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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

Synthesis of Tetrasubstituted 1*H*-Pyrazoles by Copper-mediated Coupling of Enaminones with Nitriles

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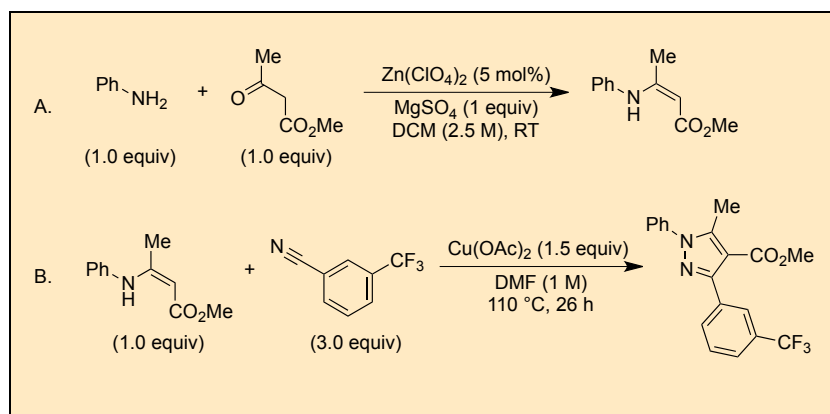
Procedure

A. *(Z)-Methyl 3-(phenylamino)but-2-enoate*.[2] A flame-dried round-bottomed, single-neck flask (capacity: 166 mL, diameter: 45 mm) is equipped with a 3 cm rod-shaped, Teflon-coated magnetic stir bar under an argon atmosphere (Note 1). Zinc perchlorate-hexahydrate ($Zn(ClO_4)_2 \cdot 6H_2O$) (1.6 g, 4.4 mmol, 5 mol%) (Note 2) and magnesium sulfate (10.7 g, 88.5 mmol, 1 equiv) (Note 3) are weighed into the flask under air. Dichloromethane (35 mL, 2.5 M), methyl acetoacetate (9.5 mL, 88.5 mmol, 1.0 equiv) and aniline (8.1 mL, 88.5 mmol, 1.0 equiv) (Note 4) are added via cannula in the respective order into the flask resulting in a white suspension. The flask is tightly closed with a glass stopper and the

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suspension is stirred at room temperature for 24 h (Note 5). Upon completion of the reaction, dichloromethane (20 mL) is added and the resulting mixture is filtered through a short pad of sand (approx. 0.5 cm x 2.5 cm) and Celite (approx. 3 cm x 2.5 cm), prepacked with dichloromethane. The solid is washed thoroughly with dichloromethane (4 × 30 mL) and the combined filtrates are concentrated by rotary evaporation (40 °C water bath, 700-600 mmHg) to obtain a viscous paste (Notes 6 and 7). The crude product was purified by re-crystallization (Note 8) to furnish 13.5–13.6 g (80–81%) of (Z)-methyl 3-(phenylamino)but-2-enoate as colorless needle-shape crystalline solid (Note 9).

B. *Methyl 5-methyl-1-phenyl-3-(3-(trifluoromethyl)phenyl)-1H-pyrazole-4-carboxylate:* A flame-dried, single-necked, 250-mL round bottomed flask is equipped with a 3 cm rod-shaped, Teflon-coated magnetic stir bar under an argon atmosphere (Note 1). Copper(II) acetate (5.40 g, 29.7 mmol, 1.5 equiv) (Note 10) and (Z)-methyl 3-(phenylamino)but-2-enoate (3.80 g, 19.8 mmol, 1.0 equiv) are weighed into the flask under air. *N,N*-Dimethylformamide (19.8 mL, 1.0 M) and 3-(trifluoromethyl)benzonitrile (7.90 mL, 59.4 mmol, 3.0 equiv) (Note 11) are added via cannula into the flask resulting in a blue-green suspension. The flask is tightly closed with a glass stopper and the suspension is stirred in a pre-heated oil bath at 110 °C for 26 h (Note 12). The reaction mixture is allowed to cool to room temperature, EtOAc (20 mL) is added and filtered through a short pad of sand approx. 0.5 cm x 2.5 cm) and Celite (approx. 3 cm x 2.5 cm), prepacked with EtOAc (Note 13). The solid is washed thoroughly with EtOAc (4 × 30 mL) and the combined filtrates are concentrated to approx. 30 mL by rotary evaporation (40 °C water bath, 200-70 mmHg) to provide a blue-green suspension. *N,N*-Dimethylformamide and 3-(trifluoromethyl)benzonitrile were distilled off by Kugelrohr distillation resulting in a blue-green viscous paste (Notes 14, 15, 16 and 7). The crude product is then purified by flash column chromatography (Note 17 and 18). The combined eluent is concentrated by rotary evaporation (40 °C water bath, 700-70 mmHg) and then submitted to high vacuum (0.07 mmHg) overnight at room temperature (Note 19) to furnish 5.60–5.68 g (78–79%) of methyl 5-methyl-1-phenyl-3-(3-(trifluoromethyl)phenyl)-1*H*-pyrazole-4-carboxylate as a white solid (Note 20).

Notes

1. The reaction is less effective in the presence of moisture, presumably due to partial hydrolysis of enaminone, which reduces the yield of the product. With exclusion of moisture, the reaction yields the same amount of product under an atmosphere of either argon or dry air. To obtain dry air after evacuating the flask, the flask is filled with air passed through a guard tube filled with calcium chloride."

2. $Zn(ClO_4)_2 \cdot 6H_2O$ is purchased from Aldrich and used as received.

3. MgSO4 is purchased from Fischer and stored in an oven at 120 °C.

4. Methyl acetoacetate is purchased from Alfa Aesar and used as received. Aniline is purchased from Alfa Aesar, distilled under reduced pressure, and stored in a brown Schlenk bottle (protected from direct sunlight) under an argon atmosphere.

5. The consumption of the starting material was monitored by TLC analysis on Merck silica gel 60 F_{254} plates (0.25 mm, aluminum plate, visualized with 254 nm UV lamp) using 1% Et_3N and 10% ethyl acetate in n-pentane as an eluent. The TLC is pre-treated with a solution of 1% Et_3N in n-pentane and dried (to prevent the hydrolysis of product to starting material). Aniline had an $R_f = 0.19$, methyl acetoacetate had an $R_f = 0.23$ and (Z)-methyl 3-(phenylamino)but-2-enoate had an $R_f = 0.52$ (UV active).

6. GC-MS analysis of the crude material detected only the peak corresponding to the product (t_R =11.2 min (Note 7)) corresponding to the only spot ($R_f = 0.52$) on the TLC plate (n-pentane/ethyl acetate/Et_3N = 90:10:1, UV active).

7. GC-MS spectra were recorded on an Agilent Technologies 7890A GC-system with an Agilent 5975C VL MSD or an Agilent 5975 inert Mass Selective Detector (EI) and a HP-5MS column (0.25 mm × 30 m, Film: 0.25 μm). The major signals are quoted in m/z with the relative intensity in parentheses. The methods used start with the injection temperature T_0; after holding this temperature for 3 min, the column is heated to temperature T_1 (ramp) and this temperature is held for an additional time t: Method: $T_0 = 50$ °C, $T_1 = 290$ °C, ramp = 40 °C/min, t = 4 min.

8. The re-crystallization of the crude product was carried out by dissolving the crude mixture in minimum amount of dichloromethane and then adding n-hexane slowly into the mixture. The resulting turbid solution is kept tightly closed at lower temperature around 4 °C (in

refrigerator) for 24 h. The mixture is allowed to come to room temperature and the needle-shaped colorless crystals are filtered using a filter paper, washed with cold *n*-hexane (2 x 10 mL) and dried *in vacuo*.

9. (*Z*)-Methyl 3-(phenylamino)but-2-enoate has the following physicochemical and spectroscopic properties: R_f = 0.52 (*n*-pentane/ethyl acetate/Et$_3$N = 90:10:1); ^{1}H NMR (400 MHz, CDCl$_3$) δ: 2.00 (s, 3 H), 3.69 (s, 3 H), 4.70 (s, 1 H), 7.07 – 7.14 (m, 2 H), 7.16 (m, 1 H), 7.32 (m, 2 H), 10.35 (br s, 1 H,); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 20.43, 50.39, 85.71, 124.62, 125.14, 129.19, 139.41, 159.24, 170.84; Exact Mass ESI-MS: calculated *m/z* for [C$_{11}$H$_{13}$NO$_2$H]$^+$: 192.1025; found: 192.1018; ATR-FTIR (cm^{-1}): 3249, 3060, 2993, 2952, 1651, 1589, 1483, 1436, 1383, 1356, 1260, 1260, 1056, 1000, 950, 912, 823, 786, 758, 729, 704, 668, 616, 551; Anal calcd for C$_{11}$H$_{13}$NO$_2$: C, 69.09; H, 6.85; N, 7.32; Found: C, 69.06; H, 6.86; N, 7.32; mp = 45.7–47.5 °C.

10. Copper(II) acetate is obtained by heating Cu(OAc)$_2$(H$_2$O), purchased from Aldrich, at 100 °C under high vacuum (approx. 0.1 mmHg) for 60 h with occasional shaking. (Stirring should be avoided to limit the reduction of the particle size.)

11. *N,N*-Dimethylformamide (99.8%) was purchased from Acros and the solvent was stored over activated 4Å molecular sieves under an atmosphere of argon. 3-(Trifluoromethyl)benzonitrile was purchased from Acros and used as received.

12. The consumption of the starting material was monitored by TLC analysis on Merck silica gel 60 F$_{254}$ plates (0.25 mm, aluminum plate, visualized with 254 nm UV lamp) using 10% ethyl acetate in *n*-pentane as an eluent. (Z)-Methyl 3-(phenylamino)but-2-enoate had an R_f = 0.44 (UV active) and methyl 5-methyl-1-phenyl-3-(3-(trifluoromethyl)phenyl)-1*H*-pyrazole-4-carboxylate had an R_f = 0.19 (UV active).

13. A large quantitiy of brown-red metallic precipitate that is typical for Cu^I/Cu^0 species is removed.

14. *N,N*-Dimethylformamide and 3-(trifluoromethyl)benzonitrile were removed from the crude reaction mixture by Kugelrohr distillation. The crude mixture was rotated in a round-bottomed cylindrical bulb and a slow gradient of reduced pressure from 5 mmHg to 0.1 mmHg is applied at 25 °C. The vapors of *N,N*-dimethylformamide and 3-(trifluoromethyl)benzonitrile condensed together in a bulb cooled using a dry ice and acetone bath.

15. The submitters reported that removal of *N,N*-dimethylformamide by an aqueous workup leads to a lower yield of the product (75 vs 81%) presumably due to the loss of the product in the aqueous phase. Thus, Kugelrohr distillation is preferred.

16. GC-MS analysis (Note 7) of the crude material detected only a single peak corresponding to the product (t_R = 10.2 min), corresponding to the only spot (R_f = 0.19) on the TLC plate (*n*-pentane/ethyl acetate = 9:1, UV active).

17. The submitters purchased silica gel (0.040-0.063) from Merck.

18. The crude mixture was dissolved in CH_2Cl_2 (approx. 10 mL), adsorbed on silica (approx. 15 g) and then charged onto a column (diameter = 5 cm, height = 15 cm) of 100 g (300 mL) of silica gel. The column was eluted with a gradient of *n*-pentane/EtOAc = 19:1 (1 L) to 3:2 (3 L) and 40-mL fractions were collected.

19. This represents a convenient way to remove trace impurities of solvents, furnishing analytically pure product as a white solid.

20. Methyl 5-methyl-1-phenyl-3-(3-(trifluoromethyl)phenyl)-1*H*- pyrazole-4-carboxylate (**3ad**) has the following physicochemical and spectroscopic properties: R_f = 0.19 (*n*-pentane/ethyl acetate = 9:1); ^{1}H NMR (400 MHz, CDCl$_3$) δ: 2.60 (s, 3 H), 3.77 (s, 3 H), 7.48 – 7.54 (m, 6 H), 7.63–7.65 (m, 1 H), 7.89 (m, 1 H), 7.98 (m, 1 H); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 12.8, 51.2, 110.5, 124.3 (q, $^1J_{CF3}$ = 270.1 Hz), 125.0 (q, $^3J_{CF3}$ = 3.8 Hz), 125.9, 126.6 (q, $^3J_{CF3}$ = 3.9 Hz), 128.2, 129.0, 129.4, 130.2 (q, $^2J_{CF3}$ = 32.1 Hz), 132.9, 134.0, 138.6, 145.5, 152.2, 164.3; ^{19}F NMR (376 MHz, CDCl$_3$) δ: –62.53 (s, CF$_3$); Exact Mass ESI-MS: calculated *m/z* for $[C_{19}H_{15}F_3N_2O_2H]^+$: 361.1164, found: 361.1158; ATR-FTIR (cm^{-1}): 3065, 2951, 2362, 1710, 1597, 1540, 1502, 1417, 1322, 1255, 1166, 1069, 995, 808, 766, 701, 684, 662; Anal calcd for $C_{19}H_{15}F_3N_2O_2$: C, 63.33; H, 4.20; N, 7.77; Found: C, 63.31; H, 4.35; N, 7.82; mp = 103.1–104.9 °C.

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Discussion

Pyrazoles belong to an important class of heterocycles. Although rarely found in natural products, they are motifs of many biologically important compounds such as Celecoxib, Sildenafil and Fipronil.[3] The classical methods for the syntheses of the pyrazole moiety involve either the condensation of hydrazine derivatives with 1,3-dicarbonyl compounds, the 1,3-dipolar [3 + 2] cycloadditions or C–N and/or C–C cross coupling of the preformed pyrazoles.[4] However, these methods face synthetic limitations owing to either the use of carcinogenic hydrazines, generation of regioisomeric mixtures of products and/or the limited substrate scope.

Recently, we have developed an efficient and highly modular synthesis of tetrasubstituted pyrazoles by copper-mediated coupling of enaminones and nitriles via an oxidative C-C/N-N bond formation cascade.[5] From the optimized reaction conditions, it was found that $Cu(OAc)_2$ is required for this transformation, the reaction is sensitive to moisture, however, the reaction can be run conveniently under an atmosphere of air (or argon) in good yields.

Initially, the substrate scope of the reaction was studied using nitrile as the solvent for the synthesis of pyrazoles, limiting this method to the use of liquid nitriles only. Later, using *N,N*-dimethylformamide as the solvent, the amount of the nitriles can be reduced. Under the optimized reaction conditions, the substrate scope has been found to be impressively broad. With (*Z*)-methyl 3-(phenylamino)but-2-enoate (**1a**) as the coupling partner, various nitriles - aromatic, heteroaromatic as well as aliphatic nitriles - can be coupled in good yields (**3aa-3ao**). However, for aliphatic nitriles the reaction is comparatively more efficient under neat reaction conditions
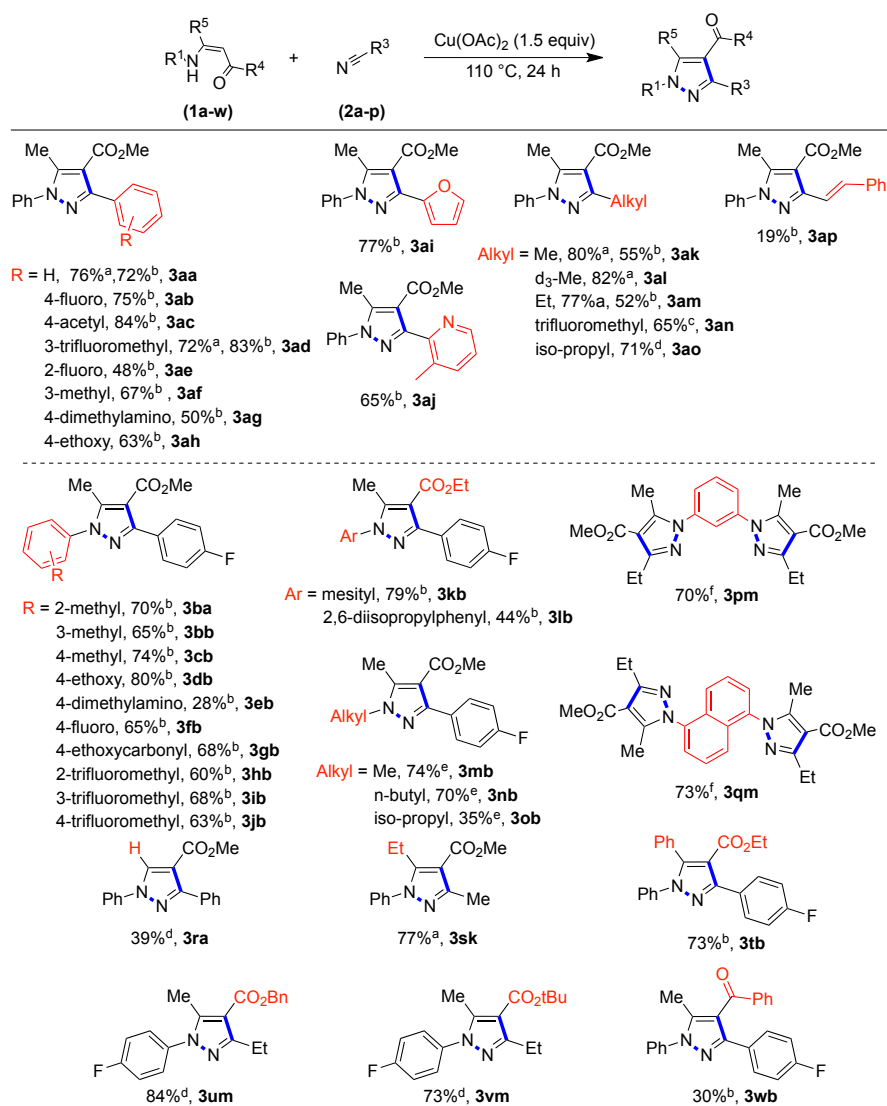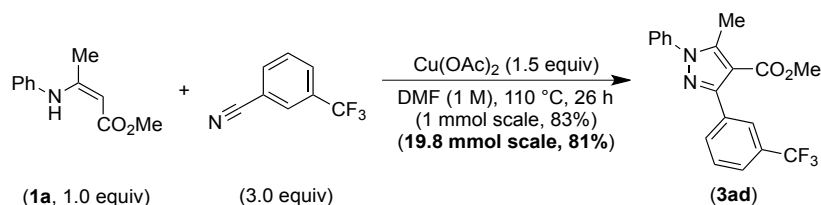
Scheme 1. Copper-mediated coupling of enaminones with nitriles. Reactions were run on a 1 mmol scale.[5] [a]**1** (1.0 equiv), Cu(OAc)$_2$ (1.5 equiv) and **2** (0.66 M), 110 °C, 24 h, air (closed tube). [b]**1** (1.0 equiv), Cu(OAc)$_2$ (1.5 equiv), **2** (3.0 equiv) and *N,N*-dimethylformamide (1 M), 110 °C, 24 h, air (closed tube). [c]Reaction conditions (B) after adding all the reagents and the solvent to a Schlenk tube (10 mL, 0.5 mmol scale), the tube was evacuated at 0 °C and then refilled with trifluoroacetonitrile gas. [d]Same as (A), **2** (0.33 M). [e]Same as (B), **2** (7.0 equiv) and *N,N*-dimethylacetamide (1 M). [f]**1** (1.0 mmol), Cu(OAc)$_2$ (6.0 equiv) and **2** (6.0 mL), 120 °C, 24 h, air (closed tube).

(**3ak**-**3ao**). To our delight, the gaseous nitrile trifluoroacetonitrile has also been coupled in good yield (**3an**). A styryl group can also be introduced at the 3-position of the pyrazole moiety, allowing further modifications at this position (**3ap**).

With 4-fluorobenzonitrile as the coupling partner the scope of the reaction with respect to the enaminone was studied. At 1-position of pyrazole moiety, various electron-rich as well as electron-poor groups bearing different functional groups were well tolerated (**3ba**-**3wb**). The sterically demanding groups such as mesityl and diisopropylphenyl could also be introduced in good yield (**3kb** and **3lb**). In addition to this, aliphatic substituents at R^1 position provided product in good yield (**3mb** and **3ob**). Bis-pyrazoles derivatives can also be obtained in good yield (**3pm** and **3qm**). The substituents at the 5-position of pyrazole products can also be varied from alkyl, aryl to hydrogen (**3pm** and **3qm**). R^4 can be varied providing pyrazole esters and ketone (**3aa**-**3wb**).

While studying the practicality and applicability of this efficient and modular transformation, the reaction was carried out on a 20 mmol scale. For the reaction conditions using *N,N*-dimethylformamide as the solvent, the reaction can be carried out at a 19.8 mmol scale, with **1a** and 3-(trifluoromethyl)benzonitrile (**2d**) as the coupling partner providing 79% yield of the product (as compared to 83% obtained on a 1 mmol scale), after elongating the reaction time to 26 h and distilling off excess of *N,N*-dimethylformamide and 3-(trifluoromethyl)benzonitrile by Kugelrohr distillation.

Scheme 2. Copper-mediated synthesis of tetrasubstituted pyrazole

In conclusion, we have developed an efficient and modular synthesis of pyrazoles by copper-mediated coupling of enaminones with nitriles with high regioselectivity and broad substrate scope. The convenient up-scaling of the reaction to 20 mmol scale shows the practicality of this transformation and its applicability in organic synthesis.

References

1. Organisch-Chemisches Institut der Westfälischen Wilhelms-Universität Münster, Corrensstrasse 40, 48149 Münster (Germany), E-mail: glorius@uni-muenster.de. The Int. NRW Graduate School of Chemistry (M.S.) and the European Research Council (ERC) under the European Community's Seventh Framework Program (FP7 2007-2013)/ERC grant agreement no. 25936 are gratefully acknowledged for financial support.
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Appendix
Chemical Abstracts Nomenclature (Registry Number)

Zinc perchlorate hexahydrate; (10025-64-6)
Magnesium sulfate; (7487-88-9)
Methyl acetoacetate; (105-45-3)
Aniline; (62-53-3)
(*Z*)-Methyl 3-(phenylamino)but-2-enoate; (4916-22-7)
Copper(II) acetate monohydrate; (6046-93-1)
Copper(II) acetate, anhydrous; (142-71-2)
Methyl 5-methyl-1-phenyl-3-(3-(trifluoromethyl)phenyl)-1*H*-pyrazole-4-carboxylate; (1259438-02-0)
N,*N*-Dimethylformamide; (68-12-2)
3-(Trifluoromethyl)benzonitrile; (368-77-4)

Frank Glorius was educated in chemistry at the Universität Hannover, Stanford University (Prof. Paul A. Wender), Max-Planck-Institut für Kohlenforschung and Universität Basel (Prof. Andreas Pfaltz) and Harvard University (Prof. David A. Evans). In 2001 he began his independent research career at the Max-Planck-Institut für Kohlenforschung in Germany (Mentor: Prof. Alois Fürstner). In 2004 he became Assoc. Prof. at the Philipps-Universität Marburg and since 2007 he is a Full Prof. for Organic Chemistry at the Westfälische Wilhelms-Universität Münster, Germany. His research program focuses on the development of new concepts for catalysis and their implementation in organic synthesis.

Mamta Suri obtained her bachelor's degree in chemistry in 2007 from St. Stephen's College at University of Delhi (India). She moved to Indian Institute of Technology Guwahati (India) and completed her master's degree (2009) in the group of Prof. T. Punniyamurthy there. She then joined the group of Prof. F. Glorius at Westfälische Wilhelms-Universität Münster (Germany) in the Int. NRW Graduate School of Chemistry, where she obtained her doctoral degree in April 2013. Currently, she is working at BASF SE at Ludwigshafen, Germany.

Lan-Ting Xu received her BS degree from West China School of Pharmacy, Sichuan University in 2008, and her Ph.D. degree from Fudan University in 2013, under the supervision of Dawei Ma. She is now a MSD China R&D Postdoc Research Fellow in Shanghai Institute of Organic Chemistry. Her research interests include copper-catalyzed coupling reactions, metal-catalyzed direct C-H functionalization and heterocycle synthesis.

(Z)-Methyl 3-(phenylamino)but-2-enoate
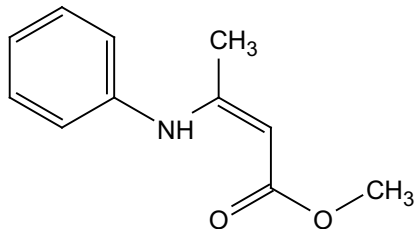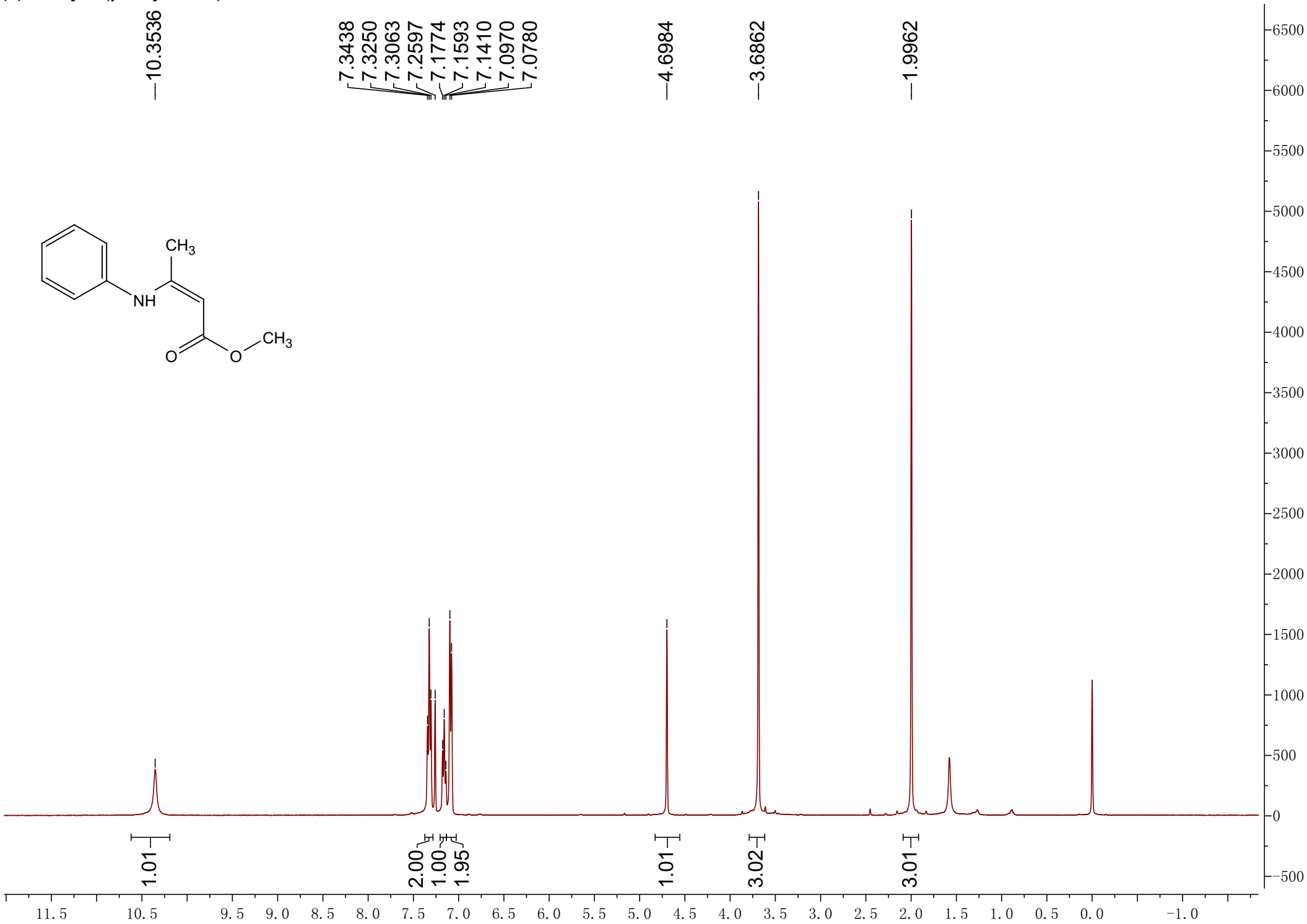
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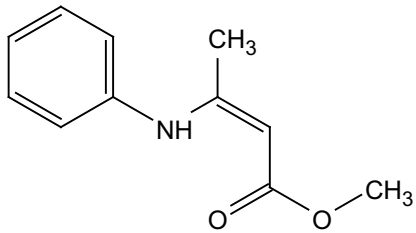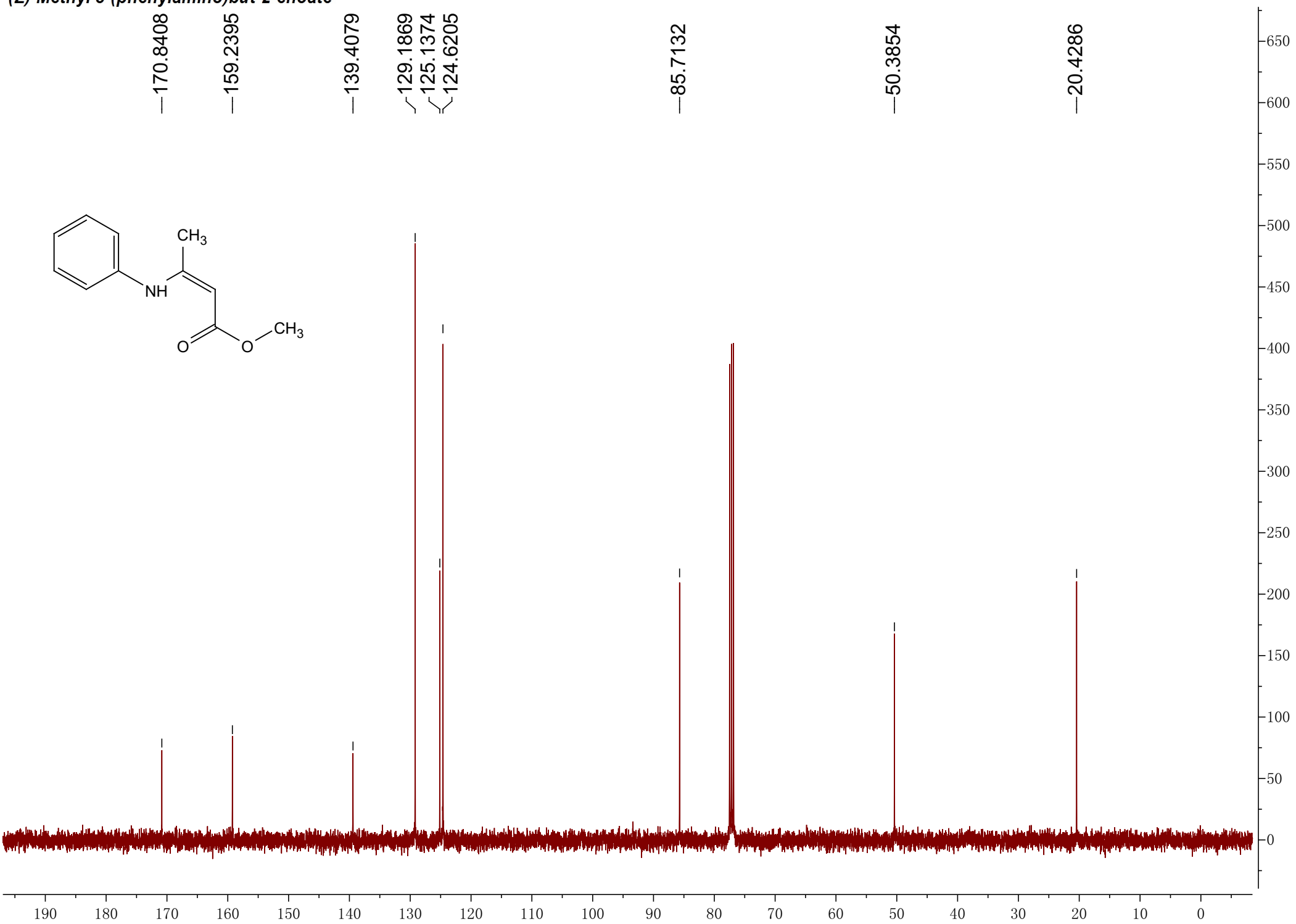
5-methyl-1-phenyl-3-(3-(trifluoromethyl)phenyl)-1H- pyrazole-4-carboxylate

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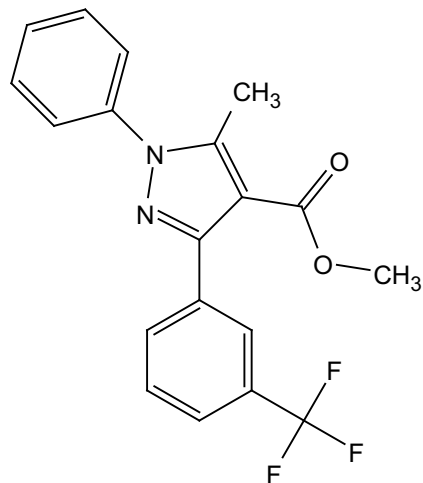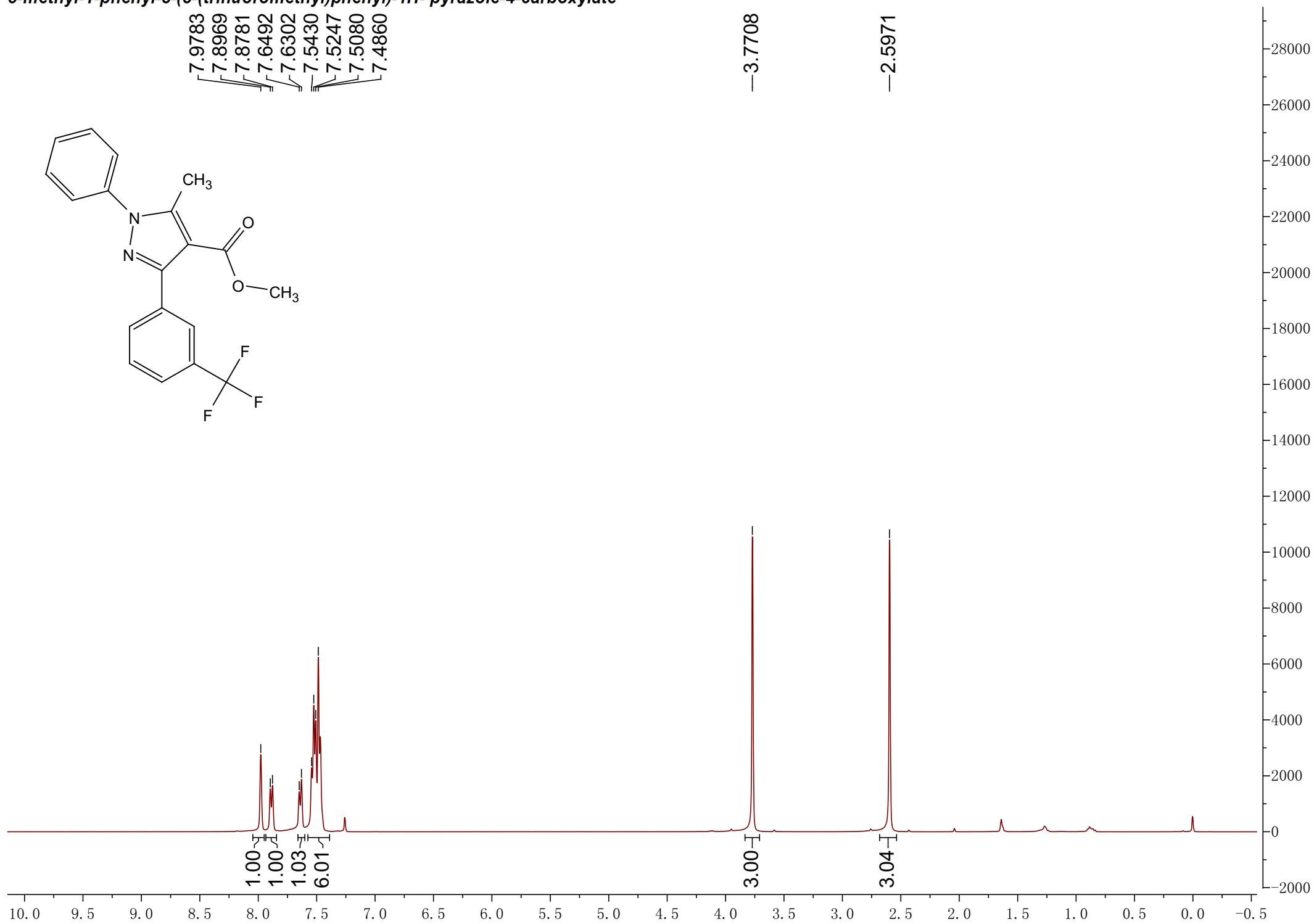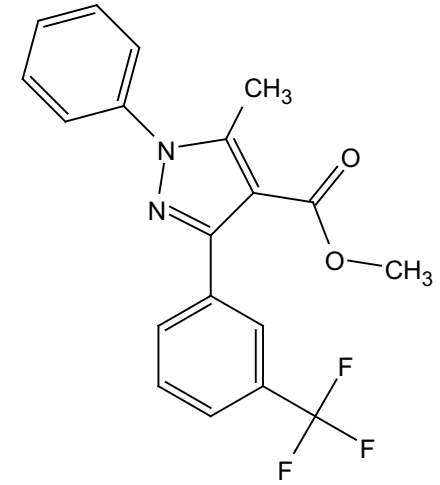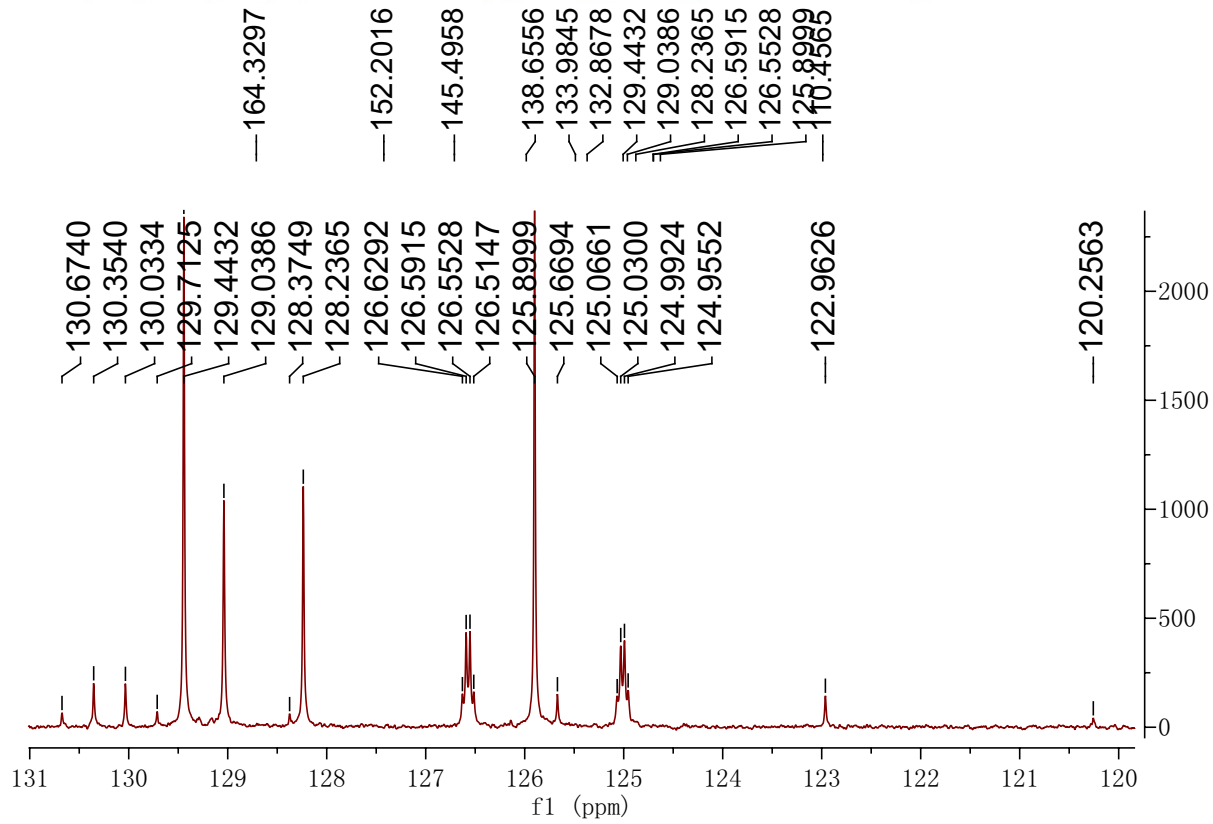
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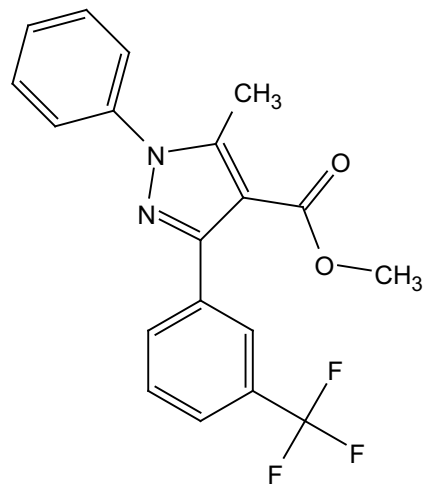
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5-methyl-1-phenyl-3-(3-(trifluoromethyl)phenyl)-1H- pyrazole-4-carboxylate

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