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# Supporting Information



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# Copper-Promoted Cyloaddition of Diazocarbonyl Compounds and Acetylides

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## Notes

Representative examples of biologically active pyrazoles: a) β-Adrenergic blocking activity: M. S. Large, L. H. Smith, *J. Med. Chem.* **1982**, *25*, 1417-1422. b) antipsychotic activity: L. D. Wise, D. E. Butler, H. A. DeWald, D. M. Lustgarten, I. C. Pattison, D. N. Schweiss, L. L. Coughenour, D. A. Downs, T. G. Heffner, T. A. Pugsley *J. Med. Chem.* **1987**, *30*, 1807-1812. c) Antibacterial activity: P. G. Baraldi, B. Cacciari, A. Leoni, M. Recanatini, R. Marinella, S. Manfredini, V. Periotto, D. Simoni, *Farmaco*, **1991**, *46*, 1337-1350. d) antitumor activity: S. Manfredini, R. Bazzanini, P. G. Baraldi, M. Guarneri, D. Simoni, M. E. Marongiu, A. Pani, E. Tramontano, P. L Colla, *J. Med. Chem.* **1992**, *35*, 917-924. e) Phosphodiesterase inhibition (Viagra): N. K. Terrett, A. S. Bell, D. Brown, P. Ellis, *Bioorg. Med. Chem. Lett.* **1996**, *6,* 1819-1824. f) Cyclooxygenase inhibition (Celebrex): T. D. Penning J. J. Talley, S. R. Bertenshaw, J. S. Carter, P. W. Collins, S. Docter, M. J. Graneto, L. F. Lee, J. W. Malecha, J. M. Miyashiro, R. S. Rogers, J. J. Rogier, S. S. Yu, G. D. Anderson, E. G. Burton, J. N. Cogburn, S. A. Gregory, C. M. Koboldt, W. E. Perkins, K Seibert, A. W. Veenhuizen, Y. Y. Zhang, P. C. Isakson, *J. Med. Chem.* **1997**, *40*, 1347-1365. g) Insecticidal activity: B. L. Finkelstein, C. J. Strock, *Pestic. Sci*. **1997**, *50*, 324-328. h) herbicidal activity: J. J. Parlow, *J. Heterocycl. Chem*. **1998**, *35*, 1493-1499. i) PPARγ Agonists: J. L. Collins, S. G. Glanchard, G. E. Boswell, P. S. Charifson, J. E. Cobb, B. R. Henke, E. A. Hull-Ryde, W. M. Kazmierski, D. H. Lake, L. M. Leesnitzer, J. Lehmann, J. M. Lenhard, L. A. Orband-Miller, Y. Gray-Nunez, D. J. Parks, K. D. Plunkett, Wei-Qin Tong, *J. Med. Chem.* **1998**, *41*, 5037-5054. j) Cannabinoid receptor agonists and antagonists: R. Lan, Q. Liu, P. Fan, S. Lin, S. R. Fernando, D. McCallion, R. Pertwee, A. Makriyannis *J. Med. Chem*. **1999**, *42*, 769-776. k) Review: J. Elguero in *Comprehensive Heterocyclic Chemistry*; A. R. Katritzky, C. W. Rees, E. F. V. Scriven, Eds.: Pergamon Oxford, **1996**; Vol 5.

Comparison to alternative reaction conditions. (a) (Alkynyl)MgCl reagents produced many unidentified side products. Deprotonation with LiHMDS gave similar ratios of **1a** to BnOH as BuLi while NaHMDS and KHMDS yielded more BnOH. (b) Other lithium salts provided increased amounts of benzyl alcohol while other chloride sources ($ZnCl_2$, $MgCl_2$) inhibited the reaction. (d) CuBr, CuCl and CuTc were similar to CuI; CuSCN was similar to CuCN. (e) The reaction was qualitatively similar in THF, toluene, $CH_2Cl_2$ and ether and glime.

### Method and Materials

**General.** Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly purified solvents. Solvents were purified using solvent purification columns purchased from Glass Contour, Laguna Beach, CA. All reactions were monitored by thin-layer chromatography with Merck silica gel 60 F254 pre-coated plates (0.25 mm). Flash chromatography was performed with indicated solvents using silica gel (particle size 0.032-0.063 μm) purchased from Sorbent Technologies. $^1$H and $^{13}$C NMR spectra were recorded on Varian Inova-400 or Mercury-300 spectrometer. Chemical shift are reported relative to internal chloroform or DMSO-$d_6$ ($CDCl_3$: $^1$H, δ = 7.27, $^{13}$C, δ = 77.26 and DMSO-$d_6$: $^1$H, δ = 2.50, $^{13}$C, δ = 39.51). Coupling constants are in Hz and are reported as d (doublet), t (triplet), q (quartet). For signals having multiple coupling patterns, the coupling constants are listed in the same order as the pattern (e.g. dt, $J$ = 2.0, 4.0; 2.0 is the coupling constant for the doublet and 4.0 is for the coupling constant for the triplet). Infrared spectra were recorded on a Perkin- Elmer 1000 series FTIR. Low-resolution mass spectra were acquired on a Shimadzu QP5000 GC/MS or Agilent LC/MS using the indicated ionization method.

**Materials**

All alkynes and ethyl diazoacetate were used as received from Sigma-Aldrich and Alfa Aesar, respectively. Other diazo compounds were prepared as indicated.

**General procedure for synthesis of diazo compounds.[1]**

**Benzyl diazoacetate:** Benzyl alcohol (0.54 g, 5 mmol) and ethyl acetoacetate (6.5 g, 50 mmol) were combined, sparged with $N_2$ for 10 min, and then heated at reflux for 5h. Unreacted ethyl acetoacetate was removed under reduced pressure, and benzyl acetoacetate was purified by flash chromatography (5% ethyl estate in hexanes). To a solution of benzyl acetoacetate (192 mg, 1 mmol) in acetonitrile (1.2 ml) was added $Et_3N$ (131.5 mg, 1.3 mmol). The reaction mixture was cooled in an ice bath and a solution of tosyl azide (217 mg, 1.1 mmol) in acetonitrile (1.2 ml) was added slowly. The reaction mixture was allowed to warm to rt. After stirring for 10h, solvent was removed under reduced pressure. The residue was dissolved in ether and washed with 5% aqueous KOH solution. To a solution of the crude benzyl 2-diazo-acetoacetate (1.87 g, 9 mmol) in acetonitrile (30 ml) was added 5% KOH (30 ml), and the reaction mixture was stirred for 1h. The reaction mixture was extracted with ether, and the organic phase was separated, dried over $Mg_2SO_4$, and concentrated under reduced pressure. Purification by flash chromatography (5% ethyl acetate in hexanes) provided the desired benzyl diazoacetate (yield: 68% from benzyl 2-diazo-3-acetoacetate ) as a yellow liquid.

***Tert*-butyl diazoacetate:** same procedure as benzyl diazoacetate but starting from *tert*-butyl acetoacetate (two step yield: 64%).

**Diazo-N-methoxy-N-methylacetamide:** same procedure as for benzyl diazoacetate but starting from *N,O*-dimethylhydroxylamine (three step yield: 22%).

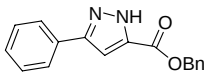
**Characterization data for diazo compounds:**
**Benzyl diazoacetate**[2]**:** Yellow liquid, $^1$H NMR ($CDCl_3$) = 4.79 (s, *1*H), 5.20 (s, 2H), 7.35 (m, 5H). EI-MS (m/z): 176 $[M]^+$.
***Tert*-butyl diazoacetate**[3]**:** Yellow liquid, $^1$H NMR ($CDCl_3$) = 1.49 (s, *9*H), 4.61 (s, 1H). EI-MS (m/z): 142 $[M]^+$.
**Diazo-N-methoxy-N-methylacetamide:** Yellow liquid, $^1$H NMR ($CDCl_3$) = 3.17 (s, *3*H), 3.68 (s, 3H), 5.32 (s, *1*H). EI-MS (m/z): 129 $[M]^+$.

**CuCN·6LiCl:** CuCN (1eq) and LiCl (6eq) were mixed and heated (160 $^o$C) under vacuum (0.1 mm Hg) for 10 h.

**General procedure for the formation of pyrazole. (Figure 1).**
BuLi (0.625 mL of 1.6M in hexane, 1.0 mmol, 1.0 equiv) was added to a solution of alkyne (1.0 mmol) in THF (4 mL) at –78 $^o$C. After 1 hour this solution was transferred to solution of CuCN·6LiCl (345 mg, 1.0 mmol) in THF (6 mL). The reaction mixture was warmed up to –17 $^o$C (dry ice/brine) and stirred for 1 h. A solution of diazo compound (1.0 mmol) in THF (4 mL) was added and the cold bath was removed. The resulting solution was stirred for 2-4 h at room temperature. After TLC analysis indicated complete consumption of the diazo carbonyl compound, aqueous ammonium chloride and ether were added. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic phases were washed with brine, dried over $MgSO_4$, concentrated and purified by flash chromatography on silica gel. Characterization data are provided below for all entries in Figure 1.

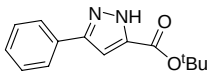
**Characterization data for synthetic compounds.** Pyrazoles display concentration-dependent NMR spectra (See figure S1). The largest changes are observed for the pyrazole methine proton and the methylene of the ester. $^1$H NMR data was collected at approximately 5 mg/mL; $^{13}$C NMR data was collected at approximately 20 mg/mL.

**Benzyl 3-phenyl-1H-pyrazole-5-carboxylate (1a)**:



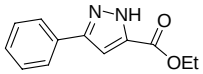
White solid, $^1$H NMR ($CDCl_3$) = 5.29 (s, *2*H), 7.11 (s, 1H), 7.38 (m, 8H), 7.70 (d, *J* = 7.6, 2H), 11.92 (bs, NH). $^{13}$C NMR ($CDCl_3$) = 67.0, 105.7, 125.9, 128.6, 128.8, 129.1, 130.4, 135.5, 140.0, 148.5, 160.9. FTIR (thin film) 3101, 3013, 1727, 1415, 1236, 1136, 1009, 760.8, 693.7cm$^{-1}$. EI-MS (m/z): 278 $[M]^+$.

**Tert-butyl 3-phenyl-1H-pyrazole-5-carboxylate (1b)**:



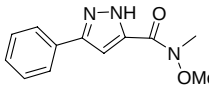
White solid, $^1$H NMR ($CDCl_3$) = 1.52 (s, 9H), 7.01 (s, 1H), 7.32 (t, *J* = 7.2 1H), 7.38 (t, *J* = 7.2, 2H), 7.76 (d, *J* = 7.6, 2H), 12.89 (NH).$^{13}$C NMR ($CDCl_3$) = 28.4, 82.5, 105.6, 125.9, 128.6, 129.1, 131.2, 140.5, 149.5, 160.3. FTIR (thin film): 2978, 1720, 1459, 1413, 1368, 1253, 1139, 841, 763, 691cm$^{-1}$. EI-MS (*m/z*): 244 $[M]^+$

**Ethyl 3-phenyl-1H-pyrazole-5-carboxylate (1c)**[4]:



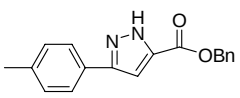
Tan solid, $^1$H NMR ($CDCl_3$) = 1.44 (t, *J* = 7.2, 3H), 4.44 (q, J = 7.2, 2H), 7.14 (s 1H), 7.38 (t, J = 7.6, 1H), 7.46 (t, J = 7.6, 2H), 7.77 (d, *J* = 7.6, 2H), 10.68 (NH). $^{13}$C NMR ($CDCl_3$) = 14.2, 61.1, 105.1, 125.8, 128.7, 129.1, 130.0, 140.9, 147.9, 161.5. FTIR (thin film): 3140, 2980, 1726, 1466, 1415, 1276, 1244, 1140, 1025, 762, 691cm$^{-1}$. EI-MS (*m/z*): 216 $[M]^+$

**N-methoxy-N-methyl-3-phenyl-1H-pyrazole-5-carboxamide (1d)**:



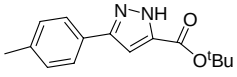
Tan solid, $^1$H NMR ($CDCl_3$) = 3.41 (s, 3H), 3.78 (s, 3H), 7.14(s 1H), 7.32 (t, *J* = 7.6 1H), 7. 41 (t, J = 7.6, 2H) 7.91 (d, *J* = 7.6, 2H), 11.99 (bs, NH). $^{13}$C NMR ($CDCl_3$) = 33.2, 61.9, 106.0, 126.0, 128.3, 129.0, 132.9, 136.3, 152.3, 159.8. FTIR (thin film): 3102, 2978, 1720, 1482, 1414, 1368, 1279, 1252, 1171, 1138, 1007, 840, 762, 691cm$^{-1}$. EI-MS (*m/z*): 231 $[M]^+$

**Benzyl 3-p-tolyl-1H-pyrazole-5-carboxylate (1e)**:



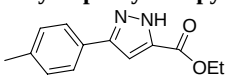
Tan solid, $^1$H NMR ($CDCl_3$) = 2.35 (s, 3H), 5.22 (s, 2H), 6.98 (br. s, 1H), 7.15 (t, *J* = 7.5, 2H), 7.28-7.32 (m, 5H), 7.55 (d, J = 7.8, 2H), 12.33 (bs, NH). $^{13}$C NMR ($CDCl_3$) = 21.5, 66.9, 105.4, 125.8, 128.5, 128.8, 129.8, 135.6, 138.7, 140.2, 148.3, 161.0. FTIR (thin film) 2923, 1727, 1417, 1236, 1134, 1009cm$^{-1}$.EI-MS (m/z): 292 $[M]^+$.

**tert-butyl 3-p-tolyl-1H-pyrazole-5-carboxylate (1f)**:



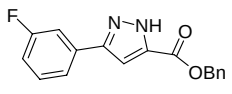
White solid, $^1$H NMR ($CDCl_3$) = 1.60 (s, 9H), 2.37 (s, 3H), 7.00 (s, 1H), 7.22 (d, *J* = 7.2, 2H), 7.66 (d, *J* = 7.2, 2H), 10.69 (bs, NH). $^{13}$C NMR ($CDCl_3$) = 21.5, 28.4, 82.8, 105.5, 125.8, 128.9, 129.8, 138.6, 139.5, 150.8, 159.8. FTIR (thin film): 2924, 2870, 1718, 1415, 1368, 1277, 1137, 1008cm$^{-1}$. EI-MS (*m/z*): 258 $[M]^+$

**Ethyl 3-p-tolyl-1H-pyrazole-5-carboxylate (1g)**:



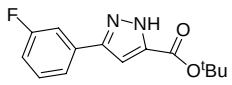
Tan solid, $^1$H NMR ($CDCl_3$) = 1.28 (t, *J* = 6.8, 3H), 2.35(s, 3H), 4.27 (q, *J* = 6.8, 2H), 6.99 (s 1H), 7.18 (d, *J* = 7.2, 2H), 7.6 (d, *J* = 7.2, 2H), 12.9 (bs, NH). $^{13}$C NMR ($CDCl_3$) = 14.2, 21.5, 61.1, 104.9, 125.8, 127.0, 129.7, 138.6, 141.3, 147.2, 161.75. FTIR (thin film):3416, 2982, 1725, 1419, 1273, 1242, 1138, 1025, 817, 775cm$^{-1}$. EI-MS (*m/z*): 230 $[M]^+$

**Benzyl 3-(3-fluorophenyl)-1H-pyrazole-5-carboxylate (1h)** (NMR data for the HCl salt)[Error! Bookmark not defined.]:



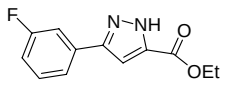
White solid, $^1$H NMR ($CDCl_3$) = 5.40 (s, 2H), 7.06 (dt, *J* = 1.6, 8.4, 1H), 7.15 (s, 1H), 7.37-7.52 (m, 7H), 7.56 (d, *J* = 7.6, 1H), 10.48 (bs, NH). $^{13}$C NMR (DMSO-$d_6$) = 66.6, 106.9, 112.8 (d, J = 23), 115.7 (d, J = 21), 122.1, 128.8, 128.9, 129.2, 131.7 (d, J = 9), 133.4, 136.6, 140.2, 146.8, 161.0, 163.2 (d, J = 241). FTIR (thin film): 3136, 1726, 1591, 1458, 1248, 1213, 1180, 1132, 1012, 857, 776, 696cm$^{-1}$. EI-MS (*m/z*): 296 $[M]^+$.

**tert-butyl 3-(3-fluorophenyl)-1H-pyrazole-5-carboxylate (1i)**:



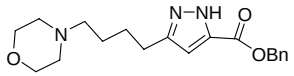
White solid, $^1$H NMR ($CDCl_3$) = 1.61 (s, 9H), 7.00-7.09 (m, 2H), 7.38 (dt, J = 7.6, 10.8, 1H), 7.56 (d, *J* = 7.6, 1H), 7.60 (d, *J* = 10, 1H), 10.94 (bs, NH). $^{13}$C NMR ($CDCl_3$) = 28.4, 83.1, 106.0, 112.9 (d, J = 20), 115.3 (d, J = 20), 121.6, 130.6 (d, J = 9), 134.4, 138.3, 150.2, 159.6, 164.7 (d, J = 250). FTIR (thin film): 3138, 2980, 1720, 1591, 1478, 1369, 1255, 1217, 1162, 1134, 1010, 864, 779cm$^{-1}$. EI-MS (*m/z*): 262 $[M]^+$

**Ethyl 3-(3-fluorophenyl)-1H-pyrazole-5-carboxylate (1j)**:



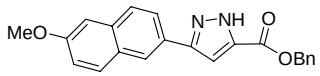
Blue solid, $^1$H NMR ($CDCl_3$) = 1.29 (t, *J* = 9.6, 3H), 4.30 (q, *J* = 9.6, 2H), 6.97-7.18 (m, 2H), 7.35 (dd, *J* =8.0, 10, 1H), 7.47 (d, *J* =14.2, 1H), 7.53 (d, *J* = 10, 1H). 12.70 (bs, NH). $^{13}$C NMR ($CDCl_3$) = 14.3, 61.6, 105.9, 112.9 (d, J = 30), 115.6 (d, J = 29), 121.6, 130.7 (d, J = 10), 133.1, 138.9, 148.8, 160.7, 165.0 (d, J = 330). FTIR (thin film): 2983, 1726, 1419, 1273, 1242, 1138, 1025, 817, 775cm$^{-1}$. EI-MS (*m/z*): 234 $[M]^+$

**Benzyl 3-(4-morpholinobutyl)-1H-pyrazole-5-carboxylate (1k)**:



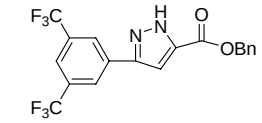
Tan oil, $^1$H NMR ($CDCl_3$) = 1.46-1.56 (m, 2H), 1.57-1.66 (m, 2H), 2.37 (dt, *J* = 4.8, 7.2, 2H), 2.37-2.48 (m, 4H), 2.71 (dt, *J* = 3.9, 7.5, 2H), 3.73 (q, *J* = 4.5, 4H), 5.34 (s, 2H), 6.60 (d, J = 4.5, 1H), 7.30-7.45 (m, 5H), 9.25 (bs, NH). $^{13}$C NMR ($CDCl_3$) = 25.9, 26.0, 27.0, 53.8, 58.6, 66.7, 67.0, 106.8, 128.5, 128.8, 136.0, 141.8, 147.5, 162.3. FTIR (thin film): 3202, 2948, 2862, 1724, 1451, 1233, 1115, 865, 780, 699cm$^{-1}$. EI-MS (*m/z*): 343 $[M]^+$.

**Benzyl 3-(6-methoxynaphthalen-2-yl)-1H-pyrazole-5-carboxylate (1l)** (NMR data for HCl salt)[5]:



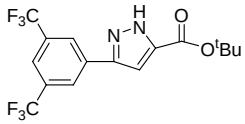
White solid $^1$H NMR (DMSO-$d_6$) = 3.85 (s, 3H), 5.34 (s, 2H), 7.16 (dd, J = 2.0, 8.8, 1H), 7.33 (dt, J = 1.4, 8.3, 3H), 7.38 (t, J = 7.0, 2H), 7.46 (d, J = 7.3, 2H), 7.81 (d, J = 9.0, 1H), 7.84, (d, J = 8.8, 1H), 7.93 (d, J = 7.8, 1H), 8.33 (s, 1H), 13.4, (bs, 2H). $^{13}$C NMR (DMSO-$d_6$) = 55.9, 66.5, 106.0, 106.7, 120.0, 124.6, 124.7, 125.9, 128.0, 128.8, 128.8, 129.1, 129.2, 130.3, 134.7, 136.7, 141.0, 147.4, 158.4, 161.5. FTIR (thin film): 3237, 1691, 1488, 1275, 1254, 1146, 856, 770, 695cm$^{-1}$. ESI-MS (*m/z*): 359 $[M+H]^+$.

**Benzyl 3-(3,5-bis(trifluoromethyl)phenyl)-1H-pyrazole-5-carboxylate (1m)**:



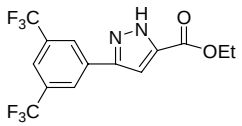
White solid, $^1$H NMR ($CDCl_3$) = 5.40 (s, 2H), 7.26 (bs, 1H), 7.25-7.47 (m, 5H), 7.84 (s, 1H), 8.30 (bs, 2H), 12.0 (bs, 1H). $^{13}$C NMR ($CDCl_3$) = 67.9, 106.7, 122.0, 124.9 (q, J = 270), 125.9, 128.8, 129.0, 129.1, 132.4, (q, J = 33), 134.3, 135.0, 135.9, 150.0, 159.78. FTIR (thin film): 3294, 3099, 3070, 1733, 1709, 1345, 1279, 1174, 1136, 1016, 897, 698, 682cm$^{-1}$. EI-MS (*m/z*): 414 $[M]^+$.

**tert-butyl 3-(3,5-bis(trifluoromethyl)phenyl)-1H-pyrazole-5-carboxylate (1n)**:



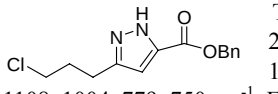
White solid, $^1$H NMR ($CDCl_3$) = 1.68 (s, 9H), 7.20 (s, 1H), 7.86 (s, 1H), 8.38 (s, 2H), 12.88 (s, 1H). $^{13}$C NMR ($CDCl_3$) = 28.40, 83.83, 106.2, 121.77, 123.6 (q, J = 270), 125.9, 132.4 (q, J = 45), 134.80, 137.46, 149.84, 159.10. FTIR (thin film): 2984, 1726, 1348, 1279, 1139, 1012, 895, 773, 707, 682cm$^{-1}$. EI-MS (*m/z*): 380 $[M]^+$

**ethyl 3-(3,5-bis(trifluoromethyl)phenyl)-1H-pyrazole-5-carboxylate (1o)**:



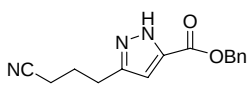
White solid $^1$H NMR ($CDCl_3$) = 1.44 (t, *J* = 7.2, 3H), 4.45 (q, *J* = 7.2, 2H), 7.26 (s 1H), 7.85 (s, 1H), 8.29 (s, 2H), 11.2 (br, s, 1H). $^{13}$C NMR ($CDCl_3$) = 14.4, 62.2, 106.5, 122.0, 123.5 (q, J = 270), 125.9, 132.5 (q, J = 34), 134.6, 136.0, 150.0, 159.8. FTIR (thin film): 3273, 1745, 1703, 1461, 1348, 1282, 1130, 1026, 897, 682cm$^{-1}$. EI-MS (*m/z*): 352 $[M]^+$

**Benzyl 3-(3-chloropropyl)-1H-pyrazole-5-carboxylate (1p)**:



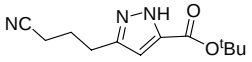
Tan solid, $^1$H NMR ($CDCl_3$) = 1.99 (quintet, J = 6.5, 2H), 2.77 (t, *J* = 6.4, 2H), 3.43 (t, *J* = 6.4, 2H), 5.31 (s, 2H), 6.59 (s, 1H), 7.31-7.43 (m, 5H), 12.6 (bs, NH). $^{13}$C NMR ($CDCl_3$) = 23.3, 31.9, 44.1, 66.8, 107.0, 128.57, 128.62, 128.8, 135.8, 141.6, 146.4, 161.9. FTIR (thin film): 3187, 3093, 2870, 1726, 1453, 1420, 1226, 1162, 1108, 1004, 779, 750 cm$^{-1}$. EI-MS (*m/z*): 278 $[M]^+$.

**Benzyl 3-(3-cyanopropyl)-1H-pyrazole-5-carboxylate (1q)**:



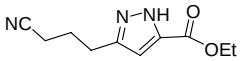
Tan solid, $^1$H NMR ($CDCl_3$) = 1.91 (quintet, J = 7.4, 2H), 2.26 (t, *J* = 7.2, 2H), 2.78 (t, *J* = 7.6, 2H), 5.32 (s, 2H), 6.61 (s, 1H), 7.30-7.39 (m, 5H), 11.8 (bs, NH). $^{13}$C NMR ($CDCl_3$) = 16.6, 25.1, 25.1, 66.9, 107.2, 119.5, 128.5, 128.7, 128.9, 135.8, 141.4, 146.0, 161.8. FTIR (thin film): 3191, 2963, 1725, 1454, 1421, 1226, 1161, 1003, 779, 751 cm$^{-1}$. EI-MS (*m/z*): 269 $[M]^+$.

**tert-butyl 3-(3-cyanopropyl)-1H-pyrazole-5-carboxylate (1r)**:



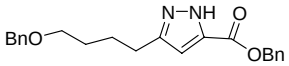
Tan solid, $^1$H NMR ($CDCl_3$) = 1.51 (s, 9H), 1.91-2.04 (m, 2H), 2.34 (t, *J* = 7.2 2H), 2.83 (t, *J* = 7.2, 2H), 6.51 (s, 1H), 10.7 (bs, NH). $^{13}$C NMR ($CDCl_3$) = 16.6, 25.3, 25.6, 28.4, 82.2, 107.0, 119.6, 141.5, 147.2, 160.7. FTIR (thin film): 2978, 1714, 1415, 1368, 1248, 1152, 999, 841, 782cm$^{-1}$. EI-MS (*m/z*): 179 [M-$^t$Bu]$^+$

**ethyl 3-(3-cyanopropyl)-1H-pyrazole-5-carboxylate (1s)**:



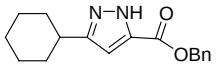
White solid, $^1$H NMR ($CDCl_3$) = 1.31 (t, *J* = 7.2, 3H), 1.94-2.03 (m, 2H), 2.35 (t, *J* = 7.2, 2H) 2.86 (t, *J* = 7.2, 2H), 4.31 (q, *J* = 7.2, 2H), 6.58 (s 1H), 10.45 (bs, NH) $^{13}$C NMR ($CDCl_3$) = 14.5, 16.6, 25.2, 25.2, 61.3, 107.0, 119.5, 141.5, 146.4, 161.9. FTIR (thin film): 3134, 2980, 1717, 1422, 1241, 1174, 1110, 784cm$^{-1}$. EI-MS (*m/z*): 207 [M]$^+$

**Benzyl 3-(4-(benzyloxy)butyl)-1H-pyrazole-5-carboxylate (1t)**:



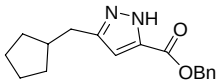
Tan solid, $^1$H NMR ($CDCl_3$) = 1.59-1.64 (m, 2H), 1.66-1.71(m, 2H), 2.64 (t, *J* = 7.2, 2H), 3.46 (t, *J* = 6.4, 2H), 4.48 (s, 2H), 5.32 (s, 2H), 6.59 (s, 1H), 7.25-7.40 (m, 10H), 10.91, (bs, NH). $^{13}$C NMR ($CDCl_3$) = 25.8, 26.2, 29.2, 66.7, 70.2, 73.2, 106.7, 127.86, 127.92, 128.49, 128.55, 128.6, 128.8, 136.0, 138.6, 142.2, 147.8, 162.2. FTIR (thin film): 3190, 2942, 1725, 1453, 1420, 1231, 1162, 737, 697cm$^{-1}$. EI-MS (*m/z*): 364 [M]$^+$.

**Benzyl 3-cyclohexyl-1H-pyrazole-5-carboxylate (1u)**:



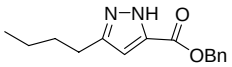
Tan solid, $^1$H NMR ($CDCl_3$) = 1.04-1.26 (m, 5H), 1.58-1.73 (m, 3H), 1.82-1.88 (m, 2H), 2.41-2.52 (m, 1H), 5.29 (s, 2H), 6.55 (s, 1H), 7.29 (m, 5H), 10.68 (bs, NH). $^{13}$C NMR ($CDCl_3$) = 26.0, 26.1, 32.5, 35.4, 66.6, 104.9, 128.4, 128.4, 128.7, 135.9, 141.9, 152.2, 162.4. FTIR (thin film): 3089, 2929, 1725, 1450, 1231, 1162, 1008, 778, 749, 697 cm$^{-1}$. EI-MS (*m/z*): 284 [M]$^+$.

**Benzyl 3-(cyclopentylmethyl)-1H-pyrazole-5-carboxylate (1v)**:



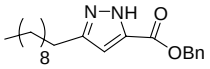
Tan solid, $^1$H NMR ($CDCl_3$) = 1.06-1.18 (m, 2H), 1.49- 1.59 (m, 4H), 1.62-1.71 (m, 2H), 2.10 (sep, *J* = 7.6, 1H), 2.66 (d, *J* = 7.6, 2H), 5.33 (s, 2H), 6.63 (s, 1H), 7.25-7.41 (m, 5H), 12.63 (bs, NH). $^{13}$C NMR ($CDCl_3$) = 25.2, 32.0, 32.6, 40.0, 66.6, 106.9, 128.46, 128.52, 128.8, 136.0, 142.0, 147.1, 162.3. FTIR (thin film):3092, 1726, 1453, 1417, 1224, 1161, 1104, 778, 749, 697 cm$^{-1}$. EI-MS (*m/z*): 284 [M]$^+$.

**Benzyl 3-butyl-1H-pyrazole-5-carboxylate (1w)**:



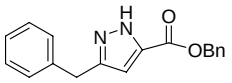
Tan solid, $^1$H NMR ($CDCl_3$) = 0.86 (t, *J* = 7.2, 3H), 1.26 (sextuplet, *J* = 7.2, 2H), 1.51 (quintet, *J* = 7.2, 2H), 2.58 (t, *J* = 7.2, 2H), 5.31 (s, 2H), 6.56 (s, 1H), 7.3-7.37 (m, 5H), 11.5, (bs, NH). $^{13}$C NMR ($CDCl_3$) = 14.0, 22.4, 22.6, 31.3, 66.6, 106.5, 128.5, 128.5, 128.8, 136.1, 142.0, 147.5, 162.3. FTIR (thin film): 3185, 2959, 1726, 1455, 1224, 1160, 1005, 750, 778, 697 cm$^{-1}$. EI-MS (*m/z*): 258 [M]$^+$.

**Benzyl 3-decyl-1H-pyrazole-5-carboxylate** (not shown in Figure 1)



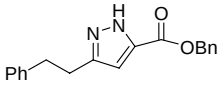
Tan solid, $^1$H NMR ($CDCl_3$) = 0.89 (t, *J* = 6.8, 3H), 1.20-1.35 (m, 14H), 1.51-1.60 (br, 2H), 2.59 (t, *J* = 7.6, 2H), 5.33 (s, 2H), 6.58 (s, 1H), 7.3-7.4 (m, 5H), 11.04 (bs, NH). $^{13}$C NMR ($CDCl_3$) = 14.4, 22.9, 26.0, 29.3, 29.4, 29.6, 29.8, 29.8, 32.2, 66.6, 106.6, 128.45, 128.49, 128.8, 136.0, 141.9, 147.5, 162.3. FTIR (thin film): 2925, 1727, 1452, 1159, 1005, 778, 749, 696 cm$^{-1}$. EI-MS (*m/z*): 342 [M]$^+$.

**Benzyl 3-benzyl-1H-pyrazole-5-carboxylate (1x)**:



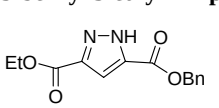
Tan solid, $^1$H NMR ($CDCl_3$) = 4.00 (s, 2H), 5.30 (s, 2H), 6.57 (s, 1H), 7.16-7.38 (m, 10 H), 12.67 (bs, NH). $^{13}$C NMR ($CDCl_3$) = 32.6, 66.8, 107.7, 128.6, 128.7, 128.8, 128.9, 129.0, 135.8, 138.4, 141.4, 147.1, 162.0. FTIR (thin film) 3185, 3066, 2962, 1725, 1455, 1416, 1495, 1224, 1160, 1108, 697 cm$^{-1}$. EI-MS (*m/z*): 292 [M]$^+$.

**Benzyl 3-phenethyl-1H-pyrazole-5-carboxylate (1y)**:



Tan solid, $^1$H NMR ($CDCl_3$) = 2.85-3.03 (m, 4H), 5.30 (s, 2H), 6.63 (s, 1H), 7.18 (t, *J* = 6.4, 2H), 7.22 (d, *J* =7.2, 2H), 7.28 (t, *J* =7.2, 2H), 7.33 (m, 4H), 11.10 (bs, NH). $^{13}$C NMR ($CDCl_3$) = 27.9, 35.6, 66.7, 106.9, 126.5, 127.4, 128.5, 128.6, 128.7, 128.8, 136.0, 141.0, 142.2, 146.7, 162.3. FTIR (thin film): 3089, 2960, 1725, 1454, 1226, 1161, 1108, 1004, 750, 698 cm$^{-1}$. EI-MS (*m/z*): 306 [M]$^+$.

**5-benzyl 3-ethyl 1H-pyrazole-3,5-dicarboxylate (1z)**:



White solid, $^1$H NMR ($CDCl_3$) = 1.29 (t, *J* = 7.2, 3H), 4.31 (q, *J* = 7.2, 2H), 5.3 (s 2H), 7.28-7.37 (m 6H), 11.41 (bs, NH). $^{13}$C NMR ($CDCl_3$) = 14.33, 61.81, 67.34, 111.69, 128.68, 128.78, 135.35, 140 (bs), 160.43, 160.52 FTIR (thin film): 3145, 2983, 1729, 1455, 1315, 129, 1169, 1086, 1019, 767, 698cm$^{-1}$. EI-MS (*m/z*): 274 [M]$^+$

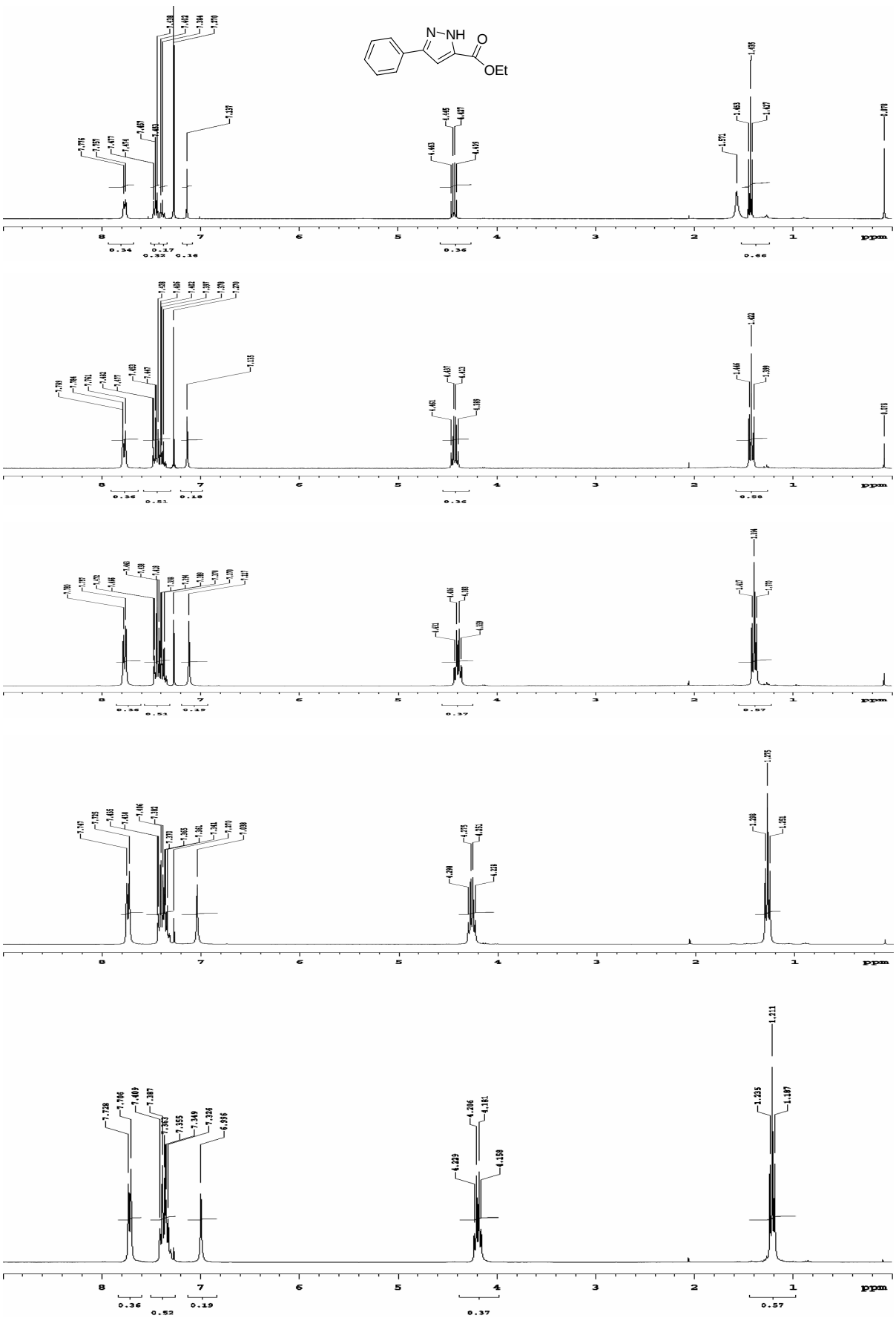



**Figure S1**. Concentration –dependent NMR spectra of **1c**. The largest changes are observed for the ethyl methylene (4.44 → 4.19 ppm) and the pyrazole methine (7.14 → 7.00 ppm).

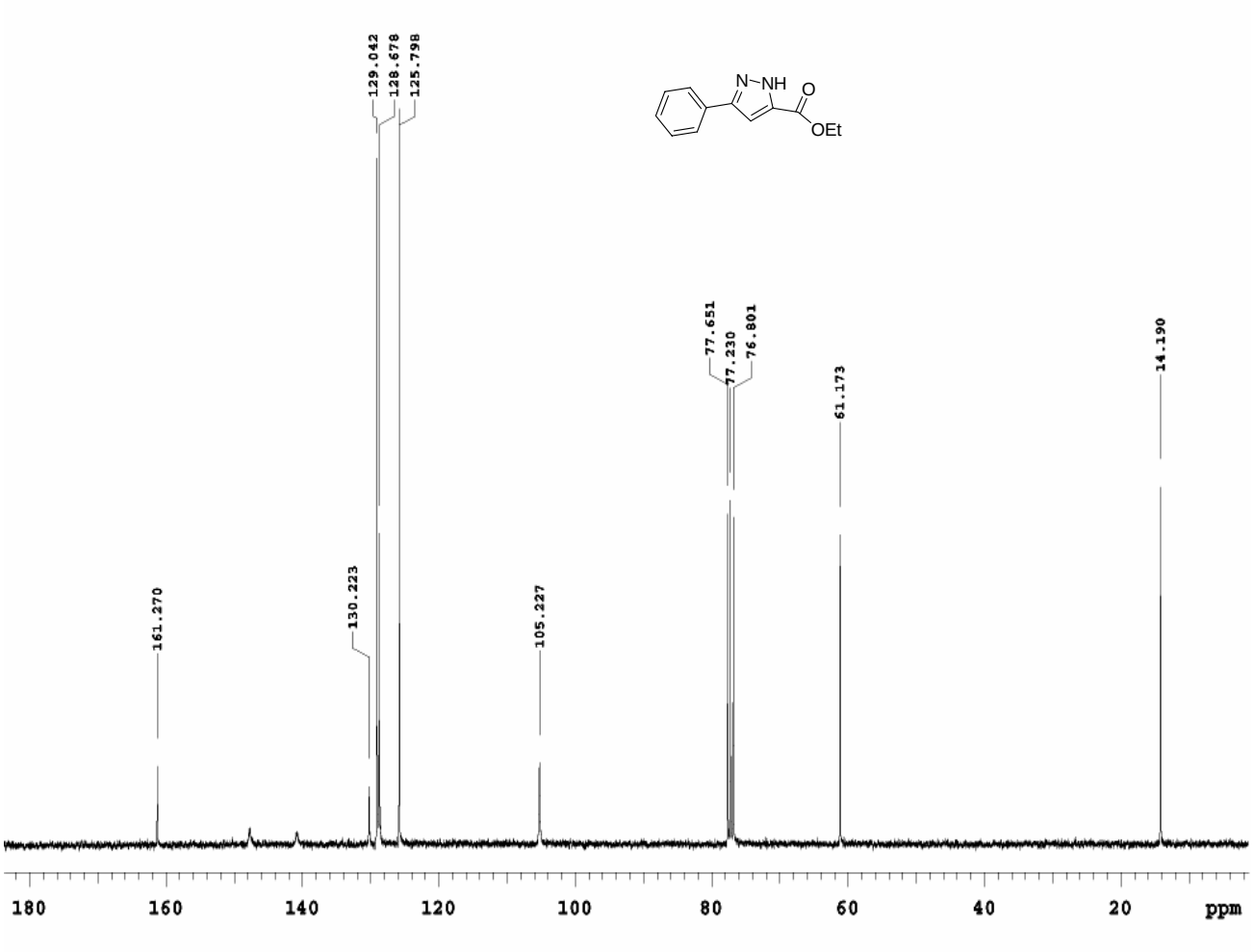



**Figure S2**. $^{13}C$ NMR for **1c**. The broad peaks at 141 and 148 ppm are the quaternary pyrazole carbons.

**Notes and references:**


[1] Z. Qu, J. Wang, *Chinese J. Org. Chem.* **2003**, *23*, 988-995.

[2] M. Schroen, S. Braese, *Tetrahedron* **2005,** *61,* 12186 - 12192.

[3] T. Dominh, O. P. Strausz, H. E. Gunning, *Tetrahedron Lett.* **1968,** *9*, 5237-5242.

[4] M. A. P. Martins, R. Freitag, N. Zanatta, *Synthesis*, **1995**, 1491-1492.


[5] Formed by adding 2M solution of HCl in $Et_2O$ to solution of pyrazole in $Et_2O$. Filtration provided the HCl salt.