TBD-Organocatalyzed Synthesis of Pyrazolines

Olivier Mahé,[a] Denis Frath,[a] Isabelle Dez,[b] Francis Marsais,[a] Vincent Levacher,[a] and Jean-François Brière[a]

[a]*INSA et Université de Rouen, UMR CNRS COBRA, IRCOF (Research Institute in Fine Organic Chemistry), rue Tesnière, BP 08, 76131 Mont Saint Aignan, France.*
[b]*LCMT (Laboratoire de Chimie Moléculaire et Thio-organique), UMR CNRS 6507, ENSICaen-Université de Caen, 14050 Caen, France*

I General experimental procedures

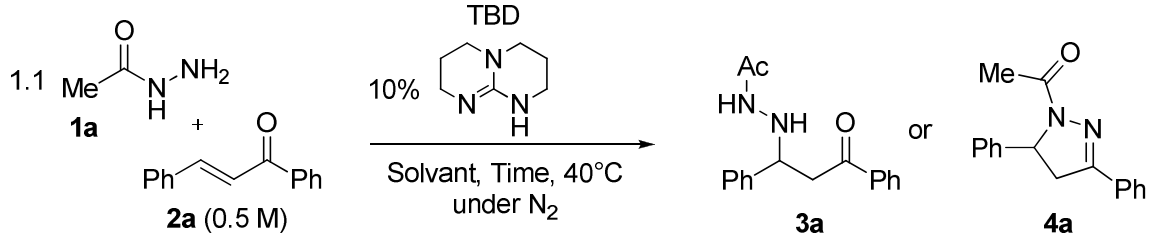
Chromatographic purification of compounds was achieved with Merck 60 silica gel (40-63 μm).[1] Thin layer chromatography was carried out on silica gel 60 F_{254} (1.1 mm, Merck) with spot detection under UV light or phosphomolybdic acid or $KMnO_4$ oxidation. ^{1}H NMR spectra were recorded at 300 MHz. Data appear in the following order: chemical shifts in ppm, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant *J*

[1] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

in Hz, number of protons. ^{13}C NMR spectra were acquired at 75.4 MHz operating with broad band ^{1}H decoupling. ^{19}F NMR spectra were acquired at 282.4 MHz. The hydrogen multiplicity was obtained by DEPT135. IR spectra were recorded on ELMER IRTF 1650 spectrometer. Mp's stand uncorrected. In situ IR spectroscopic spectra were recorded using a ReactIR^{TM} 4000 from ASI Applied Systems (Mettler Toledo) fitted with an immersible DiComp ATR probe optimized for sensitivity. The spectra were acquired in 64 scans per spectrum collected every 30 seconds at a gain of 1 and a resolution of 8 using system ReactIR^{TM} 3.0 software. The chalcones are commercially available and used without further purification, except for chalcones **2o** and **2q** which were synthesized via a Claisen-Schmidt condensation with respect to a known procedure.[2]

[2] Bhagat, S.; Sharma, R.; Sawant, D. M.; Sharma, L.; Chakraborti, A. *J. Mol. Catal. A: Chemical* **2006**, *244*, 20.

II Optimization of solvent and temperature



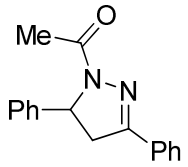
entry	Dry Solvents (0.5 M)	time (h)	Temp (°C)	Aza-michael **3a** (%)[b]	Pyrazoline **4a** (%)[b]
1	THF	5.5	40	49	23
2	Toluene	5.5	40	49	31
3	Toluene	23	40	23	52
4	Toluene[a]	23	20	38	22
5	Toluene	23	60	9	86
6	CH_2Cl_2	5.5	40	44	28
7	CH_2Cl_2	23	40	36	42
8	DMF	5.5	40	24	25
9	*t*-AmylOH	5.5	40	51	11
10	*t*-AmylOH	23	40	44	26
11	MeCN	5.5	40	36	42
12	MeCN	23	40	16	67
13	MeCN (1M)	23	40	5	79

[a] 0.23 equiv of TBD. [b] Yield determined by ^{1}H NMR of the crude product by an internal standard.

III Representative procedure for the synthesis of 1-acetyl-3,5-diphenyl-4,5-dihydro-1*H*-pyrazole 4a

Chalcone (214.5 mg, 1.0 mmol, 1 equiv), acetylhydrazine (98.8 mg, 1.2 mmol, 1.2 equiv) and triazabicyclo[4.4.0]dec-5-ene (TBD, 13.9 mg, 0.1 mmol, 0.1 equiv) were introduced into a Schlenk under nitrogen. Then, 1 mL of anhydrous acetonitrile was added at room temperature and the solution was heating at 60°C (oil bath temperature) for 24 hours. The reaction mixture was allowed to stand at room temperature and concentrated *in vacuo*. The residue was purified by flash column chromatography (by default AcOEt/Petrol Ether 2:3, otherwise indicated) afforded the desired pyrazoline **4a** as described in the following characterizations. *Remark*: the obtained solids tend to retain solvents as AcOEt or CH_2Cl_2, so they have to be dried for long period of time under vacuum.

III.1 1-acetyl-3,5-diphenyl-4,5-dihydro-1*H*-pyrazole: 4a

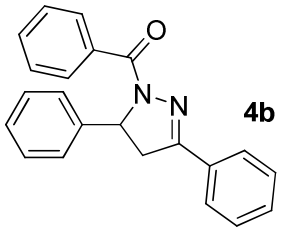


Following the general procedure, the pyrazoline **4a** was obtained as a white powder (216.4 mg, 82%) after purification (AcOEt/PE 2:3, $R_f = 0.33$) by flash column chromatography. M.p. 124-126°C (lit.,[3] 125-125.5°C). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.44 (s, 3H), 3.14-3.22 (dd, J = 4.5 Hz and 17.7 Hz, 1H), 3.72-3.82 (dd, J = 11.8 Hz and 17.7 Hz, 1H), 5.58-5.63 (dd, J = 4.5 Hz and 11.8 Hz, 1H), 7.23-7.36 (m, 5H), 7.42-7.46 (m, 3H), 7.74-7.77 (m, 2H). ^{13}C NMR ($CDCl_3$, 63 MHz) δ 22.1 (CH3), 42.4 (CH), 60.0 (CH2), 125.6 (CH), 126.6 (CH), 127.67 (CH), 128.8 (CH), 128.9 (CH), 130.4 (CH), 131.5 (C), 141.9 (C), 153.9 (C), 168.9 (C). IR

[3] Overberger, C. G.; Anselme, J.-P. *J. Am. Chem. Soc.* **1964**, *86*, 658.

(KBr) ν (cm^{-1}) 1656, 1645, 1596, 1455, 1443, 1410, 1360, 1327, 762, 691. HRMS *m/z* calcd for $C_{17}H_{17}N_2O_1$ $[M+H]^+$: 265.1341, found: 265.1349.

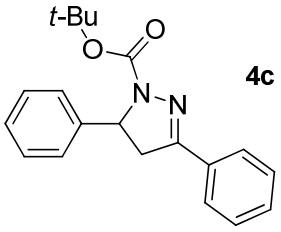
III.2 1-benzoyl-3,5-diphenyl-4,5-dihydro-1*H*-pyrazole: 4b



4b

Following the general procedure but the reaction was performed at 0.5 M for solubility reasons (the product precipitated out of the solution after 1 hour and get slowly into the solution), the pyrazoline **4b** was obtained as a white powder (262.7 mg, 80%) after purification (AcOEt/PE 1:3, R_f = 0.27) by flash column chromatography. M.p. 159-161°C. (lit.,[4] 158-160°C). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.22 (dd, J = 5.0 Hz and J = 17.7 Hz, 1H), 3.81 (dd, J = 11.8 Hz and J = 17.7 Hz, 1H), 5.83 (dd, J = 5.0 Hz and J = 11.8 Hz, 1H), 7.26-7.52 (m, 11H), 7.70-7.73 (m, 2H), 8.02-8.03 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 41.67 (CH2), 61.31 (CH), 125.78 (CH), 126.85 (CH), 127.72 (CH), 127.80 (CH), 128.80 (CH), 129.04 (CH), 130.22 (CH), 130.47 (CH), 131.03 (CH), 131.42 (C), 134.42 (C), 141.93 (C), 154.74 (C), 166.44 (C). IR (KBr) ν (cm^{-1}) 1634, 1594, 1494, 1450, 1422, 1338, 1133, 1077, 835, 788, 699. HRMS *m/z* calcd for $C_{22}H_{19}N_2O_1$ $[M+H]^+$: 327.1497, found: 327.1481.

III.3 *tert*-butyl 3,5-diphenyl-4,5-dihydro-1*H*-pyrazole-1-carboxylate: 4c

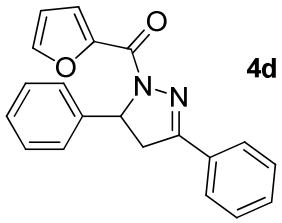


4c

[4] Khan, S. S.; Hasan, A. *Heterocl. Comm.* **2006**, *12*, 377.

Following the general procedure, the pyrazoline **4c** was obtained as a white powder (285.5 mg, 88%) after purification (AcOEt/PE 1:4, R_f = 0.31) by flash column chromatography. M.p. 146-148°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.31 (s, 9H), 3.17 (dd, J = 5.4 Hz and J = 17.5 Hz, 1H), 3.76 (dd, J = 12.1 Hz and J = 17.5 Hz, 1H), 5.30-5.37 (m, 1H), 7.22-7.4 (m, 8H), 7.75-7.79 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.2 (CH3), 42.9 (CH2), 61.9 (CH), 81.3 (C), 125.7 (CH), 126.8 (CH), 127.7 (CH), 128.6 (CH), 128.8 (CH), 130.0 (CH), 131.6 (C), 143.2 (C), 151.9 (C), 152.4 (C). IR (KBr) ν (cm^{-1}) 1702, 1449, 1403, 1326, 1150, 1133, 904, 763, 754, 694. HRMS *m/z* calcd for $C_{20}H_{23}N_2O_2$ $[M+H]^+$: 323.1760, found: 323.1761.

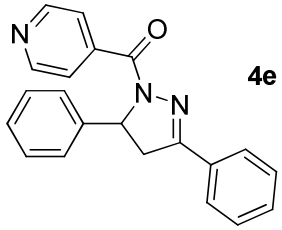
III.4 1-(2-furoyl)-3,5-diphenyl-4,5-dihydro-1*H*-pyrazole: 4d



4d

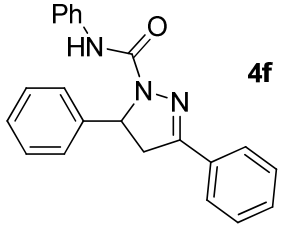
Following the general procedure, the pyrazoline **4d** was obtained as a yellowish-white (250.1 mg, 79%) after purification (AcOEt/PE 2:3, R_f = 0.31) by flash column chromatography. M.p. 135-138°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.23 (dd, J = 17.7 Hz and 4.5 Hz, 1H), 3.79 (dd, J = 17.6 and 11.7 Hz, 1H), 5.82 (dd, J = 11.7 Hz and 4.5 Hz, 1H), 6.57 (dd, J = 3.5 Hz and 1.7 Hz, 1H), 7.22-7.36 (m, 5H), 7.45-7.50 (m, 3H), 7.62-7.63 (m, 1H), 7.70-7.71 (m, 1H), 7.78-7.82 –m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 41.4 (CH2), 61.1 (CH), 111.6 (CH), 119.1 (CH), 125.75 (CH), 126.8 (CH), 127.8 (CH), 128.92 (CH), 128.97 (CH), 130.6 (CH), 131.3 (C), 141.5 (CH), 145.5 (C), 146.3 (C), 155.5 (C), 155.9 (C). IR (KBr) ν (cm^{-1}) 1642, 1557, 1471, 1431, 1337, 809, 754, 691. HRMS *m/z* calcd for $C_{20}H_{17}N_2O_2$ $[M+H]^+$: 317.1290, found: 317.1285.

III.5 4-[(3,5-diphenyl-4,5-dihydro-1*H*-pyrazol-1-yl)carbonyl]pyridine: 4e



Following the general procedure with 20% of TBD, the pyrazoline **4e** was obtained as a white powder in (215.4 mg, 66%) after purification (AcOEt/PE 1:1, R_f = 0.33) by flash column chromatography. M.p. 148-150°C. (lit.,[5] 146-148°C). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.27 (dd, J = 4.8 Hz, J = 170.8 Hz, 1H), 3.84 (dd, J = 17.8 and 11.8 Hz, 1H), 5.81 (dd, J = 4.8 Hz and J = 11.7 Hz, 1H), 7.27-7.50 (m, 8H), 7.70-7.73 (m, 2H), 7.84-7.86 (m, 2H), 8.76 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 41.8 (CH2), 61.3 (CH), 123.7 (CH), 125.7 (CH), 126.9 (CH), 128.1 (CH), 128.9 (CH), 129.12 (2×CH), 130.9 (CH), 141.22 (C), 141.75 (C), 149.76 (CH), 156.1 (C), 164.3 (C). IR (KBr) ν (cm^{-1}) 1637, 1593, 1549, 1430, 1339, 835, 768, 752, 700, 693. HRMS *m/z* calcd for $C_{21}H_{18}N_3O_1$ $[M+H]^+$: 328.1450, found: 328.1452. Anal. Calcd for $C_{21}H_{17}N_3O_1$: C, 77.04; H, 5.23; N, 12.84. Found: C, 76.81; H, 5.18; N, 12.75.

III.6 *N*,3,5-triphenyl-4,5-dihydro-1*H*-pyrazole-1-carboxamide: 4f

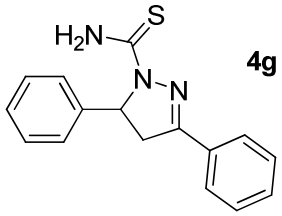


Following the general procedure (the product precipitated out of the solution), the pyrazoline **4f**[6] was obtained as a white powder in (332.0 mg , 97%) after purification (AcOEt/PE 1:5, R_f = 0.35) by flash column chromatography. M.p. 164-166°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ

[5] Khan, S. S.; Hasan, A. *Heterocl. Comm.* **2006**, *12*, 377.
[6] (a) Shishikura, J.-i.; Inami, H.; Kaku, H.; Tsutsumi, R.; Yamashita, H.; Ohno, K.; (Yamanouchi Pharmaceutical Co., Ltd., Japan). Application: WO, 2001, p 50 pp. (b) Weber, F. G.; Brosche, K. *Zeitschrift fuer Chemie* **1972**, *12*, 132.

3.24 (dd, *J* = 5.6 and *J* = 17.7 Hz, 1H), 3.85 (dd, *J* = 12.1 Hz and *J* = 17.7 Hz, 1H), 5.60 (dd, *J* = 5.6 Hz and *J* = 12.1 Hz, 1H), 6.99-7.05 (m, 1H), 7.24-7.37 (m, 7H), 7.43-7.47 (m, 3H), 7,50-7.54 (m, 2H), 7.73-7.77 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 43.1 (CH2), 60.5 (CH), 119.0 (CH), 122.9 (CH), 125.7 (CH), 126.6 (CH), 127.8 (CH), 128.9 (CH), 129.0 (CH), 129.1 (CH), 130.4 (CH), 131.3 (C), 138.6 (C), 142.4 (C), 151.6 (C), 151.9 (C). IR (KBr) ν (cm^{-1}) 3372, 1681, 1602, 1592, 1531, 1444, 1389, 1313, 1295, 1129, 1074, 874, 750, 704, 692, 623. HRMS *m/z* calcd for $C_{22}H_{20}N_3O_1$ $[M+H]^+$: 342.1606, found: 342.1613.

III.7 3,5-diphenyl-4,5-dihydro-1*H*-pyrazole-1-carbothioamide: 4g

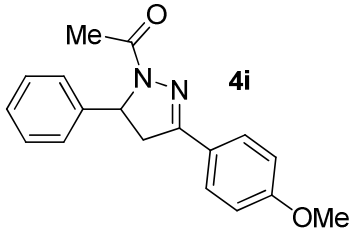


4g

Following the general procedure, the pyrazoline **4g** was obtained as a white powder in (229.0 mg, 81%) after purification (AcOEt/PE 1:2, R_f = 0.33) by flash column chromatography. M.p. 196-199°C. (lit.,[7] 204-206°C). 1H NMR (CDCl3, 300 MHz) δ 3.22 (dd, *J* = 17.7 and 3.7 Hz, 1H), 3.85 (dd, *J* = 11.5 and 17.7 Hz, 1H), 6.05 (dd, *J* = 11.5 and 3.6 Hz, 1H), 7.21-7.36 (m, 5H), 7.40-7.47 (m, 3H), 7.72-7.75 (m, 2H). ^{13}C NMR ($CDCl_3$, 63 MHz) δ 43.2 (CH2), 63.5 (CH), 125.5 (CH), 127.0 (CH), 127.7 (CH), 128.96 (CH), 129.0 (CH), 130.7 (C), 131.1 (CH), 141.9 (C), 158.1 (C), 176.8 (C). IR (KBr) ν (cm^{-1}) 3484, 3350, 1574, 1471, 1443, 1364, 1342, 1069, 819, 753, 695, 689. HRMS *m/z* calcd for $C_{16}H_{16}N_3S$ $[M+H]^+$: 282.1065, found: 282.1060. Anal. Calcd for $C_{16}H_{15}N_3S_1$: C, 68.30; H, 5.37; N, 14.93, S, 11.40. Found: C, 68.54; H, 5.39; N, 14.84, S, 11.17.

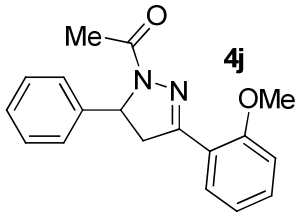
[7] Rezessy, B.; Zubovics, Z.; Kovacs, J.; Toth, G. *Tetrahedron* **1999**, *55*, 5909.

III.8 1-acetyl-3-(4-methoxyphenyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole: 4i



Following the general procedure, the pyrazoline **4i**[8] was obtained as a white powder (234.4 mg, 81%) after purification (AcOEt/PE 2:3, R_f = 0.24) by flash column chromatography. M.p. 134-136°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.49 (s, 3H), 3.17 (dd, J = 17.6 and 4.5 Hz, 1H), 3.74 (dd, J = 17.6 and 11.8 Hz, 1H), 3.89 (s, 3H), 5.62 (dd, J = 11.8 and 4.5 Hz, 1H), 6.98-7.01 (m, 2H), 7.27-7.40 (m, 5H), 7.73-7.76 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.9 (CH3), 42.3 (CH2), 55.3 (CH), 59.7 (CH), 114.0 (CH), 123.9 (C), 125.4 (CH), 127.4 (CH), 128.1 (CH), 128.7 (CH), 141.9 (C), 153.6 (C), 161.2 (C), 168.4 (C). IR (KBr) ν (cm^{-1}) 1660, 1607, 1594, 1518, 1426, 1360, 1247, 1179, 1037, 839, 761, 701. HRMS *m/z* calcd for $C_{18}H_{19}N_2O_2$ $[M+H]^+$: 295.1447, found: 295.1452.

III.9 1-acetyl-3-(2-methoxyphenyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole: 4j

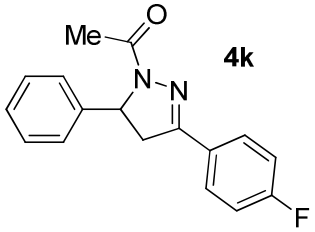


Following the general procedure, the pyrazoline **4j**[9] was obtained as a white powder (229.6 mg, 78%) after purification (AcOEt/PE 2:3, R_f = 0.27) by flash column chromatography. M.p. 127-129°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.41 (s, 3H), 3.32 (dd, J = 4.5 Hz, J = 18.6 Hz, 1H), 3.82 (s, 3H), 3.90 (dd, J = 11.8 Hz and J = 18.6 Hz, 1H), 5.54 (dd, J = 4.5 Hz and J = 11.8 Hz, 1H), 6.94 (d, J = 8.4 Hz, 1H), 7.02 (td, J = 0.95 Hz, J = 7.55 Hz, 1H), 7.21-7.35 (m,

[8] Mehta, K. H.; Desai, K. R. *Orient. J. Chem.* **2002**, *18*, 539.
[9] Cox, C. D.; Breslin, M. J.; Mariano, B. J.; Coleman, P. J.; Buser, C. A.; Walsh, E. S.; Hamilton, K.; Huber, H. E.; Kohl, N. E.; Torrent, M.; Yan, Y.; Kuod, L. C.; Hartman, G. D. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2041.

5H), 7.36-7.42 (m, 1H), 7.95 (dd, J = 1.7 Hz and J = 7.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.0 (CH3), 45.6 (CH2), 55.4 (CH or CH3), 59.9 (CH or CH3), 111.6 (CH), 120.5 (C), 120.8 (CH), 125.6 (CH), 127.4 (CH), 128.7 (CH), 129.0 (CH), 131.6 (CH), 142.2 (C), 154.2 (C), 158.2 (C), 168.7 (C). IR (KBr) ν (cm^{-1}) 1656, 1600, 1495, 1441, 1416, 1250, 1026, 758, 702. HRMS *m/z* calcd for $C_{18}H_{19}N_2O_2$ $[M+H]^+$: 295.1447, found: 295.1432.

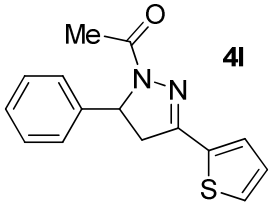
III.10 1-acetyl-3-(2-fluorophenyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole: 4k



4k

Following the general procedure, the pyrazoline **4k** was obtained as a slightly yellow (237.1 mg, 84%) after purification (AcOEt/PE 1:2, R_f = 0.31) by flash column chromatography. M.p. 121-124°C. (lit.,[10] 140-141°C). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.42 (s, 3H), 3.13 (dd, J = 17.6 Hz and 4.6 Hz, 1H), 3.74 (dd, J = 17.6 and 11.8 Hz, 1H), 5.60 (dd, J = 11.8 Hz and 4.6 Hz, 1H), 7.08-7.14 (m, 2H), 7.21-7.36 (m, 5H), 7.71-7.76 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.0 (CH3), 42.5 (CH2), 60.1 (CH), 116.0 (J = 21.9 Hz, CH), 126.6 (CH), 127.8 (CH), 128.6 (J = 8.5 Hz, CH), 129.0 (CH), 141.8 (C), 155.9 (2×C), 165.6 (J = 251.1 Hz, C), 168.9 (C). ^{19}F ($CDCl_3$, 282 MHz) δ 109.4. IR (KBr) ν (cm^{-1}) 1664, 1605, 1515, 1424, 1365, 1324, 1231, 114, 1025, 959, 870, 835, 755, 699. HRMS *m/z* calcd for $C_{17}H_{16}F_1N_2O$ $[M+H]^+$: 283.1247, found: 283.1234.

III.11 1-acetyl-5-phenyl-3-(2-thienyl)-4,5-dihydro-1*H*-pyrazole: 4l

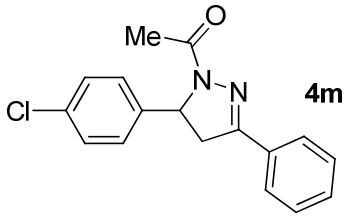


4l

[10] Joshi, K. C.; Pathak, V. N.; Sharma, S. *J. Indian Chem. Soc.* **1984**, *61*, 1014.

Following the general procedure, the pyrazoline **4l** was obtained as a white powder (208.0 mg, 69%) after purification (AcOEt/PE 1:4, R_f = 0.23) by flash column chromatography. M.p. 120-123°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.41 (s, 3H), 3.16 (dd, J = 4.6 Hz and J = 17.5 Hz, 1H), 3.77 (dd, J = 11.8 Hz, J = 17.6 Hz, 1H), 5.60 (dd, J = 4.6 Hz and J = 11.8 Hz, 1H), 7.07 (dd, J = 3.7 Hz and J = 5.1 Hz, 1H), 7.21-7.29 (m, 4H), 7.32-7.37 (m, 2H), 7.44 (dd, J = 1.1 Hz and J = 5.1 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.0 (CH3), 43.1 (CH2), 60.1 (CH), 125.6 (CH), 127.7 (CH), 127.8 (CH), 128.8 (CH), 128.8 (CH), 129.0 (CH), 135.0 (C), 141.7 (C), 149.6 (C), 168.7 (C). IR (KBr) ν (cm^{-1}) 1667, 1450, 1405, 1318, 952, 837, 760, 700, 695. HRMS *m/z* calcd for $C_{15}H_{15}N_2O_1S_1$ $[M+H]^+$: 271.0905, found: 271.0916. Anal. Calcd for $C_{15}H_{15}N_2O_2S_1$: C, 66.64; H, 5.22; N, 10.36; S, 11.86. Found: C, 66.69; H, 5.15; N, 10.27; S, 11.71.

III.12 1-acetyl-5-(4-chlorophenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazole: 4m

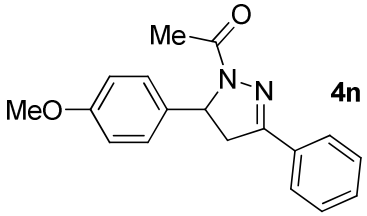


Following the general procedure, the pyrazoline **4m** was obtained as a yellowish-white in (203.0 mg, 68%) after purification (AcOEt/PE 1:3, R_f = 0.29) by flash column chromatography. M.p. 83-86°C. (lit.,[11] 108-109°C). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.42 (s, 3H), 3.13 (dd, J = 4.7 Hz and J = 17.7 Hz, 1H), 3.76 (dd, J = 11.9 Hz and J = 17.7 Hz, 1H), 5.55 (dd, J = 4.7 Hz and J = 11.9 Hz, 1H), 7.16-7.19 (m, 2H), 7.26-7.30 (m, 2H), 7.41-7.46 (m, 3H), 7.72-7.76 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.0 (CH3), 42.2 (CH2), 59.3 (CH), 126.6 (CH), 127.1 (CH), 128.8 (CH), 129.0 (CH), 130.5 (CH), 131.1 (C), 133.4 (C), 140.4 (C), 153.8 (C), 168.9 (C). IR (KBr) ν (cm^{-1}) 1667, 1594, 1492, 1439, 1411, 1361, 1324,

[11] Levai, A. *ARKIVOC* **2005**, 344.

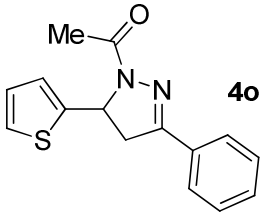
1011, 823, 760, 691. HRMS *m/z* calcd for $C_{17}H_{16}N_2O_1Cl$ $[M+H]^+$: 299.0951, found: 299.0949. Anal. Calcd for $C_{17}H_{15}N_2O_1Cl$: C, 68.34; H, 5.06; N, 9.38. Found: C, 68.25; H, 5.08; N, 9.09.

III.13 1-acetyl-5-(4-methoxyphenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazole: 4n



Following the general procedure, the pyrazoline **4n** was obtained as a white powder (238.4 mg, 81%) after purification (AcOEt/PE 2:3, $R_f = 0.27$) by flash column chromatography. M.p. 104-106°C. (lit.,[12] 105-107°C). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.41 (s, 3H), 3.16 (dd, J = 6.6 Hz and J = 17.7 Hz, 1H), 3.73 (dd, J = 11.8 Hz and J = 17.7 Hz, 1H), 3.77 (s, 3H), 5.55 (dd, J = 4.5 Hz and J = 11.8 Hz, 1H), 6.83-6.86 (m, 2H), 7.15-7.18 (m, 2H), 7.41-7.45 (m, 3H), 7.73-7.76 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.0 (CH3), 42.3 (CH2), 55.3 (CH or CH3), 59.4 (CH or CH3), 114.2 (CH), 126.6 (CH), 126.9 (CH), 128.8 (CH), 130.3 (CH), 131.5 (C), 134.1 (C), 153.9 (C), 159.0 (C), 168.8 (C). IR (KBr) ν (cm^{-1}) 1660, 1515, 1453, 1443, 1415, 1250, 1175, 1030, 823, 767, 692. HRMS *m/z* calcd for $C_{18}H_{19}N_2O_2$ $[M+H]^+$: 295.1447, found: 295.1440. Anal. Calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.81; H, 6.25; N, 9.48.

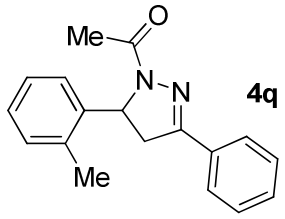
III.14 1-acetyl-3-phenyl-5-(2-thienyl)-4,5-dihydro-1*H*-pyrazole: 4o



[12] Manna, F.; Chimenti, F.; Fioravanti, R.; Bolasco, A.; Secci, D.; Chimenti, P.; Ferlini, C.; Scambia, G. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4632.

Following the general procedure, the pyrazoline **4o**[13] was obtained as a yellow (208.0 mg, 77%) after purification (AcOEt/PE 1:8, R_f = 0.29) by flash column chromatography. Due to some instability of pyrazoline **4o** during column chromatography, 5% (v/v) of triethylamine was added to the solvents for deactivation of silicagel. M.p. 98-100°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.41 (s, 3H), 3.35 (dd, J = 4.1 Hz and J = 17.6 Hz, 1H), 3.72 (dd, J = 11.4 Hz and J = 17.6 Hz, 1H), 5.91 (dd, J = 4 Hz and J = 11.4 Hz, 1H), 6.92 (dd, J = 3.5 Hz and J = 5.1 Hz, 1H), 7.02-7.03 (m, 1H), 7.18 (dd, J = 1.2 Hz and J = 5.1 Hz, 1H), 7.42-7.46 (m, 3H), 7,73-7.78 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.1 (CH3), 42.1 (CH2), 55.3 (CH), 124.7 (CH), 124.8 (CH), 126.7 (CH), 126.9 (CH), 128.9 (CH), 130.5 (CH), 131.4 (C), 144.4 (C), 154.0 (C), 169.1 (C). IR (KBr) ν (cm^{-1}) 1651, 1445, 1411, 1360, 1327, 1249, 853, 844, 763, 721, 708, 690. HRMS *m/z* calcd for $C_{15}H_{15}N_2O_1S_1$ $[M+H]^+$: 271.0905, found: 271.0901.

III.15 1-acetyl-5-(2-methylphenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazole: 4q



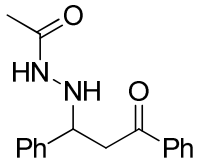
4q

Following the general procedure, the pyrazoline **4q**[14] was obtained as a white powder in (232 mg, 83%) after purification (AcOEt/PE 1:3, R_f = 0.35) by flash column chromatography. M.p. 112-114°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.45 (s, 3H), 2.46 (s, 3H), 3.02 (dd, J = 17.4 Hz and 4.8 Hz, 1H), 3.77 (dd, J = 17.4 and 11.8 Hz, 1H), 5.76 (dd, J = 11.8 Hz and 4.8 Hz, 1H), 6.97-7.01 (m, 1H), 7.02-7.20 (m, 3H), 7.40-7.44 (m, 3H), 7.72-7.75 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.6 (CH3), 22.1 (CH3), 41.7 (CH2), 57.1 (CH), 124.0 (CH), 126.67

[13] Keki, S.; Nagy, L.; Torok, J.; Toth, K.; Levai, A.; Zsuga, M. *Rapid Commun. Mass Spectrom.* **2007**, *21*, 1799.
[14] Cox, C. D.; Breslin, M. J.; Mariano, B. J.; Coleman, P. J.; Buser, C. A.; Walsh, E. S.; Hamilton, K.; Huber, H. E.; Kohl, N. E.; Torrent, M.; Yan, Y.; Kuod, L. C.; Hartman, G. D. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2041.

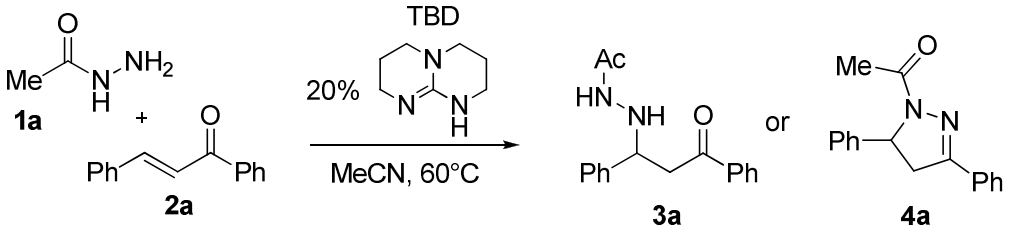
(CH), 126.76 (CH), 127.5 (CH), 128.8 (CH), 130.4 (CH), 130.9 (C), 131.6 (C), 134.1 (C), 139.9 (C), 154.0 (0), 168.9 (C). IR (powder) ν (cm^{-1}) 1660, 1597, 1434, 1360, 1328, 1148, 761, 691. HRMS *m/z* calcd for $C_{18}H_{19}N_2O_1$ $[M+H]^+$: 279.1497, found: 279.1488. Anal. Calcd for $C_{18}H_{18}N_2O_1$: C, 77.67; H, 6.54; N, 10.06. Found: C, 77.59; H, 6.54; N, 10.02.

IV *N*'-(3-oxo-1,3-diphenylpropyl)acetohydrazide: 3a



Chalcone (107.4 mg, 0.5 mmol, 1 equiv), acetylhydrazine (45.4 mg, 1.1 mmol, 1.1 equiv) were introduced into a Schlenk under nitrogen. Then, 1 mL of anhydrous toluene was added at room temperature and the solution was heating at 60°C (oil bath temperature) for 17 hours. The reaction mixture was allowed to stand at room temperature and concentrated *in vacuo*. The residue was purified by flash column chromatography (AcOEt/MeOH 20:1, R_f = 0.4) afforded the desired aza-Michael derivatives **3a** (55.0 mg, 39%) as an oil. *Two rotamers A (major) and B (minor) appeared on the ^1H NMR spectra.* ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.81 (s, 3H, A), 1.95 (s, 3H, B), 3.30-3.50 (m, 2H, A+B), 4.43-4.48 (m, 1H, B), 4.58 (br, 1H, B), 4.67-4.71 (m, 1H, A), 6.58 (br, 1H, B), 6.88 (br, 1H, A), 7.29-7.59 (m, 8H, A+B), 7.89-7.94 (m, 2H, A+B). *Two rotamers A (major) and B (minor) appeared on the ^{13}C NMR spectra but the minor one cannot bet always characterized and the main pics will only be described.* ^{13}C NMR ($CDCl_3$, 75 MHz) *rotamer A* δ 21.2 (CH3), 44.6 (CH2), 60.7 (CH), 127.7 (CH), 128.0 (CH), 128.2 (CH), 128.7 (CH), 128.8 (CH), 133.4 (CH), 136.7 (C), 141.0 (C), 169.4 (C), 198.2 (C). *rotamer B* δ 19.7 (CH3), 43.1 (CH2), 61.8 (CH), 128.2 (CH), 128.4 (CH), 128.8 (CH), 129.0 (CH), 133.7 (CH), 136.5 (C). IR (powder) ν (cm^{-1}) 3280, 1681, 1651, 1597, 1449, 1371, 1227, 1206, 989, 911, 749, 794, 700. HRMS *m/z* calcd for $C_{17}H_{19}N_2O_2$ $[M+H]^+$: 283.1447, found: 283.1433.

V IR in situ study of pyrazoline 3a formation – mechanistic investigations

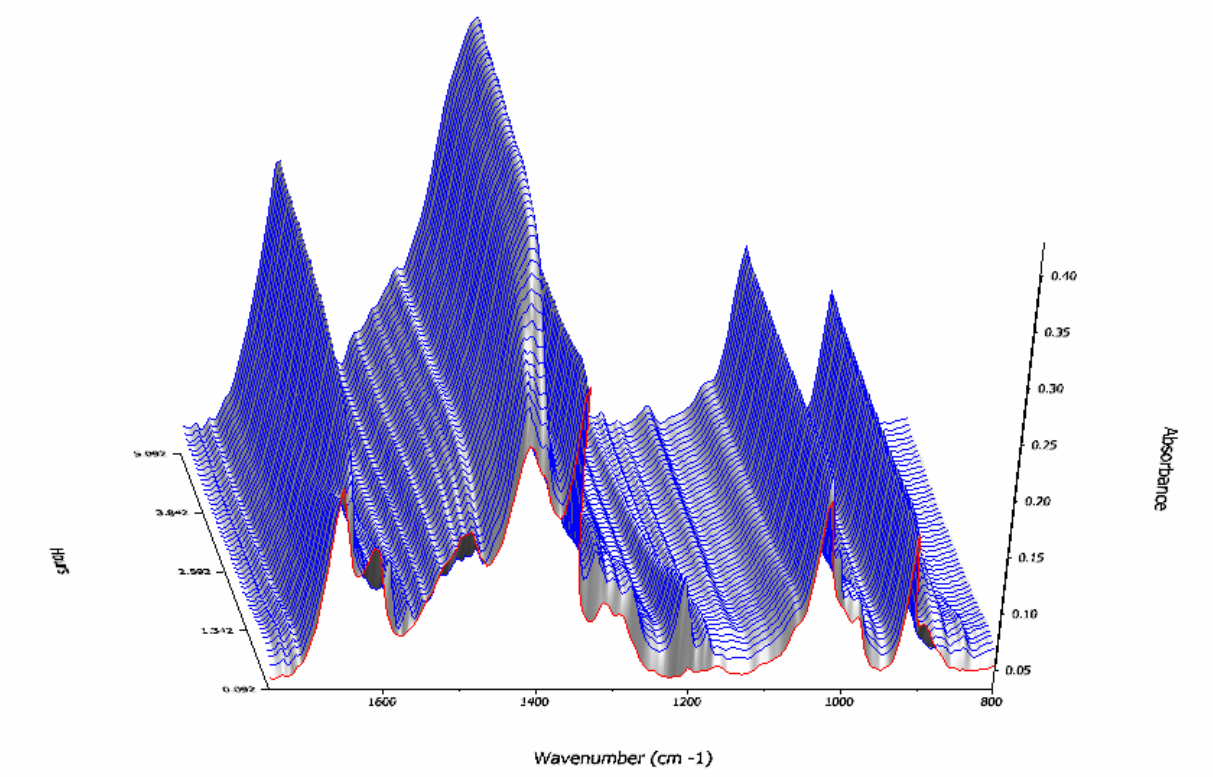


The IR probe was inserted through a nylon adapter and O-ring seal into an oven-dried, cylindrical flask fitted with a magnetic stir bar and T-joint capped with a septum. Acetylhydrazine **1a** (136.4 mg, 1.7 mmol, 1.1 equiv) and triazabicyclo[4.4.0]dec-5-ene **TBD** (40.6 mg, 0.29 mmol, 0.2 equiv) was introduced into a Schlenk under nitrogen. Then, anhydrous acetonitrile (2 mL) was added at room temperature and the solution was heating at 60°C (oil bath temperature). The Infra Red spectra were recorded at that point. When 60°C was reached, a solution of Chalcone **2a** (322.4 mg, 1.5 mmol, 1 equiv) in 1 mL of anhydrous acetonitrile was rapidly added. After 3 minutes a small reaction sample was filtered though a silica gel pad. After evaporation to dryness, the residue was analyzed by ^{1}H NMR.

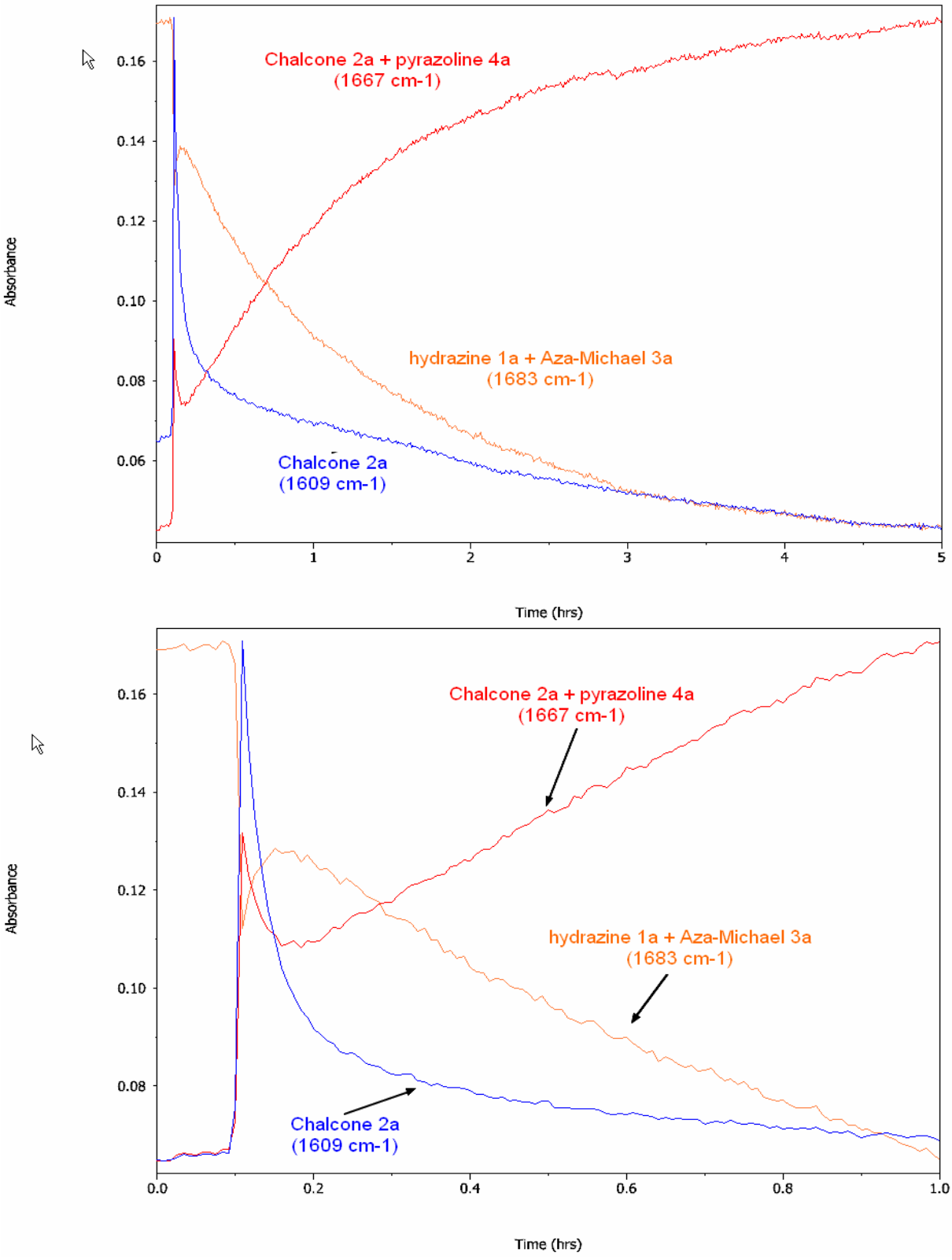
A sample was analyzed by ^{1}H NMR after 3 minutes (subsequent to the addition of chalcone) revealing the presence **2a**/**3a**/**4a** in a ratio of 51/40/9 respectively. By carrying out the same reaction but with one equivalent of TBD (instead of 0.2 equiv) a ratio of 27/37/36 **2a**/**3a**/**4a**, showing that TBD accelerates the formation of pyrazoline **3a**.

V.1 IR spectra versus time

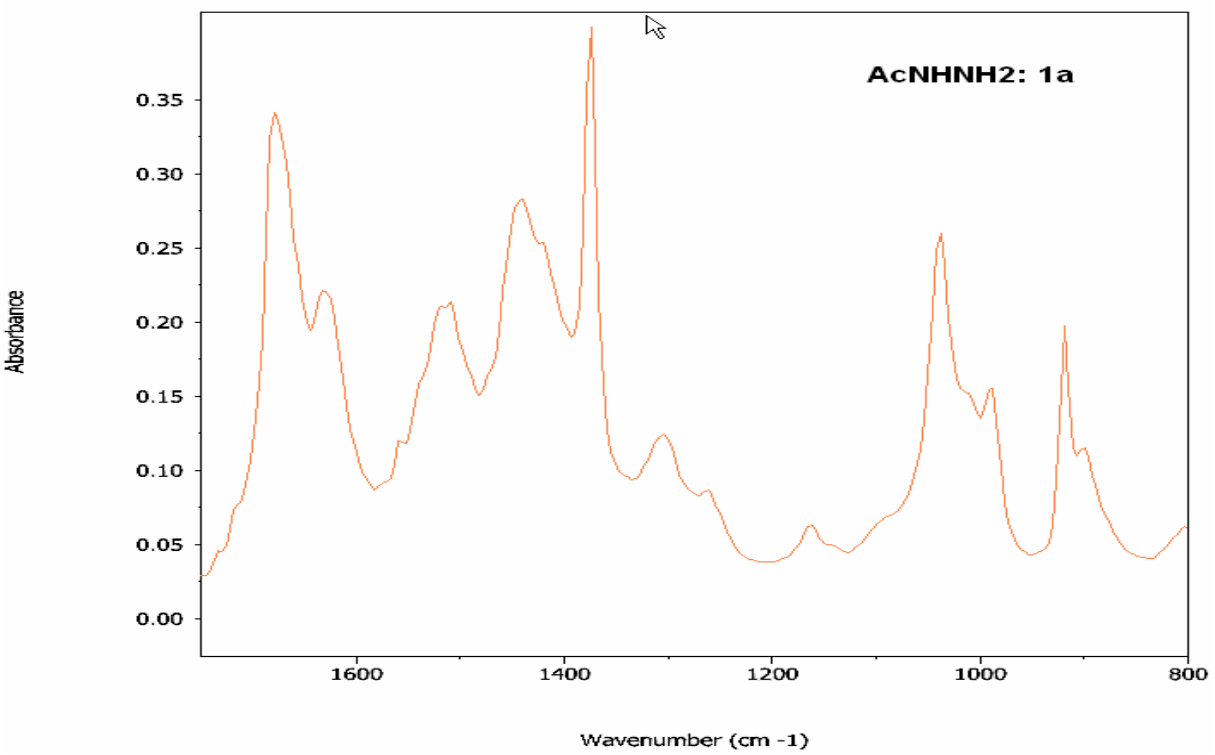
Spectra from *1750 to 800 cm^{-1}* roughly over 5 hours are displayed with a skip factor of 7 (1 spectra being recorded every 30 seconds). The first two spectra (red line) displayed correspond to the solution of Acetylhydrazine **1a** and triazabicyclo[4.4.0]dec-5-ene **TBD** in acetonitrile before the addition of chalcone (the first spectra being in red).

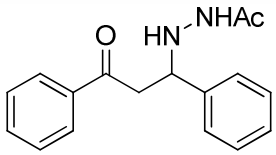


V.2 Species versus time

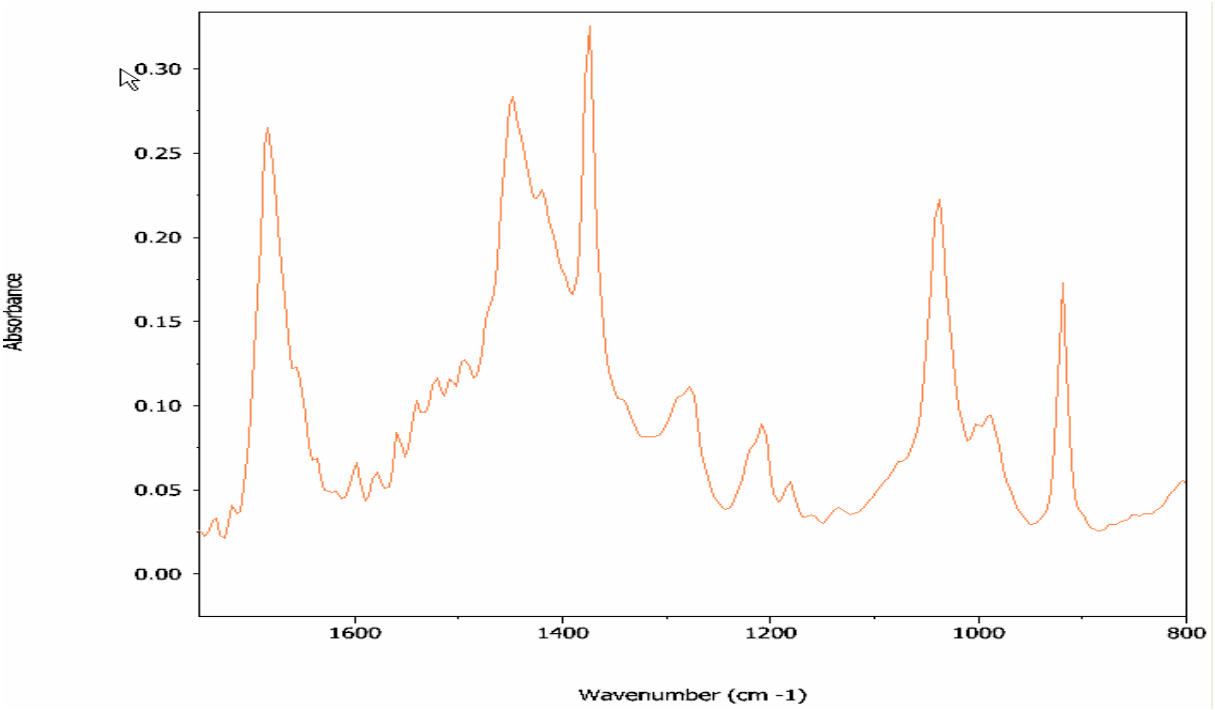


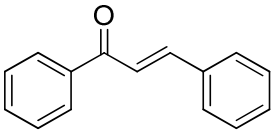
V.3 IR spectra in acetonitrile



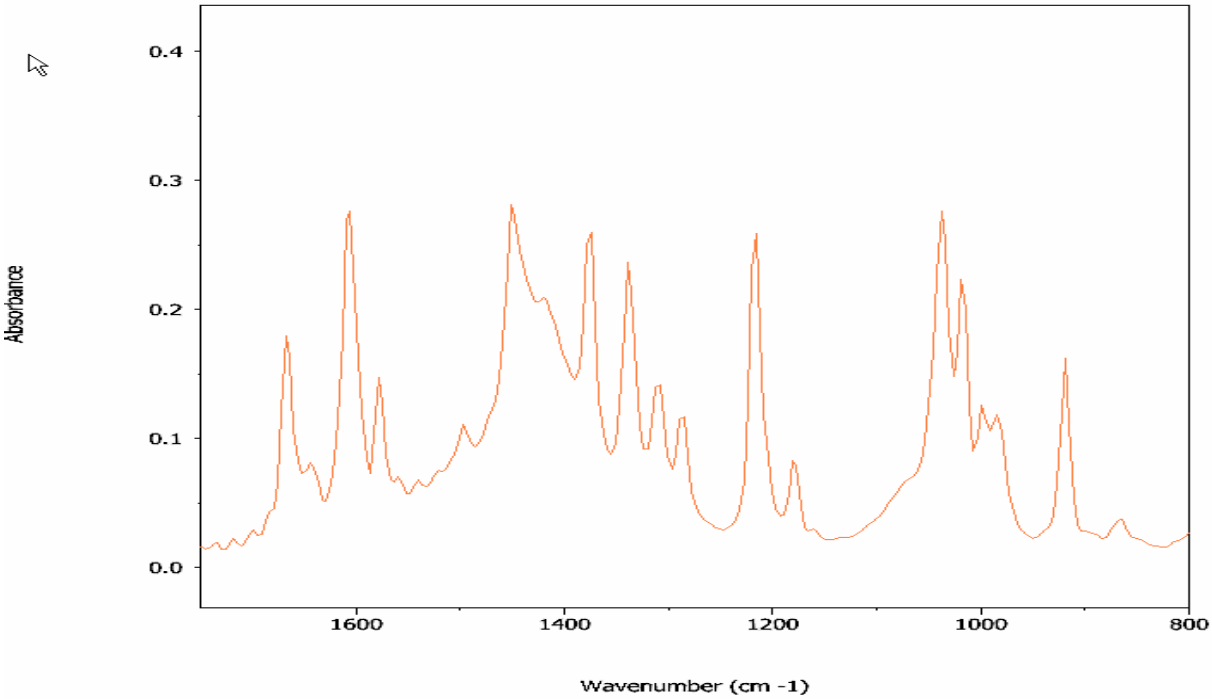


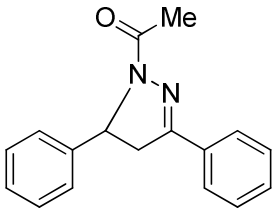
3a



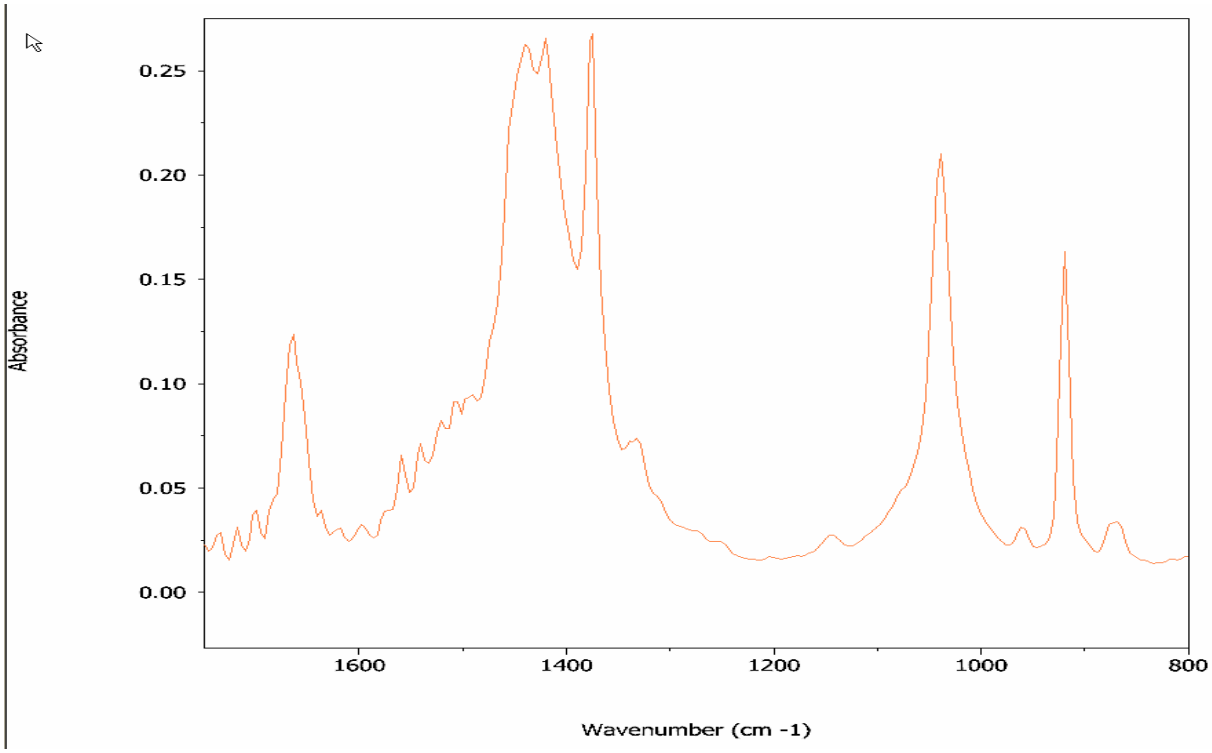

O

2a


Absorbance
0.4
0.3
0.2
0.1
0.0
1600
1400
1200
1000
800
Wavenumber (cm -1)

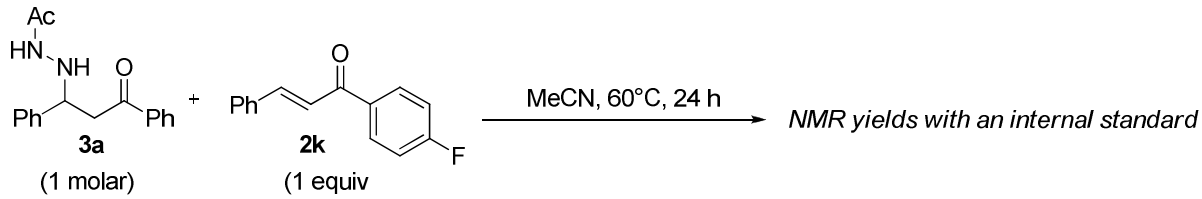

O
Me
N
N

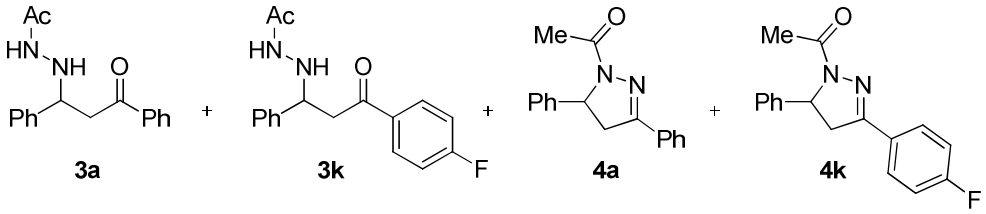
4a


Absorbance
0.25
0.20
0.15
0.10
0.05
0.00
1600
1400
1200
1000
800
Wavenumber (cm -1)

V.4 Cross-over experiments

The following experiments could be interpreted by equilibrium between **3a** and acetylhydrazine which allows the formation of aza-Michael adduct **3k** without base, and pyrazoline **4k** in the presence of TBD.



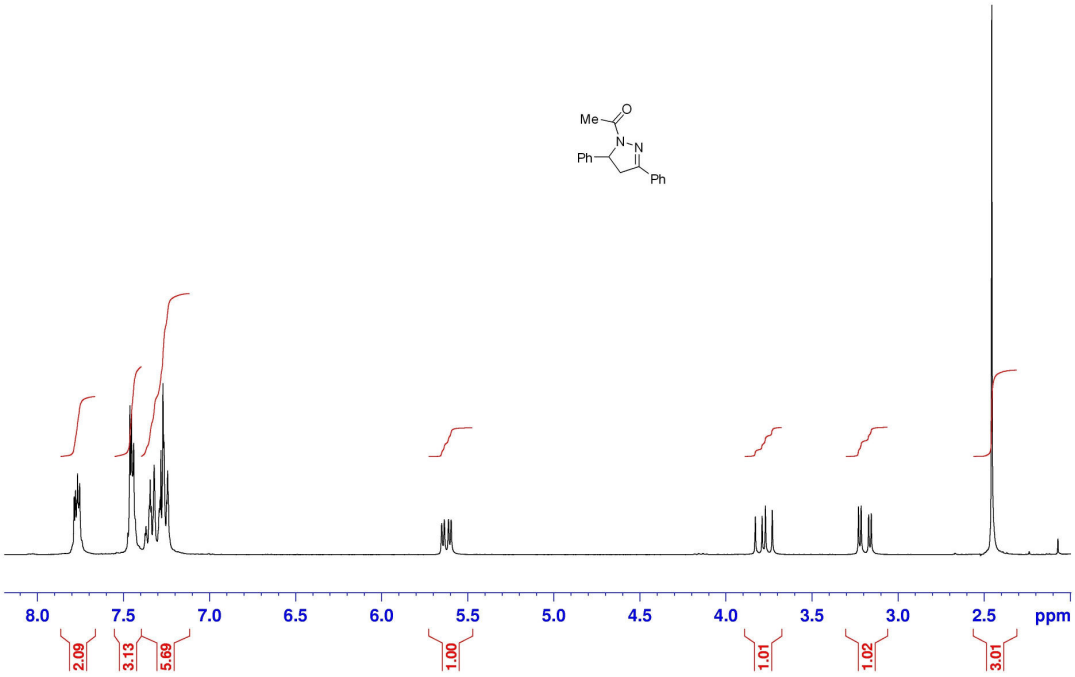


Without base:	33%	53%	0	0
TBD (0.2 equiv):	traces	traces	33%	39%

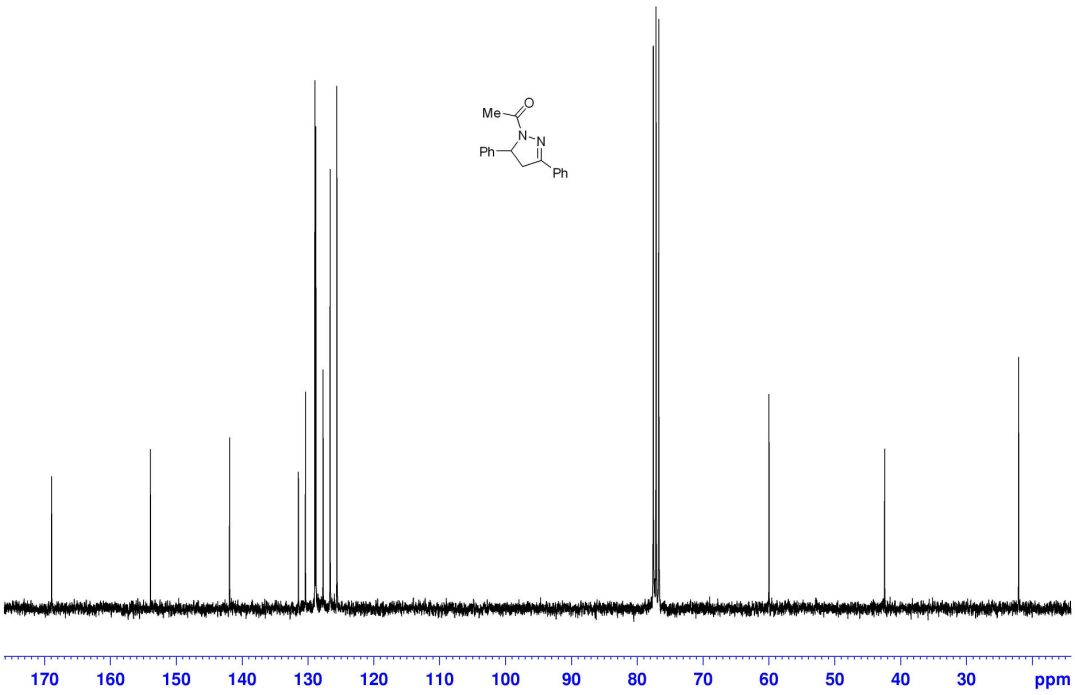
In the presence of TBD, the reactions are less clean (with respect to the RMN of the crude product) starting from the aza-Michael adduct **3a** than in the optimized conditions from acetylhydrazine and chalcone **3a**. This suggests a relative instability of the aza-Michael compound **3a** in the basic conditions exacerbated by its high concentration during the cross-over experiment.

VI NMR spectra

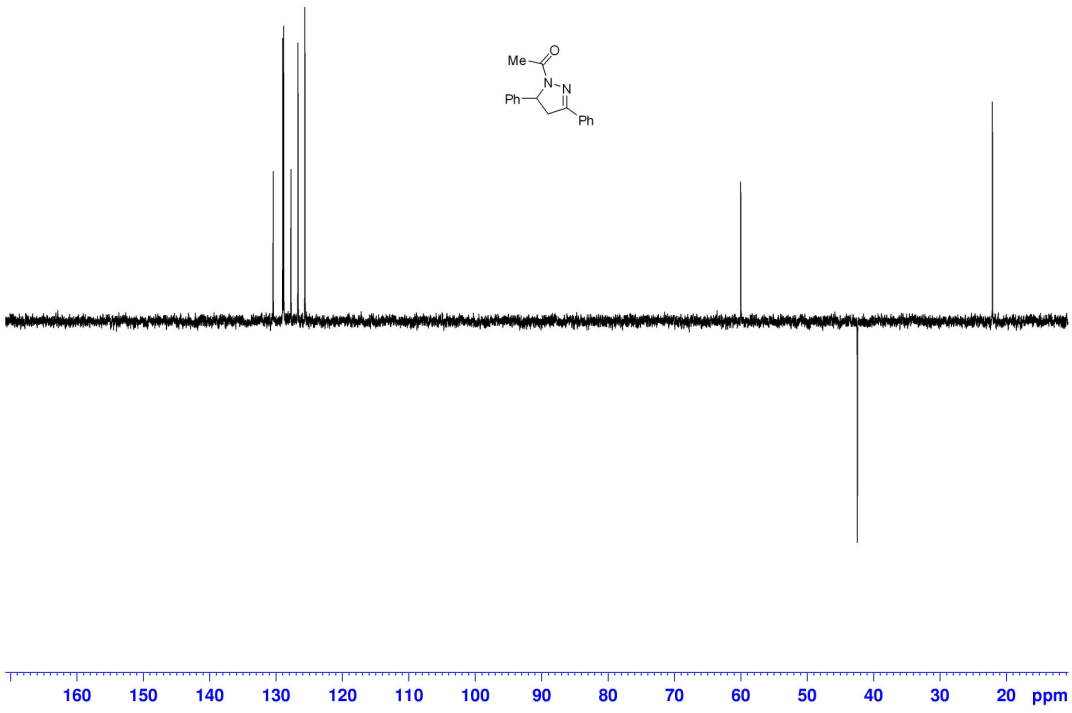
VI.1 1-acetyl-3,5-diphenyl-4,5-dihydro-1*H*-pyrazole (^{1}H): 4a



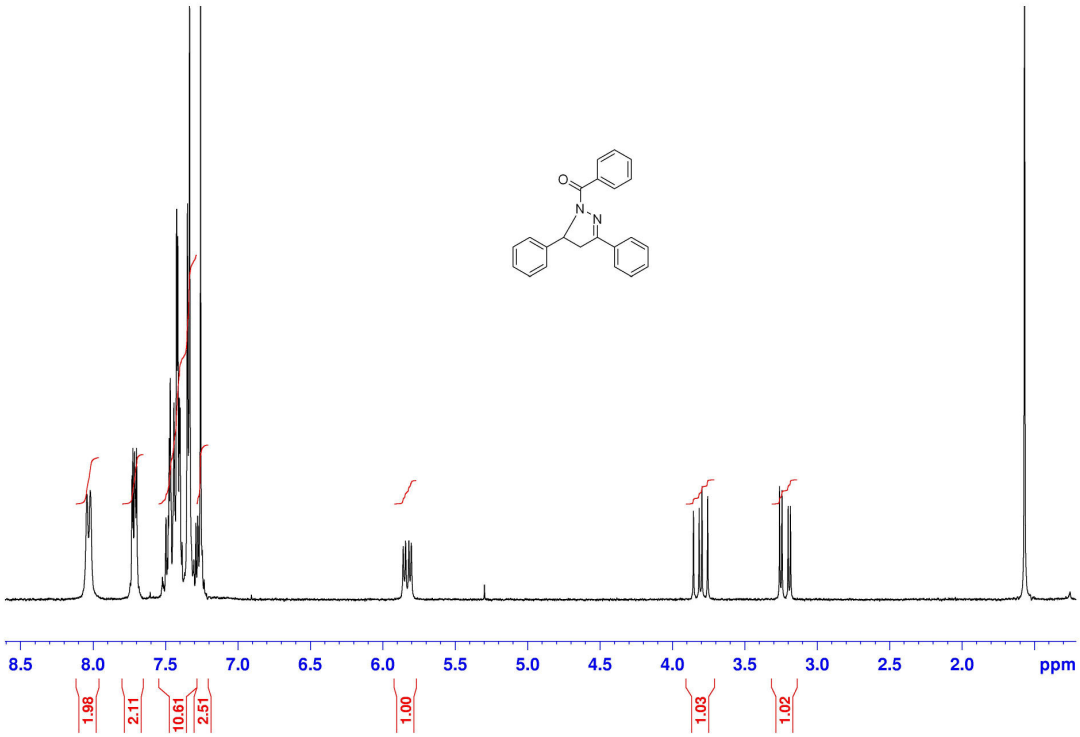
VI.1 1-acetyl-3,5-diphenyl-4,5-dihydro-1*H*-pyrazole (^{13}C): 4a



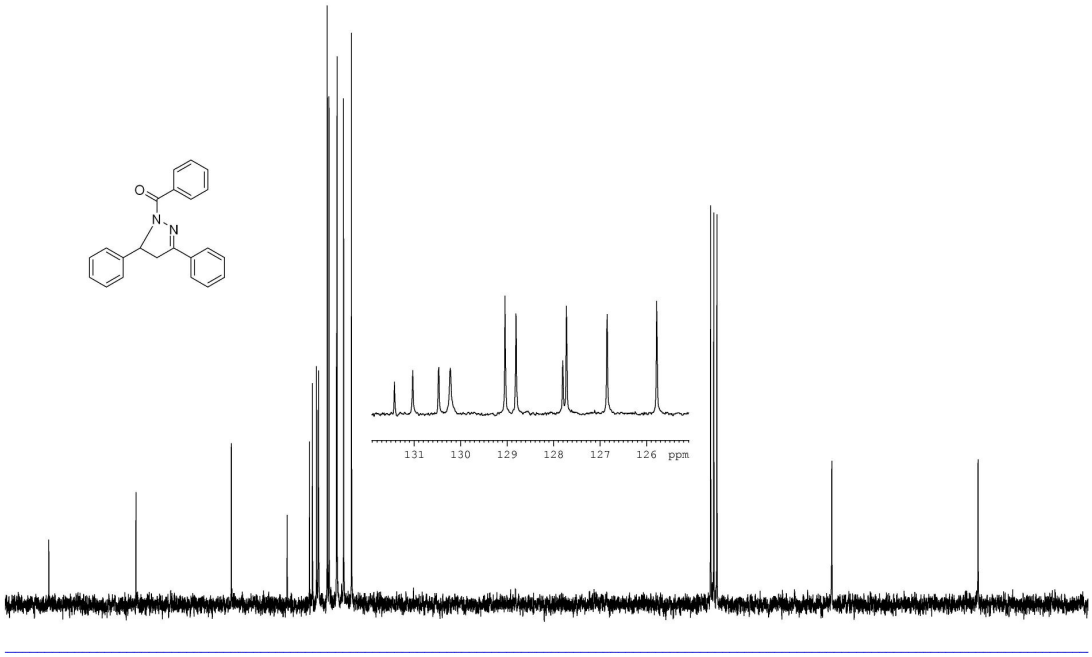
VI.1 1-acetyl-3,5-diphenyl-4,5-dihydro-1*H*-pyrazole (DEPT135): 4a



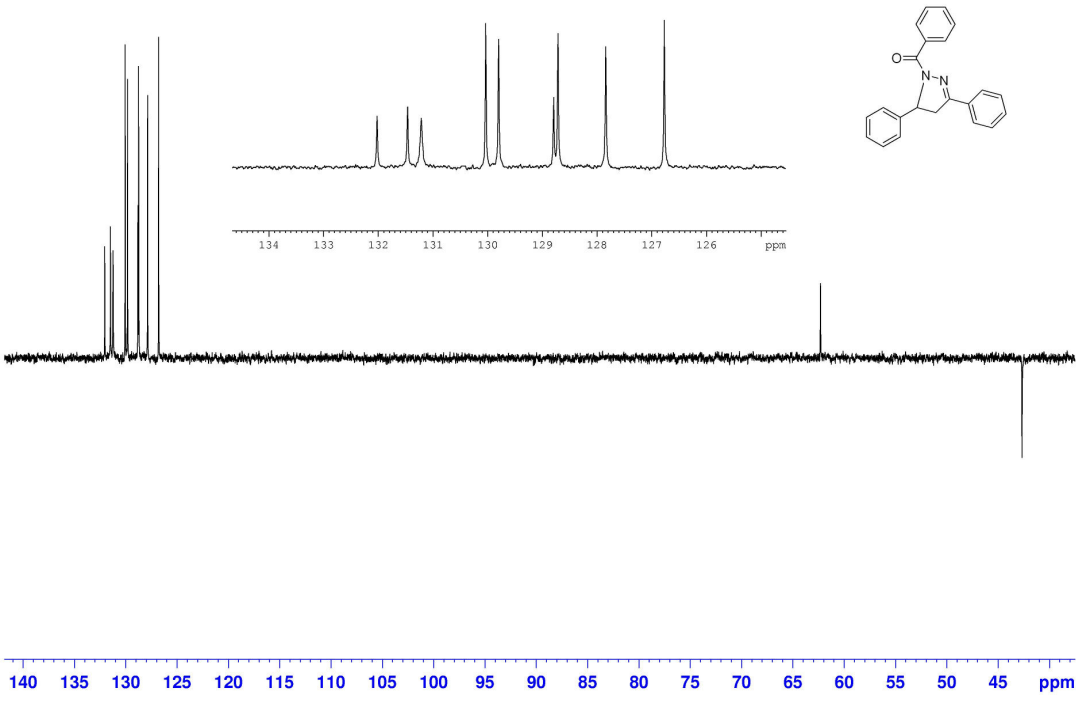
VI.2 1-benzoyl-3,5-diphenyl-4,5-dihydro-1*H*-pyrazole (^{1}H): 4b



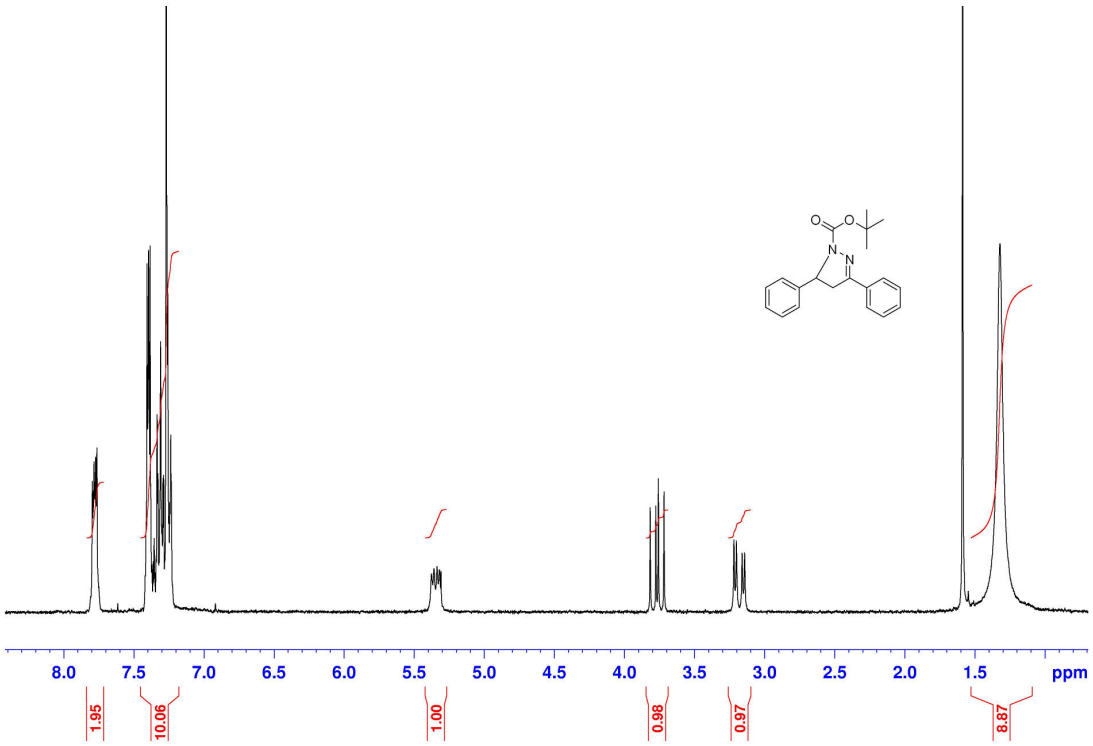
VI.2 1-benzoyl-3,5-diphenyl-4,5-dihydro-1*H*-pyrazole (^{13}C): 4b



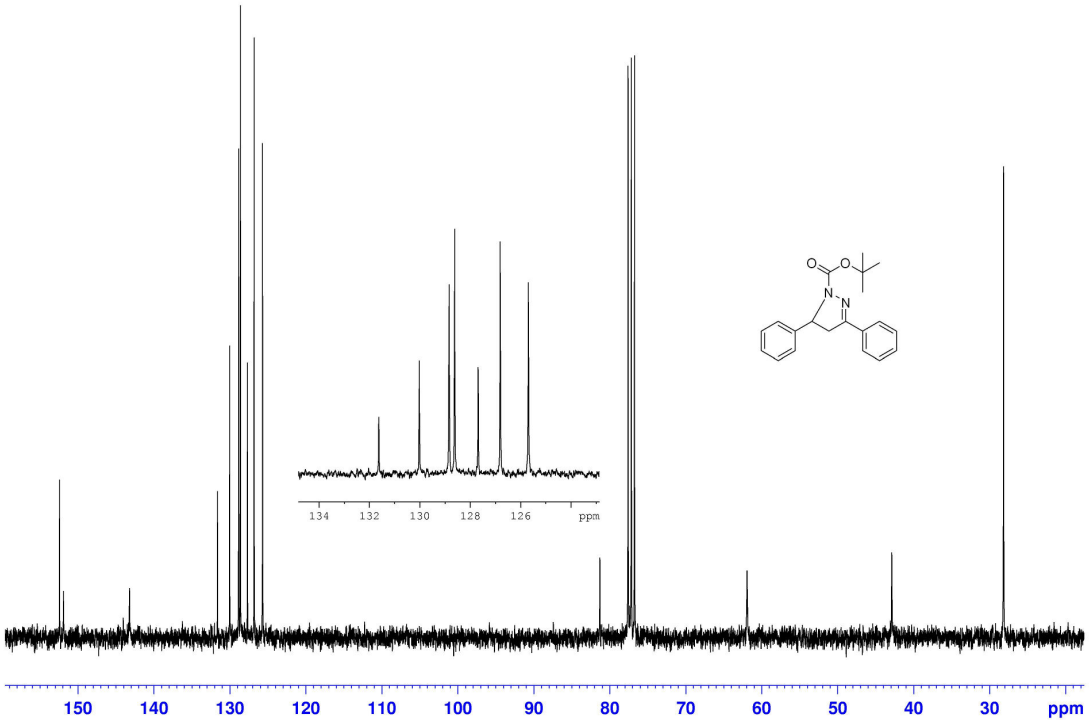
VI.2 1-benzoyl-3,5-diphenyl-4,5-dihydro-1*H*-pyrazole (DEPT135): 4b



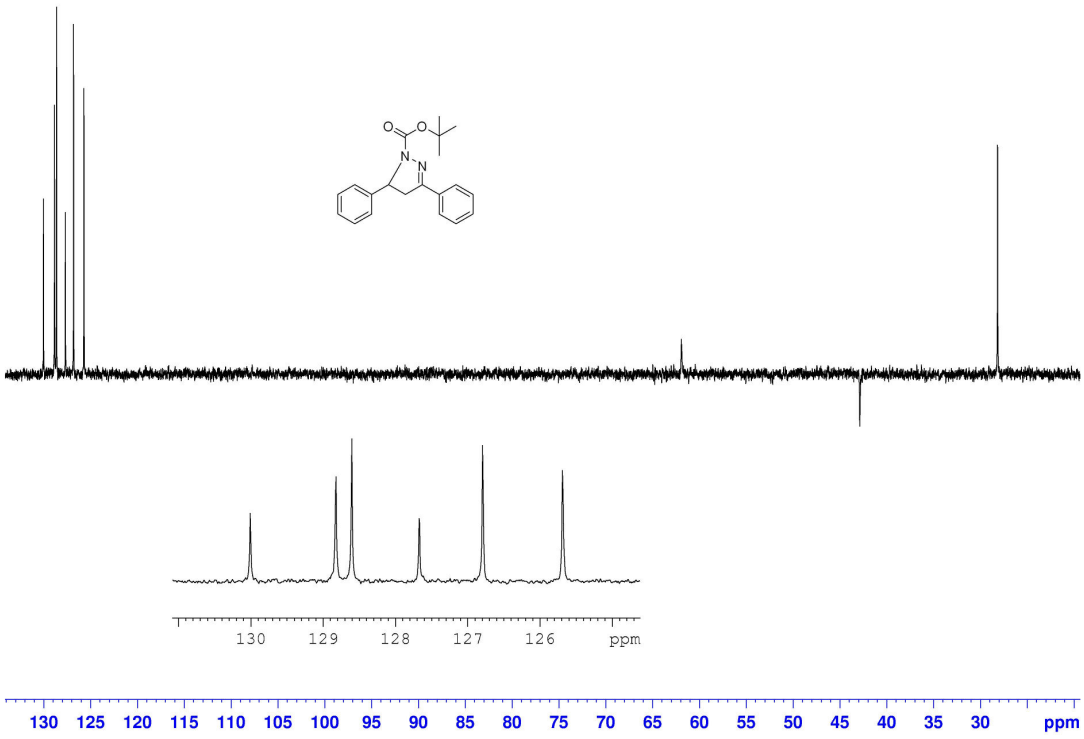
VI.3 *tert*-butyl 3,5-diphenyl-4,5-dihydro-1*H*-pyrazole-1-carboxylate (^{1}H): 4c



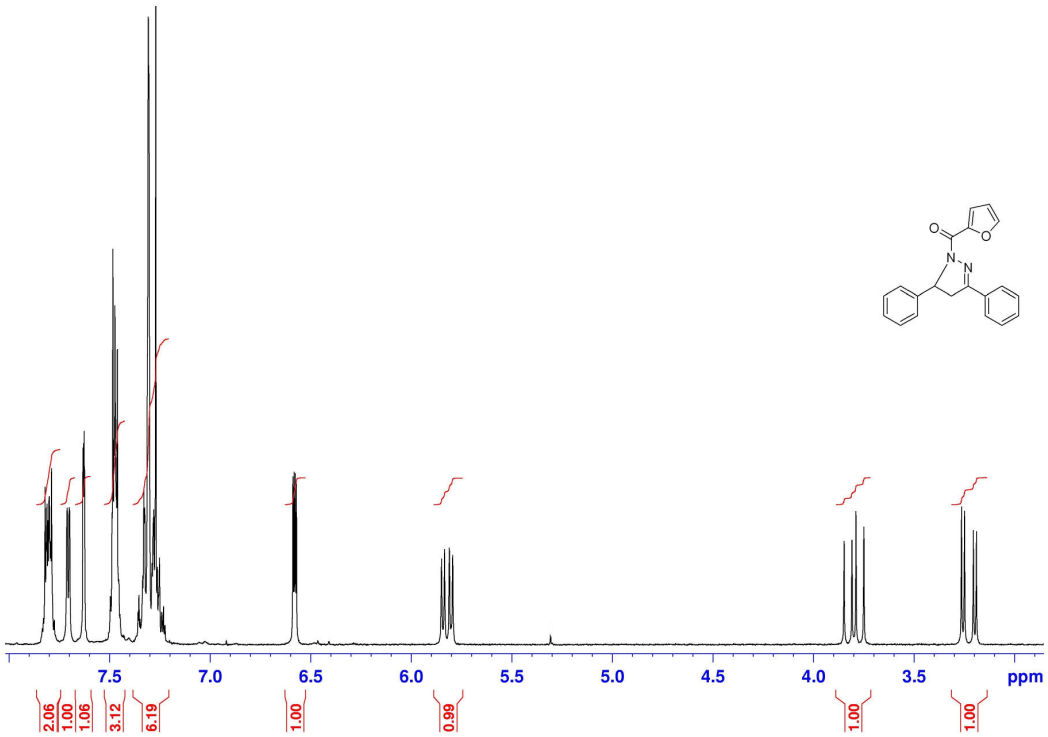
VI.3 *tert*-butyl 3,5-diphenyl-4,5-dihydro-1*H*-pyrazole-1-carboxylate (^{13}C): 4c



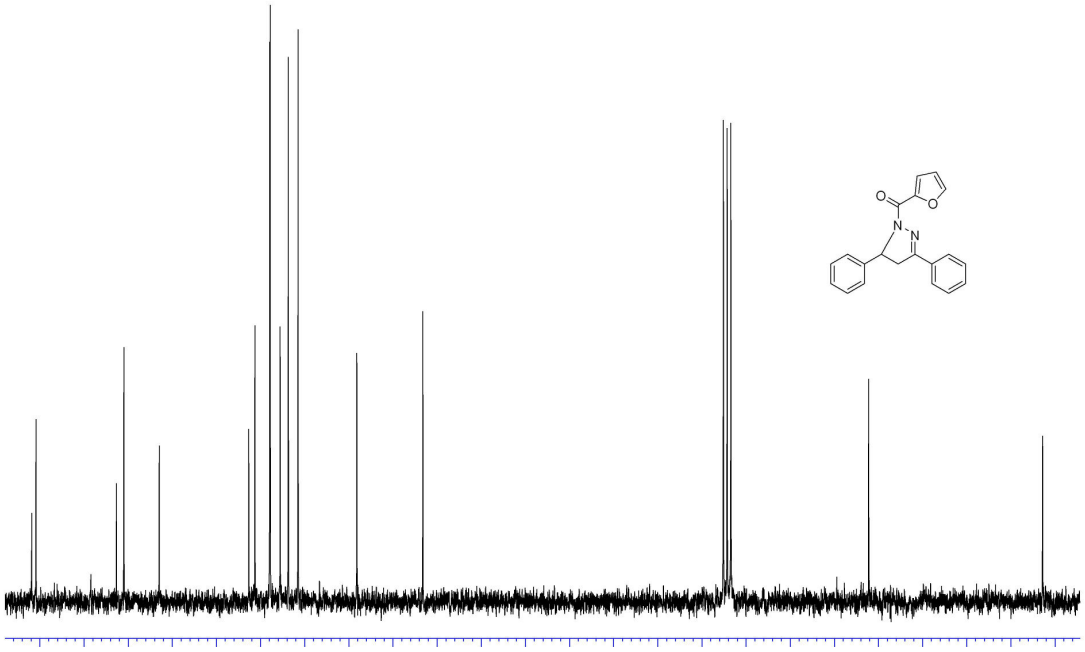
VI.3 *tert*-butyl 3,5-diphenyl-4,5-dihydro-1*H*-pyrazole-1-carboxylate (DEPT135): 4c



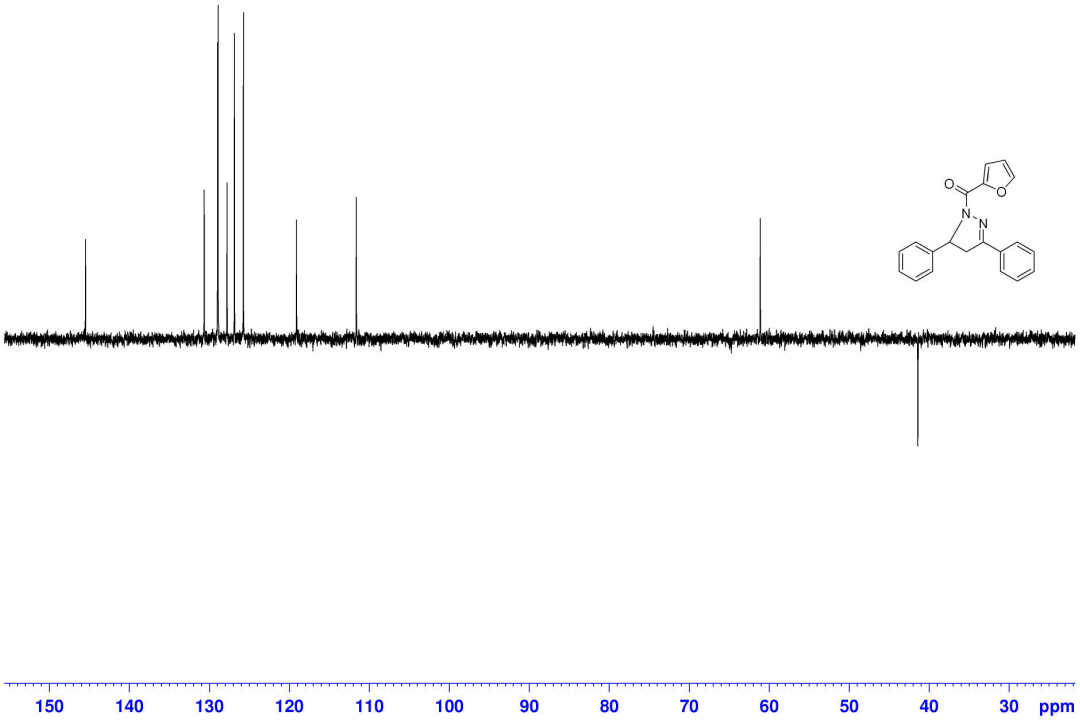
VI.4 1-(2-furoyl)-3,5-diphenyl-4,5-dihydro-1*H*-pyrazole (^{1}H): 4d



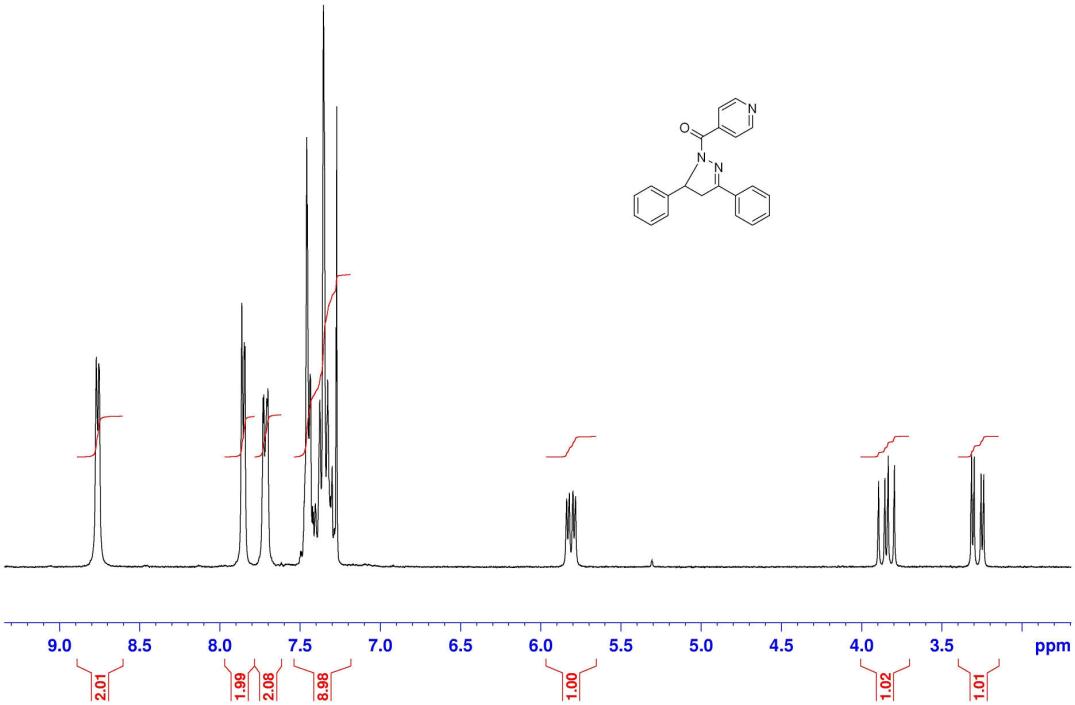
VI.4 1-(2-furoyl)-3,5-diphenyl-4,5-dihydro-1*H*-pyrazole (^{13}C): 4d



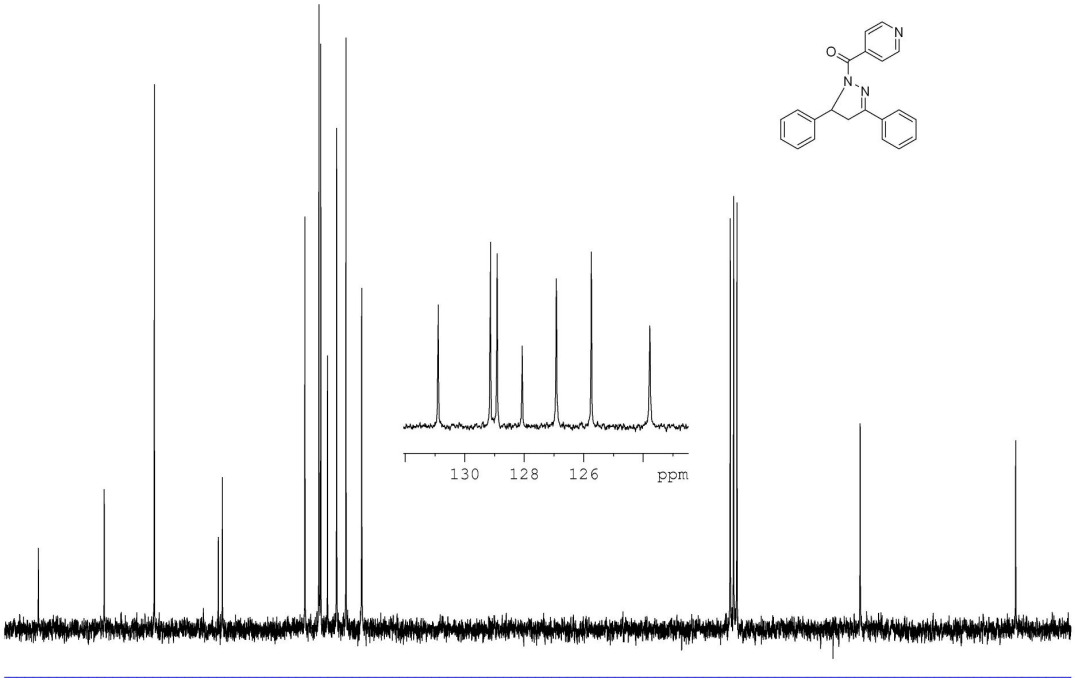
VI.4 1-(2-furoyl)-3,5-diphenyl-4,5-dihydro-1*H*-pyrazole (DEPT135): 4d



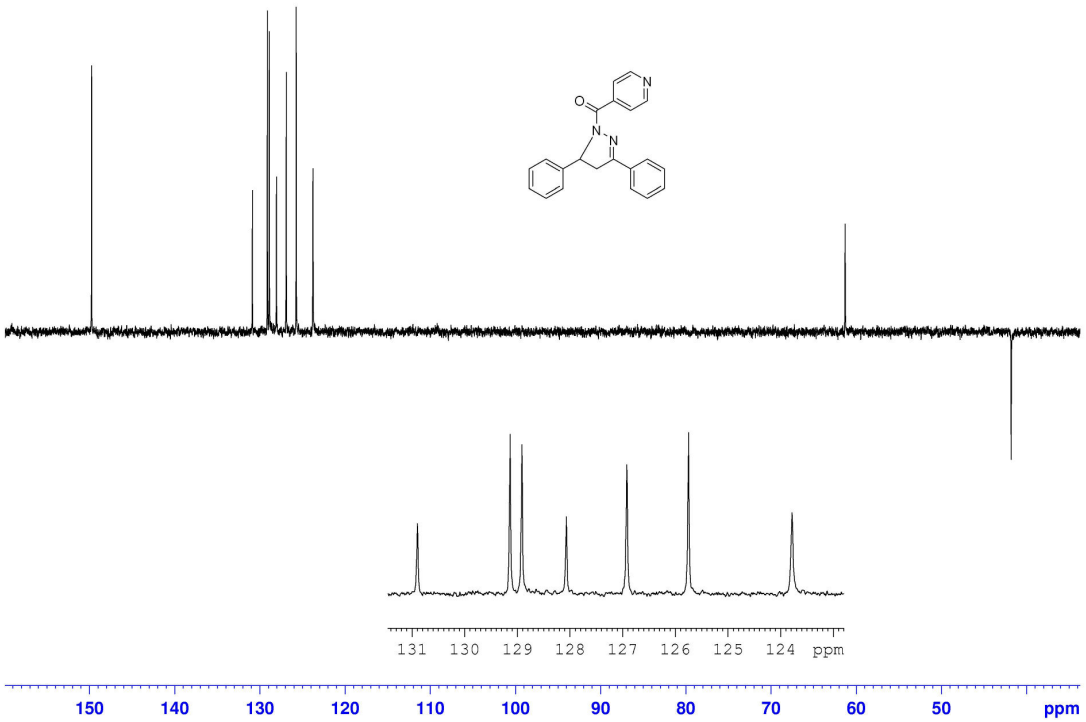
VI.5 4-[(3,5-diphenyl-4,5-dihydro-1*H*-pyrazol-1-yl)carbonyl]pyridine (^{1}H): 4e



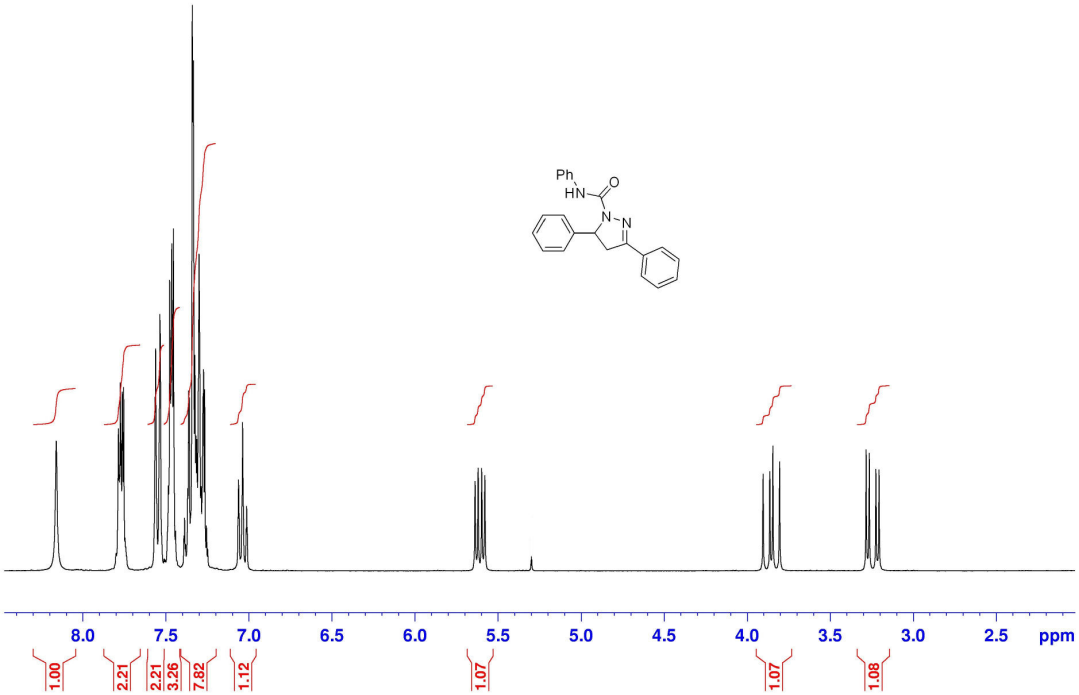
VI.5 4-[(3,5-diphenyl-4,5-dihydro-1*H*-pyrazol-1-yl)carbonyl]pyridine (^{13}C): 4e



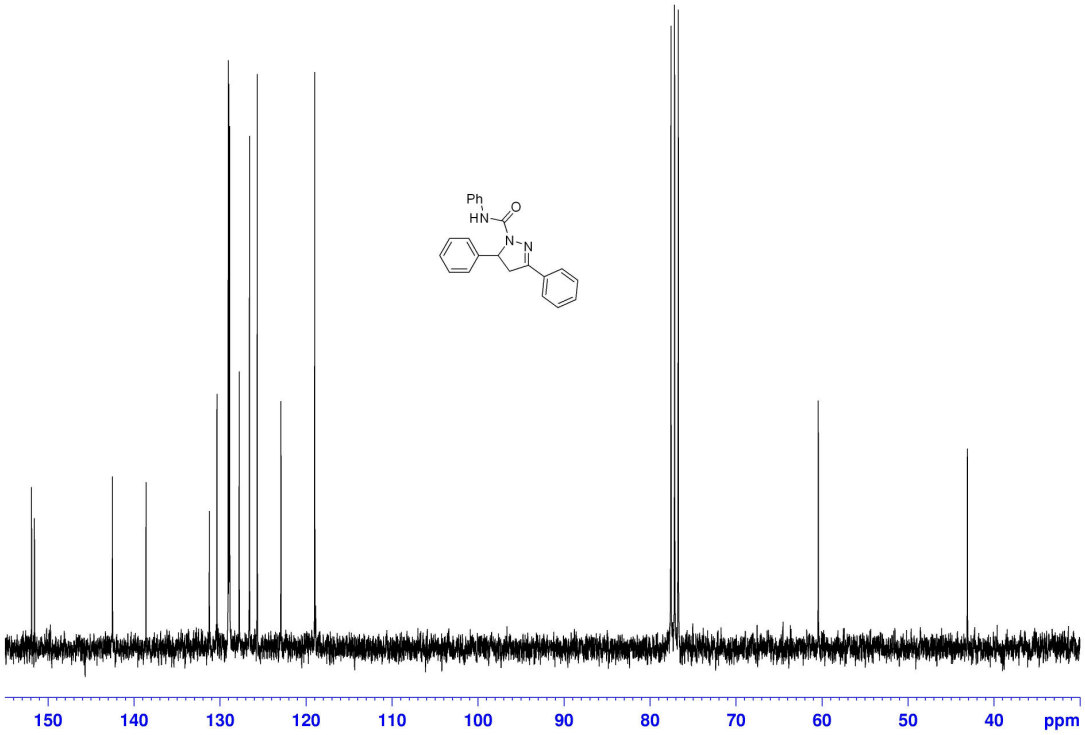
VI.5 4-[(3,5-diphenyl-4,5-dihydro-1*H*-pyrazol-1-yl)carbonyl]pyridine (DEPT135): 4e



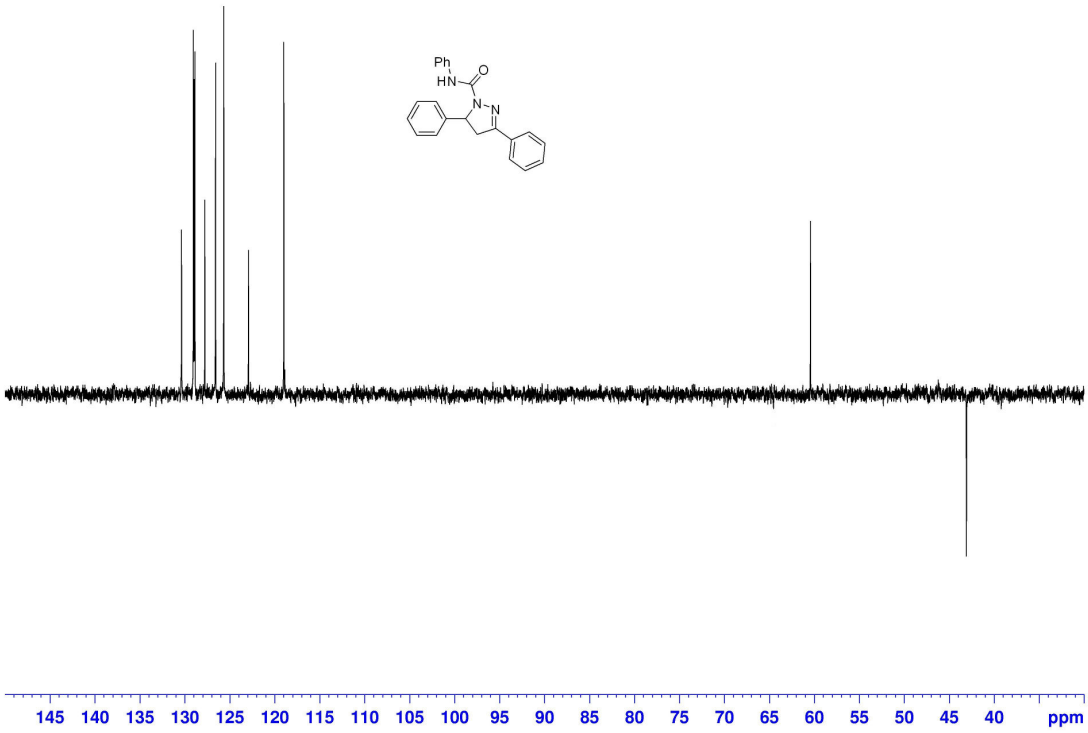
VI.6 *N*,3,5-triphenyl-4,5-dihydro-1*H*-pyrazole-1-carboxamide (^{1}H): 4f



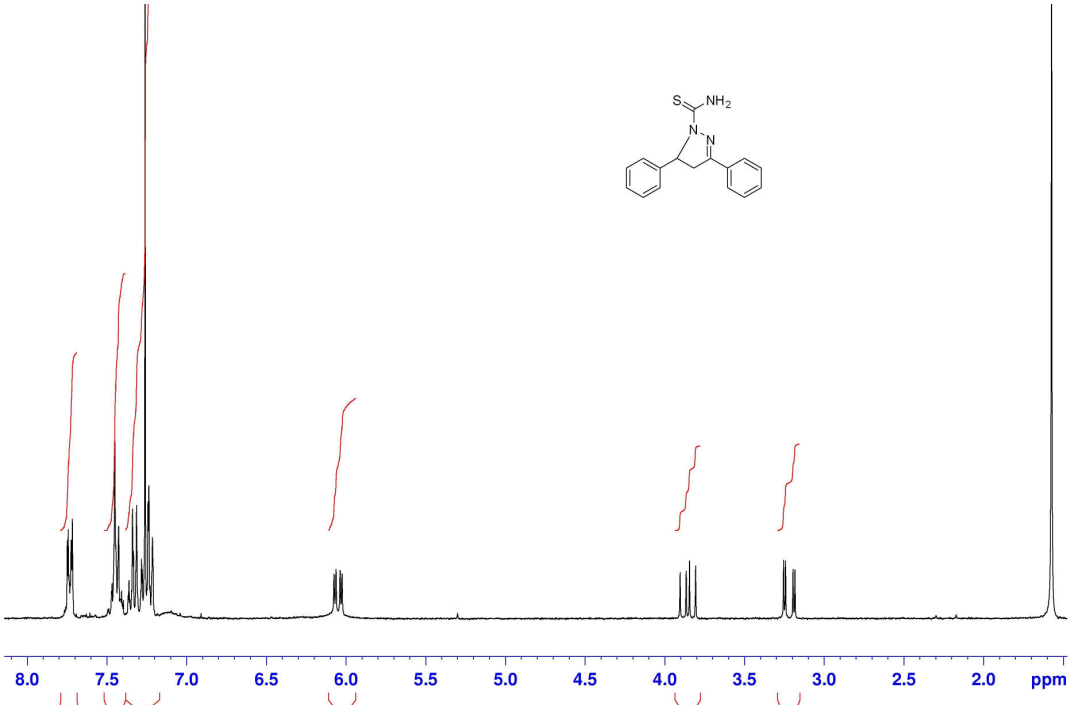
VI.6 *N*,3,5-triphenyl-4,5-dihydro-1*H*-pyrazole-1-carboxamide (^{13}C): 4f



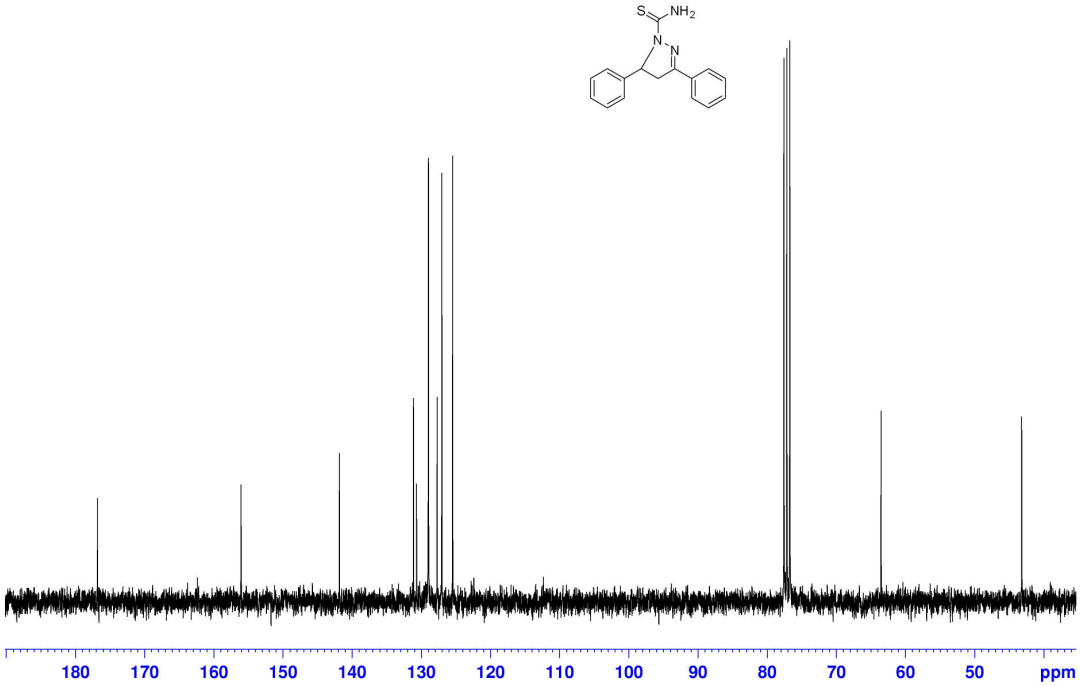
VI.6 3,5-diphenyl-4,5-dihydro-1*H*-pyrazole-1-carbothioamide (DEPT135): 4f



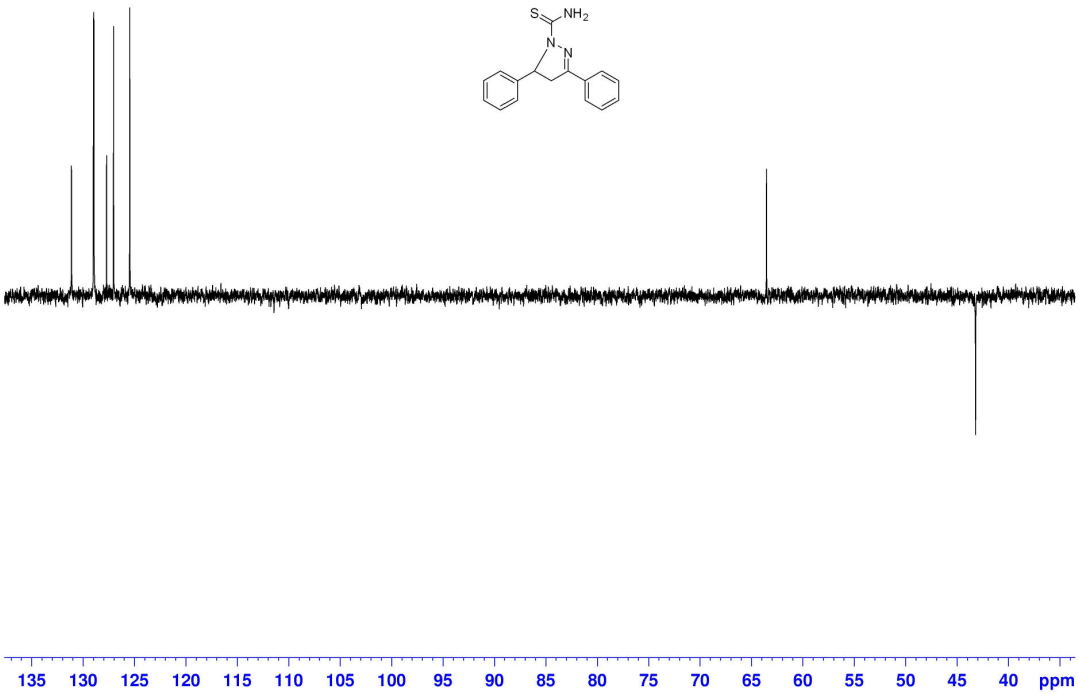
VI.7 3,5-diphenyl-4,5-dihydro-1*H*-pyrazole-1-carbothioamide (^{1}H): 4g



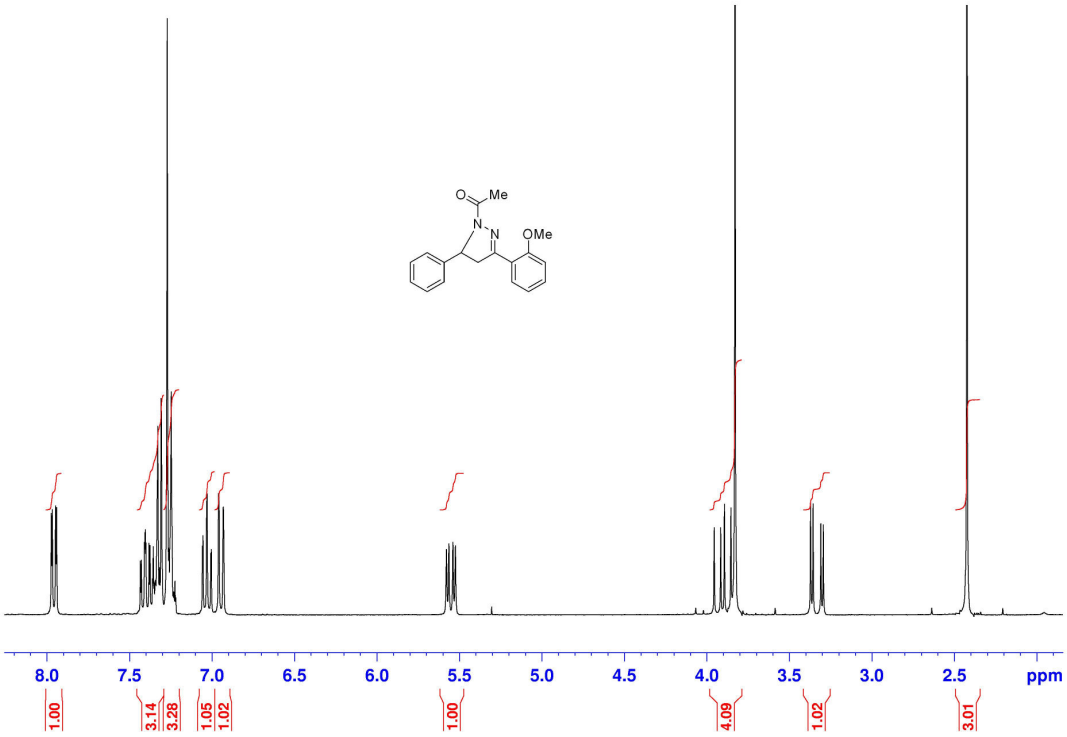
VI.7 3,5-diphenyl-4,5-dihydro-1*H*-pyrazole-1-carbothioamide (^{13}C): 4g



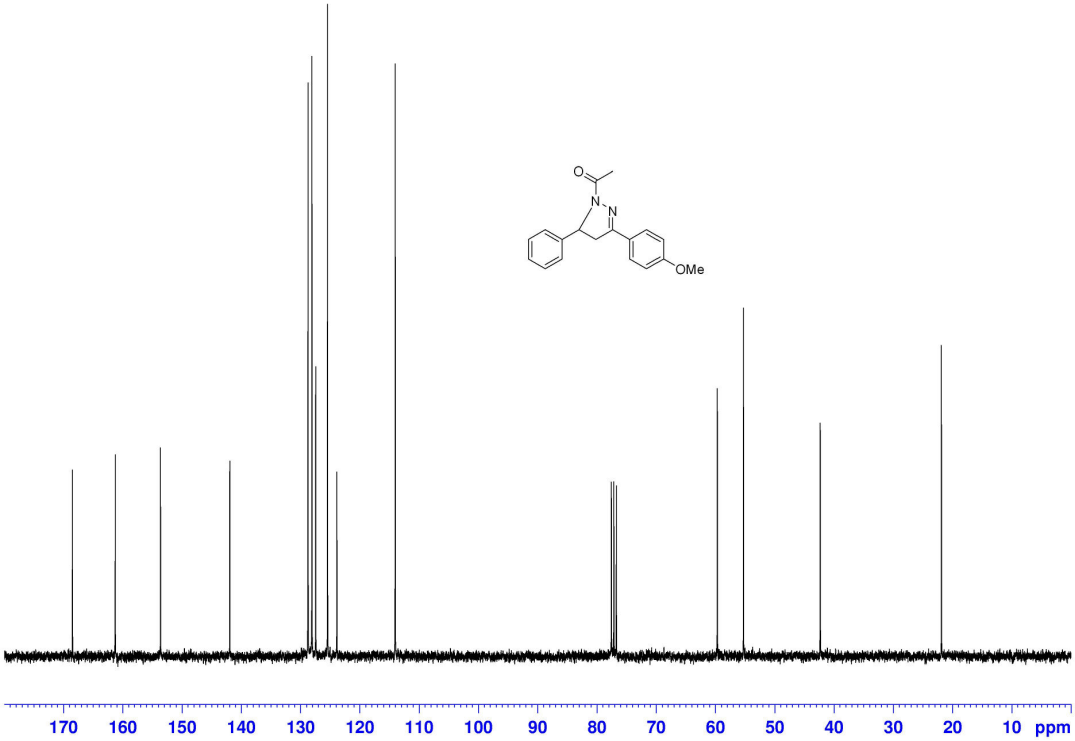
VI.7 3,5-diphenyl-4,5-dihydro-1*H*-pyrazole-1-carbothioamide (DEPT135): 4g



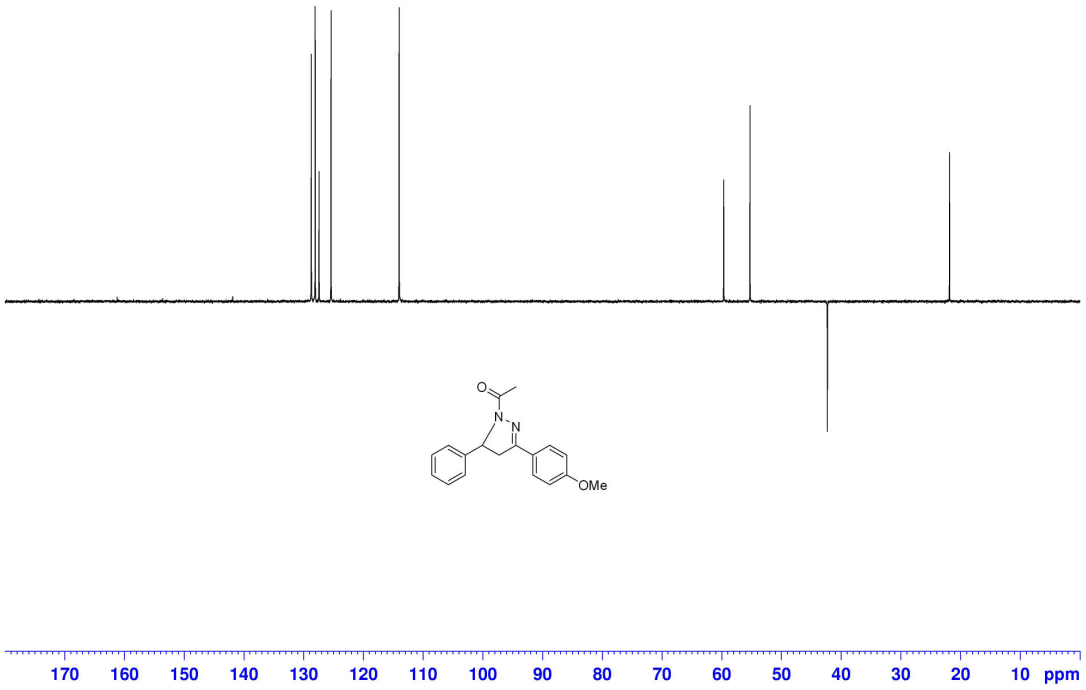
VI.8 1-acetyl-3-(4-methoxyphenyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole (^{1}H): 4i



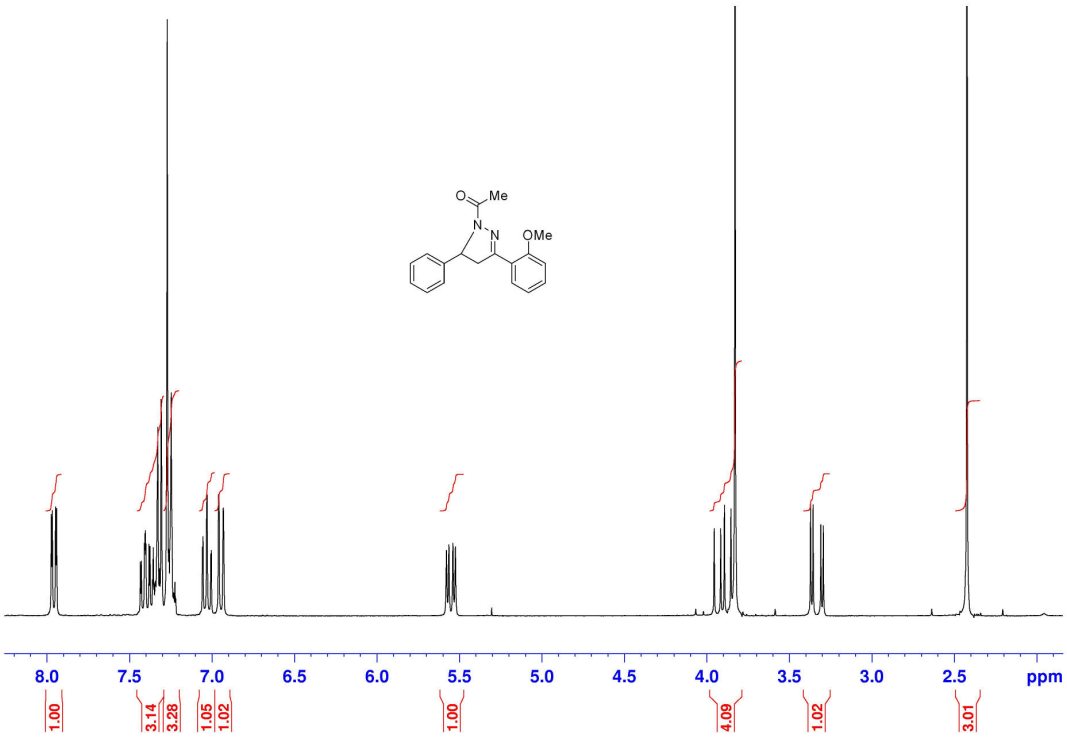
VI.8 1-acetyl-3-(4-methoxyphenyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole (^{13}C): 4i



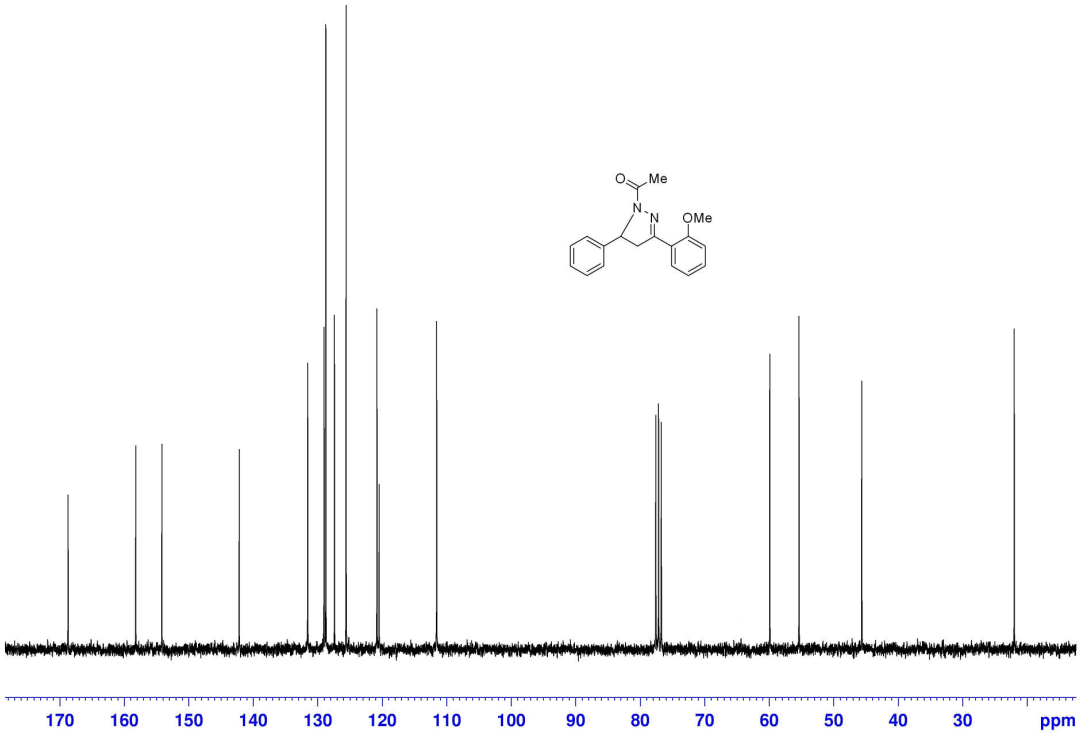
VI.8 1-acetyl-3-(4-methoxyphenyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole (DEPT135): 4i



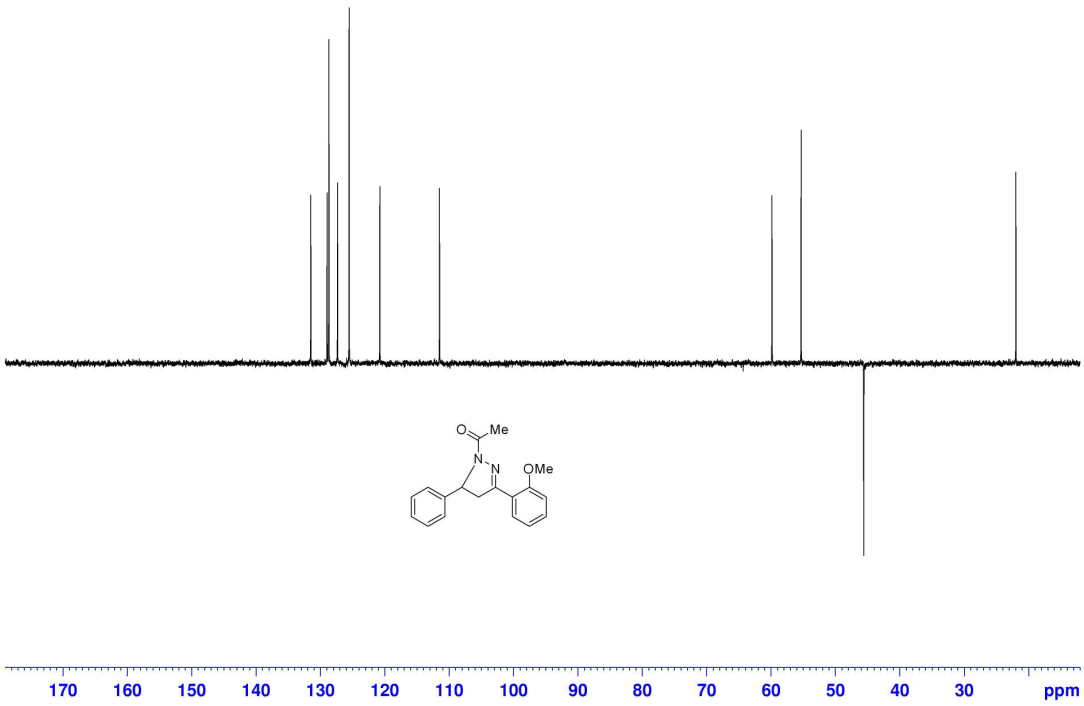
VI.9 1-acetyl-3-(2-methoxyphenyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole (^{1}H): 4j



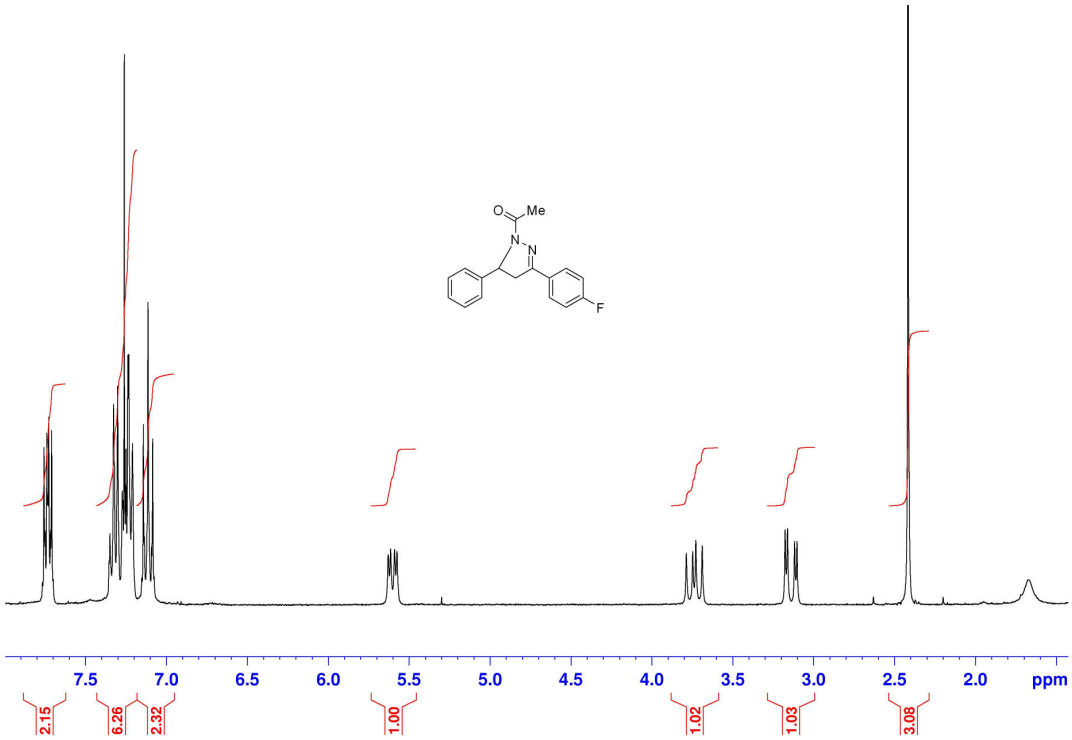
VI.9 1-acetyl-3-(2-methoxyphenyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole (^{13}C): 4j



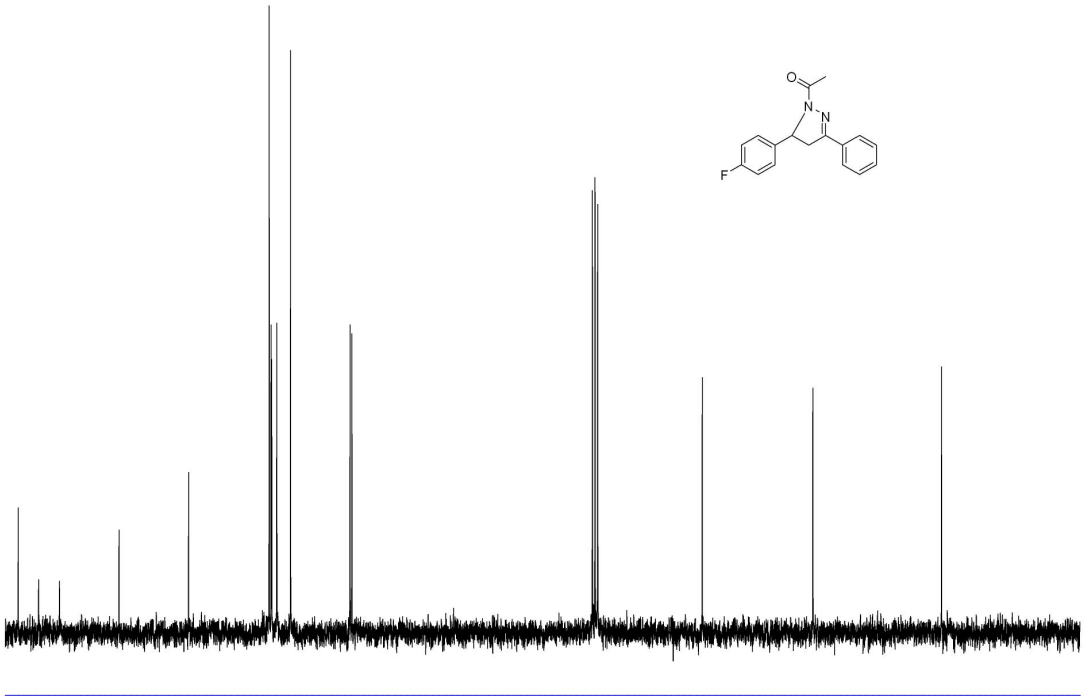
VI.9 1-acetyl-3-(2-methoxyphenyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole (DEPT135): 4j



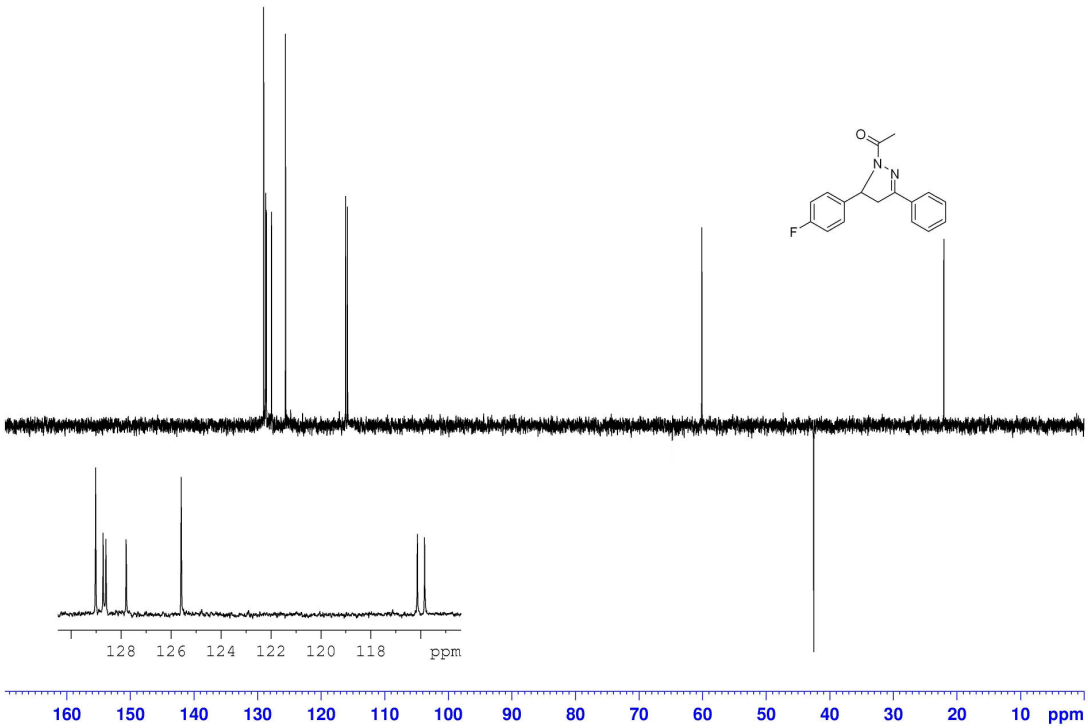
VI.10 1-acetyl-3-(2-fluorophenyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole (1H): 4k



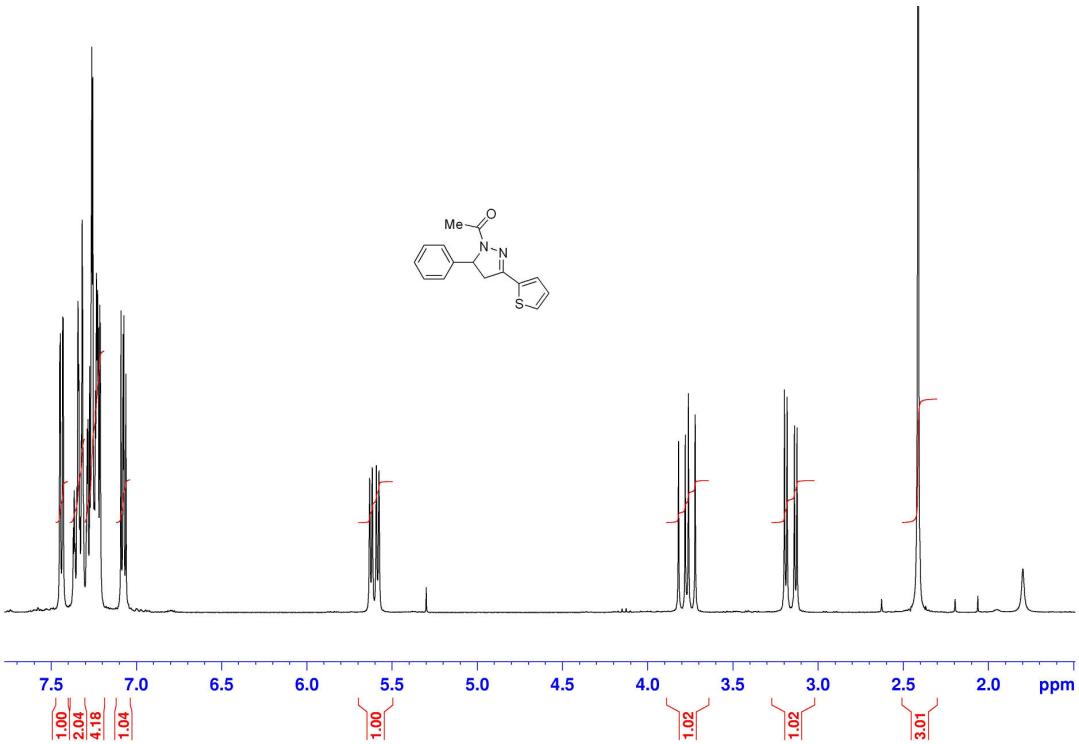
VI.10 1-acetyl-3-(2-fluorophenyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole (^{13}C): 4k



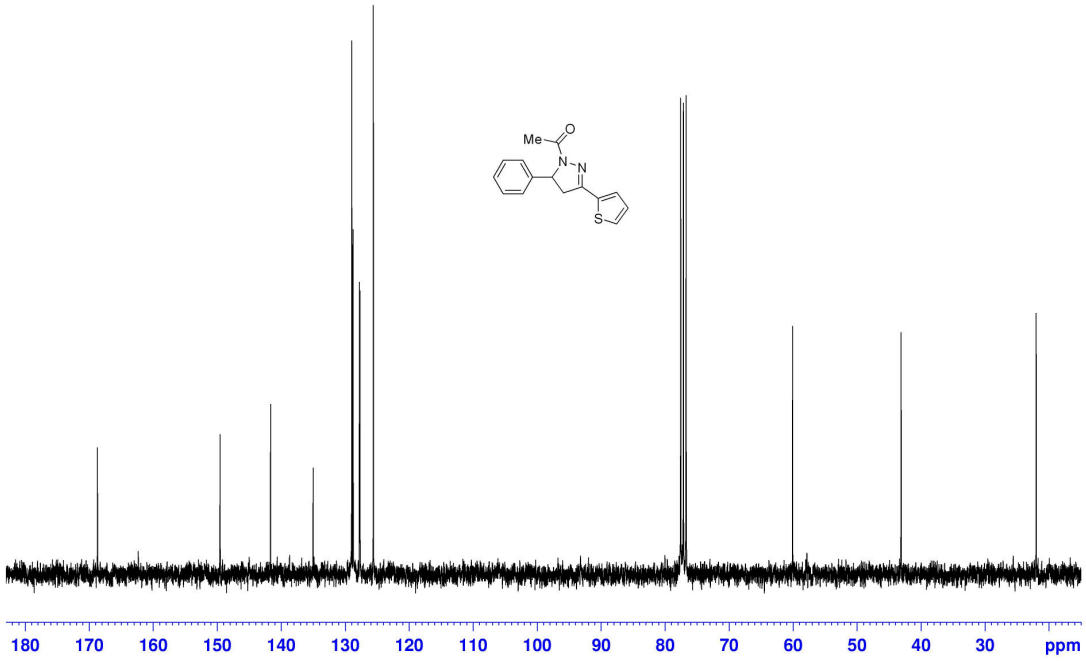
VI.10 1-acetyl-3-(2-fluorophenyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole (DEPT135): 4k



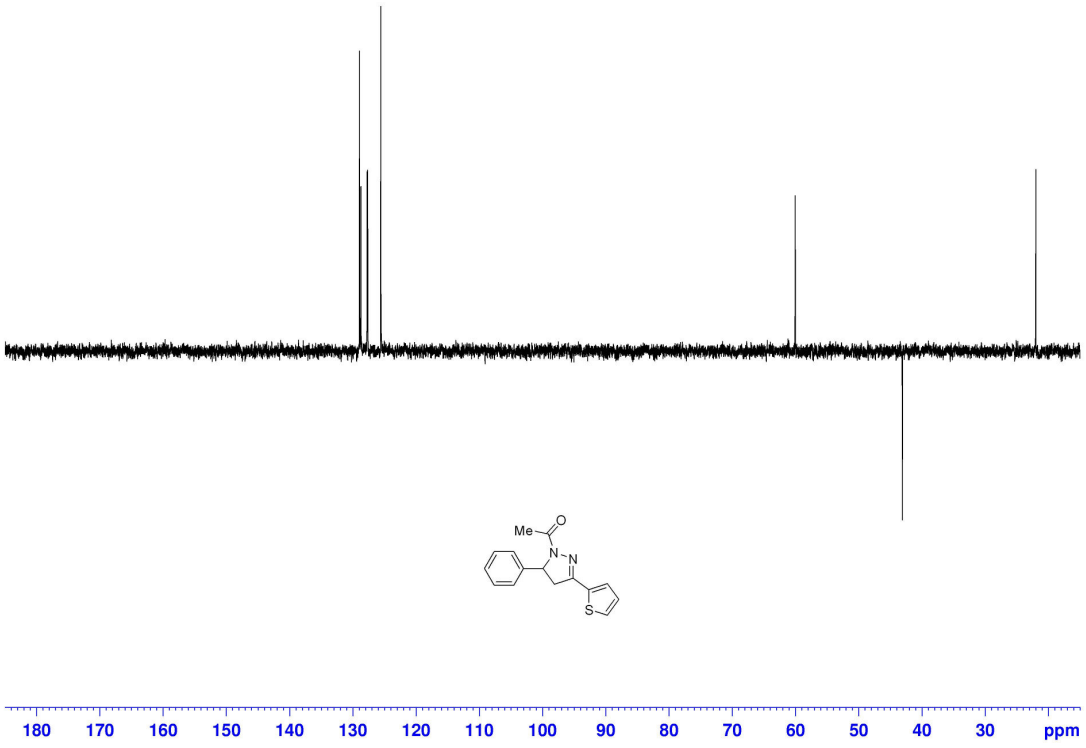
VI.11 1-acetyl-5-phenyl-3-(2-thienyl)-4,5-dihydro-1*H*-pyrazole (^{1}H): 4l



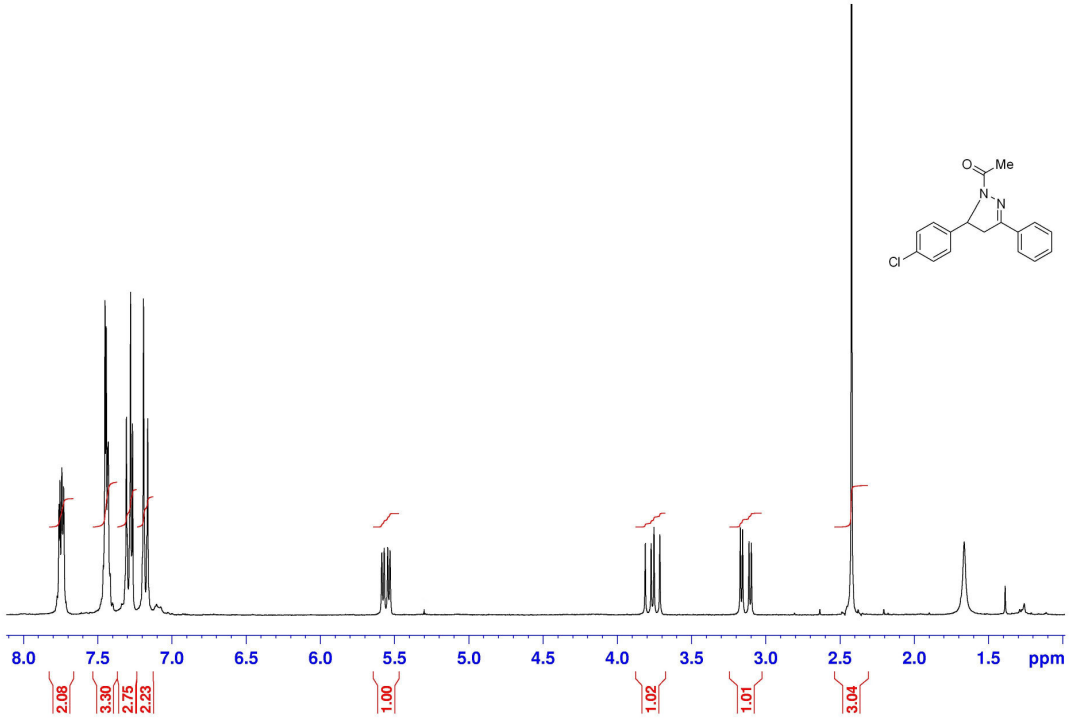
VI.11 1-acetyl-5-phenyl-3-(2-thienyl)-4,5-dihydro-1*H*-pyrazole (13C): 4l



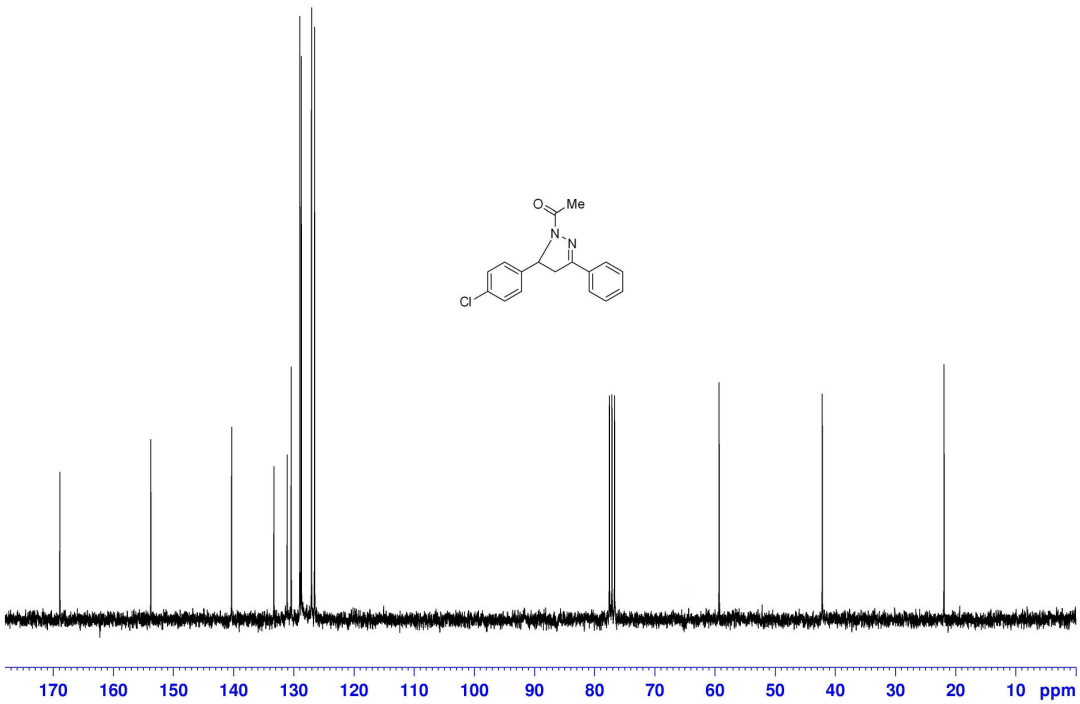
VI.11 1-acetyl-5-phenyl-3-(2-thienyl)-4,5-dihydro-1*H*-pyrazole (DEPT135): 4l



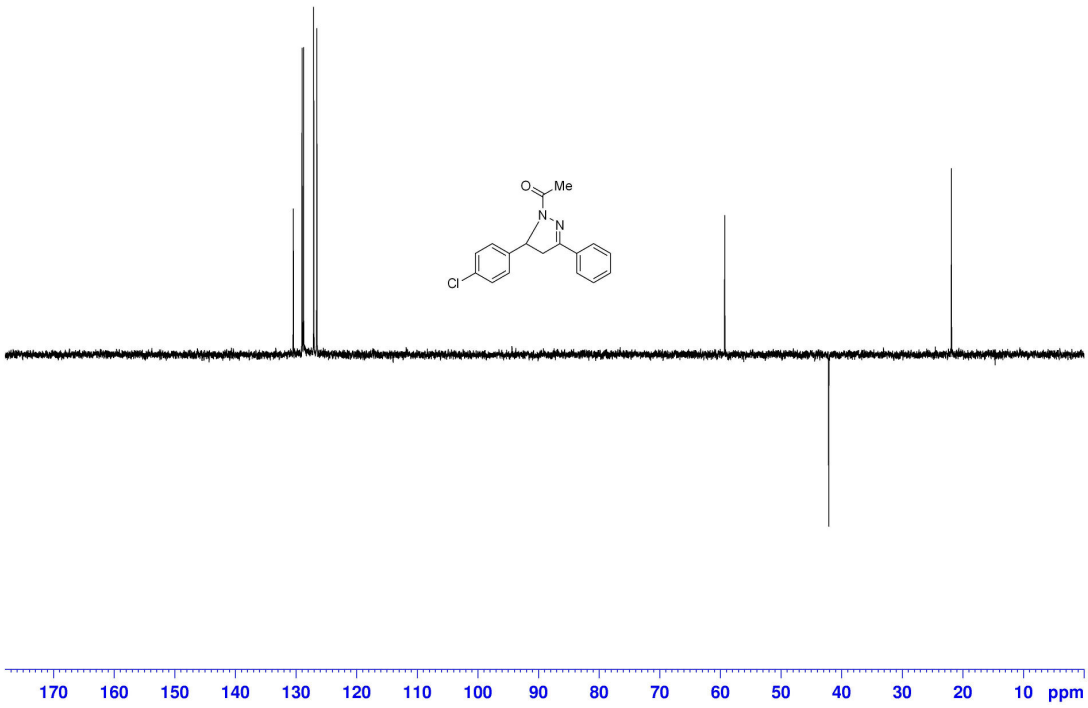
VI.12 1-acetyl-5-(4-chlorophenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazole (^{1}H): 4m



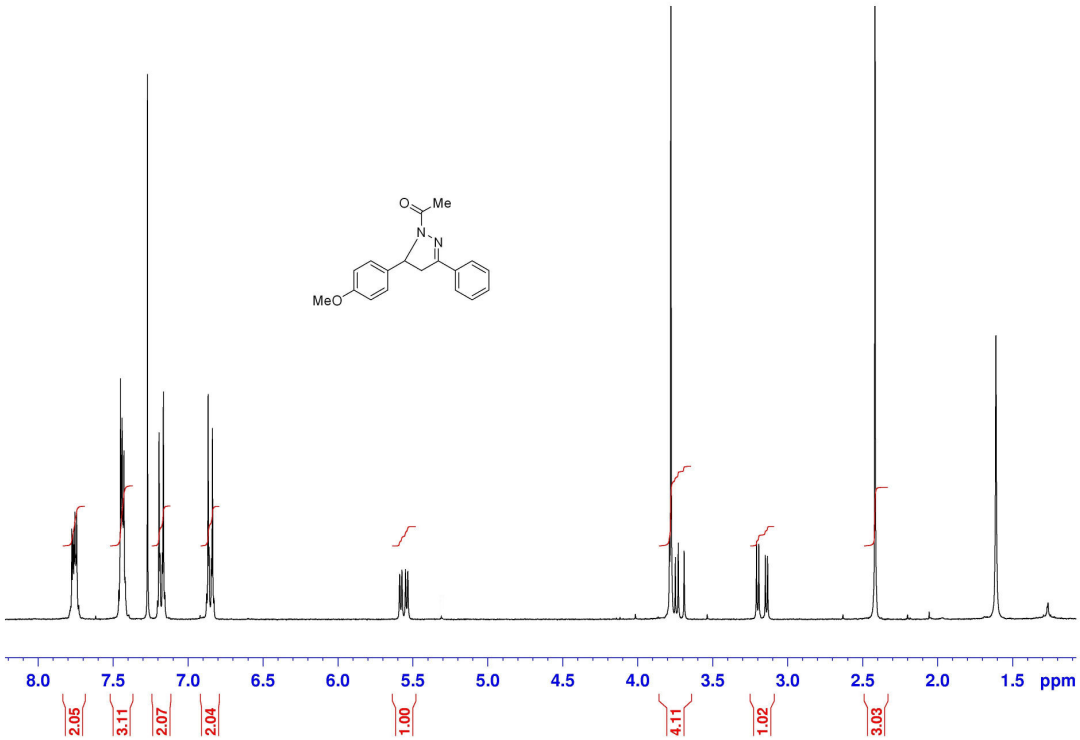
VI.12 1-acetyl-5-(4-chlorophenyl)-3-phenyl-4,5-dihydro-1H-pyrazole (13C): 4m



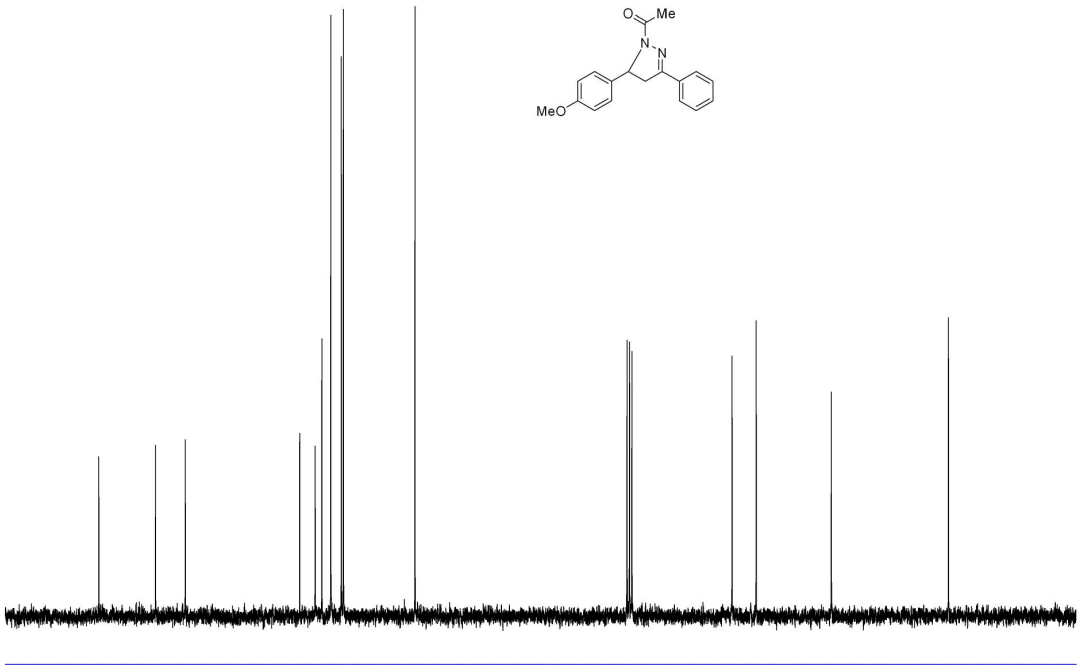
VI.12 1-acetyl-5-(4-chlorophenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazole (DEPT135): 4m



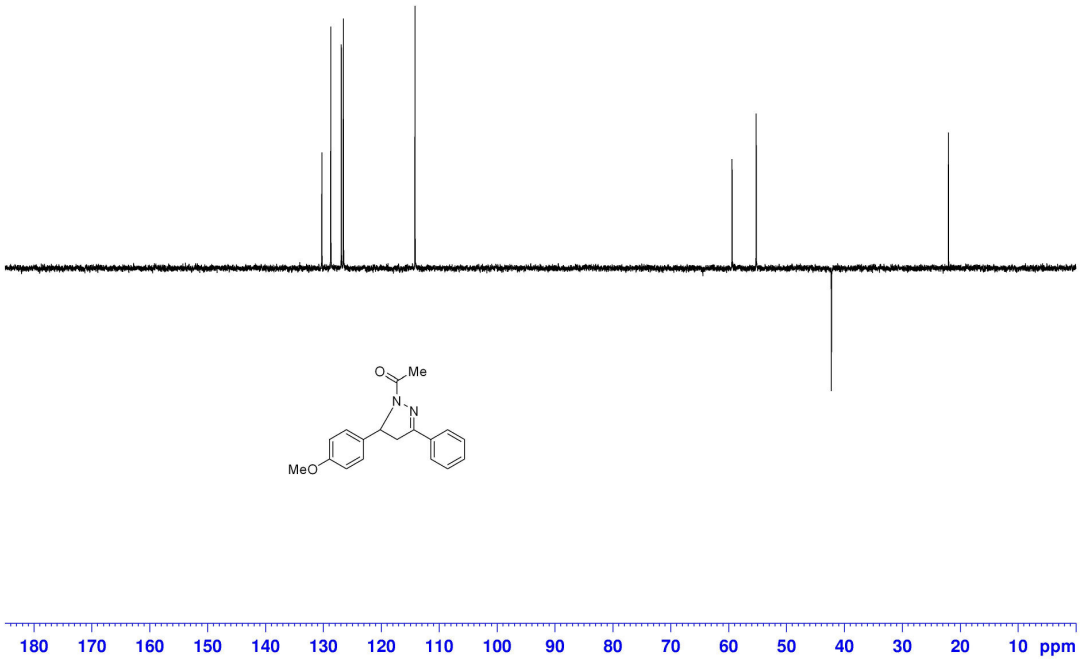
VI.13 1-acetyl-5-(4-methoxyphenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazole (^{1}H): 4n



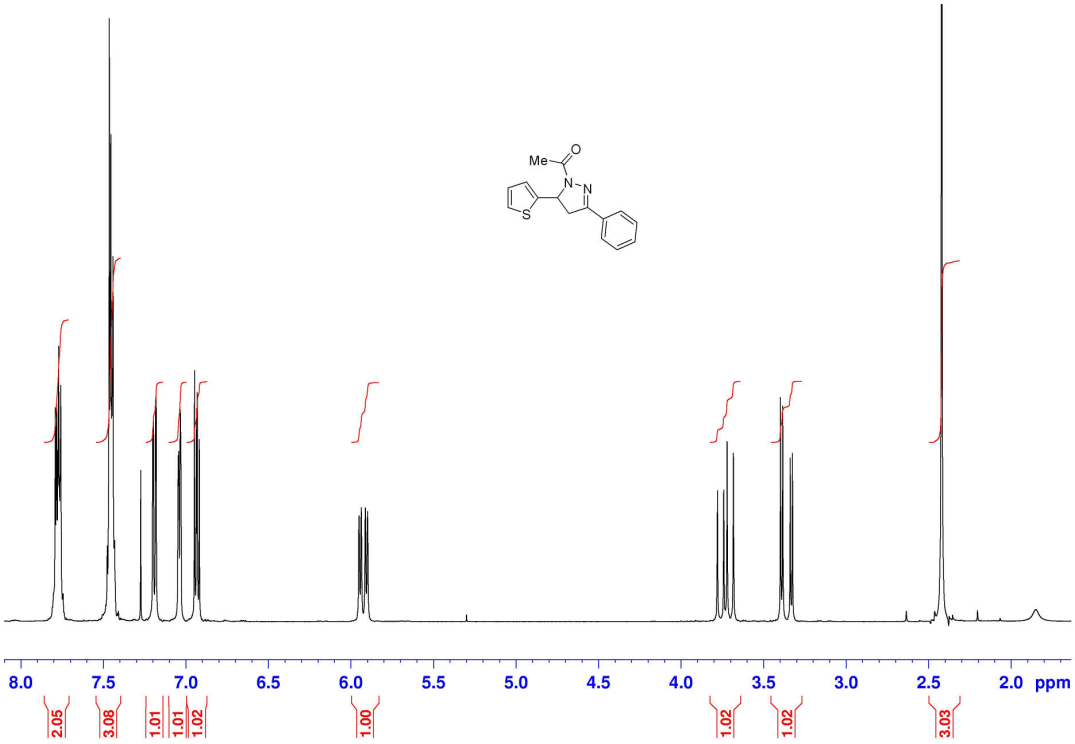
VI.13 1-acetyl-5-(4-methoxyphenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazole (^{13}C): 4n



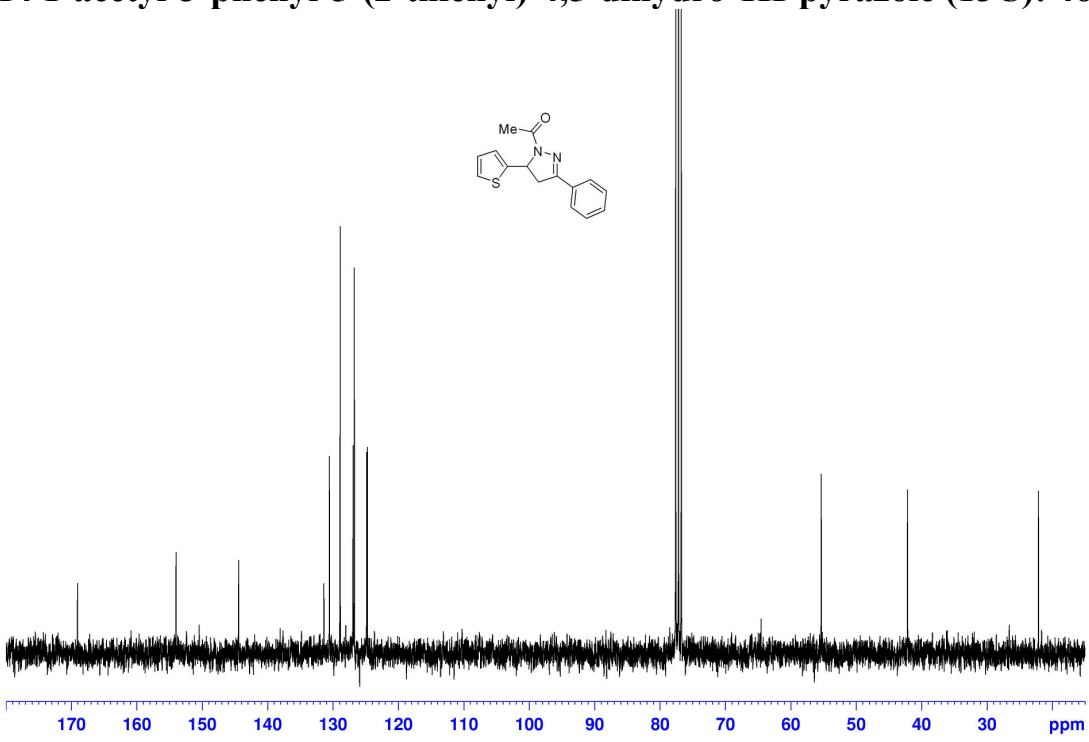
VI.13 1-acetyl-5-(4-methoxyphenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazole (DEPT135): 4n



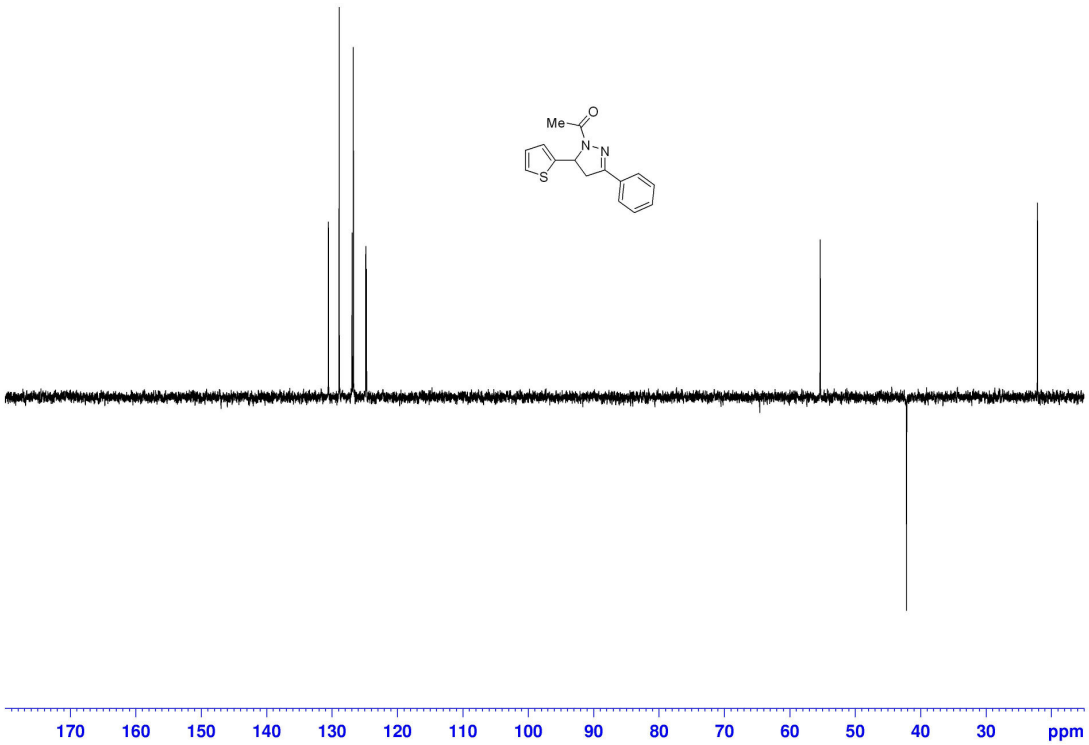
VI.14 1-acetyl-3-phenyl-5-(2-thienyl)-4,5-dihydro-1*H*-pyrazole (^{1}H): 4o



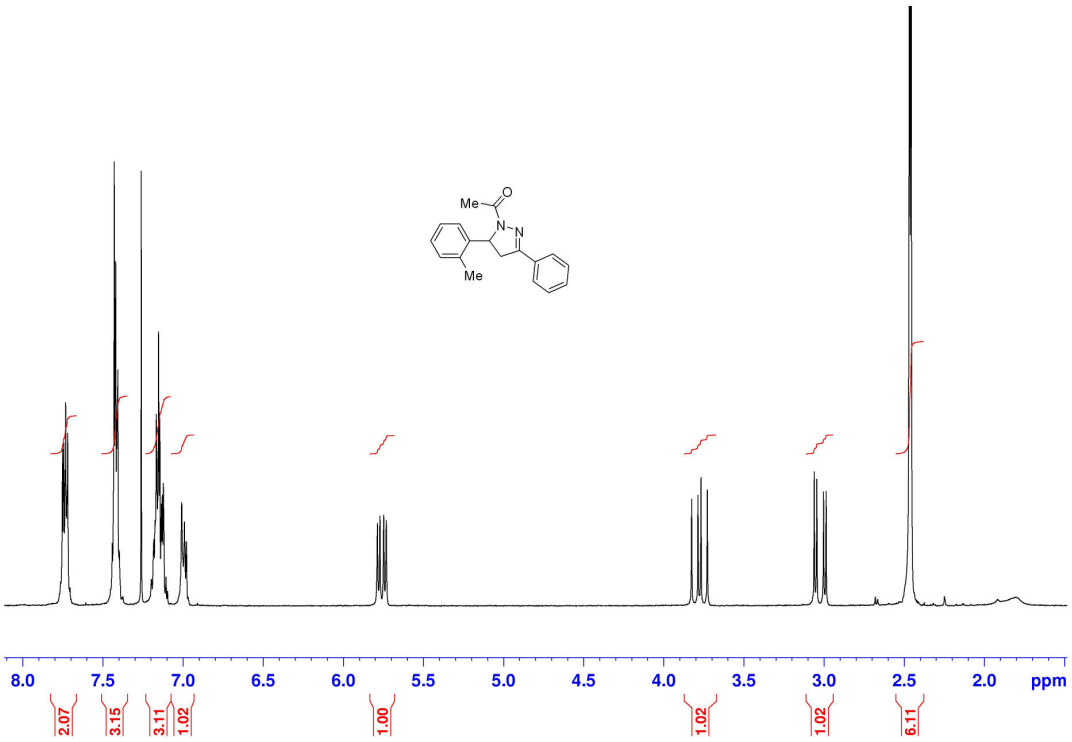
VI.14 1-acetyl-3-phenyl-5-(2-thienyl)-4,5-dihydro-1H-pyrazole (13C): 4o



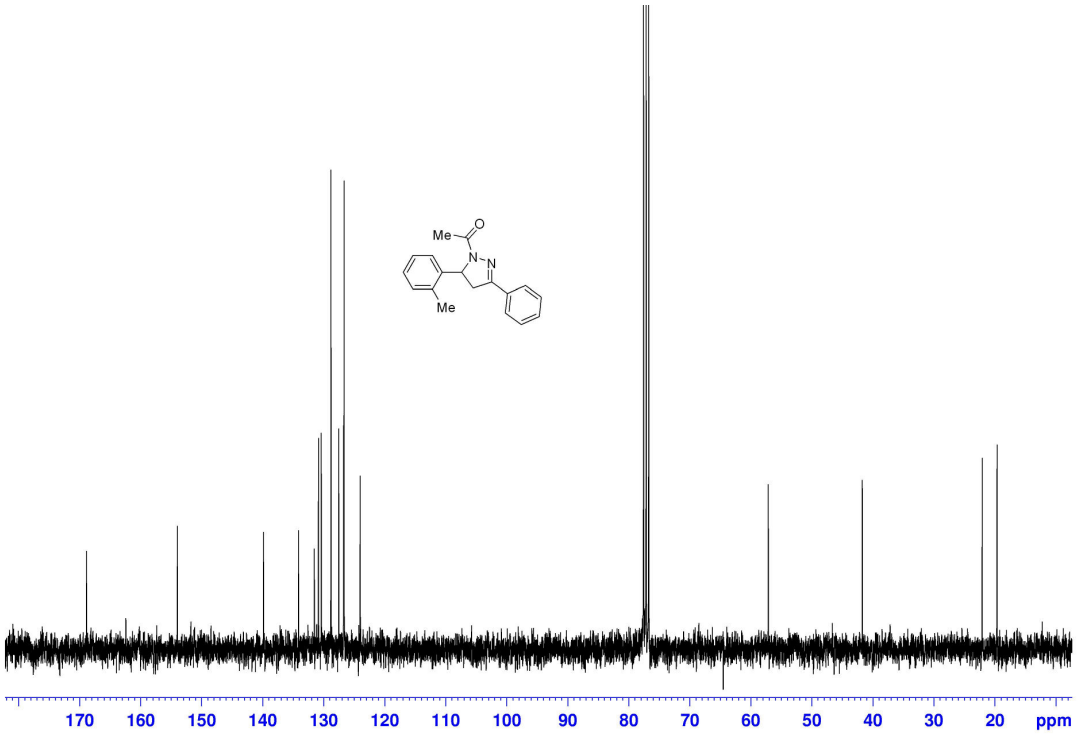
VI.14 1-acetyl-3-phenyl-5-(2-thienyl)-4,5-dihydro-1*H*-pyrazole (DEPT135): 4o



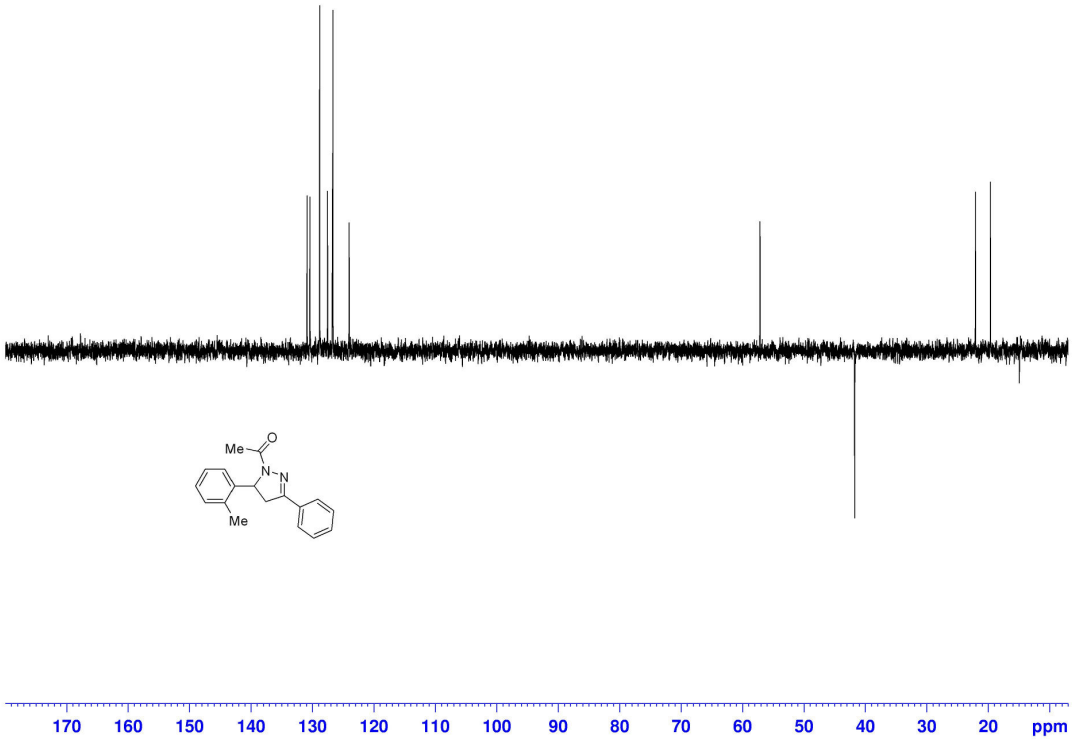
VI.15 1-acetyl-5-(2-methylphenyl)-3-phenyl-4,5-dihydro-1H-pyrazole (1H): 4q



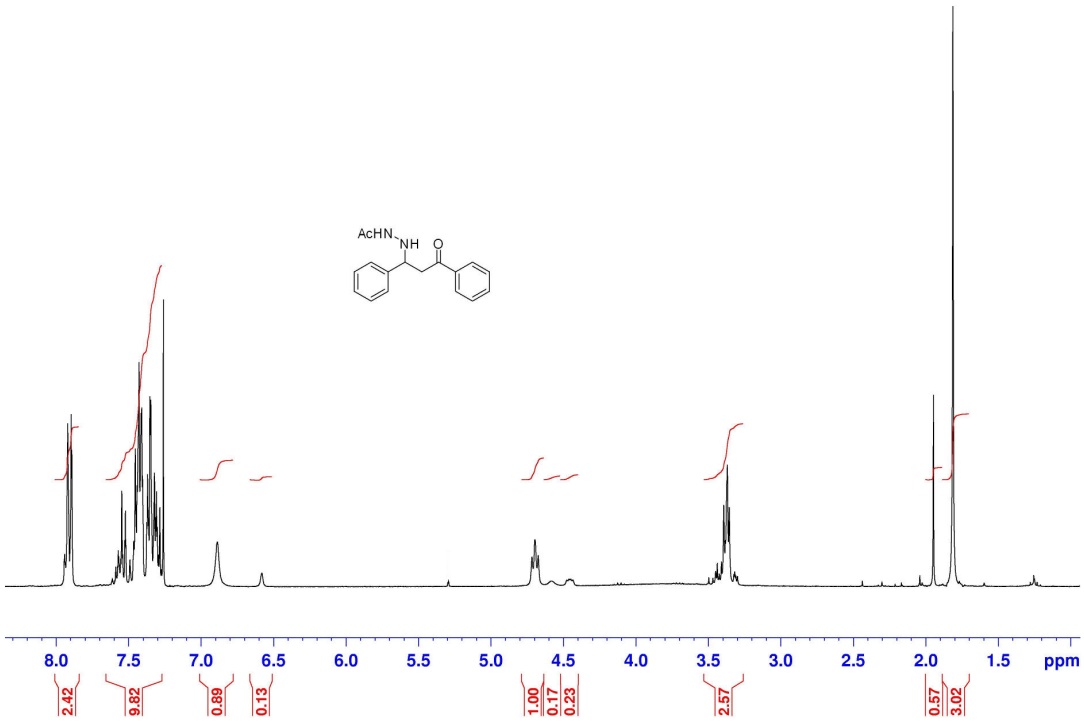
VI.15 1-acetyl-5-(2-methylphenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazole (^{13}C): 4q



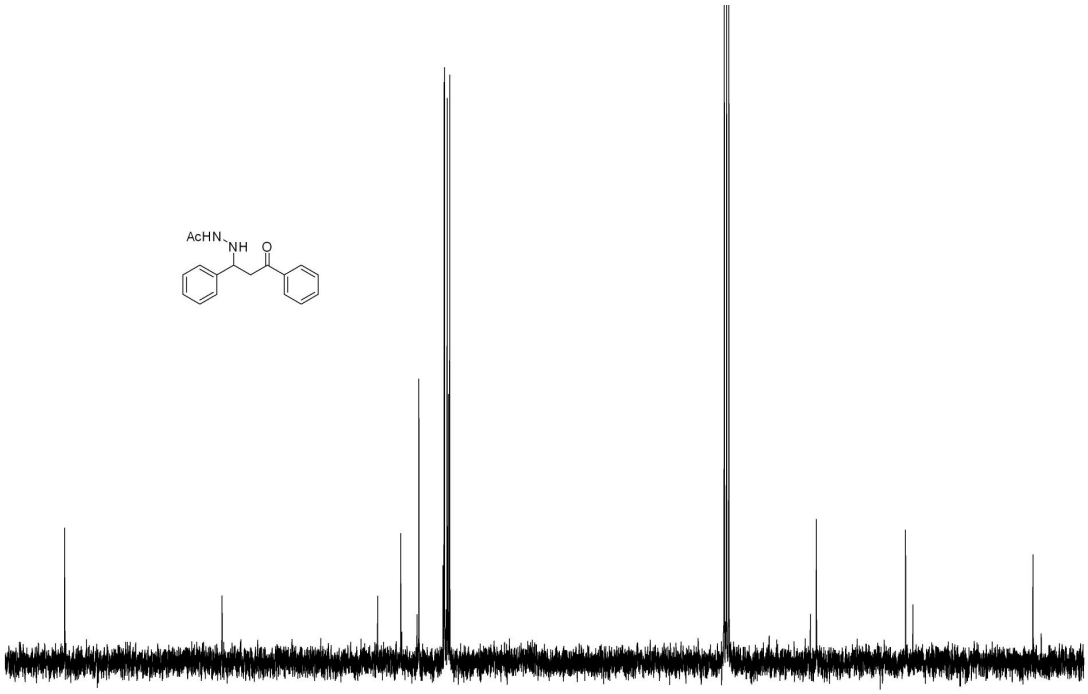
VI.15 1-acetyl-5-(2-methylphenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazole (DEPT135): 4q



VI.16 *N*'-(3-oxo-1,3-diphenylpropyl)acetohydrazide (1H): 3a



VI.16 *N*'-(3-oxo-1,3-diphenylpropyl)acetohydrazide (13C): 3a



VI.16 *N*'-(3-oxo-1,3-diphenylpropyl)acetohydrazide (DEPT135): 3a