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Parallel synthesis of structurally diverse aminobenzimidazole tethered sultams and benzothiazepinones

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ABSTRACT

A solid-phase methodology to construct aminobenzimidazole tethered sultams and benzothiazepinones from commercial amino acids, amines, carboxylic acids, and sulfonyl chlorides is described. Coupling of Fmoc-Cys(Trt)-OH to resin-bound aminobenzimidazole scaffold provided an essential precursor for the construction of a variety of seven membered benzofused cyclic sulfonamides and thiazepinones via palladium catalyzed Buchwald–Hartwig type intramolecular cyclization.

Introduction

Solid phase organic synthesis (SPOS) is a valuable tool for the expedited parallel synthesis of structurally diverse compounds of drug discovery interest.[1–7] Continuing with our long standing interest in the development of heterocyclic libraries utilizing resin-bound peptidyl-,[5–7] and heterocyclic scaffolds[7–9] as starting materials, we describe an efficient methodology for the parallel synthesis of structurally diverse aminobenzimidazole tethered sultams and benzothiazepinones. Sultams or cyclic sulfonamides are useful structural motifs in heterocyclic synthesis,[4] applied as chiral auxiliaries in asymmetric synthesis,[10] and are actively sought in the areas of antimalarial,[11] antiviral,[12] anticancer,[13] antimicrobial,[14] and antileukemic research.[15,16] Likewise, aminobenzimidazole is a recurring template in the design and for the development of combinatorial libraries of drugs and drug-like molecules.[17,18]

We previously reported the application of resin-bound aminobenzimidazoles as a template for the synthesis of a variety of fused and/or tethered heterocyclic compounds such as tetracyclic benzimidazoles,[8b] triazino-benzimidazoles,[8c] branched thiohydantoin benzimidazolinethiones,[9] and aminobenzimidazole tethered hydantoins, thiohydantoins,[19] and thiazoles.[20] In this Letter, we extend the application of this practical methodology toward the synthesis of aminobenzimidazole tethered sultams and benzothiazepinones.

Our retrosynthetic rationale for the synthesis of aminobenzimidazole derived cyclic sulfonamides is illustrated in Scheme 1. We envisioned the construction of benzofused cyclic sulfonamides **1** from the resin-bound free amine **2** via palladium catalyzed cyclization.[21]

The parallel synthesis of the desired sulfonamides was pursued using the tea-bag approach, wherein the resin is packed within sealed polypropylene mesh packets.[22] The synthesis of diversified resin-bound aminobenzimidazoles **3** via nucleophilic substitution of 4-fluoro-3-nitrobenzoic acid was carried out according to the literature precendents.[8b,c,9,19,20] The resin-bound aminobenzimidazole was later coupled to Fmoc-Cys(Trt)-OH **4** in the presence of PyBOP. Following Fmoc deprotection, the generated free amine **2**[19,20] was treated with 2-bromoarylsulfonyl chlorides to furnish the intermediate sulfonamides which, upon trityl group deprotection generated a thiol **5**. The treatment of resin-bound sulfonamides in the presence of Cs_2CO_3 and palladium led the following intramolecular cyclization in a Buchwald–Hartwig fashion to the resin-bound sultams **6**.[7,23,24] Additional third position of diversity (R_3) was introduced by the treatment of sultams with several aryl and alkyl halides **7** (Scheme 2). Following cleavage of the resin with anhydrous HF, the desired cyclic sultams **1**[25] were isolated in reasonable yields (Table 1).

On the basis of this result, we decided to extend the application of this protocol toward the synthesis of benzothiazepinones (Scheme 3) **8**. The reaction of the cysteine coupled to resin-bound aminobenzimidazole **2** with substituted 2-chlorobenzoic acids in the presence of DIC/HOBT, followed by cleavage of the trityl group

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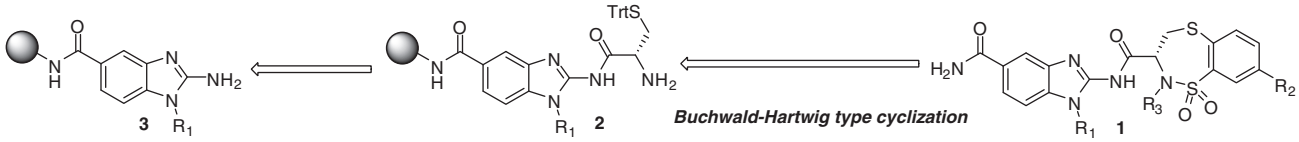
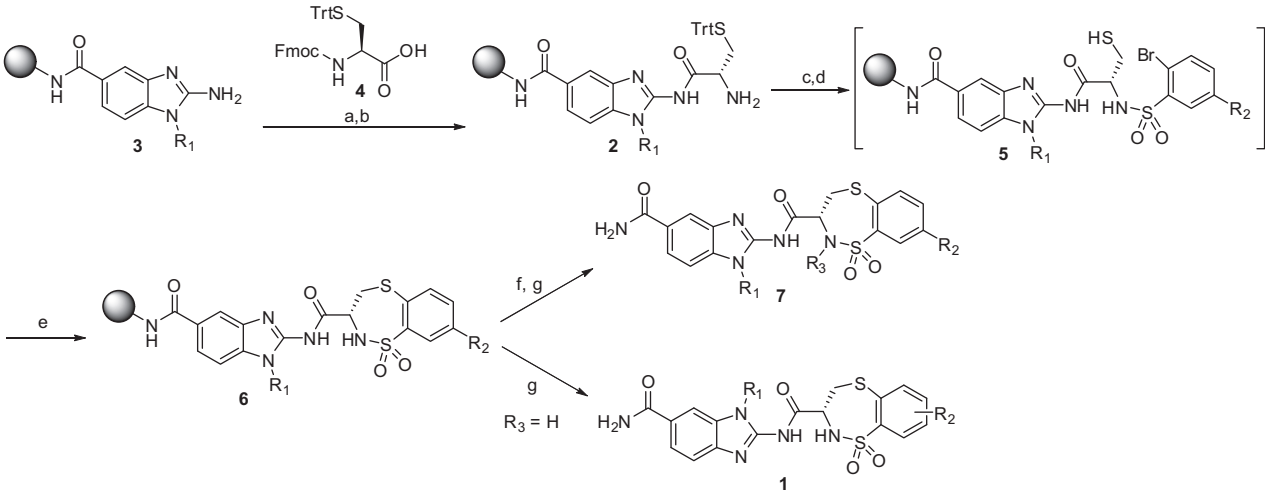
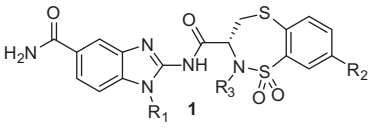


Scheme 1. Retrosynthetic illustration of aminobenzimidazole tethered sultams.



Scheme 2. (a) PyBOP (8 equiv, 0.5 M anhyd. DMF), HOBt (8 equiv), DIEA (8 equiv), 12 h, rt; (b) 20% piperidine/DMF, 15 min (2×), rt; (c) DIEA (10 equiv), R_2SO_2Cl (10 equiv) 12 h, rt; (d) 6% TFA/DCM (1% TIPS), 15 min (2×); (e) Cs_2CO_3 (10 equiv), $Pd(PPh_3)_4$ (0.2 equiv), (±)-BINAP (0.4 equiv), anhydrous DMF, 100 °C, 16 h; (f) R_3I, DIEA (8 equiv, in 0.2 M DMF); (g) HF, anisole (99:5), 0 °C, 90 min.

Table 1



Entry	Ri	R_2	R_3	Mass calcd./found	Yield[a] (%)
1a	Cyclopentyl	H	H	485.6/486.4 (MH^+)	44
1b	*n*-Butyl	H	H	473.5/474.3 (MH^+)	47
1c	*i*-Butyl	H	H	473.5/474.4 (MH^+)	53
1d	Cyclohexanemethyl	H	H	513.6/514.5 (MH^+)	42
1e	3-(trifluoromethyl)benzyl	H	H	575.6/576.5 (MH^+)	56
1f	Cyclopentyl	CF_3	H	553.6/554.5 (MH^+)	22
19	*n*-Butyl	CF_3	H	541.5/542.4 (MH^+)	24
1h	*i*-Butyl	CF_3	H	541.5/542.4 (MH^+)	18
1i	Cyclohexanemethyl	CF_3	H	581.6/582.4 (MH^+)	25
1j	3-(trifluoromethyl)benzyl	CF_3	H	643.6/644.4 (MH^+)	15
1k	*i*-Butyl	H	4-OMe-Bn	593.7/594.5 (MH^+)	16
11	*i*-Butyl	CF_3	4-OMe-Bn	661.7/662.5 (MH^+)	18
1m	*n*-Butyl	H	Bn	563.7/564.6 (MH^+)	32
1n	*n*-Butyl	CF_3	Bn	631.7/632.5 (MH^+)	36
1o	3-(trifluoromethyl)benzyl	H	Et	603.6/604.5 (MH^+)	23
1p	3-(trifluoromethyl)benzyl	CF_3	Et	671.6/672.5 (MH^+)	12

Isolated yields of aminobenzimidazole tethered sultams: The products were run on a Vydac column, gradients 5–95% formic acid in ACN in 7 min.

[a] The yields are based on the weight of purified products and are relative to the initial loading of the resin.

generated the intermediate thiol which under Buchwald–Hartwig type conditions proceeded smoothly to yield the resin-bound thiazepinones **10**. Finally, the desired benzothiazepinones **8** were obtained in moderate yields after cleavage of the resin using anhydrous HF (Scheme 3).[26] The results are summarized in Table 2. All these above synthesized products were confirmed by LC-MS and NMR spectroscopy. The incorporated heterocyclic core in the final products, is a useful pharmacophore prevalent in many bioactive compounds endowed with an array of pharmacological properties.[27,28]

Conclusions

In conclusion, we have developed a multistep solid-phase strategy for the parallel synthesis of aminobenzimidazole tethered sultams and benzothiazepinones via palladium-catalyzed