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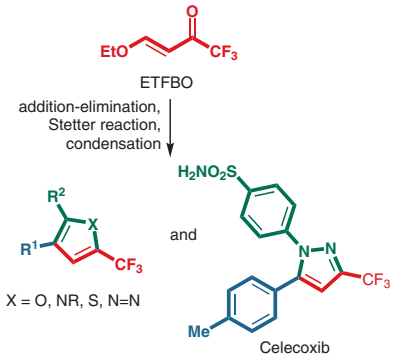
4-Ethoxy-1,1,1-trifluoro-3-buten-2-one (ETFBO), a Versatile Precursor for Trifluoromethyl-Substituted Heteroarenes – a Short Synthesis of Celebrex® (Celecoxib)

Heiko Sommer[a]
Max Braun[b]
Benjamin Schröder[a]
Andreas Kirschning*[a]

[a] Institut für Organische Chemie und Biomolekulares Wirkstoffzentrum (BMWZ) der Leibniz Universität Hannover, Schneiderberg 1B, 30167 Hannover, Germany
andreas.kirschning@oci.uni-hannover.de
[b] Solvay Fluor GmbH, Hans-Böckler-Allee 20, 30173 Hannover, Germany



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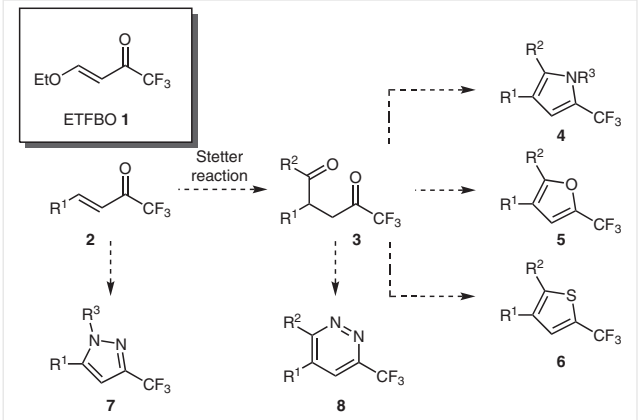
Abstract 4-Ethoxy-1,1,1-trifluoro-3-buten-2-one (ETFBO) serves as a trifluoromethyl-containing building block for the preparation of trifluoromethyl-substituted thiophenes, furans, pyrrols, and piperazines. Key steps are an addition–elimination reaction to ETFBO followed by the thiazolium-catalyzed Stetter reaction. The scope of this chemistry was demonstrated in a new synthetic approach towards the COX-2 selective, nonsteroidal anti-inflammatory drug Celebrex® (celecoxib).

Key words antiinflammation, heteroarenes, Stetter reaction, organocatalysis, trifluoromethyl group

Fluorinated compounds play an important role in the development of novel biologically active agents in pharmaceutical and agrochemical research.[1] Typical examples are doravirine, a non-nucleoside reverse transcriptase inhibitor, Sustiva® used in HIV-1 therapy and sitagliptin an orally employed drug against diabetes mellitus type 2.[1–5]

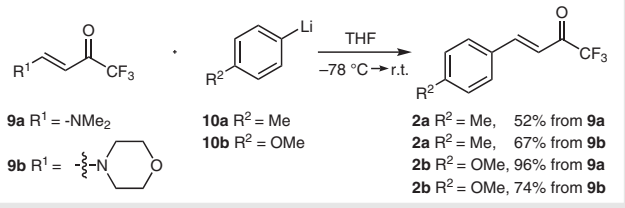
Over the last few decades a large arsenal of methods for the introduction of fluorine into organic molecules has been reported.[6,7] Recently, the properties of difluoromethylene and trifluoromethyl groups received great attention.[8] Consequently, the trifluoromethylation of aromatic compounds has emerged as a useful tool in the repertoire of the practicing medicinal chemist.[9–11] As an alternative strategy to the chemoselective introduction of the trifluoromethyl group at a late stage using transfer reagents such as Togni's reagent[12] the use of easily accessable building blocks that contain the trifluoromethyl group can provide a way to prepare trifluoromethyl-functionalized targets.[9] For the transformation of this precursor into the desired target molecules, reliable methods have to be developed to meet the unique reactivity profile of fluorinated hydrocarbons. Among suitable building blocks we envisaged 4-ethoxy-1,1,1-trifluoro-3-buten-2-one (ETFBO, **1**) to be highly versatile for the following reasons. ETFBO is a commercially available industrial product that is already used for the preparation of trifluoromethyl-substituted pyridines, pyrazoles, and arenes which represent common scaffolds in agrochemical and pharmaceutical research.[13] Importantly, it bears several sites of different reactivity useful for further chemoselective transformations. Besides the keto group the olefinic double bond is remarkable as it is substituted with the trifluoromethylacyl group and at the same time it bears an electron-rich enol ether moiety. Especially the condensation with 1,3-dicarbonyl compounds, ureas, and hydrazines provides scalable access to various trifluoromethylated arenes.[13–16] Though only few examples are found in the literature for the preparation of five-membered heterocycles which are based on the use of α,β-unsaturated trifluo-



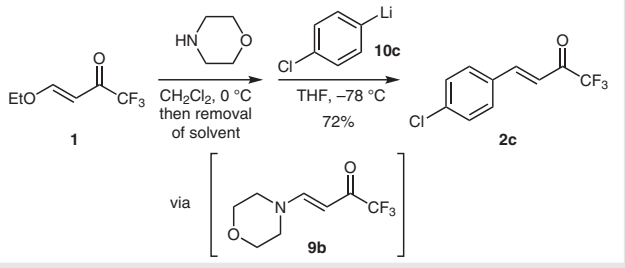
Scheme 1 ETFBO (**1**), corresponding β-substituted α,β-unsaturated trifluoromethyl ketones **2**, and synthetic sequence towards trifluoromethyl-substituted heterocycles **4–8**

romethyl ketones as building blocks,[17–20] no reports have appeared on utilizing ETFBO (**1**) in the synthesis of five-membered heteroarenes so far.

As a part of our research to evaluate the scope of this fluorinated synthetic building block, in this article we disclose robust transformations for preparing a variety of trifluoromethylated heteroarenes in gram scale. Specifically, this report covers synthetic avenues towards new trifluoromethyl-substituted pyrroles **4**, furans **5**, thiophenes **6**, pyrazoles **7**, and pyridazines **8** (Scheme 1). As an initial step towards diversity we developed a short sequence that starts from ETFBO (**1**) and yields a variety of new trifluoromethyl ketones **2**. By employing the Stetter reaction, the number of new trifluoroketones can be further increased yielding 1,4-dicarbonyl compounds **3**. These serve as precursors for various trifluoromethyl-substituted heterocycles. Additionally, we apply the chemistry described in this report in a short synthesis of the COX inhibitor Celebrex®(Celecoxib).[21]



Scheme 2 Formation of new trifluoromethyl ketones **2** by nucleophilic addition of lithiated arenes **10** to β-amino-α,β-unsaturated trifluoromethyl ketones **9** (isolated yields)



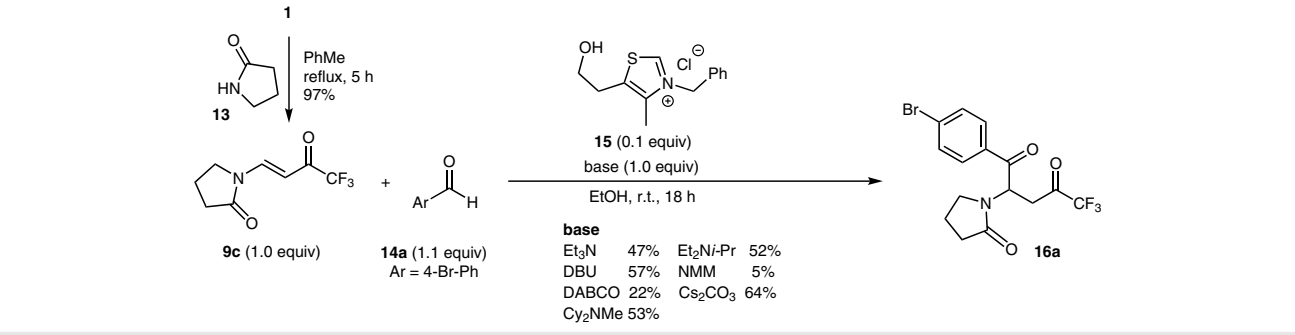
Scheme 3 One-pot synthesis of trifluoromethyl ketone **2c** (isolated yield)

One of the most reliable methods for preparing α,β-unsaturated trifluoromethyl ketones **2** is based on the addition of organometallic agents to the corresponding vinylogous amides **9** of ETFBO.[20–24] These amides **9** have to be prepared first in order to avoid 1,2-addition of the organometallic agent.[25] We found that the morpholine derived *E*-configured analogue **9b** is readily available in good yield and with excellent regioselectivity (Scheme 2). We favor morpholine over the more toxic dimethylamine which has been the amine of choice so far. Practically, the two steps can be carried out as a one-pot procedure avoiding purification or isolation of the amide **9b** by simply removing the solvent after amide formation (Scheme 3). The crude product is taken up in dry THF and treated with the organolithium agent such as **10c** to yield new trifluoromethyl ketone **2c**.

Instead of secondary amines indole derivatives **11a–c** can also serve as nucleophiles that react via C3 of the indole system with ETFBO (**1**) to yield trifluoromethyl ketones **12a–c** (Table 1). This is achieved by Lewis acid activation and we found that scandium triflate is better suited than zinc dichloride.[26] Furthermore, it can be employed in catalytic amounts as low as 0.5 mol%.

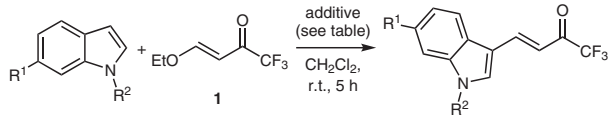
In the following, we envisaged the Stetter reaction[27] as a second derivatization protocol to gain access to valuable trifluoromethyl-substituted 1,4-diketones. This Umpolung-type C–C coupling reaction should proceed between an aldehyde **14** and the β-position of the enone moiety of the trifluoromethylketone moiety. We used the thiazolium salt **15** as organocatalyst and optimized the reaction conditions with bromobenzaldehyde **14a** and enone **9c** as model reaction, yielding 1,4-diketone **16a** (Scheme 4).

Enone **9c** was obtained from ETFBO (**1**) and pyrrolidinone **13** by simply heating both compounds in toluene under refluxing conditions (see Supporting Information). We found that ethanol is the solvent of choice for this Stetter reaction, while in toluene or acetonitrile yields were lower, irrespective of which base was used. Good yields were obtained with DBU, Cs_2CO_3, and Cy_2NMe. For practical reasons DBU was chosen as base of choice. The optimization relied



Scheme 4 Optimization of the Stetter reaction (determined by HPLC-MS analysis of the crude product)

Table 1 Preparation of Indole-Substituted α,β-Unsaturated Trifluoromethyl Ketones **12a–c**



11a R^1 = Br, R^2 = H
11b R^1 = H, R^2 = H
11c R^1 = Br, R^2 = Me

12a R^1 = Br, R^2 = H
12b R^1 = H, R^2 = H
12c R^1 = Br, R^2 = Me

Entry	Indole	Conditions	Product	Yield (%)[a]
1	**11a**	**1** (1.0 equiv), $ZnCl_2$ (20 mol%)	**12a**	41
2	**11a**	**1** (1.0 equiv), $Sc(OTf)_3$ (10 mol%)	**12a**	62
3	**11b**	**1** (2.0 equiv), $Sc(OTf)_3$ (2.5 mol%)	**12b**	80
4	**11a**	**1** (2.0 equiv), $Sc(OTf)_3$ (1.0 mol%)	**12a**	75
5	**11b**	**1** (2.0 equiv), $Sc(OTf)_3$ (0.5 mol%)	**12b**	75
6	**11a**	**1** (2.0 equiv), $Sc(OTf)_3$ (0.5 mol%)	**12a**	63
7	**11c**	**1** (2.0 equiv), $Sc(OTf)_3$ (0.5 mol%)	**12c**	63

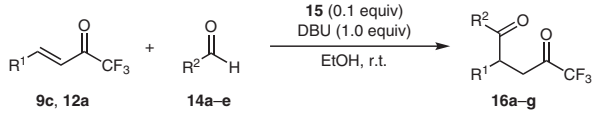
[a] Isolated yields.

on HPLC-MS analysis conducted with the crude product which contained different keto-enol tautomers. Therefore, the Stetter products were directly subjected for the reactions to follow (vide infra).

Having established the reaction conditions, we extended the scope of the Stetter reaction to additional aldehydes **14b–e** and trifluoromethyl ketones **9c** and **12a** (Table 2). Principally, the scope of the reaction is broad. However, isolated yields differed with respect to the electronic properties of the chosen aldehyde. Electron-deficient aldehydes such as **14a**,**c** and **14e** delivered the corresponding ketones **16a–c**,**e**,**g** in moderate to good yields, whereas electron-rich aldehydes **14b** and **14d** provided C–C coupling products in only moderate yields. The same trend was observed regarding the nature of the unsaturated trifluoromethyl ketone. Aliphatic aldehydes failed to undergo the Stetter reaction under the described conditions.

With these new trifluoromethyl-substituted 1,4-diketones **16** in hand, we investigated their suitability to undergo condensation reactions to yield different heteroarenes. Formation of thiophenes was conducted on diketones **16a** and **16b**. The synthesis was accompanied with the evaluation whether the amide group can chemoselectively be sulfurized in the presence of the 1,4-diketo moiety. However, this transformation was not straightforward. Using the Lawesson's reagent alone provided the thioamide but instead of the thiophene only the furan ring was generated. P_4S_{10} yielded a mixture of the thioketone and the thiophene. Consequently, we first employed P_4S_{10} and afterwards added Lawesson's reagent to achieve thiophenes **17a** and **17b** in moderate yield, proving the scope of modifications that are possible with these diketones (Scheme 5).[28]

Table 2 Synthesis of Trifluoromethyl Ketones **16a–g** by the Stetter Reaction

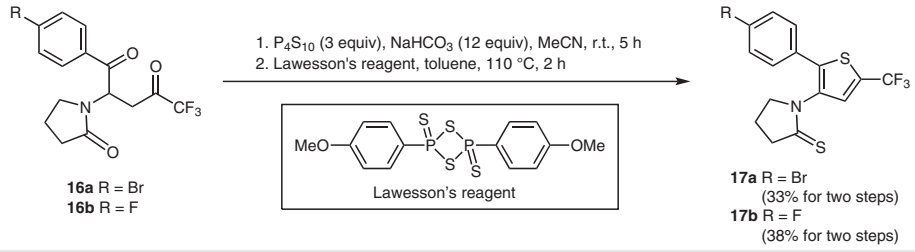


9c, **12a** **14a–e** **16a–g**

Entry	R^1	R^2	Product	Conversion (%)[a]
1	**9c**	**14a**	**16a**	70[b]
2	**9c**	**14c**	**16b**	38
3	**12a**	**14a**	**16c**	80
4	**12a**	**14b**	**16d**	51
5	**12a**	**14c**	**16e**	72
6	**12a**	**14d**	**16f**	29
7	**12a**	**14e**	**16g**	71

[a] Conversion determined by HPLC-MS of the crude product.
[b] Conversion was higher compared to the one reported for the optimization (see Scheme 4), because the transformation was repeated on a larger scale.

Likewise, diketones **16c** and **16d** were transformed to the trifluoromethyl-substituted furans **18a** and **18b**, respectively, under dehydrating conditions (Table 3, entries 1 and 2). Pyrrole **19** was obtained from diketone **16a** in the presence of allyl amine (Table 3, entry 3). Finally, also pyridazines **20a** and **20b** were accessible from diketones **16a** and **16h**, respectively, in the presence of hydrazine liberated from the corresponding hydrochloride salt (Table 3, entries 4 and 5).

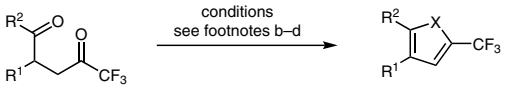


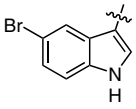
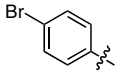
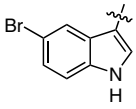
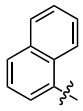
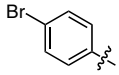
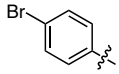
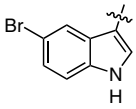
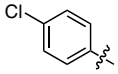
Scheme 5 Sulfuration and cyclization of 1,4-diketones **16a** and **16b**, respectively, to thiophenes **17a** and **17b**

Having established a synthetic sequence that starts from ETFBO (**1**) with an addition–elimination step, followed by a Stetter reaction and finalized by a condensation reaction with intermediate 1,4-diketones, we finalized these studies with the preparation of Celebrex® (celecoxib, **22**), a COX-2 selective, nonsteroidal anti-inflammatory drug used to relieve pain, swelling, and joint stiffness (Scheme 6).[29] Recent disclosures on the synthesis of celecoxib either use the trifluoromethyl-substituted 1,3-diketone as precursor[30] or form the pyrazole ring by a 1,3-dipolar cycloaddition between between a nitrile imine and an enamine.[31]

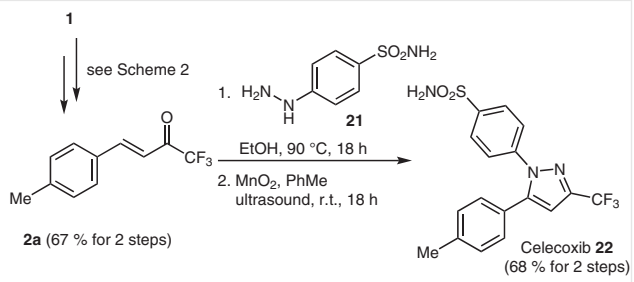
We devised a new short approach towards this trifluoromethyl-substituted pyrazole derivative starting from ETFBO (**1**). A two-step protocol provided trifluoromethyl ketone **2a** which was transformed into the Celecoxib (**22**) after treatment with sulfonamide **21** and MnO_2-promoted oxidation.

Table 3 Formation of Furans **18a**,**b**, Pyrrole **19**, and Pyridazines **20a**,**b** by Cyclization of 1,4-Diketones **16**



Entry	Diketone	R^1	R^2	X	Product	Yield (%)[a]
1	**16c**[b]			O	**18a**	69
2	**16d**[b]			O	**18b**	56
3	**16a**[c]				**19**	60
4	**16a**[d]	H[e]		-N=N-	**20a**	65
5	**16h**[d]			-N=N-	**20b**	30

[a] Isolated yield.
[b] Conditions for furan formation: **16d** or **16e**, 1 equiv Lawesson's reagent, 0.1 M in PhMe, 110 °C.
[c] Conditions for pyrrole formation: **16a**, 2 equiv allyl amine, cat. PTSA, 0.1 M in toluene, r.t. to 110 °C.
[d] Conditions for pyridazine formation: **16a** or **16h**, 2 equiv ClH_3NNH_3Cl, 4 equiv NaOAc, 0.1 M in toluene, r.t. to 110 °C.
[e] **16a** served as the starting material, however, the product lacks the γ-lactam substituent due to elimination and aromatization.



Scheme 6 A short synthesis of the COX-2 inhibitor Celebrex® (Celecoxib, **22**)

In summary, we reported on the utilization of 4-ethoxy-1,1,1-trifluoro-3-buten-2-one as a trifluoromethyl-containing building block ideally suited for the preparation of different trifluoromethyl-substituted heteroarenes such as thiophenes, furans, pyrrols, and piperazines.[32] The key steps towards the corresponding 1,4-diketo precursors are based on an addition–elimination reaction to 4-ethoxy-1,1,1-trifluoro-3-buten-2-one using N- as well as C-nucleophiles, followed by the organocatalytically promoted Stetter reaction. The scope of this chemistry was demonstrated in a new synthetic approach towards the COX-2 selective, non-steroidal anti-inflammatory drug Celebrex® (celecoxib).

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1589097.

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(32) **4-[5-*p*-Tolyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (Celecoxib®) (22)**
(*E*)-1,1,1-Trifluoro-4-*p*-tolylbut-3-en-2-one (**2a**, 856 mg, 4.00 mmol, 1.0 equiv) and 4-hydrazinylbenzenesulfonamide hydrochloride (**21**, 941 mg, 4.20 mmol, 1.05 equiv) were heated in 10 mL of EtOH for 18 h at 90 °C. After cooling to r.t. the reaction was terminated by addition of a sat. NH_4Cl solution. The mixture was extracted twice with EtOAc, the combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude material was dissolved in 50 mL toluene, equipped with activated MnO_2 (3.48 g, 40.0 mmol, 10 equiv), and sonicated for 18 h at r.t. The mixture was then filtered over Celite® with the aid of 100 mL EtOAc. The volatiles were removed under reduced pressure, and the residue was purified by flash chromatography (PE–EtOAc = 2:1 to 1:1) to give the title compound 22 (1.03 g, 2.70 mmol; 68% yield) as a colourless solid.
^{1}H NMR (400 MHz, $CDCl_3$, $CHCl_3$= 7.26 ppm): δ = 2.39 (s, 3 H, CH_3), 4.91 (s, 2 H, NH_2), 6.76 (s, 1 H, pyrazol-H), 7.13 (m, 2 H, ArH), 7.20 (m, 2 H, ArH), 7.50 (m, 2 H, ArH), 7.92 (m, 2 H, ArH) ppm. ^{13}C NMR (200 MHz, $CDCl_3$, $CDCl_3$ = 77.2 ppm): δ = 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* calcd for $C_{17}H_{15}O_2F_3N_3S$ [M + H$^+$]: 382.0832; found: 382.0839.