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Solid Phase Synthesis of 5-Aminopyrazoles and Derivatives Part II

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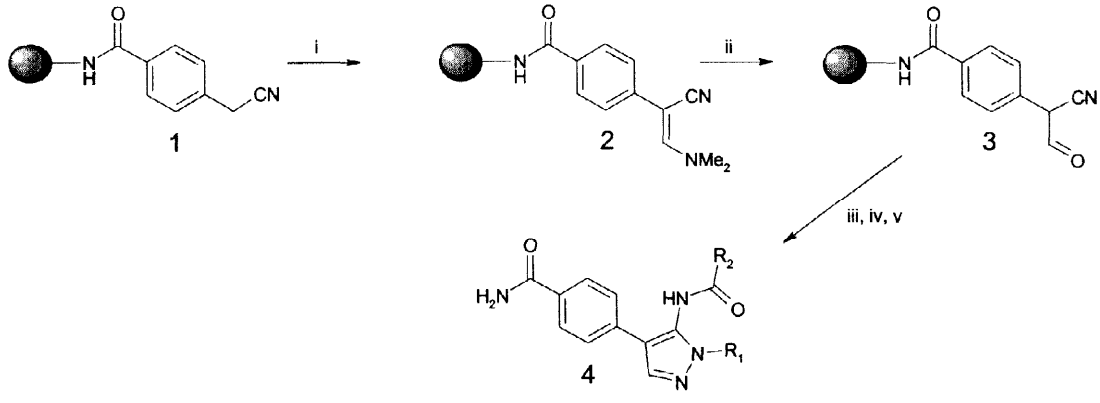
Abstract: A new synthesis of 5-amino pyrazoles on a solid support via in situ generation of a resin bound aldehyde nitrile is described. The synthesis is more versatile and efficient than the method that we had previously described and the new route yields complementary structures.

Solid phase combinatorial synthesis has been shown to be a powerful tool in the area of drug discovery, with a multitude of chemistries now having been adapted to the solid support[1]. In this context we have previously[2] described the solid phase synthesis of some 5-aminopyrazoles and derivatives. We have further expanded and developed this chemistry and can now report a second solid phase synthesis of 5-aminopyrazoles. This synthesis makes use of Bredereck's reagent[3] to convert solid supported benzyl nitrile, (1), into an enamine nitrile (2), The enamine (2) is readily hydrolysed to afford the aldehyde nitrile (3) which reacts efficiently with hydrazines to the give corresponding 5-aminopyrazoles. Subsequent acylation and cleavage from the resin affords N-acyl-5-aminopyrazoles (4). This new 5-aminopyrazole synthesis is more versatile than its predecessor, in that it has the greater potential for variation of the first position in the synthesis, namely the nitrile component, and in that it avoids the use of troublesome β-keto nitrile functionality. This new route is ideally suited for the synthesis of combinatorial libraries for screening against drug targets.

Scheme 1



Reagents and Conditions - i. Bredereck's reagent; ii. 2N HCl; iii. R_1NHNH_2; iv. R_2CO_2H; v. TFA

Expanding upon our initial 5-aminopyrazole synthesis, we were keen to develop substrates that could be converted, in situ, into 5-aminopyrazole precusors on the solid support. In this context, the potential

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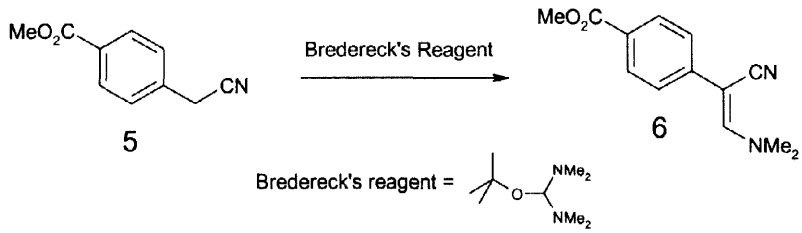
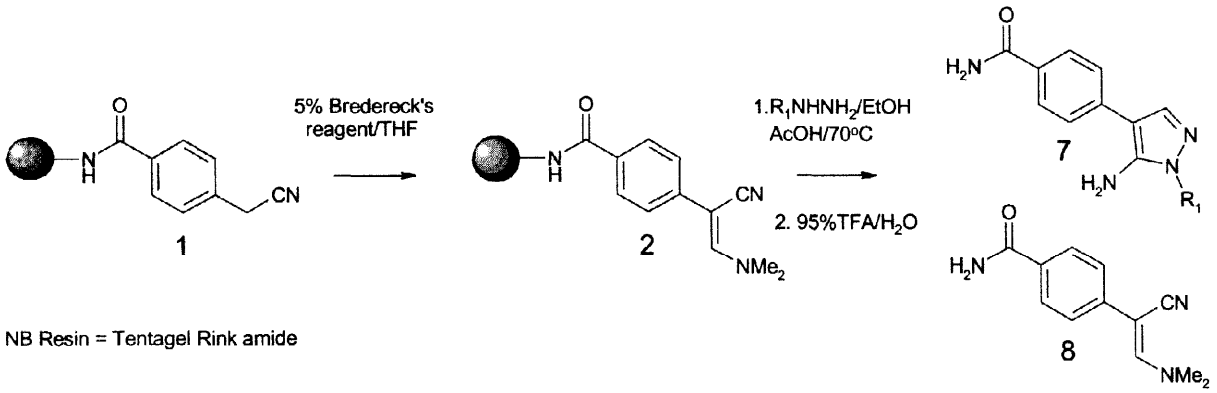
reaction of Bredereck's reagent with benzyl nitriles to give enamine nitriles such as (6) (a potential 5-aminopyrazole precursor), was attractive. Bredereck's reagent offers a mild and neutral method for introduction of enamine functionality and is hence ideally suited to solid phase synthesis (especially when compared to more traditional reagents such as DMFDMA[4], which often require higher temperatures and more forcing conditions). Solution phase experiments successfully demonstrated the feasibility of the strategy using Bredereck's reagent. Methyl-4-cyanomethyl benzoate (5) reacts cleanly with Bredereck's reagent in THF at ambient temperature to yield the corresponding enamine (6).



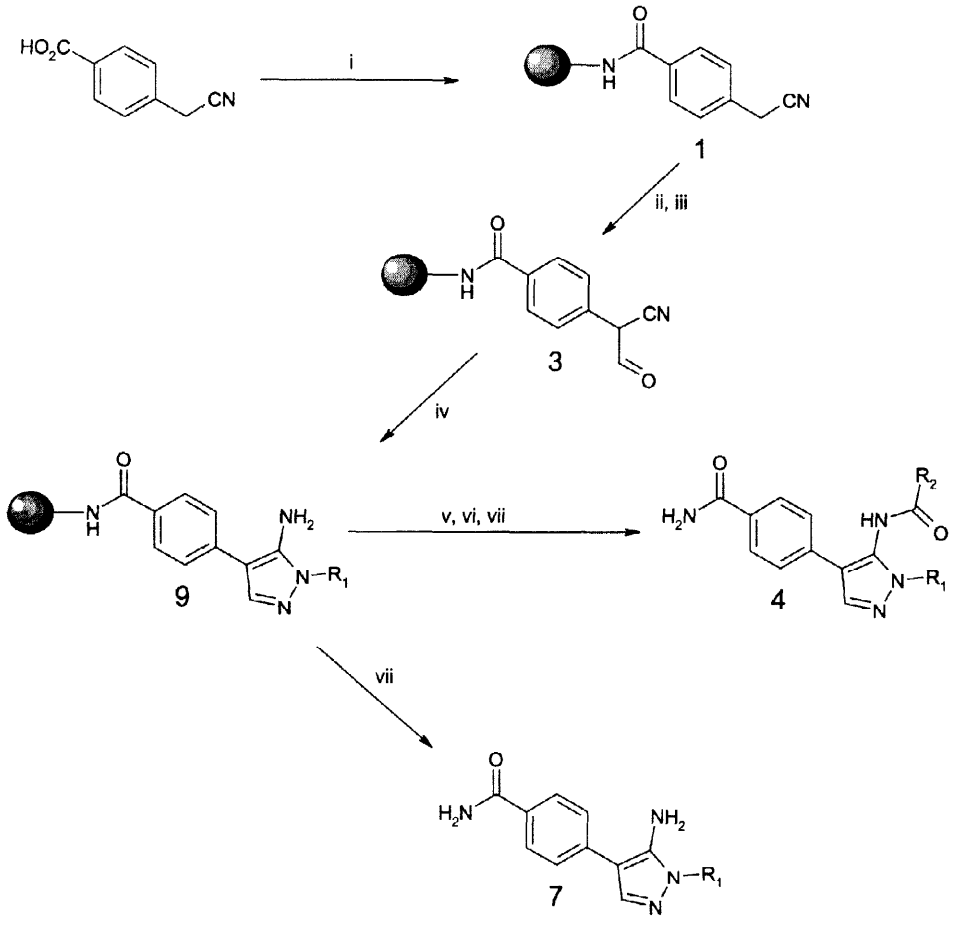
Enamine (6) subsequently undergoes reaction with hydrazines to give 4-substituted 5-amino pyrazoles. Furthermore this chemistry was readily transferred to the solid support. Treatment of the resin supported nitrile (1) with a 5% solution of Bredereck's reagent in THF yields the corresponding enamine (2) in quantitative yield[5]. However it proved difficult to drive the pyrazole formation to completion when electron rich hydrazines were employed. Interestingly, after cleavage with 95% TFA/water the only component present, other than the desired product (7), was the unreacted enamine (8).



Whilst the above protocol was suitable for the synthesis of 5-aminopyrazoles, we would only have a limited selection of hydrazines at our disposal. This limitation was overcome by hydrolysis of the solid supported enamine (2), with 2N HCl/THF (1:2). This gives the corresponding aldehyde (3), which reacts with both electron rich and electron poor hydrazines allowing access to a much broader range of 5-aminopyrazoles. Incorporating this finding into our strategy gives the overall synthesis of N-acyl-4-(4-carboxamidophenyl)-5-aminopyrazoles (4), as shown in scheme 2. Resin bound nitrile (1) is converted through to the aldehyde (3) in two steps as described above. Aldehyde (3) is then reacted with hydrazines to give 5-aminopyrazoles (9) which are in turn N-acylated and cleaved to give products (4) in good yield and excellent purity[6]. The previously described cyclisation and acylation conditions are employed thus allowing rapid entry into a complementary class of aminopyrazoles, with a different spacial display of substituents. It

is worth noting that in stark contrast to the previous β-ketonitrile route, 20g of enamine[7] resin was synthesised in one day for only modest effort.

Scheme 2



Reagents and Conditions - i. Tentagel S Rink amide resin/HATU/DIPEA/DMF; ii. Bredereck's reagent/THF/RT; iii. 2NHCl/THF; iv. R_1NHNH_2/EtOH/AcOH/70°; v. R_2CO_2H/DIC/DMAP/Pyridine/80°/DOUBLE COUPLE; vi. 20% Piperidine/DMF; vii. 95%TFA/water

It is interesting to contrast the apparent stability of the resin bound enamine (2) to 95% TFA/water and 2N HCl/THF. Whilst the former conditions leave the enamine intact, they completely cleave it from the solid support via the Rink amide linker. Conversely 2N HCl/THF completely hydrolyses the enamine on solid support in 4h, and yet leaves the Rink linker intact (as observed from post cleavage yield measurements and from ^{1}H Magic Angle Spinning NMR of the support).

Table 2 shows analytical data for a range of both free amino, and N-acylated 5-aminopyrazoles synthesised according to scheme 2, and analysed by HPLC[8], high resolution mass spectrometry[9] and LC coupled mass spectrometry (to confirm the identity of the HPLC peaks). Purities are measured directly after cleavage from the solid support, and without any purification. In all cases the products are >80% pure.

Table 1: 5-Aminopyrazoles (4 and 7) Prepared According to Scheme 2

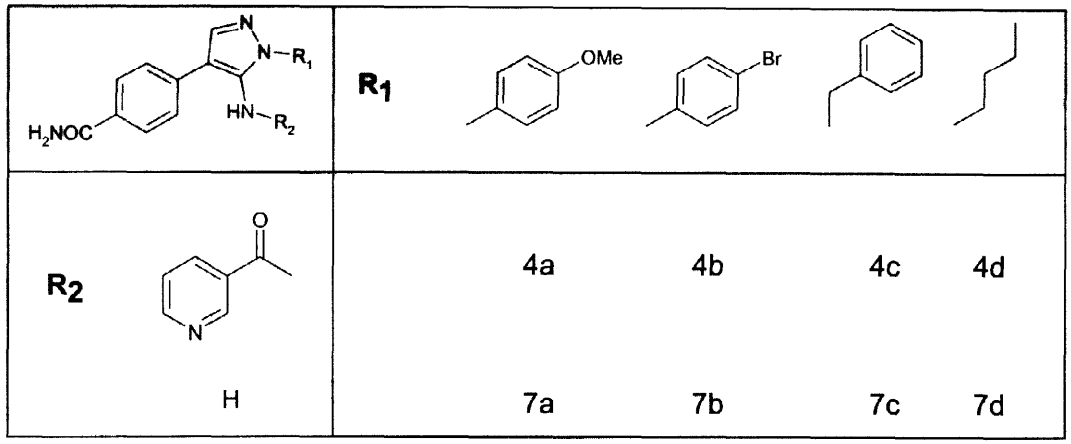


Table 2: HPLC Purity and High Resolution Mass Spectral Data for Aminopyrazoles of Table 1

Sample	Purity (%)	Molecular Formula	Theoretical Mass[a]	Measured Mass[a]	Sample	Purity[a] (%)	Molecular Formula	Theoretical Mass[a]	Measured Mass[a]
4a	88	$C_{23}H_{20}N_5O_3$	414.156615	414.155486	7a	96	$C_{17}H_{17}N_4O_2$	309.135151	309.135153
4b	83	$C_{22}H_{17}BrN_5O_2$	462.056561	462.057182	7b	100	$C_{16}H_{14}BrN_4O$	357.035097	357.034730
4c	88[b]	$C_{23}H_{20}N_5O_2$	398.161700	398.161334	7c	100	$C_{17}H_{17}N_4O$	293.140236	293.141111
4d	97[c]	$C_{20}H_{22}N_5O_2$	364.177350	364.177794	7d	100[c]	$C_{14}H_{19}N_4O$	259.155886	259.155538

a. Mass corresponds to molecular ion MH^+; b. *ca* 3:1 mix of regioisomers by HPLC; c. *ca* 1:1 mix of regioisomers by HPLC

In summary, we have described the synthesis of libraries of 4-(4-carboxamido phenyl)-5-aminopyrazoles (4) starting from a benzyl nitrile. Through the use of Bredereck's reagent, followed by subsequent acidic hydrolysis, such nitriles represent excellent intermediates for the solid phase synthesis of libraries of 5-aminopyrazoles. This new synthesis is more versatile than, and generates compounds which are of a complementary structure to those accessed by our earlier work. In addition this method allows the generation of a complex di-electrophilic species (namely an aldehyde nitrile) on the solid support, under very mild conditions from a chemically benign precursor.

References and Notes

1 For recent reviews of solid phase organic synthesis see - Früchtel J.S., Jung G., *Angew. Chem. Intl. Ed. Engl.* **1996**, *35*, 17 and Hermkens P.H.H., Ottenheijm H.C.J., Rees D. Tetrahedron Report No. 394 *Tetrahedron* **1996**, *52*, 4527

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3 Bredereck H., Effenberger F., Botsch H., *Chem.Ber.* **1964**, *97*, 3397

4 Bailey N., Cooper A.W.J., Deal M.J., Dean A.W., Gore A.L., Hawes M.C., Judd D.B., Merritt A.T., Storer R., Travers S., Watson S.P. *Chimia*, **1997**, *51*, 832

5 Yields were determined by taking ^1H NMR spectrum of cleaved product in DMSO - d6 containing 5mM *p*-nitro phenol as an internal standard.

6 Purities judged by lc/ms - Hewlett Packard HP1050 HPLC system, 10cm, 3μm hypersil BDS column coupled to a VG Platform Mass Spectrometer operating in positive electrospray mode.

7 The resin is stored at the enamine stage, due to long term instability of the resin bound aldehyde.

8 Hewlett Packard HP 1050 HPLC system, 3μm Supelcosil column, UV detection at 280nm.

9 VG Autospec Mass Spectrometer operating in positive electrospray mode, 8000 resolution