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LETTERS

Combinatorial Modification of 2-Ketopiperazine with Solid Phase C-Alkylation and N-Acylations.

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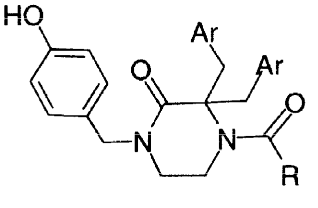
Abstract: 2-Chlorotrityl resin bound 2-ketopiperazine was modified by C-alkylation followed by acylation with acid chlorides. © 1998 Elsevier Science Ltd. All rights reserved.

KEYWORDS: Solid-Phase Synthesis: Benzylation: Acylation.

Solid phase chemistry has flourished in recent years in the wake of wide applications of combinatorial synthesis in industrial as well as academic laboratories[1] and many solution reactions have been optimized on the solid phase. In our efforts to study the application of ketopiperazine as a conformationally constrained peptidomimetic[2] in drug discovery, we have developed a two-point modification including a solid phase C-alkylation[3] procedure which gives access to a combinatorial synthesis of molecules with general structure shown below(**1**).



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The ketopiperazine[4] **2** was converted to **3** by first protecting the secondary amine with trimethylsilylethoxycarbamide and by N-alkylation with p-benzyloxybenzyl chloride followed by hydrogenation. The phenol **3** was then loaded on to 0.83 equivalent of 2-chlorotrityl

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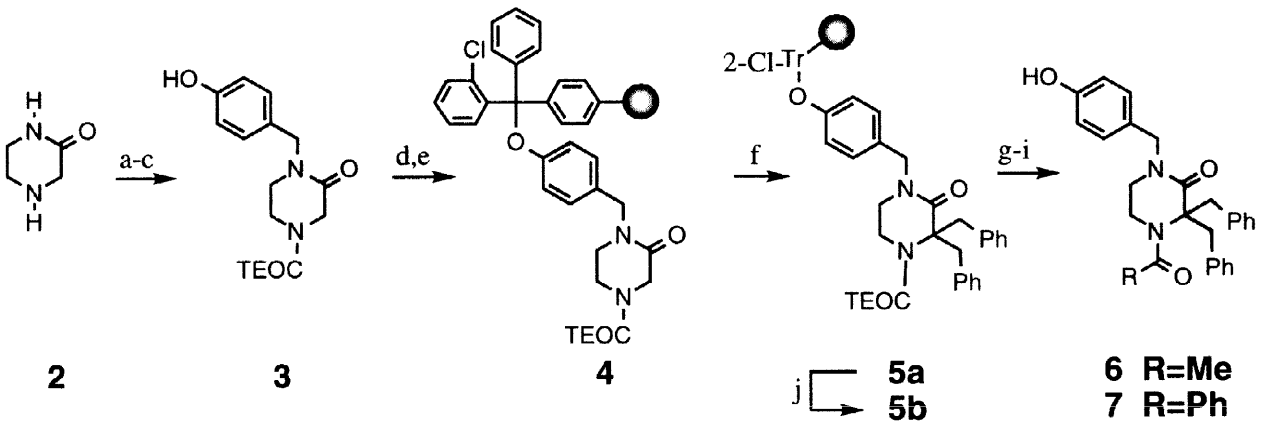
resin(1.3 meq/g) in the presence of 2.5 equivalents of diisopropylethylamine in DCM followed by capping of the resin with methanol. Clean di-benzylation of **4** was achieved with five equivalents of benzylchloride and lithium bis(trimethylsilyl)amide at room temperature overnight to give **5a** (Scheme 1).[5] Attempts to achieve selective monoalkylation through control of stoichiometry of either base[6] or alkylating reagent led to roughly a 1:1:1 product ratio of dialkylation, monoalkylation vs starting amide **3**. Preformation of the enolate of **4** before alkylation was precluded due to the finding that similar enolates decompose in solution even at low temperature (-78 °C)[7]. Other simple alkyl halides such as methyl iodide were not effective in the alkylation reactions.

Resin bound compound **5a** was deprotected with TBAF to give the secondary amine which was used for further modification. Not unexpectedly, the sterically hindered amine was very resistent toward various derivatizations, such as reactions with isocyanates, sulfonyl chlorides, alkylations with alkyl halides and reductive alkylations with aldehydes. However, upon treatment with benzoyl chloride or acetyl chloride, **5a** gave the corresponding resin bound amides **6** and **7** with high purity .

Scheme 1.



a) p-nitrophenyl-(2-trimethylsilylethyl)carbonate, b) p-BnOBnCl, NaH, THF, c) H_2, Pd/C, overall yield 67%, d) DIEA, DCM, 2-chlorotritylchloride resin, e) MeOH capping, f) 5 eq. BnCl, 5 eq LiHMDS, THF, r.t., g) TBAF/THF, h) RCOCl, Et_3N, DCM, i) cleavage with 7:1:2 DCM:MeOH:TFA, isolated yields from **4**: 95% for **6**, 90% for **7**. j) cleavage with 7:1:2 DCM:MeOH:TFA, isolated yield from 4 92%.

A thirty member library was constructed to explore the scope of these two solid phase reaction sequences utilizing the IRORI™ radio frequency tag technology.[8] Resin **4** was dispensed into 30 microcans (70 mg each) which were then split into equal portions for six alkylation reactions. Cleavage of the intermediate beads showed that all alkylation reactions were complete within 12 hr. The microcans were pooled together, washed with THF, DCM and MeOH and then treated with 1M TBAF in THF for 2h. After washing, the microcans containing the deprotected amines were split into five equal portions for acylations overnight with 5 equivalents of acid chlorides. After being washed with DMF, THF, DCM and MeOH, these microcans were then sorted according to the radio-frequency tags to retrieve the history of each can and the corresponding structures. The final products were obtained by TFA cleavage and the analytical results are listed in Table 1.

Table 1.

Entry	AR[i]	R[ii]	Purity[iii]	MS[iv]	MS[v]	Entry	AR[i]	R[ii]	Purity[iii]	MS[iv]	MS[v]
1	Ar1	R1	78.5%	517	516	16	Ar4	R1	83.4%	541	540
2	Ar1	R2	91.8%	579	578	17	Ar4	R2	95.8%	604	602
3	Ar1	R3	100%	580	579	18	Ar4	R3	85.6%	520	519
4	Ar1	R4	94.2%	580	579	19	Ar4	R4	78.2%	520	519
5	Ar1	R5	100%	543	542	20	Ar4	R5	93.4%	483	482
6	Ar2	R1	72.5%	641	640	21	Ar5	R1	80.6%	429	428
7	Ar2	R2	82.1%	703	702	22	Ar5	R2	90.7%	491	490
8	Ar2	R3	72.1%	704	703	23	Ar5	R3	90.3%	492	491
9	Ar2	R4	80.4%	704	703	24	Ar5	R4	100%	492	491
10	Ar2	R5	100%	667	666	25[vi]	Ar5	R5	83.7%	455	454
11	Ar3	R1	76.6%	529	528	26	Ar6	R1	100%	557	557
12	Ar3	R2	100%	591	590	27	Ar6	R2	100%	619	619
13	Ar3	R3	100%	592	591	28	Ar6	R3	100%	620	620
14	Ar3	R4	83.2%	592	591	29	Ar6	R4	76.3%	620	620
15	Ar3	R5	90.0%	555	554	30	Ar6	R5	89.0%	583	583

i) Ar1, o-3,4-methylenedioxybenzyl; Ar2, p-benzyloxybenzyl; Ar3, 2-naphthylmethyl; Ar4 4-tert-butylbenzyl; Ar5, Benzyl; Ar6, m-Cl-p-MeO-Benzyl. ii) R1, Acetyl; R2, Benzoyl; R3, Nicotinoyl; R4, Picolinoyl; R5, cyclopropylcarbonyl. iii) LC-Electrospray-Mass spectroscopy was used to determine the molecular mass and purity. iv) Observed Mass v) Predicted Mass. vi) A representative NMR Spectra of entry 25: H^{1}NMR(CDCl$_3$) δ 7.1-7.25 ppm, m, 10 H; δ 6.9 ppm, d, 2H; δ 6.7 ppm, d, 2H; δ 4.28 ppm, s, 2H; δ 4.13 ppm, d, 2H; δ 3.45 ppm, d, 2H; δ 2.7 ppm, m, 2H; δ 2.0 ppm, m, 2H; δ 1.45 ppm, m, 1H; δ 1.08 ppm, m, 2H; δ 0.70 ppm, m, 2H.

We have demonstrated a facile solid phase C-dibenzylation of ketopiperazine at room temperature and its successful application in a combinatorial library of modified 2-

ketopiperazine. Further explorations into other modifications of the same scaffold are underway.

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[5] Detailed procedure for dibenzylation of **4**: To a slurry of 2-chlorotrityl Resin **4** (200 mg, 1.3 mmol/g loading) swelled for 5 min in 3 ml anh. THF in a 10 ml cartridge capped with a rubber septa was added 0.22 ml (1.87 mmol) benzyl bromide. After shaking for 5 min, 2.0 ml of a 1M THF solution of lithium hexamethyldisilazide was added and the mixture was shaken overnight. The beads were then washed with THF X 2, DCM X 2, MeOH X 2 and DCM X 2 and cleaved with 2 ml of 7:1:2 DCM:MeOH:TFA to generate 80 mg of crystalline solid **5b** as the only product.

[6] We also examined the use of Schwesenger's bases without success. See O'Donnell, M. J.; Zhou, C. and Scott, W. L. *J. Am. Chem. Soc.* **1996**, *118*, 6070 for related studies.

[7] Unpulished result from Mckittrick, B.

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