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A new synthesis of 4′-trifluoromethyl-2,2′:6′,2″-terpyridine

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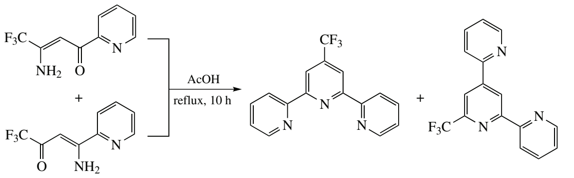
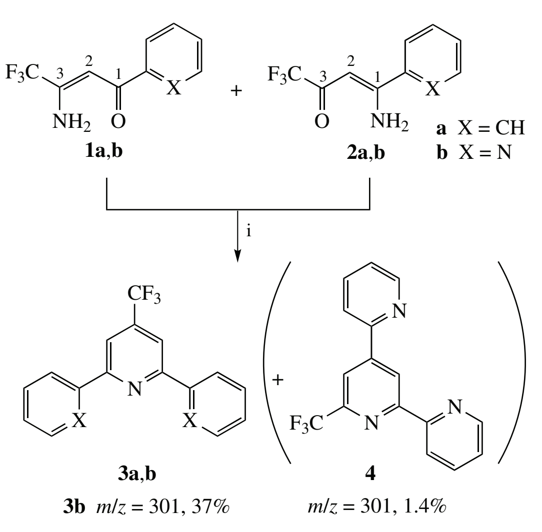
Reflux of two isomeric 3-amino-4,4,4-trifluoro-1-(2-pyridyl)-but-2-en-1-one and 3-amino-1,1,1-trifluoro-4-(2-pyridyl)-but-3-en-2-one in acetic acid affords 4′-trifluoromethyl-2,2′:6′,2″-terpyridine (37%) with 1.4% admixture of 6′-trifluoromethyl-2,2′:4′,2″-terpyridine.



Keywords: organofluorine compounds, β-aminovinyl ketones, regioisomerism, heterocyclization, pyridines, 2,2′:6′,2″-terpyridines.

Tridentate ligand 2,2′:6′,2″-terpyridine (Tpy) and its derivatives being good chelating agents have been used to prepare homo- and multinuclear metal complexes[1–9] and to construct coordination polymers.[10,11] Modification of organic-inorganic platforms with terpyridine fragments makes it possible to obtain components of solar cells, OLED devices and chemosensors.[1–3,12–14] In the family of Tpy ligands, the derivatives bearing substituents at $C^{4'}$ position appear to be of special interest since this pattern does not provide the basis for the formation of enantiomeric isomers as this type of Tpy retains its plane of symmetry.[1–3] Meanwhile, the only reported example of 4′-trifluoromethyl-2,2′:6′,2″-terpyridine was used as a ligand in the Negishi nickel-catalyzed cross-coupling of secondary alkylzinc halides with aryl/heteroaryl iodides. This particular Tpy was obtained in 30% yield by the Stille cross-coupling of 2,6-dichloro-4-(trifluoromethyl)pyridine with (2-pyridyl)tributylstannane.[15]

Earlier,[16] we have shown that refluxing β-aminovinyl ketone (AVK) **1a** in glacial acetic acid caused its isomerization into AVK **2a**, and the subsequent condensation of compounds **1a** and **2a** produced 2,6-diphenyl-4-(trifluoromethyl)pyridine **3a** (Scheme 1).[16] It was logical to assume that under similar reaction conditions the condensation of AVK **1b** and **2b** would lead to 4′-trifluoromethyl-2,2′:6′,2″-terpyridine **3b** (Tpy **3b**). In this work we found that this assumption was true.



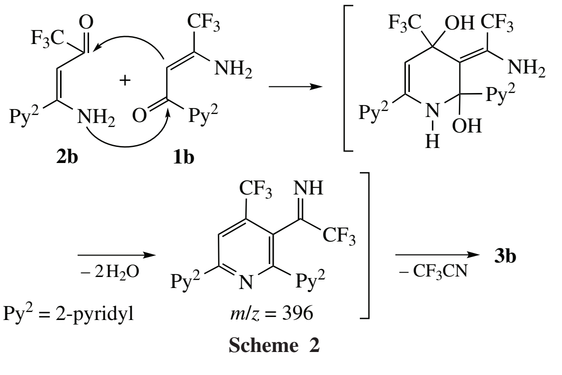
Scheme 1 *Reagents and conditions*: i, AcOH, reflux.

In fact, refluxing a mixture of AVKs **1b** and **2b** in glacial acetic acid for 10 h gave Tpy **3b** in 37% yield. In addition, isomeric 6′-trifluoromethyl-2,2′:4′,2″-terpyridine **4** (Tpy **4**), was isolated in 1.4% yield (see Scheme 1). Products **3b** and **4** were characterized by elemental analysis, GC-MS, IR, ^{1}H, ^{13}C and ^{19}F NMR spectroscopy (see Online Supplementary Materials).

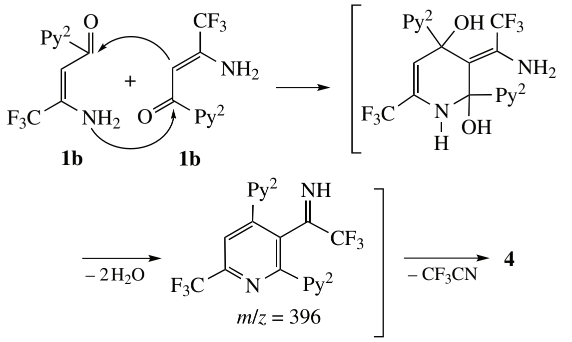
We believe that the formation of Tpy **3b** occurs through condensation of AVK **1b** and AVK **2b** with participation of electrophilic C^1 and C^3 and nucleophilic C^2 and N centres (Scheme 2).

In a similar way, the formation of compound **4** takes place through condensation of two molecules of AVK **1b** with the participation of electrophilic C^1 and C^3 and nucleophilic C^2 and N centers (Scheme 3). A low yield of compound **4** is due to a reduced reactivity of NH_2 bearing the geminal CF_3 fragment.

In order to elucidate some chemical features of this reaction, we have investigated composition of the residue after preparative isolation of compounds **3b** and **4** by GC-MS. The chromatogram proved to contain 5 peaks corresponding to the AVK **2b**,[17] Tpy **3b** and presumably to compounds **5** (or **7**), **6** and **8** (see Online Supplementary Materials, Schemes S1, S2 and Figures S9–S14). The absence of starting AVK **1b** in the reaction mixture was attributed to its participation not only in condensations leading to

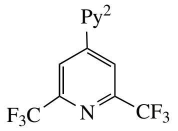


Scheme 2



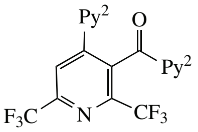
Scheme 3

compounds **3b**, **4–8** but also in isomerization[18–20] into AVK **2b**, thus providing an excess of the latter in the reaction mixture (see Online Supplementary Materials, Scheme S3).



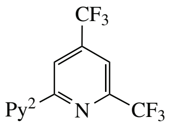
5

$m/z = 292$



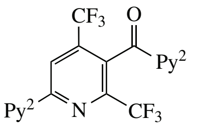
6

$m/z = 397$



7

$m/z = 292$



8

$m/z = 397$

Heating AVK **1b**[†] at 110 °C for 2 h resulted in formation of small amounts of AVK **2b**. Prolongation of the incubation time to 10 h caused significant growth of the content of AVK **2b** and Tpy **3b** along with formation of small amounts of Tpy **4** and 4,4,4-trifluoro-3-hydroxy-1-(2-pyridyl)but-2-en-1-one (see Online Supplementary Materials, Figures S15–S28). These results are in favor of the important role of isomerization of AVK **1** into AVK **2** for the formation of the pyridine ring. The mechanism explaining the formation of products **3b**, **4–8** is in good agreement with that suggested earlier[16] for the formation of 2,6-diphenyl-4-(trifluoromethyl)pyridine **3a** and its by-products.

In conclusion, starting from easily available regioisomeric fluoroalkyl-substituted β-aminovinyl ketones **1b** and **2b**[17] we have performed one-stage assembling of 4′-trifluoromethyl-2,2′:6′,2″-terpyridine **3b** in ~37% yield. In addition, isomeric Tpy **4** was isolated in ~1.4% yield. Compounds **5–8** were also detected as by-products, whose presence in the reaction mixtures is important for understanding the chemical features of such reactions.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2021.05.035.

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[†] The presence of the Tpy **3b** impurity in this sample does not interfere with the study of the isomerization process.