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Mendeleev Commun., 2012, **22**, 87–89
Mendeleev Communications

Unusual C-alkylation of pyrazolines with 2-(het)arylcyclopropane-1,1-dicarboxylates in the presence of $GaCl_3$

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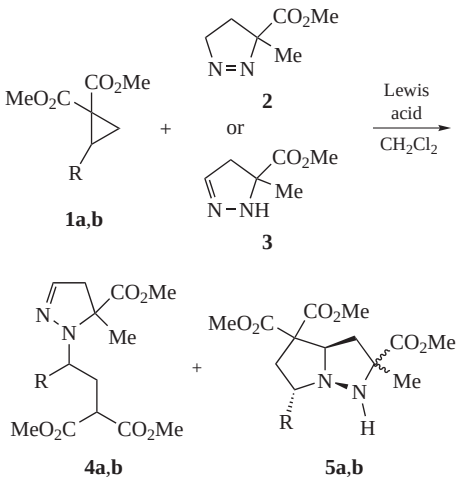
DOI: 10.1016/j.mencom.2012.03.012

The reaction outcome between 2-(het)arylcyclopropane-1,1-dicarboxylates and 1- and 2-pyrazolinecarboxylates in the presence of $GaCl_3$ is temperature-dependent: at 5 °C 1:1 adducts are formed, whereas at 40 °C 2:1 adducts would predominate.

It is known that cyclopropanes bearing electron-donating and electron-withdrawing substituents at the vicinal position can undergo opening of the three-membered ring[1,2] upon thermolysis or under catalysis by Lewis acids. The dipolar intermediate thus resulting can enter formal [2+3]- or [3+3]-cycloaddition with double and triple bonds and with 1,3-dipoles to give five- or six-membered rings, including rings containing heteroatoms.

We have recently found[3] that reactions of 2-substituted cyclopropane-1,1-dicarboxylates **1** with 1- or 2-pyrazolines (such as, *e.g.*, **2** or **3**) are efficiently catalyzed by scandium and ytterbium triflates. The reaction with 1-pyrazolines at 0–5 °C predominantly gives N-substituted 2-pyrazolines **4** (60–95% yields), whereas the reaction with 2-pyrazolines at 20 °C predominantly gives diazabicyclooctanes **5** (Scheme 1). The use of anhydrous $GaCl_3$ also ensured the reaction of cyclopropanedicarboxylates **1** with 1-pyrazolines, but this required an equimolar amount of $GaCl_3$ and cooling to 0 °C, providing exclusively N-substituted 2-pyrazolines **4** being 1:1 adducts. Unlike 1-pyrazolines, the reaction of cyclopropanes **1** with 2-pyrazolines **3** in the presence of $GaCl_3$ was found to be more complex and, *e.g.*, the use of equimolar amounts of **1a**, **3** and $GaCl_3$ afforded a mixture of compounds in which the content of pyrazoline **4a** did not exceed 20%.

These reactions were carried out at temperatures no higher than ambient. However, it was found that even a small temperature increase (to 40 °C) changed the composition of the products and allowed a number of new compounds to be obtained along with monoadducts **4** and **5**. In fact, the reaction of cyclopropane **1a** with 1-pyrazoline **2** in the presence of $GaCl_3$ (molar ratio 1.3:1:1) at 0–5 °C results in N-substituted pyrazoline **4a** in 72% yield along with minor amounts of conversion products of cyclopropane itself.[3,4] As the temperature is increased to 20 °C, other conditions being the same, the yield of compound **4a** decreases to 59%, while substituted pyrazoline **6a**, a product of double addition of cyclopropane **1a** appeared.† Raising the temperature



a R = Ph
b R = 2-thienyl

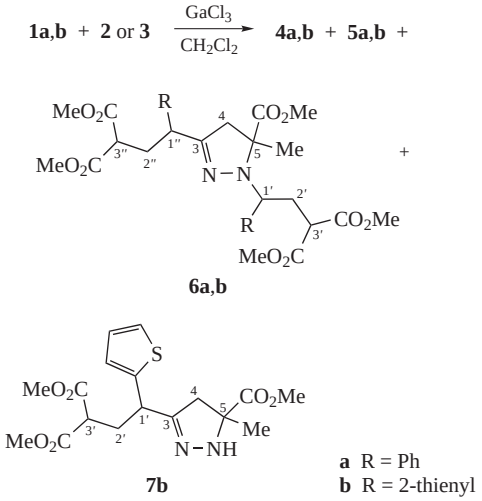
Scheme 1

† ^1H and ^{13}C NMR spectra were recorded on Bruker AMX-400 (400.1 and 100.6 MHz, respectively) and Bruker AVANCE II 300 (300 and 75 MHz, respectively) spectrometers in $CDCl_3$ containing 0.05% Me_4Si as the internal standard. Assignment of ^1H and ^{13}C signals was made with the aid of 1D DEPT-135 and 2D COSY, NOESY, HSQC and HMBC spectra.

General procedure. A solution of $GaCl_3$ (1.45 mmol) in dry dichloromethane (1 ml) was added in one portion under argon to a solution of cyclopropane **1** (1.45 mmol) and pyrazoline **2** or **3** (1.12 or 0.48 mmol; the ratios are specified in Table 1) in dry dichloromethane (5 ml) at a specified temperature and the reaction mixture was stirred for a period of time indicated in Table 1. After that, an aqueous HCl solution (5%) was added at 0 °C to attain pH 3 and the reaction mixture was extracted with dichloromethane (3×10 ml). The organic layers were combined and dried with $MgSO_4$; the solvent was evaporated *in vacuo*. The residue was separated by means of column chromatography on silica gel to isolate pure compounds **4**–**7**.

*Methyl 1,3-bis[4-methoxy-3-(methoxycarbonyl)-4-oxo-1-phenylbutyl]-5-methyl-4,5-dihydro-1*H*-pyrazole-5-carboxylate* **6a**: The residue from the reaction of compounds **1a** (281 mg, 1.2 mmol) and **3** (57 mg, 0.4 mmol) in the presence of $GaCl_3$ (211 mg, 1.2 mmol) carried out at 40 °C for 5 min was purified by column chromatography on silica gel (benzene–EtOAc, 10:1) to give compounds **4a** (9 mg, yield 6%), **5a** (9 mg, yield 6%) and **6a** (190 mg total, yield 78%, as four diastereomers **6aa**–**6ad** in approximately equal amounts; one of these was isolated in individual form and the three others, as a mixture of diastereomers). The isolated compounds **4a** and **5a** were identical to the samples obtained previously.[3]

*(5*R**,1′*R**)*-**6aa**. Thick colourless oil. HRMS calculated for $C_{32}H_{38}N_2O_{10}$, *m*/*z*: $[M+H]^+$, 611.2599; $[M+Na]^+$, 633.2419; $[M+K]^+$, 649.2158. Found, *m*/*z*: 611.2592, 633.2415, 649.2167. ^1H NMR ($CDCl_3$, 400.1 MHz) δ: 0.78 (s, 3H, Me), 2.15 [d, 1H, H_a(4), ^2J 16.7 Hz], 2.35 [ddd, 1H, H_a(2′), ^2J 14.0 Hz, ^3J 9.3 and 4.8 Hz], 2.43 [ddd, 1H, H_a(2″), ^2J 14.6 Hz, ^3J 7.5 and 7.4 Hz], 2.75 [ddd, 1H, H_b(2″), ^2J 14.6 Hz, ^3J 7.5 and 7.4 Hz], 2.80 [ddd, 1H, H_b(2′), ^2J 14.0 Hz, ^3J 10.3 and 5.0 Hz], 3.04 [d, 1H, H_b(4), ^2J 16.7 Hz], 3.50 [dd, 1H, H(1″), ^3J 7.5 and 7.4 Hz], 3.57 [dd, 1H, H(3″), ^3J 7.5 and 7.4 Hz], 3.71, 3.731, 3.735, 3.737 and 3.76 (all s, 5×3H, 5OMe), 3.77 [dd, 1H, H(3′), ^3J 9.3 and 5.0 Hz], 4.28 [dd, 1H, H(1′), ^3J 10.3 and 4.8 Hz], 7.13 [m, 2H, 2*o*-Ph at C(1″)], 7.20 [m, 1H, *p*-Ph at C(1″)], 7.26 [m, 3H, 2*m*-Ph at C(1″) and *p*-Ph at C(1′)], 7.30 [m, 2H, 2*m*-Ph at C(1′)], 7.53 [m, 2H, 2*o*-Ph at C(1′)]. ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ: 22.0 (Me), 32.9 [C(2″)], 36.5 [C(2′)], 44.7 [C(1″)], 46.5 [C(4)], 49.2 [C(3′)], 49.8 [C(3″)], 52.41 (2OMe), 52.44, 52.57 and 52.59 (3OMe), 60.6 [C(1′)], 71.4 [C(5)], 127.27 [*p*-C, Ph at C(1′)], 127.29 [*p*-C, Ph at C(1″)], 128.0 [2*o*-C, Ph at C(1″)], 128.1 [2*o*-C, Ph at C(1′)], 128.3



Scheme 2

to 40 °C results in the rise in the yield of compound **6a** to 24% (Scheme 2). According to ^{1}H and ^{13}C NMR spectra, it is formed as a mixture of four diastereomers in nearly equal amounts. Surprisingly, the use of excess cyclopropane (**1a**:**2** = 3:1) at 40 °C does not alter significantly the ratio of the reaction products (Table 1). Thus, the yield of 1:1 or 2:1 adducts **4a** and **6a** is mostly determined by the process temperature rather than by the ratio of the starting reactants.

Nearly the same behaviour was observed for cyclopropanedicarboxylate **1b** containing a 2-thienyl substituent at the cyclopropane ring. Its reaction with 1-pyrazoline **2** at 5 °C in the presence of an equimolar amount of $GaCl_3$ gave exclusively compound **4b** (Scheme 1). The reaction selectivity decreased at 40 °C, and a number of other compounds were obtained along with compound **4b**, including diadduct **6b**‡ (Scheme 2). However, in this case 3-substituted pyrazoline **7b** (two diastereomers, 1:1),§ was also formed (as distinct from the reaction between **1a** and **2**).

Table 1 Yields of compounds **4**–**7** in $GaCl_3$ catalyzed reactions of cyclopropanes **1a** and **1b** with pyrazolines **2** and **3** (CH_2Cl_2 as the solvent, molar ratio $GaCl_3$: cyclopropane = 1:1).

Cyclopropane	Pyrazoline	Molar ratio	*T*/°C	*t*/min	Yield (%)			
					4a,**b**	**5a**,**b**[a]	**6a**,**b**[b]	**7b**
1a	**2**	1.3:1	5	5	72	—	—	—
		1.3:1	20	5	59	—	9	—
		1.3:1	40	5	47	3 (1:1)	24	—
		3:1	40	5	45	3 (1:1)	28	—
	3	1.3:1	20	5	17	9 (1:3.9)	36	—
		1.3:1	40	5	8	7 (1:6.5)	48	—
		3:1	40	5	6	6 (1:3.5)	78	—
1b	**2**	1.3:1	5	5	72	—	—	—
		1.3:1	40	1	32	24 (1:2.2)	14	11
		3:1	40	1	33	25 (1:1.9)	27	<2
	3	3:1	40	1	14	22 (1:2.1)	49	<2

[a]The numbers in parentheses specify the ratio of *anti*- and *syn*-isomers. [b]A mixture of four diastereomers in nearly equal amounts.

The yield of pyrazoline **4b** remained nearly unchanged in the presence of excess cyclopropane **1b**, whereas the yield of pyrazoline **7b** decreased, which was accompanied by a simultaneous increase in the yield of double addition product **6b** (Table 1). These data, along with the fact that N-substituted pyrazolines **4** and cyclopropanes **1** in the presence of $GaCl_3$ at 40 °C did not give diadducts **6**, indicated that the latter were

[2*m*-C, Ph at C(1′)], 128.9 [2*m*-C, Ph at C(1″)], 140.6 [*i*-C, Ph at C(1″)], 144.1 [*i*-C, Ph at C(1′)], 147.8 [C(3)], 169.95, 170.02, 170.06 and 170.4 (4 COO), 173.6 [COO at C(5)].

*A mixture of diastereomers (5*R**,1′*S**)-***6ab***, *(5*R**,1′*S**)-***6ac*** *and (5*R**,1′*R**)-***6ad***. Thick colourless oil. HRMS calculated for $C_{32}H_{38}N_2O_{10}$, *m*/*z*: $[M+H]^+$, 611.2599; $[M+Na]^+$, 633.2419; $[M+K]^+$, 649.2158. Found, *m*/*z*: 611.2593, 633.2410, 649.2161.

*(5*R**,1′*S**)-***6ab***: ^{1}H NMR ($CDCl_3$, 400.1 MHz), δ: 1.38 (s, 3 H, Me), 2.35 [d, 1H, H_a(4), ^2J 16.8 Hz], 2.39 [m, 1H, H_a(2′)], 2.44 [m, 1H, H_a(2″)], 2.69 [m, 1H, H_b(2″)], 2.75 [m, 1H, H_b(2′)], 2.71 [s, 3 H, OMe at C(5)], 2.85 [d, 1H, H_b(4), ^2J 16.8 Hz], 3.54–3.64 [m, 3 H, H(3′), H(1″) and H(3″)], 3.71, 3.736, 3.739 and 3.77 (all s, 4×3 H, 4 OMe), 4.03 [dd, 1H, H(1′), ^3J 9.9 and 5.5 Hz], 7.17–7.48 (m, 10 H, 2 Ph). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ: 21.5 (Me), 32.4 [C(2″)], 36.5 [C(2′)], 44.6 [C(1″)], 45.8 [C(4)], 49.3 [C(3′)], 49.6 [C(3″)], 50.9 [OMe at C(5)], 52.5 (OMe), 52.60 (2 OMe), 52.62 (OMe), 59.3 [C(1′)], 68.7 [C(5)], 127.2 and 127.4 (2*p*-C), 128.0, 128.2, 128.5 and 128.6 (2×2*o*-C and 2×2*m*-C), 140.2 and 140.6 (2*i*-C), 149.4 [C(3)], 169.9 (COO), 170.0 (3 COO), 172.2 [COO at C(5)].

*(5*R**,1′*S**)-***6ac***: ^{1}H NMR ($CDCl_3$, 400.1 MHz) δ: 1.32 (s, 3 H, Me), 2.35 [d, 1H, H_a(4), ^2J 16.8 Hz], 2.38 [m, 1H, H_a(2′)], 2.44 [m, 1H, H_a(2″)], 2.69 [m, 1H, H_b(2″)], 2.80 [m, 1H, H_b(2′)], 2.86 [s, 3 H, OMe at C(5)], 2.87 [d, 1H, H_b(4), ^2J 16.8 Hz], 3.49–3.62 [m, 3 H, H(3′), H(3″) and H(1″)], 3.727, 3.732, 3.78 and 3.84 (all s, 4×3 H, 4 OMe), 4.07 [dd, 1H, H(1′), ^3J 9.5 and 6.2 Hz], 7.00–7.50 (m, 10 H, 2 Ph). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ: 20.8 (Me), 33.0 [C(2″)], 36.5 [C(2′)], 44.8 [C(1″)], 46.9 [C(4)], 49.4 [C(3′)], 49.9 [C(3″)], 51.3 [OMe at C(5)], 52.50, 52.53, 52.59 and 52.64 (4 OMe), 59.6 [C(1′)], 69.2 [C(5)], 127.2 and 127.5 (2*p*-C), 128.1, 128.4, 128.5 and 128.9 (2×2*o*-C and 2×2*m*-C), 140.4 and 140.5 (2*i*-C), 149.7 [C(3)], 169.8 (COO), 170.0 (3 COO), 172.6 [COO at C(5)].

*(5*R**,1′*R**)-***6ad***: ^{1}H NMR ($CDCl_3$, 400.1 MHz) δ: 0.65 (s, 3 H, Me), 1.89 [d, 1H, H_a(4), ^2J 16.9 Hz], 2.24 [ddd, 1H, H_a(2′), ^2J 14.3 Hz, ^3J 9.6 and 4.4 Hz], 2.39 [m, 1H, H_a(2″)], 2.61 [ddd, 1H, H_b(2′), ^2J 14.3 Hz, ^3J 10.9 and 3.9 Hz], 2.78 [m, 1H, H_b(2″)], 3.08 [d, 1H, H_b(4), ^2J 16.9 Hz], 3.58 [dd, 1H, H(3′), ^3J 9.6 and 3.9 Hz], 3.54–3.62 [m, 2 H, H(1″) and H(3″)], 3.69, 3.71, 3.74, 3.76 and 3.77 (all s, 5×3 H, 5 OMe), 4.22 [dd, 1H, H(1′), ^3J 10.9 and 4.4 Hz], 7.04–7.45 (m, 10 H, 2 Ph).

‡ *Methyl 1,3-bis[4-methoxy-3-(methoxycarbonyl)-4-oxo-1-(2-thienyl)-butyl]-5-methyl-4,5-dihydro-1*H*-pyrazole-5-carboxylate* **6b**: the residue from the reaction of compounds **1b** (240 mg, 1.0 mmol) and **3** (47 mg, 0.33 mmol) in the presence of $GaCl_3$ (176 mg, 1.0 mmol) carried out for 1 min at 40 °C was purified by column chromatography on silica gel (benzene–EtOAc, gradient from 20:1 to 5:1) to give compounds **4b** (18 mg, yield 14%), **5b** (28 mg, yield 22%, a mixture of *anti* and *syn* isomers in a ratio of ~1:2.1) and **6b** {100 mg total, yield 49%, as four diastereomers in approximately equal amounts, two of which [(5*R**,1′*R**)-**6ba** and (5*R**,1′*R**)-**6bb**] were isolated in individual form and the two others, as a mixture of diastereomers}. The isolated compounds **4b** and **5b** were identical to the samples obtained previously.[3]

For NMR spectra of compounds **6ba**–**6bd**, see Online Supplementary Materials.

§ *Methyl 3-[4-methoxy-3-(methoxycarbonyl)-4-oxo-1-(2-thienyl)butyl]-5-methyl-4,5-dihydro-1*H*-pyrazole-5-carboxylate* **7b**: The residue from the reaction of compounds **1b** (165 mg, 0.69 mmol) and **2** (75 mg, 0.53 mmol) in the presence of $GaCl_3$ (122 mg, 0.69 mmol) carried out at 40 °C for 1 min was purified by column chromatography on silica gel (benzene–EtOAc, gradient from 20:1 to 1:1) to give compounds **4b** (65 mg, yield 32%), **5b** (48 mg, yield 24%, as a mixture of *anti* and *syn* isomers in a ratio of ~1:2.2), **6b** (46 mg, yield 14%) and **7b** (22 mg, yield 11%, as a mixture of diastereomers in a ratio of ~1:1). The isolated compounds **4b** and **5b** were identical to the samples synthesised previously.[3]

Compound **7b** (a mixture of two diastereomers in a ratio of ~1:1). Thick colourless oil. HRMS calculated for $C_{17}H_{22}N_2O_6S$, *m*/*z*: $[M+H]^+$, 383.1271; $[M+Na]^+$, 405.1091. Found, *m*/*z*: 383.1267, 405.1084.

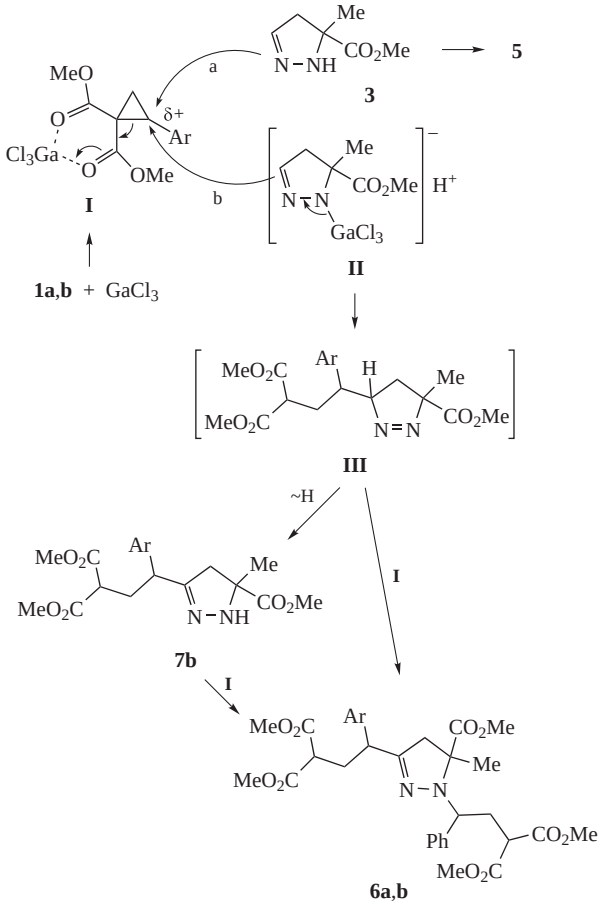
Diastereomer **7ba**: ^{1}H NMR ($CDCl_3$, 400.1 MHz) δ: 1.43 (s, 3 H, Me), 2.45 [d, 1H, H_a(4), ^2J 16.8 Hz], 2.46 [ddd, 1H, H_a(2′), ^2J 13.9 Hz, ^3J 8.2 and 6.6 Hz], 2.64 [ddd, 1H, H_b(2′), ^2J 13.9 Hz, ^3J 8.2 and 7.8 Hz], 3.05 [d, 1H, H_b(4), ^2J 16.8 Hz], 3.43 [dd, 1H, H(3′), ^3J 8.2 and 6.6 Hz], 3.696, 3.72 and 3.741 (all s, 3×3 H, 3 OMe), 3.93 [dd, 1H, H(1′), ^3J 8.2 and 7.8 Hz], 6.05 (br. s, 1H, NH), 6.86 [dd, 1H, H_{thi}(3), ^3J 3.3 Hz, ^4J 1.2 Hz], 6.95 [dd, 1H, H_{thi}(4), ^3J 5.3 and 3.3 Hz], 7.21 [dd, 1H, H_{thi}(5), ^3J 5.3 Hz, ^4J 1.2 Hz]. ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ: 23.7 (Me), 32.6 [C(2′)], 39.8 [C(1′)], 43.5 [C(4)], 49.3 [C(3′)], 52.48, 52.51 and 52.6 [3 OMe], 68.2 [C(5)], 124.7 [C_{thi}(5)], 125.4 [C_{thi}(3)], 126.9 [C_{thi}(4)], 142.8 [C_{thi}(2)], 155.2 [C(3)], 169.2 and 169.3 (2 COO), 175.3 [COO at C(5)].

exclusively formed by insertion of molecules of activated cyclopropanes **1** into the N–H bond of pyrazolines **7**. In turn, the formation of pyrazolines **7** upon increasing the reaction temperature from 5 to 40 °C presumably occurred due to an increase in the rate of isomerization of the starting 1-pyrazoline **2** to 2-pyrazoline **3** and alkylation of the latter at position 3 of the pyrazoline ring. In fact, the yield of diadducts **6a**,**b** increased abruptly if 2-pyrazoline **3** and cyclopropanes **1a** or **1b** were used, and they became the major products (Table 1). In the case of cyclopropane **1a** containing a phenyl substituent, the absence of C-substituted pyrazoline **7a** similar to pyrazoline **7b** in the reaction mixture apparently results from its faster conversion to diadduct **6a** in comparison with pyrazoline **7b**, in which the nucleophilicity of the nitrogen atom for the second alkylation by activated cyclopropane may be lower due to possible coordination of $GaCl_3$ to the sulfur atom of the thienyl moiety.

Thus, the formation of substituted pyrazolines **6** and **7** implies the participation of 2-pyrazoline **3** taken as the reactant or partially formed due to the isomerization of 1-pyrazoline **2**. If the temperature is increased to 40 °C, along with electrophilic attack of activated cyclopropane **I** on the N(2) atom of pyrazoline **3** followed by formation of diazabicyclooctane **5**, activation of the pyrazoline itself can apparently occur to give, *e.g.*, intermediate **II** (Scheme 3). This intermediate undoubtedly manifests an increased nucleophilicity of the C(3) atom of the pyrazoline ring, which in turn allows us to explain the partial formation of 2-pyrazolines substituted at position 3 of the heterocycle due to attack of activated cyclopropane on this molecule position. Further, similarly to 1-pyrazolines,[3] the resulting adducts **III** are either directly converted to 2-pyrazolines **6a**,**b** in the reaction with the second molecule of activated cyclopropane **I**, or first undergo isomerization to 3-substituted 2-pyrazolines **7** followed by alkylation with cyclopropane at the nitrogen atom. If a small excess of thienyl-substituted cyclopropane **1b** is used, 2-pyrazoline **7b** can be isolated from the reaction mixture. The suggested reaction scheme excludes the necessity of involving N-substituted pyrazolines **4** to explain the formation of 1,3-bis-substituted pyrazolines **6a**,**b**.

Note that raising the temperature of the reaction of donor-acceptor cyclopropanes **1a**,**b** with pyrazoline **3** in the presence of $GaCl_3$ not only changes the pyrazoline reactivity to produce compounds **6** and **7** but also modifies the isomeric composition of concurrently formed 1,2-diazabicyclooctanes **5a**,**b** (Table 1), which will be the subject of our next study. It should only be noted in the context of this communication that the formation of 3-substituted pyrazolines **6a**,**b** and **7b** is not related to reactions of isomeric diazabicyclooctanes **5a**,**b**.

Thus, we have discovered yet another pathway of the reaction of activated cyclopropanes with 2-pyrazoline **3** under the action of $GaCl_3$, which occurs on increasing the reaction temperature from 5 to 40 °C and whose driving force may involve not only coordination of the employed Lewis acid to the oxygen atoms of cyclopropanedicarboxylates **1** but also $GaCl_3$ bonding with a pyrazoline molecule with possible replacement of the NH proton and nucleophilicity enhancement of the C(3) heterocycle atom.



Scheme 3

This study was supported by the Ministry of Education and Science (Government Contract no. 02.740.11.0258) and the Division of Chemistry and Materials Science of the Russian Academy of Sciences (Program for Basic Research 'Theoretical and Experimental Study of the Nature of Chemical Bonds and Mechanisms of Important Chemical Reactions and Processes').

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2012.03.012.

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Diastereomer **7bb**: ^{1}H NMR ($CDCl_3$, 400.1 MHz) δ: 1.46 (s, 3H, Me), 2.44 [d, 1H, H_a(4), ^2J 16.8 Hz], 2.43 [ddd, 1H, H_a(2′), ^2J 14.0 Hz, ^3J 8.2 and 7.1 Hz], 2.61 [dt, 1H, H_b(2′), ^2J 14.0 Hz, ^3J 7.8 Hz], 3.09 [d, 1H, H_b(4), ^2J 16.8 Hz], 3.42 [dd, 1H, H(3′), ^3J 7.8 and 7.1 Hz], 3.698, 3.699 and 3.737 (all s, 3×3H, 3OMe), 3.95 [dd, 1H, H(1′), ^3J 8.2 and 7.8 Hz], 6.05 (br.s, 1H, NH), 6.85 [dd, 1H, H_{thi}(3), ^3J 3.4 Hz, ^4J 0.9 Hz], 6.94 [dd, 1H, H_{thi}(4), ^3J 5.2 and 3.4 Hz], 7.19 [dd, 1H, H_{thi}(5), ^3J 5.2 Hz, ^4J 0.9 Hz]. ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ: 23.5 (Me), 32.6 [C(2′)], 39.7 [C(1′)], 43.1 [C(4)], 49.3 [C(3′)], 52.48, 52.51 and 52.6 (3OMe), 68.5 [C(5)], 124.7 [C_{thi}(5)], 125.4 [C_{thi}(3)], 126.9 [C_{thi}(4)], 142.8 [C_{thi}(2)], 155.5 [C(3)], 169.2 and 169.3 (2COO), 175.5 [COO at C(5)].

Received: 5th September 2011; Com. 11/3794