

Facile Preparation of 3-Acetamido-5-acetylfuran from *N*-Acetyl-D-glucosamine Using Commercially Available Aluminum Salts

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Experimental

Materials

All solvents, *N*-acetylglucosamine (NAG), NaCl, B(OH)₃ and metal chloride hydrated salts were purchased from Wako. Metal triflate salts were purchased from Sigma-Aldrich. All reactants were used as received.

NAG conversion in batch reactor

Typically, 5 g of 5 wt. % NAG solution in DMF were loaded in a 2-necks 50 mL round bottom flask, equipped with a water reflux condenser. To ensure that all NAG was solubilized, pre-heating of the solution at 100 °C for ca. 5 min could be necessary. Successively, the appropriate amount of catalyst and/or salts was added, and the reaction was started by placing the flask in the oil bath at the set temperature. During time online experiments, aliquots of reactions mixture were taken at defined interval of time.

Analytical procedure

All substrates were quantified by means of HPLC using calibration curves obtained by analysis of standard solutions at different concentration. Prior HPLC analysis, 0.5 mL of reaction mixture were weighted inside a 1 mL volumetric flask and diluted in water. A Shimadzu HPLC system equipped with a refractive index and single wavelength UV (300 nm) detector was used for quantification. Reactions component were separated by means of a Rezex RPM-Monosaccharide Pb+2 column held at 70 °C, water was used as mobile phase with a flow rate of 0.6 mL min⁻¹. GC-MS analysis were conducted on a Shimadzu GC-MS 2010 system using a DB-5MS column. NMR analysis were perform using a JEOL 600 MHz.

Purification of 3A5AF and AEF

100 g scale reaction was performed by simple linear scale-up of the above procedure. Specifically, 5 g of NAG were dissolved in 95 g of DMF and 5.46 g of AlCl₃.6H₂O were added. The reaction was conducted in a 200 ml round bottom flask equipped with a water reflux condenser, performed at 120 °C (oil bath temperature) for 30 min. After the reaction was concluded, DMF was evaporated by applying reduced pressure and 60 °C. The obtained black solid was re-dissolved in ethanol and about 15 g of SiO₂ was added in order to adsorb the products. Solvent was evaporated by rotavapor and a fine black powder was obtained. Purification of products was performed by column chromatography, about 150 g of SiO₂ was added into a 5 cm of diameter glass column, a mixture of ethyl acetate and hexane (1:1 v/v) was used at the beginning of the process. Product collection was followed by thin layer chromatography (TLC) analysis, retardation factor (R_f) of AEF and 3A5AF in EtOAc:hexane 1:1 were 0.59 and 0.15, respectively. Once AEF was eluted, the mobile phase polarity was

increased (EtOAc:hexane 3:1) in order to accelerate the elution of 3A5AF. Fractions containing same component were combined and the solvent was evaporated at rotavapor in order to obtain the dry solid product. AEF and 3A5AF were obtained in quantitative yield of 1.5 and 18 %, respectively. Purity of 3A5AF was calculated > 98% by NMR and GC-MS analysis.

Supplementary figures

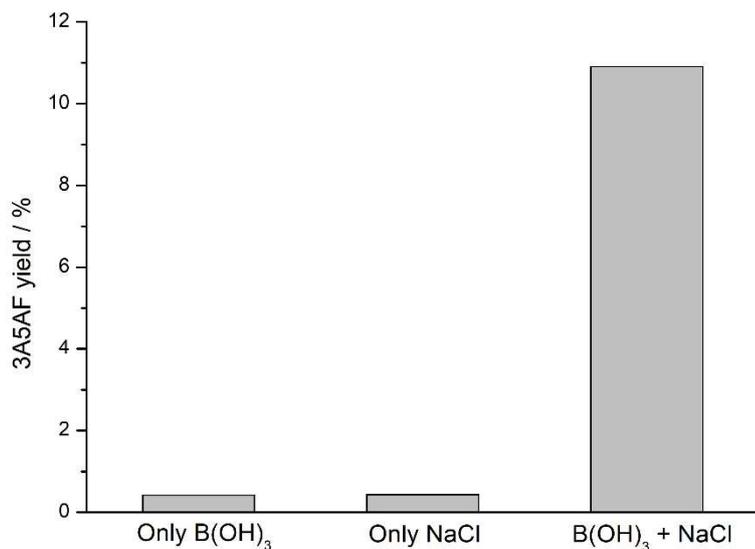


Figure S1. NAG dehydration control test, effect of chloride salt and boric acid. Reaction conditions: 5 mL of 5 wt. % of NAG in DMA at 160 °C, 1 h, B(OH)₃, 1 eq. and NaCl 2 eq.

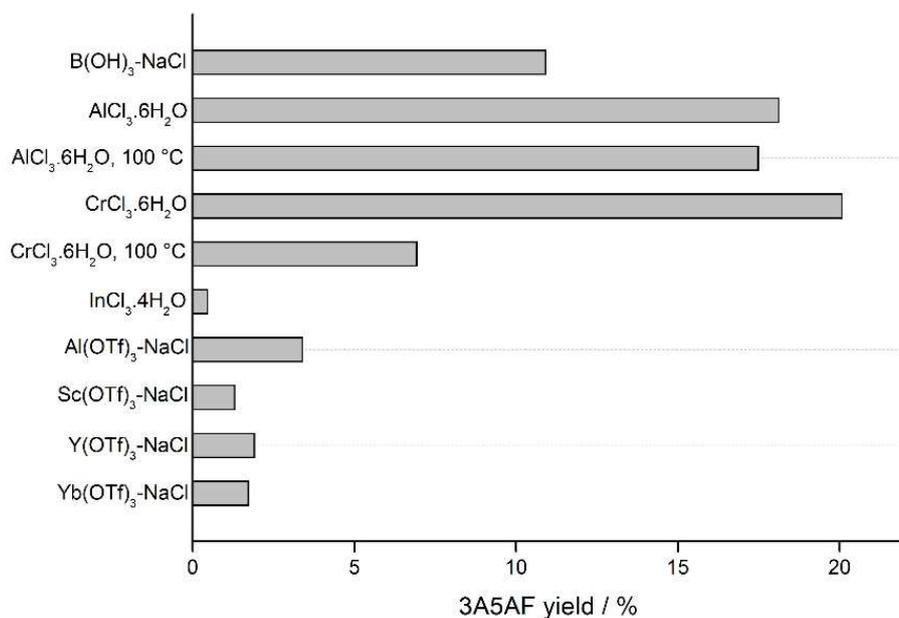


Figure S2. Catalyst screening of several metal complexes for 3A5AF production by NAG dehydration. Reaction conditions: 5 mL of 5 wt. % of NAG in DMA, 1 h, 160 °C (unless stated otherwise), 1 eq. of metal and 2 eq. of NaCl if present.

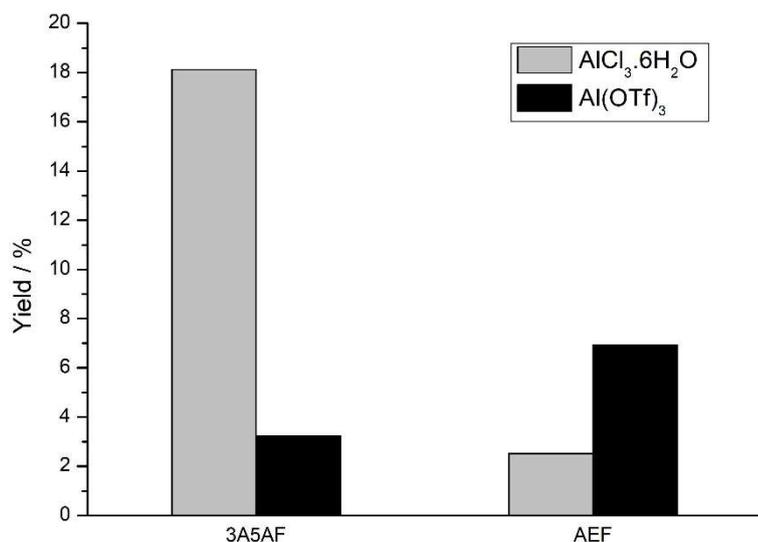


Figure S3. NAG dehydration performed with two different Al complexes at same reaction conditions. Reaction conditions: 5 mL of 5 wt. % of NAG in DMA, 160 °C, 1 h, AlCl₃·6H₂O (1 eq.), or Al(OTf)₃ (1 eq.) and NaCl (2 eq.).

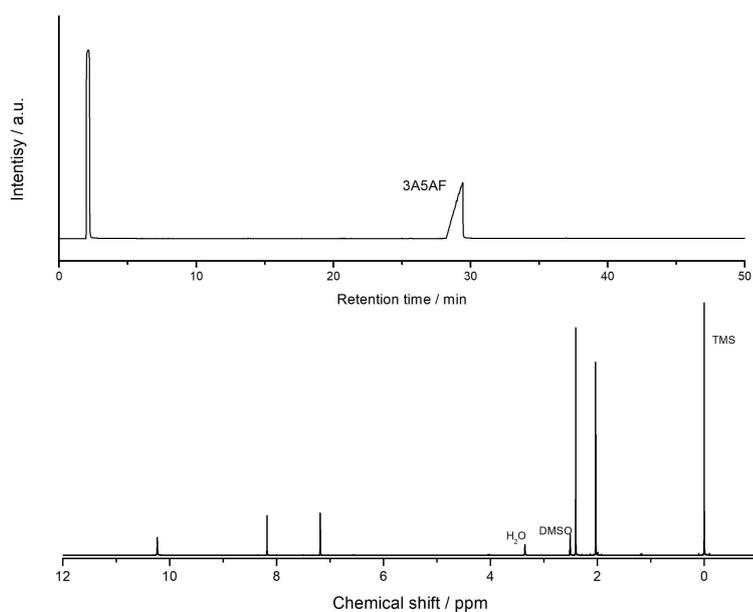


Figure S4. 3A5AF purity check by GC-MS (top) and ¹H NMR (bottom) analysis.

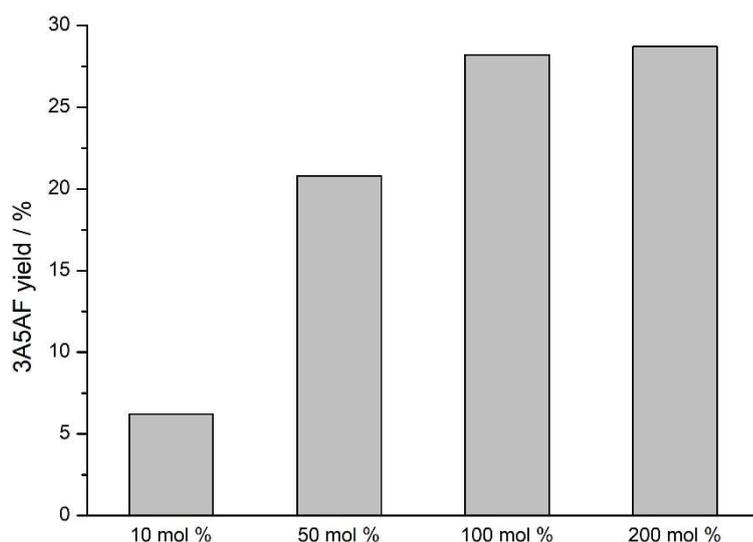


Figure S5. Effect of AlCl₃.6H₂O molar quantity relative to NAG. Reaction conditions: 5 mL of 5 wt. % of NAG in DMF, 1 h, AlCl₃.6H₂O at variable amount.

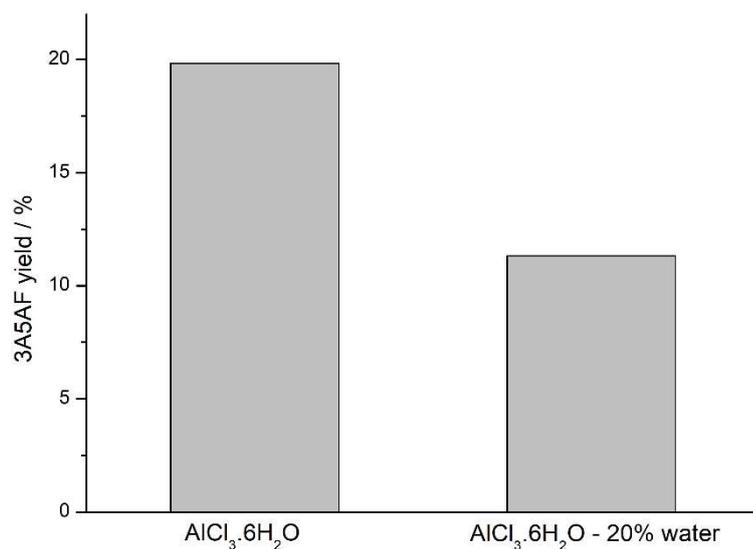


Figure S6. Effect of water addition on the reaction mixture for 3A5AF production during NAG dehydration performed at 160 °C for 1 h in the presence of AlCl₃.6H₂O.

3-acetamido-5-ethylidene furanone (AEF) characterization

^1H NMR δ_{H} (298K, 600 MHz, DMSO- d_6) 1.85 (d, J = 7.45 Hz, 3H), 2.10 (s, 3H), 5.44 (q, J = 7.45 Hz, 1H), 7.57 (s, 1H), 10.36 (s, 1H).

^{13}C NMR δ_{C} (298K, 600 MHz, DMSO- d_6) 11.44, 23.08, 108.76, 119.61, 126.02, 148.29, 165.57, 169.67.

MS, m/z (% ion) 167 (22), 125 (100), 97 (10), 69 (25), 43 (33).

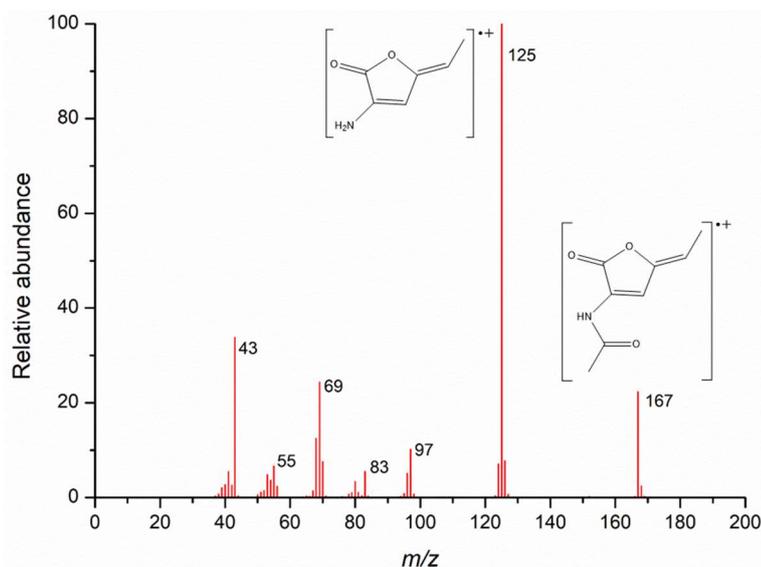


Figure S7. Mass spectrum of AEF generated by electron ionization.

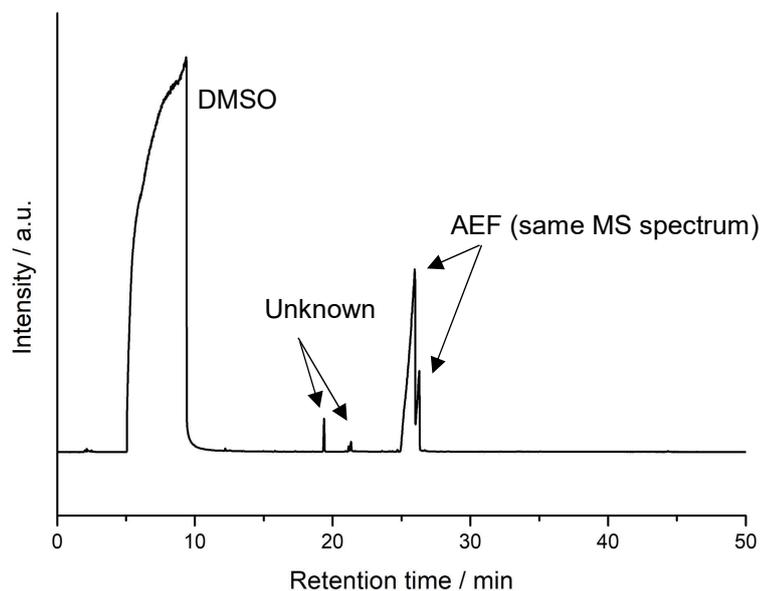


Figure S8. GC chromatogram of AEF in DMSO.

Table S1. Relative energy of Z isomer of AEF to that of E isomer.

Method	ΔE for Z isomer ^a /kJ mol ⁻¹
CBS-QB3	-2.1 ($\Delta G^\circ(393\text{K}) = -3.1$ kJ mol ⁻¹ , E:Z ratio = 28:72)
PBE0-D3/6-311+G(d,p)	-2.5 ^b
M06-2X/aug-cc-pVTZ	-2.2 ^b
MN15/aug-cc-pVTZ	-1.9 ^b
MP2/aug-cc-pVTZ ^c	-1.9 ^b

^aDifference in sum of electronic energy and zero-point-vibration energy (ZPE), compared to that of E isomer. Solvent effect: SMD, *N,N*-dimethylformamide.

^bWe used ZPE determined at the PBE0-D3/6-311+G(d,p) level at the optimized structure with PBE0-D3/6-311+G(d,p).

^cFrozen core.

Even though the energy difference is small, all the methods tested gave similar values, indicating good reliability.

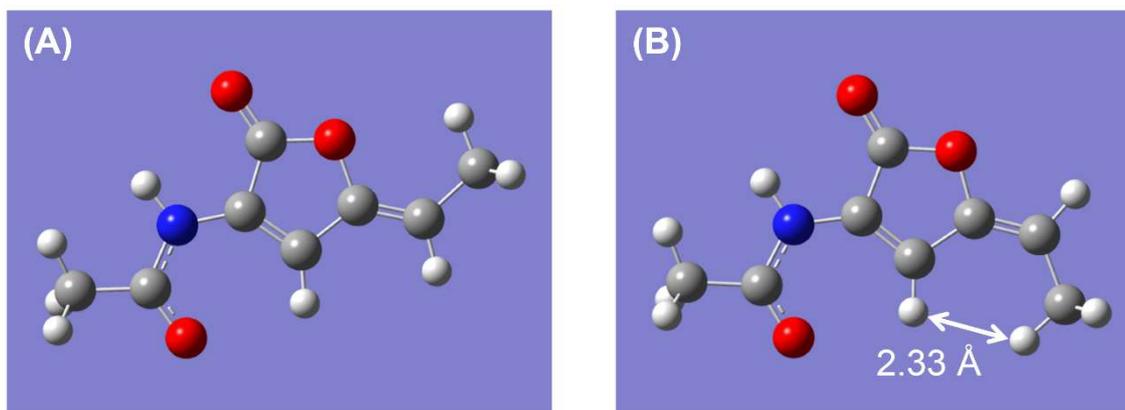


Figure S9. Structure of AEF determined by MP2/aug-cc-pVTZ, (A) Z isomer, (B) E isomer.

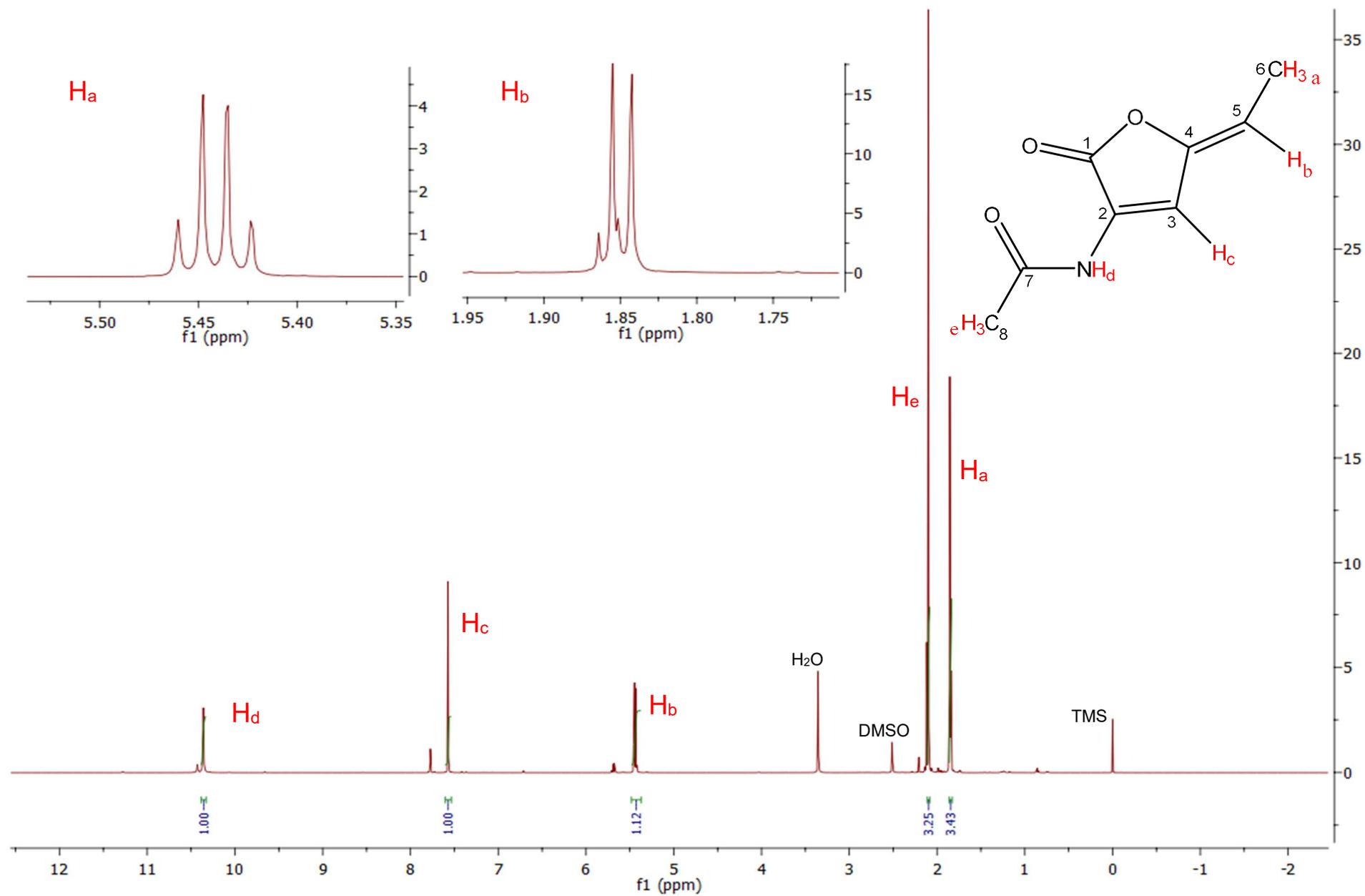


Figure S10. ^1H NMR of AEF in DMSO-d_6 with TMS as reference. In the inset protons a) and b) are shown .

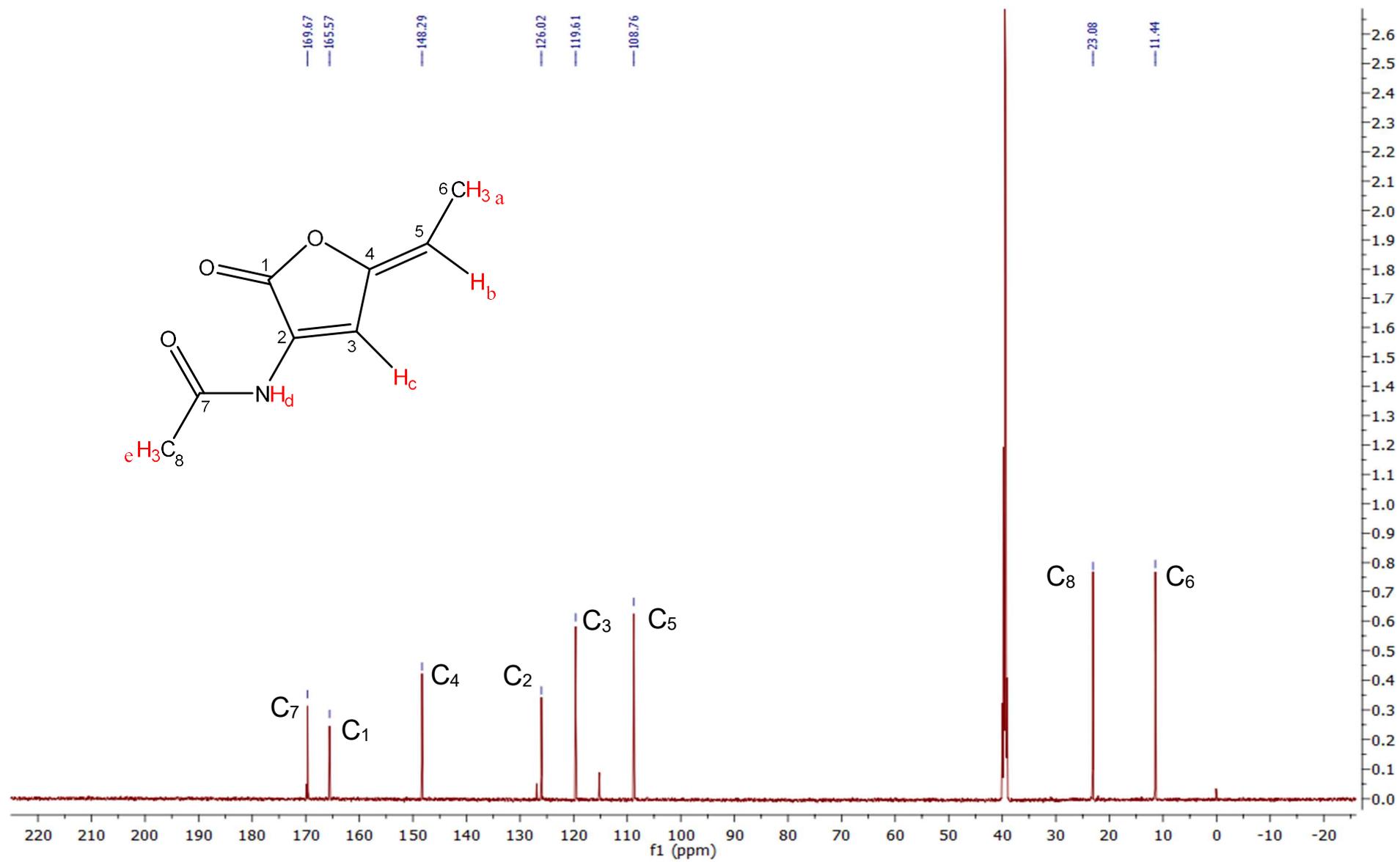


Figure S11. ^{13}C NMR of AEF in DMSO-d_6 with TMS as reference.

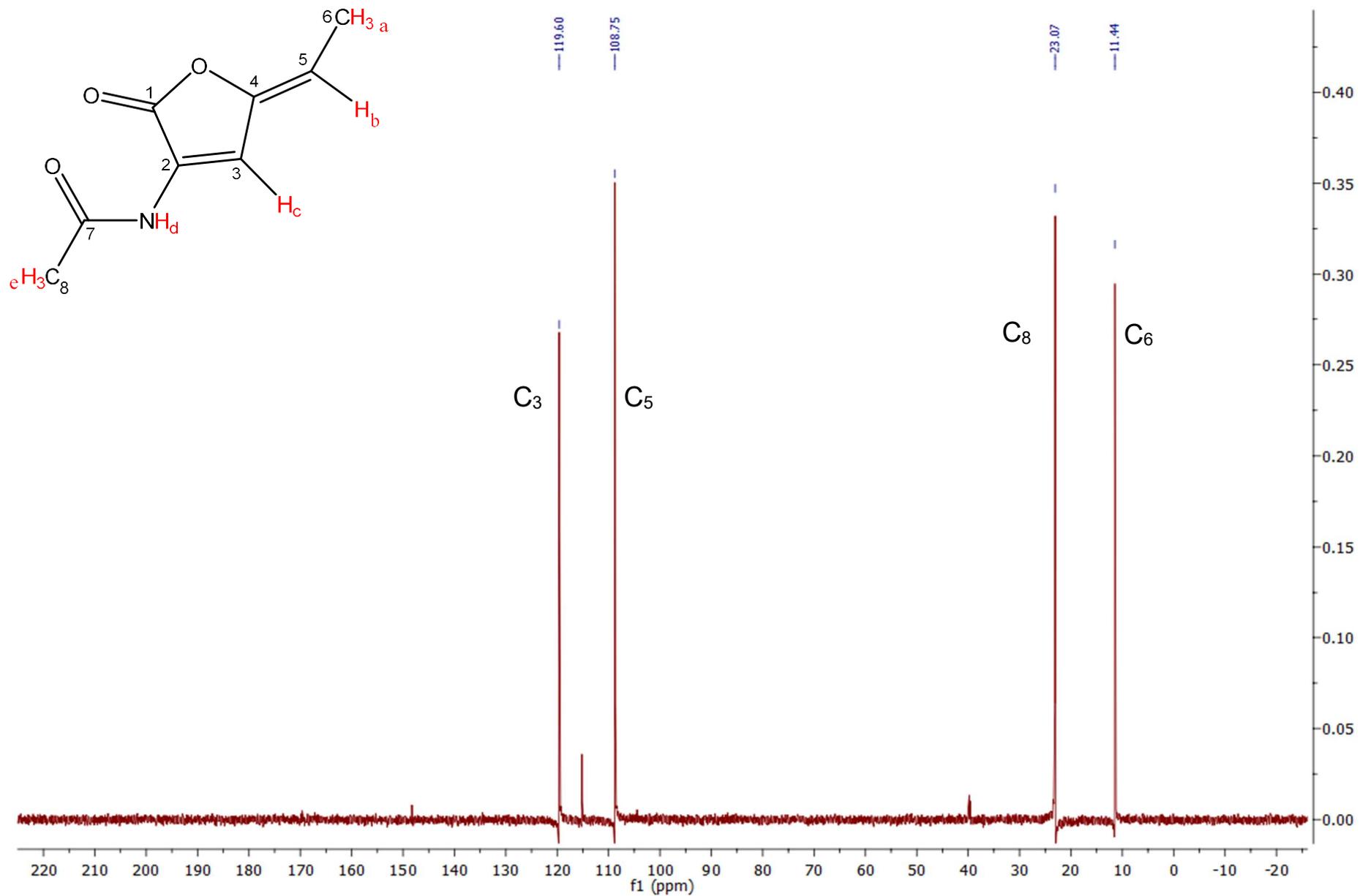


Figure S12. DEPT 45 carbon NMR spectra of AEF in DMSO-d₆.

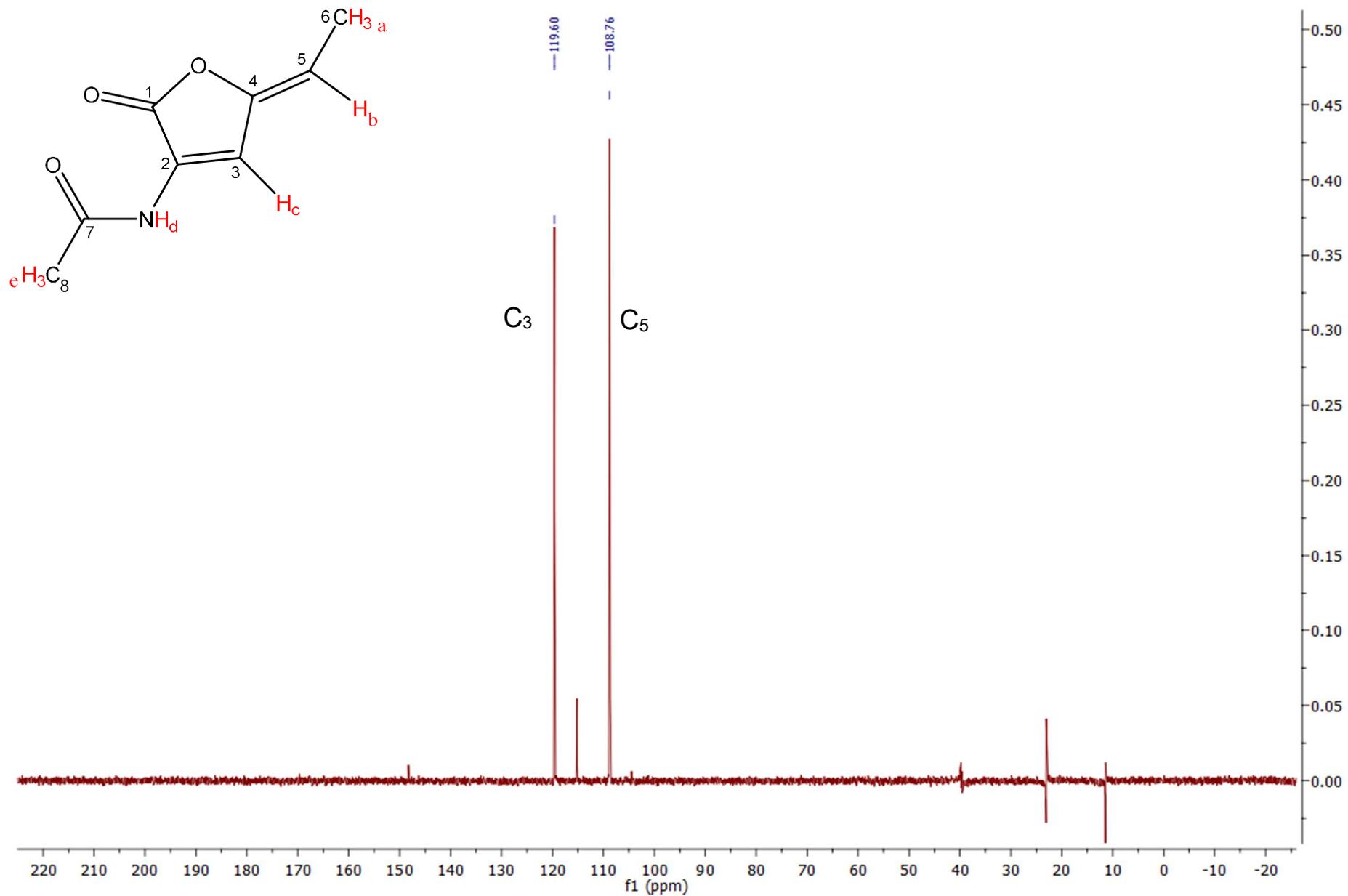


Figure S13. DEPT 45 (top) and DEPT 90 (bottom) NMR spectra of AEF in DMSO-d₆.

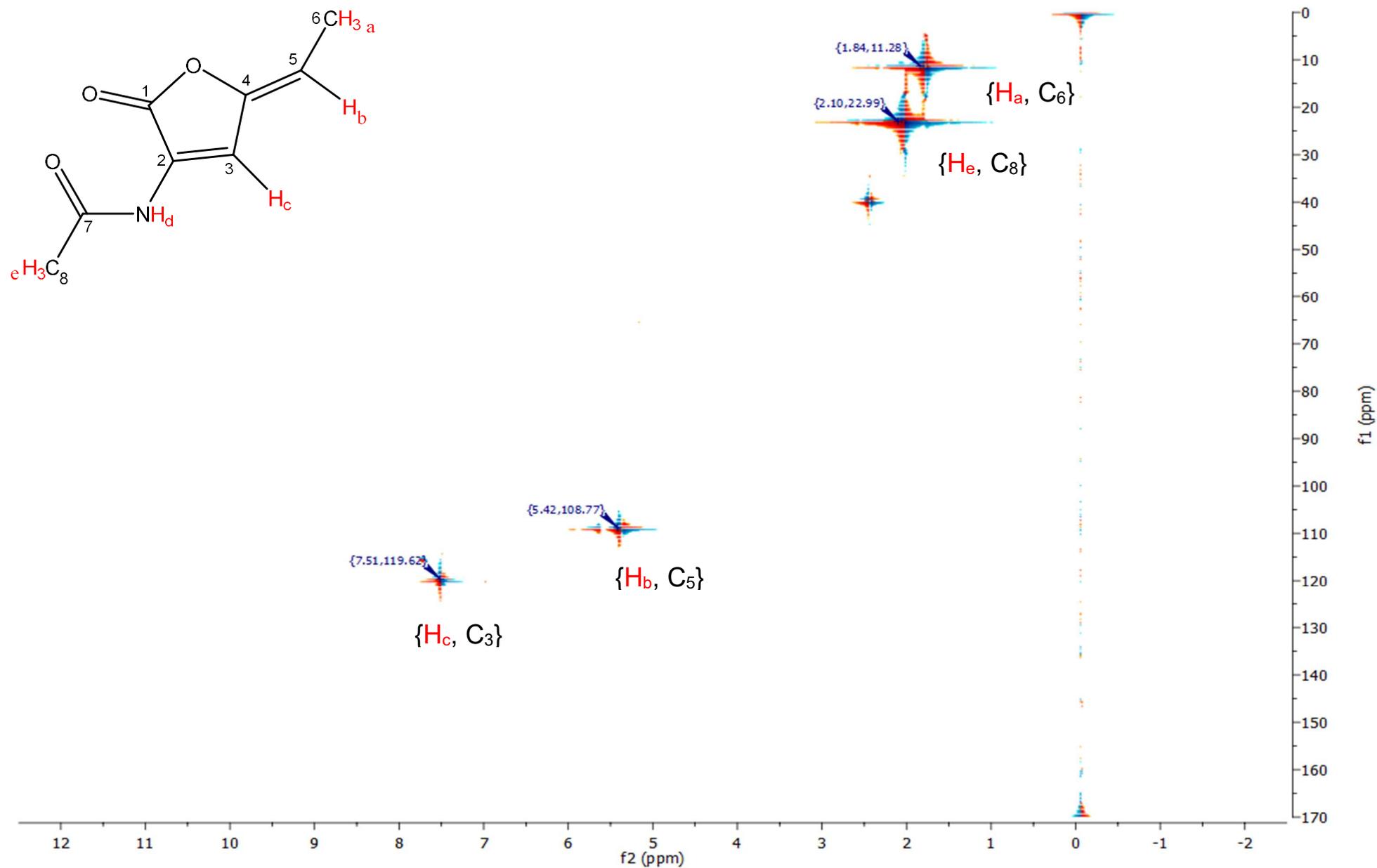


Figure S14. HSQC 2D spectra of AEF in DMSO-d₆ with TMS as reference.

S#569956
DPFGSE NOE 1d

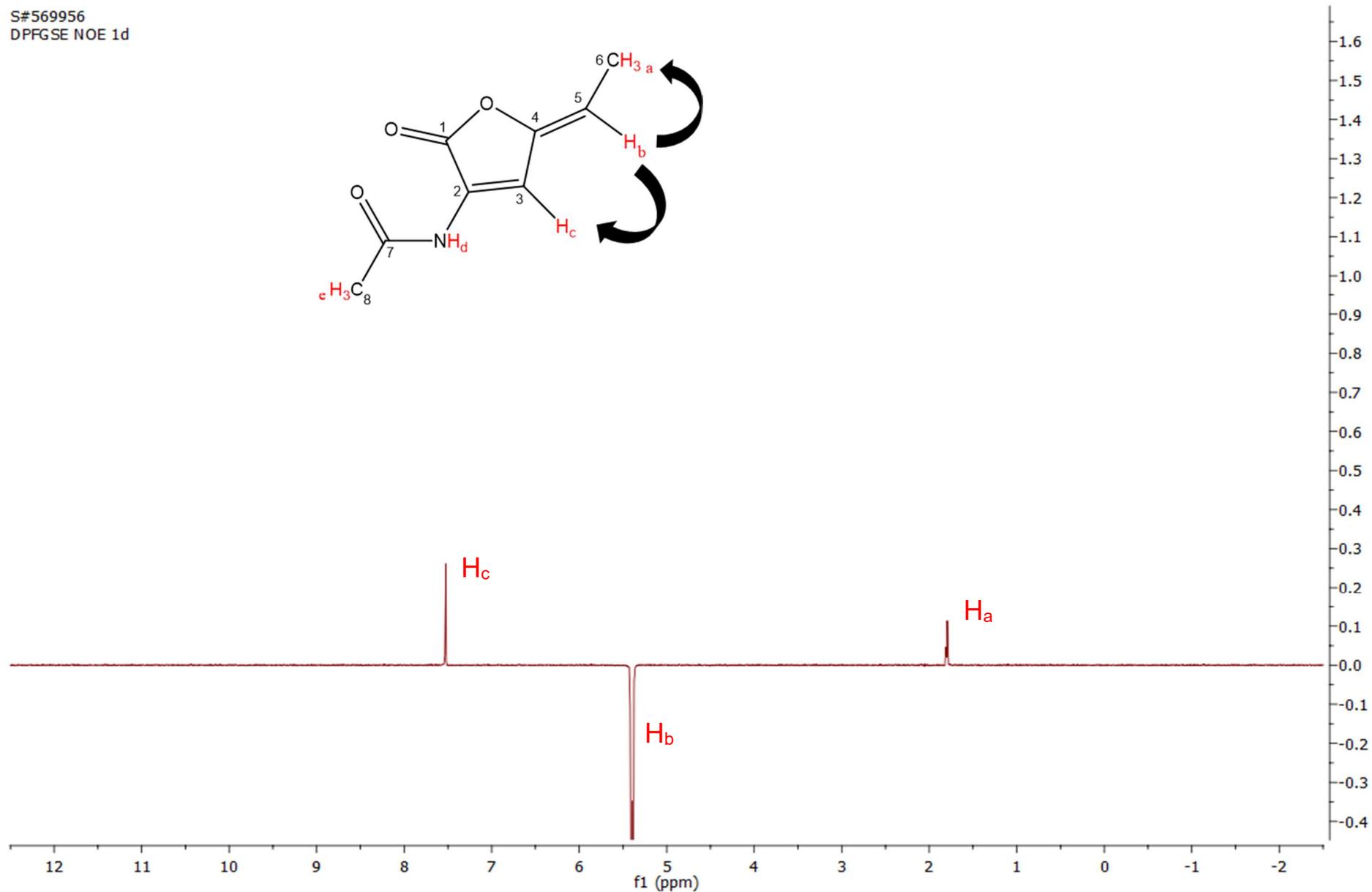
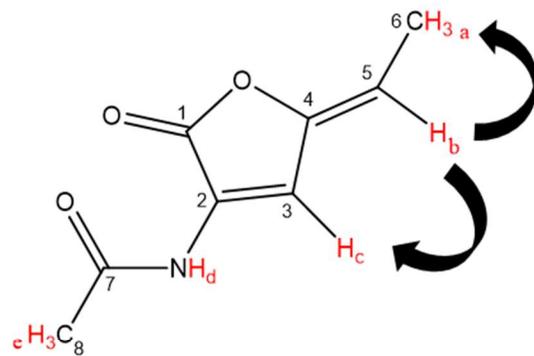


Figure S15. 1D NOE experiment on AEF in DMSO-d₆. Excited frequency: 5.44 ppm.