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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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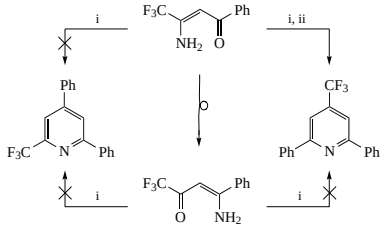
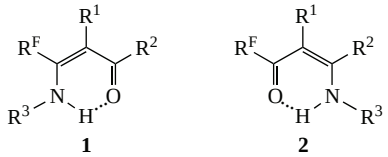
On heating in glacial acetic acid (or ethanol in the presence of manganese(II) acetate), 3-amino-4,4,4-trifluoro-1-phenylbut-2-en-1-one undergoes unusual transformation into 2,6-diphenyl-4-trifluoromethylpyridine. The regioisomeric β-aminovinyl ketone, *viz*. 1-amino-4,4,4-trifluoro-1-phenylbut-1-en-3-one, remains unchanged under similar reaction conditions.



Keywords: organofluorine compounds, β-aminovinyl ketones, regioisomerism, heterocyclization, pyridines.

Due to the presence of conjugated C=C and C=O bonds, two electrophilic [C(1) and C(3)] and three nucleophilic [N, C(2) and O] centers, fluoroalkyl-substituted β-aminovinyl ketones (AVKs) are considered to be valuable polyfunctional building blocks for the synthesis of a variety of heterocyclic compounds, including pyridine family.[1–7] Also, they are used as effective ligands for metal complexes.[8–16]

Earlier, effective syntheses[10,17–23] of regioisomeric AVKs **1** and/or **2**, their unusual **1** → **2** isomerization[24–26] and exchange by functional groups between AVKs **1** and β-diketones or β-aminovinyl thiones[27] were documented.

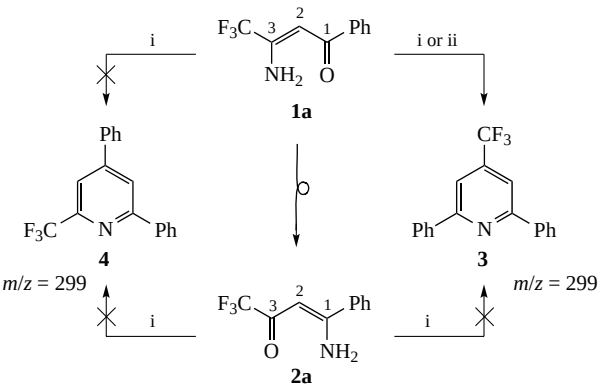


1 **2**

R^F = CF_3–C_4F_9, $H(CF_2)_n$; n = 1, 2, 4
$R^1 + R^2$ = $(CH_2)_3$, $(CH_2)_4$
R^1 = H; R^2 = Me, Bu^t, Ar
R^3 = H, Alk, Ar, Het

In this communication we report an unusual transformation of 3-amino-4,4,4-trifluoro-1-phenylbut-2-en-1-one **1a** into 2,6-diphenyl-4-trifluoromethylpyridine **3**. Refluxing AVK **1a** in glacial acetic acid afforded 2,6-diphenyl-4-(trifluoromethyl)-pyridine **3** in 72% yield (Scheme 1). Regioisomeric AVK **2a** proved to be unchanged under similar reaction conditions, as found previously[18] and also confirmed in this study. The structure of compound **3** was confirmed by elemental analysis, GC-MS, ^{1}H, ^{19}F and ^{13}C NMR and IR spectroscopy (for details, see Online Supplementary Materials). Ultimately its structure was established by X-ray study (Figure 1).[†]

It is worth noting that condensation of two molecules of AVK **1a** through the participation of electrophilic [C(1) and C(3)] and



Scheme 1 *Reagents and conditions*: i, AcOH, reflux, 5 h; ii, $Mn(OAc)_2$, EtOH, reflux, 1 h.

[†] *Crystal data for* **3**. Monoclinic, space group $P2_1/c$, a = 10.1800(10), b = 16.9898(15) and c = 8.5869(7) Å, β = 104.199(7)°, 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, wR_2 = 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 Å^{-3}. The XRD analysis was performed on an Xcalibur 3 automatic four-circle diffractometer with CCD detector along the usual procedure (MoKα-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.[28] 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.

CCDC 2005153 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Center *via* http://www.ccdc.cam.ac.uk.

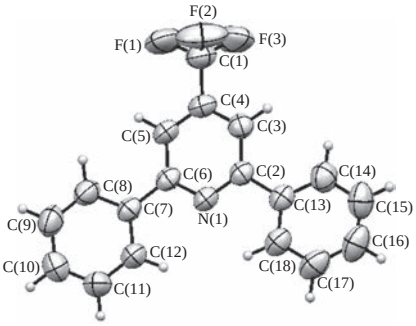
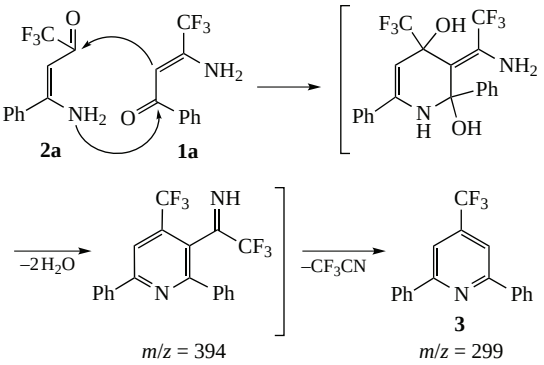


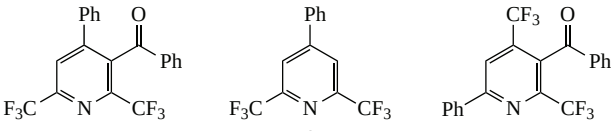
Figure 1 Molecular structure of compound **3** shown in the thermal ellipsoids of 50% probability.



Scheme 2

nucleophilic [C(2) and N] centers can result in the formation of pyridines **4**–**6** but not pyridine **3** (see Online Supplementary Materials, Schemes S1 and S2).

Monitoring the process of the formation of pyridine **3** from AVK **1a** by GC-MS revealed that after 1 h of refluxing AVK **1a** in glacial acetic acid both AVK **2a** and pyridine **3** were present in the reaction mixture (product **3** was even isolated preparatively). Prolongation of the reaction time up to 5 h results in a lower content of AVK **1a** with simultaneous growth of the content of **2a** and pyridine **3**. Also, peaks corresponding to compounds **5** and **7** with *m/z* = 395 were observed (see Online Supplementary Materials, Figures S6–S16 and Schemes S2, S3).



The feature of reactions of this type is the formation of pyridine **6**, as indicated by detection of the peak with *m/z* = 291 (see Online Supplementary Materials, Scheme S2). Pyridines **5**–**7** have also been registered by GC–MS method, and their presence in the reaction mixtures is very important for understanding the reaction mechanism.

Analysis of the previously obtained results,[24–27] and the data of this study has enabled us to state that isomerization of AVK **1a** into AVK **2a**[24–26] took place as the first step, followed by condensation of AVK **1a** and AVK **2a** into pyridine **3** (Scheme 2). Isomerization of AVK **1a** into AVK **2a** involves a nucleophilic attack of the NH_2 group of one molecule of AVK **1a** at the electrophilic carbon C(3) of another molecule of AVK **1a**[26] (see Online Supplementary Materials, Scheme S4). Therefore, we believe that the formation of pyridine **3** occurs through the condensation of AVK **1a** with AVK **2a** with participation of electrophilic [C(1) and C(3)] and nucleophilic [C(2) and N] centers (see Scheme 2).

Alternative schemes involving a nucleophilic attack of NH_2 group of AVK **1a** at one of electrophilic centers of AVK **2a** seem unlikely due to a low nucleophilicity of NH_2 bearing a geminal CF_3 fragment. Indeed, products **5**–**7** arising from such interactions were detected only in trace amounts (see Online Supplementary Materials, Schemes S2, S3).

Refluxing AVK **1a** in ethanol in the presence of an equimolar amount of manganese(II) acetate enhances yield of pyridine **3** up to 96%, while the reactions of AVKs with metal acetates usually result in the corresponding metal chelates.[10] We believe that in these transformations manganese acetate reacts with AVK **1a** and **2a** to give unstable complexes, playing the role of templates, which facilitate coordination of reagents, thus enhancing yields of pyridine **3**.

It is worth to note that melting point, IR and ^{1}H NMR spectra of pyridine **3** proved to be identical to those of pyridine isolated from condensation of the corresponding 1,3-diketone (4,4,4-trifluoro-1-phenylbutane-1,3-dione) with ammonia. The latter compound was mistakenly considered to have the structure of pyridine **4**.[18]

In summary, starting from a preparatively available fluorinated synthon, 3-amino-4,4,4-trifluoro-1-phenylbut-2-en-1-one **1a**, we have synthesized 2,6-diphenyl-4-(trifluoromethyl)pyridine **3** and determined its structure by X-ray analysis. Apparently, the isomerization of AVK **1a** into AVK **2a** occurs as the first step, followed by condensation of AVK **1a** and AVK **2a** into pyridine **3**. Taking into account that syntheses of pyridines bearing fluoroalkyl substituents are of interest for agrochemistry[29] and medicine,[30] we intend to continue our research in this direction.

The work was carried out within the framework of the theme of the state task no. AAAA-A19-119011790134-1. Analytical studies were performed using equipment of the Center for Joint Use ‘Spectroscopy and Analysis of Organic Compounds’.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2020.09.042.

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