SHORT PAPER

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Synthesis of trifluoromethyl heterocyclic compounds †

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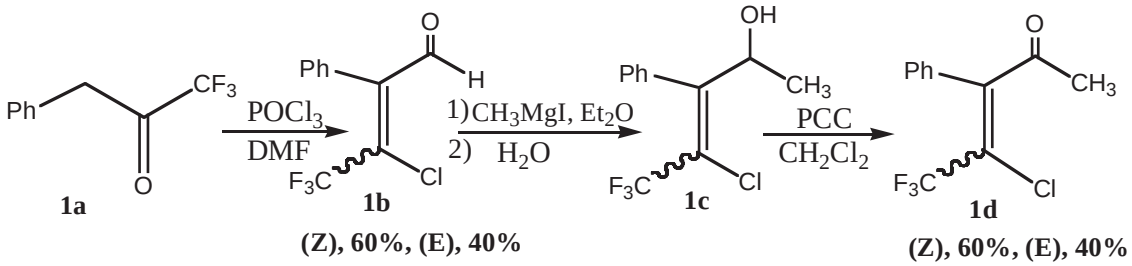
The synthesis of trifluoromethyl pyrazoles, 1,5-benzodiazepines, and 1,5-benzothiazepines is described. The regiochemistry of the pyrazole synthesis was investigated using 2D NMR methods.

Keywords: trifluoromethyl compounds, pyrazoles, 1,5-benzodiazepines, 1,5-benzothiazepines



Scheme 1

Heterocyclic compounds bearing a trifluoromethyl group are one of the most important classes of organofluorocompounds. They play a distinctive role in organic synthesis, in medicine and in agriculture [1–10] and they exhibit frequently biological activities.[11–15] As a continuation of our research program focused on the synthesis and the reactivity study of fluoromethylated derivatives prepared from Vilsmeier methods,[16–18] we report in this paper a straightforward access to the trifluoromethyl heterocyclic compounds **2**, **4** and **5** by condensation of trifluoromethyl enone **1d** with a variety of bidentate nucleophiles.

Results and discussion

Preparation of the 4-chloro-3-phenyl-5,5,5-trifluoropent-3-en-2-one **1d**: The 4-chloro-3-phenyl-5,5,5-trifluoropent-3-en-2-one **1d** was prepared in three steps. Firstly, the chlorotrifluoromethylacrolein **1b** was obtained in a mixture of stereoisomers Z (60%) and E (40%) by Vilsmeier reaction from benzylketone **1a**[18]. The reaction of this aldehyde with CH_3MgI and oxidation of the resulting alcohol **1c** by pyridinium chlorochromate gave in 80% yield the trifluoromethylated enone **1d,** *Z* (60%), *E* (40%) (Scheme 1).

Preparation of pyrazoles **2a–e**: On treatment with hydrazine and some derivatives ($RNHNH_2$) in refluxing solvent (acetonitrile or toluene), the enone **1d** gave regioselectively in one step the trifluoromethyl pyrazoles **2a–e** in moderate to good yields (Scheme 2).

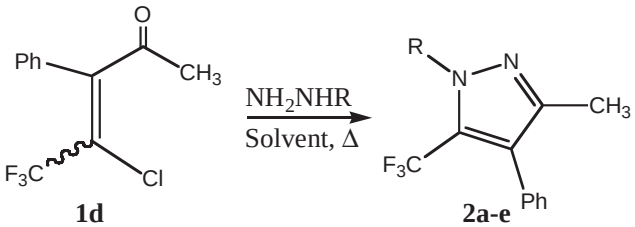
In every case, this cyclocondensation afforded a single regioisomer among the two pyrazoles **2** and **3** which could be obtained. Considering the fact that there are four possible modes of initial addition of an alkylhydrazine to the β-trifluoromethyl αβ-unsaturated ketone **1d**, the observed selectivity is not easy to rationalise (Scheme 3).

It is worth nothing that the ^1H NMR spectroscopic data do not allow discrimination between the pyrazole structures **2** and **3**. Moreover, in all the cases of the addition of alkylhydrazines to the compound **1d**, we could not detect any of the intermediates (**Ia**) or (**Ib**) or (**II a**) or (**II b**).

In order to remove this ambiguity, we have used the 2D NMR technique to elucidate the structure of the compound (**2b** or **3b**) obtained from the reaction of *N*-methylhydrazine and enone **1d** (Scheme 4).

The structure of the unique regioisomer prepared in this manner was deduced from its HMBC 2D-NMR spectra. Indeed, the trifluoromethyl fluorines correlate both with the NCH_3 protons and with the protons in the *ortho* positions of the phenyl ring, showing that the CF_3 group is situated between the positions carrying the phenyl and the *N*-methyl groups (Scheme 4). The HMBC 2D-NMR spectra are therefore in favor of the pyrazole **2b**. The other monosubstituted hydrazines are assumed to react in the same way, to form the pyrazoles **2c–e**.

Preparation of 1,5-benzodiazepine **4** *and 1,5-benzothiazepine* **5**: In order to explore the reactivity of enone **1d** towards other nucleophiles, it seemed attractive to try with some 1,4-nucleophiles. Condensation of **1d** and 1,2-diaminobenzene, in refluxing benzene, showed that the diazepine **4** could be prepared in moderate yield (50%) (Scheme 5).



Scheme 2

2	a	b	c	d	e
R	H	Me	Ph	CH_2CO_2Et	COPh
Solvent	MeCN	MeCN	MeCN	MeCN	toluene
Yield/%	76	77	48	75	70

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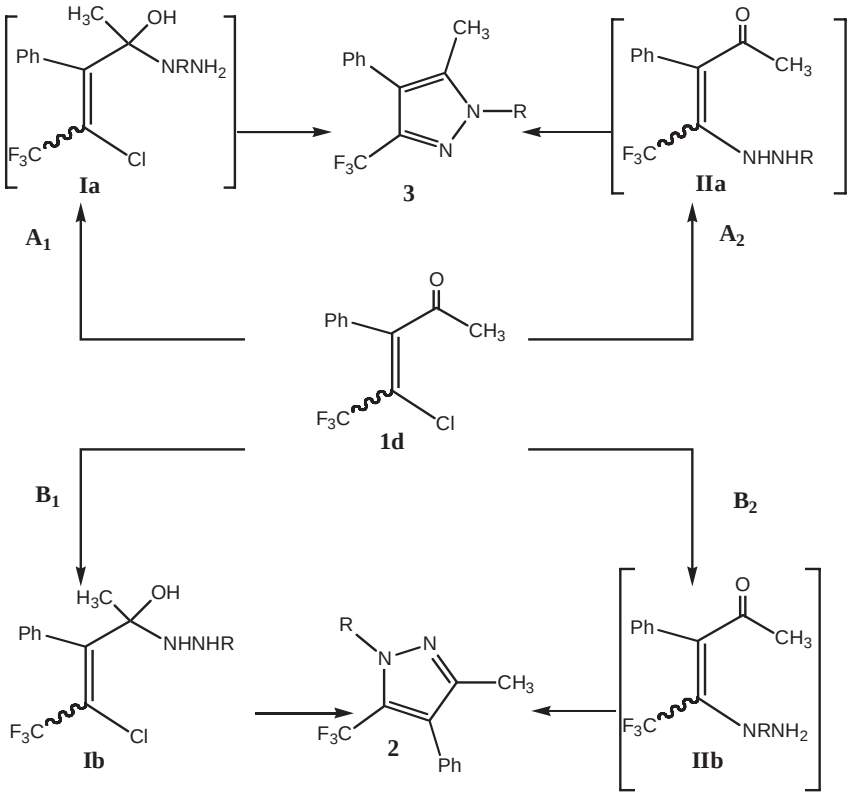
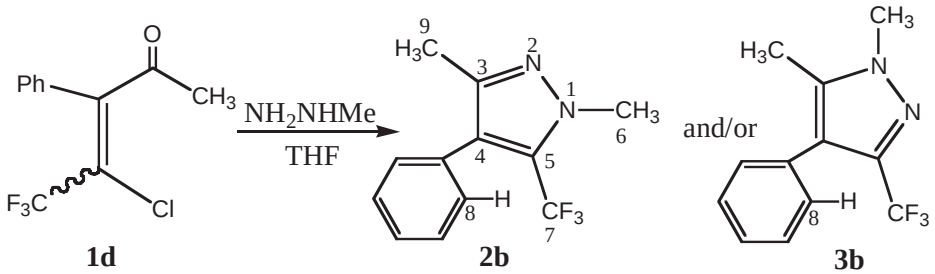
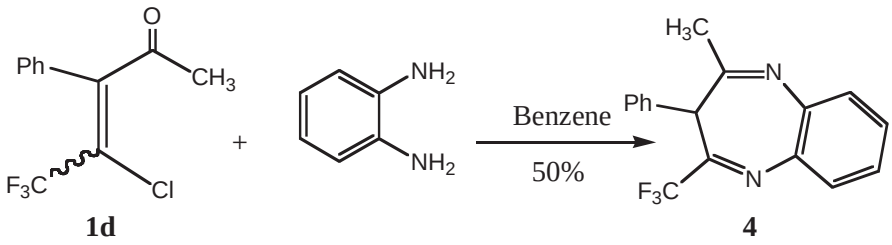


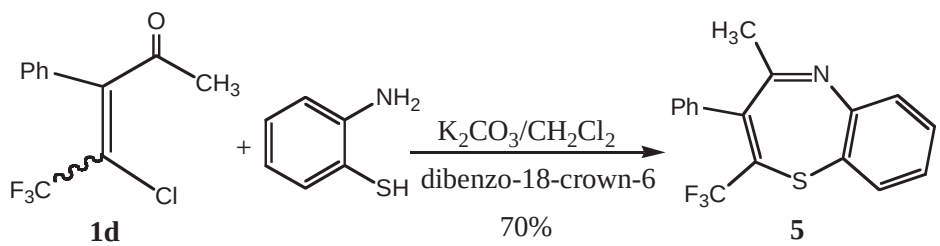
Scheme 3



Scheme 4

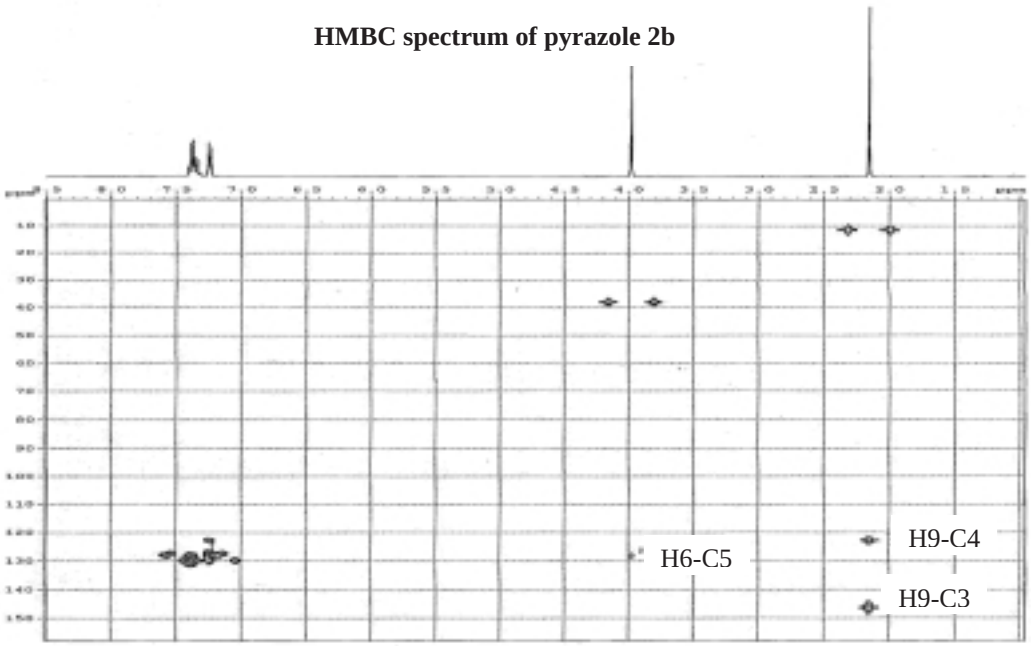


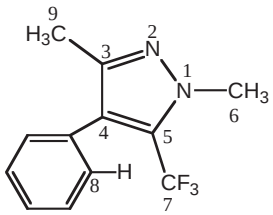
Scheme 5



Scheme 6

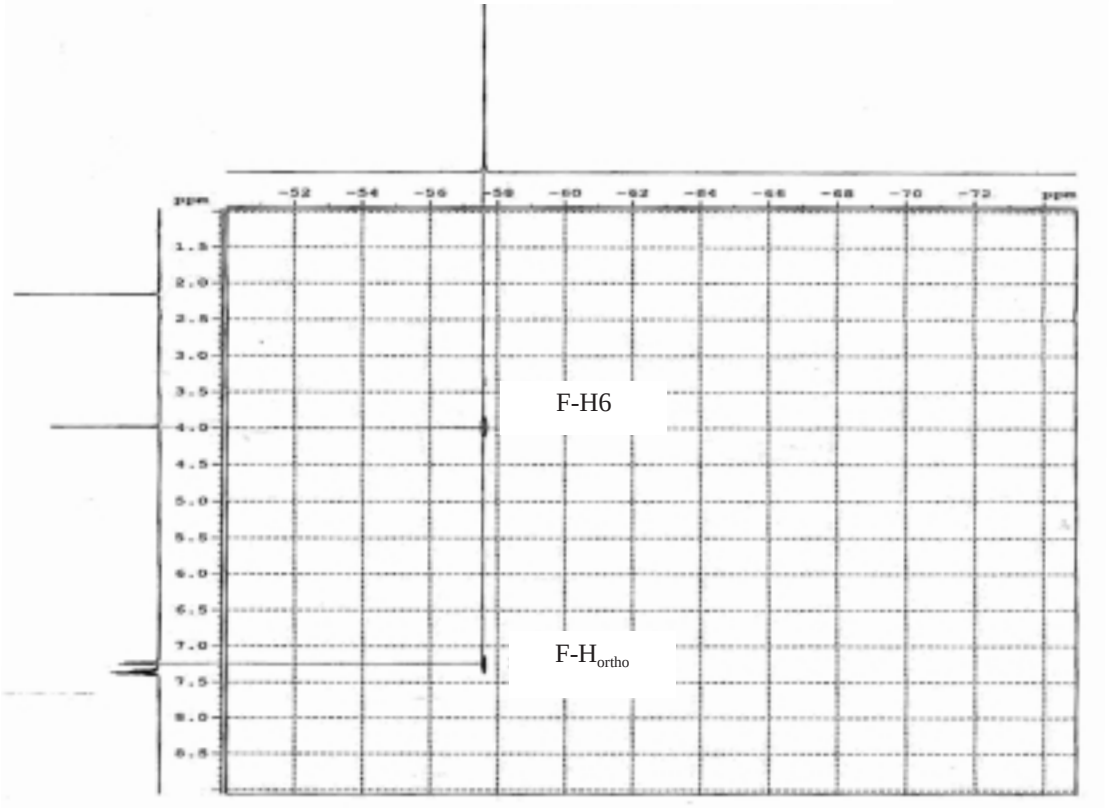
HMBC spectrum of pyrazole 2b

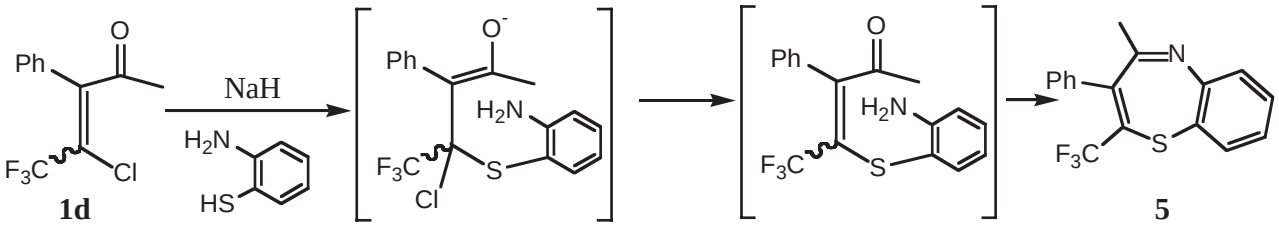




2b

NOESY spectrum of pyrazole 2b





Scheme 7

The same methodology was also used to prepare the thiazepine **5** in 70% yield by reaction of enone **1d** and 2-thio-1-aminobenzene in the presence of K_2CO_3 and dibenzo-18-crown-6 in refluxing methylene chloride (Scheme 6).

The regiochemistry of thiazepine **5** was assigned according to previous work.[19] Similarly, we assume that the reaction of enone **1d** with 2-thioaminophenol afforded a tetrahedral intermediate by 1,4-addition of thiolate ion and elimination of chloride. Subsequent intramolecular cyclisation, involving the amino group, led to the corresponding thiazepine 5 (Scheme 7).

In summary, we have developed in this paper a regioselective method for the preparation of the trifluoromethyl heterocyclic compounds **2**, **4** and **5** by reaction of derivative **1d** and a variety of ambident nucleophiles under mild conditions.

Experimental

All reactions progress was monitored by thin-layer chromatography (TLC) analysis (Merck Kieselgel 60 F_{254}). All compounds were purified by chromatography column (Silica gel 60, 70–230 mesh ASTM). IR spectra were obtained on Perkin-Elmer Paragon 1000 PC. ^{1}H NMR spectra were recorded on a Bruker AC-300 (300 MHz) spectrometer using tetramethylsilane (TMS, δ_H = 0) as internal standard. ^{13}C NMR spectra were recorded on a Bruker AC-300 (75 MHz) spectrometer with proton decoupling. For ^{19}F spectra, C_6F_6 was used as reference and they were obtained using a Bruker AC-300 (282.36 MHz). HMBC (Heteronuclear Multiple Bond Correlation) was carried out under standard conditions.[20] Mass spectra were carried out on a Hewlett-Packard model (70 eV) by the staff of the Faculté de Médecine, Département de Biochimie, Monastir, Tunisia, under electronic impact (EI). Coupling constants (*J* values) are given in Hertz and spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet).

4-Chloro-3-phenyl-5,5,5-trifluoropent-3-en-2-ol (**1c**): To a solution of methylmagnesium (5mmol of Mg and 6,7 mmol of CH_3I) under N_2, was added slowly the aldehyde **1b** (1.0 g, 4.2 mmol). After one hour in refuxing solvent (ethyl ether, 20 ml), the mixture was allowed to room temperature and quenched with a saturated NH_4Cl solution.

The organic layer was separaed and the aqueous phase was extracted with ether (3×15ml). After drying over $MgSO_4$, the solvent was removed under reduced pressure to give crude alcohol **1c** which was purified by column chromatography filled with silica gel upon elution with ethyl ether-petroleum ether (20/80).

Yield 70%; IR ($CHCl_3$) ν/cm^{-1}: 3417 (O-H) ; 1630 (C=C); 1180–1135 (CF_3); δ_H (60 MHz, $CDCl_3$) 1.2 (d, $^3J_{HH}$ = 3 Hz, 3H); 5.1 (q, $^3J_{HH}$ = 3 Hz, 1H); (6.9–7.0) (m, 5H, C_6H_5); δ_C (75 MHz, $CDCl_3$): (20.45–22.04) (2s, CH_3); (65.76–65.66) (2s, CH) ; 121.50 (q, CF_3, $^1J_{CF}$ = 211.01 Hz); (127.35–129.34) (m, C-Ph, C-CF_3, C_6H_5), δ_F (282.4 MHz, $CDCl_3$): 102.7 (s, CF_3) ; 104.7 (s, CF_3) ; MS (*m/z*): 250(7) ; 215(36) ; 206(65) ; 170(100); 151(81); 75(9); (found: C, 53.1; H, 3.4. $C_{11}H_{10}ClF_3O$ requires C, 52.9; H, 3.6).

4-Chloro-3-phenyl-5,5,5-trifluoropent-3-en-2-one (**1d**): To a solution of pyridinium chlorochromate (1.3 g, 6mmol) in CH_2Cl_2 (20 ml) was added (at 0°C), the alcohol **1c** (1.0 g, 4 mmol). After stirring at room temperature during 24 hours, the reaction mixture was concentrated, the organic residue was purified on column chromatography by using silica gel upon elution with ethyl ether-petroleum ether (20/80).

Yield 80%; IR ($CHCl_3$) ν/cm^{-1}: 1713 (C=O); 1144 (CF_3).

Steroisomer (*Z*): δ_H (300 MHz, $CDCl_3$), 2.35 (s, CH_3); (7.26–7.46) (m, C_6H_5); δ_C (75 MHz, $CDCl_3$): 27.93 (s, CH_3); 120.04 (q, CF_3, $^1J_{CF}$ = 272.92 Hz); (127.53–130.5) (m, C-CF_3; C-Ph; C_6H_5); 198.48 (s, CHO); δ_F (282.4 MHz, $CDCl_3$): 100.82 (CF_3); MS (*m/z*): 248 (36); 185 (22); 170 (100); 151 (29); 120 (9); 75 (10).

Steroisomer (*E*): δ_H (300 MHz, $CDCl_3$), 2.28 (s, CH_3); (7.26–7.46) (m, C_6H_5); δ_C (75 MHz, $CDCl_3$): 28.96 (s, CH_3); 120.32 (q, CF_3, $^1J_{CF}$ = 272.92 Hz); (127.53–130.5) (m, C-CF_3; C-Ph; C_6H_5); 197.82 (s, CHO); δ_F (282.4 MHz, $CDCl_3$): 198.41 (CF_3); MS (*m/z*): 248 (40); 185 (26); 170 (100); 151 (31); 120 (9); 75 (11). (Found: C, 53.03; H, 3.63. $C_{11}H_8ClF_3O$ requires C, 53.11; H, 3.21).

Pyrazoles **2a-e**: A mixture of one equivalent of the enone **1d** (4mmol) and two equivalents of the alkylhydrazine (8 mmol) was stirred in refluxing solvent (acetonitrile or toluene) (20mL). After evaporation of the solvent, the crude product was treated on silica gel by flash chromatography to afford a pure fraction (ethyl ether - petroleum ether : 20 / 80).

3-Methyl-4-phenyl-5-trifluoromethyl-1H-pyrazole (**2a**): Yield 76%; colourless solid; *m.p.*: 126 °C; IR ($CHCl_3$) δ/cm^{-1}: 3441 (N–H); 1609 (C=C); 1135–1165 (CF_3); δ_H (300 MHz, $CDCl_3$): 2.30 (s, 3H, CH_3); (7.00–7.40) (m, 5H, C_6H_5); δ_C (75 MHz, $CDCl_3$): 9.4 (s, CH_3–C=N); 118.7 (s); 121.8 (q, CF_3, $^1J_{CF}$ = 269.4 Hz); (127.5; 128.3; 129.7; 130.5) (C_6H_5); 139.6 (q, C–CF_3, $^2J_{CF}$ = 35.5 Hz); δ_F (282.4 MHz, $CDCl_3$): 102.7 (s, CF_3) ; MS (*m/z*): 226 (M^+, 100) 205(16); 157 (14); 130 (9); 103 (6); 77 (6); 69 (7); 51 (7). (Found: C, 58.70; H, 3.79; N, 12.10. $C_{11}H_9F_3N_2$ requires C, 58.40; H, 3.98; N, 12.39).

1,3-Dimethyl-4-phenyl-5-trifluoromethylpyrazole (**2b**): Yield 77%; colourless oil, IR ($CHCl_3$) ν/cm^{-1}: 1610 (C=N); 1565 (C=C); 1127–1163 (CF_3); δ_H (300 MHz, $CDCl_3$): 2.16 (s, 3H, CH_3); 3.96 (s, 3H, CH_3); 7.30 (m, 5H, C_6H_5); δ_C (75 MHz, $CDCl_3$): 11.7 (s, CH_3); 38.4 (q, CH_3, $^4J_{CF}$ = 2.4 Hz); 123 (q, CF_3, $^1J_{CF}$ = 274.0 Hz); 118.6 (s); (127.5; 128.1; 129.9; 131.2) (C_6H_5); 146.4 (s, C=N); δ_F (282.4 MHz, $CDCl_3$): 104.7 (s, CF_3); MS (*m/z*): 240 (M^+, 100); 178 (5); 171 (13); 130 (8); 103 (7); 77 (8); 68 (9); 51 (5). (Found: C, 60.25; H, 4.91; N, 11.30. $C_{12}H_{11}F_3N_2$ requires: C, 60.00; H, 4.58; N, 11.66).

3-Methyl-1,4-diphenyl-5-trifluoromethylpyrazole (**2c**): Yield 48%; yellow oil; IR ($CHCl_3$) ν/cm^{-1}: 1600 (C=N); 1502 (C=C); 1134–1170 (CF_3); δ_H (300 MHz, $CDCl_3$): 2.26 (s, 3H, CH_3); (7.10–7.40) (m, 10H, 2C_6H_5); δ_C (75 MHz, $CDCl_3$) 28.2 (s, CH_3–C=N);(127.5–130.9) (m, 2 C_6H_5); 128.7 (q, CF_3, $^1J_{CF}$ = 242.37 Hz); δ_F (282.4 MHz, $CDCl_3$): 107.51 (s, CF_3); MS (*m/z*): 302 (M^+, 100); 233 (9); 77 (18); 51 (10). (Found: C, 67.92; H, 4.12; N, 9.54. $C_{17}H_{13}F_3N_2$ requires: C, 67.55; H, 4.30; N, 9.27).

Ethyl 3-methyl-4-phenyl-5-trifluoromethylpyrazole-1-acetate (**2d**): Yield 75%; colourless oil; IR($CHCl_3$) ν/cm^{-1}: 1753 (CO_2Et); 1159–1132 (CF_3); δ_H (300 MHz, $CDCl_3$): 1.30 (t, 3H, $OCH_2\underline{CH}_3$); 2.19 (s, 3H, CH_3); 4.26 (q, 2H, $OC\underline{H}_2CH_3$); 4.96 (s, 2H, $NC\underline{H}_2CO$); (7.28–7.41) (m, 5H, C_6H_5); δ_C (75 MHz, $CDCl_3$): 23.7 (s, CH_3); 29.0 (s, CH_2-CH_3); 62.0 (s, CH_2–N) ; 67.4 (s, CH_2-O); (127.4–130.7) (m, C_6H_5); 139.4 (s, C=N); 166.84 (s, CO_2Et); δ_F (282.4 MHz, $CDCl_3$): 102.28 (s, CF_3); MS (*m/z*): 312 (M^+, 62); 239 (100); 103 (10). (Found: C, 57.52; H, 4.40; N, 8.77. $C_{15}H_{15}F_3N_2O_2$ requires: C, 57.69; H, 4.80; N, 8.97).

1-Benzoyl-3-methyl-4-phenyl-5-trifluoromethylpyrazole (**2e**): Yield 70%; white solid; M.p.:161–163 C; IR($CHCl_3$) ν/cm^{-1}: 1670 (C=O); 1580 (C=N); 1136–1169 (CF_3);δ_H (300 MHz, $CDCl_3$): 2.36 (s, 3H, CH_3); (7.10–7.55) (m, 10H, 2C_6H_5); δ_C (75 MHz, $CDCl_3$) 28.2 (s, CH_3C=N); (126.5–135.6) (m, 2 C_6H_5); 200.9 (s, C=O); δ_F (282.4 MHz, $CDCl_3$): 104.89 (s, CF_3); MS (*m/z*): 233 (100); 205 (8); 184 (43); 151(14); 131(12); 109 (12); 90 (17); 77 (15); 51 (8). (Found: C, 65.20; H, 3.73; N, 8.71. $C_{18}H_{13}F_3N_2O$ requires: C, 65.45; H, 3.94; N, 8.48).

Diazepine **4**: A mixture of the enone **1d** (0.5 g, 2 mmol) and 1,2-diaminobenzene (0.33 g, 3 mmol) was stirred in refluxing solvent (5mL of benzene and 2 ml of acetic acid). After evaporation of the solvent, the crude product was treated on silica gel by flash chromatography to afford a pure fraction (ethyl ether - petroleum ether: 20 / 80).

Yield 50%; yellow oil; IR ($CHCl_3$) ν/cm^{-1}: 1133–1165 (CF_3); δ_H (300 MHz, $CDCl_3$): 2.60 (s, 3H, CH_3); 5.56 (s, 1H, CHPh); (6.63–7.56) (m, 9H, C_6H_5, C_6H_4); δ_C (75 MHz, $CDCl_3$): 29.2 (s,

CH_3); 52.9 (s, CH); 119.4 (q, CF_3, $^1J_{CF}$ = 275.5 Hz); (125.2-140.2) (m, C_6H_5, C_6H_4); 145.2 (q, C-CF_3, $^2J_{CF}$= 34.0 Hz); 160.1 (s, C=N); δ_F (282.4 MHz, $CDCl_3$): 89.9 (s, CF_3); MS (*m/z*): 302 (M^+, 100); 287 (31); 233 (42); 218 (11); 165 (17); 116 (17); 91 (14); 76 (12); 51 (8); (found: C, 67.67; H, 4.67; N, 9.36. $C_{17}H_{13}F_3N_2$ requires: C, 67.55; H, 4.30; N, 9.27).

Thiazepine **5**: The enone **1d** (1.0 g, 4 mmol) was added to K_2CO_3 (1.0 g, 17.36 mmol), 2-aminothiophenol (0.52 g, 6 mmol) and (dibenzo-18-crown-6) (0.1 g) in methylene chloride (15ml). The reaction mixture was stirred at room temperature for 90 min. After evaporation of the solvent, the crude product was treated on silica gel by flash chromatography to afford a pure fraction (ethyl ether – petroleum ether : 20 / 80).

Yield 70%; white solid; m.p.: 162 °C; IR ($CHCl_3$) ν/cm^{-1}: 1624 (C=N); 1579 (C=C); 1134–1166 (CF_3); δ_H (300 MHz, $CDCl_3$): 2.21 (s, 3H, CH_3); (7.00–7.51) (m, 9H, C_6H_5, C_6H_4); δ_C (75 MHz, $CDCl_3$): 26.5 (s, CH_3); 120.6 (q, CF_3, $^1J_{CF}$ = 274.63 Hz); (127.8–129.1) (m, C_6H_5, C_6H_4); 133.9 (s); 148.0 (s); 168.2 (s, C=N); δ_F (282.4 MHz, $CDCl_3$): 103.5 (s, CF_3); MS (*m/z*): 287 (100); 272 (83); 218 (29); 176 (21); 151 (9); 88 (9); 51 (5); (found: C, 63.62; H, 3.78; N, 4.32. $C_{17}H_{12}F_3NS$ requires: C, 63.94; H, 3.76; N, 4.38).

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