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$GaCl_3$-mediated acyclic dimerization of donor–acceptor cyclopropanes using 1,2-dipole reactivity

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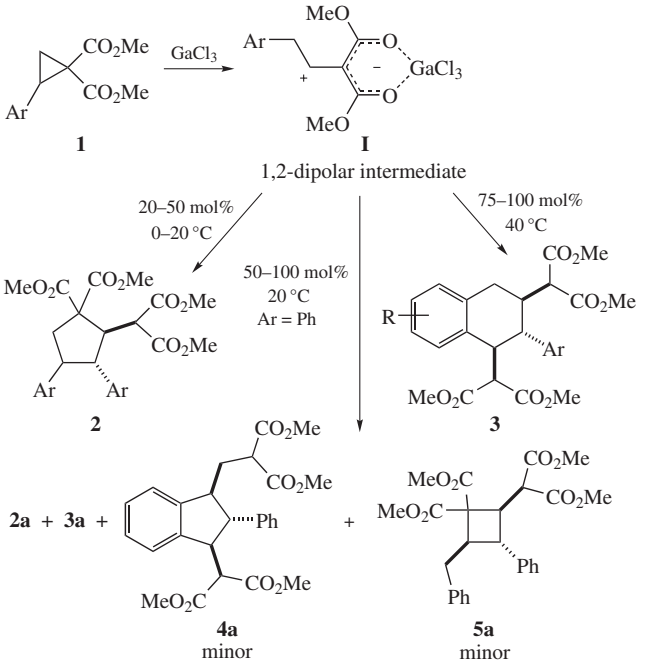
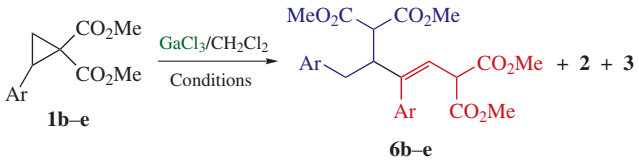
A new type of dimerization of 2-arylcyclopropane-1,1-dicarboxylates in the presence of anhydrous $GaCl_3$ to give acyclic dimers, *viz.*, substituted pent-2-ene-1,1,5,5-tetracarboxylates, occurs at room temperature. In this reaction, one molecule of the donor–acceptor cyclopropane manifests a non-classical reactivity and serves as a 1,2-dipole.

Donor–acceptor cyclopropanes (DACs) are excellent sources for generation of 1,3-dipoles in cycloaddition, annelation and dimerization reactions affording carbo- and heterocycles.[1,2] We have recently reported on $GaCl_3$-catalyzed oligomerization as a new type of DAC reactivity[3–6] where DACs act as sources of formal 1,2- and 1,4-dipoles formed by $GaCl_3$-assisted 'migration' of positive charge. In this way, 2-arylcyclopropane-1,1-dicarboxylates[3,4] underwent [2+2]- and [4+2]-cyclodimerization accompanied by elimination of malonyl moieties.[5,6]

In fact, 2-arylcyclopropane-1,1-dicarboxylates **1** in the presence of $GaCl_3$ readily give 1,2-dipolar gallium complexes **I** that are relatively stable in solution at reduced temperatures (Scheme 1).[3] In the absence of trapping agents, 1,2-dipoles **I** undergo dimerization by several different pathways depending on conditions. At 5–10 °C and with catalytic amounts of gallium trichloride, cyclopentanes **2** are formed due to formal [3+2]-cycloaddition,[3,7] whereas at 40 °C and with an equimolar amount of $GaCl_3$ [4+2]-annelation at the aromatic ring occurs to furnish substituted tetralins **3**.[4] Furthermore, in the case of substrate **1a**, minor dimers **4a** and **5a** were also formed along with compounds **2a** and **3a**[3,4] (see Scheme 1).



Scheme 1



Ar = 4-XC_6H_4
b X = F
c X = Cl
d X = Br
e X = NO_2

Conditions: for **1b–d**, $GaCl_3$ (60 mol%), 20 °C, 2 h; for **1e**, $GaCl_3$ (120 mol%), 35 °C, 3.5 h

Products: **6b** (32%, *Z*/*E* 25:1), **6c** (37%, *Z*/*E* 20:1), **6d** (45%, *Z*/*E* 30:1), **6e** (38%, *Z*/*E* 8:1)

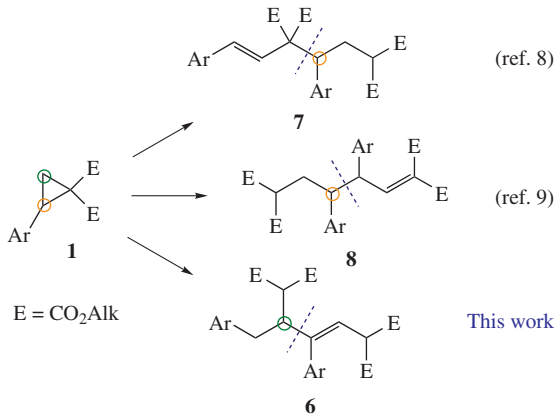
Scheme 2

In this work, we continued studying dimerization of 2-arylcyclopropane-1,1-dicarboxylates **1** in the presence of anhydrous gallium trichloride. The main focus was on the processes occurring at room temperature. We discovered a new type of DAC dimerization to give acyclic dimers **6** (Scheme 2). Dimers of this type were sometimes formed at 40 °C, although in minor or even trace amounts.

Previously, formation of acyclic dimers, namely, substituted hexenes **7** and **8**, in dimerization of 2-arylcyclopropane-1,1-dicarboxylates was reported,[8,9] however, the reaction involved classical 1,3-dipoles (Scheme 3).

We have found that addition of anhydrous $GaCl_3$ (~60 mol%) to a solution of cyclopropanedicarboxylates **1** in dry dichloromethane at 20 °C and keeping the mixture for 2 h considerably raised the yields of acyclic dimers **6**. These yields, however, did not exceed 45% since cyclic dimers **2** and **3** were also formed. The target compounds **6** were isolated by chromatography on silica gel.†

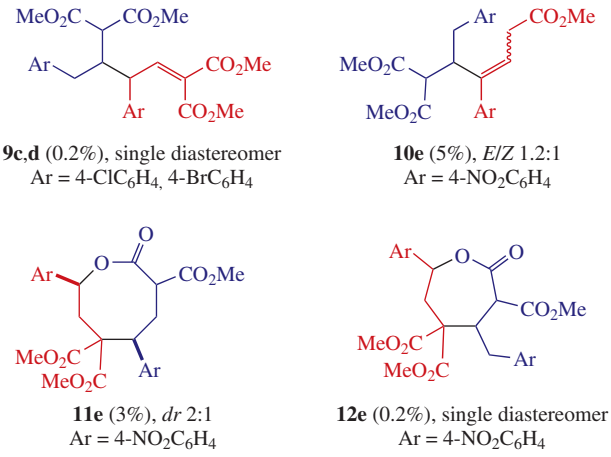
† *Synthesis of dimers* **6b–d** *(general procedure)*. Solid $GaCl_3$ (0.36 mmol, 60 mol%) was added in one portion to a solution of cyclopropane **1b–d** (0.6 mmol) in 5 ml of dry dichloromethane under argon at 20 °C with vigorous stirring. The mixture was stirred at the same temperature for 2 h. After that, aqueous solution of HCl (5%) was added at room temperature until pH 3 was reached and the reaction mixture was extracted with dichloromethane (3×10 ml). The organic layer was dried over $MgSO_4$ and the solvent was removed *in vacuo*. The residue was subjected to column chromatography on silica gel (eluent, benzene to benzene–EtOAc, 5:1) to afford cyclopropane dimers **6b–d**, **2b–d** and **3b–d** as a number of fractions with different purity. The target dimers **6b–d** were additionally purified on a Silufol chromatographic plate (20×20 cm) eluting with hexane–acetone (5:1) or benzene–EtOAc (10:1) to afford the pure product. NMR spectra of compounds **2b–d** and **3b–d** correspond to described earlier.[4,8]



Scheme 3

Dimerization of DACs to give acyclic dimers **6** occurs for rather a narrow scope of aryl-substituted cyclopropanes, mostly for *para*-halo-substituted arylcyclopropanes **1b–d** and *para*-nitro derivative **1e**. For the latter, it was best to effect the process at 35 °C for 3.5 h on using 120 mol% of $GaCl_3$.‡ The selectivity of the formation of acyclic dimers **6** was high enough. In all the cases, the dimers were formed with overwhelming predominance of only one regioisomer and almost fully as *Z*-isomer (Scheme 2). Isomeric dimers with different position of the double bond, namely, pent-1-ene-1,1,5,5-tetracarboxylates **9**, were detected in some cases only and in trace amounts (Figure 1).

On the contrary, *meta*-bromo derivative **1f** reacts oppositely. The yield of acyclic dimer **6f** drops noticeably, while alkylidene-



9c,**d** (0.2%), single diastereomer
Ar = 4-ClC_6H_4, 4-BrC_6H_4

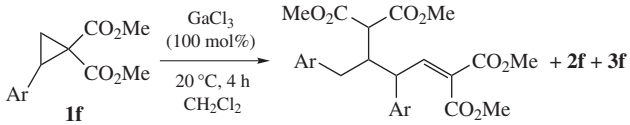
10e (5%), *E*/*Z* 1.2:1
Ar = 4-$NO_2C_6H_4$

11e (3%), *dr* 2:1
Ar = 4-$NO_2C_6H_4$

12e (0.2%), single diastereomer
Ar = 4-$NO_2C_6H_4$

Figure 1

‡ *Dimerization of cyclopropane* **1e** *in the presence of* $GaCl_3$. Solid $GaCl_3$ (127 mg, 0.72 mmol, 120 mol%) was added in one portion to a solution of cyclopropane **1e** (167 mg, 0.6 mmol) in 5 ml of dry dichloromethane at room temperature with vigorous stirring. The mixture was heated to 40 °C and refluxed with stirring for 3 h. After that, aqueous solution of HCl (5%) was added at room temperature until pH 3 was reached and the mixture was extracted with dichloromethane (3×10 ml). The organic layer was dried over $MgSO_4$ and the solvent was removed *in vacuo*. The residue was subjected to column chromatography on silica gel (eluent, benzene to benzene–EtOAc, 5:1) to afford cyclopropane dimers **2e**, **6e** and minor dimers (**10e**–**12e**) as a number of fractions of different purity. The target dimers **2e** and **6e** were additionally purified on Silufol chromatographic plates (20×20 cm) eluting with hexane–acetone (5:1) or benzene–EtOAc (10:1) to give the pure products. Minor and trace dimers (**10e**–**12e**) were isolated with different purity using a number of cascade separations and purifications (up to 4 times) on Silufol chromatographic plates [20×20 cm, eluents, hexane–acetone (5:1) and benzene–EtOAc (10:1)] of the obtained fractions from the main first column chromatography and additional purifications of major dimers.



Scheme 4

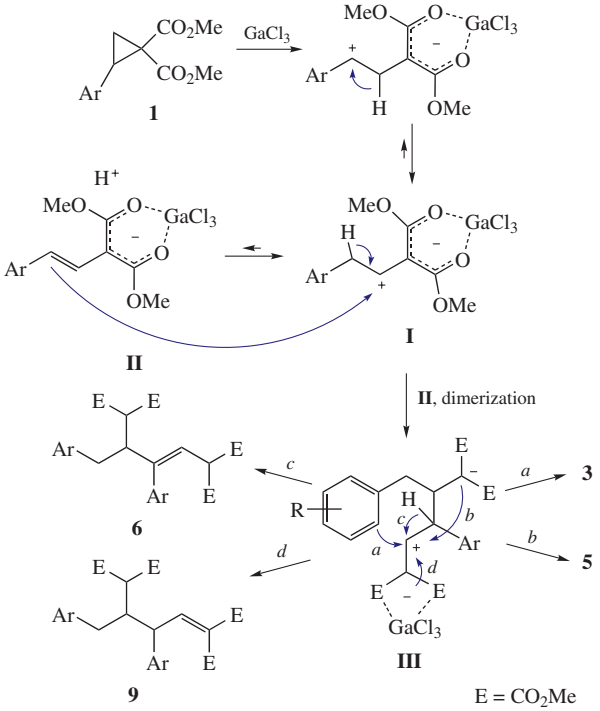
malonate **9f** formed as a single diastereomer becomes the predominating regioisomer (Scheme 4) (see Online Supplementary Materials). As before, cyclic dimers **2f** and **3f** were the main reaction products.

The structures of acyclic dimers **6** and **9** were determined by 1D and 2D COSY, TOCSY, NOESY, HSQC and HMBC ^1H and ^{13}C NMR spectra (see Online Supplementary Materials).

Using *para*-nitro derivative **1e**, we succeeded in isolating and identifying some other minor dimerization products (Figure 1). In fact, in addition to acyclic dimer **6e**, a similar product **10e** lacking one ester group was found (yield ~5%). This fact is not surprising in view of partial hydrolysis and decarboxylation of one geminal ester group. It is interesting that configuration of the double bond changed in this case. In fact, while the *E*- and *Z*-isomers of compound **6e** were formed in 1:8 ratio, this ratio for compound **10e** was ~1.2:1. This effect can be due either to differences in the decarboxylation rates of *E*- and *Z*-**6e** or to additional double bond migration to produce a structure similar to **9e**.

Furthermore, in the case of nitro derivative **6e**, two more products of dimerization involving an ester group were formed, namely, eight-membered and seven-membered cyclic lactones **11e** and **12e**. Note that lactone **11e** is similar to minor (5%) product formed during dimerization of **1b**.[1(k),10] Their structures and relative configurations were determined by 1D and 2D COSY, TOCSY, NOESY, HSQC and HMBC ^1H and ^{13}C NMR spectra (see Online Supplementary Materials) using long accumulation (up to 3 days) due to the small amounts of the compounds.

Formation of new acyclic dimers **6** and **9** allowed us to update and confirm the previously suggested mechanism of DAC dimerization as even-numbered 1,2- and 1,4-dipoles in the reaction with $GaCl_3$.[4] The general mechanism of these processes is presented in Scheme 5. The reactions occur through the relatively stable



Scheme 5

1,2-dipolar intermediate **I** that is generated from cyclopropane in the presence of gallium trichloride. Elimination of a proton from this compound leads to another intermediate, *viz*., coordination-bound styrylmalonate **II** that exists in equilibrium with dipole **I**. Coupling of these species gives aliphatic intermediate **III**, which further undergoes transformations *via* four different pathways (see Scheme 5) depending on the process conditions and the nature of the aryl substituent.

1,4-Cyclization by the malonyl anion results in cyclobutane **5** (pathway *b*), but this minor formation of a strained four-membered ring is unfavourable. The major process involves electrophilic attack at the aromatic ring to yield [4+2]-annelation product **3** (pathway *a*), however, this requires some heating (40 °C). Electrophilic attack under milder conditions occurs poorly, allowing acyclic dimers **6** and **9** to be isolated. Abstraction of a proton from the benzyl moiety in intermediate **III** produces a double bond to afford acyclic dimer **6** as a product (pathway *c*). Dimer **9** is formed upon removal of gallium from intermediate **III** (pathway *d*).

In summary, we discovered a new type of DAC acyclic dimerization that occurs due to formation of a 1,2-dipole in the presence of gallium trichloride.[3,4] This expands the scope of DAC synthetic applicability and allows one to tune reaction centers in the original cyclopropane molecule and to perform controlled syntheses of isomeric products with various topologies of the carbon skeleton.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2015.09.007.

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