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REACTION OF 1-AZABICYCLO[1.1.0]BUTANES WITH 2,3-DICYANOFUMARATES; INTERCEPTION OF THE INTERMEDIATE ZWITTERIONS WITH METHANOL

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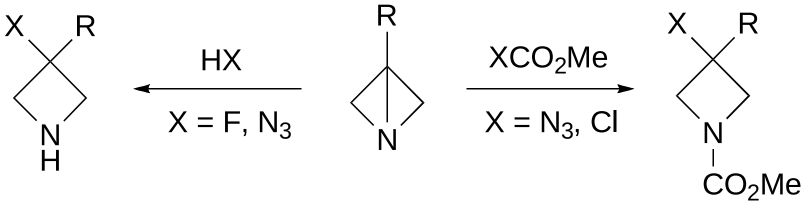
Dedicated to Professor Emeritus Keiichiro Fukumoto on the occasion of his 75th birthday

Abstract – The reaction of 3-phenyl-1-azabicyclo[1.1.0]butane (**1c**) with 2,3-dicyanofumarates ((*E*)-**5**) in dichloromethane at room temperature yields mixtures of *cis*- and *trans*-2,3-dicyano-4-phenyl-1-azabicyclo[2.1.1]hexane-2,3-dicarboxylates (*cis*,*trans*-**4**). The proposed two-step reaction mechanism *via* a zwitterionic intermediate of type (**6**) is supported by trapping experiments with methanol: when the reactions of 1-azabicyclo[1.1.0]butanes (**1**) with dimethyl 2,3-dicyanofumarate ((*E*)-**5a**) are carried out in methanol, dimethyl (*E*)-2-(azetidin-1-yl)-3-cyanobut-2-enedioates (**7**) are formed as the only products.

INTRODUCTION

The smallest bicyclic nitrogen compounds are azabicyclobutanes, and 1-azabicyclo[1.1.0]butanes (**1**) are known as relatively stable substances.[1] The parent compound (**1a**) was prepared by the two-fold intramolecular substitution of either 1,3-dibromopropan-2-amine[2] or the isomeric 2,3-dibromopropan-1-amine.[3] The cyclizations were performed by using KOH or BuLi as a base. On the other hand, 3-aryl substituted 1-azabicyclo[1.1.0]butanes (**1**) are conveniently available by the reaction of 3-aryl-2*H*-azirines with dimethylsulfonium methanide.[4,5] The strained bicyclic system (**1**) easily undergoes addition reactions with HX along the N(1),C(3) bond yielding diverse azetidine derivatives (**2**).[6] Electrophilic agents such as azido- or chloroformates add in a similar manner to **1** yielding azetidine-1-carboxylates (**3**).[7] Analogous reactions with chlorodithioformates led to hitherto unknown azetidine-1-dithiocarboxylates,[8] and sulfanyl as well as sulfinyl chlorides add easily to **1c** across the N(1),C(3) bond to give sulfenyl- and sulfinylamides, respectively.[9] In a very recent paper, the unsubstituted **1a** was shown to undergo a smooth 1,3-addition with the thiol form of azaheterocyclic thiones to give products of type **2** with X = S-Hetaryl.[10] This type of azetidine derivative is also an attractive building block for the preparation of biologically active quinolone carboxylic acids bearing an azetidine residue. In the same paper, the reactions of **1a** with nucleophilic secondary amines in the presence of $Mg(ClO_4)_2$ affording 3-aminoazetidines (**2**) (R = H, X = R_2N) are described.

Scheme 1



2

1a R = H
b R = Et
c R = Ph

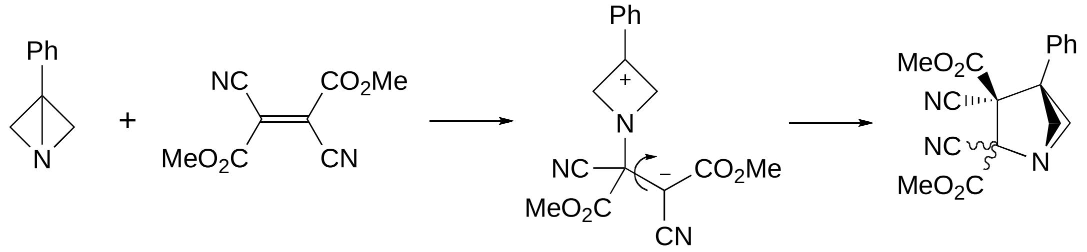
3

The first ring enlargement of **1c** to give a 1-azabicyclo[2.1.1]hexane (**4a**) was achieved by the treatment of **1c** with the extremely electron deficient dimethyl 2,3-dicyanofumarate ((*E*)-**5a**).[11] The analysis of the crude product showed that the reaction led to a mixture of *cis*- and *trans*-**4a** in a ratio of 1:3 (*Scheme 2*). The same ratio of the ring-enlarged products was obtained starting with **1c** and dimethyl 2,3-dicyanomaleate ((*Z*)-**5a**).

In the previous paper, we proposed that the reactions occur stepwise *via* the zwitterionic intermediate **6c**, which lives long enough to undergo rotation about the C(2),C(3)-bond of the former olefinic component. The subsequent 1,5-ring closure results in the formation of the same mixture of *cis*- and *trans*-**4a** starting either from (*E*)- or (*Z*)-**5a**.

To get more insight into the mechanism of this unprecedented ring enlargement, reactions of differently substituted 1-azabicyclo[1.1.0]butanes (**1**) with (*E*)-**5a** in the presence of methanol as a trapping reagent were studied.

Scheme 2



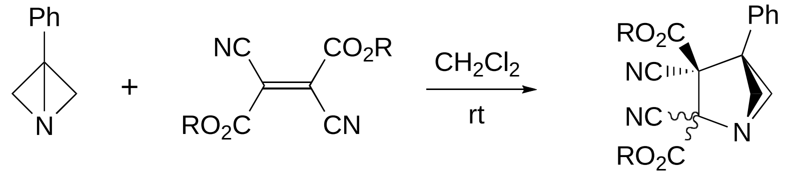
1c (*E*)-**5a** **6c** *cis*/*trans*-**4a** (*cis* : *trans* 1:3)

RESULTS AND DISCUSSION

For the present study, three different 1-azabicyclo[1.1.0]butanes were used, *i.e.*, **1b**, **1c**, and 2,2-dimethyl-3-phenyl-1-azabicyclo[1.1.0]butane (**1d**). Along with the dimethyl ester (*E*)-**5a**, the corresponding diethyl and diisopropyl esters ((*E*)-**5b**) and ((*E*)-**5c**) were also applied.

Analogously to **5a**, the reactions of **1c** with (*E*)-**5b** and (*E*)-**5c** were carried out in CH_2Cl_2 at room temperature. After *ca.* 15 h, using equimolar amounts of reagents, complete conversion of **1c** was confirmed by ^{1}H-NMR spectroscopy. Chromatographic separation of the crude mixtures gave the expected stereoisomers of 1-azabicyclo[2.1.1]hexane **4b** and **4c**, respectively, in fair yields (*Scheme 3*). In both cases, the ratio of *cis*- to *trans*-adduct was established as *ca.* 2:3 after chromatographic workup.

Scheme 3



1c (*E*)-**5b** R = Et
c R = *i*Pr
cis/*trans* -**4b** R = Et (25 and 34%)
c R = *i*Pr (19 and 28%)

In the case of **4c**, the structure of the crystalline product isolated from the less polar fraction (minor isomer), was established by X-ray crystallography as *cis*-**4c** (*Figure 1*).

For comparison, the reactions of (*E*)-**5a** with **1b** and **1d** were carried out with the aim of testing the influence of the substitution pattern of **1**. In both cases, the ^{1}H-NMR spectra of the crude products confirmed the absence of starting compounds **1b** or **1d**, and the formation of a complex mixture of polymeric products was very likely. Attempted chromatographic separations of the products, using preparative plates coated with silica, failed.

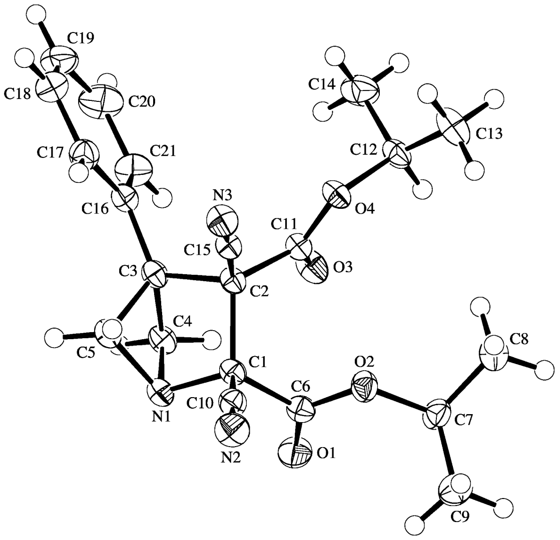


Figure 1. ORTEP plot[12] of the molecular structure of *cis*-**4c** (arbitrary numbering of the atoms; 50% probability ellipsoids)

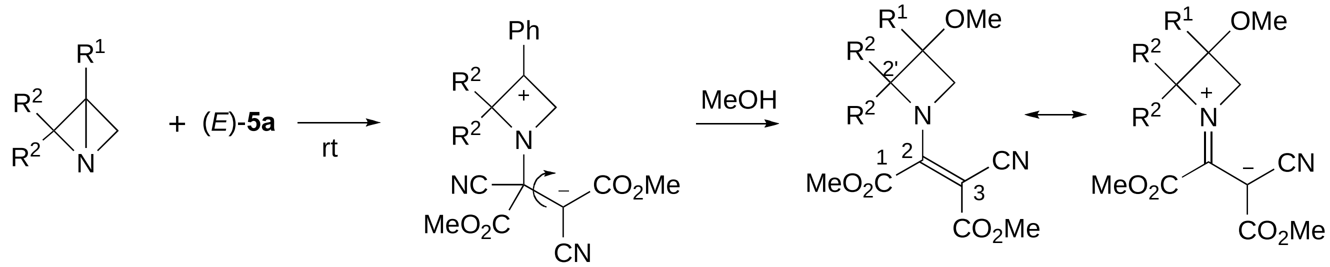
In order to trap the postulated zwitterion, which is formed from **1c** and (*E*)-**5a**, the reaction was performed in methanol, leading to a new product. The ^{1}H-NMR spectrum of the crude mixture revealed the presence of three MeO signals located at 3.05, 3.74, and 3.92 ppm. After isolation and purification of the sole product, the MeO signals in the ^{1}H-NMR were unchanged. In addition, the ^{13}C-NMR spectrum showed the presence of a single C≡N absorption at 116.7 ppm as well as three signals at 158.5, 161.8, and 165.0 ppm. Whereas two of these signals belong to the ester C=O groups, the third one is attributed to the strongly deshielded C(2)-atom. The C(3)-atom absorbs at higher field, and the corresponding signal appears at 70.8 ppm. Based on this observation and supported by the mass spectrum and the elemental analysis, the structure of 2-(azetidin-1-yl)butenedioate (**7b**) is proposed (*Scheme 4*). Neither spectroscopically nor during the workup could the presence of the previously described bicyclic products (*cis*/*trans*-**4a**) be detected.

Interestingly, analogous interception experiments performed with **1b** and **1d** also gave the corresponding products (**7b**) and (**7c**), respectively, although in the absence of the trapping agent, no products of type **4**, formed *via* the intramolecular reaction, were observed.

The configuration of the C=C bonds of **7a**–**c** is yet unknown. Surprisingly, reactions of amines with dicyanofumarates are rarely reported. The structure of the product obtained with 4-nitroaniline is believed to be the (*Z*)-isomer.[13] The reactions with 1,2-diamines led to (*Z*)-configured 3-[α-cyano-α-(alkoxycarbonyl)methylidene]piperazin-2-ones.[14] Similarly, cyanoacetic acid hydrazide and semicarbazide, respectively, reacted with dicyanofumarates to give heterocyclic products *via* an addition-cyclization-elimination sequence.[15] In all of these cases, the initially formed products were neither isolated nor detected. However, the crystal structure of the enamine obtained from the reaction of dimethyl dicyanofumarate with pyrrolidine showed the (*E*)-configuration with a *cis*-orientation of the ester groups.[16] Because the reaction of **1** and pyrrolidine, respectively, with dicyanofumarates occur *via* an analogous zwitterionic intermediate, we propose that the C=C bond in compounds (**7**) is also (*E*)-configured.

It is worth discussing the NMR-data of products (**7a**–**c**). The ^{1}H-NMR spectrum of **7c** shows two Me signals for $Me_2C(2')$ at 0.98 and 1.56 ppm and an AB-system for $H_2C(4')$. In the ^{13}C-NMR spectrum of this compound, C(2) and C(3) absorb at 157.1 and 70.4 ppm, respectively, confirming the 'push-pull effect' in the structure of **7c**. The ^{1}H-NMR spectrum of **7a** is characterized by the presence of two AB-systems at 3.94/4.09 and 4.08/4.42 ppm for $H_2C(2')$ and $H_2C(4')$, and, in the ^{13}C-NMR spectrum, C(2) and C(3) absorb at 158.7 and 75.9 ppm, respectively. The presence of two AB-systems for the two azetidine CH_2 groups is a clear evidence for hindered rotation about the N(1'),C(2)-bond, *i.e.*, its partial double bond character (*Scheme 4*). Finally, **7b** shows a similar pattern of signals in the ^{13}C-NMR spectrum (158.5 and 70.8 ppm for C(2) and C(3), resp.). On the other hand, the two azetidine CH_2 groups appear as an AB-system at 4.89/5.00 and, unexpectedly, as a broad singlet at 4.42 ppm.

Scheme 4



1b R^1 = Et, R^2 = H
c R^1 = Ph, R^2 = H
d R^1 = Ph, R^2 = Me

6

7a R^1 = Et, R^2 = H (77%)
b R^1 = Ph, R^2 = H (55%)
c R^1 = Ph, R^2 = Me (53%)

The trapping experiments with methanol confirm the proposed mechanism of the ring enlargement in the reaction of 3-phenyl-1-azabicyclo[1.1.0]butanes (**1**) with 2,3-dicyanofumarates ((*E*)-**5**). The intermediate zwitterion of type **6** (*Scheme 2*) undergoes ring closure to give **4** in the case of the phenyl derivative (**1c**). Bulkier substituents in the ester ((*E*)-**5**) do not influence the course of the reaction. On the other hand, the replacement of the phenyl group in **1c** by an ethyl group in **1b**, or the presence of two methyl groups in **1d**, prevents the formation of the ring-enlarged bicyclic product. Nevertheless, in all cases studied, the initially formed zwitterion of type **6** is efficiently trapped by methanol. The 1:1:1-adducts spontaneously eliminate HCN and could never be detected. It is worth mentioning that the formation of the final products (**7**) occurs stereoselectively to give exclusively the (*E*)-configured isomers.

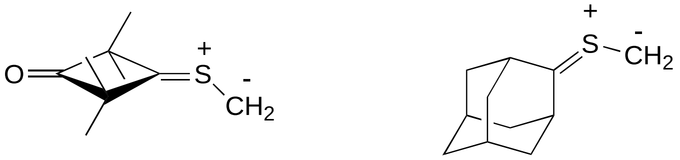
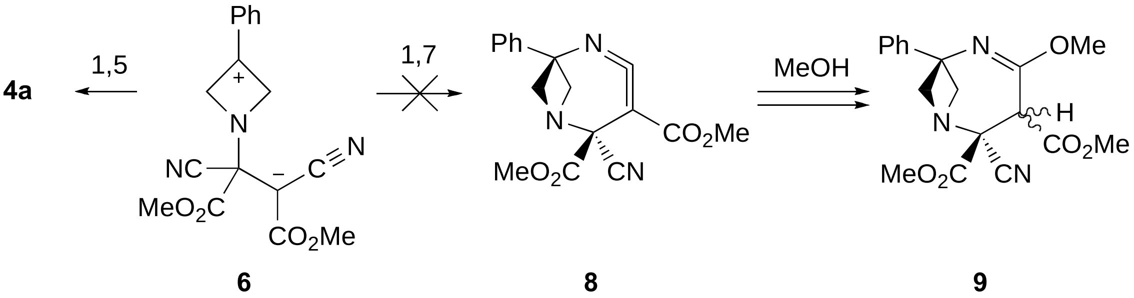


Figure 2. Electron-rich thiocarbonyl ylides derived from the sterically crowded 2,2,4,4-tetramethyl-3-thioxocyclobutanone and adamantanethione, respectively

The reactions of (*E*)-**5** with electron-rich thiocarbonyl ylides (*Figure 2*) has been studied extensively.[17] In this case, the appearance of a zwitterionic intermediate was evidenced by the 1,7-dipolar ring closure to give a reactive ketene imine, which subsequently was trapped by methanol. Based on these results, the zwitterion (**6**), in addition to the 1,5-cyclization to give **4a**, could be expected to undergo a competitive 1,7-cyclization to a ketenimine (**8**) (*Scheme 5*). Trapping of the latter with methanol would yield the bicyclic iminoether (**9**). In the present study, however, products of type **9** have never been observed, and the 1,5-cyclization of **6** is highly preferred. In contrast to the zwitterions formulated in the reaction of (*E*)-**5** with a sterically hindered thiocarbonyl ylide,[17] the intermediate of type **6** reacts with methanol quickly, and neither five- nor seven-membered bicyclic products are formed.

Scheme 5



In conclusion, the described results show that strained 1-azabicyclo[1.1.0]butanes (**1**) easily react with electron-deficient 2,3-dicyanofumarates ((*E*)-**5**), and the zwitterions of type **6** are formed as intermediates. In the absence of methanol, highly stabilized structures with the phenyl substituent at C(3) undergo 1,5-ring closure to yield 1-azabicyclo[2.1.1]hexanes (**4**). The presence of two methyl groups at C(2) of the 1-azabicyclo[1.1.0]butane prevents this ring-closure. Again, no formation of the ring-enlarged bicyclic system of type **4** was observed in the case of the 3-ethyl derivative (**1b**). However, the intermediacy of a zwitterion (**6**) is demonstrated by trapping experiments with methanol. The adducts formed thereby spontaneously eliminate HCN to yield the ‘push-pull stabilized’ products (**7**) in a stereoselective manner.

EXPERIMENTAL

General remarks. Melting points were determined in a capillary using a MEL-TEMP II apparatus (*Aldrich*) and are uncorrected. IR spectra were recorded with a FT-IR NEXUS instrument as KBr pellets or as films, and the positions of absorption bands are given in cm^{-1}. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a BRUKER-AC-300 (^{1}H at 300 MHz and ^{13}C at 75 MHz) instrument in $CDCl_3$ solutions using TMS ($\delta = 0$ ppm) as an internal standard; chemical shifts (δ) in ppm. MS spectra were recorded on a LKB-2091 spectrometer using chemical ionization (CI-MS; with NH_3) or electrospray (ESI) method; *m/z* (rel. %). Elemental analyses were performed in the Analytical Laboratory of the University of Zürich or in the Laboratory of the Polish Academy of Sciences (CBMiM) in Lodz.

Starting materials. For the preparation of the starting materials, known procedures were applied: 3-ethyl-1-azabicyclo[1.1.0]butane (**1b**),[2] 3-phenyl-1-azabicyclo[1.1.0]butane (**1c**),[4] 2,2-dimethyl-3-phenyl-1-azabicyclo[1.1.0]butane (**1d**),[4] and dimethyl 2,3-dicyanofumarates ((*E*)-**5a**).[18] Diethyl ((*E*)-**5b**) and diisopropyl 2,3-dicyanofumarate ((*E*)-**5c**) were prepared in analogy to (*E*)-**5a** using diethyl and diisopropyl cyanoacetate, respectively, as substrates for the reaction with thionyl chloride (see ref.[18]).

Synthesis of 1-azabicyclo[2.1.1]hexanes 4b and 4c. To a magnetically stirred solution of 1 mmol of (*E*)-**5b** (or (*E*)-**5c**) in 1 mL of CH_2Cl_2 at rt, 131 mg (1 mmol) of **1c** dissolved in 1 mL of CH_2Cl_2 was added in small portions. The homogenous solution was left at rt overnight. Next day, the solvent was evaporated to dryness and crude products obtained as viscous oils were separated on preparative plates covered with SiO_2 and CH_2Cl_2 as the eluent. Two well separated fractions were isolated and additionally purified by crystallization; yields refer to amounts obtained after chromatography.

trans-Diethyl 2,3-dicyano-4-phenyl-1-azabicyclo[2.1.1]hexane-2,3-dicarboxylate (*trans*-**4b**). Less polar fraction. Yield: 120 mg (34%). Colorless oil, isolated and purified chromatographically. IR (neat): 2987*s*, 2941*m*, 2245*w* (C≡N), 1767*vs* (C=O), 1750*vs* (C=O), 1501*m*, 1448*m*, 1392*m*, 1328*m*, 1261*vs* (O–C), 1243*vs*, 1095*s*, 1005*s*, 1020*m*, 1005*m*, 918*m*, 850*m*, 761*vs*, 725*m*, 700*s*. ^{1}H-NMR ($CDCl_3$): 1.33, 1.47 (2*t*, $^2J_{H,H}$ = 7.1 Hz, 2*Me*CH$_2$); 3.52–3.59 (*m*, 1H); 3.71–3.74 (*m*, 1H); 3.87–3.90 (*m*, CH_2O); 4.22–4.29 (*m*, 1H); 4.37–4.43 (*m*, 1H); 4.44–4.57 (*m*, CH_2O); 7.22–7.27 (*m*, 2H, Ph); 7.34–7.39 (*m*, 3H, Ph). ^{13}C-NMR ($CDCl_3$): 13.8 (*q*, Me); 60.7 (*s*, C_q); 64.3, 64.7 (2*t*, 2CH_2O); 64.8 (*t*, CH_2); 65.8 (*s*, C_q); 66.1 (*t*, CH_2); 68.6 (C_q); 114.4, 115.5 (2*s*, 2C≡N); 127.1, 128.7, 129.0 (3*d*, 5 arom CH); 131.2 (*s*, arom. C_q); 162.1, 163.5 (2*s*, 2C=O). CI-MS: 356 (14), 355 (22), 354 (100, $[M+1]^+$). Anal. Calcd for $C_{19}H_{19}N_3O_4$: C, 64.58; H, 5.42; N, 11.89. Found: C, 64.47; H, 5.39; N, 11.73.

cis-Diethyl 2,3-dicyano-4-phenyl-1-azabicyclo[2.1.1]hexane-2,3-dicarboxylate (*cis*-**4b**). More polar fraction. Yield: 88 mg (25%). Colorless prisms, mp 143–144 °C (hexane/CH_2Cl_2). IR (KBr): 2986*w*, 2246*w* (C≡N), 1777*s* (C=O), 1740*s* (C=O), 1451*w*, 1279*m*, 1259*vs* (C=O), 1244*vs* (C=O), 1092*s*, 1055*m*, 1022*w*, 1007*w*, 921*w*, 851*w*, 706*m*. ^{1}H-NMR ($CDCl_3$): 1.11, 1.37 (2*t*, $^2J_{H,H}$ = 7.1 Hz, 2*Me*CH_2); 3.55 (*dd*, $^2J_{H,H}$ = 8.5 Hz, 10.1 Hz, 1H); 3.78 (*dd*, $^2J_{H,H}$ = 5.6 Hz, 8.3 Hz, 2H); 4.04 (*dd*, $^2J_{H,H}$ = 8.4 Hz, 10.2 Hz, 1H); 4.20-4.34 and 4.35-4.49 (2*m*, $2CH_2O$); 7.06–7.15 (*m*, 2H, Ph); 7.35–7.44 (*m*, 3H, Ph). ^{13}C-NMR ($CDCl_3$): 13.7, 13.8 (2*q*, 2Me); 61.6, 71.5, 77.8 (3*s*, $3C_q$); 62.7, 64.3 (2*t*, $2CH_2$); 64.1, 66.3 (2*t*, $2CH_2O$); 114.8, 115.5 (2*s*, 2C≡N); 126.2, 129.0, 129.4 (3*d*, 5 arom. CH); 130.9 (*s*, arom. C_q); 161.8, 164.9 (2*s*, 2C=O). CI-MS: 356 (8), 355 (22), 354 (100, $[M+1]^+$). Anal. Calcd for $C_{19}H_{19}N_3O_4$: C, 64.58; H, 5.42; N, 11.89. Found: C, 64.29; H, 5.46; N, 11.90.

trans-Diisopropyl 2,3-dicyano-4-phenyl-1-azabicyclo[2.1.1]hexane-2,3-dicarboxylate (*trans*-**4c**). Less polar fraction. Yield: 107 mg (28%). Colorless prisms, mp 81–83 °C (hexane/CH_2Cl_2). IR (KBr): 2985*m*, 2245*w* (C≡N), 1763*vs* (C=O), 1746*vs* (C=O), 1466*m*, 1270*vs* (C=O), 1104*s*, 1054*m*, 909*w*. ^{1}H-NMR ($CDCl_3$): 1.24, 1.38, 1.45, 1.48 (4*d*, $^2J_{H,H}$ = 6.3 Hz, 2*Me*$_2$CH); 3.60–3.52 (m, 1H); 3.72–3.69 (*d*, $J_{H,H}$ = 8.4 Hz, 1H); 3.84–3.91 (*m*, 2H); 5.10–5.19, 5.27–5.35 (2*m*, 2Me$_2$C*H*O); 7.23–7.25 (*m*, 2H, Ph); 7.34–7.38 (*m*, 3H, Ph). ^{13}C-NMR ($CDCl_3$): 21.5, 21.6 (2*q*, 2*Me*$_2$CH); 60.6 (*s*, C_q); 64.8, 66.0 (2*t*, $2CH_2$); 68.4 (*s*, $2C_q$); 72.9, 73.6 (2*d*, 2Me$_2$*C*HO); 114.6, 115.6 (2*s*, 2C≡N); 127.2, 128.7, 128.9 (3*d*, 5 arom. CH); 131.3 (*s*, arom. C_q); 161.6, 163.0 (2*s*, 2C=O). CI-MS: 384 (8), 383 (25), 382 (100, $[M+1]^+$). Anal. Calcd for $C_{21}H_{23}N_3O_4$: C, 66.13; H, 6.07; N, 11.01. Found: C, 66.14; H, 6.05; N, 11.05.

cis-Diisopropyl 2,3-dicyano-4-phenyl-1-azabicyclo[2.1.1]hexane-2,3-dicarboxylate (*cis*-**4c**). More polar fraction. Yield: 73 mg (19%). Colorless prisms, mp 191–193 °C (hexane/CH_2Cl_2). IR (KBr): 2987*w*, 2248*w* (C≡N), 1767*vs* (C=O), 1731*m* (C=O), 1464*w*, 1378*w*, 1263*vs* (C=O), 1101*s*, 1056*w*, 927*w*, 701*w*. ^{1}H-NMR ($CDCl_3$): 0.86, 1.24, 1.29, 1.38 (4*d*, $^2J_{H,H}$ = 6.3 Hz, 2*Me*$_2$CH); 3.52 (*dd*, $^2J_{H,H}$ = 8.5 Hz, 10.1 Hz, 1H); 3.74 (*dd*, $^2J_{H,H}$ = 5.6 Hz, 8.3 Hz, 2H); 4.04 (*dd*, $^2J_{H,H}$ = 8.4 Hz, 10.2 Hz, 1H); 4.88–4.96, 5.14–5.23 (2*m*, 2Me$_2$C*H*O); 7.10–7.15 (*m*, 3H, Ph); 7.32–7.40 (*m*, 2H, Ph). ^{13}C-NMR ($CDCl_3$): 21.4, 21.3, 21.2 (3*q*, 2*Me*$_2$CH); 62.4, 66.2 (2*t*, $2CH_2$); 61.6, 71.6, 77.6 (3*s*, $3C_q$); 72.6, 72.9 (2*d*, 2Me$_2$*C*HO); 115.1, 115.6 (2*s*, 2C≡N); 126.2, 128.9, 129.3 (3*d*, 5 arom. CH); 131.0 (*s*, arom. C_q); 161.4, 164.2 (2*s*, 2C=O). CI-MS: 384 (8), 383 (24), 382 (100, $[M+1)^+$). Anal. Calcd for $C_{21}H_{23}N_3O_4$: C, 66.13; H, 6.07; N, 11.01. Found: C, 66.14; H, 6.05; N, 11.05.

Reactions of azabicyclobutanes 1b-d with (*E*)-5a in methanolic solutions. The solution containing 1 mmol of the corresponding **1** in 1 mL of MeOH was added at rt in small portions to a magnetically stirred solution containing 194 mg (1 mmol) of (*E*)-**5a** dissolved in 1 mL of MeOH. After 15 min, the solvent was evaporated *in vacuo* and the crude product obtained thereby was analyzed by ^{1}H-NMR spectroscopy. A preliminary purification was achieved by chromatography on a short column filled with SiO$_2$, and CHCl$_3$ was used as the eluent. The isolated fraction was additionally purified on preparative plates (CH$_2$Cl$_2$ as the eluent), and only in the case of **7c**, an analytically pure sample was obtained after crystallization. Reported yields were calculated for the products obtained after preparative LC (PLC).

Dimethyl (*E*)-2-(3'-ethyl-3'-methoxyazetidin-1-yl)-3-cyanobutanedioate (**7a**). Yield: 216 mg (77%). Colorless, thick oil isolated after chromatography (PLC, SiO$_2$, CH$_2$Cl$_2$). IR (neat): 2954*m*, 2205*s*, (C≡N), 1748*vs* (C=O), 1705*vs*, (C=O), 1569*vs* (C=C), 1456*s*, 1436*s*, 1306*s*, 1250*s*, 1193*s*, 1177*s*, 1331*s* (br), 1070*s*, 1020*w*, 769*m*. ^{1}H-NMR (CDCl$_3$): 0.91 (*t*, $^2J_{\mathrm{H,H}}$ = 7.3 Hz, *Me*CH$_2$); 1.84 (*q*, $^2J_{\mathrm{H,H}}$ = 7.3 Hz, MeCH_2); 3.21, 3.73, 3.91 (3*s*, 3MeO); 3.94, 4.09 (*AB*, *J* = 10.0 Hz, CH$_2$-azetidine); 4.08, 4.42 (*AB*, *J* = 11.5 Hz, CH$_2$-azetidine). ^{13}C-NMR (CDCl$_3$): 6.9 (*q*, *Me*CH$_2$); 26.6 (*t*, Me*C*H$_2$); 50.7, 52.1, 53.6 (3*q*, 3MeO); 62.4, 62.8 (2*t*, 2CH$_2$-azetidine); 71.0 (*s*, C$_q$); 75.9 (*s*, C$_q$-azetidine); 117.0 (*s*, C≡N); 158.7 (*s*, C$_q$); 161.9, 165.1 (2*s*, 2C=O). ESI-MS: 305 (100, [*M*+Na]$^+$). Anal. Calcd for $C_{13}H_{18}N_2O_5$: C, 55.31; H, 6.43; N, 9.92. Found: C, 55.26; H, 6.21; N, 9.87.

Dimethyl (*E*)-2-(3'-phenyl-3'-methoxyazetidin-1-yl)-3-cyanobutanedioate (**7b**). Yield: 180 mg (55%). Colorless, thick oil isolated after chromatography (PLC, SiO$_2$, CHCl$_3$). IR (neat): 2953*s*, 2206*s* (C≡N), 1747*vs* (C=O), 1709*vs* (C=O), 1569*vs* (C=C), 1450*s*, 1436*s*, 1306*s*, 1250*vs*, 1195*s*, 1138*vs*, 1065*m*, 1637*m*, 767*s*, 702*s*. ^{1}H-NMR (CDCl$_3$): 3.05, 3.74, 3.92 (3*s*, 3MeO); 4.42 (br.*s*, CH$_2$); 4.89, 5.00 (*AB*, *J* = 11.8 Hz, CH$_2$); 7.31–7.47 (*m*, 5H, Ph). ^{13}C-NMR (CDCl$_3$): 51.9, 52.1, 53.7 (3*q*, 3MeO); 63.5, 63.8 (2*t*, 2CH$_2$-azetidine); 70.8 (*s*, C$_q$); 77.3 (*s*, C$_q$-azetidine); 116.7 (*s*, C≡N); 126.1, 129.0, 129.1 (3*d*, 5 arom. CH); 137.4 (*s*, arom. C$_q$); 158.5 (*s*, C$_q$); 161.8, 165.0 (2*s*, 2C=O). ESI-MS: 353 (100, [*M*+Na]$^+$). Anal. Calcd for $C_{17}H_{18}N_2O_5$: C, 61.81; H, 5.49; N, 8.48. Found: C, 61.67; H, 5.33; N, 8.78.

Dimethyl (*E*)-2-(3'-phenyl-3'-methoxy-2,2-dimethylazetidin-1-yl)-3-cyanobutanedioate (**7c**). Yield: 190 mg (53%). Colorless prisms, mp 107–109 °C (MeOH). IR (KBr): 2953*s*, 2205*m* (C≡N), 1751*vs* (C=O), 1702*s* (C=O), 1549*vs* (C=C), 1440*m* (br), 1302*m*, 1265*s*, 1246*s*, 1193*m*, 1146*s*, 1133*s*, 769*m*, 703*m*. ^{1}H-NMR (CDCl$_3$): 0.98, 1.56 (2*s*, 2Me); 3.04, 3.74, 3.88 (3*s*, 3MeO); 4.78, 5.21 (*AB*, *J* = 12.3 Hz, CH$_2$); 7.26–7.46 (*m*, 5H, Ph). ^{13}C-NMR (CDCl$_3$): 21.4, 25.6 (2*q*, 2Me); 52.0, 53.3 (2*q*, 3MeO); 56.8 (*t*, CH$_2$); 70.4, 81.2, 83.0 (3*s*, 3C$_q$); 117.9 (*s*, C≡N); 127.1, 128.8, 128.9 (3*d*, 5 arom. CH); 135.4 (*s*, arom. C$_q$); 157.1 (s, C$_q$); 162.6, 165.3 (2*s*, 2C=O). ESI-MS: 381 (100, [*M*+Na]$^+$). Anal. Calcd for $C_{19}H_{22}N_2O_5$: C, 63.67; H, 6.19; N, 7.82. Found: C, 63.47; H, 5.93; N, 7.76.

X-Ray Crystal-Structure Determination of *cis*-**4c** (*Figure 1*).[19] All measurements were made on a *Nonius KappaCCD diffractometer*[20] using graphite-monochromated MoK_{α} radiation (λ = 0.71073 Å) and an Oxford Cryosystems Cryostream 700 cooler. Data reduction was performed with *HKL Denzo and Scalepack*.[21] The intensities were corrected for *Lorentz* and polarization effects, but not for absorption. Equivalent reflections were merged. The data collection and refinement parameters are given below, and a view of the molecule is shown in *Figure 1*. The structure was solved by direct methods using SIR92,[22] which revealed the positions of all non-hydrogen atoms. The non-hydrogen atoms were refined anisotropically. All of the hydrogen-atoms were placed in geometrically calculated positions and refined using a riding model where each hydrogen-atom was assigned a fixed isotropic displacement parameter with a value equal to $1.2U_{\text{eq}}$ of its parent C-atom ($1.5U_{\text{eq}}$ for the methyl groups). The refinement of the structure was carried out on F^2 using full-matrix least-squares procedures, which minimized the function $\Sigma w(F_o^2 - F_c^2)^2$. A correction for secondary extinction was applied. Five reflections, whose intensities were considered to be extreme outliers, were omitted from the final refinement. Neutral atom scattering factors for non-hydrogen atoms were taken from ref.[23], and the scattering factors for hydrogen-atoms were taken from ref.[24] Anomalous dispersion effects were included in F_c;[25] the values for f' and f'' were those of ref.[26] The values of the mass attenuation coefficients are those of ref.[27] All calculations were performed using the SHELXL97 program.[28] Crystal data for *cis*-**4c**: Crystallized from hexane/CH_2Cl_2, $C_{21}H_{23}N_3O_4$, M = 381.43, colorless, prism, crystal dimensions 0.23 × 0.25 × 0.30 mm, triclinic, space group $P\bar{1}$, Z = 2, reflections for cell determination 5715, a = 10.1892(3) Å, b = 10.5551(2) Å, c = 10.7555(3) Å, α = 61.812(1)°, β = 77.635(1)°, γ = 84.420(2), V = 995.88(5) Å^3, D_X = 1.272 g·cm^{-3}, μ(MoK_{α}) = 0.0892 mm^{-1}, T = 160(1) K, ϕ and ω scans, $2\theta_{\max}$ = 60°, total reflections measured 26597, symmetry independent reflections 5827, reflections with $I > 2\sigma(I)$ 4451, reflections used in refinement 5822, parameters refined 258, R (on F; $I > 2\sigma(I)$ reflections) = 0.0465, $wR(F^2)$ (all reflections) = 0.1234 ($w = (\sigma^2(F_o^2) + (0.0517P)^2 + 0.2317P)^{-1}$, where $P = (F_o^2 + 2F_c^2)/3$), goodness of fit 1.042, secondary extinction coefficient 0.029(5), final $\Delta_{\max}/\sigma$ 0.001, $\Delta\rho$ (max; min) = 0.29; –0.23 e Å^{-3}.

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