

# Functionalized Cyclobutenes via Multicomponent Thermal [2 + 2] Cycloaddition Reactions

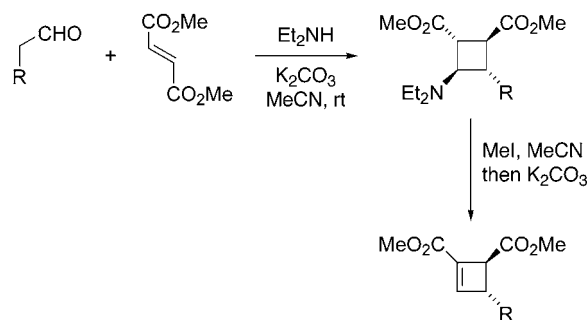
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## ABSTRACT



Enamine [2 + 2] cycloadditions can be achieved in useful yields simply by stirring a mixture of an aldehyde, diethylamine, a dialkyl fumarate, and potassium carbonate in acetonitrile at 25 °C, conditions that are compatible with the presence of a potential leaving group on the  $\beta$ -position of the intermediate enamine. Methylation and elimination of the product cyclobutanes completes a mild nonphotochemical route to functionalized cyclobutenes.

The unique features of the cyclobutene ring have provided a focus for the development of some fundamental structural principles over the years, notably those that underpin the electrocyclic reactions.<sup>1</sup> This has in turn ensured a sustained interest in the preparation of cyclobutenes<sup>2,3</sup> and their exploitation in synthesis, e.g., as diene precursors.<sup>4</sup>

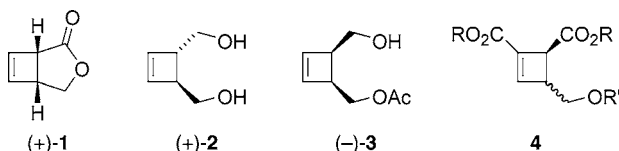
Our interest in this area<sup>5</sup> led us to seek an alternative to the [2 + 2] photoaddition methods<sup>6</sup> that have traditionally provided access to key intermediates such as **1–3**, from which various targets (e.g., geometrically pure polyenes,<sup>5</sup> nucleoside analogues<sup>7</sup>) can be prepared. We were attracted

by the substitution patterns that emerge from the [2 + 2] thermal cycloadditions of enamines to electron-deficient alkenes, a process studied in depth by Brannock et al. some 40 years ago<sup>8</sup> and occasionally exploited for cyclobutene synthesis.<sup>9</sup> We chose to reevaluate this process and herein report that it can be run as a multicomponent reaction<sup>10</sup> under

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(2) (a) *Carbocyclic Four-Membered Ring Compounds*, Houben-Weyl *Methods of Organic Chemistry*; de Meijere, A., Ed.; Thieme: Stuttgart, 1997; Vol. 17f, E17e–f. (b) Negishi, E.-i.; Liu, F.; Choueiry, D.; Mohamud, M. M.; Silveira, A., Jr.; Reeves, M. *J. Org. Chem.* **1996**, *61*, 8325–8328. (c) Liu, F.; Negishi, E.-i. *Tetrahedron Lett.* **1997**, *38*, 1149–1152. (d) Maughon, B. R.; Grubbs, R. H. *Macromolecules* **1997**, *30*, 3459–3469. (e) Kowalczyk, B. A.; Smith, T. C.; Dauben, W. G. *J. Org. Chem.* **1998**, *63*, 1379–1389. (f) Knölker, H.-J.; Baum, G.; Schmitt, O. *Tetrahedron Lett.* **1998**, *39*, 7705–7708. (g) Limanto, J.; Snapper, M. L. *J. Org. Chem.* **1998**, *63*, 6440–6441. (h) Barbero, A.; Cuadrado, P.; Garcia, C.; Rincon, J. A.; Pulido, F. J. *J. Org. Chem.* **1998**, *63*, 7531–7533.

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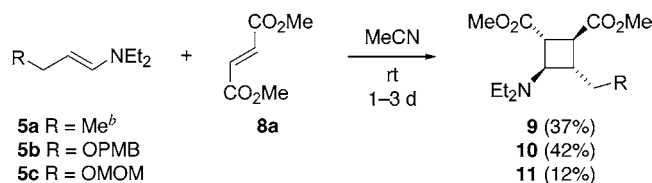


**Figure 1.** Synthetically useful cyclobutene derivatives.

mild conditions that are compatible with the presence of a potential leaving group, viz., a protected hydroxyl, in the enamine component, making it a simple and convenient source of 2-cyclobutene-1,2-dicarboxylates of the form **4**.

In initial experiments we used the conventional method,<sup>8</sup> reacting enamines **5a–c**, prepared by condensation of the respective aldehydes **6a–c** and diethylamine **7a**, with the fumarate **8a** (Scheme 1). Although quantities of the desired

**Scheme 1.** Reactions of Enamines **5** with Dimethyl Fumarate<sup>a</sup>



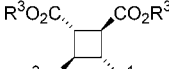
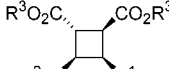
<sup>a</sup> Enamines prepared with  $K_2CO_3$  using the method in ref 8. All yields based on starting aldehyde **6**. <sup>b</sup> The enamine was distilled.

products **9**, **10**, and **11** were obtained, in our hands the sequence suffered from irreproducibility associated with manipulating the enamines, especially **5b** and **5c**.

To address the problems associated with the isolation of enamines, we developed a one-pot, multicomponent variant of these cycloadditions in which the enamine precursors **6**

and **7** are stirred with the diester **8** and potassium carbonate in acetonitrile at room temperature. The results using this mild and straightforward procedure are shown in Table 1.

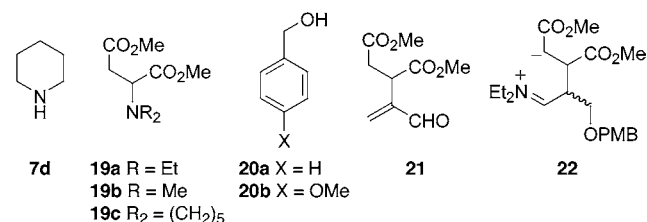
**Table 1.** One-Pot Access to Cyclobutane-1,2-dicarboxylates<sup>a</sup>

$R^1-CHO + R^2NH_2 + \begin{array}{c} CO_2R^3 \\   \\ CO_2R^3 \end{array} \quad \text{or} \quad \begin{array}{c} CO_2Me \\   \\ CO_2Me \end{array}$				
<b>6a</b> $R^1 = Et$ <b>6b</b> $R^1 = PMBOCH_2$ <b>6c</b> $R^1 = MOMOCH_2$ <b>6d</b> $R^1 = BnOCH_2$ <b>6e</b> $R^1 = Ph$	<b>7a</b> $R^2 = Et$ <b>7b</b> $R^2 = Me$ <b>7c</b> $R^2 = Pr^i$	<b>8a</b> $R^3 = Me$ <b>8b</b> $R^3 = Et$	<b>8c</b>	
$\downarrow K_2CO_3, MeCN, rt, 2-3 d$				
				
<b>9-15</b>		<b>16-18</b>		
		<b>R<sup>1</sup></b> <b>9, 16</b> Et <b>10, 17</b> CH <sub>2</sub> OPMB <b>11</b> CH <sub>2</sub> OMOM <b>12, 18</b> CH <sub>2</sub> OPMB <b>13</b> CH <sub>2</sub> OBn <b>14</b> CH <sub>2</sub> OBn <b>15</b> Ph	<b>R<sup>2</sup></b> Et Et Et Et Me Me Me	<b>R<sup>3</sup></b> Me Me Et Et Me Me Me

entry	aldehyde (mmol)	amine (equiv)	ester	isolated products (yield %) <sup>b</sup>	method
1	<b>6a</b> (2.2)	<b>7a</b> (2)	<b>8a</b>	<b>9</b> (65), <b>16</b> (15)	A
2	<b>6b</b> (18)	<b>7a</b> (2)	<b>8a</b>	<b>10</b> (64), <b>17</b> (9)	A
3	<b>6b</b> (0.6)	<b>7a</b> (1)	<b>8a</b>	<b>10</b> (62), <b>17</b> (16)	B
4	<b>6b</b> (0.7)	<b>7a</b> (2)	<b>8b</b>	<b>12</b> (63), <b>18</b> (10)	A
5	<b>6b</b> (0.6)	<b>7a</b> (2)	<b>8c</b>	<b>10</b> (65) <sup>c</sup>	A
6	<b>6c</b> (0.9)	<b>7a</b> (2)	<b>8a</b>	<b>11</b> (39)	A
7	<b>6d</b> (15)	<b>7a</b> (2)	<b>8a</b>	<b>13</b> (58) <sup>c</sup>	A
8	<b>6d</b> (0.9)	<b>7b</b> (1) <sup>d</sup>	<b>8a</b>	<b>14</b> (36), <b>19b</b> (36) <sup>c,e</sup>	A
9	<b>6d</b> (0.9)	<b>7b</b> (1) <sup>d</sup>	<b>8a</b>	<b>14</b> (61) <sup>c</sup>	B
10	<b>6e</b> (1.4)	<b>7a</b> (2)	<b>8a</b>	<b>15</b> (26)	A

<sup>a</sup> Method A: a mixture of **6**, **7**,  $K_2CO_3$  (1 mol per mol of **7**), and **8** (1.2 mol per mol of **6**) in MeCN (1 mL per mmol of **6**) was stirred at room temperature for 2–3 d. Method B: as method A, but with **8** added after 1 h. <sup>b</sup> Yield based on **6**. <sup>c</sup> No other products were investigated. <sup>d</sup> The amine was added as a 2 M solution in THF. <sup>e</sup> Yield based on **8a**.

The initial targets **9–11** were obtained in improved and consistent yields working on various scales (entries 1–6). The products with fumarate **8a** and maleate **8c** (entry 5) were the same, a feature of this type of reaction<sup>8,11</sup> that can be attributed to the rapid isomerization of maleate into fumarate on contact with the enamine or a related species.<sup>12</sup> The minor stereoisomers formed in the cycloadditions with **6a** and **6b**



**Figure 2.** Structures relating to Table 1 and other experiments.

(4) For examples, see: (a) Namyslo, J. C.; Kaufmann, D. E. *Chem. Rev.* **2003**, *103*, 1485–1537. (b) Paquette, L. A.; Geng, F. *Org. Lett.* **2002**, *4*, 4547–4549. (c) Geng, F.; Liu, J.; Paquette, L. A. *Org. Lett.* **2002**, *4*, 71–73. (d) Nicolaou, K. C.; Vega, J. A.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2001**, *40*, 4441–4445.

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(6) (a) Bloomfield, J. J.; Owsley, D. C. *Org. Photochem. Synth.* **1976**, *2*, 36–40 and references therein. (b) Gauvry, N.; Comoy, C.; Lescop, C.; Huet, F. *Synthesis* **1999**, 574–576.

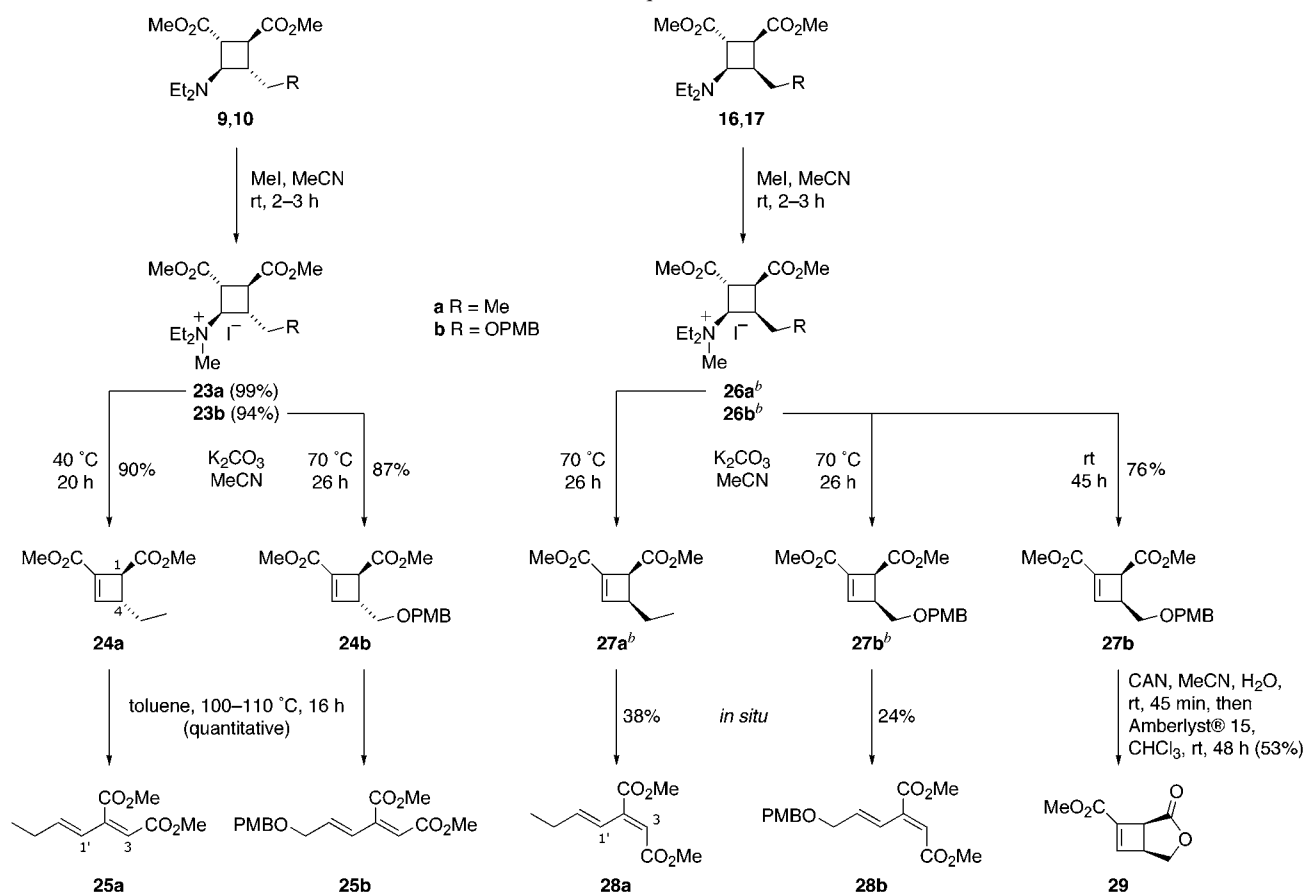
(7) (a) Jung, M. E.; Sledeski, A. W. *J. Chem. Soc., Chem. Commun.* **1993**, 589–591. (b) Gourdel-Martin, M.-E.; Comoy, C.; Huet, F. *Tetrahedron: Asymmetry* **1999**, *10*, 403–410. (c) Pichon, C.; Hubert, C.; Alexandre, C.; Huet, F. *Tetrahedron: Asymmetry* **2000**, *11*, 2429–2434. (d) Hubert, C.; Alexandre, C.; Aubertin, A.-M.; Huet, F. *Tetrahedron* **2002**, *58*, 3775–3778. (e) Gharbaoui, T.; Legraverend, M.; Bisagni, E. *Tetrahedron Lett.* **1992**, *33*, 7141–7144.

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**Scheme 2.** Elimination Sequences with **9**, **10**, **16**, and **17**<sup>a</sup>



<sup>a</sup> CAN = Ce(NH<sub>4</sub>)<sub>2</sub>(NO<sub>3</sub>)<sub>6</sub>. <sup>b</sup> Not isolated pure.

(and probably **6d**) were not observed when using preformed enamines (Scheme 1). Further experiments revealed that the efficiency of the multicomponent method is finely balanced. Imine formation with diethylamine **7a** is evidently rapid, allowing enamine formation and [2 + 2] cycloaddition to compete successfully with the conjugate addition of the amine to the fumarate to produce **19a**. On changing to dimethylamine **7b**, conjugate addition to give **19b** and elimination to give **20a** become more significant (entry 8). These side reactions are inhibited and the yield of **14** improved if the introduction of the fumarate **8a** is delayed for 1 h (entry 9). However, such a delay provided no obvious benefit with **7a** as the amine (entry 3).

In other experiments with the aldehyde **6b**, the use of an additional equivalent of the amine **7a** merely promoted the formation of **19a**, while attempts to use less solvent caused a considerable rise in the yields of the usual byproducts **20b** and **21**. These compounds are presumed to arise via the elimination of **20b** from the zwitterion **22** formed in the first step of the [2 + 2] addition process. In experiments with

**6d**, the use of the hindered amine **7c** led mainly to the elimination product **20a** (63%), whereas the use of piperidine **7d** gave **19c** and **20a** as the only identifiable products.

For the dual purpose of determining the structures of the cycloadducts listed in Table 1 and establishing access to cyclobutenes of the desired type, the cycloadducts derived from aldehydes **6a** and **6b** were taken through Hofmann elimination sequences using mild modifications of known procedures<sup>8,9b</sup> (Scheme 2). Thus, the methylation of **9** gave a crystalline salt **23a** whose stereochemistry was confirmed by X-ray crystallography.<sup>13</sup> The corresponding salt **23b** obtained from **10** was not crystalline but is presumed to be analogous to **9** on the basis of the following observations.

Treating either of the salts **23** with potassium carbonate in acetonitrile gave the respective cyclobutene **24** in good yield, and heating **24a** or **24b** to 100–110 °C brought about thermal electrocyclic ring opening, which yielded a single diene **25** in quantitative yield. The (*Z,E*)-geometry of **25a** and **25b**, evident from their <sup>1</sup>H NMR spectra (H-1' at δ 6.1–6.4 ppm), is consistent with the 1,4-*trans* relationship in **24a**<sup>14</sup>

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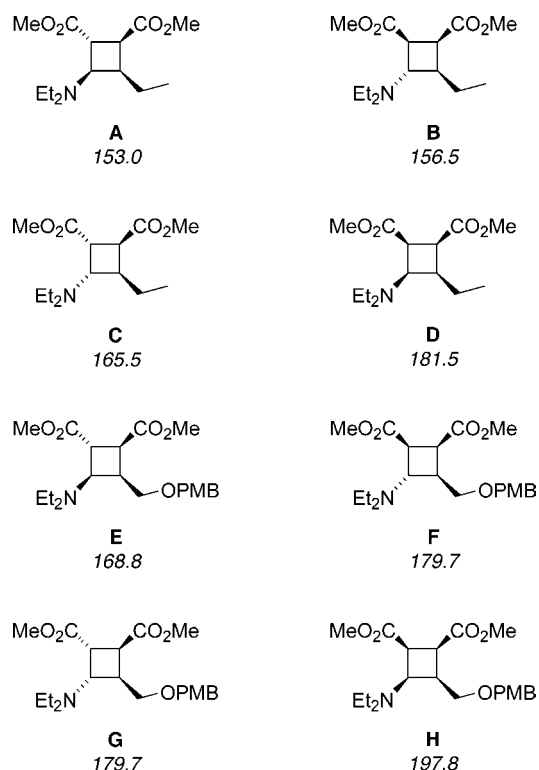
(13) Crystallographic data (excluding structure factors) for compound **22a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 276887. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, U.K. (fax: +44–1223–336033; e-mail: deposit@ccdc.cam.ac.uk).

and **24b**. When the cycloadducts **16** and **17** were taken through the same elimination sequence, the resulting cyclobutenes **27** were different from their analogues **24** and also more prone to electrocyclic ring opening. This lability of **27** compared to **24** and the exclusive (*E,E*)-geometry of the derived dienes **28** (H-1' at  $\delta$  7.3–7.5 ppm) is consistent with a 1,4-*cis* relationship in **27** and illustrates the ability of cyclobutenes bearing substituents with complementary conrotatory preferences to undergo thermal electrocyclic ring-opening with enhanced rates and stereoselectivity.<sup>5</sup> The 1,4-*cis* relationship in **27b** was confirmed by its ready conversion into the lactone **29**.

Although the above sequences confirm the 1,4-*cis* nature of **16** and **17**, the other stereochemical relationships in this pair are open to question. The structures are tentatively assigned as depicted on the basis of computer modeling of the four possible 1,4-*cis* diastereoisomers for each (Figure 3). The structures **A** and **E** are predicted to possess the lowest minimum steric energies in their respective series and would be expected to predominate if formed reversibly or under product development (i.e., kinetic) control.

Although there is evidence in some cases that both steps of the enamine [2 + 2] cycloaddition are reversible,<sup>11</sup> we speculate that the 1,4-*cis* structures **16** and **17** formed in these reactions are a consequence of the presence of (*Z*)-enamines in the reaction mixtures, since they were not observed in reactions with isolated enamines. We saw no decomposition or equilibration of **9** and **16** or **10** and **17** when they were subjected to the conditions of the one-pot procedure, indicating that the first step of the cycloaddition process, i.e., the formation of **22**, is not significantly reversible under these conditions. However, reversibility in the second (ring closure) step is a distinct possibility.

In summary, thermal [2 + 2] cycloadditions of aldehyde-derived enamines to fumarates can be carried out in multi-component fashion by stirring the aldehyde, secondary amine, and fumarate components with potassium carbonate in acetonitrile. The procedure is a convenient source of 4-substituted 3-dialkylaminocyclobutane-1,2-dicarboxylates that can be converted into functionalized cyclobutenes via methylation and elimination. The mildness of the overall sequence is compatible with the use of protected forms of 3-hydroxypropanal as the starting aldehyde and thus provides



**Figure 3.** Calculated minimum steric energies (kJ mol<sup>-1</sup>) of the 1,4-*cis* diastereoisomers of **16** and **17** (Macromodel 8.0, MM3).

access to cyclobutenes with the functionality normally generated using alkyne [2 + 2] photoadditions. Various mechanistic aspects and the synthetic potential of this methodology are under investigation in our laboratory.

**Acknowledgment.** We thank the EPSRC for financial support, and are also grateful to Stacy Lloyd for carrying out preliminary experiments and to Robin Pritchard for the X-ray analysis.

**Supporting Information Available:** Experimental procedures and characterization of compounds, including X-ray data for compound **23a** and molecular modeling parameters (CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(14) The diethyl ester analogous to **24a** was reported by Ichihara et al.,<sup>9a</sup> who wrongly attributed its preparation to Brannock et al.<sup>8</sup>