Distillable ionic liquids for a new multicomponent reaction*

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Abstract: Adducts of dimethylamine and carbon dioxide form a "distillable ionic liquid" (DIMCARB) that may used as both a reaction medium and catalyst in the direct, atom-economical synthesis of useful synthetic building blocks, such as mono-condensed α,β-unsaturated ketones. The utilization of such building blocks in the synthesis of two new classes of versatile macrocycles, by a sequence of condensation reactions (H_2O by-product), is described. Investigation into the mechanism of action of DIMCARB catalysis and observation of an aniline impurity arising from a competing reaction sequence led to development of a new multicomponent reaction for the direct preparation of 2- or 4-substituted anilines. Some of the macrocycles and anilines are, respectively, supramolecular host compounds and ligands for the preparation of metal complexes.

Keywords: ionic liquids; green chemistry; sustainability; DIMCARB; substituted anilines.

INTRODUCTION

Green chemistry may be described as the philosophy of sustainability applied to the practice of chemistry. Ideally it is a "leave no footprint" approach where the impact on the environment of all parts of the process and product is taken into account. It is useful to consider the chemical value chain of raw materials, transformed via processes to products, which are ultimately disposed of, post use, in one way or another. As is illustrated schematically in Fig. 1, ALL inputs in the form of reagents, auxiliaries, or energy must be taken into account as must ALL outputs in the form of waste, fugative emissions (resulting in pollution), and the product itself, as well as any hazards (e.g., toxic reagents or process hazards).
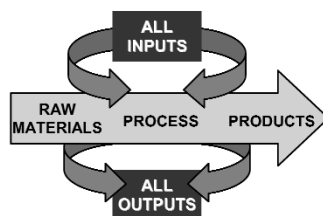

Fig. 1 The desired chemical product is not the only output from a process; all wastes, energy use, and inherent hazards must be considered.

To achieve this holistic approach, it is necessary to develop new tools which may include: auxiliaries such as solvents, catalysts, or reagents; technologies, such as novel modes of chemical activation or heating; new processes, including new reactions designed with the principles of green chemistry in mind; and new products or classes of molecules.

Here we present the progression from applying a self-associated adduct of two gases as a solvent and catalyst to prepare useful synthetic building blocks, leading to new classes of macrocycles (amongst other molecular structures), to a new multicomponent reaction allowing access to a previously somewhat underexplored region of "molecular structure space".

A "DISTILLABLE IONIC LIQUID"

The class of low-temperature molten salts described by the evocative name "ionic liquids" (ILs) is characterized by extremely low vapor pressures [1] and salts which are not readily distillable (although some of the more thermally stable "traditional" ILs may be distilled at reduced pressure [2]). A number of salts, formed by acid/base neutralization reactions, which have low melting points and negligible vapor pressures at ambient temperature, may be distilled by reversal of the salt-forming reaction, i.e., volatilized as their constituent acids and bases [3]. These may be described as switchable solvents, where the "switch" is a proton transfer reaction, Scheme 1. Jessop has described a switchable solvent system in which a mixture of base and alcohol are transformed into an IL upon addition of CO_2 [4], Scheme 2.

$$HA + B \rightleftharpoons A^- + BH^+$$
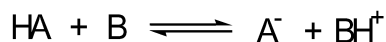
Scheme 1 "Protic ionic liquids" may be formed by acid/base neutralization reactions [3].
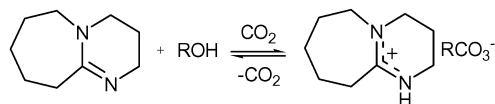
Scheme 2 Jessop's DBU/alcohol/CO_2-based switchable solvent. The reaction with CO_2 to yield the polar liquid salt is reversible by bubbling N_2 through the solvent to remove CO_2 [4].

Self-associating, or reactive systems, based on amines, have been known for some time [5], and one of the simplest is that formed by the exothermic reaction of the gases dimethylamine and carbon dioxide [6]. Simply allowing $(CH_3)_2NH$ and CO_2 gases to come into contact yields an immediate reaction from which a liquid adduct may be condensed, Scheme 3. While this product is frequently described as the salt dimethylammonium dimethylcarbamate **2**, this is clearly not the correct constitution of the liquid, as this salt is a crystalline solid at ambient temperature [7], albeit one which rapidly loses $(CH_3)_2NH$, forming the liquid that is a mixture of the neutral carbamic acid **1** and the salt **2** [8]. Similar salts (or mixtures of salts and carbamic acids) may be formed from a variety of secondary amines, although many are solids at ambient temperature [9].
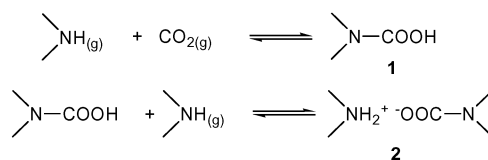
Scheme 3 Reaction between dimethylamine and CO_2 gases yields a liquid, which is a mixture with amine:CO_2 ratio of ca. 1.8:1. Thus, the liquid is composed of the neutral carbamic acid **1** mixed with the ammonium carbamate salt **2**.

While the liquid formed from dimethylamine and CO_2 (DIMCARB) is not, strictly speaking, an IL, if one takes the definition of "composed of 100 % ions" as the basis for the term, it exhibits reasonable conductivity and may be used as both a solvent and electrolyte in electrochemistry [10]. The liquid has been used as an additive in rubber vulcanization [9], an extraction solvent in oil-refining processes [11], and an easily handled and delivered form of methylamine [12] (b.p. 7.4 °C [13]), obviating the need for gas lines and pressurized cylinder storage. Additionally, DIMCARB has been used in the syntheses of ureas [14] and amides [15] and, as a catalyst, in the preparation of silanes [16] and polysilazanes [17].

DIMCARB may be decomposed, reverting to the constituent gases and subsequently rereacted in a condenser, yielding a process that is no more complex than is, effectively, a distillation, Fig. 2. Thus, the liquid has been described as a "distillable ionic liquid" with properties midway between conventional ILs and molecular solvents, as illustrated schematically in Fig. 3 [18].
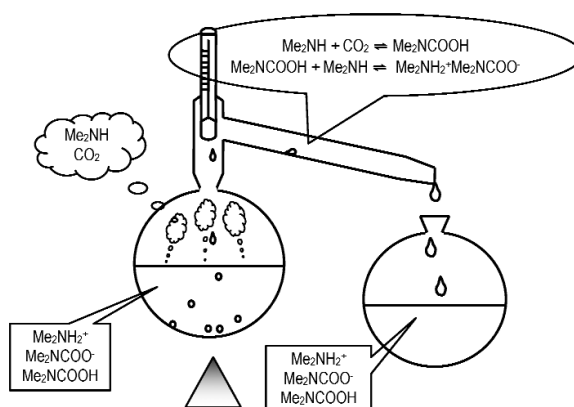

Fig. 2 DIMCARB dissociates into its constituent gases at ca. 60 °C and recombines in the condenser in a process analogous to conventional distillation.
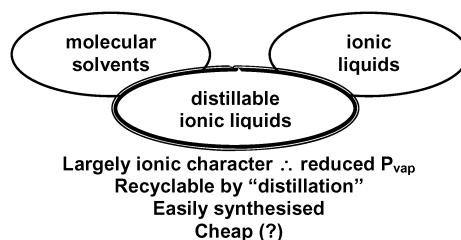

Fig. 3 A liquid that is largely ionic in character (an electrolyte) and yet may be volatilized, exhibits properties of both molecular solvents and ILs. While "cheap" is not to be equated with "green", it is important if the process/solvent/catalyst is to be accepted and used industrially.

## BUILDING BLOCKS FOR COMPLEX MOLECULAR STRUCTURES

As part of a research program to develop direct, green routes to complex molecular structures and hence to greener materials, we required access to mono-substituted α,β-unsaturated ketones **4** derived from symmetrical ketones with two potentially reactive α-methylene groups **3** such as cyclohexanone or cyclopentanone. While the direct condensation of aldehyde and ketone in a Claisen–Schmidt reaction is clearly a desirable route with respect to atom economy (1 mol of water is produced as by-product per mol of product) and energy consumption (the Claisen–Schmidt condensation reaction often proceeds at ambient temperature), it is almost impossible to isolate good yields of the mono-condensed product **4** due to the now enhanced reactivity of the second α-methylene group, which reacts rapidly to form the symmetrical products **5**, Scheme 4 [19].
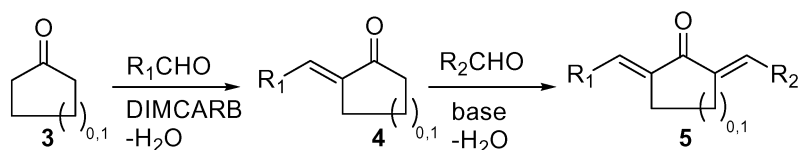
Scheme 4

A number of synthetic approaches to **4** may be applied, with the most oft used requiring the formation of a silyl enol ether. However, this introduces a second reaction step and significantly lowers the atom economy of the reaction [20]. Application of DIMCARB as catalyst and/or solvent allows the preparation of a range of α,β-unsaturated ketones **4** in a single direct reaction, in good to excellent yields [21]. Most reactions proceed at temperatures between 0 and 50 °C, and DIMCARB, which may be used in bulk as a solvent, is recovered post-reaction by distillation.

Indirect evidence, in the form of the identity of isolated by-products, leads to the supposition that the reaction proceeds via an enamine (such as **11**) formed by reaction of dimethylamine with the ketone in a reaction analogous to that employing preformed enamines [22]. The *N,N*-dimethylxanthenamine by-product **10** was isolated (as an HCl salt, post-acid workup) as a significant product from the DIMCARB-mediated reaction of 1-naphthaldehyde **6** with cyclohexanone **7**, and it is proposed that this results from the sequence of reactions depicted in Scheme 5. Preformed enamines have been employed in the synthesis of analogous products [23].
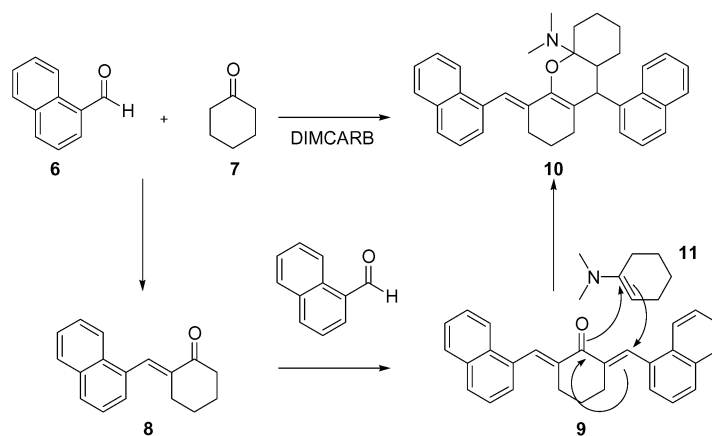
Scheme 5 Proposed route to the *N,N*-dimethylxanthenamine **10** by-product isolated in the DIMCARB-mediated reaction of 1-naphthaldehyde **6** with cyclohexanone **7**.

Enamine intermediates, formed in situ, are described in reactions mediated by the organocatalyst proline [24], and it is noteworthy that this amine/CO_2 (DIMCARB) system is buffered in a similar manner to proline or its derivatives (where an added acid is usually required if nonspecific base catalysis is to be avoided). Shortly after our report of the use of DIMCARB for the direct preparation of mono-substituted α,β-unsaturated ketones from ketones bearing two reactive α-methylene groups, Wang et al. described a proline derivative for similar purposes [25].

With access to the building blocks **4**, it is possible to use a traditional base-catalyzed Claisen–Schmidt condensation to generate unsymmetrically substituted bis(arylidene)cycloalkanones **12** in two atom-economical steps [26]. Application of yet another highly atom-economical reaction, isoaromatization [27], provides variously decorated 2,6-benzyl phenols **13** (Scheme 6) which are of interest as ligands in the formation of main group and lanthanoid metal complexes [28].
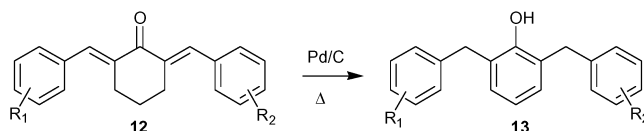
Scheme 6 Isoaromatization of unsymmetrically substituted bis(arylidene)cycloalkanones **12** provides unsymmetrically substituted 2,6-benzyl phenols **13**.

NEW CLASSES OF MACROCYCLES

With a judicious choice of building blocks, direct base-catalyzed condensation reactions, which yield water as a by-product, may be utilized to provide large macrocyclic structures. For example, linking salicylaldehyde moieties by Williamson etherification provides a flexible dialdehyde **14** which may be condensed with cyclohexanones or cyclopentanones to yield macrocycles of varied size and shape, Scheme 7 [29]. The length of the ether linker in **14** defines whether the condensation to the semi-circular macrocycle **15** or the rectangular macrocycle **16** predominates.
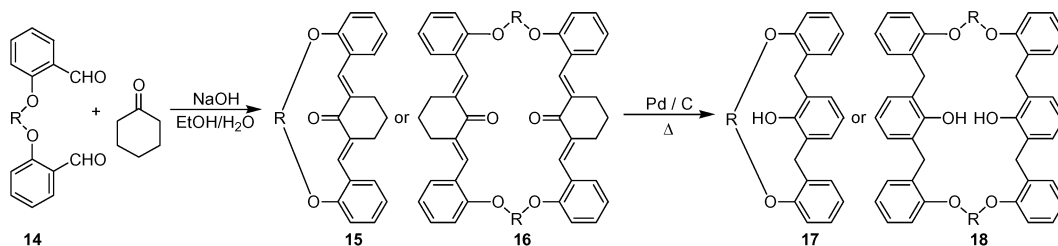
Scheme 7 Synthesis of rigid "dienone-ether" **15**, **16** and Horning-crown macrocycles **17**, **18**.

The rather rigid "dienone-ether" macrocycles **15**, **16** may be isoaromatized to yield Horning-crown macrocycles **17**, **18** (Scheme 7) [30], which exhibit some similar structural elements to the well-known complexing agents and supramolecular hosts crown ethers and calixarenes, Fig. 4. The largely inflexible rectangular dienone-ether macrocycles are transformed into flexible phenol-ether macrocycles, and this is associated by a marked change in physicochemical properties such as solubility. It is possible to alter each structural element: linker, corner piece, and cycloalkanone, and a vast range of molecular motifs become accessible using a series of available building blocks and simple, atom-economical reactions.
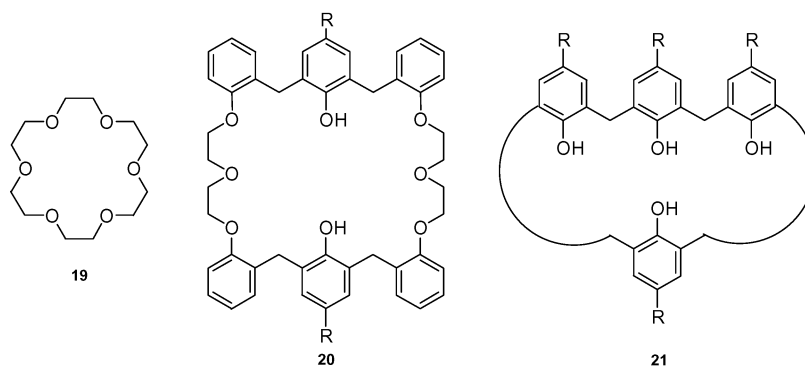
Fig. 4 A crown ether, 18-crown-6 **19**, one of the accessible Horning-crown macrocyclic structures **20** and a calix[4]arene **21**. The Horning-crown macrocycle has some structural elements in common with each of the other two well-known classes of host molecules.

With such a potentially large number of supramolecular host compounds accessible by direct and potentially green synthetic methods, it is of interest to compare the supramolecular chemistry of the semi-rigid dienone ether macrocycles and the flexible Horning-crowns. The former have a tendency to form porous solids (Fig. 5), while the latter may dimerize forming clasped ball-like structures (Fig. 6) [31], which, due to a poor ability to close-pack, tend to include a range of solvent or guest molecules [32].
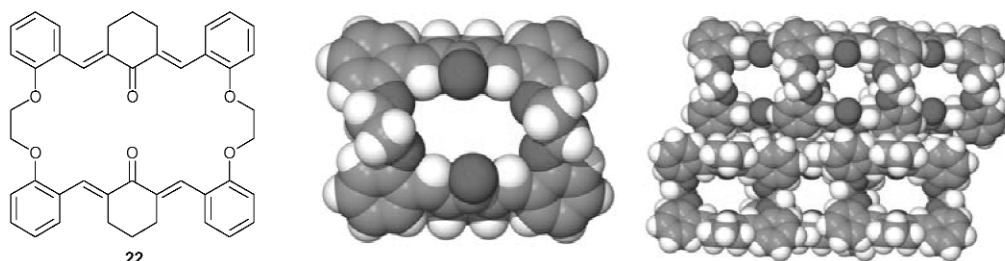

Fig. 5 Ethyl-linked dienone-ether macrocycle **22** has a rectangular shape (middle) which is slightly folded at the ethyl linker. When crystallized from solvents such as acetonitrile/dichloromethane, a solvate results, with guest solvent molecules contained in channels (right; guest molecules are removed to show channels) [29].
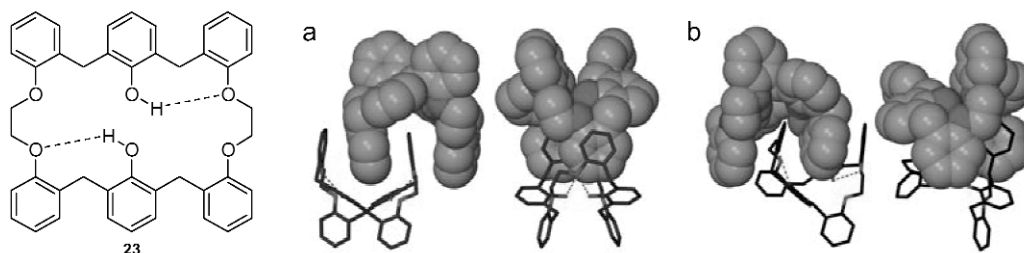

Fig. 6 Horning-crown macrocycle **23** forms clasped dimers [31], which are not readily close-packed and so tend to yield clathrates or inclusion complexes: (a) the symmetrical clasped dimer found in the crystalline pyridine-*d*5 solvate (two views); (b) the twisted clasped dimer formed in inclusion complex crystals with anthracene-9-carboxaldehyde/heptane/DCM complex (two views) [32].

The use of DIMCARB-mediated condensation reactions allows sequential preparation of each side of the macrocycle, allowing for structures with linkers of different lengths or identities. Similarly, different substituents may be included selectively at the corners of one or other side, increasing, yet further, the number of possible macrocyclic structures available from a small number of building blocks. This, combined with the rich supramolecular chemistry displayed by these new classes of macrocycles, is being explored in a number of applications.
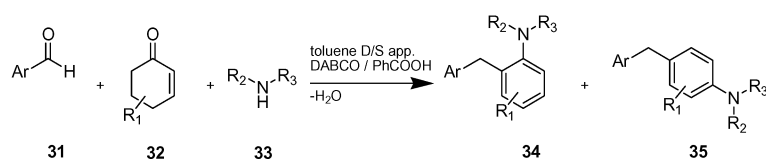
A NEW MULTICOMPONENT REACTION

Following from the direct mono-condensation of aldehyde and ketone to yield α,β-unsaturated ketones and isoaromatization of products to yield phenols, we proposed the DIMCARB-mediated synthesis of "masked phenols" such as **29**, by condensation of cyclohexenone with benzaldehyde derivatives, according to Scheme 8. (The masked phenol **29** would be converted to the phenol **30** in analogous manner to the previously described isoaromatization reactions.) While rather low conversion to **29** was observed, 2-benzyl *N,N*-dimethylaniline (**28**) was isolated as a by-product in 14 % yield. This product is thought to arise from the reaction sequence illustrated in Scheme 8 where aromatization of **27** to yield the aniline **28** competes with hydrolysis, which would yield the desired product **29**.
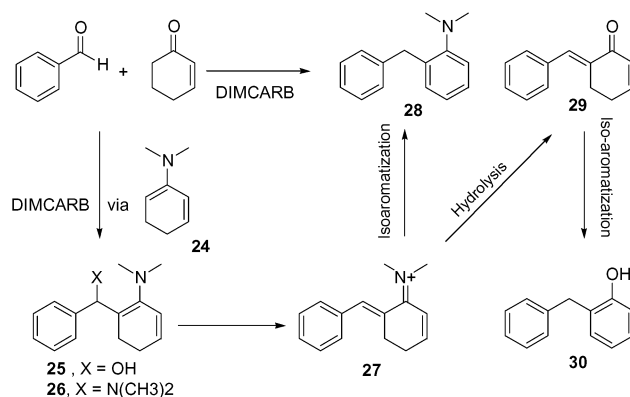
Scheme 8 DIMCARB-mediated reaction of benzaldehyde with cyclohexenone yields a significant quantity of 2-benzyl *N,N*-dimethylaniline **28**.

Exploration revealed that the 3-component coupling reaction of aromatic aldehydes **31**, cyclohexenone derivatives **32**, and primary or secondary amines **33** was best achieved in toluene with water removal and proceeded to give 2- or 4-substituted anilines in varying yields. While relatively few examples of such 2-substituted anilines had been previously reported, molecules of similar structure have been employed as antioxidants in lubricants [33], tested as potential pharmacological agents [34], and used as synthetic precursors [35].

As it was noted that excess base was required to drive the reaction and that the most rapid conversion occurred with benzaldehyde substrates bearing COOH substituents, addition of a strong base and/or acid catalyst was tested, leading to the choice of benzoic acid/DABCO as the most effective combination, both in reaction and post-reaction separation, Scheme 9 [36]. Regioselectivity is reasonably predictable with bulky secondary amines favoring *para* arylmethyl products **35**, while sterically less demanding primary amines tend to yield *ortho* arylmethyl-substituted anilines **34**. The simplicity of the reaction lends itself to the preparation of libraries, and the scope of possible starting materials provides for a wide array of molecular structures previously only accessible by wasteful, multistep synthetic routes.

Scheme 9 Preparation of 2- and 4-arylmethyl *N*- or *N,N*-substituted anilines via a multicomponent reaction [36].

CONCLUSIONS

Using the principles of green chemistry as "design rules" for developing new reactions to known or novel products can lead to innovation that might not occur if "known" transformations are applied. For example: there exists well-developed chemistry for the synthesis of the mono-substituted γ,β-unsaturated ketones described here, but, although easy to apply and widely used, most methods exhibit poor atom economy. Application of DIMCARB (a material described nearly a century ago!) as solvent and catalyst led to a single-step atom-economical route to these useful building blocks. Extension of the methodology to larger molecules provided routes to novel classes of macrocycles with huge potential for structural diversity and thus to useful "green" supramolecular building blocks for development of new materials.

The serendipitous discovery of a multicomponent reaction for the preparation of complex anilines followed from careful analysis of the products of a "failed" reaction, and this, in turn, provided yet another class of structurally rich molecules which may be synthesized by green methodology.

ACKNOWLEDGMENTS

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