Cycloaddition of nitrile imines to resin-bound enamines: a solid phase synthesis of 1,4-diarylpyrazoles

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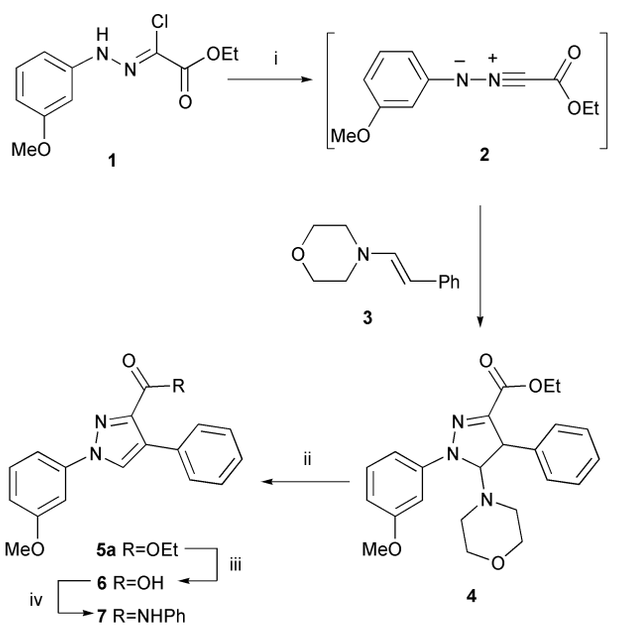
The 1,3-dipolar cycloaddition reaction between nitrile imines and resin-bound enamines gives resin-bound pyrazoline intermediates. The piperazine resin functions as a traceless linker and allows these intermediates to be cleaved directly from the resin under mild acid conditions to afford 1,4-diarylpyrazoles. Alternatively they may be chemically modified on the resin prior to elimination from the polymer. The cycloaddition–elimination sequence is regiospecific for the 3,4-disubstituted pyrazole isomer and the products are obtained in good to high yield and in high purity.

As part of our drug discovery program we needed to synthesise a range of 1,4-diarylpyrazoles such as pyrazole amide **7** (Scheme 1). A review of the literature indicated that 1,4-diarylpyrazole-3-carboxylates could be prepared *via* the cycloaddition of an appropriately substituted nitrile imine and phenylacetaldehyde enamines followed by elimination.[1] We sought to apply this chemistry in order to prepare our target compounds and, using solution phase chemistry, the reaction sequence outlined in Scheme 1 proved to be particularly efficient for this purpose. Thus, commercially available ethyl 2-chloroacetoacetate underwent a Japp–Klingemann reaction with the diazonium salt derived from 3-methoxyaniline to give the shelf stable hydrazonyl chloride **1**.[2] Exposure of the hydrazonyl chloride **1** to basic conditions generated the nitrile imine **2** *in situ* which underwent a 1,3-dipolar cycloaddition reaction with compound **3**, the morpholine enamine of phenylacetaldehyde. Pyrazoline **4** was obtained in 85% yield and acid catalysed elimination of morpholine from cycloadduct **4** gave the pyrazole **5a** in quantitative yield. Saponification of ester **5a** afforded acid **6** which, upon treatment with aniline and HBTU, gave the desired amide adduct **7** in 56% yield for the two steps.[3]



Scheme 1 *Reagents and conditions*: (i) NEt_3, $CHCl_3$, reflux, 3 h to RT 16 h; (ii) 2 M aq. HCl, dioxane, 100 °C, 90 min; (iii) NaOH, DMSO, H_2O, 100 °C, 4 h; (iv) $N(^iPr)_2Et$, HBTU, aniline, DMF, RT, 16 h.

In order to streamline the generation of a library of pyrazole adducts we sought to transfer the above methodology to the solid phase (Scheme 2). While the two aromatic rings at the 1 and 4 positions of the pyrazole core offered no obvious point of attachment to a resin, we were intrigued by the possibility of using the amino group of the phenylacetaldehyde enamine as a traceless linker.[4] In this way the product would be released from the resin at the end of the synthesis and would simultaneously regenerate the amino functionalised resin. Despite the advances in solid phase organic chemistry, there are few examples of the formation of resin-bound enamines[5] and no examples of nitrile imine cycloaddition methodology being transferred to the solid phase.[6] This paper describes our results in this area.

Results and discussion

The piperazine resin **8** was chosen as the starting point of the synthesis. It is easy to prepare from Merrifield's resin[7] and has recently become commercially available.[8] Reaction of resin **8** with phenylacetaldehyde under Dean–Stark conditions gave product **9** (Y = H). Formation of the desired enamine was supported by infrared analysis which showed the presence of an enamine C=C absorption at 1636 cm^{-1}. Treatment of this resin with 2 mol equivalents of the *in situ* generated nitrile imine **2** gave a product that, by infrared analysis, showed a peak at 1726 cm^{-1} and the absence of an absorption maximum at 1636 cm^{-1}. The structure of this product was presumed to be compound **12a** (X = 3-MeO, Y = H, R = OEt). Ultimately, the success of the enamine formation–cycloaddition sequence was confirmed by subjecting the crude product to acidic conditions (3% TFA–DCM) which resulted in elimination of resin **8** as its TFA salt and formation of the pyrazole **5a**. The latter material was obtained in 95% purity and in 79% yield for the three steps (Table 1, entry 1).

Having successfully demonstrated the transfer of the enamine formation–cycloaddition methodology to the solid

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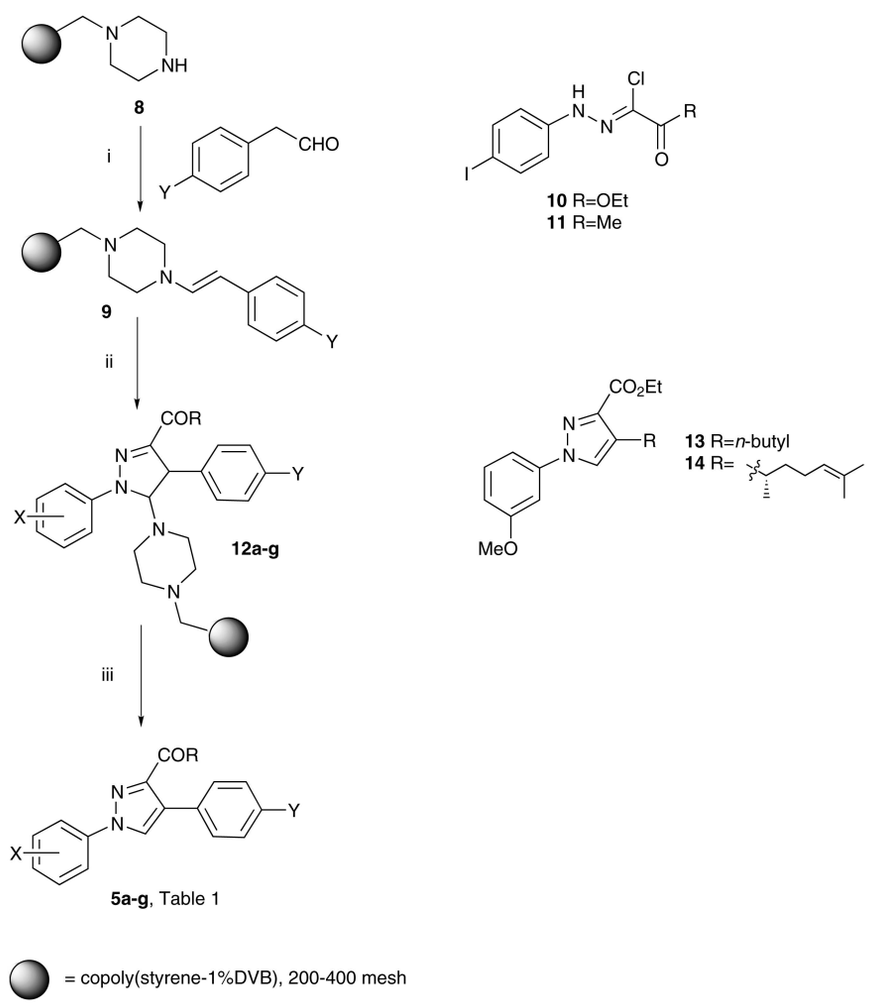


Scheme 2 *Reagents and conditions*: (i) benzene, Dean–Stark, 22 h; (ii) NEt_3, **1**, **10** or **11**, $CHCl_3$, reflux, 16 h; (iii) 3% TFA in DCM, RT, 10–20 min.

phase, we briefly examined if additional points of diversity (*i.e.* at positions 1, 3 and/or 4 of the pyrazole ring) could be incorporated into the synthetic sequence. To this end, we modified the nitrile imine component to include an iodine atom (*i.e.* compounds **10** and **11**) thereby allowing access to palladium catalysed coupling chemistry (Table 1, entries 2–4). A ketone functionality was also tolerated within the nitrile imine component (Table 1, entry 4) and offers an additional point of diversity through either imine formation or reductive amination protocols. Electron deficient phenylacetaldehydes also participated readily in the enamine formation–cycloaddition chemistry (Table 1, entries 3, 5 and 6).‡ The presence of a nitro group[9] also introduces further potential for chemical modification *via* a range of methods (*e.g.* reduction and acylation).

In addition to preparing 1,4-diarylpyrazoles, we attempted to incorporate non-aromatic acetaldehyde derivatives in order to prepare pyrazoles with an alkyl group in the 4-position. Thus, the resin-bound enamines of hexanal and (*R*)-(+)-citronellal were prepared, reacted with dipole **2** then cleaved with TFA following the general procedure outlined in Scheme 2. This gave the 4-alkyl-1-arylpyrazole adducts **13** and **14** in yields of 15–20% and 36% respectively. While the purities of these products were comparable to that of the 1,4-diarylpyrazoles (>95%), the yields were significantly lower.§

Table 1 Yield and purity of 1,4-diarylpyrazoles

Entry	Cmpd	Y	X	R	Yield[a]	Purity[b]
1	**5a**	H	3-MeO	OEt	79	>95%
2	**5b**	H	4-I	OEt	64	>95%
3	**5c**	NO_2	4-I	OEt	55	>95%
4	**5d**	H	4-I	Me	59	>95%
5	**5e**	Br	3-MeO	OEt	62	>90%
6	**5f**	Cl	3-MeO	OEt	61	>90%
7	**5g**	Me	3-MeO	OEt	52	>90%

[a] Over the 3 steps from **8**. [b] Determined by ^1H and ^{13}C NMR spectroscopy.

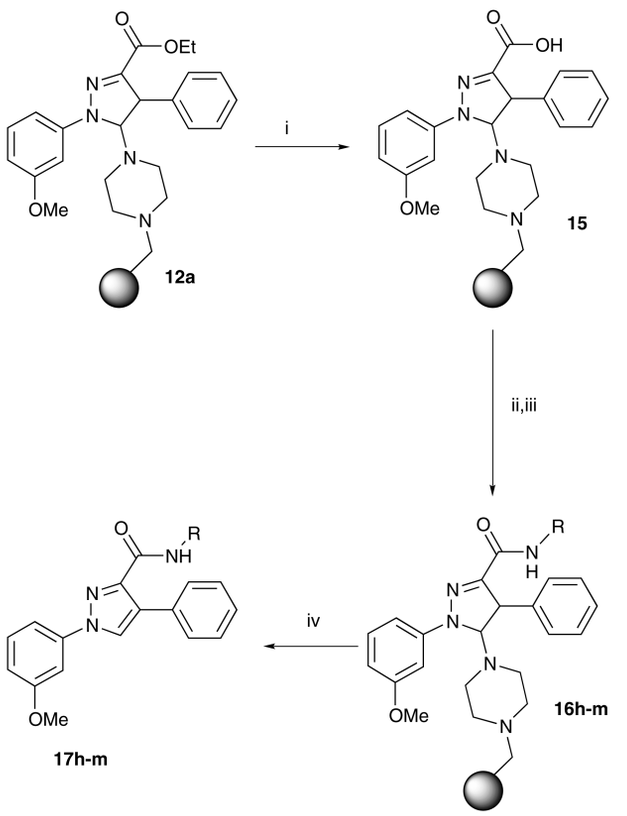
In all the cases studied, only one of the two possible regioisomeric products was detected after analysis by ^1H and ^{13}C NMR spectroscopy. Pyrazole **5a** was subjected to a series of 2D NMR experiments (COSY, HSQC, HMBC, NOE difference) that strongly suggested that the expected 1,3,4-substituted pyrazole had been obtained. An authentic sample of the alternate possible regioisomer, the 1,3,5-substituted pyrazole, was

‡ In general, enamine formation was performed in refluxing benzene with a Dean–Stark apparatus (see the Experimental section). These conditions, however, were found not to be optimal for the 4-bromo or 4-chlorophenylacetaldehydes. For these examples better results (higher yields and greater purities) were obtained when the acetaldehyde and piperazine resin were stirred gently at room temperature or 40 °C for 24 h. Removal of water by azeotropic distillation or addition of a dehydrating agent (*e.g.* sieves or K_2CO_3) was found to be unnecessary.

§ This result is not entirely unexpected as conjugation of a double bond leads to a significant increase in dipolarophilic reactivity. The rate constants for the 1,3-dipolar cycloaddition of some monosubstituted ethylenes to a number of dipoles, including nitrile imines, have been measured and shows a rate increase of 1.5 to 20 times when the double bond is conjugated with an aromatic ring.[10,11]

prepared¶ and its 1D and 2D NMR spectral data analysed and then compared with that of pyrazole **5a**. This confirmed that the 1,3,4-substituted pyrazole was the exclusive product of the cycloaddition. Similar work by Huisgen on the cycloaddition of β-pyrrolidinostyrenes to nitrile oxides and nitrile imines shows the same regiospecificity with only the 3,4-disubstituted isoxazoles or pyrazoles being formed.[11,14]

With confidence in our ability to form resin-bound pyrazolines, conversion to their corresponding amide derivatives was investigated next (Scheme 3). Initially we tried to convert



Scheme 3 *Reagents and conditions*: (i) 1 M LiOH, THF, reflux, 18 h; (ii) pentafluorophenol, pyridine, TFAA, 4 h, RT; (iii) NH_2R (see Table 2), DMF, RT, 18 h; (iv) 3% TFA in DCM, RT, 10–20 min.

ester **12a** (Y = H, X = 3-MeO, R = OEt) to carboxamide derivative **16h** (R = CH_2Ph) by a direct amidation protocol. This involved heating the resin ester **12a** in the presence of excess benzylamine under a variety of conditions and it invariably led to partial amide formation.‖ We then investigated a two-step saponification–amidation process. LiOH mediated hydrolysis of resin **12a** cleanly gave the acid **15**, however, when it was treated with benzylamine in the presence of HBTU, again, incomplete amide bond formation was observed. Eventually we applied methods developed by chemists at Glaxo Wellcome[15] and treated resin acid **15** with pentafluorophenol and trifluoroacetic anhydride to give the pentafluorophenyl active ester intermediate. Subsequent treatment of this material with a limited range of primary amines generated compounds of the general type **16** (Table 2). TFA-mediated cleavage of each of the resin-bound adducts furnished amides **17** (Table 2) in varying yields but with a high degree of purity. Future work in this area will include examining other reactions of resin-bound enamines (*e.g.* nitrile oxide cycloadditions).

Table 2 Yield and purity of amides **17h–m**

Entry	Cmpd	R	Yield[a]	Purity[b]
1	**17h**	$PhCH_2$	49	>95%
2	**17i**	$4\text{-}CF_3(C_6H_4)CH_2$	70	>95%
3	**17j**	$4\text{-}NO_2(C_6H_4)CH_2$	80	>95%
4	**17k**	CH_3OCOCH_2	48	>95%
5	**17l**	$CH_2{=}CHCH_2$	88	>95%
6	**17m**	$(CH_2)_7CH_3$	18[c]	>95%

[a] Over the 5 steps from **9** (Y = H). [b] Determined by ^1H and ^{13}C NMR spectroscopy. [c] The yield was low due to handling difficulties as the resin developed a waxy texture after amide bond formation.

Experimental

General

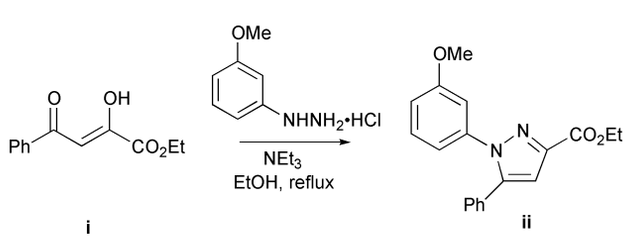
Short-path distillations were performed using a Kugelrohr (bulb-to-bulb) distillation apparatus. IR spectra were recorded as KBr disks (unless stated otherwise) using either a Perkin-Elmer 842 spectrometer or a Bio-Rad Excalibur Series spectrometer. ^1H NMR spectra were recorded at 200 MHz with a Bruker AC-200, 250 MHz with a Bruker ACP-250 or at 500 MHz with a Bruker DRX-500 spectrometer. Spectra were acquired in deuteriochloroform solution with residual chloroform as the internal standard (δ_H 7.27), unless otherwise stated. ^{13}C NMR spectra were recorded at either 50 MHz with a Bruker AC-200 spectrometer or at 63 MHz with a Bruker DRX-500 spectrometer. Spectra were acquired in deuterio-chloroform solution with residual chloroform as the internal standard (δ_C 77.0). Accurate mass determinations were recorded on a Finnigan MA95XL mass spectrometer. Atmospheric pressure chemical ionisation (APCI) MS were recorded on a FISONS Instrument VG Platform quadrupole mass spectrometer. Elemental analyses were performed by the Campbell Microanalytical Laboratory, University of Otago, Dunedin, New Zealand. Unless otherwise stated, all reagents were purchased from Aldrich Chemical Company, Inc. and used without further purification.

Substituted phenylacetaldehydes were prepared according to the known literature procedure,[9] and were purified by distillation and characterised by ^1H NMR, ^{13}C NMR and MS. The yields of cleaved products were calculated based upon the commercial resin loading specification for the piperazinomethyl polystyrene **8** (Novabiochem catalogue number 01–64–0310) of 0.69 mmol g^{-1}.

Solution phase chemistry

1-(3-Methoxyphenyl)-5-morpholin-4-yl-4-phenyl-4,5-dihydro-1*H*-pyrazole-3-carboxylic acid ethyl ester (4). A solution of the hydrazonyl chloride **1**[2a] (2.47 g, 9.64 mmol) in $CHCl_3$ (20 ml) was added to a stirred solution of morpholine enamine **3** (2.0 g, 10.6 mmol) and triethylamine (1.47 ml, 10.6 mmol) in $CHCl_3$ (30 ml) under an atmosphere of nitrogen. The reaction mixture

¶ The 1,3,5-substituted pyrazole was prepared using standard literature procedures for the synthesis of pyrazoles. Thus, ethyl 4-phenyl-2,4-dioxobutanoate **i** (CAS 6296-54-4) was prepared as its enol tautomer, from acetophenone and diethyl oxalate following the procedure outlined by Brecker *et al.*[12] This material was then reacted with 3-methoxyphenylhydrazine hydrochloride (Lancaster Cat. No. 8091) following a method similar to that described by Zhang *et al.*[13] to give the 1-(3-methoxyphenyl)-5-phenyl-1*H*-pyrazole-3-carboxylic acid ethyl ester **ii** (see Experimental for details).



‖ Conditions included heating of the resin at temperatures of 60, 80 and 120 °C for times ranging from 2–36 h in either neat benzylamine or in the presence of a co-solvent (chloroform or dioxane).

was heated at reflux for 3 h and then stirred at room temperature overnight. The reaction mixture was washed with water (150 ml) and the organic phase separated and dried ($MgSO_4$). Removal of the solvent gave an orange oil which was triturated with ether–petroleum ether to give the title compound **4** (3.45 g, 85%) as an orange solid, mp 126–127 °C (Found: C, 67.5; H, 6.5; N, 10.3. $C_{23}H_{27}N_3O_4$ requires C, 67.5; H, 6.65; N, 10.3%). ν_{max}(KBr)/cm^{-1} 1691, 1597, 1541, 1429, 1282, 1145, 1097. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.22 (t, *J* 7.1 Hz, 3H), 2.43–2.65 (m, 4H), 3.65 (br s, 4H), 3.81 (s, 3H), 4.19 (q, *J* 7.1 Hz, 2H), 4.46 (d, *J* 3.2 Hz, 1H), 4.98 (d, *J* 3.2 Hz, 1H), 6.55 (dd, *J* 2.1 and 7.9 Hz, 1H), 7.02–7.32 (m, 8H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.1, 45.7, 48.5, 55.3, 61.1, 66.6, 89.9, 101.5, 107.5, 108.1, 127.0, 127.4, 129.2, 129.7, 139.8, 141.3, 143.4, 160.3, 161.9. *m/z* (APCI) 410 (MH$^+$, 10%), 323 (100). HRMS calcd for $C_{23}H_{27}N_3O_4$ 409.2001, found 409.1999.

1-(3-Methoxyphenyl)-4-phenyl-1*H*-pyrazole-3-carboxylic acid ethyl ester (5a). A solution of dihydropyrazole **4** (3.0 g, 7.3 mmol) and 2 M HCl (11.0 ml, 22.0 mmol) in 1,4-dioxane (40 ml) was heated at 100 °C for 90 min. The solvent was removed and the residue taken up in EtOAc (100 ml) and washed with saturated $NaHCO_3$ solution (200 ml) and water (200 ml). The organic layer was dried ($MgSO_4$), filtered and concentrated to give the desired product **5a** (2.35 g, 100%) as a yellow solid, mp 121.5–122.5 °C (Found: C, 70.7; H, 5.8; N, 8.7. $C_{19}H_{18}N_2O_3$ requires C, 70.8; H, 5.6; N, 8.7%). ν_{max}(film)/cm^{-1} 1723, 1608, 1487, 1280, 1170, 1134, 1038, 761. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.20 (t, *J* 7.1 Hz, 3H), 3.76 (s, 3H), 4.25 (q, *J* 7.1 Hz, 2H), 6.78 (ddd, *J* 1.5, 2.6 and 7.6 Hz, 1H), 7.14–7.43 (m, 8H), 7.84 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.1, 55.5, 61.0, 105.8, 111.8, 113.5, 127.3, 127.5, 127.7, 127.9, 129.3, 130.2, 131.3, 140.4, 141.2, 160.4, 162.4. *m/z* (APCI) 323 (MH$^+$, 52%), 309 (100). HRMS calcd for $C_{19}H_{18}N_2O_3$ 322.1317, found 322.1315.

1-(3-Methoxyphenyl)-4-phenyl-1*H*-pyrazole-3-carboxylic acid (6). The ester **5a** (174 mg, 0.54 mmol) in DMSO (5.0 ml) was treated with NaOH (240 mg, 60.0 mmol) in water (3.0 ml) following the procedure of Biere *et al.*[16] to give the acid **6** (136 mg, 85%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.86 (s, 3H), 6.90 (br d, *J* 7.5 Hz, 1H), 7.20–7.47 (m, 6H), 7.47–7.62 (m, 2H), 7.95 (s, 1H), 11.01 (br s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 55.7, 105.8, 111.9, 113.9, 127.9, 128.16, 128.20, 128.3, 129.4, 130.4, 130.9, 140.1, 140.3, 160.6, 166.5. *m/z* (APCI) 295 (MH$^+$, 41%), 277 (31). HRMS calcd for $C_{19}H_{18}N_2O_3$ 294.1004, found 294.1011.

1-(3-Methoxyphenyl)-4-phenyl-1*H*-pyrazole-3-carboxylic acid phenylamide (7). Diisopropylethylamine (1.4 ml, 8.2 mmol) was added dropwise to a solution of the acid **6** (1.0 g, 3.4 mmol), HBTU (1.53 g, 4.1 mmol) and aniline (381 mg, 4.1 mmol) in dry DMF (20 ml) and stirred at room temperature for 16 h. The reaction mixture was diluted with ethyl acetate (100 ml) and water (150 ml) and the phases separated. The organic layer was washed sequentially with 10% aqueous citric acid (100 ml), saturated $NaHCO_3$ solution (100 ml) and brine (100 ml). The organic fraction was dried ($MgSO_4$), filtered and concentrated to give the crude product, which was triturated (diethyl ether) to give the product **7** (826 mg, 66%) as a yellow solid, mp 141–142.5 °C (from diethyl ether–hexane) (Found: C, 74.6; H, 5.5; N, 11.25. $C_{23}H_{19}N_3O_2$ requires C, 74.8; H, 5.2; N, 11.4%). ν_{max}(KBr)/cm^{-1} 3313, 1666, 1597, 1530, 1500, 1424, 1211, 1046, 976, 837, 754, 692. ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.92 (s, 3H), 6.94 (ddd, *J* 1.2, 2.4 and 8.0 Hz, 1H), 7.05–7.19 (m, 1H), 7.28–7.54 (m, 8H), 7.61–7.77 (m, 4H), 8.00 (s, 1H), 8.90 (br s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 55.5, 104.4, 110.7, 112.4, 118.5, 119.7, 123.3, 123.9, 126.7, 127.7, 127.9, 128.2, 130.1, 130.8, 138.3, 139.7, 143.9, 159.7, 160.6. *m/z* (APCI) 370 (MH$^+$, 100%). HRMS calcd for $C_{23}H_{19}N_3O_2$ 369.1477, found 369.1480.

Solid phase chemistry

The following methods were used to prepare compounds **9**, **12a**–**g** and **5a**–**g**.

Preparation of resin bound enamines: representative procedure. Phenylacetaldehyde (2.0 ml, 17.25 mmol) was added to a gently stirred suspension of piperazinomethyl polystyrene (Novabiochem catalogue no. 01–64–0310) (5.0 g, 0.69 mmol g^{-1}, 3.45 mmol) in dry benzene (50.0 ml). The reaction flask was fitted with a Dean–Stark apparatus and heated at reflux for 22 h under a nitrogen atmosphere. The reaction was cooled to room temperature and filtered (sinter funnel). The resin was washed successively with 150 ml portions of benzene, DCM, MeOH, DCM, acetone and ether before being dried overnight in a vacuum oven (60 °C, 20 mmHg) to give a straw coloured resin **9** (Y = H) (5.37 g).

Cycloadditions: representative procedure. A solution of hydrazonyl chloride **2** (354 mg, 1.38 mmol) in dry $CHCl_3$ (3.0 ml) was added to a mixture of enamine resin **9** (Y = H) (1.1 g, approx. 0.69 mmol) and triethylamine (192 μl, 1.38 mmol) in dry $CHCl_3$ (12.0 ml). The mixture was heated at reflux under a nitrogen atmosphere for 16 h. The reaction mixture was cooled to room temperature, filtered and the resin was washed successively with 25 ml portions of $CHCl_3$, DCM, MeOH, 1 : 1 MeOH–H_2O, DCM, acetone and ether before being dried overnight in a vacuum oven (60 °C, 20 mmHg) (1.24 g).

Cleavage of resin bound pyrazoline adducts: representative procedure. A solution of 3% TFA in DCM (2.0 ml) was added rapidly to resin-bound cycloadduct **12a** (R = OEt, X = 3-MeO, Y = H) (0.62 g, approx. 0.345 mmol) in dry DCM (10.0 ml). The red solution was stirred at room temperature for 10 min before being filtered. The resin was washed well with DCM (5 × 20 ml) and the filtrate concentrated to give the pyrazole **5a** (88 mg, 79%) as a yellow solid. Analysis by ^{1}H and ^{13}C NMR spectroscopy showed the product to be of >95% purity and was identical in all respects to the sample prepared *via* solution phase chemistry.

*1-(4-Iodophenyl)-4-phenyl-1H-pyrazole-3-carboxylic acid ethyl ester (**5b**).* ν_{max}(film)/cm^{-1} 1721, 1498, 1485, 1390, 1283, 1226, 1137, 960, 825, 761, 698. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.31 (t, *J* 7.1 Hz, 3H), 4.37 (q, *J* 7.1 Hz, 2H), 7.55 (d, *J* 8.9 Hz, 2H), 7.29–7.51 (m, 5H), 7.81 (d, *J* 8.9 Hz, 2H), 7.94 (s, 1H).^{13}C NMR (50 MHz, $CDCl_3$) δ 14.1, 61.2, 92.2, 121.4, 127.3, 127.7, 127.8, 128.0, 129.3, 131.1, 138.5, 139.0, 141.7, 162.3. *m/z* (APCI) 419 (MH$^+$, 52%), 405 (100), 373 (100). HRMS calcd for $C_{18}H_{15}IN_2O_2$ 418.0178, found 418.0177.

*1-(4-Iodophenyl)-4-(4-nitrophenyl)-1H-pyrazole-3-carboxylic acid ethyl ester (**5c**).* ν_{max}(film)/cm^{-1} 1714, 1604, 1496, 1339, 1309, 1299, 1230, 1149, 858, 816, 698. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.33 (t, *J* 7.1 Hz, 3H), 4.37 (q, *J* 7.1 Hz, 2H), 7.54 (d, *J* 8.9 Hz, 2H), 7.68 (d, *J* 8.9 Hz, 2H), 7.82 (d, *J* 8.9 Hz, 2H), 8.05 (s, 1H), 8.24 (d, *J* 8.9 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.2, 61.6, 92.8, 121.5, 123.3, 125.6, 127.9, 130.1, 138.1, 138.7, 141.5, 147.1, 161.9. *m/z* (APCI) 464 (MH$^+$, 75%), 450 (100). HRMS calcd for $C_{18}H_{14}IN_3O_4$ 463.0029, found 463.0037.

*1-[1-(4-Iodophenyl)-4-phenyl-1H-pyrazol-3-yl]ethanone (**5d**).* ν_{max}(film)/ cm^{-1} 1677, 1496, 1484, 1220, 825, 766, 698. ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.69 (s, 3H), 7.34–7.50 (m, 3H), 7.49–7.60 (m, 2H), 7.55 (d, *J* 8.7 Hz, 2H), 7.82 (d, *J* 8.7 Hz, 2H), 7.94 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 28.0, 92.0, 121.0, 126.7, 127.5, 127.7, 128.1, 129.2, 131.1, 138.6, 139.1, 147.5, 194.5. *m/z* (APCI) 389 (MH$^+$, 100%). HRMS calcd for $C_{17}H_{13}IN_2O$ 388.0073, found 388.0069.

*4-(4-Bromophenyl)-1-(3-methoxyphenyl)-1H-pyrazole-3-carboxylic acid ethyl ester (**5e**).* ν_{max}(KBr)/cm^{-1} 1721, 1609, 1595, 1485, 1277, 1205, 1174, 1136, 1072, 684. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.32 (t, *J* 7.1 Hz, 3H), 3.88 (s, 3H), 4.36 (q, *J* 7.1

Hz, 2H), 6.91 (ddd, *J* 1.0, 2.3 and 7.9 Hz, 1H), 7.16–7.67 (m, 7H), 7.92 (s, 1H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 14.2, 55.6, 61.3, 106.0, 112.1, 113.6, 121.7, 126.3, 127.9, 130.4, 131.0, 131.2, 140.4, 141.1, 160.6, 162.3. *m/z* (APCI) 403, 401 (MH^+, 27, 28%), 389, 387 (53, 53), 357, 355 (92, 100). HRMS calcd for $C_{19}H_{17}{}^{79}BrN_2O_3$ 400.0422, found 400.0421.

*4-(4-Chlorophenyl)-1-(3-methoxyphenyl)-1H-pyrazole-3-carboxylic acid ethyl ester (**5f**).* ν_{max}(KBr)/cm^{-1} 1721, 1606, 1595, 1487, 1277, 1207, 1174, 1136, 1092, 850, 835, 685. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.32 (t, *J* 7.1 Hz, 3H), 3.88 (s, 3H), 4.36 (q, *J* 7.1 Hz, 2H), 6.93 (ddd, *J*1.0, 2.3 and 7.9 Hz, 1H), 7.20–7.51 (m, 7H), 7.93 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.1, 55.6, 61.4, 106.1, 112.2, 114.0, 126.3, 128.3, 129.7, 130.4, 130.7, 133.7, 140.2, 141.0, 160.6, 162.3. *m/z* (APCI) 359, 357 (MH^+, 5, 15%), 345, 343 (20, 60), 313, 311 (30, 100). HRMS calcd for $C_{19}H_{17}{}^{35}ClN_2O_3$ 356.0927, found 356.0928.

*1-(3-Methoxyphenyl)-4-(4-tolyl)-1H-pyrazole-3-carboxylic acid ethyl ester (**5g**).* ν_{max}(KBr)/cm^{-1} 1723, 1609, 1493, 1279, 1205, 1175, 1133, 1031, 807, 685. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.34 (t, *J* 7.1 Hz, 3H), 2.39 (s, 3H), 3.88 (s, 3H), 4.38 (q, *J* 7.1 Hz, 2H), 6.86–6.98 (m, 1H), 7.00–7.70 (m, 7H), 7.93 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.2, 21.2, 55.6, 61.1, 105.9, 112.0, 113.6, 127.4, 127.7, 128.4, 128.7, 129.2, 130.2, 137.4, 140.6, 160.5, 162.5. HRMS calcd for $C_{20}H_{20}N_2O_3$ 336.1473, found 336.1470.

*4-(Butyl)-1-(3-methoxyphenyl)-1H-pyrazole-3-carboxylic acid ethyl ester (**13**).* ν_{max}(KBr)/cm^{-1} 2957, 2929, 1723, 1606, 1497, 1225, 1171, 1106. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.95 (t, *J* 7.2 Hz, 3H), 1.21–1.35 (m, 2H), 1.42 (t, *J* 7.1 Hz, 3H), 1.57–1.67 (m, 2H), 2.80 (t, *J* 7.5 Hz, 2H), 3.86 (s, 3H), 4.43 (q, *J* 7.1 Hz, 2H), 6.88 (dd, *J* 1.8 and 8.1 Hz, 1H), 7.20–7.38 (m, 3H), 7.71 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 14.4, 22.5, 24.2, 32.4, 55.6, 60.8, 105.9, 112.0, 113.4, 127.2, 127.6, 130.2, 140.9, 142.2, 160.6, 162.9.*m/z* (APCI) 303 (MH^+, 48%), 289 (100), 257 (90). HRMS calcd for $C_{17}H_{22}N_2O_3$ 302.1630, found 302.1637.

*4-[(1R)-1,5-Dimethylhex-4-enyl]-1-(3-methoxyphenyl)-1H-pyrazole-3-carboxylic acid ethyl ester (**14**).* ν_{max}(KBr)/cm^{-1} 1719, 1609, 1497, 1478, 1370, 1223, 1174, 1088, 978, 686. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.18 (d, *J* 6.9 Hz, 3H), 1.35 (t, *J* 7.1 Hz, 3H), 1.48 (s, 3H), 1.60 (s, 3H), 1.60–1.78 (m, 2H), 1.88–2.00 (m, 2H), 3.30 (m, 1H), 3.79 (s, 3H), 4.35 (q, *J* 7.1 Hz, 2H), 5.04 (m, 1H), 6.77 (m, 1H), 7.15–7.30 (m, 3H), 7.65 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.3, 17.6, 21.6, 25.7, 26.0, 29.0, 37.9, 55.6, 60.8, 105.7, 111.9, 113.2, 124.3, 125.7, 130.1, 131.5, 133.4, 140.8, 141.8, 160.4, 162.8. *m/z* (APCI) 357 (MH^+, 100%), 311 (57). HRMS calcd for $C_{21}H_{28}N_2O_3$ 356.2099, found 356.2089.

Preparation of amides: representative procedure. A suspension of the resin bound cycloadduct **12a** (R = OEt, X = 3-MeO, Y = H) (665 mg), 1 M aq. LiOH (5.0 ml) in THF (5.0 ml) was heated at reflux for 18 h. The mixture was filtered and the resin washed successively with 25 ml portions of water, THF, 1 : 1 THF–10% aq. citric acid solution, 10% aq. citric acid and acetone. The resin **15** was dried overnight in a vacuum oven (60 °C, 20 mmHg).

The resin-bound acid **15** (105 mg, approx. 0.06 mmol) was added to a solution of pentafluorophenol (135.4 mg, 0.74 mmol) and pyridine (100 μl, 1.24 mmol) in dry DMF (1.0 ml). Trifluoroacetic anhydride (85 μl, 0.60 mmol) was added and the mixture was stirred for 4 h at room temperature. The reaction mixture was filtered and washed successively with 20 ml portions of DMF, THF and DCM. After suction drying for 30 min the resin was re-suspended in DMF (1.0 ml) and treated with 4-(trifluoromethyl)benzylamine (86 μl, 0.60 mmol). Stirring was continued at room temperature for 18 h after which time the resin was filtered and washed successively with 20 ml portions of DMF, MeOH, 1 : 1 MeOH–10% aq. citric acid solution, MeOH, acetone, DCM and ether. The resin was treated with 3% TFA in DCM as described above to give the carboxamide **17i** (R = 4-$CF_3(C_6H_5)CH_2$) (19 mg, 70%).

*1-(3-Methoxyphenyl)-4-phenyl-1H-pyrazole-3-carboxylic acid benzylamide (**17h**).* ν_{max}(KBr)/cm^{-1} 3410 br w, 3330 br w, 1669, 1608, 1528, 1500, 1209, 1172, 762, 699. ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.88 (s, 3H), 4.64 (d, *J* 5.9 Hz, 1H), 6.90 (m, 1H), 7.21–7.53 (m, 12H), 7.57–7.68 (m, 2H), 7.97 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 43.4, 55.6, 105.7, 111.6, 113.1, 126.3, 127.6, 127.7, 127.9, 128.2, 128.7, 129.3, 130.4, 131.0, 137.8, 140.3, 142.7, 160.5, 162.4. *m/z* (APCI) 384 (MH^+, 100%) HRMS calcd for $C_{24}H_{21}N_3O_2$ 383.1633, found 383.1637.

*1-(3-Methoxyphenyl)-4-phenyl-1H-pyrazole-3-carboxylic acid 4-trifluoromethylbenzylamide (**17i**).* ν_{max}(KBr)/cm^{-1} 3414 br w, 3333 br w, 1668, 1608, 1529, 1501, 1326, 1163, 1120, 1067, 850, 761, 696. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.88 (s, 3H), 4.69 (d, *J* 6.2 Hz, 2H), 6.90 (ddd, *J* 0.7, 2.4 and 8.3 Hz, 1H), 7.24–7.43 (m, 6H), 7.45 (br m, 1H, NH), 7.48 (d, *J* 8.1 Hz, 2H), 7.59 (d, *J* 8.1 Hz, 2H), 7.63–7.68 (m, 2H), 7.98 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 42.7, 55.7, 106.0, 111.7, 113.0, 124.2 (q, *J* 272 Hz), 125.7 (q, *J* 4 Hz), 126.5, 127.7, 128.0, 128.1, 128.2, 129.4, 129.7 (q, *J* 32 Hz), 130.5, 131.2, 140.5, 142.6, 143.0, 160.7, 162.1. *m/z* (APCI) 452 (MH^+, 100%). HRMS calcd for $C_{25}H_{20}N_3O_2F_3$ 451.1507, found 451.1498.

*1-(3-Methoxyphenyl)-4-phenyl-1H-pyrazole-3-carboxylic acid 4-nitrobenzylamide (**17j**).* ν_{max}(KBr)/cm^{-1} 3402 br w, 3321 br w, 1669, 1607, 1519, 1344, 1212, 979, 762, 697. ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.89 (s, 3H), 4.73 (d, *J* 6.3 Hz, 2H), 6.91 (m, 1H), 7.28–7.60 (m, 6H), 7.53 (d, *J* 8.6 Hz, 2H), 7.64 (dd, *J* 1.4 and 8.0 Hz, 2H), 8.00 (s, 1H), 8.19 (d, *J* 8.6 Hz, 2H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 42.4, 55.6, 105.9, 111.6, 112.9, 123.8, 126.6, 127.7, 128.15, 128.17, 128.24, 129.4, 130.5, 131.0, 140.3, 142.6, 146.1, 147.2, 160.6, 162.2. *m/z* (APCI) 429 (MH^+, 95%). HRMS calcd for $C_{24}H_{20}N_4O_4$ 428.1484, found 428.1485.

*{[1-(3-Methoxyphenyl)-4-phenyl-1H-pyrazol-3-yl-3-carbonyl]-amino}acetic acid methyl ester (**17k**).* ν_{max}(KBr)/cm^{-1} 3403 br w, 1748, 1672, 1606, 1529, 1501, 1206, 1170, 982, 852, 762, 697. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.79 (s, 3H), 3.90 (s, 3H), 4.21–4.26 (m, 2H), 6.91 (ddd, *J* 0.7, 2.3 and 8.3 Hz, 1H), 7.28–7.46 (m, 6H), 7.51 (t, *J* 5.5 Hz, 1H), 7.61–7.65 (m, 2H), 7.97 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 41.0, 52.4, 55.7, 105.8, 111.6, 113.2, 126.5, 127.6, 127.9, 128.1, 129.4, 130.4, 131.2, 140.5, 142.7, 160.7, 162.2, 170.4. *m/z* (APCI) 366 (MH^+, 95%). HRMS calcd for $C_{20}H_{19}N_3O_4$ 365.1375, found 365.1382.

*1-(3-Methoxyphenyl)-4-phenyl-1H-pyrazole-3-carboxylic acid allylamide (**17l**).* ν_{max}(KBr)/cm^{-1} 3412 w, 3335 br w, 1669, 1608, 1595, 1528, 1501, 1208, 1166, 761, 696. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.90 (s, 3H), 4.07 (dddd, *J* 1.5, 1.5, 5.8, 5.8 Hz, 2H), 5.17 (dddd, *J* 1.5, 1.5, 1.5 and 10.2 Hz, 1H), 5.28 (dddd, *J* 1.4, 1.6, 1.7 and 17.1 Hz, 1H), 5.94 (dddd, *J* 5.5, 5.7, 10.3 and 17.2 Hz, 1H), 6.91 (ddd, *J* 0.9, 2.5 and 8.3 Hz, 1H), 7.12 (br s, 1H), 7.27–7.35 (m, 3H), 7.36–7.45 (m, 3H), 7.63–7.68 (m, 2H), 7.97 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 41.6, 55.7, 105.8, 111.6, 113.0, 116.5, 126.3, 127.6, 127.9, 128.1, 129.4, 130.5, 131.3, 134.3, 140.6, 143.4, 160.7, 162.0. *m/z* (APCI) 334 (MH^+, 100%). HRMS calcd for $C_{20}H_{19}N_3O_2$ 333.1477, found 333.1482.

*1-(3-Methoxyphenyl)-4-phenyl-1H-pyrazole-3-carboxylic acid octylamide (**17m**).* ν_{max}(KBr)/cm^{-1} 3417 w, 3333 br w, 2927, 1666, 1607, 1595, 1531, 1501, 1209, 1165, 852, 760, 696. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J* 7.0 Hz, 3H), 1.21–1.45 (m, 10H), 1.56–1.66 (m, 2H), 3.42 (app dd, *J* 7.2, 13.3 Hz, 2H), 3.90 (s, 3H), 6.91 (ddd, *J* 0.5, 2.3 and 8.3 Hz, 1H), 7.01 (br t, *J* ~5 Hz, 1H, NH), 7.27–7.43 (m, 6H), 7.61–7.67 (m, 2H), 7.96 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 22.7, 27.1, 29.2, 29.3, 29.7, 31.8, 39.4, 55.7, 105.9, 111.7, 113.0, 126.2, 127.6, 127.9, 128.2, 129.4, 130.4, 131.4, 140.6, 143.7, 160.7, 162.1. *m/z* (APCI) 406 (MH^+, 100%). HRMS calcd for $C_{25}H_{31}N_3O_2$ 405.2416, found 405.2421.

Ethyl 4-phenyl-2,4-dioxobutanoate (i)

Ethyl 4-phenyl-2,4-dioxobutanoate **i** was prepared in 59% yield following the procedure of Brecker *et al.*[12] Spectral data acquired on this compound (^{1}H NMR, ^{13}C NMR and MS) were identical to that reported in the literature.

1-(3-Methoxyphenyl)-5-phenyl-1*H*-pyrazole-3-carboxylic acid ethyl ester (ii)

Triethylamine (60 μl, 46 mg, 0.45 mmol) was added dropwise to a solution of ethyl 4-phenyl-2,4-dioxobutanoate (100 mg, 0.45 mmol) and 3-methoxyphenyl hydrazine hydrochloride (79 mg, 0.45 mmol) in dry ethanol (5.0 ml) under a nitrogen atmosphere. The mixture was heated at reflux for 14 h, cooled to ambient temperature and then the solvent removed *in vacuo*. The residue was subjected to flash chromatography (silica, 40% ethyl acetate–hexane elution, R_f = 0.32) to give the title compound as a brown oil (52 mg, 36%). ν_{max} (KBr)/cm^{-1} 1732, 1720, 1607, 1593, 1489, 1468, 1437, 1243, 1217, 1027, 763. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.42 (t, *J* 7.1 Hz, 3H), 3.70 (s, 3H), 4.45 (q, *J* 7.1 Hz, 2H), 6.84 (dd, *J* 0.9 and 7.9 Hz, 1H), 6.88 (dd, *J* 1.9 and 8.3 Hz, 1H), 6.91 (app t, *J* 2.0 Hz), 7.03 (s, 1H), 7.19 (t, *J* 8.1 Hz, 1H), 7.21–7.25 (m, 2H), 7.28–7.34 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.5, 55.5, 61.2, 110.0, 111.1, 114.8, 118.1, 128.6, 128.8, 129.6, 129.7, 140.5, 144.3, 144.7, 160.0, 162.5. *m/z* (APCI) 323 (MH^+, 100%). HRMS calcd for $C_{19}H_{18}N_2O_3$ 322.317, found 322.1315.

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References

1 H. Biere, E. Schröder, H. Ahrens, J.-F. Kapp and I. Böttcher, *Eur. J. Med. Chem.*, 1982, **17**, 27.
2 (*a*) G. Broggini and G. Molteni, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1685; (*b*) there is a range of conditions (solvent, base, temperature) described in the literature for this type of Japp–Klingemann reaction. We found the most convenient method (aqueous pyridine, 0 °C) to be that described by El-Abadelah *et al.* as the hydrazonyl chloride precipitated from the reaction mixture and after filtration could be used without further purification. See M. M. El-Abadelah, A. Q. Hussein and B. A. Thaher, *Heterocycles*, 1991, **32**, 1879.
3 Incorporating the amide functionality within the starting hydrazonyl chloride is a less convergent strategy and, in addition, α-chloro-β-ketoamides have been reported to be unstable and the precursor β-ketoamide has to be prepared. *e.g.* L. Garanti, A. Sala and G. Zecchi, *Synth. Commun.*, 1976, **6**, 269.
4 For a lead paper into the area of traceless linkers see F. Zaragoza, *Angew. Chem., Int. Ed.*, 2000, **39**, 2077 and references cited therein.
5 (*a*) F. Aznar, C. Valdés and M.-P. Cabal, *Tetrahedron Lett.*, 2000, **41**, 5683; (*b*) N. W. Hird, K. Irie and K. Nagai, *Tetrahedron Lett.*, 1997, **38**, 7111.
6 Other 1,3-dipolar cycloaddition reactions have been applied to solid phase organic chemistry K.-I. Washizuka, K. Nagai, S. Minakata, I. Ryu and M. Komatsu, *Tetrahedron Lett.*, 2000, **41**, 691 and references cited therein.
7 (*a*) L. A. Carpino, E. M. E. Mansour, C. H. Cheng, J. R. Williams, R. MacDonald, J. Knapczyk, M. Carman and A. Lopusiñski, *J. Org. Chem.*, 1983, **48**, 661; (*b*) J. Simpson, D. L. Rathbone and D. C. Billington, *Tetrahedron Lett.*, 1999, **40**, 7031 and corrigendum J. Simpson, D. L. Rathbone and D. C. Billington, *Tetrahedron Lett.*, 2000, **41**, 283; (*c*) S. Bräse, D. Enders, J. Köbberling and F. Avemaria, *Angew. Chem., Int. Ed.*, 1998, **37**, 3413.
8 Piperazinomethyl polystyrene; Novabiochem catalogue number 01-64-0310. Novabiochem also sell a piperidine-4-carboxylic acid polyamine resin, catalogue number 01-64-0256. Piperazine bound to a Wang resin *via* a carbamate has also been described F. Zaragoza and S. V. Petersen, *Tetrahedron*, 1996, **52**, 10823.
9 We found the most convenient preparation of 4-nitrophenylacetaldehyde to be the $Pb(OAc)_4$ oxidation of 4-nitrostyrene A. Lethbridge, R. O. C. Norman and C. B. Thomas, *J. Chem. Soc., Perkin Trans. 1*, 1973, 35 As a range of substituted styrenes are commercially available, this process represents a convenient route to a diverse range of phenylacetaldehydes and we have used this method to prepare 4-methyl-, 4-chloro- and 4-bromophenylacetaldehyde.
10 R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, 1963, **2**, 633.
11 P. Caramella, and P. Grünanger, in *1,3-Dipolar Cycloaddition Chemistry*, ed. by A. Padwa, Wiley, New York, 1984, vo1. 1, pp. 291–387.
12 L. Brecker, M. Pogorevc, H. Griengl, W. Steiner, T. Kappe and D. W. Ribbons, *New J. Chem.*, 1999, **23**, 437.
13 J. Zhang, S. Didierlaurent, M. Fortin, D. Lefrançois, E. Uridat and J. P. Vevert, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 2575.
14 (*a*) K. Bast, M. Christl, R. Huisgen, W. Mack and R. Sustmann, *Chem. Ber.*, 1973, **106**, 3258; (*b*) R. Huisgen, R. Sustmann and G. Wallbillich, *Chem. Ber.*, 1967, **100**, 1786.
15 J. A. Linn, S. W. Gerritz, A. L. Handlon, C. E. Hyman and D. Heyer, *Tetrahedron Lett.*, 1999, **40**, 2227 and references cited therein.
16 H. Biere, J.-F. Kapp and I. Böttcher, *Arch. Pharm. (Weinheim, Ger.)*, 1983, **316**, 588.