Haloacetylated Enol Ethers. 11 [16]. Synthesis of 1-Methyl- and 1-Phenyl pyrazole-3(5)-ethyl Esters. A One-Pot Procedure

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A one-pot synthesis of 1-methyl- and 1-phenylpyrazole-3(5)-ethyl esters **2,3a-e** by the cyclocondensation of β-alkoxyvinyl trichloromethyl ketones **1a-e** with methyl and phenyl hydrazine hydrochloride under mild conditions, is reported. A study using compounds **1a-e** with different substituents proved that these are versatile building blocks for the synthesis of pyrazole derivatives, having a 3(5)-ethoxycarbonyl substituent in good yields (60-89%). The hydrazine and β-alkoxyvinyl trichloromethyl ketone substituent effects on the reaction regiochemistry on the formation of the 1,3- and 1,5-isomer were observed.

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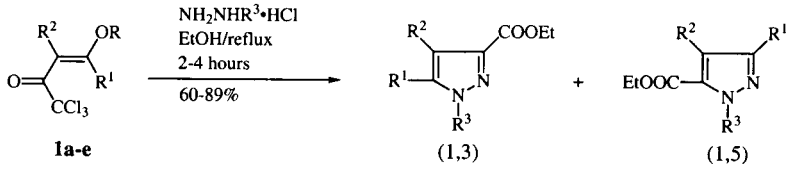
The pyrazole-3(5)-ethyl esters and their derivatives are known to be important intermediates in the preparation of agrochemicals, microbicides, herbicides [1], plant growth regulators and protectants [2]. v. Auwers and Cauer [3] have synthesized pyrazole-3(5)-alkyl esters by the reaction of an appropriate α-ethylenic ester and diazomethane, followed by oxidation of the pyrazoline intermediate with bromine. This method was improved by Elguero *et al.* [4] who obtained a series of pyrazole-3(5)-alkyl esters in moderate overall yields. These authors [5] also have developed a method to synthesize a series of substituted 3- and 5-ethoxycarbonyl-1-methylpyrazoles from the reaction of the sodium salt of 1-ethoxycarbonyl-butane-1,3-dione and methylhydrazine sulfate. Padwa *et. al.* [6] reported the synthesis of 3(5)-methyl-5(3)-ethoxycarbonylpyrazoles by the cyclization of vinyl diazo esters. All the reactions mentioned above, are limited to the synthesis of one compound, or they involve several step syntheses, or they use precursors that are not readily synthesized.

β-haloacetylated enol ethers (or β-alkoxyvinyl halomethyl ketones), with functionalized acyl groups of the type CX_3CO [7], CHX_2CO [8]. These compounds are of general interest as precursor for a variety of halo-substituted five- and six-membered heterocyclic compounds, *e.g.*, isoxazoles [7-11], dihydroisoxazoles[7-11], pyrazoles [12,13,16], pyrimidinones [14], and pyrimidine derivatives [15,16].

In a previous short paper [13] we have reported a one-pot procedure to synthesize ethoxycarbonylpyrazoles by the reaction of β-alkoxyvinyl trichloromethyl ketones with hydrazine. The aim of this work is to report the application of this one-pot procedure for the synthesis of 1-methyl- and 1-phenylpyrazole-3(5)-ethyl esters **2, 3a-e,** by the reaction of β-alkoxyvinyl trichloromethyl ketones **1a-e**, with methyl and phenyl hydrazine hydrochloride. Also, we intend to observe the effect of hydrazine and β-alkoxyvinyl trichloromethyl ketone substituents on the reaction regiochemistry to the formation of the 1,3- and 1,5-isomer (Scheme).

Scheme



1a-e (1,3) (1,5)

2,3 a-e

Compound	R	R^1	R^2		R^3
a	Et	H	H	**2**	Me
b	Me	Me	H	**3**	Ph
c	Et	H	Me		
d	Me	Ph	H		
e	Et/H	$-(CH_2)_4-$			

As a part of our research program, we developed a general one-step procedure for preparing analytically pure

The β-alkoxyvinyl trichloromethyl ketones **1a-e** were synthesized from the reaction of the respective car-

bonyl acetal or enamine with trichloroacetyl chloride [17].

The cyclocondensation of **1a-e** with methyl or phenylhydrazine hydrochloride was carried out in a molar ratio 1:1.2 using 96% ethanol as the solvent. The use of a small excess of the hydrazine derivative was essential to obtain a saturated solution during the reaction resulting in an improvement of the yield. The reaction was monitored by hplc and the best reaction time was found to be 2 hours for methylhydrazine, and 4 hours for phenylhydrazine. Thus, all reaction mixtures were stirred under reflux for 2 hours (methylhydrazine) or 4 hours (phenylhydrazine, 78°), then the excess hydrazine hydrochloride was filtered and the solvent was evaporated under reduced pressure. The product was taken up in dichloromethane and was purified chromatographically. The mixture of 1,3- and 1,5-isomers of 1-methylpyrazole-3(5)-ethyl esters **2a-e** and 1-phenylpyrazole-3(5)-ethyl esters **3a-e** are obtained in 60-89% yield (Scheme, Tables 1 and 2).

Table 1

Yield and (1,3):(1,5) Isomer Ratio [a] of Compounds **2,3a-e**

Compound	Isomer ratio 1,3:1,5	Yield %	Compound	Isomer ratio 1,3:1,5	Yield %
2a	3:1	70	**3a**	9:1	70
2b	4:1	81	**3b**	1:1	81
2c	1:1	60	**3c**	8:1	87
2d	10:1	63	**3d**	11:1	83
2e	1:6	89	**3e**	1:2	77

[a] The isomer ratio was obtained by gc-ms. The assignments of 1,3- and 1,5-isomers were made from the aromatic solvent induced shift data [4].

The mechanism proposed for the formation of compound **2,3** involves conjugate addition of the nucleophilic nitrogen (Michael type) followed by cyclic ring closure to form the pyrazole derivatives. The transformation of the trichloromethyl group into the ethoxycarbonyl group remains unclear. Although mild conditions had been used, we believe the mechanism for this transformation was possible because during ring closure the carbonyl oxygen of the β-alkoxyvinyl trichloromethyl ketone begins the chlorine substitutions with attack on the carbon atom of the trichloromethyl group similar to those of neighboring assistance reported for the reaction of α-haloketones with alkoxide groups [18].

The 1,3:1,5 isomer ratio is determined in the first step of the mechanism. The major proportion for 1,3-isomer of products **2,3** is to be expected because the substituted nitrogen in both hydrazines is more nucleophilic [19]. This statement was found experimentally since the reaction of methyl and phenylhydrazine with 3-, 4-unsubstituted β-alkoxyvinyl trichloromethyl ketone **1a** led a predominance of the 1,3-isomer. The presence of a 4-phenyl group in β-alkoxyvinyl trichloromethyl ketone **1d** increases the yield of 1,3-isomer in both *N*-substituted pyrazoles series (**2, 3**). In the case of the 3,4-disubstituted β-alkoxyvinyl trichloromethyl ketone **1e** a dramatic increase of the proportion of the 1,5-isomer was observed when it reacted with methyl- or phenylhydrazine. The reaction regiochemistry in 3- or 4-monosubstituted β-alkoxyvinyl trichloromethyl ketones **1b,c** depends on the dinucleophile used. In the reaction with methylhydrazine the 3-methyl substituent increases the proportion of the 1,5-isomer and the 4-methyl substituent shows

Table 2

Selected Physical and Spectra Data of **2,3a-e**

Compound	mp (°C) found [a]	Isomer: 1,3/1,5 bp(°C)/mBar (mp °C)) Reported [reference]	GC-MS m/z (%) Isomer: 1,3/1,5	Elemental Analysis (%) C Calcd./Found	H Calcd./Found	^{1}H NMR δ, J (Hz) Isomer: 1,3/1,5	^{13}C NMR δ Isomer: 1,3/1,5
2a	oil	...	154 (M^+, 11/0), 126 (22/0), 109 (100/100), 81 (25/12)	54.54 54.32	6.54 6.50	7.40/7.42 (d, 1H, J = 2.0, H5/H3), 6.79/6.81 (d, 1H, J = 2.0, H4), 3.98/4.17 (s, 3H, NCH_3)	143.4/137.3 (C5/C3), 110.6/108.7 (C4),131.1/132.2 (C3/C5), 162.0/159.5 (C=O)
2b	oil	1,3:129/0.3 [20] 1,5:134/10 1,3:77/0.3 [21] 1,5:98/10	169 ($M+H^+$, 100/9), 139 (13/1), 123 (58/100), 95 (11/7)	...	...	2.28/2.26 (d, 3H, J <0.5, CH_3), 6.54/6.59 (q, 1 H, J <0.5, 114), 3.84/4. 10 (s, 3H, NCH_3)	141.9/146.5 (C5/C3), 110.0/107.9 (C4), 139.6/132.8 (C3/C5), 162.2/159.6 (C=O)
2c	oil	...	169 ($M+H^+$, 100/63), 139 (24/1), 123 (45/100), 95 (17/4)	57.13 57.09	7.19 7.18	7.35/7.37 (q, 1H, J <0.5, H5/H3), 2.31 (d, 3H, J <0.5, CH_3), 3.90/4.12 (s, 3H, NCH_3)	140.6/138.6 (C5/C3), 122.4/120.8 (C4),130.6/129.5 (C3/C5), 162.6/160.3 (C=O)
2d	oil	...	230 (M^+, 31/100), 202 (4/53), 185 (100/29), 157 (87/28)	67.81 67.78	6.13 6.11	7.43/...[b] (m, 5H, Arom), 6.84/...[b] (s, 1H, H4), 3.94/...[b] (s, 3H, NCH_3)	144.9/...[b] (C5), 108.6/ ...[b] (C4), 142.5/...[b] (C3), 162.2/...[b] (C=O)
2e	oil	...	209 ($M+H^+$, 100/100), 179 (1/6), 163 (23/0), 135 (16/10)	63.44 63.39	7.74 7.71	...[b]/1.58-2.00 (m, 4H, -$CH_2CH_2CH_2CH_2$-), ...[b]/2.50-2.90 (m, 4H, -$CH_2CH_2CH_2CH_2$-), 3.79/4.10 (s, 3H, NCH_3)	139.7/147.5 (C5/C3), 121.6/119.7 (C4), 138.6/128.3 (C3/C5), 162.2/160.2 (C=O)

Table 2 (continued)

Compound	mp (°C) found [a]	Isomer: 1,3/1,5 bp(°C)/mBar (mp (°C)) Reported [reference]	GC-MS m/z (%) Isomer: 1,3/1,5	Elemental Analysis (%) C H Calcd./Found	^{1}H NMR δ, J (Hz) Isomer: 1,3/1,5	^{13}C NMR δ Isomer: 1,3/1,5
3a	oil	...	216 (M^+, 100/0), 187 (20/0), 171 (62/0),143 (16/7) 77 (51/42)	62.49 6.29 62.44 6.25	7.93/...[c] (d, 1H, J = 2.0, H5), 6.95/...[c] (d, 1 H, J = 2.0, H4), 7.31-7.91 (m, 5H, NPh)	144.8/...[b] (C5), 109.9/...[b] (C4), 119.6/...[b] (C3), 161.9/...[b] (C--O)
3b	oil	1,3: 128-130/0.1 1,5:106-108/0.1 [22]	230 (M^+, 100/18),201 (14/0), 185 (31/46), 158 (31/100),77 (38/44)	...	2.30/2.34 (d, 3H, J <0.5, CH_3), 6.72/6.79 (q, 1 H, J <0.5, H4), 7.28-7.43 (s, 5H, NPh)	143.4/148.3 (C5/C3), 111.6/108.7 (C4), 133.5/...[c] (C3), 162.3/158.7 (C=O)
3c	79-80	1,3: (79-80) 1,5: (43-44) [23]	231 ($M+H^+$, 100/9), 201 (4/26), 185 (53/12), 157 (22/17), 77 (73/100)	...	7.70/...[c] (q, 1H, J <0.5, H5), 2.27/...[c] (d, 3H, J <0.5, CH_3), 7.31-7.91 (m, 5H, NPh)	142.1/ ...[b] (C5), 121.5/...[b] (C4), 118.9/...[b] (C3), 162.3/...[b] (C=O)
3d	78-79	1,3: (98) [24]	292 (M^+, 59/100), 263 (1/16), 247 (29/13), 219 (82/27), 77 (82/49)	...	7.20-7.28 (m, 5H, Arom), 7.03/...[b] (s, 1 H, H4) 7.20-7.28 (m, 5H, NPh)	144.4/...[b] (C5), 109.7/...[b] (C4), 129.4/...[b] (C3), 162.2/...[b] (C=O)
3e	oil	1,3: (103-104.5) [25]	270 (M^+,71/70), 241 (93/90), 225 (9/16), 197 (44/46), 77 100/100)	...	1.24-1.69 (m, 4H, -$CH_2CH_2CH_2CH_2$-), 2.67-2.82 (m, 4H, -$CH_2CH_2CH_2CH_2$-), 7.26-7.48 (m, 5H, NPh)	140.7/149.8 (C5/C3), 123.8/120.7 (C4), 129.1/...[c] (C3), 162.8/159.2 (C=O)

[a] Melting points determined with a Reichert Thermovar apparatus, and are uncorrected. [b] It was not possible to observe the isomer 1,3 or 1,5. [c] The signal is superimposed to others signals.

similar results compared to that of the non-substituted β-alkoxyvinyl trichloromethyl ketone **1a**. In the case of the reaction of **1b,c** with phenylhydrazine the trend observed was reversed.

Unless otherwise indicated all common reagents and solvents were used as obtained from commercial suppliers without further purification. All melting points were determined on a Reichert Thermovar apparatus and are uncorrected. Elemental analysis was carried out on a Vario EL Foss Heraeus apparatus. The ^{1}H and ^{13}C nmr spectra were recorded on a Brucker AC-80 spectrometer (^{1}H at 80 MHz and ^{13}C at 20 MHz) in chloroform-d_1/-tetramethylsilane.

EXPERIMENTAL

Synthesis of 1-Methyl- and 1-Phenyl-1*H*-pyrazole-3(5)-ethyl Esters **2,3a-e**. General Procedure.

To a stirred solution of methyl- or phenylhydrazine hydrochloride (12 mmoles) in ethanol (10 ml) was added rapidly at room temperature, the appropriate β-alkoxyvinyl trichloromethyl ketones **1** (10 mmoles). The mixture was stirred under reflux for 2 hours (4 hours for phenylhydrazine), at 78°. The excess methyl or phenylhydrazine hydrocloride was filtered and the solvent was evaporated under reduced pressure. The product was taken up in dichloromethane, and the solution was washed with 0.1 *N* chloridric acid (3 x 15 ml), then with water (15 ml) and dried overnight over sodium carbonate. After removal of the solvent under reduced pressure, the oily residue was purified chromatographically (silica gel 60, 230-400 mesh, 30 cm column, eluent, hexane) (Tables 1 and 2).

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