A new route to β-trifluoromethylenaminones

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New β-trifluoromethylenaminones have been prepared in moderate to good yields by regioselective reaction of a variety of primary and secondary amines on the corresponding β-chlorovinyl-β-trifluoromethylketone.

Keywords: trifluoromethyl compounds, Vilsmeier derivatives, β-chlorovinyl-β-trifluoromethyl ketones, β-trifluoromethylenaminones, Michael addition.

We have shown that the addition of primary amines to the β-trifluoromethyl-β-chloroacroleins in THF at room temperature afforded regioselectively the 1-aza-1,3-dienes[1] whereas the reaction of an excess of secondary amines on the same functionalised aldehydes, in refluxing THF, afforded the corresponding β-trifluoromethyl enaminoaldehydes. These intermediates are slowly converted *in situ* into a variety of enaminoketones, by reaction of a second equivalent of amine followed by hydrolysis (Scheme 1).[2]

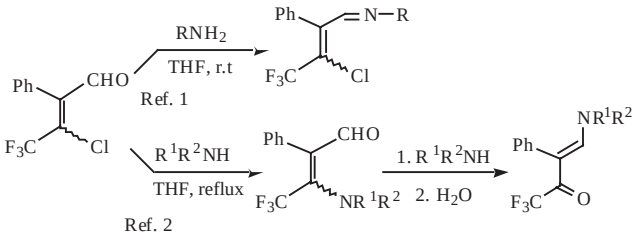
More recently, we have reported that, on treatment with hydrazine and its derivatives in refluxing acetonitrile or toluene, the β-trifluoromethyl enone **1** gave regioselectively, *via* a *one-pot* procedure, a variety of pyrazoles.[3] In connection with our ongoing interests in the synthesis and the reactivity of trifluoromethylated Vilsmeier adducts, we report here our results concerning the behaviour of enone **1** towards both primary and secondary amines, as a new route to β-trifluoromethylenaminones **2** and **3.**

The β-chlorovinyl ketone **1**[4,5] was prepared as a mixture of *Z* and *E* diastereomers (*E* :*Z* = 60 : 40) which were not readily separable. On treatment with secondary alkyl- and aryl amines, in THF at room temperature, the ketone (*E*,*Z*)-**1** gave regioselectively, *via* a tandem 1,4-addition-ion chloride elimination, the β-trifluoromethylenaminones **2**; each one was formed as a mixture of *Z* and *E* diastereomers**.**[6] The yields are in the range 41–77%. We have observed that the *E*:*Z* ratios of compounds **2** depend on the nature of the alkyl- and aryl amines and can be determined by ^{19}F NMR spectroscopy. An anisotropic effect for the phenyl moiety to the CF_3 group was observed in the case of the (*Z*)-**2** diastereomers (Scheme 2).

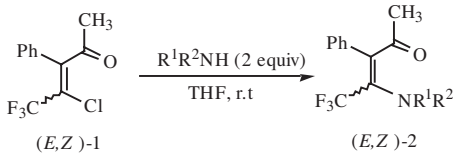
Under the reaction conditions (THF/r.t) mentioned above, aliphatic and aromatic primary amines similarly displace the β-chlorine atom of the β-chlorovinyl ketone **1**, affording the expected β-trifluoromethylenaminones **3** in moderate to good yields. In contrast to secondary amines, the reaction of primary ones on the (*E*,*Z*)-enone **1** gave exclusively the (*Z*)-enaminones **3** (Scheme 3).[7,8]

The uniform configuration of enaminones **3a–e** is proved by NMR spectroscopy. Indeed, the ^{19}F NMR spectrum of each enaminone shows only one signal corresponding to a single diastereomer (Table 2). Moreover, the ^{1}H NMR spectrum of each compound revealed at the high field, one singlet assigned to the methyl group (*i.e.* $COCH_3$). Accordingly, the carbonyl group (C=O) of each compound gives just one signal in the ^{13}C NMR spectrum.

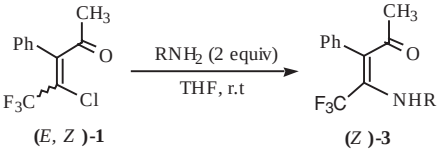
For the assignment of the (*Z)*-configuration of enaminones **3a–e**, examination of hetero nOe spectrum of compound **2a**, after irradation of the CF_3 group, resulted in 3 % enhancement of the *ortho* positions' protons, showing that the enaminone **3a** was in the (*Z*)-configuration (Fig.1).



Scheme 1 Reaction of amines on a β-trifluoromethyl-β-chloroacrolein derivative.



Scheme 2 Synthesis of β-trifluoromethylenaminones (*E,Z*)-**2**.



Scheme 3 Synthesis of β-trifluoromethylenaminones (*Z*)-**3**.

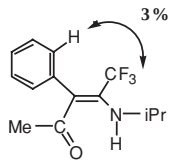


Fig.1 NOe effect between CF_3 group and H_{ortho} in compound (Z)-**2a**.

Table 1 Yields, *E* :*Z* ratios, IR and ^{19}F NMR spectra of β-trifluoromethylenaminones (*E,Z*)-**2**

2	R^1	R^2	yield (%)	*E* :*Z* (%)	IR/cm^{-1}	^{19}F NMR (δ, ppm) Minor (*E*)	Major (*Z*)
a	Me	Bn	41	38 : 62	1700 (C=O); 1128–1165 (C–F)	101.4	105.0
b	–$(CH^2)^5$–	–	77	16 : 84	1695 (C=O); 1171–1155 (C–F)	103.7	106.3
c	Et	Et	70	17 : 83	1697 (C=O); 1125–1099 (C–F)	104.0	105.2

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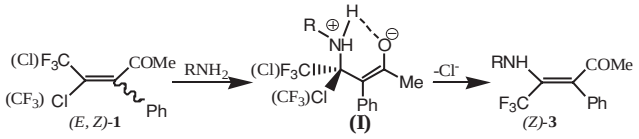
Table 2 Yields, IR and ^{19}F NMR spectra of β-trifluoromethyl enaminones (*Z*)-**3**

(*Z*)-**3**	**a**	**b**	**c**	**d**	**e**
R	*i*Pr	Bn	Me	Et	c–C_6H_{11}
Yield/%	74	51	51	70	75
IR/cm^{-1}	1700 ;	1713 ;	1701	1709;	1705 ;
(C=O; C–F)	1128–1165	1135–1158	1138–1159	1140–1162	1130–1162
^{19}F NMR/δ, ppm	104.0	104.5	103.5		



Scheme 4 Synthesis of (*Z*)-**3** via the hypothetical intermediate (**I**).

Finally, the high stereoselectivity in favour of the (*Z*)-diastereomer is believed to result from the six-membered intermediate **(I)** which could be stabilised by intramolecular hydrogen bonding involving the amino group and oxygen atom of enolate**.** Thus, the formation of enaminones (*Z*)-**3** could be described according to the following Scheme 4.

In summary, new β-trifluoromethylenaminones were easily prepared by reaction of amines on the corresponding β-chlorovinylkenones in mild conditions and in moderate to good yields. The addition of primary ones on *(E, Z)*-**1** especially constitute a simple and efficient route to prepare pure (*Z*)-enaminones **3** in moderate to good yields.

Enaminones are currently useful intermediates for the preparation of a number of biologically active heterocyclic compounds including alkaloids,[9] quinolines,[10] quinolizines,[11] pyrimidines,[12,13] pyrroles[14] and pyrazoles.[15,16]

Experimental

General experimental procedures

All reaction progress was monitored by thin-layer chromatography (TLC) analysis (Merck Kieselgel 60 F_{254}). All compounds were purified on a chromatography column (Silica gel 60, 70–230 mesh ASTM). IR spectra were obtained on a Perkin-Elmer Paragon 1000 PC instrument. ^1H NMR spectra were recorded on a Bruker AC-300 (300 MHz) spectrometer using tetramethylsilane (TMS, δ_H=0) as internal standard. ^{13}C NMR spectra were recorded on a Bruker AC-300 (75 MHz) spectrometer with proton decoupling. For ^{19}F spectra, C_6F_6 was used as reference and the spectra were recorded on a Bruker AC-300 (282.36 MHz) spectrometer. Mass spectra were carried out on a Hewlett-Packard model (70 eV) by the staff of the Faculté de Médecine, Département de biochimie, Monastir, Tunisia, under electronic impact (EI) using NH_3 as the carrier gas.

Typical procedure for the synthesis of compound (*Z*)-**3a**: To a stirred solution of **1** (4 mmol) in THF (20 ml), Primary amine (8 mmol) was added. The mixture was stirred overnight at room temperature. After evaporation of the solvent, the resulting residue was purified by column chromatography, using 20 % ethyl ether-petroleum ether as eluent to give the compound **3a** as a colourless oil in 74 % yield.

4-(N,N-methylbenzylamino)-3-phenyl-5,5,5-trifluoropent-3-en-2-one (*E, Z*)- **2a**: Oil; yield=41%; IR ($CHCl_3$): ν (cm^{-1}) 1700 (C=O); 1128.34–1165.46 (CF_3); ^1H NMR (300 MHz, $CDCl_3$): δ_H 2.10 and 2.20 (2s, 3H, CH_3); 2.36 and 2.56 (2s, 3H, CH_3); 3.63 and 4.00 (2s, 2H, CH_2); 7.00–7.16 (m, 10H, 2 C_6H_5); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 29.7 and 29.8 ($\underline{C}H_3$–CO); 40.0 and 40.2 ($\underline{C}$H3–N); 60.5 and 65.8 ($\underline{C}H_2$–Ph); 128.3 (q, $\underline{C}F_3$, $^1J_{CF}$ = 272 Hz); 128.4 (q, $\underline{C}$–CF3, $^2J_{C-F}$ = 18.4 Hz); 128.5–128.9 (C=$\underline{C}$–Ph and C_6H_5); 200.5 and 201.3 (C=O); ^{19}F NMR (282.4 MHz $CDCl_3$)**:** δ_F 101.0 (s, CF_3); 101.4 (s, CF_3); Anal. calcd for $C_{19}H_{18}F_3NO$ (333): C, 68.47; H, 5.40; N, 4.20%. Found: C, 68.28; H, 5.62; N, 3.99%.

3-Phenyl-4-(piperidin-1-yl)-5,5,5-trifluoropent-3-en-2-one (*E,Z*)- **2b**: Oil; yield=77%; IR ($CHCl_3$)**:** ν (cm^{-1}) 1695 (C=O); 1171.48–1155.23 (C–F); ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.46 (m, 6H); 2.16 and 2.28 (2s, 3H, CH3); 2.76 (m, 4H); 7.00–7.26 (m, 5H, C6H5); ^{13}C NMR (75 MHz, $CDCl_3$)**:** δ_C 22.3 and 22.5 ($\underline{C}$H3–CO); 29.2 (–CH_2–); 44.4 (–CH_2–); 50.1 (–CH_2–); 127.0–129.3 (m, $C_{ethylenic}$, CF_3 and C_6H_5); 205.4 and 206.5 (2s, C=O); ^{19}F NMR (282.4 MHz, $CDCl_3$): δ_F 83.7 (s, CF_3); 86.3 (s, CF_3); M.S: 51(26); 69(15); 75(17); 101(12); 151(100); 170(83); 195(16); 206(63); 215(37); 250(9). Anal. calcd for $C_{16}H_{18}F_3NO$ (297): C, 64.65; H, 6.06; N, 4.71%. Found: C, 64.49; H, 5.92; N, 4.62%.

4-(N,N-diethylamino)-3-phenyl-5,5,5-trifluoropent-3-en-2-one (*E,Z*)- **2c**: Oil; yield=70%; IR ($CHCl_3$): ν (cm^{-1}) 1697.54 (C=O); 1124.98–1098.98 (C–F); ^1H NMR (300 MHz, $CDCl_3$): δ_H 0.96 and 1.14 (2t, 3H, CH_3, *J* = 7.1 Hz); 2.17 and 2.22 (2s, 3H, CH_3); 2.66 and 2.95 (2q, 4H, CH_2, *J* = 7.1 Hz); 7.33 (m, 5H, C_6H_5); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 13.4 and 13.6 (2s, $\underline{C}H_3$–CH_2); 29.7 and 29.7 (2s, $\underline{C}H_3$–CO); 46.8 and 47.5 (2s, –CH_2–); 128.4 (q; CF_3–C=$\underline{C}$; $^3J_{CF}$ = 8.7 Hz); 128.4 (q; CF_3–$\underline{C}$=C; $^2J_{CF}$ = 66.2 Hz); 132.0 (q; CF_3, $^1J_{CF}$ = 281.5 Hz); (128.5, 128.6, 128.7, 128.8) C_{arom}; 201.0 and 201.5 (2s, C=O); ^{19}F NMR (282.4 MHz, $CDCl_3$): δ_F 104.0 (s, CF_3); 105.5 (s, CF_3); Anal. calcd for $C_{15}H_{18}F_3NO$ (285)**:** C, 63.16; H, 6.32; N, 4.91%. Found: C, 62.98; H, 6.50; N, 5.03%.

3-Phenyl-4-isopropylamino-5,5,5-trifluoropent-3-en-2-one (*Z*)- **3a**: Oil; yield=74% ; IR ($CHCl_3$)**:** ν (cm^{-1}) 3576 (N–H); 1713.26 (C=O); 1158–1135 (CF_3); ^1H NMR (300 MHz, $CDCl_3$)**:** δ_H 1.31 (d, 6H, *J* = 6.0 Hz, *i*Pr), 1.83 (s, 3H, CH_3); 3.63–4.20 (m, 1H, C–H) ; 7.30 (m, 5H, C_6H_5); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 24.7 (s, CH–($\underline{C}H_3$)$_2$); 30.1 (s, $\underline{C}H_3$–CO) ; 47.6 (q, $\underline{C}$H–(CH_3)$_2$), $^4J_{CF}$ = 3.7 Hz) ; (127.1–138.0) (m, $C_{ethylenic}$, CF_3 and C_6H_5) ; 146.4 (q, CF_3–$\underline{C}$=C, $^2J_{CF}$ = 29.1 Hz); 199.7 (s, C=O); ^{19}F NMR (282.4 MHz, $CDCl_3$): δ_F 104.0 (s, CF_3); M.S: 271(M^+, 100); 57(14); 89(19); 117(31); 160(36); 170(39); 186(65); 214(77); 228(24); 256(30); Anal. calcd for $C_{14}H_{16}F_3NO$ (271): C, 61.99; H, 5.90; N, 5.17%. Found: C, 61.90; H, 5.76; N, 5.08%.

4-Benzylamino-3-phenyl-5,5,5-trifluoropent-3-en-2-one (*Z*)- **3b**: Oil; yield=51%; IR ($CHCl_3$): ν (cm^{-1}) 3650 (N–H); 1701 (C=O); ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.83 (s, 3H, CH_3); 4.53 (s, 2H, CH_2); 4.80 (s, 1H, N–H); 7.20 (m, 10H, 2C_6H_5); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 29.5 (s, CH_3–CO); 64.5 (s, CH_2–Ph); 128.5 (q, CF_3, $^1J_{CF}$ = 274.8 Hz); 128.5–131.0 (m, C_6H_5 and $C_{ethylenic}$); 201.5 (C=O); ^{19}F NMR (282.4 MHz, $CDCl_3$): δ_F 104.5 (s, CF_3). Anal. calcd for $C_{18}H_{16}F_3NO$ (319): C, 67.71; H, 5.02; N, 4.39. Found: C, 67.83; H, 5.12; N, 4.27%.

4-Methylamino-3-phenyl-5,5,5-trifluoropent-3-en-2-one (*Z*)- **3c**: Oil; yield=51%; IR ($CHCl_3$): ν (cm^{-1}) 3370 (N–H); 1709.12 (C=O); 1162.79–1140.05 (C–F); ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.83 (s, 3H, CH_3CO); 3.10 (m, 3H, CH_3N); 7.06 (m, 5H, C_6H_5); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 30.1 (s, $\underline{C}H_3$–CO); 31.3 (s, CH_3–NH); 127.1–131.3 (m, C=$\underline{C}$(Ph), CF_3 and C_6H_5); 147.6 (q, CF_3–$\underline{C}$=C, $^2J_{CF}$ = 22.6 Hz); 199.9 (s, C=O); ^{19}F NMR (282.4 MHz, $CDCl_3$): δ_F 103.5 (s, CF_3); MS: *m/z* 57(29); 77(13); 91(24); 121(29); 149(49); 161(74); 177(100); 228(3). Anal. calcd for $C_{12}H_{12}F_3NO$ (243): C, 59.26; H, 4.94; N, 5.76. Found: C, 59.07; H, 4.83; N, 5.63%.

4-Ethylamino-3-phenyl-5,5,5-trifluoropent-3-en-2-one (*Z*)- **3d**: Oil; yield=70%; IR ($CHCl_3$): ν (cm^{-1}) 3410 (NH); 1705 (C=O); 1162–1130–(C–F); ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.25 (t, 3H, CH_2–$\underline{C}H_3$, *J* = 7.1 Hz); 1.80 (s, 3H, CH_3CO); 3.50 (q, 2H, *J* = 7.0 Hz, $\underline{C}H_2$–CH_3); 7.30 (m, 5H, C_6H_5); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 13.6 (s, CH_2–$\underline{C}H_3$); 29.7 (s, $\underline{C}H_3$–CO); 47.5 (s, $\underline{C}H_2$–CH_3); 128.5 (q, CF_3–$\underline{C}$=C; $^2J_{CF}$ = 66.2 Hz); 131.0 (q, CF_3, $^1J_{CF}$ = 282 Hz); 128.5 (q, CF_3–C=$\underline{C}$, $^3J_{CF}$ = 8.8 Hz); 128.5– 128.9 (m, CF_3–$\underline{C}$=C and C_{arom}); 199.8 (s, C=O); ^{19}F NMR (282.4 MHz, $CDCl_3$): δ_F 104.2 (s, CF_3)**.** Anal. calcd for $C_{13}H_{14}F_3NO$ (257): C, 60.70, H, 5.45; N, 5.45. Found: C, 60.83; H, 5.53; N, 5.34%.

4-Cyclohexylamino-3-phenyl-5,5,5-trifluoropent-3-en-2-one (*Z*)- **3e**: Oil; yield = 75%; IR ($CHCl_3$): ν (cm^{-1}) 3650 (NH); 1700 (C=O); 1157.17–1137.14 (C–F); ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.70 (m, 10H, c–C_6H_{10}); 1.90 (s, 3H, CH_3); 3.50 (m, 1H, CH); 4.1 (s, 1H, NH); 7.16 (m, 5H, C_6H_5); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 24.3 (s, CH_3); 25.2 and 30.0 and 34.6 (3s, –CH_2–); 54.2 (s, –CH); 120.7 (q, CF_3, $^1J_{CF}$ = 282.7 Hz); (127.0–138.0) (m, $C_{ethylenic}$ and C_6H_5); 146.4 (q, $\underline{C}$–CF_3, $^2J_{CF}$ = 29.3 Hz); 199.5 (C=O); ^{19}F NMR (282.4 MHz, $CDCl_3$): δ_F 104.60 (CF_3). MS: *m/z* 311(M^+); 214(100); 55 (80); 97(42); 134(57); 170(28); 186(43); 268(34); 311(74). Anal. calcd for $C_{17}H_{20}F_3NO$ (311): C, 65.59; H, 6.43; N, 4.50. Found: C, 65.49; H, 6.27; N, 4.37%.

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