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Solid-phase synthesis of 'diverse' heterocycles

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Abstract—A novel and efficient solid-phase synthetic methodology for constructing 'diverse' heterocycles from *ortho*-fluoronitrobenzoic acid has been developed.

The utility of combinatorial technology to drug discovery has been well demonstrated in recent years.[1] Towards achieving this objective, significant progress has been made in the development of solid-phase and solution-phase methodologies for the synthesis of large numbers of compounds.[2] Most of the approaches reported so far have made use of linear or convergent reaction sequence strategies (Fig. 1) to arrive at the targeted structures. The diversity in these molecules has been introduced by carefully selecting the reagents using various algorithms.[3] Recently Houghton has reported 'library of library approach' to further diversify the initial library.[4] Herein we report a novel strategy (Fig. 2) that maximally utilizes divergent efficiency, which ultimately leads to the synthesis of *six heterocyclic cores from a single commercially available starting material*.

These heterocycles, as represented by general structures ($n=0$, 1 in Fig. 3), have been claimed in the literature to have a wide range of therapeutic activities.[5]

We envisaged that such a strategy would require a synthetic sequence leading to a common intermediate, which in turn could diverge into different products. The resin bound secondary amine (**1**, R1 = -CH2Ph) was acylated with 4-fluoro-3-nitro-benzoic acid (Scheme 1) to afford **2**.

Displacement of the fluorine with a primary amine (R2 = *n*-butyl) gave the common intermediate, *o*-nitroaniline (**3a**). We embarked upon the construction of six cores from this common intermediate.

Treatment of **3a** with ethyl oxalyl chloride in toluene at 40°C followed by tin chloride reduction and resin cleavage gave the 4-hydroxy-quinoxalin-2-one (**4a**) and not the quinoxalin-2-one.[6,7] The NMR and mass spectral analysis confirmed the structure of the product. These results (see Table 1) indicated that the preferred reaction pathway was partial reduction of the nitro group to the hydroxylamine followed immediately by intramolecular cyclization.

Figure 1.

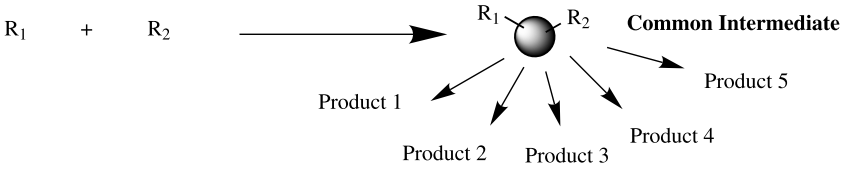

Figure 2.

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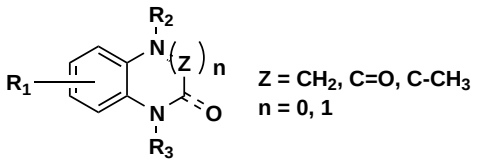
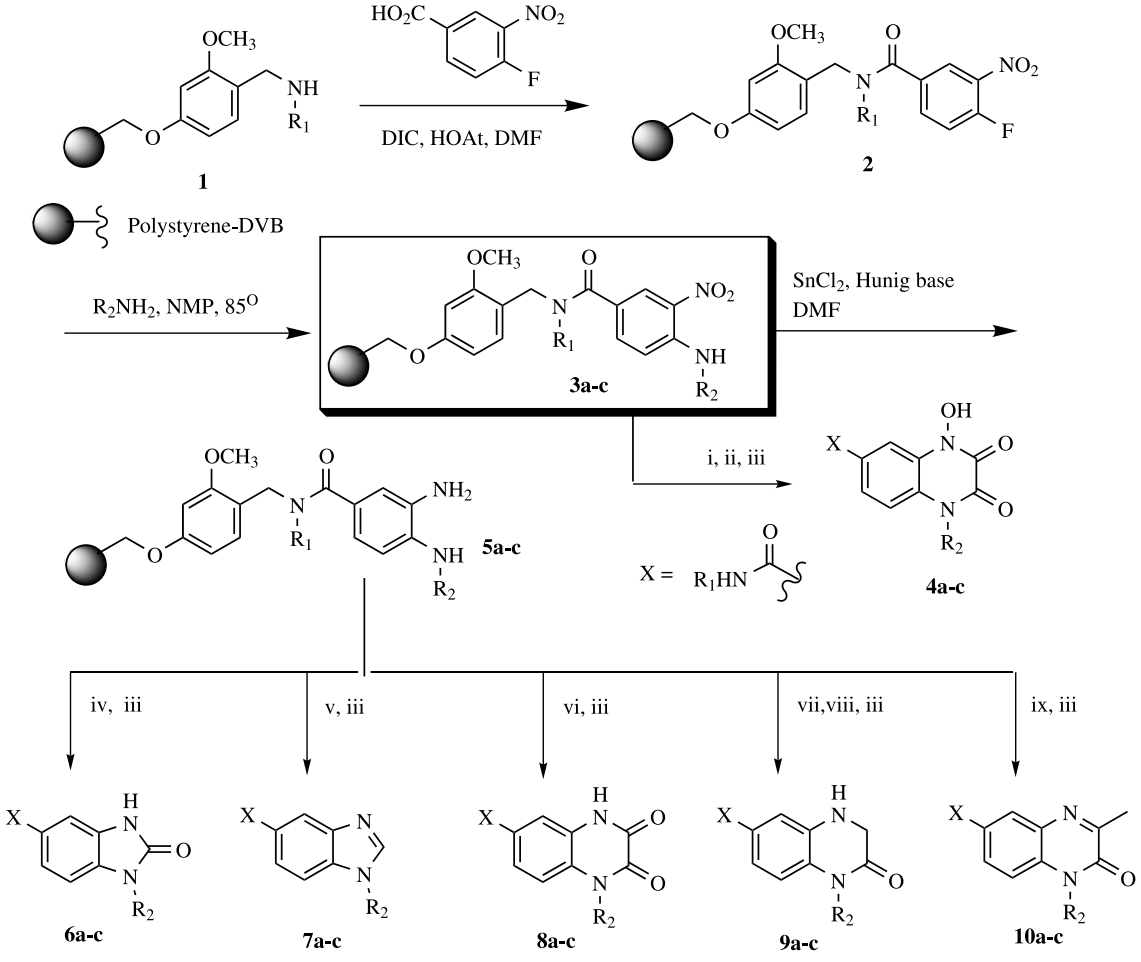


Figure 3.

To access the remaining five cores, the nitro group in the adduct **3a** was reduced with buffered tin chloride in DMF to furnish the phenylenediamine (**5a**). Attempts to cyclize **5a** to imidazolidone using either carbonyl diimidazole or disuccinimidyl carbonate[8] were only partially successful. The cyclization was efficiently carried out using triphosgene,[9] the product of which upon cleavage furnished the benzoimidazol-2-one (**6a**) derivative.[6,7] Heating the suspension of **5a** in trimethylorthoformate followed by the resin cleavage gave the benzoimidazole (**7a**).[6,7,10] Quinoxaline-2,3-dione (**8a**) was readily assembled by careful addition of oxalyl chloride to the cooled suspension (−15°C) of **5a** and 2,6-lutidine in dichloroethane followed by the cleavage. Synthesis of the corresponding quinoxalin-2-one (**9a**) derivative was found to be relatively difficult.[11] All our initial attempts to carry out the reductive amination with methyl glyoxylate followed by cyclization in one step were unsuccessful. Ultimately **5a** was allowed to react with methyl glyoxylate for an extended period (40 h) to ensure imine formation and then subjected to reductive amination followed by concurrent cyclization to afford the quinoxalin-2-one (**9a**) after cleavage. Heating **5a** with methyl pyruvate in dimethylformamide–trimethyl orthoformate (1:1) at 60°C followed by cleavage from the resin gave the 3-methyl-quinoxalin-2-one (**10a**).

Once the strategy was established, we decided to examine the scope and limitations using different R2 groups while keeping the R1 group constant as benzyl. The results (purity and yield of crude) of these as well as the validation experiments are as shown in Table 1.



Scheme 1. *Reagents and conditions*: (i) ethyl oxalyl chloride (3 equiv.), Hunig base (3 equiv.), toluene, rt to 40°C, 40 h; (ii) $SnCl_2 \cdot 2H_2O$ (10 equiv.), Hunig base (10 equiv.), DMF, rt, 24 h; (iii) TFA–CH_2Cl_2 (1:1), 1 h; (iv) triphosgene (2 equiv.), Hunig base (2 equiv.), CH_2Cl_2, 0°C to rt, 20 h; (v) trimethylorthoformate (neat), 70°C, 24 h; (vi) oxalyl chloride (8 equiv.), 2,6-lutidine (8 equiv.), CH_2Cl_2, −15°C to rt, 20 h; (vii) methyl glyoxylate (12 equiv.), DMF–trimethylorthoformate (1:1), 40°C, 40 h; (viii) $NaCNBH_3$ (12 equiv.), AcOH (cat), THF, rt, 48 h; (ix) methyl pyruvate (10 equiv.), DMF–trimethylorthoformate (1:1), AcOH (cat.), 40°C, 40 h.

Table 1.

Compound #	R2	Purity (%) (crude)	Yield (%) (crude)
4a	*n*-Butyl	95	74
6a	*n*-Butyl	92	79
7a	*n*-Butyl	98	84
8a	*n*-Butyl	89	70
9a	*n*-Butyl	90	68
10a	*n*-Butyl	96	80
4b	Cyclohexyl	92	71
6b	Cyclohexyl	89	76
7b	Cyclohexyl	95	79
8b	Cyclohexyl	87	62
9b	Cyclohexyl	88	60
10b	Cyclohexyl	93	75
4c	Phenyl	92	68
6c	Phenyl	91	65
7c	Phenyl	93	72
8c	Phenyl	73	58[a]
9c	Phenyl	70	55[a]
10c	Phenyl	90	75

[a] Yield calculated based upon purified material.

Overall, the reaction sequence using a straight chain amine (R2 = *n*-butyl) worked well across all the cores. On the other hand, when a branched chain amine or aniline (R2 = cyclohexyl or phenyl) was used; the results differed depending upon the core. For instance, results of the benzoimidazole (**6b–c** and **7b–c**) as well as the quinoxalin (**4b–c** and **10b–c**) derivatives were comparable to that obtained from the straight chain amine. But, in the case of the quinoxalin (**8b–c** and **9b–c**), the yield and purity were always lower than the corresponding straight chain amine. These results could be easily explained by decreased reactivity of the aniline nitrogen towards intramolecular cyclization in lieu of steric bulk and electron deficiency (in the case of R2 = phenyl).

In conclusion, we have demonstrated the utility of a novel *divergent* synthetic strategy for the construction of six related cores for rapid product and SAR generation.

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6. All compounds were characterized by LC-MS analysis of the crude product. In addition, compounds **4a–10a** gave satisfactory NMR spectra. The yields were based on weight of crude product unless mentioned otherwise.
7. A typical experimental procedure (illustrated for compound **4a–10a**):

   Resin **3a** was prepared by the method similar to described in Ref. 8

   To the resin **3a** (50 mg, 0.050 mmol) suspended in toluene (0.5 mL) was added diisopropylethylamine (26 μL, 0.150 mmol) and ethyl oxalyl chloride (17 μL, 0.150 mmol). The mixture was heated at 40°C for 40 h. The solution was removed and the resin was washed with toluene (2×20 mL), DMF (3×10 mL), CH_2Cl_2 (3×20 mL) and dried under vacuum. To this resin was added DMF (0.5 mL), diisopropylethylamine (90 μL, 0.50 mmol) and tin chloride dihydrate (112 mg, 0.50 mmol). The mixture was shaken at room temperature for 24 h. The resin was washed with DMF (3×10 mL), CH_2Cl_2 (3×20 mL) and dried under vacuum. The resin was treated with CH_2Cl_2–TFA (1:1) solution (1.0 mL) for 1 h. The solution was drained and the resin was rinsed with CH_2Cl_2 (0.5 mL). The combined cleavage solution was concentrated under vacuum to afford **4a**.

   To the resin **3a** (1.0 g, 1.0 mmol) in DMF (40 mL) and diisopropylethylamine (1.6 mL, 10 mmol) was added tin chloride dihydrate (2.25 g, 10 mmol). The mixture was vortexed for 20 h. The solvent was drained, and the resin was washed sequentially with DMF (2×50 mL), DMF–H_2O (3:1) (2×25 mL), DMF (2×50 mL), CH_2Cl_2 (2×50 mL), MeOH (2×50 mL), and dried under vacuum to give **5a**.

   Triphosgene (32 mg, 0.1 mmol) was added to the suspension of resin **3a** (50 mg, 0.050 mmol) and diisopropylethylamine (20 μL, 0.1 mmol) in CH_2Cl_2 (0.5 mL) at 0°C. The mixture was kept at 0°C for 1 h and then continued to shake for additional 20 h at room temperature. The resin was washed with DMF (2×5 mL), CH_2Cl_2 (3×5 mL) and dried under vacuum. The resin was treated with CH_2Cl_2–TFA (1:1) solution (1.0 mL) and shaken for 1 h. The solution was drained and rinsed with CH_2Cl_2 (0.5 mL). The combined cleavage solution was concentrated under vacuum to furnish **6a**.

   Resin **3a** (50 mg, 0.050 mmol) suspended in trimethylorthoformate (1.0 mL) was shaken at 70°C for 24 h. The resin was washed with DMF (2×5 mL) and CH_2Cl_2 (3×5 mL) and dried under vacuum. The resin was treated with CH_2Cl_2–TFA (1:1) solution (1.0 mL) and shaken for 1 h. The solution was drained and rinsed with CH_2Cl_2 (0.5 mL). The combined cleavage solution was concentrated under vacuum to afford **7a**.

   To the resin **3a** (50 mg, 0.050 mmol) suspended in CH_2Cl_2 (1.0 mL) was added 2,6-lutidine (46 μL, 0.4 mmol) and 2 M oxalyl chloride (200 μl, 0.4 mmol) at −15°C. The mixture gradually warmed to 0°C in 1 h and then shaken at room temperature for 20 h. The resin was washed with DMF (2×5 mL), CH_2Cl_2 (3×5 mL) and dried under vacuum. The product was cleaved by treatment (1 h) with CH_2Cl_2–TFA (1:1) solution (1.0 mL) The resin was rinsed with CH_2Cl_2 (0.5 mL) and the combined cleavage solution was concentrated under vacuum to afford **8a**.

Methyl glyoxlate in toluene (140 μL, 0.6 mmol) was added to the suspension of resin **3a** (50 mg, 0.050 mmol) in DMF–trimethylorthoformate (1:1) (1 mL). The mixture was shaken at 40°C for 40 h. The solvent was drained and the resin was washed with anhydrous THF (2×5 mL). The resin was resuspended in THF (0.5 mL) and to which was added $NaCNBH_3$ (1 M, 600 μL, 0.6 mmol) and HOAc (15 μL). The mixture was shaken at room temperature for 48 h. The solution was removed and the resin was washed with THF (2×5 mL), DMF (2×5 mL), CH_2Cl_2 (3×5 mL) and dried under vacuum. The resin was treated with CH_2Cl_2–TFA (1:1) solution (1.0 mL) and shaken for 1 h. The solution was drained and rinsed with CH_2Cl_2 (0.5 mL). The combined cleavage solution was concentrated under vacuum to afford **9a**.

To the resin **4a** (50 mg, 0.050 mmol) suspended in DMF–trimethylorthoformate (1:1) (1 mL) was added methyl pyruvate (56 μL, 0.50 mmol) and HOAc (15 μL). The mixture was shaken at 40°C for 40 h. The resin was washed with DMF (3×5 mL), THF (2×5 mL), DCM (3×5 mL) and dried under vacuum. The resin was then treated with CH_2Cl_2–TFA (1:1) solution (1.0 mL) and shaken for 1 h. The solution was drained and rinsed with CH_2Cl_2 (0.5 mL). The combined cleavage solution was concentrated under vacuum to afford **10a**.

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