Synthesis of dimethyl 1-(trifluoromethyl)-3*H*-pyrrolizine-2,3-dicarboxylate using phosphorus compounds

Maryam Kalantari, Mohammad Reza Islami*, Zahra Hassani, and Kazem Saidi

Department of Chemistry, Shahid Bahonar Uuniversity of Kerman, Kerman 76169, Iran
E-mail: mrislami@mail.uk.ac.ir

Abstract

A general and practical route for the synthesis of phosphorus compounds containing trifluoromethyl or trichloromethyl groups by a one-pot condensation triphenylphosphine and dialkyl acetylenedicarboxylate in the presence of an NH-acid such as 2,2,2-trifluoro-1-(1*H*-pyrrol-2-yl)ethanone or 2,2,2-trichloro-1-(1*H*-pyrrol-2-yl)ethanone is described. The product obtained from the fluorinated compound undergoes an intramolecular Wittig reaction in boiling THF. This method offers a simple procedure for the preparation of dimethyl 1-(trifluoromethyl)-3H-pyrrolizine-2, 3-dicarboxylate.

Keywords: Pyrrolizine derivatives, acetylenic esters, triphenylphosphine

Introduction

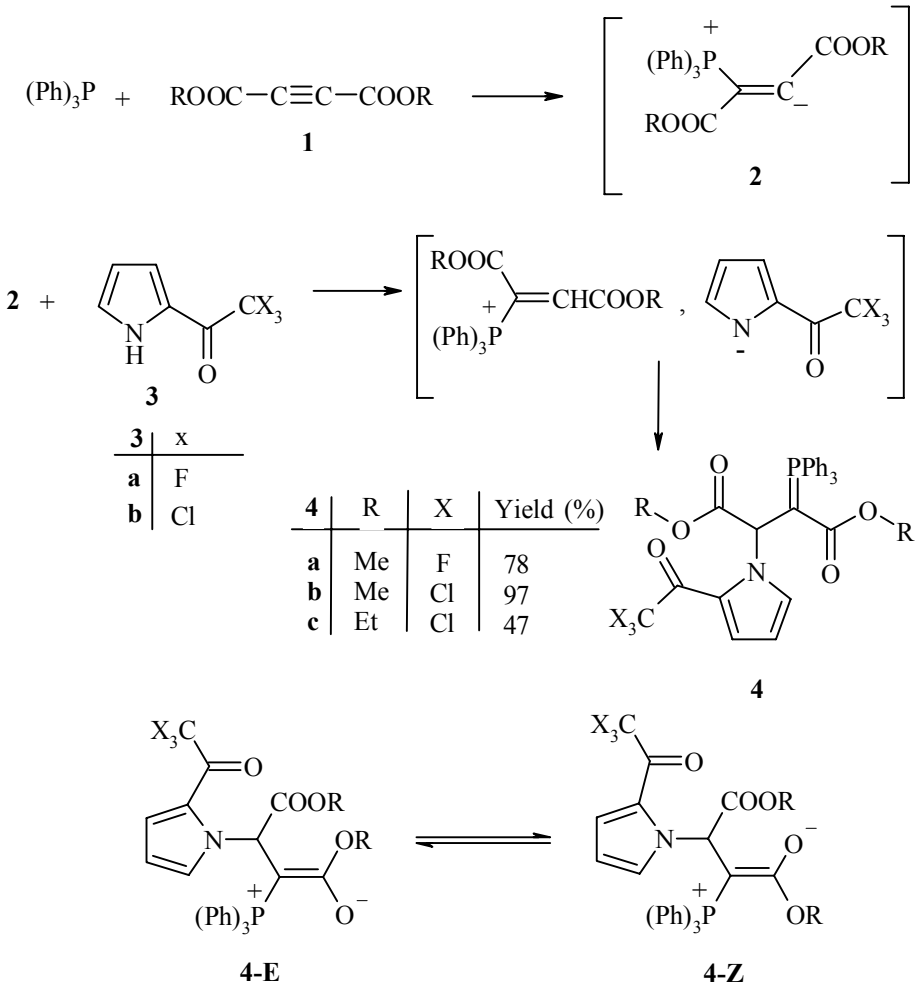
The pyrrolizine derivatives have attracted considerable attention since they are used for antiinflammation, and analgesia[1], as aromatase [2] and tumor inhibitors [3]. Recently, a very large family of natural products such as alkaloides containing pyrrolizine systems which are isolated from plants, insects, animals, marine organisms and microbes having biological activities occupy an important place in the realm of natural and synthetic organic chemistry [4]. Although there are some reports regarding the chemistry and synthesis of such compounds, [5-11] in view of the above observations, and as part of our program that involves the synthesis of new heterocyclic compounds,[12,13] we report here the preparation of new phosphorus compounds and dimethyl 1-(trifluoromethyl)-3*H*-pyrrolizine-2,3-dicarboxylate in good to excellent yields.

Results and Discussion

It is known that the reaction of acetylenic esters and Ph_3P produces the intermediate **2** which is sufficiently stabilized by resonance [14, 15]. Thus, compounds **4a-c** were apparently obtained from

initial addition of triphenylphosphine as a good nucleophile [16-19] to acetylenic esters as a Michael acceptor [20] and concomitant protonation of the intermediate **2** by the NH-acid. Then the positively charged ion is attacked by the nitrogen of the conjugated base of the NH-acid to form phosphoranes containing several functional groups **4**.

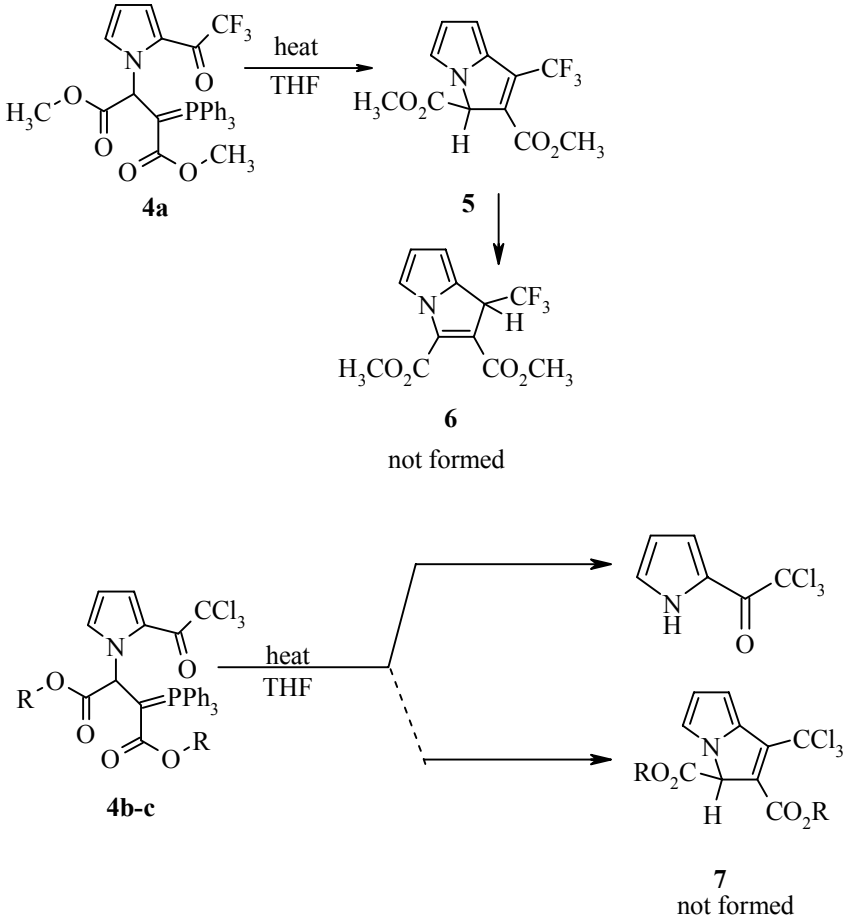
It is worthy to mention that although the reaction of PPh_3 with compounds containing Cl groups, such as CCl_4 and hexachloroacetone, has been reported in the literature, [21-23] during the course of our studies we have not observed the products derived from the nucleophilic attack of the PPh_3 at the Cl groups in compound **3a**. Apparently, under the present reaction conditions the intermediate **2**, in which the phosphonium ion is conjugated with α,β-unsaturated esters, is formed faster than Ph_3P^+-Cl. However, the reaction conditions that we were used are much milder than in the Ph_3P/CCl_4 procedure which typically is run at ambient temperature for 1-2 days or at 60-80 °C for several hours.[21]



Scheme 1

Compounds **4a-c** were characterized on the basis of their spectroscopic data such as the ^{1}H NMR, ^{13}C NMR, IR, mass spectra and analyses data. These data are consistent with the presence of two rotational isomers. The ylide moiety in these compounds is strongly conjugated with adjacent carbonyl group and rotation about the partial double bond in **4-(*E*)** and **4-(*Z*)** geometrical isomers is slow at the room temperature.

Thus the ^{1}H NMR spectrum of compound **4a** showed four sharp lines due to the methoxy protons at δ= 3.23, 3.60, 3.72 and 3.73 ppm along with signals for methine protons at δ= 5.65 and 5.59 ppm, which appear as two doublets ($^3J_{PH}$ 17.6 Hz) and ($^3J_{PH}$ 19.0 Hz) respectively for the *Z* and *E* geometrical isomers. The aromatic protons appear as a multiplet at δ= 6.28-7.97 ppm. The ^{13}C NMR spectrum of **4a** displayed twenty nine distinct resonances in agreement with the mixture of two rotational isomers. Although the presence of the ^{31}P nucleus complicates both the ^{1}H and ^{13}C NMR spectra of **4a**, it helps in assignment of signals by long-range spin-spin couplings with ^{1}H and ^{13}C nuclei. The ^{1}H and ^{13}C NMR spectra of compound **4b** are similar to those of **4a**, except for the signal from the CCl_3 group in ^{13}C NMR, which appears in the corresponding chemical shift and the absence of the CF_3 group. The ^{1}H and ^{13}C NMR spectra of compound **4c** are similar to those of **4b**, except for the signals from the ester groups, which appear as characteristic resonance lines with the corresponding chemical shifts.



Scheme 2

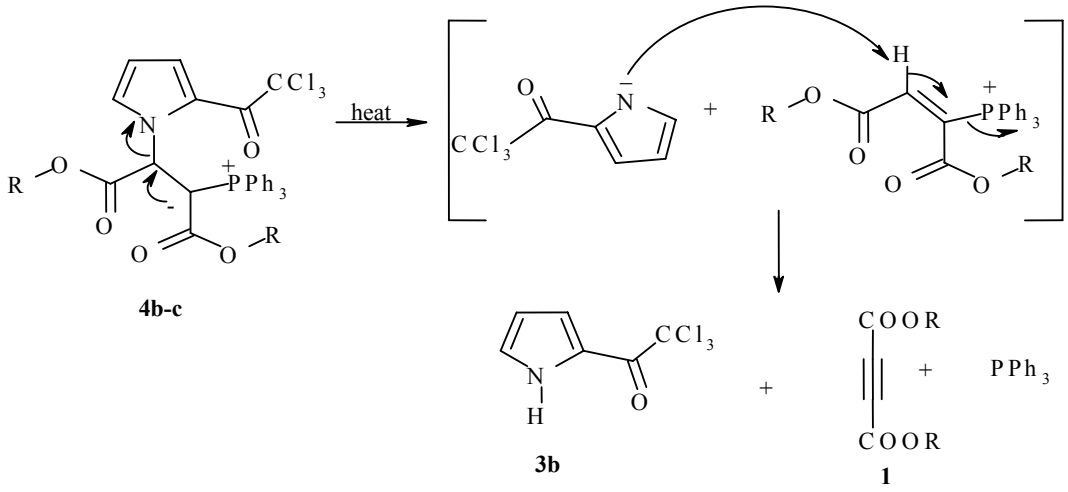
Compound **4a** undergoes a smooth reaction in boiling THF to produce triphenylphosphine oxide and dimethyl 1-(trifluoromethyl)-3H-pyrrolizine-2,3-dicarboxylate (Scheme 2) **5**. Structure **5** was assigned on the basis of their elemental analyses, IR, ^{1}H, ^{13}C NMR and mass spectral data. Thus the ^{1}H NMR spectrum of **5** in $CDCl_3$ exhibits two signals at δ= 3.88 and 3.91 ppm for the methoxy groups along with a signal at δ= 4.76 ppm due to methine proton. The aromatic protons appear as a multiplet signal at δ= 6.71-7.69 ppm. Several examples are known in which a heterocyclic compound is produced from a phosphorus ylide connected to a carbonyl group by a chain containing a heteroatom.[24,25] Thus pyrrolizine derivative **5** may be considered as a product of an intramolecular Wittig reaction.

It is known that the 3*H*-pyrrolizine derivatives can be tautomerised to other isomers such as 1*H*-pyrrolizine and there are evidences in which 3*H*-pyrrolizine derivatives were reported as intermediates in the synthesis of 1*H*-pyrrozilines. [26] It is important to note that only compound **5** was isolated from the reaction mixture and compound **6** was not formed. ^{1}H NMR data were used to distinguish between structure **5** and **6**.

A singlet for methine proton at the ^{1}H NMR spectrum at 4.76 ppm with the integration of 1H is a good evidence for the formation of compound **5**, while in the case of compound **6** the corresponding methine proton should reveal a quartet due to the effect of three adjacent fluorine atoms.

With these results in hand, we next tried to study whether functionalized phosphoranes containing CCl_3 group could be used as intermediates in the preparation of pyrrolizine derivatives including trichloromethyl group. It was assumed that heating of phosphoranes **4b-c** could be used for this purpose and dialkyl 1-(trichloromethyl)-3*H*-pyrrolizine-2,3-dicarboxylate **7** is the product through an identical pathway, the same reaction observed in the case of compound **5** (Scheme 2). However, the expected pyrrolizine **7** was not formed when phosphorus ylides **4b-c** heated in THF, and the 2,2,2-trichloro 1-(1*H*-pyrrol-2-yl)ethanone **3b,** acetylenic esters **1** and PPh_3 were obtained instead, although CCl_3 group is similar to CF_3 group and can act as an electron withdrawing group by inductive effect and thus the connected carbonyl group to it is very active for attacking of the ylide moiety. The reason for such a difference between products from compounds **4b-c** and product from the reactant **4a** is not clear to us, but steric hindrance of CCl_3 group might play an important role in these reactions.

Although we have not established a mechanism for the formation of compound **3b** in an experimental manner, a reasonable possibility has been shown in Scheme 3. In this mechanism it is assumed that the fragmentation of compounds **4b-c** has occurred by the formation of a double bond as driving force in intermediate salt.



Scheme 3

In conclusion, we have revealed a novel and efficient multiple component condensation reactions for the synthesis of heterocyclic compounds including an ylide moiety, which can be employed for the preparation of pyrrolizine derivative containing trifluoromethyl group.

Experimental Section

General Procedures. Dialkyl acetylenedicarboxylates and triphenylphosphine were obtained from Merck Chemical Co. and were used without further purification. Compounds **3a-b** were prepared according to the reported procedure in the literature.[27] Melting points were obtained on a Gallenkamp melting point apparatus and were uncorrected. Elemental analyses for C, H and N were performed by the University of Tehran using a Heracus CHN-O-Rapid analyzer. IR spectra were measured on a Mattson 1000 FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a BRUKER DRX-500 AVANCE spectrometer at 500 and 125.77 MHz, respectively. Mass spectra were recorded on MS-QP2000A Shimadzu mass spectrometer operating at an ionization potential of 70 eV.

Dimethyl 2-(2-(2,2,2-trifluoroacetyel)-1H-pyrrol-1- yl) -3-(1,1,1-triphenyl-λ^{5}-phosphanyl -idene) succinate(4a). At ambient temperature dimethyl acetylenedicarboxylate (0.24 mL, 2 mmol) was added dropwise to a stirred solution of triphenylphosphine (0.53 g, 2 mmol) and 2,2,2-trifluoro-1-(1H-pyrrol-2-yl)ethanone (0.32 g, 2 mmol) in a mixture of hexane-ethyl acetate (6 mL, 1:2). After the addition was complete (approximately 5 minutes) the mixture was stirred for an additional 1hr and was subsequently filtered. The solid collected in the filter was washed thoroughly with ethyl acetate to give a pale yellow powder. (0.9 g, m.p 129-132 ˚C. yield 78 %); IR (KBr) (ν_{max} , cm^{-1}): 1765 and 1641 (C=O). MS, m/z (%): 566 (28), 498 (35), 473 (30),

277 (36), 94 (25), 77 (15), 44 (36). Anal. Calcd. for $C_{30}H_{25}NO_5F_3P$ (567.57): C, 63.48; H, 4.44; N, 2.47 %. Found: C, 63.50; H, 4.60; N, 2.50 %

Major isomer, **4a**-(Z) (51.2%), ^{1}H NMR: δ 3.22 and 3.73 (6H, 2s, 2 OCH_3), 5.65 (1H, d, $^3J_{PH}$ 17.6 Hz, P=C-CH), 6.28-7.97 (36H, m, arom)*. ^{13}C NMR: δ 43.67 (d, $^1J_{PC}$ 126.2 Hz, P=C), 49.42 and 50.38 (2 OCH_3), 61.82 (d, $^2J_{PC}$ 17.8 Hz, P=C-CH), 109.98 (CH), 110.11 (CH), 116.95 (q, $^1J_{CF}$ 290.8 Hz, CF_3)*, 123.88 (C), 124.34 (CH) 126.16 (d, $^1J_{PC}$ 91.8 Hz, C^{ipso}), 128.93 (d, $^3J_{PC}$ 11.5 Hz, C^{meta}), 132.40 (C^{para})*, 133.39 (d, $^2J_{PC}$ 9.8 Hz, C^{ortho}), 169.02 (d, $^2J_{PC}$ 22.3 Hz, C=O), 170.54 (d, $^3J_{PC}$ 18.6 Hz, C=O),171.64 (C=O).

Minor isomer, **4a**-(E) (48.8%),^{1}H NMR: δ 3.60 and 3.72 (6H, 2s, 2 OCH_3), 5.59 (1H, d, $^3J_{PH}$ 19.0 Hz, P=C-CH). ^{13}C NMR: δ 43.94 (d, $^1J_{PC}$ 135.2 Hz, P=C), 52.48 and 52.67 (2 OCH_3), 61.76 (d, $^2J_{PC}$ 17.4 Hz, P=C-CH), 124.34 (C), 125.5 (d, $^1J_{PC}$ 92.1Hz, C^{ipso}), 128.96 (d, $^3J_{PC}$ 11.5 Hz, C^{meta}),132.96 (CH), 133.47 (d, $^2J_{PC}$ 9.7 Hz, C^{ortho}), 133.79 (CH), 168.74 (d, $^2J_{PC}$ 22.3 Hz, C=O), 170.02 (d, $^3J_{PC}$ 13.4 Hz, C=O), 171.74 (C=O).

Dimethyl 2-(2-(2,2,2-tricholoroacetyel)-1H-pyrrol-1-yl) -3-(1,1,1-triphenyl-λ^5-phosphanylidene) succinate(4b). (1.2 g, m.p. 154-156 °C, yield 97 %); IR (KBr) (ν_{max} , cm^{-1}): 1765 and 1641 (C=O). MS, m/z (%): 607 (1), 329 (3), 277 (100), 262 (29), 211 (5), 183 (36), 77 (49), 51 (31), 45 (23). Anal. Calcd. for $C_{30}H_{25}NO_5Cl_3P$ (617.04): C, 58.41; H, 4.09; N, 2.27 %. Found: C, 58.65; H, 3.93; N, 2.12 %

Major isomer, **4b**-(Z) (50%), ^{1}H NMR: δ 3.22 and 3.72 (6H, 2s, 2 OCH_3), 5.64 (1H, d, $^3J_{PH}$ 18.9 Hz, P=C-CH), 6.25-7.91 (36H, m, arom)*. ^{13}C NMR: δ 43.98 (d, $^1J_{PC}$ 134.7 Hz, P=C), 49.37 and 50.34 (2 OCH_3), 61.97 (d, $^2J_{PC}$ 17.7 Hz, P=C-CH)*, 96.55 ($2CCl_3$)*, 108.69 (CH), 108.82 (CH), 121.16 (C), 124.27 (CH) 125.65 (d, $^1J_{PC}$ 92.4 Hz, C^{ipso}), 128.97 (d, $^3J_{PC}$ 12.2Hz, C^{meta})*, 132.37 (C^{para})*, 133.38 (d, $^2J_{PC}$ 10.6 Hz, C^{ortho}), 169.96 (d, $^2J_{PC}$ 13.2 Hz, C=O), 171.75 (d, $^3J_{PC}$ 12.6 Hz, C=O), 171.73 (C=O).

Minor isomer, **4b**-(E) (50%),^{1}H NMR: δ 3.59 and 3.73 (6H, 2s, 2 OCH_3), 5.68 (1H, d, $^3J_{PH}$ 17.6 Hz, P=C-CH). ^{13}C NMR: δ 43.69 (d, $^1J_{PC}$ 126.1 Hz, P=C), 52.47 and 52.62 (2 OCH_3), 120.91 (C), 124.59 (CH), 126.28 (d, $^1J_{PC}$ 91.9 Hz, C^{ipso}), 131.72 (CH), 132.59 (CH), 133.47 (d, $^2J_{PC}$ 10.4 Hz, C^{ortho}), 170.61 (d, $^2J_{PC}$ 18.5 Hz, C=O), 171.86 (d, $^3J_{PC}$ 12.7 Hz, C=O), 171.89 (C=O).

Diethyl 2-(2-(2,2,2-tricholoroacetyel)-1H-pyrrol-1-yl) -3-(1,1,1-triphenyl-λ^5-phosphanylidene) succinate(4c). (0.6 g, m.p. 157-160 °C, yield 47 %); IR (KBr) (ν_{max} , cm^{-1}): 1765 and 1641 (C=O). MS, m/z (%): 645 (25), 526 (23), 277 (42), 262 (99), 183 (98), 73 (10), 77 (10), 44 (50). Anal. Calcd. for $C_{32}H_{29}NO_5Cl_3P$ (645.09): C, 59.57; H, 4.53; N, 2.17 %. Found: C, 59.70; H, 4.90; N, 2.20 %

Major isomer, **4c**-(Z) (51.2%), ^{1}H NMR: δ 0.52 (3H, t, $^3J_{HH}$ 6.9 Hz, CH_3), 1.23 (3H, t, $^3J_{HH}$ 6.8 Hz, CH_3), 3.73-4.35 (8H, m, $4CH_2$)*, 5.69 (1H, d, $^3J_{PH}$ 18.5 Hz, P=C-CH), , 6.25-7.93 (36H, m, arom)*. ^{13}C NMR: δ 14.06 and 14.14 ($2CH_3$), 43.50 (d, $^1J_{PC}$ 126.2 Hz, P=C), 60.96 and 60.98 (2 OCH_2), 62.08 (d, $^2J_{PC}$ 18.9 Hz, P=C-CH), 96.67 ($2CCl_3$)*, 108.58 (CH), 108.74 (CH), 120.88 (C), 124.31 (CH) 126.54 (d, $^1J_{PC}$ 92.2 Hz, C^{ipso}), 128.89 (d, $^3J_{PC}$ 11.8 Hz, C^{meta}), 132.29 (C^{para})*, 133.47 (d, $^2J_{PC}$ 9.3 Hz, C^{ortho})*, 169.53 (d, $^2J_{PC}$ 13.2 Hz, C=O), 171.11 (C=O), 171.16 (d, $^3J_{PC}$ 12.7 Hz, C=O).

Minor isomer, **4c**-(E) (48.8%),^{1}H NMR: δ 1.17 (3H, t, $^{3}J_{HH}$ 6.9 Hz, CH_3), 1.28 (3H, t, $^{3}J_{HH}$ 6.8 Hz, CH_3), 5.64 (1H, d, $^{3}J_{PH}$ 20.3Hz, P=C-CH). ^{13}C NMR: δ 14.16 and 14.87 (2CH_3), 43.98 (d, $^{1}J_{PC}$ 135.3 Hz, P=C), 57.98 and 58.60 (2 OCH_2), 61.93 (d, $^{2}J_{PC}$ 19.1Hz, P=C-CH), 121.11 (C), 124.58 (CH), 125.91 (d, $^{1}J_{PC}$ 92.2 Hz, C^{ipso}), 131.91 (CH), 132.67 (CH), 170.36 (d, $^{2}J_{PC}$ 18.2 Hz, C=O), 171.21 (C=O), 171.70 (d, $^{3}J_{PC}$ 12.7 Hz, C=O).

Dimethyl 1-(trifluoromethyl)-3*H*-pyrrolizine-2,3-dicarboxylate. (0.2 g, m.p 75-78˚C. yield 79 %); IR (KBr) (ν_{max} , cm^{-1}): 1741 and 1716 (C=O). MS, *m/z* (%): 163 (42), 102 (25), 66 (36), 69 (50) 59 (25), 39 (40). Anal. Calcd. for $C_{12}H_{10}NO_4F_3$ (289.24): C, 49.83; H, 3.48; N 4.84 %. Found: C, 49.40; H, 3.70; N, 4.4 %. ^{1}H NMR: δ 3.88 and 3.91 (6H, 2s, 2 OCH_3), 4.76 (1H, s, CH), 6.71-7.69 (3H, m, arom)*. ^{13}C NMR: δ 52.12 and 52.66 (2 OCH_3), 55.39 (CH), 122.66 (q, $^{1}J_{CF}$ 267.0 Hz, CF_3), 119.64 and 121.43 (CH), 132.95 (C), 135.59 (CH), 143.40 (C), 143.43 (C), 160.00 and 164.08 (2C=O).

*For two rotamers.

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