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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.

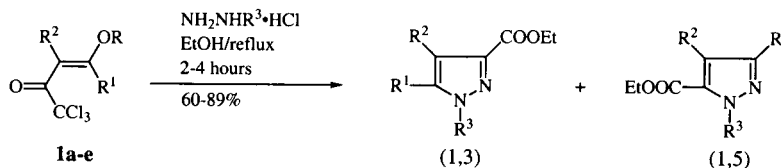
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The pyrazole-3(5)-ethyl esters and their derivatives are known to be important intermediates in the preparation of agrochemicals, microbicides, herbicides [1], plant growth regulators and protectants [2]. v. Auwers and Cauer [3] have synthesized pyrazole-3(5)-alkyl 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



2,3 a-e

Compound	R	R ¹	R ²	R ³
a	Et	H	H	2
b	Me	Me	H	3
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].

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

Compound	mp (°C)	Isomer: 1,3/1,5 bp(°C)/mBar (mp °C))	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
	found	Reported [reference] [a]				
2a	oil	...	154 (M ⁺ , 11/0), 126 (22/0), 109 (100/100), 81 (25/12)	54.54 6.54 54.32 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 7.19 57.09 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 6.13 67.78 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 7.74 63.39 7.71	...[b]/1.58-2.00 (m, 4H, -CH ₂ CH ₂ CH ₂ CH ₂ -), ...[b]/2.50-2.90 (m, 4H, -CH ₂ CH ₂ CH ₂ CH 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)	Isomer: 1,3/1,5 bp(°C)/mBar (mp (°C)) found Reported [reference] [a]	GC-MS m/z (%) Isomer: 1,3/1,5	Elemental Analysis (%)		¹ H NMR δ, J (Hz) Isomer: 1,3/1,5	¹³ C NMR δ Isomer: 1,3/1,5
				C	H		
3a	oil	...	216 (M ⁺ , 100/0), 187 (20/0), 171 (62/0), 143 (16/7) 77 (51/42)	62.49	6.29	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 ₂ CH ₂ CH ₂ CH ₂ -), 2.67-2.82 (m, 4H, -CH ₂ CH ₂ CH ₂ CH 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 ¹H and ¹³C nmr spectra were recorded on a Bruker AC-80 spectrometer (¹H at 80 MHz and ¹³C at 20 MHz) in chloroform-d₁/tetramethylsilane.

EXPERIMENTAL

Synthesis of 1-Methyl- and 1-Phenyl-1H-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 hydrochloride 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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