 3.86 (3H, s), 4.50 (1H, dddd, J = 12.3, 6.4, 5.8, 5.2), 7.05–7.15 (4H, m); δ_C ($CDCl_3$) 13.96 (q), 20.59 (q), 22.45 (t), 26.55 (t), 31.55 (t), 36.50 (t), 52.02 (q), 61.41 (d), 113.90–115.10, 130.84 (s), 137.24 (s), 139.72 (s), 167.58 (s); m/z (EI) 274 (M^+).

1-(4-Bromophenyl)-3-methoxycarbonyl-5-cyano-4,5-dihydropyrazole **4db** (0.18 g, 30%) was a yellow solid, mp 105 °C (from iPrOH/iPr_2O) (Found: C, 46.81; H, 3.24; N, 13.70. $C_{12}H_{10}BrN_3O_2$ requires C, 46.78; H, 3.27; N, 13.64%); ν_{max} (Nujol)/cm^{-1} 1730; δ_H ($CDCl_3$) 3.57 (1H, dd, J = 17.8, 8.7), 3.63 (1H, dd, J = 17.8, 8.7), 3.92 (3H, s), 5.08 (1H, t, J = 8.7), 7.10–7.50 (4H, m); δ_C ($CDCl_3$) 35.28 (t), 51.06 (q), 65.90 (d), 116.38 (d), 125.95 (s), 127.80–130.16, 132.40 (s), 133.84 (s), 140.76 (s), 168.88 (s); m/z (EI) 308 (M^+).

In the case of entries 8, 12 and 16 the mixture was taken up with CH_2Cl_2 (75 cm^3). The organic layer was washed with water (100 cm^3), dried over Na_2SO_4 and evaporated. The residue was chromatographed on a silica gel column with Et_2O–CH_2Cl_2 10:1. Tetrazine **5b**, **5c** or **5d** was eluted first, followed by the corresponding pyrazoles **6b**, **6c** and **6d**.

Further elution gave **4bd**, **4cd** and **4dd**, respectively.

1-(4-Methylphenyl)-3-methoxycarbonylpyrazole **6b** (65 mg, 15%) was a white solid, mp 115 °C (from hexane–benzene) (Found: C, 63.64; H, 9.84; N, 12.44. $C_{12}H_{12}N_2O_2$ requires C, 63.69; H, 9.80; N, 12.38%); ν_{max} (Nujol)/cm^{-1} 1730; δ_H ($CDCl_3$) 2.32 (3H, s), 3.95 (3H, s), 6.95 (1H, d, J = 2.7), 7.14–7.60 (4H, m), 7.88 (1H, d, J = 2.7); δ_C ($CDCl_3$) 21.12 (q), 52.56 (q), 105.31 (d), 115.86 (d), 128.58–130.59, 133.15 (s), 139.18 (s), 169.16 (s); m/z (EI) 216 (M^+).

1-(4-Methoxyphenyl)-3-methoxycarbonylpyrazole **6c** (0.13 g, 28%) was a white solid, mp 73 °C (from hexane–benzene) (Found: C, 62.10; H, 5.17; N, 12.12. $C_{12}H_{12}N_2O_3$ requires C, 62.06; H, 5.21; N, 12.06%); ν_{max} (Nujol)/cm^{-1} 1735; δ_H ($CDCl_3$) 3.80 (3H, s), 3.91 (3H, s), 6.92 (1H, d, J = 3.0), 7.00–7.60 (4H, m), 7.86 (1H, d, J = 3.0); δ_C ($CDCl_3$) 52.38 (q), 55.72 (q), 105.84 (d), 115.50 (d), 127.60–130.00, 135.12 (s), 140.31 (s), 168.18 (s); m/z (EI) 232 (M^+).

1-(4-Bromophenyl)-3-methoxycarbonylpyrazole **6d** (0.16 mg, 29%) was a white solid, mp 144 °C (from hexane–benzene) (Found: C, 46.94; H, 3.26; N, 10.04. $C_{11}H_9BrN_2O_2$ requires C, 47.00; H, 3.23; N, 9.97%); ν_{max} (Nujol)/cm^{-1} 1735; δ_H ($CDCl_3$) 3.90 (3H, s), 6.90 (1H, d, J = 3.0), 7.50–7.70 (4H, m), 7.90 (1H, d, J = 3.0); δ_C ($CDCl_3$) 51.80 (q), 104.28 (d), 117.21 (d), 128.90–131.20, 132.83 (s), 140.76 (s), 168.31 (s); m/z (EI) 2816 (M^+).

1-(4-Methylphenyl)-3-methoxycarbonyl-5-butoxy-4,5-dihydropyrazole **4bd** (0.14 g, 24%) was a pale yellow solid, mp 68 °C (from iPrOH/iPr_2O) (Found: C, 66.22; H, 7.70; N, 9.71. $C_{16}H_{22}N_2O_3$ requires C, 66.18; H, 7.64; N, 9.65%); ν_{max} (Nujol)/cm^{-1} 1730; δ_H ($CDCl_3$) 0.90 (3H, t, J = 6.0), 1.20–1.60 (4H, m), 2.28 (3H, s), 2.90 (1H, dd, J = 18.0, 6.6), 3.20 (1H, dd, J = 18.0, 12.4), 3.45 (2H, t, J = 6.3), 3.88 (3H, s), 5.84 (1H, dd, J = 12.4, 6.3), 7.10–7.30 (4H, m); δ_C ($CDCl_3$) 16.03 (q), 20.37 (q), 22.30 (t), 27.53 (t), 35.38 (t), 51.85 (q), 55.30 (t), 67.28 (d), 116.36 (d), 128.80–130.70, 132.40 (s), 133.21 (s), 140.21 (s), 168.90 (s); m/z (EI) 290 (M^+).

1-(4-Methoxyphenyl)-3-methoxycarbonyl-5-butoxy-4,5-dihydropyrazole **4cd** (0.17 g, 27%) was a white solid, mp 58 °C (from iPrOH) (Found: C, 62.77; H, 7.27; N, 9.21. $C_{16}H_{22}N_2O_4$ requires C, 62.73; H, 7.24; N, 9.14%); ν_{max} (Nujol)/cm^{-1} 1730; δ_H ($CDCl_3$) 0.85 (3H, t, J = 6.0), 1.20–1.40 (4H, m), 3.05 (1H, dd, J = 18.0, 6.7), 3.18 (1H, dd, J = 18.0, 12.1), 3.40 (2H, t, J = 6.4), 3.75 (3H, s), 3.84 (3H, s), 5.80 (1H, dd, J = 12.1, 6.7), 6.80–7.30 (4H, m); δ_C ($CDCl_3$) 17.11 (q), 21.70 (t), 25.14 (t), 36.18 (t), 52.31 (q), 55.20 (t), 55.95 (q), 66.58 (d), 115.19 (d), 128.10–130.20, 131.94 (s), 135.16 (s), 140.38 (s), 169.25 (s); m/z (EI) 306 (M^+).

1-(4-Bromophenyl)-3-methoxycarbonyl-5-butoxy-4,5-dihydropyrazole **4dd** (0.18 g, 25%) was a yellow solid, mp 74 °C (from iPrOH/iPr_2O) (Found: C, 50.76; H, 5.43; N, 7.95. $C_{15}H_{19}BrN_2O_3$ requires C, 50.72; H, 5.39; N, 7.89%); ν_{max} (Nujol)/cm^{-1} 1730; δ_H ($CDCl_3$) 0.80 (3H, t, J = 6.2), 1.20–1.45 (4H, m), 3.10 (1H, dd, J = 18.0, 6.7), 3.18 (1H, dd, J = 18.0, 12.2), 3.40 (2H, t, J = 6.7), 3.88 (3H, s), 5.83 (1H, dd, J = 12.2, 6.7), 7.20–7.50 (4H, m); δ_C ($CDCl_3$) 16.74 (q), 20.90 (t), 26.18 (t), 36.16 (t), 52.73 (q), 55.24 (t), 67.15 (d), 116.16 (d), 128.40–130.12, 130.76 (s), 134.08 (s), 139.85 (s), 168.94 (s); m/z (EI) 355 (M^+).

In the case of entries 4, 17, 19 and 20 the mixture was taken up with CH_2Cl_2 (75 cm^3). The organic layer was washed with water (100 cm^3), dried over Na_2SO_4 and evaporated. The residue was chromatographed on a silica gel column with Et_2O.

1-Phenyl-3-methoxycarbonyl-pyrazole **6a** (61 mg, 15%) was obtained (entry 4) as a white solid, mp 76 °C (from hexane–benzene) (Found: C, 65.38; H, 5.02; N, 13.92. $C_{11}H_{10}N_2O_2$ requires C, 65.34; H, 4.98; N, 13.85%); ν_{max} (Nujol)/cm^{-1} 1730; δ_H ($CDCl_3$) 3.92 (3H, s), 7.00 (1H, d, J = 2.8), 7.05–7.40 (5H, m), 7.90 (1H, d, J = 2.8); δ_C ($CDCl_3$) 52.28 (q),

105.27 (d), 116.12 (d), 128.60–130.86, 133.15 (s), 140.21 (s), 168.18 (s); m/z (EI) 202 (M^+).

1-(4-Nitrophenyl)-3-methoxycarbonyl-5-ethoxycarbonyl-4,5-dihydropyrazole **4ea** (19 mg, 3%) was obtained (entry 17) as a white solid, mp 97 °C (from MeOH) (Found: C, 52.30; H, 4.67; N, 13.13. $C_{14}H_{15}N_3O_6$ requires C, 52.34; H, 4.71; N, 13.08%); ν_{max} (Nujol)/cm^{-1} 1740, 1725; δ_H ($CDCl_3$) 1.24 (3H, t, $J = 7.2$), 3.34 (1H, dd, $J = 17.8$, 6.8), 3.61 (1H, dd, $J = 17.8$, 12.5), 3.95 (3H, s), 4.25 (2H, q, $J = 7.2$), 5.02 (1H, dd, $J = 12.5$, 6.8), 7.30–8.30 (4H, m); δ_C ($CDCl_3$) 23.70 (q), 36.16 (t), 51.05 (t), 52.66 (q), 67.32 (d), 118.28 (d), 131.80 (d), 134.15 (s), 138.80 (s), 140.89 (s), 169.58 (s), 170.07 (s); m/z (EI) 321 (M^+).

In the case of entry 19, unreacted **1e** was obtained.

In the case of entry 20, first fractions the pyrazole **6e**; further elution gave **4ed**.

1-(4-Nitrophenyl)-3-methoxycarbonylpyrazole **6e** (50 mg, 10%) was a dark yellow solid, mp 153 °C (from hexane–benzene) (Found: C, 53.39; H, 3.63; N, 16.63. $C_{11}H_9N_3O_4$ requires C, 53.44; H, 3.67; N, 17.00%); ν_{max} (Nujol)/cm^{-1} 1740; δ_H ($CDCl_3$) 3.88 (3H, s), 6.94 (1H, d, $J = 2.8$), 7.30–7.40 (2H, m), 7.96 (1H, d, $J = 2.8$), 8.00–8.20 (2H, m); δ_C ($CDCl_3$) 52.13 (q), 105.68 (d), 118.31 (d), 123.35 (d), 131.18 (d), 133.16 (s), 138.57 (s), 140.51 (s), 168.90 (s); m/z (EI) 247 (M^+).

1-(4-Nitrophenyl)-3-methoxycarbonyl-5-butoxy-4,5-dihydropyrazole **4ed** (65 mg, 10%) was a yellow solid, mp 67 °C (from iPrOH) (Found: C, 56.11; H, 6.00; N, 13.14. $C_{15}H_{19}N_3O_5$ requires C, 56.07; H, 5.96; N, 13.08%); ν_{max} (Nujol)/cm^{-1} 1740; δ_H ($CDCl_3$) 0.85 (3H, t, $J = 6.3$), 1.20–1.50 (4H, m), 3.10 (1H, dd, $J = 18.0$, 6.7), 3.20 (1H, dd, $J = 18.0$, 12.4), 3.36 (2H, t, $J = 6.7$), 3.92 (3H, s), 5.96 (1H, dd, $J = 12.4$, 6.7), 7.30–8.20 (4H, m); δ_C ($CDCl_3$) 16.80 (q), 21.38 (t), 27.03 (t), 36.58 (t), 52.12 (q), 55.38 (t), 67.98 (d), 119.25 (d), 132.14 (d), 133.20 (s), 138.96 (s), 140.71 (s), 169.85 (s); m/z (EI) 321 (M^+).

In the case of entry 18 the mixture was taken up with CH_2Cl_2 (75 cm^3). The organic layer was washed with water (100 cm^3), dried over Na_2SO_4 and evaporated giving untractable tarry material.

Reaction between hydrazonoyl chloride 1b and 1-hexene 3c in aqueous media

A mixture of methyl 2-chloro-2-(4-methylphenyl-hydrazono) acetate **1b** (0.45 g, 2.0 mmol), 1-hexene **3c** (0.67 g, 8.0 mmol), n-$Hex_4N^+Cl^-$ (75 mg, 0.2 mmol) and aqueous 0.1 M base (25 cm^3), (see Table 1) was mechanically shaken at room temperature for 90 min.

In the case of entries 1–5, the mixture was taken up with CH_2Cl_2 (100 cm^3). The organic layer was washed with water (2×50 cm^3), dried over Na_2SO_4 and evaporated. The residue was chromatographed on a silica gel column with AcOEt–CH_2Cl_2 1:5. Unreacted **1b** was eluted first, followed by the corresponding tetrazine **5b**. Further elution gave pyrazoline **4bc**.

In the case of entry 6 the mixture was filtered; the solid material was washed with water (100 cm^3) and dried giving tetrazine **5b**.

Reaction between hydrazonoyl chloride 1b and acrylonitrile 3b in aqueous media

A mixture of methyl 2-chloro-2-(4-methylphenyl-hydrazono) acetate **1b** (0.45 g, 2.0 mmol), acrylonitrile **3b** (0.42 g, 8.0 mmol), phase-transfer catalyst (see Table 2) and aqueous 0.1 M Na_2CO_3 (25 cm^3), was mechanically shaken at room temperature for the time indicated in Table 2.

In the case of entry 2, entries 4–10 and 13–16 the mixture was filtered; the solid material was washed with water (100 cm^3) and dried giving the pyrazoline **4bb**.

In the case of entries 1, 3 and 11, 12, the mixture was taken up with CH_2Cl_2 (100 cm^3). The organic layer was washed with water (2×50 cm^3), dried over Na_2SO_4 and evaporated. The residue was chromatographed on a silica gel column with AcOEt–light petroleum 2:1. Unreacted **1b** was eluted first, followed by the pyrazoline **4bb**.

Treatment of hydrazonoyl chloride 1b with ethyl acrylate 3a in aqueous media

A mixture of methyl 2-chloro-2-(4-methylphenyl-hydrazono) acetate **1b** (0.30 g, 1.3 mmol), ethyl acrylate **3a** (0.53 g, 5.3 mmol) and aqueous 0.1 M Na_2CO_3 (16 cm^3), was mechanically shaken at room temperature for 24 h. The mixture was filtered; the solid material was washed firstly with water (40 mL), then with hexane (40 mL) and dried giving unreacted **1b** (0.28 g, 94%).

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References

1 For a monograph: *Organic Synthesis in Water*, ed. P. A Grieco, Blackie, Glasgow, 1998.
2 For reviews(*a*) J. B. F. N. Engberts and M. J. Blandamer, *Chem. Commun.*, 2001, 1701; (*b*) A. R. Katritzky and D. A. Nichols, *Chem. Rev.*, 2001, **101**, 825; (*c*) A. R. Katritzky, D. A. Nichols, M. Siskin, R. Murugan and M. Balasubramanian, *Chem. Rev.*, 2001, **101**, 837; (*d*) S. Ribe and P. Wipf, *J. Chem. Soc., Chem. Commun.*, 2001, 299; (*e*) A. Lubineau, J. Augé and Y. Queneau, *Synthesis*, 1994, 741; (*f*) C.-J. Li, *Chem. Rev*, 1993, **93**, 2023; (*g*) R. Breslow, *Acc. Chem. Res.*, 1991, **24**, 159; (*h*) P. A. Grieco, *Aldrichimica Acta*, 1991, **24**, 59.
3 W. E. Doering and W. R. Roth, *Tetrahedron*, 1962, **18**, 67.
4 D. C. Rideout and R. Breslow, *J. Am. Chem. Soc.*, 1980, **102**, 7816.
5 (*a*) R. Breslow, U. Maitra and D. C. Rideout, *Tetrahedron Lett.*, 1983, **24**, 1901; (*b*) L. A. Van Royen, R. Mijngheer and P. J. De Clercq, *Tetrahedron*, 1985, **41**, 4667; (*c*) H. Waldmann, *Angew. Chem., Int. Ed. Engl.*, 1988, **27**, 274; (*d*) H. Waldmann and M. Braun, *Liebigs Ann. Chem.*, 1991, 1045; (*e*) W. Blokzijl, M. J. Blandamer and J. B. F. N. Engberts, *J. Am. Chem. Soc.*, 1991, **113**, 4241; (*f*) J. W. Wijnen and J. B. F. N. Engberts, *J. Org. Chem.*, 1997, **62**, 2039; (*g*) F. Fringuelli, O. Piermatti and F. Pizzo, *Targets Heterocycl. Syst.*, 1997, **1**, 57; (*h*) D. Amantini, F. Fringuelli, O. Piermatti, F. Pizzo and L. Vaccaro, *Green Chem.*, 2001, 229; (*i*) F. Fringuelli, O. Piermatti, F. Pizzo and L. Vaccaro, *Eur. J. Org. Chem.*, 2001, 439.
6 (*a*) C. Grundmann and R. Richter, *J. Org. Chem.*, 1967, **32**, 2308; (*b*) C. Grundmann and S. K. Datta, *J. Org. Chem.*, 1969, **34**, 2016; (*c*) K. J. Dignam, A. F. Hegarty and P. L. Quain, *J. Org. Chem.*, 1978, **43**, 388; (*d*) Y. Inoue, K. Araki and S. Shiraishi, *Bull. Chem. Soc. Jpn.*, 1991, **64**, 3079; (*e*) J. C. Rohloff, J. Robinson III and J. O. Gardner, *Tetrahedron Lett.*, 1992, **33**, 3113; (*f*) D. van Mersbergen, J. W. Wijnen and J. B. F. N. Engberts, *J. Org. Chem.*, 1998, **63**, 8801.
7 (*a*) Z. Demko and K. B. Sharpless, *J. Org. Chem.*, 2001, **66**, 7945; (*b*) J. W. Wijnen, R. A. Steiner and J. B. F. N. Engberts, *Tetrahedron Lett.*, 1995, **36**, 5389.
8 (*a*) R. Grigg, T. Mongkolaussavaratana, C. A. Pounds and S. Sivagnanam, *Tetrahedron Lett.*, 1990, **31**, 7215; (*b*) A. Lubineau, G. Bouchain and Y. Queneau, *J. Chem. Soc., Perkin Trans. 1*, 1995, 2433.
9 G. Broggini, G. Molteni and M. Orlandi, *J. Chem. Soc., Perkin Trans. 1*, 2000, 3742.
10 S. W. Djuric, N. Y. BaMaung, A. Basha, H. Liu, J. R. Luly, D. J. Madar, R. J. Sciotti, N. P. Tu, F. L. Wagenaar, P. E. Wiedeman, X. Zhou, S. Ballaron, J. Bauch, Y.-W. Chen, X. G. Chiou, T. Fey, D. Gauvin, E. Gubbins, G. C. Hsieh, K. C. Marsh, K. V. Mollison, M. Pong, T. K. Shaughnessy, M. P. Sheets, M. Smith, J. M. Trevillyan, U. Warrior, C. D. Wegner and G. W. Carter, *J. Med. Chem.*, 2000, **43**, 2975.

11 S. R. Stauffer, C. J. Coletta, R. Tedesco, G. Nishiguchi, K. Carlson, J. Sun, B. S. Katzenellenbogen and J. A. Katzenellenbogen, *J. Med. Chem.*, 2000, **43**, 4934.
12 D. L. Selwood, D. G. Brummell, J. Budworth, G. E. Burtin, R. O. Campbell, S. S. Chana, I. G. Charles, P. A. Fernandez, R. C. Glen, M. C. Goggin, A. J. Hobbs, M. R. Kling, Q. Liu, D. J. Madge, S. Meillerais, K. L. Powell, K. Reynolds, G. D. Spacey, J. N. Stables, M. A. Tatlock, K. A. Wheeler, G. Wishart and C.-K. Woo, *J. Med. Chem.*, 2001, **44**, 78.
13 D. J. P. Pinto, M. J. Orwat, S. Wang, J. M. Fevig, M. L. Quan, E. Amparo, J. Cacciola, K. A. Rossi, R. S. Alexander, A. M. Smallwood, J. M. Luettgen, L. Liang, B. J. Aungst, M. R. Wright, R. M. Knabb, P. C. Wong, R. R. Wexler and P. Y. S. Lam, *J. Med. Chem.*, 2001, **44**, 566.
14 (*a*) J. S. Clovis, A. Eckell, R. Huisgen and R. Sustmann, *Chem. Ber.*, 1967, **100**, 60; (*b*) R. Huisgen, M. Seidel, G. Wallbillich and H. Knupfer, *Tetrahedron*, 1962, **17**, 3.
15 (*a*) R. Paul and S. Tchelitcheff, *Bull. Soc. Chim. Fr.*, 1967, 4179; (*b*) T. Shimizu, Y. Hayashi, T. Nishio and K. Teramura, *Bull. Chem. Soc. Jpn.*, 1984, **57**, 787; (*c*) A. S. Shawali and S. T. Ezmirly, *J. Heterocycl. Chem.*, 1988, **25**, 257.
16 (*a*) K. N. Houk, J. Sims, R. E. Duke, R. W. Strozier and J. K. George, *J. Am. Chem. Soc.*, 1973, **95**, 7287; (*b*) K. N. Houk, J. Sims, C. R. Watts and L. J. Luskus, *J. Am. Chem. Soc.*, 1973, **95**, 7301; (*c*) K. N. Houk and P. Caramella, *J. Am. Chem. Soc.*, 1976, **98**, 6397.
17 S. Vojutsky, *Colloid Chemistry*, Mir Publishers, Moscow, 1985.
18 (*a*) Compound **2a**: R. Fusco and R. Romani, *Gazz. Chim. Ital.*, 1946, **76**, 419; (*b*) Compounds **2b,d**: M. M. El-Abadelah, A. Q. Hussein, m. R. Kamal and K. H. Al-Adhami, *Heterocycles*, 1988, **27**, 917; (*c*) Compound **2c**: G. Broggini and G. Molteni, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1685; (*d*) Compound **2e**: M. T. Cocco, A. Maccioni and A. Plumitallo, *Farmaco, Ed. Sci.*, 1985, **40**, 272.
19 (*a*) Compound **5a**: P. Dalla Croce, M. Ioannisci and E. Licandro, *J. Chem. Soc., Perkin Trans. 1*, 1979, 330; (*b*) Compound **5b**: see ref. 9.