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Efficient approach for the parallel solid-phase synthesis of 1,1,3,4-tetrasubstituted-5-oxopiperazin-1-ium compounds

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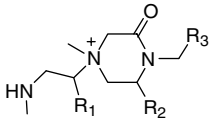
Abstract—An efficient approach for the design and parallel solid-phase synthesis of unique tetrasubstituted oxopiperazinium derivatives is presented. The synthetic procedure involved a seven-step sequence carried out starting from resin-bound dipeptides. The desired compounds were obtained in good yields and high purity.

1. Introduction

Over the last few years, combinatorial chemistry has emerged as an exciting new paradigm for drug discovery.[1] In a very short time, the topic has become the focus of considerable scientific interest and research efforts. Small molecule combinatorial synthesis for the generation and optimization of leads for a variety of applications continues to be a powerful way to discover new drugs, catalysts, and materials.[2] In a continuation of our ongoing studies for the generation of new heterocyclic compounds starting from resin-bound short peptides,[3] we describe herein, the synthesis of unique 1,1,3,4-tetrasubstituted-5-oxopiperazin-1-ium compounds. The expected improved solubility and bioavailability induced by the presence of the quaternary ammonium moiety and the reduced flexibility of the structural backbone render them of special interest to chemists and medicinal chemists alike. Recently, the solution phase synthesis of a 3-oxopiperazinium library was reported.[4] Reported activities of oxopiperazinium pharmacophores include activity on the central nervous system,[5] inhibition of the activity of the vanilloid receptor TRPV1 and modulation of the multidrug resistance phenomenon.[4]

2. Results and discussion

The strategy leading to the desired 1,1,3,4-tetrasubstituted-5-oxopiperazin-1-ium salts **5** is outlined in Scheme 1. Starting from *p*-methylbenzhydrylamine (MBHA) resin-bound dipeptide **1**, the N-terminal primary amine was protected with triphenylmethyl chloride (Trt-Cl). The two secondary amides were methylated following treatment of the resin-bound protected dipeptide with litium *tert*-butoxide and methyl iodide.[6] Following cleavage of the trityl protecting group, the free amine was acylated with a variety of carboxylic acids. The amide groups were then reduced using BH_3–THF to generate the corresponding resin-bound triamines having two tertiary amines and one secondary amine.[7] The secondary amine was then coupled with bromoacetic acid overnight in the presence of diisopropylcarbodiimide (DIC). Following acylation, an energetically favorable spontaneous intramolecular displacement of the bromo group occurred to yield the resin-bound epimeric mixture of the desired tetrasubstituted-5-oxopiperazinium salt. Following cleavage of the solid support, extraction, and lyophilization, all compounds were characterized by LC–MS. Selected compounds were characterized by ^{1}H NMR.



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Using the tea bag method,[8] which facilitates the handling of many different resins under the same reaction conditions, the parallel synthesis of individual 1,1,3,4-tetrasubstituted-5-oxopiperazin-1-ium salts was

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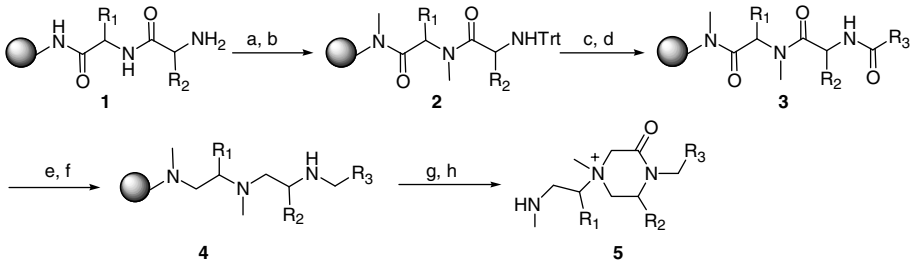

Scheme 1. Reagents and conditions: (a) Trt-Cl, DCM/DMF (9:1), overnight; (b) Li^{t}BuO, MeI, DMSO; (c) 2% TFA in DCM; (d) R_3COOH, DIPCDI, HOBt, DMF; (e) BH_3–THF, 65 °C, 3 days; (f) Piperidine, 65 °C, overnight; (g) $BrCH_2CO_2H$, DMF; (h) HF/anisole (95:5), 90 min.

Table 1.

Entry	R_1	R_2	R_3	HPLC purity[a] (%)	Obtained MW
5a	$-CH_2Ph$	$-CH_2Ph$	$-CH_2CH_2Ph$	83	456.3 (M^+)
5b	$-CH_2Ph$	$-CH_2Ph$	$-CH_2C(CH_3)_2$	85	408.3 (M^+)
5c	$-CH_2Ph$	$-CH(CH_3)_2$	$-CH_2CH_2Ph$	90	408.3 (M^+)
5d	$-CH_2Ph$	$-CH(CH_3)_2$	$-CH_2C(CH_3)_2$	86	360.3 (M^+)
5e	$-CH_2Ph$	$-CH_3$	$-CH_2CH_2Ph$	82	380.3 (M^+)
5f	$-CH_2Ph$	$-CH_3$	$-CH_2C(CH_3)_2$	84	332.3 (M^+)
5g	$-CH_3$	$-CH_2Ph$	$-CH_2CH_2Ph$	90	380.3 (M^+)
5h	$-CH_3$	$-CH_2Ph$	$-CH_2C(CH_3)_2$	>95	332.3 (M^+)
5i	$-CH_3$	$-CH(CH_3)_2$	$-CH_2CH_2Ph$	>95	323.3 (M^+)
5j	$-CH_3$	$-CH(CH_3)_2$	$-CH_2C(CH_3)_2$	85	284.3 (M^+)
5k	$-CH_3$	$-CH_3$	$-CH_2CH_2Ph$	90	304.3 (M^+)
5l	$-CH_3$	$-CH_3$	$-CH_2C(CH_3)_2$	85	256.3 (M^+)
5m	$-CH(CH_3)_2$	$-CH_2Ph$	$-CH_2CH_2Ph$	>95	408.3 (M^+)
5n	$-CH(CH_3)_2$	$-CH_2Ph$	$-CH_2C(CH_3)_2$	90	360.3 (M^+)
5o	$-CH(CH_3)_2$	$-CH(CH_3)_2$	$-CH_2CH_2Ph$	88	360.3 (M^+)
5p	$-CH(CH_3)_2$	$-CH(CH_3)_2$	$-CH_2C(CH_3)_2$	91	312.3 (M^+)
5q	$-CH(CH_3)_2$	$-CH_3$	$-CH_2CH_2Ph$	>95	332.3 (M^+)
5r	$-CH(CH_3)_2$	$-CH_3$	$-CH_2C(CH_3)_2$	90	284.3 (M^+)

[a] Purity was based on the peak area of HPLC spectra of crude products at 214 nm.

achieved. As a first attempt, we initially optimized the reaction conditions of this synthetic route by the parallel synthesis of eighteen individual compounds (Table 1). We chose phenylacetic acid and isobutyric acid as the R_3 acylating carboxylic acids, and three different L-amino acids (Ala, Val, and Phe) for the R_1 and R_2 diversities. Good purities and yields were obtained in all cases. We and an other group previously reported that the borane reduction of amide bonds was free of racemization by comparing the relative absorbances of different pairs of diastereomers that do not coelute by RP-HPLC.[9] As expected, following the cationic oxopiperazinium intramolecular cyclization, a new stereocenter was generated and an epimeric mixture was obtained. Two peaks with different ratios were observed in RP-HPLC for all samples depending on the side chains of the amino acids. Representative compounds were purified and characterized as epimeric mixtures. ^{1}H NMR spectra showed distinct signals for specific protons, such as the singlet of the methyl at position 1 and the aliphatic side chains of amino acids.[12]

3. Conclusion

In conclusion, an efficient approach for the parallel solid-phase synthesis of 1,1,3,4-tetrasubsitituted-5-oxopiperazinium was presented. Using different alkylating reagents, natural and non-natural amino acids, and different carboxylic acids, the described chemistry will be applied for the generation of a large number of individual compounds and mixture-based libraries.

4. Experimental

All amino acids, carboxylic acids, and reagents were obtained from commercial suppliers and used without further purification.

General procedure for the synthesis of individual 1,1,3,4-tetrasubstituted-5-oxopiperazin-1-ium salts **5**: 100 mg sample of *p*-methylbenzhydrylamine (MBHA) resin (1.15 mequiv/g, 100–200 mesh) was contained within a sealed polypropylene mesh packet (tea bag). Reactions were carried out in polyethylene bottles. Following neutralization with 5% diisopropylethylamine (DIEA) in dichloromethane (DCM), the first amino acid (Fmoc-Xaa-OH, 6 equiv) was coupled using the conventional reagents hydroxybenzotriazole (HOBt, 6 equiv) and diisopropylcarbodiimide (DIC, 6 equiv) in anhydrous DMF for 60 min. Completion of the coupling was monitored using the ninhydrin test.[10] Following removal of the protecting group with 20% piperidine in DMF (two times, 2×10 min) and washing with DMF (six times), the second amino acid was coupled

using the same reaction conditions. Following removal of the Fmoc protecting group with 20% piperidine in DMF (2 × 10 min) and washing with DMF (8×), the mesh packet was shaken overnight in a solution of trityl chloride (5 equiv) in DCM/DMF (9:1) in the presence of DIPEA (10 equiv). Completeness of the trityl coupling was verified using the bromophenol blue color test.[11] N-Methylation of the amide bonds was performed by treatment of the resin packet with 0.5 M lithium *tert*-butoxide in THF (20 equiv) for 10 min at room temperature. Excess base was removed by decantation, followed by addition of methyl iodide (20 equiv) in anhydrous DMSO. The solution was vigorously shaken for 2 h at room temperature (this operation was repeated three times). Upon removal of the trityl from the α-amino group with 2% TFA in DCM (2 × 10 min), the resin packet was washed, neutralized with a solution of 5% DIEA in DCM, and the dipeptide was N-acylated with a carboxylic acid (10 equiv) overnight in the presence of DIPCDI (10 equiv) and HOBt (10 equiv) in anhydrous DMF. Exhaustive reduction of the amide bonds was performed in 50 ml kimax tubes under nitrogen. To each tube was added the resin packet, followed by the addition of 1 M BH_3–THF (40-fold excess over each amide bond). The kimax tubes were capped and heated at 65 °C for 72 h, followed by quenching with MeOH. The resin was then washed with methanol (4×), and the borane disproportionated by treatment with neat piperidine at 65 °C overnight. The resin was then washed with methanol (2×) and DMF (6×) and dried. The completeness of the reaction was verified by cleavage and LC–MS analysis of sample controls. In order to shorten the time of the reduction, we have successfully performed the reaction using microwave conditions. We have determined that we can reduce the time to just a couple hours. Currently, the polypropylene mesh is sensitive to melting under microwave conditions and cannot be used at the temperature and pressure employed, limiting the potential usefulness of the procedure when making large numbers of compounds.

The resin-bound secondary triamine **4** was treated overnight with 10 equiv of bromoacetic acid and 10 equiv of DIPCDI in anhydrous DMF. Completion of the coupling was verified by cleavage and LC–MS analysis of sample controls. Results have shown completion of the coupling, followed by an intramolecular displacement of the bromo group to yield the desired oxopiperazinium ring system. The desired product **5** was obtained following cleavage of the solid support with anhydrous HF. The crude material was extracted with acetic acid, freezed, and lyophilized. The product was purified by preparative HPLC.

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12. *(3S)-1-[1-Benzyl-2-(methylamino)ethyl]-1,3-dimethyl-5-oxo-4-(2-phenylethyl)piperazin-1-ium* (**5e**): ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.19–7.48 (m, 10 H), 4.54 (d, $J = 16.4$ Hz, 1H, diastereomer), 4.34 (d, $J = 16.4$ Hz, diastereomer), 4.16 (m, 1H, diastereomer), 4.25 (m, 1H), 3.82 (m, 1H), 3.4–3.7 (m, 4H), 3.26 (m, 1H), 3.21 (s, 3H, diastereomer), 2.95 (m, 1H), 2.92 (s, 3H, diastereomer), 2.81 (s, 3H, diastereomer), 2.80 (m, 1H), 2.63 (m, 1H), 2.54 (m, 2H), 2.36 (s, 3H, diastereomer), 1.26 (d, $J = 6.1$ Hz, 3H, diastereomer), 1.33 (d, $J = 5.6$ Hz, 3H, diastereomer).
(3S)-3-Benzyl-1-methyl-1-[1-methyl-2-(methylamino)ethyl]-5-oxo-4-(2-phenylethyl)piperazin-1-ium (**5g**): ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.13–45 (m, 10H), 4.52 (d, $J = 16.1$ Hz, 1H, diastereomer), 4.30 (t, $J = 16.9$ Hz, 1H, diastereomer), 4.10 (m, 1H), 3.92 (m, 1H), 3.86 (m, 1H), 3.77 (m, 1H), 3.62 (m, 1H), 3.50 (m, 1H), 3.31–350 (m, 2H), 3.25 (dd, $J = 14.0$ Hz, 4.8 Hz, 1H), 3.24 (m, 1H), 2.96 (s, 3H, diastereomer), 2.93 (m, 1H), 2.82 (s, 3H, diastereomer), 2.79 (m, 1H), 2.70 (m, 1H), 2.62 (s, 3H, diastereomer), 2.59 (s, 3H), 1.45 (d, $J = 6.5$ Hz, 3H, diastereomer), 1.27 (d, $J = 6.3$ Hz, 3H, diastereomer).
(3S)-1-[1-Benzyl-2-(methylamino)ethyl]-3-isopropyl-1-methyl-5-oxo-4-(2-phenylethyl)piperazin-1-ium (**5c**): ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.19–7.48 (m, 10H), 4.57 (dd, $J = 3.3$ Hz, 15.1 Hz, 1H, diastereomer), 4.31 (d, $J = 15.1$ Hz, 1H, diastereomer), 4.10 (m, 2H), 3.64 (m, 1H), 3.30–3.58 (m, 2H), 3.27 (s, 3H, diastereomer), 3.22 (m, 1H), 3.05 (m, 1H), 2.92 (m, 1H), 2.83 (s, 3H, diastereomer), 2.79 (m, 1H), 2.63 (m, 1H), 2.40 (s, 3H, diastereomer), 2.33 (s, 3H, diastereomer), 0.90 (d, $J = 6.9$ Hz, 3H, diastereomer), 0.83 (d, $J = 6.95$ Hz, 3H, diastereomer), 0.81 (d, $J = 7.0$ Hz, 3H, diastereomer), 0.76 (d, $J = 6.8$ Hz,

3H, diastereomer), 0.71 (d, $J = 6.45$ Hz, 1H, diastereomer), 0.58 (m, 1H, diastereomer).

(3S)-1-[1-Benzyl-2-(methylamino)ethyl]-4-isobutyl-3-isopropyl-1-methyl-5-oxopiperazin-1-ium (**5d**): ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.30–7.47 (m, 5H), 4.59 (m, 1H, diastereomer), 4.41 (d, $J = 16.7$ Hz, 1H, diastereomer), 4.30 (m, 1H, diastereomer), 4.23 (dd, $J = 16.7$ Hz, 2.8 Hz, 1H, diastereomer), 3.98 (m, 1H), 3.72 (m, 1H), 3.4–3.7 (m, 3H), 3.38 (s, 3H, diastereomer), 3.18 (s, 3H, diastereomer), 2.85 (dd, $J = 14.0$ Hz, 5.7 Hz, 1H, diastereomer), 2.68 (dd, $J = 14.0$ Hz, 5.7 Hz, 1H, diastereomer), 2.63 (s, 3H, $J = 14.0$ Hz, 5.7 Hz, 1H, diastereomer), 2.45 (s, 3H, diastereomer), 2.85 (m, 1H, diastereomer), 1.93 (m, 1H), 1.48 (m, 1H, diastereomer), 0.89 (d, $J = 6.6$ Hz, 3H, diastereomer), 0.83 (d, $J = 6.3$ Hz, 3H, diastereomer), 0.81 (d, $J = 6.5$ Hz, 3H, diastereomer), (0.79 (d, $J = 6.4$ Hz, 3H, diastereomer), 0.73 (d, $J = 6.7$ Hz, 3H, diastereomer), 0.66 (d, $J = 6.7$ Hz, 3H, diastereomer), 0.52 (d, $J = 6.7$ Hz, 3H, diastereomer).

(3S)-3-Isopropyl-1-methyl-1-[1-methyl-2-(methylamino)ethyl]-5-oxo-4-(2-phenylethyl)piperazin-1-ium (**5i**): ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.23–7.34 (m, 5H), 4.45 (m, 1H, diastereomer), 4.38 (m, 1H, diastereomer), 3.92 (m, 1H, diastereomer), 3.93 (m, 1H), 3.92 (m, 1H), 3.63 (m, 2H), 3.40–3.60 (m, 2H), 3.10–3.3.40 (m, 3H), 3.05 (s, 3H, diastereomer), 2.95 (m, 1H), 2.80 (m, 1H), 2.66 (s, 3H, diastereomer), 2.64 (s, 3H, diastereomer), 2.61 (s, 3H, diastereomer), 1.50 (d, $J = 6.7$ Hz, 1H), 1.48 (d, $J = 6.7$ Hz, 1H), 0.97 (d, $J = 7.1$ Hz, 3H, diastereomer), 0.95 (d, $J = 7.0$ Hz, diastereomer), 0.93 (d, $J = 6.2$ Hz, diastereomer), 0.91 (m, 3H, diastereomer), 0.81 (d, $J = 6.8$ Hz, 3H).

(3S)-3-Benzyl-1-[1-benzyl-2-(methylamino)ethyl]-4-isobutyl-1-methyl-5-oxopiperazin-1-ium (**5b**): ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.13–7.41 (m, 10H), 4.5 (2d, $J = 15.6$ Hz, 1H, diastereomer), 4.29 (m, 1H), 4.10 (m, 1H), 3.85 (m, 1H), 3.50–3.75 (m, 4H, diastereomers), 3.24 (s, 3H, diastereomer), 3.22 (s, 3H, diastereomer), 3.17 (m, 1H), 2.91 (m, 1H, diastereomer), 2.82 (m, 1H, diastereomer), 2.69 (m, 1H, diastereomer), 2.47 (s, 3H, diastereomer), 2.43 (s, 3H, diastereomer), 1.83 (m, 1H, diastereomer), 1.72 (m, 1H, diastereomer), 0.78 (d, $J = 6.4$ Hz, 3H, diastereomer), 0.74 (d, $J = 6.9$ Hz, 3H, diastereomer), 0.72 (d, $J = 7.2$ Hz, 3H, diastereomer).