Reactions of 1,1,1-Trifluoro[chloro]-4-ethoxybut-3-en-2-ones with 1,3-Dicarbonyl Compounds: Synthesis of 5-Acetyl[carboxyethyl]-1,1,1-trifluoro[chloro]hept-3-ene-2,6-diones and their Cyclic Derivatives Phenol, Pyridines, and Azetone

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Received 11 September 1998; revised 3 December1998

Abstract: The synthesis of 5-acetyl[carboxyethyl] 1,1,1-trifluoro[chloro]hept-3-ene-2,6-diones (**3a,b**, **4a,b**) and their cyclic derivatives 1-[2-hydroxy-4-(trifluoromethyl)phenyl]ethanone (**5a**), 1-[2-hydroxy-6-(trichloro[fluoro]methyl)pyridin-3-yl]ethanone (**6c**, **7c**), and 3-acetylazet-2(1*H*)-one (**8**), obtained from the reactions of 1,1,1-trifluoro[chloro]-4-ethoxybut-3-en-2-one **(1**, **2),** with 1,3-dicarbonyl compounds such as acetylacetone **(a),** ethyl acetoacetate (**b)**, and acetoacetamide **(c)** and sodium hydride in anhydrous THF, is reported.

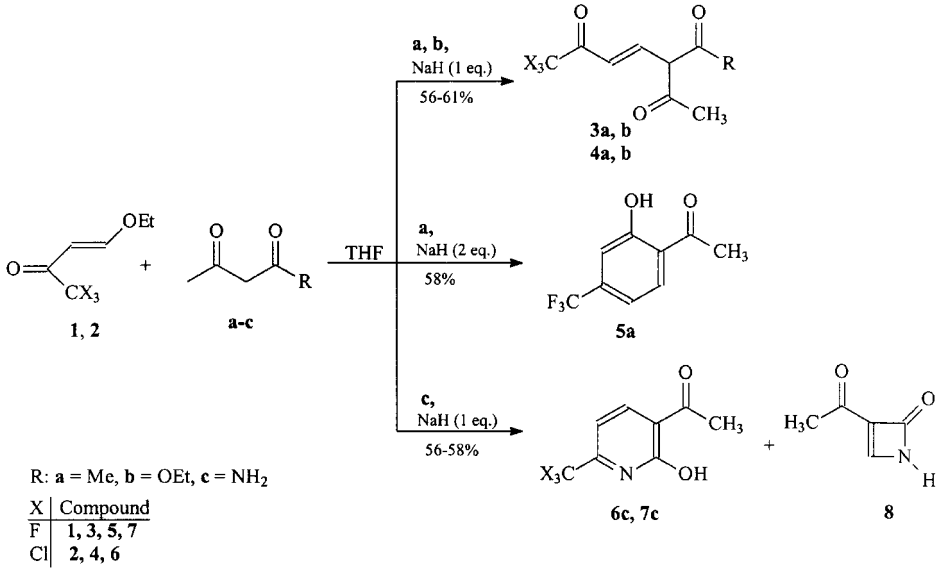
Key words: 1,1,1-Trifluoro[chloro]-4-ethoxybut-3-en-2-ones, dicarbonyl compounds, pyridines, phenols, azetones

The Michael reaction is an efficient and important method for the formation of new C–C bonds,[1,2] The Michael reaction was originally described as the addition of an enolate (electron donor) coming from a –CHCO system to an alkenic group (electron acceptor) of an α,β-unsaturated carbonyl compound.[3,4] More recently, the reaction was extended to α,β-unsaturated nitriles and nitro compounds.[5] In addition to the traditional methods described above, the use of ruthenium,[6] rhodium,[7] scandium,[8] and ytterbium[9] complexes has been reported as stereoselective catalysts of the Michael reaction. Also the application of microwave radiation decreases the reaction time of the Michael reaction from hours, by the conventional method, to minutes.[10]

It is relatively rare to find Michael adducts that preserve the unsaturation on the α,β-carbons. Only two citations were found in the literature where α,β-unsaturated Michael adducts were obtained using methyl 3-chloroacrylate[11] and ethyl propiolate[6] as Michael acceptors. The reaction of methyl 3-chloroacrylate with 2-methylcyclohexanone was accomplished with 20% yield and the low yield of this reaction was attributed to polymerization reactions and the formation of other non-identified products. The reaction of ethyl propiolate with ethyl cyanoacetate furnished the α,β-unsaturated Michael adduct in a mixture of *E/Z* isomers (65/35), in 80% yield.

The β-alkoxyvinyl trihalomethyl ketones, which have been extensively used by our research group in the synthesis of heterocycles of five,[12–17] six[18–22] and seven[23] membered rings, show favorable structural features for use as substrate acceptors to obtain α,β-unsaturated Michael adducts.

Until now α,β-unsaturated Michael adducts derived from β-alkoxyvinyl trihalomethyl ketones have not been reported in the literature. The aim of this work is to report the synthesis of 5-acetyl[carboxyethyl]-1,1,1-trifluo-



ro[chloro]hept-3-ene-2,6-diones and their cyclic derivatives from the reactions of 4-ethoxy-1,1,1-trifluorobut-3-en-2-one **(1)** and 1,1,1-trichloro-4-ethoxybut-3-en-2-one (**2**) with acetylacetone **(a),** ethyl acetoacetate (**b)**, and acetoacetamide **(c)** (Scheme). Compounds **3a,b** and **4a,b** could be useful precursors for the synthesis of pyrimidinylacrylates.[24] Compound **4a,** especially, is a potential key intermediate for a one pot synthesis of the pyrimidinylacrylate residue of sparsomycin,[25] a metabolite isolated from *Streptomyces sparsogenes* and *Streptomyce cuspidosporus*,[26] which shows many kinds of biological activities.[27–32] Compounds **3a,b** and **4a,b** could also work as convenient building blocks for the synthesis of a series of heterocycles and bis-heterocycles.

The most satisfactory conditions with which to obtain the α,β-unsaturated Michael adducts 5-acetyl[carboxyethyl]-1,1,1-trifluorohept-3-ene-2,6-diones **(3a,b)** and 5-acetyl[carboxyethyl]-1,1,1-trichlorohept-3-ene-2,6-diones **(4a,b)** were when β-alkoxyvinyl trihalomethyl ketones **1** and **2,** sodium hydride in anhydrous THF and the 1,3-dicarbonyl compounds **a** and **b**, were used in the same molar ratio. These reactions were stereoselective, and only the E isomers of compounds **3a,b** and **4a,b** were obtained. The coupling constant of 16 Hz among the two vinyl protons in the ^{1}H NMR spectra of compounds **3a,b** and **4a,b** (see Table) allowed for the assignment of the E configuration about the double bond.

Many other reaction conditions and bases such as potassium *t*-butoxide/*t*-butanol,[11] sodium ethoxide/ethanol,[33] and

Table Selected Physical and Spectral Data of **3a-b, 4a-b, 5a, 6c, 7c,** and **8**

Compound	Yield[a] (%)	Mp[b] (°C)	MS (*m/z*) (Intesity %)	IR (KBr), *ν* (cm^{-1})	^{1}H NMR, *δ*, *J* (Hz)[c]	^{13}C- NMR, *δ*, J_{C-F} (Hz)[c]
3a	58	Oil	222 (M, 6), 206 (100), 196 (42), 159 (27)	2987, 1580 (O-H, C=O enol form), 1680 (C=O)	2.44 (s, 6H), 6.40 (d, 1H, *J* = 16) 8.02 (d, 1H, *J* = 16), 18.17 (s, 1H)	25.4 (C-7, C-9), 110.0 (C-5), 114.5 (C-3), 116.5 (C-1, $^1J_{C-F}$ = 290.8), 144.6 (C-4), 179.4 (C-2, $^2J_{C-F}$ = 34.8), 196.7 (C-6, C-8)
3b	59	Oil	252 (M, 2), 235 (70), 183 (62), 120 (76), 92 (100)	2921, 1582 (O-H, C=O enol form), 1702 (C=O)	1.40 (t, 3H, *J* = 7), 2.43 (s, 3H), 4.41 (q, 2H, *J* = 7), 6.96 (d, 1H, *J* = 16), 7.89 (d, 1H, *J* = 16), 14.82 (s, 1H)	14.0 (C-10), 20.1 (C-7), 62.1 (C-9), 100.9 (C-5), 111.1 (C-1, $^1J_{C-F}$ = 289), 113.8 (C-3), 142.7 (C-4), 172.2 (C-8), 180.3 (C-2, $^2J_{C-F}$ = 34,1), 187.0 (C-6)
4a	56	50–51	271 (M, 4), 254 (100), 219 (26), 125 (18)	2908, 1574 (O-H, C=O enol form), 1718 (C=O)	2.41 (s, 6H), 6.70 (d, 1H, *J* = 16), 7.97 (d, 1H, *J* = 16), 17.95 (s, 1H)	25.2 (C-7, C-9), 96.5 (C-1), 110.2 (C-5), 114.9 (C-3), 143.9 (C-4), 179.8 (C-2), 195.6 (C-6, C-8)
4b	61	74–75	301 (M, 2), 259 (15), 184 (100)	2910, 1570 (O-H, C=O enol form), 1704 ((C=O)	1.44 (t, 3H, *J* = 7), 2.41 (s, 3H), 4.39 (q, 2H, *J* = 7), 7.27 (d, 1H, *J* = 16), 7.85 (d, 1H, *J* = 16), 14.55 (s, 1H)	13.9 (C-10), 20.6 (C-7), 62.0 (C-9), 97.0 (C-1), 101.2 (C-5), 113.6 (C-3), 142.0 (C-4), 172.3 (C-8) 181.0 (C-2), 185.3 (C-6)
5a	58	Oil	204 (M, 42), 189 (100), 161 (18), 63 (18)	2960 (O-H), 1657 (C=O), 1508, 1580, 1600 (C=C)	2.68 (s, 3H), 7.14 (d, 1H, ^3J = 8), 7.26 (d, 1H, ^4J = 2), 7.86 (d/d, 1H, ^3J = 8, ^4J = 2), 12.28 (s, 1H)	26.8 (C-8), 115.3 (C-6), 115.9 (C-4), 121.5 (C-2), 122.9 (C-9, $^1J_{C-F}$ = 271.6), 131.3 (C-3), 137.3 (C-5, $^2J_{C-F}$ = 32.9), 162.2 (C-1), 204.2 (C-7)
6c	56	121–122	254 (M, 3), 220 (79), 185 (100) 166 (70), 127 (26)	2930 (O-H), 1654 (C=O)	2.74 (s, 3H), 7.62 (d, 1H, *J* = 8), 8.31 (d, 1H, *J* = 8), 12.6 (s, 1H)	29.2 (C-8), 95.3 (C-9), 111.1 (C-5), 116.3 (C-3), 142.2 (C-4), 161.4 (C-6), 164.2 (C-2), 201.8 (C-7)
7c	58	94–95	206 (M+1, 100)	2931 (O-H), 1664 (C=O)	2.74 (s, 3H), 7.34 (d, 1H, *J* = 8), 8.34 (d, 1H, *J* = 8), 12.7 (s, 1H)	26.6 (C-8), 112.3 (C-5), 117.3 (C-3), 120.2 (C-9, $^1J_{C-F}$ = 271.6), 142.1 (C-4), 151.6 (C-6, $^2J_{C-F}$ = 32.9), 165.1 (C-2), 202.4 (C-7)
8[d]	24	194–195	111 (M, 6), 100 (83), 80 (100)	3482 (N-H), 1660, 1656 (C=O)	2.4 (s, 3H), 5.8 (d, 1H, *J* = 10), 7.7 (d, 1H, *J* = 10)	21.5 (C-6), 139.9 (C-3), 163.7 (C-4), 168.8 (C-2), 192.1 (C-5)

[a] Yields after purification.
[b] Satisfactory Elemental Analysis C ± 0.30, H ± 0.20, N ± 0.10.
[c] Spectra acquired in $CDCl_3$/TMS.
[d] Spectra acquired in DMSO-d_6/TMS.

aluminum oxide[34] which have been successfully used in other related Michael reactions, either gave poor yields, side products, polymerization, or failed to react with our substrate.

The 1-[2-hydroxy-4-(trifluoromethyl)phenyl]ethanone (**5a**) was obtained from the reaction of ketone **1** with acetylacetone and sodium hydride in a molar ratio of 1:1:2 respectively, under reflux for three hours. Using these conditions the compounds **3b**, **4a**,**b** were not converted to the corresponding phenols.

The reaction of ketone **1** or **2** with acetylacetamide (**c**) and sodium hydride in anhyd THF, carried out at room temperature and equal molar ratio, resulted in a 1:1 mixture of the cyclic compounds 1-[2-hydroxy-6-(trifluoromethyl)pyridin-3-yl]ethanone **(7c)** and 3-acetylazet-2(1*H*)-one (**8**) or 1-[2-hydroxy-6-(trichloromethyl)pyridin-3-yl]ethanone **(6c)** and **8**. Compound **8** is probably formed by the internal attack of the amidic nitrogen on the β-carbon with the subsequent elimination of trihalomethylacetone. The compounds **6c** or **7c** were obtained as pure compounds when the reactions were carried out at room temperature and with catalytic amounts of sodium hydride (20%).

Unless otherwise indicated all common reagents and solvents were used as obtained from commercial suppliers without further purification. The β-alkoxyvinyl trifluoro[chloro]methyl ketones (**1a**, **2a)** were prepared according to reference 11. All melting points were determined on a Reichert Thermovar apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were acquired on a Bruker DPX 400 spectrometer (^{1}H at 400.13 MHz and ^{13}C at 100.62 MHz) or on a Bruker DPX 200 spectrometer (^{1}H at 200.13 MHz and ^{13}C at 50.32 MHz) in $CDCl_3$ (or DMSO-d_6 for compound **8**) using TMS as the internal reference. IR spectra were recorded on a Bruker IFS 28 FT-IR spectrometer. The mass spectra were recorded on a Finnigan Mat 80A ion trap detector connected to a Varian 3400 GC equipped with a SE-30 fused silica capillary column, 50 m, 0.32 mm ID. Elemental analysis was performed on a Vario EL Elementar Analysensysteme.

(*E*)-5-Acetyl[carboxyethyl]-1,1,1-trifluoro[chloro]hept-3-ene-2,6-diones (3a,b, 4a,b); General Procedure

In a two necked round-bottomed flask of 50 mL a mixture of β-alkoxyvinyl trihalomethyl ketones **1** or **2** (5.0 mmol), NaH (0.12 g, 5.0 mmol), and anhyd THF (10 mL) was added with stirring. To this mixture was added the dicarbonyl compound **a** or **b** (5.0 mmol) in anhyd THF (10 mL) dropwise from an addition funnel. After stirring for 30 min at r.t., the mixture was acidified with 1 M solution of HCl to pH 3 and the organic layer extracted with CH_2Cl_2 (3 x 40 mL). The combined CH_2Cl_2 layers were dried ($MgSO_4$) and concentrated in vacuo to obtain a dark oil that was filtered through silica gel 60 with hexane. On removal of solvent the compounds **4a** and **4b** crystallized and were further recrystallized from hexane. The compounds **3a** and **3b** did not crystallize and were purified by column chromatography using silica gel 60 and hexane.

The 1-[2-hydroxy-4-(trifluoromethyl)phenyl]ethanone (**5a**) was obtained when the reaction of **1** (0.84 g, 5.0 mmol), acetylacetone (0.50 g, 5.0 mmol), and NaH (0.24 g, 10.0 mmol), was refluxed for 3 h after the addition of the reactants. The compound **5a** was isolated by the same procedure adopted for the compounds **3a** and **3b**. Compound **5a** was obtained as a dark oil which was purified by column chromatography using silica gel and hexane as the mobile phase. Pure **5a (**0.52 g, 58% yield) was obtained.

1-[2-Hydroxy-6-(trichloro[fluoro]methyl)pyridin-3-yl]ethanone (6c, 7c) and 3-Acetylazet-2(1*H*)-one (8); General Procedure

In a two necked round-bottomed flask of 50 mL β-alkoxyvinyl trihalomethyl ketones **1** or **2** (5.0 mmol), NaH (0.024 g, 1.0 mmol), and anhyd THF (10 mL) was added with stirring. To this mixture the dicarbonyl compound **c** (0.50 g, 5.0 mmol) in anhyd THF (10 mL) was added dropwise from an addition funnel. After stirring for 30 min at r.t., the mixture was acidified with 1M HCl until pH 3 and extracted with CH_2Cl_2 (3 x 40 mL). The combined CH_2Cl_2 layers were dried ($MgSO_4$) and concentrated under vacuum to obtain **6c** or **7c** as brown solids which were purified by recrystallization from $CHCl_3$. Yield of **6c** was 0.71 g (56%) and **7c** was 0.59 g (58%).

Compound **8** was obtained together with compounds **6c** or **7c** when the reaction was carried out with an equivalent amount of NaH. The compound **8** was isolated from the compounds **6c** and **7c** by their different solubility. Compounds **6c** and **7c** are soluble in $CHCl_3$ while compound **8** is soluble in MeOH. After compound **8** was separated from **6c** or **7c**, it was recrystallized from MeOH. Yield of pure **8** was 0.13 g (24%).

Acknowledgement

The authors thank the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), PADCT-II/FINEP, and Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul (FAPERGS) for financial support.

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Article Identifier:
1437-210X,E;1999,0,05,0765,0768,ftx,en;C05998SS.pdf