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Solid phase synthesis of 5,6,7,8-tetrahydro-1*H*-imidazo[4,5-*g*]quinoxalin-6-ones [†]

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Abstract

Traceless solid phase synthesis of 5,6,7,8-tetrahydro-1*H*-imidazo[4,5-*g*]quinoxalin-6-ones with three points of diversity is described. Primary amines attached to 2-(4-formyl-3-methoxyphenoxy)ethyl polystyrene react with 1,5-difluoro-2,4-dinitrobenzene followed by displacement of second fluorine with amino acid ester, reduction of nitro groups, acylation and ring closure. A library of 60 title compounds has been prepared. © 1999 Elsevier Science Ltd. All rights reserved.

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The application of solid phase approaches in combinatorial chemistry has created vast opportunities in the synthesis of diverse multifunctional libraries (for recent reviews on solid phase synthesis and combinatorial libraries, see lit.[1–5]). This approach highlights potential prospects for the construction of organic molecules via novel routes, which are feasible for parallel application. Much of the published work relies upon direct conversion of known solution phase chemistry to the solid phase. As a result, extraneous functional groups left in the products after cleavage level physico-chemical and biological properties and limit investigation of structure–activity relationship. A number of approaches have been developed to circumvent this problem resulting in so-called traceless solid phase synthesis. Herein, we describe the traceless synthetic methodology employing 4-formyl-3-methoxyphenoxy linker. To our knowledge, the traceless synthesis of aromatic heterocycles on an aldehyde functionalized resin has not been published before. The acid sensitive 4-formyl-3-methoxyphenoxy linker and its derivatives have been applied for solid phase preparation of *N*-substituted amides, ureas, sulfonamides, carbamates[6] and lactams.[7–9]

We report the efficient solid phase synthesis of imidazo[4,5-*g*]quinoxalines with three points of diversity from versatile building blocks which include primary amines, carboxylic acids and amino acid esters. The method described below is a part of our continuing effort to adapt traceless synthetic methodology to

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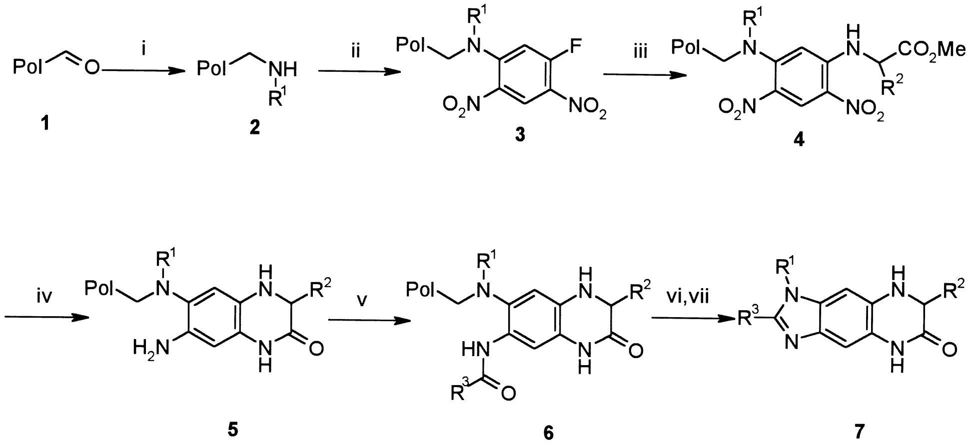
the synthesis of heterocycles. A solid phase approach gives advantage to employ the proposed inexpensive symmetric scaffold 1,5-difluoro-2,4-dinitrobenzene for straightforward construction of asymmetric fused heterocycles. For the purposes of library generation, the multistep synthesis described below is conveniently carried out on solid support since the effort spent upon product isolation following each reaction is minimized. The use of 4-fluoro-3-nitrobenzoic acid and 3-fluoro-4-nitrophenol has been published for solid phase synthesis of benzimidazoles[10–16] and quinoxalin-2-ones[17,18] containing extraneous functional groups.

The solid phase synthesis of 5,6,7,8-tetrahydro-1*H*-imidazo[4,5-*g*]quinoxalin-6-ones is outlined in Scheme 1. Cleavage of numerous 1–2 mg samples of the resin-bound intermediates with subsequent HPLC and LC–MS analysis of the resultant products accompanied each step during optimization of reaction conditions.



Scheme 1. (i) R^{1}NH$_2$, HC(OEt)$_3$, NaCNBH$_3$; (ii) 1,5-F$_2$-2,4-(NO$_2$)$_2$C$_6$H$_2$, Et$_3$N; (iii) H$_2$NCHR^{2}CO$_2$Me; (iv) SnCl$_2$·2H$_2$O, NMM; (v) R^{2}CO$_2$H, DIC; (vi) CF$_3$CO$_2$H:CH$_2$Cl$_2$:Et$_3$SiH (10:30:1); (vii) 4N HCl/dioxane–MeOH (2:1), 50°C

In the first step, 2-(4-formyl-3-methoxyphenoxy)ethyl polystyrene was loaded with a primary amine using reductive amination procedure. Treatment of the resin-bound amine **2** with an excess of 1,5-difluoro-2,4-dinitrobenzene in the presence of triethylamine resulted in nucleophilic aromatic substitution of only one fluorine atom.

The presence of the two nitro groups facilitates the displacement of the second fluorine atom by an amino acid ester, which was obtained from the corresponding hydrochloride salt. Quinoxaline **5** was formed by the reduction of both nitro groups using tin chloride in *N*-methylpyrrolidin-2-one in the presence of *N*-methylmorpholine and concomitant ring closure of compound **4**. Acylation of the primary aromatic amino group was carried out by symmetric anhydrides which were generated in situ from *N*,*N*′-diisopropylcarbodiimide and corresponding carboxylic acids. Acidolysis of acylamidoquinoxaline **6** by cleavage cocktail trifluoroacetic acid (TFA)/methylene chloride/triethylsilane for 1 h and/or the subsequent treatment of cleaved product by TFA overnight was insufficient for complete formation of the imidazole ring. According to LC–MS analysis, cleaved samples consist of both 7-acylamido-6-alkylamino-1,2,3,4-tetrahydroquinoxalin-2-ones and 1,2,7-trisubstituted 5,6,7,8-tetrahydro-1*H*-imidazo[4,5-*g*]quinoxalin-6-ones **7** in ratios depending on the substituents. Alternative release from the polymer by incubation of resin **6** at 50°C in mixture dioxane/methanol/HCl resulted in complete ring closure. We compared the purity and yield of imidazo[4,5-*g*]quinoxalines that were isolated by two ways: (i) treatment of the resin **6** by cleavage cocktail TFA–CH$_2$Cl$_2$–Et$_3$SiH, evaporation of the collected solution and incubation of the residue in dioxane/methanol/HCl at 50°C; (ii) direct

Table 1
Purity and yields of representative compounds

Compound	R^1	R^2	R^3	Yield(%)[a]	Purity(%)[b]
7a	3-(4-methylpiperazin-1-yl)propyl	H	methyl	76	85
7b	3-(pyrrolidin-2-on-1-yl)propyl	benzyl	benzyl	82	87
7c	cyclohexyl	benzyl	cyclohexyl	90	93
7d	2-(2-chloro-phenyl)ethyl	*i*-propyl	3-chlorophenyl	92	89
7e	2-(2-chloro-phenyl)ethyl	H	3-pyridyl	72	76
7f	3-(pyrrolidin-2-on-1-yl)propyl	benzyl	benzyl	91	85
7g	cyclohexyl	benzyl	3-chlorophenyl	90	95

[a] Crude yields based on the original loading capacity of the resin
[b] Purity based on the integration area on HPLC (detection at 215 and 254 nm)

treatment of the resin **6** by mixture dioxane/methanol/HCl at 50°C. While the yield of crude material isolated by the two methods was approximately the same (~80%), the purity of samples obtained by the first method was greater.

We synthesized a representative library of sixty 5,6,7,8-tetrahydro-1*H*-imidazo[4,5-*g*]quinoxalin-6-ones containing substituents in positions 1, 2 and 7. The first four steps of the synthetic scheme were accomplished in polypropylene fritted columns where the resin was agitated by nitrogen through bubbling. The N_2 atmosphere was sufficient to prevent oxidation of resin-bound diaminoquinoxaline **5** by air. Acylation, cleavage and cyclization have been performed in a 96-deep well plate in a Charibdis® reaction block. The purity (72–95%) of the synthesized library was assessed based on the integration area on HPLC (detection at 215 and 254 nm) and identity was confirmed by LC–MS analysis (Table 1).

In summary, imidazo[4,5-*g*]quinoxalin represents a worthwhile combinatorial scaffold and our method allows for the introduction of three points of chemical diversity through the manipulation of commercially available amines, carboxylic acids and amino acid esters. The methodology is ideally suited for automated application. The heterocycle **7** obtained after cleavage has no extraneous functional groups, which have been utilized for attachment of starting building blocks to the initial polymer. Therefore, the developed method for preparation of 5,6,7,8-tetrahydro-1*H*-imidazo[4,5-*g*]quinoxalin-6-ones might be considered as traceless synthesis on solid phase.

General procedure for the synthesis of 5,6,7,8-tetrahydro-1*H*-imidazo[4,5-*g*]quinoxalin-6-ones **7**:

2-(4-Formyl-3-methoxyphenoxy)ethyl polystyrene[‡] (50 mg) was mixed with $HC(OEt)_3$ (1 ml) and 1 M primary amine in 1,2-dichloroethane (1 ml). N_2 was bubbled into the slurry for 2 h. The solution was removed by suction, and the resin was treated with 1 M $NaCNBH_3$/THF (1 ml) and 1% AcOH/DMF (1 ml) overnight under N_2. After washing of the resin, the procedure was repeated. The resin was washed five times with DMF, MeOH, CH_2Cl_2 after each reaction step. 1 M 1,5-Difluoro-2,4-dinitrobenzene in mixture triethylamine/*N*-methylpyrrolidin-2-one (1:1) (2 ml) was added to dry resin **2**. N_2 was bubbled into the slurry overnight. Resin **3** was treated with 1 M amino acid ester in *N*-methylpyrrolidin-2-one. The support bound dinitrobenzene **4** was reduced with 1 M $SnCl_2 \cdot 2H_2O$ and 1 M *N*-methylmorpholine in *N*-methylpyrrolidin-2-one (2 ml) overnight at rt. After washing of the resin, the reduction procedure

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[‡] The resin with loading capacity 0.5 mmol/g was purchased from Calbiochem-Novabiochem Corp.

was repeated. Carboxylic anhydride (0.25 M) (2 ml, prepared in situ from a carboxylic acid and DIC in DMF) was added to the resin bound quinoxaline **5**. N_2 was bubbled into the slurry overnight. Resin **6** was treated with 2 ml of $CF_3CO_2H:CH_2Cl_2:Et_3SiH$ (10:30:1) for 1 h at rt. The solution was collected, and the resin was washed with MeCN (2 ml). The combined filtrates were collected and concentrated in vacuo. The residue was dissolved in 1 ml of 4N HCl/dioxane–MeOH (2:1). The solution was kept at 50°C for 3 h and was concentrated in vacuo to give 5,6,7,8-tetrahydro-1*H*-imidazo[4,5-*g*]quinoxalin-6-one **7**.

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References

1.. Booth, S.; Hermkens, P. H. H.; Ottenhejm, H. C. J.; Rees, D. C. *Tetrahedron* **1998**, *54*, 15385–15443.
1. Brown, R. D. *J. Chem. Soc. Perkin Trans. 1* **1998**, 3293–3320.
2. Dolle, R. E. *Mol. Diversity* **1998**, *3*, 199–233.
3. *Combinatorial Chemistry and Molecular Diversity in Drug Discovery*; Gordon, E. M.; Kerwin, J. F. J., Eds.; John Wiley & Sons: New York, 1998.
5.. Hall, S. E. *Mol. Diversity* **1998**, *4*, 131–142.
6.. For example, see: Fivush, A. M.; Willson, T. M. *Tetrahedron Lett*. **1997**, *38*, 7151–7154.
7.. Boojamra, C. G.; Burow, K. M.; Thompson, L. A.; Ellman, J. A. *J. Org. Chem*. **1997**, *62*, 1240–1256.
4. del Fresno, M.; Alsina, J.; Royo, M.; Barany, G.; Albericio, F. *Tetrahedron Lett*. **1998**, *39*, 2639–2642.
9.. Ouyang, X.; Tamayo, N.; Kiselyov, A. S. *Tetrahedron* **1999**, *55*, 2827–2834.
10.. Phillips, G. B.; Wei, G. P. *Tetrahedron Lett*. **1996**, *37*, 4887–4890.
5. Wei, G. P.; Phillips, G. B. *Tetrahedron Lett*. **1998**, *39*, 179–182.
6. Sun, Q.; Yan, B. *Bioorg. Med. Chem. Lett*. **1998**, *8*, 361–364.
7. Lee, J.; Gauthier, D.; Rivero, R. A. *Tetrahedron Lett*. **1998**, *39*, 201–204.
8. Mayer, J. P.; Lewis, G. S.; McGee, C.; Bankaitis-Davis, D. *Tetrahedron Lett*. **1998**, *39*, 6655–6658.
9. Tumelty, D.; Schwarz, K.; Needels, M. C. *Tetrahedron Lett*. **1998**, *39*, 7467–7470.
16.. Tumelty, D.; Schwarz, K.; Cao, K.; Needels, M. C. *Tetrahedron Lett*. **1999**, *40*, 6185–6188.
17.. Lee, J.; Murra, W. V.; Rivero, R. A. *J. Org. Chem*. **1997**, *62*, 3874–3879.
18.. Morales, G. A.; Corbett, J. W.; DeGrado, W. F. *J. Org. Chem*. **1998**, *63*, 1172–1177.