One-Pot Synthesis of Trifluoromethyl-Containing Pyrazoles via Sequential Yb(PFO)$_3$-Catalyzed Three-Component Reaction and IBX-Mediated Oxidation

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Abstract: Fourteen trifluoromethyl-containing fully substituted pyrazoles were synthesized via Yb(PFO)$_3$-catalyzed three-component condensations of aromatic hydrazines, aldehydes, and ethyl trifluoroacetoacetate, followed by IBX-mediated oxidation of pyrazolines. A possible mechanism is suggested.

Key words: trifluoromethyl-containing pyrazole, IBX, Yb(PFO)$_3$, three-component synthesis

Pyrazoles and, in particular, trifluoromethyl-containing pyrazoles have been shown to be an increasingly important class of biologically active compounds for the access to agricultural chemicals and pharmaceutical products.[1] For example, fluazolate is a new trifluoromethyl-containing phenylpyrazole herbicide, intended for pre-emergence use to control a range of annual grasses and broad-leaved weeds in winter wheat.[2] Others can act as potential anti-inflammatory drugs **I**[3] or antihyperglycemic agents **II**[4] (Figure 1).

There are two main methods for the synthesis of fluorine-containing organic compounds: the direct introduction of fluorine replacing hydrogen[5] and the usage of simple reactive fluoro-containing building blocks.[6] However, the first is associated with several shortcomings such as harsh reaction conditions, high toxicity, tedious work-up procedures, and co-occurrence of several side reactions. With the increasing number of new fluoro-containing building blocks, the second is becoming an important and popular tool to construct the fluoro-containing compounds.

Nowadays, multicomponent reactions have attracted great interest due to the fact that the products are formed in a single step and the diversity can be simply achieved by varying the reacting components.[7] When searching in the literature, we found that there were only a few reports on the use of fluoro-containing building block as one of the components in the multicomponent reactions.[8] Therefore, we believe that the strategy, multicomponent reactions including fluoro-containing building blocks (MCR-FBB), will prove to be a powerful tool for the construction of fluoro-containing compounds. The fascinating scope of this strategy lies in the straightforward assembly of complex fluorinated compounds from simple and available fluoro-containing building blocks as well as the high level of diversity that can be obtained by varying the fluoro-containing components taking part in the MCR.

Recently, much attention has been paid to the synthesis of trifluoromethyl-containing pyrazoles starting from different fluoro-containing building blocks.[9] However, there are few reports on the synthesis of trifluoromethyl-containing fully substituted pyrazoles. Herein we describe the application of this MCR-FBB strategy for the straightforward synthesis of fourteen trifluoromethyl-containing fully substituted pyrazoles via sequential Yb(PFO)$_3$-catalyzed three-component condensations of aromatic hydra-

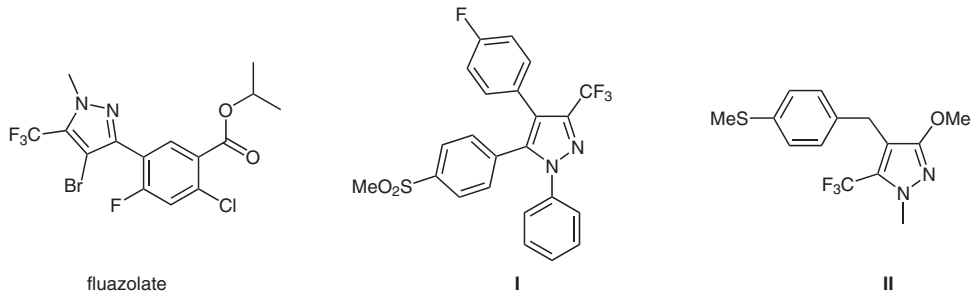

Figure 1 Bioactive trifluoromethyl-containing pyrazoles

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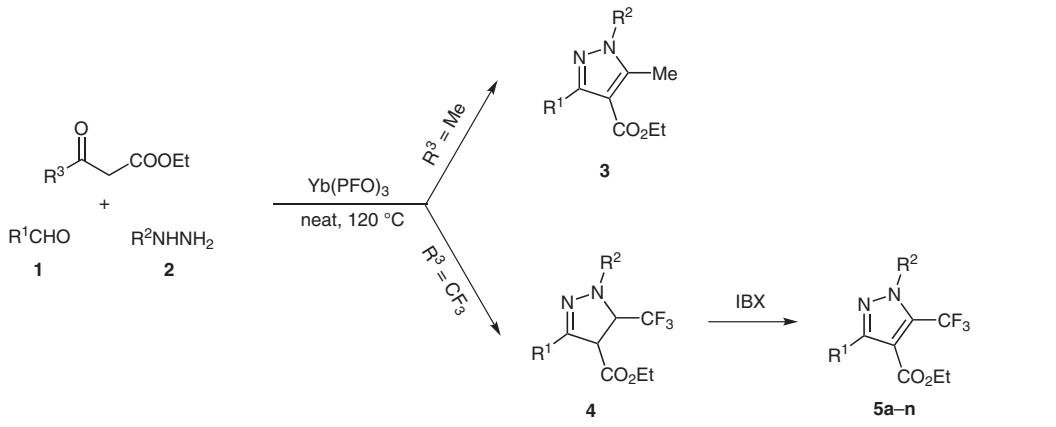


5a R^1 = Ph, R^2 = Ph
5b R^1 = 4-$CF_3OC_6H_4$, R^2 = Ph
5c R^1 = 4-MeC_6H_4 , R^2 = Ph
5d R^1 = 4-CNC_6H_4, R^2 = Ph
5e R^1 = 3-(6-Clpyridinyl), R^2 = Ph
5f R^1 = $MeCH_2CH_2$, R^2 = Ph
5g R^1 = Me_2CHCH_2, R^2 = Ph
5h R^1 = Me_2CH, R^2 = Ph
5i R^1 = $MeCH_2$, R^2 = Ph
5j R^1 = Ph, R^2 = 4-FC_6H_4
5k R^1 = 4-BrC_6H_4, R^2 = 4-FC_6H_4
5l R^1 = 4-$CF_3OC_6H_4$, R^2 = 4-MeC_6H_4
5m R^1 = Ph, R^2 = 4-MeC_6H_4
5n R^1 = $MeCH_2CH_2$, R^2 = 4-MeC_6H_4

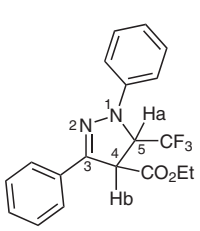
Scheme 1

zines, aldehydes, and ethyl trifluoroacetoacetate followed by IBX-mediated oxidation (Scheme 1, $R^3 = CF_3$).

In our preceding paper, we briefly reported a novel approach to fully substituted pyrazoles via three-component condensations of phenylhydrazine, aldehydes, and ethyl acetoacetate using ytterbium perfluorooctanoate [$Yb(PFO)_3$] as catalyst under solvent-free conditions (Scheme 1, R^3 = Me).[10] To extend our previous work, we try to prepare trifluoromethyl-containing pyrazole by the replacement of ethyl acetoacetate with a simple and available trifluoromethyl-containing building block, ethyl trifluoroacetoacetate. But this reaction only afforded an unexpected product – pyrazoline **4** in moderate to good yield, whereas the anticipated trifluoromethyl-containing pyrazole **5** was not obtained. Therefore, our initial efforts were directed toward isolating two representative intermediates **4a** (Figure 2) and **4f** and determination of their structures by ^{1}H NMR, ^{13}C NMR, ^{19}F NMR spectroscopy and HRMS studies.

The position of hydrogen atom in the pyrazoline ring of **4a** was also identified on the basis of the ^{1}H NMR, ^{13}C NMR, and HMQC (two-dimensional heteronuclear multiple quantum coherence) spectrum of **4a** (see Supporting Information).

In the ^{1}H NMR spectrum of **4a**, the proton of pyrazoline ring Hb appeared at δ = 4.50 ppm, as a doublet with a coupling constant of 3.6 Hz due to coupling with Ha, whereas Ha appeared as quadruplet of doublets (qd, δ = 5.05 ppm), indicating *ortho* coupling between the proton Ha and Hb ($^3J_{HaHb}$ = 3.6 Hz) and *ortho* coupling between the proton Ha and the fluoro atom ($^3J_{HaF}$ = 6.8 Hz). In the ^{13}C NMR spectrum of **4a**, C-5 (δ = 65.6 ppm) was split into a quadruplet because of coupling with CF_3. The coupling constant ($^2J_{C-F}$) was 31 Hz. The CF_3 group resonated at δ = 124.4 ppm and was split into a quartet with $^1J_{C-F}$ = 281 Hz due to one-bond C–F coupling. The signal from C-4 atom was a doublet at δ = 53.1 ppm, indicating that it is a saturated carbon in the pyrazoline ring.

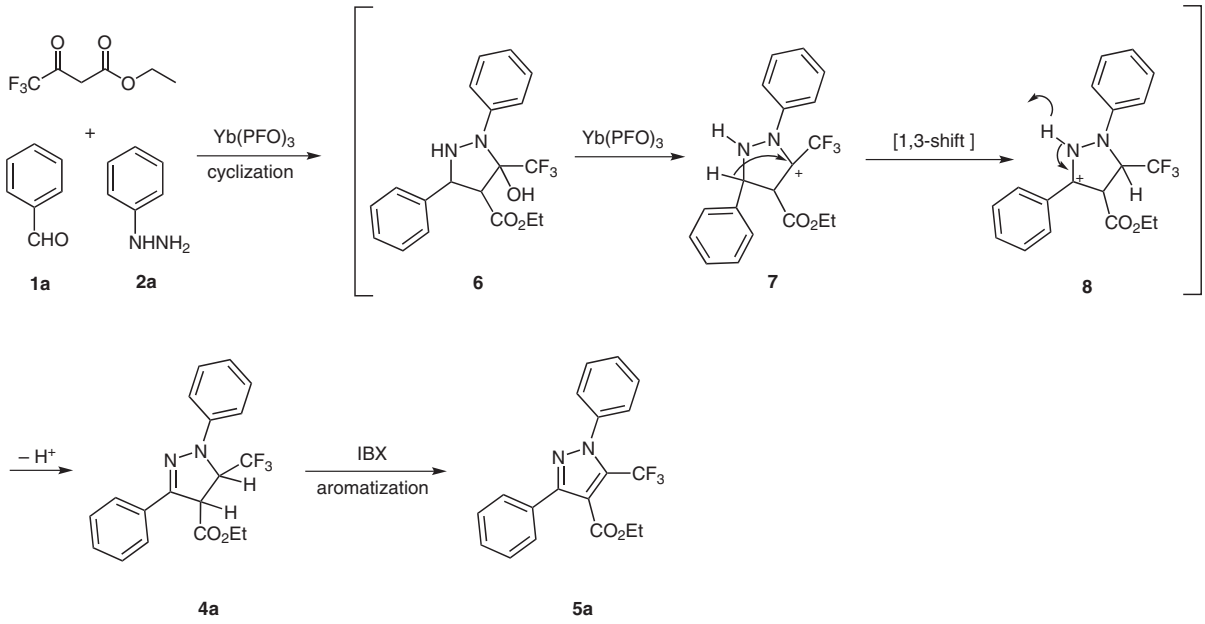


4a

Figure 2 Structure of **4a**

Moreover, heteronuclear (^{1}H–^{13}C) correlation further confirmed the conclusions drawn from the ^{1}H and ^{13}C NMR, and clearly showed coupling between the Ha (δ = 5.05 ppm) and C-5 (δ = 65.6 ppm) and the Hb (δ = 4.50 ppm) and C-4 (δ = 53.1 ppm). The determination of the position of hydrogen atom in the pyrazoline ring should be helpful to understand the mechanism of the reaction.

After the confirmation of the structure of the product, we then envisaged the transformation of the pyrazoline to the corresponding pyrazoles by simply adding a supplementary oxidant in one-pot process without any purification of the crude pyrazoline intermediates **4**. Although a variety of oxidants, such as DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone),[11] Pd/C,[12] $Zr(NO_3)_4$,[13] cobalt soap of fatty acids,[14] MnO_2,[15] trichloroisocyanuric acid[16] and 4-(*p*-chloro)phenyl-1,2,4-triazole-3,5-dione,[17] can be used to oxide pyrazoline, as far as current one-pot reaction system is concerned, a suitable oxidant should be properly screened. Our next efforts focused on the search of a practical oxidant. To achieve this projected transformation, the oxidant has to be stable enough at present reaction temperature (120 °C) and be compatible with the solvent-free conditions. Thus, benzaldehyde, phenylhydrazine, and ethyl trifluoroacetoacetate were chosen as model compounds to accomplish the one-pot, three component



Scheme 2

Table 1 One-Pot Reaction of Benzaldehyde, Phenylhydrazine, and Ethyl Trifluoroacetoacetate Using Different Oxidants

Entry	Oxidant	Oxidant (equiv)	Yield (%)[a]
1	H_2O_2	10	–
2	CAN[b]	2	15.3
3	MnO_2	10	30.1
4	PCC	2.5	50.5
5	IBX	1.5	54.5

[a] Yields were based on GC analysis.
[b] CAN: ceric (IV) ammonium nitrate.

process that involves first cyclization, followed by oxidative aromatization. Several oxidants were used to aromatize the pyrazoline. The results are summarized in Table 1.

Among various oxidants tested, both PCC and IBX gave moderate yield (ca. 50%) of the expected product in the one-pot procedure. Pyridinium chlorochromate (PCC), a chromium-based oxidant, is useful in the research laboratory, but its large-scale use generates toxic heavy-metal waste product. It is not all eco-friendly and often entail severe environment pollution during the process of waste disposal. Even worse, compared with IBX, nearly twice the amount of PCC was required. On the other hand, as a safe, economical, and environmentally friendly oxidizing agent, IBX has attracted increasing interest in organic synthesis in recent years.[18] It is proved that IBX is a versatile oxidizing agent for synthetic organic chemistry. Therefore, we used it as oxidant to perform the aromatization of the pyrazoline.

To investigate the generality of this novel one-pot reaction, we applied this protocol to a variety of aldehydes **1**, and aromatic hydrazines **2**. In the case of aliphatic aldehydes, the reaction proceeded efficiently giving the corresponding pyrazoles in good yield. Aromatic aldehydes produced only moderate yield of pyrazoles irrespective of electronic effects. However, heterocyclic aromatic aldehyde (such as **5e**) yielded only 40% of the desired product. When furan aldehyde and thiophene aldehyde were used, few products were observed. The substituted phenylhydrazine having electron-donating group on the aromatic moiety is favorable for the reaction and afforded pyrazoles in good yield.

A mechanism for the formation of **5**[23,24] is outlined in Scheme 2. Unlike previously proposed mechanisms involving the reaction of the phenylhydrazines, aldehydes, and ethyl acetoacetate[10] and known mechanisms of the condensation of substituted hydrazine with ethyl acetoacetate (or ethyl trifluoroacetoacetate),[19] a novel intermediate, pyrazoline **4**,[20–22] can be isolated in moderate to good yield. The successful isolation of **4** can provide a lot of insight into the mechanism of the reaction. The 5-hydroxyl pyrazolidine **6**, which is formed from the cyclization of hydrazone with enol tautomer of ethyl trifluoroacetoacetate, is converted by the Lewis acid to the carbenium ion **7**. Because of the strong electronic-withdrawing effect of the trifluoromethyl group, this intermediate is unstable and rapidly undergoes a 1,3-proton migration to form relatively stable benzyl carbenium ion **8**, followed by loss of another proton to generate pyrazoline **4**. This key intermediate can be further oxidized and subsequent aromatized to afford the desired product in the presence of IBX.

In summary, a novel one-pot, three-component synthesis of trifluoromethyl-containing pyrazoles via sequential $Yb(PFO)_3$-catalyzed cyclization followed by IBX-mediated oxidation is described. The combination of multicomponent reactions and fluoro-containing building-

block strategy provide an efficient and practical method to the access of fully substituted trifluoromethyl-containing pyrazoles as well as a useful trifluoromethyl-containing pyrazoline synthon.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(20) **Experimental**
All chemicals were purchased commercially and used without further purification. Melting points were measured in open capillary using Büchi melting point B540 apparatus and were uncorrected. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AM-400 spectrometer (400 MHz and 100 MHz, respectively) using TMS as internal standard. The ^{19}F NMR and HMQC spectra were obtained using a Bruker Avance-500 spectrometer (470 MHz), and the ^{19}F NMR spectra were measured with external CF_3CO_2H as the standard. High-resolution mass spectra (HRMS) were recorded under electron-impact conditions using a MicroMass GCT CA 055 instrument.

(21) **General Procedure for the One-Pot Synthesis of Trifluoromethyl-Substituted Pyrazolines**
Aldehydes **1** (1 mmol) and aromatic hydrazines **2** (1 mmol) were stirred for 20 min before ethyl trifluoroacetoacetate (2.5 mmol) and $Yb(PFO)_3$ (0.05 mmol) were added. The mixture was heated at 120 °C for 0.5 h. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to r.t. Dichloromethane (3 mL) was added and then filtered. The filtrate was washed with sat. aq NaCl solution and dried over anhyd Na_2SO_4, filtered, and concentrated under reduced pressure to leave the crude product which was recrystallized by EtOH to give the pure compound. If necessary, the product was purified by chromatography over SiO_2.

(22) **Typical Data for Representative Compound: Ethyl 1,3-Diphenyl-5-trifluoromethyl-Δ^2-pyrazolin-4-carboxylate (4a)**
Yield 70.4%; white solid; mp 82.2–82.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89–7.86 (2 H, m, Ph), 7.45–7.40 (3 H, m, Ph), 7.38–7.29 (4 H, m, Ph), 7.03–6.98 (1 H, m, Ph), 5.05 (1 H, qd, $^3J_{HF}$ = 6.8 Hz, J_{HH} = 3.6 Hz, C*H*CF_3), 4.50 (1 H, d, *J* = 3.6 Hz, 4-*H*), 4.20–4.09 (2 H, m, $CO_2CH_2CH_3$, nonequivalent geminal hydrogens), 1.12 (3 H, t, *J* = 7.2 Hz, $CO_2CH_2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.9, 145.9, 144.7, 130.4, 129.6, 129.1, 128.5, 126.9, 124.4 (q, $^1J_{CF}$ = 281 Hz), 121.5, 114.9, 65.6 (q, $^2J_{CF}$ = 31 Hz), 62.5, 53.1 (d, $^3J_{CF}$ = 1.5 Hz), 13.8. ^{19}F NMR (470 MHz, $CDCl_3$): δ = –76.33 (d, $^3J_{HF}$ = 6.6 Hz). HRMS: *m/z* calcd for $C_{19}H_{17}N_2O_2F_3$ [M$^+$]: 362.1242; found: 362.1242.

(23) **General Procedure for the One-Pot Synthesis of Trifluoromethyl-Substituted Pyrazoles**
Aldehydes **1** (1 mmol) and aromatic hydrazines **2** (1 mmol) were stirred for 20 min before ethyl trifluoroacetoacetate (2.5 mmol) and $Yb(PFO)_3$ (0.05 mmol) were added. The mixture was heated at 120 °C for 0.5 h and stirred for another 10 min after IBX (1.5 mmol) was added. After completion of

the reaction (monitored by TLC), the reaction mixture was cooled to r.t. Dichloromethane (3 mL) was added, and the mixture was passed through a Celite pad, which was successively washed with PE and EtOAc. The filtrate was washed with sat. aq NaCl solution and dried over anhyd Na_2SO_4, filtered, and concentrated under reduced pressure to leave the crude product which was recrystallized by EtOH to give the pure compound. If necessary, the product was purified by chromatography over SiO_2.

(24) **Typical Data for Representative Compound: Ethyl 1,3-Diphenyl-5-trifluoromethyl-1*H*-pyrazole-4-carboxylate (5a)**

Yield 54.5%; white solid; mp 83.1–83.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73–7.71 (2 H, m, Ph), 7.53 (5 H, s, Ph), 7.44–7.42 (3 H, m, Ph), 4.36 (2 H, q, *J* = 7.2 Hz, $CO_2CH_2CH_3$), 1.31 (3 H, t, *J* = 7.2 Hz, $CO_2CH_2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.8, 151.5, 139.0, 132.5 (q, $^2J_{CF}$ = 39 Hz), 131.9, 130.9, 129.8, 129.2, 129.0, 128.4, 125.9, 119.1 (q, $^1J_{CF}$ = 270 Hz), 115.1, 61.9, 13.8. ^{19}F NMR (470 MHz, $CDCl_3$): δ = –56.87. HRMS: *m/z* calcd for $C_{19}H_{15}N_2O_2F_3$ [M^+]: 360.1086; found: 360.1086.