Nitrilimine cycloadditions in aqueous media

Giorgio Molteni,*[a] Marco Orlandi[b] and Gianluigi Broggini[c]

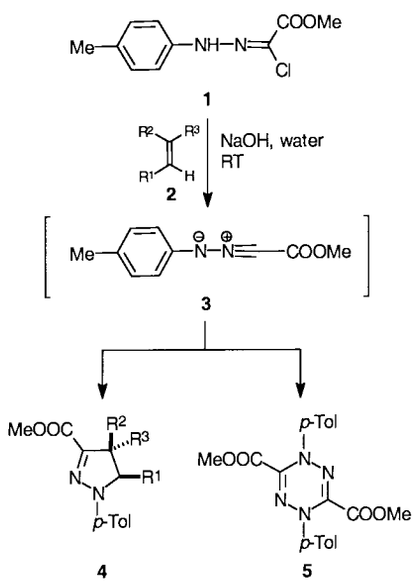
[a] *Dipartimento di Chimica Organica e Industriale, Università di Milano, via Golgi 19, 20133 Milano, Italy*
[b] *Dipartimento di Scienze dell'Ambiente e del Territorio, Piazza della Scienza 1, Università di Milano-Bicocca, 20126 Milano, Italy*
[c] *Dipartimento di Scienze Chimiche, Fisiche e Matematiche, Università dell'Insubria, via Lucini 3, 22100 Como, Italy*

Received (in Cambridge, UK) 10th July 2000, Accepted 7th September 2000
First published as an Advance Article on the web 27th October 2000

Nitrilimine cycloadditions onto a variety of alkenyl dipolarophiles were performed for the first time in aqueous media. The observed cycloaddition outcome was markedly dependent on several factors, including the electronic features and the solubility in water of the dipolarophiles, as well as the presence of a cationic surfactant or an organic cosolvent in the reaction mixture.

Introduction

Although water has been long regarded as an uncommon reaction medium by the majority of organic chemists, it displays a number of desirable features. The search for environmentally friendly procedures and the exploration of new synthetic approaches fully justify its use. Despite the aggressive nature of water towards many classes of organic functionalities, a growing number of organic transformations have been successfully performed in aqueous media,[1] including cycloadditions.[2] Among the latter reactions, which are traditionally regarded as solvent-insensitive processes,[3] a striking example of rate acceleration in aqueous medium was reported by Breslow in a typical Diels–Alder reaction.[4] In focusing on 1,3-dipolar cycloadditions, early contributions by Grundmann which describe nitrile oxide cycloadditions in biphasic aqueous–organic mixtures,[5] should be acknowledged. Later, further examples of dipolar cycloadditions in water or aqueous media have been expanded to cover nitrile oxide,[6] azomethine ylide[7] and azide[8] cycloaddition chemistry. In this work we undertook the first study on the feasibility of nitrilimine cycloadditions in an aqueous medium. Various alkene dipolarophiles were tested towards nitrilimine **3**, generated *in situ* from the corresponding hydrazonoyl chloride **1** (Scheme 1).



2,4	R^1	R^2	R^3
a	COOEt	H	H
b	-$OCH_2CH_2CH_2$-		H
c	CN	H	H
d	COOMe	H	COOMe
e	COOEt	H	Me
f	CH_2OH	H	H
g	COONa	H	H

Scheme 1

Results and discussion

Firstly, we investigated the reaction of nitrilimine **3** with ethyl acrylate **2a** and 2,3-dihydropyran **2b**. The choice of such dipolarophilic reactants was dictated by their opposite electronic features. Ethyl acrylate **2a** is a typical electron poor dipolarophile, while 2,3-dihydropyran **2b** belongs to the class of electron rich dipolarophiles.[9] Since the *in situ* generation of nitrilimines from the corresponding hydrazonoyl chlorides is generally performed by base treatment of the latter,[10] we perceived sodium hydroxide solution as the most suitable base in an aqueous medium. However, three different procedures were tested: (*i*) aqueous 0.1 M sodium hydroxide (method A); (*ii*) aqueous 0.1 M sodium hydroxide in the presence of tetrahexylammonium chloride as a catalyst (method B) and (*iii*) 80:20 mixture of aqueous 0.1 M sodium hydroxide and THF (method C). All reactions were performed at room temperature by stirring a heterogeneous (methods A and B) or homogeneous (method C) mixture of the reactants. For the sake of comparison, the generation of nitrilimine **3** was also accomplished by treating **1** with an excess of triethylamine in dry toluene at room temperature (method D), thus following the classic nitrilimine cycloaddition protocol.[11] Times, products and yields are collected in Table 1. Cycloadducts **4**, which were formed as the only regioisomers, and tetrazine **5** were fully characterised by analytical and spectroscopic methods. In particular, the ^{1}H NMR spectra of products **4** are in full agreement with those reported in the literature for

 DOI: 10.1039/b005567k

Table 1 Reaction between hydrazonoyl chloride **1** and dipolarophiles **2a** and **2b**

Entry	Dipolarophile	Equiv. of **2**	Method	*t*/h	Products and yields (%)[f]		
					4	**5**	**1**
1	**2a**	4	A[a]	24	4[g]	—	96[g]
2	**2a**	4	B[b]	24	100	—	—
3	**2a**	4	B[c]	0.75	100	—	—
4	**2a**	2	C[d]	0.5	80	10	—
5	**2a**	5	D[e]	24	55	—	41
6	**2b**	4	A[a]	24	0	—	100[g]
7	**2b**	4	B[b]	24	7	—	84
8	**2b**	4	B[c]	3.5	0	90	—
9	**2b**	2	C[d]	0.5	0	80	—
10	**2b**	5	D[e]	24	2	—	95

[a] In 0.1 M sodium hydroxide. [b] In 0.1 M sodium hydroxide and 0.1 mol. equiv. of tetrahexylammonium chloride, under magnetic stirring. [c] Method B, under mechanical shaking. [d] In 80:20 mixture of 0.1 M sodium hydroxide–THF. [e] In dry toluene with 5 mol equiv. of Et_3N. [f] Isolation yields unless otherwise stated. [g] Deduced from ^1H NMR analysis.

similar 1-aryl-3-alkoxycarbonyl-5-substituted pyrazolines.[12] The diagnostic ^1H NMR peaks of **4**, which unequivocally establish the regiochemistry of the cycloaddition, are those of the hydrogens bonded to the C5 of the pyrazolinic ring (denoted as C_5-H in the Experimental section).

In the absence of additives (catalyst or cosolvent), little or no reaction occurred and starting materials were recovered almost quantitatively (Table 1, entries 1 and 6). The presence of tetrahexylammonium chloride clearly promoted the cycloaddition, but the extent of the reaction was markedly dependent on the dipolarophile. In fact, quantitative yields of the cycloadduct **4a** was achieved from ethyl acrylate, while 2,3-dihydropyran reacted only slightly giving the cycloadduct **4b** in 7% yield (Table 1, entries 2 and 7). A dramatic acceleration was experienced when the heterogeneous reaction mixtures were mechanically shaken (Table 1, entries 3 and 8). Unfortunately, in the case of **2b**, the only product was the tetrazine **5**, resulting from the dimerisation of nitrilimine **3**. When hydrazonoyl chloride **1** was treated with **2a** or **2b** according to Method C (Table 1, entries 4 and 9) its disappearance was complete in 30 minutes: ethyl acrylate gave the cycloadduct **4a** as the largely predominant product, while 2,3-dihydropyran did not show any cycloaddition. Variable amounts of the tetrazine **5** were formed in both cases.

These preliminary results deserve some comments. It is apparent that, unexpectedly, the nitrilimine intermediate is no longer generated from hydrazonoyl chloride **1** in 0.1 M NaOH alone. Considering that the organic reactants are fully insoluble in water, the role played by tetrahexylammonium chloride may be related to some kind of micellar catalysis.[13] Electrostatic attraction due to the cationic surfactant can drive hydroxide ions from the bulk aqueous medium to the surface of the micellar aggregate. Alternatively, within such an aggregate, hydrophobic interactions can facilitate the association of the organic reactants during the activation process. This type of acceleration is well documented for Diels–Alder cycloadditions.[2,14] The strongly dipolarophilic behaviour of ethyl acrylate in contrast to the weak one of 2,3-dihydropyran towards nitrilimine **3** reflects the usual HOMO-dipole (LUMO-dipolarophile) controlled nature of nitrilimine cycloadditions.[15] Within this picture, the manner of stirring the heterogeneous reaction mixtures strongly influences the generation rate of labile intermediates **3**, which determines the overall reaction rate. Weak magnetic stirring promotes only a slow generation of **3**, and the cycloaddition outcome just reflects with the better dipolarophilic character of ethyl acrylate with respect to 2,3-dihydropyran. On the other hand, fast generation of **3** occurred with vigorous mechanical shaking, and cycloadditions were strongly accelerated (Table 1, entries 3 and 8). In the latter case, ethyl acrylate gave quantitatively the corresponding cycloadduct **4a**, while the far less reactive 2,3-dihydropyran gave no cycloaddition; the formation of tetrazine **5** being the kinetically favoured process. In this regard, the formation of 1,2,4,5-tetrazines is a well-known drawback of nitrilimine reactions when they are generated in the presence of strong basic agents and in the absence of efficient dipolarophiles.[10] As a control experiment, we treated hydrazonoyl chloride **1** according to method B (Table 1) and in the absence of the dipolarophile. Unreacted **1** was recovered quantitatively after 24 hours under magnetic stirring, while quantitative amounts of **5** were recovered after 4 hours under mechanical shaking. It can be inferred from Table 1 that the reactions in aqueous conditions are much better in term of rates and yields than under the classical anhydrous conditions (method D).

On the basis of the findings outlined above, hydrazonoyl chloride **1** was reacted with a number of alkenyl dipolarophiles, namely **2c**–**g**. The generation of nitrilimine **3** was performed according to methods B and C (see Table 2). Mechanical shaking of the reaction mixtures promoted fast generation of **3**, which implies the formation of variable amounts of **5** at the expense of cycloadducts **4**. Here again, increased formation of **5** can be related to the decreasing of the dipolarophilic activity of **2**. Irrespective of the experimental procedure, the cycloaddition extent was satisfactory with the electron-poor dipolarophiles acrylonitrile **2c** and dimethyl fumarate **2d**, while allyl alcohol **2f** gave expectedly poor results. Ethyl crotonate **2e** and sodium acrylate **2g** showed an intermediate behaviour. Some kind of steric encumbrance of the dipolarophilic fragment could intervene in the case of **2e**, while the behaviour of the very unusual dipolarophile **2g**, which is very soluble in the aqueous medium, can hardly be effectively bound by the organic aggregate to give cycloaddition.

Conclusions

The present work has demonstrated that pyrazoline synthesis by nitrilimine cycloadditions in an aqueous medium proceeds in a satisfactory manner provided that: (*i*) a quantity of organic cosolvent is added to obtain an homogeneous medium, or (*ii*) a micellar-type catalysis is operative due to the presence of a cationic surfactant. In every case, owing to the use of small amount (or even the absence) of organic solvents as well as to the very cheap experimental procedures, the generation and reaction of nitrilimines in an aqueous medium seems to offer a valid alternative to the classical protocols.

Experimental

Mps were determined with a Büchi apparatus and are uncorrected. IR spectra were recorded on a FT IR Perkin-Elmer

Table 2 Reaction between hydrazonoyl chloride **1** and dipolarophiles **2c**–**g** in aqueous media

Entry	Dipolarophile	Equiv. of **2**	Method	*t*/h	Products and yields (%)[e]		
					4	**5**	**1**
1	**2c**	4	B[a]	24	92	—	—
2	**2c**	4	B[b]	1	83	7	—
3	**2c**	2	C[c]	0.25	65	15	—
4	**2d**	4	B[a]	24	28[d]	—	60[d]
5	**2d**	4	B[b]	3.5	26[f]	43[f]	—
6	**2d**	2	C[c]	0.16	75	—	—
7	**2e**	4	B[a]	24	27	—	56
8	**2e**	4	B[b]	4	18[f]	52[f]	—
9	**2e**	2	C[c]	0.75	5	75	—
10	**2f**	4	B[a]	24	0	—	93
11	**2f**	2	C[c]	0.1	18	38	—
12	**2g**	4	B[a]	24	19	—	66
13	**2g**	2	C[c]	1.15	36	42	—

[a] In 0.1 M sodium hydroxide and 0.1 mol equiv. of tetrahexylammonium chloride, under magnetic stirring. [b] Method B, under mechanical shaking. [c] In 80 : 20 mixture of 0.1 M sodium hydroxide–THF. [d] After 140 h, isolation yields were 62% for **4d** and 19% for **1**. [e] Isolation yields, unless otherwise stated. [f] Deduced from ^{1}H NMR analysis.

1725 X spectrophotometer. MS spectra were determined with a VG-70EQ apparatus. ^{1}H and ^{13}C NMR spectra were taken with a Bruker AC 300 or AMX 300 instrument in $CDCl_3$ solutions; chemical shifts are given as ppm from tetramethylsilane and *J*-values are given in Hz. All new compounds **4**, **5** gave satisfactory elemental analyses.

Compound **1** was synthesised according to literature procedures.[16]

Reaction between hydrazonoyl chloride 1 and alkenyl dipolarophiles 2 in aqueous media

Method A. A mixture of **1** (0.30 g, 1.32 mmol), **2** (5.28 mmol) and aqueous 0.1 M NaOH (21 cm^3), was stirred at room temperature for 24 h. The mixture was filtered; the solid material was washed with water (40 cm^3) and dried giving unreacted **1** (entry 6, Table 1) or a 96 : 4 mixture of **1**:**4a** (entry 1, Table 1) on the basis of ^{1}H-NMR analysis.

Method B. A mixture of **1** (0.30 g, 1.32 mmol), **2** (5.28 mmol), *n*-$Hex_4N^+Cl^{-1}$ (50 mg, 0.13 mmol) and aqueous 0.1 M NaOH (21 cm^3), was magnetically stirred or mechanically shaken at room temperature for the time indicated in Tables 1 and 2.

In the case of entries 2,3 (Table 1) and entry 1 (Table 2), the mixture was filtered; the solid material was washed with water (30 cm^3) and dried giving pure **4a** or **4c**.

1-(4-Methylphenyl)-3-methoxycarbonyl-5-ethoxycarbonyl-4,5-dihydropyrazole **4a** (0.38 g, 100%). Yellow solid, mp 118 °C. ^{1}H NMR ($CDCl_3$) δ: 1.19 (3H, t, J = 7.5), 2.28 (3H, s), 3.28 (1H, dd, J = 18.1, 6.9), 3.51 (1H, dd, J = 18.1, 13.6), 3.86 (3H, s), 4.17 (2H, q, J = 7.5), 4.90 (C_5-H, dd, J = 13.6, 6.9), 7.00–7.10 (4H, m). ^{13}C NMR ($CDCl_3$) δ: 21.02 (q), 23.11 (q), 34.36 (t), 52.80 (q), 54.50 (t), 67.05 (d), 114.90 (d), 130.24 (d), 132.59 (s), 134.87 (s), 139.77 (s), 169.23 (s), 169.44 (s). IR (Nujol) 1725, 1710 cm^{-1}. MS *m*/*z*: 290 (M). Anal. Calcd for $C_{15}H_{18}N_2O_4$: C, 62.04; H, 6.25; N, 9.65. Found: C, 62.10; H, 6.22; N, 9.70%.

1-(4-Methylphenyl)-3-methoxycarbonyl-5-cyano-4,5-dihydropyrazole **4c** (0.30 g, 92%). Dark yellow solid, mp 91 °C. ^{1}H NMR ($CDCl_3$) δ: 2.32 (3H, s), 3.49 (1H, dd, J = 18.6, 8.9), 3.56 (1H, dd, J = 18.6, 8.9), 3.90 (3H, s), 5.10 (C_5-H, t, J = 8.9), 7.10–7.20 (4H, m). ^{13}C NMR ($CDCl_3$) δ: 20.96 (q), 34.77 (t), 52.42 (q), 62.95 (d), 115.06 (d), 125.27 (s), 130.20 (d), 131.47 (s), 138.97 (s), 140.41 (s), 163.67 (s). IR (Nujol) 1730 cm^{-1}. MS *m*/*z*: 243 (M). Anal. Calcd for $C_{13}H_{13}N_3O_2$: C, 64.17; H, 5.39; N, 17.28. Found: C, 64.21; H, 5.42; N, 17.21%.

In the case of entries 4,7 (Table 2), the mixture was filtered; the solid material was washed with water (50 cm^3) and dried. Crystallisation from MeOH gave pure **4d** or **4e**. Evaporation of the mother liquor and subsequent crystallisation from i-Pr_2O gave unreacted **1**.

1-(4-Methylphenyl)-3,4,5-tris(methoxycarbonyl)-4,5-dihydropyrazole **4d** (0.12 g, 28%). Pale yellow solid, mp 83 °C. ^{1}H NMR ($CDCl_3$) δ: 2.30 (3H, s), 3.75 (3H, s), 3.79 (3H, s), 3.88 (3H, s), 4.38 (1H, d, J = 5.8), 5.16 (C_5-H, d, J = 5.8), 7.06–7.12 (4H, m). ^{13}C NMR ($CDCl_3$) δ: 22.31 (q), 39.18 (d), 51.16 (q), 53.12 (q), 53.85 (q), 65.93 (d), 117.28 (d), 128.65 (d), 130.70 (s), 133.91 (s), 139.85 (s), 167.83 (s), 168.61 (s), 169.94 (s). IR (Nujol) 1735, 1720, 1715 cm^{-1}. MS *m*/*z*: 334 (M). Anal. Calcd for $C_{16}H_{18}N_2O_6$: C, 57.46; H, 5.43; N, 8.38. Found: C, 57.41; H, 5.40; N, 8.33%.

1-(4-Methylphenyl)-3-methoxycarbonyl-4-methyl-5-ethoxycarbonyl-4,5-dihydropyrazole **4e** (0.11 g, 27%). Yellow solid, mp 76 °C. ^{1}H NMR ($CDCl_3$) δ: 1.27 (3H, t, J = 7.1), 1.42 (3H, d, J = 7.2), 2.28 (3H, s), 3.58 (1H, dq, J = 7.2, 5.1), 3.86 (3H, s), 4.16 (2H, q, J = 7.1), 4.46 (C_5-H, d, J = 5.1), 7.00–7.16 (4H, m). ^{13}C NMR ($CDCl_3$) δ: 19.80 (q), 21.08 (q), 21.22 (q), 31.62 (d), 52.41 (q), 53.16 (t), 66.85 (d), 115.80 (d), 129.80 (d), 133.11 (s), 135.10 (s), 140.10 (s), 168.21 (s), 169.82 (s). IR (Nujol) 1725, 1720 cm^{-1}. MS *m*/*z*: 304 (M). Anal. Calcd for $C_{16}H_{20}N_2O_4$: C, 63.13; H, 6.63; N, 9.21. Found: C, 63.10; H, 6.60; N, 9.27%.

In the case of entry 7 (Table 1), the mixture was taken up with AcOEt (50 cm^3). The organic layer was washed with water (50 cm^3), dried over Na_2SO_4 and evaporated. The residue was chromatographed on a silica gel column with AcOEt–hexane 2 : 1. Unreacted **1** was eluted first, further elution gave 1-(4-methylphenyl)-3-methoxycarbonyl-1,3a,4,5,6,7a-hexahydropyrano[2,3-*c*]pyrazole **4b** (25 mg, 7%). Pale yellow solid, mp 58 °C. ^{1}H NMR ($CDCl_3$) δ: 1.74–2.00 (4H, m), 2.37 (3H, s), 2.96 (1H, ddd, J = 10.8, 8.6, 5.2), 3.64–3.71 (2H, m), 3.92 (3H, s), 5.87 (C_5-H, d, J = 8.6), 7.06–7.18 (4H, m). ^{13}C NMR ($CDCl_3$) δ: 19.24 (t), 21.16 (t), 22.36 (q), 30.98 (d), 50.21 (t), 54.16 (q), 70.63 (d), 116.85 (d), 128.30 (d), 132.16 (s), 133.95 (s), 141.75 (s), 165.59 (s). IR (Nujol) 1725 cm^{-1}. MS *m*/*z*: 274 (M). Anal. Calcd for $C_{15}H_{18}N_2O_3$: C, 65.66; H, 6.62; N, 10.22. Found: C, 65.70; H, 6.59; N, 10.17%.

In the case of entry 12 (Table 2), the mixture was adjusted to pH 2 with 1 M aqueous hydrochloric acid. AcOEt (50 cm^3) was added, the organic layer was washed with water (40 cm^3), dried over Na_2SO_4 and evaporated. Crystallisation of the residue with MeOH gave pure **4g**. Evaporation of the mother liquour and subsequent crystallisation from i-Pr_2O gave unreacted **1**.

Sodium 1-(4-methylphenyl)-3-methoxycarbonyl-4,5-dihydropyrazole-5-carboxylate **4g** (66 mg, 19%). White solid, mp 294 °C. ^{1}H NMR ($CDCl_3$) δ: 2.28 (3H, s), 3.30 (1H, dd, J = 18.0, 6.6), 3.51 (1H, dd, J = 18.0, 13.5), 3.87 (3H, s), 4.93 (C_5-H, dd, J = 13.5, 6.6), 7.02–7.13 (4H, m), 10.65 (1H, br s). ^{13}C NMR

($CDCl_3$) δ: 21.16 (q), 33.96 (t), 52.59 (q), 65.28 (d), 116.67 (d), 126.80 (d), 132.35 (s), 134.21 (s), 139.84 (s), 165.12 (s), 169.21 (s). IR (Nujol) 3430, 1725, 1715 cm^{-1}. MS *m*/*z*: 262 (M). Anal. Calcd for $C_{13}H_{14}N_2O_4$: C, 59.52; H, 5.38; N, 10.69. Found: C, 59.49; H, 5.40; N, 10.74%.

In the case of entry 8 (Table 1), the mixture was filtered; the solid material was washed with water (50 cm^3) and dried. Crystallisation from hexane–benzene gave 1,4-bis(4-methylphenyl)-3,6-bis(methoxycarbonyl)-1,4-dihydro-1,2,4,5-tetrazine **5**. Dark red solid, mp 161 °C. ^1H NMR ($CDCl_3$) δ: 2.32 (6H, s), 3.72 (6H, s), 7.04–7.19 (8H, m). IR (Nujol) 1730 cm^{-1}. MS *m*/*z*: 380 (M). Anal. Calcd for $C_{20}H_{20}N_4O_4$: C, 62.87; H, 6.50; N, 11.29. Found: C, 62.91; H, 6.53; N, 11.34%.

In the case of entry 10 (Table 2), the mixture was filtered; the solid material was washed with water (30 cm^3) and dried. Crystallisation from i-Pr_2O gave unreacted **1**.

Method C. Compound **1** (0.20 g, 0.88 ml) was added portionwise to a solution of **2** (1.76 mmol) in aqueous 0.1 M NaOH (14.0 ml) and THF (3.5 cm^{-3}) under stirring at room temperature for the time indicated in Tables 1 and 2.

In the case of entry 13 (Table 2), the mixture was adjusted to pH 2 with 1 M aqueous hydrochloric acid. AcOEt (50 cm^3) was added, the organic layer was washed with water (40 cm^3), dried over Na_2SO_4, and the solvent was evaporated. Crystallisation of the residue with MeOH gave 83 mg of **4g** (36%). Evaporation of the mother liquour gave 140 mg of **5** (42%).

In all the other cases, the mixture was taken up with AcOEt (50 cm^3). The organic layer was washed with water (50 cm^3), dried over Na_2SO_4 and evaporated.

In the case of entry 4 (Table 1) and entries 3,6 (Table 2), crystallisation of the residue from i-Pr_2O gave **4**. Evaporation of the mother liquour and subsequent crystallisation from hexane–benzene gave **5**.

In the case of entry 9 (Table 1) and 9 (Table 2), crystallisation of the residue with hexane–benzene gave **5**.

In the case of entry 11 (Table 2), the residue was chromatographed on a silica gel column with AcOEt–hexane 2:1. The first fractions contained 128 mg (38%) of **5**. Further elution gave 40 mg (18%) of 1-(4-methylphenyl)-3-methoxycarbonyl-5-hydroxymethyl-4,5-dihydropyrazole **4f**. White solid, mp 164 °C. ^1H NMR ($CDCl_3$) δ: 2.28 (3H, s), 2.90 (1H, br s), 3.21 (1H, dd, J = 17.4, 6.5), 3.29 (1H, dd, J = 17.4, 10.9), 3.66 (1H, dd, J = 11.3, 4.3), 3.80 (3H, s), 3.91 (1H, dd, J = 11.3, 6.1), 4.57–4.65 (C_5-H, m), 7.03–7.12 (4H, m). ^{13}C NMR ($CDCl_3$) δ: 22.18 (q), 32.30 (t), 43.28 (t), 53.85 (q), 60.10 (d), 117.85 (d), 128.60 (d), 131.85 (s), 134.38 (s), 142.12 (s), 169.11 (s). IR (Nujol) 3500, 1710 cm^{-1}. MS *m*/*z*: 248 (M). Anal. Calcd for $C_{13}H_{16}N_2O_3$: C, 62.87; H, 6.50; N, 11.29. Found: C, 62.90; H, 6.52; N, 11.33%.

Reaction between hydrazonoyl chloride 1 and alkenyl dipolarophiles 2a,b in toluene (Method D)

A solution of **1** (0.30 g, 1.33 mmol) and **2a** or **2b** (6.65 mmol) in dry toluene (30 cm^3) was added with triethylamine (0.67 g, 6.65 mmol) and stirred at room temperature for 24 h. The solvent was evaporated and the residue was chromatographed on a silica gel column with AcOEt–hexane 2:1. Products and isolation yields were as reported in Table 1, entries 5 and 10.

Acknowledgements

Thanks are due to MURST and CNR for financial support. The authors are grateful to Professor Luisa Garanti and Professor Gaetano Zecchi for helpful suggestions.

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