A new example of the three-component reaction: nucleophilic ring opening in cyclopropenones by cyanide ions in the presence of water or alcohols

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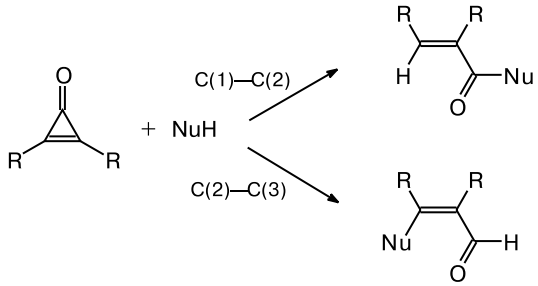
3-Methyl-2,3-diphenyl- and 3-methyl-2-phenylcyclopropenones react with NaCN and water or alcohols as nucleophiles in the presence of $NaHSO_4$ to give novel compounds, namely, 3-cyano-2,3-diphenylpropionic acid or alkyl 3-cyano-2,3-diphenyl- and alkyl 3-cyano-2-methyl-3-phenylpropionates. A reaction mechanism was proposed. The *anti*-(*R***R**)-diastereomer was found to be the major reaction product.

Key words: 2,3-diphenylcyclopropenone, 3-methyl-2-phenylcyclopropenone, nucleophilic opening of the ring, cyanide ion.

Recent interest in the chemistry of cyclopropenones and products of their reactions with various reagents is due to the use of these structures, which are now quite accessible, as building blocks for design of complex molecules with biogenic properties. Some cyclopropenone derivatives are selective inhibitors of cysteine proteinase[1,2] or exhibit antibiotic[3,4] and immunomodulating activities.[5—7]

It is known that cyclopropenones are attacked by a nucleophile on either the carbonyl or the olefin C atom.[8] Reaction intermediates undergo complex multistep transformations often resulting in opening of the three-membered ring *via* cleavage of the C(1)—C(2) or, rarely, C(2)—C(3) bonds[9] (Scheme 1).

Scheme 1

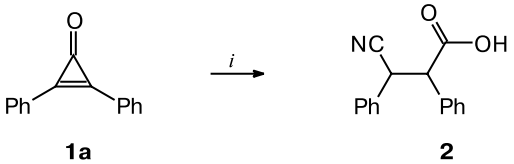


However, only few nucleophiles react directly with the cyclopropenone ring.[10] Most nucleophilic agents react with the activated form of cyclopropenone (so-called cyclopropenylium salts). Cyclopropenones themselves are inert toward water and alcohols over a wide range of conditions.[10]

Results and Discussion

In inert solvents (diethyl ether, THF, and CH_2Cl_2), even such a strong C-nucleophile as cyanide did not react with 2,3-diphenyl- (**1a**) or 2-methyl-3-phenylcyclopropenones (**1b**). However, in solvents exhibiting nucleophilic properties, the three-membered ring underwent opening to give a product of a sequential attack by two nucleophilic agents on the cyclopropenone fragment. For instance, a reaction of cyclopropenone **1a** with two equivalents of NaCN and $NaHSO_4$ in water—dioxane yielded 3-cyano-2,3-diphenylpropionic acid (**2**) (Scheme 2).

Scheme 2



Reagents and conditions: *i*. 2 NaCN, 2 $NaHSO_4$, water—dioxane.

With alcohols as solvents, cyclopropenone **1a** was converted into esters **3a**—**c**. Analogous reactions with cyclopropenone **1b** afforded alkyl 3-cyano-2-methyl-3-phenyl-

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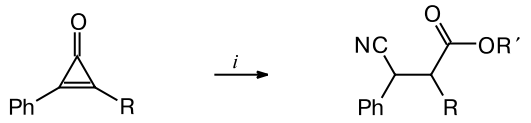
propionates **4a—c** (Scheme 3). In all cases, two moles of sodium cyanide should be used since the conversion of cyclopropenones **1a,b** in the reaction with an equimolar amount of NaCN did not exceed 50% (GC-MS data).

Scheme 3



1a,b **3a—c, 4a—c**

R = Ph (**1a**, **3**), Me (**1b**, **4**);
R′ = Me (**a**), Et (**b**), Pr^i (**c**)

Reagents and conditions: *i*. 2 NaCN, 2 $NaHSO_4$, R′OH.

An analysis of the ^1H and ^{13}C NMR spectra of compounds **2—4** revealed that out of two possible diastereomers, namely, 2*R**,3*R** (*anti*) and 2*R**,3*S** (*syn*), the *anti*-diastereomer is dominant. Its content in the mixture depends on the nucleophilicity of the alcohol and the reaction temperature. In the reaction of 2,3-diphenylcyclopropenone (**1**) with NaCN in methanol at room temperature, the content of the *anti*-isomer reached 90%. An increase in the temperature and a decrease in the alcohol nucleophilicity (from methanol to propan-2-ol) made the reaction less diastereoselective (Table 1). A low selectivity was also observed in the reaction with water: the content of the *anti*-isomer was 65%.

The ratio of the diastereomers was estimated from the integral intensities of the respective signals in the ^1H and ^{13}C NMR spectra. The chemical shifts were assigned to a particular pair by addition of a chiral paramagnetic shifting reagent, namely, europium tris(heptafluorobutyrylcamphorate) ($Eu(hfc)_3$) (50—100 mol. %).[11] Lanthanide-based paramagnetic shifting reagents are known to readily form complexes with molecules containing fragments with the properties of Lewis bases.[12] The enantiomeric ratio is commonly determined from ^1H NMR spectra.[13] However, we found it more convenient to employ here ^{13}C NMR spectra since the chiral centers are not directly bound to the atoms involved in complex formation.[14]

Table 1. Effect of the solvent on the content of the *anti*-diastereomer in the reaction product

Solvent	Product	Content of the *anti*-diastereomer (%)
H_2O—dioxane	**2**	65
MeOH	**3a**	90
EtOH	**3b**	65
Pr^{i}OH	**3c**	58—60
MeOH	**4a**	70
EtOH	**4b**	60—63
Pr^{i}OH	**4c**	55—58

The ^{13}C NMR spectra contain, owing to complexation between the compound under examination and $Eu(hfc)_3$, slightly broadened resonance signals for the sp^2- and sp-hybridized C atoms of the carboxy and cyano groups for the *syn*-isomer and the corresponding distinct doublets for the *anti*-isomer. This effect is due to a compensation of the chiral shift difference between the *R*,*S*- and *S*,*R*-isomers, which is absent for the *anti*-isomer. This experiment allowed unambiguous assignment of the signals for either diastereomer in the ^{13}C NMR spectrum. The diastereomer ratio of the reaction products was determined by comparing the integral signal intensities for the identical carbon and hydrogen atoms in the ^{13}C and ^1H NMR spectra.

Our initial assumption of sequential processes, namely, an attack by a nucleophile (water or alcohol) that results in opening of the three-membered ring in cyclopropenone **1** and the formation of substituted acryl ester followed by the Michael addition of HCN to this system, proved to be false. It was found that no Michael reaction of alkyl 2,3-diphenylacrylates with cyanide occur under the conditions of the reaction under study. Apparently, cyclopropenone **1a** is initially attacked by HCN to give an equilibrium mixture of adducts **5** and **5′**. Cyclopropanone **5′**, which is characterized by *anti*-arrangement of the benzene rings and thus is sterically most favorable, rapidly reacts with alcohol (or water) to form hemiketal **6**. The easy formation of compound **6** is explained by lowering of the ring strain when passing from the sp^2-hybridized C atom in cyclopropanone **5′** to the sp^3-hybridized one. Opening of hemiketal **6** yields diastereomer **3**. A parallel slow opening of the ring in adducts **5** and **5′** gave ketene **7**, which rapidly and nonselectively adds an alcohol (water) to give a mixture of diastereomers **3** and **3′** (Scheme 4).

The reaction with 2-methyl-3-phenylcyclopropenone **1b** proceeded analogously, with exclusive cleavage of the C(1)—C(3) bond in the three-membered ring. This is explained by the higher stability of benzyl ions compared to alkyl ones in heterolytic opening of the ring. It should be noted that the reactions with 2-methyl-3-phenylcyclopropenone are less diastereoselective than those with 2,3-diphenylcyclopropenone. This is indirect evidence for our suggested mechanism. The corresponding cyclopropanone (similar to compound **5′**) is sterically less hindered; for this reason, the equilibrium mixture can contain its spatial isomer with *syn*-arrangement of the methyl and phenyl groups. When attacked by an alcohol (water), this form will yield the *syn*-isomer.

The structures of the compounds obtained were proved by IR and ^1H and ^{13}C NMR spectroscopy; their compositions were confirmed by elemental analysis.

Scheme 4

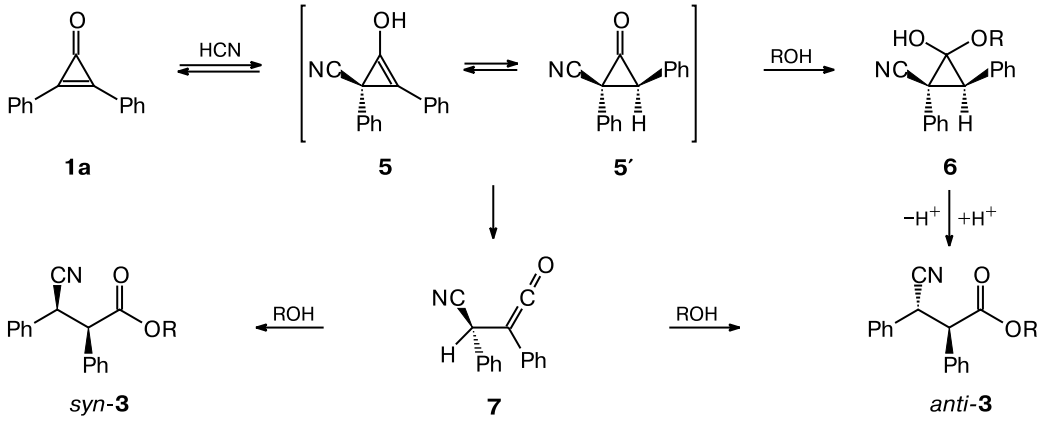


Table 2. ^{1}H and ^{13}C NMR spectra of compounds **2**, **3a**—**c**, and **4a**—**c** (δ, *J*/Hz, $CDCl_3$)

Compound	Isomer	^{1}H			^{13}C				
		H(2)	H(3), d	R′	C(1)	C(2)	C(3)	CN	R′
2	*anti*	4.04 (d, *J* = 10)	4.57 (*J* = 10)	10.3 (s)	174.4	41.0	56.2	118.7	—
	syn	4.06 (d, *J* = 10)	4.32 (*J* = 10)	10.3 (s)	174.9	40.6	56.3	119.6	—
3a	*anti*	4.01 (d, *J* = 10)	4.60 (*J* = 10)	3.57 (s)	170.7	41.3	52.4	118.8	56.4
	syn	4.02 (d, *J* = 10)	4.35 (*J* = 10)	3.79 (s)	171.1	40.9	52.7	119.6	56.4
3b	*anti*	4.00 (d, *J* = 10)	4.55 (*J* = 10)	1.03 (t, *J* = 6.9), 4.02 (q, *J* = 6.9)	170.1	41.4	56.4	118.9	13.7, 61.4
	syn	4.01 (d, *J* = 10)	4.31 (*J* = 10)	1.25 (t, *J* = 6.9), 4.24 (q, *J* = 6.9)	170.6	40.9	56.5	119.6	13.9, 61.8
3c	*anti*	3.97 (d, *J* = 10)	4.53 (*J* = 10)	1.01 (d, *J* = 6.1), 4.87 (sept, *J* = 6.1)	169.7	41.5	56.7	119.0	21.3, 69.3
	syn	3.97 (d, *J* = 10)	4.31 (*J* = 10)	1.25 (d, *J* = 6.1), 5.12 (sept, *J* = 6.1)	170.2	41.1	56.8	119.7	21.7, 69.6
4a	*anti*	3.41 (q, *J* = 7)	3.75 (*J* = 7)	3.62 (s)	171.2	29.7	54.3	120.5	52.5
	syn	3.30 (q, *J* = 7)	3.60 (*J* = 7)	3.70 (s)	171.4	28.4	54.5	121.4	52.5
4b	*anti*	3.40 (q, *J* = 7)	3.64 (*J* = 7)	1.23 (t, *J* = 6.9), 4.18 (q, *J* = 6.9)	170.7	29.7	54.5	120.6	13.9, 61.5
	syn	3.28 (q, *J* = 7)	3.69 (*J* = 7)	1.23 (t, *J* = 6.9), 4.19 (q, *J* = 6.9)	170.9	28.5	54.7	121.3	13.9, 61.5
4c	*anti*	3.39 (q, *J* = 6)	3.60 (*J* = 6)	1.01 (d, *J* = 6.1), 4.85 (sept, *J* = 6.1)	170.1	29.6	54.5	120.6	16.8, 69.1
	syn	3.27 (q, *J* = 6)	3.63 (*J* = 6)	1.20 (d, *J* = 6.1), 5.08 (sept, *J* = 6.1)	170.2	28.4	54.8	121.3	15.4, 69.1

Experimental

IR spectra were recorded on a Specord UR-20 instrument (Nujol and thin film). ^{1}H and ^{13}C NMR spectra were recorded on Bruker AC-200 and Bruker AC-500 spectrometers in $CDCl_3$. Mass spectra were recorded on an HP 5995 A spectrometer (direct inlet probe, EI, 70 eV, 60 °C).

Cyclopropenones **1a,b** were prepared according to a known procedure.[15]

The ^{1}H and ^{13}C NMR spectra of compounds **2**—**4** are given in Table 2.

3-Cyano-2,3-diphenylpropionic acid (2). Diphenylcyclopropenone **1a** (0.51 g, 2.5 mmol) was added to a stirred suspension of NaCN (0.24 g, 5 mmol) and $NaHSO_4$ (0.60 g, 5 mmol) in dioxane (20 mL) with water (1 mL). The reaction mixture was stirred and refluxed for 4 to 5 h. After the starting cyclopropenone was consumed completely (TLC, silica gel, $CHCl_3$—ethyl acetate (7 : 2), R_f = 0.3), the resulting mixture was treated with cold water (50 mL) and the product was extracted with CH_2Cl_2 (2×20 mL). The combined organic extracts were washed with water (20 mL), dried with $MgSO_4$, and concentrated. The resulting yellowish crystalline substance was dried *in vacuo* at ~20 °C to give 3-cyano-2,3-diphenylpropionic acid (0.30 g, 45%)

as a mixture of diastereomers, m.p. 167—168 °C. Found (%): C, 76.75; H, 5.30; N, 5.24. $C_{16}H_{13}NO_2$. Calculated (%): C, 76.48; H, 5.21; N, 5.57.

Methyl 3-cyano-2,3-diphenylpropionate (3a). Cyclopropenone **1a** (0.51 g, 2.5 mmol) was added to a stirred suspension of NaCN (0.24 g, 5 mmol) and $NaHSO_4$ (0.60 g, 5 mmol) in methanol (20 mL). The reaction mixture was stirred at room temperature for 4 to 5 h until the diphenylcyclopropenone disappeared (monitoring by TLC) and then treated with cold water (50 mL). The product was extracted with dichloromethane (2×20 mL). The combined organic extracts were washed with water (20 mL), dried with $MgSO_4$, and concentrated. The resulting yellowish crystalline substance was dried *in vacuo* at 20 °C to give methyl 3-cyano-2,3-diphenylpropionate (**3a**) (0.6 g, 90%) as a mixture of diastereomers, m.p. 165—166 °C. Found (%): C, 77.13; H, 5.46; N, 5.10. $C_{17}H_{15}NO_2$. Calculated (%): C, 76.96; H, 5.70; N, 5.28.

Ethyl 3-cyano-2,3-diphenylpropionate (3b) was obtained as a mixture of diastereomers from cyclopropenone **1a** (0.51 g, 2.5 mmol) and ethanol (20 mL) as described for compound **3a**. The yield of compound **3b** was 0.60 g (86%), m.p. 135—136 °C. Found (%): C, 77.49; H, 5.94; N, 4.80. $C_{18}H_{17}NO_2$. Calculated (%): C, 77.40; H, 6.13; N, 5.01.

The physicochemical constants and spectroscopic data for compound **3b** agree with the literature data.[16]

Isopropyl 3-cyano-2,3-diphenylpropionate (3c) was obtained as a mixture of diastereomers from cyclopropenone **1a** (0.51 g, 2.5 mmol) and propan-2-ol (20 mL) as described for compound **3a**. The yield of compound **3c** was 0.55 g (75%), m.p. 125—128 °C. Found (%): C, 77.51; H, 6.39; N, 4.65. $C_{19}H_{19}NO_2$. Calculated (%): C, 77.79; H, 6.53; N, 4.77.

Methyl 3-cyano-2-methyl-3-phenylpropionate (4a). A mixture of cyclopropenone **1b** (0.72 g, 5 mmol), NaCN (0.49 g, 10 mmol), and $NaHSO_4$ (1.20 g, 10 mmol) in methanol (40 mL) was stirred at 20 °C for 4 h (monitoring by TLC) and then treated with cold water (50 mL). The product was extracted with CH_2Cl_2 (2×20 mL). The combined organic extracts were washed with water (20 mL), dried with $MgSO_4$, and concentrated to give compound **4a** (0.90 g, 88%) as a yellowish oil (mixture of diastereomers). Found (%): C, 71.05; H, 6.50; N, 6.70. $C_{12}H_{13}NO_2$. Calculated (%): C, 70.92; H, 6.45; N, 6.89.

Ethyl 3-cyano-2-methyl-3-phenylpropionate (4b) was obtained as a viscous yellowish oil (mixture of diastereomers) from cyclopropenone **1b** (0.72 g, 5 mmol) and ethanol (30 mL) as described for compound **4a**. The yield of compound **4b** was 0.87 g (80%). Found (%): C, 71.61; H, 6.89; N, 6.29. $C_{13}H_{15}NO_2$. Calculated (%): C, 71.87; H, 6.96; N, 6.45.

The physicochemical constants and spectroscopic data for compound **4b** (see Table 2) agree with the literature data.[17]

Isopropyl 3-cyano-2-methyl-3-phenylpropionate (4c) was obtained as a viscous yellowish oil (mixture of diastereomers) from cyclopropenone **1b** (0.72 g, 5 mmol) and propan-2-ol (30 mL) as described for compound **4a**. The yield of compound **4c** was 0.86 g (75%). Found (%): C, 72.45; H, 7.32; N, 6.19. $C_{14}H_{17}NO_2$. Calculated (%): C, 72.70; H, 7.41; N, 6.06.

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