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Report

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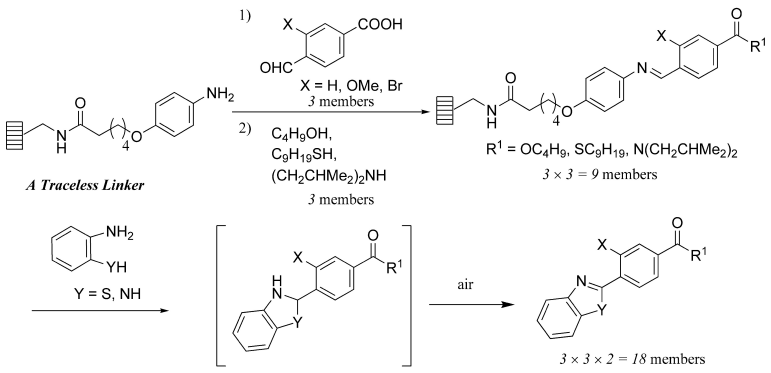

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Combinatorial Synthesis of Benzothiazoles and Benzimidazoles Using a Traceless Aniline Linker

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Solid-phase synthesis is easily performed and is particularly effective for split/mix combinatorial synthesis to generate a large number of compounds. Therefore, solid-phase combinatorial synthesis is commonly used for the rapid discovering of new drugs and materials. The selection of an adequate linker in the solid-phase synthesis is one of the key factors for efficiently building the desired libraries.[1] In particular, traceless linkers have advantages, because the point of attachment on the solid support is not apparent in the target molecules.[2] We recently developed a new traceless linker **1** suitable for the synthesis of compounds possessing azomethines and applied it to the synthesis of a rod-shaped, liquid crystalline library.[3] In previous studies, the product yields were dependent on the stability balance of the resin-bound azomethines. The overall yields of azomethines were low to moderate because the resin-bound azomethine **3** suffered partial alcoholysis during condensation with alcohols. On the other hand, a resin-bound azomethine **5**, which was loaded on the 4-alkoxyaniline linker **2**, was more stable against alcoholysis, but the equilibrium was not shifted effectively in favor of the final product **6** at the cleaving step due to comparable stability of **5** and **6**. In the latter case, the product yields are expected to improve when the resin-bound substrates are cleaved by an irreversible process. Using this approach, we report the combinatorial synthesis of benzothioazoles and benzimidazoles, which exhibit many pharmacological and biological activities (see Figure 1 and Scheme 1).

Our synthetic plan is shown in Scheme 2. In the first step, *l* members of 4-formylbenzoic acids **7** are condensed with a 4-alkoxyaniline linker **2** on the solid support to afford resin-bound azomethine **8** (step 1). In the second step, *m* members of alcohols, thiols, and amines **9** are reacted with **8** to give azomethine **10** (step 2). Finally, the azomethines on the solid support are cleaved by *n* members of 2-aminothiophenols or 1,2-phenylenediamines **11** through an imine-exchange process coupled with oxidation to give 2-arylbenzothioazoles **13** (Y = S) or 2-arylbenzimidazoles **13** (Y = NH) (step 3). The final cleaving step would proceed smoothly because the oxidation process is irreversible. In the subsequent procedure, $l \times m \times n$ members of compounds are synthesized using these three steps.

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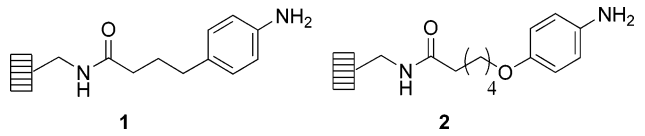
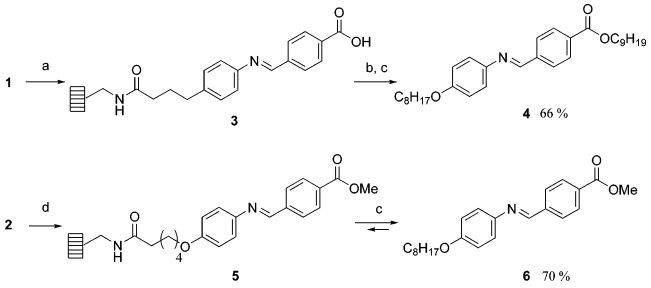


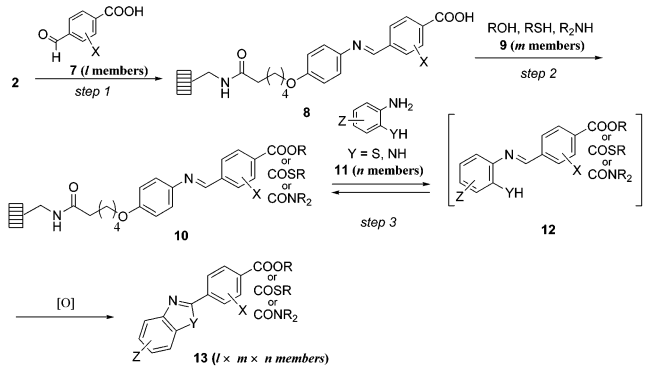
Figure 1. Two traceless aniline linkers.

Scheme 1. Synthesis of Azomethines Using Traceless Aniline Linkers[a]



[a] Reagents: (a) 4-formylbenzoic acid; (b) 1-nonanol, DIC, DMAP; (c) 4-octyloxyaniline; (d) methyl 4-formylbenzoate.

Scheme 2. Synthetic Plan of 2-Arylbenzothiazole and 2-Arylbenzimidazole Library



First, we investigated oxidative cleavage of the resin-bound azomethines. The results are summarized in Scheme 3 and Table 1. A solid-supported azomethine ester **14** was prepared according to the previously reported procedure.[3] By treating **14** with 4 equiv of 2-aminothiophenol at room temperature for 18 h, 2-arylbenzothiazole **15** (Y = S) was obtained without any oxidizing agent but air in 68% yield (entry 1). Air oxidation was concomitant with imine exchange to release the product.[4] The yield improved to 90% at a higher temperature (entries 2 and 3). The reaction completed within 20 min at 100 °C (entries 3−6). Reducing the equivalents of 2-aminothiophenol resulted in lower product yield (entry 7). A substantial amount of 2-aminothiophenol might be oxidatively decomposed in the reaction conditions.[5] 2-Arylbenzimidazole was also obtained in good yield, although a longer reaction time was required (entries 8−10).

Next, we started the synthesis of a small combinatorial library consisting of 18 members using the building blocks shown in Scheme 4. The yields are summarized in Table 2. When X was hydrogen, esters and thioesters were obtained in good yield. When X was a bromine or methoxy group,

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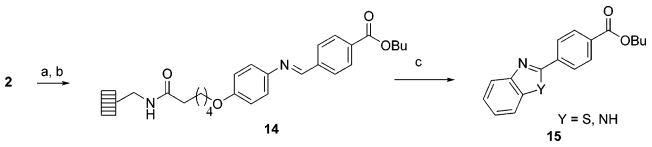
Scheme 3. Solid-Phase Syntheses of a 2-Arylbenzothiazole and a 2-Arylbenzimidazole Using a Traceless Aniline Linker[a]



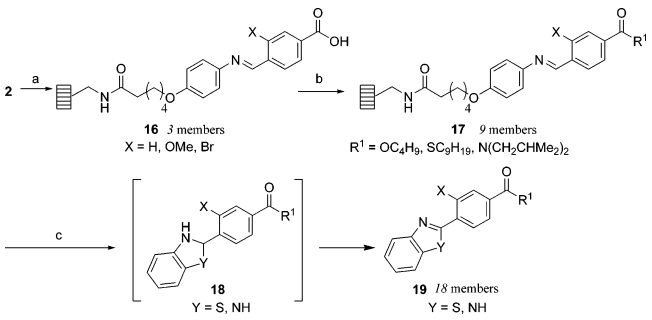
[a] Reagents and conditions: (a) 4-formylbenzoic acid, DMF, r.t., 24 h; (b) 1-butanol, DIC, DMAP, DCM, r.t., 3 h; (c) 4 equiv of 2-aminothiophenol (Y = S) or 1,2-phenylenediamine (Y = NH), air, DMF. See Table 1.

Table 1. Syntheses of a 2-Arylbenzothiazoles **15** (Y = S) and a 2-Arylbenzimidazoles **15** (Y = NH) from Solid Supported Azomethine **14**

entry	Y	period	temp (°C)	yield (%)
1	S	18 h	rt	68
2		18 h	50	82
3		18 h	100	90
4		5 min	100	76
5		20 min	100	91
6		1 h	100	90
7[a]		20 min	100	51
8	NH	20 min	100	5
9		1 h	100	14
10		18 h	100	84

[a] 2 equiv of 2-aminophenol was used.

Scheme 4. Synthesis of 2-Arylbenzothiazole and 2-Arylbenzimidazole Library[a]



[a] Reagents and conditions: (a) three kinds of 4-formylbenzoic acids (4-formylbenzoic, 4-formyl-3-methoxybenzoic, and 3-bromo-4-formylbenzoic acids), DMF, r.t., 24 h; (b) *n*-C_4H_9OH, *n*-$C_9H_{19}SH$, or $(Me_2CHCH_2)_2NH$); DIC; DMAP; DCM, r.t.; 3 h; (c) 2-aminothiophenol or 1,2-phenylenediamine, air, DMF, 100 °C, 18 h.

Table 2. Isolated Yields (%) of All Library Members **19**

	Y = S			Y = NH		
R^1	X = H	X = OMe	X = Br	X = H	X = OMe	X = Br
OBu	87	72	70	84	80	64
SC_9H_{19}	88	70	60	82	70	74
$N(CH_2CHMe_2)_2$	47	33	31	40	38	37

however, the yields were slightly reduced. The reduced yields reflect the stability of resin-bound azomethines **16** and **17**, presumably because steric hindrance between X and the azomethine linkage causes out-of-plane distortion of the two aromatic rings. Amides were synthesized in 31−47% yields, which indicated that the partial imine-exchange reaction between **16** and diisobutylamine could not be suppressed perfectly, even using the 4-alkoxyaniline linker **2**. The reaction rate in the final step was highly dependent on the substitution at the aromatic nuclei. When X was a methoxy group, all of the six reactions, which were monitored by TLC, were complete within 2 h. On the other hand, when X was a bromine, the reaction was the slowest of the series. The order seems to reflect the oxidizing potential of 2-arylbenzothiazoline or 2-arylbenzimidazoline intermediates **18**. All 18 reactions in the final step were complete within 18 h.

In summary, we demonstrated combinatorial synthesis of 2-arylbenzothioazoles and 2-arylbenzimidazoles using a traceless aniline linker. Solid-phase combinatorial syntheses of these compounds have been reported,[6] and some approaches utilized traceless linkers.[7] However, this synthetic method has the advantage that the products are cleavable without the aid of oxidants under neutral conditions. Syntheses of other heterocyclic compounds are under investigation.

Supporting Information Available. General procedures for the synthesis of the library and spectroscopic data of all 18 library members. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Guillier, F.; Orain, D.; Bradley, M. *Chem. Rev.* **2000**, *100*, 2091−2157.

(2) (a) Blaney, P.; Grigg, R.; Sridharan, V. *Chem. Rev.* **2002**, *102*, 2607−2624. (b) Bräse, S.; Dahmen, S. *Chem.−Eur. J.* **2000**, *6*, 1899−1905.

(3) (a) Hioki, H.; Fukutaka, M.; Takahashi, H.; Kodama, M.; Kubo, K.; Ideta, K.; Mori, A. *Tetrahedron Lett.* **2004**, *45*, 7591−7594. (b) Hioki, H.; Fukutaka, M.; Takahashi, H.; Kubo, M.; Matsushita, K.; Kodama, M.; Kubo, K.; Ideta, K.; Mori, A. *Tetrahedron* **2005**, *61*, 10643−10651.

(4) Direct synthesis of 2-arylbenzothiazoles or 2-arylbenzimidazoles from corresponding aromatic aldehydes and 2-aminothiophenols or 1,2-phenylenediamines in the presence of a Lewis acid or activated carbon under an oxygen atmosphere has been reported. In our case, however, neither additives nor a complete oxygen atmosphere was required for the oxidation. See: (a) Kawashita, Y.; Nakamichi, N.; Kawabata, H.; Hayashi, M. *Org. Lett.* **2003**, *5*, 3713−3715. (b) Itoh, T.; Nagata, H.; Ishikawa, H.; Ohsawa, A. *Hetrocycles* **2004**, *63*, 2769−2783.

(5) When only 2-aminothiophenol was stirred for 20 min under an air atmosphere at 100 °C in DMF, a substantial amount of decomposition products (a disulfide compound and so on) was observed by TLC.

(6) (a) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893−930. (b) Yokum, T. S.; Alsina, J.; Barany, G. *J. Comb. Chem.* **2000**, *2*, 282−292. (c) Wu, Z.; Ede, N. J.; Mathieu, M. N. *Tetrahedron Lett.* **2003**, *44*, 2293−2296. (d) Matsushita, H.; Lee, S.-H.; Joung, M.; Clapham, B.; Janda, K. D. *Tetrahedron Lett.* **2004**, *45*, 313−316. (e) Kilburn, J. P.; Lau, J.; Jones, R. C. F. *Tetrahedron Lett.* **2000**, *41*, 5419−5421.

(7) (a) Mazurov, A. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 67−70. (b) Krchnak, V.; Smith, J.; Vagner, J. *Tetrahedron Lett.* **2001**, *42*, 1627−1630. (c) Huang, W.; Scarborough, R. M. *Tetrahedron Lett.* **1999**, *40*, 2665−2668. (d) Smith, J. M.; Krchnak, V. *Tetrahedron Lett.* **1999**, *40*, 7633−7636. (e) Huang, X.; Tang, J. *Tetrahedron* **2003**, *59*, 4851−4856.

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