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Solid-Phase Synthesis of Imidazo[1,2-a]pyridine Using Sodium Benzenesulfinate as a Traceless Linker

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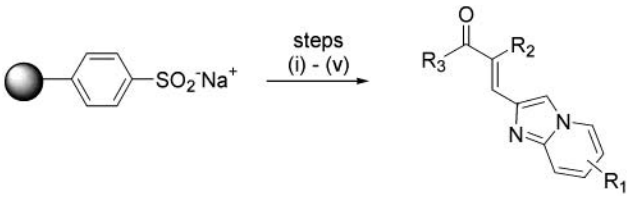
ABSTRACT



The preparation of the first library of imidazo[1,2-a]pyridine derivatives on a solid support is described. A sulfone linker strategy was applied in the synthesis. Key steps involved in the solid-phase synthetic procedure include (i) α-haloketone resin formation by sulfinate → sulfone alkylation, (ii) imidazo[1,2-a]pyridine ring formation by treatment with 2-aminopyridine, (iii) sulfone anion alkylation, and (iv) traceless product release by oxidation–elimination. A library of 12 imidazo[1,2-a]pyridines was synthesized.

Central to the effective application of solid-phase organic synthesis (SPOS) is the choice of linker, through which the reactive intermediates are attached to the solid support and from which the target molecules can be efficiently cleaved from the resin.[1] Methods of immobilizing compounds to the solid phase for combinatorial synthesis initially relied upon traditional solid-phase peptide linkers, which resulted in the release of carboxylic acids, esters, or amides from the ester- or amide-bound substrate.[2] Immobilization techniques that afford alternative residual functional groups are highly desirable. In this regard, one of our interests is to develop the sulfone linker via polymer-bound sodium benzenesulfinate **1** and explore new applications for it in SPOS. Sodium benzenesulfinate has been widely used in the preparation of sulfone, which plays an important role in organic synthesis,[3] but the application of **1** in solid-phase synthesis has received relatively less attention. Previous reports from other laboratories[4,5] and ours[6] have demonstrated the use of **1** as a solid support for SPOS and shown the resulting sulfone linker derived from **1** to be a versatile and robust tether that offers various on-resin functionalization or cleavage with additional changes.

Imidazo[1,2-a]pyridine moieties represent important building blocks in both natural and synthetic bioactive compounds, which have been shown to possess diverse therapeutic activities.[7] Hence they are interesting targets in the development of new drug leads. A large number of solution-phase synthetic pathways are available for the preparation of imidazo[1,2-a]pyridines but, to our knowledge, there have been no previous reports on the solid-phase synthesis of these

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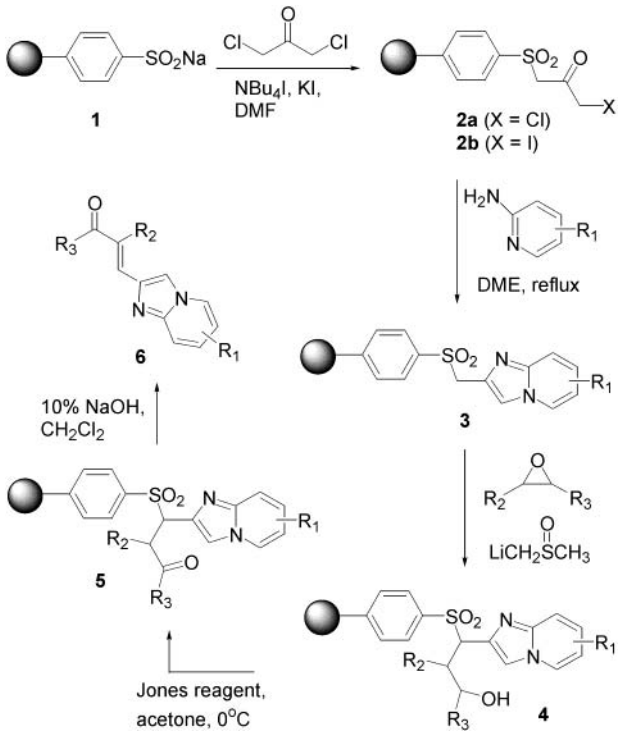
compounds. Herein, we describe the utilization of **1** as a linker for the synthesis of imidazo[1,2-a]pyridine derivatives.

Key steps in the synthesis of imidazo[1,2-a]pyridines from **1** include (i) α-haloketone resin formation by sulfinate → sulfone alkylation, (ii) imidazo[1,2-a]pyridine ring formation by treatment with 2-aminopyridines, (iii) sulfone anion alkylation with epoxides, and (iv) traceless product release by oxidation−elimination (Scheme 1). Since a variety of

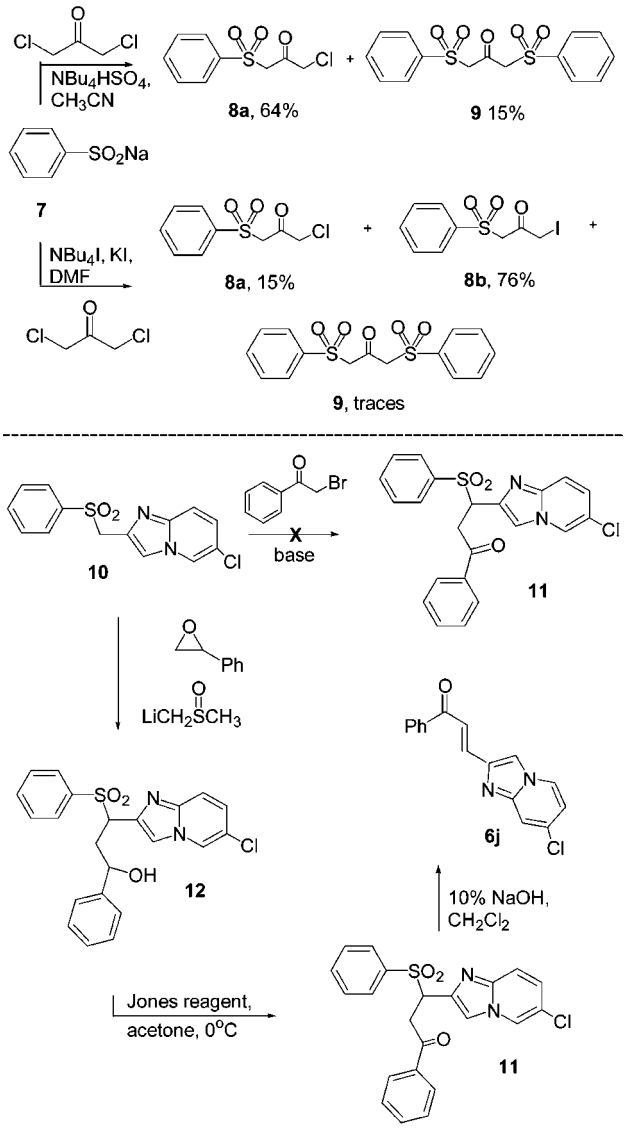
Scheme 1. Sulfinate SPOS to Imidazo[1,2-a]pyridine



reagents can be used in steps ii and iii, the overall strategy appears to be applicable for library generation.

Solution-Phase Synthesis of Imidazo[1,2-a]pyridine. In a preliminary solution-phase study, two reaction systems were analyzed for step i (Scheme 2). Treatment of sodium benzenesulfinate **7** with 1,3-dichloropropan-2-one in the presence of NBu_4HSO_4 and CH_3CN at room temperature gave 1-benzenesulfonyl-3-chloropropan-2-one **8a** and the undesired product, 1,3-bis-benzenesulfonylpropan-2-one, **9** in 64 and 15% yields, respectively. However, replacement of NBu_4HSO_4/CH_3CN with NBu_4I/KI/DMF resulted in almost quantitative formation of **8a** and 1-benzenesulfonyl-3-iodopropan-2-one **8b** and only traces of **9**. Refluxing a 1 equiv mixture of **8a** and **8b** with 2 equiv of 2-amino-5-

Scheme 2. Solution-Phase Study



chloropyridine in anhydrous DME gave 2-benzenesulfonylmethyl-6-chloroimidazo[1,2-a]pyridine **10** in 66% yield. Attempts to α-alkylate **10** with 2-bromoacetophenone under various conditions (NaOEt/THF, NaOEt/MeOH/DMF, BuLi/HMPA/THF, K_2CO_3/DMF, or NaH/NBu_4Br/DMF) did not provide the desired 3-benzenesulfonyl-3-(6-chloroimidazo-[1,2-a]pyridin-2-yl)-1-phenylpropan-1-one **11**, and compound **10** was recovered. To effect the formation of **11**, compound **10** was treated with epoxystyrene according to the procedure of Kurth and co-workers[4b] to provide **12**. Subsequent oxidation with the Jones reagent[8] gave **11**, which was not very stable and thus immediately treated with 10% NaOH to give **6j** in 85% yield. Oxidation of **12** via the Swern oxidation gave less clean products, although the reaction proceeded with concomitant elimination of the sulfone linker.

Solid-Phase Synthesis of Imidazo[1,2-a]pyridine. With the solution-phase synthetic pathway to imidazo[1,2-

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a]pyridine established, we proceeded to develop the solid-phase route to these compounds. Sodium benzenesulfinate resin **1** in NBu_4I/KI/DMF was allowed to react with 1,3-dichloro-propan-2-one at room temperature (Scheme 1). The formation of the supported α-haloketones **2a** and **2b** could be monitored by KBr FTIR for the appearance of a new carbonyl stretch (ν_{max}, 1740 cm^{-1}). Treatment of **2a** or **2b** with substituted 2-aminopyridines in anhydrous DME afforded the imidazo[1,2-a]pyridine resin **3**. This transformation was monitored by FTIR for the disappearance of the carbonyl stretch. Alkylation of resin **3** with epoxides gave resin **4**, which could not be reliably analyzed by FTIR. Hence, we proceeded to oxidize resin **4** with Jones reagent followed by sulfinate elimination with 10% NaOH to release the target molecule from the solid support. To illustrate the versatility of this chemistry, a library of 12 compounds (**6a**−**l**) was prepared (Figure 1). ^1H NMR analysis of these

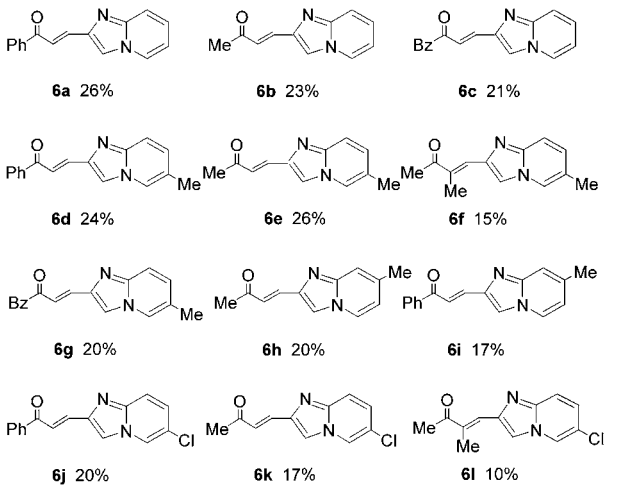


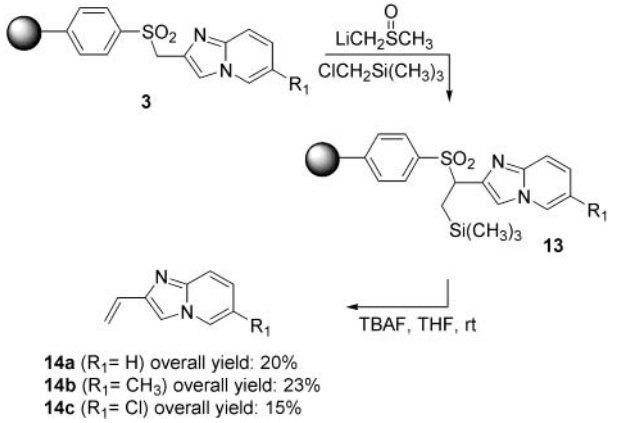
Figure 1. Library of Imidazo[1,2-a]pyridines.

compounds indicates that only the (*E*)-stereoisomer was obtained (J = 15.6 Hz and NOESY data). Except for **6f** and **6l**, the overall yields of all other compounds were 17−26% (purities >95% by NMR), indicating an average yield of greater than 70% for each step of the five solid-phase reactions.

For the alkylation of resin **3** with epoxides, we have used both *cis*-2,3-epoxybutane and *trans*-2,3-epoxybutane in our efforts to eventually obtain **6f** and **6l**. However, we found that the reaction proceeds with *cis*-2,3-epoxybutane but not with *trans*-2,3-epoxybutane. This may presumably be due to the greater steric hindrance in *trans*-2,3-epoxybutane.

In addition to the alkylation via sulfone anion epoxide-opening reaction, we have also examined the use of chloromethyltrimethylsilane as an alkylating agent (Scheme 3).[4b]

Scheme 3. Alkylation via β-Silyl Sulfone Formation



Resin **3** was allowed to react with dimsyl anion (5 equiv) followed by chloromethyltrimethylsilane (10 equiv) in THF. The formation of the β-silyl sulfone resin **13** was easily monitored for the appearance of a new Si−C stretch by KBr FTIR (ν_{max}, 1249 cm^{-1}). The product **14** was cleaved from the resin by treatment with TBAF/THF to provide an overall yield of 15−23%.

In summary, we have developed the first example of a solid-phase synthesis of imidazo[1,2-a]pyridines. The use of a sulfone moiety as a linker in the reaction benefits the solid-phase synthetic route as it not only makes isolation of the product easier but its chemical versatility also adds to the diversity of the library.

Acknowledgment. We thank the National University of Singapore for financial support of this work.

Supporting Information Available: Detailed experimental procedure, NMR and MS data of all compounds, and ^1H and ^{13}C NMR spectra of **6a**, **6f**, **6j**, and **14b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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