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Unexpected transformation of 3-amino-4,4,4-trifluoro-1-phenylbut-2-en-1-one into 2,6-diphenyl-4-trifluoromethylpyridine

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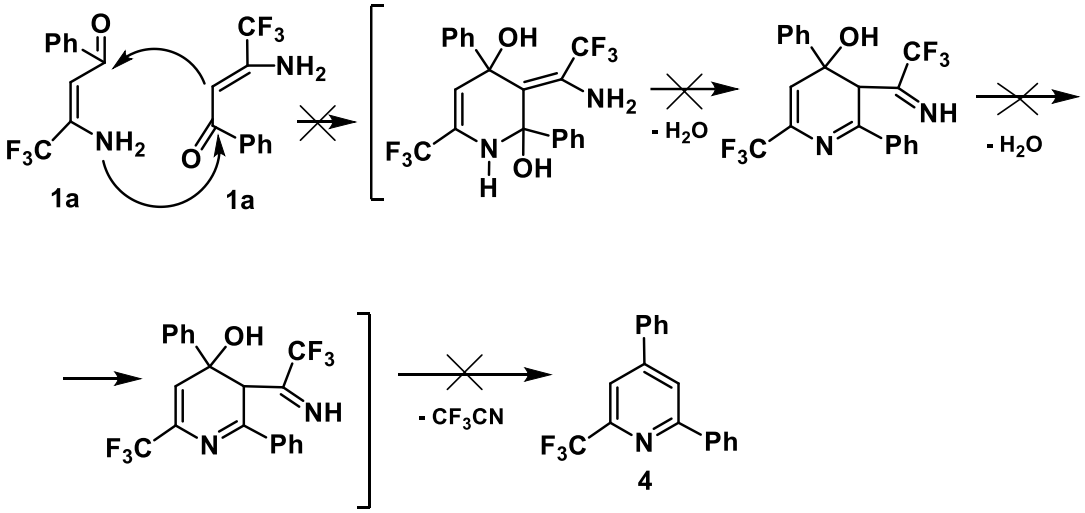
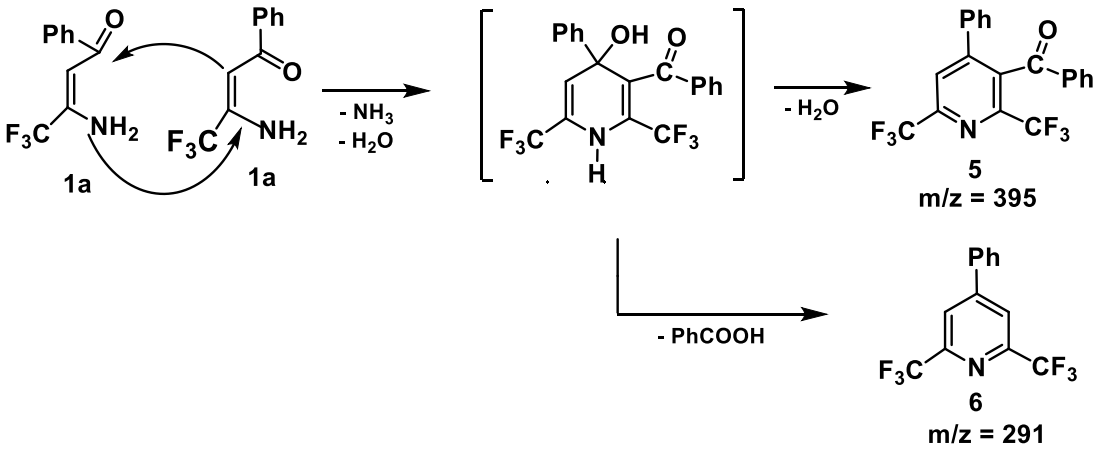
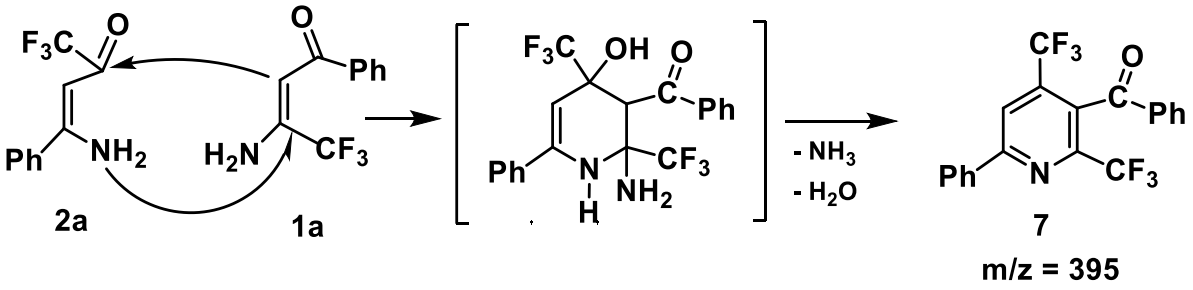


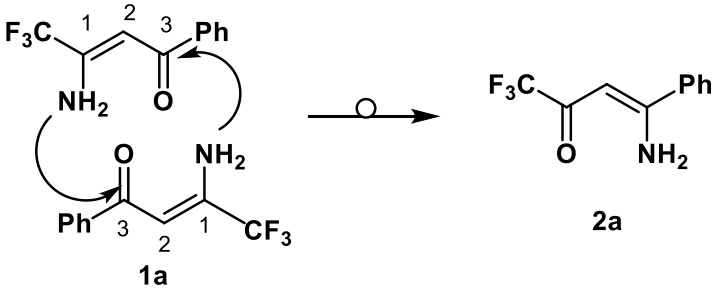
Scheme S1



Scheme S2



Scheme S3



Scheme S4 Isomerization of AVK **1a** into AVK **2a**.

Materials and methods.

AVK **1a** was obtained as described [S1], mp 80-81 °C. AVK **2a**, mp 103-104 °C, was obtained by reamination of 4,4,4-trifluoro-1-(*N*-phenylamino)-1-phenyl-but-2-en-3-one [S2].

The purity of compounds were monitored by TLC on Sorbfil plates (UV-254, eluent $CHCl_3$). Spots on the plates were detected by UV light and a treatment with $Cu(OAc)_2$ aqueous solution. ^1H and ^{13}C spectra were recorded on Bruker DRX-400 и Bruker AVANCE-500 spectrometers using TMS as internal standards. ^{19}F NMR spectra were recorded on Bruker DRX-400 spectrometer in $CDCl_3$ solutions using C_6F_6 as the external standard and converted to the $CFCl_3$ standard by the calculation of $\delta(CFCl_3) = \delta(C_6F_6) - 162.93$. IR spectra were recorded on a Perkin-Elmer Spectrum One FT-IR instrument equipped with attenuated total reflection (ATR) or the diffusion reflection accessory (DRA) units for the 400–4000 cm^{-1} range in solid form. Elemental analysis was carried out using a Perkin Elmer PE 2400 element analyzer. The GC-MS analysis was performed on GC-MS spectrometer Trace GC Ultra DSQ II (USA) with a quartz capillary column Thermo TR-5ms (polydimethylsiloxane, 5 wt % of phenyl groups, 30 m x 0.25 mm, film thickness 0.25 μm), a quadrupole mass-spectrometric detector with electron ionization (70 eV). Carrier gas helium, split ratio 1:50, flow through the column 1.0 ml min^{-1}. Scan of the total ionic current in the range 20–1000 Da. The initial column temperature

was 40°C (storige 3 min), programming rate was 10 °C min^{-1} to 280 °C (storage 30 min). The temperatures of the injector 250°C, of the source 200°C, of the transfer line 200 °C. Solutions of the samples with a concentration of 4-5 mg ml^{-1} were prepared in ethanol.

*Synthesis of 2,6-diphenyl-4-(trifluoromethyl)pyridine **3***

Method 1. A solution of **1a** (0.25 g, 1.2 mmol) in glacial AcOH (5 ml) was refluxed for 5 h, and the mixture was left overnight. The mixture was poured into water, the precipitate was filtered off and recrystallized from hexane to give 0.13 g (72%) of white powder **3**, mp 85 - 86 °C. Found: C, 71.97; H, 4.10; F, 19.20; N, 4.73. Calc. for $C_{18}H_{12}F_3N$: C, 72.23; H, 4.04; F, 19.04; N, 4.68. IR (nujol suspension, cm^{-1}): 1600 (C=N), 1560 (C=C). ^{1}H NMR ($CDCl_3$): 7.87 (2H, s, H(C3) and H(C5)), [7.47–7.54 (6H, m), 8.13–8.17 (4H, m) Ph];. ^{19}F NMR ($CDCl_3$): δ -65.87 (s, CF_3); ^{13}C NMR ($CDCl_3$) 113.98 (q, *J* 3.6), 123.18 (q, *J* 273.4), 127.11 (s), 128.88 (s), 129.82 (s), 138.19 (s), 139.98 (q, *J* 33.4), 158.21 (s). MS (EI) *m*/*z* (rel. intensity, %) 299 (M; 100.0%), 298 (52), 280 (4.6), 258 (4.0), 230 (20.0), 202 (14.5), 174 (4.0), 149 (6.0), 126 (14.0), 102 (24.0), 77 (49.0), 51 (50.0), 39 (16.0).

Analogously from AVK **2a** (0.20 g, 0.93 mmol) in glacial AcOH (3 ml), 0.18 g (90%) of the initial compound **2a** with mp 103-104 °C was recovered. GC-MS revealed that the reaction mixture contained only the initial AVK **2a** (τ_R 17.88). MS (EI) *m*/*z* (rel. intensity, %) 215 (M^+, 4.0), 196 (76.0), 176 (14.0), 146 (32.0), 128 (15.0), 120 (51.0), 105 (38.0), 91.0 (16.0), 78 (28.0), 77 (100.0), 68 (35), 51 (82.0), 50.0 (30.0), 41.0 (16.0), 28.0 (21.0).

Method 2. A mixture of **1a** (0.78 g, 3.6 mmol)and manganese(II) acetate (0.62 g, 3.6 mmol) in ethanol (4 ml) was refluxed until the initial compound fully disappeared (1 h, TLC control), and the mixture was left overnight. The crystals precipitated were filtered off and recrystallized from ethanol, to afford 0.52 g (96%) of a white powder of **3**, mp 85-86 °C identical to that obtained by *Method 1*.

*Monitoring of the formation of pyridine **3** from AVK **1a***

Monitoring 1. A solution of **1a** (0.25 g, 1.2 mmol) in glacial AcOH (5 ml) was refluxed for 1 h. The mixture was poured into water, the precipitate was filtered off to give 0.03 g of a white powder **3** in 16.5 % yield, mp 85 - 86 ºC. The mother liquor was extracted three times with CH_2Cl_2. The extracts were combined, the solvent was evaporated. The oily residue was analyzed by GC-MS (Figures S6-S9).

Monitoring 2 was carried out in a similar way, but the reaction mixture was boiled for 5 hours to give 0.12 g (68%) of a white powder **3**, mp 85-86 °C. The oily residue was analyzed by GC-MS (Figures S10-S16).

*Crystal data for pyridine **3**.*

The XRD analysis of compound **3** was performed on an automatic four-circle diffractometer Xcalibur 3 with CCD detector along the usual procedure (Mo*K*α-radiation, graphite monochromator, 295(2)K, ω/2θ-scannning, the scan step 1°). Corrections for absorption were not introduced because of its smallness. The structure was solved and refined using the SHELXTL software [S3]. All non-hydrogen atoms were refined in the anisotropic approximation, the part of hydrogen atoms were placed in the geometrically calculated positions and included in the refinement using the riding model with the dependent isotropic thermal parameters, the other hydrogen atoms were solved and refined independently in the isotropic approximation.

According to the X-ray analysis the crystal of compound **3** is monoclinic, space symmetry group $P2_1/c$. The unit cell parameters are: a= 10.1800(10) Å, b= 16.9898(15) Å, c= 8.5869(7) Å, β= 104.199(7)º, V= 1439.8(2) $Å^3$, Z= 4, $d_{calc.}$= 1.381 g cm^{-3}. The final refinement parameters are as follows: R_1= 0.0496, *w*R2= 0.1313 [for reflections with $I > 2\sigma(I)$], R_1= 0.1172, wR_2= 0.1480 (all reflections) with the *Q* parameter *S* = 1.007. Peaks of maximum and minimum of the residual electron density $\Delta\rho_e$= 0.361/-0.230 $ē \cdot Å^{-3}$.

The X_ray diffraction data obtained have been deposited with the Cambridge Crystallographic Data Center (No. 2005153) and are available from www.ccdc.cam.ac.uk/data_request/cif*www.ccdc.cam.ac.uk/data_request/cif.*

According to the data of XRD, in molecule of compound **3** non planar phenyl rings are expanded relative to the pyridine ring at angles 16-18º. General view of the structure of **3** and the numeration of atoms accepted in the experiment are given in Figure S1.

Bond lengths and angles are typical for this kind of compounds. The relatively high values of the thermal parameters of fluorine atoms of CF_3- group are typical and can be explained by libration along the axis of C(1)-C(4) bond. Molecular packing is layered, layers are oriented in parallel to plane [1 0 0]. Significantly shortened contacts in the system are absent.

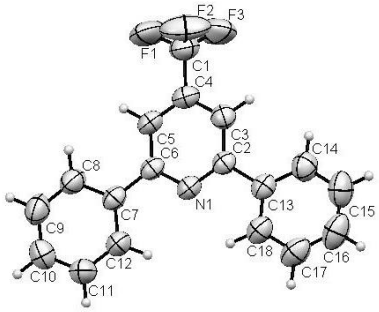


Figure S1 General view of compound **3** shown in the thermal ellipsoids of 50% probability.

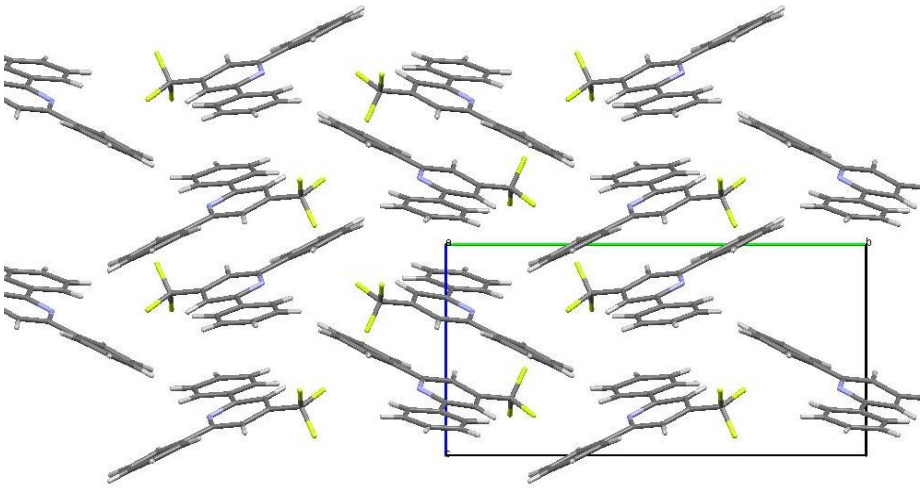


Figure S2 Fragment of molecular packing of compound **3**.

References

[S1]. N. S. Boltacheva, V. I. Filyakova and V. N. Charushin, *Russ. J. Org. Chem.* 2005, **41**, 1452 (*Zh. Org. Khim.*, 2005, **41**, 1483). doi.1070-4280/05/4110-1452

[S2]. K. I. Pashkevich and V. I. Filyakova, *Bull. Acad. Sci. USSR, Div. Chem. Sci*., 1986, **35**, 566 (*Izv. Akad. Nauk SSSR, Ser. Khim*., 1986, 620). https://doi.org/10.1007/BF00953227

[S3]. G. M. Sheldrick, *Acta Crystallogr., Sect. A*, 2008, **64**, 112.

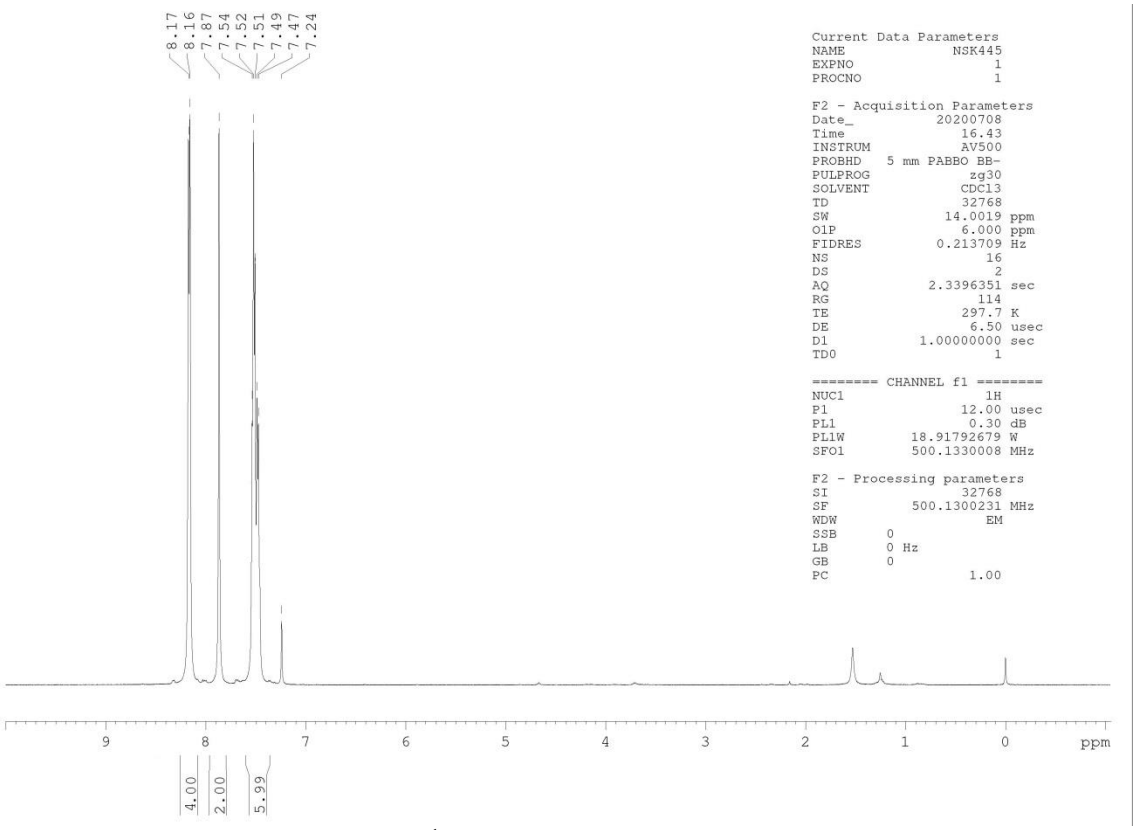


Figure S3 ^{1}H NMR spectra of pyridine **3**

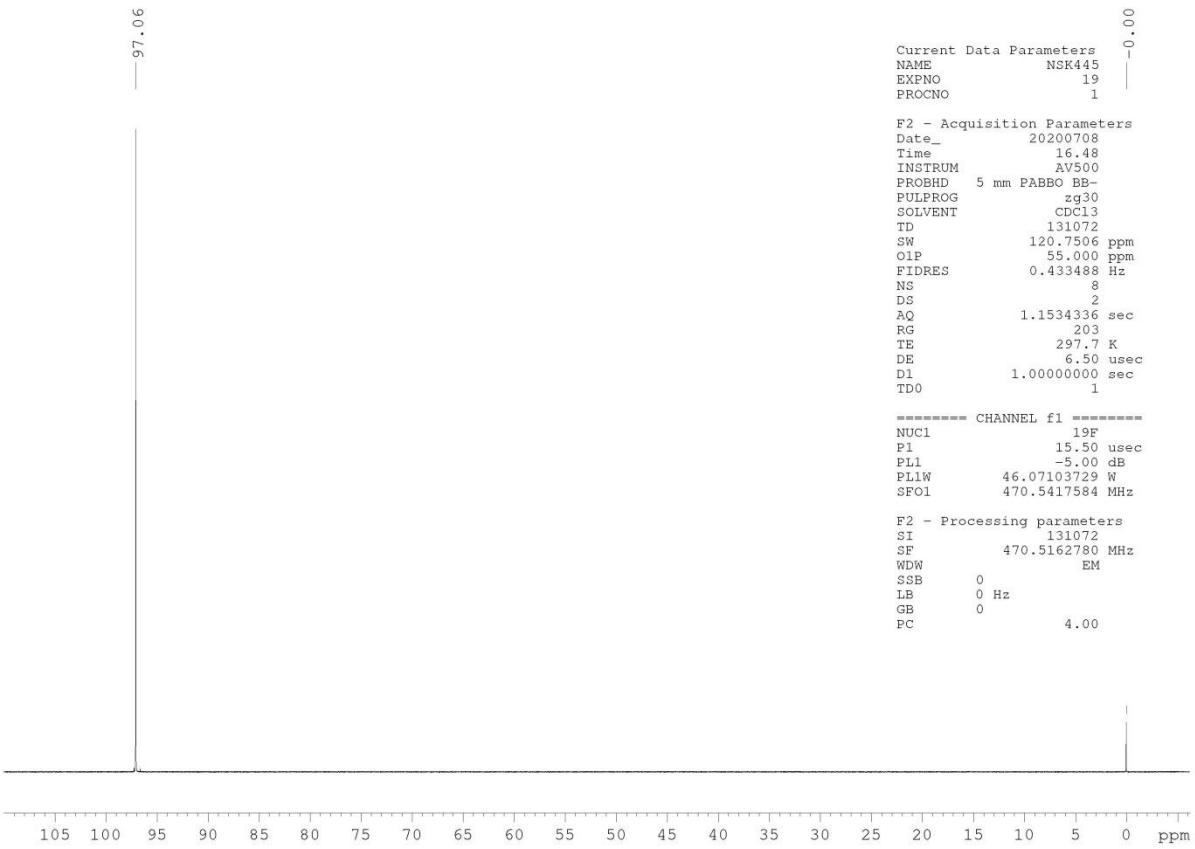


Figure S4 ^{19}F NMR spectra of pyridine **3**

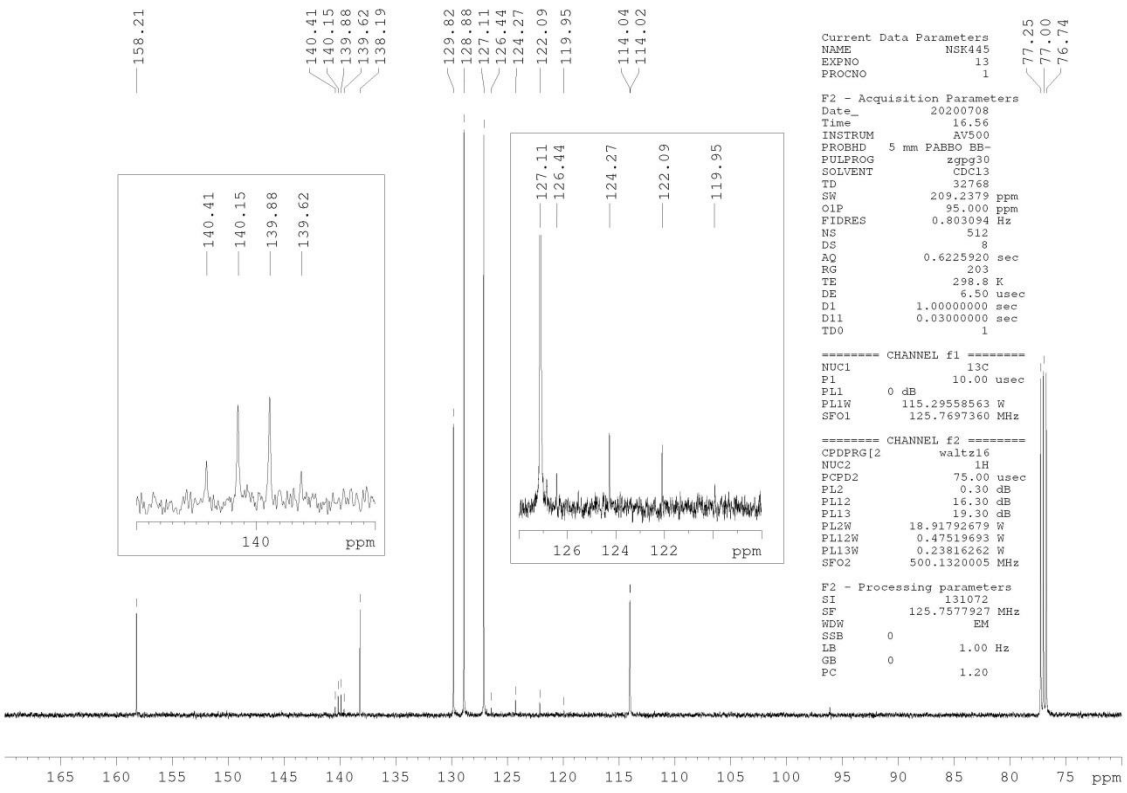
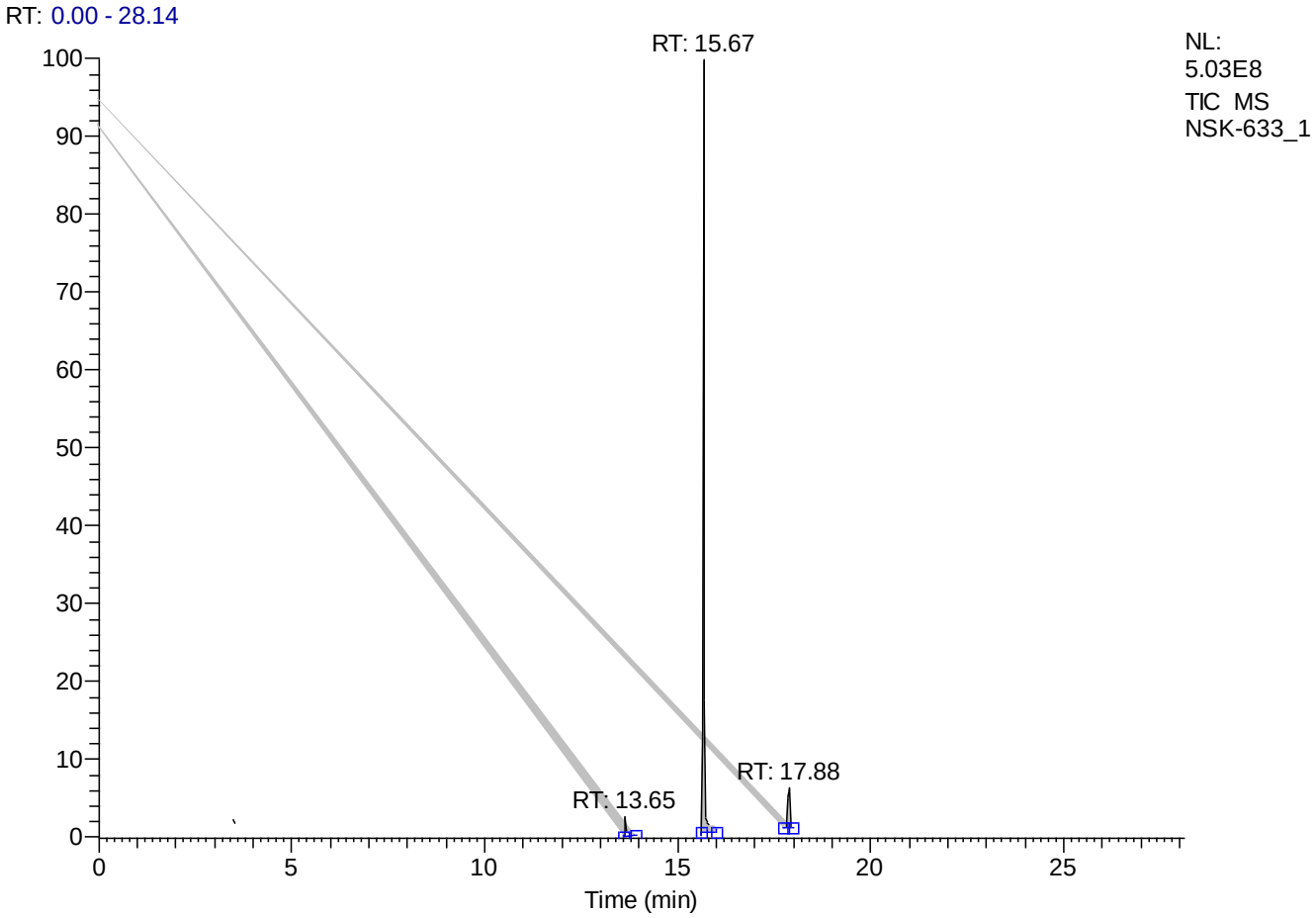


Figure S5 ^{13}C NMR spectra of pyridine **3**

Trace GC Ultra DSQ II
Column: Thermo TR-5ms 30 m x 0.25 mm ID x 0.25 mkm (5% phenyl methyl silox)
Method: **solv_contr-EI-AOC.meth**
Tkol 40/3/10/280 Tinl 250 °C, split, split flow 60 ml/min, split ratio 1:50, col flow 1.2 ml/min
MS transfer line 200 °C, Ion Source 200 °C, mass range 20-1000 Da, solvent delay 3.5 min
Sample Name: NSK-633
Data File: C:\Xcalibur\data\ labGC\Boltacheva\NSK-633_1.RAW
Instrument Method: C:\Xcalibur\methods\solv_cont-EI-AOC.meth
Acq: 13\02\2013
Vial: 1
Injection Volume (µl): 1,0
Comments: Solution in EtOH, конц. 4.6 mg ml^{-1}, injection 1.0 µl AL/AS



PEAK LIST

Apex RT	Area	%Area	Height	%Height
13.65	40854963.120	2.71	12363624.951	2.30
15.67	1356436414.146	89.85	500036380.939	92.87
17.88	112413499.137	7.45	26039812.292	4.84

Figure S6 Chromatogram of the extract from the mother liquor (after 1 hour of refluxing AVK **1a** in glacial acetic acid)

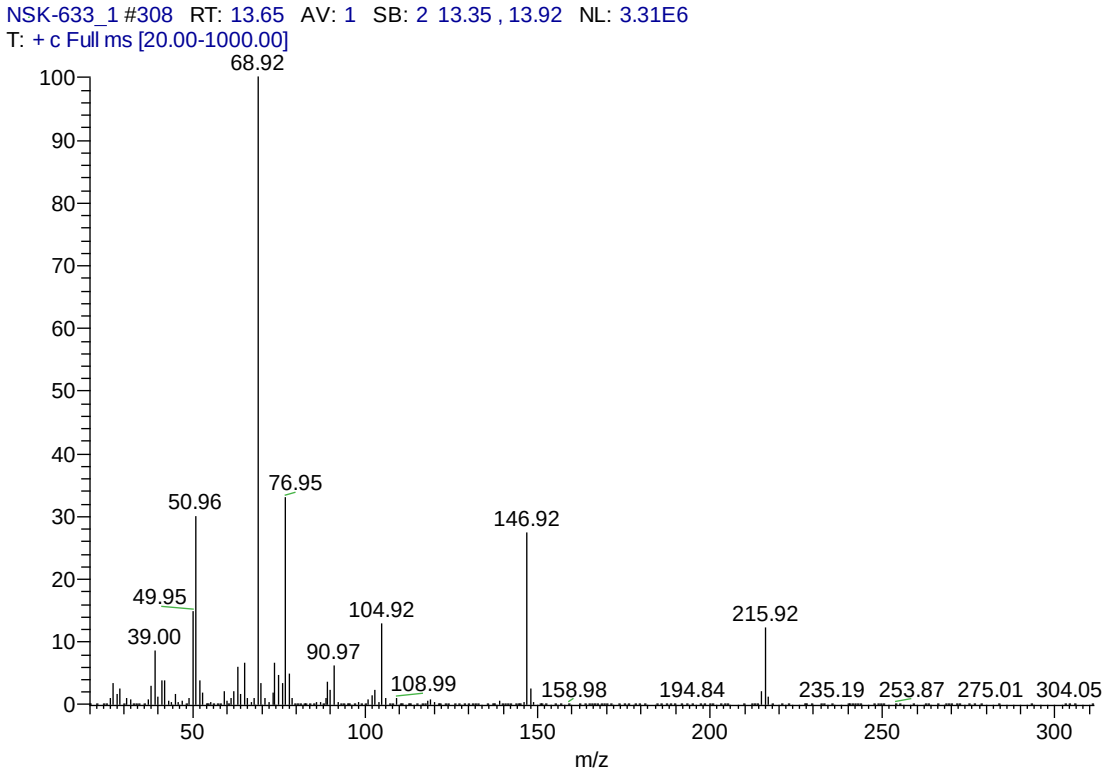


Figure S7 Mass spectrum of 4,4,4-trifluoro-1-phenyl-1,3-butanedione, hydrolysis product of **1a** and/or **2a**

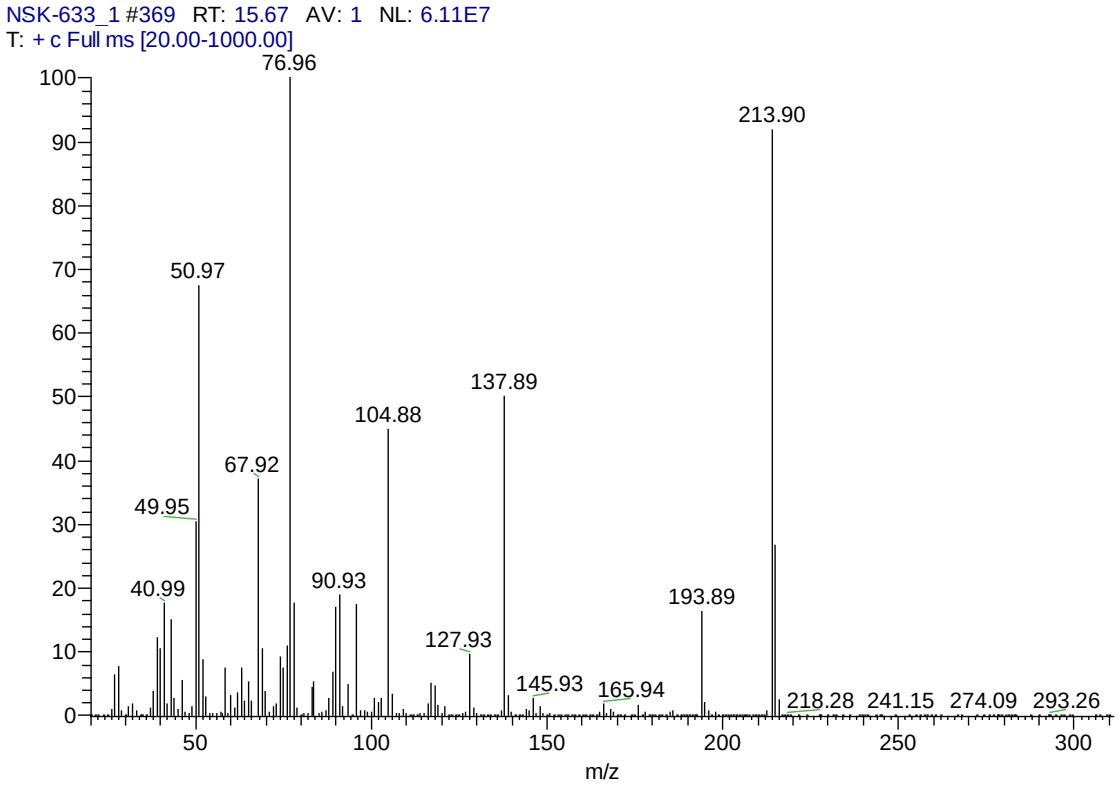


Figure S8 Mass spectrum of 3-amino-4,4,4-trifluoro-1-phenyl-but-2-en-1-one **1a**

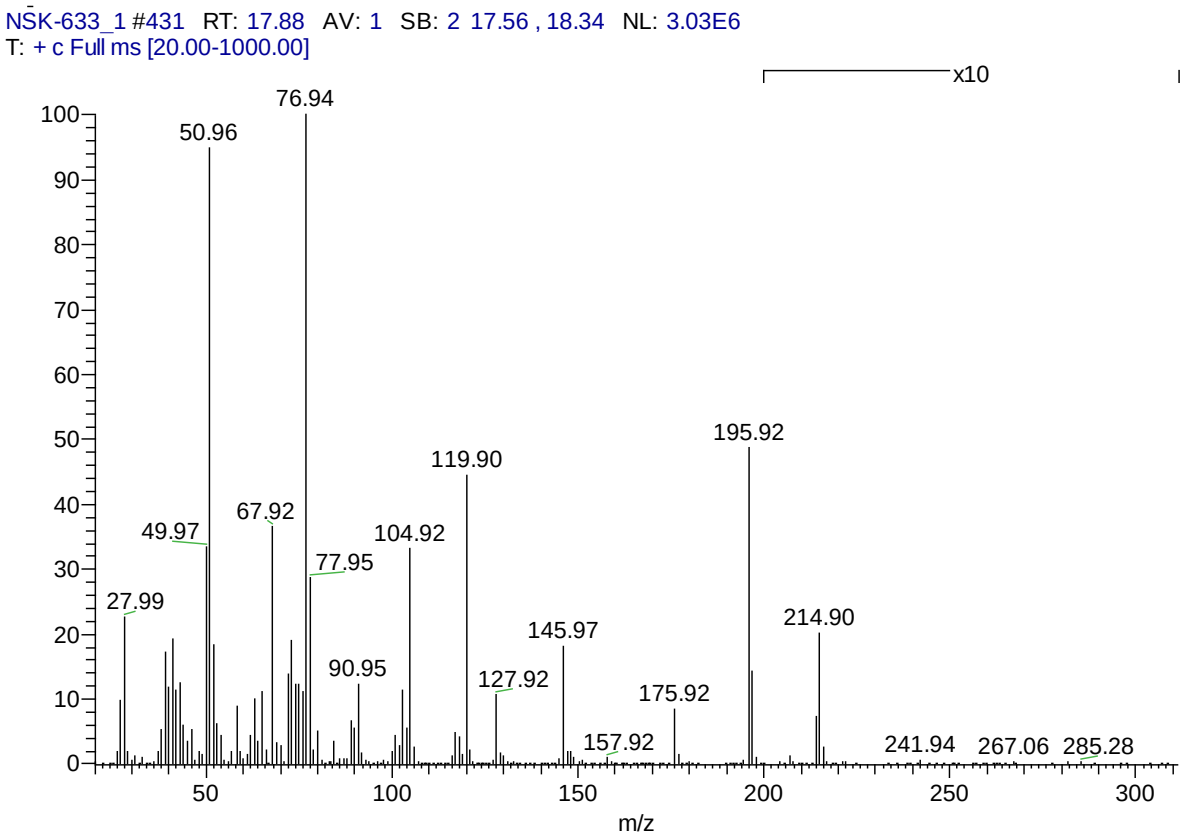
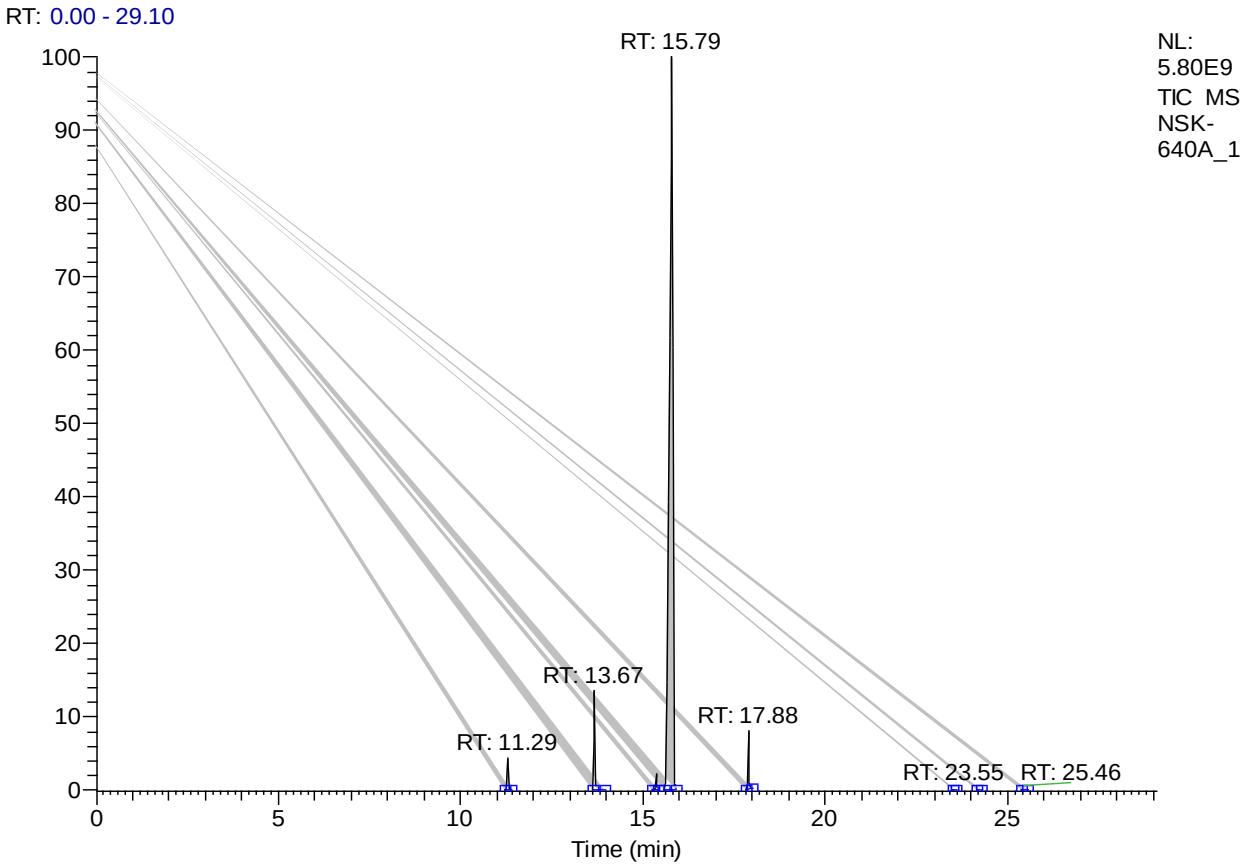


Figure S9 Mass spectrum of 1-amino-4,4,4-trifluoro-1-phenyl-but-1-en-3-one **2a**

Trace GC Ultra DSQ II
Column: Thermo TR-5ms 30 m x 0.25 mm ID x 0.25 mkm (5% phenyl methyl silox)
Method: **solv_contr-EI-AOC.meth**
Tkol 40/3/10/280 Tinl 250 °C, split, split flow 60 ml min^{-1}, split ratio 1:50, col flow 1.2 ml min^{-1}
MS transfer line 200 °C, Ion Source 200 °C, mass range 20-1000 Da, solvent delay 7.0 min
Sample Name: NSK-640A
Data File: C:\Xcalibur\data\ labGC\Boltacheva\NSK-640A_1.RAW
Instrument Method: C:\Xcalibur\methods\solv_cont-EI-AOC.meth
Acq: 14\02\2013
Vial: 1
Injection Volume (µl): 1.0
Comments: Sample NSK-640A + 0.5 ml toluene, injection 1.0 µl AL/AS



PEAK LIST

Apex RT	Area	%Area	Height	%Height
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13.67	2641790130.446	5.61	782480355.170	10.51
15.35	338800614.205	0.72	128136211.279	1.72
15.79	42256044358.578	89.79	5788767207.225	77.75
17.88	1198055784.180	2.55	461409181.750	6.20
23.55	32845941.556	0.07	15358940.159	0.21
24.21	21932056.942	0.05	8595634.369	0.12
25.46	17623159.932	0.04	6745545.385	0.09

Figure S10 Chromatogram of the extract from the mother liquor
(after 5 hour of refluxing AVK **1a** in glacial acetic acid)

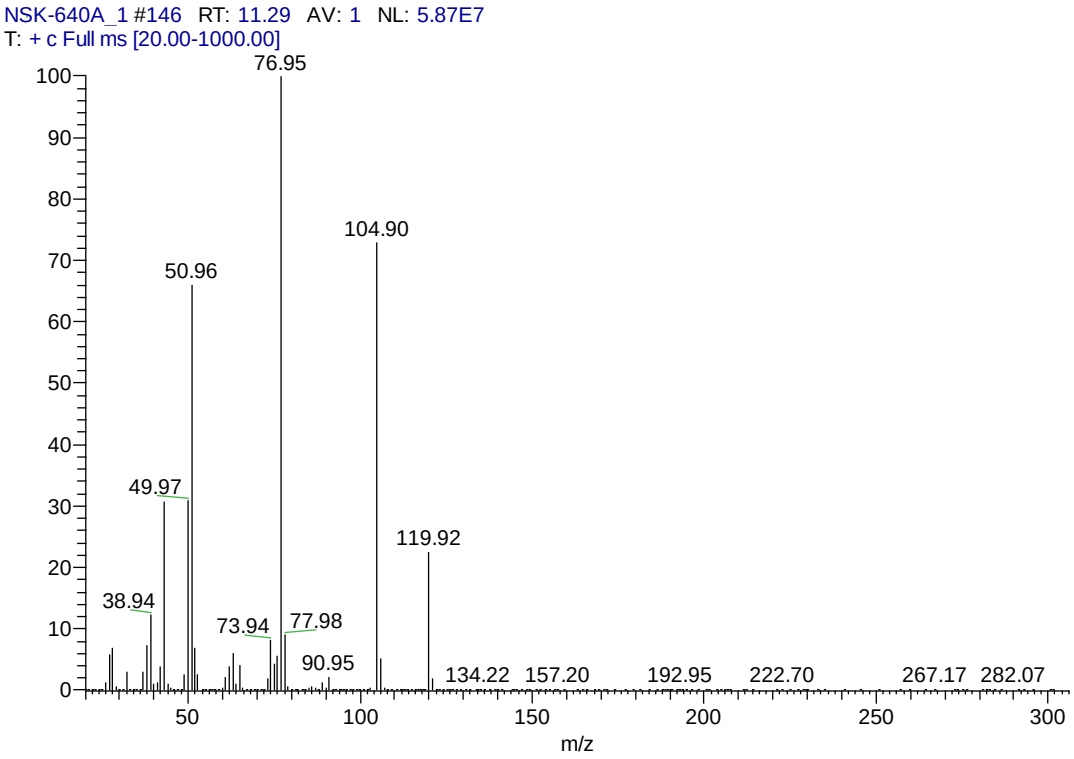

Figure S11 Mass spectrum of acetophenone, degradation product of 4,4,4-trifluoro-1-phenyl-1,3-butanedione at C(2) -C(3)

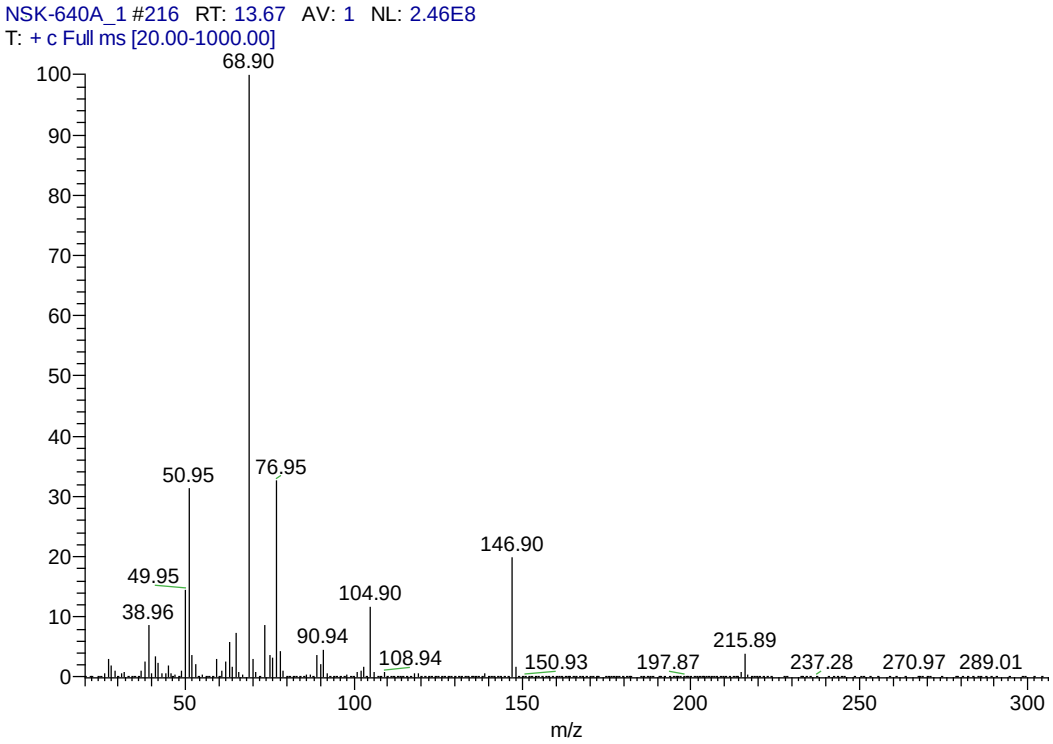

Figure S12 Mass spectrum of 4,4,4-trifluoro-1-phenyl-1,3-butanedione, hydrolysis product of **1a** and/or **2a**

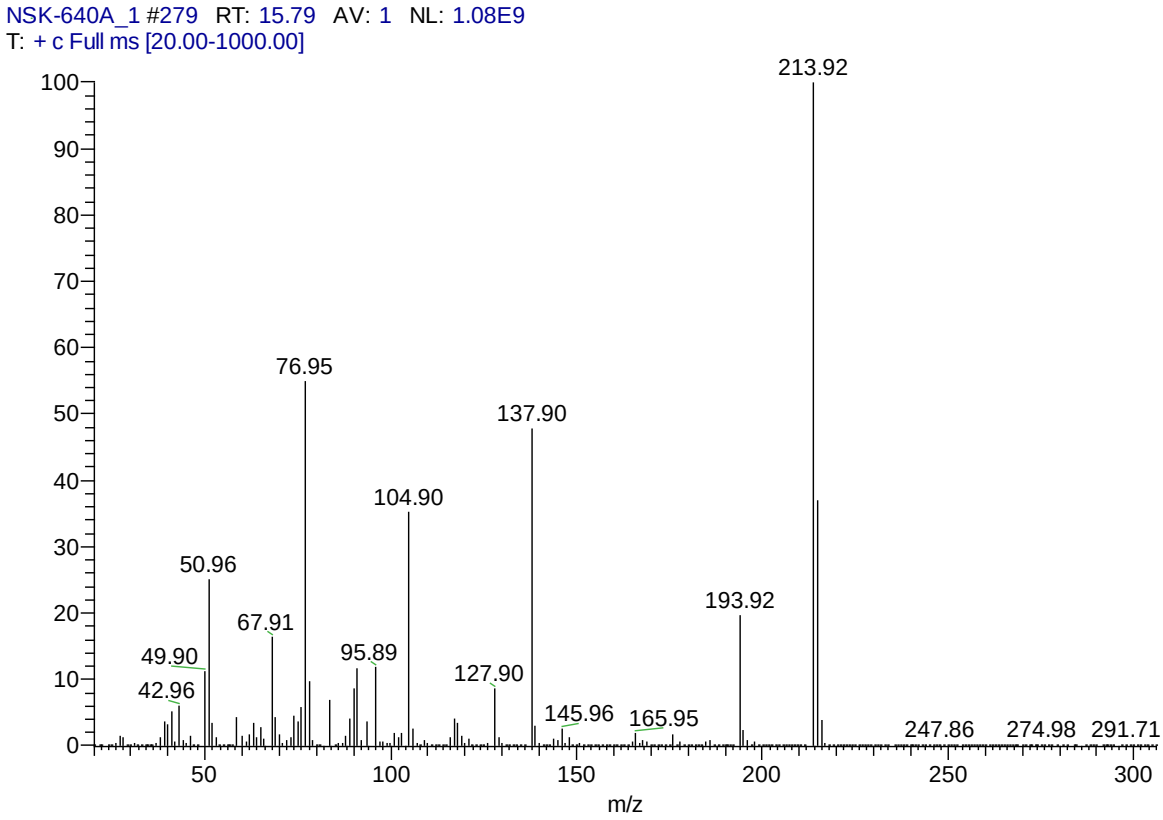

Figure S13 Mass spectrum of 3-amino-4,4,4-trifluoro-1-phenyl-but-2-en-1-one **1a**

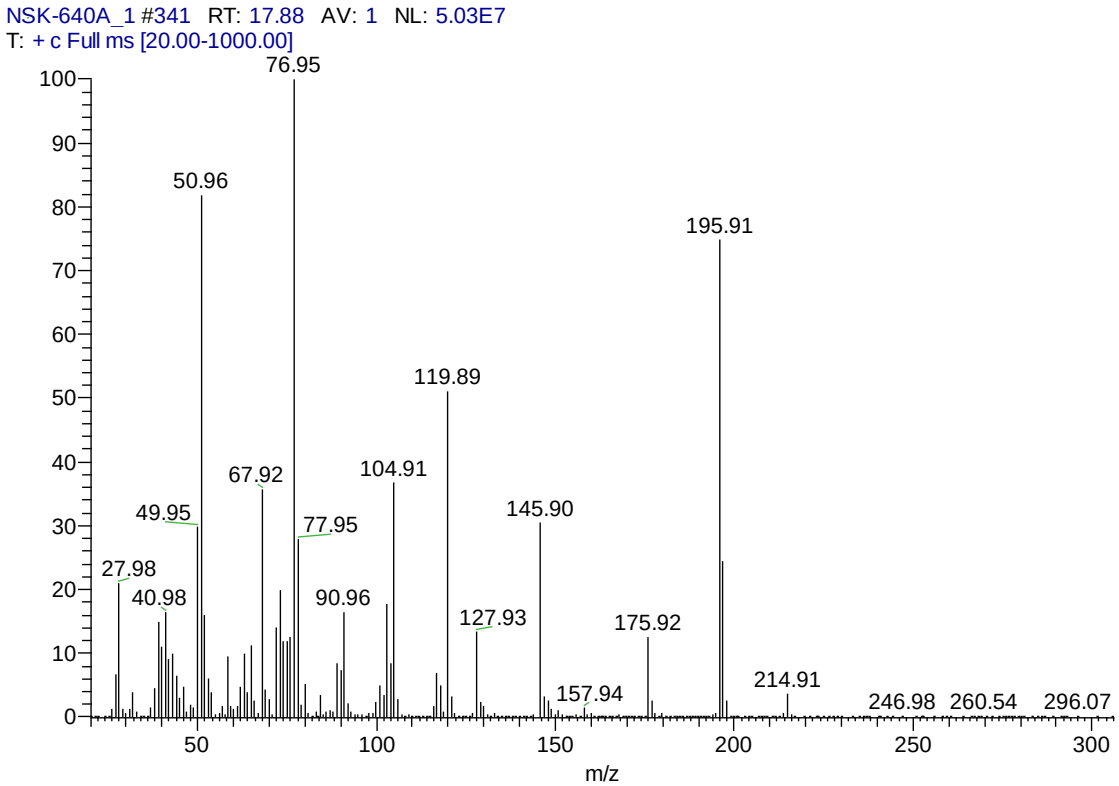

Figure S14 Mass spectrum of 1-amino-4,4,4-trifluoro-1-phenylbut-1-en-3-one **2a**

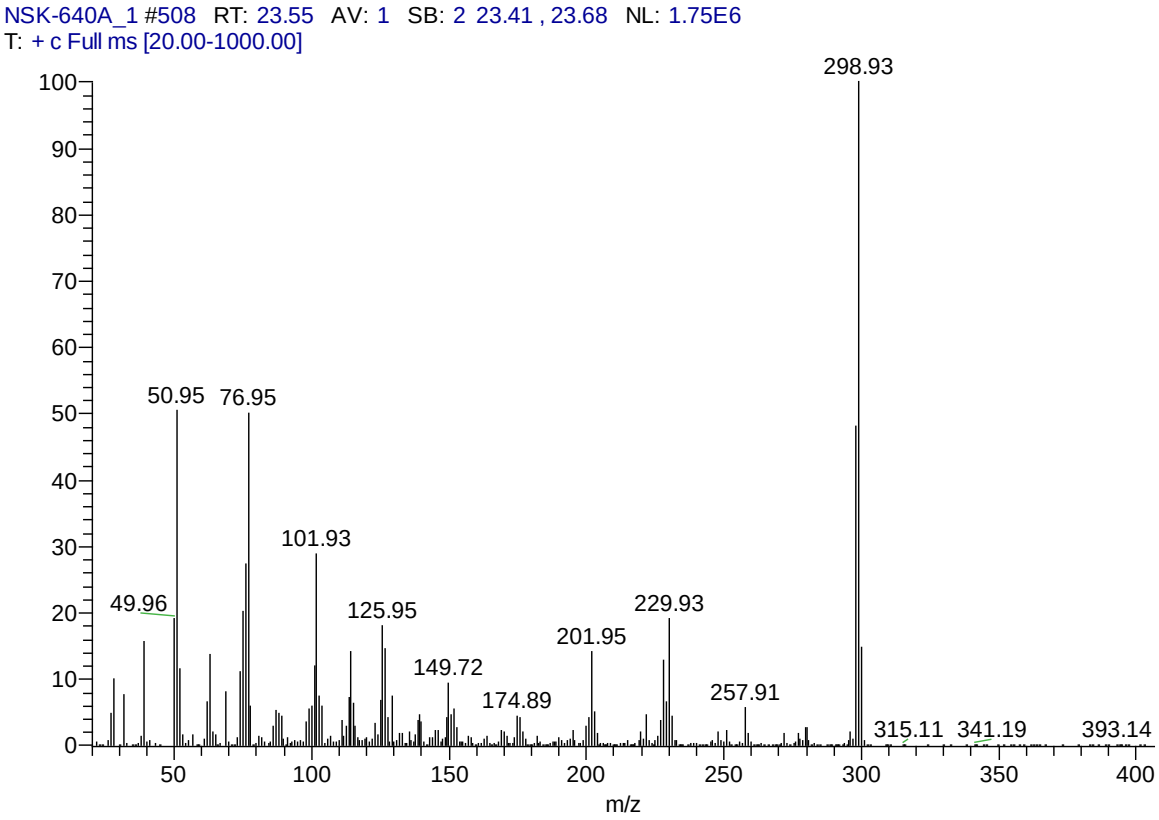

Figure S15 Mass spectrum of pyridine **3**

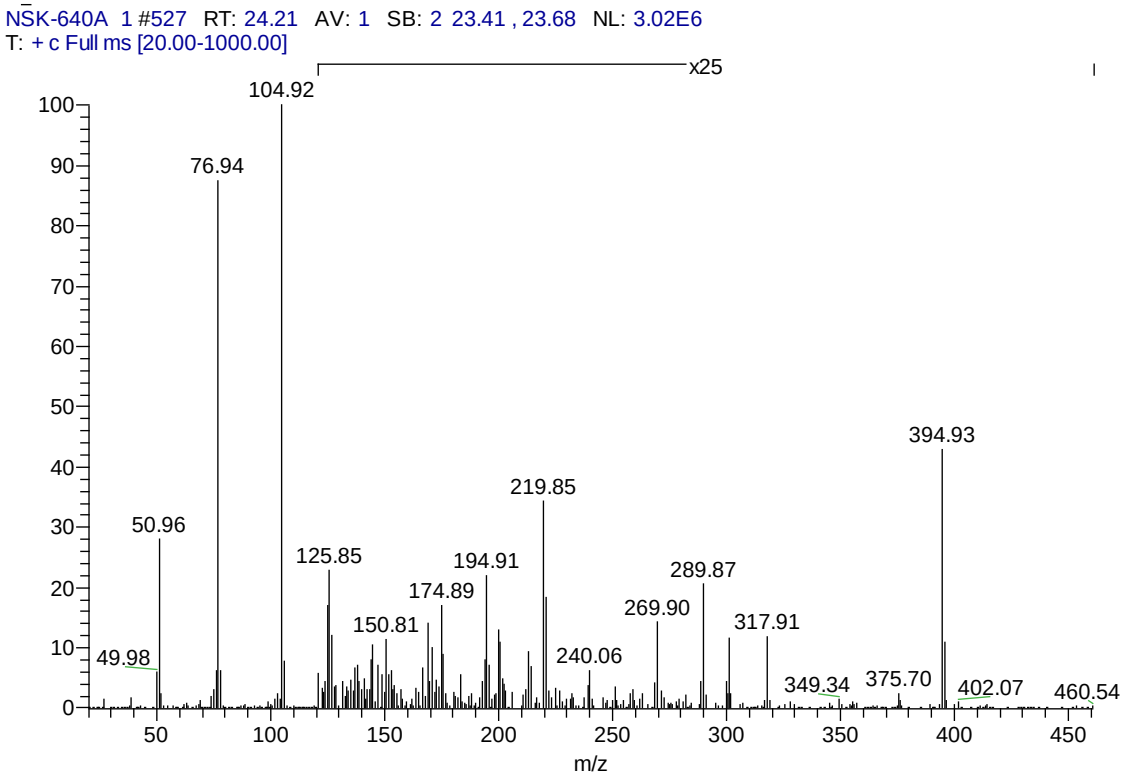

Figure S16 Mass spectrum of pyridine **5**