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Novel Intramolecular Rearrangement Leading to the Synthesis of Biheterocyclic Indole–Benzoimidazole Derivatives on Solid Phase†

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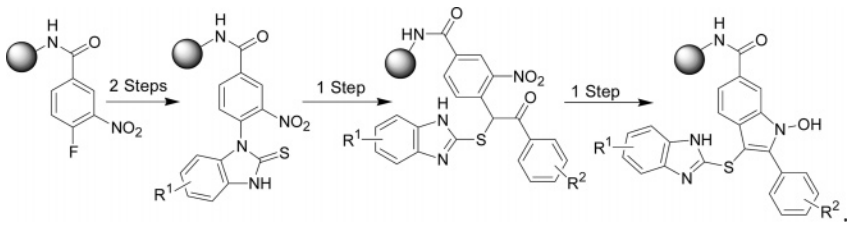
ABSTRACT



A novel intramolecular SNAr rearrangement observed during the S-alkylation of benzoimidazole-2-thione with α-haloacetophenone is reported. The rearrangement led to the formation of a new benzoimidazole-based intermediate, which is further utilized for the generation of a new biheterocyclic indole–benzimidazole derivatives with a two-point diversity.

Combinatorial synthesis of diversified heterocyclic compounds is a promising strategy for new pharmaceutical lead structures.[1] These privileged structures, when combined, may provide biheterocyclic structures with druglike properties capable of addressing various biological targets depending on their substitution pattern. To create diversified molecules in a minimum number of steps and in a shorter time scale, several heterocyclic compounds synthesized in solution phase have been transferred to solid phase. During the course of our ongoing efforts to synthesize nitrogen- and sulfur-containing heterocycles using solid-phase strategies,[2] we focused our interest on synthesizing libraries of benzoimidazole-based heterocycles.

Among the benzoimidazole-based heterocycles, the 2-alkylsulfanyl-1*H*-benzoimidazole scaffold represents one of the most important pharmacophores responsible for its role as an antiproliferative agent[3] and a proton pump inhibitor; notable clinical examples are Omeprazole,[4] Lansoprazole, Pantoprazole, and Rabeprazole.[5] In addition, benzoimidazole-based compounds have shown selective inhibition of platelet-

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derived growth factor receptor,[6] class III antiarrythmatic activity,[7] neuropeptide Y_1 receptor antagonism,[8] angiotensin II receptor antagonism,[9] and antiviral properties.[10] Moreover, the 2-alkylsulfanyl-1*H*-benzoimidazole scaffold has gained much attention recently due to its activity against cancer cell lines.[11] Thus, due to a variety of biological and pharmacological activities exhibited by these classes of compounds, we sought to develop a solid-phase synthetic strategy for biheterocycles **1** (Figure 1) derived from 2-alkylsulfanyl-1*H*-benzoimidazole.

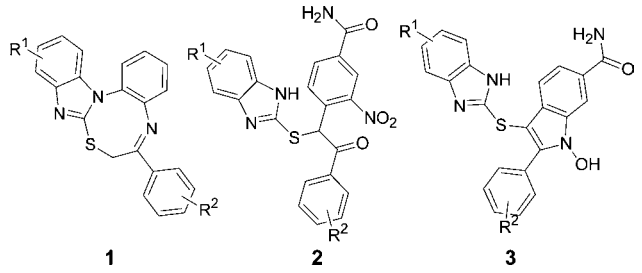
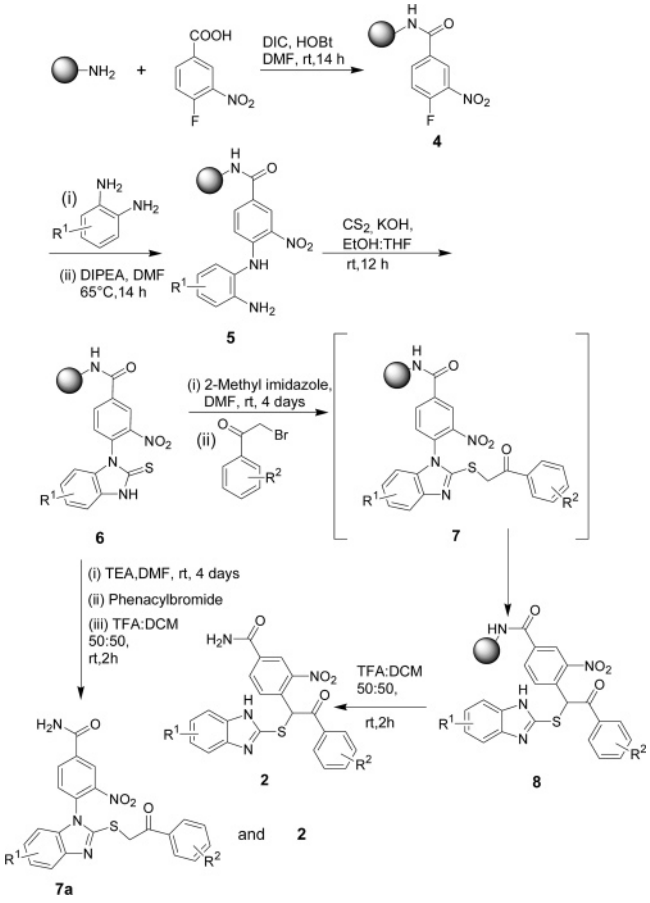


Figure 1.

To date, a number of methods have been reported for the synthesis of benzoimidazole ring and benzoimidazoles−thiones and 2-alkylsulfanyl-1*H*−benzoimidazole on solid phase.[12] However, there are no reports dealing with S-alkylation using α-haloacetophenone as an alkylating agent. For the synthesis of our target structure **1**, we proposed to alkylate the resin-bound benzoimidazole-2-thione with α-haloacetophenone in the presence of a base. Interestingly, the strategy resulted in a novel intramolecular rearrangement on solid phase to furnish a new benzoimidazole-based intermediate **2** (Figure 1) as an enantiomeric mixture. The latter was found to be an interesting intermediate, as its one-step synthetic transformation on solid phase resulted in the synthesis of substituted indole-1-ols **3** tethered with substituted 1*H*-benzimidazol-2yl-sulfanyl derivatives. The details of our findings are presented in this communication.

The synthetic methodology commenced with the anchoring of *o*-fluoro-nitrobenzoic acid to Rink amide AM resin (Scheme 1) by the help of coupling agents DIC/HOBt. The

Scheme 1



completion of the reaction was confirmed by a negative Kaiser test. The fluorine atom in resin **4** was replaced with *o*-phenyldiamine in the presence of diisoproylamine in DMF at 60 °C to give **5**. The resulting diamine so obtained was then treated with carbon disulfide and KOH in a mixture of THF−EtOH to give the intermediate 1,3-dihydrobenzoimidazole-2-thione structure **6**. The compound at this stage was cleaved and characterized using mass and NMR spectroscopy. The strategy developed by us provides an easy and a commercially viable approach for synthesizing the 1,3-dihydrobenzoimidazole-2-thione with a very high yield (>95%) and purity (>95%).

Next, the resin-bound 1-(2-nitro-phenyl)-1,3-dihydro-benzoimidazole-2-thione **6** was treated with 4-methyl phen-

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acylbromide in the presence of triethylamine as a base in DMF for 24 h at room temperature to generate the S-alkylated product. The final product was then washed and cleaved from the resin by treating it with 50% TFA−DCM. TLC of the crude final product revealed two major spots indicating formation of two compounds. The two spots were separated by column chromatography and characterized by mass and NMR. The ESMS of both spots observed in the TLC provided a similar molecular ion peak (M + H = 463). NMR analysis of the component having the higher R_f value revealed the formation of the S-alkylated product **7a**, whereas the second component, having a lower R_f value, showed certain resonance signals in the ^{1}H NMR spectrum, which suggested the formation of an unusual product. These results prompted us to explore the structure of the unusual product formed during the S-alkylation reaction.

The structure of the unexpected product was elucidated by the combined use of various one- and two-dimensional NMR experiments. The structure was thus designated to be 4-[1-(1*H*-Benzoimidazol-2-ylsulfanyl)-2-(4-methyl-phenyl)-2-oxo-ethyl]-3-nitro-benzamide (**2**).

Figure 2 highlights a few selected HMBC correlations required for the confirmation of structure **2**. On the basis of

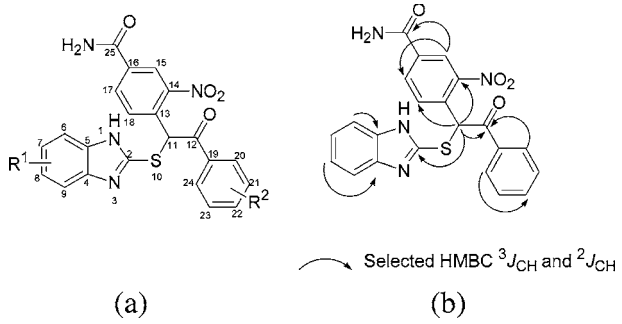


Figure 2. Numbering (a) and HMBC correlation (b) observed for **2**.

these observations, we propose a plausible mechanism for the rearrangement as shown in Figure 3. The first step of the reaction is the usual dehydration of the benzoimidazole ring proton followed by S-alkylation leading to the formation of the expected resin-bound product **7**. An excess of base present in the system would then abstract the activated methylene proton to generate a nucleophile, followed by its attack at the electrophilic carbon (C-13) resulting in a five-membered transition state. This resulted in the substitution of the nucleophilic methine carbon (C-11) at the C-13 quaternary carbon, replacing the benzoimidazole ring via an intramolecular SNAr mechanism to furnish **2**. Presence of the electron-withdrawing nitro group may contribute toward the stabilization of the cyclic transition state through charge dispersion, which may facilitate the reaction. Interestingly, the entity **2** appeared to be a useful template for the generation of a novel benzoannelated heterosystem through the reduction of the aromatic nitro group to $-NH_2$, which

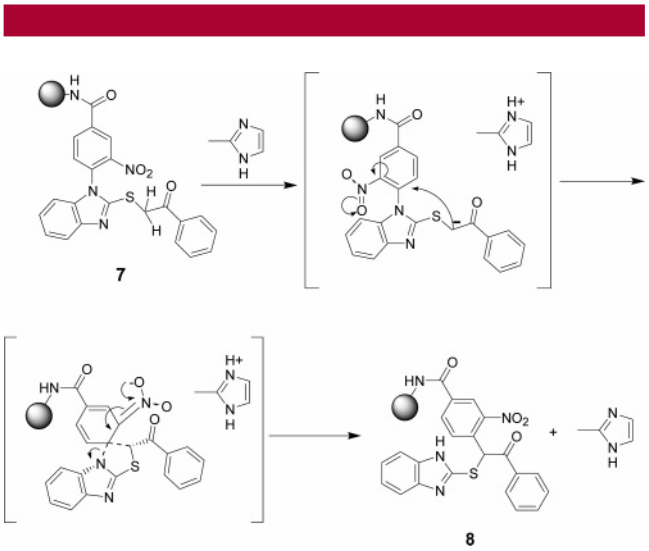


Figure 3. Proposed mechanism for base-catalyzed intramolecular SNAr reaction.

may then undergo spontaneous intramolecular cyclization with the keto group at the γ-position. This led us to optimize our reaction conditions for the selective synthesis of **2** from resin **6**, as the use of Et_3N resulted in a mixture of **2** and **7a**.

We carried out this reaction by employing a variety of bases such as DIPEA, DMAP, imidazole, 2-methylimidazole, 1-methylimidazole, and DIPA. The optimal condition that led to the selective synthesis of **2** in high yield and purity involved treatment of resin **6** with 2-methylimidazole as a base for 4 days in DMF at room temperature. Other bases furnished mixtures of **2** and **7a** in varying ratios (based on HPLC) as depicted in Table 1.

Table 1. Ratio of Products **7a** and **2** Formed during S-Alkylation of **6** with α-Haloketones and Base (Scheme 1)

	ratio of products formed	
bases used	**7a** (%)	**2** (%)
trimethylamine	75	25
diisopropylethylamine	80	20
(dimethylamino)pyridine	72	28
imidazole	45	55
2-methyl imidazole	0	100
1-methyl imidazole	30	70
diisopropylamine	35	65

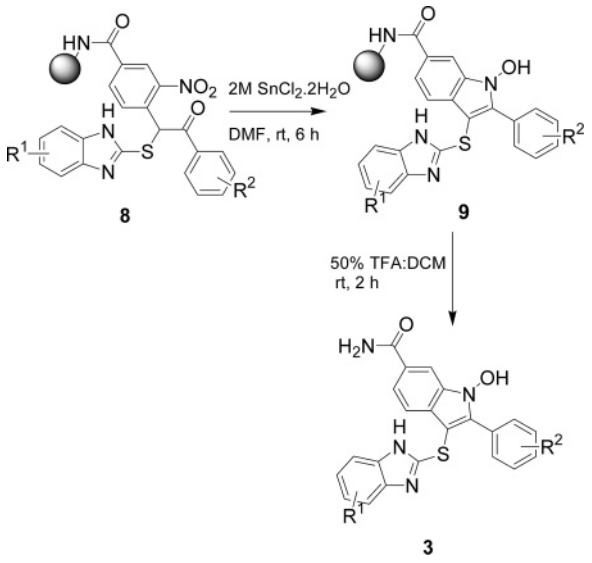
Once the reaction conditions for the selective synthesis of **2** were optimized, we then proceeded with the utility of **2** for generating a novel heterosystem. For this, the resin-bound 4-[1-(1*H*-benzoimidazol-2-ylsulfanyl)-2-oxo-2-phenyl-ethyl]-3-nitro-benzamide **8** was then treated with a 2 M solution of $SnCl_2 \cdot 2H_2O$ in DMF for 5 h. The final product **3** was cleaved with 50% TFA in DCM, and the residue obtained after evaporation of the cleavage mixture was lyophilized by dissolving in 4:1 *t*BuOH−water mixture.

The purity of crude product was assessed using HPLC, which indicated a purity of ~85%. The resulting product

was then purified using column chromatography and characterized using ESMS and two-dimensional NMR experiments.

On the basis of the NMR analysis, the structure of the final compound was elucidated as a trisubstituted indole-1-ol heterosystem tethered with benzoimidazole. A careful survey of the literature revealed only one report dealing with solid-phase synthesis of indole-1-ol;[13] however, it was associated with limited diversity. To probe the versatility and limitation of our strategy, a minilibrary of 17 compounds with two-point diversity having general structures **2** and **3** was synthesized. The purities of crude products obtained after acidolytic cleavage were found to be in the range from 78 to 98% and are presented in Table 2. The compounds were purified by silica gel chromatography and characterized by NMR.

Scheme 2. Synthesis of Trisubstituted Indole-1-ol (**3**)



In summary, we have developed an efficient method for the synthesis of a new benzoimidazole-based intermediate that resulted from an unusual rearrangement on solid phase. The utility of the intermediate has been demonstrated for the synthesis of a novel heterosystem based on indole-benzoimidazole conjugates with good yield and purity. The strategy can be successfully used for the generation of large libraries using an automated synthesizer.

Table 2. Yields and Purities of Representative Compounds Based on Prototype **2** and **3**

compd	R^1	R^2	% yield[a] (crude/isolated)	purity[b]
2a	H	4-CH_3	98/90	95
2b	H	4- OCH_3	95/85	98
2c	4,5-CH_3	4-OCH_3	85/69	78
2d	H	2-OCH_3	92/85	85
2e	H	4-Br	93/84	90
2f	H	4-Cl	88/71	82
2g	H	3-OCH_3	88/75	84
2h	H	H	85/69	75
2i	2-Br	4-OCH_3	78/66	92
3a	H	4-CH_3	95/86	92
3b	H	4-OCH_3	96/88	90
3c	H	3-OCH_3	91/77	91
3d	4,5-CH_3	4-CH_3	84/71	86
3e	4,5-CH_3	4-OCH_3	96/85	94
3f	H	4-Cl	83/72	84
3g	4,5-CH_3	H	81/65	78
3h	2-Br	4-OCH_3	80/67	77

[a] Based on initial loading. [b]Analysis of crude products was carried out on Agilent liquid chromatograph using a 5 μm, 4.8 $\times$ 150 mm C_{18} reverse-phase column with a linear gradient 10−100% ACN in water (v/v) over 25 min. The flow rate was 1.0 mL/min, and UV detection was performed at 220/254 nm.

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Supporting Information Available: Detailed experimental procedure and ^{1}H NMR spectra of compounds **2a**−**i** and **3b**−**f**, ^{13}C NMR spectra of **2a**−**f**,**h** and **3b**−**e**, and two-dimensional HSQC and HMBC NMR spectra of **2a** and **3b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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