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Solid phase synthesis of tetrahydropyrazine-2-ones by intramolecular Mitsunobu reactions

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Abstract

A novel route for the synthesis of tetrahydropyrazine-2-ones on solid support through intramolecular Mitsunobu reactions is reported. The syntheses employ reductive amination of commercially available amino alcohols to attach them to ArgoGel-MB-CHO resin. Amino acids are then coupled to the derivatized solid support for construction of the ring systems and a Mitsunobu reaction between the activated amino acids and amino alcohols forms the derivatized tetrahydropyrazine-2-one rings. © 1999 Elsevier Science Ltd. All rights reserved.

Recently, we wished to prepare libraries of non-peptidic, RNA-binding molecules for potential use as antibacterial agents. Accordingly, the tetrahydropyrazine-2-one ring was identified as a suitable template for mimicing certain dipeptide structures.[1] Other groups have reported the synthesis of this peptidomimetic through either solution[1] or solid phase[2] techniques. We now report a new, parallel, solid phase synthesis of the tetrahydropyrazine-2-one system which incorporates three combinatorial sites. Such molecules may provide new leads for the identification of novel antibacterial agents.

The coupling of various amino alcohols to ArgoGel-MB-CHO resin via reductive amination gave the corresponding support-bound amino alcohols in >95% yield as judged by gelphase ^{13}C NMR.[3] As illustrated by the example of (*S*)-(−)-2-amino-3-phenyl-1-propanol ((*S*)-phenylalaninol), this coupling proceeded through the Schiff base intermediate (**1**) instead of the possibly competing oxazole[4] (**2**), as evidenced by gelphase ^{13}C NMR.[5] Further reduction of **1** with a borane–pyridine complex[6,7] gave the desired derivatized resin (**3**) (Scheme 1).

In Scheme 2, protection of the resin **3** with *tert*-butyldimethylsilyl chloride (TBSCl) gave the silylated resin (not shown) in >95% yield as judged by gelphase ^{13}C NMR. The next step required the coupling of this relatively hindered support-bound secondary amine to an amino acid. Standard procedures for peptide coupling produced low yields (HATU/collidine/DMF, 35%) as evidenced by analysis of subsequently cleaved Fmoc residues.[8] However, use of HATU/DIPEA in dichloromethane in the presence of DMAP[9] led to a dramatic increase in the yield of the desired derivatized resin (**4**) (**4a**, 85%; **4b**, 89%; and **4c**, 88.5% from the Argogel resin). The Fmoc group of resin (**4**) was then removed under

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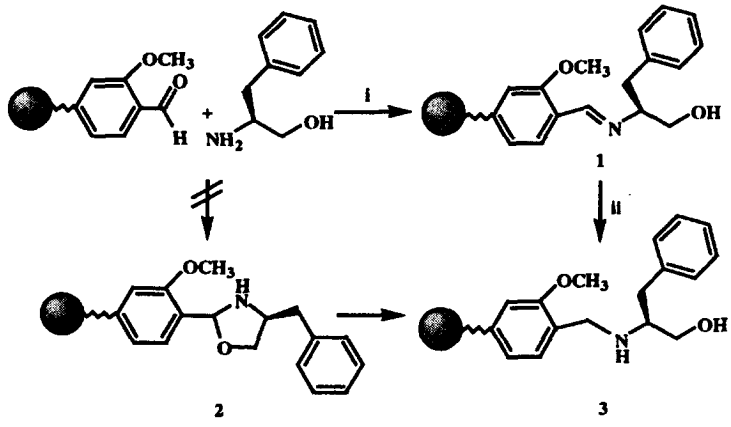
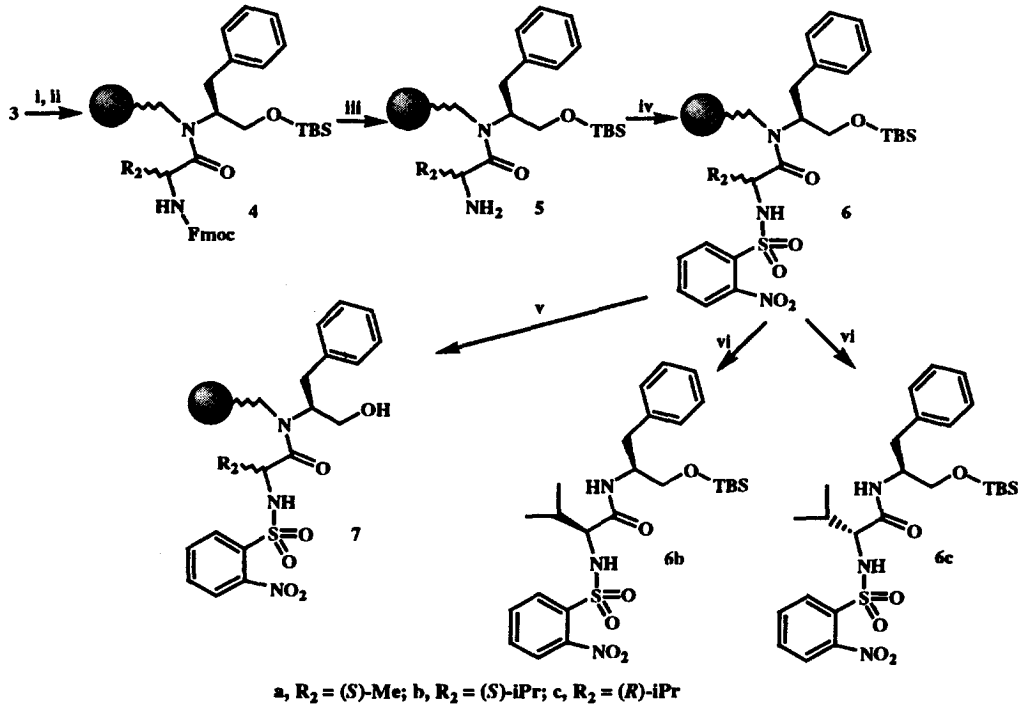


Scheme 1. (i) Trimethylorthoformate/MeOH, (ii) 2 equiv. BH_3/pyridine, 2 equiv. HOAc

basic conditions (10% piperidine in DMF) to give resin **5** which was subsequently coupled with 2-nitrobenzenesulfonyl chloride to afford resin **6**. Deprotection of the silylated hydroxyl group of **6** with 1 M TBAF in THF then gave resin **7**. As a precaution, trifluoroacetic acid cleavage of **6** was performed to investigate the extent of R_2 racemization that occurred during the amino acid coupling step. Both compounds **6b** and **6c** were examined by reverse phase HPLC[10] and both were obtained in >95% de. This result indicated that the amino acid coupling conditions[9] used did not cause significant racemization.

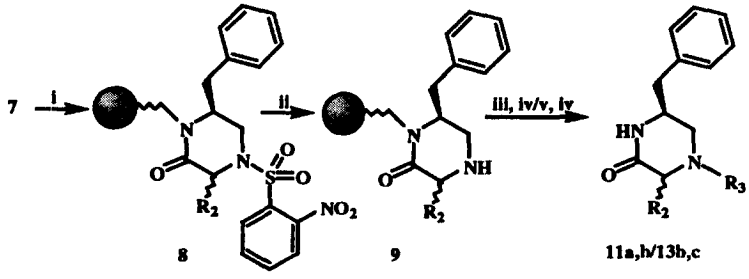


a, R_2 = (*S*)-Me; **b**, R_2 = (*S*)-iPr; **c**, R_2 = (*R*)-iPr

Scheme 2. (i) 3 Equiv. TBSCl; 3 equiv. TEA; 0.1 equiv. DMAP, (ii) 5 equiv. amino acid/5 equiv. HATU/10 equiv. DIPEA/CH_2Cl_2/1 equiv. DMAP, (iii) 10% piperidine in DMF, (iv) 3 equiv. 2-nitrobenzene sulfonyl chloride; 3 equiv. DIPEA, (v) 1 M TBAF in THF, (iv) TFA/H_2O (90/10; v/v)

As depicted in Scheme 3, intramolecular Mitsunobu reaction of resin **7** was effected by treatment with triphenylphosphine and DEAD (diethyl azodicarboxylate) and provided cyclized resin **8**. A similar

cyclization strategy using triphenylphosphine–cyclic sulfamide betaine as the activating agent was previously described for the solid-phase synthesis of constrained bicyclic structures based on the hydroxyprolinol motif.[7] Subsequent de-sulfonylation[7] generated resin **9** and reaction of this resin with phenyl isocyanate gave resin **10** (not shown). After treatment of resin **10** with TFA/H_2O (90/10; v/v), tetrahydropyrazine-2-ones **11a** and **11b** were obtained in 61% and 80% yield[11] when the amino acid employed in the synthesis was either L-alanine or L-valine, respectively. Functionalities other than phenyl isocyanate, such as carboxylic acids, were also used to derivatize resin **9**. One example was the use of nalidixic acid[12,13] which was combined with resin **9b** or **9c** using the coupling conditions[9] employed above for the derivatization of silylated resin **3** to give resin **12** (not shown). After subsequent TFA cleavage, compounds **13b** and **13c** were obtained in 75% and 90% yield,[11] respectively. Compounds **11a**, **11b**, **13b**, and **13c** were characterized by ^1H and ^{13}C NMR spectrometry, high resolution mass spectrometry[14] as well as reverse phase HPLC (Table 1). The successful preparation of compounds **13b** and **13c** demonstrates the use of the intramolecular Mitsunobu reaction to prepare both *cis* and *trans*-substituted tetrahydropyrazine-2-ones.



a, R_2 = (*S*)-Me; **b**, R_2 = (*S*)-iPr; **c**, R_2 = (*R*)-iPr

Scheme 3. (i) 4 Equiv. Ph_3P; CH_3CN/DMF; 4 equiv. DEAD, (ii) 0.5 M mercaptoacetic acid, 1 M DBU in DMF; (iii) 5 equiv. phenyl isocyanate; DMF, (iv) TFA/H_2O (90/10; v/v), (v) 5 equiv. nalidixic acid/5 equiv. HATU/10 equiv. DIPEA/CH_2Cl_2/1 equiv. DMAP

The simplicity of the described solid phase synthesis makes it readily adaptable to robotic automation. The commercial availability of other amino alcohols, amino acids (for R_2 and R_3), isocyanates (for R_3), as well as sulfonyl chlorides (for R_3), provides additional diversity for the preparation of tetrahydropyrazine-2-one combinatorial libraries. Further application of this chemistry as well as the syntheses of other peptidomimetic scaffolds are in progress.

Table 1

Compound#	R_2	R_3	%yield	Purity% (HPLC)[15]
11a	(*S*)-CH_3	$C(O)NHC_6H_5$	61	89
11b	(*S*)-$CH(CH_3)_2$	$C(O)NHC_6H_5$	80	91
13b	(*S*)-$CH(CH_3)_2$	nalidixyl*	75	94
13c	(*R*)-$CH(CH_3)_2$	nalidixyl*	90	89

*nalidixyl =

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3. Gelphase ^{13}C NMR analysis showed neither aldehyde carbonyl carbon resonance (188.0 ppm) nor the benzyl alcohol carbon resonance (69.0 ppm) of the starting MB-CHO resin.
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5. Gelphase ^{13}C NMR (CD_2Cl_2) δ 162.3, 160.4, 157.4 (imino carbon), 139.4, 129.9, 128.6, 128.3, 126.2, 118.0, 106.2, 98.8, 74.5, 65.9, 39.4.
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9. For example, DIPEA (0.6 mL, 10 equiv.) and HATU (0.68 g, 5 equiv.) were added to Fmoc-NH-Val-OH (0.6 g, 5 equiv.) in CH_2Cl_2 (3 mL) at room temperature. The mixture was vigorously stirred for 15 min and then added to silylated resin **3** (0.9 g, 0.36 mmol based on the loading of MB-CHO resin, 0.4 mmol/g). Finally, DMAP (0.04 g, 1 equiv.) was added. After shaking for 12 h, the resin was washed with DMF (3×5 mL), CH_2Cl_2 (3×5 mL) and MeOH (3×5 mL).
10. HPLC (monitored by a ELSD light scattering detector) on a 100×2 mm LUNA C-18 column, using a gradient of 5 to 80% acetonitrile to 0.1% trifluoroacetic acid in H_2O in 18 min at 0.4 mL/min.
11. Yields were calculated based on the weight of compounds cleaved from support and based on the loading of the starting resin (0.4 mmol/g).
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14. **11a**: ^1H NMR (DMSO) δ 8.50 (br s, 1H), 8.06 (br s, 1H), 7.27 (m, 9H), 6.92 (m, 1H), 4.63 (m, 1H), 4.14 (m, 1H), 3.63 (m, 2H), 2.70 (m, 2H), 1.24 (d, 3H, *J*=6.9); ^{13}C NMR (DMSO) δ 169.8, 153.7, 140.1, 136.6, 129.3, 128.4, 128.2, 126.6, 122.0, 119.9, 69.8, 52.3, 51.7, 38.1, 16.3; HRMS (FAB) *m/z* 324.1719 $(M+H)^+$ ($C_{19}H_{21}N_3O_2$ requires 324.1712). **11b**: ^1H NMR (DMSO) δ 8.54 (br s, 1H), 7.93 (br s, 1H), 7.26 (m, 9H), 6.91 (m, 1H), 4.38 (d, 1H, *J*=6.7), 4.04 (m, 2H), 3.48 (m, 1H), 2.74 (m, 3H), 0.94 (d, 3H, *J*=6.8), 0.73 (d, 3H, *J*=6.8); ^{13}C NMR (DMSO) δ 169.0, 154.7, 140.2, 136.4, 129.6, 128.2, 126.5, 121.9, 119.8, 117.3, 69.7, 59.9, 51.9, 41.7, 30.3, 19.7, 19.2; HRMS (FAB) *m/z* 352.2011 $(M+H)^+$ ($C_{21}H_{25}N_3O_2$ requires 352.2025). **13b**: ^1H NMR (DMSO) δ 8.28 (br s, 1H), 8.01 (s, 1H), 7.37 (d, 1H, *J*=8.0), 7.21 (m, 5H), 6.85 (m, 1H), 4.58 (d, 1H, *J*=7.2), 4.37 (m, 1H), 3.27 (m, 2H), 2.98 (m, 3H), 2.67 (m, 2H), 2.64 (s, 3H), 1.31 (t, 3H, *J*=7.0), 1.00 (d, 3H, *J*=6.7), 0.85 (d, 3H, *J*=6.6); ^{13}C NMR (DMSO) δ 172.9, 168.7, 165.5, 162.9, 162.3, 148.1, 143.6, 136.2, 135.7, 128.9, 127.7, 125.9, 120.4, 118.6, 60.1, 52.5, 58.7, 45.4, 37.8, 30.6, 24.8, 20.0, 19.4, 14.8; HRMS (FAB) *m/z* 447.2399 $(M+H)^+$ ($C_{26}H_{30}N_4O_3$ requires 447.2396). **13c**: ^1H NMR (DMSO) δ 8.22 (br s, 1H), 7.98 (s, 1H), 7.68 (d, 1H, *J*=11.2), 7.24 (m, 5H), 6.82 (m, 1H), 4.74 (d, 1H, *J*=7.2), 4.40 (m, 1H), 3.30 (m, 2H), 2.97 (m, 1H), 2.67 (m, 2H), 2.66 (s, 5H), 1.31 (t, 3H, *J*=7.0), 1.02 (d, 3H, *J*=6.8), 0.83 (d, 3H, *J*=7.2); ^{13}C NMR (DMSO) δ 173.9, 167.9, 163.0, 148.8, 147.0, 142.9, 138.7, 136.5, 131.4, 129.0, 127.3, 126.1, 118.4, 117.6, 64.2, 59.5, 57.1, 46.4, 37.3, 33.7, 25.2, 20.3, 19.4, 15.3; HRMS (FAB) *m/z* 469.2205 $(M+Na)^+$ ($C_{26}H_{30}N_4O_3$ requires 469.2216).
15. HPLC (monitored by a ELSD light scattering detector) on a 100×2 mm LUNA phenyl–hexyl column, using a gradient of 5 to 80% acetonitrile to 0.1% trifluoroacetic acid in H_2O in 18 min at 0.4 mL/min.