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A solid-phase synthetic route to substituted 7-azabenzimidazoles suitable for combinatorial library synthesis

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Abstract

A novel route for the solid-phase synthesis of 1,2,5-substituted 7-azabenzimidazole derivatives has been developed. Primary amines are attached to an aldehyde resin then coupled to 6-chloro-5-nitro-nicotinyl chloride. Subsequent alkylation with amines, reduction of the nitro group and cyclisation with aldehydes gives 1,2,5-substituted 7-azabenzimidazole derivatives.

Keywords: solid-phase synthesis; combinatorial chemistry.

Solid-phase organic chemistry, in particular for the synthesis of heterocyclic compounds, has become a focal point of combinatorial research due to the value of heterocyclic libraries in the drug discovery process.[1] In this paper, we wish to describe a novel solid-phase route[2] (Scheme 1) to an azabenzimidazole scaffold with three diversity sites.

Amine **1** was attached onto a 4-formyl-3-methoxyphenyloxymethyl polystyrene resin by reductive alkylation[3] with >95% loading as judged by solid-phase infra-red[4] (disappearance of the diagnostic C=O stretching at 1674 cm^{-1}). The next step, coupling of 6-chloro-5-nitropyridine-3-carboxylic acid to the supported amine **2**, proved to be more difficult. Our initial attempts, using a wide range of different coupling conditions,[5] were all unsuccessful. The conditions were eventually optimised by replacing the pyridine-3-carboxylic acid with the more reactive nicotinoyl chloride **3** and carrying out the reaction at sub-ambient temperature (Et_3N, DCM, –78°C). Under these conditions, the reaction proceeds cleanly with no evidence[6] of any impurities arising from a possible competing alkylation reaction between the electrophilic 6-chloro substitutent of heterocycle **3** and amine nucleophile **2**.

The immobilised nicotinyl intermediate **4** was then sequentially alkylated with different amines **5** (10 equiv.) and reduced ($SnCl_2$, DMF)[7] to give the diamines **7**. The diamines **7** were then treated

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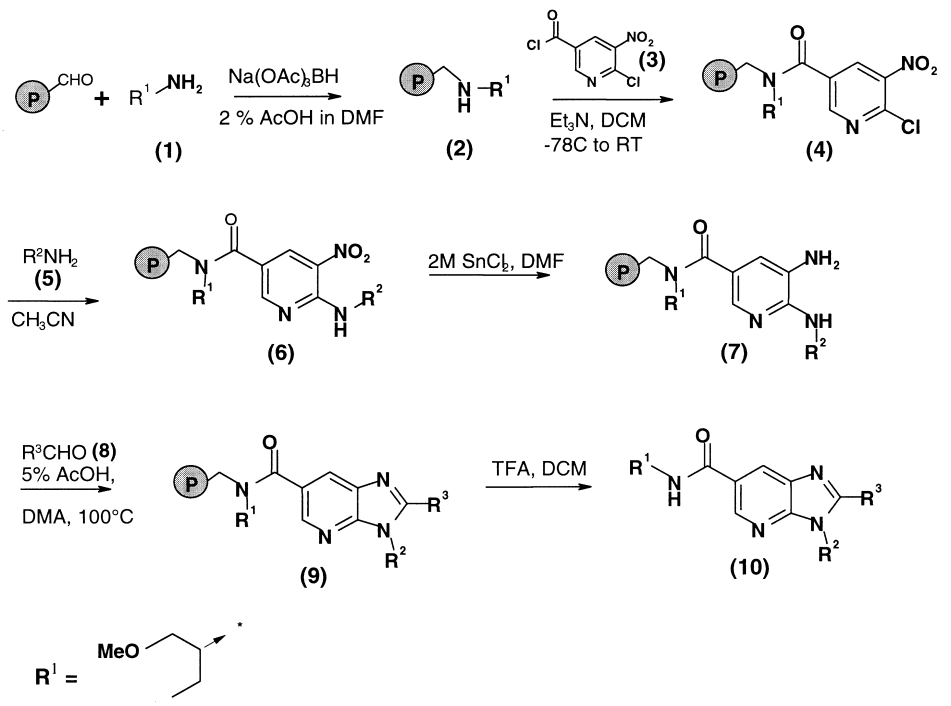


Scheme 1.

with aldehydes **8** and cyclised by heating in DMA. Dihydroazabenzimidazoles, which form initially, spontaneously aromatised[8] by aerial oxidation to give the desired azabenzimidazoles **9**.

As Table 1 shows, the procedure tolerates a range of different substituents. The products were all isolated in >50% yield[9] (average 78%). All final compounds were characterised by HPLC-MS and ^{1}H NMR. The purities of the compounds, measured by HPLC using three different modes of detection (215 nm, 254 nm and ELS), and their crude yields are shown in Table 1.

Table 1
Purity and yield of products **10a–h**

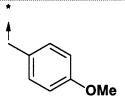
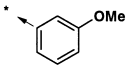
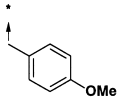
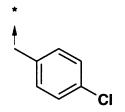
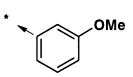
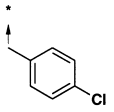
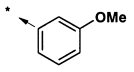
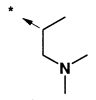
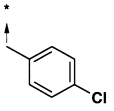
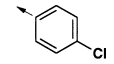
Compound	R^2	R^3	Purity	Yield
10 a			94	83
10b			97	83
10c			81	78

Table 1 (*continued*)

10d			95	84
10e			98	87
10f			96	94
10g			96	50
10h			98	62

In conclusion, the robustness of this synthetic methodology and the wide availability of diverse reagents (amines and aldehydes) makes this procedure ideally suited for high throughput synthesis. We are now using this methodology for construction of large combinatorial libraries based on the 7-azabenzimidazole template.

References

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2. General procedure for preparation of azabenzimidazoles exemplified with the synthesis of **10c**: 2-amino-1-methoxybutane (3 equiv. 34 mmol) was added to 4-benzyoxybenzaldehyde polystyrene resin (7.00 g, 1.62 mmol/g) suspended in 2% AcOH in DMF (70 mL). After agitating for 1 h at rt, sodium triacetoxyborohydride (7.2 g, 34 mmol, 3 equiv.) was added and the mixture then agitated for a further 36 h when IR showed no aldehyde absorption at 1674 cm^{-1}. The mixture was drained and the resin washed sequentially with 1:1 DCM:MeOH (3×30 mL), MeOH (1×30 mL), 1:1 DCM:MeOH (1×30 mL), DCM (1×30 mL), and Et_2O (2×30 mL) and then dried. The resin (**2**) (6×100 mg, 1.3 mmol/g) was then loaded into IRORI™ MiniKans[10] and dried by azeotroping with toluene (3×30 mL). The MiniKans were then suspended in triethylamine–DCM (100 mL), cooled to –78°C under argon then treated with a solution of the acid chloride (**3**) (1.00 g, 5 mmol) in DCM (20 mL). The mixture was then allowed to warm to rt overnight, drained and washed sequentially with DMF (30 mL), DCM (2×30 mL), 1:1 DCM:MeOH (30 mL), MeOH (1×30 mL), DCM (2×30 mL), and Et_2O (2×30 mL) and dried to give resin (**4**). The resin (**4**) in two MiniKans was suspended in CH_3CN (10 mL) and 4-chlorobenzylamine (10 equiv. 1.3 mmol) was added. The mixture was agitated overnight at room temperature, then drained and washed with DCM (2×30 mL), 1:1 DCM:MeOH (30 mL), MeOH (1×30 mL), DCM (2×30 mL), and Et_2O (2×30 mL) and dried to give resin (**6**). Resin (**6**) in a MiniKan was suspended in 2 M $SnCl{\cdot}2H_2O$ in DMF (10 mL) and agitated at room temperature for 25 h. The Kan was then drained and washed with portions of DMF (30 mL), DCM (2×30 mL), 1:1 DCM:MeOH (30 mL), MeOH (1×30 mL), DCM (2×30 mL), and Et_2O (2×30 mL) and dried to give resin (**7**). Resin (**7**) was swollen in 5% AcOH in DMA and 3-methoxybenzaldehyde (10 equiv. 1.3 mmol) was added. The MiniKan was then heated for 6 h at 120°C, drained and washed with DMF (30 mL), DCM (2×30 mL), 1:1 DCM:MeOH (30 mL), MeOH (1×30 mL), DCM (2×30 mL), and Et_2O (2×30 mL) and dried to give resin (**9**). This was cleaved with TFA:DCM:H_2O 6:3:1 (1 h). The resulting solution was collected and the resin washed with DCM (2 mL) and

DCM:MeOH 1:1 (2 mL). The combined washings were evaporated to give **10c** (47 mg, 0.10 mmol, yield 78%); ^{1}H NMR (400 MHz, CD_3SOCD_3) δ 8.88 (1H, s), 8.61 (1H, s), 8.33 (1H, d, $J=8.4$ Hz), 7.46 (1H, t, $J=7.6$ Hz), 7.33 (3H, m), 7.24 (1H, m), 7.15 (1H, m), 7.03 (2H, m), 5.66 (2H, s), 4.08 (1H, m), 3.74 (3H, +s), 3.44 (1H, dd, $J=10.6/6.4$ Hz), 3.40 (1H, dd, $J=10.6/5.6$ Hz), 3.28 (3H, s), 1.64 (1H, m), 1.53 (1H, m), 0.92 (3H, t, $J=7.6$); EI-MS m/z (M^+) found: 478.1767; $C_{26}H_{27}N_4O_3$ Cl requires: 478.1772.

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6. Purity of intermediate **4** was determined by cleaving a portion of the resin and analysing the product by HPLC-MS.
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8. To investigate the efficiency of the aerial oxidation reaction, the cyclisation reaction of diamine **7** to azabenzimidazole **10h** was investigated. After heating at 100°C for 3 h a 1:1 mixture of the oxidised and reduced product was observed (HPLC-MS of cleaved product). The oxidation was complete after 8 h.
9. Yields were calculated based on weight of compounds cleaved from support and based on the loading of the starting resin.
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