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Cyclobutane Formation by the Reaction of Ethenesulfonyl Fluoride with Dimethyl Diazomalonate

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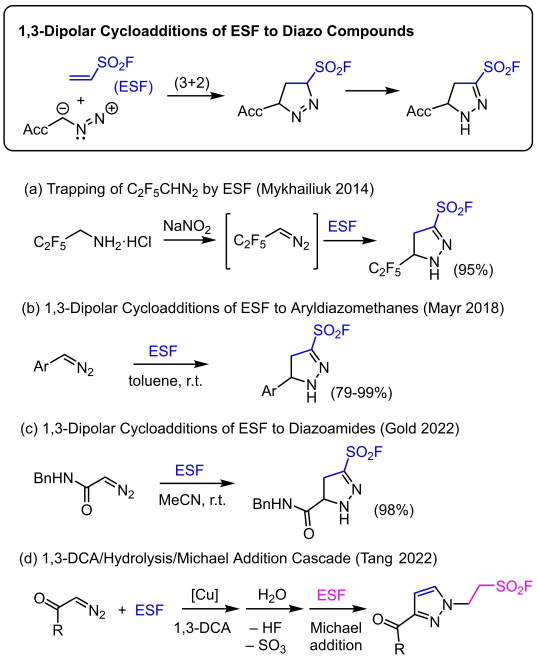
Attempts to synthesize fluorosulfonyl-substituted pyrazolines by Huisgen reactions (1,3-dipolar cycloadditions) of dimethyl diazomalonate with ethenesulfonyl fluoride led to the formation of dimethyl (2*R**,3*S**,4*R**)-2-(1,3-dimethoxy-1,3-dioxopropan-2-yl)-3-(fluorosulfonyl)-4-((fluorosulfonyl)methyl)cyclobutane-1,1-dicarboxylate, a highly substituted cyclobutane derivative, which was characterized by NMR spectroscopy and single crystal X-ray crystallography. The mechanism of its formation was elucidated by carrying out the reaction at different temperatures and workup conditions. It is shown that an initial 1,3-dipolar cycloaddition yields a pyrazoline which extrudes nitrogen with formation of 1-fluorosulfonyl-2,2-bis(methoxycarbonyl)cyclopropane and dimethyl 2-(2-(fluorosulfonyl)ethylidene)malonate, the latter of which dimerized during chromatography on silica gel with formation of the isolated cyclobutane.

Introduction

Organic sulfonyl fluorides have already been known since the 1920s.[1–3] Though the synthetic potential of alkenesulfonyl fluorides to react as Michael acceptors as well as the general ability of organic sulfonyl fluorides to undergo reactions at the SO_2F group had already been recognized in the late 1970s,[2–4] this class of organic compounds had attracted little attention until Sharpless and associates introduced sulfonyl fluoride exchange (SuFEx) reactions[5,6] as a new generation of click chemistry in 2014.[7] Since then numerous applications in organic synthesis,[8] materials chemistry,[3] polymer chemistry,[9] drug discovery,[10,11] medicinal chemistry,[12] and chemical biology[13] have been reported.[14] Furthermore, the electrophilic reactivity of alkenesulfonyl fluorides has been characterized and embedded in the currently most comprehensive reactivity scales for polar reactions.[15]

Alkenesulfonyl fluorides may also act as dipolarophiles in Huisgen reactions (1,3-dipolar cycloadditions) to provide a straightforward access to fluorosulfonyl substituted heterocycles.[16] In reactions with organic azides R-N_3, ethenesulfonyl fluoride (ESF)[6] acted as formal acetylene equivalent, however, because the initially formed cycloadducts rapidly eliminated SO_2 and HF to yield 1-alkyl or 1-aryl-1,2,3-triazoles.[17] On the other hand, the reactions of ESF with diazoalkanes were reported to generate SO_2F-functionalized heterocycles (Scheme 1). Mykhailiuk, for example, used ESF as a highly efficient trapping reagent for the in situ generated 1,3-dipole pentafluorodiazopropane ($C_2F_5CHN_2$) to yield 3-SO_2F-5-pentafluoroethyl-Δ^2-pyrazoline regioselectively (Scheme 1a).[18,19] Analogously, reactions of ESF with aryldiazomethanes gave 5-arylpyrazolines that carried an SO_2F group at position 3 (Scheme 1b).[20] Very recently, ESF was reported by Gold and coworkers to undergo an uncatalyzed 1,3-dipolar cycloaddition with *N*-benzyl-2-diazoacetamide to deliver a 3,5-disubstituted pyrazoline (Scheme 1c).[21] Copper(II) fluoride catalysis was used by Tang and coworkers to synthesize the (3 + 2)-cycloadducts of ESF with α-keto-stabilized diazoalkanes, hydrolysis of which led to HF/SO_3 elimination with formation of pyrazoles that under-



Scheme 1. Reported 1,3-dipolar cycloadditions (1,3-DCA) of ESF with diazo compounds.

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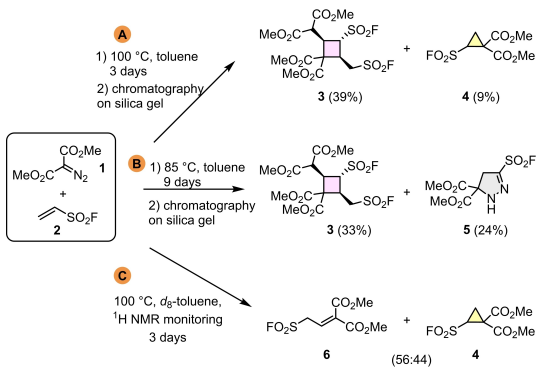
went a Michael addition to a second equivalent of ESF (Scheme 1d).[22]

During our ongoing studies to quantify the reactivities of diazo compounds,[20,23] we envisioned the cycloaddition of ESF with dimethyl diazomalonate to furnish fluorosulfonyl substituted pyrazolines without the need for metal catalysis, in analogy to the reports summarized in Scheme 1.

Herein, we report that the initially formed cycloadduct from diazomalonate and ESF underwent a cascade of subsequent reactions, which ultimately generated highly functionalized cyclobutanes. Online-NMR spectroscopic monitoring of the reaction was used to identify further intermediates in the course of the reaction, which enabled us to elucidate the individual transformations on the way to the isolated cyclobutane.

Results and Discussion

When we tried to synthesize fluorosulfonyl substituted pyrazolines by the reaction of ESF (**2**) with dimethyl diazomalonate (**1**), we isolated cyclobutane **3** as the major product along with a small amount of cyclopropane **4** (Scheme 2A). Cyclobutane **3** showed four singlets for methoxy groups in the proton NMR spectrum as well as two signals in the ^{19}F NMR spectrum, indicating that **3** is a 2:2 product of **1** and **2**.



Scheme 2. Reactions of ethenesulfonyl fluoride (**2**) with dimethyl diazomalonate (**1**) under different conditions.

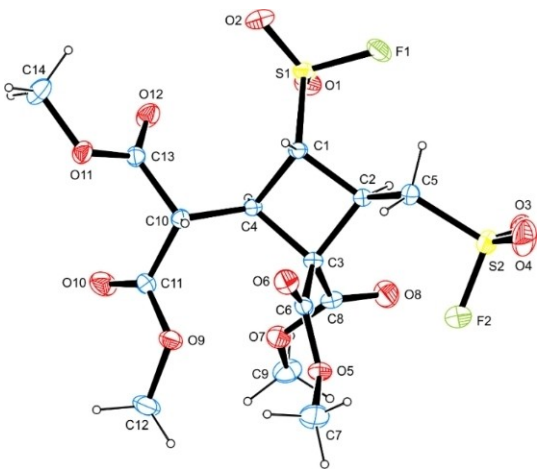


Figure 1. X-ray crystal structure of cyclobutane **3** (CCDC 2183363). Within the cyclobutane ring the atomic distances are for C1-C2 155.1(2), C2-C3 157.2(2), C3-C4 157.6(2), and C4-C1 155.2(2) pm.

Since **3** crystallized nicely after column chromatographic purification, its molecular structure could be investigated by single-crystal X-ray crystallography (Figure 1). The solid state structure shows that the cyclobutane moiety adopts a butterfly conformation with a ring puckering angle of 20.5°. Slightly elongated C–C single bonds (as compared with 153.6 pm in cyclohexane)[24] are due to the ring strain in the four-membered carbocycle. Only one diastereomer with the SO_2F group trans to the vicinal CH_2SO_2F and $CH(CO_2Me)_2$ was obtained.

Cyclobutanes with similar substitution patterns have been formed by gallium chloride-mediated (2+2) dimerization of donor-acceptor cyclopropanes.[25]

Since cyclopropanes, such as **4**, are known to be formed by thermolysis of Δ^1-pyrazolines,[26] the cycloadducts from the reactions of diazoalkanes with dipolarophiles, we repeated the reaction of **1** with **2** at lower temperature, hoping to isolate the precursors of **3** and **4**. However, as depicted in Scheme 2B, cyclobutane **3** was the main product again when the reaction was run at 85 °C, now accompanied by the Δ^2-pyrazoline **5**.

Because of the slow reaction of **1** with **2**, we did not further lower the temperature, but monitored the 100 °C reaction in a sealed tube by ^1H NMR spectroscopy. As depicted in Scheme 2C and documented by the original spectra (Supporting Information), cyclobutane **3** and Δ^2-pyrazoline **5** were not detectable. Instead, the formation of a 44:56 mixture of cyclopropane **4** and alkylidene malonate **6** was observed.

While a solution of **5** (0.128 M) in d_8-toluene remained unchanged over a period of more than 4 months when stored at ambient temperature, the assumption that both, **4** and **6**, are generated by thermolysis of pyrazoline **5** was confirmed by ^1H NMR monitoring of the thermal decomposition of isolated **5** in d_8-toluene at 95 °C. Figure 2 shows that the cyclopropane **4** and the acyclic product **6** are formed in parallel reactions. As soon as the resonances of **4** and **6** have both reached signal-to-noise levels that enable a reliable integration of the ^1H NMR signals (after 72 h), the 55/45 ratio of **4** and **6** remains constant, suggesting that **4** and **6** do not interconvert. The fact that the sum of the concentrations of **4** and **6** is smaller by about 10% than the initial concentration of the starting material **5** may indicate that thermolysis of **5** yields small amounts of further, so far not identified products.

Further experiments were undertaken to gain insight in the mechanisms that ultimately generate cyclobutane **3** from the **4**/**6**-mixture initially obtained by heating **1** and **2** in an inert solvent (Scheme 2C). In particular, we sought to clarify whether the cyclopropane **4** or the alkylidene malonate **6** or both are the precursors of **3**. A solution of equimolar amounts (2.54 mmol) of methyl diazomalonate (**1**) and ESF (**2**) in d_8-toluene was kept at 100 °C for 52 h to generate a 42:58-mixture of **4** and **6** (Figure 3). Stirring of this solution with a small amount of added silica gel at ambient temperature for 30 min did not noticeably change the composition of the mixture ([**4**]:[**6**] = 45:55, Figure 3B). A quick workup of this sample by

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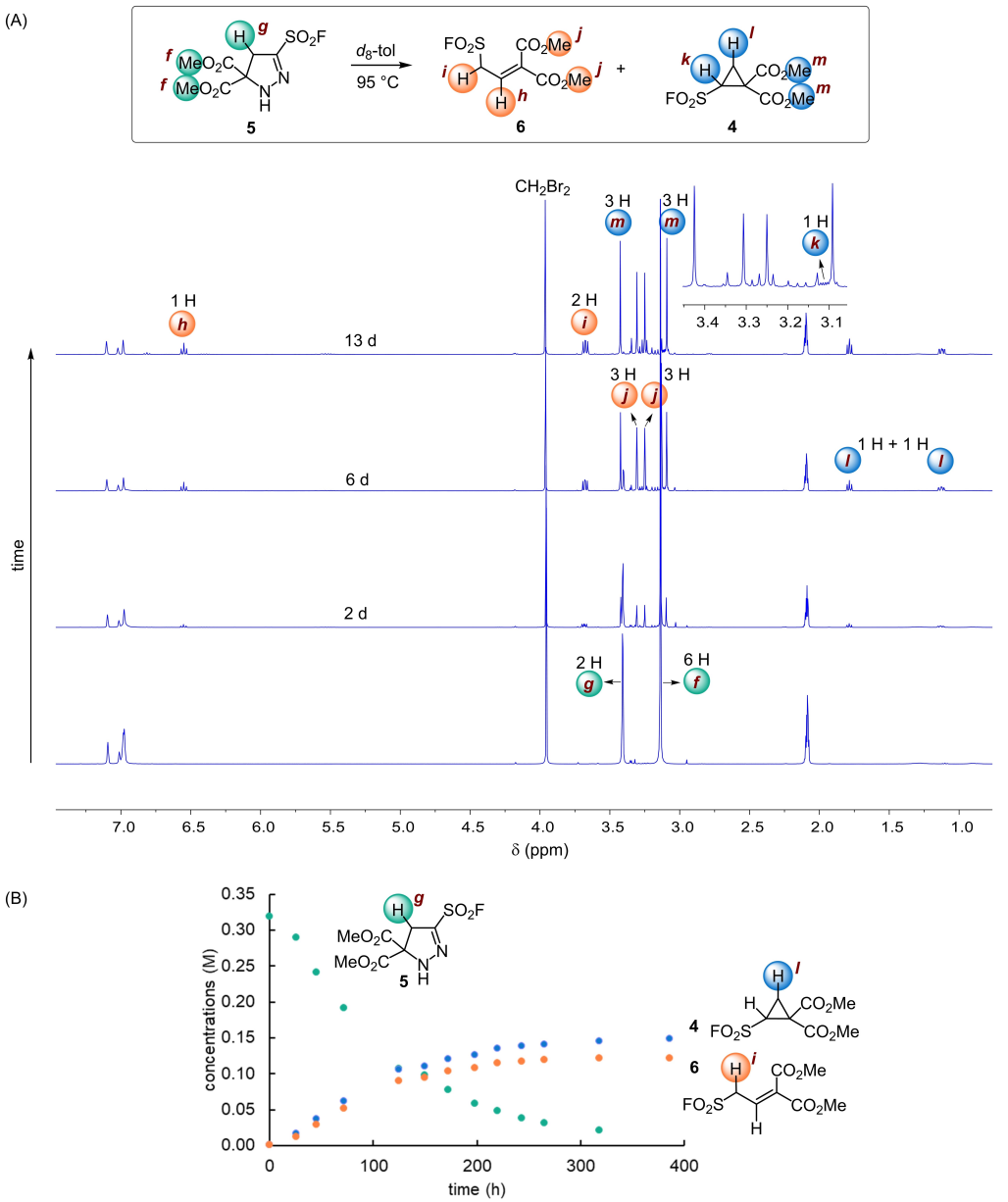

Figure 2. (A) ^{1}H NMR (400 MHz) monitoring of the transformation of **5** (c_0 = 0.318 M) in d_8-toluene at 95 °C with CH_2Br_2 (0.277 M) as the internal integration standard. (B) Concentration profiles for the starting material **5**, the alkylidene malonate **6**, and the cyclopropane **4** in d_8-toluene at 95 °C determined by monitoring the thermal decomposition of **5** by ^{1}H NMR spectroscopy [evaluated protons are marked by colored dots, the resonance at δ_H = 1.66-1.86 ppm (H^l) was used to determine the content of **4**, integrals for **4**, **5**, and **6** were normalized to 1 H and concentrations were calculated relative to CH_2Br_2 as the internal integration standard].

filtration through a plug of silica gel (pentane/ethyl acetate and dichloromethane as eluents) followed by removal of the solvents (vacuum) furnished a residue, which was dissolved in $CDCl_3$ and analyzed by ^{1}H NMR spectroscopy to contain **4** and **6** in a 45:55 ratio (Figure 3C). At this point, the NMR spectrum did not yet indicate formation of the cyclobutane **3**. Then, drops of triethylamine (NEt_3) were added to the **4**/**6**-mixture. NMR monitoring showed that the characteristic resonances for the alkylidene malonate **6** disappeared within minutes (Figure 3D). Yet, due to overlapping resonances, it was not possible to derive the selective conversion of **6** into the cyclobutane **3** from the ^{1}H NMR spectrum. Therefore, the formation of **3** was substantiated by identifying both ^{19}F resonances of **3** in the ^{19}F NMR spectrum (377 MHz) of this sample (Supporting Information, Figure S1).

In contrast to the acyclic product **6**, cyclopropane **4** was not altered by the addition of NEt_3 to the reaction mixture (Figure 3D and Figure S1). It can, therefore, be concluded that basic sites on silica used for the chromatographic purification of the product mixtures (cf. Scheme 2A or Scheme 2B) led to the formation of cyclobutane **3**. Accordingly, acidic additives, such

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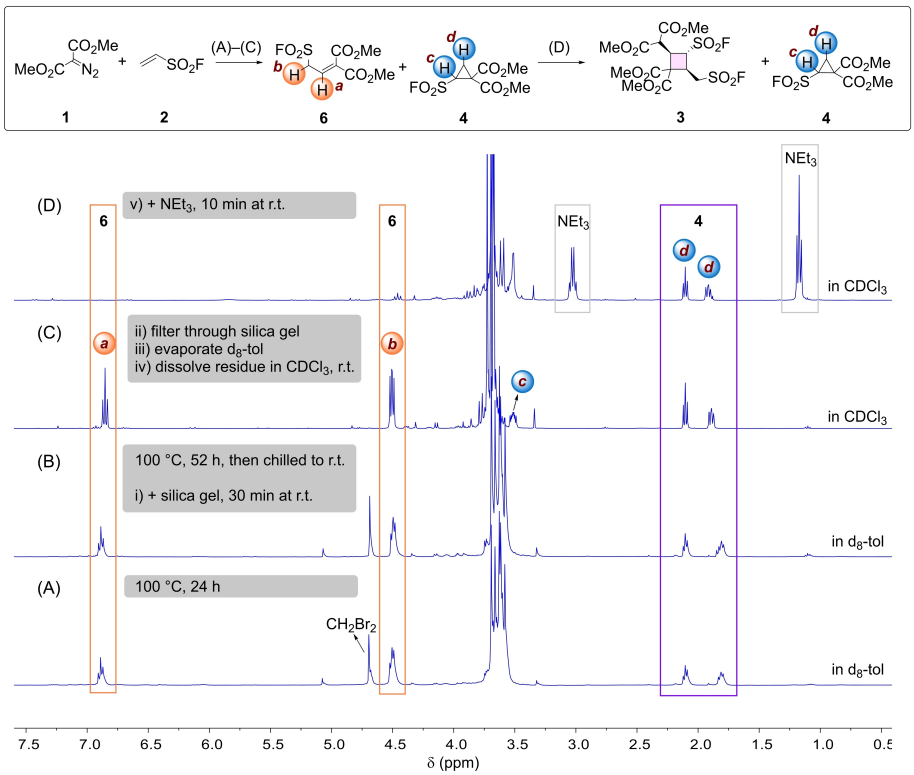
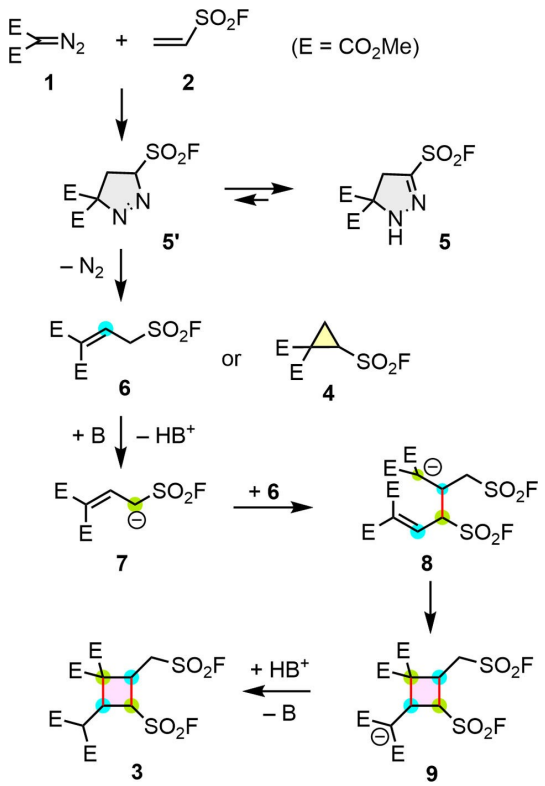


Figure 3. (A) Generation of a mixture of **4** and **6** through the reaction of **1** with **2** (100 °C, in d_8-toluene, CH_2Br_2 as the internal integration standard) with subsequent addition of (B) silica gel, (C) filtration through silica gel and solvent exchange to *d*-chloroform as well as (D) addition of triethylamine.

as acetic acid or boron trifluoride etherate, failed to induce cyclobutane formation from **4**/**6** mixtures in $CDCl_3$ within 24 h.

We, therefore, suggest the reaction mechanism described in Scheme 3. 1,3-Dipolar cycloaddition of dimethyl diazomalonate (**1**) and ESF (**2**) generates the Δ^1-pyrazoline **5′**, which is in rapid equilibrium with its thermodynamically more stable tautomer **5** that is observed by NMR spectroscopy. At higher temperatures, **5′** extrudes molecular nitrogen with formation of cyclopropane **4** and the alkylidene malonate **6**. While **4** is persistent under the reaction and workup conditions, the strong electron-withdrawing nature of the SO_2F group (Hammett substituent parameter $\sigma_p^- = 1.54$ for SO_2F, as compared to $\sigma_p^- = 1.27$ for NO_2)[27] facilitates deprotonation of the CH_2 group of **6**. The resulting allyl anion **7** is sufficiently nucleophilic to undergo a Michael addition with another equivalent of the alkylidene malonate **6** to furnish the diester stabilized anion **8**, which is intramolecularly trapped in a second Michael addition leading to the formation of the cyclobutylmalonyl anion **9**. Protonation of **9** yields the isolated and characterized cyclobutane **3**.



Scheme 3. Proposed reaction mechanism for the formation of cyclobutane **3**.

Conclusion

The highly functionalized cyclobutane **3**, isolated as the major product by the reaction of dimethyl diazomalonate (**1**) with ethenesulfonyl fluoride (**2**) is formed by a series of well-established reactions. Initial Huisgen (3 + 2)-cycloaddition of **1** with **2** yields the Δ^1-pyrazoline **5′**, which tautomerizes into the

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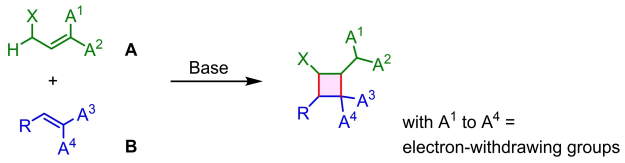


Scheme 4. Suggestion of a versatile cyclobutane synthesis.

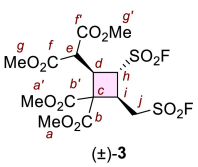
thermodynamically more stable Δ^2-pyrazoline **5** in a reversible reaction. Thermolysis of **5′** leads to extrusion of nitrogen and concomitant formation of the cyclopropane **4** and the Michael acceptor **6**, which dimerizes under basic conditions to give cyclobutane **3**, while cyclopropane **4** remained unaffected.

Scheme 4 shows a generalization of the observed dimerization of **6** which might give access to cyclobutanes of large structural variety.[28] By combining CH-acids of type **A** with Michael acceptors **B**, which are more electrophilic than **A**, mixed variants of the dimerization of **6** might become viable.[28b,29] Electrophilicity parameters of numerous types of Michael acceptors are available and can be used for designing suitable reactions.[30] An extension to acetylenic variants of **A** and **B** appears feasible.

Experimental Section

Cyclobutane 3 and cyclopropane 4. Dimethyl diazomalonate (**1**) (400 mg, 2.53 mmol) was mixed with ethenesulfonyl fluoride (ESF, **2**) (279 mg, 2.53 mmol) in toluene (0.2 mL) in an oven-dried NMR tube with screw cap under argon atmosphere at room temperature. The NMR tube was then sealed and the reaction mixture was heated at 100 °C for 3 days (TLC showed quantitative consumption of the starting material). At the end of the reaction time, the reaction mixture was transferred to a 25 mL round-bottom flask and the NMR tube was washed with CH_2Cl_2 (3×2 mL). Solvents were evaporated and the resulting crude products were then worked up by column chromatography (diameter of the column: 20 mm) on silica gel (50 mL, 0.035-0.070 mm, 60 Å) with n-pentane/EtOAc (4:1 ~ 2:1) as the eluent to give dimethyl (2*R**,3*S**,4*R**)-2-(1,3-dimethoxy-1,3-dioxopropan-2-yl)-3-(fluorosulfonyl)-4 ((fluorosulfonyl)methyl)cyclobutane-1,1-dicarboxylate (**3**) as a white solid (241 mg, yield 39%; mp 144.9 °C) and dimethyl 2-(fluorosulfonyl)cyclopropane-1,1-dicarboxylate (**4**) as a light-yellow oil (54.3 mg, yield 9%).

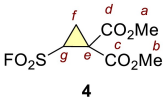
Spectroscopic characterization of cyclobutane 3:



(±)-**3**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.73–3.86 (m, 3 H, H^d, H^i, and H^j, superimposed with resonances of OCH_3 groups), 3.75, 3.78, 3.82 and 3.85 (4 s, 4×3 H, 4 OCH_3, superimposed with resonances of H^d, H^i, and H^j), 4.05 (app t, J = 9.1 Hz, 1 H, H^e), 4.13–4.20 (m, 1 H, H^j), 4.33 (t, J = 9.5 Hz, 1 H, H^h). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 37.3 (CH, C^i), 41.9 (CH, C^e), 49.2 (CH_2, d, $^2J_{C,F}$ = 19.9 Hz, C^j), 51.2 (CH, C^d), 53.39 and 53.44 (2 CH_3, C^a and $C^{a'}$), 53.82 and 53.87 (2× CH_3, C^g and $C^{g'}$), 55.5 (C_q, C^c), 57.5 (CH, d, $^2J_{C,F}$ = 19.0 Hz, C^h), 166.1 (C_q, C^b or $C^{b'}$), 166.6 (C_q, C^b or $C^{b'}$), 167.5 (C_q, C^f or $C^{f'}$), 167.8 (C_q, C^f or $C^{f'}$). ^{19}F NMR (377 MHz, $CDCl_3$): δ 50.83–50.84 (m, 1 F), 58.80–58.81 (m, 1 F). HRMS (ESI$^+$): *m/z* calcd for $C_{14}H_{18}F_2O_{12}NaS_2^+$ ($M+Na^+$): 503.0100; found 503.0100. IR (neat, ATR): 2991, 2963, 1751, 1738, 1719, 1439, 1416, 1409, 1351, 1311, 1288, 1268, 1251, 1211, 1196, 1186, 1160, 1020, 964, 889, 817, 798, 779, 770, 762, 747, 722 cm^{-1}.

Spectroscopic characterization of cyclopropane 4:



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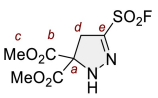
NMR spectra in $CDCl_3$: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.99 (ddd, $^3J_{H,H}$ = 9.0, $^2J_{H,H}$ = 6.2, $^4J_{H,F}$ = 1.6 Hz, 1 H, H^f), 2.26 (dd, $^3J_{H,H}$ = 6.8, $^2J_{H,H}$ = 6.2 Hz, 1 H, H^f), 3.56 (ddd, $^3J_{H,H}$ = 9.0, $^3J_{H,H}$ = 6.7, $^3J_{H,F}$ = 4.3 Hz, 1 H, H^g), 3.83 (s, 3 H, H^a or H^b), 3.84 (s, 3 H, H^a or H^b). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 18.6 (CH_2, C^f), 36.3 (C_q, C^e), 39.3 (CH, d, $^2J_{C,F}$ = 32.3 Hz, C^g), 54.0 (CH_3, C^a or C^b), 54.2 (CH_3, C^a or C^b), 163.7 (C_q, C^c or C^d), 166.9 (C_q, C^c or C^d). ^{19}F NMR (376 MHz, $CDCl_3$): δ 61.83 (dd, $^3J_{F,H}$ = 4.4, $^4J_{F,H}$ = 1.6 Hz). NMR spectra in d_8-toluene: ^{1}H NMR (400 MHz, d_8-toluene): δ = 1.10 (ddd, $^3J_{H,H}$ = 9.0, $^2J_{H,H}$ = 6.2, $^4J_{H,F}$ = 1.5 Hz, 1 H, H^f), 1.76–1.79 (m, 1 H, H^f), 3.06–3.11 (m, 1 H, H^g, superimposed with H^a or H^b resonance), 3.07 (s, 3 H, H^a or H^b, superimposed with H^g), 3.42 (s, 3 H, H^a or H^b). ^{13}C NMR (101 MHz, d_8-toluene): δ = 17.9 (CH_2, C^f), 36.3 (C_q, C^e), 39.2 (CH, d, $^2J_{C,F}$ = 32.6 Hz, C^g), 53.1 (CH_3, C^a or C^b), 53.2 (CH_3, C^a or C^b), 163.3 (C_q, C^c or C^d), 166.6 (C_q, C^c or C^d). NMR spectra in CD_2Cl_2: ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 2.01 (ddd, $^3J_{H,H}$ = 9.0, $^2J_{H,H}$ = 6.3, $^4J_{H,F}$ = 1.6 Hz, 1 H, H^f), 2.24 (app t, J = 6.5 Hz, 1 H, H^f), 3.61 (ddd, $^3J_{H,H}$ = 9.0, $^3J_{H,H}$ = 6.8, $^3J_{H,F}$ = 4.3 Hz, 1 H, H^g), 3.80 (s, 3 H, H^a or H^b), 3.81 (s, 3 H, H^a or H^b). ^{13}C NMR (101 MHz, CD_2Cl_2): δ = 18.8 (CH_2, C^f), 36.6 (C_q, C^e), 39.4 (CH, d, $^2J_{C,F}$ = 32.0 Hz, C^g), 54.1 (CH_3, C^a or C^b), 54.4 (CH_3, C^a or C^b, superimposed with resonances of the solvent CD_2Cl_2), 164.0 (C_q, C^c or C^d), 167.0 (C_q, C^c or C^d). HRMS (EI): *m/z* calcd for $C_7H_9FO_6S^{+\bullet}$ ($M^{+\bullet}$): 240.0098; found 240.0102. IR (neat, ATR): 3113, 3047, 2960, 2921, 2853, 1736, 1437, 1408, 1352, 1318, 1261, 1218, 1200, 1179, 1128, 1008, 915, 879, 793, 767, 718 cm^{-1}.

Dimethyl 5-(fluorosulfonyl)-2,4-dihydro-3*H*-pyrazole-3,3-dicarboxylate (**5**). When the product mixture obtained from the reaction of **1** (442 mg, 2.80 mmol) with **2** (296 mg, 2.69 mmol) in d_8-toluene: mesitylene = 1:1 (200 µL) at 85 °C for 9 days was worked up by column chromatography on silica gel (n-pentane/EtOAc = 5:1 ~ 1:1), we isolated cyclobutane **3** (213 mg, yield 33%) and the pyrazole **5** as a colorless oil (170 mg, yield 24%).



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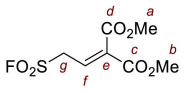
^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.77 (d, $^4J_{H,F}$ = 1.6 Hz, 2 H, H^d), 3.87 (s, 6 H, H^c), 7.51 (br s, 1 H, NH). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 38.4 (CH_2, C^d), 54.5 (CH_3, C^c), 76.3 (C_q, C^a), 141.0 (C_q, d, $^2J_{C,F}$ = 37.8 Hz, C^e), 167.0 (C_q, C^b). ^{19}F NMR (377 MHz, $CDCl_3$): δ 59.84–59.86 (m). HRMS (EI): *m/z* calcd for $C_7H_9FN_2O_6S^{+\bullet}$ ($M^{+\bullet}$): 268.0160; found 268.0166. IR (neat, ATR): 3347, 2962, 2851, 1740, 1557, 1415, 1282, 1254, 1223, 1164, 1134, 1078, 1046, 956, 879, 769 cm^{-1}.

Dimethyl 2-(2-(fluorosulfonyl)ethylidene)malonate (**6**) was characterized by analyzing the NMR spectra of the mixture of **4** and **6** obtained at the end of the reaction of **1** (404 mg, 2.56 mmol) with **2** (287 mg, 2.61 mmol) in d_8-toluene (0.2 mL) at 100 °C for 3 days.



6 (in a 56/44 mixture with **4**)

^{1}H NMR (400 MHz, d_8-toluene): δ = 3.53 (s, 3 H, H^a or H^b), 3.60 (s, 3 H, H^a or H^b), 4.39 (dd, $^3J_{H,H}$ = 7.7, $^3J_{H,F}$ = 5.6 Hz, 2 H, H^g), 6.79 (t, $^3J_{H,H}$ = 7.7 Hz, 1 H, H^f). ^{13}C NMR (101 MHz, d_8-toluene): δ = 50.2 (CH_2, d, $^2J_{C,F}$ = 19.4 Hz, C^g), 52.9 (CH_3, C^a or C^b), 53.0 (CH_3, C^a or C^b), 132.5 (CH, C^f), 135.0 (C_q, C^e), 163.6 (C_q, C^c or C^d), 164.1 (C_q, C^c or C^d). ^{19}F NMR (376 MHz, d_8-toluene): δ 54.89 (t, $^3J_{F,H}$ = 5.6 Hz).

Deposition Number CCDC 2183363

Deposition Number 2183363 (for **3**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: Azo compounds · (3 + 2)-Cycloadditions · Cyclobutanes · Reaction monitoring · Sulfonyl fluorides

[1] a) W. Steinkopf, *J. Prakt. Chem.* **1927**, *117*, 1–82; b) W. Steinkopf, P. Jaeger, *J. Prakt. Chem.* **1930**, *128*, 63–88; c) W. Steinkopf, R. Hübner, *J. Prakt. Chem.* **1934**, *141*, 193–200.
[2] P. K. Chinthakindi, P. I. Arvidsson, *Eur. J. Org. Chem.* **2018**, 3648–3666.
[3] A. S. Barrow, C. J. Smedley, Q. Zheng, S. Li, J. Dong, J. E. Moses, *Chem. Soc. Rev.* **2019**, *48*, 4731–4758.
[4] J. J. Krutak, R. D. Burpitt, W. H. Moore, J. A. Hyatt, *J. Org. Chem.* **1979**, *44*, 3847–3858.
[5] J. Dong, L. Krasnova, M. G. Finn, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2014**, *53*, 9430–9448; *Angew. Chem.* **2014**, *126*, 9584–9603.
[6] M.-C. Giel, C. J. Smedley, J. E. Moses, in *Science of Synthesis: Click Chemistry*, Vol. 1 (Ed: F. P. J. T. Rutjes), Thieme, Stuttgart, **2021**, Ch. 5, pp. 435–484..
[7] Y.-P. Meng, S.-M. Wang, W.-Y. Fang, Z.-Z. Xie, J. Leng, H. Alsulami, H.-L. Qin, *Synthesis* **2020**, *52*, 673–687.
[8] T. S.-B. Lou, M. C. Willis, *Nat. Chem. Rev.* **2022**, *6*, 146–162.
[9] T. A. Fattah, A. Saeed, F. Albericio, *J. Fluorine Chem.* **2018**, *213*, 87–112.
[10] Z. Liu, J. Li, S. Li, G. Li, K. B. Sharpless, P. Wu, *J. Am. Chem. Soc.* **2018**, *140*, 2919–2925.
[11] J. J. Rojas, R. A. Croft, A. J. Sterling, E. L. Briggs, D. Antermite, D. C. Schmitt, L. Blagojevic, P. Haycock, A. J. P. White, F. Duarte, C. Choi, J. J. Mousseau, J. A. Bull, *Nat. Chem.* **2022**, *14*, 160–169.
[12] O. O. Grygorenko, D. M. Volochnyuk, B. V. Vashchenko, *Eur. J. Org. Chem.* **2021**, 6478–6510.
[13] Q. Zheng, J. L. Woehl, S. Kitamura, D. Santos-Martins, C. J. Smedley, G. Li, S. Forli, J. E. Moses, D. W. Wolan, K. B. Sharpless, *Proc. Natl. Acad. Sci. USA* **2019**, *116*, 18808–18814.
[14] N. D. Ball in *Emerging Fluorinated Motifs: Synthesis, Properties, and Applications*, Vol. 2 (Eds: J.-A. Ma, D. Cahard), Wiley-VCH, Weinheim, **2020**, Ch. 21, pp. 621–674.
[15] Q. Chen, P. Mayer, H. Mayr, *Angew. Chem. Int. Ed.* **2016**, *55*, 12664–12667; *Angew. Chem.* **2016**, *128*, 12854–12858.
[16] a) J. Chanet-Ray, R. Vessière, A. Zéroual, *Heterocycles* **1987**, *26*, 101–108; b) V. L. Mykhalchuk, V. S. Yarmolchuk, R. O. Doroschuk, A. A. Tolmachev, O. O. Grygorenko, *Eur. J. Org. Chem.* **2018**, 2870–2876.
[17] M.-C. Giel, C. J. Smedley, E. R. R. Mackie, T. Guo, J. Dong, T. P. Soares da Costa, J. E. Moses, *Angew. Chem. Int. Ed.* **2020**, *59*, 1181–1186; *Angew. Chem.* **2020**, *132*, 1197–1202.
[18] P. K. Mykhailiuk, *Chem. Eur. J.* **2014**, *20*, 4942–4947.
[19] P. K. Mykhailiuk, *Chem. Rev.* **2021**, *121*, 1670–1715.
[20] H. Jangra, Q. Chen, E. Fuks, I. Zenz, P. Mayer, A. R. Ofial, H. Zipse, H. Mayr, *J. Am. Chem. Soc.* **2018**, *140*, 16758–16772.
[21] P. Yamanushkin, K. Kaya, M. A. M. Feliciano, B. Gold, *J. Org. Chem.* **2022**, *87*, 3868–3873.
[22] W.-F. Yang, T. Shu, H.-R. Chen, H.-L. Qin, H. Tang, *Org. Biomol. Chem.* **2022**, *20*, 3506–3510.
[23] a) T. Bug, M. Hartnagel, C. Schlierf, H. Mayr, *Chem. Eur. J.* **2003**, *9*, 4068–4076; b) J. Zhang, Q. Chen, R. J. Mayer, J.-D. Yang, A. R. Ofial, J.-P. Cheng, H. Mayr, *Angew. Chem. Int. Ed.* **2020**, *59*, 12527–12533; *Angew. Chem.* **2020**, *132*, 12628–12634; c) M. Hartnagel, A. R. Ofial, H. Mayr, *Synthesis* **2022**, *54*, doi: 10.1055/s-0041–1737327; d) L. Li, P. Mayer, D. S. Stephenson, A. R. Ofial, R. J. Mayer, H. Mayr, *Angew. Chem. Int. Ed.* **2022**, *61*, e202117047; e) L. Li, R. J. Mayer, D. S. Stephenson, P. Mayer, A. R. Ofial, H. Mayr, *Chem. Eur. J.* **2022**, doi: 10.1002/chem.202201376.
[24] K. B. Wiberg in *The Chemistry of Cyclobutanes* (Eds.: Z. Rappoport, J. F. Liebman), Wiley, **2005**, Ch. 1, pp. 1–15.
[25] R. A. Novikov, A. V. Tarasova, V. A. Korolev, V. P. Timofeev, Y. V. Tomilov, *Angew. Chem. Int. Ed.* **2014**, *53*, 3187–3191; *Angew. Chem.* **2014**, *126*, 3251–3255.
[26] a) W. M. Jones, *J. Am. Chem. Soc.* **1958**, *80*, 6687; b) W. M. Jones, *J. Am. Chem. Soc.* **1959**, *81*, 5153–5156; c) W. M. Jones, *J. Am. Chem. Soc.* **1960**, *82*, 3136–3137.
[27] C. Hansch, A. Leo, D. Hoekman, *Exploring QSAR – Hydrophobic, Electronic, and Steric Constants*, ACS Professional Reference Book, American Chemical Society, Washington D. C. (U. S. A.), **1995**.
[28] For reviews on the synthesis of functionalized cyclobutanes, see: a) F. Secci, A. Frongia, P. P. Piras, *Molecules* **2013**, *18*, 15541–15572; b) K.-G. Wen, Y.-Y. Peng, X.-P. Zeng, *Org. Chem. Front.* **2020**, *7*, 2576–2597.
[29] For a selection of organocatalytic reactions that furnish cyclobutanes, see: a) Ł. Albrecht, G. Dickmeiss, F. Cruz Acosta, C. Rodríguez-Escrich, R. L. Davis, K. A. Jørgensen, *J. Am. Chem. Soc.* **2012**, *134*, 2543–2546; b) K. Patora-Komisarska, M. Benohoud, H. Ishikawa, D. Seebach, Y. Hayashi, *Helv. Chim. Acta* **2011**, *94*, 719–745; c) G. Talavera, E. Reyes, J. L. Vicario, L. Carrillo, *Angew. Chem. Int. Ed.* **2012**, *51*, 4104–4107; *Angew. Chem.* **2012**, *124*, 4180–4183; d) P. S. Akula, B.-C. Hong, G.-H. Lee, *Org. Lett.* **2018**, *20*, 7835–7839.
[30] For a freely accessible database of electrophilicity parameters *E*, see: www.cup.lmu.de/oc/mayr/DBintro.html (accessed on August 8th, 2022).

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