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Trifluoroacetylation of unsymmetrical ketone acetals. A convenient route to obtain alkyl side chain trifluoromethylated heterocycles

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Abstract

A convenient method to obtain β-alkyl-β-methoxyvinyl trifluoromethyl ketones [$CF_3COCH{=}C(OMe)R$, where R = Et, *n*-Pr, *i*-Pr, *i*-Bu, t-Bu, $-(CH_2)_2OMe$] from the regiospecific acylation of kinetic enol ether generated in situ is reported. The unsymmetrical ketone dimethyl acetals react with trifluoroacetic anhydride in the presence of pyridine using dry chloroform as solvent with a temperature range of 25–60°C. These acetals [$R–C(OMe)_2Me$] are obtained from the reaction of alkyl methyl ketones with trimethyl orthoformate in the presence of *p*-toluenesulfonic acid as catalyst in pure methanol as solvent. The new acetylated enol ethers proved to be versatile building blocks for the construction of interesting alkyl trifluoromethyl substituted heterocycles. Thus, examples of isoxazoline, pyrazoline, pyrazole and pyrimidinone have been obtained in good yields (62–79%).

Keywords: β-Alkoxyvinyl trifluoromethyl ketones; Unsymmetrical ketone dimethyl acetals; Trifluoromethylated heterocycles

1. Introduction

Several methods for the synthesis of trifluoromethyl enones have been reported [1,2] because the attempts to perform the synthesis of a very simple trifluoromethyl containing vinyl ketones, by conventional procedures, are not yet successful. A route to obtain these compounds has been the direct haloacetylation of acyclic enol ethers described elsewhere [3–8] and by our research group [9–11], which has afforded β-alkoxyvinyl halomethyl ketones or β-diketones. These haloacetylated enol ethers have been used as a 3-atom synthetic precursor for the synthesis of 5-, 6- and 7-membered trihalomethylated heterocycles [12–23]. Conventionally, enol ethers have been prepared from symmetrical ketone or aldehyde acetals [24–26]. However, the isolation of these enol ethers involves a tedious distillation process and in some cases (e.g. those derived from unsymmetrical ketones) a mixture of kinetic and thermodynamic enol ethers are obtained. Moreover, the presence of trace acids in the acylation reaction leads to the polymerization or hydrolysis of enol ethers. Recently, an alternative one-pot procedure with advantages over the direct acylation of enol ethers was reported. In this procedure, enol ethers, generated in situ from the respective ketone acetal are acylated to obtain β-alkoxyvinyl halomethyl ketones [6–8,10–11,38]. This reaction was carried out using the ketone dimethyl acetal and the acylating reagent in a molar ratio of 1 : 2, respectively in order to generate the enol ether in situ following by its acetylation.

On the other hand, we have observed in the literature many methods to put a desired alkyl side chain in heterocyclic compounds. The great majority of these methods introduce the alkyl side chain after the isolation of the heterocyclic structure [28].

The introduction of alkyl chain plays a very important role in many heterocycles with respect to their biological activity. For example, pyroctone a pyrimidone described as an antiseborrheic agent, nabilone a 9-ketocannabinoid with antiemetic properties and nabitran that in addition of being hypotensive and sedative-hypnotic has more potent analgesic effect than codeine [29]. Also, the increase of the herbicidal activity has been investigated in 3-trifluoro-

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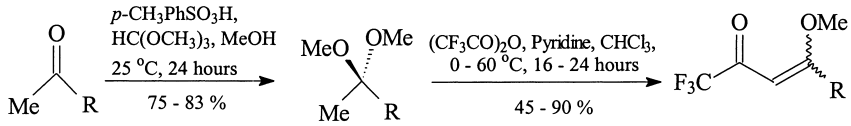


1a-f **2a-f** **3a-f**

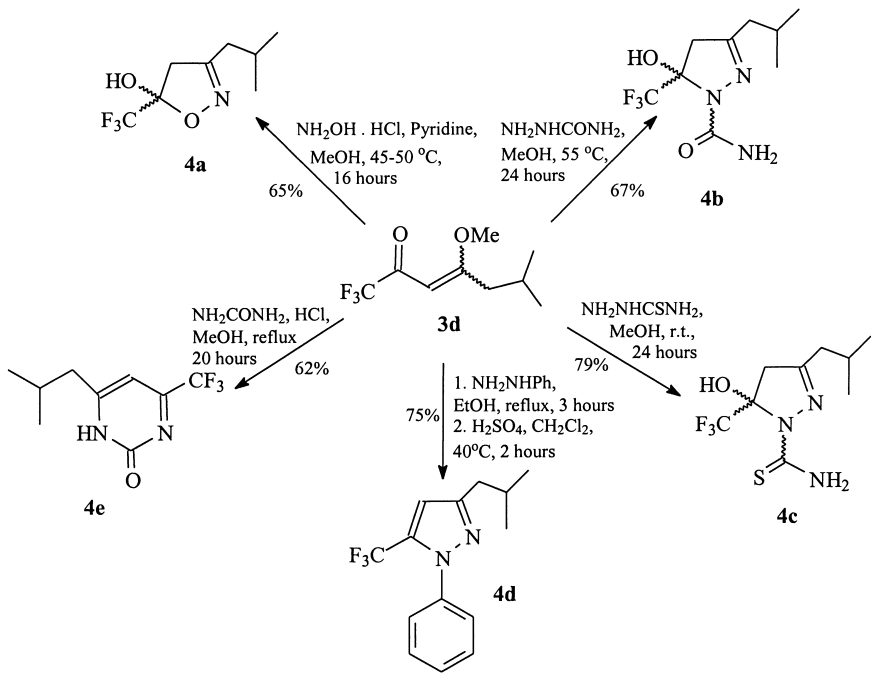
	a	b	c	d	e	f	
R	Et	*n*-Pr	*i*-Pr	*i*-Bu	*t*-Bu	vinyl	**1**
R	Et	*n*-Pr	*i*-Pr	*i*-Bu	*t*-Bu	-$(CH_2)_2$OMe	**2, 3**

Scheme 1.

methyl- and 3-t-butyl-pyrazole and pyridin–carboxamide derivatives [30]. Morever, a review of the literature showed that the synthesis of important compounds, as pirimidin-2-ones, from direct cyclization of 1,3-diketones with urea has not been reported. For example, the synthesis of uracils, involves the condensation of thiourea or alkylisothioureas with β-ketoesters [31–33]. The subsequent removal of the S atom, in order to obtain uracil, involves usually severe conditions [34,35]. Another indirect method to obtain 2-pyrimidin-ones is the condensation of β-ketoesters and *O*-methylisourea bisulfate in a slightly basic medium. The 2-methoxy-pyrimidin-4-one is then hydrolyzed to the corresponding uracils [36]. Specific and facile synthesis of trifluoromethylated pyrimidin-2-one was developed by our research group [37]. However, the introduction of an alkyl side chain has not yet been studied, because the synthesis of β-alkoxyvyniltrifluoromethyl ketones from trifluoracetylation of acetals derived from alkyl-methyl-dimethylacetals was not known.

This situation prompted us to investigate the development of a general method to obtain functionalized precursors for heterocycles which contain in their structure both an alkyl side chain and a trifluoromethyl group.

The aim of this work is (i) to use the methodology of acylation of enol ethers, generated in situ from unsymmetrical ketone dimethyl acetals (**2a–f**), as a general procedure to synthesize regiospecifically β-alkyl-β-metoxyvinyl trifluoromethyl ketones (**3a–f**) derived from unsymmetrical ketones (**1a–f**) that contain in their structure both an alkyl side chain and a trifluoromethyl group (Scheme 1); and (ii) to use one precursor (**3d**) to obtain interesting trifluoromethyl alkyl side chain heterocycles (**4a–e**) from the cyclocondensation reactions with hydroxylamine, semicarbazide, thiosemicarbazide, phenylhydrazine and urea (Scheme 2).



4a **4b** **3d** **4e** **4d** **4c**

Scheme 2.

2. Results and discussion

The alkyl methyl ketone dimethyl acetals **2a–f** were synthesized from the reaction of the respective unsymmetrical methyl ketones **1a–f** with trimethyl orthoformate in molar ratio 1 : 1.5 and in the presence of *p*-toluenesulfonic acid [7,10–11,38] as catalyst and using pure methanol as solvent. The acylation of **2a–f** with trifluoroacetic anhydride in pyridine, in molar ratio 1 : 2 : 2, was carried out in dry chloroform as solvent. Two equivalents of the acylating reagent per dimethyl acetal was necessary to obtain the β-methoxyvinyl trifluoromethyl ketones **3a–f** since one molecule of the acylating promotes the acylation and a second traps the methoxy group liberated by the ketone dimethyl acetal and to give methyl trifluoroacetate.

A mixture of distilled ketone dimethyl acetals, pyridine and dry chloroform is added to pure trifluoroacetic anhydride at 0°C or, with cooling in an ice/salt bath. After the addition, the optimal reaction time and reaction temperature for trifluoroacetylation were found to be 16 h at 25–30°C for **3a–b**, **3f** and 24 h at 60–65°C for **3c–e**. It was observed that the compounds (**2a–b**, **2f**) derived from alkyl methyl ketones with small substituents (R) could be readily converted into β-methoxyvinyl trifluoromethyl ketones **3a–b**, **3f** at ambient temperature. The same reaction must be carried out for compounds (**2c–e**), derived from alkyl methyl ketones with bulky substituent (R), at temperatures above 60°C. As expected, the Michael addition occurred at the vinyl bond of the compound **1f** and the saturated ketone dimethyl acetal **2f** was isolated in good yield. Under the conditions employed, alkyl methyl ketone dimethyl acetals react with trifluoroacetic anhydride to give trifluoroacetyl vinyl enones (**3a–f**) in good yields. The geometrical isomerism (*E*/*Z*) for compounds **3a–f** have not yet been determined. In all reactions we have not found polymerization products and all crude products were purified by distillation. The compounds **3a–f** are highly volatile at room temperature and because of this property the elemental analysis of **3a–f** could not be performed.The more satisfactory results of these reactions, selected physical (b.p.), NMR and mass spectral data of **3a–f** are presented in Table 1.

The cyclization reactions for compounds **4a–e** were carried out under similar conditions or with any modifications, as described in the literature [9,17,18,23,37] and are presented in the experimental part. An important modification was performed in the synthesis of **4b**. This compound was only obtained where previously the semicarbazide hydrochloride was treated with sodium methoxide in methanolic medium. On the other hand, the use of the procedure described in the literature [17] to obtain **4d** give a mixture of 2 : 1 of **4d** and the respective 4,5-dihydro-pyrazoline. This problem was overcome by addition of sulfuric acid in a second reaction step, where only **4d** was obtained in 75% yield.

3. Conclusion

The regiospecificity of the reaction on the methyl carbon of **2a–f** is achieved under kinetic control. For the conditions used, the kinetic enol ether is generated and reacts with the strong acylating agent [$(CF_3CO)_2O$] present in the medium. This study affords a methodology to obtain regiospecifically a series of β-methoxyvinyl trifluoromethyl ketones (**3a–f**), in regular to good yield (see Table 1). This series can be employed as a trifluoromethylated 3-atom block precursor on organic synthesis, especially to obtain new alkyl side chain substituted trifluoromethylated heterocycles **4a–e** (see Table 2), which often shown biological activity [27].

4. Experimental

Unless otherwise indicated all common reagents and solvents were used as obtained from commercial suppliers without further purification. All boiling and melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker DPX-200 spectrometer (^1H at 200.13 MHz and ^{13}C at 50.32 MHz), 298 K and 0.5 M in chloroform-d_1/TMS (**3a–f**) or in DMSO-d_6/TMS (**4a–e**). The mass spectra were performed on a GC/MS spectrometric system (HP 6890 GC coupling to HP 5973 mass selective detector).

*4.1. Preparation of unsymmetrical ketone dimethyl acetals (**2a–f**)*

The ketone dimethyl acetals were synthesized according with the literature [7,10–11,38] and purified by distillation process.

*4.2. Preparation of β-methoxyvinyl trifluoromethyl ketones (**3a–f**)*

4.2.1. General procedure

A solution of ketone dimethyl acetals **2a–f** (30 mmol) and pyridine (60 mmol) in 30 ml of chloroform was added dropwise to stirred pure trifluoroacetic anhydride (60 mmol) kept at 0°C. The mixture was stirred for 16 h at room temperature (25–30°C) for **3a–b**, **3f** or for 24 h at 60–65°C for **3c–e**. The mixture was washed with a solution of hydrochloric acid 0.1 M (once) and water (three times). The organic layer was dried with magnesium sulfate, the solvent was removed by rotatory evaporation and the products (**3a–f**) were purified by distillation under reduced pressure.

*4.3. Preparation of 5-hydroxy-3-iso-butyl-5-trifluoromethyl-4,5-dihydro-isoxazole (**4a**)*

Hydroxylamine hydrochloride (10 mmol) was added to a stirred solution of 4-methoxy-4-iso-butyl-1,1,1-trifluoro-3-

Table 1
Selected physical properties and spectral data of compounds **3a-f**

Compound[a]	Yield (%)	Boiling.point (°C) /mBar	Molecular formula (weight)	^{1}H-NMR [δ (ppm)]	^{13}C-NMR [δ (ppm), J_{CF} (Hz)]	MS [*m/z* (%)]
3a	90	49/9.0	$C_7H_9O_2F_3$ (182.14)	5.63 (s, 1H, H-3), 3.81 (s, 3H, OCH_3), 2.83 (q, 2H, H-5), 1.14 (t, 3H, H-6)	186.2 (C-4), 188.4 (q, J = 33, C-2), 116.7 (q, CF_3, J = 292), 90.5 (C-3), 56.5 (OCH_3), 27.4 (C-5), 10.7 C-6)	182 (M^+, 77), 165 (1), 150 (3), 113 (100), 85 (23), 69 (77)
3b	68	37/3.5	$C_8H_{11}O_2F_3$ (196.16)	5.64 (s, 1H, H-3), 3.80 (s, 2H, OCH_3), 2.78 (t, 2H, H-5), 1.56 (sext, 2H, H-6), 0.97 (t, 3H, H-7)	185.2 (C-4), 177.8 (q, J = 33, C-2), 116.7 (q, J = 292,CF_3), 91.0 (C-3), 56.4 (OCH_3), 35.6 (C-5), 20.3 (C-6), 13.6 (C-7)	196 (M^+, 50), 181 (33), 164 (3), 127 (100), 99 (22), 69 (66)
3c	50	70/16	$C_8H_{11}O_2F_3$ (196.16)	5.55 (s, 1H, H-3), 3.94 (sept, 1H, H-5), 3.79 (s, 3H, OCH_3), 1.11 (d, 6H, $2CH_3$)	189.2 (C-4), 178.3 (q, J = 33, C-2,), 116.8 (q, J = 292, CF_3), 89.7 (C-3), 56.5 (OCH_3), 31.2 (C-5), 10.2 ($2CH_3$)	196 (M^+, 95), 181 (17), 164 (13), 127 (100), 99 (23), 69(81)
3d	86	67/9.5	$C_9H_{13}O_2F_3$ (210.19)	5.66 (s, 1H, H-3), 3.79 (s, 3H, OCH_3), 2.71 (d, 2H, H-5), 2.01 (m, 1H, H-6), 0.95 (d, 6H, $2CH_3$)	184.6 (C-4), 178.4 (q, J = 33, C-2), 116.8 (q, J = 292, CF_3), 91.5 (C-3), 56.5 (OCH_3), 46.0 (C-5), 27.8 (C-6), 22.0 ($2CH_3$)	210 (M^+, 8),195 (81), 141 (100), 113 (32), 69 (58)
3e[b]	45	51/7.0	$C_9H_{13}O_2F_3$ (210.19)	6.05/5.78 (2s, 1H, H-3), 4.03/3.80 (2s, 3H, OCH_3), 1.23/1.19 (2s, 9H, $3CH_3$)	190.9/190.2 (2C-4), 176.5/175.2 (2q, J = 33/42, 2C-2), 117.2/116.7 (2q, J = 282/291, $2CF_3$), 91.6/90.1 (2C-3), 63.7/56.7 (2-OCH_3), 39.8/39.5 (2C-5), 27.7/26.6 [2($3CH_3$)]	210 (M^+, 6), 195 (48), 141 (100), 113 (35), 69 (58)
3f	62	87/15	$C_8H_{11}O_3F_3$ (212.16)	5.70 (s, 1H, H-3), 3.82 (s, 3H, OCH_3), 3.63 (t, 2H, H-6), 3.34 (s, 3H, H-7), 3.11 (t, 2H, H-5)	181.9 (C-4), 178.1 (q, J = 33, C-2), 116.4 (q, J = 292, CF_3), 91.6 (C-3), 68.7 (C-7), 57.78 (C-6), 56.3 (OCH_3), 33.8 (C-5)	212 (M^+, 19), 197 (54), 181 (100), 143 (36), 115 (12), 69(19)

[a]Yields of isolated compounds; volatile compounds.
[b]Mixture of *E*/*Z* isomers.

buten-2-one (5 mmol) and pyridine (10 mmol) in 15 ml of methanol at room temperature. The mixture was stirred and heated for 16 h at 45–50°C. To this mixture is added dichloromethane at room temperature. The new mixture was washed with a solution of hydrochloric acid 0.5 N (three times) and water (once). The organic layer was dried with magnesium sulfate, the solvent was removed by rotatory evaporation and the pure product was isolated.

4.4. Preparation of 5-hydroxy-3-iso-butyl-5-trifluoromethyl-4,5-dihydro-1H-1-pyrazole-carboxyamide (**4b**)

To a stirred solution of semicarbazide (10 mmol) in 10 ml of methanol, 4-methoxy-4-iso-butyl-1,1,1-trifluoro-3-buten-2-one (5 mmol) was added at 20–25°C. The mixture was stirred for 24 h at 55°C. The product precipitated by addition of 15 ml of cool water to the reaction. The crystalline solid were filtered off and recrystallized from hexane-chloroform 3 : 1.

4.5. Preparation of 5-hydroxy-3-iso-butyl-5-trifluoromethyl-4,5-dihydro-1H-1-pyrazolethio-carboxyamide (**4c**)

To stirred solution of semicarbazide (5 mmol) in 25 m1 of methanol, kept at 20–25°C, pure 4-methoxy-4-iso-butyl-1,1,1-trifluoro-3-buten-2-one (5 mmol) was added and the mixture was stirred for 24 h at 20–25°C.The solvent was evaporated and hot chloroform was added to the solid residue. The insoluble thiosecarbazide was filtered off. The product was crystallized by addition of hexane to the chloroform solution (1 : 2).

Table 2
Selected physical and spectral data of compounds **4a-e**

Compound	Yield[a] (%)	Melting point (°C)	Molecular formula[b] (weight)	^{1}H-NMR [δ (ppm), J (Hz)]	^{13}C-NMR [δ (ppm), J_{CF} (Hz)]
4a	65	99–100	$C_8H_{12}F_3NO_2$ (211.18)	8.20 (s, 1H, OH), 3.35 (d, 1H, J = 19, H4a), 3.02 (d, 1H, J = 19, H4b), 2.19 (d, 2H, H3'1, 1.88 (m, 1H, H3'2), 0.90 (d, 3H, H3'3), 0.87 (d, 3H, H3'3)	159.0 (C3), 122.7 (q, J = 284, CF_3), 102.6 (q, J = 33, C5), 44.56 (C4), 35.6 (C3'1), 25.5 (C3'2), 22.1 (1C, C3'3), 21.9 (1C, C3'3)
4b	67	100–101	$C_9H_{14}F_3N_3O_2$ (253.22)	7.30 (s, 1H, OH), 6.54 (s, 2H, NH_2), 3.30 (d, 1H, J = 19, H4a), 3.01 (d, 1H, J = 19, H4b), 2.18 (d, 2H, H3'1), 1.93 (m, 1H, H3'2), 0.91 (d, 3H, H3'3), 0.88 (d, 3H, H3'3)	155.1 (C = 0),154.1 (C3), 123.6 (q, J = 286, CF_3), 90.1 (q, J = 33, C5), 46.7 (C4), 38.0 (C3'1), 25.6 (C3'2), 22.3 (1C, C3'3), 22.1 (1C, C3'3)
4c	79	106–107	$C_9H_{14}F_3N_3OS$ (269.28)	9.15 (s, 1H, NHa), 9.02 (s,1H, OH), 8.55 (s, 1H, NHb), 4.00 (d, 1H, J = 19, H4a), 3.83 (d, 1H, J = 19, H4b), 2.70 (d, 2H, H3'1), 2.49 (m, 1H, H3'2), 1.42 (d, 3H, H3'3), 1.37 (d, 3H, H3'3)	176.1 (C5), 158.4 (C3), 123.7 (q, J = 290, CF_3), 91.9 (q, J = 33, C5), 46.4 (C4), 38.0 (C3'1), 25.4 (C3'2), 22.4 (1C, C3'3), 22.0 (1C, C3'3)
4d	75	Oil	$C_{14}H_{15}F_3N_2$ (268.28)	8.10–7.98 (m, 5H, Ar–H), 7.40 (s, 1H, H4), 3.05 (d, 2H, H3'1), 2.49 (m, 1H, H3'2), 1.45 (d, 6H, H3'3)	152.1, 129.1, 128.8, 125.5 (Ar–C), 138.7 (C3) 131.4 (q, J = 39, C5), 120.1 (q, J = 268, CF_3),108.5 (C4), 36.3 (C3'1), 28.0 (C3'2), 22.0 (C3'3)
4e	62	123–124	$C_9H_{11}F_3N_2O$ (220.19)	12.77 (s, 1H, NH), 6.78 (s, 1H, H5), 2.56 (d, 2H, H6'1), 2.07 (m, 1H, H6'2), 0.92 (d, 6H, H6'3)	168.0 (C = O),161.0 (q, J = 35, C4), 157.5 (C6), 120.0 (q, J = 277, CF_3), 99.7 (C5), 48.6 (C6'1), 29.2 (C6'2), 22.3 (2C, C6'3)

[a] Yields of isolated compounds.
[b] Sactisfactory microanalyses obtained: C ± 0.15, H ± 0.11 N ± 0 33.

4.6. Preparation of 3-iso-butyl-5-trifluoromethyl-1H-1-phenylpyrazol (**4d**)

Phenyl hydrazine (6.5 mmol) was added dropwise at room temperature to a stirred solution of the 4-methoxy-4-iso-butyl-1,1,1-trifluoro-3-buten-2-one (5 mmol) in absolute ethanol (10 ml). The mixture was stirred and heated under reflux for 3 h, then the solvent was evaporated in vacuo. To this mixture was added 5 ml of dichloromethane and 1 ml sulfuric acid 96% and heated at 40°C for 2 h. After, was added 10 ml of water and extracted with dichloromethane. The organic layer was dried with magnesium sulfate and the solvent was removed by rotatory evaporation. The crude product was passed through a column of silica gel 60, eluent dichloromethane. After evaporation of the solvent in vacuo a yellow oil was isolated, as pure product.

4.7. Preparation of 6-iso-butyl-4-trifluoromethyl-pyrimidin-2-one (**4e**)

Compound **3d** (5 mmol) and urea (10 mmol), were dissolved in 10 ml of methanol. To the mixture was added 1 ml of concentrated HC1 and refluxed for 20 h. The solvent was partially evaporated and the product was allowed to crystalize by cooling the solution. The solid was filtered, washed with cold water, and recrystalized from methanol.

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