

Electrospray Ionization Mass Spectrometry Reveals an Unexpected Coupling Product in the Copper-Promoted Synthesis of Pyrazoles

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General Experimental.

The (*Z*)-Methyl-3-(phenylamino)but-2-enoate (**1a**) and (*Z*)-methyl-3-(*p*-tolylamino)but-2-enoate (**1b**) were prepared by analogous methods described previously.¹ The synthesis of methyl 3,5-dimethyl-1-phenyl-1*H*-pyrazole-4-carboxylate (**2**) was carried out according to previous work.² Cu(OAc)₂, 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one and solvents were purchased from Sigma-Aldrich and Penta Chemicals and used as obtained without other purification.

NMR spectra were recorded on a Bruker Avance 500 (500 MHz for ¹H, 125.7 MHz for ¹³C) or Bruker Avance 400 (400 MHz for ¹H, 100.6 MHz for ¹³C) NMR spectrometer. Chemical shifts are reported in δ ppm referenced to solvent residual peak (CDCl₃: ¹H = 7.24 ppm, ¹³C = 77.23 ppm) as the internal reference unless otherwise noted. Data are reported in the following order: chemical shifts are given (δ); multiplicities are indicated br (broadened), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), app (apparent); coupling constants, *J*, are reported in Hz. Infrared spectra were measured on a Bruker EQUINOX55 (IFS55) spectrometer in CHCl₃ (cuvette width 0.118 mm). Peaks in IR are reported in cm⁻¹ with the following relative intensities: s (strong, 67-100%), m (medium, 40-67%), w (weak, 10-40%). Column chromatography procedures were followed using 70-230 mesh and 60 Å silica gel. Visualization was effected with ultraviolet light.

Unless otherwise mentioned, the condensed-phase reactions were performed by heating a solution of enaminone **1** (0.0260 mmol; 5 mg) and copper(II) acetate (1.5 eq.; 0.0384 mmol; 7.0 mg) in acetonitrile (2 mL) to 110 °C in round flask with condenser and Drierite guard tube. In given time intervals, small samples were taken (10 μL), diluted with acetonitrile in a 1:100 ratio, and probed by using of ESI-MS.

¹ Würtz, S.; Rakshit, S.; Neumann, J. J.; Dröge, T.; Glorius, F. *Angew. Chem. Int. Ed.* **2008**, *47*, 7230-7233.

² Neumann, J. J.; Suri, M.; Glorius, F. *Angew. Chem. Int. Ed.* **2010**, *49*, 7790–7794.

Catalyst solution (SYNAPT data)

High-resolution mass measurements of solution of copper(II) acetate in acetonitrile was performed with a SYNAPT G2 ion mobility instrument (WATERS, Manchester, U.K.).

Measured (m_{exp}) and calculated (m_{calc}) masses of selected copper ions from high resolution mass determination.^a

	nominal mass	m_{exp}	m_{calc}	Δm^b
[Cu] ⁺	63	62.9300	62.9296	0.4
	65	64.9279	64.9278	0.1
[Cu(CH ₃ CN)] ⁺	104	103.9546	103.9561	-1.5
	106	105.9530	105.9543	-1.3
[Cu(CH ₃ CN) ₂] ⁺	145	144.9820	144.9827	-0.7
	147	146.9797	146.9809	-1.2

^a Monoisotopic masses for the both copper isotopes. ^b $\Delta m = m_{\text{exp}} - m_{\text{calc}}$ in milli-amu.

Reaction kinetics followed via ESI-MS

The reaction was performed with 5.0 mg of the enaminone **1c** (0.026 mmol). The relative concentration is represented by sum of ions containing the reactant **1**, the product **2**, and the potential intermediate **X**, respectively. The data are normalized to $\Sigma = 1$.

time (min)	1	X	2
0	0.92	0.03	0.04
2.5	0.82	0.13	0.05
5	0.64	0.29	0.07
15	0.46	0.42	0.12
30	0.38	0.46	0.16
45	0.36	0.41	0.24
60	0.28	0.45	0.27
80	0.24	0.42	0.34
120	0.15	0.37	0.48
140	0.12	0.39	0.49
160	0.12	0.37	0.51
180	0.11	0.35	0.54
210	0.09	0.32	0.58
240	0.06	0.32	0.61
270	0.06	0.29	0.65

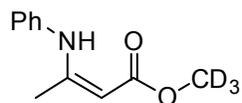
300	0.06	0.28	0.66
360	0.05	0.27	0.69
420	0.05	0.22	0.72
480	0.06	0.21	0.74

Stoichiometric oxidation of the substrate by Cu(OAc)₂ under anaerobic conditions

The enaminone **1a** (128 mg; 0.67 mmol) and copper(II) acetate were placed in a Schlenk flask. After degassing the flask, the reactants were flushed with argon and then 1 mL of degassed acetonitrile was added. The flask was closed by glass stopper with Teflon sleeve, once again flushed with argon and finally the flask valve was closed. The reaction mixture was stirred at 110 °C for 24 hours. The reaction mixture was allowed to cool down to room temperature and then was poured into 25 mL of ethyl-acetate allowing precipitation of copper(II) acetate from the reaction mixture. Copper(II) acetate was removed by filtration through 2 cm of silicagel in ethyl-acetate and washed with 75 mL of ethyl-acetate. Dimethyl terephthalate (internal standard, 154 mg) was dissolved in combined filtrates (~100 mL). 0.3 mL of this solution was taken, diluted with 1 ml of ethyl-acetate and analyzed by GC/MS. The calibration graph was made by 5 points of the various ratios of pyrazole **2** and dimethyl terephthalate with accuracy $R^2=0.9987$.

eq. of Cu(OAc) ₂	m (Cu(OAc) ₂) [mg]	GC yield of 2 [%]
0.25	31	19
0.5	61	35
1.0	122	54
1.5*	183	74
2.0*	243	74

* The reaction mixtures were not homogeneous.



d³-methyl-3-anilincrotonate (1c) Methanol-d₄ (1.5 mL; 0.037 mol) was

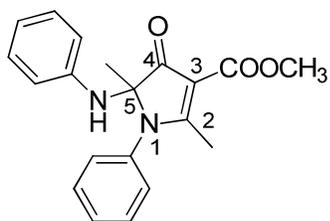
added dropwise to suspension of NaH (0.887 g; 0.037 mol) in toluene (12 mL) at 0 °C. Then reaction mixture was stirred for 15 min and during that time evolution of gas had stopped. After that glacial acetic acid (2.2 mL) was added dropwise (at 0 °C) and the reaction mixture was stirred for another 15 min. The resulting precipitate (sodium acetate) was removed by filtration and was washed with 3 ml of fresh toluene. Freshly distilled 2,2,6-trimethyl-4H-1,3-dioxin-4-one (1.3 mL; 1.422 g; 0.01 mol) and *p*-toluenesulfonic acid (35 mg; 0.

2 mmol) were added into combined filtrates and the resulting mixture was stirred at 100 °C for 2.5 h under argon. The reaction mixture was cooled down to 50 °C and aniline (950 μL; 0.01 mol) was added. The mixture was stirred at 50 °C for another 2.5 h. After that, solvent was distilled off under reduced pressure and the crude product was purified by column chromatography (silicagel 140 g, mobile phase 100:4:1 *n*-hexane:ethyl-acetate:triethylamine, $R_f=0.16$). The title product was obtained as yellowish sticky crystals (958 mg) in 49 % yield.

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 10.34 (br s, 1H), 7.33 – 7.28 (m, 2H), 7.17 – 7.11 (m, 1H), 7.09 – 7.04 (m, 2H), 4.68 (d, $J = 0.5$, 1H), 1.98 (d, $J = 0.4$, 3H). (Compare the spectrum of nondeuterated compound in ref.1)

Copper(II) d^3 -acetate monohydrate. $\text{Cu}(\text{OH})_2\cdot\text{CuCO}_3$ was prepared by quantitative precipitation of aqueous $\text{CuSO}_4\cdot 5\text{H}_2\text{O}$ solution with aqueous Na_2CO_3 solution.

$\text{Cu}(\text{OH})_2\cdot\text{CuCO}_3$ (1.125 g; 5.088 mmol) was suspended in 20 mL of water and d^4 -acetic acid was added dropwise. The reaction mixture was stirred at room temperature for 30 minutes. Then the warm reaction mixture was filtered and precipitated by pouring it dropwise into 500 mL of acetone. Resulting blue-green precipitate was collected by filtration, washed with acetone (100 mL) and dried under reduced pressure. The title product was obtained as a blue-green precipitate (1.380 g) in 66 % yield.



Methyl 2,5-dimethyl-4-oxo-1-phenyl-5-(phenylamino)-4,5-dihydro-1H-pyrrole-3-carboxylate (X). Enaminone **1a** (191 mg; 1.0 mmol) was dissolved in acetonitrile (76 mL), followed by the addition of $\text{Cu}(\text{OAc})_2$ (272 mg; 1.5 mmol). The reaction mixture was stirred at 110 °C for 15 minutes in a flask equipped with condenser

and drying tube. After that the reaction mixture was cooled down and 60 ml of solvent was distilled off. The remaining mixture was poured into solution of ethylenediaminetetraacetic acid (EDTA) (500 mg in 50 mL of water). The resulting mixture was extracted with 25 mL of ethyl-acetate. The organic layer was separated and washed with solution of EDTA of same concentration as before. The resulting combined blue aqueous phase (contains Cu^{2+}) was washed with additional ethyl-acetate (10 mL). Combined organic layers were dried over MgSO_4 , filtered

and evaporated. The residue was separated by column chromatography (silicagel 20 g, ethylacetate as a mobile phase). The title product was obtained as a brownish oil (5 mg) in 3 % yield.

^1H NMR (499.8 MHz, CDCl_3) δ 7.35 (m, 2H, H-*p*-PhN), 7.31 (m, 2H, H-*m*-PhN), 7.08 (m, 2H, H-*m*-PhNH), 6.89 (m, 2H, H-*o*-PhN), 6.72 (m, 1H, H-*p*-PhNH), 6.36 (m, 2H, H-*o*-PhNH), 4.14 (br s, 1H NH), 3.78 (s, 3H, CH_3O), 2.42 (s, 3H, $\text{CH}_3\text{-2}$), 1.42 (s, 3H, $\text{CH}_3\text{-5}$).

^{13}C NMR (125.7 MHz, CDCl_3) δ 194.03 (C-4), 178.28 (C-2), 165.14 (COOMe), 143.11 (C-*i*-PhNH), 134.27 (C-*i*-PhN), 129.66 (CH-*m*-PhNH), 129.66 (CH-*m*-PhN), 129.43 (CH-*p*-PhN), 129.35 (CH-*o*-PhN), 119.54 (CH-*p*-PhNH), 113.96 (CH-*o*-PhNH), 100.72 (C-3), 81.20 (C-5), 51.21 (CH_3O), 25.40 ($\text{CH}_3\text{-5}$), 16.21 ($\text{CH}_3\text{-2}$).

IR (cm^{-1} , CHCl_3) 1723 m (COOMe), 1201 s or 1238 m-s (C-O in COOMe), 1438 m (Me in COOMe), 3438 w (NH), 3061 w, 1604 m, 1500 s, 1415 m, 1315 m (Ph-N), 3061 w, 1604 m, 1514 vs, 1415 m, 1315 m (Ph-NH), 1386 m, 1369 m, 2953 w ($\text{CH}_3 - \text{C2}$), 1684 vs (C4=O), 1514 vs, 1500 s or 1483 m, sh (C2=C3).

HRMS +p ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_3\text{Na}^+$, 359.13661; found 359.13656.

Role of compound X as a reaction intermediate

Compound **X** (1 mg; 0.003 mmol) was dissolved in 1.5 mL of acetonitrile, followed by the addition of copper(II) acetate (1 mg; 0.0055 mmol; 1.8 eq.). The reaction mixture was stirred at 120 °C for 30 min and then sample of reaction mixture was probed using ESI-MS.

Reaction with $^{18}\text{O}_2$

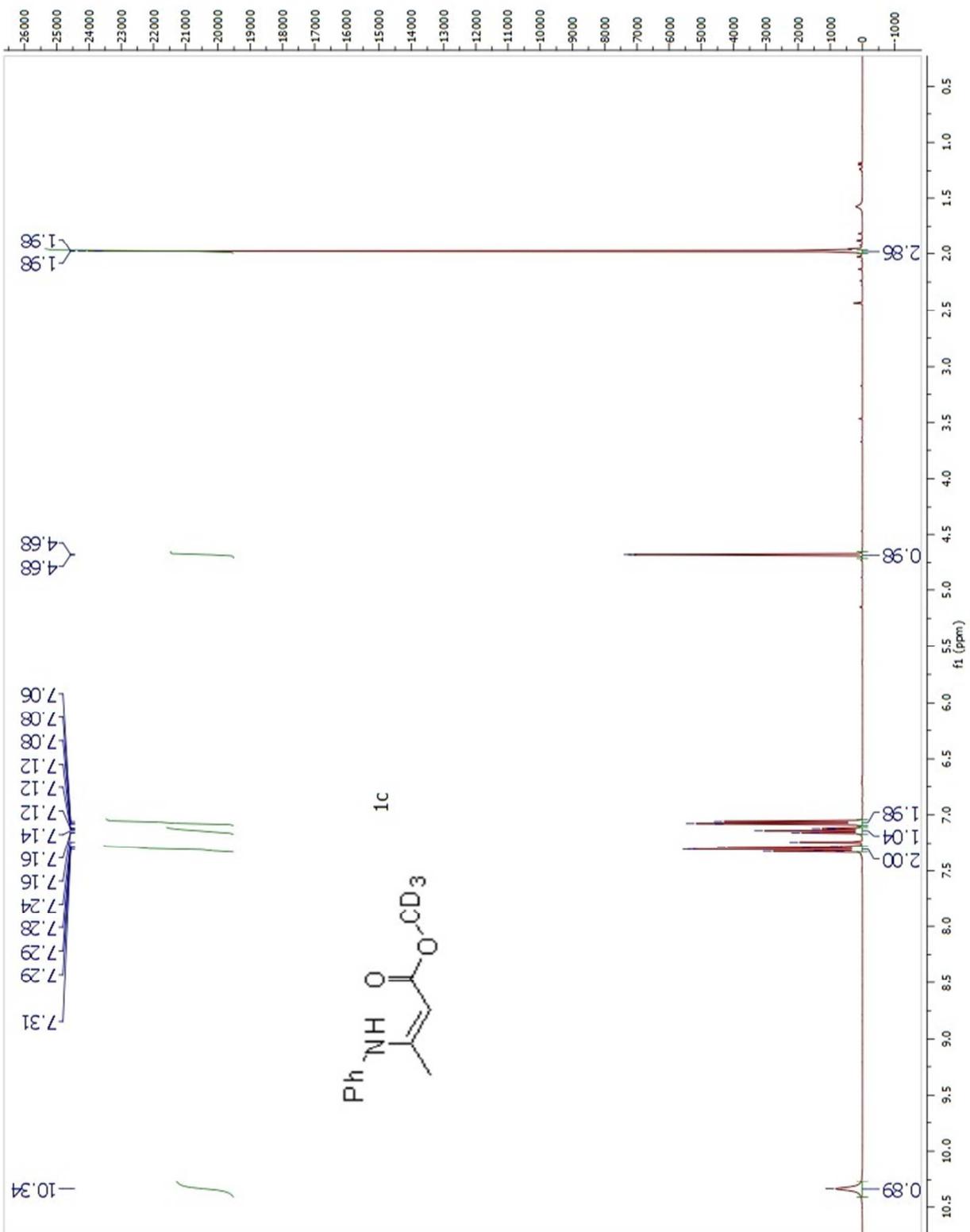
Enaminone **1a** (25 mg; 0.131 mmol) and copper(II) acetate (6 mg; 0.033 mmol; 0.25 eq.) were placed into 3-necked flask equipped with water condenser and balloon (dumping of sudden change of pressure). The apparatus was degassed and flushed with argon and degassed acetonitrile (10 mL) was added. $^{18}\text{O}_2$ was added from cylinder by 3-way valve attached to one neck of reaction flask and then the apparatus was closed. The reaction mixture was stirred at 110 °C for 5 hours and samples were taken during the progress of reaction.

Influence of X on reaction kinetics

Enaminone **1a** (10 mg; 0.0523 mmol) and copper(II) acetate (14 mg; 0.0771 mmol) were placed into flask, followed by acetonitrile (4 mL). The reaction mixture was stirred at room temperature for 30 minutes until full dissolution of all components. The resulting solution was divided into two equal parts (2+2 mL) by pipette. Compound **X** (1 mg; 0.0030 mmol; 0.11 eq. to enaminone **1a**) was added only to the one reaction mixture. The reaction mixtures were simultaneously stirred at 110 °C and the samples (10 µL) were taken during the progress of reaction, diluted with acetonitrile in a 1:100 ratio, and probed using ESI-MS.

The relative rates are represented by ratio of relative concentrations of product **2** and enaminone **1**. Relative concentrations were obtained as a sum of ions containing the reactant **1**, the product **2**, and the potential intermediate **X**, respectively. The data were normalized to $\Sigma = 1$.

Reaction without X		Reaction with X	
t (min)	Ratio 2/1	t (min)	Ratio 2/1
3	0.12	4	0.27
5	0.21	6	0.19
10	0.27	11	0.27
15	0.27	16	0.36
30	0.53	31	0.72
45	0.62	46	1.01
60	1.28	61	1.31
80	1.56	81	1.88
100	1.62	101	2.63



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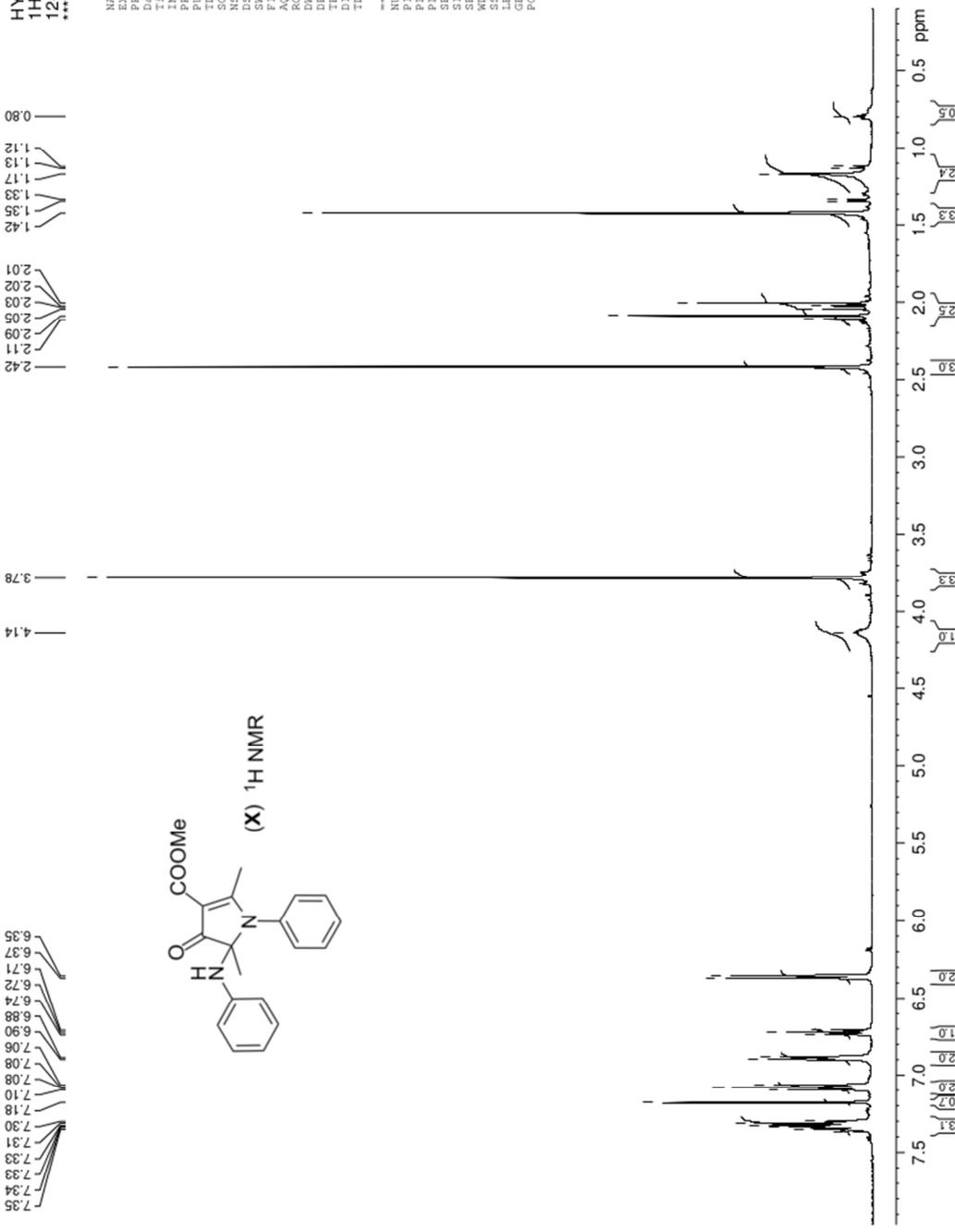
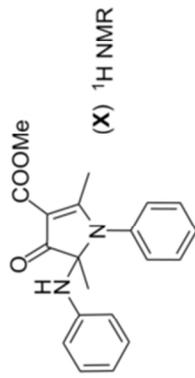
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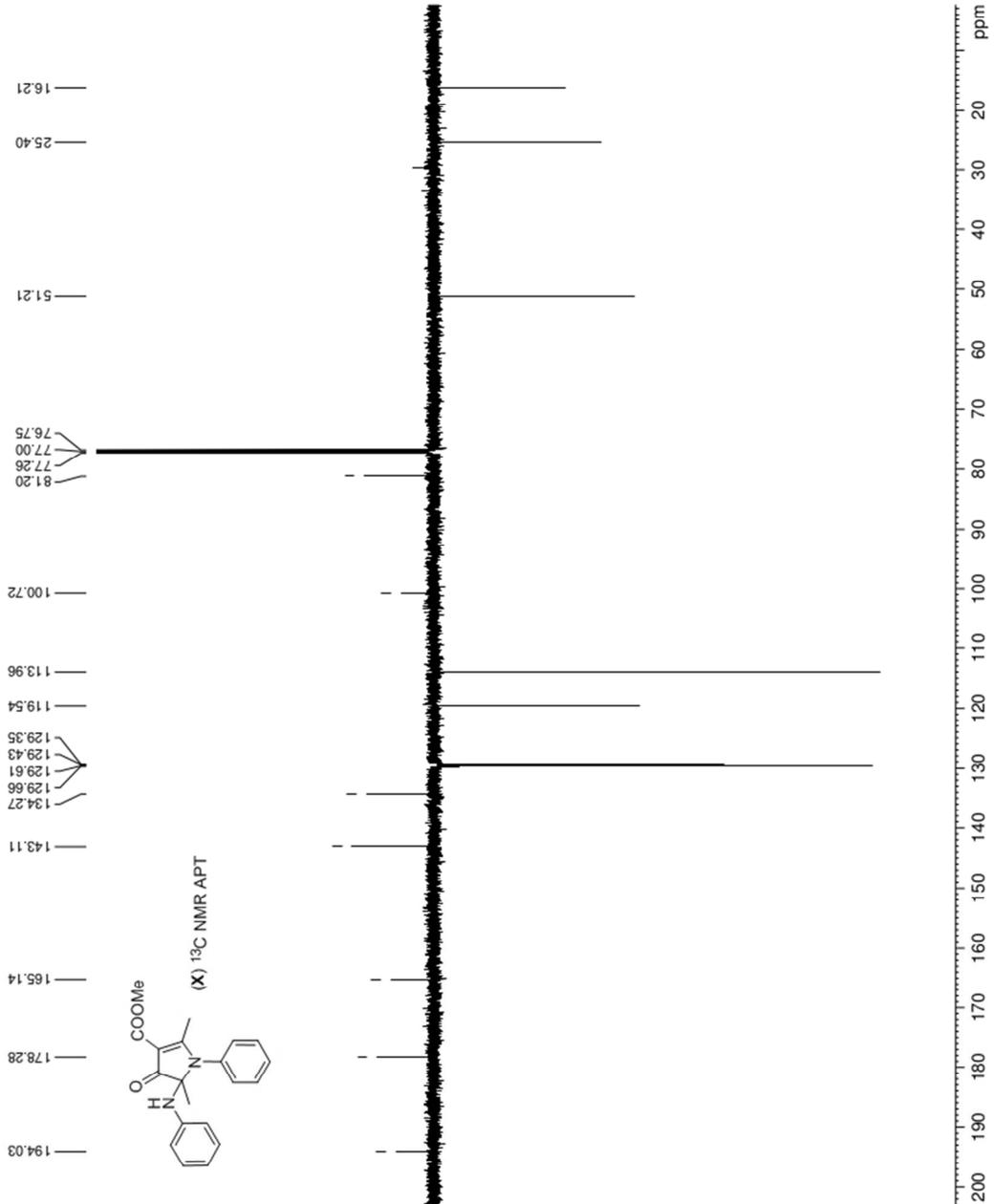
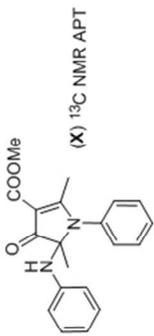
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HYVL JH028-I_3
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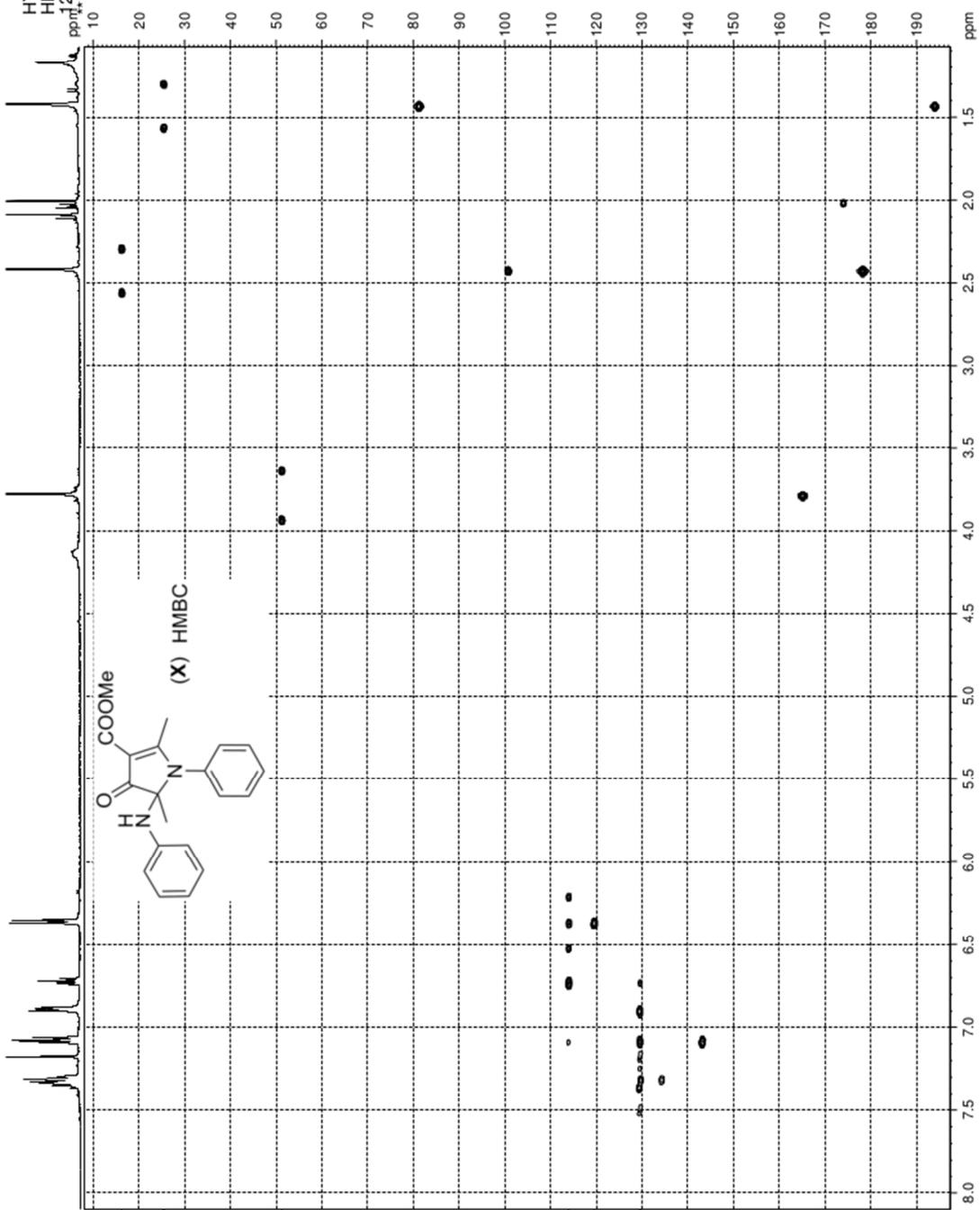
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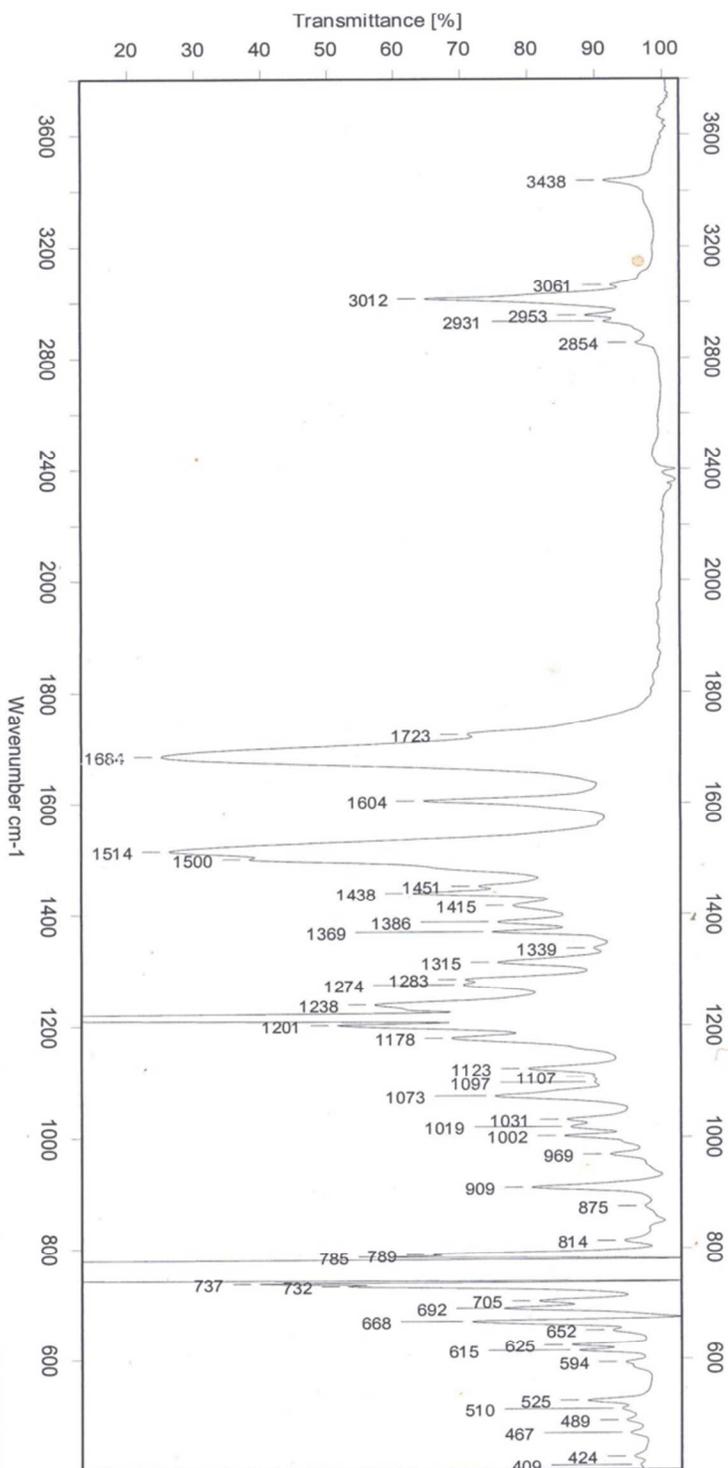
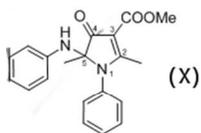
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