Supporting Information

Structure Elucidation of a Cryptic Condensation Product from Diacetyl and Arylamine - Then and Now

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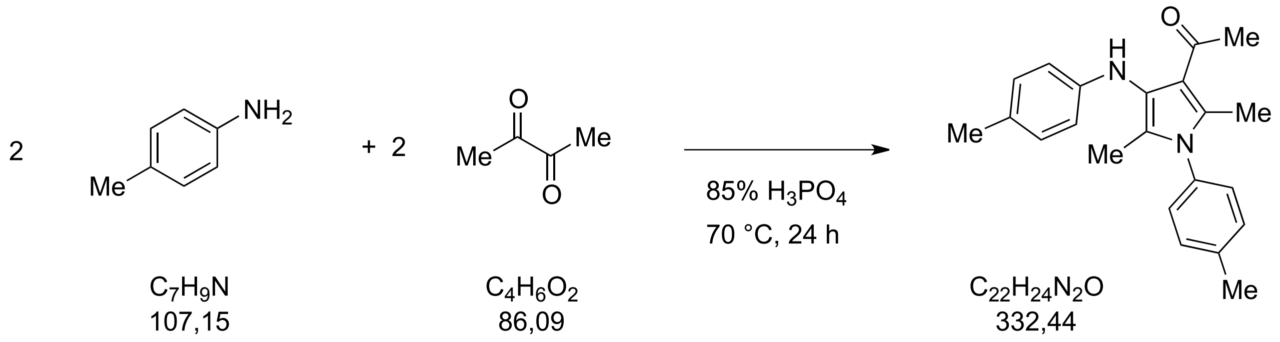
1 Syntheses and substance data

1.1 1-(2,5-Dimethyl-1-(*p*-tolyl)-4-(*p*-tolylamino)-1*H*-pyrrol-3-yl)ethanone (4a)[1,2]



p-Toluidine (5.35 g, 50 mmol) was placed into a 50 mL round-bottom flask containing a magnetic stirring bar. Concentrated 85% phosphoric acid (25 mL) was added with stirring. The flask was placed into an oil-bath at 50 °C and the suspension stirred until completely dissolved. Diacetyl (5.15 mL, 59 mmol) was added dropwise over 5 minutes with stirring. The oil-bath was heated to 70 °C and the reaction mixture stirred for 24 hours. The cooled solution was poured into 250 mL deionized water and stirred, forming a turbid suspension that was stirred for 1 d at r.t. Vacuum filtration (which took several hours, since the filter was partly blocked by the fine solid) and washing of the solid with water and a little EtOH–H_2O (1:1) gave 4.44 g of crude ochre material.[3] This material was boiled with 50 mL of EtOH and the mixture filtered through a glass-filter. The solid on the filter was washed with additional hot EtOH to leave some bright tan yellow microcrystalline solid (265 mg, m.p. 152–153 °C). The filtrate was evaporated to ca 15 mL in a rotatory evaporator. After stirring in an ice-bath, it was filtered and the solids washed with EtOH to give ochre solid (965 mg, m.p. 151–152 °C); the two fractions have identical NMR spectra; combined yield 1.23 g (15%).

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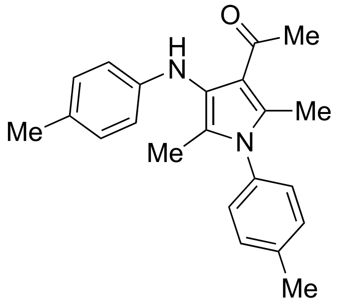
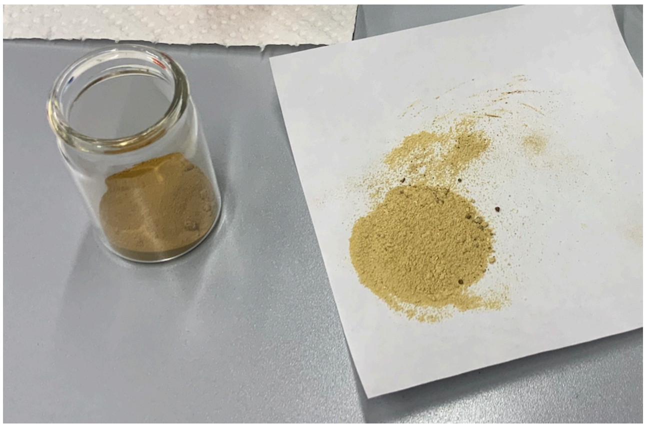
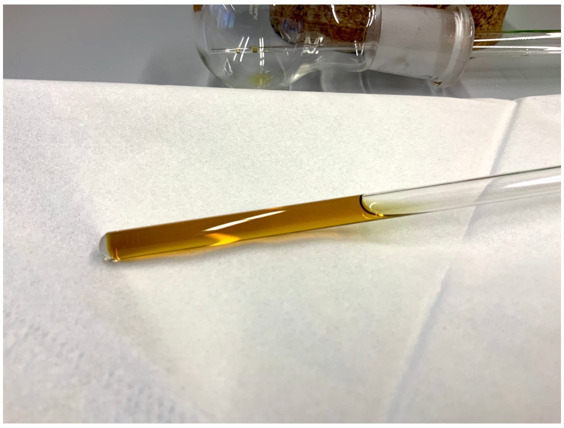
[1] F. Christen, B. Prijs, H. Lehr, *Helv. Chim. Acta* **1949**, *32*, 56.

[2] F. Christen, *Zur Kenntnis von biologisch wirksamen Kondensationsprodukten aus primären aromatischen Aminen*, Dissertation, Universität Basel, **1946**.

[3] According to ^1H NMR, the crude material consists mainly of pyrrole **4a** and a little polymeric material (broad signals) with no indication of clearly discernible signal sets for other lower molecular compounds.



R_f 0.40 (EtOAc–hexanes 1:3); m.p. 151–152 °C (from EtOH) [Lit. 146.5 °C][1]; 152–153 °C (EtOH-washed precipitate from H_2O); ^1H NMR (500 MHz, $CDCl_3$): δ 1.80 (s, 3 H, Me), 2.23 (s, 3 H, Me), 2.29 (s, 3 H, Me), 2.39 (s, 3 H, Me), 2.44 (s, 3 H, Me), 5.92 (br s, 1 H, NH), 6.56–6.61 (m, 2 H, ArH), 6.95–7.00 (m, 2 H, ArH), 7.07–7.11 (m, 2 H, ArH), 7.28–7.32 (m, 2 H, ArH); ^{13}C APT NMR (76 MHz, $CDCl_3$): δ 10.58 (CH_3), 13.60 (CH_3), 20.44 (CH_3), 21.20 (CH_3), 30.36 (CH_3), 113.97 (CH), 117.55 (C), 122.87 (C), 123.91 (C), 127.14 (C), 127.97 (CH), 129.65 (CH), 130.08 (CH), 133.73 (C), 134.73 (C), 138.70 (C), 145.06 (C), 195.65 (C=O). ^{15}N NMR (51 MHz, $CDCl_3$; by $^1H,^{15}N$-HMBC): δ 63 (R_2NH), 174 (pyrrole).

	
left: sample recrystallized from EtOH; right: partially undissolved material left on filter	NMR sample in $CDCl_3$.

^1H NMR (500 MHz, $CDCl_3$) of 4a - Excerpts

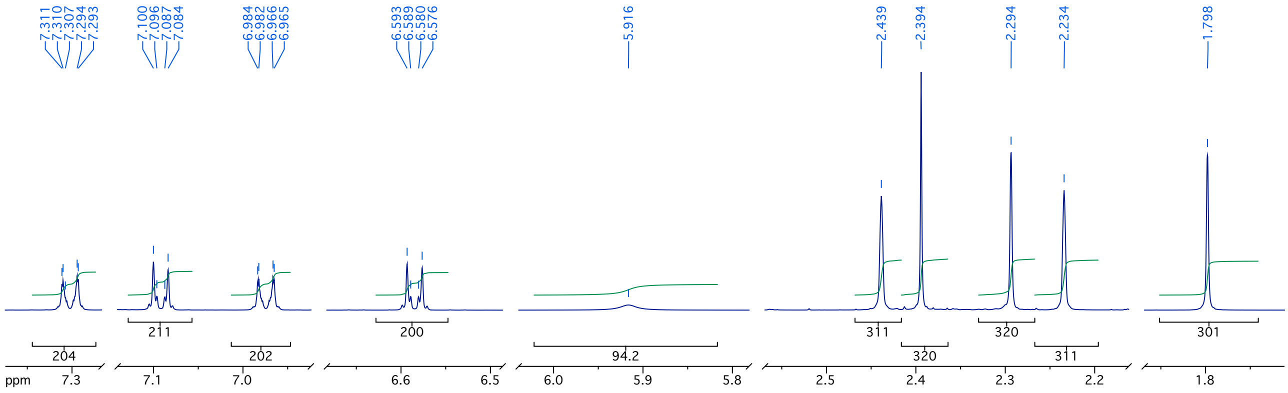
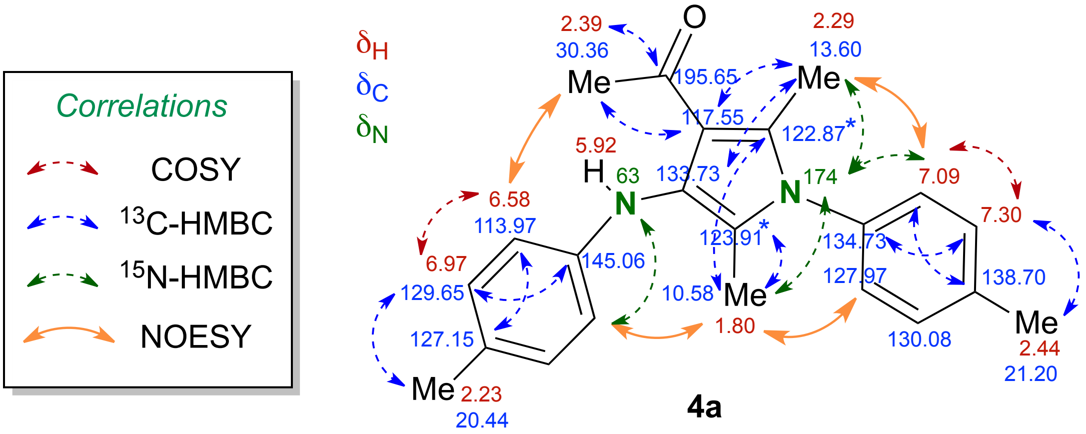


Table S-1. NMR data and assignments for 4a

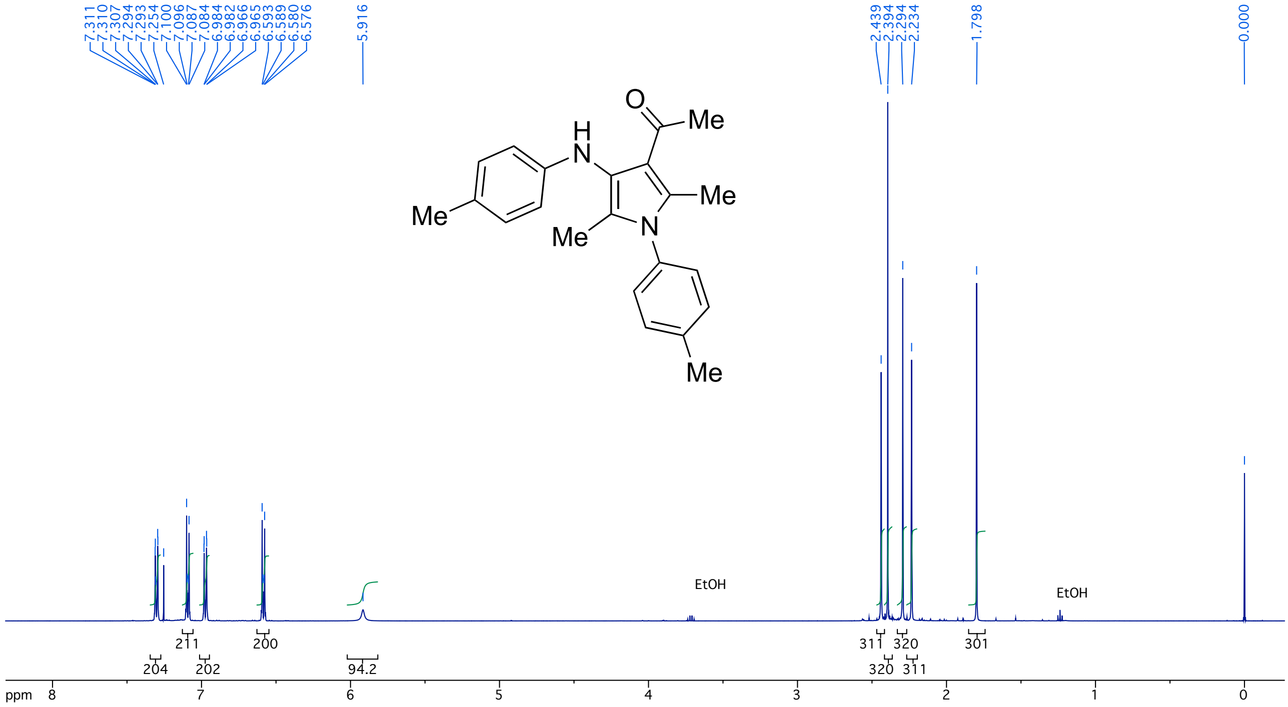
	δ(^{13}C)^{a}	n	Type	δ(^{1}H)^{b}	Mult.	H	δ(^{1}H) by HSQC^{c}	HMBC strong^{b}	HMBC weak^{b}
	$CDCl_3$		APT	500 MHz			(mult, J/Hz)		
	10.58	1	CH_3	1.80	s	3	1.80	123.9, 122.9 (?)	117.5, 144.9, 133.7 (vw)
	13.60	1	CH_3	2.29	s	3	2.30	133.7, 117.6	195.4
	20.44	1	CH_3	2.23	s	3	2.25	130.1 (129.6?), 127.2	145.1, 113.9, 138.8
	21.20	1	CH_3	2.44	s	3	2.44	130.1, 139.0	
	30.36	1	CH_3	2.39	s	3	2.40	195.4, 117.7	
	113.97	2	CH	6.58	m	2	6.59	127.15, 114.0	145.0
	117.55	1	C				–		
	122.87	1	C				–		
	123.91	1	C				–		
	127.14	1	C				–		
	127.97	2	CH	7.09	m	2	7.10	128.0, 138.7,	134.8
	129.65	2	CH	6.97	m	2	6.98	20.3, 145.0, 129.7	113.9
	130.08	2	CH	7.30	m	2	7.30	21.2, 130.1, 134.7	
	133.73	1	C				–		
	134.73	1	C				–		
	138.70	1	C				–		
	145.06	1	C				–		
	195.65	1	C=O				–		
NH			NH	5.92	s	1			
		C_{22}	$C_{22}H_{24}N_1O_1$*			H_{24}			

a) APT at 76 MHz. b) At 500 MHz. c) At 300 MHz. (lr) = long-range, (vw) = very weak. *) Partial sum formula based on spectroscopically proven fragments as listed in the column. A second nitrogen was proven by ^{1}H,^{15}N-HMBC.

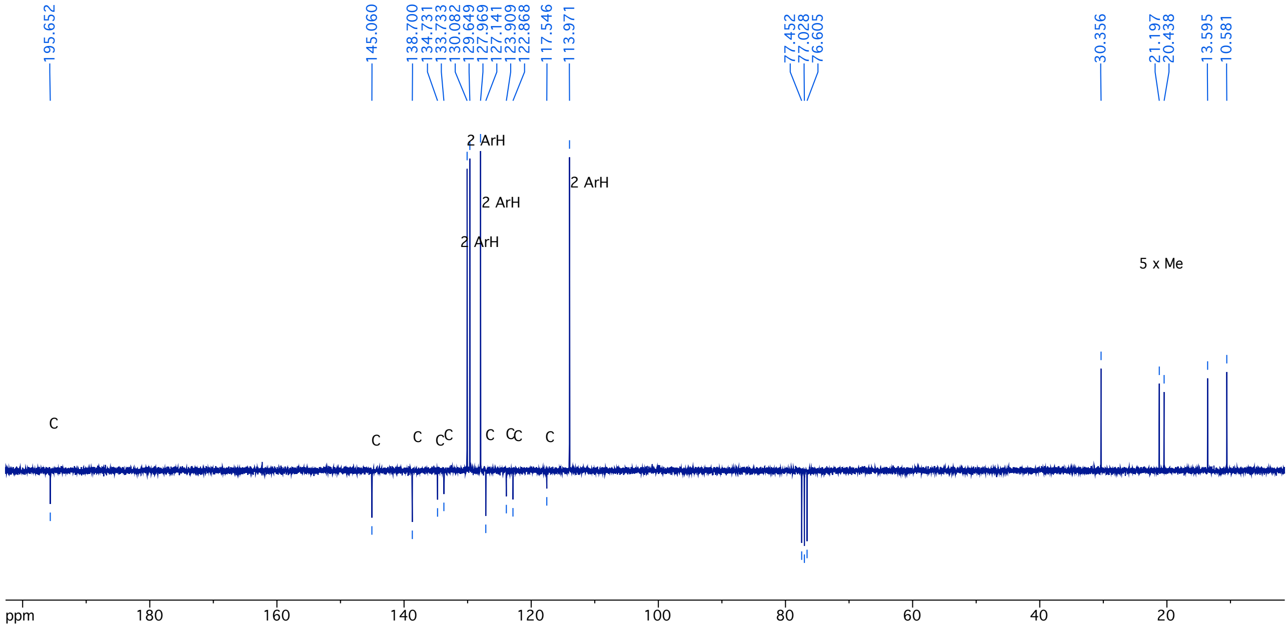


4a

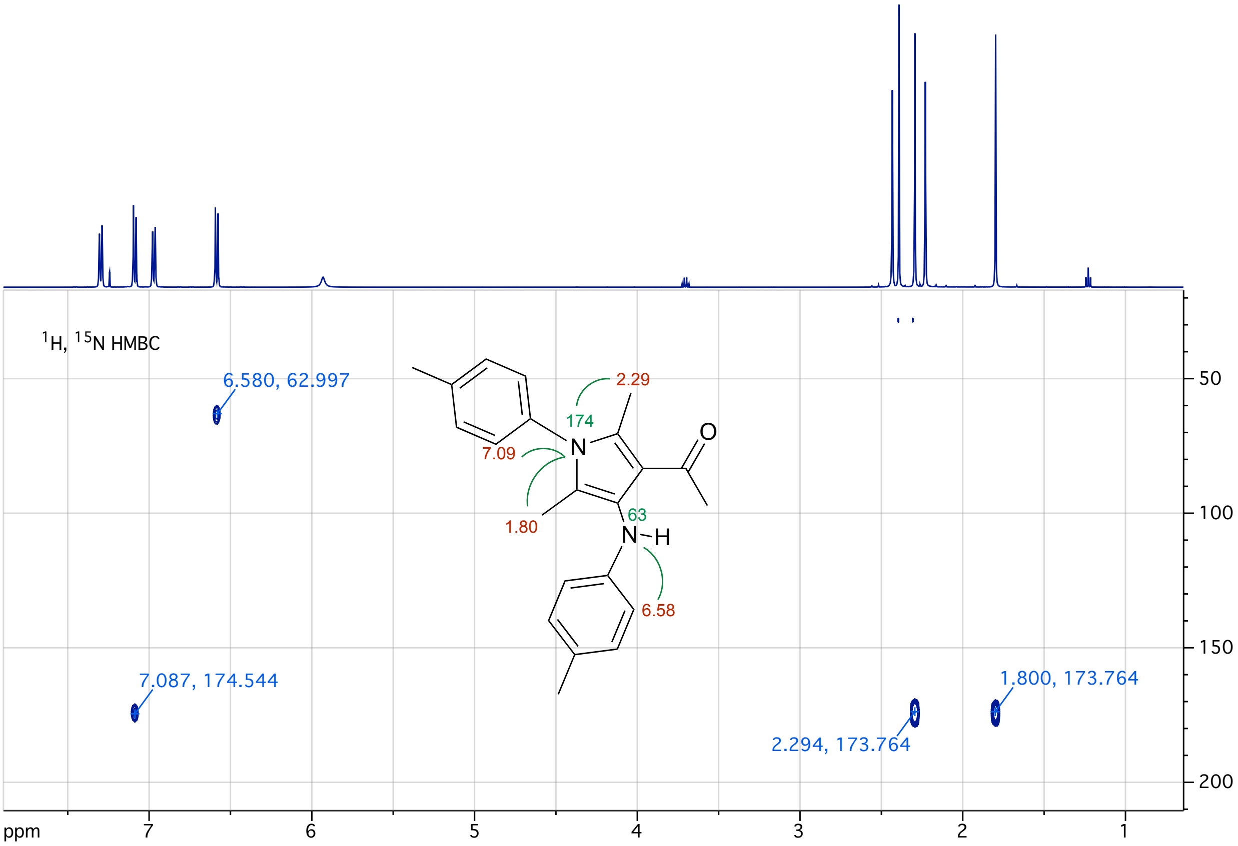
^{1}H NMR (500 MHz, CDCl$_3$) of 4a – Full range



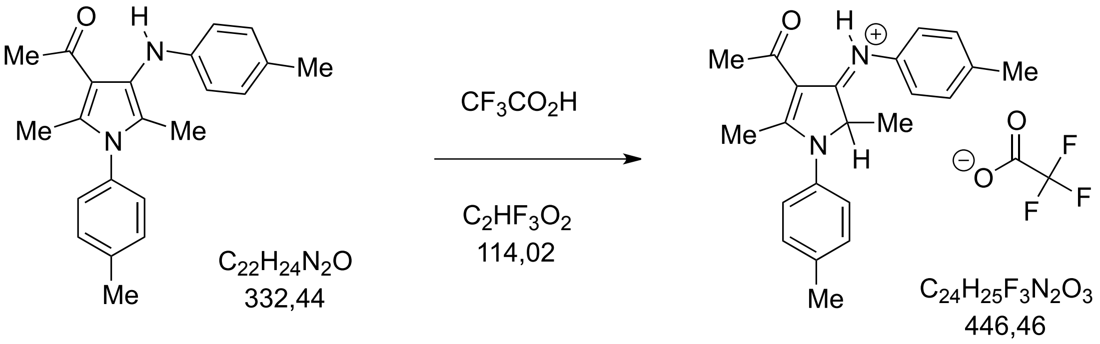
^{13}C APT NMR (76 MHz, CDCl$_3$) of 4a



^{1}H,^{15}N-HMBC (500 MHz, $CDCl_3$) of 4a



1.2 *N*-(4-Acetyl-2,5-dimethyl-1-(*p*-tolyl)-1*H*-pyrrol-3(2*H*)-ylidene)-4-methylbenzenaminium 2,2,2-trifluoroacetate (5a)



A sample of pyrrole **4a** (29.2 mg, 87.8 µmol) was placed into an NMR tube and dissolved in $CDCl_3$ (550 µL). Trifluoroacetic acid (20 µL, 260 µmol, 3 equiv.) was added by microliter syringe and the sample homogenized by shaking. The color turned from yellow to brown with yellow-red tones.

^{1}H NMR (500 MHz, $CDCl_3$) of 5a – Excerpts

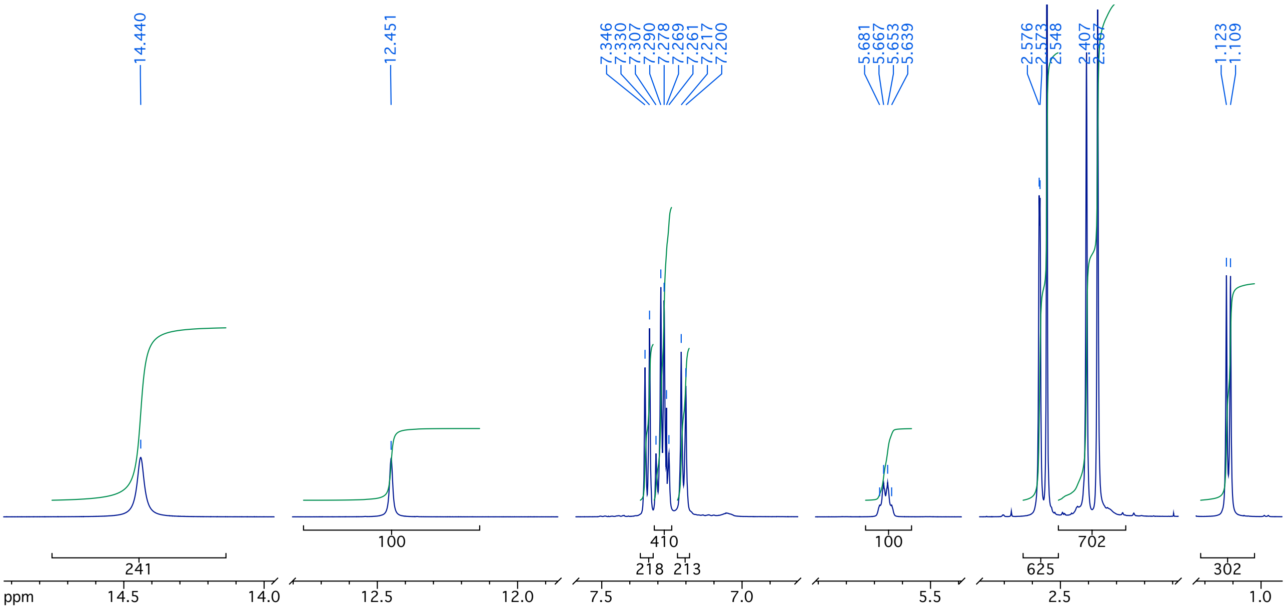
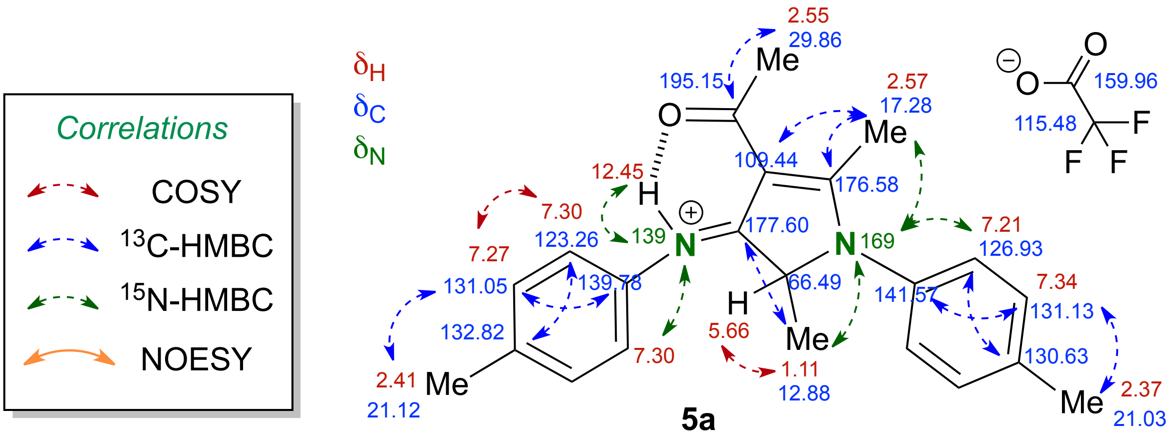


Table S-2. NMR data and assignment for 5a

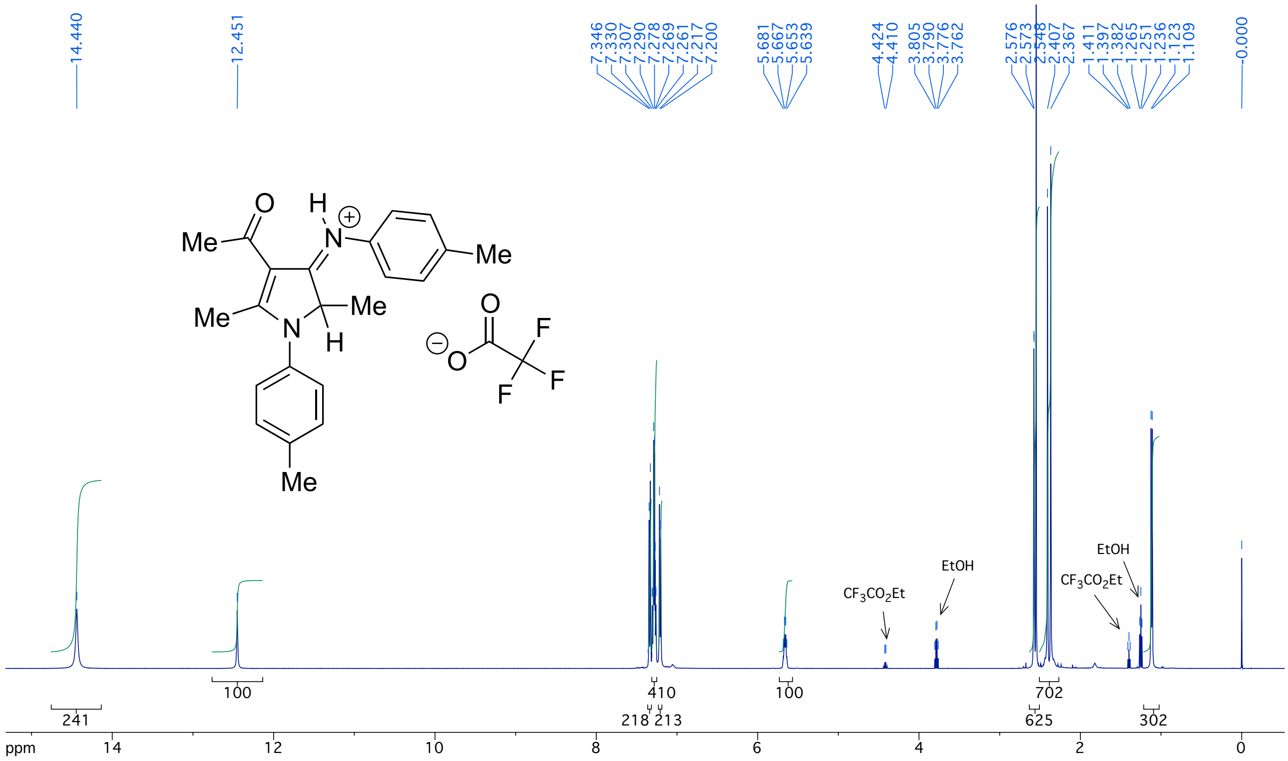
Pos.	δ(^{13}C)^a	n	Type	δ(^{1}H)^b	Multiplicity	H	δ(^{1}H) by HSQC^b
	$CDCl_3$		APT	500 MHz	(Hz)		(mult, J/Hz)
	12.88	1	CH_3	1.11	d (7.2)	3	1.11
	17.28	1	CH_3	2.57	d (1.6)	3	2.58
	21.03	1	CH_3	2.37	s	3	2.37
	21.12	1	CH_3	2.41	s	3	2.42
	29.86	1	CH_3	2.548	s	3	2.55
	66.49	1	CH	5.66	qqd, (7.2)	1	5.67
	109.44	1	C	–			–
	115.48	1	CF_3		q ($J_{F,C}$ 282)		–
	123.26	2	CH	7.30	d (8.6)	2	7.30
	126.93	2	CH	7.21	d (8.3)	2	7.20
	130.63	1	C	–			–
	131.05	2	CH	7.27	d (8.6)	2	7.27
	131.13	2	CH	7.34	d (8.1)	2	7.34
	132.82	1	C	–			–
	139.78	1	C	–			–
	141.57	1	C	–			–
	159.96	1	CF_3CO_2	–	q ($J_{F,C}$ 39.0)		–
	176.58	1	C	–			–
	177.60	1	C	–			–
	195.15	1	C=O	–			–
NH			NH	12.45	s	1	
OH			CO_2H	14.44	s	–	excess TFA, not **5a**
		C_{24}	$C_{24}H_{25}F_3N_1O_3$*			H_{25}	

a) APT at 100 MHz. b) 500 MHz. (lr) = long-range. *) Partial sum formula based on spectroscopically proven fragments as listed in the column. A second nitrogen was proven by ^{1}H,^{15}N-HMBC.



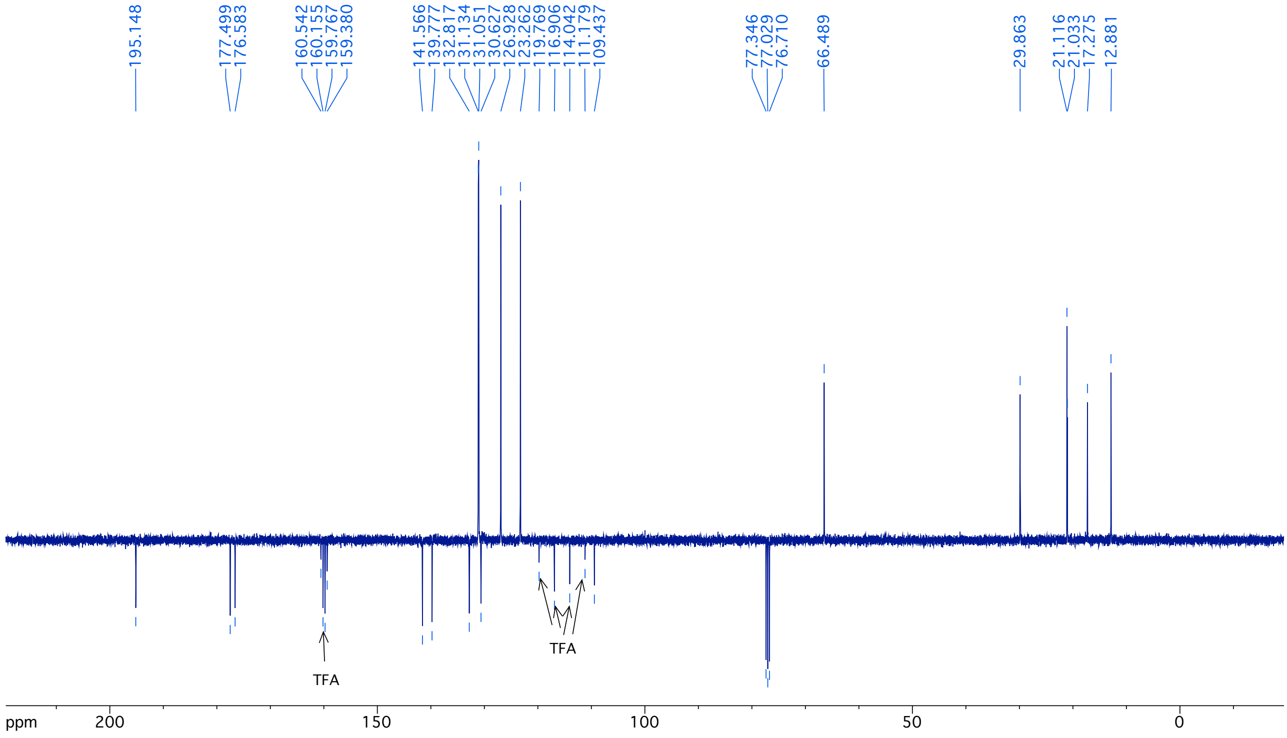
5a

^{1}H NMR (500 MHz, CDCl$_3$) of 5a – Full range



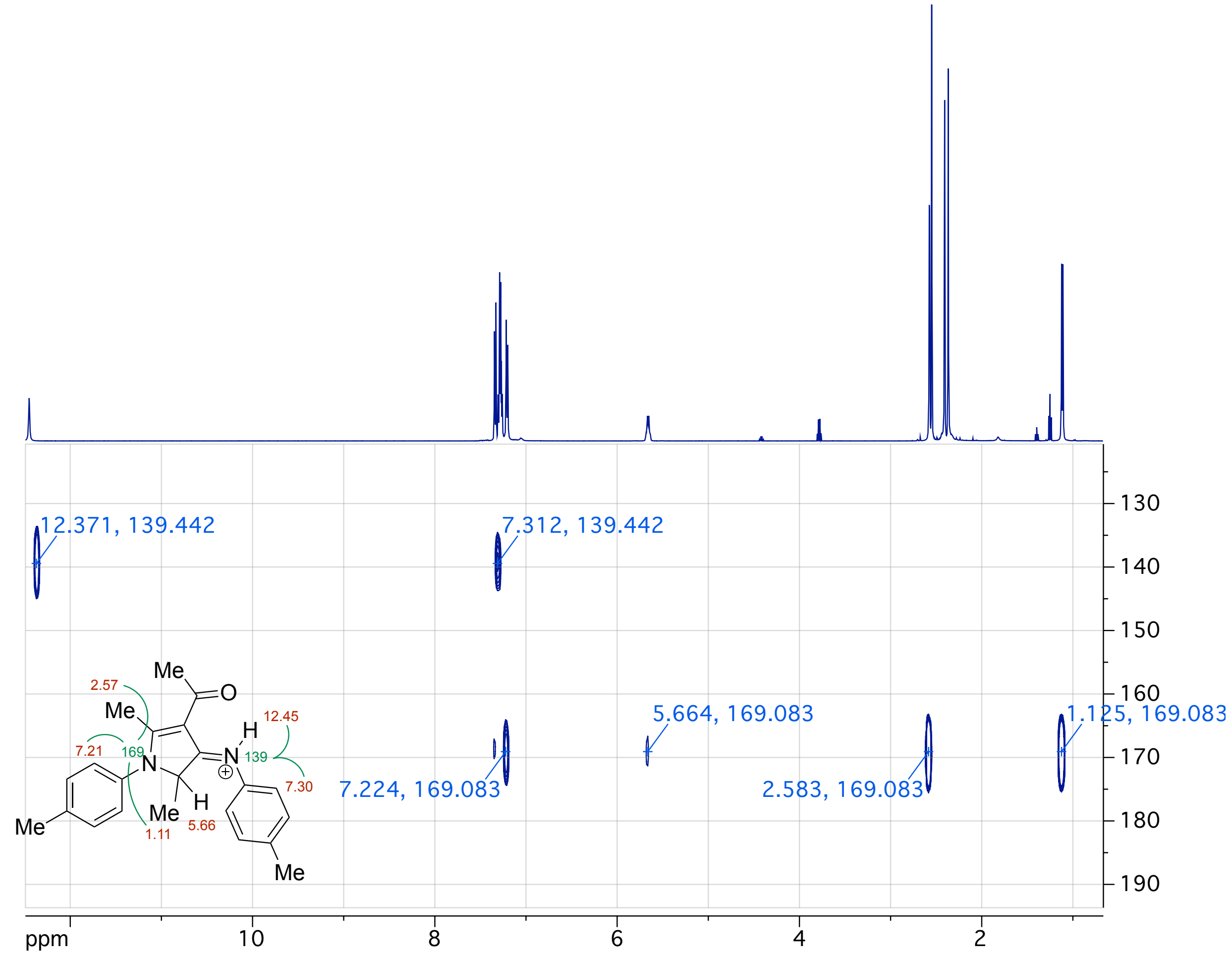
δ$_H$ 14.44 is due to excess CF$_3$CO$_2$H. EtOH is remaining recrystallization solvent in **4a**, which forms CF$_3$CO$_2$Et in situ.

^{13}C APT NMR (76 MHz, CDCl$_3$) of 5a

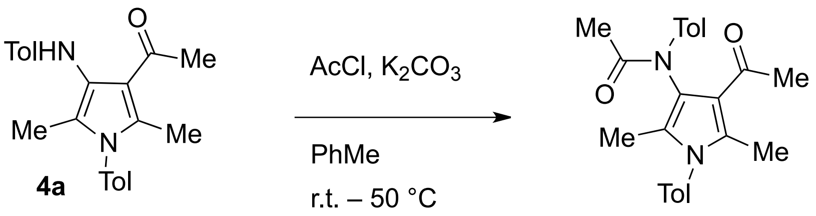


TFA = trifluoroacetate and trifluoroacetic acid

^{1}H,^{15}N-HMBC (500 MHz, CDCl$_3$) of 5a



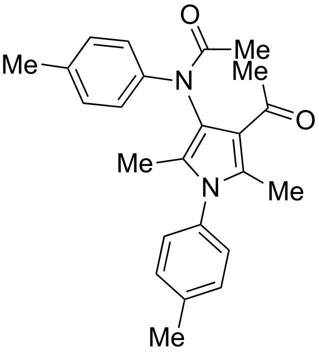
1.3 *N*-(4-Acetyl-2,5-dimethyl-1-(*p*-tolyl)-1*H*-pyrrol-3-yl)-*N*-(*p*-tolyl)acetamide (= *N*-Acetyl derivative of 4a)[1]



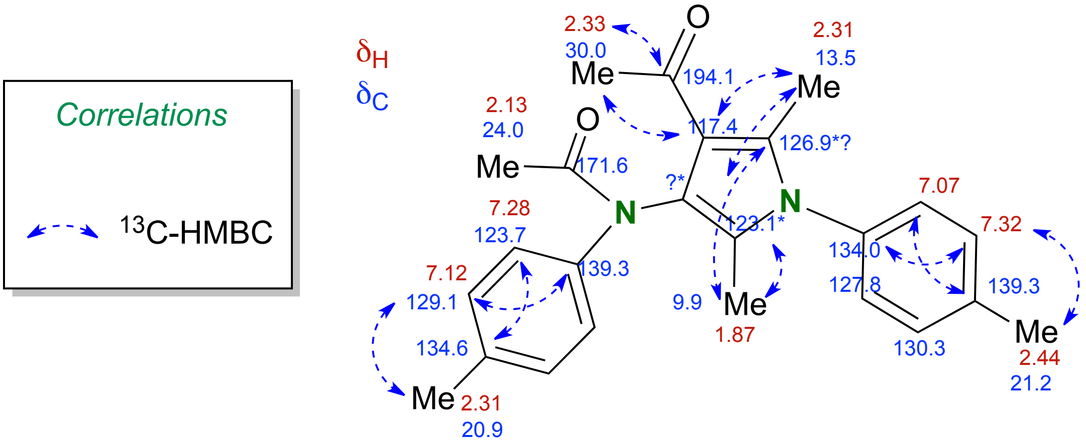
A sample of **4a** (281 mg, 0.85 mmol) was stirred in toluene (9 mL) with addition of acetyl chloride (1.5 mL, excess) to give a clear solution. Powdered K_2CO_3 (1.5 g) was added with stirring, inducing an exothermal reaction. The mixture was stirred for 15 min at r.t., then for 30 min at 50 °C. The mixture was diluted with EtOAc and transferred to a separatory funnel. Washing of the organic phase with aq Na_2CO_3, drying over Na_2SO_4, filtration, evaporation gave a brown resin which freely dissolved in EtOH without crystallization. Upon evaporation in the hood the material formed brown resin, which crystallized very slowly over 2 weeks.

The semisolid was triturated with hexanes (4 mL) and *t*BuOMe (6 mL) and set aside for 2 days. The material was irradiated in an ultrasonic cleaning bath for 2 x 40 min, and solid blocks were ground to give powdery suspended material using a spatula. Supernatant solvent was removed using a pipette and the solid was washed with *t*BuOMe. The bright tan powder was used for analysis.

The sample displayed broadened ^{1}H and ^{13}C NMR signals presumably due to chemical exchange by amide rotation. The H-Ar signals are not well separated, and methyl group singlets partially overlapping. Consequently, the material was not useful to the structure elucidation.

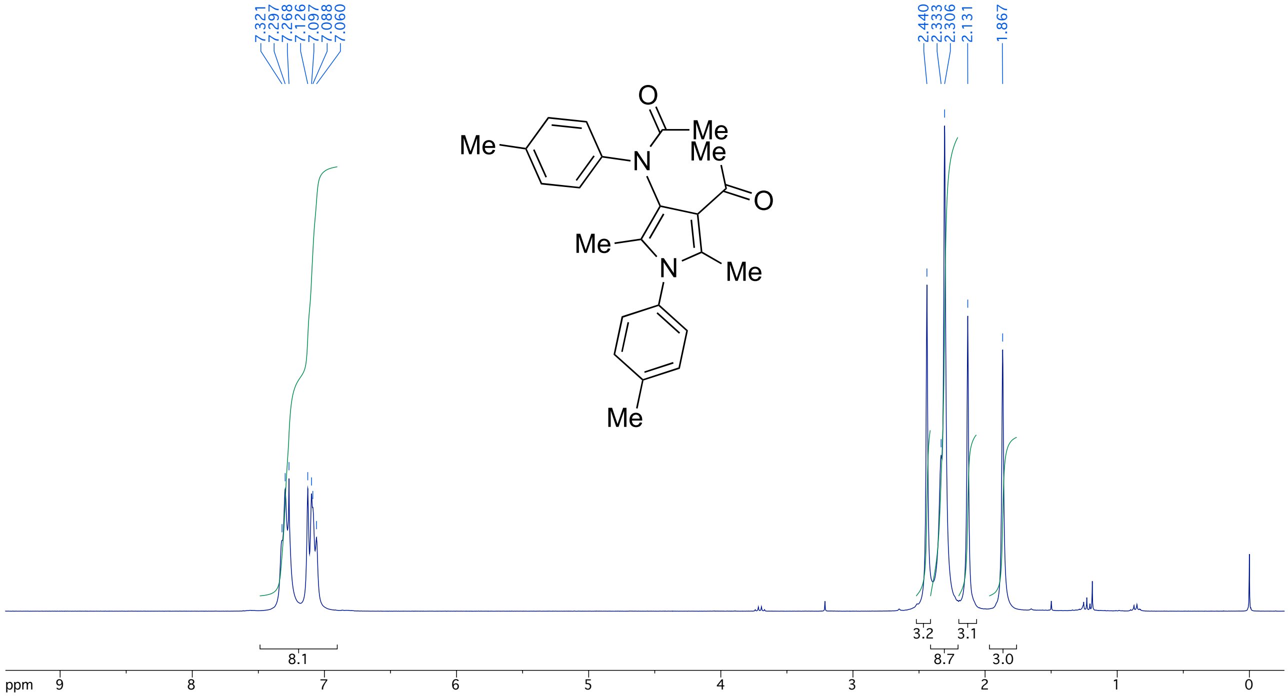


R_f = 0.19 (EtOAc–hexanes 1:1); m.p. 146.0–146.5 °C [Lit. 142.5–143.0 °C];[1] ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.87 (s, 3 H), 2.13 (s, 3 H), 2.31 (s, 6 H, 2 Me), 2.33 (br s, 3 H), 2.44 (s, 3 H), 7.03–7.15 (br m, 4 H), 7.21–7.36 (br m, 4 H). ^{13}C APT NMR (76 MHz, $CDCl_3$): δ 9.9 (br, CH_3), 13.5 (br, CH_3), 20.9 (CH_3), 21.2 (CH_3), 24.0 (br, CH_3), 30.0 (br, CH_3), 117.4 (br C), 123.1 (C), 123.7 (br, CH, 2 C), 126.9 (br, C), 127.8 (br, CH, 2 C), 129.1 (br, CH, 2 C), 130.3 (br, CH, 2 C), 134.0 (br, C), 134.5 (br, C), 139.3 (br, C, 2 C), 171.6 (C), 194.1 (C), with additional information from HSQC and HMBC; 1 signal not detected.



* Exchangeable assignments

^{1}H NMR (300 MHz, CDCl$_3$) of *N*-acetyl derivative



^{13}C APT NMR (76 MHz, CDCl$_3$) of *N*-acetyl derivative