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Use of polyfunctionalized ethylene synthons: Convenient synthesis of biologically active trifluoromethyl containing N-substituted-benzoylpyrazoles and triazole

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Ten biologically active trifluoromethyl containing N-substituted-benzoylpyrazoles (**3a-d**, **4a-d**, and **6a, b**) and one triazole analogue **5** have been conveniently synthesized from four versatile polyfunctionalized ethylene synthons and one novel synthon N-cyanoimido-S,S- dimethyldithio-carbonate (CIDT, **v**), respectively. The reactions of trifluoromethyl containing substituted benzoylhydrazine with classical synthons such as ethyl dimethylaminomethylene- malonate, acetylacetone and ethyl acetoacetate have also been investigated. Herbicidal, fungicidal and plant-growth regulation activities for all reported new compounds have been determined and reported.

Key Words: biological activity, pyrazole, triazole, synthon, synthesis

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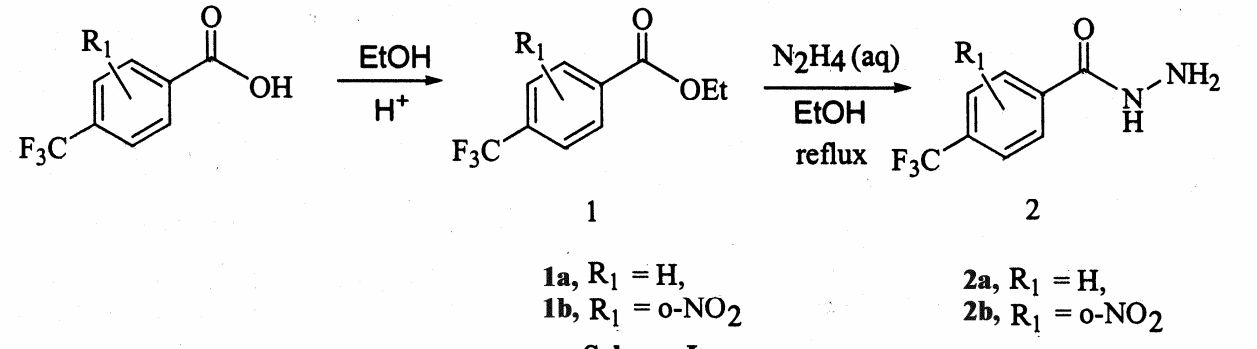
The synthesis, structure and biological activities of pyrazole and triazole derivatives have long been the focus of research interests in the fields of medicine, food and agriculture, due to the various and potent biological activities exhibited by them[1-4]. Therefore, a variety of methods have been elaborated for the synthesis of these classes of heterocycles. New challenging problems in plant protection have promoted research to discover more efficient pesticides, among which pyrazole and triazole derivatives play an important role. To the best of our knowledge, the substituents at the N-position of pyrazole and triazole rings are mainly alkyl and aryl groups, and our interest now focuses on such previously seldom reported pyrazoles and triazoles that there are benzoyl groups attached to the N atom of these frameworks, namely the N-benzoylated ones, with great expectation to find biologically active lead compounds. To improve the possibility of this goal, we employed two trifluoromethyl containing starting materials, *p*-trifluoromethyl-benzoylhydrazine **2a** and *o*-nitro-*p*-trifluoromethylbenzoylhydrazine **2b**, prepared from the corresponding acids through a conventional two-step approach (**Scheme I**). The introduction of trifluoromethyl group into molecules has become increasingly significant, because the incorporation of this functional group has frequently generated much more activity than that of the parent compounds[5-9].

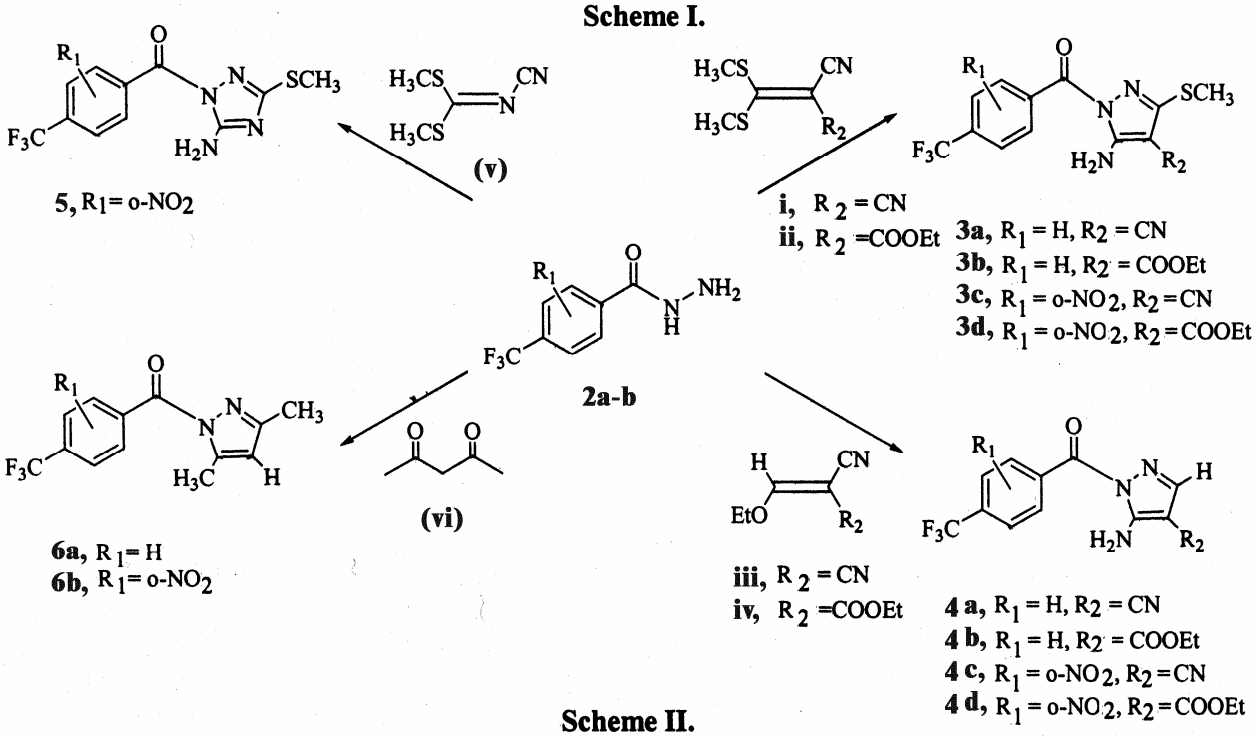
Results and Discussions

A number of versatile polyfunctionalized ethylene synthons have been employed to build the reported triazole and pyrazoles through the reactions with aforementioned compounds **2a, b**, and they were: dimethylthiomethylenemalononitrile[10,11] (**i**), ethyl dimethylthiomethylenecyanoacetate[11,12] (**ii**), ethoxy-methylenemalononitrile[13-16] (**iii**), ethyl ethoxy-methylenecyanoacetate[13,16,17] (**iv**) (**Scheme II**), and ethyl dimethylaminomethylenemalonate[18] (**vii**) (**Scheme III**). However, the isolated products **7a, b** from ethyl dimethylaminomethylenemalonate have been unambiguously identified as the uncyclized compounds, and so far all our attempts to cyclize them have been unsuccessful, and further attempts have not been carried out.

To extend the utility of the trifluoromethyl containing substituted-benzoylhydrazine **2a, b**, the reaction of **2b** with a novel synthon, N-cyanoimido-S,S-dimethyldithiocarbonate (CIDT) [19-21], has been studied, producing the expected compound **5**. Also, conventional synthons, such as acetylacetone (**vi**) and



Scheme I.



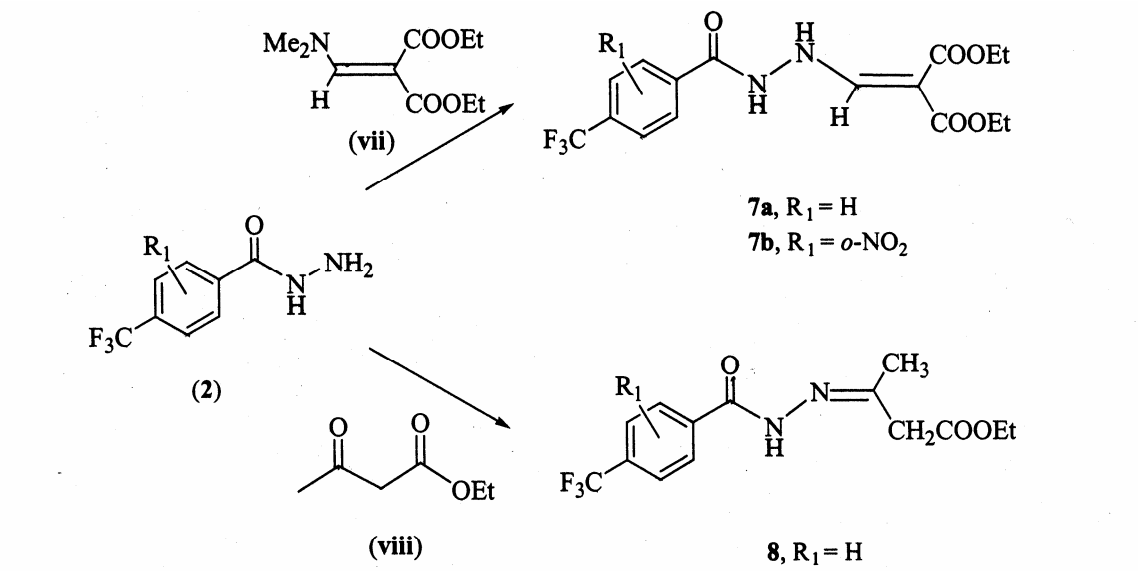
Scheme II.

ethyl acetoacetate (**viii**), have been also used to extend the utility of trifluoromethyl containing **2a,b** in the construction of pyrazoles (**Scheme II** and **Scheme III**). As described for **vii**, the procedure employing **viii** yielded uncyclized product **8**. Given the spontaneous cyclization occurring in the reactions involving the other synthons, especially those involving **viii**, we preliminarily concluded that the challenging cyclization reactions could be attributed to the absence of effective conjugated system in the cyclized products **9a, b** and **10** as existed in the products in other cases (**Scheme IV**).

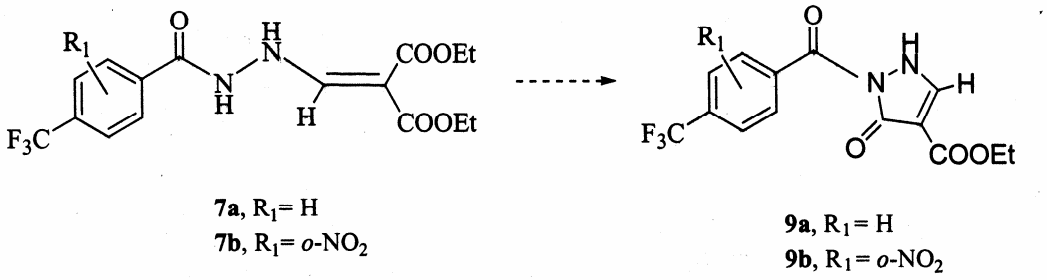
The reactions between **2** and the aforementioned synthons **i-v** proceeded highly regioselectively, with the other isomer being undetectable or ignorable in each case (**Scheme V**; using synthon **i** as example). The determination of the structure of the regiomer was based on earlier reports[10,15,22].

An alternative route to the reported molecules has initially been conceived (**Scheme VI**; using synthon **i** as example); however, further considerations and experiments favoured the route as described in **Scheme I** and **Scheme II**, since the benzoyl chlorides **2-1a-b** do not always react with 1*H*-pyrazole (**ix**) regioselectively, yielding a mixture of unidentified compounds.

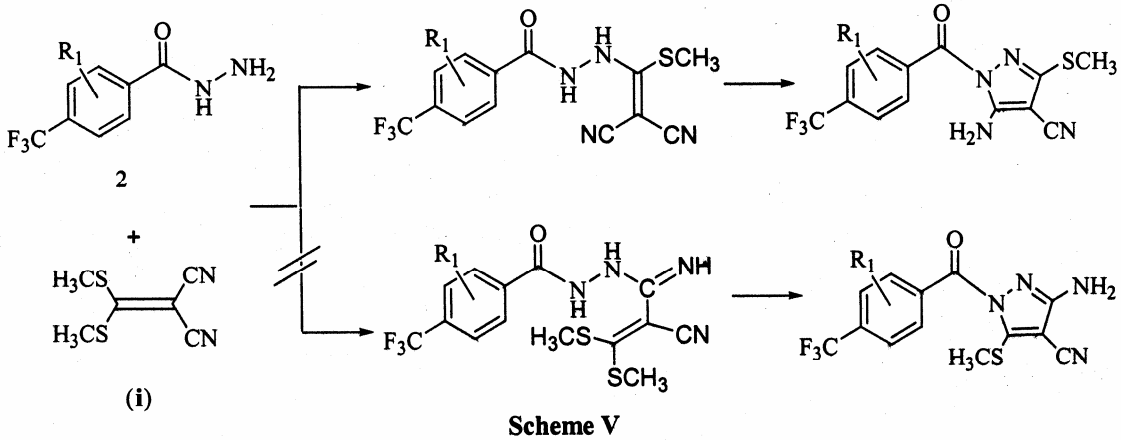
Preliminary biological tests showed that compounds **4a**, **4c** and **8** showed reasonable herbicidal activity against the model herb *Brassica napus* at the concentration of 100 μg/mL, with the inhibition rates reaching 72.3%, 77.1% and 61.8%, respectively. Nonetheless, the test results for fungicidal and plant-growth regulation activities are unsatisfactory, and none of the inhibition rates could reach 50% at the 100 μg/mL.



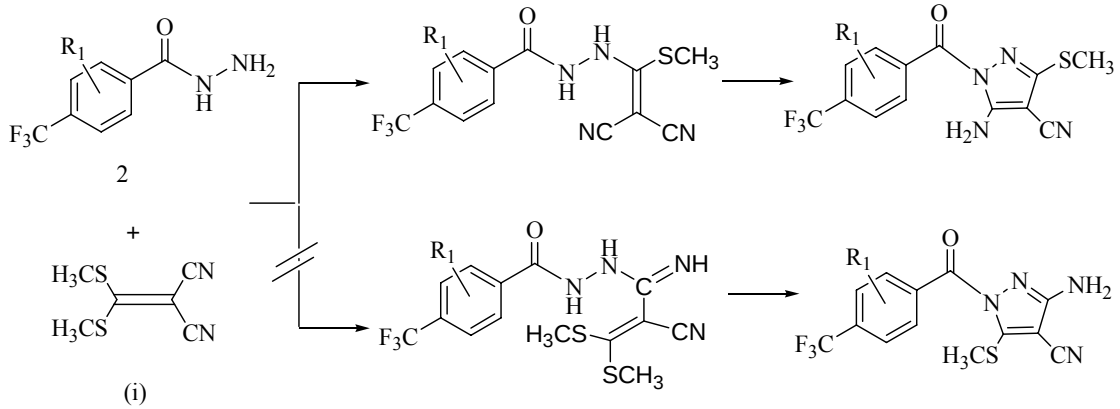
Scheme III



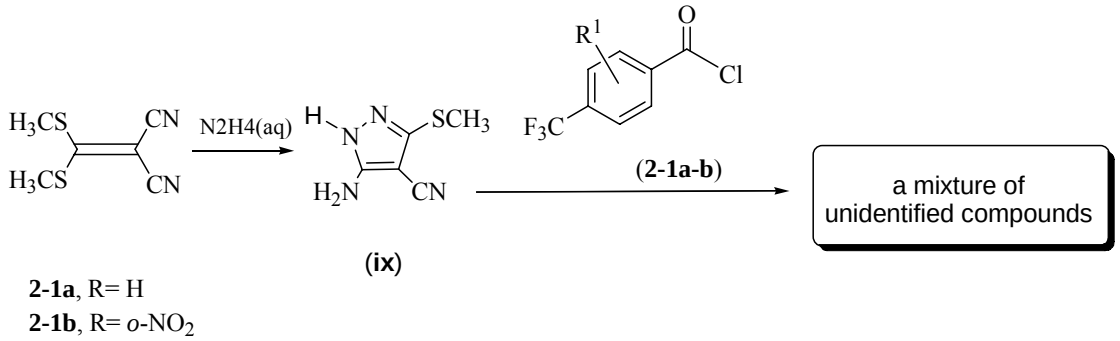
Scheme IV



Scheme V



Scheme V.



2-1a, R= H
2-1b, R= *o*-NO_2

Scheme VI.

In conclusion, we have synthesized a novel class of trifluoromethyl containing 1-substituted- benzoyl-pyrazoles, which have been seldom reported previously, from several polyfunctionalized ethylene synthons. The regioselectivity, an alternative pathway and the biological activities have been also reported.

Experimental Section

All melting points were determined with a RY-1 apparatus in capillaries and are uncorrected. IR spectra were recorded on a 501P FT-IR spectrometer as KBr pellets; ^{1}H NMR spectra on a Jeol JNM-ECP 600M or a BRUKER AC-300 spectrometer, using DMSO-d_6 or $CDCl_3$ as solvent and TMS as internal standard (chemical shifts in δ, ppm, and coupling constants (*J*) in the unit of Hz); mass spectra were recorded on a HP 5988 spectrometer employing electron impact technique at 70 eV. Elemental analyses were performed with a Yanaco MT-3 CHN analyzer. Thin Layer Chromatography (TLC; the TLC plates were coated with Silica Gel 60, 200-300 mesh, obtained commercially from Qingdao Haiyang Chemical Co., Ltd.) was used to trace the course of reactions and ascertain the purities of the products, and the detection of components was made by exposure to ultraviolet light (254 nm or 365 nm). Column chromatography (elution from silica gel, 60-100 mesh) was performed when necessary to purify the final products.

General procedure. Equal equivalents (5 mmoles) of **2a-b** and synthons **i-viii** were dissolved in suitable solvent (20 mL; absolute ethanol for **i-iv** and **vi-viii**, and acetonitrile for **v**. A few drops of conc. HCl were necessary in the case of **vi**, and the resulting solution was stirred at a specific temperature (ambient temperature for **i-iii**, and reflux for the other synthons) for a specific time period (6-10hr), until the complete consumption of the reactants as monitored by TLC. On cooling to room temperature, the products crystallized out which were recrystallized from a suitable solvent or chromatographed (in the case of **vi**) using pet.ether-ethyl acetate (3:2).

5-Amino-4-cyano-3-methylthio-1- (*p*-trifluoro-methylbenzoyl)pyrazole 3a: White needles, yield 79%, m.p. 239-41 ºC; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.22, 7.75 (dd, 4H, Ph-H), 6.62 (s, 2H, NH_2), 2.50 (s, 3H, SCH_3); IR (KBr): 3401, 3307, 2224, 1700 cm^{-1}. Anal. Calcd for $C_{13}H_9F_3N_4OS$: C, 47.85; H, 2.78; N, 17.18. Found: C, 47.75; H, 2.77; N, 17.20 %.

Ethyl 5-amino-3-methylthio-1-(*p*-trifluoromethyl-benzoyl)pyrazole-4-carboxylate 3b: Yellow powder; yield 58%, m.p. 134-36 ºC; ^{1}H NMR ($CDCl_3$, 600

MHz): δ 8.25, 7.74 (dd, 4H, Ph-H), 6.65 (s, 2H, NH_2), 4.34 (q, 2H, CH_2, J = 7.5 Hz), 2.41 (s, 3H, SCH_3), 1.38 (t, 3H, CH_3, J = 7.5 Hz); IR (KBr): 3455, 3329, 1716, 1674 cm^{-1}. Anal. Calcd for $C_{15}H_{14}F_3N_3O_3S$: C, 48.25; H, 3.78; N, 11.26. Found: C, 48.18; H, 3.75; N, 11.20 %.

5-Amino-4-cyano-3-methylthio-1-(*o*-nitro-*p*-trifluoromethylbenzoyl)pyrazole 3c: Yellow solid, yield 88%, m.p. 239-40 ºC; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.46-8.52 (m, 3H, Ph-H), 6.70 (s, 2H, NH_2), 2.58 (s, 3H, SCH_3); IR (KBr): 3419, 3307, 2225, 1693 cm^{-1}. Anal. Calcd for $C_{13}H_8F_3N_5O_3S$: C, 42.05; H, 2.17; N, 18.87. Found: C, 42.00; H, 2.15; N, 18.84 %.

Ethyl 5-amino-3-methylthio-1-(*o*-nitro-*p*-trifluoromethylbenzoyl)pyrazole-4-carboxylate 3d: Yellow powder, yield 65%, m.p. 140-42 ºC; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.83, 8.03, 8.42 (2d+s, 1H each, Ph-H, J = 8.1 Hz), 6.62 (s, 2H, NH_2), 4.34 (q, 2H, CH_2, J = 7.6 Hz), 2.48 (s, 3H, SCH_3), 1.37 (t, 3H, CH_3, J = 7.6 Hz); IR (KBr): 3483, 3361, 1716, 1674 cm^{-1}. Anal. Calcd for $C_{15}H_{14}F_3N_4O_5S$: C, 42.95; H, 3.37; N, 13.37. Found: C, 42.99; H, 3.35; N, 13.42 %.

5-Amino-4-cyano-1-(*p*-trifluoromethylbenzoyl)-pyrazole 4a: White needles, yield 66%, m.p. 199-201 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.16, 7.78 (dd, 4H, Ph-H), 7.60 (s, 1H, pyrazole-H); 6.63 (s, 2H, NH_2); IR (KBr): 3408, 3306, 2225, 1692 cm^{-1}. Anal. Calcd for $C_{12}H_7F_3N_4O$: C, 51.42; H, 2.52; N, 20.00. Found: C, 51.49; H, 2.50; N, 20.05 %.

Ethyl 5-amino-1-(*p*-trifluoromethylbenzoyl)pyrazole-4-carboxylate 4b: White solid, yield 68%, m.p. 118-20 ºC; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.19, 7.78 (dd, 4H, Ph-H), 7.77 (s, 1H, pyrazole-H), 6.66 (s, 2H, NH_2), 4.34 (q, 2H, CH_2, J = 7.5 Hz), 1.39 (t, 3H, CH_3, J = 7.5 Hz); IR (KBr): 3460, 3343, 1716, 1719, 1674 cm^{-1}. Anal. Calcd for $C_{14}H_{12}F_3N_3O_3$: C, 51.36; H, 3.70; N, 12.84. Found: C, 51.30; H, 3.72; N, 12.89 %.

5-Amino-4-cyano-1-(*o*-nitro-*p*-trifluoromethylbenzoyl)pyrazole 4c: Yellow solid, yield 73%, m.p. 202-04 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.51, 8.10, 7.80 (s+2d, 1H each, Ph-H, J = 8.0 Hz), 7.44 (s, 1H, pyrazole-H), 6.70 (s, 2H, NH_2); IR (KBr): 3302, 3226, 2225, 1719 cm^{-1}. Anal. Calcd for $C_{12}H_6F_3N_5O_3$: C, 44.30; H, 1.86; N, 21.54. Found: C, 44.35; H, 1.89; N, 21.59 %.

Ethyl 5-amino-1-(*o*-nitro-*p*-trifluoromethylbenzoyl)pyrazole-4-carboxylate 4d: Yellow powder, yield 58%, m.p. 153-155 ºC; ^{1}H NMR (DMSO-d_6, 600 MHz): δ 8.18, 8.40, 8.57 (2d+s, 1H each, Ph-H, J = 8.0 Hz), 7.70 (s, 1H, pyrazole-H), 7.20 (s, 2H, NH_2), 4.30 (q, 2H, CH_2, J = 7.6 Hz),; 1.26 (t, 3H, CH_3, J = 7.6 Hz); IR (KBr): 3463, 1719, 1683 cm^{-1}. Anal. Calcd for $C_{14}H_{12}F_3N_4O_5$: C, 45.03; H, 3.24; N, 15.01. Found: C, 45.09; H, 3.21; N, 15.06 %.

5-Amino-3-methylthio-1-(*o*-nitro-*p*-trifluoromethylbenzoyl)triazole 5: Yellow crystal, yield 77%, m.p. 201-03 ºC; ^{1}H NMR (DMSO-d_6, 600 MHz): δ 8.54 (s, 1H, Ph-H), 8.37 (d, 2H, Ph-H, J = 8.1 Hz), 7.99 (s, 2H, NH_2), 2.50 (s, 3H, SCH_3); IR (KBr): 3155, 1542, 1344 cm^{-1}. Anal. Calcd for $C_{11}H_8F_3N_5O_3S$: C, 38.04; H, 2.32; N, 20.18. Found: C, 38.12; H, 2.30; N, 20.11 %.

3,5-Dimethyl-1-(*p*-trifluoromethylbenzoyl)pyrazole 6a: Colorless crystals, yield 81%, m.p. 44-46 ºC; ^{1}H NMR (DMSO-d_6, 600 MHz): δ 8.00, 7.73 (dd, 4H, Ph-H), 6.09 (s, 1H, pyrazole-H), 2.65, 2.24 (2s, 3H each, CH_3): IR (KBr): 1704 cm^{-1}. Anal. Calcd for $C_{13}H_{11}F_3N_2O$: C, 58.19; H, 4.14; N, 10.45. Found: C, 58.10; H, 4.16; N, 10.49 %. MS: m/z 268 (M^+).

3,5-Dimethyl-1-(*o*-nitro-*p*-trifluoromethylbenzoyl)pyrazole 6b: White crystals, yield 66%, m.p. 105-06 ºC, ^{1}H NMR (DMSO-d_6, 600 MHz): δ 8.46, 8.05, 8.03 (s+2d, 1H each, Ph-H, J = 8.2 Hz), 6.06 (s, 1H, pyrazole-H), 2.72, 2.09 (2s, 3H each, CH_3); IR (KBr): 1722 cm^{-1}. Anal. Calcd for $C_{13}H_{10}F_3N_3O_3$: C, 49.83; H, 3.22; N, 13.42. Found: C, 49.80; H, 3.25; N, 13.40%.

Ethyl [(*p*-trifluoromethylbenzoylhydrazino)-methylene]malonate 7a: White powder, yield 85%, m.p. 163-65 ºC; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 11.56, 10.25 (2s, 1H each, 2NH), 8.32, 8.02 (dd, 2H each, Ph-H), 7.96 (s, 1H, =CH), 4.18 (q, 2H, CH_2, J = 7.2 Hz), 4.10 (q, 2H, CH_2, J = 7.5 Hz), 1.23 (m, 6H, $2CH_3$); IR (KBr): 3299, 3203, 1708, 1672, 1638 cm^{-1}. Anal. Calcd for $C_{16}H_{17}F_3N_2O_5$: C, 51.32; H, 4.58; N, 7.49. Found: C, 51.39; H, 4.60; N, 7.56 %.

Ethyl [(*o*-nitro-*p*-trifluoromethylbenzoylhydrazino)methylene]malonate 7b: White powder, yield 81%, m.p. 139-41 ºC; ^{1}H NMR (DMSO-d_6, 600 MHz): δ 10.1, 8.68 (2s, 1H each, 2NH), 8.52 (s, 1H, Ph-H), 8.02 (s, 1H, =CH), 7.97, 7.77 (dd, 1H each, Ph-H, J = 8.3 Hz), 4.28 (q, 2H, CH_2, J = 7.2 Hz), 4.18 (q, 2H, CH_2, J = 7.5 Hz), 1.35 (t, 3H, CH_3, J = 7.2 Hz), 1.28 (t, 3H, CH_3, J = 7.5 Hz); IR (KBr): 3168, 1719, 1652, 1639 cm^{-1}. Anal. Calcd for $C_{16}H_{16}F_3N_3O_7$: C, 45.81; H, 3.85; N, 10.02. Found: C, 45.89; H, 3.89; N, 10.09%.

Ethyl acetoacetate *p*-trifluoromethylbenzoylhydrazone 8: White powder, yield 71%, m.p. 113-15 ºC; ^{1}H NMR (DMSO-d_6, 600 MHz): δ 10.82 (s, 1H each, NH), 8.00, 7.71 (dd, 2H each, Ph-H, J = 8.0 Hz), 4.27 (q, 2H, CH_2, J = 7.6 Hz), 3.45 (s, 2H, =C-

CH_2), 2.11 (s, 3H, CH_3), 1.30 (t, 3H, CH_3, J = 7.6 Hz); IR (KBr): 3231, 1739, 1661, 1614 cm^{-1}. Anal. Calcd for $C_{14}H_{16}F_3N_2O_3$: C, 52.98; H, 5.09; N, 8.83. Found: C, 52.90; H, 5.07; N, 8.89 %.

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