ORGANIC LETTERS

2004
Vol. 6, No. 19
3257–3259

# A New Family of Macrocycles Produced by Sequential Claisen–Schmidt Condensations

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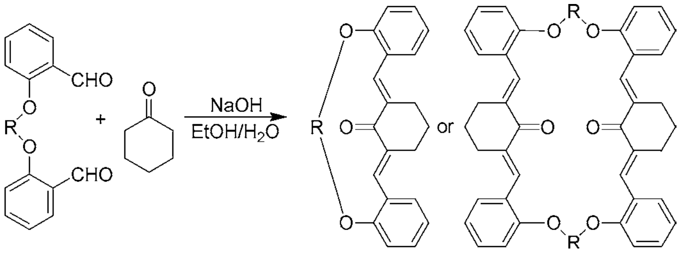
Received June 9, 2004

## ABSTRACT



**Members of a new family of macrocycles have been synthesized in one step, from simple building blocks, by sequential Claisen–Schmidt condensations.**

Claisen−Schmidt condensations proceed under either acid or base catalysis, at moderate temperature, in high atom economy and with water as the sole byproduct.[1−3] Chemoselectivity is also high.[1,2] It was first reported in 1925 that arylaldehydes and cycloalkanones afford predominantly α,α′-bisarylidenecycloalkanones instead of α-monoarylidenecycloalkanones.[4] Subsequent workers have found that this applies even when the ratio of starting ketone to aldehyde is greater than 1:1.[5] The orientation of exocyclic bonds generated is exclusively *trans* with respect to the aryl ring and the carbonyl group of the cycloalkanone.[6] Relative rates for potentially competing processes, including self-condensation of the cycloalkanone and Cannizzaro or Tischenko reactions of aryl aldehydes, are negligible.[1,2] Reported yields have typically been 75% or higher. These attributes suggest that Claisen−Schmidt condensations could be well-suited for green chemistry.[7]

In that regard, the selection of appropriate starting materials for new products and processes also is important. Salicylaldehyde is naturally occurring and is produced in high atom economy by methods including formylation of phenol[8a] and oxidation of *o*-cresol.[8b] Cyclohexanone (a key component in this work) is manufactured in high tonnages, predominantly as a synthetic precursor to caprolactam for nylon manufacture. It has low toxicity and can be prepared by aerial oxidation of cyclohexane[8c] in a process that has seen recent improvements.[9]

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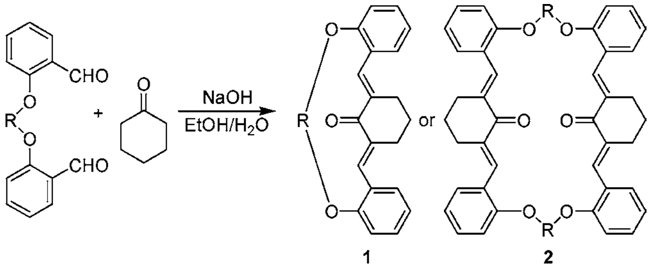
[1] Nielsen, A. T.; Houlihan, W. J. *Org. React. (N.Y.)* **1968**, *16*, 1.
[2] Heathcock, C. H. In *Comprehensive Organic Synthesis*; Fleming, I., Ed.; Pergamon Press: Oxford, 1991; p 133.
[3] Levai, A. *ARKIVOC* **2004**, *vii*, 15, http://arkat-usa.org/ark/journal/2004/Antus/SA-894B/894B.asp
[4] Garland, C. E.; Reid, E. E. *J. Am. Chem. Soc.* **1925**, *47*, 2333.
[5] For example, see: (a) Li, J.-T.; Chen, G.-F.; Wang, J.-X.; Li, T.-S. *Synth. Commun.* **1999**, *29*, 965. (b) Zheng, M.; Wang, L.; Shao, J.; Zhong, Q. *Synth. Commun.* **1997**, *27*, 351. (c) Nivalkar, K. R.; Mudaliar, C. D.; Mashraqui, S. H. *J. Chem. Res., Synop.* **1992**, 98.
[6] (a) Smith, P. J., Dimmock, J. R.; Turner, W. A. *Can. J. Chem.* **1973**, *51*, 1, 1458. (b) Hassner, A.; Mead, T. C. *Tetrahedron* **1964**, *20*, 2201. (c) Huitric, A. C.; Kumler, W. D. *J. Am. Chem. Soc.* **1956**, *78*, 614.
[7] Anastas, P. T.; Warner, J. W. *Green Chemistry−Theory and Practice*; Oxford University Press: Oxford, New York, 1998; p 30.
[8] Szmant, H. H. *Organic Building Blocks for Organic Chemistry*; Wiley: New York, 1989: (a) p 121. (b) p 520. (c) pp 413−414.
[9] For example: Wang, F.; Xu, J.; Liao, S.-J. *Chem. Commun.* **2002**, 626.

10.1021/ol048922k CCC: $27.50

These aspects of the Claisen−Schmidt condensation and green chemistry have been exploited in this work, to produce members of a new family of macrocycles in a single step as shown in Scheme 1.[10] Starting dialdehydes were prepared, in each case by linking two salicylaldehyde molecules, their derivatives or analogues, with flexible linear tethers. Published routes to such compounds (referred to herein as flexible connectors) employed Williamson etherification conditions that required long reaction times (several days at high temperatures),[11] and/or the use of activating groups such as tosylates, and the toxic base HMPA.[12] Typically, literature yields were low to moderate. Our preparations of flexible connectors also employed Williamson etherification. In this work, improved conditions were obtained for etherification, through the use of microwave heating at 220 °C. At worst, comparable, but more usually, improved yields compared to those reported previously were obtained within 6 min on a multigram scale.

**Scheme 1.** Synthesis of Macrocycles by Sequential Claisen−Schmidt Condensations[a]



[a] **1** is favored when $R \geq 7$ atoms and **2** predominates when shorter flexible linkers are employed.

Nonetheless, Williamson etherification is not environmentally benign, owing to stoichiometric amounts of salt formed for each ether linkage. Although progress has been made in some areas of etherification,[13] including from within our laboratories,[14] the need for universally applicable “green” methods to supersede the Williamson methodology remains a major synthetic challenge.

Efficient preparations of the present macrocycles depended upon α-monoarylidenecycloalkanones being more reactive than cycloalkanones toward aldehydes under Claisen−Schmidt conditions.[4,5] Flexible connectors underwent sequential Claisen−Schmidt condensation with cycloalkanones in the presence of base. The products of the reactions were highly dependent on the length of the tethering unit within the flexible connector. When the tethering unit contained seven or more atoms (excluding the oxygen atoms attached to the aryl rings), cyclization occurred through sequential inter- and intramolecular Claisen−Schmidt condensations, at positions α to the carbonyl group (Scheme 1). In cases where the tethering unit contained fewer than seven atoms, it was too short to enable intramolecular cyclization of one flexible connector with one cycloalkanone. Consequently, a macrocyclic ring made up from two cycloalkanone moieties condensed with two connectors resulted, through four sequential Claisen−Schmidt condensations, the first three being intermolecular and the final one being intramolecular.

The syntheses resulted from the propensity for Claisen−Schmidt condensations to proceed predictably and with high chemo-, stereo-, and regioselectivity, as mentioned above. The one-step process delivered 19- to 32-membered macrocyclic rings for the examples presented in Table 1. In that regard, the apparently low to moderate yields obtained already compare favorably with those for other macrocyclic ring-forming processes that may employ more steps.[15] The major byproducts obtained were mixtures of open-chain oligomers of molecular weight higher than that of the macrocycles. Variables including the nature and quantity of catalysts and solvent employed, absolute and relative concentration of reactants, reaction time, and the possibility of templating could influence the yields, which have not yet been fully optimized. Investigations into those aspects are continuing.

**Table 1.** Macrocycles Prepared by Sequential Claisen−Schmidt Condensations

| R | | yield (%) | |
|---|---|---|---|
| | | **1** | **2** |
| -$(CH_2)_8$- | **a** | 22 | |
| -$CH_2(CH_2OCH_2)_2CH_2$- | **b** | 55 | |
| -$(CH_2)_2$- | **c** | | 34 |
| -$(CH_2)_2O(CH_2)_2$- | **d** | | 25 |

Single crystal structures for members of this family of macrocycles were obtained.[16] Macrocycles **1a** and **1b**,

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[10] For examples of chalcone macrocyclizations, see: (a) Rao, M. L. N.; Houjou, H.; Hiratani, K. *Tetrahedron Lett.* **2001**, *42*, 8351. (b) Vogtle, F.; Mayenfels, P.; Luppertz, F. *Synthesis* **1984**, 580.

[11] For example: Simion, C.; Simion, A.; Mitoma, Y.; Nagashima, S.; Kawaji, T.; Hashimoto, I.; Tashiro, M. *Heterocycles* **2000**, *53*, 2459.

[12] Tirado-Rives, J.; Oliver, M. A.; Fronczek, F. R.; Gandour, R. D. *J. Org. Chem.* **1984**, *49*, 1627.

[13] For example: Peng, Y.; Song, G. *Green Chem.* **2002**, *4*, 349 and references therein.

[14] Bagnell, L.; Cablewski, T.; Strauss, C. R. *Chem. Commun.* **1999**, 283.

[15] *Macrocycle Synthesis: A Practical Approach*; Parker, D., Ed.; Oxford University Press: Oxford, New York, 1996.

[16] **Crystal data for 1a**: $C_{28}H_{32}O_3$, $M_r = 416.54$, orthorhombic, space group $P2_12_12_1$, $a = 5.8657(2)$, $b = 13.2154(4)$, $c = 30.0592(10)$ Å, $V = 2330.1(1)$ Å$^3$, $Z = 4$, $D_{calc} = 1.187$ g·cm$^{-3}$, $\mu$(Mo Kα) = 0.075 mm$^{-1}$. Of 5232 unique reflections measured, 2414 $I > 2\sigma(I)$, $R$ indices [$I > 2\sigma(I)$] $R_1 = 0.0627$, $wR_2 = 0.1200$, GoF on $F^2 = 0.901$ for 280 refined parameters and 0 restraints.

[17] **Crystal data for 1b:** $C_{26}H_{28}O_5$, $M_r = 420.48$, orthorhombic, space group $Pna2_1$, $a = 11.4843(2)$, $b = 23.5263(3)$, $c = 8.0456(1)$ Å, $V = 2173.78(5)$ Å$^3$, $Z = 4$, $D_{calc} = 1.285$ g·cm$^{-3}$, $\mu$(Mo Kα) = 0.088 mm$^{-1}$. Of 2743 unique reflections measured, 2139 $I > 2\sigma(I)$, $R$ indices [$I > 2\sigma(I)$] $R_1 = 0.0528$, $wR_2 = 0.1377$, GoF on $F^2 = 1.043$ for 280 refined parameters and 1 restraint.

[18] **Crystal data for 2c:** $(C_{44}H_{40}O_6)_2\cdot(CH_3CN)\cdot(CHCl_3)_{1.5}$, $M_r = 1497.96$, monoclinic, space group $C2/c$, $a = 18.0398(5)$, $b = 8.8290(5)$, $c = 25.0282(2)$ Å, $\beta = 107.302(3)°$, $V = 3805.9(2)$ Å$^3$, $Z = 2$, $D_{calc} = 1.307$ g·cm$^{-3}$, $\mu$(Mo Kα) = 0.187 mm$^{-1}$. Of 4537 unique reflections measured, 1596 $I > 2\sigma(I)$, $R$ indices [$I > 2\sigma(I)$] $R_1 = 0.1016$, $wR_2 = 0.2066$, GoF on $F^2 = 0.951$ for 248 refined parameters and 4 restraints

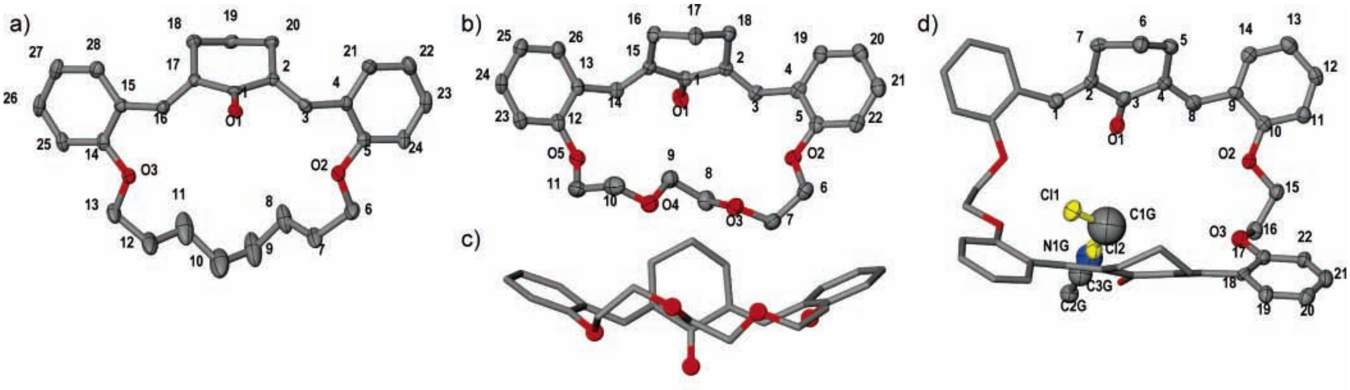

**Figure 1.** Molecular structures and numbering for (a) **1a**, an octylene-linked macrocycle; (b) **1b**, a polyether-linked macrocycle; (c) side view of **1b**, and (d) **2c**, formed by four sequential Claisen-Schmidt condensations and containing disordered mixed solvent ($CH_3CN$ and $CH_2Cl_2$) of crystallization. Atoms of the asymmetric unit are depicted as ellipsoids at the 50% probability level (disordered solvent molecules have sof = 0.25 and 0.375 for $CH_3CN$ and $CH_2Cl_2$, respectively) and hydrogen atoms have been omitted for clarity.

resulting from condensation of cyclohexanone with dialdehydes containing tethers composed of eight atoms, are illustrated in Figure 1a and 1b, respectively. Compound **1b** exhibited a slightly curved three-dimensional flattened-bowl structure (see side view in Figure 1c). Dimeric macrocycle **2c**, resulting from the condensation of two cyclohexanone molecules and two dialdehyde linkers, was approximately square in projection (Figure 1d) and folded at the $(CH_2)_2$ flexible tether hinge to provide a bent host compound that incorporated solvent molecules in the porous channel-type structure formed by stacked hosts, Figure 2. In this example, crystallized from a mixture of acetonitrile and dichloromethane, disordered solvent molecules in the ratio **2c**:$CH_3CN$:$CH_2Cl_2$ 2:1:1.5 occupied the channels and diffused out readily upon removal of the crystals from the mother liquor.

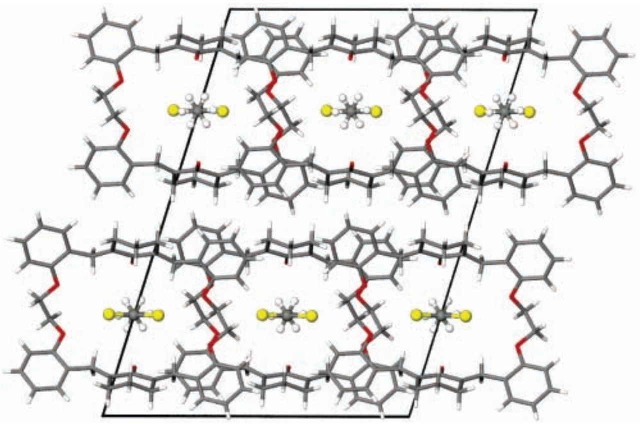

**Figure 2.** Packing diagram of 2**2c**·$CH_3CN$·1.5($CH_2Cl_2$) viewed down (010). Channels accommodate a mixture of guests.

Studies on the host–guest behavior of macrocyclic compounds **1** and **2**, belonging to the family presented herein, will be discussed elsewhere. Importantly, as demonstrated in the following manuscript, **1** and **2** are chameleon-like and can be converted readily by green chemical processes into members of distinctly different classes. Depending upon the transformations conducted, the physical and chemical properties of the new products can differ extensively from those of the present compounds.

**Acknowledgment.** We thank the Australian Research Council, Special Research Centre for Green Chemistry (CGC), Monash University for project funding. CSIRO is thanked for seconding C.R.S. to the CGC.

**Supporting Information Available:** Tables of atomic coordinates, bond lengths and angles, detailed experimental procedures and characterization, and crystal data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

OL048922K