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THREE-COMPONENT REACTIONS WITH 3-PHENYL-1-AZA-BICYCLO[1.1.0]BUTANE, DIMETHYL DICYANOFUMARATE, AND PRIMARY AROMATIC AMINES

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Dedicated to Professor Emeritus Akira Suzuki on the occasion of his 80th birthday

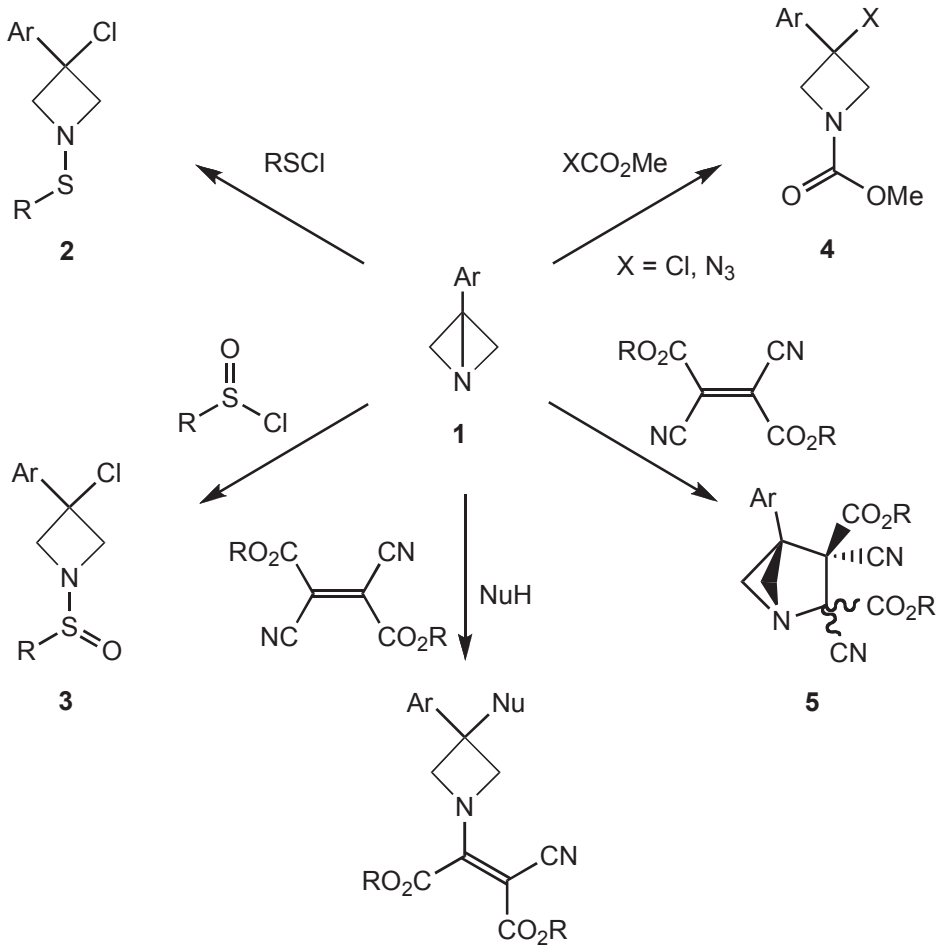
Abstract – The three-component reaction of 3-phenyl-1-azabicyclo[1.1.0]butane (**1a**) with 2,3-dicyanofumarates (DCFM) and primary aromatic amines in dichloromethane at room temperature yielded mixtures of (*Z*)-2-arylamino-3-cyanofumarates (**7**) and the corresponding (*E*)-2-(azetidin-1-yl)-3-cyanomaleates (**6**) and (**9**). In the case of anisidine (**8d**), higher oligomers containing three or four azetidine residues, e.g. **10a**, were also formed. With more nucleophilic aliphatic amines, only 1:1 adducts of type **7** were obtained. The reaction course can be rationalized by the formation of intermediate zwitterions (**11**) via addition of the N-nucleophiles onto DCFM. The results show that the nucleophilicity of **1a** toward DCFM is lower than that of aliphatic amines but exceeds that of aromatic amines.

INTRODUCTION

Reactions of 1-azabicyclo[1.1.0]butanes (**1**) leading to azetidine derivatives are of continual interest.[1,2] In some of our recent papers, reactions of **1** with diverse electrophiles, such as sulfanyl and sulfinyl chlorides[3] as well as chlorodithioformates,[4] were described. In analogy to other reactions of **1** with electrophilic agents, *e.g.* azido and chloroformates,[5] the only products obtained were azetidine derivatives of type **2**–**4** (*Scheme 1*). On the other hand, the reaction with the electron deficient dicyanofumarates yielded a mixture of stereoisomeric 1-azabicyclo[2.1.1]hexane dicarboxylates (**5**).[6] In this case, the

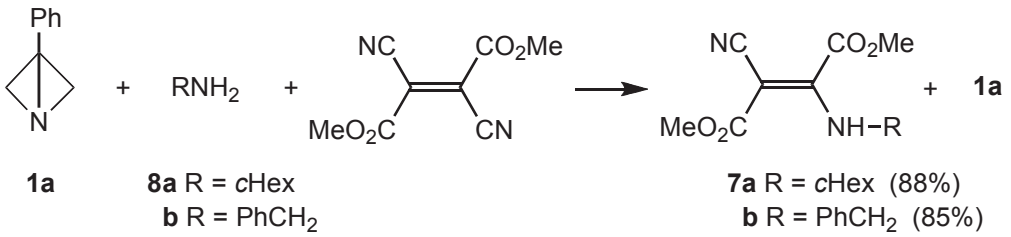
reaction was shown to occur via an intermediate zwitterion which was trapped quantitatively with methanol or morpholine to give enamines of type **6**.[7,8]

Scheme 1



The successful trapping reactions evidence that 3-phenyl-1-azabicyclo[1.1.0]butane (**1a**) exceeds both methanol and morpholine in the nucleophilicity towards the electron poor C=C bond. Whereas methanol does not react with dicyanofumarates at room temperature, a Michael type addition of morpholine, and also of other secondary and primary amines, followed by elimination of HCN to give enamines of type **7** was observed under the same conditions.[8] Interestingly, *N*-methylaniline did not react with dimethyl dicyanofumarate even at elevated temperature. Furthermore, a three-component reaction with equimolar amounts of **1a**, cyclohexylamine (**8a**), and dimethyl dicyanofumarate (DCFM)[9] resulted in the formation of only a 1:1 product, *i.e.*, the enamine (**7a**)[7] (*Scheme 2*), and not even traces of the expected 1:1:1 product of type **6** were observed. This result suggests that **8a** reacts faster with DCFM than **1a** and prompted us to examine analogous three-component reactions with less nucleophilic primary aromatic amines.

Scheme 2



RESULTS AND DISCUSSION

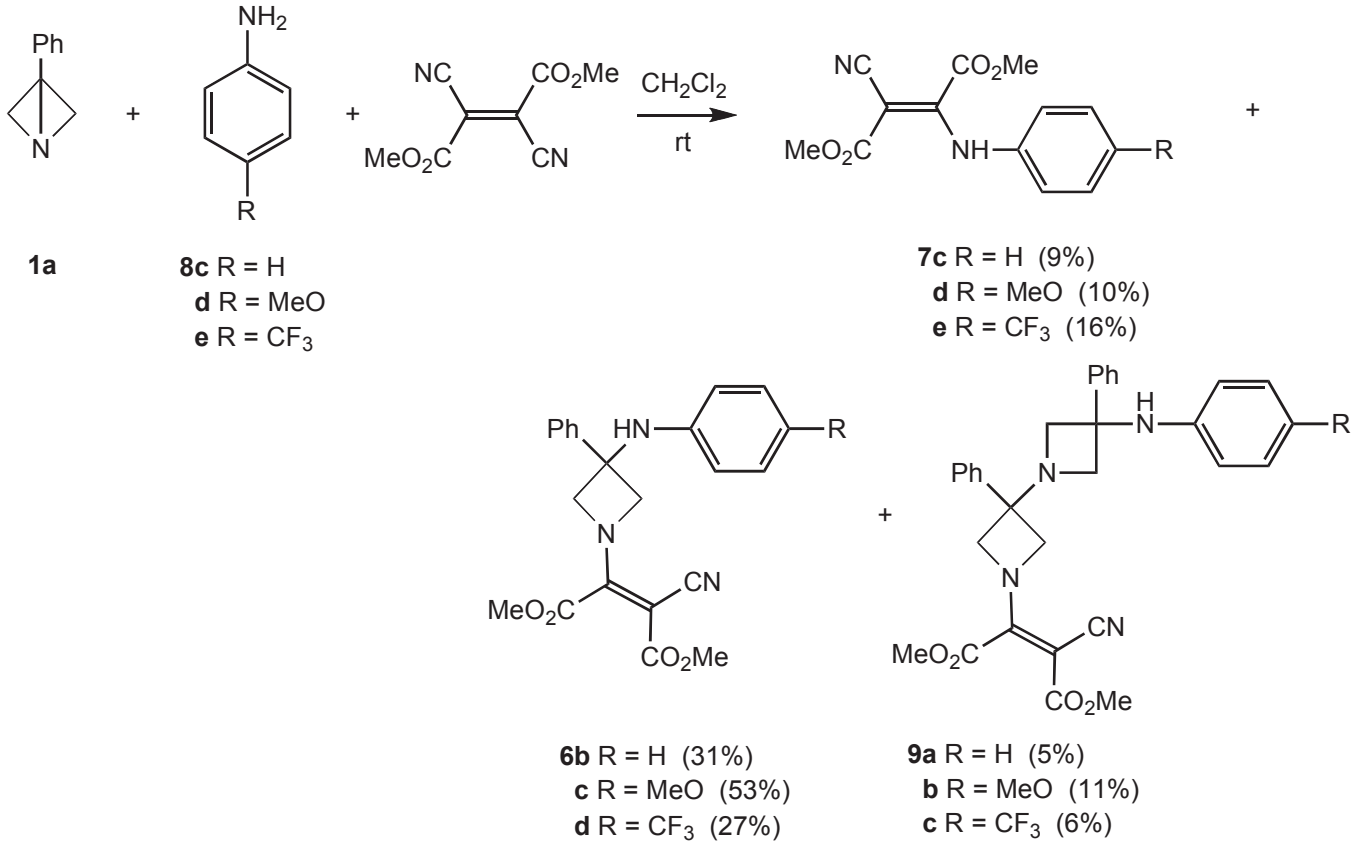
In the first series of three-component reactions, a mixture of equimolar amounts of **1a** and the corresponding primary amine, *e.g*. cyclohexylamine (**8a**), in dichloromethane at room temperature was treated with one mole equivalent of DCFM, dissolved in the same solvent. As depicted in *Scheme 2*, the mixture contained the enamine (**7a**) along with unchanged **1a**. After chromatographic purification, the already described compound (**7a**)[8] was obtained in 88% yield. The replacement of cyclohexylamine (**8a**) in the reaction mixture by benzylamine (**8b**) gave also an enamine (**7b**)[10] as the sole product of this reaction. Similarly to the case with **8a**, the yield of the enamine (**7b**), being the product of the two-component reaction, was high and was determined to 85%. Product (**7b**) was also obtained in the two-component reaction of **8b** with DCFM (94%). The results of the experiments with **8a** and **8b** showed that aliphatic primary amines with high nucleophilicity react faster with DCFM than **1a**, and no competition of the two nucleophiles, present in the solution in identical mol ratios, was observed.

The analogous reaction with aniline (**8c**) led to a more complex mixture and, according to the ^{1}H-NMR analysis, **1a** was completely consumed. The chromatographic separation gave three fractions. The compound isolated from the least polar fraction in 9% yield was identified as the enamine (**7c**).[8] The second fraction contained the 1:1:1 product (**6b**) as the major component (31%) of the reaction. Its ^{1}H-NMR spectrum was characterized by the presence of two MeO signals at 3.73 and 3.91 ppm and two AB systems at 4.38/4.63 ppm with J = 10.1 Hz and 4.91/4.96 ppm with J = 11.3Hz, respectively, for two CH_2 groups of the azetidine ring. In addition, a set of multiplets of 10 aromatic H-atoms confirmed the structure of **6b** (*Scheme 3*). The most polar fraction gave a colorless solid (**9a**) in 5% yield, which displayed a similar ^{1}H-NMR spectrum as **6b**, but differed by the presence of an additional AB system for two azetidine CH_2 groups located at 3.5/3.7 ppm. Furthermore, the integration of the aromatic H-atoms confirmed the presence of three Ph residues.

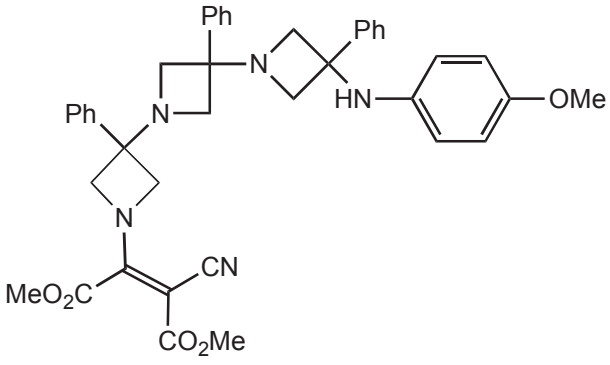
The ESI-MS revealed the $[M+Na]^+$ peak of **6b** at *m/z* 414 and for **9a** at *m/z* 545, thus confirming the structures of a 1:1:1 and 1:2:1 product of type **6** and **9**, respectively. The configuration of the C=C bonds of **6** and **9** is described as (*E*) based on the assumption presented in note 10. The simultaneous formation of **6b** and **9a** suggests that the secondary step of the reaction occurs via competitive attack of aniline

versus **1a** onto the initially formed zwitterion. The low yield of **7c** in comparison with **6b** + **9a** evidences that **1a** is a more prone nucleophile in the reaction with DCFM.

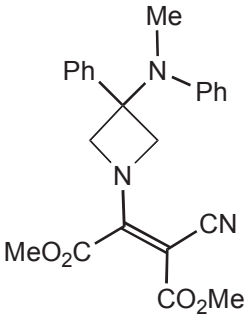
Scheme 3



Similar to aniline, the three-component reaction with anisidine (**8d**) led to the complete conversion of **1a**, and the separation of the mixture gave the corresponding products (**7d**), (**6c**) and (**9b**) (*Scheme 3*) in a ratio comparable with that observed in the case of aniline (**8c**).[11] With the aim of increasing the yield of the 'oligoazetidine' (**9b**), the stoichiometry of the reaction was modified, and a twofold (Procedure B) as well as a threefold amount (Procedure C) of **1a** was used in the following two experiments. In both cases, the formation of the 1:1 product (**7d**) was completely suppressed and, according to the ^{1}H-NMR spectra of the crude mixtures, significant amounts of **1a** were still present. The chromatographic separation yielded in each case **6c** along with **9b** and a third, even more polar fraction. In comparison with the results of the reaction with equimolar amounts of starting materials, the yields of the isolated products were increased in favor of **9b**. The most polar fraction, after additional purification, was analyzed by means of ^{1}H-NMR spectroscopy, and the data obtained confirm the structure of the 'oligoazetidine' (**10a**).[12]



10a

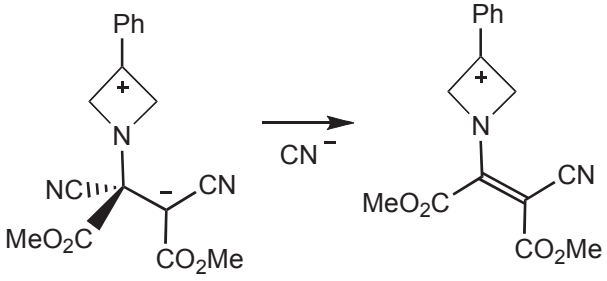


6e

In order to examine the scope of the three-component reactions with **1a**, DCFM, and an aromatic amine, the 4-trifluoromethyl- (**8e**) and 4-nitroaniline were included in the study. In spite of the fact that the basicity of the former is significantly lower when compared with aniline (pK_{BH}^{+} = 2.5 versus 4.6), the results of the reaction with equimolar amounts of reactants was comparable with that obtained for aniline, *i.e*. products (**7e**), (**6d**) and (**9c**) were isolated after chromatographic workup. In contrast, the reaction with 4-nitroaniline (pK_{BP}^{+} = 1.0) led to a complex mixture. After 30 min, **1a** was no more present in the mixture, but after attempted chromatographic separation, apart from 4-nitroaniline no defined product could be isolated.

As already mentioned, *N*-methylaniline did not react with DCMF.[8] However, the three-component reaction with **1a**, carried out in the typical manner, led to a single product. After isolation in 96% yield, its structure was elucidated as the 1:1:1 product (**6e**). In this case, neither the 1:1 nor the 1:2:1 product was formed.

Scheme 4



11 **12**

CONCLUSIONS

The present study showed that the reactivity of 3-phenyl-1-azabicyclobutane (**1a**) as a Michael donor towards DCFM is comparable with that of primary aromatic amines. On the other hand, cyclohexylamine

(**8a**) reacts much faster with DCFM, and in a competition experiment, neither the 1:1:1 product nor higher 'oligomers' **9** or **10** were formed. The reactivity of benzylamine (**8b**) is comparable with that of cyclohexylamine (**8a**). As evidenced in earlier studies, the reaction of **1a** with DCFM occurs via a zwitterion **11**, which can be trapped by a nucleophile followed by elimination of HCN.[7] On the other hand, elimination of CN^- from **11** could lead to the cation **12** (*Scheme 4*), which than can be intercepted by the nucleophile. Depending on the type of the nucleophile, the trapping product stabilizes by deprotonation (with methanol, primary and secondary amines) or, in the case of **1a** as the nucleophile, an oligomerization of the azetidine unit occurs. In each step of this oligomerization, **1a** and the aromatic amine compete as nucleophiles. A similar oligomerization was reported for the reactions of 3-ethyl and 3-phenyl-1-azabicyclo[1.1.0]butanes with tosyl azide.[13,14]

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 (δ = 0 ppm) as an internal standard; chemical shifts (δ) in ppm. The multiplicity of the ^{13}C signals was deduced from DEPT spectra. MS spectra were recorded on a LKB-2091 or Finnigan SSQ-700 spectrometer using electrospray (ESI) method; *m/z* (rel. %). ESI-HR-MS on Finnigan MAT-95. Elemental analyses were performed in the Analytical Laboratory of the University of Zurich or in the Laboratory of the Polish Academy of Sciences (CBMiM) in Łódź.

Starting materials. For the preparation of the starting materials, known procedures were applied: 3-phenyl-1-azabicyclo[1.1.0]butane (**1c**),[15] and dimethyl 2,3-dicyanofumarates (DCFM).[9] Amines **8a–e** were used as commercial reagents and purified before usage according to standard procedures.

Reactions of dimethyl dicyanofumarate (DCFM) with amines 8b, 8d and 8e. – General procedure. To a magnetically stirred solution of DCFM (184 mg, 1 mmol) in 2 mL of the appropriate solvent (MeOH or CH_2Cl_2), the corresponding amine **8** (1.1 mmol) was added in small portions at rt. The stirring was continued at rt and the progress of the reaction was monitored by TLC and ^{1}H-NMR spectroscopy. When the amine **8** was completely consumed, the solvent was evaporated and the product **7** was isolated by means of preparative layer chromatography on plates coated with SiO_2 using a mixture of petroleum ether and CH_2Cl_2 (1:9) or petroleum ether and AcOEt (8:2) as the eluent. Additional crystallization afforded analytically pure sample. Reported yields refer to the product isolated after chromatography. In the case

of **7b**, crystalline product was also obtained by crystallization of the crude material from MeOH.

Dimethyl (*Z*)-2-benzylamino-3-cyanobutanedioate (**7b**). Solvent used for the reaction: CH_2Cl_2; reaction time: 30 min. Yield: 258 mg (94%). Colorless crystals, mp 102–104 ºC (MeOH). IR (KBr): 3257*m* (NH), 2956*w*, 2215*vs* (C≡N), 1747*vs* (C=O), 1687*vs* (C=O), 1598*vs* (C=C), 1451br.*m*, 1274*vs*, 1255*s*, 1198*m*, 1159*w*, 1063*m*, 1008*w*, 788*s*, 749*m*, 698*m*. ^{1}H-NMR ($CDCl_3$): 9.70 (*br.s*, NH); 7.10–7.50 (*m*, 5 arom. H); 4.45 (*d*, $^2J_{H,H}$ = 7.5 Hz, CH_2); 3.90, 3.76 (2*s*, 2 MeO). ^{13}C-NMR ($CDCl_3$): 168.1, 161,3, 161.0 (3*s*, 2 C=O, =C(2)); 135.2 (*s*, 1 arom. C); 128.9, 128.4, 127.4 (3*d*, 5 arom. CH); 116.3 (*s*, CN); 71.1 (*s*, =C(3)); 53.6, 51.8 (2*q*, 2 MeO); 49.7 (*t*, CH_2). ESI-MS: 298 (16), 297 (100, $[M+Na]^+$), 275 (6, $[M+1]^+$). Anal. Calcd for $C_{14}H_{14}N_2O_4$: C, 61.31; H 5.14; N 10.21. Found: C, 61.31; H, 5.03; N, 10.25.

Dimethyl (*Z*)-3-cyano-2-[(4-methoxyphenyl)amino]butanedioate (**7d**). Solvent used for the reaction: CH_2Cl_2; reaction time: 4 d. Yield: 127 mg (44%). Colorless crystals, mp 93–95 ºC (MeOH). IR (KBr): 2215*vs* (C≡N), 1745*vs* (C=O), 1682*vs* (C=O), 1598*vs* (C=C), 1581*s*, 1510*s*, 1436*m*, 1275br.*s* (C–O), 1255br.*s* (C–O), 1035*s*, 849*w*, 778*m*. ^{1}H-NMR ($CDCl_3$): 10.90 (br.*s*, NH); 7.06, 6.88 (*AB*, *J* = 9 Hz, 4 arom. H); 3.85, 3.81, 3.78 (3*s*, 3 MeO). ^{13}C-NMR ($CDCl_3$): 168.2, 161.4, 159.5, 159.0 (4*s*, 2 C=O, =C(2), 1 arom. C); 129.9 (*s*, 1 arom. C); 125.0, 114.8 (2*d*, 4 arom. CH); 116.0 (*s*, CN); 73.5 (*s*, =C(3)); 55.5, 53.7, 52.3 (3*q*, 3 MeO). ESI-MS (MeOH): 314 (18), 313 (100, $[M+Na]^+$), 292 (10), 291 (62, $[M+1]^+$), 259 (52), 245 (14), 231 (11). HR-ESI-MS: 313.0793 (calcd. 313.0795 for $C_{14}H_{14}N_2NaO_5$, $[M+Na]^+$), 291.0973 (calcd. 291.0976 for $C_{14}H_{15}N_2O_5$, $[(M+1]^+$). Anal. Calcd for $C_{14}H_{14}N_2O_5$: C, 57.93; H 4.86; N 9.65. Found: C, 57.43; H, 4.80; N, 9.46.

Dimethyl (*Z*)-3-cyano-2-[(4-trifluoromethylphenyl)amino]butanedioate (**7e**). Solvent used for the reaction: MeOH; reaction time: 8 d. Yield: 138 mg (42%). Colorless crystals, mp 117–119 ºC (MeOH). IR (KBr): 2218*s* (C≡N), 1751*s* (C=O), 1686*s* (C=O), 1609*s*, 1579*vs* (C=C), 1442*m*, 1325*vs*, 1275*vs* (C–O), 1120*s*, 1068*s*, 1027*w*, 850*w*, 798*w*. ^{1}H-NMR ($CDCl_3$): 11.20 (br.*s*, NH); 7.63, 7.20 (*AB*, *J* = 8.5 Hz, 4 arom. H); 3.88, 3.86 (2*s*, 2 MeO). ^{13}C-NMR ($CDCl_3$): 167.8, 161.2, 157.8 (3*s*, 2 C=O, =C(2)); 140.2 (*s*, 1 arom. C); 124.4 (*q*, $^1J_{C,F}$ = 398 Hz, CF_3); 127.1 (*q*, $^3J_{C,F}$ = 3.6 Hz, 2 arom. CH); 122.4 (*d*, 2 arom. CH); 126.7 (*q*, $^2J_{C,F}$ = 166.7 Hz, 1 arom. C); 115.2 (*s*, CN); 76.7 (*s*, =C(3)); 54.0, 52.7, 52.3 (3*q*, 3 MeO). Anal. Calcd for $C_{14}H_{11}F_3N_2O_4$: C, 51.23; H 3.37; N 8.53. Found: C, 51.00; H, 3.33; N, 8.38.

Three component reactions with 1a, DCFM and variable amounts of amine 8. – General procedure. To a magnetically stirred solution of **1a** (131 mg, 1 mmol) and the corresponding amine (1 mmol (procedure A), 2 mmol (procedure B) or 3 mmol (procedure C)) in 3 mL of abs. CH_2Cl_2, the powdered,

crystalline DCFM (194 mg, 1 mmol) was added in small portions. Stirring was continued for 30 min to complete the reaction. Subsequently, the solvent was evaporated to dryness and the mixture obtained was controlled by ^{1}H-NMR spectroscopy. In all cases, no diagnostic multiplets of **1a** (2.79–2.76 and 1.54–1.51 ppm for 2 CH_2) were found in the spectra evidencing thereby full conversion of the starting material. Mixtures of products were separated chromatographically on SiO_2 columns or preparative plates coated with SiO_2. Mixtures of petroleum ether with AcOEt (8:2) or CH_2Cl_2 and MeOH (99:1) were used as eluents. The isolated solid products were additionally purified by crystallization.

Reaction with cyclohexylamine (8a) (procedure A). Column chromatography (SiO_2, $CHCl_3$) afforded crystalline **7a** as a sole product.

Dimethyl (*Z*)-3-cyano-2-(cyclohexylamino)butanedioate (**7a**). Yield: 235 mg (88%). Colorless crystals, mp 102–105 ºC (MeOH) (ref.[8]: mp 100–104 ºC).

Reaction with benzylamine (8b) (procedure A). Separation was achieved by column chromatography (SiO_2, CH_2Cl_2).

Dimethyl (*Z*)-2-benzylamino-3-cyanobutanedioate (**7b**). Yield: 233 mg (85%). Colorless crystals, mp 102–104 °C.

Reaction with aniline (8c) (procedure A). Separation was achieved on preparative plates coated with SiO_2; a mixture of CH_2Cl_2 and MeOH (99:1) was used as the eluent.

Dimethyl (*Z*)-3-cyano-2-(phenylamino)butanedioate (**7c**). Isolated as the least polar fraction. Yield: 24 mg (9%). Colorless crystals, mp 89–92 °C (ref.[8]: mp 90–92 °C). IR and ^{1}H-NMR data fit well with that described in the literature.[8]

Dimethyl (*E*)-3-cyano-2-[3-phenyl-3-(phenylamino)azetidin-1-yl]butanedioate (**6b**). Isolated as the more polar fraction. Yield: 159 mg (31%). Colorless crystals, mp 181–183 °C (MeOH). IR (KBr): 3365*s* (NH), 2953*w*, 2201*m* (C≡N), 1750*s* (C=O), 1707*s* (C=O), 1572*vs* (C=C), 1496*w*, 1435*m*, 1294*s*, 1269*s*, 1190*m*, 1146*m*, 1021*w*, 754*m*, 699*m*. ^{1}H-NMR ($CDCl_3$): 7.60–6.65 (*m*, 8 arom. H); 6.29 (*d*, $^2J_{H,H}$ = 8.0 Hz, 2 arom. H); 4.85 (br.*s*, NH); 4.97, 4.90 (*AB*, $^2J_{H,H}$ = 11.3 Hz, CH_2); 4.62, 4.38 (*AB*, $^2J_{H,H}$ = 11.3 Hz, CH_2); 3.91, 3.73 (2*s*, 2 MeO). ^{13}C-NMR ($CDCl_3$): 161.9, 161.7, 158.4 (3*s*, 2 C=O, =C(2)); 143.6, 140.6 (2*s*, 2 arom. C); 129.2, 129.1, 128.0, 125.1, 118.7, 114.3 (6*d*, 10 arom. CH); 116.6 (*s*, CN); 70.9 (*s*, =C(3)); 67.6, 65.8

(2*t*, 2 CH_2); 59.0 (*s*, C_q); 53.7, 52.1 (2*q*, 2 MeO). ESI-MS (MeOH): 415 (23), 414 (100, [*M*+Na]$^+$), 352 (39), 299 (9), 230 (11). Anal. Calcd for $C_{22}H_{21}N_3O_4$: C, 67.51; H 5.41; N 10.73. Found: C, 66.98; H, 5.19; N, 10.68.

Dimethyl (*E*)-3-cyano-2-{3-phenyl-3-[3-phenyl-3-(phenylamino)azetidin-1-yl]azetidin-1-yl}butanedioate (**9a**). Isolated as the most polar fraction. Yield: 29 mg (5%). Colorless solid, mp 125–130 °C (MeOH). IR (KBr): 3397br.*m* (NH), 2952*w*, 2206*m* (C≡N), 1748*s* (C=O), 1707*s* (C=O), 1603*m*, 1566*vs* (C=C), 1497*m*, 1447br.*m*, 1308*m*, 1260br.*s*, 1195*m*, 1133*s*, 1025*w*, 760*s*, 700*s*. ^{1}H-NMR($CDCl_3$): 7.60–6.60 (*m*, 13 arom. H); 6.27 (*d*, $^2J_{H,H}$ = 8.0 Hz, 2 arom. H); 4.93, 4.92 (*AB*, $^2J_{H,H}$ = 15 Hz, CH_2); 4.45 (br.*s*, CH_2); 3.92, 3.74 (2*s*, 2 MeO); 3.70 (*m*, 2H); 3.50 (*m*, 2H). ^{13}C-NMR ($CDCl_3$): 164.9, 161.7, 158.2 (3*s*, 2 C=O, =C(2)); 144.6, 142.8, 137.8 (3*s*, 3 arom. C); 128.9, 128.7, 128.5, 128.2, 127.0, 126.5, 125.4, 117.7, 114.2 (9*d*, 15 arom. CH); 116.6 (*s*, CN); 70.6 (*s*, =C(3)); 61.0, 60.9, 60.7, 60.2 (4*t*, 4 CH_2); 65.9, 63.2 (2*s*, 2 C_q); 53.6, 52.1 (2*q*, 2 MeO). ESI-MS (MeOH): 546 (16), 545 (48, [*M*+Na]$^+$), 524 (39), 523 (100, [*M*+1]$^+$), 431 (10), 430 (33), 299 (13), 298 (65). HR-ESI-MS: 545.2159 (calcd. 545.2159 for $C_{31}H_{30}N_4NaO_4$, [*M*+Na]$^+$), 523.2340 (calcd. 523.2340 for $C_{31}H_{31}N_4O_4$, [(*M*+1]$^+$).

Reaction with anisidine (8d) (procedures A, B and C). Separation of the crude mixture was achieved on preparative plates coated with SiO_2; a mixture of CH_2Cl_2 and AcOEt (7:3) was used as the eluent.

Dimethyl (*Z*)-3-cyano-2-[(4-methoxyphenyl)amino]butanedioate (**7d**). Isolated as the least polar fraction. Yield: 29 mg (10%) (procedure A), traces (procedure B), and not found (procedure C). Colorless crystals, mp 93–95 °C (MeOH) ; according to IR and ^{1}H-NMR data identical with the substance isolated form the two-component reaction.

Dimethyl (*E*)-3-cyano-2-{3-phenyl-3-[(4-methoxyphenyl)amino]azetidin-1-yl}butanedioate (**6c**). Isolated as the second polar fraction. Yield: 225 mg (53%) (procedure A), 96 mg (23%) (procedure B), and 124 mg (29%) (procedure C). Colorless crystals, mp 106–109 ºC (dec.) (MeOH). IR (KB): 3406*m* (NH), 2952*w*, 2207*m* (C≡N), 1747*s* (C=O), 1705*s* (C=O), 1566*vs* (C=C), 1513*s*, 1457*m*, 1436*m*, 1278br.*vs*, 1196*m*, 1135*m*, 1037*m*, 823*m*, 764*m*, 702*w*. ^{1}H-NMR ($CDCl_3$): 7.60–7.25 (*m*, 5 arom. H); 6.76, 6.29 (*AB*, $^3J_{H,H}$ = 8.5 Hz, 4 arom. H); 4.95, 4.80 (*AB*, $^2J_{H,H}$ = 11.5 Hz, CH_2); 4.55, 4.35 (*AB*, $^2J_{H,H}$ = 10.5 Hz, CH_2); 3.90, 3.70, 3.65 (3*s*, 3 MeO). ^{13}C-NMR ($CDCl_3$): 164.9, 161.7, 158.5 (3*s*, 2 C=O, =C(2)); 153.0, 140.9, 137.3 (3*s*, 3 arom. C); 129.1, 128.0, 125.3, 116.0, 114.9 (5*d*, 10 arom. CH); 116.5 (*s*, CN); 71.0 (*s*, =C(3)); 67.5, 65.9 (2*t*, 2 CH_2); 56.6 (*s*, C_q); 55.6, 53.8, 52.2 (3*q*, 3 MeO). ESI-MS (MeOH): 445 (37), 444 (100, [*M*+Na]$^+$), 393 (9), 225 (14). Anal. Calcd for $C_{23}H_{23}N_3O_5$: C, 65.55; H 5.50; N 9.97. Found: C,

65.45; H, 5.28; N, 9.60.

Dimethyl (*E*)-3-cyano-2-{3-phenyl-3-[3-(4-methoxyphenyl)amino-3-phenylazetidin-1-yl]azetidin-1-yl}butanedioate (**9b**). Isolated as the third polar fraction. Yield: 60 mg (11%) (procedure A), 64 mg (12%) (procedure B), and 95 mg (17%) (procedure C). Colorless crystals, mp 111–116 °C (dec.) (MeOH). IR (neat): 3393*m* (NH), 2951*w*, 2205*m* (C≡N), 1748*s* (C=O), 1706*s* (C=O), 1566*vs* (C=C), 1512*s*, 1447*m*, 1307*m*, 1249br.*s*, 1132*m*, 1030*m*, 910*w*, 822*w*, 763*w*, 734*w*, 701*w*. ^{1}H-NMR ($CDCl_3$): 7.60–7.10 (*m*, 10 arom. H); 6.65, 6.25 (*AB*, $^3J_{H,H}$ = 7.5 Hz, 4 arom. H); 4.95, 4.45 (2 br.*s*, 2 CH_2); 3.90, 3.73, 3.65 (3*s*, MeO); 3.66, 3.52 (*AB*, $^2J_{H,H}$ = 6.5 Hz, 2 CH_2). ^{13}C-NMR ($CDCl_3$): 165.0, 161.8, 158.3 (3*s*, 2 C=O, =C(2)); 152.4, 138.6, 137.9 (3*s*, 3 arom. C); 128.8, 128.6, 128.3, 127.1, 126.5, 125.6, 115.8, 114.6 (8*d*, 10 arom. CH); 116.6 (*s*, CN); 70.8 (*s*, =C(3)); 61.8, 60.6 (2*t*, 2 CH_2); 61.0 (*t*, 2 CH_2), 60.3, 55.6 (2*s*, 2 C_q); 54.8, 53.7, 52.1 (3*q*, 3 MeO). ESI-MS (MeOH): 575 (11, $[M+Na]^+$), 554 (36), 553 (100, $[M+1]^+$), 430 (31). HR-ESI-MS: 575.2259 (calcd. 575.2265 for $C_{32}H_{32}N_4NaO_5$, $[M+Na]^+$), 553.2442 (calcd. 553.2446 for $C_{32}H_{33}N_4O_5$, $[(M+1]^+$).

Dimethyl (*E*)-3-cyano-2-(3-phenyl-3-{[3-(4-methoxyphenyl)amino-3-phenylazetidin-1-yl]-3-phenylazetidin-1-yl}azetidin-1-yl)butanedioate (**10a**). Isolated as the most polar fraction. Yield: not observed (procedure A), traces (procedure B), 21 mg (3%) (procedure C). Colorless, viscous oil. IR (neat): 3382*m* (NH), 2980*s*, 2206*s* (C≡N), 1747*vs* (C=O), 1705*vs* (C=O), 1559*vs* (C=C), 1512*s*, 1447br.*m*, 1374*m*, 1249br.*vs*, 1134*s*, 927*w*, 842*m*, 762*m*, 736*s*, 701*s*. ^{1}H-NMR ($CDCl_3$): 7.70–7.10 (*m*, 15 arom. H); 6.63, 6.22 (*AB*, $^3J_{H,H}$ = 9.0 Hz, 4 arom. H); 4.90, 4.40 (2br.*s*, 2 CH_2); 3.89, 3.74, 3.66 (3*s*, 3 MeO); 3.70–3.20 (*m*, 4 CH_2). ESI-MS (MeOH): 816 (14), 815 (25), 706 (6, $[M+Na]^+$), 685 (41), 684 (100, $[M+1]^+$), 551 (18), 529 (13), 444 (16), 422 (12). HR-ESI-MS: 815.3903 (calcd. 815.3916 for $C_{50}H_{51}N_6O_5$, $[M$(**10a**)+**1a**+1$]^+$), 684.3174 (calcd. 684.3181 for $C_{41}H_{42}N_5O_5$, $[(M$(**10a**)+1$]^+$).

Reaction with 4-(trifluoromethyl)phenylamine (8e) (procedure A). Separation of the crude mixture was achieved on preparative plates coated with SiO_2; a mixture of petroleum ether and AcOEt (8:2) was used as the eluent.

Dimethyl (*Z*)-3-cyano-2-[(4-trifluoromethylphenyl)amino]butanedioate (**7e**). Isolated as the least polar fraction. Yield: 53 mg (16%). Colorless crystals, mp 117–119 °C (MeOH).

Dimethyl (*E*)-3-cyano-2-{3-phenyl-3-[(4-trifluoromethylphenyl)amino]azetidin-1-yl}butanedioate (**6d**). Isolated as the second fraction. Yield: 123 mg (27%). Colorless crystals, mp 167–169 °C (MeOH or

diisopropylether). IR (KBr): 3366*m* (NH), 2955*w*, 2204*m* (C≡N), 1747*s* (C=O), 1709*s* (C=O), 1618*m*, 1567*vs* (C=C), 1460*m*, 1438*m*, 1327*vs*, 1287*s* (C–F), 1261*s* (C–F), 1194*m*, 1134br.*s*, 1067*s*, 1015br.*w*, 930*w*, 830*m*, 763*m*, 701*m*. ^{1}H-NMR ($CDCl_3$): 7.60–7.15 (*m*, 5 arom. H); 7.35, 6.35 (*AB*, $^3J_{H,H}$ = 9.0 Hz, 4 arom. H); 4.85 (br.*s*, NH); 4.95 (br.*s*, CH_2); 4.45 (br.*s*, CH_2); 3.90, 3.70 (2*s*, 2 MeO). ^{13}C-NMR ($CDCl_3$): 164.8, 161.6, 158.5 (3*s*, 2 C=O, =C(2)); 164.5, 139.8 (2*s*, 2 arom. C); 124.5 (*q*,$^1J_{C,F}$ = 270 Hz, CF_3); 120.4 (*q*, $^2J_{C,F}$ = 32.8 Hz, 1 arom. C); 129.3, 128.4, 125.0, 113.6 (4*d*, 7 arom. CH); 126.7 (*q*, $^3J_{C,F}$ = 3.7 Hz, 2 arom. CH); 116.6 (*s*, CN); 71.3 (*s*, =C(3)); 67.6, 65.6 (2*t*, 2 CH_2); 56.0 (*s*, C_q); 53.9, 52.3 (2*q*, 2 MeO). ESI-MS (MeOH): 483 (37), 482 (100, $[M+Na]^+$), 460 (5, $[M+1]^+$), 459 (3, M^+). Anal. Calcd for $C_{23}H_{20}F_3N_3O_4$: C, 60.13; H 4.39; N 9.15. Found: C, 59.68; H, 4.16; N, 8.92.

Dimethyl (*E*)-3-cyano-2-{3-phenyl-3-[3-(4-trifluoromethylphenyl)amino-3-phenylazetidin-1-yl] azetidin-1-yl}butanedioate (**9c**). Isolated as the third, most polar fraction. Yield: 32 mg (6%). Colorless crystals, mp 97–100 °C (dec.) (MeOH). IR (KBr): 3393*m* (NH), 2955*w*, 2207*m* (C≡N), 1748*vs* (C=O), 1707*s* (C=O), 1617*s*, 1568*vs* (C=C), 1456br.*m*, 1325*s*, 1262br.*s*, 1191*w*, 1168*w*, 1114*s*, 1066*m*, 830*m*, 763*m*, 701*m*. ^{1}H-NMR ($CDCl_3$): 7.60–7.15 (*m*, 10 arom. H); 7.40, 6.40 (*AB*, $^3J_{H,H}$ = 9.0 Hz, 4 arom. H); 5.55 (br.*s*, NH); 5.95 (br.*s*, CH_2); 4.70, 4.40 (*AB*, $^2J_{H,H}$ = 9.8 Hz, CH_2); 3.90, 3.70 (2*s*, 2 MeO); 3.70, 3.50 (*AB*, $^2J_{H,H}$ = 7.5 Hz, 2 CH_2). ^{13}C-NMR ($CDCl_3$): 165.0, 161.8, 158.3 (3*s*, 2 C=O, =C(2)); 147.4.5, 141.9, 137.5 (3*s*, 3 arom. C); 124.9 (*q*,$^1J_{C,F}$ = 270 Hz, CF_3); 126.4 (*q*, $^3J_{C,F}$ = 3.7 Hz, 2 arom. CH); 127.4 (*q*, $^2J_{C,F}$ = 31.0 Hz, 1 arom. C); 129.4, 128.9, 128.8, 127.4, 126.5, 126.0, 125.4, 113.5 (7*d*, 12 arom. CH); 114.9 (*s*, CN); 71.4 (*s*, =C(3)); 68.6, 67.6 (2*t*, 2 CH_2); 66.2 (*t*, 2 CH_2); 60.9, 60.5 (2*s*, 2 C_q); 53.7, 52.2 (2*q*, 2 MeO). ESI-MS (MeOH): 629 (22, $[M+K]^+$), 614 (34), 613 (100, $[M+Na]^+$), 592 (31), 591 (87, $[M+1]^+$), 509 (28), 488 (11), 482 (13), 449 (27), 430 (28). HR-ESI-MS: 613.2026 (calcd. 613.2033 for $C_{32}H_{29}F_3N_4NaO_4$, $[M+Na]^+$), 591.2208 (calcd. 591.22214 for $C_{32}H_{30}F_3N_4O_4$, $[(M+1]^+$).

Reaction with *N*-methylaniline (8f). Separation of the crude material was achieved on PLC plates (SiO_2) using a mixture of CH_2Cl_2 and MeOH (99:1) as an eluent and gave **6e** as the sole product. The experiment was carried out using **1a**, **8f** and DCFM in the molar ratio 1:1:1 (procedure A).

Dimethyl (*E*)-3-cyano-2-{3-[(methyl)(phenyl)amino]-3-phenylazetidin-1-yl}butanedioate (**6e**). Yield: 387 mg (96%). Colorless crystals, mp 98–100 ºC (dec.) IR (KBr): 2952*w*, 2206*m* (C≡N), 1750*m* (C=O), 1708*m* (C=O), 1568*vs* (C=C), 1503*m*, 1456*m*, 1436*m*, 1267br.*s*, 1135*s*, 753*m*, 701*m*. ^{1}H-NMR ($CDCl_3$): 7.43–7.20 (*m*, 5 arom. H); 7.17 (*t*-like, 2 arom. H); 6.78 (*t*-like, 1 arom. H); 6.37 (*d*-like, 2 arom. H); 5.10, 4.88 and 4.58, 4.38 (2 *AB*, *J* = 11 and 10 Hz, resp., 2 CH_2); 3.93, 3.76 (2s, 2 MeO); 3.12 (*s*, MeN). ^{13}C-NMR ($CDCl_3$): 165.0, 161.7, 158.0 (3*s*, 2 C=O, =C(2)); 146.4, 140.7 (2*s*, 2 arom. C); 129.23, 129.17,

128.2, 125.3, 118.5, 114.6 (6*d*, 10 arom. CH); 116.5 (*s*, CN); 71.3 (*s*, =C(3)); 66.0, 65.3 (2*t*, 2 CH_2); 61.5 (*s*, C_q); 53.8, 52.2 (2*q*, 2 MeO); 36.9 (*q*, MeN). ESI-MS (MeOH): 429 (26), 428 (100, $[M+Na]^+$), 406 (10, $[M+1]^+$). HR-ESI-MS: 428.1579 (calcd. 428.1581 for $C_{23}H_{23}N_3NaO_4$, $[M+Na]^+$).

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10. The configuration of **7b** was assigned as (*Z*) based on the comparison with the analogous product obtained with aniline.[8] The (*E*)-configuration of **6b** was assigned in analogy to the structure of the corresponding product (**6a**) (Ar = Ph, Nu = $O(CH_2CH_2)_2N$, R = Me) formed with morpholine.[8]
11. Compounds (**7d**) and (**7e**) were prepared in 44% and 42% yield, respectively, in the two-component reactions of DCFM with **8d** and **8e**.
12. The ESI-MS of **10a** showed an additional peak at higher mass with *m/z* 815. According to the HR-ESI-MS, the molecular formula of this minor product corresponds with the next higher oligomer of **10a** containing an additional unit of **1a**.
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