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Diels–Alder Reaction of Ethyl 3-Benzamido-2-oxo-6-(trifluoromethyl)-2*H*-pyran-5-carboxylate with Alkoxyalkenes as an Effective Approach to Trifluoromethyl-Containing 3-Aminobenzoic Acid Derivatives

Ivan S. Kondratov,[a] Nataliya A. Tolmachova,[a] Violetta G. Dolovanyuk,[a] Igor I. Gerus,[a] Klaus Bergander,[b] Constantin-Gabriel Daniliuc,[b] and Günter Haufe*[b]

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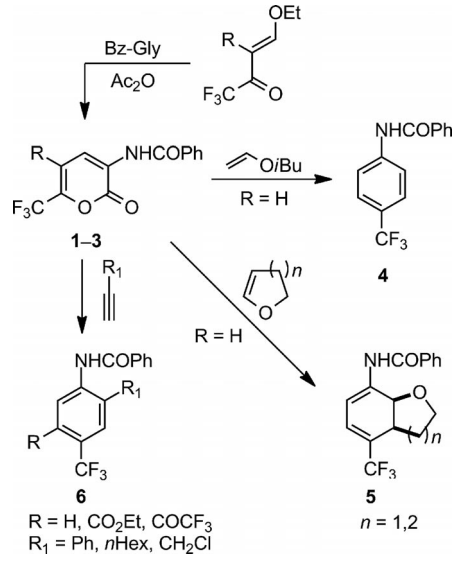
The Diels–Alder reactions of ethyl 3-benzamido-2-oxo-6-(trifluoromethyl)-2*H*-pyran-5-carboxylate with ethyl vinyl ether, 2-methoxypropene, and 1-ethoxypropene were investigated. Under different reaction conditions, intermediate oxabicyclo[2.2.2]octenones, alkoxycyclohexadienes, or aromatic products [5-benzamido-2-(trifluoromethyl)benzoates] were formed. The reaction is useful for the preparation of some hitherto unknown trifluoromethyl-containing derivatives of 3-aminobenzoic acid.

Introduction

2*H*-Pyran-2-ones are widely used in organic synthesis as convenient 1,3-dienes for Diels–Alder reactions, the cycloadducts of which usually provide aromatic compounds upon the elimination of CO_2.[1] Although there are few reports that consider Diels–Alder reactions with trifluoromethyl-containing pyrones,[2] the reaction might be a convenient method to prepare new trifluoromethylated aromatic building blocks, which include those of interest for medicinal chemistry and agrochemistry.

In addition to our earlier investigations of [4+2] cycloaddition reactions of fluorinated compounds,[3] we have described the synthesis of 3-benzamido-6-(trifluoromethyl)-2*H*-pyran-2-ones **1**–**3** from readily available β-alkoxy enones[4] and the Diels–Alder reactions[2b] of **1**–**3** with various dienophiles to lead to compounds **4**–**6** (see Scheme 1).

Herein, we present our results of the Diels–Alder reactions between pyrone **2** and vinyl ethers as well as the application of this reaction to the synthesis of trifluoromethyl-substituted 3-aminobenzoic acid **7** and its derivatives. 3-Aminobenzoic acid moieties are common structural elements of biologically active compounds. The anesthetic Metabutethamine, the antihypertensive drug Tienoxolol, and the antibiotic Ertapenem are commercialized drugs that contain this motif (see Figure 1). Therefore, compound **7** and its derivatives are of interest as building blocks for medicinal chemistry as the introduction of fluorine and fluorinated groups into biologically active compounds is a generally effective strategy to design new drugs.[5]



Scheme 1. Diels–Alder reactions of pyrones **1**–**3** with different dienophiles as described in the literature.[2b]

[a] Institute of Bioorganic Chemistry and Petrochemistry, National Ukrainian Academy of Science,
Murmanska 1, 02660 Kiev 94, Ukraine
[b] Organisch-Chemisches Institut, Universität Münster,
Corrensstraße 40, 48149 Münster, Germany
E-mail: haufe@uni-muenster.de
http://www.uni-muenster.de/Chemie.oc/haufe/haufe.html
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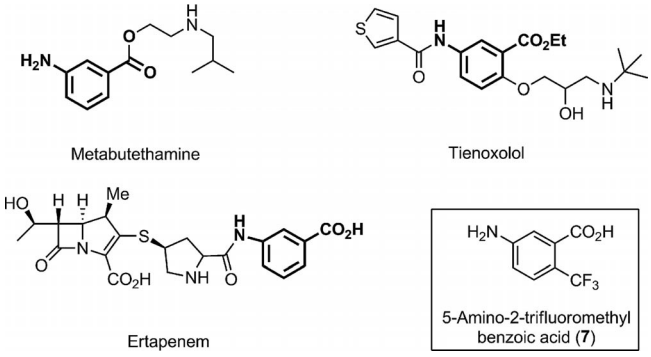


Figure 1. Commercialized drugs that contain the 3-aminobenzoic acid skeleton.

Results and Discussion

We began our investigation with the reaction of pyrone **2** and ethyl vinyl ether under conventional heating or microwave irradiation (see Scheme 2 and Table 1). The outcome of the reaction was analyzed by ^{19}F NMR spectroscopy. As expected, the reaction proceeded regioselectively to give initially a mixture of *endo*- and *exo*-bicyclic adducts **8a** and **8b**, which upon elimination of carbon dioxide formed cyclohexadiene derivative **9**. Finally, *N*-benzoyl aminobenzoic ester **10** was formed by the elimination of ethanol. Depending on the conditions, the predominant formation of one of the products **8**, **9**, or **10** was observed.

Bicyclic adduct **8a** was found as major product after gentle heating (see Table 1, Entry 1) or mild microwave irradiation (see Table 1, Entry 2). At elevated temperatures with microwave irradiation, mixtures of **8a** and up to 20% of *exo*-adduct **8b** (see Table 1, Entries 3 and 4) were formed. Products **8a** and **8b** were easily isolated and separated by column chromatography. The regiochemistry and relative configuration of these compounds were assigned by $^1H\{^1H\}$- and $^1H\{^{19}F\}$-NOE experiments (see Figure 2). Furthermore, the major product **8a** was crystallized from toluene (87% yield), and the structure was proved by X-ray crystal structure analysis (see Figure 3).

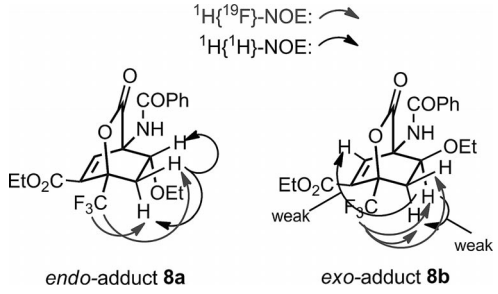


Figure 2. $^1H\{^1H\}$- and $^1H\{^{19}F\}$-NOE of compounds **8a** and **8b**.

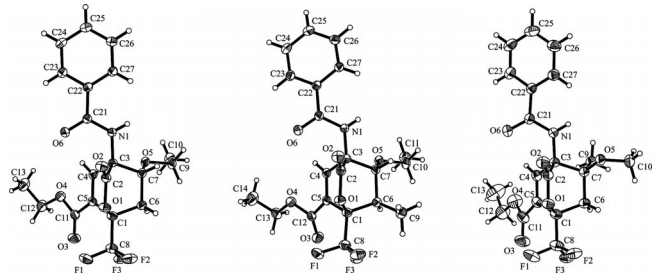
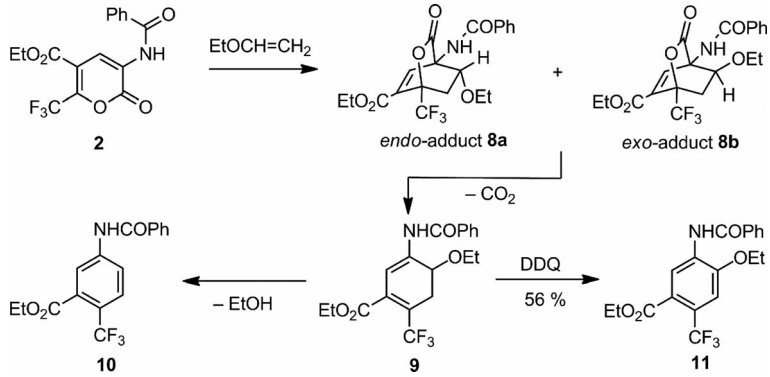


Figure 3. X-ray crystal structures of compound **8a**, **12a**, and **13b** (from left to right, 30% probability).[6]

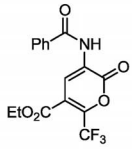
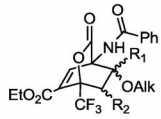
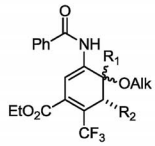
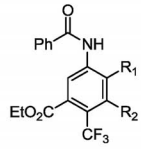
Compound **9** was formed predominantly under forced conditions (see Table 1, Entry 5) and was identified in the product mixture by using ^1H and ^{19}F NMR spectroscopic analysis as well as HRMS.[7] However, our attempts to isolate this compound by column chromatography or by recrystallization failed. Only aromatic product **10** was isolated in up to 64% yield (based on **2**, see Table 1, Entry 5). This product was also obtained in 60% yield through the reaction of pyrone **2** with ethyl vinyl ether under more forcing conditions (see Table 1, Entry 6) and even then under stronger forcing thermal conditions (see Table 1, Entry 7). The reaction could be scaled up to prepare 20 g amounts of **10** in one batch. Compound **10** was also formed by heating **8a** and **8b** at 180 °C.

Nonfluorinated cyclohexa-1,3-dienes similar to compound **9** were recently investigated by Kočevar and coworkers,[8] who were also faced with their low stability and



Scheme 2. Diels–Alder reaction of 2*H*-pyran-2-one **2** with ethyl vinyl ether (for product ratios and yields from different reaction conditions, see Table 1; DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone).

Table 1. Reaction of pyrone **2** with alkoxy alkenes (see Schemes 2 and 3).

Entry	Starting dienophile	Conditions	Components of the reaction mixture (share in the mixture/isolated yield)[a,b]			
						
1	$R_1 = R_2 = H$, Alk = Et	120 °C, 90 min	**2** (2)	**8a** (93/87), **8b** (5/–)	–	–
2	$R_1 = R_2 = H$, Alk = Et	200 W, 80 °C, 30 min	**2** (36)	**8a** (55/24), **8b** (9/–)	–	–
3	$R_1 = R_2 = H$, Alk = Et	200 W, 120 °C, 60 min	–	**8a** (76/51), **8b** (20/11)	**9** (4/–)	–
4	$R_1 = R_2 = H$, Alk = Et	200 W, 150 °C, 30 min	–	**8a** (77/60), **8b** (16/5)	**9** (7/–)	–
5	$R_1 = R_2 = H$, Alk = Et	250 W, 180 °C, 30 min	–	–	**9** (78/–)	**10** (22/64)[c]
6	$R_1 = R_2 = H$, Alk = Et	250 W, 180 °C, 60 min	–	–	**9** (31/–)	**10** (69/60)[c]
7	$R_1 = R_2 = H$, Alk = Et	180 °C, 8 h	–		**9** (13/–)	**10** (87/59)[c]
8	$R_1 = H$, $R_2 = Me$, Alk = Et	120 °C, 90 min	**2** (14)	**12a** (47/31) **12b** (39/19)	–	–
9	$R_1 = H$, $R_2 = Me$, Alk = Et	200 W, 120 °C, 60 min	**2** (21)	**12a** (53/36) **12b** (26/13)	–	–
10	$R_1 = H$, $R_2 = Me$, Alk = Et	250 W, 180 °C, 60 min[b]	–	–	**14a** (26/12) **14b** (74/59)	–
11	$R_1 = H$, $R_2 = Me$, Alk = Et	180 °C, 8 h	–	–	**14a** (17/8) **14b** (80/68)	**17** (3/–)
12	$R_1 = Me$, $R_2 = H$, Alk = Me	120 °C, 90 min	**2** (81)	**13a** (14/–) **13b** (5/–)	–	–
13	$R_1 = Me$, $R_2 = H$, Alk = Me	200 W, 120 °C, 60 min	–	**13a** (72/60) **13b** (28/11)	–	–
14	$R_1 = Me$, $R_2 = H$, Alk = Me	250 W, 180 °C, 60 min	–	–	**15** (49/–)	**16** (51/66)[c]
15	$R_1 = Me$, $R_2 = H$, Alk = Me	180 °C, 8 h	–	–	**15** (9/–)	**16** (91/64)[c]

[a] The ratios of the products were determined by ^{19}F NMR spectroscopic analysis of the crude product mixtures. [b] The starting pyrone **2** was not isolated from the product mixtures. [c] Cyclohexadienes **9** and **15** were completely transformed into compounds **10** and **16**, respectively, during isolation by column chromatography.

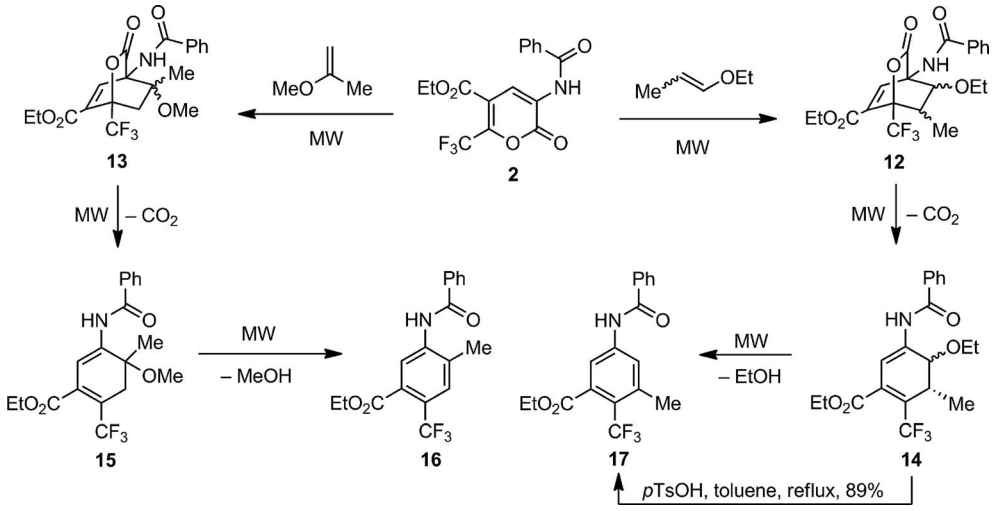
aromatization during column chromatography. The more stable bicyclic cyclohexa-1,3-dienes **5** were formed from the reaction with pyrone **1** (see Scheme 1).[2b]

Alternatively, compound **9** (in a mixture with **10**) can be thermally dehydrogenated by treatment with DDQ or microwave irradiation. Aryl ethyl ether **11** was separated from compound **10** by column chromatography and isolated in 56% yield (based on pyrone **2**). It is worth noting that upon reaction of pyrone **1** with ethyl vinyl ether, neither bicyclic adducts analogous to **8** nor cyclohexa-1,3-diene derivatives analogous to **9** were isolated.[2b]

Next, the reactions of pyrone **2** with *cis*/*trans*-1-ethoxypropene and 2-methoxypropene were investigated (see Scheme 3). Gentle heating or microwave irradiation of pyrone **2** with an excess amount of *cis*/*trans*-1-ethoxypropene (3:1) gave mixtures of diastereomers **12** (see Table 1, Entries 8 and 9). Only **12a** and **12b** with the Me and EtO groups in the *trans* orientation (see Figure 4) were isolated,[9] and their configurations were assigned according to the small vicinal coupling constants of 2.3 and 2.6 Hz, respectively, (compared to 2.0 and 2.6 Hz for **8a** and **8b**, respectively) and by using $^1H\{^1H\}$- and $^1H\{^{19}F\}$-NOE experiments (see Supporting Information). In addition, the structure of the major isomer **12a** was confirmed by X-ray crystal structure analysis (see Figure 3). Thus, *trans*-1-ethoxypropene predominantly underwent the reaction.

Heating pyrone **2** with 2-methoxypropene at 120 °C for 90 min resulted in low conversion (see Table 1, Entry 12). However, under mild microwave irradiation, a mixture of diastereomers **13a** and **13b** (see Figure 4) was formed. These compounds were separated by column chromatography and isolated in good yield (see Table 1, Entry 13). NOE data for **13a** and **13b** were not sufficient to establish the relative configuration of each of the stereoisomers unambiguously. Thus, the structure of the crystalline minor product **13b** was confirmed by using X-ray crystal analysis (see Figure 3).

Cyclohexa-1,3-dienes **14a** and **14b** (ratios from 1:3 to 1:5) with the methyl and ethoxy groups in a *cis* or *trans* orientation were formed by the reaction of pyrone **2** with *cis*/*trans*-1-ethoxypropene. Compounds **14a** and **14b** were isolated in 12 and 67% (see Table 1, Entries 10 and 11, respectively), whereas the *trans* cycloadducts **12a** and **12b** were isolated



Scheme 3. Reaction of pyrone **2** with 2-methoxypropene and *cis*/*trans*-1-ethoxypropene (for product ratios and yields from different reaction conditions, see Table 1, MW = microwave).

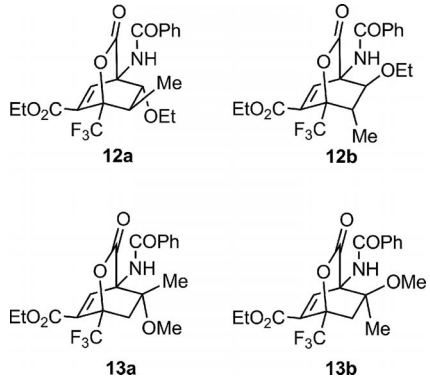
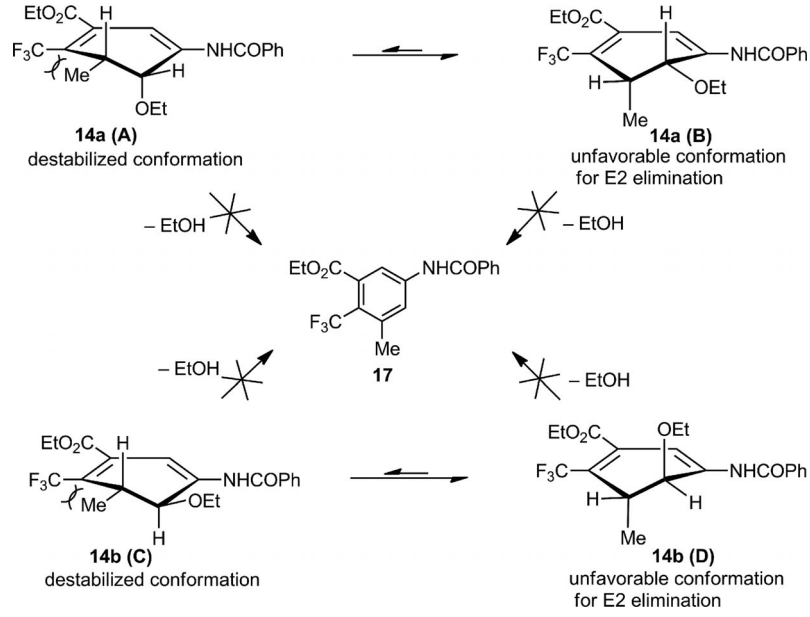


Figure 4. Confirmed structures of compounds **12a**, **12b**, **13a**, and **13b**.

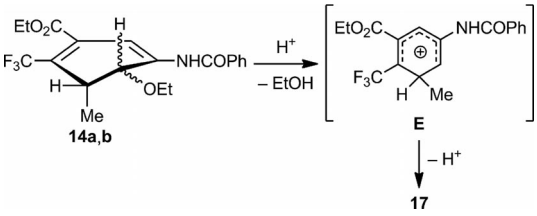
under milder conditions (see Table 1, Entries 8 and 9).[9] On the other hand, the reaction with 2-methoxypropene under the same conditions led to a mixture of cyclohexadiene **15** and aromatized product **16** (see Table 1, Entries 14 and 15). Compound **15** (just as cyclohexa-1,3-diene **9**) was identified in the mixture by ^{1}H and ^{19}F NMR spectroscopic analysis as well as HRMS,[10] but could not be isolated because of its easy aromatization into **16**. The latter compound was isolated in yields up to 66%.

In contrast, there was no significant aromatization of compounds **14a** and **14b** through the elimination of ethanol, even after further heating under forced microwave irradiation conditions (see Scheme 4). Only by heating compounds **14a** and **14b** at reflux in toluene in the presence of *p*-toluenesulfonic acid for 1 h led to the formation of aro-



Scheme 4. Steric and electronic factors that prevent thermal EtOH elimination.

matic compound **17** in 89% yield (see Scheme 5). To explain the stability of compounds **14a** and **14b** (in comparison to the thermolabile compound **9**), we examined the conformations of each isomer.



Scheme 5. Mechanism of acid-catalyzed EtOH elimination from compounds **14a** and **14b**.

For a thermal E2 elimination, the favored conformation for the elimination of EtOH is the antiperiplanar orientation of the hydrogen atom and the ethoxy group at the 3- and 4-positions, respectively. This orientation is possible in conformation **A** of the minor *cis*-isomer **14a**, but this geometry is disfavored because of the repulsive interaction between the neighboring CF_3 and Me groups. In conformation **B**, these groups are gauche to each other (see Scheme 4). In the case of *trans*-isomer **14b**, conformer **C** is also destabilized because of a steric repulsion between the bulky groups. In conformer **D**, however, the neighboring hydrogen atom and ethoxy group at the 3- and 4-positions, respectively, are again in the gauche conformation. Thus, all of the structures **A** through **D** are disfavored for the E2 elimination of ethanol. On the other hand, an E1 elimination in the absence of an acid also seems unlikely, as the C–O scission is not assisted by the conjugated double bond. This might explain the thermal stability of **14a** and **14b**.

The most stable conformations of compounds **14a** and **14b** were established by the NMR spectroscopic data (see Figure 5), which demonstrate and equatorial-axial orientation of the H-3 and H-4 atoms in compound **14a** ($J_{H,H}$ = 6.5 Hz, strong H{H}-NOE between H-4 and H-3, no H{H}-NOE between H-4 and CH_3-3) and an equatorial-equatorial orientation of the H-3 and H-4 atoms in **14b** ($J_{H,H}$ = 2.3 Hz, strong H{H}-NOE between H-4 and H-3 as well as H-4 and CH_3-3).

In the presence of *p*-toluenesulfonic acid, however, the E1 elimination becomes probable, as protonation of the ether oxygen and EtOH elimination lead to the formation of the carbocationic intermediate **E**, which deprotonates to give aromatic compound **17**. Under these conditions, the relative configuration and favored conformation of **14** do not influence the aromatization process significantly (see Scheme 5). Furthermore, compounds **14a** and **14b** (just as compound **9**) can be oxidized by treatment with DDQ to give compound **18** in 51% yield (see Scheme 6).

To obtain amino acid **7**, we hydrolyzed compound **10**. Under strong basic conditions, the hydrolysis of the ester and amide functions occurred, but the CF_3 group was also converted into a carboxylic acid to give compound **19** in 75% yield.[11] In contrast, compound **10** was entirely hydrolyzed under strong acidic conditions (6 N HCl, reflux, 48 h) to give compound **7** in 56% yield (see Scheme 7). Additionally we found that the hydrolysis of the benzamide group proceeded more easily than that of the ester function under milder acidic conditions, and this allowed the isolation of amino ester **20** with 73% yield. On the other hand, the ester group was selectively hydrolyzed by using "anhydrous hydroxide"[12] that was generated by *t*BuOK in tetrahydrofuran (THF)/H_2O to give amido ester **21** in 88% yield. The same conditions were used to hydrolyze the ester function of compound **20** to lead to compound **7** in 85% yield.

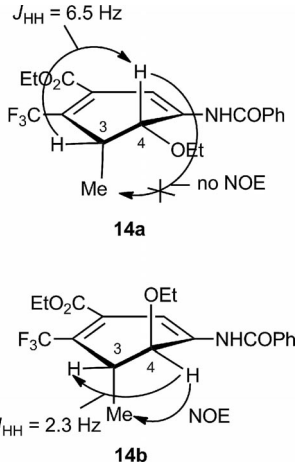
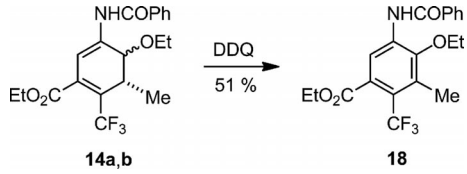
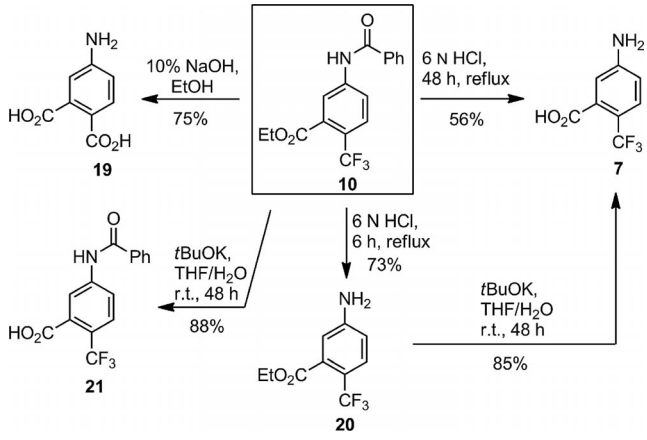


Figure 5. NMR spectroscopic data for compounds **14a** and **14b**.



Scheme 6. Dehydrogenation of compounds **14a** and **14b** by treatment with DDQ.



Scheme 7. Hydrolysis reactions of compound **10**.

Conclusions

The Diels–Alder reactions of ethyl 3-benzamido-2-oxo-6-(trifluoromethyl)-2*H*-pyran-5-carboxylate (**2**) with ethyl

vinyl ether, *cis*/*trans*-1-ethoxypropene, and 2-methoxypropene under different reaction conditions was used for the preparation of bicyclic adducts **8**, **12**, and **13**. Under forced conditions, the elimination of CO_2 from these cycloadducts formed cyclohexa-1,3-diene derivatives **9**, **14**, and **15**, respectively, followed by the elimination of ethanol to give aromatic *N*-benzoylamino esters **10** and **17** and the elimination of methanol to give **16**. Compounds **11** and **18** were formed by the oxidation of compounds **9** as well as **14a** and **14b** by treatment with DDQ. Moreover, compound **10** was selectively hydrolyzed under different reaction conditions to give either trifluoromethylated amine **20**, carboxylic acid **21**, or amino acid **7**. The Diels–Alder reactions of pyrone **2** with other dienophiles and the applications of these cycloadducts for the synthesis of promising fluorinated building blocks are under investigation.

Experimental Section

General Methods: The NMR spectroscopic data were recorded with a Bruker Avance II at 300 or 400 MHz, a Bruker DRX at 300 MHz, and an Agilent DD2 at 500 or 600 MHz (for ^{1}H NMR) at 25 °C. TMS (for ^{1}H and ^{13}C NMR) and CCl_3F (for ^{19}F NMR) were used as internal standards. IR spectra were recorded with a Bruker Vertex 70. Mass spectra (ESI-MS) were measured with a Bruker Daltonics MicroTof. The progress of the reactions was monitored by TLC (silica gel 60 F_{254}, Merck). Column chromatography was carried out on silica gel 60 (Merck, particle size 0.040–0.063 mm). Elemental analyses are correct within the limits of ±0.3% for C, H, and N. Reactions under microwave irradiation were carried out in sealed tubes. The microwave oven was a Discover BenchMate from CEM Corporation (for the conditions, see Table 1). All starting materials were of the highest commercial quality and were used without further purification. Pyrone **2** was prepared as described.[4]

General Procedure for Diels–Alder Reactions of Pyrone 2 with Alkoxyalkenes: A mixture of pyrone **2** (355 mg, 1 mmol) and the corresponding alkoxyalkene (ethyl vinyl ether, 1-ethoxypropene, or 2-methoxypropene; 0.5 mL, 5–6 equiv.) was heated without solvent in a sealed tube or microwave irradiated (see Table 1). The excess amount of the alkoxyalkene was removed, and the corresponding product was purified by crystallization or column chromatography.

Ethyl *endo*-4-Benzamido-8-ethoxy-3-oxo-1-(trifluoromethyl)-2-oxabicyclo[2.2.2]oct-5-ene-6-carboxylate (8a): The reaction of pyrone **2** and ethyl vinyl ether with conventional heating or microwave irradiation (see Table 1, Entries 1–4) gave the crude product that was purified by crystallization (toluene) or column chromatography (EtOAc/Hex, 1:2; R_f = 0.34). The most appropriate conditions were heating at 120 °C for 90 min to give the main product **8a** (372 mg, 87% yield) as a colorless solid; m.p. 206–208 °C. IR (KBr): $\tilde{\nu}$ = 1106, 1138, 1164, 1208, 1254, 1486, 1518, 1663, 1734, 1784, 2911, 2991, 3397 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.21 (t, J = 7.1 Hz, 3 H, CH_3), 1.31 (t, J = 7.1 Hz, 3 H, CH_3), 2.07 (dd, ^1J = 14.0 Hz, ^2J = 2.0 Hz, 1 H, H_a of CH_2), 2.77 (dd, ^1J = 14.0 Hz, ^2J = 7.3 Hz, 1 H, H_b of CH_2), 3.49–3.66 (m, 2 H, CH_2O), 4.22 (dd, ^1J = 7.3 Hz, ^2J = 2.0 Hz, 1 H, CHO), 4.27 (q, J = 7.1 Hz, 2 H, CH_2O), 6.81 (s, 1 H, NH), 7.47–7.50 (m, 2 H, Ph), 7.55–7.59 (m, 2 H, Ph and CH), 7.85–7.88 (m, 2 H, Ph) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 14.0, 15.1, 35.3, 61.8, 64.7, 66.1, 80.8 (q, J = 34.5 Hz), 122.0 (q, J = 285.0 Hz), 127.3, 128.8, 131.1, 132.4, 133.2, 144.8, 160.0, 165.3, 167.3 ppm. ^{19}F NMR (564 MHz, $CDCl_3$): δ = –74.92 (s, CF_3) ppm. MS (ESI): calcd. for $C_{20}H_{20}F_3NNaO_6$ 450.1135; found 450.1137.

Ethyl *exo*-4-Benzamido-8-ethoxy-3-oxo-1-(trifluoromethyl)-2-oxabicyclo[2.2.2]oct-5-ene-6-carboxylate (8b): The reaction of pyrone **2** and ethyl vinyl ether under microwave irradiation (see Table 1, Entries 3 and 4) gave the crude product that was purified by column chromatography (EtOAc/Hex, 1:2; R_f = 0.60). The most appropriate conditions were microwave heating (200 W) at 120 °C for 60 min to give the minor product **8b** (47 mg, 11% yield) as a colorless solid; m.p. 116–118 °C. IR (KBr): $\tilde{\nu}$ = 1016, 1047, 1109, 1137, 1177, 1194, 1217, 1255, 1289, 1371, 1517, 1582, 1739, 1779, 2890, 2932, 2987, 3308 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.10 (t, J = 7.0 Hz, 3 H, CH_3), 1.31 (t, J = 7.2 Hz, 3 H, CH_3), 2.32 (dd, ^1J = 13.6 Hz, ^2J = 2.6 Hz, 1 H, H_a of CH_2), 2.61 (dd, ^1J = 13.5 Hz, ^2J = 8.8 Hz, 1 H, H_b of CH_2), 3.48 (dq, ^1J = 9.7 Hz, ^2J = 6.9 Hz, 1 H, H_a of CH_2O), 3.55 (dq, ^1J = 9.7 Hz, ^2J = 6.9 Hz, 1 H, H_b of CH_2O), 4.23–4.29 (m, 2 H, CH_2O), 4.74 (dd, ^1J = 8.8 Hz, ^2J = 2.6 Hz, 1 H, CHO), 7.41 (br. s, 1 H, NH), 7.50–7.54 (m, 2 H, Ph), 7.58–7.60 (m, 1 H, Ph), 7.61 (s, 1 H, CH), 7.87–7.90 (m, 2 H, Ph) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 13.9, 15.1, 35.5, 62.0, 65.2, 67.0, 71.5, 81.4 (q, J = 35.5 Hz), 121.6 (q, J = 282.0 Hz), 127.1, 128.9, 132.5, 133.0, 133.8, 143.4, 159.9, 106.2, 167.3 ppm. ^{19}F NMR (564 MHz, $CDCl_3$): δ = –75.00 (s, CF_3) ppm. MS (ESI): calcd. for $C_{20}H_{20}F_3NNaO_6$ 450.1135; found 450.1134.

Ethyl 5-Benzamido-2-(trifluoromethyl)benzoate (10): The reaction of pyrone **2** and ethyl vinyl ether under microwave irradiation (see Table 1, Entries 5–7) gave the crude product that was purified by crystallization (toluene) or column chromatography (EtOAc/Hex, 1:4; R_f = 0.26). The most appropriate conditions were microwave heating (250 W) at 180 °C for 30 min to give the main product **10** (216 mg, 64% yield) as a colorless solid; m.p. 109–110 °C. IR (KBr): $\tilde{\nu}$ = 1111, 1141, 1265, 1320, 1596, 1659, 1723, 2995, 3296 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.38 (t, J = 7.2 Hz, 3 H, CH_3), 4.37 (q, J = 7.2 Hz, 2 H, CH_2O), 7.46–7.63 (m, 3 H, Ph), 7.74 (d, J = 8.4 Hz, 1 H, CH), 7.85–7.91 (m, 2 H, Ph), 7.96 (d, J = 2.3 Hz, 2 H, CH), 8.09 (dd, ^1J = 8.4 Hz, ^2J = 2.3 Hz, 1 H), 8.20 (s, 1 H, NH) ppm. ^{13}C NMR (76 MHz, $CDCl_3$): δ = 13.9, 62.3, 121.0, 121.5, 123.4 (q, J = 275.0 Hz), 124.0 (q, J = 33.2 Hz), 127.1, 128.1 (q, J = 5.1 Hz), 129.0, 132.5, 134.0, 141.1, 166.0, 166.6 ppm. ^{19}F NMR (283 MHz, $CDCl_3$): δ = –59.28 (s, CF_3) ppm. MS (ESI): calcd. for $C_{17}H_{14}F_3NNaO_3$ 360.0818; found 360.0818.

Ethyl 5-Benzamido-4-ethoxy-2-(trifluoromethyl)benzoate (11): A mixture of crude compound **9** [obtained from pyrone **2** and ethyl vinyl ether under microwave irradiation (250 W, 180 °C, 30 min; see General Procedure and Table 1)] and DDQ (340 mg, 1.5 mmol) in toluene (5 mL) was stirred and heated at reflux for 12 h or heated in a sealed tube under microwave heating (250 W, 120 °C, 60 min). The solvent was removed, and the corresponding product was purified by column chromatography (EtOAc/Hex, 1:4, R_f = 0.36) to give **11** (214 mg, 56%) as a colorless solid; m.p. 105–107 °C. Compound **10** (115 mg, 34%) was also isolated also as a byproduct. IR (CH_2Cl_2): $\tilde{\nu}$ = 1155, 1245, 1295, 1354, 1373, 1502, 1535, 1591, 1685, 1730, 2855, 2927, 3428 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.40 (t, J = 7.1 Hz, 3 H, CH_3), 1.55 (t, J = 7.1 Hz, 3 H, CH_3), 4.26 (q, J = 7.1 Hz, 2 H, CH_2O), 4.39 (q, J = 7.1 Hz, 2 H, CH_2O), 7.22 (s, 1 H, CH), 7.47–7.64 (m, 3 H, Ph), 7.84–7.94 (m, 2 H, Ph), 8.66 (s, 1 H, CH), 9.07 (s, 1 H, NH) ppm. ^{13}C NMR (76 MHz, $CDCl_3$): δ = 14.1, 14.7, 61.8, 65.2, 108.9, 121.3, 122.8 (q, J = 285.0 Hz), 124.5 (q, J = 33.5 Hz), 127.1, 129.0, 130.3, 132.2, 134.5, 135.2, 148.3, 165.2, 166.2 ppm. ^{19}F NMR (283 MHz, $CDCl_3$): δ = –59.19 (s, CF_3) ppm. MS (ESI): calcd. for $C_{19}H_{18}F_3NNaO_4$ 404.1080; found 404.1082.

Ethyl 5-Amino-2-(trifluoromethyl)benzoate (20): A mixture of compound **10** (3.37 g, 10 mmol) and HCl (6 N solution, 50 mL) was heated at reflux as it stirred for 6 h. Upon full conversion, the mixture was cooled, and the precipitate of benzoic acid was removed by filtration. The water solution was treated with 10% $NaHCO_3$ to give a pH > 7, and the resulting solution was then extracted with EtOAc (3× 20 mL). The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. The residue was washed with CCl_4 to give the pure compound **20** (1.70 g, 73% yield) as a light brown solid; m.p. 171–173 °C. IR [attenuated total reflectance (ATR)]: $\tilde{\nu}$ = 1034, 1098, 1247, 1271, 1306, 1580, 1610, 1630, 1719 2986, 3232, 3384 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.39 (t, J = 7.1 Hz, 3 H, CH_3), 4.38 (q, J = 7.1 Hz, 2 H, OCH_2), 4.10–5.10 (br. s, 2 H, NH_2), 6.76 (d, J = 8.1 Hz, 1 H, Ar), 6.99 (s, 1 H, Ar), 7.50 (d, J = 8.1 Hz, 1 H, Ar) ppm. ^{13}C NMR (76 MHz, $CDCl_3$): δ = 13.9, 61.9, 115.6, 117.9 (q, J = 33.2 Hz), 118.6, 124.0 (q, J = 275.0 Hz), 130.2, 132.8, 149.1, 167.4 ppm. ^{19}F NMR (283 MHz, $CDCl_3$): δ = –58.36 (s, CF_3) ppm. MS (ESI): calcd. for $C_{10}H_{10}F_3NNaO_2$ 256.0556; found 256.0555. $C_{10}H_{10}F_3NO_2$ (233.19): calcd. C 51.51, H 4.32, N 6.01; found C 51.39, H 4.25, N 5.87.

5-Amino-2-(trifluoromethyl)benzoic Acid (7)

Method A (from Compound 10): A mixture of compound **10** (3.37 g, 10 mmol) and HCl (6 N solution, 50 mL) was heated at reflux as it stirred for 48 h. The reaction progress was monitored by TLC and ^1H NMR spectroscopic analysis. Upon complete conversion, the mixture was cooled, and the precipitate of benzoic acid was removed by filtration. The water solution was evaporated, and the solid residue was washed with hot CCl_4 to give pure compound **7** as hydrochloride (1.35 g, 56% yield).

Method B (from Compound 20): To a stirred suspension of *t*BuOK (2.66 g, 26 mmol) in dry THF (50 mL) was added water (0.12 mL) through a syringe at 0 °C. This slurry was stirred for 5 min, and then compound **20** (0.70 g, 3 mmol) was added in several portions. The reaction mixture was stirred at room temp. overnight and then quenched by the addition of ice water until two clear layers were formed. The aqueous layer was separated, acidified with 15% citric acid, and then extracted with EtOAc (3× 20 mL). The combined organic layers were washed with water, dried with $MgSO_4$, and concentrated in vacuo. The residue was treated with concentrated hydrochloric acid (5 mL), and the mixture was then concentrated and washed with hot CCl_4 to give pure compound **7** as hydrochloride (0.62 g, 85% yield) as a colorless solid; m.p. 86–88 °C. IR (KBr): $\tilde{\nu}$ = 1039, 1109, 1145, 1264, 1322, 1536, 1658, 1721, 2909, 2995, 3111, 3296 cm^{-1}. ^1H NMR {300 MHz, deuterated dimethyl sulfoxide ([D_6]DMSO}: δ = 6.04–6.80 (br. s, 4 H, NH_3^+, CO_2H), 6.81 (dd, ^1J = 2.2 Hz, ^2J = 8.4 Hz, 1 H, Ar), 6.97 (d, J = 2.2 Hz, 1 H, Ar), 7.45 (d, J = 8.4 Hz, 1 H, Ar) ppm. ^{13}C NMR (76 MHz, [D_6]DMSO): δ = 113.6 (q, J = 31.9 Hz), 114.7, 114.9, 124.4 (q, J = 271.0 Hz), 127.8 (q, J = 4.9 Hz), 133.4, 150.4, 168.2 ppm. ^{19}F NMR (283 MHz, [D_6]DMSO): δ = –55.46 (s, CF_3) ppm. MS (ESI): calcd. for $C_8H_6F_3NO_2Na$ 228.0248; found 228.0243. $C_8H_7ClF_3NO_2$ (241.59): C 39.77, H 2.92, N 5.80; found C 39.91, H 2.80, N 5.88.

X-ray Crystal Structure Determination: Data sets were collected with a Nonius KappaCCD diffractometer. Programs were used for data collection (COLLECT[13]), data reduction (Denzo-SMN[14]), absorption correction (Denzo[15]), structure solution (SHELXS-97[16]), structure refinement (SHELXL-97[17]), and graphics (XP Bruker AXS, 2000). Thermals ellipsoids are shown with 30% probability. R values are given for observed reflections, and wR^2 values are given for all reflections. Exceptions and special features: For compound **13b**, over two positions, one disordered CF_3 and CO-OEt group were found in the asymmetric unit. Several restraints (SIMU, SADI, SAME, ISOR, and DFIX) were used to improve refinement stability.

X-ray Crystal Structure Analysis of 8a: Formula: $C_{20}H_{20}F_3NO_6$, M = 427.37, colorless crystal, 0.40 × 0.10 × 0.03 mm, a = 14.0597(4) Å, b = 8.6177(3) Å, c = 17.2698(5) Å, β = 111.470(2)°, V = 1947.25(10) $Å^3$, $\rho_{calcd.}$ = 1.458 $g cm^{-3}$, μ = 1.089 mm^{-1}, empirical absorption correction (0.669 ≤ T ≤ 0.968), Z = 4, monoclinic, space group $P2_1/n$ (No. 14), λ = 1.54178 Å, T = 223(2) K, ω and ϕ scans, 13697 reflections collected (±h, ±k, ±l), [(sinθ)/λ] = 0.60 $Å^{-1}$, 3378 independent (R_{int} = 0.062) and 2635 observed reflections [I > 2σ(I)], 276 refined parameters, R = 0.044, wR^2 = 0.111, max. (min.) residual electron density 0.18 (–0.20) e $Å^{-3}$, the hydrogen atom at N1 was refined freely, others were calculated and refined as riding atoms.

X-ray Crystal Structure Analysis of 12a: Formula: $C_{21}H_{22}F_3NO_6$, M = 441.40, colorless crystal, 0.40 × 0.15 × 0.02 mm, a = 14.0824(5) Å, b = 8.8231(3) Å, c = 17.3409(5) Å, β = 106.919(2)°, V = 2061.4(1) $Å^3$, $\rho_{calcd.}$ = 1.422 $g cm^{-3}$, μ = 1.047 mm^{-1}, empirical absorption correction (0.679 ≤ T ≤ 0.979), Z = 4, monoclinic, space group $P2_1/n$ (No. 14), λ = 1.54178 Å, T = 223(2) K, ω and ϕ scans, 16978 reflections collected (±h, ±k, ±l), [(sinθ)/λ] = 0.60 $Å^{-1}$, 3624 independent (R_{int} = 0.047) and 3221 observed reflections [I > 2σ(I)], 287 refined parameters, R = 0.039, wR^2 = 0.104, max. (min.) residual electron density 0.25 (–0.19) e $Å^{-3}$, the hydrogen atom at N1 was refined freely, others were calculated and refined as riding atoms.

X-ray Crystal Structure Analysis of 13b: Formula: $C_{20}H_{20}F_3NO_6$, M = 427.37, colorless crystal, 0.35 × 0.35 × 0.08 mm, a = 10.3933(2) Å, b = 16.6644(5) Å, c = 22.9674(8) Å, V = 3977.9(2) $Å^3$, $\rho_{calcd.}$ = 1.427 $g cm^{-3}$, μ = 1.066 mm^{-1}, empirical absorption correction (0.706 ≤ T ≤ 0.919), Z = 8, orthorhombic, space group $Pbca$ (No. 61), λ = 1.54178 Å, T = 223(2) K, ω and ϕ scans, 21334 reflections collected (±h, ±k, ±l), [(sinθ)/λ] = 0.60 $Å^{-1}$, 3425 independent (R_{int} = 0.045) and 2910 observed reflections [I > 2σ(I)], 345 refined parameters, R = 0.040, wR^2 = 0.111, max. (min.) residual electron density 0.17 (–0.17) e $Å^{-3}$, the hydrogen atom at N1 was refined freely, others were calculated and refined as riding atoms.

Supporting Information (see footnote on the first page of this article): Spectroscopic and mass spectrometric data, elemental analyses, and copies of ^1H, ^{13}C, and ^{19}F NMR spectra of all new compounds **1**–**18**, **20**, and **21**.

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[6] CCDC-933172 (for **8a**), -963174 (for **12a**), and -933173 (for **13b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[7] The most characteristic data of compound **9** are as follows: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.46 (tq, ^1J = 16.5 Hz, ^2J = 2.4 Hz, 1 H, H_a of CH_2), 2.81 (dd, ^1J = 16.5 Hz, ^2J = 7.9 Hz, 1 H, H_b of CH_2), 4.42 (dd, ^1J = 16.5 Hz, ^2J = 7.9 Hz, 1 H, CHOEt) ppm. ^{19}F NMR (300 MHz, $CDCl_3$): δ = –63.65 (s, CF_3) ppm. MS (ESI): calcd. for $C_{19}H_{20}F_3NNaO_4$ 406.1242; found 406.1237.

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[9] Although the formation of four diasteromeric bicyclic adducts can be expected in the reaction of pyrone **2** with *cis*/*trans*-1-ethoxypropene, only compounds **12a** and **12b** were isolated. The signals of another diastereomer (probably with the *endo-cis* configuration) were also observed in the ^{1}H NMR spectrum [The most characteristic signals are as follows: ^{1}H NMR: δ = 2.79 (dq, ^3J = 9.0 Hz, ^3J = 7.0 Hz, 1 H, CHMe), 4.62 (d, ^3J = 9.0 Hz, 1 H, CHOEt) ppm. Both signals have a large coupling constant of 9 Hz for the *cis* arrangement of the protons.] and in the ^{19}F NMR spectrum of the reaction mixture [^{19}F NMR: –69.39 (s, CF_3) ppm] with a relative integral of 5–8%. However, our attempts to isolate and confirm its structure failed.

[10] The most characteristic data of compound **15** are as follows: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.49 (d, J = 16.8 Hz, 1 H, H_a of CH_2), 2.80 (d, ^1J = 16.8 Hz, 1 H, H_b of CH_2) ppm. ^{19}F NMR (300 MHz, $CDCl_3$): δ = –64.20 (s, CF_3) ppm. MS (ESI): calcd. for $C_{19}H_{20}F_3NNaO_4$ 406.1242; found 406.1240.

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