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A Peptoid Based Synthesis of Di- and Tri-Substituted 2-Oxopiperazines On Solid Support

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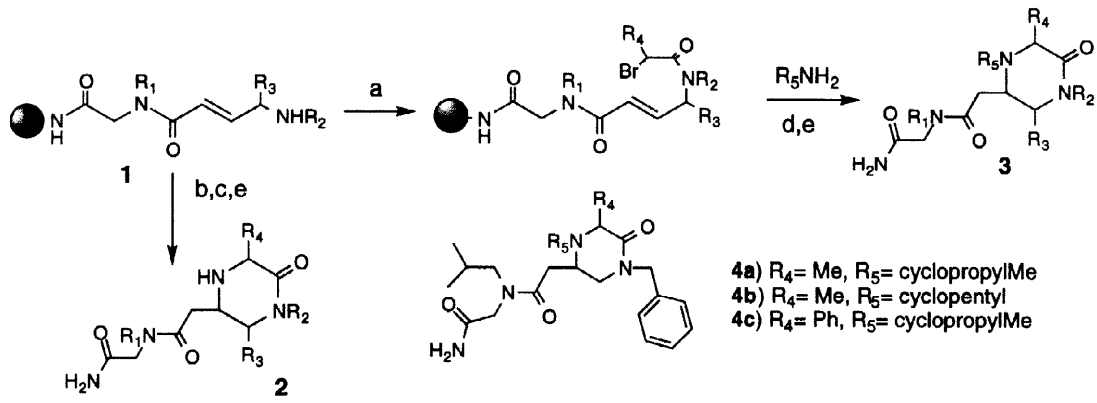
Abstract. 2-Oxopiperazines containing up to five variable ring substituents can be obtained by the tandem SN2 / Michael addition of amines to unsaturated peptoids on solid support.

We have recently reported the synthesis of 2-oxopiperazines on solid support using an intramolecular Michael addition.[1] This synthesis is based on the coupling of an FMOC-amino acid to an unsaturated peptoid anchored to the solid support. Removal of the FMOC group leads to cyclization yielding **2**, which has a free basic nitrogen which can be further functionalized (Scheme 1). It occurred to us that a simple modification of this procedure could lead to a complementary substitution pattern around the 2-oxopiperazine ring. Thus acylation of the resin bound peptoid **1** with an α-halocarboxylic acid, followed by reaction with a concentrated amine solution led to a tandem SN2 displacement / Michael addition to yield 2-oxopiperazine **3**. We were especially intrigued by the possibility of synthesizing a pentasubstituted six membered ring in such a simple fashion. Furthermore, the diversity of R groups which can be obtained from amines and α-haloacids makes this structure attractive as a scaffold for the synthesis of combinatorial libraries. A conceptually similar solution phase synthesis of disubstituted piperidines has recently been described by Bunce and co-workers.[2]



SCHEME 1: a) $R_4CHBrCO_2H$, DIC, 0.5M, DMF, 2x 30 min, room temp. b) $NH(FMOC)CHR_4CO_2H$, DIC, HOBt, 0.5M, DMF, 1h, room temp. c) 20% piperidine in DMF, 3h room temp. d) R_5NH_2, 2.0M in DMSO, 2h, room temp. e) 95/5 TFA/H_2O, 20 min, room temp.

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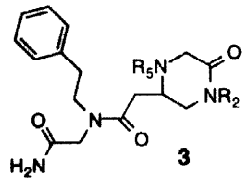
Table 1



3

3	R_2	R_5	Yield[a]	Purity[b]	RT (min)	MH^{+}[c]
a	cyclopentyl	i-Bu	58	80	22.1	443
b	cycloheptyl	i-Bu	63	90	25.0	471
c	L(-)α-MeBn	i-Bu	36	94[d]	28.7	479
d	1,2-diPhEt	i-Bu	56	88	28.5	555
e	$-CH_2$-c-C_3H_7	i-Bu	77	80	20.6	429
f	piperonyl	i-Bu	42	87	23.1	509
g	i-Bu	cyclopentyl	93	75	21.5	443
h	i-Bu	cycloheptyl	93	75	23.6	471
i	i-Bu	2,2-diPhEt	55	80	28.6	555
j	i-Bu	$-CH_2$-c-C_3H_7	60	81	21.1	429
k	i-Bu	piperonyl	47	85	23.7	509

a) Yield of crude product lyophilized three times. All products were solids except **3g** and **3h** which were oils. The yield is that of the final amine displacement/ Michael addition step and for **3a-f** is based on an experimentally determined loading of 0.36 mMol/gm for the starting dipeptoid. For **3g-k** the manufacturer's stated loading of 0.51 mMol/gm is assumed.
b) Purity was determined by C-18 RP HPLC (Vydac) using a linear gradient of 0-80% acetonitrile in 40 min with H_2O containining 1 mL/L TFA. Absorption was monitored at 214 nm.
c) Observed protonated parent ion by electrospray mass spectrometry
d) The diastereomers were not separable in this system.

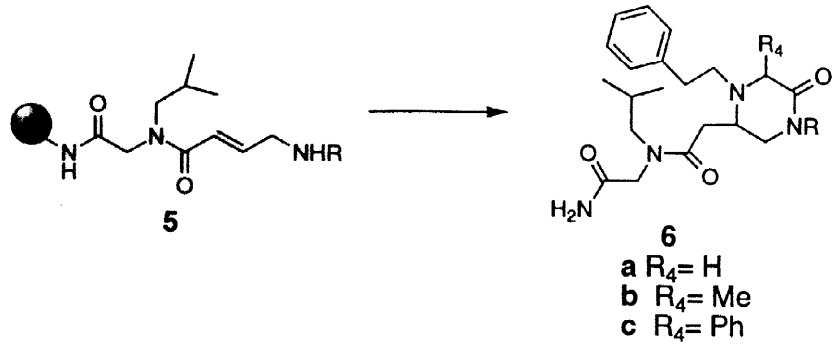
In order to assess the scope of this synthesis a series of 2-oxopiperazines differing only at R_2 and R_5 was prepared. (Table 1) Note that there are 5 pairs of compounds in which the two R groups are reversed. All these compounds gave satisfactory yields and purity as determined by hplc and electrospray mass spectrometry. ^{1}H NMR of the crude products was also entirely consistent with their structure and showed no evidence of vinylic protons due to uncyclized material. It should be noted that the hplc peaks of many of these compounds are broadened, possibly due to cis-trans amide bond rotamers at the side chain tertiary amide.

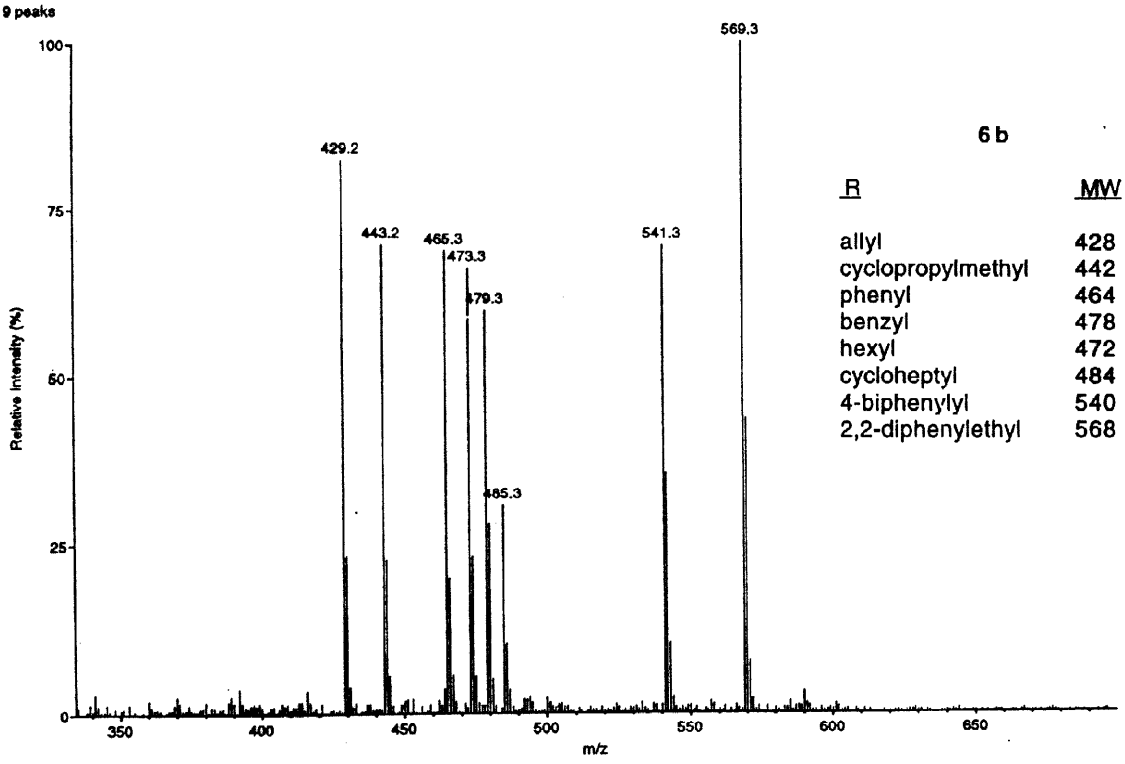
Some generalizations can also be drawn from a large number of individual compounds of type **3** which have been prepared. A wide variety of amines, including anilines can be used to provide the NR_2 residue. This is in contrast to our earlier synthesis of **2** where we experienced difficulty in acylating **1** with FMOC-amino acids when R_2 = phenyl, substituted phenyl, or diphenylmethyl. If R_2 contains reactive functionalities such as amino or alcohol these must be protected. A wide variety of amines can also be used for the cyclization step (R_5NH_2). In this case symmetrical diamines such as 1,3-diaminopropane, amino alcohols (ethanolamine, tyramine) and heterocyclic amines (2,3, or 4-aminomethylpyridines or tryptamine, for example) can be used without protection. These functional groups can be further modified after the cyclization to give still greater diversity. Hindered amines such as benzhydrylamine or 9-aminofluorene work although the hplc purity of these products is only about 60%. NMR of the crude products shows some alkylated but uncyclized material still remaining . Aniline or 4-aminobiphenyl did not cyclize at room temperature and heating at 55° C overnight was required.

We have also investigated the use of (S)- 2-bromopropionic acid and 2-bromophenylacetic acid (R_4= Me or Ph) in this synthesis (Scheme 1). Three individual compounds **4a-c** were prepared in excellent purity (>85%). All three compounds gave correct mass spectra and nmr spectra consistent with their cyclized structure. In the case of **4b** we were able to separate the two diastereomers (ratio 88:12, both giving m/e 443 as required).

In order to demonstrate the feasibility of this chemistry for combinatorial synthesis eight batches of resin **5** were prepared, each with a different R_2 residue. These resins were then mixed in equal amounts to give a mixed amine resin. This resin was divided in three portions and acylated with three different α-halo acids (R_4=H, Me, Ph). Tandem displacement / cyclization with phenethylamine followed by cleavage from the resin with 95/5 TFA/H_2O give mixtures **6a-c.** The mass spectrum of **6b** is shown in Figure 1. The spectra are surprisingly clean and show, in each case, all eight of the desired compounds. These results have encouraged us to plan the synthesis of a large scale library of 2-oxopiperazines based on this chemistry .

Figure 1





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References

1) Goff, D.A., Zuckermann, R.N., *Tetrahedron Lett.*, **1996**, *37*, 6247-6250

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