4-Ethoxy-1,1,1-trifluoro-3-buten-2-one (ETFBO), a versatile precursor for trifluoromethyl-substituted heteroarenes – a short synthesis of Celebrex® (Celecoxib)

Heiko Sommer, Max Braun, Benjamin Schröder, Andreas Kirschning*

Institute of Organic Chemistry and Center of Biomolecular Drug Research (BMWZ), Leibniz Universität Hannover, Schneiderberg 1B, 30167 Hannover (Germany)
Fax: (+49) 511-762-3011, E-mail: andreas.kirschning@oci.uni-hannover.de
Solvay GmbH, Hans-Böckler-Allee 20, 30173 Hannover (Germany)

General information: Unless otherwise stated, all chemicals and solvents were purchased in per analysis quality and used as received. All reactions were performed under an atmosphere of inert gas unless otherwise stated. Glassware was dried by heating under vacuum and flooded with nitrogen prior to use. Dry solvents were obtained by heating under refluxing conditions over sodium and subsequent distillation (THF) or by heating under refluxing conditions over KOH and subsequent distillation (Et3N) or by filtration through drying columns on a M. Braun solvent purification system (CH2Cl2, Et2O). Dry solvents were additionally stored over molecular sieves prior to use (THF, CH2Cl2, Et2O). Flash column chromatography was performed with Macherey Nagel 60M silica gel (particle size 40-63 µm) under a slight overpressure. Thin layer chromatography was performed on silica gel coated aluminium sheets Macherey Nagel Xtra SIL G/UV254. Indication was achieved with UV light (λ = 254 nm) and common dip stains (anisaldehyde, potassium permanganate or ceric ammonium molybdate).

1H NMR spectra were recorded at 400 MHz or 500 MHz, respectively, and 13C NMR spectra were recorded at 100 MHz or 125 MHz, respectively, with a BRUKER Avance 400, DPX 400 or DRX 500. Chemical shift values of NMR data are reported as values in ppm relative to (residual undeuterated) solvent signal as internal standard. Multiplicities for 1H NMR signals are described using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet; where appropriate with the addition of b = broad. 13C Multiplicities refer to the resonances in the off-resonance decoupled spectra and were elucidated using the distortionless enhancement by polarization transfer (DEPT) spectral editing technique. Multiplicities for 13C NMR signals are reported using the following abbreviation: q = quaternary (CR4), t= tertiary (R3CH), secondary = s (R2CH2) and primary = p (RCH3). Mass spectra were obtained with a type LCT (ESI) (Micromass) equipped with a lockspray
dual ion source in combination with a WATERS Alliance 2695 LC system, or with a type Q-TOF premier (Micromass) spectrometer (ESI mode) in combination with a WATERS Acquity UPLC system equipped with a Waters BEH C18 1.7 μm (SN 01473711315545) column (solvent A: water + 0.1 % (v/v) formic acid, solvent B: MeOH + 0.1 % (v/v) formic acid; flow rate = 0.4 mL/min; gradient (t [min]/solvent B [%]): (0:5) (2.5:95) (6.5:95) (6.6:5) (8:5)). Ion mass signals (m/z) are reported as values in atomic mass units. Compounds 11a-c, 13, 14a-e and 15 are commercially available. The synthesis of (E)-1,1,1-trifluoro-4-dimethylaminobut-3-en-2-one (9a) was reported in ref. [S1].

Synthesis of vinylogous trifluoromethylcarbamides

(E)-1,1,1-Trifluoro-4-morpholinobut-3-en-2-one (9b)

\[
\begin{align*}
\text{EtO} & \quad \text{O} \\
\begin{array}{c}
\text{F} \\
\text{F}
\end{array} & \quad \text{O} \\
\begin{array}{c}
\text{F} \\
\text{F}
\end{array}
\end{align*}
\]

(E)-4-Ethoxy-1,1,1-trifluorobut-3-en-2-one (1) (13.8 mL, 100 mmol, 1.0 equiv.) was stirred in 100 mL of reagent grade dichloromethane under ice cooling. Morpholine (8.79 mL, 100 mmol, 1.0 equiv.) dissolved in 50 mL of dichloromethane was added dropwise over a period of 15 minutes. After another 15 minutes of stirring the volatiles were removed under reduced pressure and the crude material 9b (20.2 g, 96.6 mmol, 97%) was used in the next step without further purification.

\(^1\)H-NMR (400 MHz, CDCl\(_3\), CHCl\(_3\) = 7.26 ppm) \(\delta\) 3.48 (d, 4H, morpholine-\(H\)), 3.79 (d, 4H, morpholine-\(H\)), 5.41 (d, 1H, CF\(_3\)COCH\(_3\)) 7.85 (d, 1H, CF\(_3\)COCH\(_3\)); \(^13\)C-NMR (100 MHz, CDCl\(_3\), CDCl\(_3\) = 77.2 ppm) \(\delta\) 46.2, 53.8, 65.6, 66.8, 116.2, 155.0. HRMS m/z calculated for C\(_8\)H\(_{11}\)O\(_2\)N\(_1\)F\(_3\) (M+H\(^+\)) : 210.0742, found: 210.0741.

The spectroscopic and physical data are in accordance with those published in the literature [S2].

Representative procedure for the synthesis of trifluoromethylketones

(E)-1,1,1-Trifluoro-4-\(p\)-tolylbut-3-en-2-one (2a)

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\begin{array}{c}
\text{F} \\
\text{F}
\end{array} & \quad \text{F} \\
\begin{array}{c}
\text{F} \\
\text{F}
\end{array}
\end{align*}
\]

Me

The spectroscopic and physical data are in accordance with those published in the literature [S2].
A flame-dried 50 mL Schlenk-flask was charged with $p$-bromotoluene (2.39 g, 14.0 mmol, 1.0 equiv.) dissolved in 15 mL of dry THF under a nitrogen atmosphere. The mixture was cooled on dry-ice and $n$-butyllithium (6.2 mL, 15.4 mmol, 2.5M in hexanes, 1.1 equiv.) was added dropwise. After being stirred at that temperature for 1 h ($E$)-1,1,1-trifluoro-4-morpholino-but-3-en-2-one (9b) (3.07 g, 14.7 mmol, 1.05 equiv.) in 10 ml THF was slowly added and stirring was continued for additional 5 minutes with dry-ice cooling. The cooling bath was removed and stirring was continued until the mixture reached room temperature. The reaction was terminated by addition of a saturated ammonium chloride solution. The mixture was extracted twice with ethyl acetate, the combined organic phases were washed with brine, dried over sodium sulfate and concentrated under reduced pressure. After flash chromatography (petroleum ether / ethyl acetate) pure products were obtained (details see below).

($E$)-1,1,1-Trifluoro-4-p-tolybut-3-en-2-one (2a)

Scale: 13.9 mmol; yield 2.00 g, 9.34 mmol, 67%.

($E$)-1,1,1-Trifluoro-4-p-tolybut-3-en-2-one (2b)

Scale: 50 mmol; yield 11.4 g, 49.5 mmol; 99%.

($E$)-1,1,1-Trifluoro-4-(4-chlorophenyl)but-3-en-2-one (2c)

Scale: 16.3 mmol; yield 1.7 g, 8.5 mmol; 52%.

The spectroscopic and physical data of all trifluoromethylketones shown are in accordance with those published in the literature [S3].

($E$)-1-(4,4,4-Trifluoro-3-oxobut-1-enyl)pyrrolidin-2-one (9c)

($E$)-4-Ethoxy-1,1,1-trifluorobut-3-en-2-one (1) (13.8 mL, 0.1 mol, 1.0 equiv.) was dissolved in 75 mL of reagent grade toluene which contained 2-pyrrolidinone (13) (7.6 ml, 0.1 mol, 1.0 equiv.).
mixture was heated under refluxing conditions for 5h before the volatiles were removed under reduced pressure. The product was obtained as an orange material in very high yield (20.0 g, 96.5 mmol, 97%).

\[
\text{\textsuperscript{1}H-NMR (500 MHz, CDCl}_3, \text{SiMe}_4= 0.0 \text{ ppm}} \] \(\delta\) 2.25 (q, 2H, NCH \_\_CH \_CO), 2.61 (t, 2H, NCH \_CH \_CO), 3.65 (t, 2H, NCH \_CH \_CO), 5.78 (d, 1H, CF \_COCH), 8.37 (d, 1H, CF \_COCH).

The spectroscopic and physical data are in accordance with those published in the literature [S4].

**Representative procedure for the vinylogous acylation of indole derivatives**

\(\text{(E)-4-(5-Bromo-1-methyl-1H-indol-3-yl)-1,1,1-trifluorobut-3-en-2-one (12c)}\)

\[\text{N-Methyl-5-bromoindol (11c) (6.3 g, 30 mmol, 1.0 equiv.) was dissolved in 60 mL reagent grade dichloromethane and stirred at room temperature. (E)-4-Ethoxy-1,1,1-trifluorobut-3-en-2-one (1) (8.26 ml, 60 mmol, 2.0 equiv.) was added followed by Sc(OTf)\_3 (74 mg, 0.15 mmol, 0.5 mol%). After being stirred for 3 h the reaction mixture was terminated by addition of water and the aqueous phase was extracted twice with dichloromethane. The combined organic phases were washed with water, dried over sodium sulfate and concentrated under reduced pressure. The residue was dissolved in a minimum amount of ethanol and treated with cyclohexane. The resulting suspension was placed in the refrigerator before the reddish solution was decanted. The solid residue was washed with cyclohexane. Pure product 12c was obtained after drying under reduced pressure.}\]

\(\text{(E)-1,1,1-Trifluoro-4-(1H-indol-3-yl)but-3-en-2-one (12a)}\)

Scale: 9.93 mmol; yield: 1.9 g, 7.94 mmol; 80% (2.5 mol% of catalyst).

\[
\text{\textsuperscript{1}H-NMR (500 MHz, CDCl}_3, \text{SiMe}_4= 0.0 \text{ ppm}} \] \(\delta\) 7.03 (d, 1H, CF\_COCH), 7.35 (m, 2H, indol-H), 7.47 (m, 1H, indol-H), 7.72 (s, 1H, indol-H), 7.95 (m, 1H, indol-H), 8.24 (d, 1H, CF\_COCHCH), 8.72 (s, 1H, NH).

\(\text{(E)-4-(5-Bromo-1H-indol-3-yl)-1,1,1-trifluorobut-3-en-2-one (12b)}\)
Representative procedure for the Stetter reaction with trifluorobutenones (16d)

\[
(E)-4-(5\text{-Bromo-1-methyl-1H-indol-3-yl})-1,1,1\text{-trifluorobut-3-en-2-one (12c)}
\]

Scale: 30.1 mmol; yield: 6.3 g, 18.97 mmol; 63%. \(^1\)H-NMR (500 MHz, DMSO, TMS= 0.0 ppm) \(\delta\) 3.86 (s, 3H, CH\(_3\)), 6.89 (d, 1 H, CF\(_3\)C(O)CHCH), 7.27 (d, 1 H, indol-H), 7.46 (d, 1 H, indol-H), 7.56 (s, 1 H, indol-H), 8.02 (s, 1 H, indol-H), 8.13 (d, 1 H, CF\(_3\)C(O)CHCH).

Representative procedure for the sulfuration of the \(\gamma\)-lactam and synthesis of thiophenes from diketones

\[
(E)-4-(5\text{-Bromo-1H-indol-3-yl})-1,1,1\text{-trifluorobut-3-en-2-one (12)}
\]

(318 mg, 1.0 mmol, 1.0 equiv.), 1-naphthaldehyde (14b) (163 \(\mu\)L, 1.2 mmol, 1.2 equiv.) and 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride (15) (27 mg, 0.1 mmol, 10 mol%) were dissolved in 2 mL of reagent grade ethanol and stirred at room temperature. DBU (150 \(\mu\)L, 1.0 mmol, 1.0 equiv.) was added and stirring was continued until completion was indicated by TLC. Then, the reaction mixture was diluted with ethyl acetate and the reaction was terminated by addition of water. The aqueous phase was extracted twice with ethyl acetate, the combined organic phases were washed with brine, dried over sodium sulfate and concentrated under reduced pressure. The crude product was purified by flash chromatography (cyclohexane / ethyl acetate) to yield the product 16c as a mixture of derivatives and the crude material was directly used as such. All other diketones were prepared likewise.
1-(4-Bromophenyl)-5,5,5-trifluoro-2-(2-oxopyrrolidin-1-yl)pentane-1,4-dione (16a) (350 mg, 0.84 mmol, 1.0 equiv.) was dissolved in 20 mL MeCN and stirred at room temperature. P₄S₁₀ (1.2 g, 2.7 mmol, 3.0 equiv.) and NaHCO₃ (920 mg, 11.0 mmol, 12 equiv.) were added and stirring was continued for 5 h. Then, the reaction was terminated by addition of water and the mixture was extracted twice with ethyl acetate. The combined organic extracts were washed with brine, dried over sodium sulfate and concentrated under reduced pressure.

The crude residue was redissolved in 20 mL of toluene, equipped with Lawesson’s reagent (404 mg, 1.0 mmol, 1.2 equiv.) and heated for 2 h at 80°C. After being cooled down to room temperature the reaction was terminated by addition of water and the mixture was extracted twice with ethyl acetate. The combined organic extracts were washed with brine, dried over sodium sulfate and concentrated under reduced pressure.

1-(2-(4-Bromophenyl)-5-(trifluoromethyl)thiophen-3-yl)pyrrolidine-2-thione (17a)

Scale: 0.89 mmol; yield: 120 mg, 0.30 mmol; 33%. ¹H-NMR (500 MHz, CDCl₃, SiMe₄= 0.0 ppm) δ 2.12 (quint, 2H, CH₂CH₂CH₂C(S)N), 3.11–3.14 (t, 2H, CH₂CH₂CH₂C(S)N), 3.65 (t, 2H, CH₂CH₂CH₂C(S)N), 7.34 (d, 2H, Ar-H), 7.50 (s, 1H, thiophene-H), 7.57 – 7.59 (d, 2H, Ar-H).

1-(2-(4-Fluorophenyl)-5-(trifluoromethyl)thiophen-3-yl)pyrrolidine-2-thione (17b)

Scale: 1.14 mmol; yield: 150 mg, 0.43 mmol; 38%; ¹H-NMR (500 MHz, CDCl₃, SiMe₄= 0.0 ppm) δ 2.10 (quint, 2H, CH₂CH₂CH₂C(S)N), 3.11–3.14 (t, 2H, CH₂CH₂CH₂C(S)N), 3.65 (t, 2H, CH₂CH₂CH₂C(S)N), 7.15 (d, 2H, Ar-H), 7.46 (d, 2H, Ar-H), 7.51 (s, 1H, thiophene-H).

**Representative procedure for the synthesis of furans from diketones**
2-(5-Bromo-1H-indol-3-yl)-1-(4-bromophenyl)-5,5,5-trifluoropentan-1,4-dione (16c) (200 mg, 0.4 mmol, 1.0 equiv.) and Lawesson’s reagent (162 mg, 0.4 mmol, 1.0 equiv.) were heated in 5 mL of dry toluene at 110 °C for 4 h. After being cooled to room temperature, the reaction was terminated by addition of water. The mixture was extracted twice with ethyl acetate, the combined organic extracts were washed with brine, dried over sodium sulfate and concentrated under reduced pressure. The crude products were purified by flash chromatography (cyclohexane / ethyl acetate).

5-Bromo-3-[2-(4-bromophenyl)-5-(trifluoromethyl)furan-3-yl]-1H-indole (18a)

Scale: 0.30 mmol; yield: 100 mg, 0.21 mmol; 69 %; ¹H-NMR (500 MHz, CDCl₃, SiMe₄= 0.0 ppm) δ 6.95 (s, 1H, furan-H), 7.24 (d, 1H, indole-H), 7.33 (s, 1H, indole-H), 7.34 (d, 1H, indole-H), 7.39 (d, 2H, Ar-H), 7.45 (d, 2H, Ar-, indole-H), 8.35 (s, 1H, NH).

(5-Bromo-3-(2-(naphthalen-1-yl)-5-(trifluoromethyl)furan-3-yl)-1H-indole (18b)

Scale: 0.51 mmol; yield: 130 mg, 0.28 mmol; 56 %; ¹H-NMR (500 MHz, CDCl₃, SiMe₄= 0.0 ppm) δ 6.80 (s, 1H, indole-H), 7.19 (d, 1H, indole-H), 7.26 (d, 1H, indole-H), 7.29 (s, 1H, indol-H), 7.37 (m, 1H, Ar-H), 7.46 (m, 2H, Ar-H), 7.57 (m, 2H, furan-H and Ar-H), 7.81 (d, 1H, Ar-H), 7.88 (d, 1H, Ar-H), 7.92 (d, 1H, Ar-H), 8.03 (s, 1H, NH).

Representative procedure for the synthesis of pyrroles from diketones
1-(4-Bromophenyl)-5,5,5-trifluoro-2-(2-oxopyrrolidin-1-yl)pentane-1,4-dione (16a) (560 mg, 70 % purity, 1.0 mmol, 1.0 equiv.) and allylamine (150 µL, 2.0 mmol, 2.0 equiv.) were stirred in 5 mL of dry dichloromethane at room temperature. The volatiles were removed under reduced pressure, the residue was dissolved in 5 mL of dry toluene and heated in the presence of PTSA (95 mg, 0.5 mmol, 0.5 equiv.) for 4 h under refluxing conditions. After being cooled to room temperature the reaction was terminated by addition of water. The mixture was extracted twice with ethyl acetate, the combined organic extracts were washed with brine, dried over sodium sulfate and concentrated under reduced pressure. The crude products were purified by flash chromatography (cyclohexane / ethyl acetate).

1-[1-Allyl-2-(4-bromophenyl)-5-(trifluoromethyl)-1H-pyrrol-3-yl]pyrrolidin-2-one (19):

Scale: 0.68 mmol; yield: 170 mg, 0.41 mmol; 60 %; \(^{1}\)H-NMR (500 MHz, CDCl\(_3\), TMS = 0.0 ppm) \(\delta\) 1.95 (quint, 2 H, CH\(_2\)C\(_6\)H\(_5\)CH\(_2\)C(O)N), 2.38 (t, 2 H, CH\(_2\)CH\(_2\)C(O)N), 3.30 (t, 2 H, C\(_6\)H\(_5\)CH\(_2\)CH\(_2\)C(O)N), 4.47 (d, 2 H, NCH\(_2\)CH\(_2\)N), 4.78 (d, 1 H, trans-H), 5.09 (d, 1 H, cis-H), 5.76 (m, 1 H, vinyl-H), 6.74 (s, 1 H, pyrrol-H), 7.23 – 7.27 (d, 2 H, Ar-H), 7.54 – 7.57 (d, 2 H, Ar-H).

Representative procedure for the synthesis of pyridazines

1-(4-bromophenyl)-5,5,5-trifluoro-2-(2-oxopyrrolidin-1-yl)pentane-1,4-dione (16a) (290 mg, 0.74 mmol, 1.0 equiv.), hydrazine-dihydrochloride (158 mg, 1.5 mmol, 2.0 equiv.) and sodium acetate (246 mg, 3.0 mmol, 4.0 equiv.) were mixed in 10 mL of toluene and the reaction mixture was stirred for 90 minutes at room temperature and then heated under refluxing conditions for 4 h. After cooling to room temperature the reaction was terminated by addition of water. The mixture was extracted twice with ethyl acetate and the combined organic extracts were washed with brine. After drying over sodium sulfate and concentration under reduced pressure, the crude material was purified by flash chromatography (cyclohexane / ethyl acetate) to yield the product 20a as a semisolid material.

3-(4-Bromophenyl)-6-(trifluoromethyl)pyridazine (20a)

Scale: 0.51 mmol; yield 100 mg, 0.33 mmol; 65%. \(^{1}\)H-NMR (500 MHz, CDCl\(_3\), TMS= 0.0 ppm) \(\delta\) 7.72 (d, 2H, Ar-H), 7.88 (d, 1H, Ar-H), 8.14 (d, 1H, Ar-H), 8.35 (s, 1H, Ar-H).

\[ \begin{align*}
\text{Br} & \quad \text{N} \quad \text{N} \\
& \quad \text{F} \quad \text{F}
\end{align*} \]
5-Bromo-3-[3-(4-chlorophenyl)-6-(trifluoromethyl)pyridazin-4-yl]-1H-indole (20b)

Scale: 0.81 mmol; yield 110 mg, 0.24 mmol; 30%. $^1$H-NMR (500 MHz, CDCl$_3$, TMS = 0.0 ppm) $\delta$ 7.16 (s, 1H, indol-H), 7.22 (d, 1H, indol-H), 7.39 (d, 1H, indol-H), 7.44 (d, 2H, Ar-H), 7.56 (d, 2H, Ar-H), 7.69 (s, 1H, indol-H), 8.30 (s, 1H, pyridazine-H), 11.96 (s, 1H, NH).

4-[5-p-Tolyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (Celecoxib®) (22)

(E)-1,1,1-Trifluoro-4-p-tolylbut-3-en-2-one (2a) (856 mg, 4.0 mmol, 1.0 equiv.) and 4-hydrazinylbenzenesulfonamide hydrochloride (21) (941 mg, 4.2 mmol, 1.05 equiv.) were heated in 10 mL of EtOH for 18 h at 90°C. At room temperature the reaction was terminated by addition of a saturated ammonium chloride solution. The mixture was extracted twice with ethyl acetate, the combined organic extracts were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The crude material was dissolved in 50 mL toluene, equipped with activated MnO$_2$ (3.9 g, 40 mmol, 10 equiv.) and sonicated for 18 h at room temperature. The mixture was then filtered over Celite® with the aid of 100 mL ethyl acetate. The volatiles were removed under reduced pressure and the residue purified by flash chromatography (petroleum ether / ethyl acetate = 2 : 1 $\rightarrow$ 1: 1) to give the title compound 22 (1.03 g, 2.7 mmol, 68% yield) as semisolid material.

$^1$H-NMR (400 MHz, CDCl$_3$, CHCl$_3$ = 7.26 ppm) $\delta$ 2.39 (s, 3H, CH$_3$), 4.91 (s, 2H, NH$_2$), 6.76 (s, 1H, pyrazol-H), 7.13 (m, 2H, Ar-H), 7.20 (m, 2H, Ar-H), 7.50 (m, 2H, Ar-H), 7.92 (m, 2H, Ar-H) ppm; $^{13}$C-NMR (200 MHz, CDCl$_3$, CDCl$_3$ = 77.2 ppm) $\delta$ 21.3, 106.4, 122.4, 125.6, 127.6, 128.7, 129.8, 139.8, 141.3, 142.6, 144.0, 144.3, 145.3 ppm; HRMS m/z calculated for C$_{17}$H$_{15}$O$_2$F$_3$N$_3$S (M+H$^+$): 382.0832, found: 382.0839.

The spectroscopic and physical data are in accordance with those published in the literature [S5].
References supporting information


