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Efficient Approaches toward the Solid-Phase Synthesis of New Heterocyclic Azoniaspiro Ring Systems: Synthesis of Tri- and Tetrasubstituted 10-Oxo-3,9-diaza-6-azoniaspiro[5.5]undecanes

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An efficient approach for the parallel solid-phase synthesis of novel heterocyclic azoniaspiro ring systems is described. The target compounds, the 1,8,9-trisubstituted 10-oxo-3,9-diaza-6-azoniaspiro[5.5]undecanes, were obtained starting from resin-bound reduced dipeptides. The azoniaspiro cation was formed by intramolecular attack of a tertiary nitrogen on pendent α-bromocarbonyl. *N*-3 acylated and *N*-3 alkylamino carbonyl derivatives of the 1,8,9-trisubstituted 10-oxo-3,9-diaza-6-azoniaspiro[5.5]undecanes were obtained following in solution treatment of the *N*-3 azoniaspiro derivatives with different carboxylic acids and isocyanates.

Combinatorial chemistry, a technology of creating molecules en masse and testing them rapidly for desirable properties, continues to be a greatly enhancing way to discover new drugs, catalysts, and materials.[1] Spiro compounds, more specifically azoniaspiro compounds, represent an important class of natural chemical structures with a wide range of biological properties.[2,3] The improved solubility and bioavailability induced by the presence of quaternary amines and the reduced flexibility of the structural backbone render them of special interest for chemists and medicinal chemists alike. Reported activities for azoniaspiro pharmacophores include antiviral, hypotensive agents and antiacetylcholinesterase activities.[4] Azoniaspiro compounds have also been reported as structure-directing agents for zeolite synthesis.[5] In this paper, we describe an unprecedented approach for the synthesis of a new class of structurally complex 1,8,9-trisubstituted-10-oxo-3,9-diaza-6-azoniaspiro[5.5]-undecane compounds **8** and their *N*-3 acylated derivatives **9** and *N*-3 alkylamino carbonyl derivatives **10**. The presented azoniaspiro-fused dipiperazine derivatives combine two important pharmacophores, the piperazine and piperazinone ring systems. These two scaffolds are very frequently found in prescribed synthetic and natural drugs covering a wide range of biological activities (Figure 1).[6]

The strategy leading to the desired 1,8,9-trisubstituted-10-oxo-3,9-diaza-6-azoniaspiro[5.5]undecane **8** is outlined in Scheme 1. Starting from *p*-methylbenzhydrylamine (MBHA) resin-bound dipeptide **1** and following exhaustive reduction of the amide bonds,[7] the N-terminal primary amine was selectively protected with 2-acetyldimedone (Dde-OH) or triphenylmethyl chloride (Trt-Cl).[8] The two secondary amines were treated with oxalyldiimidazole to generate the corresponding resin-bound 2,3-diketopiperazines **4**.[9] Following cleavage of the Dde or Trt group, the free amine was acylated with phenyl acetic acid. The oxamide and amide groups were then reduced using BH_3−THF to generate the corresponding resin-bound piperazine tethered secondary amine **5**.[7] The secondary amine was then coupled overnight with bromoacetic acid in the presence of diisopropylcarbodiimide

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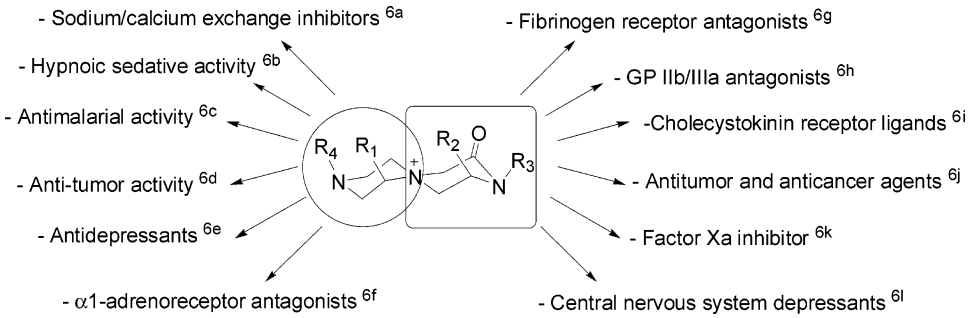
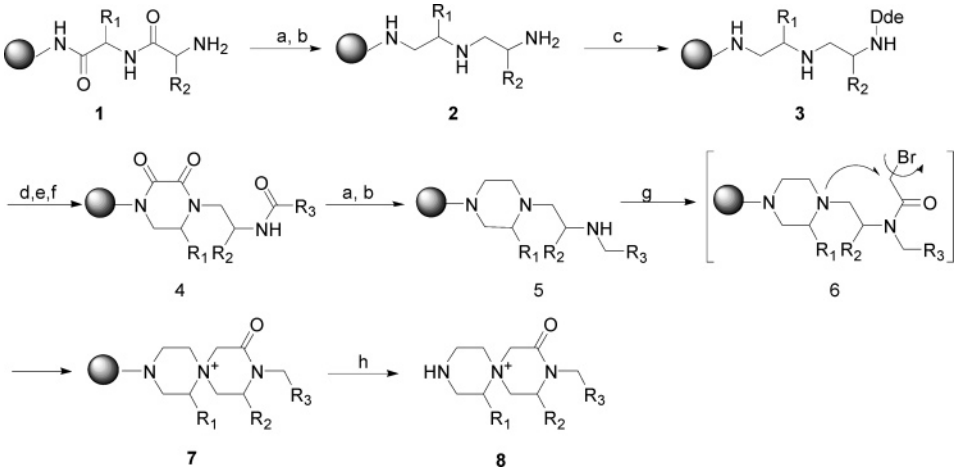


FIGURE 1. Partial list of biological properties of piperazines and oxopiperazines.

SCHEME 1[a]



[a] Key: (a) BH_3−THF, 65 °C, 3 days; (b) piperidine, 65 °C, overnight; (c) Dde-OH in DMF, rt, overnight; (d) $C_2O_2Im_2$, DMF, rt, overnight; (e) 2% hydrazine in DMF, rt, 10 min then 40 min; (f) R_3CO_2H, DIC, HOBt, DMF; (g) $BrCH_2CO_2H$, DIC, DMF, rt, overnight; (h) HF/anisole (95:5), 90 min, 0 °C.

(DIC). Following acylation, an intramolecular displacement of the bromo group occurred to yield the resin-bound diastereomeric mixture of the desired 1,8,9-trisubstituted 10-oxo-3,9-diaza-6-azoniaspiro[5.5]undecane **7**.

Following cleavage of the solid support, extraction and lyophilization, all compounds **8** were characterized by LC−MS, and selected compounds were characterized by ^{1}H NMR. Using the tea-bag method,[10] which facilitates the handling of the many different resins under the same reaction conditions, the parallel synthesis of individual diaza-azoniaspiro compounds was achieved. In a first attempt, we initially optimized the reaction conditions of this synthetic route by the parallel synthesis of 16 individual compounds. We chose phenylacetic acid as the R_3 acylating carboxylic acid and four different L-amino acids (Ala, Val, Phe, and Leu) to generate the R_1 and the R_2 groups. Good purities and yields were obtained for all cases.

We 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.[7] The same observations were later reported by other groups using different reduction work-up procedures.[11] As expected, a diastereomeric mixture was obtained during the cationic azoniaspiro intramolecular cyclization. Two major peaks were obtained in all cases, in different ratios depending on the amino acid's side chains.[12] Most compounds were purified and characterized as diastereomeric mixtures (Table 1).

To increase the diversity around the azoniaspiro template, an extra set of tea bags bearing compounds **8** were prepared in parallel. Following cleavage of the solid-support, extraction, and lyophilization, the crude products were treated with different activated carboxylic acids in the presence of DIEA to afford the corresponding N-3-acylated 1,8,9-trisubstituted 10-oxo-3,9-diaza-6-azoniaspiro[5.5]undecanes **9**.[13] We randomly selected some different diaza-6-azoniaspiro[5.5]undecanes to acylate (Scheme 2 and Table 1). Treatment of the azoniaspiro compounds **8** with ethyl or phenyl isocyanates in anhydrous DMF provided the corresponding 3-ethylaminocarbonyl or 3-anilinocarbonyl-1,8,9-trisubstituted-10-oxo-3,9-diaza-6-azoniaspiro[5.5]-undecanes **10**, respectively in good yield and purity. Excess isocyanate was scavenged using amine-substituted resin (Scheme 2 and Table 1).

Continuing with our ongoing efforts in the diversity oriented synthesis of small molecule compounds using amino acids and peptides as starting material,[14] we have explored an efficient approach for the solid-phase syn-

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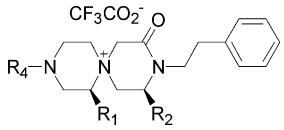
(12) Following separation of the two diastereomers, the absolute configuration of the ammonium was not determined.
(13) Acetic anhydride and benzoyl chloride were used for the *N*-3 acylation.

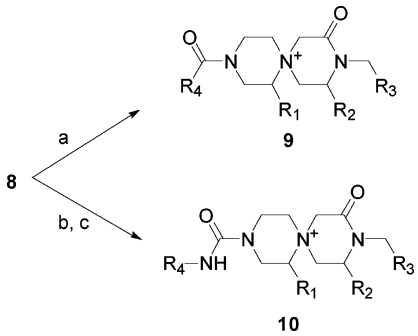
TABLE 1[a]



entry	R_1	R_2	R_4	obtained MW	yield[a] (%)
8a	$-CH_3$	$-CH_3$	$-H$	302.2 (M^+)	67
8b	$-CH_3$	$-CH(CH_3)_2$	$-H$	330.2 (M^+)	62
8c	$-CH_3$	$-CH_2Ph$	$-H$	378.2 (M^+)	59
8d	$-CH(CH_3)_2$	$-CH_3$	$-H$	330.2 (M^+)	64
8e	$-CH(CH_3)_2$	$-CH_2Ph$	$-H$	406.2 (M^+)	49
8f	$-CH_2Ph$	$-CH_3$	$-H$	378.2 (M^+)	58
8g	$-CH_2CH(CH_3)_2$	$-CH_3$	$-H$	344.2 (M^+)	69
8h	$-CH_2Ph$	$-CH_2Ph$	$-H$	454.2 (M^+)	59
9c	$CH_2CH(CH_3)_2$	CH_3	$-COCH_3$	386.2 (M^+)	47
9d	CH_3	$CH_2CH(CH_3)_2$	$-COPh$	448.2 (M+)	51
10b	$-CH(CH_3)_2$	$-CH_3$	$-CONHPh$	449.2 (M^+)	45
10c	$-CH(CH_3)_2$	$-CH(CH_3)_2$	$-CONHEt$	429.2 (M^+)	43
10d	$-CH_2CH(CH_3)_2$	$-CH(CH_3)_2$	$-CONHEt$	443.2 (M^+)	52

[a] Yields (in %) are based on the weight of purified material and are relative to the initial loading of the resin. The products were collected and characterized as pairs of diastereomers.

SCHEME 2[a]



[a] Key: (a) R_4COX, DIEA, DCM; (b) R_4NCO, DMF; (c) amino resin (MBHA resin).

thesis of unique trisubstituted and tetrasubstituted azoniaspiro derivatives. Using different amino acids, isocyanates, and carboxylic acids, the chemistry described in this paper allows the parallel synthesis of a large number of individual compounds.

Experimental Section:

Typical Procedure for the Synthesis of 1,8,9-Trisubstituted 10-Oxo-3,9-diaza-6-azoniaspiro[5.5]undecane Compounds 8. A 50 mg sample of *p*-methylbenzhydrylamine (MBHA) resin (1.15 mequiv/g, 100−200 mesh) was contained within a sealed polypropylene mesh packet. 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. 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. The Fmoc group was removed, and the amide bonds were reduced. The exhaustive reduction of the amide bonds was performed in 50 mL Kimax tubes under nitrogen. To each tube was added the resin packet (1 mequiv of resin, 50 mg of starting resin. 0.23 mequiv of carbonyl) followed by the addition of 1 M BH_3−THF (40-fold excess over each amide bond). The Kimax tubes were 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 controle.

Selective Protection of the N-Terminal Primary Amine. Trt protection: The mesh packet was shaken overnight in a solution of trityl chloride (10 equiv) in DCM/DMF (9:1) in the presence of DIEA (10 equiv). Completeness of the trityl reaction was monitored using the bromophenol blue color test. The Trt group was cleaved with 2% TFA in DCM (2 × 10 min).

Dde protection: The free amine was treated overnight with 2-acetyldimedone (Dde-OH), 5 equiv in anhydrous DMF. Completeness of the reaction was verified using the Kaiser test. The Dde group was cleaved following treatment with 2% hydrazine in DMF (10 min then 40 min).

Oxalyldiimidazole treatment: The resin was treated overnight with 5 equiv of carbonyldiimidazole in anhydrous DMF followed by washing with DMF (six times) and DCM (two times). The completeness of the reaction was verified by cleavage and LC−MS analysis of sample control.

N-Acylation. Following Trt or Dde deprotection and neutralization of the resin with a solution 5% DIEA in DCM (in the case of Trt), the resin was washed with DMF (six times) and the free amine was treated overnight with 10 equiv of carboxylic acid in the presence of DICI (10 equiv) and HOBt (10 equiv) in anhydrous DMF. Completion of the reaction was verified using Kaiser test. The oxamide and the amide groups were reduced using BH_3−THF using the same conditions described before. The resin-bound secondary amine **6** was treated overnight with 10 equiv of bromoacetic acid and 10 equiv of DICI in anhydrous DMF. Completion of the coupling was verified by cleavage and LC−MS analysis of sample control. Results have shown completion of the coupling followed by an intramolecular displacement of the bromo to yield the desired azoniaspiro ring system. All samples were purified by preparative HPLC and characterized.

(1*S*,8*S*)-1,8-Dimethyl-10-oxo-9-(2-phenylethyl)-3,9-diaza-6-azoniaspiro[5.5]undecane (8a): ^{1}H NMR (500 MHz, DMSO-d_6), mixture of diastereomers, δ (ppm) 7.22−7.33 (m, 5H), 4.77 (d, J = 16.3 Hz, 1H, diastereomer), 4.33 (d, J = 16.5 Hz, 1H, diastereomer), 4.21 (2d, J = 16.2, 15.7 Hz, 2H, diastereomer), 3.95 (m, 2H), 3.82 (m, 1H), 3.71 (m, 1H), 3.7−3.1 (m, 7H), 2.9 (m, 1H), 2.7 (m, 1H), 1.44 (d, J = 4.1 Hz, 3H, diastereomer), 1.42 (d, J = 4.2 Hz, 3H, diastereomer), 1.30 (d, J = 5.6 Hz, 3H, diastereomer), 1.27(d, J = 6.1 Hz, 3H, diastereomer).

Typical Procedure for the Synthesis of Compounds 9. The dried crude material of compound **8** was dissolved in anhydrous DMF. DIEA (3 equiv) was added followed by the addition of 1.2 equiv of acyl chloride (acetyl chloride or benzoyl chloride). The solution was stirred at room temperature overnight. Completion of the reaction was monitored by HPLC. The solution was dissolved in acetic acid, frozen, and lyophilized. The obtained product was purified by preparative HPLC.

(1*S*,8*S*)-3-[(Ethylamino)carbonyl]-1,8-diisopropyl-10-oxo-9-(2-phenylethyl)-3,9-diaza-6-azoniaspiro[5.5]undecane (10c): ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 7.33−7.21 (m, 5H), 6.88 (t, J = 5.2 Hz, 1H, diastereomer), 6.81 (t, J = 5.1 Hz, 1H, diastereomer), 6.57 (b, 1H), 4.76 (d, J = 15.5 Hz, 1H, diastereomer), 4.67 (d, J = 15.7 Hz, 1H, diastereomer), 4.21 (dd, J = 16.5, 7.8 Hz, 1H, diastereomer), 4.17 (m, 1H, diastereomer), 3.96 (m, 3H), 3.70 (m, 2H), 3.55 (m, 2H), 3.47 (m, 1H), 3.18 (m, 1H), 3.09 (m, 3H), 2.98 (m, 2H), 2.84 (m, 2H), 2.78 (m, 1H), 2.49 (m, 1H, diastereomer), 2.28 (m, 1H, diastereomer), 1.34 (d, J = 6.7 Hz, 3H, diastereomer), 1.05 (d, J = 6.9 Hz, 3H, diastereomer), 1.03 (d, J = 4.5 Hz, 3H, diastereomer), 1.01 (d, J = 4.5 Hz, diastereomer), 0.99 (m, 6H, diastereomers), 0.93 (d, J = 7.0 Hz, 3H, diastereomer), 0.90 (d, J = 6.5 Hz, 3H,

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diastereomer), 0.86 (d, J = 4.1 Hz, diastereomer), 0.85 (d, J = 4.1 Hz, 3H, diastereomer).

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Supporting Information Available: Experimental procedures for the preparation of compounds **8**−**10**. ^{1}H NMR data and spectra of **8a**−**h**, **9c**,**d**, **10b**−**d** and LC−MS of compounds **8a**−**h** (and LC−MS of other compounds **8** not presented in Table 1). This material is available free of charge via the Internet at http://pubs.acs.org.

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