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Solid-phase synthesis of skeletally diverse benzofused sultams via palladium-catalyzed cyclization

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ABSTRACT

The solid-phase synthesis of sultams from resin-bound amino acids is described. The sulfonylation of the resin-bound primary amines afforded the requisite secondary amines, after which the intramolecular Buchwald–Hartwig-type coupling forms the C–S bond. A final alkylation on the sulfonamides followed by cleavage provided the corresponding seven-membered sultams.

Sultams (cyclic sulfonamides) are one of the most important heterocyclic skeletons in organic chemistry. Due to their diverse biological properties, sultams have emerged as privileged structures in drug discovery.[1] Most recently, the significance of sultams has reached new frontiers, due in part to the discovery of promising bioactive sultams in areas such as, antiviral,[2] anticancer,[3] antimicrobial,[4] antimalarial,[5] and antileukemic therapeutics.[6] As part of the efforts toward utilizing solid-phase synthesis as a powerful methodology for the synthesis of a compound library for discovering biologically relevant compounds,[7] herein, we report on the development of a solid-phase synthetic strategy for the generation of seven-membered sultams. We utilized a Buchwald–Hartwig-type reaction[8] between a thiol group and α-haloarylsulfonamides, in part because α-haloarylsulfonamide represents an attractive building block for the production of benzofused sultams.[9]

As outlined in Scheme 1, we began our investigation on the solid-phase using the 'tea-bag' methodology.[10] Starting from *p*-methylbenzhydrylamine (MBHA) resin, a variety of Boc-L-amino acids (Boc-L-AA-OH) were coupled to the resin. The Boc group was removed by 55% TFA in DCM. The resulting primary amine was then coupled with Fmoc-L-Cys(Trt)-OH to provide the dipeptide **3**, which following a standard Fmoc deprotection afforded the primary amine. Subsequent sulfonylation of the resin-bound primary amine with 2-bromoarylsulfonyl chloride gave the resin-bound sulfonamide **4**. The palladium-catalyzed intramolecular coupling of aryl halides with the thiol group proved to be an efficient method to form the C–S bond. This C–S bond is a common functionality found in numerous pharmaceutically active compounds.[11] After optimization of the reaction conditions, we found that the resin-bound seven-membered sultams could be obtained efficiently by treatment of **5** with Cs_2CO_3 (10 equiv), $Pd(PPh_3)_4$ (0.2 equiv), and (±)-BINAP (0.4 equiv) in anhydrous DMF at 100 °C for 20 h. Further treatment with K_2CO_3 and a variety of electrophilic reagents, such as alkyl halides, benzyl halides, and phenylacyl bromide introduced the R^3 diversity element seen in the corresponding resin **7**. The desired products were obtained following cleavage from the resin using HF for 1.5 h at 0 °C. To illustrate the versatility of this chemistry, a library of 15 compounds (**8a–8o**) were prepared (Table 1). The product was characterized by electrospray LC–MS, ^1H, and ^{13}C NMR.[12]

In summary, we have demonstrated a feasible approach to facilitate the rapid parallel multistep synthesis of seven-membered sultams from amino acids and short peptides on the solid-phase via a palladium-catalyzed intramolecular cyclization reaction. This methodology is of value for the formation of a C–S bond. Furthermore, the reaction utilizes chiral amino acids, which in turn produces chiral sultams.

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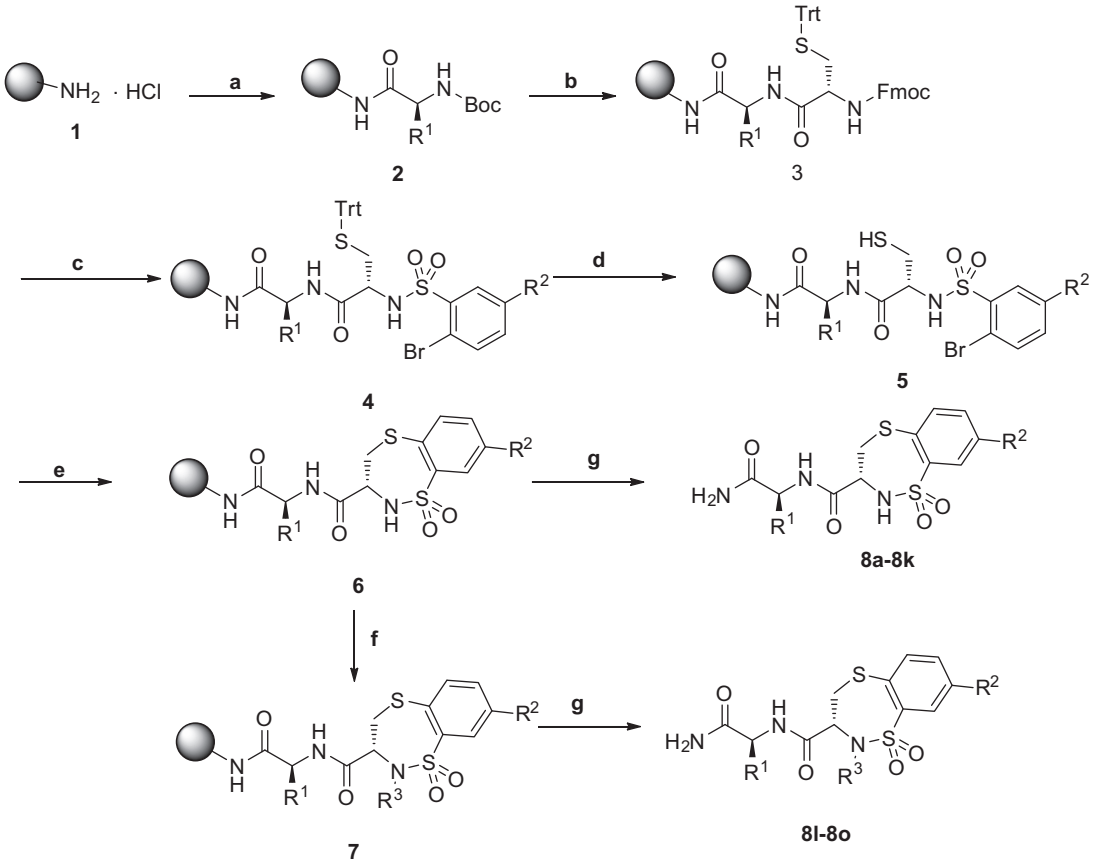

Scheme 1. Reagents and conditions: (a) (i) prewash with 5% DIEA/DCM; (ii) Boc-L-AA-OH, DIC, HOBT, DMF, rt, 2 h; (b) (i) 55% TFA/DCM; (ii) Fmoc-L-Cys(Trt)-OH, DIC, HOBT, DMF, rt, 2 h; (c) (i) 20% piperidine/DMF; (ii) R^2SO_2Cl, DIEA, DCM, rt, overnight; (d) 5% TFA/5% triisopropylsilane/90% DCM; (e) $Pd(PPh_3)_4$, (±)-BINAP, Cs_2CO_3, 100 °C, 20 h; (f) R^3X, K_2CO_3, DMF, 48 h; or R^3X, DIEA, DMF, 48 h; (g) HF, 0 °C, 1.5 h.

Table 1
Individual sultams of **8**

Entry	R^1	R^2	R^3	Yield[a] (%)	Purity[b] (%)	MW[c]
8a	H	H	H	88	98	315.9 ($[M+H]^+$)
8b	H	CF_3–	H	76	99	383.9 ($[M+H]^+$)
8c	CH_3–	H	H	85	98	329.9 ($[M+H]^+$)
8d	CH_3–	CF_3–	H	59	87	397.9 ($[M+H]^+$)
8e	$(CH_3)_2CHCH_2$–	H	H	52	94	372.0 ($[M+H]^+$)
8f	–$(CH_2)_3$–[d]	H	H	98	85	356.0 ($[M+H]^+$)
8g	–$(CH_2)_3$–[d]	CF_3–	H	75	98	446.0 ($[M+Na]^+$)
8h	$CH_3SO(CH_2)_2$–	H	H	67	91	405.9 ($[M+H]^+$)
8i	$CH_3SO(CH_2)_2$–	CF_3–	H	61	89	474.0 ($[M+H]^+$)
8j	$HOCH_2$–	H	H	54	92	345.9 ($[M+H]^+$)
8k	$HOCH_2$–	CF_3–	H	67	97	435.9 ($[M+Na]^+$)
8l	$(CH_3)_2CH$–	H	CH_3CH_2–	69	83	408.0 ($[M+Na]^+$)
8m	H	H	4-NO_2PhCH_2–	84	70	450.9 ($[M+H]^+$)
8n	CH_3–	H	2,4-Di-$FPhCH_2$–	63	62	478.0 ($[M+Na]^+$)
8o	$(CH_3)_2CH$–	H	$PhCOCH_2$–	40	91	498.1 ($[M+Na]^+$)

[a] Yields (in %) are based on the weight of crude material and are relative to the initial loading of the resin.
[b] The purity of the crude material was estimated by the peak area from analytical HPLC traces at $\lambda = 254$ nm.
[c] Confirmed by mass spectra (ESI).
[d] –$(CH_2)_3$–:

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12. *General produce for the synthesis of sultams*: 100 mg of MBHA resin was contained in a polypropylene mesh packet. Following neutralization with 5% diisopropylethylamine (DIEA), the resin was then coupled with Boc-L-amino acid, hydroxybenzotriazole (HOBt, 6.0 equiv, 0.1 M) and diisopropylcarbodiimide (DIC, 6.0 equiv, 0.1 M) in DMF at room temperature for 2 h. Upon removal of the Boc group with 55% TFA in DCM (30 min), the resin was washed with DCM (2 times), neutralized with a solution of 5% DIEA in DCM. The resin-bound amine was then coupled with Fmoc-L-Cys(Trt)-OH(6.0 equiv, 0.1 M), HOBT (6.0 equiv, 0.1 M) and DIC (6.0 equiv, 0.1 M) in DMF for 2 h. Deprotection of the Fmoc group with 20% piperidine in DMF (10 min × 2 times), the resin was washed with DMF (2 times), DCM (2 times) and lyophilized. To the dried resin, DIEA (10.0 equiv) was added into the solution of anhydrous DCM. The reaction mixture was then gently stirred for 5 min before the addition of the corresponding benzenesulfonyl chloride. The resulting mixture was then stirred at room temperature overnight. After that, the resin was washed with DMF (2 times), DCM (2 times), and methanol (2 times). Deprotection of the Trt group with 5% TFA/5% triisopropylsilane/90% DCM for 15 min (3 times), the resin was washed with DCM (6 times) and lyophilized overnight. The palladium-catalyzed cyclization reaction was performed under nitrogen. To each tube was added the resin, Cs_2CO_3 (10.0 equiv), $Pd(PPh_3)_4$ (0.2 equiv) and (±)-BINAP (0.4 equiv), followed by 10 ml of anhydrous DMF. The reaction mixture was heated at 100 °C for 20 h. The resin was then washed with DMF (2 times), DCM (2 times) and methanol (2 times). Diverse alkyl or benzyl halides were tethered to the resin-bound sultams in the presence of K_2CO_3 or DIEA in the DMF at room temperature for 48 h. After the alkylation, the resin was washed with DMF (2 times), DCM (2 times) and methanol (2 times). The final product was cleaved with HF at 0 °C for 1.5 h. The desired product was extracted with acetic acid/water (95:5) and lyophilized. The product was characterized by LC–MS under ESI conditions, ^1H and ^{13}C NMR. ESI-MS (*m*/*z*) of **8g**: 446.0 $(M+Na)^+$; ^1H NMR of **8g**: (500 MHz, DMSO-d_6): 1.85–1.91 (1H, m), 1.93–1.95 (2H, m), 2.07–2.11 (1H, m), 2.91 (1H, dd, J_1 = 10.0 Hz, J_2 = 15.0 Hz), 3.42–3.48 (1H, m), 3.70–3.75 (2H, m), 4.19 (1H, dd, J_1 = 3.0 Hz, J_2 = 9.0 Hz), 4.73 (1H. dd. J_1 = 2.0 Hz, J_2 = 10.0 Hz), 6.99 (1H, s), 7.31 (1H, s), 7.91 (1H, dd, J_1 = 2.0 Hz, J_2 = 8.5 Hz), 7.96 (1H, d, J = 8.0 Hz), 8.09 (1H, d, J = 2.0 Hz); ^{13}C NMR of **8g**: (125 MHz, DMSO-d_6): 24.1, 29.4, 34.9, 46.6, 58.1, 60.0, 123.3 (q, J = 271 Hz), 125.2, 128.3 (q, J = 33 Hz), 128.7, 135.6, 137.0, 146.7, 166.4, 173.2.