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Thermal Diels–Alder Reactions of 3-(Benzoylamino)-6-(polyfluoroalkyl)pyran-2-ones – New Synthesis of *p*-(Polyfluoroalkyl)anilines

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A new practical method for the regioselective synthesis of the *N*-benzoyl-4-(polyfluoroalkyl)anilines **5a–g** by thermal Diels–Alder cycloaddition of 5-substituted 3-(benzoylamino)-6-(polyfluoroalkyl)pyran-2-ones **1a–e** with fluorostyrenes **2** and **7**, acetylenes **8a–c** or vinyl ethers **10** and **13a** and **13b** is described. In the case of the reactions of pyrone **1a** with cyclic vinyl ethers **13a** and **13b**, the dihydrobenzenes **14a** and **14b** were obtained. Free 4-(polyfluoroalkyl)anilines **16a–c** were smoothly formed in good yields by DBU-assisted benzoyl deprotection.

Introduction

Diels–Alder reactions have attracted much interest for the syntheses of six-membered unsaturated rings, which can be applied to the synthesis of complex pharmaceuticals and other biologically active compounds.[1] 2-Pyrones have successfully been used as conjugated dienes in Diels–Alder cycloadditions[2] with alkenes or alkynes.[3,4] However, there are few [4+2] cycloadditions known that lead to fluorinated products, and only a few examples with monofluorinated dienophiles[5] or dienes[6] have been described. On the other hand, the introduction of a fluorine atom or a CF_3 group into organic molecules has often been performed to obtain new biologically active compounds,[7] but there are only a few examples of syntheses of CF_3-substituted benzenes starting from 6-CF_3-containing 2-pyrones and alkynes or alkenes.[8]

Recently, we have shown that simple vinyl fluorides such as α- or β-fluorostyrene do not react with normal dienes like furan, cyclopentadiene or Danishefsky's diene neither under thermal conditions nor at high pressure. These reactions were also unsuccessful in the presence of Lewis acids or radical cation initiators. Only with the highly reactive diene diphenylisobenzofuran were the thermal reactions successful, leading to a 60:40 mixture of the diastereomeric cycloadducts in about 80% yield.[5d,9] On the other hand, several [4+2] cycloadditions are known with α-fluorinated acroleins or acrylic esters,[5a–5c] and recently we described an enantioselective Diels–Alder reaction mediated by enantiopure titanium catalysts.[10] Moreover, inverse-electron demand [4+2] cycloadditions of polyfluorinated 2,4-cyclohexadienones with α- or β-fluorostyrenes gave the corresponding *endo*/*exo*-isomeric bicyclo[2.2.2]oct-2-en-5-ones in good yield.[11]

Until now, 4-(polyfluoroalkyl)anilines have not yet been synthesized by a Diels–Alder reaction as the key step. Such compounds have previously been prepared by the replacement of a halogen atom of halo(trifluoromethyl)benzenes with an amino group[12] or by reduction of trifluoromethylated nitroaromatics.[13] Trials to introduce a CF_3 group selectively into an aniline ring failed.[14] It is known that anilines without polyfluoroalkyl groups are available from electron-deficient 2-pyrones and electron-rich ynamines.[15]

This paper reports on a new and practical method for the general and regioselective synthesis of *N*-benzoyl-4-(polyfluoroalkyl)anilines **5a–e** by thermal Diels–Alder cycloaddition of the 2-pyrones **1a–e** with the fluorostyrenes **2** and **7**, the acetylenes **8a–c** or vinyl ethers **10** and **13a** and **13b**. Also, the physicochemical properties of synthesized 4-(polyfluoroalkyl)anilines **5a–e** and some theoretical calculations of the reaction mechanism are presented.

Results and Discussion

We found that the heating of pyrone **1a**[16] with α-fluorostyrene (**2**)[9] in toluene gave only one of the possible regioisomeric products, the phenyl-substituted *N*-benzoyl-4-(trifluoromethyl)aniline **5a** in a very slow reaction (toluene, sealed tube, 120 °C, 34 d, 43% yield, 32% of pyrone **1a** was recovered) (Scheme 1). Interestingly, the reaction of β-fluorostyrenes **7**[17] with pyrone **1a** gave the same product in

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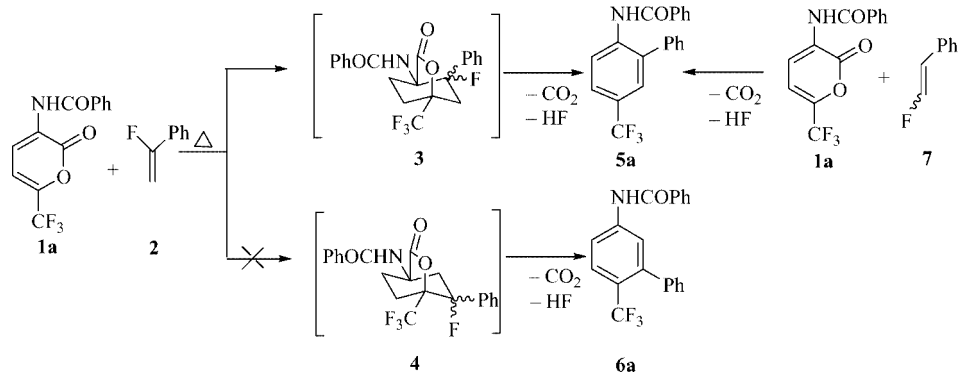
Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.



Scheme 1.

54% yield after 40 d at 120 °C (34% of pyrone **1a** was recovered).

In the key step of the synthesis, obviously only one of the possible regioisomeric intermediate bicyclic adducts, **3** or **4**, was formed. However, the bicyclic adduct was thermally labile and easily eliminated CO_2, followed by hydrogen fluoride loss, resulting in aromatization to form a 4-(trifluoromethyl)aniline **5a** or **6a**. In the ^{19}F NMR spectrum of the crude reaction mixture, only one signal of a CF_3 group at δ = –62.7 ppm was observed. Thus, the reaction proceeded regioselectively, and only one of the possible isomeric anilines **5a** or **6a** was formed (Scheme 1). The structure of the compound obtained was easily confirmed as a phenyl-substituted *N*-benzoyl-4-(trifluoromethyl)aniline by elemental analysis, GC-MS, IR and ^1H, ^{19}F and ^{13}C NMR spectra. However, the position of phenyl ring in the formed aniline could not be determined by NMR spectroscopy. The ^1H, as well as the ^{13}C NMR, spectrum of the product was quite complicated, showing many aromatic signals with very similar chemical shifts.

Consequently, we tried to get some information from semiempirical calculations. PM3 and AM1 calculations of the frontier orbital energies implied a Diels–Alder reaction with inverse-electron demand, because in all cases $\Delta[LUMO_{diene} - HOMO_{dienophile}]$ was smaller (0.84–1.44 eV) than $\Delta[HOMO_{diene} - LUMO_{dienophile}]$. However, the relevant orbital coefficients of the double bond carbon atoms are almost identical, and therefore, did not deliver unambiguous information about the regiochemistry of the cycloaddition (see Supporting Information).

Finally, crystals of the product suitable for X-ray analysis were grown and showed the structure of aniline **5a** (Figure 1), which bears the phenyl ring attached to the *ortho* position. Steric demand of the CF_3 group, which is comparable in size to an isopropyl group,[18] seems to direct the attack of the dienophiles **2** or **7** to the diene **1**.

It is known that acetylenes can react as synthetic equivalents of electron-rich haloalkene dienophiles in Diels–Alder reactions.[19,20] Thus, heating of pyrones **1** with an excess of acetylenes **8** gave the products **5** in high yields (Scheme 2 and Table 1).

The reaction of **1a** with **8a** proceeded with high regioselectivity. Similarly, the 4-(trifluoromethyl)anilides **5b** and **5c**,

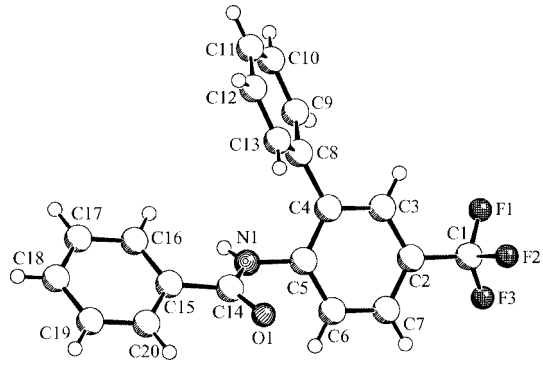
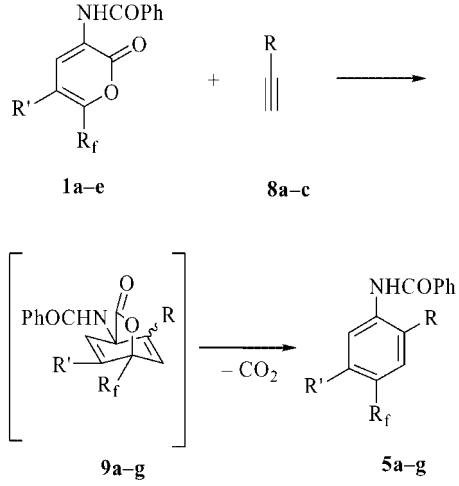


Figure 1. Single-crystal X-ray structure of *N*-benzoyl-2-phenyl-4-(trifluoromethyl)aniline (**5a**).



Scheme 2.

Table 1. Products of cycloaddition reactions of pyrones **1a**–**e** with acetylenes **8a**–**c**.

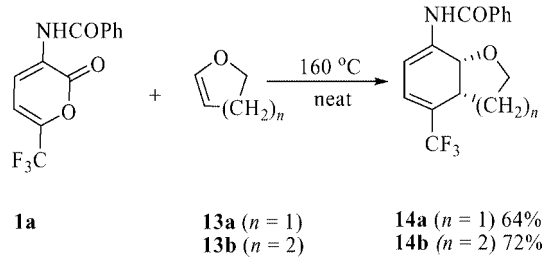
Product	R	R′	R_f	Yield [%]
5a	Ph	H	CF_3	91
5b	n-C_5H_{11}	H	CF_3	68
5c	CH_2Cl	H	CF_3	62
5d	Ph	H	CF_2Cl	86
5e	Ph	H	C_3F_7	80
5f	Ph	CO_2Et	CF_3	91
5g	Ph	$C(O)CF_3$	CF_3	76

containing alkyl groups *ortho* to the benzamido functionality, were obtained by heating **1a** with heptyne (**8b**) or propargyl chloride (**8c**) in good yields. The reaction was also successful with other 6-(polyfluoroalkyl)pyrones such as **1b** and **1c**. The yields of the corresponding derivatives **5d** and **5e** were not influenced by the different substituents. Moreover, the introduction of electron-withdrawing substituents (ethoxycarbonyl or trifluoroacetyl) in position 5 of the pyrone ring (compounds **1d** and **1e**) increased the reactivity of the pyrone **1a**, and the corresponding benzanilides **5f** and **5g** were obtained in high yields under milder conditions (1 d, 100 °C) in the reaction with phenylacetylene (**8a**) (Table 1).

The progress of the Diels–Alder reactions was easily monitored by ^{19}F NMR spectroscopy of the reaction mixtures, as the signals from polyfluoroalkyl groups of pyrones **1a**–**e** and 4-(polyfluoroalkyl)anilides **5a**–**g** are significantly different [e.g. the signal of the CF_3 group of pyrone **1a** (δ = –70.01 ppm) was shifted downfield by 8–9 ppm in the 4-(trifluoromethyl)anilides **5a**–**e**]. No other isomers have been detected in the crude reaction mixtures by this method. We suppose that intermediates **9a**–**g** are formed in the first step of the cycloaddition (Scheme 2), since the formation of similar intermediate bicyclic structures has been established for the Diels–Adler cycloaddition of other pyrones.[2b] However, we did not observe any polyfluoroalkyl group signals that could be assigned to bicyclic 1,4-hexadienes **9a**–**g** in the reaction mixtures.

It is well known that alkyl vinyl ethers react with pyrones as dienophiles under milder conditions than acetylenes.[21a,21b] Thus, we suspected that the reaction of pyrone **1a** with alkyl vinyl ethers might allow us to identify bicyclic adducts in reaction mixtures. However, after heating pyrone **1a** with isobutyl vinyl ether (**10**), only the aromatic product **12** was obtained after 48 h at 100 °C, as a result of cycloaddition with subsequent elimination of CO_2 and isobutyl alcohol (Scheme 3). As the bicyclic adduct **11** was not stable at 100 °C, we tried to find milder reaction conditions in order to detect the intermediate compound **11**. However, we did not observe any product by ^{19}F NMR spectroscopy after boiling the reactants in dichloromethane. We increased the reaction temperature gradually and found that the reaction of neat reactants did not start below 80 °C. After 12 h at this temperature, a new signal from a CF_3 group appeared at about –80 ppm in the crude reaction mixture (ca. 10%), together with signals from pyrone **1a** (ca. 72%) and the aromatic product **12** (ca. 18%). This signal can be assigned to a bicyclic 1,4-hexadiene. However, the bicyclic adduct **11** was not stable enough to be purified by column chromatography.

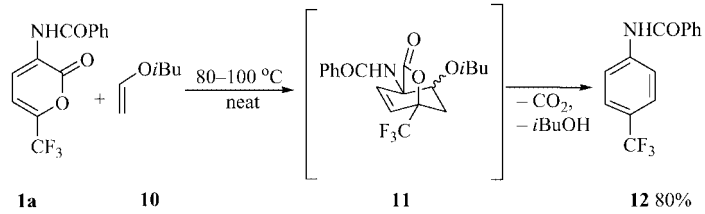
The cycloaddition of the pyrone **1a** with the cyclic vinyl ethers **13a** and **13b** required harsher conditions than those of the reactions of the above-mentioned dienophiles. The reaction did not start below 160 °C, and at this temperature, we did not expect to observe cycloadducts analogous to **11**. However, we isolated products from the reaction mixture which, in the ^{19}F NMR spectrum, exhibited signals from a CF_3 group with chemical shifts of about –66 ppm, which is slightly different from that of benzanilide **12** (δ = –60.92 ppm). Moreover, in the ^{1}H NMR spectrum, the usual signals from the three new aromatic protons were not observed. Instead, two signals in the typical region for olefinic protons appeared. For example, for **14b** a doublet of doublets was found at δ = 7.05 ppm (J = 6.3 and 1.8 Hz), and a doublet of a quartet appeared at δ = 6.47 ppm (J = 6.3 and 2.0 Hz). Obviously, in the case of the cyclic vinyl ethers **13a** and **13b**, the reaction was accompanied by CO_2 elimination but without aromatization, which would necessitate an elimination of an alcohol (Scheme 4). Earlier,[22] ethyl 2-oxo-5,6,7,8-tetrahydro-2*H*-chromene-3-carboxylate, with a similar cyclohexadiene structure to that of **14**, was obtained by the Diels–Alder reaction of methyl 2-oxo-6-(trifluoromethyl)-2*H*-pyran-4-carboxylate with dihydrofuran **13a** in a sealed tube at 160 °C.



Scheme 4.

^{1}H, ^{19}F and ^{13}C NMR spectra of products **14a** and **14b** are very similar, and their stereochemistry was proven, as exemplified for product **14b** by COSY NMR and X-ray techniques (Figure 2 and Figure 3).

In order to verify the exact structure of the bicyclic adducts **14a** and **14b** and to define the regiochemistry of the Diels–Alder cycloaddition unambiguously, we grew crystals of dihydrobenzene **14b** suitable for X-ray analysis. The X-



Scheme 3.

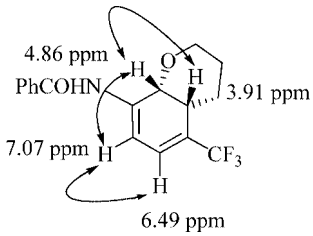


Figure 2. Characteristic COSY correlations for adduct **14b**.

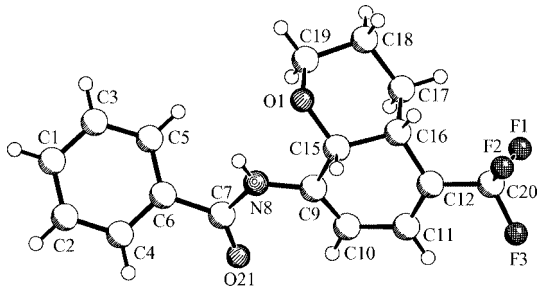
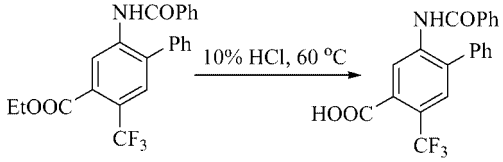


Figure 3. Single-crystal X-ray structure of *N*-[5-(trifluoromethyl)-3,4,4a,8a-tetrahydro-2*H*-chromen-8-yl]benzamide (**14b**).

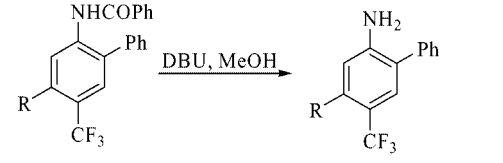
ray analysis proved that the benzamido group and the oxygen atom were attached in an *ortho* relationship, and that the H^{15} and H^{16} protons have a *cis* configuration (Figure 3).

Some chemical transformations with *p*-(trifluoromethyl) anilides **5a**, **5f** and **5g** have also been investigated. Thus, the ester **5f** gave the *N*-protected *m*-aminobenzoic acid **15** in 52% yield by heating in 10% aq. HCl at 60 °C (Scheme 5).



Scheme 5.

On the other hand, under basic conditions, the amide functionality can be deprotected. Thus, conventional heating (6–10 h) or microwave irradiation (1–3 min) of *p*-(trifluoromethyl)anilides **5a**, **5f** or **5g** with two equiv. of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[23] in methanol gave the free 4-(trifluoromethyl)anilines **16a**–**c** in good yields (Scheme 6).



Scheme 6.

Conclusion

A simple and highly regioselective method for the synthesis of various 4-(polyfluoroalkyl)anilides **5** is presented. The key reaction step is a Diels–Alder reaction of a 3-(benzoylamino)-6-(polyfluoroalkyl)-2-pyrone of type **1** with an α- or β-fluorostyrene **2** or **7** or with an acetylenes of type **8a**–**c**. Moreover, Diels–Alder reactions of the 3-(benzoylamino)-6-(polyfluoroalkyl)-2-pyrones with alkyl vinyl ethers **10** and **13a** and **13b** were studied. Gentle heating of **1a** with isobutyl vinyl ether (**10**) allowed a spectroscopic proof of the primary bicyclic Diels–Alder adduct. In case of the reactions of pyrone **1a** with cyclic alkyl vinyl ethers **13a** and **13b**, the bicyclic dihydrobenzenes **14a** and **14b** were isolated as stable products. Removal of the *N*-benzoyl group of amides **5** by heating in methanol with DBU gave the *p*-CF_3-containing anilines **16a**–**c** in high yields. These products may serve as bioactive substances themselves or as building blocks for the synthesis of fluorinated bioactive compounds.

Experimental Section

General: Melting points are uncorrected. NMR spectra were recorded with a Varian VXR-300 spectrometer at 300 MHz (^{1}H), 75.4 MHz (^{13}C) and 282.3 MHz (^{19}F) or with a Bruker AMX-400 spectrometer at 400 MHz (^{1}H) and 100.6 MHz (^{13}C) at 25 °C. TMS (for ^{1}H and ^{13}C NMR) and CCl_3F (for ^{19}F NMR) were used as internal standards. Mass spectra were recorded with a combination of a Varian GC 3400 gas chromatograph and Finnigan MAT 8230 mass spectrometer (70 eV, EI). IR spectra were recorded with a Specord M-80 spectrometer. Column chromatography was performed on silica gel 60 (Merck).

Starting Materials: Starting materials were of the highest commercial quality and were used without further purification. The *N*-[2-oxo-6-(polyfluoroalkyl)-2*H*-pyran-3-yl]benzamides[16] and fluorostyrenes[9,17] were prepared according to literature procedures.

General Procedures for Diels–Alder Reaction

Method 1. Diels–Alder Reaction of Pyrone 1a with Fluorostyrenes 2 or 7 (Benzamide 5a): α-Fluorostyrene (**2**, 49 mg, 0.40 mmol) or β-fluorostyrenes (**7**, 96 mg, 0.79 mmol) and 2-pyrone **1a** (80 mg, 0.28 mmol, or 160 mg, 0.56 mmol) in anhydrous toluene (3 mL or 6 mL) were heated in a sealed glass tube at 120 °C for 34 or 40 d (fluorostyrenes **2** or **7**, respectively). The solvent was evaporated in vacuo, and the oily residue was purified by silica gel column chromatography with cyclohexane/ethyl acetate (10:1) as the eluent. Yields: 41 mg (43%) of **5a** and 26 mg (32%) of recovered **1a** or 104 mg (54%) of **5a** and 26 mg (32%) of recovered **1a** for fluorostyrenes **2** and **7**, respectively.

Method 2. Diels–Alder Reaction of Pyrones 1a-e with Acetylenes 8a–c (Benzamides 5a–g): The acetylenes **8** (0.60 mmol) and 2-pyrone **1a** (0.28 mmol) were heated without solvent in a sealed glass tube at 100–120 °C for 1–7 d. The excess of acetylene was removed in vacuo, and the residue was dissolved and filtered through a short silica gel column with hexane/ethyl acetate (2:1) as the eluent. After evaporation of the solvent in vacuo, the products were crystallized from hexane/toluene (5:1).

***N*-(5-Trifuoromethyl)biphenyl-2-yl)benzamide (5a):** Method 1 or 2. White crystals, m.p. 155–156 °C The product was purified by

chromatography with cyclohexane/ethyl acetate as the eluent or crystallized from hexane/toluene. Yield: 829 mg (91%, method 2). ^{1}H NMR (300 MHz, [D$_6$]acetone): δ = 8.50 (d, J = 8.6 Hz, 1 H), 7.78 (m, 3 H), 7.66 (br. s, 1 H), 7.51 (m, 9 H) ppm. ^{19}F NMR (282.3 MHz, [D$_6$]acetone): δ = –62.71 (s, CF_3) ppm. ^{13}C NMR (75.4 MHz, [D$_6$]acetone): δ = 165.01, 143.22, 140.43, 138.21, 136.74, 134.35, 132.12, 129.86, 129.30, 128.93, 127.60 (q, J = 267.9 Hz), 126.91, 126.44 (q, J = 30.1 Hz), 125.82, 125.04, 120.61 ppm. GC-MS (70eV) m/z (%) = 341 (25) [M]$^+$, 235 (8), 216 (3), 167 (67), 105 (100), 77 (38), 51 (6). $C_{20}H_{14}F_3NO$ (341.3): calcd. C 70.38, H 4.13, N 4.10; found C 70.19, H 3.94, N 3.73. IR ($CHCl_3$): $\tilde{\nu}$ = 3020, 1808, 1683, 1600, 1522, 1472, 1416, 1336, 1312, 1212, 1168, 1131, 1072, 840, 704 cm^{-1}.

***N*-[4-(Trifluoromethyl)phenyl]benzamide (12):** A mixture of pyrone **1a** (320 mg, 1.13 mmol) and an excess of isobutyl vinyl ether **10** (1 mL) was heated without solvent in a sealed glass tube at 100 °C for 2 d. The product was purified by silica gel column chromatography with chloroform/hexane (2:1) as the eluent. Yield: 239 mg (80%). ^{1}H NMR (300 MHz, [D$_6$]acetone): δ = 9.85 (s, 1 H), 8.09 (d, J = 8.5 Hz, 2 H), 8.01 (m, 2 H), 7.70 (d, J = 8.5 Hz, 2 H), 7.55 (m, 3 H) ppm. ^{19}F NMR (282.3 MHz, [D$_6$]acetone): δ = –61.63 (s, CF_3) ppm. ^{13}C NMR ([D$_6$]acetone, 75.4 MHz): δ = 166.79, 143.77, 135.70, 132.66, 129.29, 128.39, 126.70 (q, J = 3.6 Hz), 125.48 (q, J = 31.7 Hz), 125.46 (q, J = 271.0 Hz), 120.74 ppm. GC-MS (70eV) m/z (%) = 266 (6) [M]$^+$, 160 (4), 141 (2), 105 (100), 77 (38), 51 (6). $C_{14}H_{10}F_3NO$ (265.24): calcd. C 63.40, H 3.80, N 5.28; found C 63.46, H 3.93, N 5.21. IR (KBr): $\tilde{\nu}$ = 3335, 1656, 1616, 1528, 1488, 1408, 1341, 1262, 1160, 1111, 1072, 1016, 834, 719 cm^{-1}.

***N*-[5-(Trifluoromethyl)-3,4,4a,8a-tetrahydro-2*H*-chromen-8-yl]-benzamide (14a):** A mixture of pyrone **1a** (766 mg, 2.70 mmol) and 2,3-dihydrofuran **13a** (227 mg, 3,24 mmol) in dry toluene (10 mL) was heated in a sealed glass tube at 160 °C for 7 d. The solvent was evaporated, and the oily residue was purified by silica gel column chromatography with chloroform/hexane (2:1) as the eluent. Yield: 535 mg (64%), white crystals, m.p. 85 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.23 (s, 1 H), 7.82 (m, 2 H), 7.51 (m, 3 H), 7.00 (d, J = 6.0 Hz, 1 H), 6.51 (dq, J = 6.7, 1.9 Hz, 1 H), 4.99 (d, J = 9.6 Hz, 1 H), 3.86 (m, 2 H), 3.03 (q, J = 9.9 Hz, 1 H), 2,40 (m, 1 H), 1.98 (m, 1 H) ppm. ^{19}F NMR (282.3 MHz, $CDCl_3$): δ = –66.32 (s, CF_3) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 166.00, 135.57, 134.28, 132.21, 128.87, 127.04, 125.56 (q, J = 6.2 Hz), 124.22 (q, J = 271.0 Hz), 122.43 (q, J = 31.3 Hz), 103.30, 76.15, 66.38, 36.31, 32.64 ppm. GC-MS (70eV) m/z (%) = 310 (3) [M]$^+$, 309 (6), 191(2), 172 (4), 105 (100), 81 (25), 78 (40), 47 (12), 31 (2). $C_{16}H_{14}F_3NO_2$ (309.29): calcd. C 62.14, H 4.56, N 4.53; found C 62.09, H 4.60, N 4.43. IR ($CHCl_3$): $\tilde{\nu}$ = 3403, 3051, 2986, 2888, 1680, 1513, 1488, 1305, 1260, 1165, 1107, 1056, 1029 cm^{-1}.

***N*-[4-(Trifluoromethyl)-2,3,3a,7a-tetrahydro-1-benzofuran-7-yl]-benzamide (14b):** A mixture of pyrone **1a** (320 mg, 1.13 mmol) and 3,4-dihydro-2*H*-pyran **13b** (0.42 mL, 1.97 mmol) was heated in a sealed glass tube at 160 °C for 5 d. The product was purified by silica gel column chromatography with chloroform/hexane (2:1) as the eluent. Yield: 262 mg (72%), white crystals, m.p. 90 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.51 (s, 1 H), 7.81 (m, 2 H), 7.56 (m, 1 H), 7.49 (s, 2 H), 7.07 (dd, J = 6.3, 2.1 Hz, 1 H), 6.49 (dq, J = 6.3, 2.1 Hz, 1 H), 4.86 (d, J = 7.7 Hz, 1 H), 3.91 (m, 1 H), 3.52 (m, 1 H), 2.70 (m, 1 H), 1.75 (m, 4 H) ppm. ^{19}F NMR (282.3 MHz, $CDCl_3$): δ = –66.28 (s, CF_3) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 165.00, 134.21, 131.24, 127.98, 125.88, 125.80 (q, J = 7.0 Hz), 123.21 (q, J = 270.0 Hz), 122.84 (q, J = 30.6 Hz), 103.70, 71.88, 62.91, 31.45 (q, J = 1.2 Hz), 24.13, 21.97 ppm. GC-MS (70eV) m/z (%) = 324 (10) [M]$^+$, 323 (6), 218 (10), 199 (3), 105 (100), 80 (39), 78 (4), 77 (46), 59 (25), 44 (3). $C_{17}H_{16}F_3NO_2$ (323.32): calcd. C 63.15, H 4.99, N 4.33; found C 63.08, H 5.00, N 4.27. IR ($CHCl_3$): $\tilde{\nu}$ = 3396, 3047, 2989, 2887, 1690, 1510, 1490, 1300, 1267, 1163, 1110, 1060, 1025 cm^{-1}.

2-(Benzoylamino)-5-(trifluoromethyl)biphenyl-4-carboxylic Acid (15): A mixture of ester **5f** (500 mg, 1.2 mmol) and HCl (10%, 15 mL) was refluxed for 6 h. The reaction mixture was cooled to room temperature, and the precipitated acid **15** was filtered and crystallized from 2-propanol: Yield: 239 mg (52%), white crystals, m.p. 163 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 10.01 (br. s, 1 H), 8.76 (d, J = 8.6 Hz, 1 H), 8.14 (br. s, 1 H), 7.67 (dd, J = 8.6, 1.4 Hz, 1 H), 7.34–7.61 (m, 10 H) ppm. ^{19}F NMR (282.3 MHz, [D$_6$]DMSO): δ = –59.10 (s, CF_3) ppm. ^{13}C NMR (75.4 MHz, [D$_6$]-DMSO): δ = 172.36, 165.45, 141.67, 140.72, 134.10, 132.73, 132.42, 132.00, 130.10, 129.71, 129.42, 129.39, 128.94 (q, J = 6.0 Hz), 127.20, 124.15 (q, J = 33.1 Hz), 122.98 (q, J = 127.1 Hz) ppm. GC-MS (70eV) m/z (%) = 386 (10) [M]$^+$, 385 (2), 265 (3), 223 (2), 105 (100), 74 (2), 73 (5), 60 (43), 59 (10) ppm. $C_{21}H_{14}F_3NO_3$ (385.35): calcd. C 65.46, H 3.66, N 3.63; found C 65.51, H 3.61, N 3.70. IR ($CHCl_3$): $\tilde{\nu}$ = 3240, 1810, 1740, 1584, 1559, 1523, 1477, 1310, 1260, 1249, 1208, 1152, 1128, 1100, 1050, 1019 cm^{-1}.

General Procedure for Deprotection of the Amides 5a,f,g to Amines 11a–c with DBU: A solution of the amide **5** (0.2 mmol) and DBU (0.091 g, 0.6 mmol) in methanol (10 mL) was refluxed until the amide was completely consumed (TLC). The reaction mixture was cooled to room temperature and poured into water (25 mL). The amine **11** was filtered, suctioned and recrystallized.

5-(Trifluoromethyl)biphenyl-2-ylamine (16a): Yield: 402 mg (85%). White crystals, m.p. 85 °C (hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33–7.51 (m, 7 H), 6.76 (dd, J = 7.8, 0.7 Hz, 1 H), 4.03 (s, 2 H) ppm. ^{19}F NMR (282.3 MHz, $CDCl_3$): δ = –61.39 (s, CF_3) ppm. ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 147.99, 138.56, 130.01, 129.77, 129.43, 128.09 (q, J = 3.6 Hz), 127.43, 126.02 (q, J = 3.6 Hz), 125.33 (q, J = 270.3 Hz), 120.60 (q, J = 32.6 Hz), 115.21 ppm. GC-MS (70eV) m/z (%) = 238 (2) [M]$^+$, 237 (6), 224 (10), 205 (4), 156 (61), 79 (17). $C_{13}H_{10}F_3N$ (237.23): calcd. C 65.82, H 4.25, N 5.90; found C 66.00, H 4.14, N 5.73. IR ($CHCl_3$): $\tilde{\nu}$ = 3500, 3407, 1684, 1625, 1523, 1492, 1423, 1335, 1261, 1206, 1168, 1149, 1117, 1078, 1040, 1020, 907, 824, 704 cm^{-1}.

X-ray Crystallographic Study: Data sets were collected with Enraf–Nonius CAD4 and Nonius KappaCCD diffractometers. Programs used: data collection: EXPRESS (Nonius B.V., 1994) and COLLECT (Nonius B.V., 1998), data reduction: MolEN (K. Fair, Enraf–Nonius B.V., 1990) and Denzo-SMN,[24] absorption correction for CCD data: SORTAV,[25] structure solution: SHELXS-97,[26] structure refinement: SHELXL-97,[27] graphics: SCHAKAL.[28]

CCDC-600000 and -600001 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.

Theoretical Calculations: The semiempirical calculations (AM1 and PM3) were performed with MOPAC93, as implemented in Chem3D.[29]

Supporting Information (see also the footnote on the first page of this article): i. Melting points, NMR, IR, mass spectroscopic data of benzanilides **5b**–**g** and anilines **16b** and **16c**. ii. X-ray Crystallographic Study data of compounds **5a** and **14b**. iii. Theoretical calculation data for the Diels–Alder reaction. iv. COSY experiment data for adduct **14b**.

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