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# Gallium(III)-mediated dimerization routes for (5-phenyl-2-thienyl)cyclopropane-1,1-dicarboxylate

**Denis D. Borisov, Roman A. Novikov* and Yury V. Tomilov***

*N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation. Fax: +7 499 135 6390; e-mail: novikovfff@bk.ru; tom@ioc.ac.ru*

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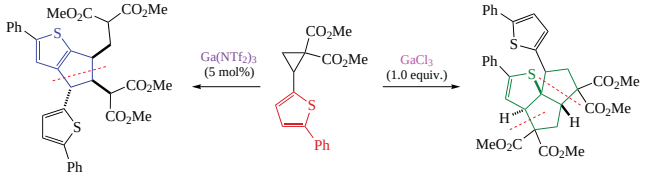
**A selectivity-switched dimerization process for (5-phenyl-2-thienyl)cyclopropane-1,1-dicarboxylate under activation conditions with anhydrous $Ga^{III}$ salts was developed. Using $GaCl_3$ or $Ga(NTf_2)_3$ as catalysts, 3a,4,5a,6,7,8-hexahydro-5*H*-pentaleno[6a,1-*b*]thiophene and 5,6-dihydro-4*H*-cyclopenta[*b*]thiophene derivatives can be selectively obtained as a result of *ipso*-type and [3+2]-annulation type dimerization. The crucial role of a phenyl substituent at position 5 of the thiophene ring and some regularities are discussed.**



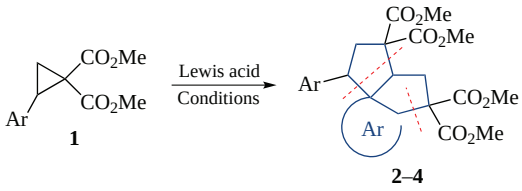

*Keywords*: donor–acceptor cyclopropanes, gallium salts, (thiophen-2-yl)cyclopropane dicarboxylate, *ipso*-dimerization, pentaleno[6a,1-*b*]-thiophenes.

One of the unique capabilities of donor–acceptor (D–A) cyclopropanes[1–8] is that they readily undergo diverse controlled dimerization processes[9] and related reactions.[10,11] As a result, complex polyfunctional compounds are obtained in one stage from available cyclopropane derivatives. Dimerization processes have been comprehensively described for 2-(hetero)aryl-cyclopropane-1,1-dicarboxylates **1**.[9]

One of the most complex cascade dimerization processes is probably the reaction involving an *ipso* attack on the (hetero)-aromatic substituent, in which the molecular complexity of products increases significantly to give fused tri- and tetracyclic systems **2**–**4** (Scheme 1).[12–14] This dimerization type is very interesting. The skeletal moieties of the resulting products are met in various natural compounds and are of interest for medicinal chemistry.[12,13] However, a very limited range of D–A cyclopropanes undergo dimerization of this type, apparently due to the complexity of the process mechanism[12–14] and easier concurrent dimerization of other types. Therefore, expanding the structural range and development of approaches for this reaction appear to be an urgent goal that can enrich the chemistry of D–A cyclopropanes and its synthetic applications.

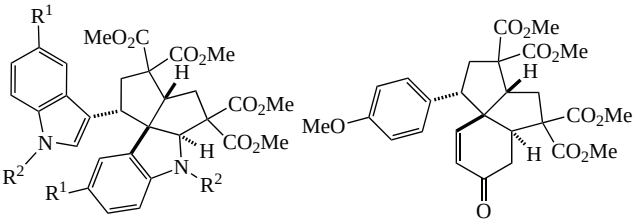
To date, it is known that D–A cyclopropanes with 3-indolyl substituent derivatives (7 examples),[12] one substituted 4-methoxyphenyl[13] and one 1-naphthyl substituted cyclopropane-1,1-dicarboxylate **1**[14] can enter into this domino process (see Scheme 1); the reaction conditions vary considerably.

In this work, we performed rather an extensive study and succeeded in expanding this series of examples with yet another important D–A cyclopropane containing a thienyl substituent as a donor fragment, which opens access to sulfur-containing fused heterocycles. It should be noted that D–A cyclopropanes with thiophene-containing 'donor' substituents have been studied rather widely before,[10,15–17] including their behavior in dimerization reactions.[13,18–20] However, no '*ipso*-type' dimers have been then detected. Dimerization processes along the [3+2]-cycloaddition,[18] [3+2]-annulation,[19] and [3+3]-annulation[13,20] pathways were known for thiophene-containing D–A cyclopropanes.




**2–4**

Ar = 5-$R^1$-1-$R^2$-3-indolyl, 4-$MeOC_6H_4$, 1-naphthyl

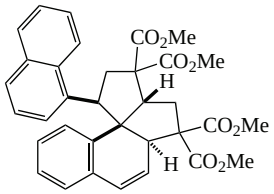



**2** (57–75%, *dr* > 95:5) [i]

$R^1$ = H, F, Cl, Br, CN

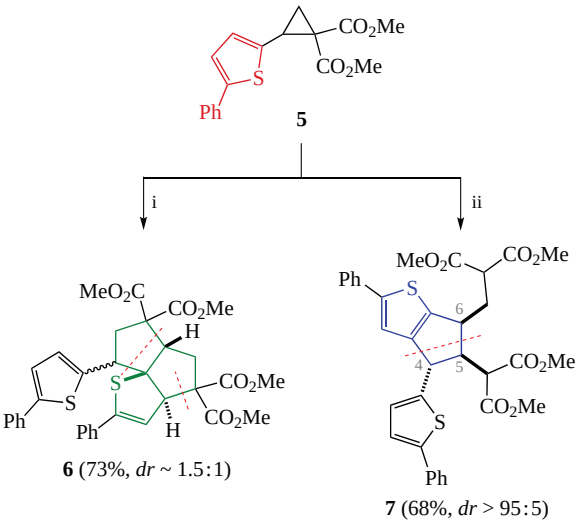
$R^2$ = Me, Bn, $(CH_2)_3Ph$

**3** (30%, *dr* > 95:5) [ii]
(55%, *dr* 4.5:1) [iii]




**4** (50%, *dr* > 95:5) [iv]

**Scheme 1** *Reagents and conditions*: i, $SnCl_4$ (120 mol%), $MeNO_2$, 60 °C, 2–3 h; ii, $SnCl_4$ (150 mol%), $C_6H_6$, 40 °C, 2 h; iii, $GaCl_3$ (20 mol%), 3,5-bis(alkoxycarbonyl)-3,5-dimethyl-1-pyrazoline (20 mol%), $CH_2Cl_2$, –30 °C, 1.5 h; iv, $GaCl_3$ (20 mol%), 3,5-bis(alkoxycarbonyl)-3,5-dimethyl-1-pyrazoline (20 mol%), $CH_2Cl_2$, 30 °C, 1.5 h.




**Scheme 2** *Reagents and conditions*: i, $GaCl_3$ (1.0 equiv.), $CH_2Cl_2$, –20 °C, 15 min; ii, $Ga(NTf_2)_3$ (5 mol%), $HNTf_2$ (1 mol%), PhCl, 130 °C, 60 min.

We succeeded by adding a phenyl substituent into the structure of (2-thienyl)cyclopropane-1,1-dicarboxylate at position 5 of the thiophenyl substituent (a previously unreported D–A cyclopropane **5**) (Scheme 2). This compound was synthesized using the standard synthetic Knoevenagel condensation/Corey–Chaykovsky cyclopropanation from commercially available 5-phenylthiophene-2-carbaldehyde (see Online Supplementary Materials).

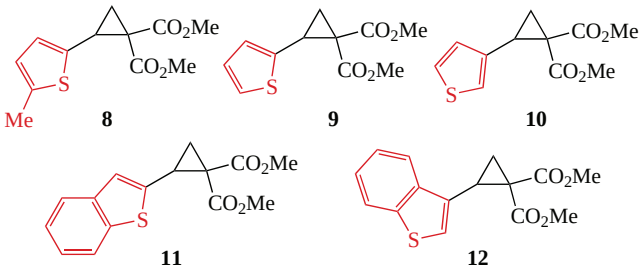
After studying and optimizing the conditions, it was found that cyclopropane **5** could successfully undergo two main types of dimerization, both catalyzed by gallium(III) salts.[21–24] The target '*ipso*-dimer' (3a,4,5a,6,7,8-hexahydro-5*H*-pentaleno-[6a,1-*b*]thiophene skeleton **6**) is regioselectively formed in the presence of anhydrous $GaCl_3$ under controlled mild conditions. Interestingly, compound **6** is formed as a mixture of two diastereomers (~1.5:1), in contrast to the other '*ipso* dimers' where, depending on the type of the substituent in the D–A cyclopropane, one of the diastereomers predominates considerably (see Scheme 1).

In the case of catalysis with anhydrous $Ga(NTf_2)_3$,[20] the dimerization is chemoselectively changed and proceeds as [3+2]-annulation (see Scheme 2) with high 4,5,6-*cis*,*trans* diastereoselectivity to give compound **7** containing the 5,6-dihydro-4*H*-cyclopenta[*b*]thiophene skeleton. This is a known dimerization type,[19,25] but its diastereoselectivity is different (4,5,6-*trans*,*cis*). In particular, this reaction with thiophene derivatives of D–A cyclopropanes is known only for (5-methylthiophen-2-yl)cyclopropane-1,1-dicarboxylate **8**. It was implemented as cross-dimerization with (4-methoxyphenyl)-cyclopropane-1,1-dicarboxylate.[19]

Other Lewis acids that are popular for similar purposes, such as $SnCl_4$, $TiCl_4$, $AlCl_3$, $EtAlCl_2$, $BF_3{\cdot}Et_2O$, $Sn(OTf)_2$ and $Sc(OTf)_3$, give much poorer results and usually bring about complex mixtures with low yields, which, among other things, is due to the rather low stability of the thiophene ring under strongly acidic conditions.

The phenyl substituent at position 5 of the thiophene ring has a decisive effect on the possibility of the *ipso*-type dimerization reaction and apparently directs and stabilizes the transition carbocation intermediates required for it.[12–14] It should be noted that we failed to perform this reaction with other related D–A cyclopropanes **8**–**12** containing a thiophene moiety under any conditions, including those in the presence of gallium salts.

If we consider the key stages of the process mechanism (Scheme 3), the conversion of intermediate **A** into **B** is the step

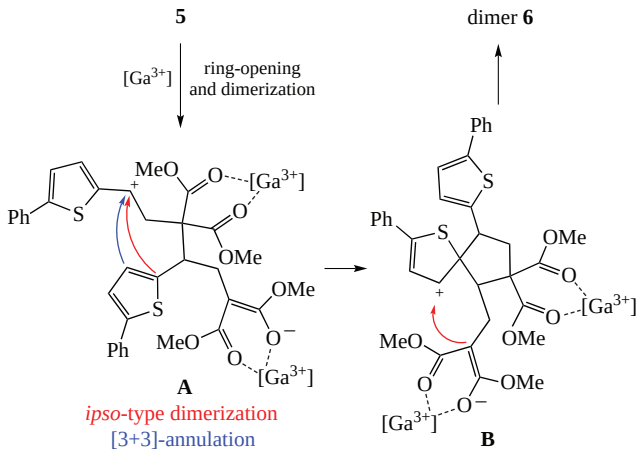



determining the reaction direction.[12–14] Accordingly, electronic and steric factors should direct the cyclization of intermediate **A** to the '*ipso*' position, which explains such a crucial effect of the phenyl substituent at position 5. Moreover, this Ph-substituent stabilizes the carbocationic center formed in intermediate **B**. (It should be noted that the most typical cyclization direction in intermediates of type **A** is cyclization to the '*ortho*' position to produce a six-membered ring in dimers[13,20]).

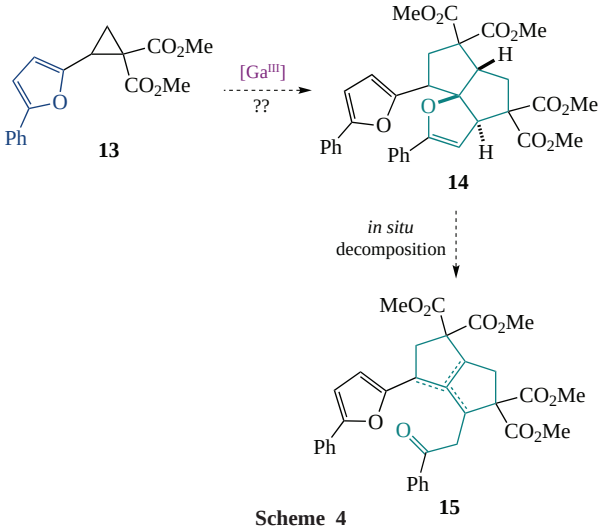
The formation of dihydrocyclopenta[*b*]thiophene **7** occurs *via* a different mechanism[18,19,25] which involves *in situ* isomerization of one D–A cyclopropane molecule into the corresponding styryl malonate[26–28] followed by its annulation. As a rule, the process is determined by the stage of initial isomerization in the presence of less reactive Lewis acids (for example, metal triflates), $Ga(NTf_2)_3$ in this case.

The question on the possible participation of related (5-phenylfuran-2-yl)cyclopropane-1,1-dicarboxylate **13** in the '*ipso*'-type dimerization is still open (Scheme 4). To date, the corresponding dimer **14** has not been isolated from the resulting complex reaction mixtures. The main problem in performing such processes is that the furan ring (even with a stabilizing phenyl substituent) is readily opened in the presence of gallium salts to give 1,4-dicarbonyl compounds, for example, **15**.[29] The structural data are based on NMR studies of the reaction mixtures, the position of the double bond in the cycles of **15** is presented as a mixture of three isomers.

In conclusion, two chemoselective dimerization routes for (5-phenylthiophen-2-yl)cyclopropane dicarboxylate with activation by anhydrous $Ga^{III}$ salts were developed. Using $GaCl_3$ or $Ga(NTf_2)_3$ as catalysts, 3a,4,5a,6,7,8-hexahydro-5*H*-pentaleno[6a,1-*b*]thiophene and 5,6-dihydro-4*H*-cyclo-penta[*b*]thiophene derivatives can be selectively obtained as a result of *ipso*-type dimerization and [3+2]-annulation type dimerization, respectively. The crucial role of the Ph-substituent at position 5 of the thiophene ring has been demonstrated. The data and regularities that we have found may be useful in the further development of the chemistry of D–A cyclopropanes, their controlled cascade reactions, and their further synthetic utilization.




**Scheme 3**




**Scheme 4**

High resolution mass spectra were recorded at the Department of Structural Studies of N. D. Zelinsky Institute of Organic Chemistry of the RAS, Moscow.

*Online Supplementary Materials*

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2022.03.005.

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