Synthesis of Pyrazolines by a Site Isolated Resin-Bound Reagents Methodology

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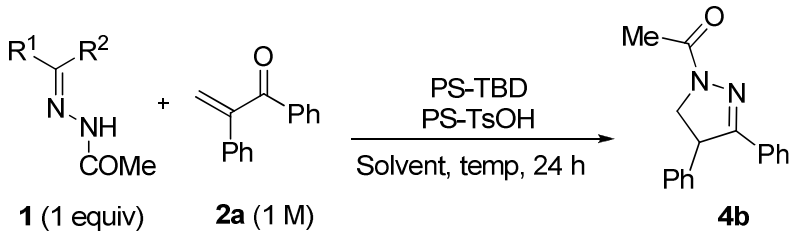
I Various procedures and optimizations

I.1 Optimization of pyrazolines syntheses



1 (1 equiv) **2a** (1 M) **4b**

Entry	Hydrazone **1** R^1, R^2 (equiv)	Solvent	Temp (°C)	PS-TBD (%)	PS-TsOH (%)	Pyrazoline **4b**[a] (%)	Enone **2a**[a] (%)
1	Me, H (1.2)	THF	50	20	100	9	39
2	Me, H (1.2)	MeCN	50	20	100	40	16
3	Me, H (1.2)	DMF	50	20	100	50	4
4	Me, H (1.2)	MeCN	25	20	100	20	29
5	Me, H (1.5)	MeCN	50	20	100	55	10
6	Me, H (1.5)	DMF	50	20	100	59	2
7	Me, H (1.5)	MeCN	50	20	40	33[b]	6
8	Me, H (1.5)	MeCN	50	20	10	-[c]	6
9	Et, H (1.5)	MeCN	50	20	100	62	8
10	Me, Me (1.5)	MeCN	50	20	100	52	18
11	Ph, H (1.5)	MeCN	50	20	100	73	2
12	4-$MeOC_6H_4$, H (1.5)	MeCN	50	20	100	78	1
13	4-$MeOC_6H_4$, H (1.5)	MeCN[d]	50	20	100	51	26
14	4-$MeOC_6H_4$, H (1.5)	MeCN	50	40	100	69	1
15	4-$MeOC_6H_4$, H (1.5)	MeCN	50	10	100	77	1

[a] Yield determined by ^{1}H NMR of the crude product by an internal standard. [b] 27% of aza-Michael product **3** was obtained. [c] 59% of aza-Michael product **3** was obtained. [d] 1 equivalent of H_2O.

Remark: in optimized conditions the hydrazones could be recovered.

I.2 Synthesis of enones and aza-Michael product 3b

Representative standard procedures for the synthesis of enones (adapted from the litterature).[1] Method A – for 1,2-diarylprop-2-en-1-ones synthesis. To a stirred solution of deoxybenzoin (1.96 g, 10 mmol) in MeOH (25 mL) was successively added formaline (3.57 mL: 37% aqueous solution), piperidine (0.128 mL, 1.3 mmol) and AcOH (0.128 mL, 2.2 mmol). The resulting mixture was refluxed for 3 h and concentrated *in vacuo*. Water was added and the obtained mixture was extracted with CH_2Cl_2. The combined organic layers were washed with water, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give 1,2-diphenylprop-2-en-1-one as colorless oil (2.08 g, quantitative crude yield). The rather unstable crude product was used rapidly without further purification. The analytical data are in accordance with literatures. **Method B – for 1- or 2-monoarylprop-2-en-1-ones synthesis.** To a stirred solution of propiophenone (1.34 g, 10 mmol) in DMF (25 mL) was successively added paraformaldehyde (1.5 g), piperidine (0.128 mL, 1.3 mmol) and AcOH (0.128 mL, 2.2 mmol). The resulting mixture was heating at 90 °C for 1 h. After cooling, water was added to the residue and the mixture was extracted with Et_2O. The combined organic layers were washed with water, dried over $MgSO_4$, filtered, and concentrated to give *in vacuo* 2-methyl-1-phenylprop-2-en-1-one as colorless oil (1.46 g, quantitative yield). The rather unstable crude product was used rapidly without further purification. The analytical data are in accordance with literatures.

Analysis data of unknown enone 2

1,2-bis(4-methoxyphenyl)prop-2-en-1-one (Table 3, entry 13). Pale yellow oil; δ_H(300 MHz; $CDCl_3$) 7.94-7.89 (2 H, m), 7.36-7.32 (2 H, m), 6.91-6.84 (4 H, m), 5.89 (1 H, s), 5.44 (1 H, s), 3.84 (3 H, s), 3.79 (3 H, s); δ_C(75.4 MHz; $CDCl_3$) 196.7 (C), 163.7 (C), 159.8 (C), 147.9 (C), 132.5 (CH), 129.9 (C), 129.7 (C), 128.1 (CH), 117.1 (CH_2), 114.1 (CH), 113.7 (CH), 55.5 (CH_3), 55.3 (CH_3); MS (EI) m/z : 268, 240, 225, 209, 165, 135, 118, 107, 92, 77.

4-methyl-2-phenylpent-1-en-3-one (Table 3, entries 17-18). Colorless oil; δ_H(300 MHz; $CDCl_3$) 7.27-7.18 (5 H, m), 5.89 (1 H, s), 5.75 (1 H, s), 3.20-3.06 (1 H, m), 1.05 (3 H, d, *J* 6.9); δ_C(75.4 MHz; $CDCl_3$) 207.0 (C), 149.1 (C), 137.5 (C), 128.3 (CH), 128.2 (CH), 128.1 (CH), 122.7 (CH_2), 36.8 (CH), 18.8 (CH_3); MS (EI) m/z : 174, 159, 131, 115, 103, 91, 77.

Analysis data for aza-Michael product (Table 1, entry 8).

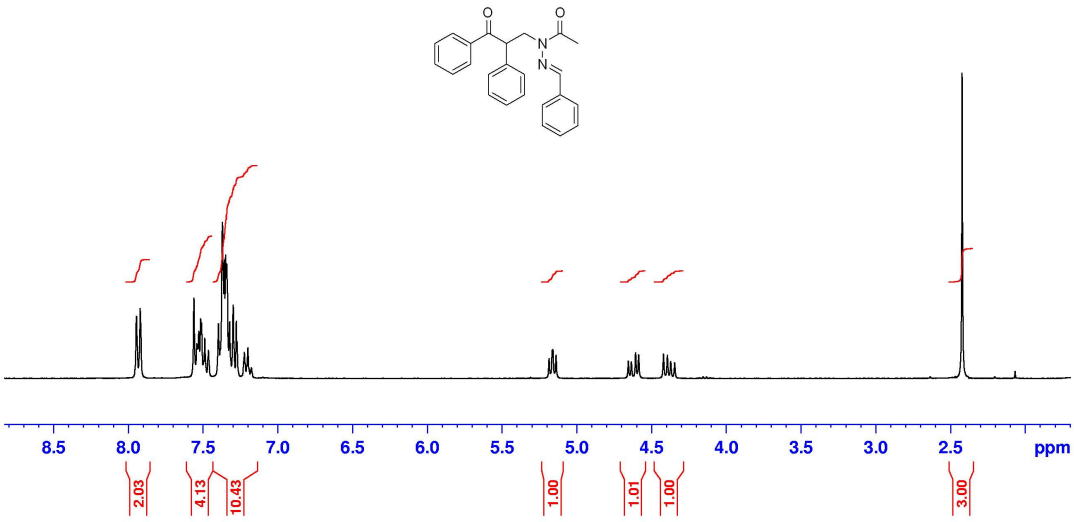
(*E*)-*N*'-benzylidene-*N*-(3-oxo-2,3-diphenylpropyl)acetohydrazide (3b). White solid (150.0 mg, 81 %); R_f = 0.46 (Petroleum ether/EtOAc: 2/1); mp 126-128 °C; IR (KBr) ν_{max}/cm^{-1} 1672, 1612, 1596, 1578, 1493, 1440, 1408, 1359, 1215, 1146, 1036, 975, 749,

[1] (*a*) A. C. Arnold, C. Grosscurt, R. van Hes and K. Wellinga, *J. Agric. Food Chem.*, 1979, **27**, 406; (*b*) J. H. M. Lange, H. K. A. C. Coolen, H. H. van Stuivenberg, J. A. R. Dijksman, A. H. J. Herremans, E. Ronken, H. G. Keizer, K. Tipker, A. C. McCreary, W. Veerman, H. C. Wals, B. Stork, P. C. Verveer, A. P. den Hartog, N. M. J. de Jong, T. J. P. Adolfs, J. Hoogendoorn and C. G. Kruse, *J. Med. Chem.*, 2004, **47**, 627; (*c*) J. A. R. Rodrigues, E. P. Siqueira-Filho, M. de Mancilha and P. J. S. Moran, *Synth. Commun.*, 2003, **33**, 331.

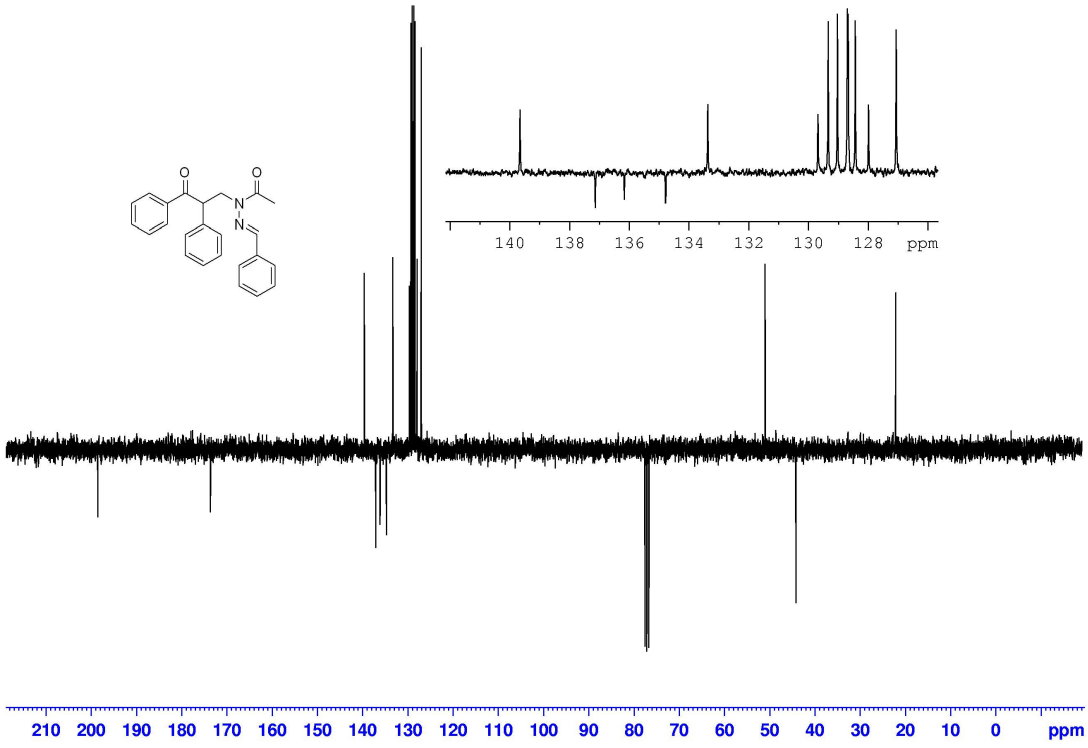
702; δ_H(300 MHz; $CDCl_3$) 7.94-7.91 (2 H, m), 7.56-7.17 (14 H, m), 5.16 (1 H, t, *J* 7.7), 4.61 (1 H, dd, *J* 14.5 and *J* 6.2), 4.38 (1 H, dd, *J* 14.5 and *J* 7.9), 2.42 (3 H, s); δ_C(75.4 MHz; $CDCl_3$) 198.6 (C), 173.7 (C), 139.6 (CH), 137.1 (C), 136.1 (C), 134.7 (C), 133.3 (CH), 129.7 (CH), 129.3 (CH), 129.0 (CH), 128.7 (CH), 128.6 (CH), 128.4 (CH), 128.0 (CH), 127.0 (CH), 51.0 (CH), 44.2 (CH_2), 22.1 (CH_3); HRMS (ESI+): Calcd for $C_{24}H_{23}N_2O_2$ [M+H]+: 371.1760; Found: 371.1767.

II NMR spectra

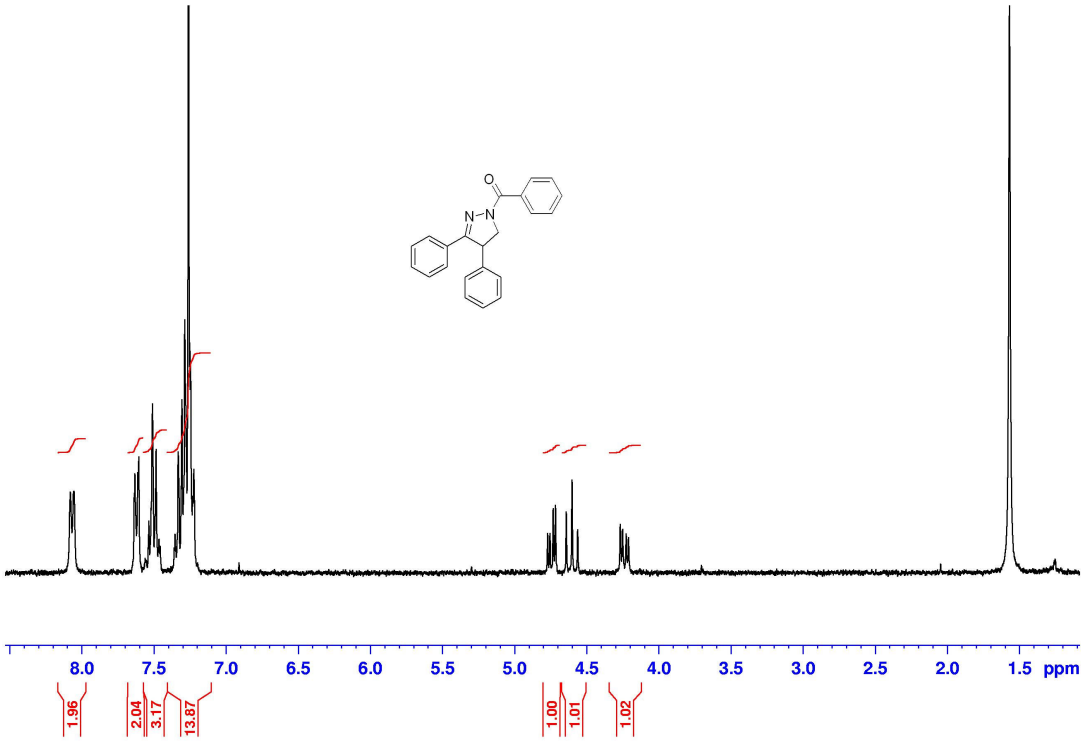
II.1 (E)-N'-benzylidene-N-(3-oxo-2,3-diphenylpropyl)acetohydrazide (^{1}H) 3b



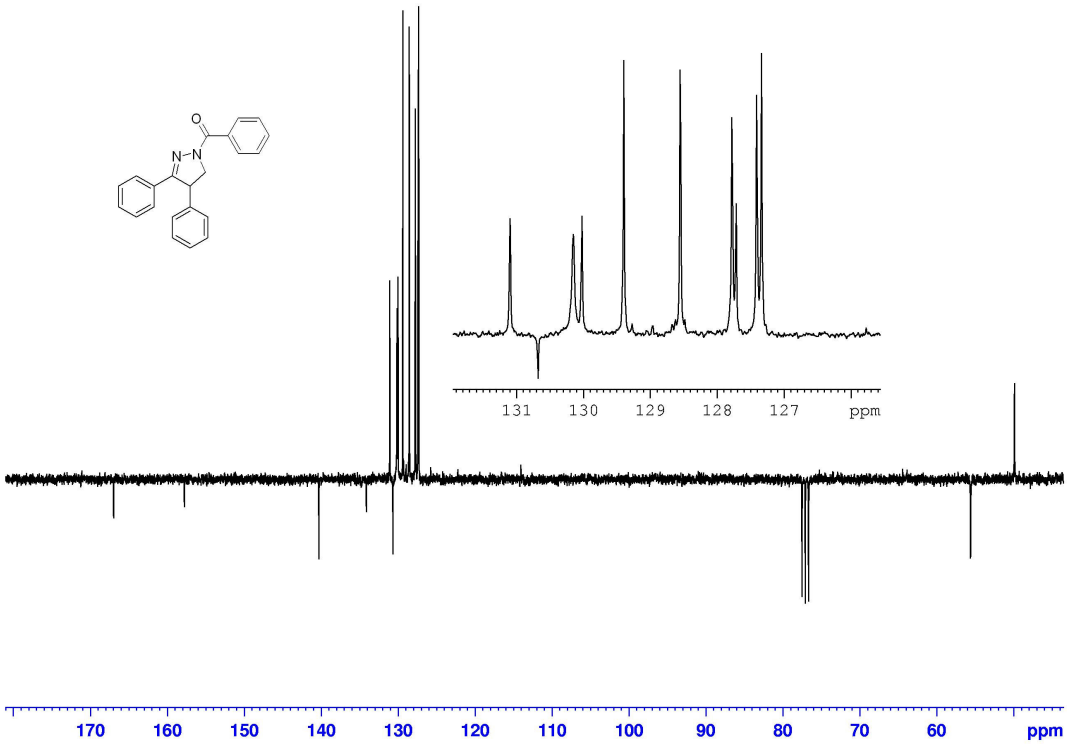
II.1 (E)-N'-benzylidene-N-(3-oxo-2,3-diphenylpropyl)acetohydrazide (JMOD) 3b



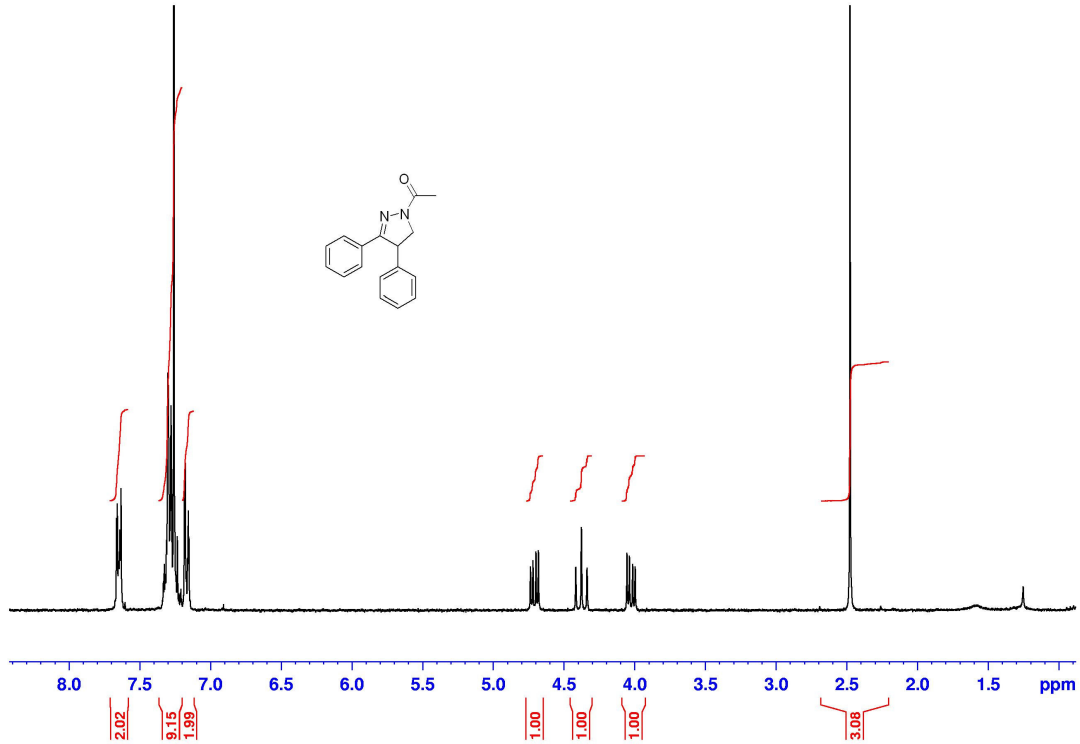
II.2 (3,4-diphenyl-4,5-dihydro-1H-pyrazol-1-yl)(phenyl)methanone (1H) 4a



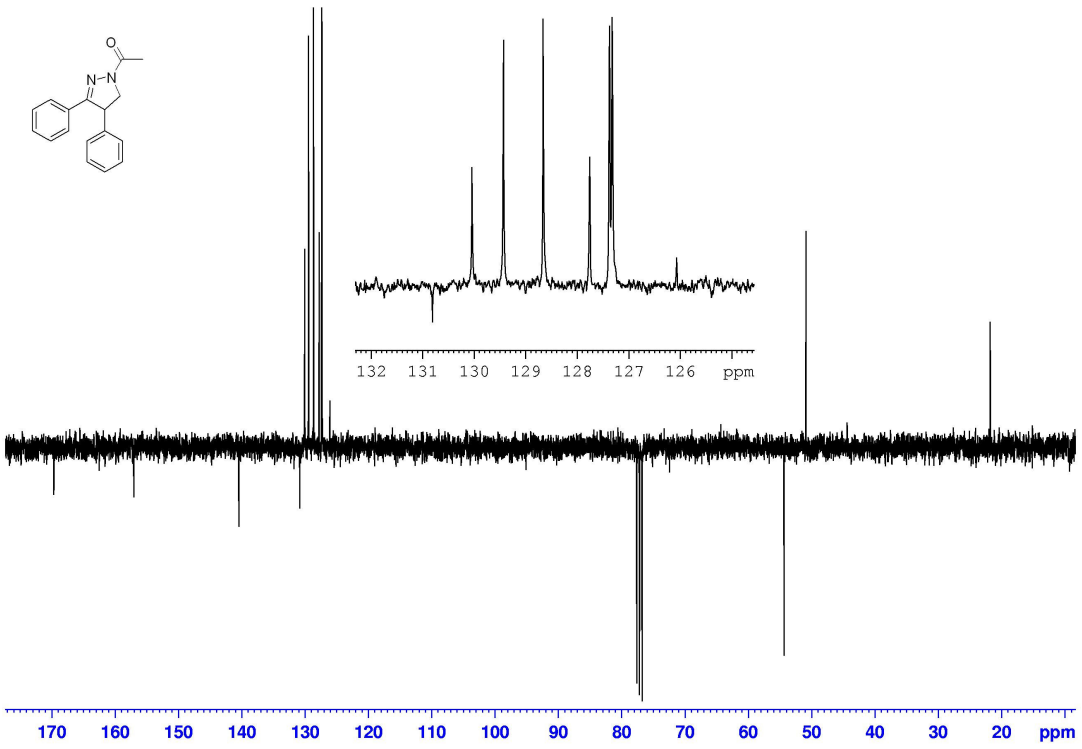
II.2 (3,4-diphenyl-4,5-dihydro-1H-pyrazol-1-yl)(phenyl)methanone (JMOD) 4a



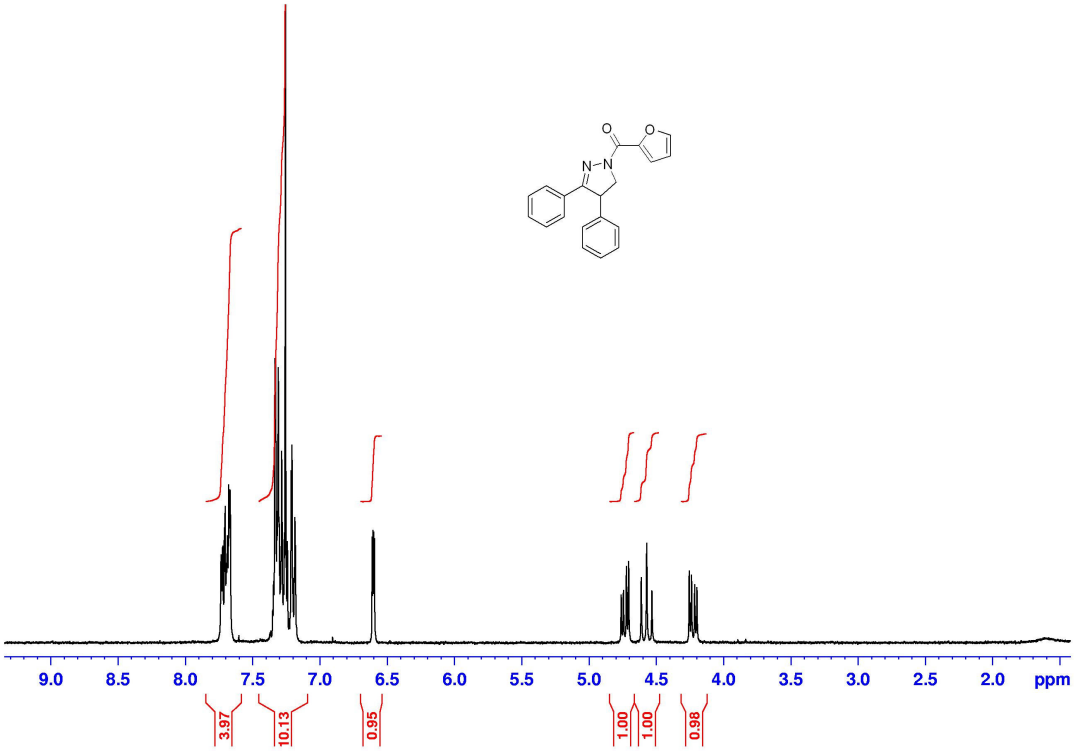
II.3 1-(3,4-diphenyl-4,5-dihydro-1H-pyrazol-1-yl)ethanone (1H) 4b



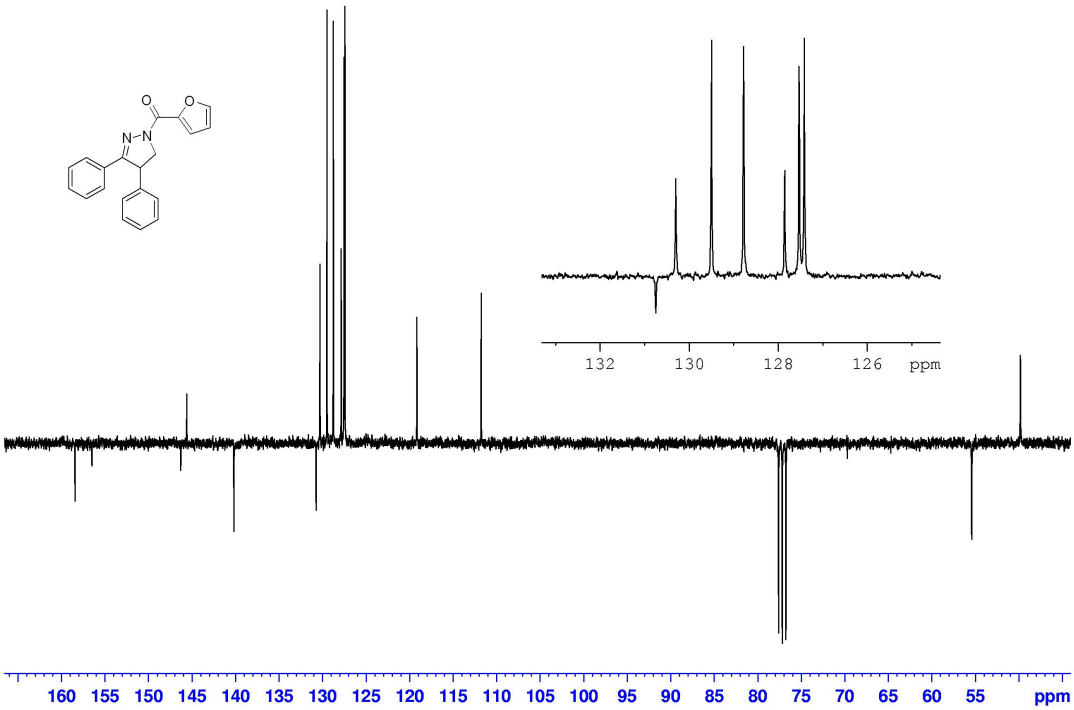
II.3 1-(3,4-diphenyl-4,5-dihydro-1H-pyrazol-1-yl)ethanone (JMOD) 4b



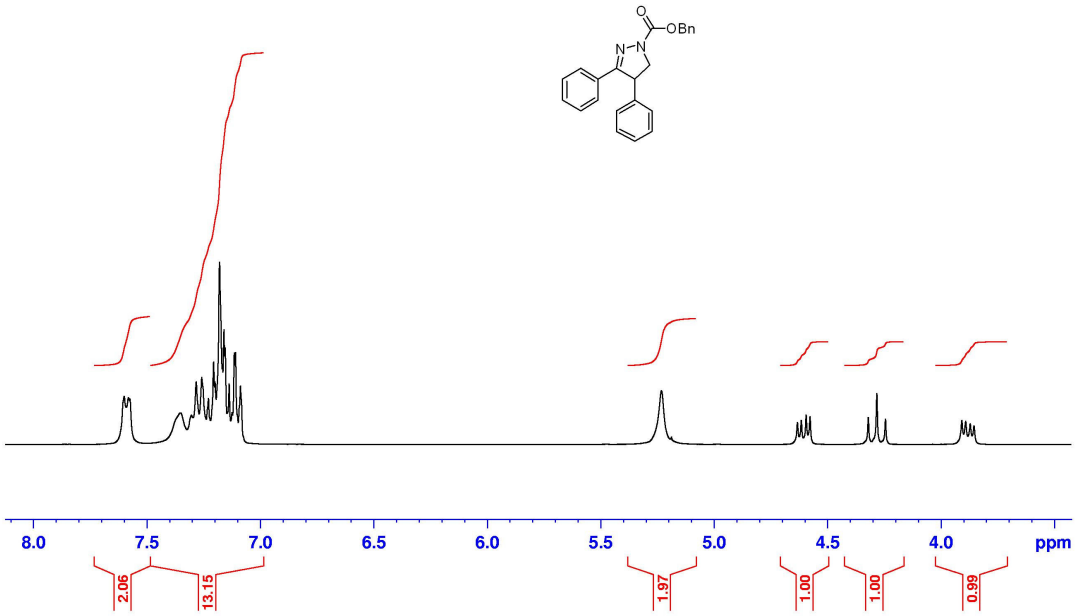
II.4 (3,4-diphenyl-4,5-dihydro-1H-pyrazol-1-yl)(furan-2-yl)methanone (1H) 4c



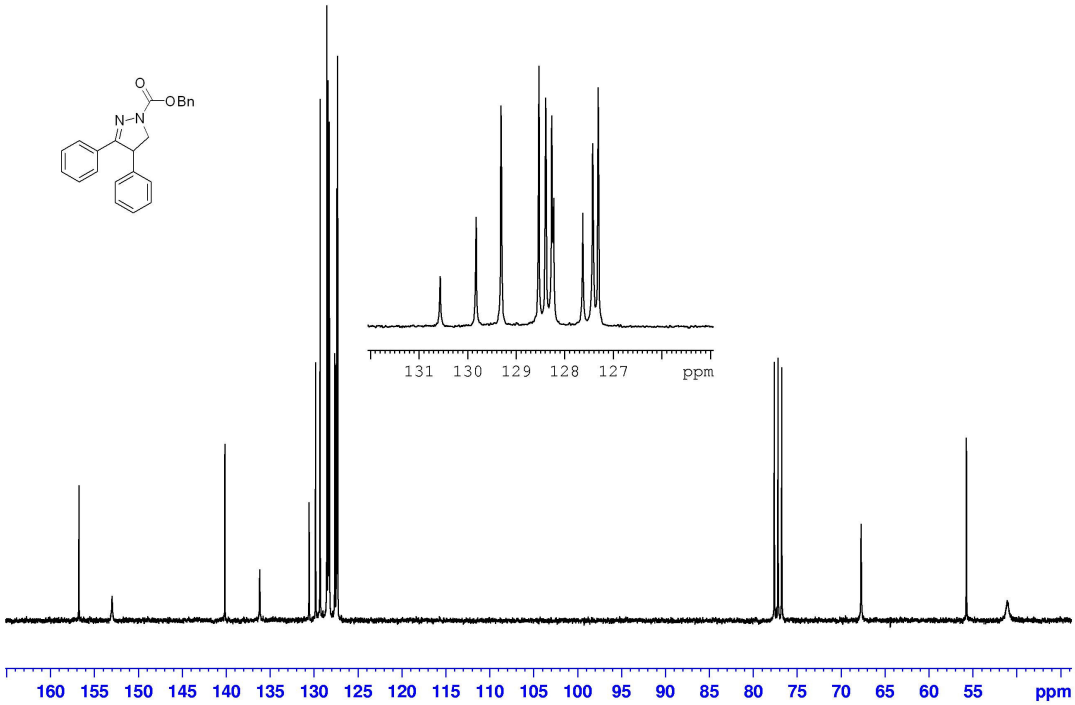
II.4 (3,4-diphenyl-4,5-dihydro-1H-pyrazol-1-yl)(furan-2-yl)methanone (JMOD) 4c



II.5 benzyl 3,4-diphenyl-4,5-dihydro-1H-pyrazole-1-carboxylate (1H) 4d

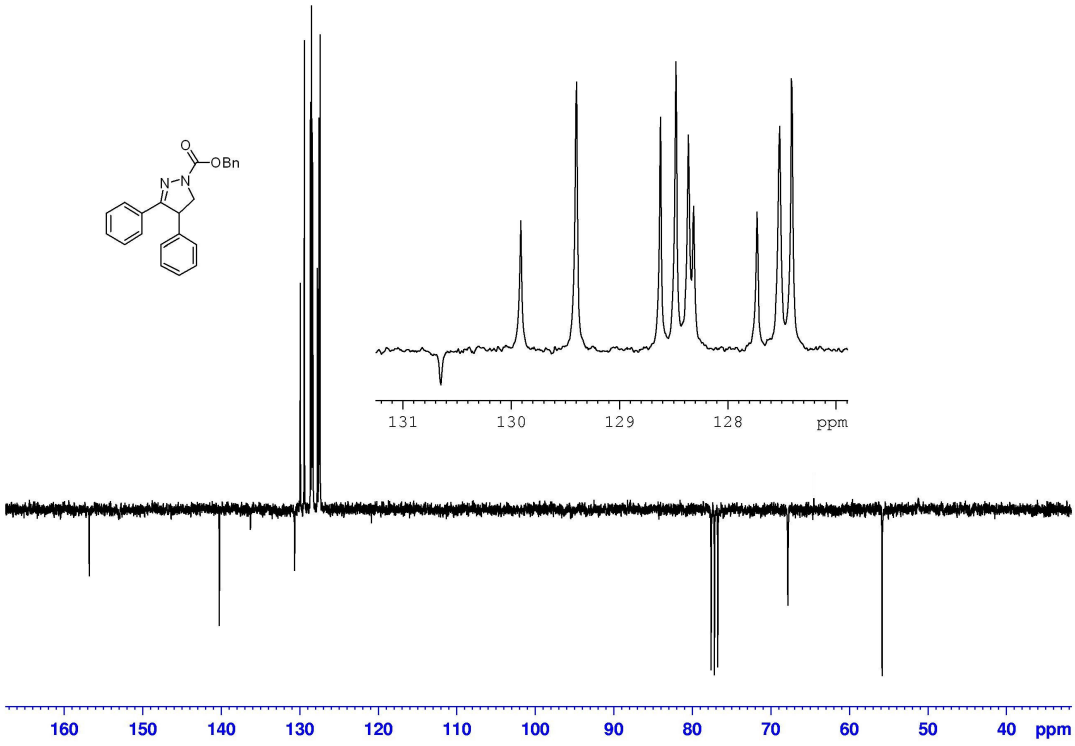


II.5 benzyl 3,4-diphenyl-4,5-dihydro-1H-pyrazole-1-carboxylate (13C) 4d

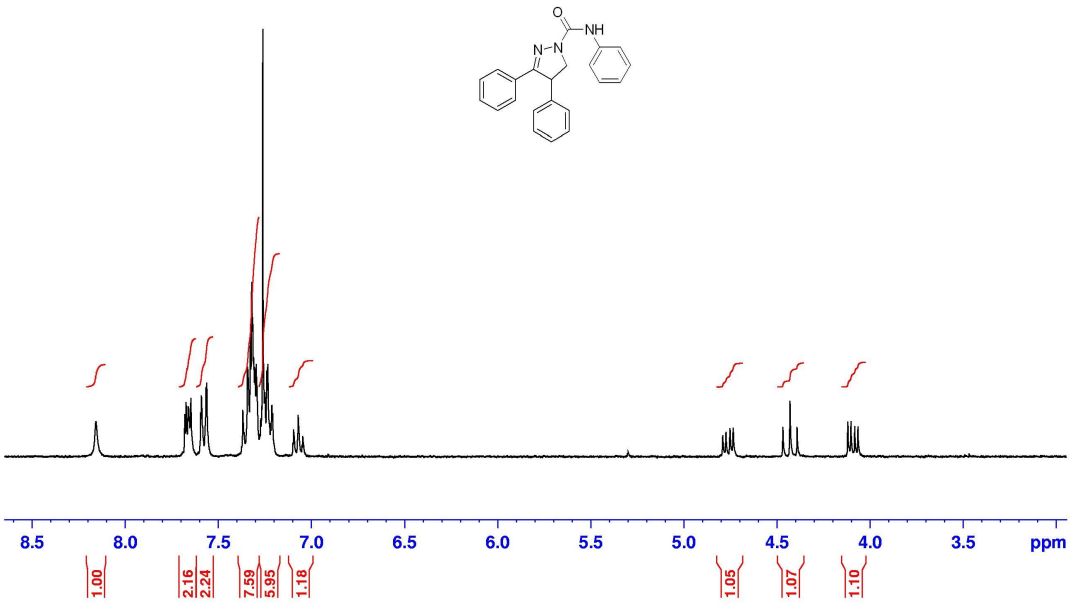


Remark: the peak corresponding to carbon 3 (CH) appeared as a small broad signal due to relaxation issue in pyrazoline-NCbz series.

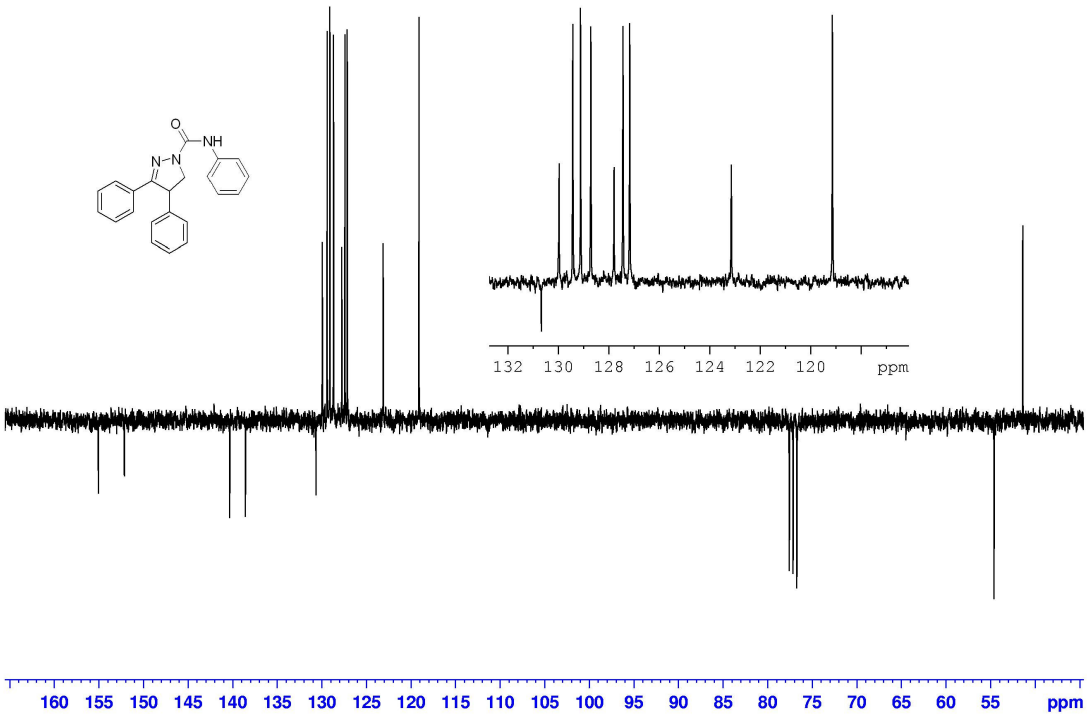
II.5 benzyl 3,4-diphenyl-4,5-dihydro-1H-pyrazole-1-carboxylate (JMOD) 4d



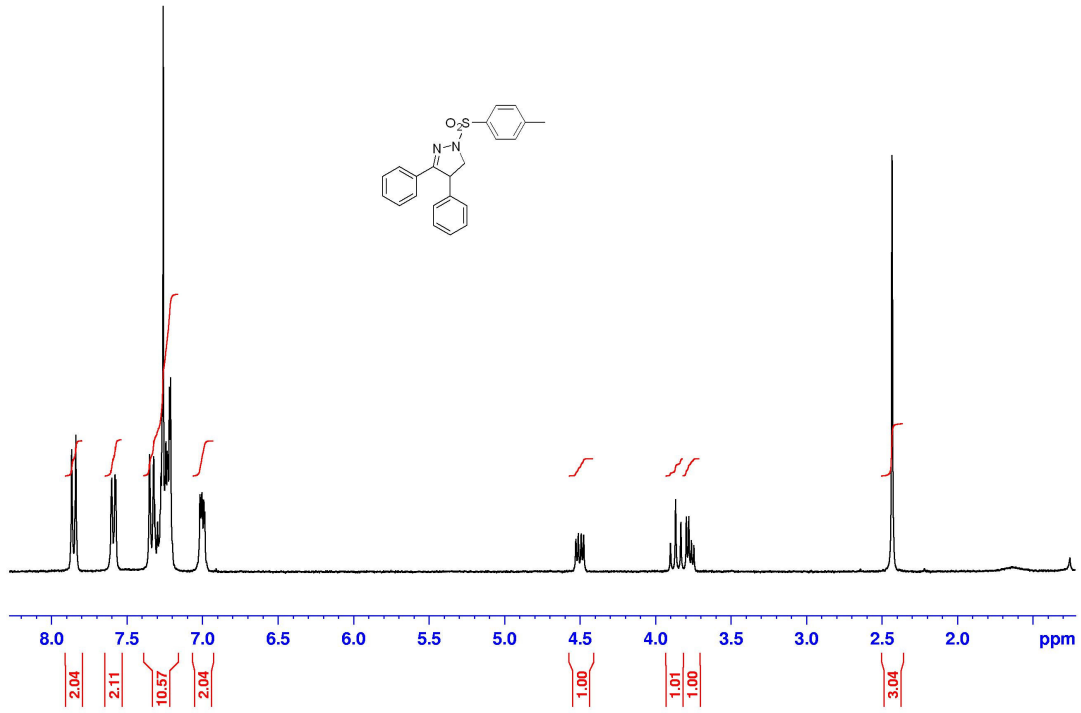
II.6 N,3,4-triphenyl-4,5-dihydro-1H-pyrazole-1-carboxamide (1H) 4e



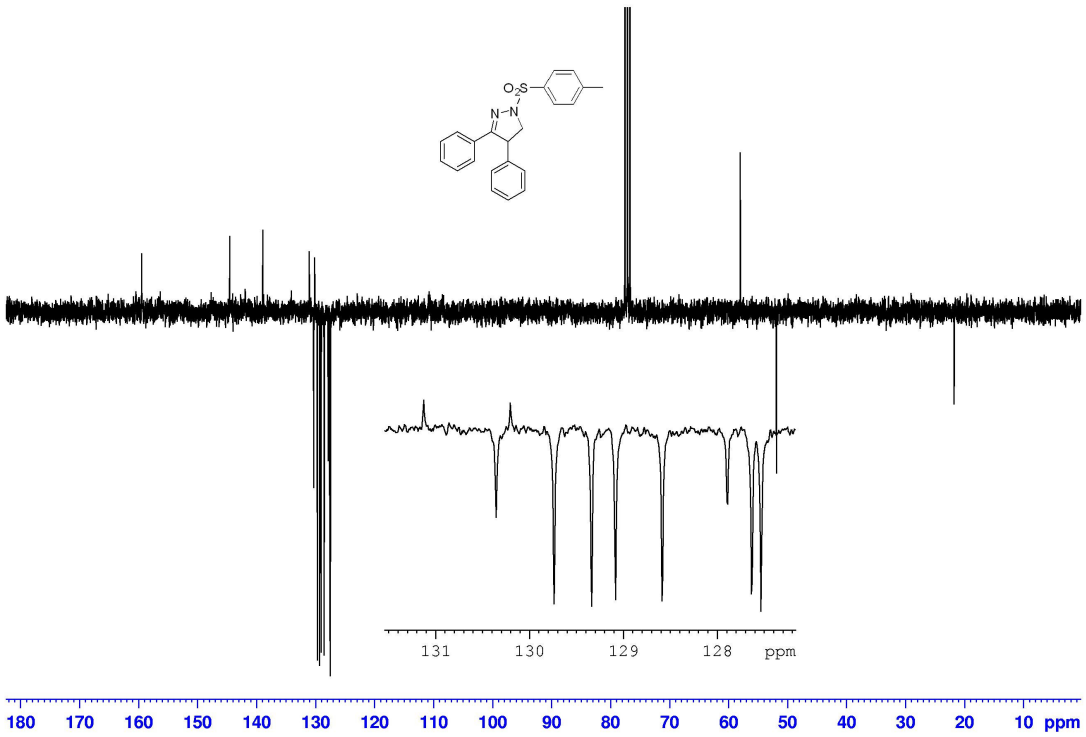
II.6 N,3,4-triphenyl-4,5-dihydro-1H-pyrazole-1-carboxamide (JMOD) 4e



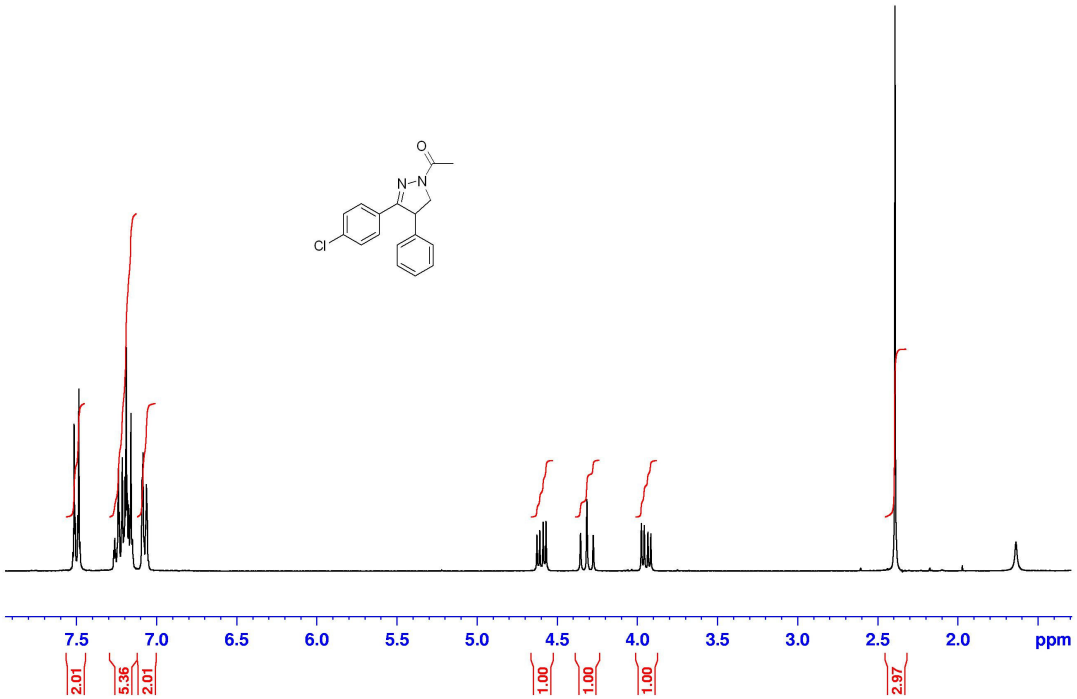
II.7 3,4-diphenyl-1-tosyl-4,5-dihydro-1H-pyrazole (1H) 4f



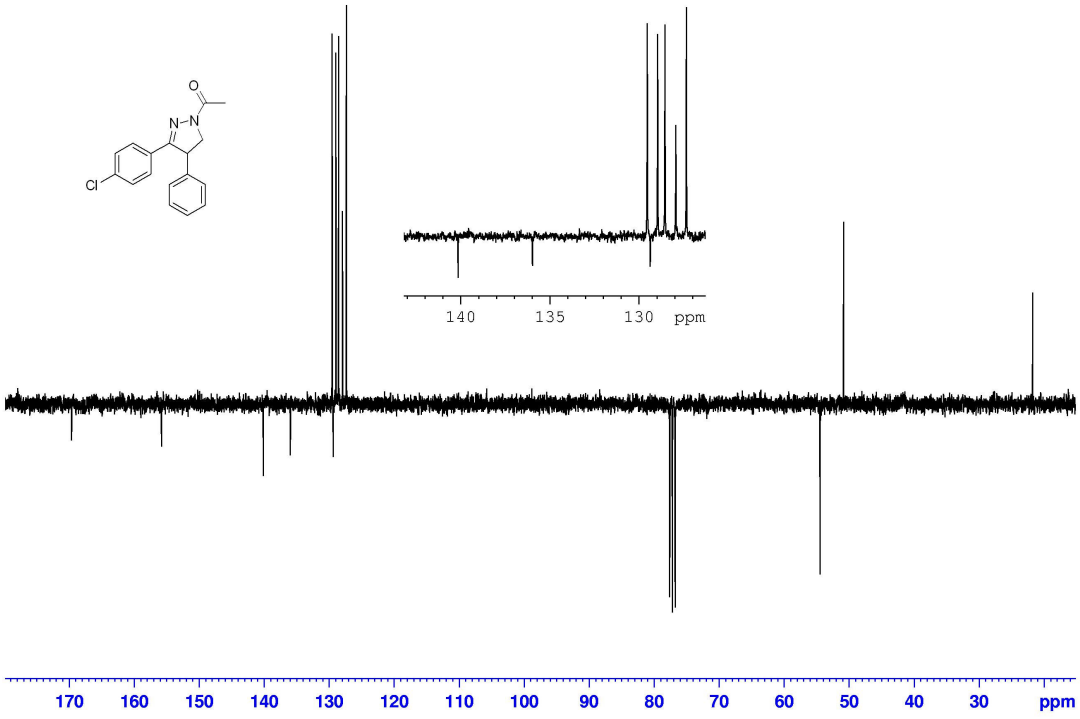
II.7 3,4-diphenyl-1-tosyl-4,5-dihydro-1H-pyrazole (JMOD) 4f



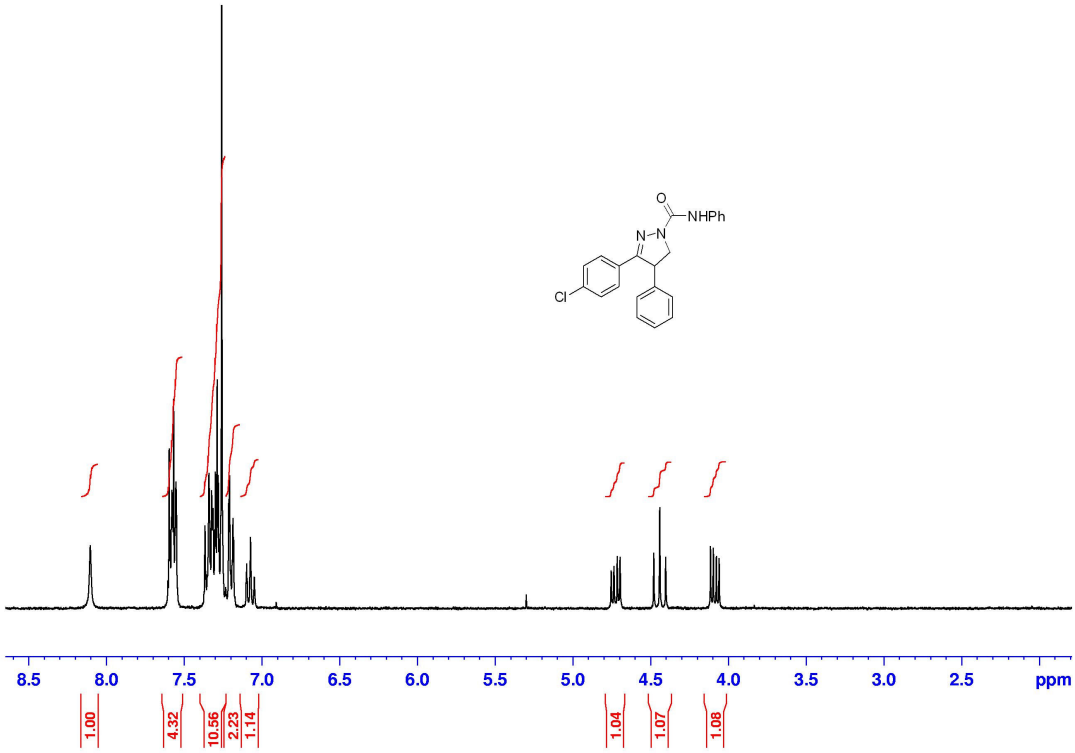
II.8 1-(3-(4-chlorophenyl)-4-phenyl-4,5-dihydro-1H-pyrazol-1-yl)ethanone (1H) 4h



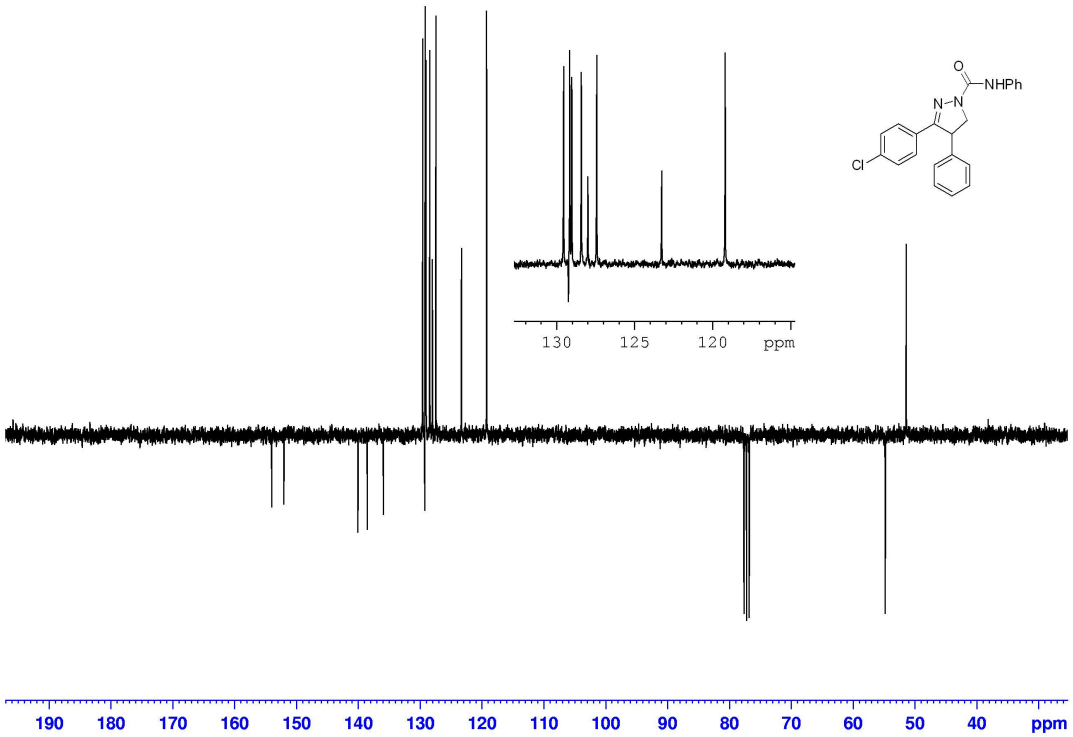
II.8 1-(3-(4-chlorophenyl)-4-phenyl-4,5-dihydro-1H-pyrazol-1-yl)ethanone (JMOD) 4h



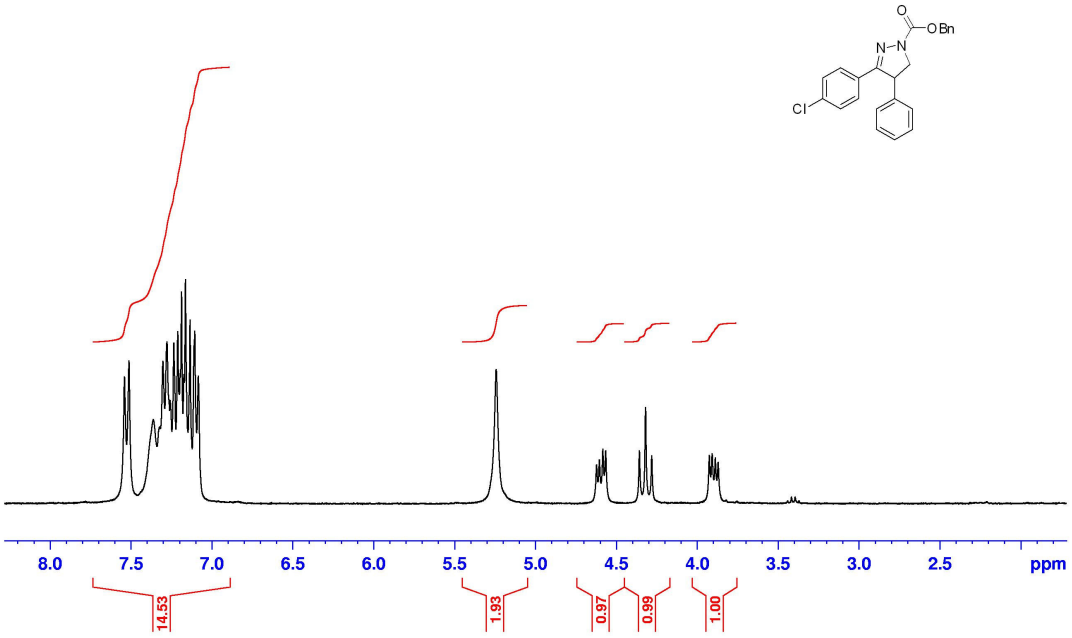
II.9 3-(4-chlorophenyl)-N,4-diphenyl-4,5-dihydro-1H-pyrazole-1-carboxamide (1H) 4i



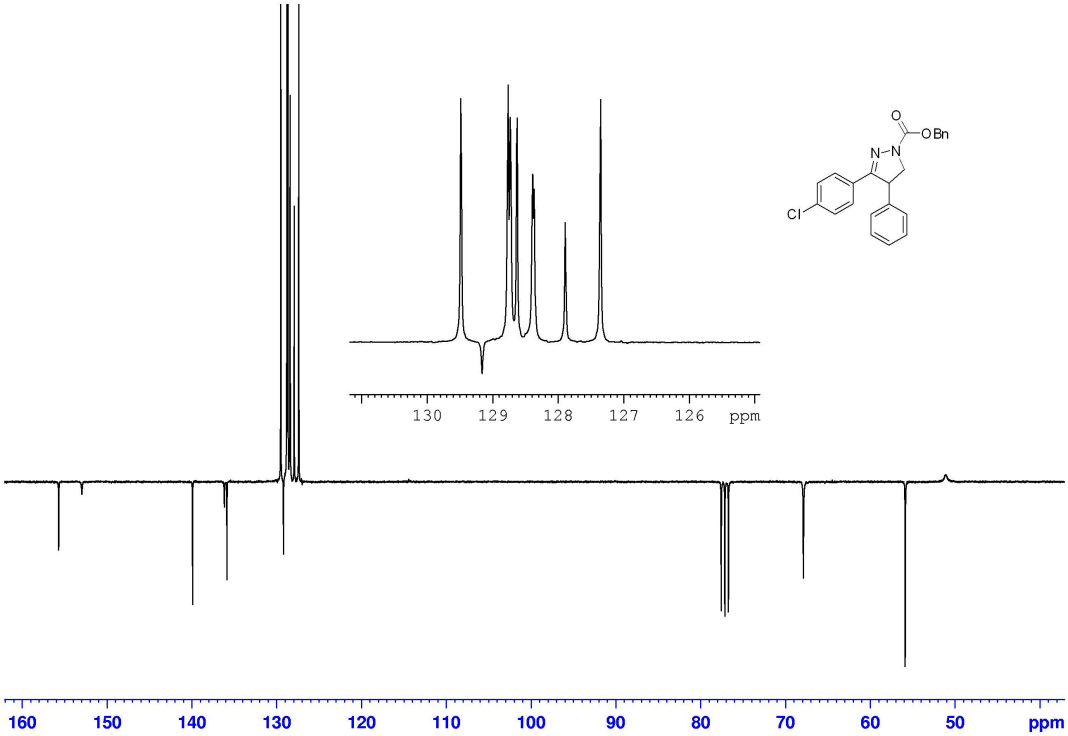
II.9 3-(4-chlorophenyl)-N,4-diphenyl-4,5-dihydro-1H-pyrazole-1-carboxamide (JMOD) 4i



II.10 benzyl 3-(4-chlorophenyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxylate (1H) 4j

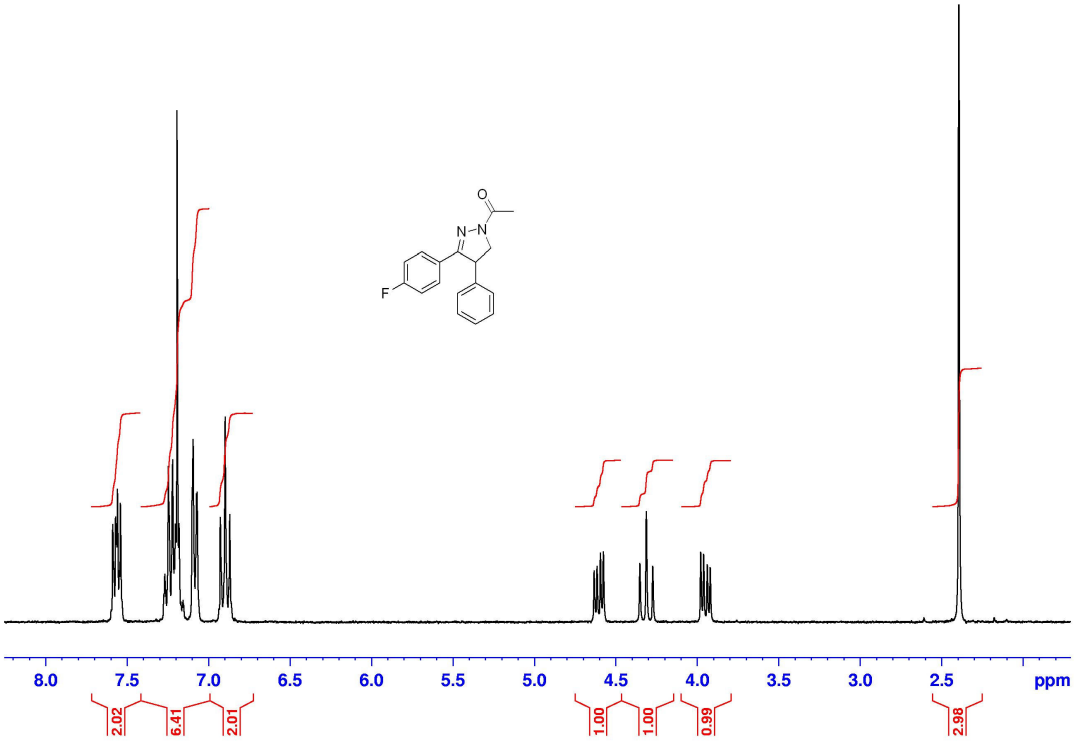


II.10 benzyl 3-(4-chlorophenyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxylate (JMOD) 4j

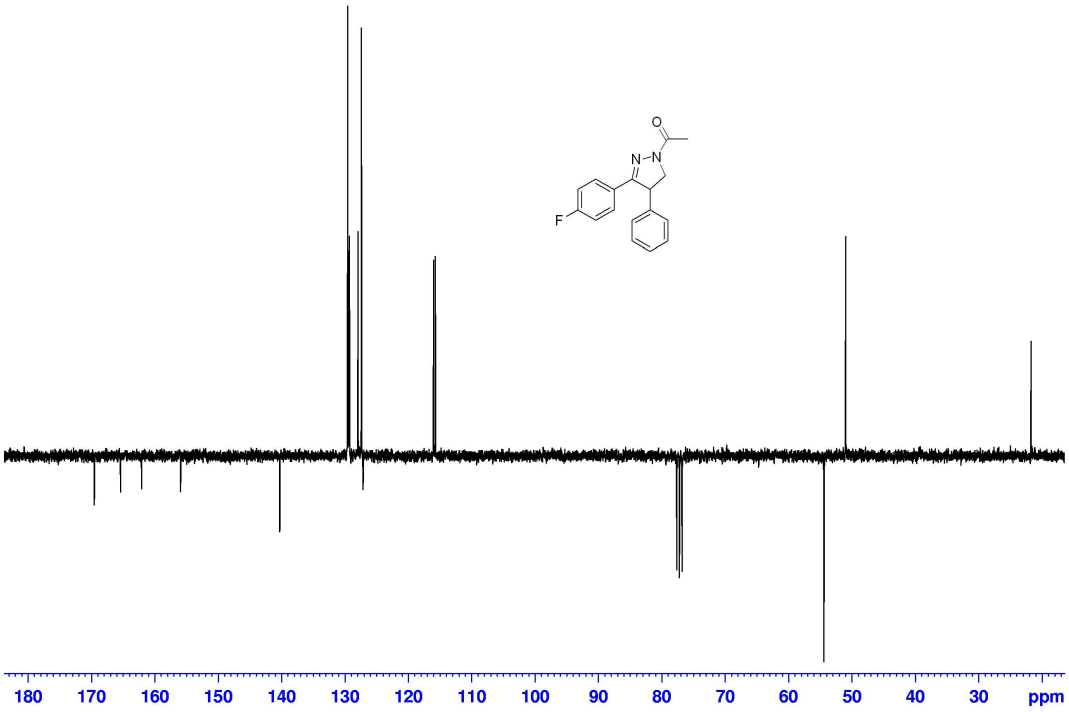


Remark: the peak corresponding to carbon 3 (CH) appeared as a small broad signal due to relaxation issue in pyrazoline-NCbz series.

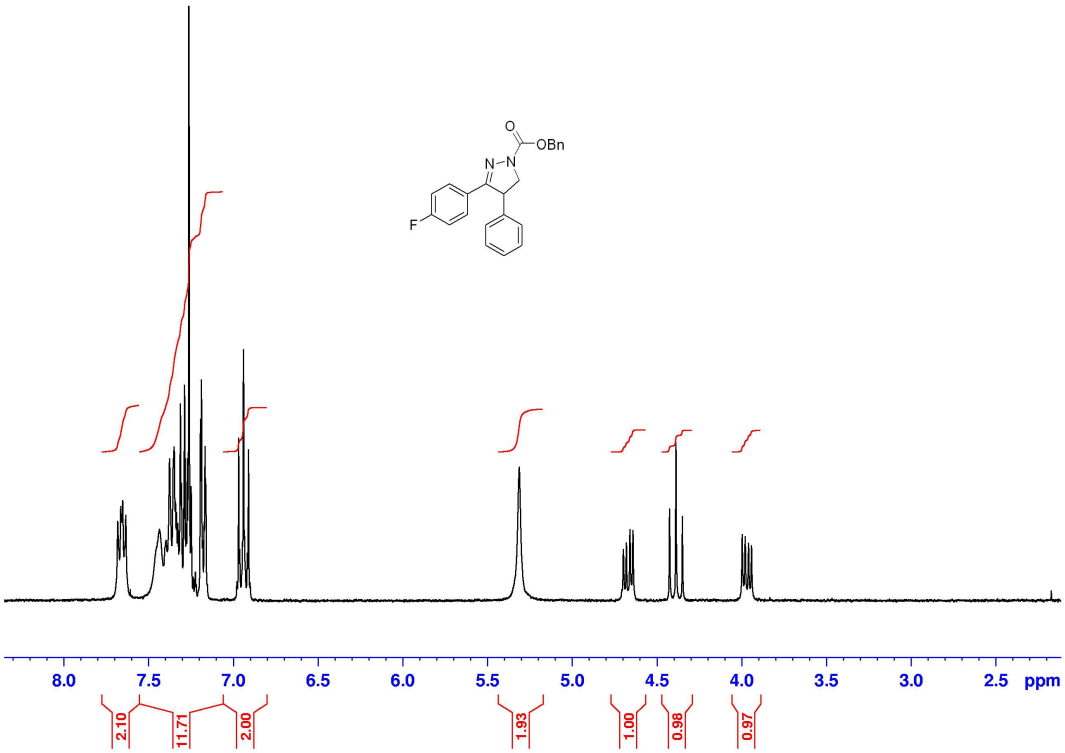
II.11 1-(3-(4-fluorophenyl)-4-phenyl-4,5-dihydro-1H-pyrazol-1-yl)ethanone (1H) 4k



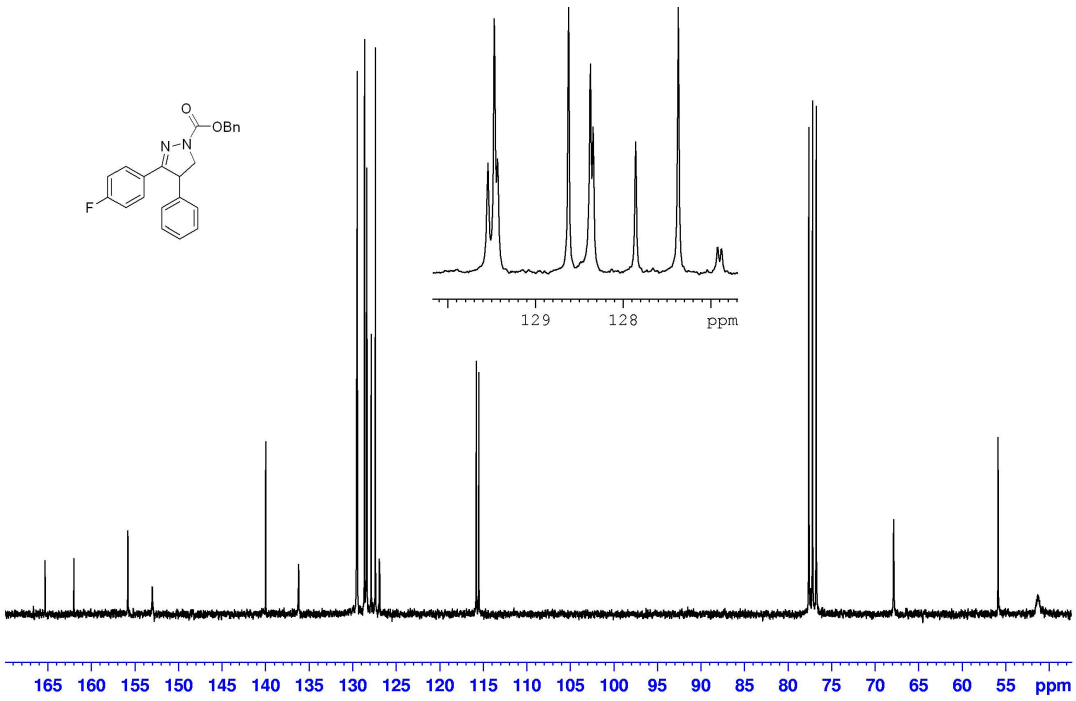
II.11 VI.11 1-(3-(4-fluorophenyl)-4-phenyl-4,5-dihydro-1H-pyrazol-1-yl)ethanone (JMOD) 4k



II.12 benzyl 3-(4-fluorophenyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxylate (1H) 4l

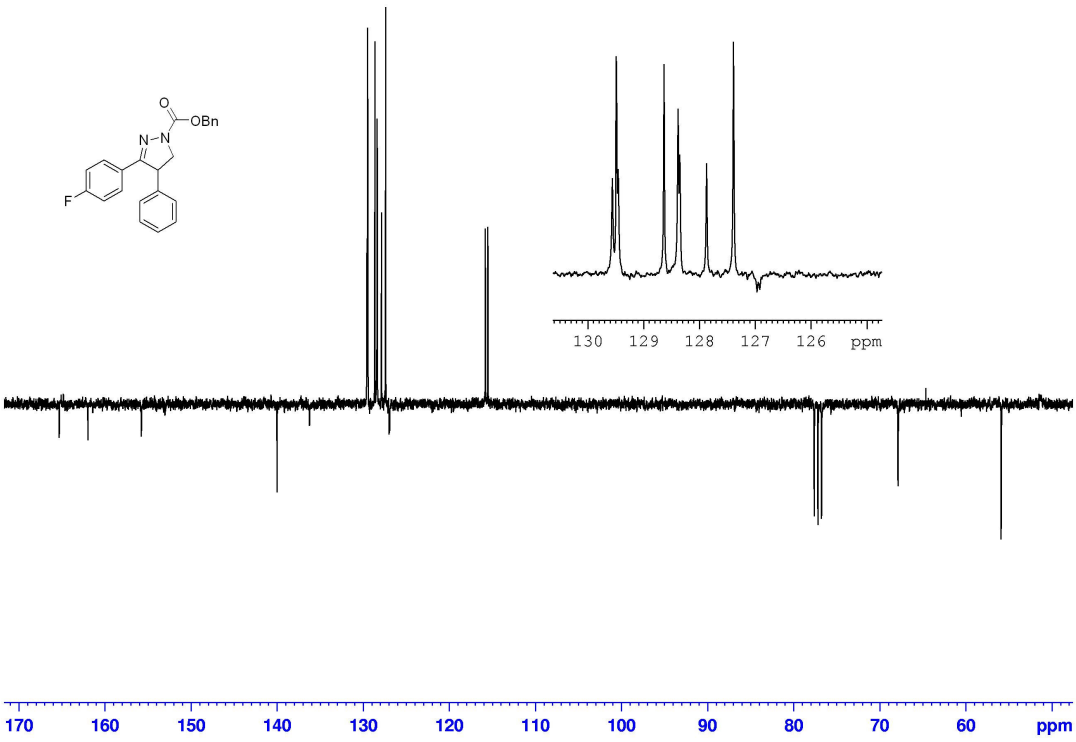


II.12 benzyl 3-(4-fluorophenyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxylate (13C) 4l

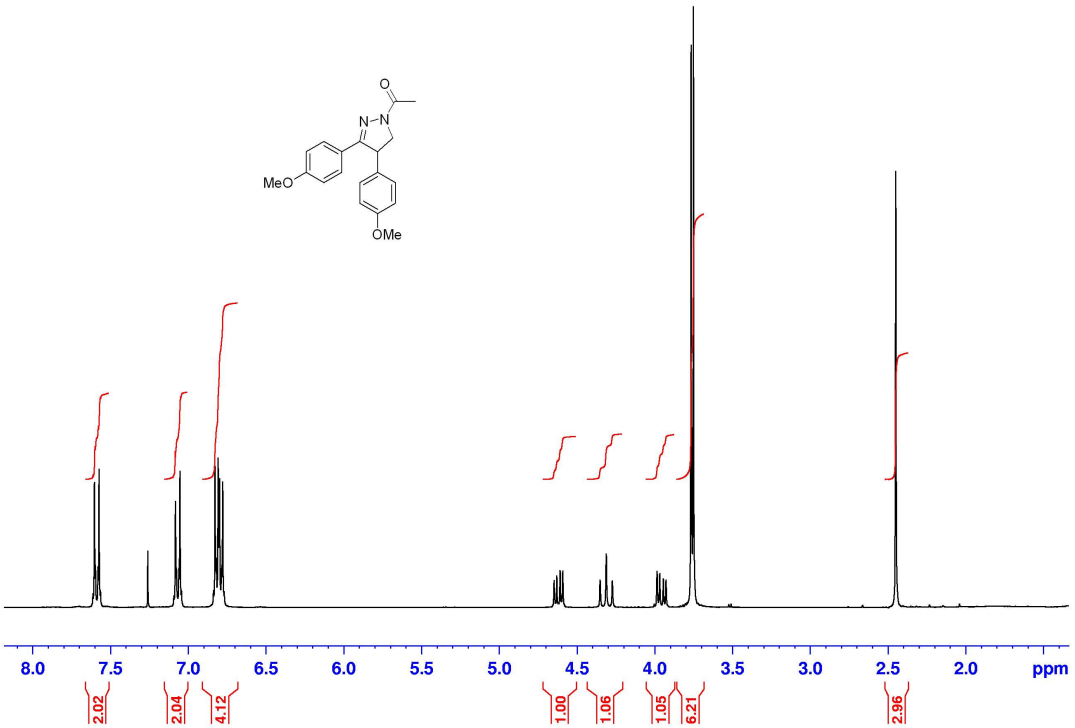


Remark: the peak corresponding to carbon 3 (CH) appeared as a small broad signal due to relaxation issue in pyrazoline-NCbz series.

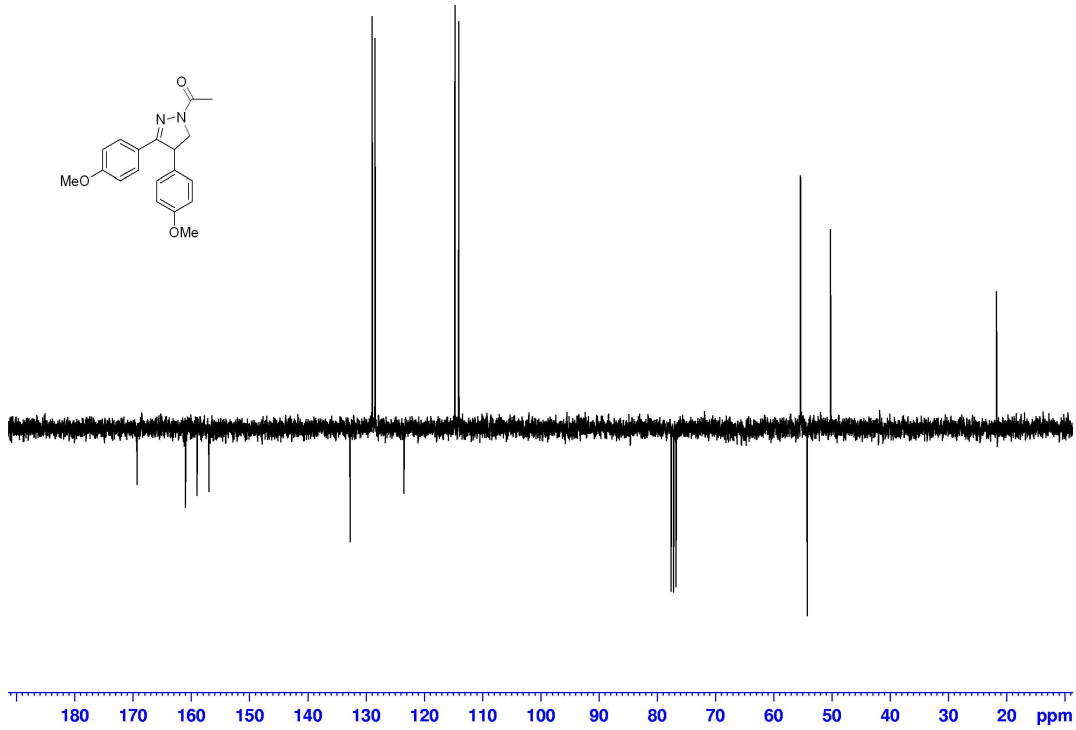
II.12 benzyl 3-(4-fluorophenyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxylate (JMOD) 4l



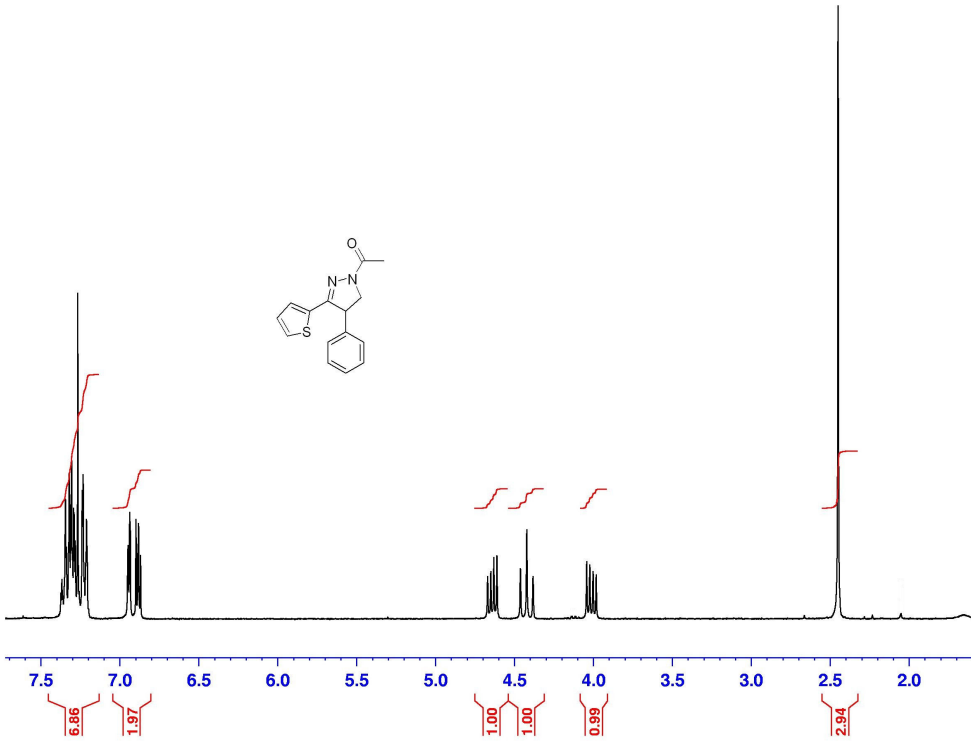
II.13 1-(3,4-bis(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)ethanone (1H) 4m



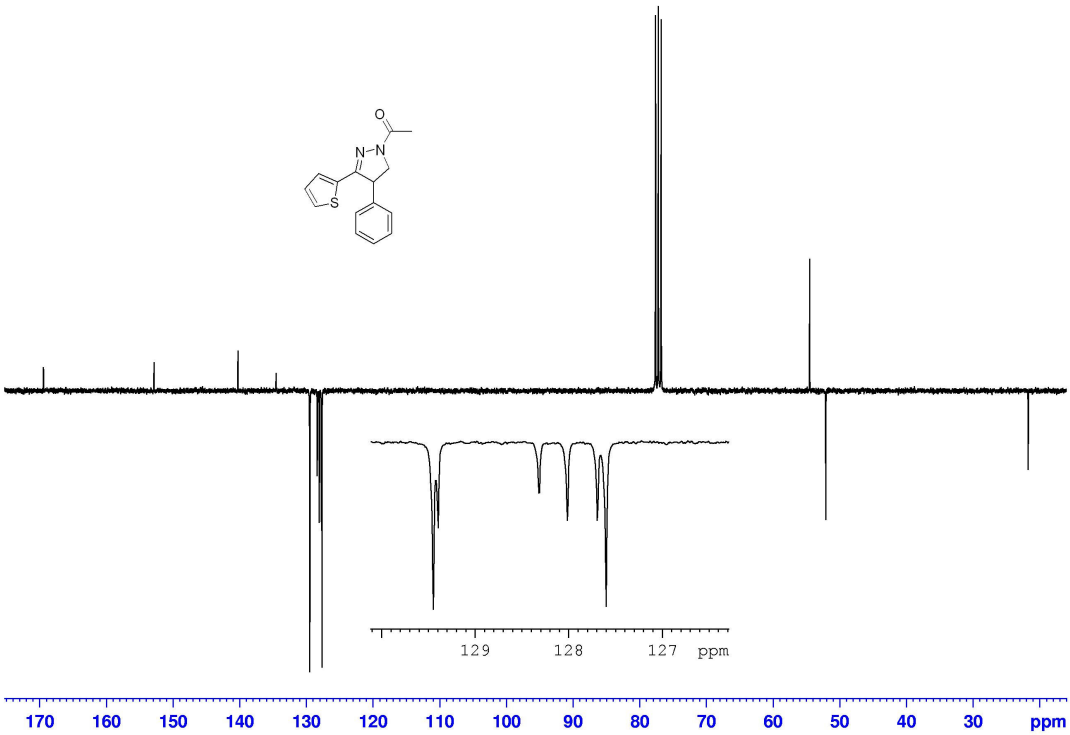
II.13 1-(3,4-bis(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)ethanone (JMOD) 4m



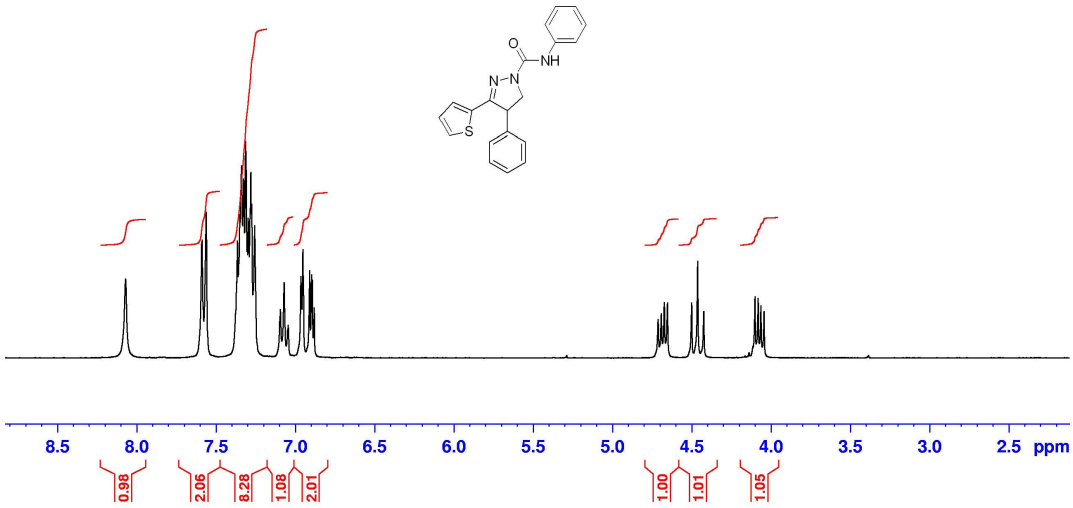
II.14 1-(4-phenyl-3-(thiophen-2-yl)-4,5-dihydro-1H-pyrazol-1-yl)ethanone (1H) 4n



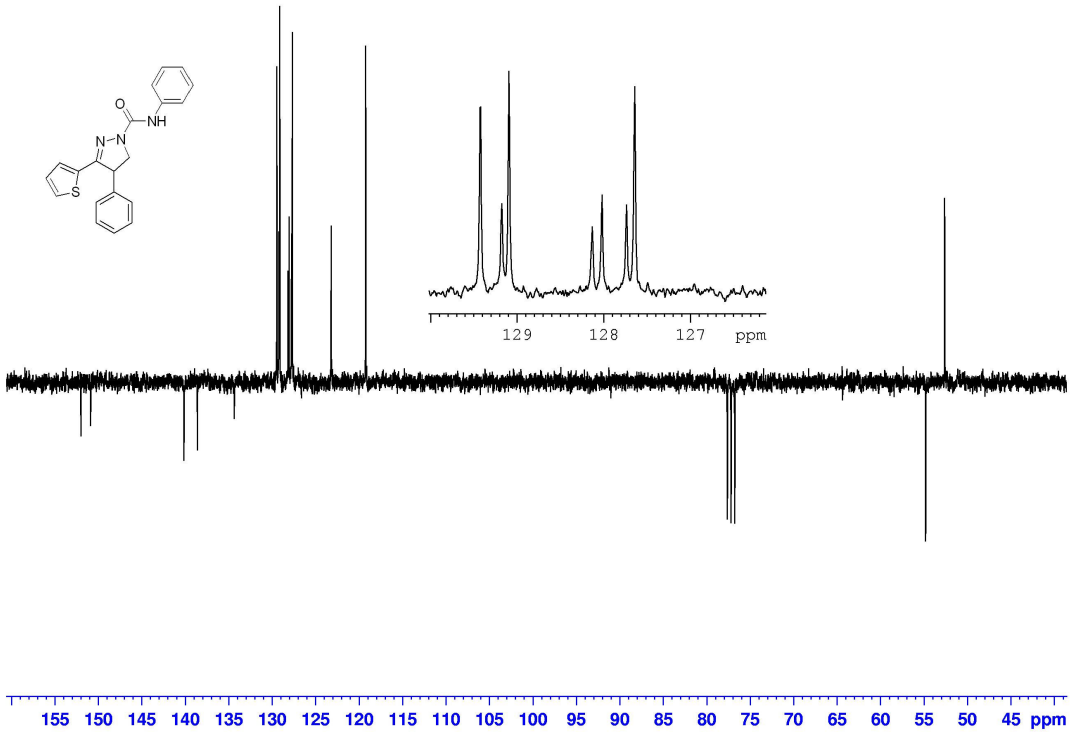
II.14 1-(4-phenyl-3-(thiophen-2-yl)-4,5-dihydro-1H-pyrazol-1-yl)ethanone (JMOD) 4n



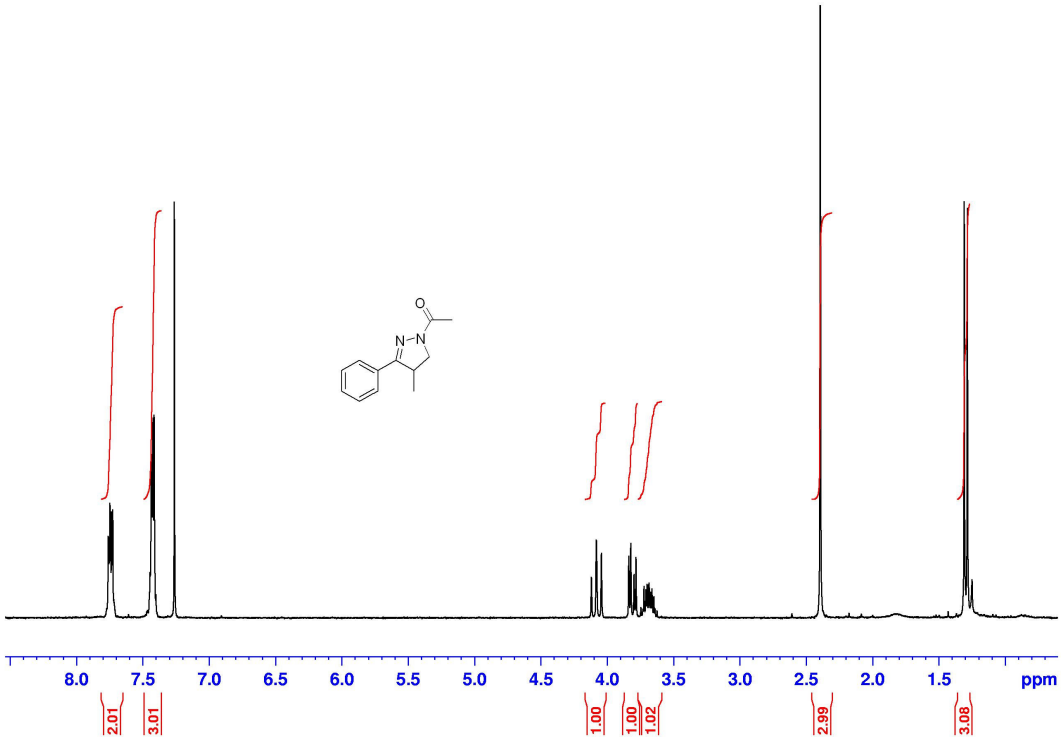
II.15 N,4-diphenyl-3-(thiophen-2-yl)-4,5-dihydro-1H-pyrazole-1-carboxamide (1H) 4o



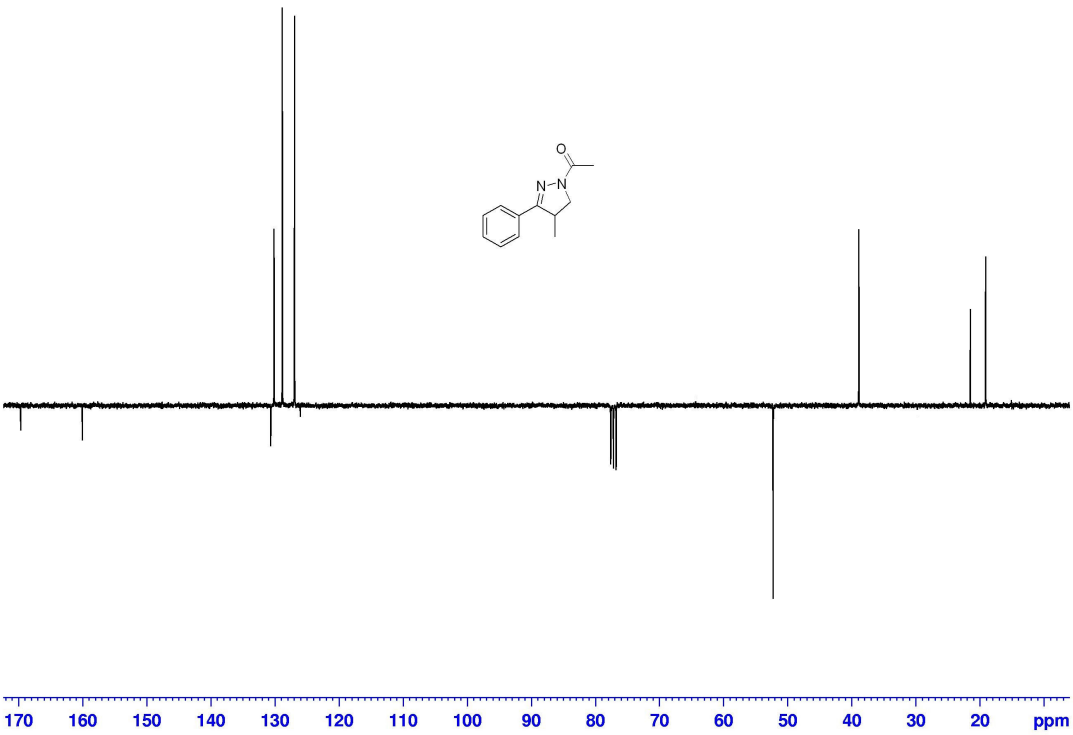
II.15 N,4-diphenyl-3-(thiophen-2-yl)-4,5-dihydro-1H-pyrazole-1-carboxamide (JMOD) 4o



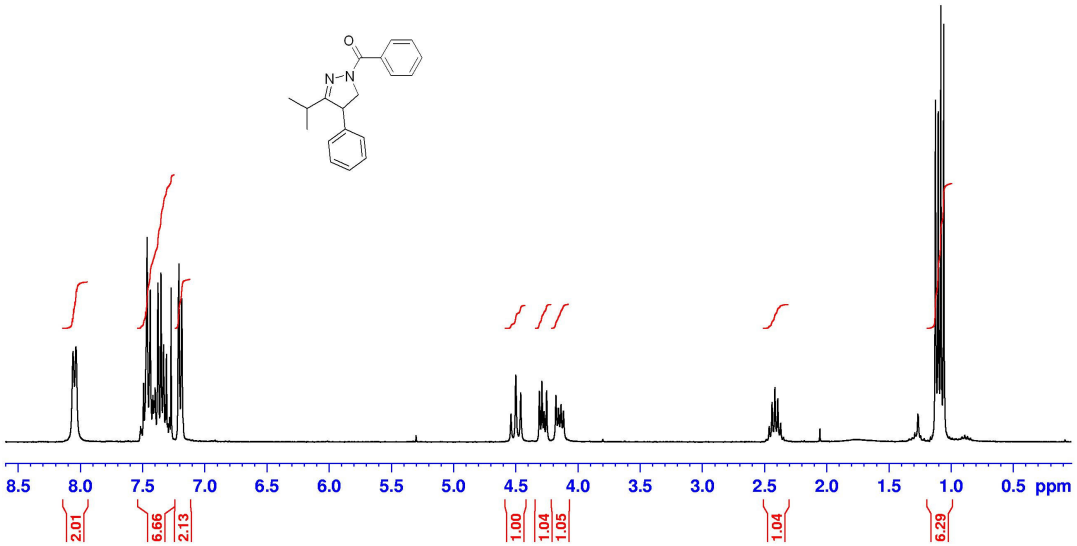
II.16 1-(4-methyl-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)ethanone (1H) 4p



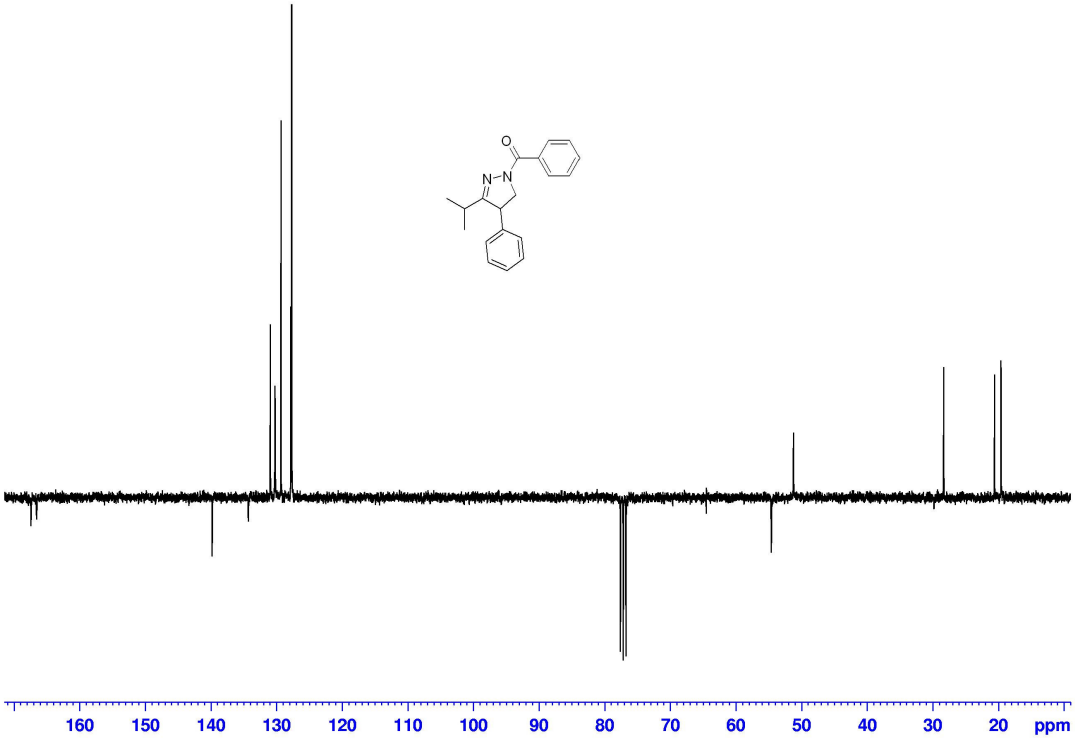
II.16 1-(4-methyl-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)ethanone (JMOD) 4p



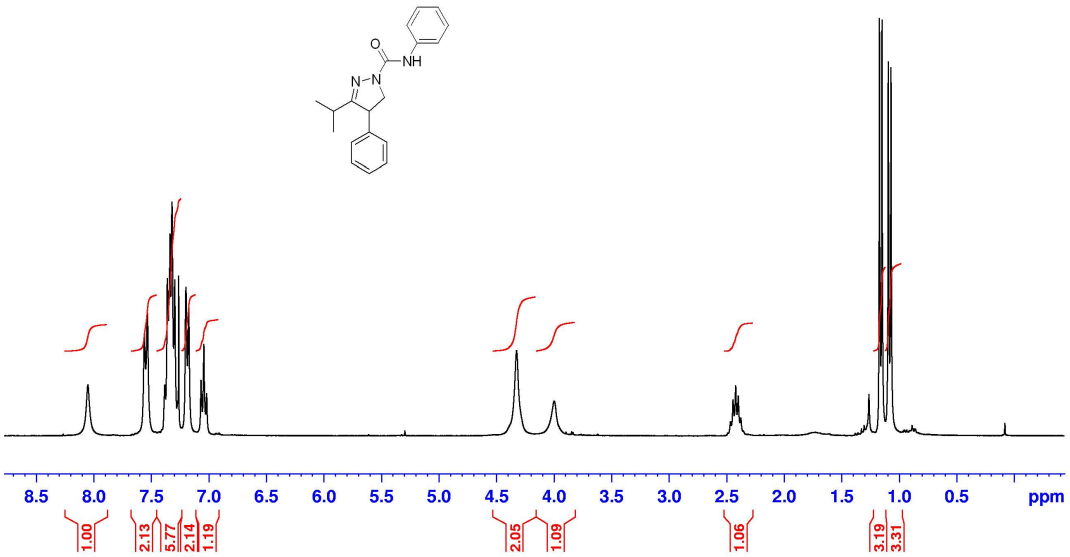
II.17 (3-isopropyl-4-phenyl-4,5-dihydro-1H-pyrazol-1-yl)(phenyl)methanone (1H) 4q



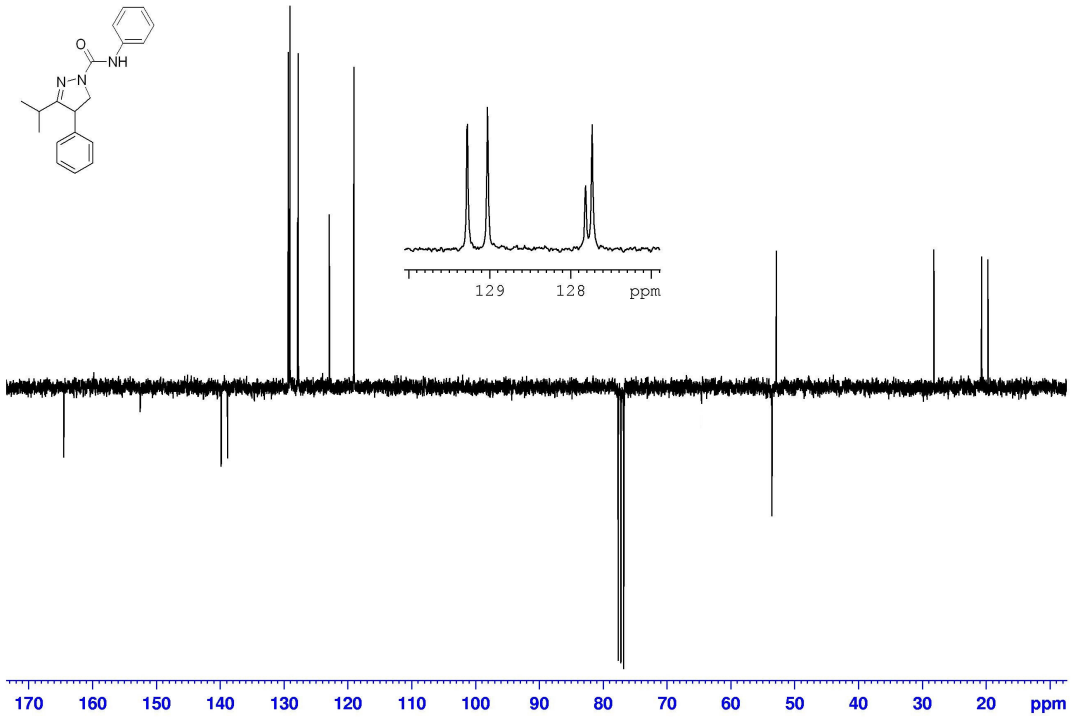
II.17 (3-isopropyl-4-phenyl-4,5-dihydro-1H-pyrazol-1-yl)(phenyl)methanone (JMOD) 4q



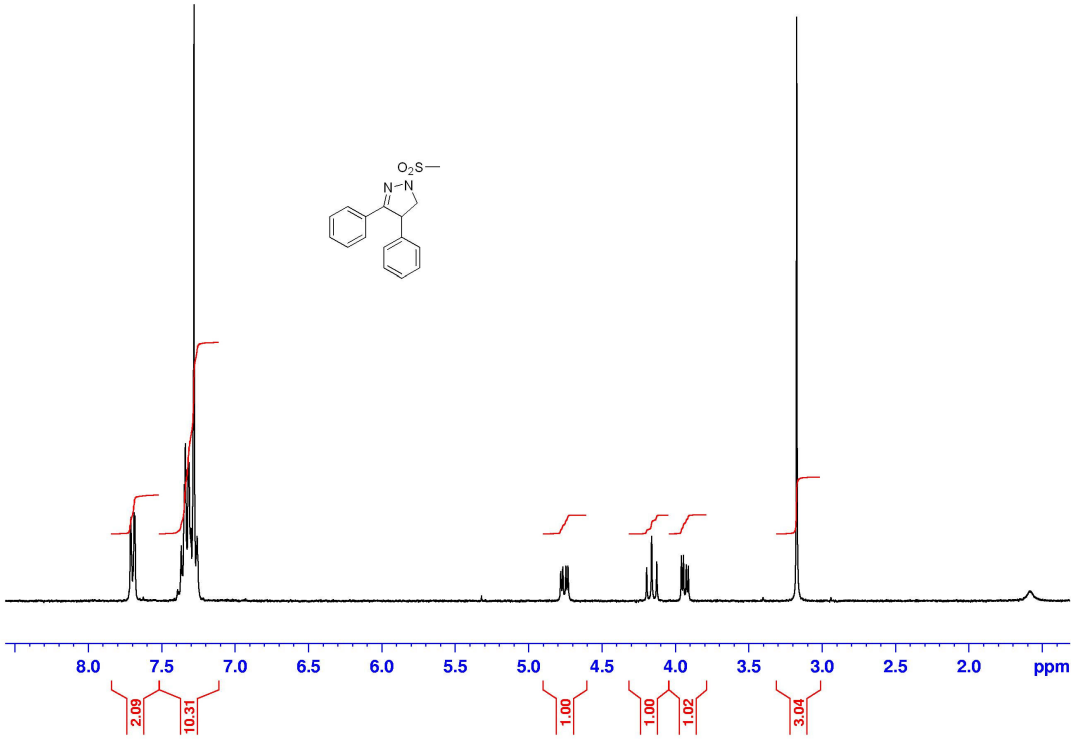
II.18 3-isopropyl-N,4-diphenyl-4,5-dihydro-1H-pyrazole-1-carboxamide (1H) 4r



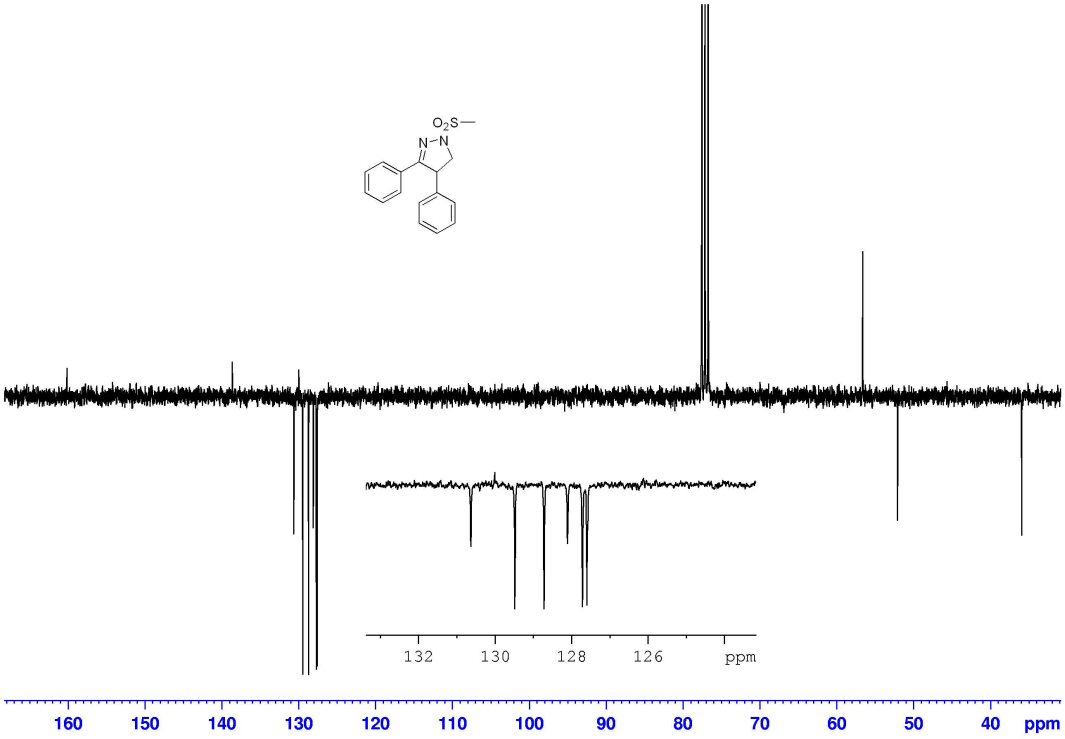
II.18 3-isopropyl-N,4-diphenyl-4,5-dihydro-1H-pyrazole-1-carboxamide (JMOD) 4r



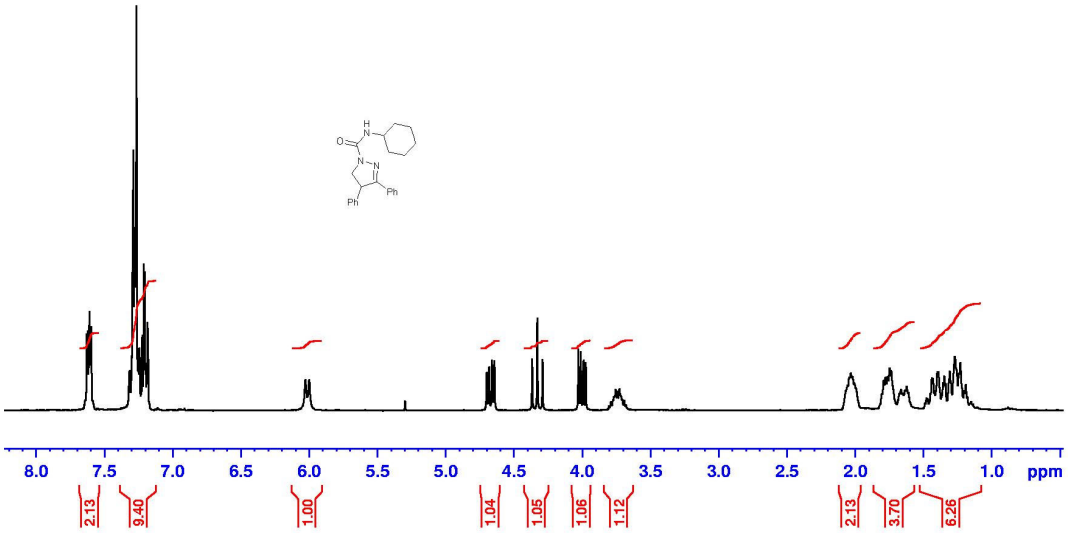
II.19 1-(methylsulfonyl)-3,4-diphenyl-4,5-dihydro-1H-pyrazole (1H) 4s



II.19 1-(methylsulfonyl)-3,4-diphenyl-4,5-dihydro-1H-pyrazole (JMOD) 4s



II.20 N-cyclohexyl-3,4-diphenyl-4,5-dihydro-1H-pyrazole-1-carboxamide (1H) 4t



II.20 N-cyclohexyl-3,4-diphenyl-4,5-dihydro-1H-pyrazole-1-carboxamide (13C) 4t