Anodic Synthesis of Euglobal and Robustadial Derivatives in Thermomorphic Electrolyte Solutions

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Euglobal and robustadials were isolated from Eucalyptus spp. as inhibitors of the Epstein-Barr virus activation, or as antimalarial compounds. Previously we reported an electrochemical generation of *o*-quinomethane and their cycloaddition with α-phellandrene to yield the euglobal Ia_1 and Ia_2 skeletons.[1] Furthermore, the first, concise synthesis of natural euglobals has been accomplished by biomimetic cycloaddition of monotermpenes and quinomethanes generated *in situ* by oxidation of grandinol. In this paper, we introduced novel thermomorphic reaction systems that enable high-throughput synthesis of eublobal and robustadial skeletons via intermolecular hetero Diels-Alder reaction of terpenes and anodically generated *o*-quinomethanes.

Construction of biphasic themomorphic reaction systems for high-throughput liquid-phase synthesis

Much of the current research has utilized the solid-phase as a platform for organic reactions. The solid-phase resins offer many advantages with regard to compound isolation and ease of handling. The insoluble nature of the resins has, however, complicated the characterization of compounds attached to them and led to reagent accessibility problems. One successful merging of solid- and liquid-phase chemistry is the use of soluble polymer platforms that selectively remove excess reaction reagents and byproducts. On the other hand, the use of a liquid-liquid biphasic thermomorphic process, in which a reagent or a catalyst is designed as a residue in one of the liquid phases and as a product in the other liquid phase, can be an enabling approach for a commercial application of chemical reactions with high selectivity, efficiency, and ease of handling for the separation of solutes.[2] Based on the immiscibility of perfluorinated hydrocarbons with both organic and inorganic solvents, a novel "fluorous biphasic system" for catalysis has been proposed.[3] On the other hand, the thermomorphic liquid-liquid separation system composed of organic solvents of different polarity might allow for extremely efficient reactions, for example, by the association of apolar products and polar substrates or catalysts in a one-phase solution, which could be spatially separated after the completion of reactions. It should further open the door for the construction of liquid-phase combinatorial chemistry, industrial and green chemistry by the ease of the separation of products, catalyses, reagents, electrolytes, and/or soluble platforms for organic synthesis. This gave us the incentive to explore a novel thermomorphic reaction system using typical organic solvents. We first explored extensively solvent-constructions for the thermomorphic solutions that could be reversibly immixed at "desired" temperatures in "arbitrary ratios" of upper and lower layer volumes. Among numerous compositions of organic solvents, an appropriate mixture of cyclohexane (CH) and nitroalkane (NA) was initially found to show the desired function, that is, a 75:25 (v/v) mixture of CH and NA [a 20:80 v/v mixture of nitromethane (NM) and nitroethane (NE)]. At 25 °C, the solvent mixture was separated into an upper CH(main) phase and a lower NA(main) phase

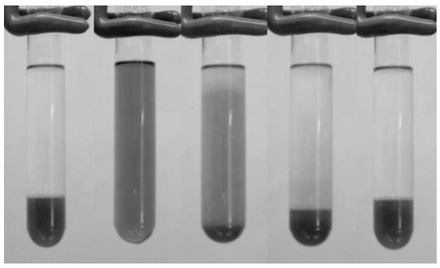

Figure 1. a) An organic solvent mixture composed of CH-NE-NM (75:20:5 v/v/v) formed the biphasic system at 25 °C (a lower NA layer was colored by methylene blue). b) The solvent mixture was immixed at 45 °C. c,d) After cooling back to 25 °C, it immediately began to exclude the CH phase. e) Finally, it formed the initial biphasic solution to recover methylene blue in the lower layer.

(Figure 1, colored by methylene blue, MB). temperature with an increase in the CH ratio to complete the one-phase formation.[4]

Application for the combinatorial synthesis of euglobal and robustadial skeletons

The solvent mixture of CH and NA showed the biphasic thermomorphic property even in the presence of several kinds of catalysts or electrolytes such as lithium perchlorate.[5] The result suggested that a convenient, *liquid-phase reaction and isolation system*, can be constructed under the thermomorphic phase separation and immixing conditions as shown in Figure 2. By using this system, several euglobal and robustadial skeletons could be synthesized just by changing alkenes

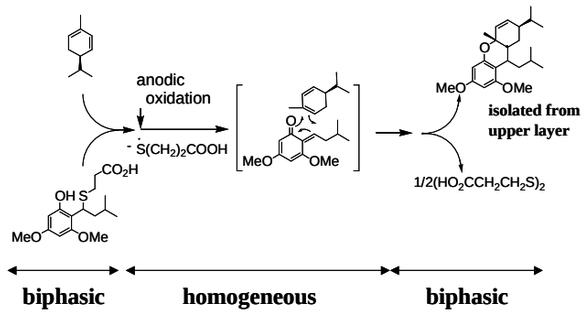

Figure 2. An example for the anodic chroman synthesis using the biphasic thermomorphic system.

(dienophiles for intermolecular hetero-Diels-Alder reaction), and most of the products were isolated from upper layer just by cooling to form the biphasic solution system after the completion of the reaction.

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