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# Solid Phase Synthesis of 5-Aminopyrazoles and Derivatives

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***Abstract:*** The development of a novel solid phase synthesis of some 5-aminopyrazoles and derivatives is described. Reaction of hydrazines with solid supported β-keto-nitrile (1) affords 5-aminopyrazoles (2) the amino group of which is readily acylated or sulphonylated. Generation of the solid supported β-keto-nitrile (1) is non trivial and represents a key step in the overall synthesis.
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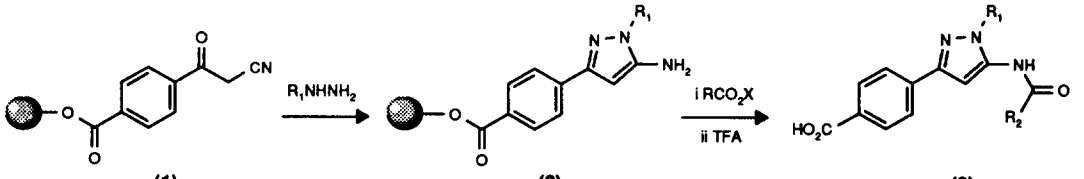
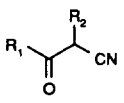
The scope and potential of Combinatorial Chemistry and Combinatorial Libraries in the drug discovery process is now well recognised and the current state of the art has been extensively reviewed[1]. Impressive as the achievements of solid supported combinatorial chemistry are, the range of chemistries available for library synthesis is limited. In particular there is a dearth of solid supported heterocyclic ring forming chemistries. Given the prevelance of heterocycles in drug molecules solid supported heterocyclic ring forming chemistries are of great utility in the preparation of libraries for testing against drug targets. In this context, in these laboratories we have devoted considerable effort towards developing new solid supported heterocyclic ring forming chemistries. Herein we describe the development of a versatile solid supported synthesis of 5-aminopyrazoles which is ideally suited to combinatorial library synthesis. Solid supported β-keto-nitrile (1) is reacted with hydrazines to form 5-aminopyrazoles (2). These are readily acylated or sulphonylated to afford, after cleavage from the solid support, N-acyl or N-sulphonyl 5-amino-3-(4-carboxyphenyl)pyrazoles (3 or 13). Generation of the solid supported β-keto-nitrile (1) is non trivial and represents a key step in the synthesis.




(1) (2) (3)

In our efforts to develop new solid supported heterocyclic ring forming chemistries the reaction of β-keto-nitriles (4) with hydrazines to afford regioselectively 5-aminopyrazoles[2,3] (5) was particularly attractive. The reaction is chemically efficient and versatile and is also powerful in that the ring formation generates a new reactive centre, the 5-amino group, which would be suitable for further functionalisation[2,3]. Futhermore 5-aminopyrazoles are well precedented templates in biologically active molecules (a search of the Derwent World Drug Index reveals over 20 known pharmacologically active structures based on the 5-aminopyrazole template) which would make this chemistry particularly attractive for the synthesis of libraries for assay

against drug targets. Additionally the structures which this 5-aminopyrazole chemistry would afford would complement those which could be accessed via the existing solid phase pyrazole synthesis developed by Marzinzik and Felder[4]



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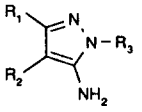

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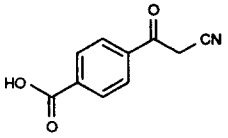

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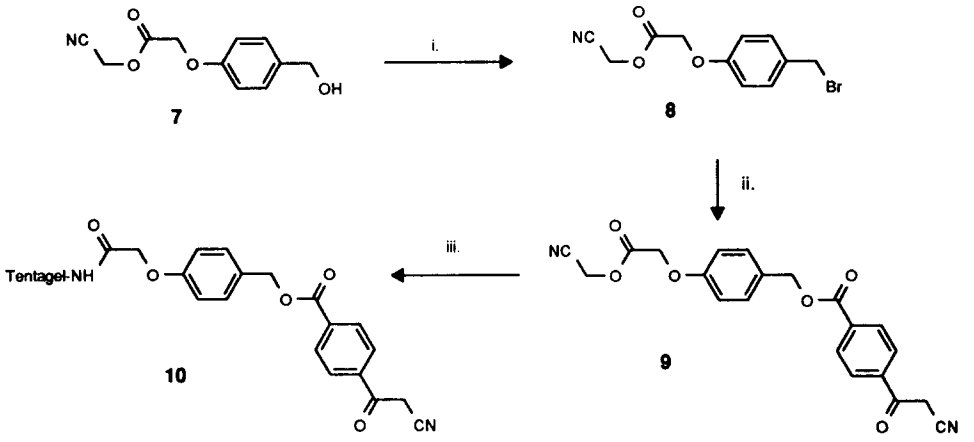
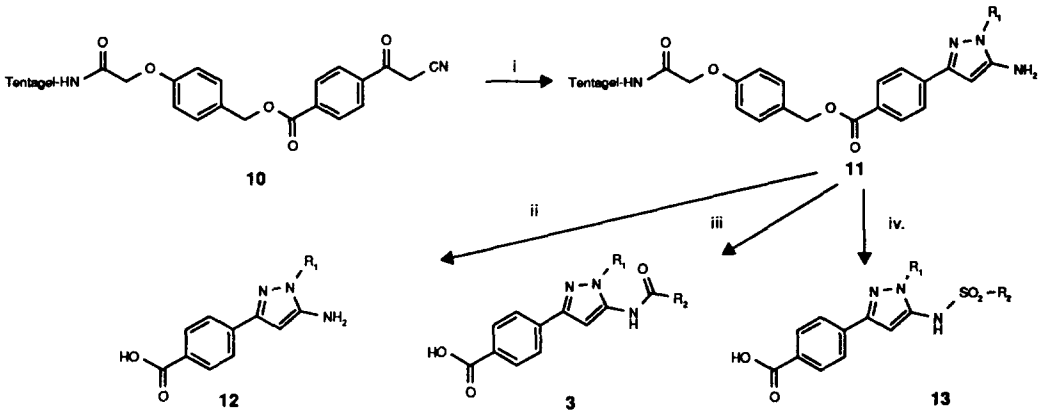
Our initial investigations in this area focused on use of β-keto-nitrile (6) (obtained from its commercially available methyl ester) which we envisaged could be attached to a resin through the carboxylic acid group. However all attempts to attach the carboxylic acid to a resin support via conventional means were unsuccessful. Myriad coupling procedures and numerous different types of resin and linker were examined all without success. We attributed these difficulties to the enolisable nature of the β-keto-nitrile system, however attempts to protect the keto-nitrile (e.g. as enol ethers) and liberate the ketonitrile on resin were similarly unsuccessful. The problem was overcome by assembling the entire β-keto-nitrile/linker ensemble (9) in solution and then coupling this to an amino resin (scheme 1). The cyanomethyl benzyl alcohol[5] (7) is converted to the corresponding benzyl bromide (8) with which β-keto-nitrile acid (6) is alkylated. The combined keto-nitrile/linker (9) obtained is then purified[6] to remove side products and treated with Tentagel S $NH_2$ resin to afford the resin supported β-keto-nitrile (10) with a TFA labile ester linkage.




Reagents and Conditions: i. $PPh_3.Br_2/CH_2Cl_2$, 75%; ii. DIPEA/(6)/Reflux then chromatography, 24%; iii. 0.5eq.Tentagel S $NH_2$ Resin/DMF/DMAP

**Scheme 1**

Treatment of the solid supported β-keto-nitrile (10) with hydrazines readily affords the corresponding supported 5-aminopyrazoles (11) which can be cleaved to give 5-amino-3-(4-carboxyphenyl)-pyrazoles (12). The supported 5-aminopyrazoles (11) are readily N-acylated or N-sulphonylated to afford, after cleavage, N-acyl 5-amino-3-(4-carboxyphenyl)pyrazoles (3) or N-sulphonyl-5-amino-3-(4-carboxyphenyl)pyrazoles (13).




Reagents and Conditions: i. $RNHNH_2.HCl/EtOH,10\%AcOH$; ii 95%TFA, iii (a) $R_2CO_2H$/DIC/DMAP/Pyridine 80°C. Double Couple, (b) 20% piperidine/DMF (c) 95%TFA; iv. (a) $R_2SO_2Cl$/DMAP/Pyridine 80°C. Double Couple, (b) 20% piperidine/DMF, (c) 95%TFA.

**Scheme 2**

**Table 1: 5-Aminopyrazoles (3,12 and 13) Prepared According to Scheme 2**

| | $R_1$ | | | | |
|---|---|---|---|---|---|
| | | | | | |
| H | 12a | 12b | 12c | 12d |
| | 3a | 3b | 3c | 3d |
| $R_2$ | 3e | 3f | 3g | 3h |
| | 3i | 3j | 3k | 3l |
| | 13a | 13b | 13c | 13d |

* Synthesis performed with N-t-BOC-Sarcosine

Table 1 shows twenty 5-aminopyrazoles prepared according to scheme 2, and table 2 contains analytical data for the samples obtained directly from this synthesis. Compounds were characterised by high resolution mass spectrometry[8] and HPLC[7]; LC coupled mass spectrometry[9] confirmed that in each case the principle component had a molecular ion corresponding to the appropriate product. The supported β-ketonitrile (10) is heated at 70°C for 5h. in $0.40molL^{-1}$ ethanol solutions of the appropriate hydrazine hydrochloride DIPEA and 10% acetic acid. After washing, cleavage with TFA/water (95:5) affords the corresponding 5-aminopyrazoles (12) in high yield and purity (table 2). N-Acylation of the resin supported 5-aminopyrazoles (11) is not straightforward. The 5-amino group is particularly unreactive and attempts to effect acylation using conventional peptide coupling procedures proved unsuccessful. However acylation

was readily effected by double coupling at 80°C for 8h in pyridine with DMAP and in-situ anhydride generation from the corresponding carboxylic acid and di-i-propylcarbodiimide. Similarly the 5-amino group is sulphonylated by double coupling at 80°C in pyridine with sulphonyl chlorides. Under these acylation/sulphonylation conditions, formation of imides and di-sulphonamides was observed in some instances. However washing with 20% piperidine in DMF readily cleaves any imide or di-sulphonamide back to the amide/mono-sulphonamide.

**Table 2: HPLC Purity[7] and High Resolution Mass Spectral Data[8] for Aminopyrazoles of Table 1**

| Sample | Purity (%) | Molecular Formula | Theoretical Mass[a] | Measured Mass[a] | Sample | Purity[a] (%) | Molecular Formula | Theoretical Mass[a] | Measured Mass[a] |
|---|---|---|---|---|---|---|---|---|---|
| 12a[b] | >95 | $C_{17}H_{15}N_3O_3$ | n/a | n/a | 3g | >95 | $C_{23}H_{18}N_4O_3$ | 399.145716 | 399.146713 |
| 12b | >95 | $C_{16}H_{12}BrN_3O_2$ | 358.019113 | 358.019843 | 3h | >95 | $C_{21}H_{15}N_5O_3$ | 386.125315 | 386.125381 |
| 12c | 91 | $C_{17}H_{15}N_3O_2$ | 294.124252 | 294.123220 | 3i | 86 | $C_{20}H_{20}N_4O_4$ | 381.156280 | 381.156842 |
| 12d | 89 | $C_{15}H_{12}N_4O_2$ | 281.103851 | 281.102866 | 3j | 89 | $C_{19}H_{17}BrN_4O_3$ | 429.056227 | 429.057356 |
| 3a | >95 | $C_{22}H_{23}N_3O_4$ | 394.176682 | 394.176560 | 3k | 80 | $C_{20}H_{20}N_4O_3$ | 365.161366 | 365.160627 |
| 3b | >95 | $C_{21}H_{20}BrN_3O_3$ | 442.076628 | 442.076703 | 3l | >95 | $C_{18}H_{17}N_5O_3$ | 352.140965 | 352.141376 |
| 3c | 90 | $C_{22}H_{23}N_3O_3$ | 378.181767 | 378.182016 | 13a | >95 | $C_{24}H_{21}N_3O_5S$ | 464.128018 | 464.129073 |
| 3d | 90 | $C_{20}H_{20}N_4O_3$ | 365.161366 | 365.161649 | 13b | 77 | $C_{23}H_{18}BrN_3O_4S$ | 512.027964 | 512.027899 |
| 3e | >95 | $C_{23}H_{18}N_4O_4$ | 415.140630 | 415.141202 | 13c | >95 | $C_{24}H_{21}N_3O_4S$ | 448.133103 | 448.133397 |
| 3f | >95 | $C_{22}H_{15}BrN_4O_3$ | 463.040577 | 463.040540 | 13d | >95 | $C_{22}H_{18}N_4O_4S$ | 435.112702 | 435.111775 |

a. Mass corresponds to molecular ion $MH^+$. b. Ion too weak for high resolution characterisation

The data of table 2 clearly illustrate the versatility and efficiency of the 5-aminopyrazole syntheses described herein. All compounds are produced in purities of greater than 75% and the wide structural variety of hydrazines and acids accomodated is clearly demonstrated.

In summary a novel solid phase syntheses of some 5-aminopyrazoles and their N-Acyl and N-sulphonyl derivatives has been developed. The syntheses are versatile, afford compounds based around a known pharmacophoric template and are ideally suited for combinatorial library generation. Further exploration of this and related chemistry is ongoing and will be published in due course.

## References and Notes


1. For excellent recent reviews of the combinatorial libraries/chemistry area see; Terret, N.K.; Gardner, M.; Gordon, D.W.; Kobylecki, R.J.; Steele, J. Tetrahedron Report Number 377,. and Balkenhol, F.;von dem Bussche-Hunnefeld, C.; Lansky, A. and Zechel, C. *Angew. Chem. Int. Ed. Engl.***1996**,*35*,2288
2. For a review of the chemistry of β-ketonitriles see; Elnagdi, M.H.;El-Moghayar, M.R.H. and Elgemeie, G.E.H., *Synthesis*,**1984**,1
3. See for example; Elnagdi, M.H.;El-Moghayar, M.R.H. and Fleita, D.H., *Tetrahedron*,**1974**,*31*,63
4. Marzinzik, A.L. and Felder, E.R. *Tet. Lett*, **1996**,*37*,1003
5. Plunkett, M.J. and Ellman, J.A. *J. Amer. Chem. Soc.*,**1995**,*117*,3306
6. The Alkylation is accompanied by a number of side reactions (e.g. C-alkylation) which precludes direct alkylation of **6** with a resin supported alkylating agent
7. Hewlett Packard HP1050 HPLC system, 3µm Supelcosil column, UV detection at 280nm
8. VG Autospec Mass Spectrometer operating in positive electrospray mode, 8000 resolution.
9. Hewlett Packard HP1050 HPLC system, 10cm, 3µm hypersil BDS column coupled to a VG Platform Mass spectrometer operating in positive electrospray mode.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