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Pentafluoronitrobenzene a novel scaffold for the solid-phase synthesis of 2,4,6-substituted-3,5-difluoronitrobenzene libraries

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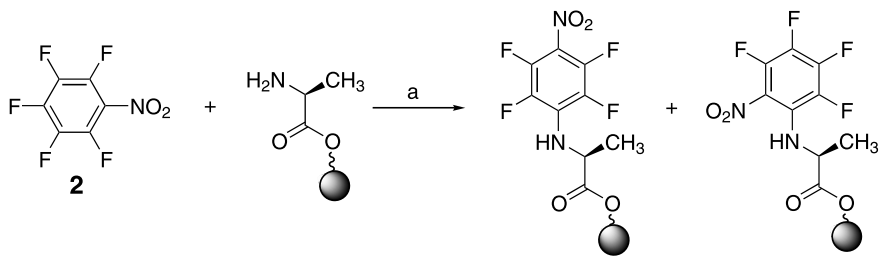
Abstract—The use of pentafluoronitrobenzene as a scaffold for solid-phase synthesis of 2,4,6-substituted-3,5-difluoronitrobenzenes is described. The scaffold is amenable to the synthesis of structurally diverse combinatorial libraries. Primary and secondary amines can be introduced to the scaffold via three successive nucleophilic aromatic substitutions under increasingly forcing conditions. The synthesis of a 36-member validation library is described as follows. Displacement of the *para*-fluorine was achieved in solution with a set of primary and secondary amines. Following purification, the *para*-substituted scaffold was attached to an amino acid-loaded hydroxymethylbenzyloxypolystyrene resin via a second substitution of one of the *ortho*-fluorines. The final reactive *ortho*-fluorine was then displaced by a second set of amines. After cleavage from the solid support the library was furnished in good overall purity, as determined by LCMS.

The use of combinatorial chemistry to provide libraries of small molecules for high-throughput screening against biological targets is now well established for drug discovery.[1,2] Libraries have been synthesised in solution or attached to a solid support using a variety of assembly strategies.[3,4] The use of polyhalogenated heteroaromatic scaffolds, which have been functionalised by successive S_NAr reactions, has proved popular, as exemplified by *s*-triazines,[5–7] pyrimidines,[8] and pyridazines.[9] One feature of this approach is that the biological activity of the library may be dominated by the heterocyclic scaffold. This can be beneficial where focussed lead optimisation libraries are required, e.g. the 2,6,9-trisubstituted purine cyclin-dependent kinase inhibitors,[10] but may limit the effective biological diversity of structurally diverse 'prospecting' libraries. For this reason, the development of combinatorial libraries based on scaffolds with unexplored biological activities is a priority in drug discovery.

We have recently employed pentafluoroarenes as starting materials in the synthesis of farnesyl transferase and geranylgeranyl transferase I inhibitors.[11–13] Stepwise S_NAr substitution of the activated fluorines of perfluoroarenes was employed in these studies. The use of fluorinated aromatics as scaffolds in combinatorial solid-phase chemistry has been described for the synthesis of a number of focussed libraries.[14–18] However, perfluoroarenes have not been fully exploited as scaffolds for the synthesis of combinatorial libraries. In this paper, we describe the synthetic methodology for the generation of libraries of compounds (**1**) using penta-



Scheme 1. Direct loading of **2** onto L-alanine HMB ester resin. *Reagents and conditions*: (a) DMF, rt.

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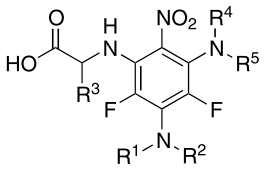
fluoronitrobenzene (**2**) as the scaffold, which can incorporate primary and secondary amine building blocks with widely different structures.

The scaffold was chosen for solid-phase combinatorial synthesis for a number of reasons: (a) novelty; (b) the potential for functionalisation by sequential S_NAr reactions to give 2,4,6-substituted products; (c) the availability of structurally diverse amines; (d) the ease of reaction monitoring by ^{19}F NMR spectroscopy, and (e) the possibility of further reactions at the nitro group.



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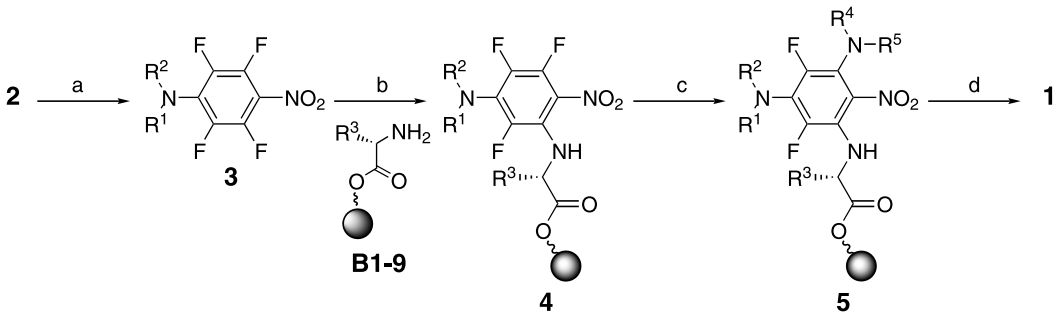
Preliminary experiments demonstrated the ease of attaching the scaffold to a solid support via reaction with L-alanine HMP ester resin (Scheme 1). However, gel phase ^{19}F NMR of the resin-bound intermediates revealed the presence of a mixture of *ortho*- and *para*-isomers, and was confirmed by LCMS of the cleaved products. Polar or hydroxylic solvents have been demonstrated to favour *para*-substitution in S_NAr reactions with pentafluoronitrobenzene.[19,20] A variety of solvents, e.g. DCM, DMF, EtOH, $MeNO_2$, were used for the reaction, however, the best *ortho* to *para* ratio obtained was 4:5, with DMF. In order to circumvent the regioselectivity problem, a different sequence was adopted in which the first substitution reaction was carried out in solution at room temperature, using a primary or secondary amine (Scheme 2). Nitromethane was the solvent of choice for these reactions giving the best ratio of the desired *para*-isomers (**3**).

Introduction of a solid supported amino acid in the second substitution required more forcing conditions (5 equiv. of **3**, DMF, 60°C, 24 h) to give the solid supported intermediate (**4**).[21] Unreacted **3** was recovered and could be recycled for future reactions with no significant loss of purity in the final products. Substitution of the final reactive fluorine was achieved by reaction of a second amine (100-fold excess, DMSO, rt, 24 h) to give (**5**).[15] Cleavage was effected under standard conditions (TFA, DCM) to give compounds **1** in good purity.[21]

Validation of the method for combinatorial library synthesis was achieved by the preparation of a small sample library (Scheme 2). Three amines were chosen as the first set of building blocks (**A1**–**3**), three natural amino acids were chosen for the second set (**B1**–**3**), and four amines (**C1**–**4**) were chosen to exemplify the third substitution reaction (Fig. 1).

The first substitution was carried as described, the desired *para*-isomer was isolated using silica chromatography, giving **3**{**A1**–**3**} in 85, 34, and 86% yields, respectively. In a typical procedure for parallel synthesis the reactions were carried out in fritted PTFE tubes. The substituted scaffold **3** (5 equiv.) was reacted with amino acid loaded HMP-resin **B1**–**3** (20 mg; 1% DVB polystyrene; 0.7 mmol/g loading; side-chain protected with *t*-Bu for **B1** and Boc for **B3**) in DMF at 60°C for 24 h, followed by washing (DMF, DCM) to give **4**{**A**,**B**}. The final substitution with amines **C1**–**4** (100



Scheme 2. Solid-phase synthesis of a perfluoronitrobenzene library. *Reagents and conditions*: (a) R^1R^2NH (**A1**–**3**), $MeNO_2$; (b) **B1**–**3**, DMF, 60°C, 4 h; (c) R^4R^5NH (**C1**–**4**, 100 equiv.), DMSO, rt, 24 h; (d) TFA, DCM, rt, 1 h.

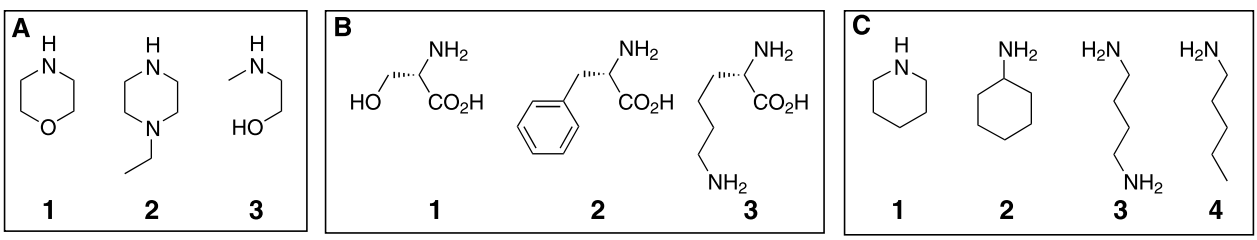


Figure 1. Reagent sets used for the validation library synthesis.

equiv.) was achieved at rt in DMSO for 24 h, followed by washing (DMF, DCM). The products **1**{**A**,**B**,**C**} were cleaved (TFA, DCM; rt) and evaporated, samples were redissolved in DMSO and the purity analysed by LCMS,[21] the results are detailed in Table 1. All of the combinations gave the desired product, typical purities were >80% and many combinations gave a single product. Lower purities, e.g. 54% for **1**{**A3**,**B2**,**C3**} were sporadic and not repeated in other similar combinations.

In summary, we have demonstrated the versatility of the pentafluoronitrobenzene scaffold **2** by the synthesis of a library of 2,4,6-substituted 3,5-difluoronitrobenzenes **1**{**A**,**B**,**C**} by successive S_NAr reactions. Our strategy involved the attachment of a *para*-substituted amino scaffold **3** to a solid support strategy via an amino acid. A small validation library has been produced with good overall purities, as determined by LCMS analysis. Further development of this approach is ongoing.

Table 1. Results from the validation library synthesis

Amine **1**	Amino acid	Amine **2**	Purity[a] (%)	ESI $[M+H]^+$
A1	**B1**	**C1**	92	458
		C2	100	472
		C3	100	446
		C4	80	461
	B2	**C1**	94	491
		C2	100	505
		C3	100	479
		C4	100	582
	B3	**C1**	100	472
		C2	91	460
		C3	86	460
		C4	73	562
A2	**B1**	**C1**	78	419
		C2	87	433
		C3	70	407
		C4	80	422
	B2	**C1**	82	480
		C2	87	494
		C3	88	467
		C4	68	420
	B3	**C1**	66	460
		C2	84	474
		C3	85	448
		C4	84	463
A3	**B1**	**C1**	74	431
		C2	89	445
		C3	93	419
		C4	80	434
	B2	**C1**	89	623
		C2	100	532
		C3	54	506
		C4	63	521
	B3	**C1**	92	604
		C2	100	513
		C3	100	487
		C4	80	502

[a] Approximate purities were determined from the UV peak area at 254 nm.[21]

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21. LCMS analysis was conducted using gradient elution (MeOH, aq. HCO_2H (0.1%)) with a Supelco Discovery C18 column (5 cm, 4.6 mm, 5 μm). Analysis by UV was recorded at 254 nm, MS was conducted on an LCQ ion trap mass spectrometer (Finnigan MAT) operating in electrospray ionisation mode. Crude yields were calculated post cleavage and were found to be greater than the theoretical yield, indicating the presence of residual solvent.