Cyclobutenedione Derivatives on Solid Support: Toward Multiple Core Structure Libraries

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With the expectation that small-molecule combinatorial libraries can facilitate the identification of new leads of therapeutic value, interest in small-molecule library synthesis continues to grow.[1,2] In contrast to arrays of biopolymers,[3] these libraries allow greater flexibility of inputs and a wider range of core structures. Many small-molecule libraries[4,5] are designed around a single core scaffold, the diversity of which derives from the number and availability of substituent groups. Using this standard methodology, different compounds are generated by altering the substituents, but all the compounds have the same core structure. To address the diversity of the core scaffold, some approaches involve the use of reaction-based templates[6] or reaction intermediates[7] that can be converted in subsequent steps into a highly diverse set of structures. An alternative strategy to the single-core library is to employ a fluid core structure system to generate a multiple core structure library (MCSL). Varying the core scaffold as well as the substituents further increases the flexibility of small-molecule libraries (see Figure 1).

We have identified the squaric acid derived synthesis of fused aromatic and heteroaromatic cores (Scheme 1) as a reaction platform to generate MCSLs. Transformations involving squaric acid derivatives[8−11] can provide libraries containing two variable sites prior to commitment to a final core structure. For example, quinones, phenols, naphthylfurans,[12] pyrones,[13] indoles, quinolizin-4-ones,[14] and multicyclic systems[15,16] containing identical substituents can be generated from a common precursor. Subsequent manipulation of the differentiated hydroxyls or the use of substituted nucleophiles readily provides a library with up to six variable sites. Described herein is the generation of a multiple core structure library from a single cyclobutenedione-based precursor.

Our first route to generating squaric acid derivatives on a solid support involved a palladium-mediated coupling reaction (Scheme 2). A halogenated aryl ether on Wang resin[17,18] (**1a**), generated through a Mitsunobu reaction, is coupled with

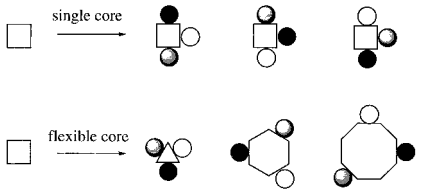
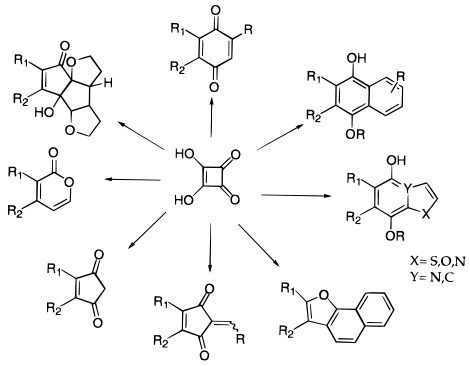
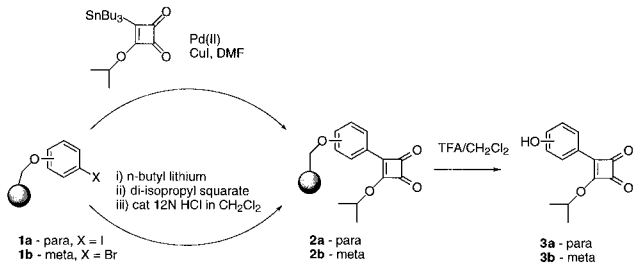


Figure 1. Single core structure libraries generate different compounds by changing the functionalities displayed, while flexible core structure libraries vary not only the functionalities but also the orientation of the display.

Scheme 1. Squaric Acid as a Versatile Precursor to Various Compound Shapes



Scheme 2. Two Routes for 3-Aryl 4-Heteroatom Squarates on Solid Support



tributyltin isopropyl squarate under Stille conditions.[19] This reaction proceeded very well, and after TFA cleavage from the resin, only the expected product **2a** was seen by ^{1}H NMR and ^{13}C NMR with a yield of 95%. A second route was developed which avoids the synthesis of the stannylated squarate. Liebeskind[20] and Moore[21] have synthesized squaric acid derivatives through 1,2-addition to squarates followed by acid-mediated rearrangement. By coupling halogenated phenols to Wang resin, we hoped to generate an anion on solid support through lithium−halogen exchange.[22] Reacting **1a,b** with 10 equiv of *n*-butyllithium in THF at −78 °C for 15 min led to complete exchange of the halogen. After the anion was formed on solid support, it was quenched with excess diisopropyl squarate. The 1,2-addition product rearranged under acid catalysis and was cleaved from the polymer with TFA to give **3a,b**, both proceeding in excellent yields.

We initially completed two versions of resin-mediated synthesis of substituted naphthylenes (Scheme 3). The first (**A**)

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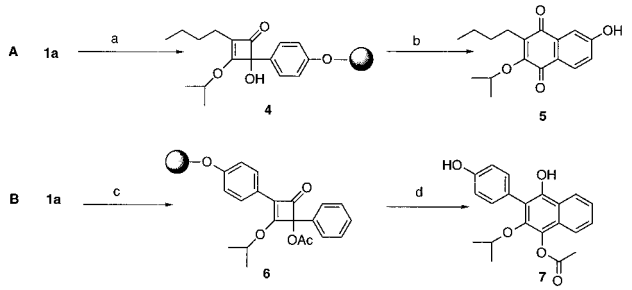
Scheme 3. Naphthyl Products from Squaric Acid Precursors through Two Different Routes[a]



[a] (**A**) (a) *n*-BuLi, THF, −78 °C, 15 min., then 3-(*n*-butyl) 4-isopropoxy squarate 15 min. (i) Toluene reflux in air 20 h. (ii) 20% TFA/DCM. (**B**) (c) (i) *n*-BuLi, THF, −78 °C, 30 min, then di-^{i}Pr squarate, cat. HCl rearrangement. (ii) PhLi, THF, −78 °C, then Ac_2O. (d) (i) Toluene reflux in air 20 h. (ii) 20% TFA/DCM.

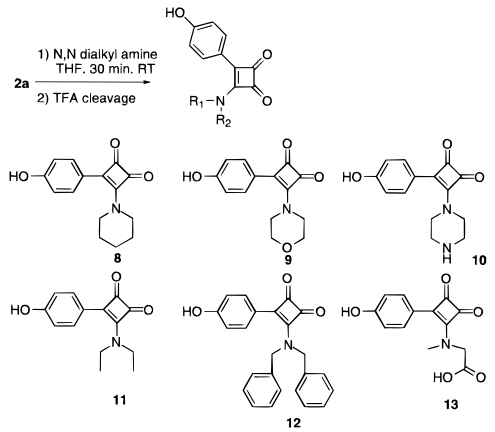


Figure 2. Vinylogous tertiary amines generated on solid support.

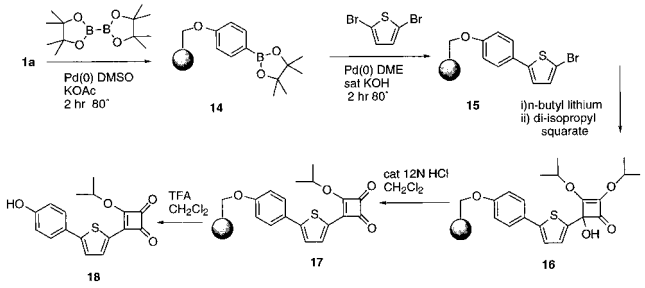
(ion on solid support) involved the condensation of a resin-bound organolithium species with a squaric acid precursor followed by thermolysis and oxidation to generate **5**. The second (**B**) (ion in solution) involved the addition of a solution organolithium compound to a squaric acid derivative covalently linked to the resin, followed by acetylation and thermolysis to generate **7**. Method **A** contains the drawback of requiring scarce, bifunctional, orthogonaly reactive substituents on solid support to generate diverse structures, while method **B** proved difficult to reproduce due to variability of titration with the alkyllithium reagent. To overcome these obstacles, we generated aminated squaric acid derivatives on solid support.

The method of generating the library described below offers two sites of variability previous to commitment to a final core structure. For the first site, we investigated the Michael addition of various mono- and disubstituted amines. Figure 2 shows the disubstituted amine products.[23] Monosubstituted amines (isobutylamine, (3-ethoxypropyl)amine, phenethylamine, 1-(2-aminoethyl)pyrrolidine, and norephedrine) all added to **2a** within 30 min in THF at 23 °C. The products cleaved from the resin showed complete disappearance of the isopropyl group and no imine formation by ^{1}H NMR.

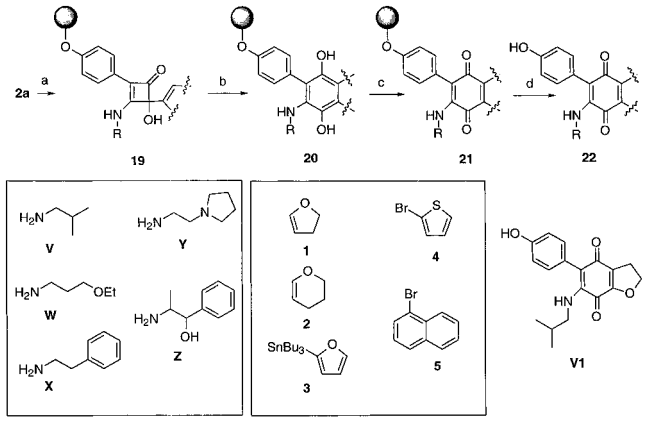
To address variability of the second site, we looked at using Suzuki coupling on solid support[24] to generate biaryl substrates as shown in Scheme 4. To prove this methodology, we coupled 2,5-dibromothiophene to a resin-bound boronate (**14**). Post-coupling lithium−halogen exchange followed by quenching and acid-catalyzed rearrangement gave **18**, which is a substrate for the amination procedure described above. Using this reaction series, we can extend the inputs for this site to include dihalogenated aryl compounds.

A library using the aminated squarates and various lithium ions was produced, as shown in Scheme 5. The monosubstituted

Scheme 4. Reaction Series To Generate Variability at the Second Site before Commitment to Core Structure



Scheme 5. Library Synthesis and Inputs for the 25-Compound Library[a]



[a] (a) (i) Amine **V**−**Z**/THF 30 min. (ii) Ion **1**−**5.** (b) Toluene reflux. (c) Oxidation. (d) 20% TFA/DCM.

amines were used, as they proved effective at directing the ion addition to the vicinal carbonyl **19** in the presence of excess ion. The ions (8 equiv) were added to the resin at −78 °C, stirred for 30 min at −78 °C, quenched with saturated NH_4Cl, rinsed, and heated in refluxing toluene in air. The cleaved products, purified by chromatography, were verified by HRMS. While trapping of the tertiary alcohol intermediate can lead to differentiated hydroquinones, we chose to air oxidize the compounds to recover the 1,4-quinones. The yields[25] ranged from 30 to 50% over seven steps from the Wang-bound iodophenol. The nonaromatic vinyl anion systems had the highest yields due to the lower temperatures required to cyclize the products of the nonaromatic systems. Compared to the other amines, lower yields were observed for norephedrine.

The synthesis of squaric acid derivatives on solid support and the conversion of a single precursor to multiple products has been completed. Aryl isopropyl squarates are generated on solid support though lithium−halogen exchange or Stille coupling, both forming carbon−carbon bonds on solid support. Mono- and disubstituted amines add to aryl isopropyl squarates in a Michael fashion, readily displacing the isopropoxy group, forming vinylogous secondary or tertiary amines. The vinylogous secondary amines allow the selective addition of an ion to the squarate on solid support in the presence of excess ion.

Supporting Information Available: Experimental data (7 pages). See any current masthead page for ordering or Internet access instructions.

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(25) Isolated yields: **V1,** 45%**; W1,** 50%; **X1,** 43%; **Y1,** 53%; **Z1,** 10%; **V2,** 43%; **W2,** 44%; **X2,** 17%; **Y2,** 27%; **Z2,** 12%; **V3,** 5%; **W3,** 14%; **X3,** 13%; **Y3,** 11%; **Z3,** 0%; **V4,** 11%; **W4,** 10%; **X4,** 5%; **Y4,** 5%; **Z4,** 0%; **V5,** 35%; **W5,** 20%; **X5,** 19%; **Y5,** 12%; **Z5,** 11%.