Nitrilimine cycloadditions to MeOPEG-bounded alkenyl dipolarophiles

Luisa Garanti,* Giorgio Molteni and Pietro Casati

Dipartimento di Chimica Organica e Industriale, Università di Milano, via Golgi 19, 20133 Milano, Italy

Received (in Cambridge, UK) 10th July 2002, Accepted 9th September 2002
First published as an Advance Article on the web 24th October 2002

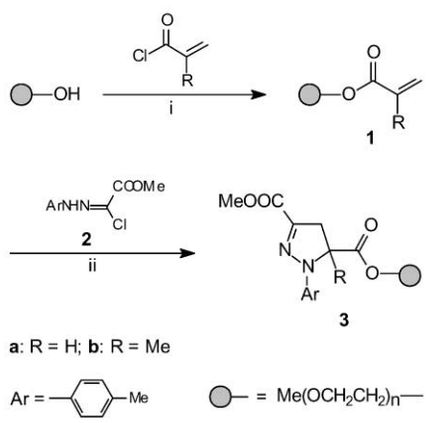
Base treatment of hydrazonoyl chloride **2** with MeOPEG-supported acrylates **1** and acrylamides **5** gave the corresponding MeOPEG-supported 4,5-dihydropyrazoles **3** and **6**. Basic hydrolysis of the cycloadducts caused the removal of the MeOPEG pendant giving 5-carboxy- or 5-aminocarbonyl-4,5-dihydropyrazoles **7** and **8**, respectively. Cycloaddition between **2** and enantiopure MeOPEG-supported acrylamide **10** gave a mixture of MeOPEG-supported cycloadducts **11** and **12** with low diastereoselectivity.

Introduction

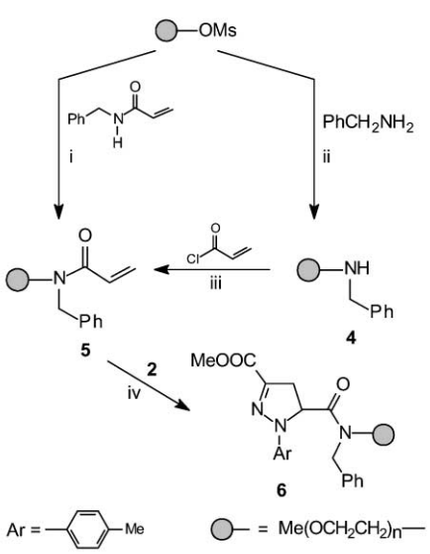
According to the Huisgen 1,3-dipolar cycloaddition protocol, the behaviour of nitrilimines towards alkenyl dipolarophiles represents a versatile method for the direct synthesis of variously substituted 4,5-dihydropyrazoles.[1] Due to their biological activity as anti-inflammatory[2] or anti-coagulating[3] agents, new methods for the regio- and/or stereoselective synthesis of these compounds should be highly valuable. In this context, the two following points should be considered: (*i*) the polymer-supported synthesis of small heterocyclic molecules is the subject of intense research activity,[4] since it represents one of the most promising ways to generate small molecular libraries in the field of combinatorial chemistry,[5] (*ii*) only one example of nitrilimine cycloaddition to resin-bound dipolarophiles (enamines) has been recently reported.[6] In the above-mentioned paper, however, the dipolarophilic enamine was prepared from Merrifield's resin,[7] and was therefor completely insoluble in organic media. Recently, soluble polymers have gained popularity among organic chemists due to a number of advantageous features. Analytical simplicity, high reactivity and low price of the starting materials usually compete with that of solution chemistry,[8] while the easy reaction workup parallels one of the most appreciated features of solid-supported synthesis. Thus, we decided to undertake the first study on the feasibility of nitrilimine cycloadditions onto soluble-polymer-supported alkenyl dipolarophiles.

Results and discussion

First of all, we devised the monomethyl ether of poly(ethylene glycol) with a M_w of 5000 (MeOPEG) as a suitable soluble support for our purposes. MeOPEG-supported acryloyl esters **1** were easily obtained as illustrated in Scheme 1, while acrylamide **5** was synthesised from MeOPEG-mesylate[9] by the two different sequences *i* and *ii*, *iii* depicted in Scheme 2. Both supported dipolarophiles **1** and **5** were reacted with hydrazonoyl chloride **2**[10] in the presence of trioctylamine. 5-MeOPEG-supported-4,5-dihydropyrazoles **3** and **6** were obtained as white solids, in nearly quantitative yields, simply by addition of diethyl ether to the crude reaction mixtures. Structural assignments of the cycloadducts rely upon ^{1}H NMR analyses and are fully consistent with those of similar 1-aryl-3-alkoxycarbonyl-5-substituted-4,5-dihydropyrazoles reported in the literature.[11] In particular, the proton on C_5 of the 4,5-dihydropyrazole ring of **3a** resonates at 4.93 δ as a doublet of doublets, thus accounting for the depicted regiochemistry of the cycloaddition.



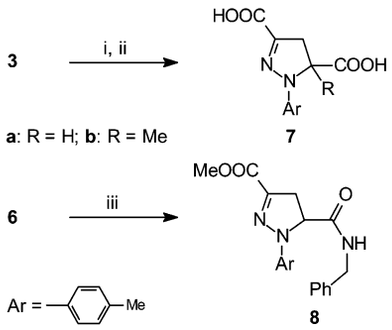
Scheme 1 *Reagents and conditions* : i, trioctylamine–CH_2Cl_2, room temp.; ii, trioctylamine–CH_2Cl_2, Δ.



Scheme 2 *Reagents and conditions* : i, NaOH–Na_2CO_3–*n*-Bu_4NBr–CH_2Cl_2, Δ; ii, CH_2Cl_2, room temp; iii, trioctylamine–CH_2Cl_2, room temp; iv, trioctylamine–CH_2Cl_2, Δ.

The removal of the MeOPEG pendant from the 4,5-dihydropyrazoles **3** and **6** was accomplished under particularly mild conditions (see Scheme 3) giving 5-carboxy- or 5-carboxy-

 DOI: 10.1039/b206629g



Scheme 3 *Reagents and conditions*: i, 1 M NaOH–THF 1 : 1, room temp.; ii, aq. 1 M HCl, room temp.; iii, 5% aq. $NaHCO_3$–THF 1 : 1, room temp.

amino-4,5-dihydropyrazoles **7** and **8**, respectively. In the next stage of our work we developed the first example of stereoselective cycloaddition between nitrilimines and enantiopure MeOPEG-supported acrylamide **10**. The latter compound was synthesised starting from MeOPEG-mesylate and (*S*)-1-phenylethylamine as the chiral building block. We followed two different synthetic sequences *i*, *iii* [(*S*)-1-phenylethylamine route] and *ii* [*N*-[(*S*)-1-phenylethyl]acrylamide[12] route] as depicted in Scheme 4. Clean nitrilimine cycloaddition to enantiopure **10** was performed by treatment with hydrazonoyl chloride **2** in the presence of trioctylamine. The usual reaction workup gave a mixture of inseparable 5-MeOPEG-supported 4,5-dihydropyrazoles **11** and **12**, the former of which was recognised as the major cycloadduct on the basis of ^{1}H NMR analysis (see Experimental). The assignement of the absolute configuration to C_5 of the 4,5-dihydropyrazole ring of both **11** and **12** was performed as follows. First, mild basic hydrolysis of the mixture **11** + **12** gave 5-{*N*-[(*S*)-1-phenylethyl]aminocarbonyl}-4,5-dihydropyrazoles **13** and **14**, respectively, which were separated by column chromatography. Then, the latter products were further hydrolysed (see Experimental) giving, respectively, (*S*)-1-(4-methylphenyl)-3,5-dicarboxy-4,5-dihydropyrazole and (*R*)-1-(4-methylphenyl)-3,5-dicarboxy-4,5-dihydropyrazole which are known in the literature.[13] At this point, it can be noted that, although the latter 5-MeOPEG-supported 4,5-dihydropyrazoles were obtained with satisfactory overall yield (96%), cycloaddition stereoselectivity was disappointing, being the ratio **11** : **12** = 57 :43. Due to the good hydrolysis yield (87%), however, it was possible to perform the **10** ⟶ **13** + **14** "MeOPEG-supported" sequence with an overall yield of 84%. For the sake of comparison, *N*-[(*S*)-1-phenylethyl]acrylamide was reacted with **2** in the presence of a large excess of triethylamine in boiling toluene (see Scheme 4), thus following the classic nitrilimine cycloaddition protocol.[1] This genuine example of homogeneous phase synthesis allowed us to perform the sequence *N*-[(*S*)-1-phenylethyl]acrylamide ⟶ **13** + **14** with a 69% overall yield and a stereoselectivity outcome **13** : **14** = 53 : 47.

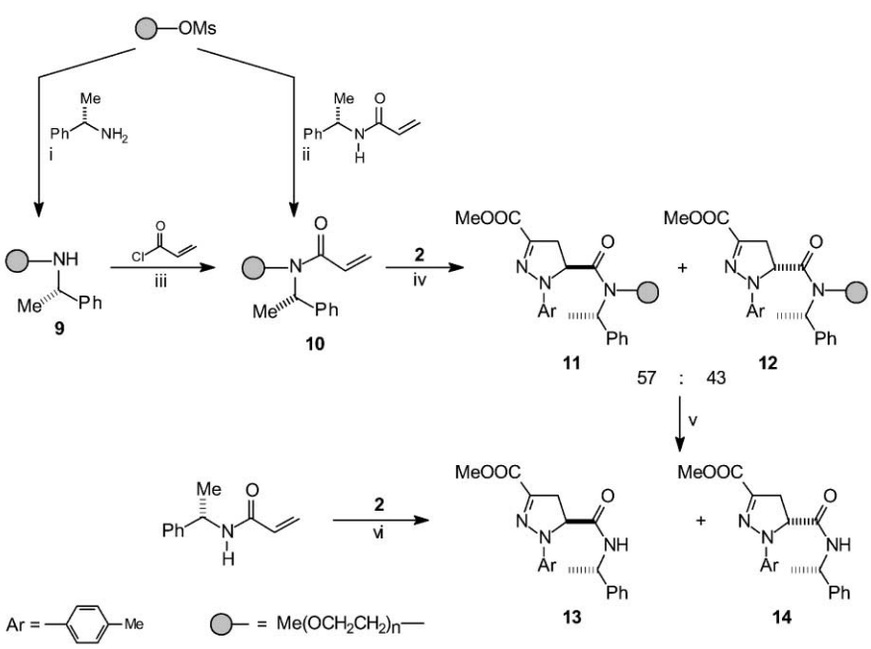
Conclusions

This first example of the behaviour of MeOPEG-supported acrylates or acrylamides towards nitrilimines reflects all the advantages concerned with soluble polymer-supported synthesis. In fact, all cycloadditions were fully satisfactory in terms of product yield, easy workup and facile removal of the PEG pendant. As far as stereoselectivity is concerned, the cycloaddition outcome for enantiopure MeOPEG-supported **10** is identical to that of *N*-[(*S*)-1-phenylethyl]acrylamide, showing that the MeOPEG pendant has little or no influence on cycloaddition stereoselectivity.

Experimental

Mps were measured with a Büchi apparatus in open capillary tubes and are uncorrected. IR Spectra were recorded with a Perkin-Elmer 1725X spectrophotometer. Mass spectra were determined with a VG-70EQ apparatus. ^{1}H-NMR and ^{13}C-NMR Spectra were taken with a Bruker AC 200 or AC 300 instruments in $CDCl_3$ solutions at room temperature unless otherwise stated. Chemical shifts are given as ppm from tetramethylsilane, *J* values are given in Hz. Optical rotations, $[\alpha]_D^{25}$, were recorded on a Perkin-Elmer Model 241 polarimeter at the sodium D line.

Before use, all MeOPEG-bounded materials were melted at 90 °C at 1 mmHg for 1 h to remove moisture.



Scheme 4 *Reagents and conditions*: i, NaH–toluene, Δ; ii, NaOH–Na_2CO_3–*n*-Bu_4NBr–toluene, 80 °C; iii, trioctylamine–toluene, 80 °C; iv, trioctylamine–CH_2Cl_2, Δ; v, 5% aq. $NaHCO_3$–THF 1 : 1, room temp.; vi, Et_3N–toluene, Δ.

MeOPEG-methanesulfonate,[9] *N*-[(*S*)-1-phenylethyl]acrylamide,[12] and *N*-benzylacrylamide[14] were synthesised according to literature procedures.

Yields and ^{1}H-NMR purity determination of MeOPEG-bounded compounds

The yields of MeOPEG-bounded materials were determined from the weight of the pure compounds. It was assumed that the average M_w of MeOPEG monomethyl ether residue is 5000 Da, while the M_w actually encompasses the range between 4500 and 5500 Da. The purity of MeOPEG-bounded compounds was determined by ^{1}H-NMR analyses with pre-saturation of the MeOPEG methylene signals at 3.64 δ. In order to ensure complete relaxation of the proton nuclei and integration accuracy, we set relaxation delay (RD) to 6 s and aquisition time (AQ) to 4 s. The integrations of the PEG fragment CH_3OCH_2, which were found between 3.30 and 3.37 δ, were used as internal standards with an estimated integration error of ±4%.

In the case of compound **3a** the signals due to the AB part of the ABX system (pyrazoline C_4-*H*, 2H) are lacking, probably because they fall under the PEG signal at 3.64 δ. The same argument applies to compounds **3b** (pyrazoline C_4-*H*, 2H and CH_3OCO, 3H) and **6** (CH_3OCO, 3H).

MeOPEG-Supported acrylates 1

A solution of MeOPEG-monomethyl ether (5.00 g, 1.0 mmol) and trioctylamine (5.30 g, 15.0 mmol) in dry CH_2Cl_2 (35 cm^3) was added to acryloyl chloride (0.9 g, 10.0 mmol) or methacryloyl chloride (1.04 g, 10.0 mmol) and stirred at room temperature for 4 h. The solvent was partly removed under reduced pressure and Et_2O (30 cm^3) was added. The white solid was collected by filtration giving pure **1**.

1a (4.80 g, 95%) δ_H ($CDCl_3$) 3.34 (3H, s, CH_3OCH_2-), 3.37 (2H, t, *J* 7.0, CH_3OCH_2-), 3.85 (3H, t, *J* 7.0, -CH_2CH_2O-), 4.30 (2H, t, *J* 7.2, -CH_2OCO-) 5.82 (1H, dd, *J* 10.3, 1.7, CH_2=), 6.13 (1H, dd, *J* 17.3, 10.3, -CO-*CH*=), 6.42 (1H, dd, *J* 17.3, 1.7, CH_2=).

1b (4.86 g, 96%) δ_H ($CDCl_3$) 1.95 (3H, s, CH_3-C), 3.30 (3H, s, CH_3OCH_2-), 3.37 (2H, t, *J* 7.0, CH_3OCH_2-), 3.85 (3H, t, *J* 7.0, -CH_2CH_2O-), 4.30 (2H, t, *J* 7.2, -CH_2OCO-), 5.54 (1H, s, CH_2=), 6.11 (1H, s, CH_2=).

MeOPEG-Supported 4,5-dihydropyrazoles 3

A solution of MeOPEG-acrylate **1** (0.9 mmol), hydrazonoyl chloride **2** (0.32 g, 1.4 mmol) and trioctylamine (1.59 g, 4.5 mmol) in dry CH_2Cl_2 (18 cm^3) was refluxed with stirring for 36 h. The solvent was partly removed under reduced pressure and Et_2O (15 cm^3) was added. The white solid was collected by filtration giving pure **3**.

3a (4.39 g, 93%) δ_H ($CDCl_3$) 2.28 (3H, s, CH_3-C_6H_4-), 3.30 (2H, t, *J* 7.0, CH_3OCH_2-), 3.37 (3H, s, CH_3OCH_2-), 3.83 (3H, s, CH_3OCO-), 4.00 (3H, t, *J* 7.0, -CH_2CH_2O-), 4.30 (2H, t, *J* 7.2, -CH_2OCO-), 4.93 (1H, dd, *J* 12.6, 8.1, pyrazole C_5-H), 6.95–7.10 (4H, m, aromatics).

3b (4.26 g, 90%) δ_H ($CDCl_3$) 1.62 (3H, s, CH_3-C), 2.27 (3H, s, CH_3-C_6H_4-), 3.34 (3H, s, CH_3OCH_2-), 3.37 (2H, t, *J* 7.0, CH_3OCH_2-), 3.85 (2H, t, *J* 7.0, -CH_2CH_2O-), 4.27–4.32 (2H, m, -CH_2OCO-), 6.95–7.05 (4H, m, aromatics).

MeOPEG-Supported benzylamine 4

A solution of MeOPEG-methanesulfonate (5.08 g, 1.0 mmol) and benzylamine (1.07 g, 10.0 mmol) in dry CH_2Cl_2 (25 cm^3) was stirred at room temperature for 18 h. The solvent was partly removed under reduced pressure and Et_2O (15 cm^3) was added. The white solid was collected by filtration giving pure **4** (5.04 g, 99%) δ_H ($CDCl_3$) 3.04 (2H, s, -NHCH_2Ph), 3.35 (3H, s, CH_3OCH_2-), 3.38 (2H, t, *J* 7.0, CH_3OCH_2-), 3.85 (2H, t, *J* 7.0, -CH_2CH_2O-), 4.33 (2H, t, *J* 7.2, -CH_2CH_2NH-), 7.35–7.45 (5H, m, aromatics).

MeOPEG-Supported *N*-benzylacrylamide 5

Method A. A solution of MeOPEG-methanesulfonate (5.08 g, 1.0 mmol) and *N*-benzylacrylamide (0.18 g, 1.1 mmol) in dry CH_2Cl_2 (25 cm^3) was treated with NaOH (0.16 g, 4.0 mmol), Na_2CO_3 (0.13 g, 1.2 mmol) and tetrabutylammoniun bromide (0.16 g, 0.5 mmol). The mixture was refluxed for 16 h. The undissolved material was filtered off, the solvent was partly removed under reduced pressure and Et_2O (15 cm^3) was added. The white solid was collected by filtration giving pure **5** (4.42 g, 86%) δ_H ($CDCl_3$) 3.02 (2H, s, >NCH_2Ph), 3.25 (2H, t, *J* 7.0, CH_3OCH_2-), 3.34 (3H, s, CH_3OCH_2-), 3.95 (2H, t, *J* 7.0, -CH_2CH_2N<), 4.34 (2H, t, *J* 7.0, -CH_2CH_2N<), 5.67 (1H, dd, *J* 10.5, 1.8, CH_2=), 6.10 (1H, dd, *J* 17.6, 10.5, -CH=), 6.28 (1H, dd, *J* 17.6, 1.8, CH_2=), 7.20–7.30 (5H, m, aromatics).

Method B. A solution of MeOPEG-supported benzylamine **4** (5.09 g, 1.0 mmol) and trioctylamine (0.53 g, 1.5 mmol) in dry CH_2Cl_2 (25 cm^3) was added to acryloyl chloride (0.11 g, 1.2 mmol) and stirred at room temperature for 10 h. The solvent was partly removed under reduced pressure and Et_2O (20 cm^3) was added. The white solid was collected by filtration giving pure **5** (4.78 g, 93%).

MeOPEG-Supported 5-aminocarbonyl-4,5-dihydropyrazole 6

A solution of MeOPEG-supported *N*-benzylacrylamide **5** (4.11 g, 0.8 mmol), hydrazonoyl chloride **2** (0.36 g, 1.6 mmol) and trioctylamine (1.42 g, 4.0 mmol) in dry CH_2Cl_2 (22 cm^3) was refluxed with stirring for 28 h. The solvent was partly removed under reduced pressure and Et_2O (15 cm^3) was added. The white solid was collected by filtration giving pure **6** (3.80 g, 92%) δ_H ($CDCl_3$) 2.24 (3H, s, $CH_3C_6H_4$-), 2.80–2.95 (2H, m, pyrazoline C_4-H), 3.02 (2H, s, >N-CH_2Ph), 3.30 (3H, s, CH_3OCH_2-), 3.37 (2H, t, *J* 7.0, CH_3OCH_2-), 3.75–3.82 (2H, m, -CH_2-CH_2-N<), 4.30 (2H, t, *J* 7.2, -CH_2-CH_2-N<), 4.88 (1H, dd, *J* 11.6, 7.8, pyrazoline C_5-H), 6.95–7.05 (4H, m, -C_6H_4-), 7.10–7.20 (5H, m, Ph-).

1-(4-Methylphenyl)-3,5-dicarboxy-4,5-dihydropyrazole 7a and 1-(4-methylphenyl)-3,5-dicarboxy-5-methyl-4,5-dihydro pyrazole 7b

A solution of **3** (0.7 mmol) in tetrahydrofuran (15 cm^3) and 1 M NaOH (15 cm^3) was stirred at room temperature for 4 h. 1 M HCl was added until the pH reached 2 and AcOEt (150 cm^3) was added. The organic layer was washed with water (30 cm^3), dried over Na_2SO_4 and evaporated under reduced pressure. The residue was crystallised from MeOH giving pure **7**.

7a (0.13 g, 76%).[13]

7b (0.14 g, 77%) was a white solid. Mp 190 °C (Found: C, 59.58; H, 5.42; N, 10.73; $C_{13}H_{14}N_2O_4$ requires C, 59.54; H, 5.38; N, 10.68%); ν_{max} (Nujol)/cm^{-1} 3400, 1750, 1665; δ_H ($CDCl_3$) 1.48 (3H, s), 2.23 (3H, s), 3.18 (1H, d, *J* 17.8), 3.42 (1H, d, *J* 17.8), 6.90–7.10 (4H, m), 13.20 (2H, br s); δ_C ($CDCl_3$) 20.1 (q), 22.8 (q), 37.4 (t), 62.6 (s), 112.4 (d), 130.1 (d), 137.8 (s), 140.1 (s), 140.9 (s), 165.7 (s), 167.6 (s); *m*/*z* (EI) 351 (M$^+$).

1-(4-Methylphenyl)-3-methoxycarbonyl-5-(*N*-benzyl)amino-carbonyl-4,5-dihydropyrazole 8

A solution of **6** (3.80 g, 0.7 mmol) in tetrahydrofuran (15 cm^3) and 5% aqueous $NaHCO_3$ (15 cm^3) was stirred at room temperature for 6 h. Et_2O (100 cm^3) was added, the organic layer was washed with water (2 × 50 cm^3), dried over Na_2SO_4 and evaporated under reduced pressure. The residue was crystallised from i-Pr_2O giving pure **8** (0.80 g, 74%) as a white solid. Mp 188 °C (Found: C, 68.41; H, 6.06; N, 12.02; $C_{20}H_{21}N_3O_3$ requires C, 68.36; H, 6.02; N, 11.96%); ν_{max} (Nujol)/cm^{-1}

3280, 1720, 1660; δ_H ($CDCl_3$) 2.23 (3H, s), 3.20 (1H, dd, *J* 18.4, 9.3), 3.60 (1H, dd, *J* 18.6, 13.8), 3.78 (3H, s), 4.30 (1H, dd, *J* 15.2, 6.7), 4.36 (1H, dd, *J* 15.2, 6.7), 4.70 (1H, dd, *J* 13.8, 9.3), 6.20 (1H, br t, *J* 6.7), 6.95–7.10 (9H, m); δ_C ($CDCl_3$) 20.1 (q), 27.7 (t), 38.6 (t), 53.3 (q), 59.0 (d), 116.7 (d), 128.0–131.3, 132.3 (s), 136.6 (s), 140.0 (s), 162.2 (s), 166.3 (s), 167.9 (s); *m*/*z* (EI) 351 (M^+).

MeOPEG-Supported (*S*)-1-phenylethylamine 9

A solution of (*S*)-1-phenylethylamine (0.24 g, 2.0 mmol) in dry toluene (40 cm^3) was treated with NaH (90 mg, 3.8 mmol) and then refluxed for 1 h. MeOPEG-methanesulfonate (5.08 g, 1.0 mmol) in hot (60 °C) dry toluene was added and the mixture was refluxed for 2 h. The solvent was partly removed under reduced pressure and Et_2O (35 cm^3) was added. The white solid was collected by filtration giving pure **9** (4.92 g, 96%) δ_H ($CDCl_3$) 1.40 (3H, d, *J* 6.8, *CH*$_3$CH<), 1.62 (1H, br s, -CH$_2$-*NH*-), 3.34 (3H, s, *CH*$_3$OCH$_2$-), 3.37 (2H, t, *J* 7.0, CH$_3$O*CH*$_2$–), 3.85 (2H, t, *J* 7.0, -*CH*$_2$CH$_2$N<), 4.34 (2H, t, *J* 7.2, -CH$_2$*CH*$_2$N<), 5.12–5.22 (1H, m, CH$_3$*CH*<), 7.30–7.35 (5H, m, aromatics).

MeOPEG-Supported *N*-[(*S*)-1-phenylethyl]acrylamide 10

Method A. A solution of *N*-[(*S*)-1-phenylethyl]acrylamide[12] (0.14 g, 1.2 mmol) in dry toluene (50 cm^3) was treated with NaOH (0.16 g, 4.0 mmol), Na_2CO_3 (0.13 g, 1.2 mmol) and tetrabutylammoniun bromide (0.16 g, 0.5 mmol). The mixture was warmed to 80 °C for 0.5 h, and MeOPEG-methanesulfonate (5.08 g, 1.0 mmol) in hot (60 °C) dry toluene (20 cm^3) was added. After warming (80 °C) and stirring for 4 h, the undissolved material was filtered off, the solvent was partly removed under reduced pressure and Et_2O (25 cm^3) was added. The white solid was collected by filtration giving pure **10** (4.14 g, 80%) δ_H ($CDCl_3$) 1.40 (3H, d, *J* 6.8, *CH*$_3$CH<), 3.34 (3H, s, *CH*$_3$OCH$_2$-), 3.37 (2H, t, *J* 7.0, CH$_3$O*CH*$_2$-), 3.85 (2H, t, J 7.0, -*CH*$_2$CH$_2$N<), 4.34 (2H, t, *J* 7.2, -CH$_2$*CH*$_2$N<), 5.12–5.22 (1H, m, CH$_3$*CH*<), 5.60 (1H, dd, *J* 10.3, 1.6, *CH*$_2$=), 6.08 (1H, dd, *J* 17.5, 10.3, -*CH*=), 6.25 (1H, dd, *J* 17.5, 1.6, *CH*$_2$=), 7.30–7.35 (5H, m, aromatics).

Method B. A solution of MeOPEG-supported (*S*)-1-phenylethylamine **9** (5.10 g, 1.0 mmol) and trioctylamine (0.53 g, 1.5 mmol) in hot (60 °C) dry toluene (30 cm^3) was added to acryloyl chloride (0.11 g, 1.2 mmol) and stirred at 80 °C for 6 h. The solvent was partly removed under reduced pressure and Et_2O (25 cm^3) was added. The white solid was collected by filtration giving pure **5** (4.85 g, 94%).

MeOPEG-Supported 5-{*N*-[(*S*)-1-phenylethyl]amino}carbonyl-4,5-dihydropyrazoles 11 and 12

A solution of MeOPEG-supported *N*-[(*S*)-1-phenylethyl]-acrylamide **10** (6.21 g, 1.2 mmol), hydrazonoyl chloride **2** (0.36 g, 1.6 mmol) and trioctylamine (1.42 g, 4.0 mmol) in dry CH_2Cl_2 (25 cm^3) was refluxed with stirring for 50 h. The solvent was partly removed under reduced pressure and Et_2O (25 cm^3) was added. The white solid was collected by filtration giving a 57 : 43 mixture of cycloadducts **11** and **12** (6.18 g, 96%). Cycloadduct ratio was deduced from integration of the ^1H NMR resonance signals due to the –COO*CH*$_3$ group placed in the 3- position of the 4,5-dihydropyrazole ring: δ_H ($CDCl_3$) 3.79 (3H, s) (for **11**), and 3.82 (3H, s) (for **12**).

1-(4-Methylphenyl)-3-methoxycarbonyl-5-{*N*-[(*S*)-1-phenylethyl]amino}carbonyl-4,5-dihydropyrazoles 13 and 14

A mixture of MeOPEG-supported cycloadducts **11** and **12** (6.18 g, 1.15 mmol) was dissolved in tetrahydrofuran (35 cm^3) and 5% aqueous $NaHCO_3$ (35 cm^3) and stirred at room temperature for 5 h. Et_2O (80 cm^3) was added, the organic layer was washed with water (2 × 50 cm^3), dried over Na_2SO_4 and evaporated under reduced pressure. The residue was chromatographed on a silica gel column with AcOEt–hexane–CH_2Cl_2 3 : 6 : 1. The major isomer (5*S*)-1-(4-methylphenyl)-3-methoxycarbonyl-5-{*N*-[(*S*)-1-phenylethyl]amino}carbonyl-4,5-dihydropyrazole **13** was eluted first, followed by the minor isomer (5*R*)-1-(4-methylphenyl)-3-methoxycarbonyl-5-{*N*-[(*S*)-1-phenylethyl]amino}carbonyl-4,5-dihydropyrazole **14**.

13 (0.19 g, 50%) was a white solid. Mp 89 °C from i-Pr_2O (Found: C, 69.07; H, 6.30; N, 11.56; $C_{21}H_{23}N_3O_3$ requires C, 69.02; H, 6.34; N, 11.50%); $[\alpha]_D^{25}$ +123.0 ($CHCl_3$, *c* = 0.22); ν_{max} (Nujol)/cm^{-1} 3180, 1730, 1665; δ_H ($CDCl_3$) 1.26 (3H, d, *J* 7.2), 2.25 (3H, s), 3.16 (1H, dd, *J* 18.0, 13.1), 3.58 (1H, dd, *J* 18.0, 6.7), 3.83 (3H, s), 4.68 (1H, dd, *J* 13.1, 6.7), 5.16 (1H, dq, *J* 9.8, 7.2), 6.20 (1H, br d, *J* 9.8), 7.0–7.3 (9H, m) δ_C ($CDCl_3$) 20.5 (q), 22.8 (q), 27.2 (t), 37.3 (d), 52.8 (q), 59.4 (d), 116.1 (d), 129.0–131.0, 131.8 (s), 137.2 (s), 140.9 (s), 163.2 (s), 167.6 (s), 169.4 (s); *m*/*z* (EI) 365 (M^+).

14 (0.15 g, 37%) was a white solid. Mp 79 °C from i-Pr_2O (Found: C, 69.04; H, 6.37; N, 11.44; $C_{21}H_{23}N_3O_3$ requires C, 69.02; H, 6.34; N, 11.50%); $[\alpha]_D^{25}$ −77.2 ($CHCl_3$, *c* = 0.28); ν_{max} (Nujol)/cm^{-1} 3180, 1720, 1660; δ_H ($CDCl_3$) 1.30 (3H, d, *J* 7.2), 2.28 (3H, s), 3.25 (1H, dd, *J* 18.4, 12.7), 3.59 (1H, dd, *J* 18.4, 6.5), 3.86 (3H, s), 4.70 (1H, dd, *J* 12.7, 6.5), 5.16 (1H, dq, *J* 9.8, 7.2), 6.20 (1H, br d, *J* 9.8), 7.0–7.3 (9H, m); δ_C ($CDCl_3$) 20.1 (q), 24.3 (q), 28.8 (t), 39.6 (d), 53.3 (q), 58.5 (d), 116.8 (d), 129.0–131.0, 131.3 (s), 136.6 (s), 139.9 (s), 162.3 (s), 166.6 (s), 170.1 (s); *m*/*z* (EI) 365 (M^+).

Homogeneous phase synthesis of cycloadducts 13 and 14

A solution of *N*-[(*S*)-1-phenylethyl]acrylamide (0.88 g, 5.0 mmol) and hydrazonoyl chloride **2** (1.30 g, 5.8 mmol) in dry toluene was added to triethylamine (2.93 g, 29.0 mmol) and then refluxed for 6 h. The solvent was evaporated and the residue was chromatographed on a silica gel column with AcOEt–hexane–CH_2Cl_2 3 : 6 : 1. The major isomer **13** (0.66 g, 36%) was eluted first, followed by the minor isomer **14** (0.60 g, 33%). Ratio **13** : **14** = 53 : 47.

(5*S*)-1-(4-Methylphenyl)-3,5-dicarboxy-4,5-dihydropyrazole and (5*R*)-1-(4-methylphenyl)-3,5-dicarboxy-4,5-dihydropyrazole

A solution of **13** (0.73 g, 2.0 mmol) in tetrahydrofuran (2.5 cm^3) and 2 M NaOH (2.5 cm^3) was stirred at 50 °C for 4 h. 1 M HCl was added until the pH 2 reached and AcOEt (50 cm^3) was added. The organic layer was washed with water (20 cm^3), dried over Na_2SO_4 and evaporated under reduced pressure. The residue was crystallised from MeOH giving (5*S*)-1-(4-methylphenyl)-3,5-dicarboxy-4,5-dihydropyrazole[13] (0.34 g, 69%).

The same procedure applied to **14** gave (5*R*)-1-(4-methylphenyl)-3,5-dicarboxy-4,5-dihydropyrazole[13] (0.33 g, 66%).

Acknowledgements

We thank MURST and CNR for financial support. C.I.N.M.P.I.S. is gratefully acknowledged for a grant that enabled Dr Pietro Casati to work on this project.

References

1 (*a*) R. Huisgen, M. Seidel, G. Wallbillich and H. Knupfer, *Tetrahedron*, 1962, **17**, 3; (*b*) J. S. Clovis, A. Eckell, R. Huisgen and R. Sustmann, *Chem. Ber.*, 1967, **100**, 60–1593.

2 (*a*) F. C. Copp, P. J. Islip and J. E. Tateson, *Biochem. Pharmacol.*, 1984, **33**, 339; (*b*) J. Frígola, A. Colombo, J. Parés, L. Martínez, R. Sagarra and R. Roser, *Eur. J. Med. Chem.*, 1989, **24**, 435.

3 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.

4 (*a*) J. S. Früchtel and G. Jung, *Angew. Chem., Int. Engl. Ed.*, 1996, **35**, 17; (*b*) S. M. Allin and P. K. Sharma, *Synthesis*, 1997, 1217; (*c*) J. A. Ellmann, *Chem. Rev.*, 1996, **96**, 555; (*d*) V. Krcňák and M. W. Holladay, *Chem. Rev*, 2002, **102**, 61.
5 A. Nefzi, J. M. Otresh and R. A. Houghten, *Chem. Rev.*, 1997, **97**, 449.
6 A. C. Donohue, S. Pallich and T. D. McCarthy, *J. Chem. Soc., Perkin Trans. 1*, 2001, 2817.
7 S. Bräse, D. Enders, J. Köbberling and F. Avemaria, *Angew. Chem., Int. Ed.*, 1998, **37**, 3413.
8 (*a*) D. J. Gravert and K. D. Janda, *Chem. Rev.*, 1997, **97**, 489; (*b*) P. H. Toy and K. D. Janda, *Acc. Chem. Res.*, 2000, **33**, 546.
9 M. Benaglia, M. Cinquini and F. Cozzi, *Tetrahedron Lett.*, 1999, **40**, 2019.
10 M. M. Abadelah, A. Q. Hussein, M. R. Kamal and K. H. Al-Adhami, *Heterocycles*, 1988, **27**, 917.
11 (*a*) R. Paul and S. Tchelicheff, *Bull. Soc. Chim. Fr.*, 1967, 4179; (*b*) T. Shimizu, Y. Hayashi, T. Nishio and T. Teramura, *Bull. Chim. Soc. Jpn.*, 1984, **57**, 787; (*c*) A. S. Shawali and S. T. Ezmirly, *J. Heterocycl. Chem.*, 1988, **25**, 257.
12 J. Szumoskovicz and M. Greig, *J. Med. Pharm. Chem.*, 1961, **4**, 259.
13 L. Garanti, G. Molteni and T. Pilati, *Tetrahedron: Asymmetry*, 2002, **13**, 1285.
14 G. Anzuino, M. d'Alagni and F. Quadrifoglio, *Ric. Sci. Sez. A*, 1963, **3**, 957 (*Chem. Abstr.*, 1964, **60**, 5293h).