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Three-component synthesis of substituted β-(trifluoromethyl)pyrroles via Grob cyclization of 1,1,1-trifluoro-3-nitrobut-2-ene with 1,3-dicarbonylic compounds and ammonia or primary amines

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ABSTRACT

A variety of substituted β-(trifluoromethyl)pyrroles were easily synthesized in good yields by a one-pot, three-component Grob cyclization of 1,1,1-trifluoro-3-nitrobut-2-ene with 1,3-dicarbonyls (ethyl acetoacetate, acetylacetone, benzoylacetone) and ammonia or primary aliphatic amines.

1. Introduction

Much attention has been addressed to trifluoromethylated heterocyclic compounds because they often show unique biological and physiological activities [1]. In particular, trifluoromethyl-substituted pyrroles and other five-membered heterocycles have drawn considerable attention [2]. The search for a simple and efficient access to such compounds with a CF_3 group at a specific position is one of the important goals in this area. However, there are a limited number of regioselective syntheses of CF_3-containing heteroaromatic compounds in good yield. In the case of β-(trifluoromethyl)pyrroles, only a few synthetic concepts have been developed [1e].

These compounds have been synthesized by the modified Knorr condensation from ethyl trifluoroacetoacetate and 1,3-dicarbonyls in strong acid media [3]. Reaction of α-(trifluoromethyl)alkenyl sulfones with ethyl isocyanoacetate in the presence of a base gave 4-(trifluoromethyl)pyrrole-2-carboxylates in moderate to good yields [4]. A one-step formation of the pyrrole ring from Michael acceptors and tosylmethylisocyanide under basic conditions was reported by van Leusen et al. [5]. The application of this procedure to the alkyl (*E*)-4,4,4-trifluorobutenoates led to the corresponding 4-(trifluoromethyl)pyrrole-3-carboxylates [6]. Ogoshi and coworkers applied this procedure to the preparation of 3-acetyl-4-(polyfluoroalkyl)pyrroles in somewhat lower yields [7]. 1,3-Dipolar cycloaddition of munchnones (1,3-oxazolium 5-olates) to β-chloro-β-(trifluoromethyl)vinyl phenyl ketone, butyl β-chloro-γ,γ,γ-trifluorocrotonate and polyfluoroacetylenic esters proceeds in a regiospecific manner under mild reaction conditions, followed by simultaneous decarboxylation to afford 4-(polyfluoroalkyl)pyrrole-3-carboxylate derivatives [8]. Cyclodehydration of the products obtained by oxygen-nitrogen exchange reaction of 4-alkoxy-1,1,1-trifluoro-3-buten-2-ones with esters of α-aminoacids, α-aminoacetophenone and 2,2-dimethoxyethylamine into fluorine-containing pyrroles is also described [9]. In addition, the introduction of a polyfluoroalkyl group in moderate yield was achieved by 1,2-addition of Me_3SiCN to β-alkoxyvinyl polyfluoroalkyl ketones, followed by reduction with $LiAlH_4$ and subsequent hydrolysis with intramolecular cyclization [10]. Although these reaction sequences have been developed for the regioselective introduction of a R^F group in the pyrrole ring, there are remaining problems to be solved, such as the handling of the materials and availability of reagents. Herein we wish to demonstrate utility of readily available (*E*)-1,1,1-trifluoro-3-nitrobut-2-ene **1** [11] as a novel building block for the construction of 4-(trifluoromethyl)-pyrroles bearing different electron-withdrawing substituents at the 3-position via addition of push–pull enamines.

Nucleophilic addition of enamines to conjugated nitroalkenes is an efficient method for preparation of cyclobutanes, 1,2-oxazine *N*-oxides and nitroalkylated enamines or γ-nitroketones [12] that, in

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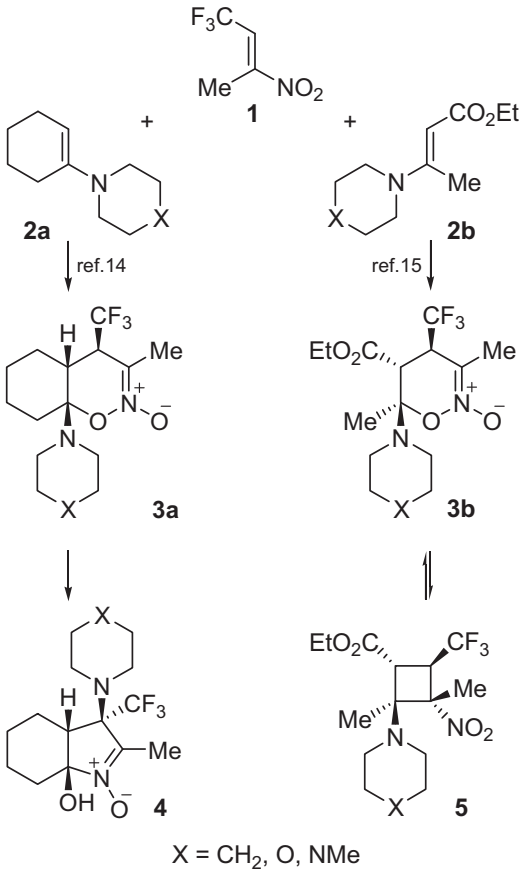


Scheme 1. Compounds **3–5** obtained previously from nitrobutene **1**.

turn, are widely used in organic synthesis [12,13]. We have recently investigated the reaction of nitrobutene **1** with tertiary enamines **2a,b** and described the first example of spontaneous ring-contraction–rearrangement of 1,2-oxazine *N*-oxides **3a** into 1-pyrroline *N*-oxides **4** [14] and a new type of ring-ring tautomerism between 1,2-oxazine *N*-oxides **3b** and cyclobutanes **5** [15] (Scheme 1).

In this paper we report a general method for the preparation of β-(trifluoromethyl)pyrroles, which is based on the three-component variant of Grob cyclization. In this pyrrole synthesis, nitroalkenes are commonly employed because the nitro group can act both as a powerful stabilizer of the intermediate anion and as a good nucleofuge in the aromatization forming a pyrrole ring. In view of the utility of this reaction in synthetic chemistry [16], we envisioned the use of nitrobutene **1** as a synthon for trifluoromethylated pyrroles, some of which represent a new class of insect control agents [17]. Although there is one report on the preparation of β-(trifluoromethyl)pyrroles by reaction of active methylene compounds with 3,3,3-trifluoro-1-nitropropene, followed by the reduction of the nitro group and subsequent cyclization [18], the use of nitrobutene **1** in the synthesis of CF_3-containing heterocycles has not been reported, except for compounds **3** and **4**.

2. Results and discussion

We found that nitrobutene **1**, which is easily obtainable from fluoral hydrate and nitroethane [11], reacted with 1,3-dicarbonyls (ethyl acetoacetate, acetylacetone and benzoylacetone) and primary aliphatic amines at reflux in ethanol to give β-(trifluoromethyl)pyrroles **7** in 42–75% yields. In most cases, the reaction was complete after 1 h and the products could be isolated by column chromatography over silica gel. The similar reaction of 25% aqueous solution of ammonia afforded *N*-unsubstituted pyrroles **7a,h,o**, albeit in lower yields (24–28%). The progress of the reaction was monitored by ^1H and ^{19}F NMR spectroscopy, and the results are summarized in Table 1. In the case of benzoylacetone, the regiochemistry was controlled by the more reactive acetyl group, which underwent preferential attack on the amine. The structure of the benzoyl derivative **7q** was confirmed by X-ray crystal structure analysis (Fig. 1) [19]. A plausible pathway leading to the formation of these compounds via intermediate aminoenones **6** is outlined in Scheme 2 [16b]. In contrast to its homologue **1**, (*E*)-3,3,3-trifluoro-1-nitropropene, lacking the methyl group, failed to give the corresponding pyrroles on reaction with 1,3-dicarbonyls and aliphatic amines under the same conditions. This indicated that cyclization in the case of a primary nitronate is not efficient.

Table 1
Synthesis of compounds **7a–r**.

7	R^1	R^2	Yield (%)[a]
a	OEt	H	28
b	OEt	Me	66
c	OEt	Et	42
d	OEt	$HO(CH_2)_2$	50
e	OEt	Bn	75
f	OEt	$Ph(CH_2)_2$	69
g	OEt	$3,4\text{-}(MeO)_2C_6H_3(CH_2)_2$	57
h	Me	H	24
i	Me	Me	48
j	Me	Et	51
k	Me	$HO(CH_2)_2$	66
l	Me	Bn	64
m	Me	$Ph(CH_2)_2$	52
n	Me	$3,4\text{-}(MeO)_2C_6H_3(CH_2)_2$	48
o	Ph	H	25[b]
p	Ph	Bn	54
q	Ph	$Ph(CH_2)_2$	50
r	Ph	$3,4\text{-}(MeO)_2C_6H_3(CH_2)_2$	48

[a] Isolated yield.
[b] In propan-1-ol.

This approach is the first example of successful three-component Grob synthesis of fully substituted β-(trifluoromethyl)pyrroles **7** and has advantages with regard to ease of operation and the ready availability of starting materials. It should be noted that primary and secondary push–pull enamines **6** could be employed directly under these conditions to give pyrroles **7** in 40–65% yields, however, a one-pot three-component reaction is much more convenient. Note that in contrast to enamines **6**,

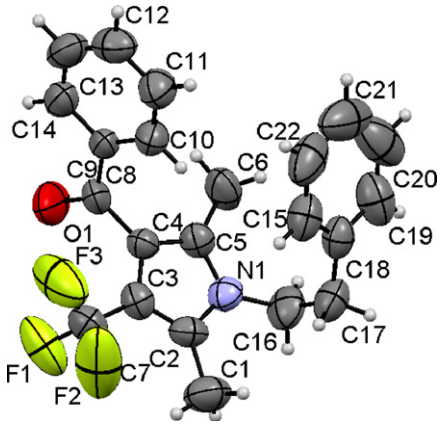
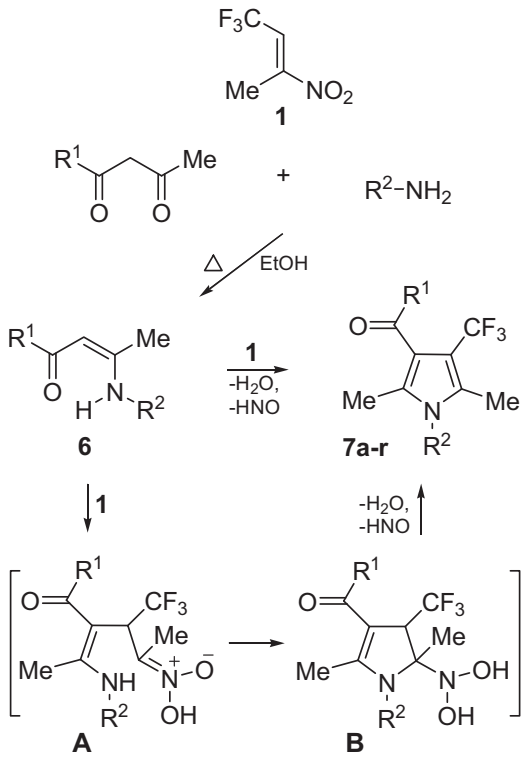


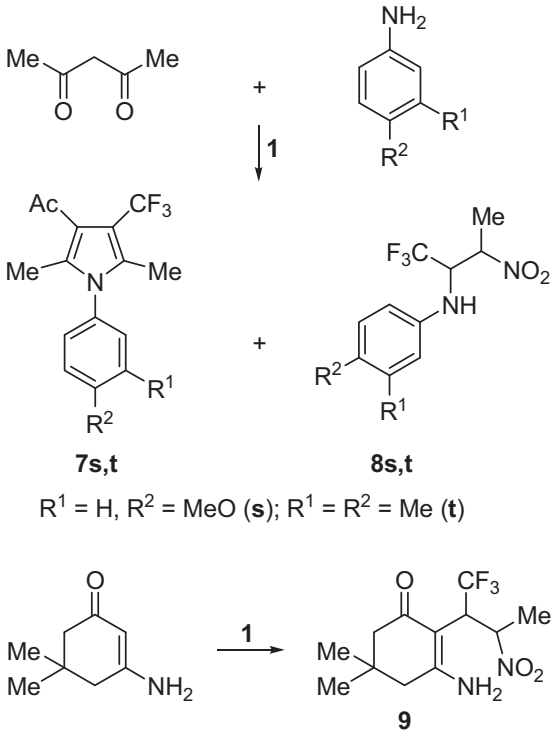
Fig. 1. Molecular structure of pyrrole **7q**.



Scheme 2. Synthesis of β-(trifluoromethyl)pyrroles **7a–r**.

tertiary push–pull enamines **2b**, lacking the labile hydrogen atom, react with **1** to give compounds **3b** and **5** (Scheme 1).

The reaction slightly depends on the substituent of the active methylene compound. One possible explanation is a greater capacity in delocalizing the electron pair of enamine nitrogen atom onto the acyl group in intermediates **A** (R^1 = Me, Ph) than in **A**, which bearing ethoxycarbonyl substituent. This delocalization may prevent nucleophilic intramolecular attack and ring closure [16f]. Substituents R^2 on amine had no great effect on the reaction course to give pyrroles **7a–r** (Scheme 2, Table 1).



Scheme 3. Reactions of **1** with anilines and dimedone enamine.

The above results prompted us to examine the reaction with aromatic amines. However, in the case of nitroalkene **1**, acetylacetone and anisidine or 3,4-xylidine, the reaction resulted in preferential formation of the previously known diastereomeric adducts **8s,t** [20], with formation of β-(trifluoromethyl)pyrroles **7s,t** in 18–27% yields, based on the ^{1}H NMR spectra of a crude reaction mixture. All our attempts to obtain **7s,t** as the sole products were fruitless. Thus, β-(trifluoromethyl)pyrroles from anilines are formed more slowly than the corresponding Michael adducts. A similar reaction of dimedone enamine with **1** yielded exclusively compound **9** in 31% yield as a 75:25 mixture of diastereomers without formation of any detectable amounts of the corresponding pyrrole (Scheme 3).

The structures of pyrroles **7** were confirmed by elemental analysis, ^{1}H, ^{19}F, ^{13}C NMR, and IR spectroscopy. In the ^{19}F NMR spectra the trifluoromethyl group appeared as a quartet at δ 107.4–108.6 ppm (C_6F_6) with $^5J_{F,H}$ = 1.7–2.5 Hz for **7a–g** and 109.4–111.1 ppm with $^5J_{F,H}$ = 1.3–1.5 Hz for **7o–r**; the CF_3 group of **7i–n** manifests itself as a slightly broadened singlet at δ 110.5–111.0 ppm. The ^{13}C NMR spectra of **7b,f,n** showed that the C-3, C-5 and C-4 atoms were coupled with the fluorine atoms of the trifluoromethyl group with $^3J_{C,F}$ = 1.7–1.8, 3.5–3.7 Hz and $^2J_{C,F}$ = 34.7–35.1 Hz, respectively; the Me-5 group was also coupled with $^4J_{C,F}$ = 2.7–3.1 Hz. The intensive absorption bands in the IR spectra in the ranges 1684–1706 cm^{-1} and 1616–1665 cm^{-1} were attributed to the ester and ketone carbonyl groups.

3. Conclusion

In conclusion, we have shown that the three-component Grob cyclization of (*E*)-1,1,1-trifluoro-3-nitrobut-2-ene with 1,3-dicarbonyls and primary aliphatic amines provides a simple and convenient approach to substituted 4-(trifluoromethyl)pyrroles bearing different electron-withdrawing substituents at the 3-position. This new synthesis of β-(trifluoromethyl)pyrroles proceeds under mild conditions and the starting materials are readily available.

4. Experimental

NMR spectra were recorded on a Bruker DRX-400 (^{1}H – 400 MHz, ^{13}C – 100 MHz, and ^{19}F – 376 MHz) and AVANCE-500 (^{1}H – 500 MHz and ^{13}C – 126 MHz) spectrometers in DMSO-d_6 and $CDCl_3$ with TMS and C_6F_6 as internal standards, respectively. IR spectra were recorded on a Perkin-Elmer Spectrum BX-II instrument as KBr discs. Elemental analyses were performed at the Microanalysis Services of the Institute of Organic Synthesis, Ural Branch, Russian Academy of Sciences. All solvents used were dried and distilled per standard procedures. The starting (*E*)-1,1,1-trifluoro-3-nitrobut-2-ene **1** was prepared according to described procedure in 53% overall yield [11].

4.1. General procedure for the synthesis of pyrroles 7a–r

A solution of the corresponding 1,3-dicarbonyl (2.0 mmol), amine (2.0 mmol) and nitroalkene **1** (0.31 g, 2.0 mmol) in ethanol (1 mL) was refluxed for 1 h. After removal of the solvent under reduced pressure, the residue was chromatographed on silica gel (eluted with chloroform) to give compound **7** as an yellow oil or solid. The solid formed was recrystallized from the corresponding solvent to yield a colourless powder or needles.

*4.1.1. 3-Ethoxycarbonyl-2,5-dimethyl-4-(trifluoromethyl)-1H-pyrrole (**7a**)*

Yield 28%, mp 151–152 °C (CH_2Cl_2–hexane), colourless needles; IR (KBr) 3312, 1687, 1608, 1559, 1544, 1478, 1449 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.34 (t, J = 7.1 Hz, 3H, Me), 2.32 (q, $^5J_{H,F}$ = 2.4 Hz, 3H, Me-5), 2.45 (s, 3H, Me-2), 4.28 (q, J = 7.1 Hz, 2H, CH_2O), 8.08 (br s, 1H, NH); ^{19}F NMR (376 MHz, $CDCl_3$) δ 107.4 (q, $^5J_{F,H}$ = 2.5 Hz, CF_3). Anal. Calcd for $C_{10}H_{12}F_3NO_2$: C, 51.07; H, 5.14; N, 5.96. Found: C, 50.84; H, 5.03; N, 5.85.

*4.1.2. 3-Ethoxycarbonyl-1,2,5-trimethyl-4-(trifluoromethyl)-1H-pyrrole (**7b**)*

Yield 66%, mp 75–76 °C (60% propan-1-ol), colourless needles; IR (KBr) 1706, 1583, 1539, 1460, 1441 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.33 (t, J = 7.1 Hz, 3H, Me), 2.32 (q, $^5J_{H,F}$ = 1.7 Hz, 3H, Me-5), 2.47 (s, 3H, Me-2), 3.41 (s, 3H, MeN), 4.27 (q, J = 7.1 Hz, 2H, CH_2O); ^{19}F NMR (376 MHz, $CDCl_3$) δ 108.4 (q, $^5J_{F,H}$ = 1.7 Hz, CF_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 11.0 (q, $^4J_{C,F}$ = 3.1 Hz, Me-5), 11.4, 14.0, 30.3, 59.9, 109.1 (q, $^2J_{C,F}$ = 35.1 Hz, C-4), 109.7 (q, $^3J_{C,F}$ = 1.7 Hz, C-3), 124.1 (q, $^1J_{C,F}$ = 267.1 Hz, CF_3), 129.8 (q, $^3J_{C,F}$ = 3.5 Hz, C-5), 136.1 (C-2), 164.4 (C=O). Anal. Calcd for $C_{11}H_{14}F_3NO_2$: C, 53.01; H, 5.66; N, 5.62. Found: C, 52.88; H, 5.59; N, 5.65.

*4.1.3. 3-Ethoxycarbonyl-1-ethyl-2,5-dimethyl-4-(trifluoromethyl)-1H-pyrrole (**7c**)*

Yield 42%, yellow oil; IR (KBr) 1704, 1578, 1548, 1436, 1408 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.26 (t, J = 7.3 Hz, 3H, *Me*CH_2), 1.33 (t, J = 7.1 Hz, 3H, *Me*CH_2O), 2.34 (q, $^5J_{H,F}$ = 1.9 Hz, 3H, Me-5), 2.48 (s, 3H, Me-2), 3.87 (q, J = 7.3 Hz, 2H, CH_2N), 4.27 (q, J = 7.1 Hz, 2H, CH_2O); ^{19}F NMR (376 MHz, $CDCl_3$) δ 108.6 (q, $^5J_{F,H}$ = 1.9 Hz, CF_3). Anal. Calcd for $C_{12}H_{16}F_3NO_2$: C, 54.75; H, 6.13; N, 5.32. Found: C, 54.73; H, 6.30; N, 5.44.

*4.1.4. 3-Ethoxycarbonyl-1-(2-hydroxyethyl)-2,5-dimethyl-4-(trifluoromethyl)-1H-pyrrole (**7d**)*

Yield 50%, yellow oil; IR (KBr) 3447, 1733, 1698, 1578, 1548, 1436, 1405 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.33 (t, J = 7.1 Hz, 3H, Me), 2.36 (q, $^5J_{H,F}$ = 1.8 Hz, 3H, Me-5), 2.49 (s, 3H, Me-2), 3.83, 4.00 (both t, J = 5.7 Hz, 2H, CH_2), 4.27 (q, J = 7.1 Hz, 2H, CH_2O); ^{19}F NMR (376 MHz, $CDCl_3$) δ 108.4 (q, $^5J_{F,H}$ = 1.8 Hz, CF_3). Anal. Calcd for $C_{12}H_{16}F_3NO_3$: C, 51.61; H, 5.78; N, 5.02. Found: C, 51.32; H, 6.08; N, 4.79.

*4.1.5. 1-Benzyl-3-ethoxycarbonyl-2,5-dimethyl-4-(trifluoromethyl)-1H-pyrrole (**7e**)*

Yield 75%, yellow oil; IR (KBr) 1705, 1651, 1601, 1583, 1548, 1434, 1407 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.35 (t, J = 7.1 Hz, 3H, Me), 2.25 (q, $^5J_{H,F}$ = 1.9 Hz, 3H, Me-5), 2.42 (s, 3H, Me-2), 4.30 (q, J = 7.1 Hz, 2H, CH_2O), 5.08 (s, 2H, CH_2), 6.89 (d, J = 7.2 Hz, 2H, Ph), 7.26–7.35 (m, 3H, Ph); ^{19}F NMR (376 MHz, $CDCl_3$) δ 108.5 (q, $^5J_{F,H}$ = 1.9 Hz, CF_3). Anal. Calcd for $C_{17}H_{18}F_3NO_2$: C, 62.76; H, 5.58; N, 4.31. Found: C, 62.53; H, 5.36; N, 4.74.

*4.1.6. 3-Ethoxycarbonyl-2,5-dimethyl-4-(trifluoromethyl)-1-phenethyl-1H-pyrrole (**7f**)*

Yield 69%, mp 90–91 °C (hexane), colourless powder; IR (KBr) 1687, 1647, 1595, 1550, 1499, 1455, 1430 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.34 (t, J = 7.1 Hz, 3H, Me), 2.20 (q, $^5J_{H,F}$ = 2.0 Hz, 3H, Me-5), 2.39 (s, 3H, Me-2), 2.88, 4.01 (both t, J = 7.6 Hz, 2H, CH_2), 4.28 (q, J = 7.1 Hz, 2H, CH_2O), 7.04–7.08 (m, 2H, Ph), 7.25–7.33 (m, 3H, Ph); ^{19}F NMR (376 MHz, $CDCl_3$) δ 108.5 (q, $^5J_{F,H}$ = 2.0 Hz, CF_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 10.8 (q, $^4J_{C,F}$ = 3.1 Hz, Me-5), 11.2, 14.0, 36.7, 45.1, 60.0, 109.5 (q, $^2J_{C,F}$ = 35.0 Hz, C-4), 110.1 (q, $^3J_{C,F}$ = 1.7 Hz, C-3), 124.1 (q, $^1J_{C,F}$ = 267.3 Hz, CF_3), 127.2, 128.7, 128.9, 129.4 (q, $^3J_{C,F}$ = 3.5 Hz, C-5), 135.7, 137.2, 164.5 (C=O). Anal. Calcd for $C_{18}H_{20}F_3NO_2$: C, 63.71; H, 5.94; N, 4.13. Found: C, 63.76; H, 5.88; N, 4.23.

*4.1.7. 3-Ethoxycarbonyl-1-(3,4-dimethoxyphenethyl)-2,5-dimethyl-4-(trifluoromethyl)-1H-pyrrole (**7g**)*

Yield 57%, mp 67–68 °C (hexane), colourless powder; IR (KBr) 1684, 1592, 1545, 1516, 1434 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.33 (t, J = 7.1 Hz, 3H, Me), 2.16 (q, 3H, Me-5, $^5J_{H,F}$ = 2.0 Hz), 2.32 (s, 3H, Me-2), 2.83 (t, J = 7.0 Hz, 2H, CH_2), 3.77 (s, 3H, MeO), 3.86 (s, 3H, MeO), 4.00 (t, J = 7.0 Hz, 2H, CH_2), 4.27 (q, J = 7.1 Hz, 2H, CH_2O), 6.31 (d, J = 1.9 Hz, 1H, H-2′), 6.63 (dd, J = 8.1, 1.9 Hz, 1H, H-6′), 6.79 (d, J = 8.1 Hz, 1H, H-5′); ^{19}F NMR (376 MHz, $CDCl_3$) δ 108.6 (q, $^5J_{F,H}$ = 2.0 Hz, CF_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 10.8 (q, $^4J_{C,F}$ = 3.1 Hz, Me-5), 11.2 (Me), 14.0 (Me), 36.1, 45.1, 55.8, 56.0, 60.0, 109.5 (q, $^2J_{C,F}$ = 35.0 Hz, C-4), 110.2 (q, $^3J_{C,F}$ = 1.8 Hz, C-3), 111.6, 112.0, 120.7, 124.1 (q, $^1J_{C,F}$ = 267.3 Hz, CF_3), 129.5 (q, $^3J_{C,F}$ = 3.5 Hz, C-5), 129.7, 135.8, 148.3, 149.2, 164.5 (C=O). Anal. Calcd for $C_{20}H_{24}F_3NO_4$: C, 60.14; H, 6.06; N, 3.51. Found: C, 59.97; H, 6.17; N, 3.59.

*4.1.8. 3-Acetyl-2,5-dimethyl-4-(trifluoromethyl)-1H-pyrrole (**7h**)*

Yield 24%, mp 212–213 °C (ethanol), colourless needles; IR (KBr) 3230, 3183, 1633, 1604, 1530, 1441, 1418 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.23 (q, $^5J_{H,F}$ = 2.6 Hz, 3H, Me-5), 2.32 (s, 3H, Me-2), 2.38 (s, 3H, Ac), 11.54 (br s, 1H, NH); ^{19}F NMR (376 MHz, $CDCl_3$) δ 111.0 (q, $^5J_{F,H}$ = 2.7 Hz, CF_3). Anal. Calcd for $C_9H_{10}F_3NO$: C, 52.69; H, 4.91; N, 6.83. Found: C, 52.59; H, 4.72; N, 6.69.

*4.1.9. 3-Acetyl-1,2,5-trimethyl-4-(trifluoromethyl)-1H-pyrrole (**7i**)*

Yield 48%, colourless crystals; IR (KBr) 1662, 1573, 1540, 1432 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.32 (q, $^5J_{H,F}$ = 1.8 Hz, 3H, Me-5), 2.35 (s, 3H, Me-2), 2.43 (q, $^6J_{H,F}$ = 1.2 Hz, 3H, Ac), 3.41 (s, 3H, MeN); ^{19}F NMR (376 MHz, $CDCl_3$) δ 110.6 (s, CF_3). Anal. Calcd for $C_{10}H_{12}F_3NO$: C, 54.79; H, 5.52; N, 6.39. Found: C, 54.59; H, 5.51; N, 6.35.

*4.1.10. 3-Acetyl-1-ethyl-2,5-dimethyl-4-(trifluoromethyl)-1H-pyrrole (**7j**)*

Yield 51%, yellow oil; IR (KBr) 1664, 1569, 1531, 1433, 1403 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, J = 7.3 Hz, 3H, *Me*CH_2), 2.34 (q, 3H, Me-5, $^5J_{H,F}$ = 1.8 Hz), 2.37 (s, 3H, Me-2), 2.44 (q, $^6J_{H,F}$ = 1.2 Hz, 3H, Ac), 3.86 (q, J = 7.3 Hz, 2H, CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ 110.7 (sept, $J_{F,H}$ = 1.4 Hz, CF_3). Anal. Calcd for $C_{11}H_{14}F_3NO$: C, 56.65; H, 6.05; N, 6.01. Found: C, 56.27; H, 6.10; N, 5.88.

*4.1.11. 3-Acetyl-1-(2-hydroxyethyl)-2,5-dimethyl-4-(trifluoromethyl)-1H-pyrrole (**7k**)*

Yield 66%, mp 73–74 °C (CH_2Cl_2–hexane), colourless powder; IR (KBr) 3330, 1639, 1568, 1528, 1432, 1396 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.00 (br s, 1H, OH), 2.35 (q, $^5J_{H,F}$ = 1.9 Hz, 3H, Me-5), 2.36 (s, 3H, Me-2), 2.43 (q, $^6J_{H,F}$ = 1.1 Hz, 3H, MeCO), 3.83, 3.99 (both t, J = 5.6 Hz, 2H, CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ 110.5 (s, CF_3). Anal. Calcd for $C_{11}H_{14}F_3NO_2$: C, 53.01; H, 5.66; N, 5.62. Found: C, 52.71; H, 5.46; N, 5.75.

*4.1.12. 3-Acetyl-1-benzyl-2,5-dimethyl-4-(trifluoromethyl)-1H-pyrrole (**7l**)*

Yield 64%, yellow oil; IR (KBr) 1665, 1607, 1563, 1532, 1432, 1402 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.25 (q, $^5J_{H,F}$ = 1.6 Hz, 3H, Me-5), 2.30 (s, 3H, Me-2), 2.48 (q, $^6J_{H,F}$ = 0.6 Hz, 3H, Ac), 5.07 (s, 2H, CH_2), 6.90 (d, J = 7.4 Hz, 2H, Ph), 7.27 – 7.37 (m, 3H, Ph); ^{19}F NMR (376 MHz, $CDCl_3$) δ 110.6 (s, CF_3). Anal. Calcd for $C_{16}H_{16}F_3NO$: C, 65.08; H, 5.46; N, 4.74. Found: C, 64.94; H, 5.36; N, 4.98.

*4.1.13. 3-Acetyl-2,5-dimethyl-4-(trifluoromethyl)-1-phenethyl-1H-pyrrole (**7m**)*

Yield 52%, mp 70–71 °C (hexane), colourless powder; IR (KBr) 1655, 1577, 1526, 1498, 1452, 1436 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.19 (s, 3H, Me-5), 2.27 (s, 3H, Me-2), 2.44 (s, 3H, Ac), 2.89,

4.00 (both t, J = 7.5 Hz, 2H, CH_2), 7.06 (d, J = 6.4 Hz, 2H, Ph), 7.25 – 7.34 (m, 3H, Ph); ^{19}F NMR (376 MHz, $CDCl_3$) δ 110.6 (s, CF_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 10.6 (q, $^4J_{C,F}$ = 2.6 Hz, Me-5), 11.3, 31.0 ($^4J_{C,F}$ = 3.7 Hz, MeCO), 36.7, 45.1, 108.5 (q, $^2J_{C,F}$ = 34.7 Hz, C-4), 120.8 (q, $^3J_{C,F}$ = 1.5 Hz, C-3), 124.4 (q, $^1J_{C,F}$ = 267.3 Hz, CF_3), 127.2, 128.7, 128.9, 129.4 (q, $^3J_{C,F}$ = 3.7 Hz, C-5), 133.1, 137.1, 196.9 (C=O). Anal. Calcd for $C_{17}H_{18}F_3NO$: C, 66.01; H, 5.87; N, 4.53. Found: C, 66.00; H, 5.88; N, 4.55.

4.1.14. 3-Acetyl-1-(3,4-dimethoxyphenethyl)-2,5-dimethyl-4-(trifluoromethyl)-1H-pyrrole (7n)

Yield 48%, mp 92–93 °C (hexane), colourless powder; IR (KBr) 1661, 1591, 1579, 1516, 1467, 1436 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.14 (q, $^5J_{H,F}$ = 1.8 Hz, 3H, Me-5), 2.24 (s, 3H, Me-2), 2.43 (q, $^6J_{H,F}$ = 1.1 Hz, 3H, Ac), 2.84 (t, J = 7.1 Hz, 2H, CH_2), 3.78, 3.86 (both s, 3H, MeO), 4.00 (t, J = 7.1 Hz, 2H, CH_2), 6.34 (d, J = 1.9 Hz, 1H, H-2′), 6.62 (dd, J = 8.1, 1.9 Hz, 1H, H-6′), 6.80 (d, J = 8.1 Hz, 1H, H-5′); ^{19}F NMR (376 MHz, $CDCl_3$) δ 110.6 (s, CF_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 10.7 (q, $^4J_{C,F}$ = 2.7 Hz, Me-5), 11.4 (Me-2), 31.0 (q, $^5J_{C,F}$ = 3.7 Hz, *Me*CO), 36.1, 45.1, 55.8, 55.9, 108.4 (q, $^2J_{C,F}$ = 34.7 Hz, C-4), 111.5, 111.9, 120.7 (q, $^3J_{C,F}$ = 1.8 Hz, C-3), 120.8, 124.4 (q, $^1J_{C,F}$ = 267.4 Hz, CF_3), 129.5 (q, $^3J_{C,F}$ = 3.7 Hz, C-5), 129.6, 133.3, 148.2, 149.1, 196.8 (C=O). Anal. Calcd for $C_{19}H_{22}F_3NO_3$: C, 61.78; H, 6.00; N, 3.79. Found: C, 61.69; H, 5.94; N, 3.81.

4.1.15. 3-Benzoyl-2,5-dimethyl-4-(trifluoromethyl)-1H-pyrrole (7o)

Yield 25%, mp 182–183 °C (ethanol), colourless powder; IR (KBr) 3243, 3196, 1616, 1596, 1580, 1535, 1450, 1423 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.90 (s, 3H, Me-2), 2.29 (q, $^5J_{H,F}$ = 1.5 Hz, 3H, Me-5), 7.46–7.68 (m, 5H, Ph), 11.63 (br s, 1H, NH); ^{19}F NMR (376 MHz, DMSO-d_6) δ 111.1 (q, $^5J_{F,H}$ = 1.5 Hz, CF_3); ^{13}C NMR (126 MHz, DMSO-d_6) δ 11.6 (q, $^4J_{C,F}$ = 1.5 Hz, Me-5), 12.3 (Me-2), 108.0 (q, $^2J_{C,F}$ = 34.7 Hz, C-4), 118.0 (q, $^3J_{C,F}$ = 1.6 Hz, C-3), 124.4 (q, $^1J_{C,F}$ = 266.9 Hz, CF_3), 128.4, 128.7, 128.9 (q, $^3J_{C,F}$ = 4.2 Hz, C-5), 131.3, 132.3, 139.6, 191.4 (C=O). Anal. Calcd for $C_{14}H_{12}F_3NO$: C, 62.92; H, 4.53; N, 5.24. Found: C, 62.71; H, 4.30; N, 5.33.

4.1.16. 3-Benzoyl-1-benzyl-2,5-dimethyl-4-(trifluoromethyl)-1H-pyrrole (7p)

Yield 54%, yellow oil; IR (KBr) 1651, 1599, 1582, 1557, 1497, 1449, 1435 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.04 (s, 3H, Me-2), 2.29 (q, $^5J_{H,F}$ = 1.4 Hz, 3H, Me-5), 5.09 (s, 2H, CH_2), 6.95 (d, J = 7.2 Hz, 2H, Ph), 7.28–7.85 (m, 8H, Ph); ^{19}F NMR (376 MHz, $CDCl_3$) δ 109.5 (q, $^5J_{F,H}$ = 1.4 Hz, CF_3). Anal. Calcd for $C_{21}H_{18}F_3NO$: C, 70.58; H, 5.08; N, 3.92. Found: C, 70.78; H, 5.37; N, 4.29.

4.1.17. 3-Benzoyl-2,5-dimethyl-4-(trifluoromethyl)-1-phenethyl-1H-pyrrole (7q)

Yield 50%, mp 85–86 °C (CH_2Cl_2–hexane), colourless prisms; IR (KBr) 1659, 1646, 1623, 1597, 1580, 1542, 1450, 1440, 1406 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.89 (s, 3H, Me-2), 2.25 (q, 3H, Me-5, $^5J_{H,F}$ = 1.4 Hz), 2.95, 4.03 (both t, J = 7.2 Hz, 2H, CH_2), 7.07 (d, J = 7.0 Hz, 2H, Ph), 7.27–7.56 (m, 6H, Ph), 7.77 (dd, J = 7.0, 8.2 Hz, 2H, Ph); ^{19}F NMR (376 MHz, $CDCl_3$) δ 109.4 (q, $^5J_{F,H}$ = 1.4 Hz, CF_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 10.5 (q, $^4J_{C,F}$ = 1.7 Hz, Me-5), 11.1, 36.8, 45.3, 110.1 (q, $^2J_{C,F}$ = 35.1 Hz, C-4), 118.8 (q, $^3J_{C,F}$ = 1.7 Hz, C-3), 124.1 (q, $^1J_{C,F}$ = 267.7 Hz, CF_3), 127.2, 128.2, 128.9, 129.0, 129.2 (q, $^3J_{C,F}$ = 3.9 Hz, C-5), 129.6, 130.7, 132.6, 137.3, 139.5, 193.3 (C=O). Anal. Calcd for $C_{22}H_{20}F_3NO$: C, 71.15; H, 5.43; N, 3.77. Found: C, 71.41; H, 5.28; N, 3.97.

4.1.18. 3-Benzoyl-1-(3,4-dimethoxyphenethyl)-2,5-dimethyl-1H-pyrrole (7r)

Yield 48%, mp 81–82 °C (CH_2Cl_2–hexane), colourless powder; IR (KBr) 1639, 1595, 1579, 1530, 1515, 1466, 1446, 1398 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.88 (s, 3H, Me-2), 2.23 (q, $^5J_{H,F}$ = 1.3 Hz, 3H, Me-5), 2.89 (t, J = 6.8 Hz, 2H, CH_2), 3.81 (s, 3H, MeO), 3.87 (s, 3H, MeO), 4.03 (t, J = 6.8 Hz, 2H, CH_2), 6.41 (s, 1H, H-2′), 6.63 (d, J = 8.2 Hz, 1H, H-6′), 6.81 (d, J = 8.2 Hz, 1H, H-5′), 7.41 (t, J = 7.5 Hz, 2H, H-3″, H-5″), 7.53 (t, J = 7.4 Hz, 1H, H-4″), 7.75 (d, J = 7.5 Hz, 2H, H-2″, H-6″); ^{19}F NMR (376 MHz, $CDCl_3$) δ 109.4 (q, $^5J_{F,H}$ = 1.3 Hz, CF_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 10.6 (q, $^4J_{C,F}$ = 1.7 Hz, Me-5), 11.3 (Me-2), 36.2, 45.3, 55.8, 56.0, 110.0 (q, $^2J_{C,F}$ = 35.0 Hz, C-4), 111.6, 112.1, 118.8 (q, $^3J_{C,F}$ = 1.7 Hz, C-3), 120.9, 124.1 (q, $^1J_{C,F}$ = 267.8 Hz, CF_3), 128.2, 129.4 (q, $^3J_{C,F}$ = 3.8 Hz, C-5), 129.5, 129.8, 130.7, 132.6, 139.4, 148.3, 149.2, 193.1 (C=O). Anal. Calcd for $C_{24}H_{24}F_3NO_3$: C, 66.81; H, 5.61; N, 3.25. Found: C, 66.65; H, 5.51; N, 3.38.

4.1.19. 3-Amino-5,5-dimethyl-2-[2-nitro-1-(trifluoromethyl)propyl]-2-cyclohexen-1-one (9)

Yield 31%, mp 212–213 °C (decomp.) (propan-1-ol), colourless powder; IR (KBr) 3432, 3356, 3186, 1677, 1608, 1548, 1454, 1422, 1410, 1390, 1369, 1361 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) major isomer (75%) δ 0.96 (s, 6H, 2Me), 1.29 (d, J = 6.5 Hz, 3H, Me), 2.04 (s, 2H, CH_2), 2.31 (d, J = 16.6 Hz, 1H, C*H*H), 2.33 (d, J = 16.6 Hz, 1H, CH*H*), 4.06 (dq, $^3J_{H,H}$ = 9.9 Hz, $^3J_{F,H}$ = 9.0 Hz, 1H, H-1′), 5.84 (dq, ^3J = 9.9, 6.5 Hz, 1H, H-2′), 7.38 (br s, 2H, NH_2); minor isomer (25%) 0.94 (s, 6H, 2Me), 1.27 (d, J = 7.1 Hz, 3H, Me), 2.15 (s, 2H, CH_2), 2.31 (d, J = 16.6 Hz, 1H, C*H*H), 2.33 (d, J = 16.6 Hz, 1H, CH*H*), 5.23 (quint, J = 10.8 Hz, 1H, H-1′), 5.90–6.00 (m, 1H, H-2′), 6.81 (br s, 2H, NH_2); ^{19}F NMR (376 MHz, DMSO-d_6) major isomer (75%) δ 96.8 (d, $^3J_{F,H}$ = 9.0 Hz, CF_3), minor isomer (25%) 97.2 (d, $^3J_{F,H}$ = 11.0 Hz, CF_3). Anal. Calcd for $C_{12}H_{17}F_3N_2O_3$: C, 48.98; H, 5.82; N, 9.52. Found: C, 48.59; H, 5.72; N, 9.31.

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References

[1] (a) R. Filler, Y. Kobayashi, L.M. Yagupolskii (Eds.), Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications, Elsevier, Amsterdam, 1993;
(b) P. Kirsch, Modern Fluoroorganic Chemistry, VCH, Weinheim, 2004;
(c) R.D. Chambers, Fluorine in Organic Chemistry, Blackwell Publishing/CRC Press, Boca Raton, 2004;
(d) T. Hiyama, Organofluorine Compounds. Chemistry and Application, Springer-Verlag, Berlin, 2000;
(e) V.M. Muzalevskiy, A.V. Shastin, E.S. Balenkova, G. Haufe, V.G. Nenajdenko, Synthesis (2009) 3905.
[2] (a) E. Okada, R. Masuda, M. Hojo, Heterocycles 34 (1992) 791;
(b) B. Jiang, F. Zhang, W. Xiong, Tetrahedron Lett. 43 (2002) 665;
(c) C.M. Nunes, M.R. Silva, A.M. Beja, R. Fausto, T.M.V.D. Pinho e Melo, Tetrahedron Lett. 51 (2010) 411;
(d) W. Tian, Y. Luo, Y. Chen, A. Yu, J. Chem. Soc. Chem. Commun. (1993) 101;
(e) V. Kameswaran, B. Jiang, Synthesis (1997) 530;
(f) Y. Kamitori, M. Hojo, R. Masuda, M. Wada, T. Takahashi, Heterocycles 37 (1994) 153;
(g) Y. Kamitori, M. Hojo, R. Masuda, T. Takahashi, M. Wada, Heterocycles 34 (1992) 1047;
(h) M.G. Hoffmann, E. Wenkert, Tetrahedron 49 (1993) 1057;
(i) M. Kawase, M. Hirabayashi, S. Saito, K. Yamamoto, Tetrahedron Lett. 40 (1999) 2541;
(j) N. Zanatta, J.M.F.M. Schneider, P.H. Schneider, A.D. Wouters, H.G. Bonacorso, M.A.P. Martins, L.A. Wessjohann, J. Org. Chem. 71 (2006) 6996.
[3] (a) H. Ogoshi, M. Homma, K. Yokota, H. Toi, Y. Aoyama, Tetrahedron Lett. 24 (1983) 929;
(b) R.A. Jones, D.C. Rustidge, S.M. Cushman, Synth. Commun. 14 (1984) 575.
[4] (a) H. Uno, M. Tanaka, T. Inoue, N. Ono, Synthesis (1999) 471;
(b) H. Uno, K. Inoue, T. Inoue, Y. Fumoto, N. Ono, Synthesis (2001) 2255.
[5] (a) A.M. van Leusen, H. Siderius, B.E. Hoogenboom, D. van Leusen, Tetrahedron Lett. (1972) 5337;
(b) A.V. Gulevich, A.G. Zhdanko, R.V.A. Orru, V.G. Nenajdenko, Chem. Rev. 110 (2010) 5235.
[6] J. Leroy, J. Fluorine Chem. 53 (1991) 61.
[7] K. Aoyagi, H. Toi, Y. Aoyama, H. Ogoshi, Chem. Lett. (1988) 1891.
[8] (a) T. Okano, T. Uekawa, N. Morishima, S. Eguchi, J. Org. Chem. 56 (1991) 5259;
(b) K. Funabiki, T. Ishihara, H. Yamanaka, J. Fluorine Chem. 71 (1995) 5.

[9] (a) R.J. Andrew, J.M. Mellor, Tetrahedron 56 (2000) 7267;
(b) E. Okada, R. Masuda, M. Hojo, R. Yoshida, Heterocycles 34 (1992) 1435;
(c) M. Soufyane, C. Mirand, J. Lévy, Tetrahedron Lett. 34 (1993) 7737;
(d) E. Okada, R. Masuda, M. Hojo, R. Inoue, Synthesis (1992) 533;
(e) R. Bartnik, A. Bensadat, D. Cal, R. Faure, N. Khatimi, A. Laurent, E. Laurent, C. Rizzon, Bull. Soc. Chim. France (1997) 725.
[10] E.N. Shaitanova, I.I. Gerus, V.P. Kukhar, Tetrahedron Lett. 49 (2008) 1184.
[11] E.T. McBee, C.E. Hathaway, C.W. Roberts, J. Am. Chem. Soc. 78 (1956) 4053.
[12] S.L. Ioffe, in: H. Feuer (Ed.), Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis: Novel Strategies in Synthesis, 2nd edition, John Wiley & Sons, Chichester, 2008, pp. 435–748.
[13] (a) N. Ono, The Nitro Group in Organic Synthesis, Wiley-VCH, New York, 2001;
(b) A. Yoshikoshi, M. Miyashita, Acc. Chem. Res. 18 (1985) 284.
[14] V.Y. Korotaev, A.Y. Barkov, P.A. Slepukhin, M.I. Kodess, V.Y. Sosnovskikh, Mendeleev Commun. 21 (2011) 277.
[15] V.Y. Korotaev, A.Y. Barkov, P.A. Slepukhin, M.I. Kodess, V.Y. Sosnovskikh, Tetrahedron Lett. 52 (2011) 5764.
[16] (a) C.A. Grob, K. Camenisch, Helv. Chim. Acta 36 (1953) 49;
(b) C.A. Grob, H.P. Schad, Helv. Chim. Acta 38 (1955) 1121;
(c) H. Meyer, Liebigs Ann. Chem. (1981) 1534;
(d) A. Gómez-Sánchez, M. Mancera, F. Rosado, J. Chem. Soc. Perkin Trans. 1 (1980) 1199;
(e) S. Lim, I. Jabin, G. Revial, Tetrahedron Lett. 40 (1999) 4177;
(f) G. Revial, S. Lim, B. Viossat, P. Lemoine, A. Tomas, A.F. Duprat, M. Pfau, J. Org. Chem. 65 (2000) 4593;
(g) C. Baldoli, G. Cremonesi, P.D. Croce, C. La Rosa, E. Licandro, Heterocycles 64 (2004) 491;
(h) A. Alizadeh, A. Rezvanian, H.R. Bijanzadeh, Synthesis (2008) 725;
(i) V.Y. Korotaev, V.Y. Sosnovskikh, I.B. Kutyashev, A.Y. Barkov, Y.V. Shklyaev, Tetrahedron Lett. 49 (2008) 5376;
(j) V.Y. Korotaev, V.Y. Sosnovskikh, E.S. Yasnova, A.Y. Barkov, Y.V. Shklyaev, Mendeleev Commun. 20 (2010) 321;
(k) V.Y. Korotaev, V.Y. Sosnovskikh, A.Y. Barkov, P.A. Slepukhin, M.A. Ezhikova, M.I. Kodess, Y.V. Shklyaev, Tetrahedron 67 (2011) 8685.
[17] D.G. Kuhn, V.M. Kamhi, J.A. Furch, R.E. Diehl, G.T. Lowen, V. Kameswaran, Pestic. Sci. 41 (1994) 279.
[18] S. Iwata, Y. Ishiguro, M. Utsugi, K. Mitsuhashi, K. Tanaka, Bull. Chem. Soc. Jpn. 66 (1993) 2432.
[19] The X-ray diffraction analysis for the structure **7q** was performed on an Xcalibur 3 automatic four-circle diffractometer (CCD detector) employing graphite monochromated Mo Kα radiation (λ = 0.71073 Å) at temperature 295 (2) K and operating in the $\omega/2\theta$ scan mode ($2\theta < 52.7$). The structure was solved by direct methods and refined with full-matrix least-squares calculation on F^2 using SHELX-97 [21]. All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were located geometrically using a riding model. Crystal data for compound **7q** $C_{22}H_{20}F_3NO$: M = 371.39, collourless prism, triclinic crystals space group $P-1$, a = 10.1911(8) Å, b = 10.4231(11) Å, c = 18.644(3) Å, α = 84.088(10)°, β = 81.408(9)°, γ = 77.059(8)°, V = 1903.5(4) Å^3, Z = 4, D_{calc} = 1.296, 7581 independent reflections (R_{int} = 0.0354), $R1$ = 0.0518, $wR2$ = 0.0955, GOF = 1.000. Crystallographic data (excluding structure factors), reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 858061 can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; deposit@ccdc.cam.ac.uk, or via www.ccdc.cam.ac.uk/data_request/cif.
[20] V.Y. Korotaev, A.Y. Barkov, M.I. Kodess, I.B. Kutyashev, P.A. Slepukhin, A.Y. Zapevalov, Izv. Akad. Nauk Ser. Khim. (2009) 1827 (Russ. Chem. Bull. Int. Ed. 58 (2009) 1886).
[21] G.M. Sheldrick, Acta Crystallogr. Sect. A 64 (2008) 112.