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4-Phenylspiro[2.2]pentane-1,1-dicarboxylate: synthesis and reactions with $EtAlCl_2$ and 4,5-diazaspiro[2.4]hept-4-ene derivative

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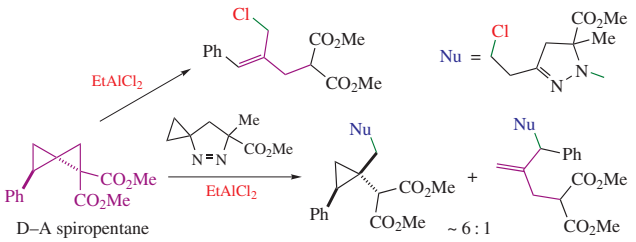
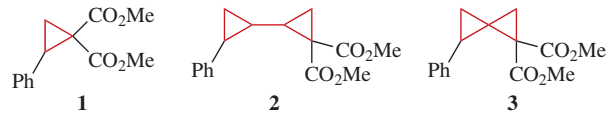
Cyclopropanation of 1-methylidene-2-phenylcyclopropane with dimethyl diazomalonate affords new dimethyl 4-phenylspiro[2.2]pentane-1,1-dicarboxylate. On contact with $EtAlCl_2$, this compound undergoes opening of both cyclopropane rings to give dimethyl (2-chloromethyl-3-phenylallyl)malonate. Its $EtAlCl_2$-assisted reaction with methyl 5′-methylspiro[cyclopropane-1,3′-pyrazoline]-5′-carboxylate proceeds as the 1,3:1′,5′-addition to afford mainly 3-(2-chloroethyl)-1-cyclopropylmethyl-1*H*-pyrazoline derivative.



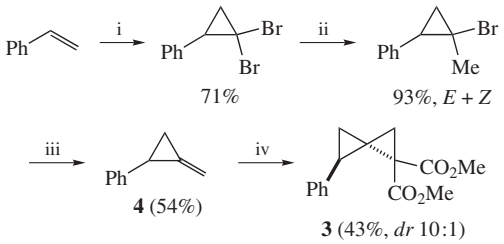
Incorporation of donor and acceptor substituents at vicinal positions of cyclopropane strongly activates this three-membered ring thus ensuring its easy opening.[1] 2-Arylcyclopropane-1,1-dicarboxylates, and primarily phenylcyclopropanedicarboxylate **1**, are among the most abundant donor–acceptor cyclopropanes (DACs).[2–6] Their activation is commonly performed by catalysis with Lewis acids[7–10] to promote reactions with diverse substrates, in particular with N-nucleophiles.[11] Various types of DAC reactivity are also documented.[12,13]

One of the trends of DAC chemistry[14,15] involves expanding the reactive carbocyclic system by adding further three-membered rings with retention of the concept of activation by donor and acceptor substituents. For example, we have recently synthesized new donor–acceptor bicyclopropane **2**[16] which proved to be a highly reactive compound whose bicyclopropyl system was strongly activated due to a favorable arrangement of donor and acceptor substituents and its entire six-membered system could react as an integral whole. Nucleophilic 1,6-addition with the opening of both cyclopropane rings was typical of such a system.[16]



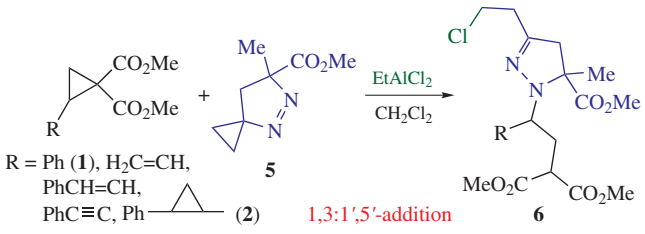
In this work, we concentrated on another novel promising chemotype of similar systems, *viz*., donor–acceptor spiropentanes of type **3**. To obtain the particular compound **3**, we developed a simple and convenient synthetic scheme based on [Rh]-catalyzed cyclopropanation of 1-methylidene-2-phenylcyclopropane **4** with diazomalonate (Scheme 1). Compound **4** was easily synthesized from styrene using reported techniques.[17,18] The target spiropentane **3** is mainly formed as the *trans*-isomer (the *trans*/*cis*-isomer ratio is ~10:1).

The reactivity of donor–acceptor spiropentane **3** was studied in the model reaction of ordinary DACs with spiro[cyclopropanepyrazoline] derivative **5**. Compound **5** is a convenient and reactive substrate that can react with various DACs as 1,3-zwitterions (Scheme 2).[19] With substrate **5**, even bicyclopropane **2** reacts as a 1,3-zwitterion. In this process, spiro[cyclopropanepyrazoline] **5** also undergoes cyclopropane ring opening that occurs as 1,5-addition.[20,21] The overall process can be represented as 1,3:1′,5′-addition that eventually results in polysubstituted 2-pyrazolines **6** (see Scheme 2).

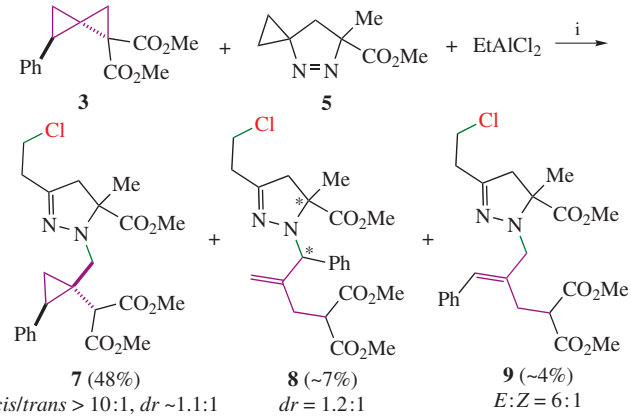


Scheme 1 *Reagents and conditions*: i, $CHBr_3$, NaOH, Et_3BnNCl, EtOH–H_2O; ii, BuLi, then MeI; iii, Bu^tOK, DMSO; iv, $N_2=C(CO_2Me)_2$, $Rh_2(OAc)_4$ (cat.).

In this study, spiropentane **3** also reacted very well with spiro[cyclopropanepyrazoline] **5** in the presence of $EtAlCl_2$ (Scheme 3) when pyrazoline **5** was added as a nucleophile and its cyclopropane ring underwent opening with addition of a chloride anion from the Lewis acid. The reaction afforded a mixture of three products **7**–**9**, indicating different types of reactivity that donor–acceptor spiropentane **3** manifested in their formation. Pyrazoline **7** is the main product (yield up to 48%) that is formed with opening of only one three-membered ring in spiropentane **3**. Note that it is opened with nucleophile addition to the least



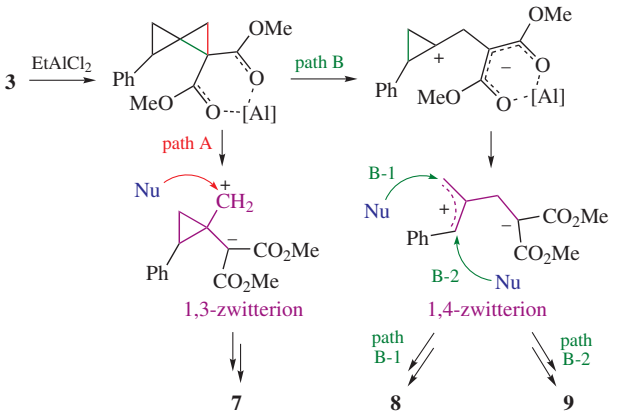
Scheme 2



Scheme 3 *Reagents and conditions*: i, **3**:**5**:$EtAlCl_2$ (1:1.3:2), CH_2Cl_2, 40 °C, 30 min.

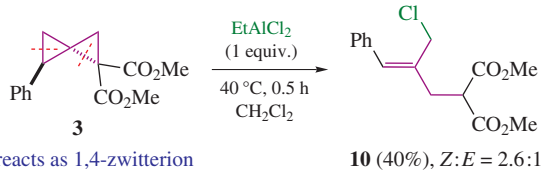
substituted position of the cyclopropanedicarboxylate moiety (Scheme 4, path A and Scheme 5), which is quite untypical of DACs including strongly substituted ones.[1,2–6,19,22] According to ^1H, ^{13}C and 2D NMR spectra, despite three chiral centers, 2-pyrazolines **7** are mainly formed as two diastereomers in approximately equal ratio owing to the retention of the configuration of the phenylcyclopropane moiety (>10:1) that has mainly *trans*-orientation in the starting spiropentane **3**.

The formation of minor co-products **8** and **9** is more interesting. In this process, the entire activated spiropentane system reacts as an integral whole. The two three-membered rings in spiropentane **3** are opened stepwise and in this case DAC acts as a synthetic equivalent of a 1,4-zwitterion (Scheme 4, path B). After coordination of the Lewis acid to both ester groups, the cyclopropane ring bound to them is first opened to give a cyclopropyl cation that is not trapped by the nucleophile but undergoes instant isomerization to the corresponding allylic cation. This cation can subsequently be attacked by the nucleophile (pyrazoline **5**) at two positions to furnish two corresponding unsaturated compounds **8** and **9** in a total yield of ~11% (see Scheme 3).



Scheme 4 Nu is compound **5**.

When the reaction of D–A spiropentane **3** with $EtAlCl_2$ under the same conditions was performed in the absence of nucleophile **5**, 2-(chloromethyl)-3-(phenylallyl)malonate **10** was formed as the main product (see Scheme 5), which was similar in the mode of formation of compound **9**, the very minor product in the reaction with pyrazoline. Thus, opening of both cyclopropane rings mostly occurs on treatment of D–A spiropentane **3** with $EtAlCl_2$: in this case, the 1,3-bond breaks in the acceptor cyclopropane ring and the resulting cyclopropyl cation is instantly converted to an allylic one with addition of a chloride anion from the Lewis acid to the least substituted allyl position of the generated 1,4-zwitterionic intermediate (see Scheme 4, path B-1).



Scheme 5

In conclusion, we synthesized dimethyl 4-phenylspiropentane-1,1-dicarboxylate (a donor–acceptor spiropentane) and studied its reactions with $EtAlCl_2$ both in the absence and in the presence of spiro[cyclopropanepyrazoline] **5**. In the presence of $EtAlCl_2$, a typical process with cleavage of the most substituted 1,3-bond in the spiropentane moiety occurred, which resulted in instant opening of the second cyclopropane ring to give an allylic system. This process also partially occurs if spiro[cyclopropanepyrazoline] is used in the reaction, but the main path of the reaction with pyrazoline is the cleavage of the less substituted 1,2-bond that is non-typical of the majority of DACs, while the second cyclopropane ring remains unchanged.

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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.2019.07.020.

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