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Synthesis of Trifluoromethyl-Containing Polysubstituted Aromatic Compounds by Diels–Alder Reaction of Ethyl 3-Benzamido-2-oxo-6-(trifluoromethyl)-2*H*-pyran-5-carboxylate

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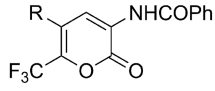
Diels–Alder reactions of ethyl 3-benzamido-2-oxo-6-(trifluoromethyl)-2*H*-pyran-5-carboxylate (**1a**) with electronically different dienophiles, including cyclic enol ethers, cycloalkenes, α,β-unsaturated ketones, and terminal acetylenes, are useful for the efficient and selective three-step preparation of trifluoromethyl-containing aromatic compounds such as 3-aminobenzoic acid derivatives. We presume that the presence of the trifluoromethyl group is the main factor in determining the regioselectivity of the initial cycloaddition.

Introduction

Trifluoromethyl-containing aromatic compounds are of considerable interest for medicinal chemistry, agrochemistry, and materials science since the selective introduction of a CF_3 group at a key position of a particular molecule can result in desirable changes of its biological and physical-chemical properties.[1] Consequently, a variety of synthetic methods for the formation of trifluoromethyl-containing aromatic compounds have been developed. The direct trifluoromethylation of aromatic compounds[2] and also several building-block-based methods[3] are among the most useful of these methods. The latter protocols are most suitable for the preparation of polyfunctionalised aromatic compounds, whose synthesis by other methods is rare.

2-Pyrones are important building blocks in organic synthesis, especially as diene components for Diels–Alder reactions with alkenes (with subsequent CO_2 elimination and dehydrogenation) or with alkynes (followed by CO_2 elimination) for the synthesis of substituted benzenes.[4] However, there are only a few examples of the use of this strategy to synthesise polyfluoroalkylated aromatic compounds using polyfluoroalkylated pyrones as dienes.[5]

Previously, we have reported a couple of Diels–Alder reactions of CF_3-containing pyrones **1a**–**1c**[6] (Figure 1) with selected dienophiles.[5b,7] In particular, the reactions of pyrone **1a** with 1-alkoxy alkenes were studied in detail, and were shown to be an effective synthetic approach to trifluoromethyl-containing 3-aminobenzoic acid derivatives.[7] Continuing our investigations in this field, in this paper we describe Diels–Alder reactions of pyrone **1a** with a variety of electronically different alkenes such as cyclic enol ethers, cycloalkenes, and cyclic α,β-unsaturated ketones and alkynes. In this way, we explore the scope and limitations of this approach for the synthesis of new trifluoromethyl-containing aromatic amino acid derivatives.



1a–c

R = CO_2Et (**a**); H (**b**); $COCF_3$ (**c**)

Figure 1. Pyrones **1a**–**1c** as potent dienes for Diels–Alder reactions.[5b,7]

Results and Discussion

Initially, we studied the reactions of **1a** with cyclic dienophiles **2a**–**2e** under microwave irradiation. The initially formed bicyclic adducts (i.e., *endo*/*exo*-**3a**–**3e**) eliminated CO_2 under forcing conditions to form stable cyclohexadienes **4a**–**4e** as the major products (Scheme 1). Compounds *endo*-**3a** and *exo*-**3a** (*dr* ≈ 30:70 by ^{19}F NMR spectroscopic analysis of the reaction mixture) were obtained under mild conditions (120 W, 120 °C, 10 min) as the major products. These products were separated and fully charac-

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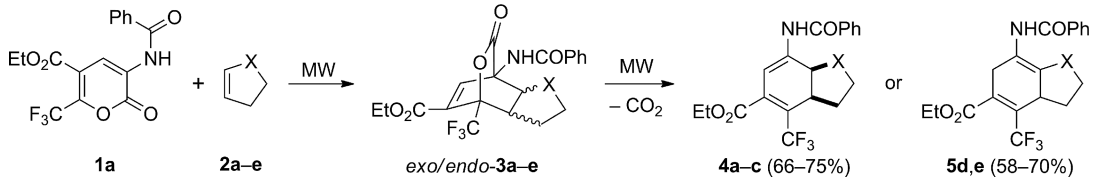


1a **2a–e** *exo/endo*-**3a–e** **4a–c** (66–75%) **5d,e** (58–70%)

Scheme 1. Reaction of pyrone **1a** with cyclic alkenes **2a**–**2e** (see text and Table 1).

terised. The *exo* configuration of *exo*-**3a** was confirmed by X-ray analysis (Figure 2).[8] Similar products have previously been isolated and characterised from the reactions of pyrone **1a** with other alkoxyalkenes,[7] whereas similar compounds were not isolated from the reactions of pyrone **1b** with dienophiles **2a** and **2b**.[5b]

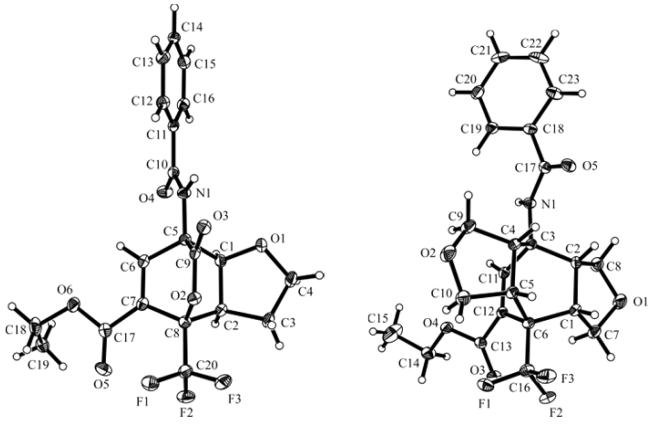
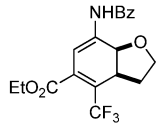
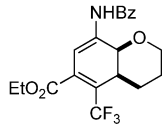
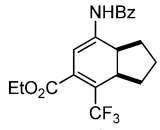
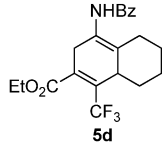
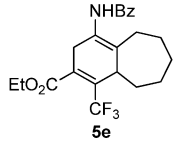


Figure 2. Crystal structure of compounds *exo*-**3a** and **8** (thermal ellipsoids are shown at 50% probability).[8]

We aimed to find conditions for the transformation of compounds **3** into dienes **4** (Table 1), and also for their further transformation into aromatic compounds **9** (Table 2). Bicyclic adducts **3** were easily formed in all cases, but the subsequent elimination of CO_2 required prolonged microwave irradiation (1–2 h, see Table 1). The reactions with dienophiles **2a**–**2c** proceeded smoothly to give the expected dienes (i.e., **4a**–**4c**) in moderate yields. In contrast, the reactions with cyclohexene (**2d**) and cycloheptene (**2e**) led to the isomeric dienes (i.e., **5d** and **5e**), which are supposed to be more stable than isomers **4**. The spectra of compounds **4** and **5** are similar, but the presence or absence of particular peaks allows the two structures to be distinguished. For compounds **4a** and **4c**, the ^{1}H NMR spectra contain a singlet (1 H, CH) between δ = 6.90 and 7.14 ppm, and the ^{13}C NMR spectra have a characteristic signal between δ = 103.1 and 104.4 ppm; neither of these signals is present in the spectra of compounds **5**. The ^{1}H NMR spectra of **5** contain an AB system (2 H, CH_2) between δ = 3.00 and 3.60 ppm with $J_{H,H}$ = 20.5–21.7 Hz. The corresponding signal in the ^{13}C NMR spectra appears between δ = 31.6 and 32.2 ppm. In addition, the structures of compounds **5d** and **5e** were confirmed by ^{1}H,^{13}C HMBC and ^{1}H,^{13}C HSQC spectra.

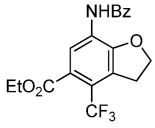
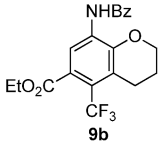
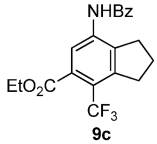
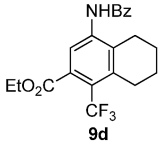
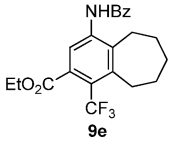
Table 1. Synthesis of compounds **4a**–**4c**, **5d**, and **5e**: conditions and yields.

Entry	Starting alkene **2**	Conditions	Products **4** or **5**	Yield [%]
1	 **2a**	150 W, 150 °C, 1 h	 **4a**	75
2	 **2b**	150 W, 150 °C, 1 h	 **4b**	71
3	 **2c**	150 W, 150 °C, 1.5 h	 **4c**	66
4	 **2d**	250 W, 150 °C, 2 h	 **5d**	58
5	 **2e**	150 W, 150 °C, 1 h	 **5e**	70

Most time-consuming was the reaction of cyclohexene (**2d**), which required ca. 2 h heating for complete conversion (Table 1, entry 4). Products **4a**–**4c** as well as **5d** and **5e** are stable, and were isolated in moderate yield and characterised. The reaction conditions can be used for the multigram preparation of compounds **4** and **5**.

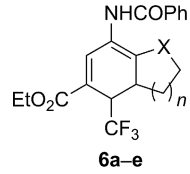
Besides other side-products, 3–12% (by ^{19}F NMR spectroscopy) of **6a**–**6e** were also identified in each of the crude reaction mixtures. We presume that these products are formed by partial isomerisation of **4** at elevated temperature (Figure 3). Compounds **6a**–**6e** could easily be identified in the reaction mixtures by ^{19}F NMR spectroscopy,[9] but all attempts to isolate them in pure form failed.

Table 2. Synthesis of compounds **9** by DDQ-mediated dehydrogenation starting from pure cyclohexenes **4a**–**4c**, **5d**, or **5e**, or the crude mixtures from the Diels–Alder reaction.

Entry	Starting diene	Product	One-step yield [%][a]	Two-steps yield [%][b]
1	**4a**	 **9a**	80	69
2	**4b**	 **9b**	75	64
3	**4c**	 **9c**	73	66
4	**5d**	 **9d**	68	59
5	**5e**	 **9e**	92	72

[a] Yield of products **9a**–**9e** by DDQ-mediated dehydrogenation of dienes **4a**–**4c**, **5d**, or **5e**. [b] Overall yield of **9a**–**9e** (based on **1a**) by the "one-pot" approach.

Unexpectedly, the reaction of **1a** with 2,5-dihydrofuran (**2f**) took a different route (Scheme 2). Under mild conditions (120 W, 120 °C, 10 min), the formation of bicyclic adducts *exo*/*endo*-**3f** was observed (the major product, i.e., *exo*-**3f**, was isolated), whereas under forcing conditions (150 W, 150 °C, 60 min), a complex mixture of products was formed. Cyclohexadiene **4f** was isolated in 6% yield. The



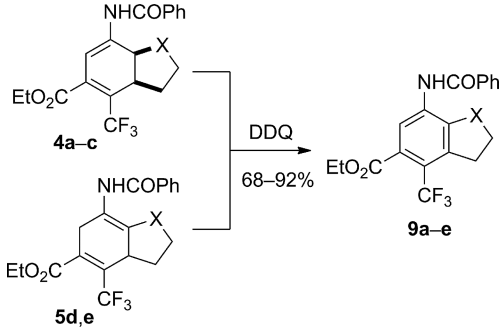
6a–e

Figure 3. General structure of by-products **6a**–**6e** (for the nature of X, see Table 1).

major product under these conditions was aromatic compound **7** (38% yield). The structure of **7** was proved by the fact that its spectroscopic data were identical to those of an authentic sample obtained earlier by the reaction of pyrone **1a** with 2-methoxypropene.[7]

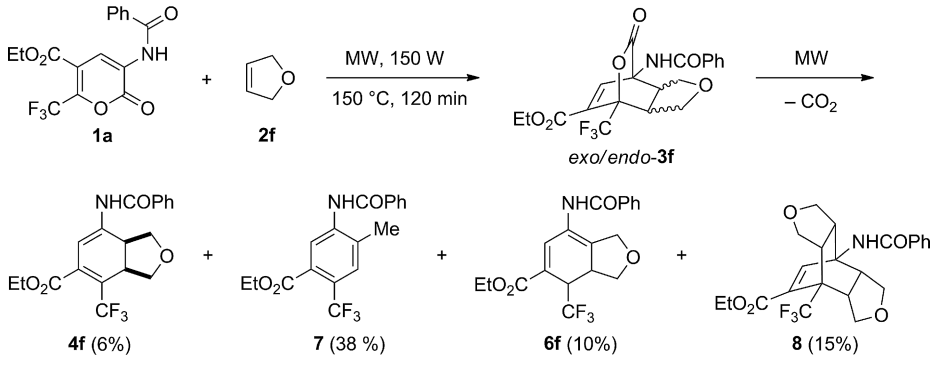
Two more isolated side-products were diene **6f** (10% yield) and bis-adduct **8** (15% yield). The simplicity of the NMR spectra of **8** indicated that this compound had a *meso* structure, and this was confirmed by X-ray analysis (Figure 2).[8] All our attempts to optimise the reaction conditions for selective formation of diene **4f** from pyrone **1a** and 2,5-dihydrofuran (**2f**) failed. Compound **7** was always formed as the major product.

Compounds **4a**–**4c**, **5d**, and **5e** were easily transformed into aromatic amino acid derivatives **9a**–**9e** (68–92% yield) by heating with DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone; Scheme 3, Table 2).



Scheme 3. Synthesis of compounds **9a**–**9e**.

Despite the anomalous results of the cycloaddition of **1a** with 2,5-dihydrofuran (**2f**), the two-step approach, i.e., Diels–Alder reaction of **1a** with alkenes **2a**–**2e**, with imme-



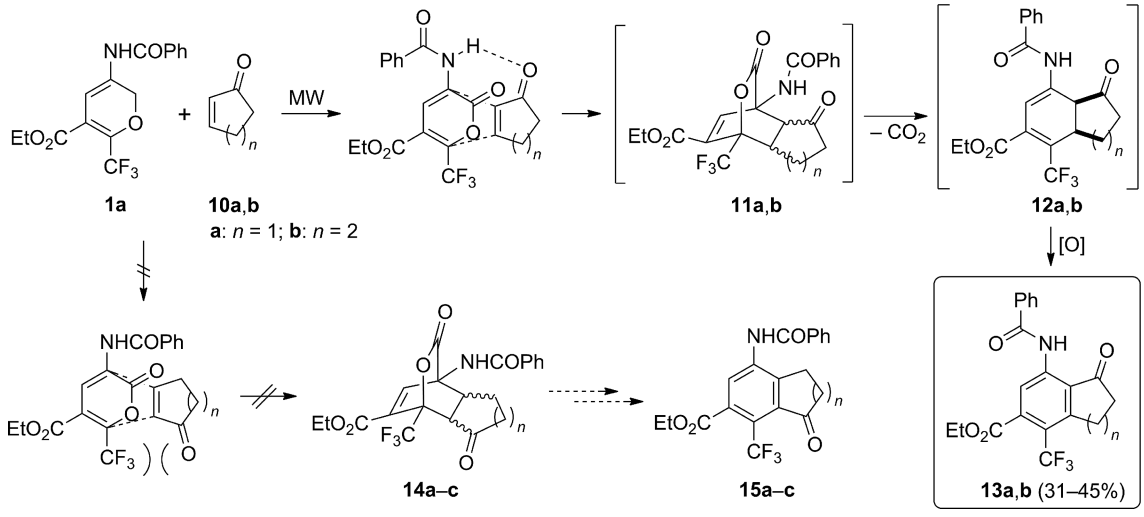
Scheme 2. Reaction of pyrone **1a** with 2,5-dihydrofuran (**2f**) (isolated yields are given in parentheses).

diate elimination of CO_2 to form compounds **4** or **5**, and subsequent DDQ-mediated dehydrogenation, is a convenient method for the synthesis of protected bicyclic aromatic amino acids such as **9**. Moreover, we found that this approach can be realised as a "one-pot" process without isolating cyclohexadienes **4** or **5**. In this case, the crude mixture from the Diels–Alder reaction (after removing the excess of **2a**–**2e**) was directly dehydrogenated by treatment with DDQ to give the corresponding products (i.e., **9**). The overall yield (based on starting compound **1a**) of the "one-pot" process was higher than that of the reaction sequence including the purification of compound **4** or **5**. The "one-pot" approach can be used for the multigram synthesis of compounds **9a**–**9e**.

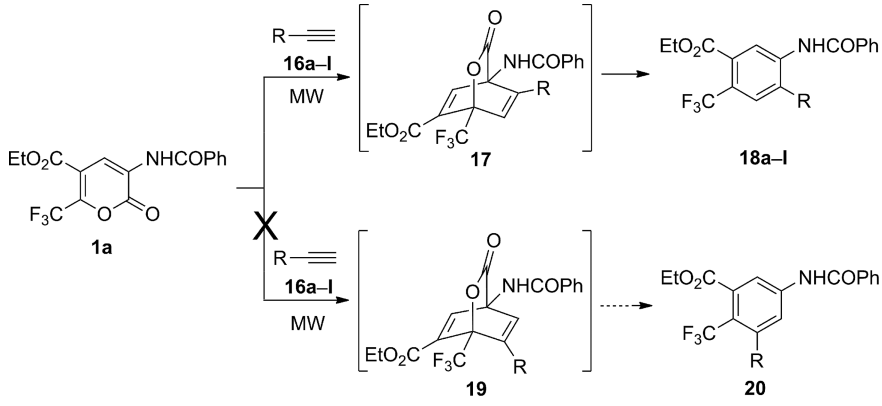
We also studied the reaction of **1a** with cycloalkenones **10a** and **10b**. Only a few examples of Diels–Alder reactions of 2-pyrones with α,β-unsaturated ketones have been reported in the literature.[10] In this way, we could synthesise CF_3-containing 1-indanones and 1-tetralones **13**. The reactions were carried out under microwave irradiation (150 W, 150 °C, 60 min), with the addition of a catalytic amount of hydroquinone in order to avoid polymerisation of compounds **10a** and **10b** (Scheme 4). Under these conditions, the corresponding intermediate tricyclic adducts (i.e., **11a** and **11b**) were not isolated. Unexpectedly, we also failed to isolate the corresponding cyclohexadienes (i.e., **12a** and **12b**), which were not stable under the reaction conditions. Dehydrogenation took place immediately to give the corresponding aromatic compounds (i.e., **13a** and **13b**) in 31–45% yield.[11]

Most intriguing, considering the electronic structures of diene **1a** and dienophiles **10a** and **10b**, the reverse regioselectivity was expected. However, regioisomers **15a** and **15b** were not isolated. Presumably, repulsion between the electron-rich C=O and CF_3 groups disfavours the transition state leading to tricyclic intermediates **14a** and **14b**, and thus prevents the formation of **15a** and **15b** (Scheme 4). On the other hand, hydrogen bonding between the NHCOPh moiety and the ketone group might facilitate the formation of intermediates **11a** and **11b**.

Bearing in mind that pyrone **1a** is a good diene for reactions with electron-rich enol ethers, ordinary alkenes, and α,β-unsaturated cyclic ketones, we were also interested in reactions with terminal acetylenes **16a**–**16l** as dienophiles. With these substrates, the oxidation step to give the final aromatic compounds can be avoided.



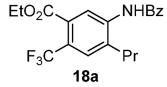
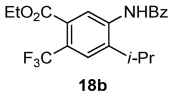
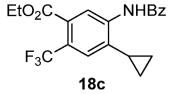
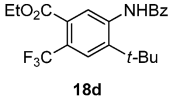
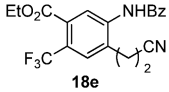
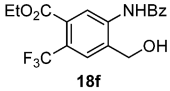
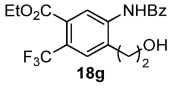
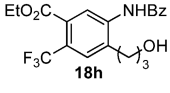
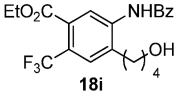
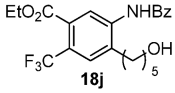
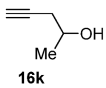
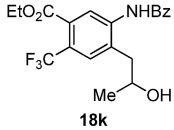
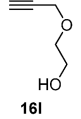
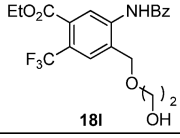
Scheme 4. Reaction of pyrone **1a** with cycloalkenones **10a** and **10b**.



Scheme 5. Regioselectivity of the Diels–Alder reaction between pyrone **1a** and acetylenes **18a**–**18l**.

The reactions took place regioselectively under mild microwave irradiation (Scheme 5) via non-isolable intermediates **17** to give aromatic products **18a**–**18l** in moderate to high yields (Table 3). The other regioisomers (i.e., **20**) were not observed.

Table 3. Synthesis of compounds **18a**–**18l**: conditions and yields.

Entry	Starting alkyne **16**	Conditions	Product **18**	Isolated yield, %
1	 **16a**	150 W, 150°C, 60 min	 **18a**	90
2	 **16b**	150 W, 150 °C, 90 min	 **18b**	64
3	 **16c**	150 W, 150 °C, 90 min	 **18c**	68
4	 **16d**	150 W, 150 °C,3 h	 **18d**	55
5	 **16e**	150 W, 150 °C, 60 min	 **18e**	73
6	 **16f**	150 W, 120 °C, 30 min	 **18f**	58
7	 **16g**	150 W, 150 °C, 60 min	 **18g**	74
8	 **16h**	150 W, 150 °C, 60 min	 **18h**	81
9	 **16i**	150 W, 150 °C, 60 min	 **18i**	70
10	 **16j**	150 W, 150 °C, 60 min	 **18j**	89
11	 **16k**	150 W, 150 °C, 90 min	 **18k**	67
12	 **16l**	150 W, 150 °C, 30 min	 **18l**	84

We suppose that in this case, the high regioselectivity is due to a steric repulsion between the CF_3 group and the alkyl chain of the acetylenes, which disfavours the formation of intermediate **19**. Single crystals of compound **18g** were grown from toluene/hexane (1:1), and X-ray analysis confirmed the substituent pattern on the benzene ring (Figure 4).[8]

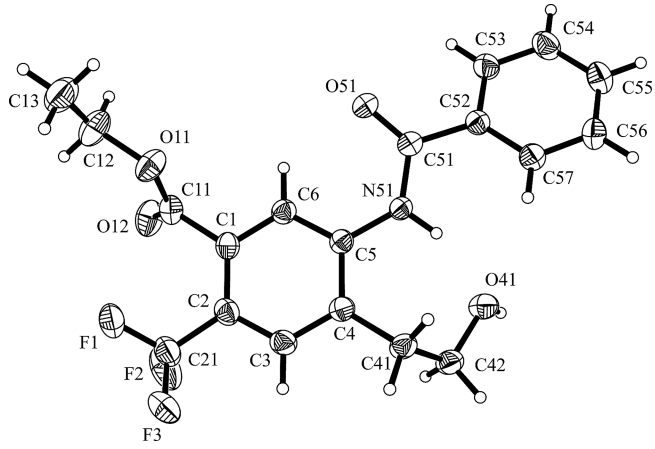
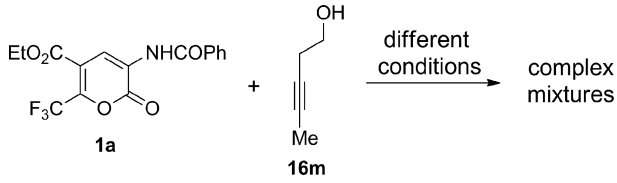


Figure 4. Crystal structure of compound **18g** (thermal ellipsoids are shown at 30% probability).[8]

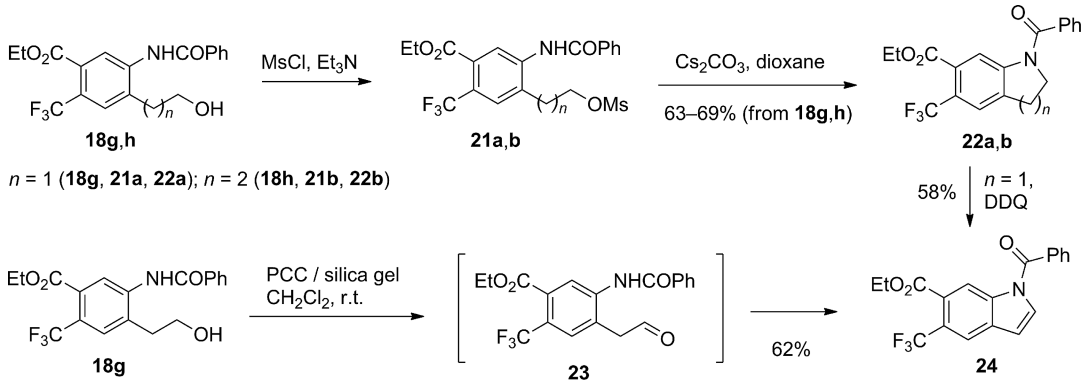
Most of the acetylenes reacted smoothly, and the method can be used for multigram syntheses of compounds **18a**–**18l**. Only in the case of *tert*-butylacetylene (**16d**) (Table 3, entry 4) did the reaction require a longer heating time (3 h) for complete conversion. In the reaction of propargyl alcohol **16f** (Table 3, entry 6), it was important to use milder conditions to obtain a reasonable yield, since at 150 °C resinification occurred.

In contrast, all attempted reactions between **1a** and pent-3-yn-1-ol (**16m**) failed. Under different conditions, inseparable complex mixtures were formed (Scheme 6). Presumably, once again, unfavourable repulsion between the CF_3 group and the alkyl groups of the acetylene prevents the formation of the transition state.



Scheme 6. Attempted reaction between pyrone **1a** and pent-3-yn-1-ol (**16m**).

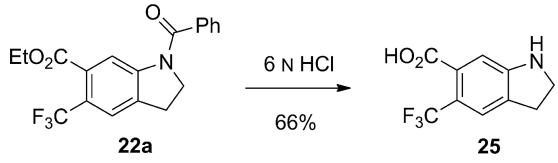
Compounds **18g**–**18l** contain neighbouring *N*-benzoylamido and hydroxyalkyl groups, which might be involved in an intramolecular cyclisation to form bicyclic compounds **22** (Scheme 7). The most efficient approach to such a cyclisation involved an initial mesylation of the hydroxy group, and subsequent intramolecular nucleophilic substitution promoted by Cs_2CO_3 in dioxane.[12] This sequence was used to cyclise compounds **18g** and **18h** to give indoline **22a** and the tetrahydroquinoline **22b**, respectively. In contrast, our attempts to cyclise compounds **18i**–**18l** failed. The corresponding mesylates did not undergo further transformation under the conditions used.



Scheme 7. Synthesis of compounds **22a**, **22b**, and **24** by intramolecular cyclisation.

Furthermore, compound **18g** could be used for the synthesis of indole **24**. Oxidation of the OH group with PCC (pyridinium chlorochromate) led directly to **24** via intermediate aldehyde **23**, which could not be isolated. Compound **24** was also obtained by dehydrogenation of **22a** with DDQ.

Formally, the compounds obtained (i.e., **9a**–**9e**, **13a**, **13b**, **18a**–**18l**, **22a**, and **22b**) are aromatic γ-amino acid derivatives. We have previously shown for similar compounds that the *N*-benzoyl group and/or the ethyl ester moiety can be hydrolysed selectively (or both in one step) under acidic or basic conditions.[7] For instance, compound **22a** was hydrolysed by heating in refluxing aqueous (6 N) HCl to give 5-(trifluoromethyl)indole-6-carboxylic acid (**25**) in 66% yield (Scheme 8).



Scheme 8. Complete hydrolysis of compound **22a**.

Conclusions

Diels–Alder reactions of trifluoromethyl-substituted pyrone **1a** with cycloalkenes and acetylenes represent a convenient method for the preparation of a variety of trifluoromethyl-substituted, polyfunctionalised aromatic compounds. Compounds accessible by this method include protected bicyclic 5-amino-2-(trifluoromethyl)benzoic acids **9a**–**9e** (via bicyclic cyclohexadienes **4a**–**4c**, **5d**, or **5e**), indanone and tetralone derivatives **13a** and **13b**, 4-alkyl-5-benzoylamino-2-(trifluoromethyl)-benzoates **18a**–**18l**, and **22a** and **22b**. The reactions proceed with high regioselectivity. We presume that the presence of the CF_3 group determines the regioselectivity of the reaction.

Experimental Section

General Remarks: NMR spectra were recorded with a Bruker Avance II instrument at 300 and 400 MHz, a Bruker DRX instrument at 300 MHz, and an Agilent DD2 instrument at 500 and 600 MHz (^{1}H), at 25 °C. Tetramethylsilane (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 instrument. Mass spectra (ESI-MS) were measured with a MicroTof Bruker Daltonics instrument. The progress of 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, N. Reactions under microwave irradiation were carried out in sealed tubes. Reactions using microwave heating were carried out using a Discover BenchMate from CEM Corporation (for the conditions, see Tables 1 and 3). All starting materials were of the highest commercially available quality, and were used as supplied. Pyrone **1a** was prepared as described.[5b]

General Procedure for the Diels–Alder Reaction of Pyrone 1a with Alkenes 2a–2e, 10a, 10b, and 16a–16m: A mixture of pyrone **1a** (355 mg, 1 mmol) and the corresponding dienophile **2a**–**2e**, **10a**, **10b**, and **16a**–**16m** (0.5 mL, 5–6 equiv.) was heated without solvent in a sealed tube under microwave irradiation (see Tables 1 and 3, main text). The excess of the dienophile was removed under reduced pressure, and the product was purified by crystallisation or by column chromatography.

Ethyl *exo*-1-Benzamido-9-oxo-7-(trifluoromethyl)-3,8-dioxatricyclo-[5.2.2.0^{2,6}]undec-10-ene-11-carboxylate (*exo*-3a): Obtained as the major product from pyrone **1a** and 2,3-dihydrofuran (**2a**) under mild microwave irradiation (120 W, 120 °C, 10 min) as a mixture with isomer *endo*-**3a** (*exo*-**3a**/*endo*-**3a** ca. 30:70 by ^{19}F NMR spectroscopic analysis of the crude reaction mixture), and isolated by column chromatography (EtOAc/cyclohexane, 1:4, R_f = 0.32), yield 89 mg (21%), colourless solid, m.p. 122 °C. IR (KBr): $\tilde{\nu}$ = 3403, 2992, 2846, 1790, 1741, 1662, 1580, 1512, 1484, 1318, 1284, 1195, 1099, 979, 895, 725, 630, 524 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.32 (t, J = 7.2 Hz, 3 H, CH_3), 2.07–2.34 (m, 2 H, CH_2), 3.22 (dd, J = 16.8, J = 9.0 Hz, 1 H, CH), 3.79 (ddd, J = 15.6, J = 9.7, J = 5.9 Hz, 1 H, H_a of CH_2O), 4.14 (ddd, J = 9.7, J = 7.7, J = 3.2 Hz, 1 H, H_b of CH_2O), 4.21–4.33 (m, 2 H, CH_2O), 5.10 (d, J = 9.0 Hz, 1 H, CHO), 7.38 (br. s, 1 H, NH), 7.45–7.55 (m, 4 H, Ph and CH), 7.84–7.95 (m, 2 H, Ph) ppm. ^{13}C NMR (76 MHz, $CDCl_3$): δ = 13.9, 26.2, 46.1, 62.1, 64.7, 71.6, 78.4, 83.0 (q, J = 31.5 Hz), 121.8 (q, J = 281.0 Hz), 127.3, 128.8, 132.6, 132.8, 135.5, 142.2, 160.9, 166.0, 167.2 ppm. ^{19}F NMR (283 MHz, $CDCl_3$): δ = –70.99 (s, CF_3) ppm. HRMS (ESI): calcd. for $C_{20}H_{19}F_3NO_6$ 426.1159; found 426.1157. $C_{20}H_{18}F_3NO_6$ (425.36): calcd. C 56.47, H 4.27, N 3.29; found C 56.33, H 4.38, N 3.26.

Ethyl *endo*-1-Benzamido-9-oxo-7-(trifluoromethyl)-3,8-dioxatricyclo[5.2.2.0^{2,6}]undec-10-ene-11-carboxylate (*endo*-3a): Obtained as the major product from pyrone **1a** and 2,3-dihydrofuran (**2a**) under mild microwave irradiation (120 W, 120 °C, 10 min) as a mixture with isomer *endo*-**3a** (*exo*-**3a**/*endo*-**3a** ca. 30:70 by ^{19}F NMR spectroscopic analysis of the reaction mixture), and isolated by column chromatography (EtOAc/cyclohexane, 1:4, R_f = 0.15), yield 191 mg (45%), colourless solid, m.p. 98 °C. IR (KBr): $\tilde{\nu}$ = 3336, 3260, 1799, 1715, 1528, 1489, 1369, 1271, 1194, 1165, 1138, 1100, 1078, 1011, 960, 713, 696, 628 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.33 (t, J = 7.1 Hz, 3 H, CH_3), 1.75–1.92 (m, 1 H, H_a of CH_2), 2.20–2.34 (m, 1 H, H_b of CH_2), 3.40 (ddd, J = 17.0, J = 9.2, J = 7.9 Hz, 1 H, CH), 3.78 (dt, J = 9.3, J = 6.6 Hz, 1 H, H_a of CH_2O), 4.05 (td, J = 8.6, J = 3.4 Hz, 1 H, H_b of CH_2O), 4.22–4.36 (m, 2 H, CH_2O), 4.51 (d, J = 7.9 Hz, 1 H, CH), 6.94 (s, 1 H, NH), 7.44–7.61 (m, 3 H, Ph), 7.63 (s, 1 H, CH), 7.87–7.93 (m, 2 H, Ar) ppm. ^{13}C NMR (76 MHz, $CDCl_3$): δ = 14.0, 28.4, 46.0, 62.1, 64.7, 70.6, 79.6, 82.9 (q, J = 31.0 Hz), 121.0 (q, J = 280.0 Hz), 127.4, 128.7, 129.8, 132.5, 144.5, 161.1, 165.1, 167.3 ppm. ^{19}F NMR (283 MHz, $CDCl_3$): δ = –73.61 (s, CF_3) ppm. HRMS (ESI): calcd. for $C_{20}H_{19}F_3NO_6$ 426.1159; found 426.1158. $C_{20}H_{18}F_3NO_6$ (425.36): calcd. C 56.47, H 4.27, N 3.29; found C 56.40, H 4.21, N 3.41.

Ethyl *cis*-7-Benzamido-4-(trifluoromethyl)-2,3,3a,7a-tetrahydrobenzofuran-6-carboxylate (4a): Obtained as the major product from pyrone **1a** and 2,3-dihydrofuran (**2a**) under microwave conditions (150 W, 150 °C, 60 min, see Table 1, entry 1), and purified by crystallisation from CCl_4, yield 285 mg (75%), colourless solid, m.p. 81 °C. IR (KBr): $\tilde{\nu}$ = 3275, 3098, 2985, 2901, 1729, 1682, 1601, 1531, 1448, 1373, 1290, 1227, 1192, 1143, 1112, 1078, 1047, 1020, 854, 792, 506 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.33 (t, J = 7.2 Hz, 3 H, CH_3), 2.06 (dt, J = 11.9, J = 9.2 Hz, 1 H, H_a of CH_2), 2.29–2.51 (m, 1 H, H_b of CH_2), 3.09 (dd, J = 18.8, J = 10.0 Hz, 1 H, CH), 3.74–4.01 (m, 2 H, CH_2O), 4.29 (q, J = 7.2 Hz, 2 H, CH_2O), 4.98 (d, J = 10.0 Hz, 1 H, CH), 7.09 (s, 1 H, CH), 7.38–7.67 (m, 3 H, Ar), 7.72–7.93 (m, 2 H, Ar), 8.30 (s, 1 H, NH) ppm. ^{13}C NMR (76 MHz, $CDCl_3$): δ = 13.9, 31.7, 36.7, 61.9, 66.3, 75.4, 103.1, 119.6 (q, J = 34.2 Hz), 123.3 (q, J = 273.5 Hz), 127.0, 128.9, 132.4, 132.9 (q, J = 4.5 Hz), 133.9, 136.2, 166.0, 166.9 ppm. ^{19}F NMR (283 MHz, $CDCl_3$): δ = –62.20 (s, CF_3) ppm. HRMS (ESI): calcd. for $C_{19}H_{18}F_3NNaO_4$ 404.1080; found 404.1078. $C_{19}H_{18}F_3NO_4$ (381.35): calcd. C 59.84, H 4.76, N 3.67; found C 59.70, H 4.86, N 3.60.

Ethyl 4-Benzamido-1-(trifluoromethyl)-3,5,6,7,8,8a-hexahydronaphthalene-2-carboxylate (5d): Obtained as the major product from pyrone **1a** and cyclopentene (**2d**) under microwave conditions (250 W, 150 °C, 120 min, see Table 1, entry 4), and purified by crystallisation from CCl_4, yield 228 mg (58%), colourless solid, m.p. 84 °C. IR (KBr): $\tilde{\nu}$ = 3271, 3063, 2936, 2855, 1730, 1639, 1515, 1486, 1368, 1288, 1268, 1184, 1128, 1094, 1072, 1011, 749, 710 cm^{-1}. ^{1}H NMR (300 MHz, CD_2Cl_2): δ = 1.31 (t, J = 7.1 Hz, 3 H, CH_3), 1.33–1.43 (m, 2 H, CH_2), 1.49–1.59 (m, 1 H, H of CH_2), 1.81–1.91 (m, 2 H, CH_2), 2.18 (d, J = 11.9 Hz, 1 H, H of CH_2), 2.73 (d, J = 11.5 Hz, 1 H, H of CH_2), 3.03–3.10 (m, 1 H, CH), 3.39 (d, J = 20.5 Hz, 1 H, H_a of CH_2), 7.30 (br. s, 1 H, NH), 7.45–7.57 (m, 3 H, Ph), 7.79–7.84 (m, 2 H, Ph) ppm. ^{13}C NMR (76 MHz, CD_2Cl_2): δ = 13.6, 26.2, 27.3, 28.7, 31.6, 34.0, 39.5, 61.7, 120.0, 123.2 (q, J = 275.5 Hz), 126.6 (q, J = 28.0 Hz), 127.0, 128.6, 130.4, 131.7, 134.3 (q, J = 4.0 Hz), 134.4, 166.0, 167.5 ppm. ^{19}F NMR (283 MHz, CD_2Cl_2): δ = –60.31 (s, CF_3) ppm. HRMS (ESI): calcd. for $C_{21}H_{22}F_3NNaO_3$ 416.1444; found 416.1449. $C_{21}H_{22}F_3NO_3$ (393.40): calcd. C 64.11, H 5.64, N 3.56; found C 64.02, H 5.70, N 3.68.

General Procedure for the Aromatisation of Compounds 4a–4c, 5d, and 5e

Method A: A mixture of DDQ (340 mg, 1.5 mmol) and the appropriate pure compound **4a**–**4c**, **5d**, or **5e** (1 mmol) was stirred in toluene (5 mL) under reflux (4–18 h). Reaction progress was monitored by TLC and NMR spectroscopic analysis of the crude mixtures. After conversion was complete, the solvent was removed, and the corresponding product (i.e., **9a**–**9e**) was purified by column chromatography or crystallisation.

Method B: As for Method A, but instead of pure compound **4a**–**4c**, **5d**, or **5e**, the crude product of the Diels–Alder reaction of pyrone **1a** with cycloalkene **2a**–**2e** (see general procedure above) was used after removing the excess cycloalkene **2a**–**2e**.

Ethyl 7-Benzamido-4-(trifluoromethyl)-2,3-dihydrobenzofuran-6-carboxylate (9a): Obtained by Method A from compound **4a** (381 mg, 1 mmol) or by Method B from the crude product of the Diels–Alder reaction of pyrone **1a** (355 mg, 1 mmol) with 2,3-dihydrofuran (**2a**) (reaction time: 5 h), and isolated by column chromatography (EtOAc/cyclohexane, 1:4, R_f = 0.38), yield by Method A (from **4a**): 303 mg (80%); yield by Method B (from **1a**): 262 mg (69%), colourless solid, m.p. 76 °C. IR (KBr): $\tilde{\nu}$ = 3226, 2980, 1727, 1652, 1616, 1533, 1488, 1427, 1374, 1337, 1286, 1244, 1193, 1126, 1016, 987, 912, 884, 691 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.38 (t, J = 7.1 Hz, 3 H, CH_3), 3.48 (td, J = 8.8, J = 1.6 Hz, 2 H, CH_2), 4.36 (q, J = 7.1 Hz, 2 H, CH_2O), 4.74 (t, J = 8.8 Hz, 2 H, CH_2O), 7.45–7.61 (m, 3 H, Ph), 7.83–7.91 (m, 2 H, Ph), 8.09 (s, 1 H, NH), 8.70 (s, 1 H, Ar) ppm. ^{13}C NMR (76 MHz, $CDCl_3$): δ = 14.0, 30.6, 61.8, 72.7, 120.5 (q, J = 31.5 Hz), 120.7, 123.6 (q, J = 273.5 Hz), 124.9, 125.4 (q, J = 2.2 Hz), 126.3 (q, J = 2.5 Hz), 127.1, 128.9, 132.4, 133.9, 150.7, 165.4, 167.1 ppm. ^{19}F NMR (283 MHz, $CDCl_3$): δ = –57.40 (s, CF_3) ppm. HRMS (ESI): calcd. for $C_{19}H_{16}F_3NNaO_4$ 402.0924; found 402.0920. $C_{19}H_{16}F_3NO_4$ (379.33): calcd. C 60.16, H 4.25, N 3.69; found C 60.02, H 4.36, N 3.80.

Ethyl 7-Benzamido-1-oxo-4-(trifluoromethyl)-2,3-dihydro-1*H*-indene-5-carboxylate (13a): Obtained as the major product from pyrone **1a** and cyclopent-2-enone (**10a**) by the general procedure for a Diels–Alder reaction in the presence of hydroquinone (3–5 mg) under microwave conditions (150 W, 150 °C, 60 min, see Scheme 4). After concentration in vacuo, the mixture was dissolved in Et_2O, the insoluble solid was removed by filtration, the filtrate was concentrated in vacuo, and the resulting residue was crystallised from Et_2O/cyclohexane, 2:1, yield 176 mg (45%), yellow solid, m.p. 52 °C. IR (KBr): $\tilde{\nu}$ = 3276, 2955, 1729, 1682, 1591, 1523, 1493, 1408, 1285, 1244, 1132, 1056, 1026, 901, 838, 713, 611 cm^{-1}. ^{1}H NMR (300 MHz, CD_2Cl_2): δ = 1.40 (t, J = 7.2 Hz, 3 H, CH_3), 2.84–2.87 (m, 2 H, CH_2), 3.34–3.38 (m, 2 H, CH_2), 4.43 (q, J = 7.2 Hz, 2 H, CH_2O), 7.55–7.67 (m, 3 H, Ph), 8.04–8.08 (m, 2 H, Ph), 8.81 (s, 1 H, CH), 11.72 (s, 1 H, NH) ppm. ^{13}C NMR (76 MHz, CD_2Cl_2): δ = 13.7, 25.4 (q, J = 3.0 Hz), 36.1, 62.6, 116.7, 118.5 (q, J = 32.5 Hz), 123.6 (q, J = 276.0 Hz), 123.9, 127.4, 129.0, 132.7, 133.3, 140.2, 141.5, 154.7, 165.7, 166.9, 208.2 ppm. ^{19}F NMR (283 MHz, CD_2Cl_2): δ = –59.20 (s, CF_3) ppm. HRMS (ESI): calcd. for $C_{20}H_{16}F_3NNaO_4$ 414.0924; found 414.0927. $C_{20}H_{16}F_3NO_4$ (391.34): calcd. C 61.38, H 4.12, N 3.58; found C 61.46, H 4.00, N 3.72.

Ethyl 5-(Benzamido)-4-propyl-2-(trifluoromethyl)benzoate (18a): Obtained as the major product from pyrone **1a** and pent-1-yne (**16a**) under microwave irradiation (150 W, 150 °C, 60 min, see Table 3, entry 1), and purified by column chromatography (EtOAc/cyclohexane, 1:4, R_f = 0.45), yield 340 mg (90%), pale yellow solid, m.p. 77 °C. IR (KBr): $\tilde{\nu}$ = 3277, 2970, 2934, 1718, 1645, 1573, 1521,

1482, 1408, 1316, 1132, 1029, 926, 910, 692, 501 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.03 (t, J = 7.3 Hz, 3 H, CH_3), 1.39 (t, J = 7.1 Hz, 3 H, CH_3), 1.65–1.80 (m, 2 H, CH_2), 2.70 (t, J = 7.6 Hz, 2 H, CH_2), 4.39 (q, J = 7.1 Hz, 2 H, CH_2O), 7.48–7.65 (m, 4 H, CH and Ph), 7.83–7.94 (m, 3 H, CH and Ar), 8.61 (s, 1 H, NH) ppm. ^{13}C NMR (76 MHz, $CDCl_3$): δ = 13.9, 14.0, 22.5, 33.3, 61.9, 123.4 (q, J = 272.0 Hz), 124.0, 124.6 (q, J = 31.5 Hz), 127.0, 128.1 (q, J = 6.0 Hz), 129.1, 130.3 (q, J = 1.8 Hz), 132.5, 134.5, 135.1, 138.4, 165.5, 166.4 ppm. ^{19}F NMR (283 MHz, $CDCl_3$): δ = –58.90 (s, CF_3) ppm. HRMS (ESI): calcd. for $C_{20}H_{20}F_3NNaO_3$ 402.1287; found 402.1282. $C_{20}H_{20}F_3NO_3$ (379.37): calcd. C 63.32, H 5.31, N 3.69; found C 63.20, H 5.44, N 3.80.

Ethyl 5-(Benzamido)-4-(2-hydroxyethyl)-2-(trifluoromethyl)benzoate (18g): Obtained from pyrone **1a** and homopropargyl alcohol (**16g**) under microwave conditions (150 W, 150 °C, 60 min, see Table 3, entry 7), and purified by column chromatography (EtOAc/hexane, 1:2, R_f = 0.45), yield 282 mg (74%), colourless solid, m.p. 64–65 °C. IR (KBr): $\tilde{\nu}$ = 3384, 2992, 1740, 1662, 1589, 1550, 1369, 1345, 1317, 1269, 1232, 1018, 910, 715 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.36 (t, J = 7.1 Hz, 3 H, CH_3), 2.92 (t, J = 5.2 Hz, 2 H, CH_2Ar), 3.50 (br. s, 1 H, OH), 4.02 (t, J = 5.2 Hz, 2 H, CH_2OH), 4.35 (q, J = 7.1 Hz, 2 H, OCH_2Me), 7.36–7.50 (m, 3 H, Ph), 7.51 (s, 1 H, Ar), 7.86–7.91 (m, 2 H, Ph), 8.44 (s, 1 H, Ar), 10.27 (s, 1 H, NH) ppm. ^{13}C NMR (76 MHz, $CDCl_3$): δ = 13.9, 35.0, 62.1, 64.5, 123.3 (q, J = 272.9 Hz), 124. 3 (q, J = 32.1 Hz), 124.9, 127.3, 128.7, 129.2 (q, J = 5.3 Hz), 130.3, 132.2, 133.8, 134.9, 140.4, 165.9, 166.8 ppm. ^{19}F NMR (283 MHz, $CDCl_3$): δ = –59.37 (s, CF_3) ppm. HRMS (ESI): calcd. for $C_{19}H_{18}F_3NNaO_4$ 404.1080; found 404.1084. $C_{19}H_{18}F_3NO_4$ (381.35): calcd. C 59.84, H 4.76, N 3.67; found C 59.76, H 4.69, N 3.91.

Synthesis of Compounds 22a and 22b: Mesyl chloride (124 mg, 1.1 mmol) was added to a solution of compound **18g** (381 mg, 1 mmol) or **18h** (395 mg, 1 mmol) and Et_3N (111 mg, 1.1 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The reaction mixture was stirred overnight at room temp., then it was poured into water, and the mixture was extracted with CH_2Cl_2 (3× 20 mL). The organic layer was dried with $MgSO_4$, and concentrated in vacuo to give crude **21a** (410 mg) or **21b** (425 mg), which were used for the next step without purification.

A mixture of crude compound **21a** (410 mg) or **21b** (425 mg) and Cs_2CO_3 (390 mg, 1.2 mmol) was heated at reflux with vigorous stirring for 6 h. The reaction was monitored by TLC and NMR spectroscopy of the crude mixtures. After conversion was complete, the solvent was removed, and the product (i.e., **22a** or **22b**) was purified by column chromatography.

2-(Benzamido)-4-(ethoxycarbonyl)-5-(trifluoromethyl)phenethyl Methanesulfonate (21a): ^1H NMR (300 MHz, $CDCl_3$): δ = 1.38 (t, J = 7.1 Hz, 3 H, CH_3), 2.94 (s, 3 H, CH_3), 3.20 (t, J = 6.2 Hz, 2 H, CH_2), 4.40 (q, J = 7.1 Hz, 2 H, CH_2O), 4.53 (t, J = 6.2 Hz, 2 H, CH_2O), 7.48–7.66 (m, 4 H, Ar), 7.93–8.01 (m, 2 H, Ar), 8.38 (s, 1 H, Ar), 8.43 (s, 1 H, NH) ppm. HRMS (ESI): calcd. for $C_{20}H_{20}F_3NNaO_6S$ 482.0861; found 482.0856.

Ethyl 1-Benzoyl-5-(trifluoromethyl)indoline-6-carboxylate (22a): Purified by column chromatography (EtOAc/cyclohexane, 1:1, R_f = 0.34), yield 230 mg (63% from **18g**), colourless solid, m.p. 37–38 °C. IR (CH_2Cl_2): $\tilde{\nu}$ = 2985, 1733, 1657, 1614, 1496, 1394, 1337, 1294, 1134, 1106, 1079, 965 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.33 (t, J = 6.9 Hz, 3 H, CH_3), 3.19 (t, J = 7.8 Hz, 2 H, CH_2), 4.15 (t, J = 7.8 Hz, 2 H, CH_2N), 4.33 (q, J = 6.9 Hz, 2 H, CH_2O), 7.40–7.60 (m, 7 H, Ar) ppm. ^{13}C NMR (76 MHz, $CDCl_3$): δ = 13.5, 27.6, 50.3, 61.6, 117.4, 122.8, 123.0 (q, J = 275.0 Hz), 123.4 (q, J = 36.2 Hz), 126.6, 128.4, 130.5, 131.2, 134.7, 145.1, 166.2, 169.0 ppm. ^{19}F NMR (283 MHz, $CDCl_3$): δ = –59.16 (s, CF_3) ppm. HRMS (ESI): calcd. for $C_{19}H_{16}F_3NNaO_3$ 386.0980; found 386.0976. $C_{19}H_{16}F_3NO_3$ (363.33): calcd. C 62.81, H 4.44, N 3.86; found C 62.68, H 4.59, N 3.98.

Ethyl 1-Benzoyl-5-(trifluoromethyl)-1*H*-indole-6-carboxylate (24)

Method A. From 18g: A mixture of compound **18g** (381 mg, 1 mmol) and PCC/silica gel (1:1; 450 mg) in CH_2Cl_2 (10 mL) was stirred at room temp. for 8 h. Reaction progress was monitored by TLC and NMR spectroscopic analysis of the crude mixture. After the conversion was complete, the mixture was filtered through a short pad of silica gel. The filtrate was evaporated in vacuo, and the residue was purified by column chromatography (EtOAc/cyclohexane, 1:2, R_f = 0.66), yield 225 mg (62%).

Method B. From 22a: A mixture of compound **22a** (363 mg, 1 mmol) and DDQ (340 mg, 1.5 mmol) in toluene (5 mL) was stirred at room temp. for 8 h. Reaction progress was monitored by TLC and NMR spectroscopic analysis of the crude mixture. After the conversion was complete, the solvent was removed in vacuo, and the residue was purified by column chromatography, yield 210 mg (58%), colourless solid, m.p. 54–55 °C. IR (KBr): $\tilde{\nu}$ = 3295, 1721, 1658, 1613, 1593, 1536, 13212, 1232, 1142, 1109, 1039, 1019, 847, 714, 691 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.39 (t, J = 6.9 Hz, 3 H, CH_3), 4.40 (q, J = 6.9 Hz, 2 H, CH_2O), 7.49–7.64 (m, 3 H, Ph), 7.75 (d, J = 8.7 Hz, 1 H, Ar), 7.85–7.91 (m, 2 H, Ph), 7.96 (s, 1 H, Ar), 8.05 (s, 1 H, Ar), 8.07 (d, J = 8.7 Hz, 1 H, Ar) ppm. ^{13}C NMR (76 MHz, $CDCl_3$): δ = 13.5, 61.8, 120.5, 121.0, 122.9 (q, J = 272.0 Hz), 123.7 (q, J = 31.2 Hz), 126.7, 127.7 (q, J = 5.4 Hz), 128.6, 132.0, 132.1, 132.3, 133.7, 140.6, 165.3, 165.9 ppm. ^{19}F NMR (283 MHz, $CDCl_3$): δ = –59.27 (s, CF_3) ppm. HRMS (ESI): $C_{19}H_{14}F_3NNaO_3$ 384.3038; found 384.3042. $C_{19}H_{14}F_3NO_3$ (361.31): calcd. C 63.16, H 3.91, N 3.88; found C 63.02, H 4.07, N 3.68.

5-(Trifluoromethyl)indoline-6-carboxylic Acid (25): A mixture of compound **22a** (3.63 g, 10 mmol) and HCl (6 N; 50 mL) was stirred at reflux for 48 h. Reaction progress was monitored by TLC and ^1H NMR spectroscopic analysis of the reaction mixture. After the conversion was complete, the mixture was cooled, and the precipitate of benzoic acid was removed by filtration. The water solution was evaporated. The resulting solid residue was washed with hot CCl_4 to give pure compound **25** (as its hydrochloride salt), yield 1.77 g (66%), pale brown solid, m.p. 66 °C. IR (KBr): $\tilde{\nu}$ = 3393, 2858, 1727, 1697, 1623, 1594, 1503, 1428, 1382, 1298, 1252, 1215, 1136, 1100, 1025, 964, 901, 836, 745, 713, 645, 612, 536, 457, 419 cm^{-1}. ^1H NMR (300 MHz, D_2O): δ = 3.25 (t, J = 7.2 Hz, 2 H, CH_2), 3.84 (t, J = 7.2 Hz, 2 H, CH_2), 7.72 (s, 1 H, Ar), 7.73 (s, 1 H, Ar) ppm. ^{13}C NMR (76 MHz, D_2O): δ = 28.5, 46.1, 120.0, 122.3 (q, J = 275.1 Hz), 124.7 (q, J = 5.5 Hz), 128.5 (q, J = 32.5 Hz), 131.8, 138.5, 139.4, 169.0 ppm. ^{19}F NMR (283 MHz, $CDCl_3$): δ = –59.68 (s, CF_3) ppm. HRMS (ESI): calcd. for $C_{10}H_8F_3NNaO_2$ 254.0399; found 254.0401. $C_{10}H_8F_3NO_2$·HCl (267.63): calcd. C 44.88, H 3.39, N 5.23; found C 44.99, H 3.25, N 5.11.

X-ray Diffraction: Data sets for compounds **3a** and **8** were collected with a D8 Venture Dual Source 100 CMOS diffractometer. Programs used: data collection: APEX2 V2014.5–0 (Bruker AXS Inc., 2014); cell refinement: SAINT V8.34A (Bruker AXS Inc., 2013); data reduction: SAINT V8.34A (Bruker AXS Inc., 2013); absorption correction, SADABS V2014/2 (Bruker AXS Inc., 2014); structure solution SHELXT-2014 (Sheldrick, 2014); structure refinement SHELXL-2014 (Sheldrick, 2014); and graphics, XP (Bruker AXS Inc., 2014). For compound **18g**, the data sets were collected with a Nonius KappaCCD diffractometer. Programs used: data collection, COLLECT (R. W. W. Hooft, Bruker AXS, 2008, Delft,

The Netherlands); data reduction Denzo-SMN;[13a] absorption correction, Denzo;[13b] structure solution SHELXS-97;[13c] structure refinement SHELXL-97.[13d] *R* values are given for observed reflections, and wR_2 values are given for all reflections.

X-ray Crystal Structure Analysis of *exo*-3a: A colourless prism-like specimen of $C_{20}H_{18}F_3NO_6$, approximate dimensions $0.114 \times 0.178 \times 0.328$ mm^3, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured. A total of 1674 frames were collected. The total exposure time was 13.12 h. The frames were integrated with the Bruker SAINT software package using a wide-frame algorithm. The integration of the data using a triclinic unit cell yielded a total of 23043 reflections to a maximum θ angle of 68.35° (0.83 Å resolution), of which 3333 were independent (average redundancy 6.914, completeness: 99.8%, R_{int} = 3.93%, R_{sig} = 2.35%) and 3128 (93.85%) were greater than $2\sigma(F^2)$. The final cell constants of a = 7.9321(3) Å, b = 10.7244(3) Å, c = 11.5725(4) Å, α = 70.9960(10)°, β = 88.2530(10)°, γ = 77.8510(10)°, volume: 909.16(5) Å^3, are based upon the refinement of the *XYZ* centroids of 9906 reflections above $20\sigma(I)$ with $8.087° < 2\theta < 136.7°$. Data were corrected for absorption effects using the multi-scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.934. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.7010 and 0.8790. The final anisotropic full-matrix least-squares refinement on F^2 with 276 variables converged at $R1$ = 3.03%, for the observed data and wR_2 = 7.57% for all data. The goodness-of-fit was 1.054. The largest peak in the final difference electron density synthesis was 0.311 e Å^{-3} and the largest hole was –0.235 e Å^{-3} with an RMS deviation of 0.043 e Å^{-3}. On the basis of the final model, the calculated density was 1.554 g cm^{-3} and F(000), 440 e.

X-ray Crystal Structure Analysis of 8: A colourless prism-like specimen of $C_{23}H_{24}F_3NO_5$, approximate dimensions $0.250 \times 0.270 \times 0.291$ mm^3, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured. A total of 498 frames were collected. The total exposure time was 3.59 h. The frames were integrated with the Bruker SAINT software package using a wide-frame algorithm. The integration of the data using an orthorhombic unit cell yielded a total of 10906 reflections to a maximum θ angle of 68.21° (0.83 Å resolution), of which 3684 were independent (average redundancy 2.960, completeness: 99.7%, R_{int} = 2.20%, R_{sig} = 2.49%) and 3638 (98.75%) were greater than $2\sigma(F^2)$. The final cell constants of a = 9.6869(3) Å, b = 14.1210(5) Å, c = 15.0292(5) Å, volume: 2055.82(12) Å^3, are based upon the refinement of the *XYZ* centroids of 9928 reflections above $20\sigma(I)$ with $5.880° < 2\theta < 136.7°$. Data were corrected for absorption effects using the multi-scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.909. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.7550 and 0.7840. The final anisotropic full-matrix least-squares refinement on F^2 with 294 variables converged at $R1$ = 2.42%, for the observed data and wR_2 = 6.07% for all data. The goodness-of-fit was 1.074. The largest peak in the final difference electron density synthesis was 0.222 e Å^{-3} and the largest hole was –0.166 e Å^{-3} with an RMS deviation of 0.034 e Å^{-3}. On the basis of the final model, the calculated density was 1.459 g cm^{-3} and F(000), 944 e.

X-ray Crystal Structure Analysis of 18g: Formula $C_{19}H_{18}F_3NO_4$, M = 381.34, colourless crystal, $0.25 \times 0.20 \times 0.05$ mm, a = 13.2281(7), b = 10.4600(7), c = 13.7512(9) Å, β = 107.237(5)°, V = 1817.2(2) Å^3, ρ_{calc} = 1.394 g cm^{-3}, μ = 1.013 mm^{-1}, empirical absorption correction ($0.785 \leq T \leq 0.951$), Z = 4, monoclinic, space group $P2_1/c$ (No. 14), λ = 1.54178 Å, T = 223(2) K, ω and ϕ scans, 12725 reflections collected ($\pm h$, $\pm k$, $\pm l$), 3213 independent (R_{int} = 0.053) and 2617 observed reflections [$I > 2\sigma(I)$], 250 refined parameters, R = 0.051, wR_2 = 0.144, max. (min.) residual electron density 0.27 (–0.21) e Å^{-3}. The hydrogen at N1 was refined freely; others were calculated and refined as riding atoms.

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[8] CCDC-1037629 (for *exo*-**3a**), -1037630 (for **8**), and -1037631 (for **18g**) 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.

[9] The most characteristic signals in the NMR spectra of compounds **6** are the doublets in the ^{19}F NMR spectra between δ = –64.5 and –67.5 (J = 8.5–9.0 Hz) ppm. These can easily be identified in the NMR spectra of the reaction mixtures.

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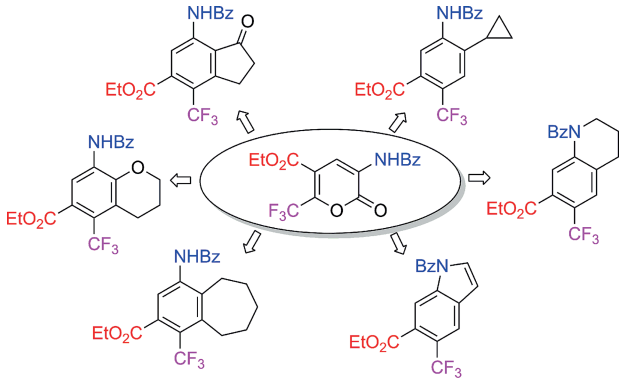
Fluorinated Compounds



Reactions of ethyl 3-benzamido-2-oxo-6-(trifluoromethyl)-2*H*-pyran-5-carboxylate with cyclic alkenes and terminal acetylenes are useful for the efficient and selective preparation of trifluoromethyl-containing polyfunctionalised aromatic amino acid derivatives.

Keywords: Synthetic methods / Alkenes / Alkynes / Cycloaddition / Carbocycles / Amino acids / Fluorine

