Contents lists available at GrowingScience

Current Chemistry Letters

homepage: www.GrowingScience.com

A new route to synthesis 3-trifluoromethyl substituted pyrrole and 4-trifluoromethyl substituted 2-(1H)-Pyridinone

Fatima Youssoufi[a*], Abouelhaoul El Alami[a], Assiya Atif[a] and Mustapha Soufyane[a]

[a]*Bioorganic Chemistry Team, Faculty of Sciences, Chouaib Doukkali University, P.O. Box 20, El Jadida, 24000, Morocco*

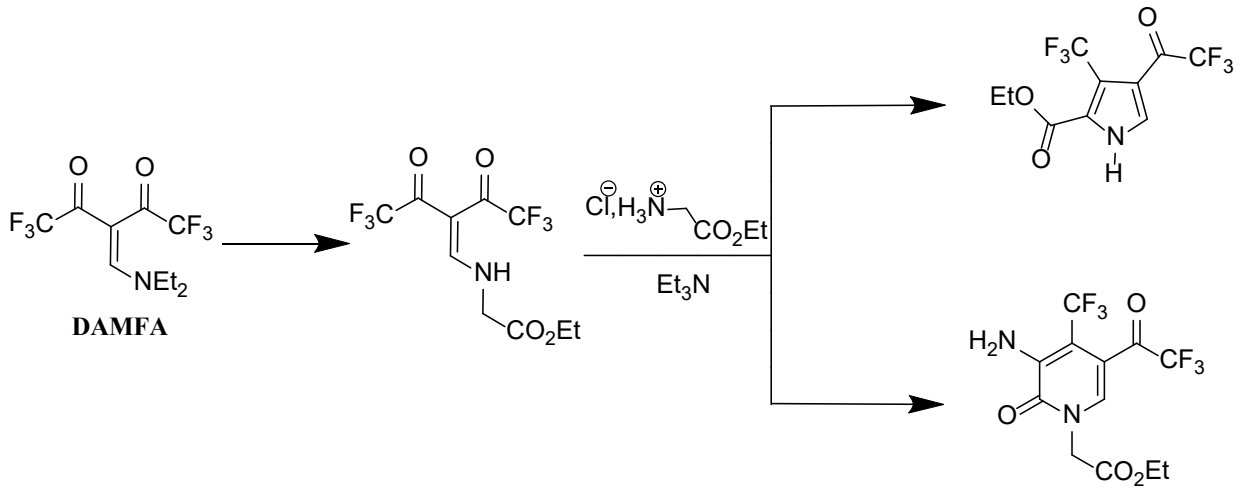
C H R O N I C L E

Article history:
Received October 4, 2024
Received in revised form
November 4, 2024
Accepted February 14, 2025
Available online
February 14, 2025

Keywords:
DAMFA
Enaminedione
Trifluoromethyl pyrrole
Trifluoromethyl-1H-pyridine-2-one

A B S T R A C T

In the present work, an enaminedione **2** was easily obtained in excellent yield (92 %) by the *N-N* exchange reaction of DAMFA (diethylaminomethylenehexafluoroacetylacetone) **1** with ethyl glycinate hydrochloride using the Michael 1,4-addition/elimination approach. The obtained compound **2** was used as a precursor in the development of a new synthesis of 3-trifluoromethyl pyrrole **3** and 4-trifluoromethyl-(1*H*)-2-pyridinone **4**. A mechanism involving nucleophilic substitution and intramolecular cyclization is proposed. The obtained compounds were identified and confirmed by Fourier transform infrared spectroscopy, proton and carbon nuclear magnetic resonance spectroscopy, and high-resolution mass spectrometry. The results of the analyses are in good agreement with the proposed structures of the synthesized compounds.



Graphical Abstract

1. Introduction

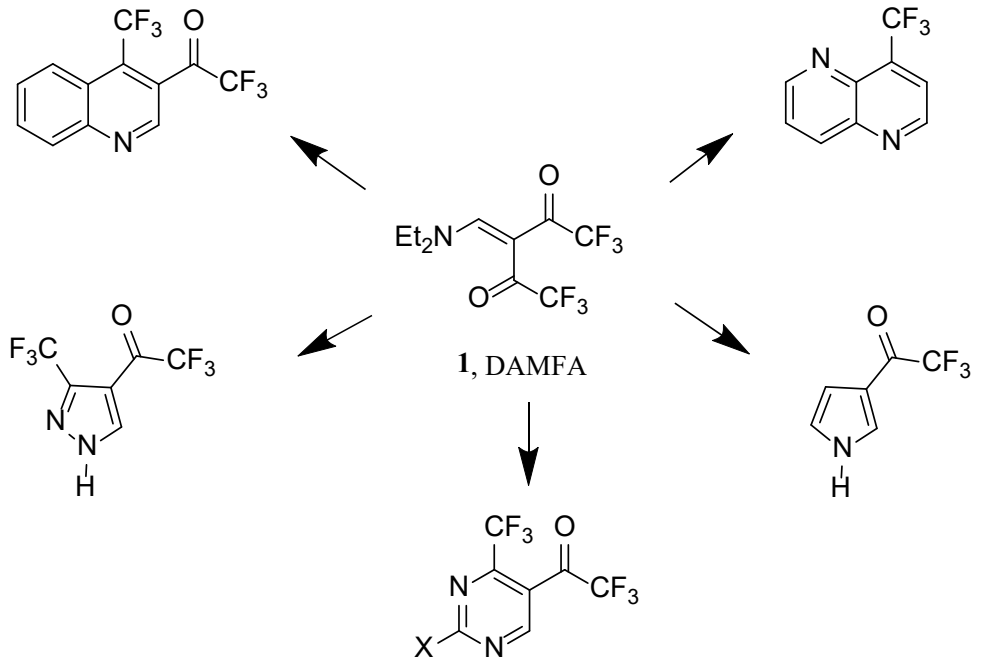
Fluoro-heterocyclic compounds are an interesting class of organic compounds due to their potent biological and pharmacological activities.[1–3] In fact, fluorine chemistry has really taken off, thanks to the special properties resulting from the introduction of fluorine atoms into an organic molecule. Moreover, fluorination of a molecule induces profound

* Corresponding author
E-mail address fyoussoufi04@gmail.com (F. Youssoufi)

doi: 10.5267/j.ccl.2025.2.004

modifications in its physical and chemical properties, which can lead to profound repercussions on its biological activities.[1,3,4]

Given the importance of fluorinated compounds, α,β-unsaturated ketones with a trifluoromethyl substituent represent interesting building blocks for the synthesis of trifluoromethyl containing compounds, especially heterocyclic systems, which often show high biological activities.[5–8] In fact, the synthesis of fluorinated N-heterocyclic compounds has drawn much more attention indicating that fluorine medicinal chemistry research is prosperous.[9] For that reason, we have putting interesting efforts into developing novel and practical methodologies to construct potential new systems dependent on the cyclization of an acyclic building block incorporating a trifluoromethyl group. The literature has reported a series of CF_3-substituted pyrrole, pyrrolidine, pyrido-pyridines, pyrimidines, pyrazoles and quinolines obtained from the reactions of enaminediones such as β-ethoxyvinyl-trifluoromethyl-ketone or diethylaminomethylene hexafluoroacetylacetone (DAMFA) **1** with the corresponding nitrogen nucleophiles (**Scheme 1**).[10–14]



Scheme 1. Heterocycles obtained from DAMFA **1**

Among these interesting compounds, pyrrole and 2-(1*H*)-pyridinone units are widely involved in natural and synthetic heterocycles with an extensive range of medicinal properties.[15–18]

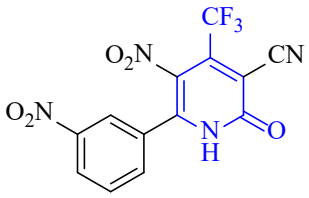
In recent decades, trifluoromethylated pyrroles and 2-(1*H*)-pyridinones have been the subject of many works due to their potential biological and pharmacological activities such as antibacterial, antifungal, analgesic, anti-aggregative activity, anti-HIV, anti-fibrosis, anticancer, anti-inflammatory and so many others.[19–27] For example, 5-nitro-6-(3-nitrophenyl)-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile (SynuClean-D) (**A**), is a promising drug candidate from the family of trifluoromethylpyridin-2-ones used for the treatment of Parkinson/s disease. It inhibits α-synuclein aggregation in cultured human cells and prevents degeneration of dopaminergic neurons in a *Caenorhabditis elegans* model of Parkinson's disease (**Figure 1**).[27] 4-fluoro-3-(4-fluorophenyl)-2-(4-(methylsulfonyl)phenyl)-1*H*-pyrrole (**B**) is a fluorinated pyrrole analogue known with his optimized anti-inflammatory activity.[26]

Moreover, diethyl (1-benzyl-4-phenyl-3-(trifluoromethyl)-1*H*-pyrrol-2-yl)phosphonate (**C**) with trifluorophosphonyl and phenyl group exhibited significant inhibition cell cycle arrest at G1 and showed prompted apoptosis in these cell line (**Figure 1**).[25] Another pyridinone derivative, 3-chloro-5-((1-((4-methyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)methyl)-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridin-3-yl)oxy)benzonitrile (Doravirin) (**D**), is a non-nucleoside reverse transcriptase inhibitor (NNRTI) with potent in vitro activity against HIV-1, blocking HIV replication through non-competitive inhibition of reverse transcriptase (**Fig. 1**).[22]

In the preliminary papers, the synthesis of trifluoromethylated pyrroles have been reported.[28] Moreover, authors mentioned some examples, dealing with the use of the enaminedione synthons for the construction of trifluoromethyl

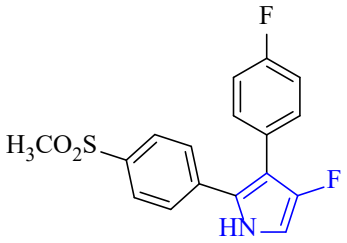
substituted pyrroles in good yields.[29–35] Furthermore, a reaction of DAMFA **1** with 2,2-dimethoxyethylamine and ethyl N-benzylglycinate giving, directly and in only one step, the trifluoroacetyl trifluoromethylpyrroles in good yields, has been documented.[11] In contrast, despite the great potential of the trifluoromethylated pyridine-2-ones, their synthesis and relative chemistry have rarely been explored. Hence, only a few efficient and general methods for their synthesis have been documented.[20,21]

In this present work, we have to think of condensing the ethyl glycinate with the DAMFA under conditions which can enable us to stop at the stage of condensation, then to target cyclization of the obtained enaminedione according to different conditions in order to lead to potent trifluoromethylated nitrogen heterocycles. Indeed, the reaction of DAMFA **1** with ethyl glycinate hydrochloride leads to the formation of fluorinated pyrrole and 2-(1*H*)-pyridinone derivatives. We report this simple and efficient process for the preparation of 3-trifluoromethyl pyrrole **3** and 4-trifluoromethyl 2-(1*H*)-pyridinone **4** from a previously prepared enaminedione **2**.



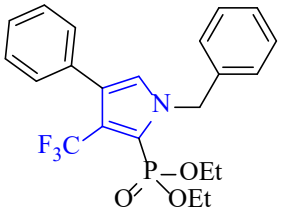
5-nitro-6-(3-nitrophenyl)-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile

(A)



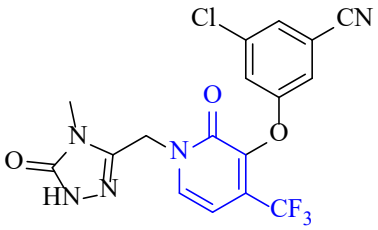
4-fluoro-3-(4-fluorophenyl)-2-(4-(methylsulfonyl)phenyl)-1*H*-pyrrole

(B)



diethyl (1-benzyl-4-phenyl-3-(trifluoromethyl)-1*H*-pyrrol-2-yl)phosphonate

(C)



3-chloro-5-((1-((4-methyl-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)methyl)-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridin-3-yl)oxy)benzonitrile

(D)

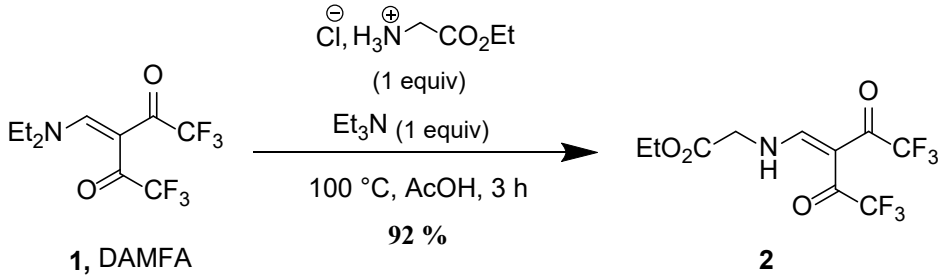
Fig. 1. Representative structures of clinically applied fluorinated and trifluoromethylated pyrroles and pyridine-2-ones

2. Results and Discussion

The N,N-diethylaminomethylene-1,1,1,5,5,5-hexafluoroacetylacetone (DAMFA) **1** was obtained by trifluoroacetylation of triethylamine with trifluoroacetic anhydride.[36,37] This enaminedione is of great interest in organic synthesis. Hence, the preparation of new fluorinated enaminedione, by substituting the N-diethylamino group (NEt_2) in DAMFA **1** with various nitrogen nucleophiles according to the Michael-type 1,4-addition-elimination approach, is of interest for the synthesis of new fluorinated nitrogen heterocycles.

*2.1 Preparation of trifluoromethylated enaminedione **2***

The preparation and isolation of enaminedione **2** was of interest to orientate the formation of fluorinated heterocycles towards perfect selectivity. For this reason, a nucleophilic N-N-exchange reaction of DAMFA **1** with ethyl glycinate hydrochloride occurred readily in the presence of triethylamine in acetic acid at 100 °C for 3 h. The target compound **2** was obtained with oily aspect in excellent yield (92 %) (**Scheme 2**).

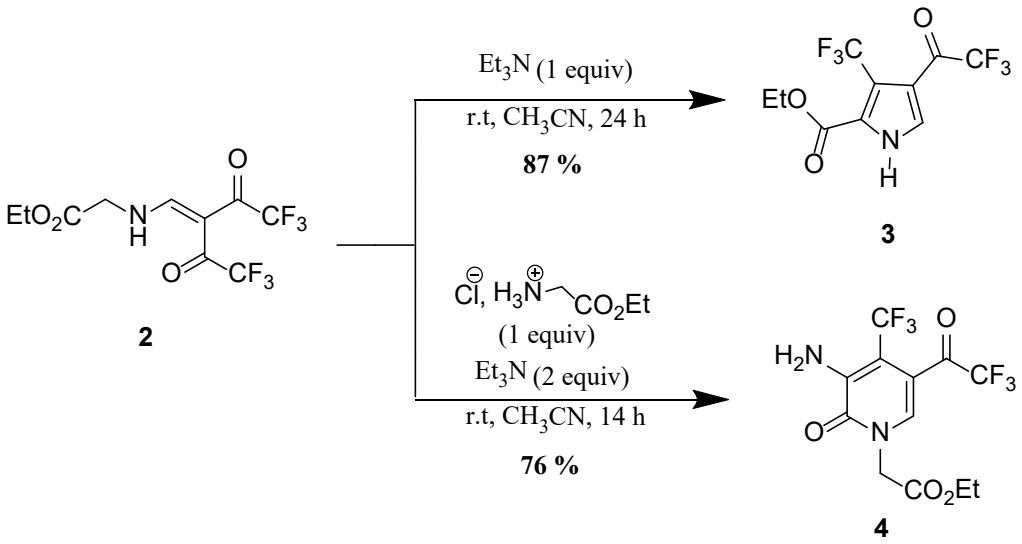


Scheme 2. Synthesis of trifluoromethylated enaminedione **2**

The structure of product **2** was identified on the basis of spectral analysis. The ^{1}H-NMR spectrum (**Figure S1**), taken in $CDCl_3$, shows the presence of a triplet at 1.31 ppm attributed to the tree protons of the methyl group, a singlet at 4.24 ppm relating to the two protons of the methylene group (CO**CH$_2$**-NH), a quadruplet signal, with an amplitude of two protons from the CH_2O group, was recorded at 4.33 ppm, a double signal with an amplitude of one proton resonates at 7.94 ppm representing the ethylenic proton (C=**CH**) and a broad singlet at 10.9 ppm corresponding to the proton carried by the secondary amine nitrogen (NH). The ^{13}C-NMR spectrum (**Figure S2**) also gave information, it reveals signals at 11.8, 50.6, 62.8 and 101.6 ppm assigned to the carbons of CH_3, CH_2, CH_2O and CH= groups, respectively. Two signals were recorded at 116.2 and 116.7 ppm attributed to the trifluoromethyl groups (CF_3) with coupling constants $^{1}J_{C\text{-}F}$ = 285 Hz and 291 Hz, respectively. In addition, the spectrum shows the presence of signals at 162.4, 167.1, 175.3 and 180.4 ppm corresponding to quaternary carbons (C=O and C=C). Furthermore, the IR spectrum (**Figure S3**) of product **2** shows, in particular, the appearance of an absorption band at 2996 cm^{-1} characteristic of the secondary amine group (N-H), absorption bands at 1744 and 1670 cm^{-1} attributed to the carbonyl groups (C=O), and an absorption band at 1612 cm^{-1} corresponding to the double bond (C=C). Finally, the mass spectrum of compound **2** (**Figure S4**), taken in electron impact (IE) mode, shows the presence of a molecular peak at *m/z* = 321 $[M]^+$ and a base peak at *m/z* = 252 corresponding to the loss of the CF_3 group, thus confirming the proposed structure.

2.2 Reactivity of the enaminedione **2**

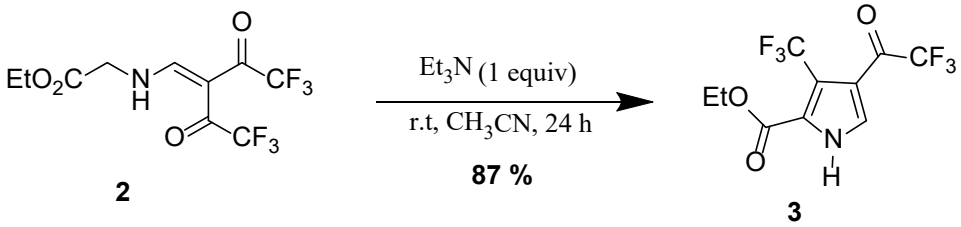
The obtained enaminedione **2** was used in two ways depending on the reaction conditions (**Scheme 3**). To target the formation of pyrrole **3**, the cyclization of the enaminedione **2** was stirred with triethylamine in acetonitrile at room temperature (25 °C). Whereas to obtain a pyridone ring **4** a further equivalent of ethyl glycinate hydrochloride was required in the presence of two equivalents of triethylamine.



Scheme 3: Synthesis of pyrrole **3** and pyridone **4**

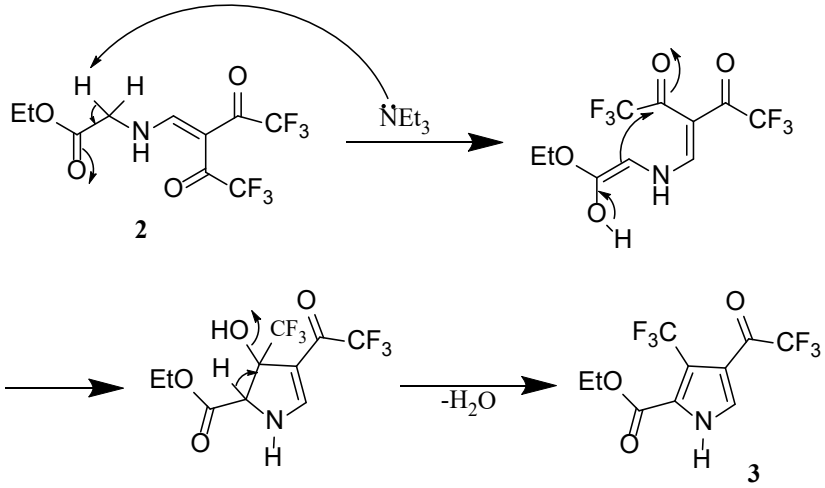
2.2.1 Synthesis of trifluoromethylated pyrrole **3**

In our strategy for the synthesis of trifluoromethylated pyrroles, a single pyrrole **3** was obtained, by reacting the enaminedione **2** with 1 equivalent of triethylamine in the acetonitrile at room temperature for 24 h (**Scheme 4**). The pyrrole ring **3** was obtained according to an intramolecular cyclization reaction, in excellent yield (87 %). Its formation is interpreted by the enolization of the ester followed by cyclodehydration according to the mechanism detailed in **Scheme 5**.



Scheme 4: Synthesis of trifluoromethylated pyrole **3**

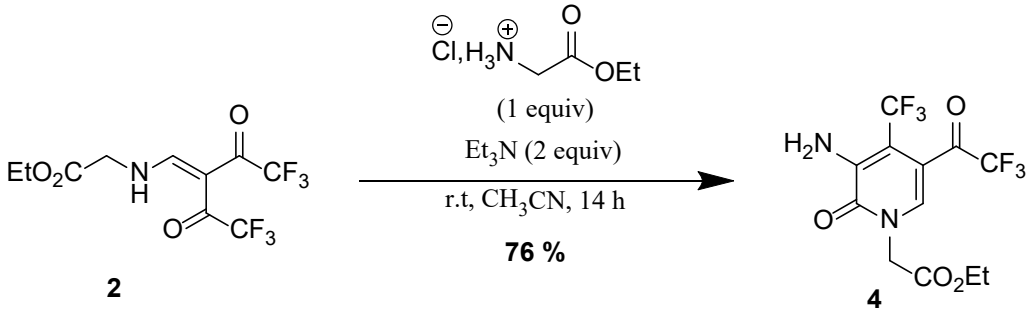
The structure of the product **3** was confirmed by the presence of signals in its ^{1}H-NMR spectrum (**Fig. S5**). The pyrrole ring proton resonates significantly downfield at 7.70 ppm. The ethyl acetate group and the N-H are observed as triplet, quadruplet and singlet at 1.38; 4.44 and 10.46 ppm, respectively. The ^{13}C-NMR spectrum (**Fig. S6**) reveals the presence of two signals at 13.9 and 62.8 ppm relating respectively to the CH_3 and CH_2 groups of the ester function, three signals at 111.2; 118.1; and 129.6 ppm attributable respectively to the ethylenic carbons of the enamine in positions 4, 5 and 3 of the pyrrole ring, as well as a signal at 142.4 ppm corresponding to the quaternary ethylenic carbon of the enamine in α of the nitrogen in the pyrrole ring. We also note the presence of two signals in the form of two quadruplets, one at 116.2 ppm with a coupling constant ($^{1}J_{C\text{-}F}$ = 285 Hz) and the other at 121.2 ppm with a coupling constant ($^{1}J_{C\text{-}F}$ = 272 Hz), attributed respectively to the quaternary carbon (CF_3), as well as two signals at 159.2 and 174.8 ppm relating respectively to the carbonyl group (C=O) of the ester function and to the carbonyl of the trifluoroacetyl group. In addition, the IR spectrum (**Fig. S7**) of product **3** shows, in particular, an absorption band at 3383 cm^{-1} due to the presence of the amine group (NH), two absorption bands at 1744 and 1679 cm^{-1} characteristic of the two carbonyl groups (C=O). Finally, the mass spectrum (**Fig. S8**) of compound **3**, taken in electron impact (IE) mode, shows the molecular peak relating to the molecular ion at *m/z* = 303 $[M]^+$ and a base peak at *m/z* = 234 corresponding to the loss of the CF_3 group, thus confirming the proposed structure.



Scheme 5. Mechanism for the formation of trifluoromethylated pyrrole **3**

2.2.2 Synthesis of trifluoromethylated pyridin-2-(1H)-one **4**

The treatment of the enaminedione **2** with 1 equivalent of the ethyl glycinate hydrochloride in the acetonitrile in the presence of 2 equivalents of triethylamine at room temperature during 14 h enabled us to obtain with 76 % of yield 2-(1*H*)-pyridinone **4** (**Scheme 6**).

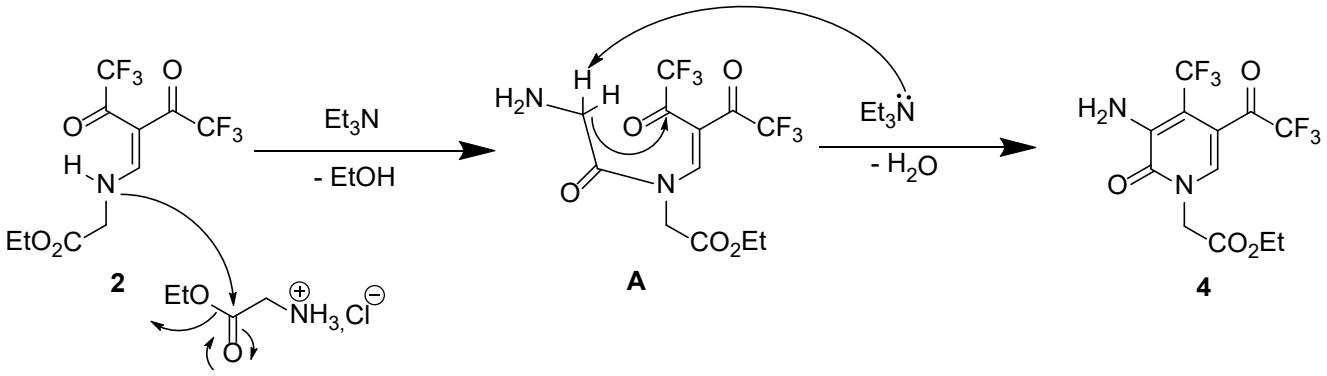


Scheme 6. Synthesis of trifluoromethylated pyridin-2-(1*H*)-one **4**

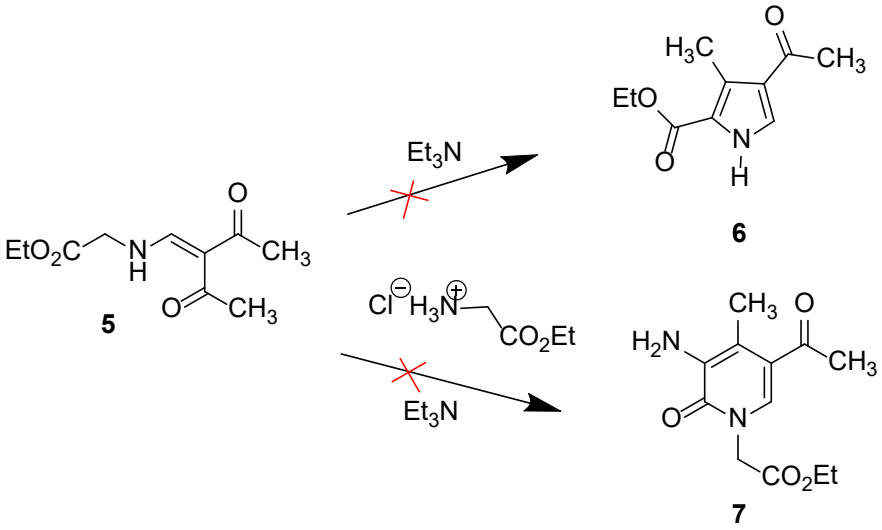
The structure of 3-amino-4-trifluoromethyl-5-trifluoroacetyl-2-(1*H*)-pyridinone **4** was deduced from the obtained spectral data. On the ^{1}H-NMR spectrum (**Fig. S9**), we revealed a singlet with 7.23 ppm allotted to the H-6 proton of the cycle 2-(1*H*)-pyridinone, broad singlet at 5.52 ppm assigned to the two primary amine protons (NH_2). The spectrum also shows a triplet at 1.31 ppm relating to the methyl group, a quadruplet at 4.28 ppm attributed to the protons of the CH_2O group of the ester function, and a singlet at 4.72 ppm corresponding to the two methyl protons linked to the pyridonic ring (CH_2N). For the ^{13}C-NMR spectrum, it showed the carbonyl carbon as a singlet at 166.4 ppm for ethyl-ester and a quadruplet at 178.6 ppm ($^{2}J_{C\text{-}F}$ = 36 Hz) for trifluoroacetyle group, in addition to a signal at 157.3 ppm due to the carbonyl of the pyridone ring. The spectrum also reveals the presence of two signals at 13.7 and 62.3 ppm assigned respectively to the CH_3 and CH_2 groups of the ester function, a signal at 51.1 ppm due to the carbon attached to the pyridone nitrogen (CH_2N), three signals at 103.5, 111.3, and 137.9 ppm, respectively attributed to the quaternary ethylenic carbons of the pyridone ring, as well as a signal at 129.3 ppm corresponding to the ethylenic carbon at α of the nitrogen in the pyridone ring. We also note the presence of two signals in the form of two quadruplets, one at 115.7 ppm with a coupling constant ($^{1}J_{C\text{-}F}$ = 289 Hz) and the other at 123.5 ppm with a coupling constant ($^{1}J_{C\text{-}F}$ = 272 Hz), attributed respectively to the quaternary carbons of the (CF_3) group. As regards the mass spectrum of compound **5** (**Fig. S10**), taken in electrospray ionization (ESI) mode, we observed the presence of a basic peak with m/z = 360 $[M]^{\cdot+}$ corresponding to the molecular peak $C_{12}H_{10}F_6N_2O_4$. The peak with m/z = 291 corresponds to the loss of the CF_3 group. Furthermore, the IR(ATR) spectrum of compound **4** reveals an absorption band at 3366 cm^{-1} characteristic of the amine function (NH_2) and an absorption band at 1665 cm^{-1} due to the presence of the pyridone carbonyl group (C=O).

More information and detailed results of the structures analysis data can be found in the *Supporting Information*.

The formation of ethyl 2-(3-amino-2-oxo-5-(2,2,2-trifluoroacetyl)-4-(trifluoromethyl)pyridin-1(2*H*)-yl)acetate **4** can be explained by the mechanism represented in Scheme 7. The initial stage of the reaction involves nucleophilic attack of the amine group of enaminedione **2** on the carbonyl of the glycine moiety. The intermediate **A** which is formed undergoes deprotonation of the glycine moiety in the presence of triethylamine. A subsequent intramolecular cyclization of the intermediate **A** yields, after loss of one molecule of water, compound **4** (**Scheme 7**).



Scheme 7. Mechanism for the formation of trifluoromethylated 2-pyridone **4**



Scheme. 8

2-(1*H*)-Pyridinone moiety is a crucial structural component of numerous biologically active natural products. Therefore, the 2-(1*H*)-pyridinone system is a common intermediate for the synthesis of a wide variety of nitrogen heterocycles boasting a broad spectrum of biological activities.[38] In particular, they constitute the skeleton of elfamycin antibiotics[39] and the antifungal compounds ilicolicin.[40] Simple 2-(1*H*)-pyridinones find applications in pharmacology due to their antimicrobial activity.[41]

In order to confirm the necessity of the trifluoroacetyl group in **2** on the effectiveness of this reaction, the comparison with non-fluorinated compounds **5** is interesting. Attempts to synthesis non-fluorinated systems showed that compound **5** does not provide, according to conditions described previously, the non-fluorinated derivatives of the pyrrole **6** and 2-(1*H*)-pyridinone **7** waited (**Scheme 8**). These results can be explained by the presence of the fluorine atom in the structures of the obtained fluorinated products, which makes changes on the reactivity of the molecules due to its potent physico-chemical and biological properties.[6]

3. Conclusion

The present work was undertaken to apply a new and efficient synthesis of fluorinated heterocyclic systems using a highly functionalized substrate named DAMFA **1**. The adopted method provides a facile and convenient access to an enamine-dione **2** from DAMFA **1**, which are useful precursor of fluorine-containing pyrrole **3** and 2-(1*H*)-pyridinone **4**. The synthetic route involved a Michael addition/heterocyclization reaction of the fluorinated 1,3-difuctional compounds and building-blocks as starting materials. On the other hand, work is still in hand with an aim of more functionalizing the 2-(1*H*)-pyridinone and pyrrole rings in order to approach towards biologically active compounds.

4. Experimental

4.1 Materials and Methods

Melting points were taken on a Stuart Scientific melting point apparatus (smp3) and were uncorrected. IR spectra were recorded on a BOMEM MB Series apparatus. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a Bruker AC 300 spectrometer. Chemical shifts are expressed in ppm from TMS (^{1}H and ^{13}C) as internal reference. Mass spectra (EIMS) were recorded on a Micromass GCT spectrometer. Elemental analyses were performed with a Perkin Elmer CHN 2400 analyser. Thin layer chromatography (TLC) was carried out on aluminium-baked Merck silica gel 60 F254. Column chromatography was performed on silica gel.

4.2 General procedure

*4.2.1 Synthesis of enaminedione **2** from DAMFA **1***

Triethylamine (488 µL, 3.45 mmol) and a solution of DAMFA **1 (**1000 mg, 3.44 mmol) in acetic acid (1.5 mL) were added subsequently at 0 °C to a mixture of ethyl glycinate hydrochloride (485 mg, 3.45 mmol) in acetic acid (15 mL). This mixture was stirred at 100 °C for 3 h (the reaction was followed by TLC), then cooled, and poured into water (100 mL). The aqueous layer was extracted with CH_2Cl_2 (3×30 mL), the combined organic phases were dried over anhydrous Na_2SO_4, and the solvent was evaporated under vacuum. Chromatography of the residue on silica gel and elution with CH_2Cl_2/cyclohexane (7:3) afforded 1015 mg of enaminedione **2**.

[4,4,4-Trifluoro-3-oxo-2-(2,2,2-trifluoro-acetyl)-but-1-enylamino]-acetic acid ethyl ester 2

Brown oil; 92 %; IR-ATR (cm^{-1}): 2996, 1744, 1670, 1612, 1571, 1267, 1193, 1143; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.31 (t, $^{3}J_{H-H}$ = 7.1 Hz, 3H; CH_3), 4.24 (s, 2H; CH_2), 4.32 (q, ^{3}J = 7.1 Hz, 2H; CH_2O), 7.94 (d, ^{3}J = 14 Hz, 1H; HC=), 10.90 (br s, 1H; NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.8, 50.6, 62.8, 101.6, 116.2 (q, $^{1}J_{C-F}$ = 285 Hz, CF_3), 116.7 (q, $^{1}J_{C-F}$ = 291 Hz, CF_3), 162.4, 167.1, 175.3 (q, $^{2}J_{C-F}$ = 34 Hz, C=O), 180.4 (q, $^{2}J_{C-F}$ = 37 Hz, C=O); ^{19}F NMR (235 MHz, $CDCl_3$): δ -70.4 (s, 3F, CF_3), -74.4 ppm (s, 3F, CF_3); EIMS, *m/z*: 321 $[M]^+$ (13), 252 (100), 248 (48), 178 (96), 128 (15), 110 (14); Anal. Calcd for $C_{10}H_9F_6NO_4$: C, 37.40; H, 2.82; N, 4.36; Found: C, 37.34; H, 2.92; N, 4.47.

4.2.2 Synthesis of pyrrole derivative

A mixture of enaminedione **2** (960 mg, 3 mmol) and triethylamine (425 µL, 3 mmol) in acetonitrile (15 mL) was stirred for 24 h at r.t (25 °C). The mixture was then evaporated and the residue was purified by chromatography on silica gel and elution was realized with a mixture of CH_2Cl_2/cyclohexane (8:2) to afford 790 mg of pyrrole **3**.

4-(2,2,2-Trifluoro-acetyl)-3-trifluoromethyl-1H-pyrrole-2-carboxylic acid ethyl ester 3

Yellow oil; 87 %; IR-ATR (cm^{-1}): 3383, 1744, 1679, 1604, 1218, 1143, 1036; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.38 (t, ^{3}J = 7.2 Hz, 3H, CH_3), 4.44 (q, ^{3}J = 7.2 Hz, 2H, CH_2O), 7.70 (s, 1H, H-5), 10.46 (br s, 1H; NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9, 62.8, 111.2, 116.2 (q, $^{1}J_{C-F}$ = 285 Hz, CF_3), 118.1, 121.2 (q, $^{1}J_{C-F}$ = 272 Hz, CF_3), 129.6 (q, $^{2}J_{C-F}$ = 34 Hz, C-3), 142.4, 159.2, 174.8 (q, $^{2}J_{C-F}$ = 36 Hz, C=O); EIMS, m/z: 303 $[M]^+$ (13), 258 (9), 234 (62), 188 (100), 130 (72); HRMS Calcd for $C_{10}H_7F_6NO_3$: 303.0330, Found : 303.0330.

4.2.3 Synthesis of 2-(1H)-pyridinone derivative

To a solution of enaminedione **2** (800 mg, 2.5 mmol) and ethyl glycinate hydrochloride (420 mg, 3 mmol) in acetonitrile (15 mL), was added dropwise triethylamine (710 µL, 5 mmol) at 0 °C. After stirring for 14 h at r.t (25 °C), the solvent was evaporated under vacuum. Chromatography of the residue on silica gel and elution with CH_2Cl_2 afforded 680 mg of 2-(1*H*)-pyridinone **4**.

[3-Amino-2-oxo-5-(2,2,2-trifluoroacetyl)-4-trifluoromethyl-2H-pyridin-1-yl]-acetic acid ethyl ester 4

White solid; 76 %; mp 132-135 °C; IR-ATR (cm^{-1}): 3366, 1745, 1665, 1604, 1266, 1208, 1142; ^1H NMR (300 MHz, $CDCl_3$): δ 1.31 (t, ^3J = 7.2 Hz, 3H; CH_3), 4.28 (q, ^3J = 7.2 Hz, 2H; CH_2O), 4.72 (s, 2H; CH_2), 5.53 (br s, 2H; NH_2), 7.23 (s, 1H; H-6); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.7, 51.1, 62.3, 103.5 (q, $^2J_{C-F}$ = 33 Hz, C-4), 111.3, 115.7 (q, $^1J_{C-F}$ = 289 Hz, CF_3), 123.5 (q, $^1J_{C-F}$ = 272 Hz, CF_3), 129.3, 137.9, 157.3, 166.4, 178.6 (q, $^2J_{C-F}$ = 36 Hz, C=O); ^{19}F NMR (235 MHz, $CDCl_3$): δ -58.1 (s, 3F, CF_3), -72.2 (s, 3F, CF_3); EIMS, m/z: 360 $[M]^+$ (100), 291 (82), 263 (9); Anal. Calcd for $C_{12}H_{10}F_6N_2O_4$: C, 40.01; H, 2.80; N, 7.78; Found: C, 40.06; H, 2.84; N, 7.97.

Supplementary materials: Supplementary data supporting the outcomes of this research are available via the "Supplementary information" section of this article's webpage.

Acknowledgement

The authors acknowledge the Department of Chemistry, Chouaib Doukkali University (El Jadida-Morocco) for providing facilities to carry out this research work, the National Center for Scientific Research and Technical (CNRST) for performing spectral analysis of the compounds.

References

1. Meyer F. (**2016)** Trifluoromethyl nitrogen heterocycles: synthetic aspects and potential biological targets. *Chem. Commun.*, 52(15), 3077-3094. doi:10.1039/C5CC09414C
2. Shabir Gh., et al. (**2023**) Chemistry and Pharmacology of Fluorinated Drugs Approved by the FDA (2016-2022). *Pharmaceuticals*, 16, 1162. doi.org/10.3390/ph16081162
3. Liu Y, Tian Q, Ge J, Wu X, Li Z, Cheng G. (**2024**) Recent advances in the synthesis of trifluoromethyl-containing heterocyclic compounds via trifluoromethyl building blocks. *Org. Biomol. Chem*. 22(31), 6246-6276. doi:10.1039/D4OB00877D
4. Prakash C, Singh R. (**2024**) Synthesis of fluorinated six-membered nitrogen heterocycles using microwave irradiation. *Chem. Heterocycl. Compd*. 60(5), 216-229. doi:10.1007/s10593-024-03323-1
5. Kirk KL. (**2006)** Fluorine in medicinal chemistry: Recent therapeutic applications of fluorinated small molecules. *J. Fluor. Chem*.,127(8), 1013-1029. doi:10.1016/j.jfluchem.2006.06.007
6. Bégué JP, Bonnet-Delpon D. (**2006)** Recent advances (1995–2005) in fluorinated pharmaceuticals based on natural products. *J. Fluor. Chem*., 127(8), 992-1012. doi:10.1016/j.jfluchem.2006.05.006
7. Kalar PL, Agrawal S, Kushwaha S, Gayen S, Das K. (**2023)** Recent Developments on Synthesis of Organofluorine Compounds Using Green Approaches. *Curr. Org. Chem*., 27(3), 190-205. doi:10.2174/1385272827666230516100739
8. Shabir G, Saeed A, Zahid W, et al. (**2023**) Chemistry and Pharmacology of Fluorinated Drugs Approved by the FDA (2016–2022). *Pharmaceuticals*., 16(8), 1162. doi:10.3390/ph16081162
9. Caron S. (**2020**) Where Does the Fluorine Come From: A Review on the Challenges Associated with the Synthesis of Organofluorine Compounds. *Org. Process. Res. Dev*., 24(4), 470-480. doi:10.1021/acs.oprd.0c00030
10. Kondratov IS, Dolovanyuk VG, Tolmachova NA, et al. (**2012)** Reactions of β-alkoxyvinyl polyfluoroalkyl ketones with ethyl isocyanoacetate and its use for the synthesis of new polyfluoroalkyl pyrroles and pyrrolidines. *Org. Biomol. Chem*., 10 (44), 8778. doi:10.1039/c2ob26176f
11. Soufyane M, Mirand C, Levy J. (**1993**) Synthesis of some fluorinated nitrogen heterocycles from (diethylaminomethylene) hexafluoroacetylacetone (DAMFA). *Tetrahedron Lett*., 34 (48), 7737-7740. doi:10.1016/S0040-4039(00)61552-6
12. Schlosser M. (**2006)** CF3 -Bearing Aromatic and Heterocyclic Building Blocks. *Angew. Chem. Int. Ed.,* 45 (33), 5432-5446. doi:10.1002/anie.200600449
13. Mustapha S, Broek SVD, Layachi K. (**1999**) Synthesis of Trifluoromethylpyrimidines from Fluorinated Enaminodiketones. *Heterocycles Int. J. Rev. Commun. Heterocycl. Chem.*, 51 (10), 2445-2451.
14. Obydennov DL, Chernyshova EV, Sosnovskikh VYa. (**2020)** Acyclic Enaminodiones in the Synthesis of Heterocyclic Compounds. *Chem. Heterocycl. Compd*., 56 (10), 1241-1253. doi:10.1007/s10593-020-02807-0
15. Ganesh BH, Raj AG, Aruchamy B, Nanjan P, Drago C, Ramani P. (**2024**) Pyrrole: A Decisive Scaffold for the Development of Therapeutic Agents and Structure-Activity Relationship. *Chem. Med. Chem*. 19(1), e202300447. doi:10.1002/cmdc.202300447

16. Sahu B, Sahu R, Gidwani B, Mishra A. (**2024**) Pyrrole: An Essential Framework in the Development of Therapeutic Agents and Insightful Analysis of Structure-Active Relationships. *Chem. Select*. 9(31), e202401604. doi:10.1002/slct.202401604
17. Verma KK, Kapoor S, Kushwaha VK, Mishra A, Upadhyay A. (**2024**) Synthesis and Biological Activity of 2-pyridone Derivatives: A Mini Review. *Lett. Drug. Des. Discov*. 21(10), 1617-1631. doi:10.2174/1570180820666230417084456
18. Jeelan Basha N, Basavarajaiah SM, Shyamsunder K. (**2022**) Therapeutic potential of pyrrole and pyrrolidine analogs: an update. *Mol. Divers*. 26(5), 2915-2937. doi:10.1007/s11030-022-10387-8
19. Hodyna D, Klipkov A, Kachaeva M, et al. (**2024**) In Silico Design and In Vitro Assessment of Bicyclic Trifluoromethylated Pyrroles as New Antibacterial and Antifungal Agents. *Chem. Biodivers*.21(8), e202400638. doi:10.1002/cbdv.202400638
20. Kushch SO, Goryaeva MV, Burgart YaV, et al. (**2022**) Facile synthesis of 6-organyl-4-(trifluoromethyl)pyridin-2(1H)-ones and their polyfluoroalkyl-containing analogs. *Russ. Chem. Bull*. 71(8), 1687-1700. doi:10.1007/s11172-022-3579-y
21. Gupta J. and Sashidhara K. V. (**2023**) Recent advances in natural products targeting α-synuclein aggregation or clearance in Parkinson's disease. *Eur. J. Med. Chem.* 9, 100114. doi.org/10.1016/j.ejmcr.2023.100114
22. Williams V, Cory TJ. (**2025**) Doravirine/islatravir for the treatment of HIV. *Expert. Opin. Pharmacother*. 26(1), 9-15. doi:10.1080/14656566.2024.2440000
23. Curreli F, Ahmed S, Benedict Victor SM, et al. (**2020**) Preclinical Optimization of gp120 Entry Antagonists as anti-HIV-1 Agents with Improved Cytotoxicity and ADME Properties through Rational Design, Synthesis, and Antiviral Evaluation. *J. Med. Chem*. 63(4), 1724-1749. doi:10.1021/acs.jmedchem.9b02149
24. Ammar YA, Ismail MMF, El-Sehrawi HM, Noaman E, Bayomi AH, Shawer TZ. (**2006**) Novel Pirfenidone Analogues: Synthesis of Pyridin-2-ones for the Treatment of Pulmonary Fibrosis. *Arch. Pharm. (Weinheim)*.339(8), 429-436. doi:10.1002/ardp.200600017
25. Olszewska P. (**2020**) A novel trifluoromethyl 2-phosphonopyrrole analogue inhibits human cancer cell migration and growth by cell cycle arrest at G1 phase and apoptosis. *Euro. J. Pharm.* 871, 15, 172943. doi.org/10.1016/j.ejphar.2020.172943
26. Wang D, Tian YT, Nie J, Jasiński M, Tang X, Ma JA. (**2023**) Traceless Directing Group Enabled One-Pot Regiospecific Synthesis of 2,3-Diaryl-4-Fluoropyrroles. *Adv. Synth. Catal*. 365(19), 3260-3264. doi:10.1002/adsc.202300625
27. Mahía A, Peña-Díaz S, Navarro S, et al. (**2021**) Design, synthesis and structure-activity evaluation of novel 2-pyridone-based inhibitors of α-synuclein aggregation with potentially improved BBB permeability. *Bioorganic Chem*. 117:105472. doi:10.1016/j.bioorg.2021.105472
28. Marrec O. (**2009**) Synthèse de pyrroles fluoroalkylés : nouvelles réactions de trifluorométhoxylation nucléophile : application à la synthèse d'hétérocycles trifluorométhoxylés. Université Claude Bernard - Lyon I.
29. Zachow LL, Mittersteiner M, Aquino EC, Bonacorso HG, Martins MAP, Zanatta N. (**2021**) Synthesis of Highly Functionalized 4-Amino-2-(trifluoromethyl)-1H-pyrroles. *Synthesis*., 53: 2841-2849. doi:10.1055/a-1503-9057
30. Muzalevskiy V, Shastin A, Balenkova E, Haufe G, Nenajdenko V. (**2009**) Synthesis of Trifluoromethyl Pyrroles and Their Benzo Analogues. *Synthesis*., 2009 (23), 3905-3929. doi:10.1055/s-0029-1217080
31. Hayashi T, Nakashima Y, Ito K, et al. (**2003**) Synthesis, Structure, and Chemical Property of the First Fluorine-Containing Porphycene. *Org. Lett*. 5(16), 2845-2848. doi:10.1021/ol0348452
32. Okada E, Masuda R, Hojo M, Inoue R. (**1992**) A Facile and Convenient Synthetic Method for N-β-Trifluoroacetylvinyl Amino Acid Esters, α-Aminoacetophenones and Aminoacetonitriles as Potentially Useful Precursors of Fluorine-Containing Pyrroles. *Synthesis*. (06), 533-535. doi:10.1055/s-1992-26155
33. Andrew RJ, Mellor JM. (**2000**) Synthesis of Trifluoromethylpyrroles and Related Heterocycles from 4-Ethyloxy-1,1,1-trifluorobut-3-ene-2-one. *Tetrahedron*., 56 (37), 7267-7272. doi:10.1016/S0040-4020(00)00598-6
34. Kuhn DG, Kamhi VM, Furch JA, Diehl RE, Lowen GT, Kameswaran V. (**1994**) The synthesis of pyrroles with insecticidal activity. *Pestic. Sci*. 41(3), 279-286. doi:10.1002/ps.2780410312
35. Okada E, Masuda R, Hojo M, Yoshida R. (**1992**) A facile and convenient synthetic method for 3-trifluoroacetyl-pyrroles. *Facile Conv Synth Method 3-Trifluoroacetyl-Pyrroles*.34(7), 1435-1441.
36. Schreiber SL. (**1980**) Hydrogen transfer from tertiary amines to trifluoroacetic anhydride. *Tetrahedron Lett*. 21 (11), 1027-1030. doi:10.1016/S0040-4039(00)78830-7
37. Sanin AV. (**1998**) A Novel Synthesis of Trifluoromethyl Enones and Enediones. *Synthesis*., 1998(06), 842-846. doi:10.1055/s-1998-2077
38. Amer MMK, Aziz MA, Shehab WS, Abdellattif MH, Mouneir SM. (**2021)** Recent advances in chemistry and pharmacological aspects of 2-pyridone scaffolds. *J. Saudi. Chem. Soc*., 25 (6), 101259. doi:10.1016/j.jscs.2021.101259
39. Zhang, Q., Liu, X., Xin, X., Zhang, R., Liang, Y., & Dong, D. (2014). Formal [4+ 2] annulation of enaminones and cyanomethyl sulfur ylide: one-pot access to polysubstituted pyridin-2 (1 H)-ones. *Chem. Commun.*, 50 (97), 15378–15380. doi:10.1039/c4cc06665k
40. Hurtado-Rodríguez D, Salinas-Torres A, Rojas H, Becerra D, Castillo JC. (**2022**) Bioactive 2-pyridone-containing heterocycle syntheses using multicomponent reactions. *RSC Adv.*, 12 (54), 34965-34983. doi:10.1039/D2RA07056A

41. Sangwan S, Yadav N, Kumar R, et al. (**2022**) A score years' update in the synthesis and biological evaluation of medicinally important 2-pyridones. *Eur. J. Med. Chem*., 232: 114199. doi:10.1016/j.ejmech.2022.114199