

An Efficient One-Pot Synthesis of Substituted 1*H*-Naphtho[2,1-*b*]pyrans and 4*H*-1-Benzopyrans (= Chromenes) under Solvent-Free Microwave-Irradiation Conditions

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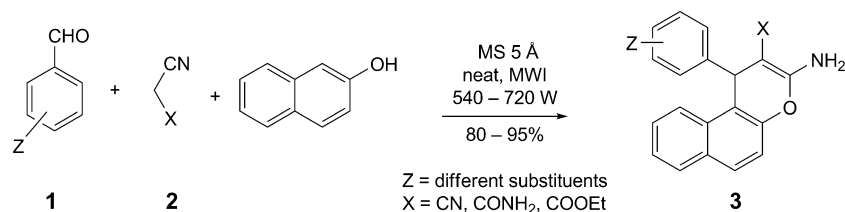
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A facile heterogeneous synthesis of 3-amino-1-aryl-1*H*-naphtho[2,1-*b*]pyran and 2-amino-4-aryl-4*H*-1-benzopyran derivatives **3** and **5**, respectively, was carried out efficiently by one-pot three-component coupling of an aromatic aldehyde **1**, an active methylene compound **2**, and naphthalen-2-ol or a phenol **4** in the presence of 5-Å molecular sieves under solvent-free microwave-irradiation conditions (*Scheme 1* and 2, *Tables 1* and 2). The catalyst was recovered and recycled (*Table 3*).

Introduction. – Substituted chromenes (= benzopyrans) are important compounds due to their applications in pigments, cosmetics, and agrochemicals, and also they are integral part of many natural products [1–5] and many therapeutic agents such as antibacterials [6], antivirals [7], mutagenics [8], and antitumor [9] and CNS-active agents [10]. Conventional method for the synthesis of substituted chromenes are mainly based on benzaldehyde, malononitrile, and naphthalen-2-ol by using various catalysts *viz.*, cetyltrimethylammonium chloride (CTACl) [11], benzyltrimethylammonium chloride (TEBA) [12], K₂CO₃ [6], γ -alumina [13], piperidine [14], TiCl₄ [15], 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) [16], ceric ammonium nitrate (CAN) [17], methyltriocetyl ammonium chloride (*Aliquat*[®] 336) [18], or CaNa₂P₂O₇ [19]. However, all these methods have disadvantages in terms of cost, longer reaction times, complex workup procedures, and usage of solvents. As a result, they are not environmentally benign, and hence, there is an urgent need to develop an efficient ecologic method for the synthesis of benzochromene (= naphthopyran) derivatives.

Results and Discussion. – In continuation of our efforts in the synthesis of heterocyclic bioactive molecules by efficient procedures, we wish to report herein a three-component one-pot synthesis of 1*H*-naphtho[2,1-*b*]pyrans (= benzo[*f*]chromenes) **3** from naphthalen-2-ol, an aldehyde **1**, and an active methylene compound **2** in the presence of 5-Å molecular sieves (MS) as catalyst under solvent-free microwave-irradiation (MWI) conditions (*Scheme 1*). A model reaction was performed with stoichiometric quantities of benzaldehyde (**1a**), malononitrile (**2**, X = CN) and naphthalen-2-ol in the presence of a catalytic amount of finely powdered 5-Å

Scheme 1. Synthesis of 1H-Naphtho[2,1-b]pyrans in the Presence of Molecular Sieves and under Microwave Irradiation



molecular sieves without solvent and under microwave irradiation. The reaction mixture was cooled, dissolved in AcOEt, and filtered to recover the catalyst. Concentration of the filtrate afforded the corresponding naphthopyran derivative **3a** in excellent yield (95%; *Table 1*). Encouraged by this result, the reaction was extended to various substituted aldehydes **1** and active methylene compounds **2** to give the corresponding naphthopyran derivatives **3b–3n** mostly in excellent yields (*Table 1*). The reaction cascade for the formation of the pyran derivatives **3** involves initial *Knoevenagel* reaction, by which the aldehyde **1** reacts with the active methylene compound **2** to give the benzyldenemalononitrile intermediate (X = CN), followed by alkylation of naphthalen-2-ol and subsequent cyclization. The 5-Å molecular sieve is an alkali aluminosilicate, and its role is presumably to act as an acidic dehydrating agent during the formation of the benzyldene intermediate.

 Table 1. Molecular-Sieves-Catalyzed Synthesis of Substituted 1H-Naphtho[2,1-b]pyrans (= Benzo-chromenes)^{a)}

1 (Z)	2 (X)	Product	Power [W]	Time [min]	Yield [%] ^{b)}
H	CN	3a	540	5	95
H	COOEt	3b	540	9	80
H	CONH ₂	3c	540	7	89
4-Me	CN	3d	720	7	85
4-Cl	CN	3e	540	4	90
4-F	CN	3f	540	4	95
2,4,6-F	CN	3g	540	7	90
2-CF ₃	CN	3h	540	8	90
4-NO ₂	CN	3i	540	4	90
4-MeO	CN	3j	720	7	88
3-MeO	CN	3k	720	8	85
^{c)}	CN	3l	720	7	85
^{d)}	CN	3m	720	9	85
^{e)}	CN	3n	720	15	60

^{a)} Reaction conditions: benzaldehyde **1** (1.0 mmol), active methylene compound **2** (1.0 mmol), naphthalen-2-ol (1.0 mmol), 5-Å molecular sieves (0.5–1.0 g weight-equiv. rel. to naphthalen-2-ol).

^{b)} Yield of isolated product **3**. ^{c)} Naphthalene-1-carboxaldehyde. ^{d)} Thiophen-2-carboxaldehyde. ^{e)} Cinnamaldehyde.

The above described condensation reaction proceeded well also with phenols **4** under 5-Å MS catalysis producing the corresponding 4*H*-1-benzopyrans **5** in 70–80% yield (Scheme 2 and Table 2).

Scheme 2. Synthesis of 4*H*-1-Benzopyrans in the Presence of Molecular Sieves and under Microwave Irradiation

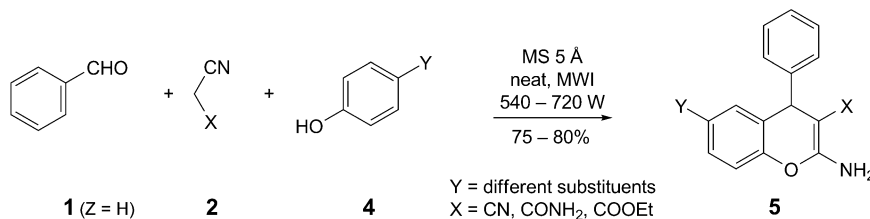


Table 2. Synthesis of 4*H*-Benzopyrans in the Presence of Molecular Sieves under Microwave Irradiation^{a)}

2 (X)	4 (Y)	Product	Time [min]	Yield [%] ^{b)}
CN	H	5a	4	80
CONH ₂	H	5b	6	80
COOEt	H	5c	9	75
CN	Me	5d	4	75
CONH ₂	Me	5e	8	70
COOEt	Me	5f	10	70
CN	Br	5g	4	80
CONH ₂	Br	5h	5	80
COOEt	Br	5i	8	80

^{a)} Reaction conditions: benzaldehyde (**1**, Z = H; 1.0 mmol), active methylene compound **2** (1.0 mmol), substituted phenol **4** (1.0 mmol), 5-Å molecular sieves (0.5–1.0 g weight equiv. rel. to phenol), microwave power 540 W. ^{b)} Yield of isolated product **5**.

The versatility of the reaction was tested by applying substituted aromatic and heteroaromatic aldehydes. Benzaldehydes **1** having electron-withdrawing or -donating groups gave the pyran derivatives **3** in good yields in a short reaction time. But in the case of cinnamaldehyde, the yield of **3n** was only 60% (Table 1), possibly due to a concomitant aldol reaction [20]. The reaction was regioselective with naphthalen-2-ol giving exclusively the angularly fused regioisomers **3** [1]. The angular fusion of the naphtho[2,1-*b*]pyrans **3** was further supported by the X-ray crystal-structure determination of **3h** (Fig.). The optimized reaction conditions for the formation of the naphtho- and benzopyran derivatives was 720 W microwave power and 5–7 min reaction time under solvent-free conditions. We tried different irradiation levels: at lower radiation power, exclusive formation of the *Knoevenagel* products was observed, while pyran derivatives were formed at high irradiation power.

We finally concentrated on the recyclability of the catalyst. The recycled 5-Å molecular sieves were used for further runs, and it was found that the catalytic activity was good, as shown by the yields of the product (Table 3).

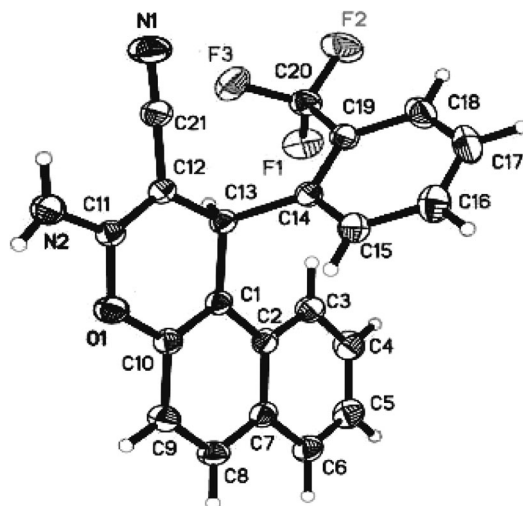


Figure. X-Ray crystal structure of 3-amino-1-[2-(trifluoromethyl)phenyl]-1H-naphtho[2,1-b]pyran-2-carbonitrile (**3h**)

Table 3. Recycling of MS Catalyst^{a)}

Run	1	2	3
Time [min]	5	5	5
Yield [%] ^{a)}	95	90	90

^{a)} Yield of compound **3a**.

In conclusion, we demonstrated a facile and environmentally benign method for the synthesis of highly functionalized naphtho- and benzopyran compounds by a single-pot three-component condensation reaction of naphthalen-2-ol or a phenol, an aldehyde, and an active methylene compound in the presence of 5-Å molecular sieves as catalyst under solvent-free conditions. The presented method is superior to existing methods for the preparation of 4*H*-1-benzopyrans as the yields are high, the catalyst is inexpensive, and toxic solvents are avoided in this green synthesis.

We are thankful to Dr. J. S. Yadav, Director, IICT, for his constant encouragement, and A. C. S., A. R. K., G. S., and K. R. are thankful to the Council of Scientific and Industrial Research (CSIR), India, for the financial assistance in the form of SRF fellowships.

Experimental Part

General. Column chromatography (CC): silica gel (SiO₂; 60–120 mesh; Merck). TLC: precoated SiO₂ (60–120 mesh); visualization under UV light. M.p.: Casia-Siamia (VMP-AM) melting-point apparatus; uncorrected. IR Spectra: Perkin-Elmer-240-C FT-IR spectrophotometer; KBr discs; $\tilde{\nu}$ in cm⁻¹. ¹H- and ¹³C-NMR Spectra: Bruker-AV spectrometers; at 300 and 75 MHz, resp.; in CDCl₃; δ in ppm rel. to Me₄Si as internal standard, *J* in Hz. EI-MS: VG-7070-H instrument; at 70 eV; in *m/z*. Elemental analyses (C, H, N): Vario-EL analyzer.

1H-Naphtho[2,1-b]pyrans (= *Benzo[f]chromenes*) **3** and *4H-1-Benzopyrans* (= *Chromenes*) **5**: *Typical Procedure*. To a mixture of benzaldehyde **1** (1.0 mmol), an active methylene compound **2** (1.0 mmol), and naphthalen-2-ol or phenol **4** (1.0 mmol) in a microwave tube, finely powdered 5-Å MS (0.5–1.0 g weight-equiv. rel. to naphthalenol or phenol) was added. The mixture was subjected to microwave irradiation at moderate power (540–720 W) for 5–10 min (TLC monitoring). Then AcOEt was added, the MS filtered, the AcOEt layer washed with H₂O, dried (Na₂SO₄), and concentrated, and the residue subjected to CC (AcOEt/hexane 5:95): **3** or **5**. The recovered catalyst was washed with acetone and dried at 100° to constant weight and used in subsequent reactions. The catalyst activity was good up to three recycles, the yields of the products being in the range 75–85%.

3-Amino-1-phenyl-1H-naphtho[2,1-b]pyran-2-carboxamide (3c): M.p. 210–212°. IR: 3476, 3442 (NH₂), 1680 (C=O). ¹H-NMR: 4.75 (s, CH); 6.82 (br. s, NH₂); 7.04 (br. s, CONH₂); 7.16–7.40 (m, 5 arom. H); 7.56 (d, *J* = 7.7, 1 arom. H); 7.67 (d, *J* = 7.7, 1 arom. H); 7.75–8.13 (m, 4 arom. H). ¹³C-NMR: 171.0; 151.8; 140.3; 137.2; 133.5; 129.3; 129.1; 128.8; 128.6; 128.4; 128.3; 128.1; 127.0; 127.2; 126.6; 126.3; 122.5; 118.9; 83.8; 38.4. MS: 316 (*M*⁺), 300 ([*M* – NH₂]⁺), 239 ([*M* – Ph]⁺). Anal. calc. for C₂₀H₁₆N₂O₂ (316.12): C 75.93, H 5.10, N 8.86; found: C 75.90, H 5.11, N 8.83.

3-Amino-1-(2,4,5-trifluorophenyl)-1H-naphtho[2,1-b]pyran-2-carbonitrile (3g): M.p. 199–201°. IR: 3448, 3339 (NH₂), 2187 (CN). ¹H-NMR: 5.5 (s, CH); 6.7 (br. s, NH₂); 6.9 (d, *J* = 7.2, 1 arom. H); 7.1 (d, *J* = 7.2, 1 arom. H); 7.3–7.85 (m, 6 arom. H). ¹³C-NMR: 179.8; 166.8; 151.8; 150.3; 149.3; 148.6; 146.7; 145.6; 144.3; 141.7; 139.2; 136.9; 133.5; 132.8; 127.2; 125.6; 117.3; 106.8; 59.2; 20.9. MS: 352 (*M*⁺), 221 ([*M* – Ph – 3F]⁺). Anal. calc. for C₂₀H₁₁F₃N₂O (352.08): C 68.18, H 3.15, N 7.95; found: C 68.17, H 3.16, N 7.93.

3-Amino-1-[2-(trifluoromethyl)phenyl]-1H-naphtho[2,1-b]pyran-2-carbonitrile (3h): M.p. 231–233°. IR: 3476, 3442 (NH₂), 2198 (CN). ¹H-NMR: 5.5 (s, CH); 6.7 (br. s, NH₂); 7.05 (d, 1 arom. H); 7.3–7.6 (m, 5 arom. H); 7.7–7.9 (m, 4 arom. H). ¹³C-NMR: 161; 148; 145; 133.6; 131.6; 130.8; 130.4; 129.0; 128.3; 127.2; 126.3; 125.1; 123.2; 122.5; 122.4; 122.1; 119.9; 117.3; 115.6; 58.3; 24.8. EI-MS (70 eV): 366 (*M*⁺), 297 ([*M* – CF₃]⁺), 221 ([*M* – Ph – CF₃]⁺). Anal. calc. for C₂₁H₁₃F₃N₂O (366.10): C 68.85, H 3.58, N 7.65; found: C 68.83, H 3.56, N 7.63.

3-Amino-1-(naphthalen-1-yl)-1H-naphtho[2,1-b]pyran-2-carbonitrile (3i): M.p. 221–223°. IR: 3477, 3440 (NH₂), 2216 (CN). ¹H-NMR: 4.74 (s, CH); 6.82 (br. s, NH₂); 7.10–8.27 (m, 13 arom. H). ¹³C-NMR: 177.1; 151.9; 134.2; 133.6; 133.5; 133.4; 132.6; 128.6; 128.4; 128.3; 128.2; 128.1; 126.9; 126.7; 126.4; 125.8; 125.6; 124.2; 123.2; 122.1; 118.9; 117.3; 59.2; 26.0. MS: 348 (*M*⁺), 221 ([*M* – naphthalenyl]⁺). Anal. calc. for C₂₄H₁₆N₂O (348.13): C 82.74, H 4.63, N 8.04; found: C 82.75, H 4.60, N 8.01.

2-Amino-4-phenyl-4H-1-benzopyran-3-carboxamide (5b): M.p. 210–212°. IR: 3477, 3441 (NH₂), 1677 (C=O). ¹H-NMR: 4.82 (s, CH); 5.2 (br. s, NH₂); 6.0 (br. s, CONH₂); 6.61–6.90 (m, 4 arom. H); 7.06–7.36 (m, 5 arom. H). ¹³C-NMR: 171.1; 156.6; 153.1; 140.2; 129.3; 129.2; 128.9; 128.3; 128.2; 128.1; 127.0; 125.0; 123.5; 117.0; 83.8; 40.1. MS: 266 (*M*⁺), 189 ([*M* – Ph]⁺). Anal. calc. for C₁₆H₁₄N₂O₂ (266.11): C 72.16, H 5.30, N 10.52; found: C 72.19, H 5.27, N 10.51.

Ethyl 2-Amino-4-phenyl-4H-1-benzopyran-3-carboxylate (5c): M.p. 195–197°. IR: 3477, 3440 (NH₂), 1726 (C=O), 1025 (C–O–C). ¹H-NMR: 1.32 (t, *J* = 7.46, MeCH₂); 4.20 (q, *J* = 7.46, MeCH₂); 4.74 (s, CH); 6.61–6.75 (m, 4 arom. H); 6.89 (br. s, NH₂); 7.06–7.40 (m, 5 arom. H). ¹³C-NMR: 167.2; 160.0; 153.1; 140.3; 129.7; 129.3; 128.9; 128.7; 128.2; 127.0; 126.3; 123.5; 120.2; 81.3; 78.9; 61.7; 39.8; 14.2. MS: 295 (*M*⁺), 218 ([*M* – COOEt]⁺). Anal. calc. for C₁₈H₁₇NO₃ (295.12): C 73.20, H 5.80, N 4.74; found: C 73.19, H 5.77, N 4.73.

2-Amino-6-methyl-4-phenyl-4H-1-benzopyran-3-carbonitrile (5d): M.p. 205–206°. IR: 3440, 3430 (NH₂), 2216 (CN). ¹H-NMR: 2.35 (s, Me); 4.74 (s, CH); 6.22 (br. s, NH₂); 6.49–6.70 (m, 3 arom. H); 7.06–7.37 (m, 5 arom. H). ¹³C-NMR: 177.1; 150.1; 140.3; 133.1; 130.8; 129.5; 129.3; 128.4; 128.2; 127.2; 126.3; 120.2; 117.6; 117.3; 59.2; 29.7; 24.6. MS: 262 (*M*⁺), 247 ([*M* – Me]⁺), 185 ([*M* – Ph]⁺). Anal. calc. for C₁₇H₁₄N₂O (262.11): C 77.84, H 5.38, N 10.68; found: C 77.80, H 5.37, N 10.65.

2-Amino-6-methyl-4-phenyl-4H-1-benzopyran-3-carboxamide (5e): M.p. 215–217°. IR: 3476, 3434 (NH₂), 1660 (C=O). ¹H-NMR: 2.35 (s, Me); 4.74 (s, CH); 6.48 (br. s, NH₂); 6.50–6.70 (m, 3 arom. H); 6.96 (br. s, CONH₂); 7.06–7.40 (m, 5 arom. H). ¹³C-NMR: 172.0; 158.8; 152.1; 140.3; 133.7; 129.8; 129.5; 129.3; 128.4; 128.2; 126.3; 122.5; 119.9; 119.7; 117.8; 83.8; 39.4. MS: 280 (*M*⁺), 203 ([*M* – Ph]⁺). Anal. calc. for C₁₇H₁₆N₂O₂ (280.12): C 72.84, H 5.75, N 9.99; found: C 72.80, H 5.73, N 9.98.

Ethyl 2-Amino-6-methyl-4-phenyl-4H-1-benzopyran-3-carboxylate (5f): M.p. 198–200°. IR: 3477, 3441 (NH₂), 1726 (C=O), 1010 (C–O–C). ¹H-NMR: 1.30 (t, *J* = 7.4, MeCH₂); 2.40 (s, MeAr); 4.19 (q, *J* = 7.4, MeCH₂); 4.74 (s, CH); 6.40 (br. s, NH₂); 6.49–6.70 (*m*, 3 arom. H); 7.07–7.37 (*m*, 5 arom. H). ¹³C-NMR: 167.2; 160.0; 150.1; 140.3; 133.1; 130.8; 129.5; 129.3; 128.4; 128.2; 127.2; 126.3; 120.2; 117.6; 78.9; 62.0; 40.2; 25.2; 14.2. EI-MS (70 eV): 309 (*M*⁺), 294 ([*M* – Me]⁺), 264 ([*M* – EtO]⁺). Anal. calc. for C₁₉H₁₉NO₃ (309.14): C 73.77, H 6.19, N 4.53; found: C 73.75, H 6.20, N 4.50.

2-Amino-6-bromo-4-phenyl-4H-1-benzopyran-3-carbonitrile (5g): M.p. 189–190°. IR: 3476, 3440 (NH₂), 2216 (CN). ¹H-NMR: 4.74 (s, CH); 6.42 (br. s, NH₂); 6.50–7.37 (*m*, 8 arom. H). ¹³C-NMR: 178.2; 152.1; 141.2; 140.3; 133.7; 129.8; 129.5; 129.3; 128.5; 126.3; 122.5; 120.9; 117.8; 117.3; 59.2; 28.7. MS: 326 (*M*⁺), 328 ([*M* + 2]⁺), 249 ([*M* – Ph]⁺). Anal. calc. for C₁₆H₁₁BrN₂O (326.01): C 58.74, H 3.39, N 8.56; found: C 58.72, H 3.40, N 8.55.

2-Amino-6-bromo-4-phenyl-4H-1-benzopyran-3-carboxamide (5h): M.p. 199–203°. IR: 3476, 3440 (NH₂), 1686 (C=O). ¹H-NMR: 4.75 (s, 1 H); 6.49 (br. s, NH₂); 6.50–7.07 (*m*, 3 H); 6.96 (br. s, CONH₂); 7.08 (br. s, 2 H); 7.12–7.38 (*m*, 5 H). ¹³C-NMR: 171.0; 158.8; 152.1; 140.3; 133.7; 129.8; 129.5; 129.3; 128.4; 128.2; 126.3; 122.5; 119.9; 117.8; 83.8; 39.4. MS: 344 (*M*⁺), 346 ([*M* + 2]⁺), 267 ([*M* – Ph]⁺). Anal. calc. for C₁₆H₁₃BrN₂O₂ (344.02): C 55.67, H 3.80, N 8.12; found: C 55.65, H 3.77, N 8.10.

Ethyl 2-Amino-6-bromo-4-phenyl-4H-1-benzopyran-3-carboxylate (5i): M.p. 170–172°. IR: 3477, 3441 (NH₂), 1726 (C=O), 1075 (C–O–C). ¹H-NMR: 1.30 (t, *J* = 7.4, MeCH₂); 4.19 (q, *J* = 7.4, MeCH₂); 4.74 (s, CH); 6.42 (br. s, NH₂); 6.50–7.07 (*m*, 3 arom. H); 7.08–7.37 (*m*, 5 arom. H). ¹³C-NMR: 168.4; 160.0; 152.1; 141.2; 133.7; 129.8; 129.4; 129.2; 128.4; 128.2; 126.2; 122.5; 120.0; 117.8; 78.0; 61.7; 39.1; 14.2. MS: 373 (*M*⁺), 375 ([*M* + 2]⁺), 328 ([*M* – EtO]⁺), 296 ([*M* – COOEt]⁺). Anal. calc. for C₁₈H₁₆BrNO₃ (373.03): C 57.77, H 4.31, N 3.74; found: C 57.70, H 4.30, N 3.78.

X-Ray Crystal Structure of 3h. The data were collected at room temperature with a Bruker-Smart-Apex-CCD diffractometer and graphite monochromated MoK_α radiation (λ 0.71073 Å) by means of the ω-scan method [21]. Preliminary lattice parameters and orientation matrices were obtained from four sets of frames. Unit cell dimensions were determined with 5971 reflections in the range 2.45 < θ < 27.93°. Integration and scaling of intensity data were accomplished with the SAINT program [21]. The structure was solved by direct methods with SHELXS97 [22], and refinement was carried out by full-matrix least-squares technique with SHELXL97 [22]. Anisotropic displacement parameters were included for all non-H-atoms. The H-atoms attached to N-atoms were located in a difference density map and refined isotropically. All other H-atoms were positioned geometrically and treated as riding on their parent C-atoms with C–H = 0.93 Å and U_{iso}(H) = 1.2 U_{eq}(C). Data: C₂₁H₁₃F₃N₂O, *M*_r 366.33, triclinic, space group *P*1̄, *a* = 8.6016(6) Å, *b* = 10.0533(7) Å, *c* = 10.2070(7) Å, α = 101.857(1)°, β = 96.315(1)°, γ = 102.062(1)°, *V* = 833.89(10) Å³, *Z* = 2, *D*_{calc} = 1.459 mg m^{−3}, *T* 294(2) K, μ = 0.114 mm^{−1}, *F*(000) = 376. Data collection yielded 8006 reflections resulting in 2921 unique, averaged reflections, 2696 with *I* > 2σ(*I*). Full-matrix least-squares refinement led to a final *R* = 0.0366, *wR* = 0.0979, and g.o.f. = 1.043. CCDC-839725 contains supplementary crystallographic data for the structure. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/data_request/cif.

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Received August 19, 2011