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Regiospecific acylation of acetals. A convenient method to obtain β-methoxyvinyl trichloromethyl ketones

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Abstract

The regiochemistry of the acylation of enol ethers, generated in situ, from acetals of unsymmetrical ketones is reported. These results demonstrate a convenient one-pot method to obtain a series of β-methoxyvinyl trichloromethyl ketones [$CCl_3COCH{=}C(OMe)R$, where R=Et, *n*-Bu, *i*-Pr, $(CH_2)_2C(OMe){=}CHC(O)CCl_3$ and $(CH_2)_5CO_2CH_3$)] in high yields.

1. Introduction

The haloacetylation of acyclic enol ethers described elsewhere[1,2] and by our research group,[3] affords β-alkoxyvinyl halomethyl ketones or β-diketones, which have been used as precursors for the synthesis of 5-, 6- and 7-membered heterocycles.[4–6] Enol ethers, prepared from ketone or aldehyde acetals,[7–10] are precursors for β-alkoxyvinyl halomethyl ketones. The isolation of these enol ethers is a tedious process and in some cases, (e.g., those derived from unsymmetrical ketones) a mixture of enol ethers is obtained. Furthermore, the presence of traces of acids in the reaction results in the polymerization or hydrolysis of enol ethers.[9] Recently, the acylation of the enol ethers generated in situ from the respective acetal of propanone,[2] acetophenone[2] or cyclohexanone,[3] as an alternative one-pot procedure to obtain β-alkoxyvinyl halomethyl ketones was reported[2,3] with great advantages over the direct acylation of enol ethers. This reaction was carried out using the acetal and the acylating agent in a molar ratio of 1:2, respectively, in order to generate the enol ether in situ followed by its acylation.

Thus, the possibility of obtaining trichloromethyl-substituted heterocycles[3–5] and the transformation of this group into carboxyl groups (under mild conditions)[4] prompted us to pay special attention to the synthesis of a series of β-alkoxyvinyl trichloromethyl ketones. The aim of this work is: (i) to study

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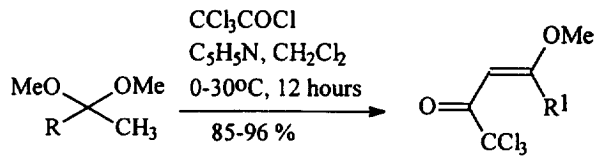
the regiochemistry of the acylation of enol ethers, generated in situ, from the acetals of unsymmetrical ketones; and (ii) to develop a general procedure to synthesize, regiospecifically, a series of β-alkoxyvinyl trichloromethyl ketones (**2a–e**, Scheme 1).



1a-e **2a-e**

	a	b	c	d	e
R	Et	*n*-Bu	*i*-Pr	$-(CH_2)_2C(OMe)_2CH_3$	$-(CH_2)_5CO_2CH_3$
R^1				$-(CH_2)_2C(OMe)=CHC(O)CCl_3$	
Yield (%), **2**	96	90	85	87	86

Scheme 1.

2. Discussion

The methyl ketone acetals **1a–e** were synthesized from the reaction of the respective ketone with trimethyl orthoformate in the presence of *p*-toluenesulfonic acid.[3] The acylation of compounds **1a–e** with trichloroacetyl chloride in pyridine and dichloromethane as solvent was carried out in a molar ratio 1:2:2 (for **1d**, 1:4:4), respectively. Two equivalents of trichloroacetyl chloride per acetal was necessary to obtain the β-alkoxyvinyl trichloromethyl ketones since one molecule of the acylant promotes the acylation and the second molecule traps the alkoxy group liberated by the acetal. The reaction was monitored by HPLC and the most satisfactory reaction time was found to be 12 hours at room temperature (25–30°C).

The regiospecificity of the reaction on the methyl carbon of **1a–e** is achieved under kinetic control. For the conditions used, only the kinetic enol ether is generated and reacts with the strong acylating agent present in the medium. The compounds **2a–e** present the *E*-configuration. The isomer configurations assigned were based on $^3J_{C5-H3}$ coupling constants and X-ray data of similar compounds.[11] Selected physical and spectral data of compounds **2a–e** are presented in Table 1.

Unless otherwise indicated all common reagents and solvents were used as obtained from commercial suppliers without further purification. Elemental analysis was carried out on an Elemental Analysensysteme Vario EL apparatus. ^1H and ^{13}C NMR spectra were recorded on a Bruker DPX-400 (^1H at 400.13 MHz and ^{13}C at 100.62 MHz), 298 K, digital resolution ±0.01 ppm, 0.5 M in chloroform-d_1/TMS. IR spectra were obtained on a Perkin–Elmer 599-B.

2.1. β-Alkoxyvinyl trichloromethyl ketones 2a–e: general procedure

To a stirred solution of acetals **1a–e** (30 mmol) and pyridine (60 mmol) in 30 ml of dichloromethane kept at 0°C a solution of trichloroacetyl chloride (60 mmol) was added dropwise. The mixture was

Table 1
Selected physical and spectral data of **2a–e**

Product	Molecular Formula	Elemental Analysis (%) C calcd. / found	H	b.p./Torr (°C)	IR (film) ν (cm^{-1})	^{1}H δ	^{13}C δ
2a	$C_7H_9Cl_3O_2$	36.32	3.92	87-89/0.4	1765, 1695,	5.92 (s, H3),	97.4 (C1), 179.2
	231.50	36.59	4.03		1580	2.80 (q, H5)	(C2), 88.7 (C3),
						3.77 (s, OMe)	184.1 (C4), 26.2
							(C5), 55.6 (OMe)
2b	$C_9H_{13}Cl_3O_2$	41.65	5.05	115/0.4	1765, 1700,	5.96 (s, H3),	98.1 (C1), 180.0
	259.56	41.59	4.83		1575	2.78 (t, H5)	(C2), 89.7 (C3),
						3.79 (s, OMe)	184.1 (C4), 33.2
							(C5), 55.2 (OMe)
2c	$C_8H_{11}Cl_3O_2$	39.13	4.52	125-126/0.4	1780, 1695,	5.97 (s, H3),	97.5 (C1), 178.9
	245.53	39.28	4.58		1570	3.95 (sept, H5),	(C2), 87.7 (C3),
						3.88 (s, OMe)	186.6 (C4), 29.9
							(C5), 55.6 (OMe)
2d	$C_{12}H_{12}Cl_6O_4$	33.29	2.79	oil	1700, 1590	5.95 (s, H3),	97.2 (C1), 179.1
	432.94	33.58	2.85			3.09 (s, H5)	(C2), 89.9 (C3),
						3.77 (s, OMe)	180.5 (C4), 29.3
							(C5), 55.8 (OMe)
2e	$C_{12}H_{17}Cl_3O_4$	43.46	5.17	oil	1760, 1575	5.90 (s, H3),	97.9 (C1), 180.0
	331.62	43.66	5.19			2.78 (t, H5)	(C2), 89.8 (C3),
						3.80 (s, OMe)	183.6 (C4), 33.2
							(C5), 55.3 (OMe)

stirred for 12 h at room temperature (25–30°C). The mixture was washed with a solution of hydrochloric acid 0.1 N (once) and water (three times). The organic layer was dried with sodium sulfate, the solvent was removed by rotary evaporation and the product was purified by either distillation (**2a**) or chromatographically (**2b–e**) with silica gel 60, in a 30 cm column and hexane:chloroform (1:1) as eluent (see Table 1).

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