One-Pot Synthesis of 3(5)-Ethoxycarbonylpyrazoles

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A one-pot synthesis of ethoxycarbonylpyrazoles **2a–e**, by the cyclocondensation of β-alkoxyvinyl trichloromethyl ketones **1a–e** with 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 (70–91%).

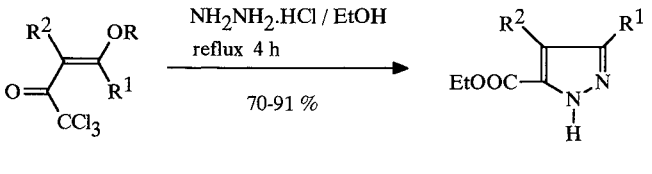
The 3(5)-alkoxycarbonylpyrazoles and their derivatives are important intermediates in the preparation of agrochemicals, microbicides, herbicides,[1] plant growth regulators and protectants.[2]

v. Auwers and Cauer[3] have synthesized 3(5)-alkoxycarbonylpyrazolines 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 3-alkoxycarbonylpyrazoles in moderate overall yields. These authors[5] also developed a method to synthesize a series of substituted 3- and 5-ethoxycarbonyl-1-methylpyrazoles from the reaction of the sodium salt of 1-ethoxycarbonylbutan-1,3-dione and methyl hydrazine sulfate, in good yields. Recently, Padwa et al.[6] reported the synthesis of 3(5)-methyl-5(3)-ethoxycarbonylpyrazoles by the cyclization of vinyl diazo esters, in good yields.

All 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.

As a part of our research program, we developed a general one-step procedure for preparing analytically pure β-alkoxyvinyl trichloromethyl ketones **1a–e**, by the acylation of several enol ethers (or acetals) in molar quantities.[7–9] These compounds have been used as precursors to a variety of substituted five- and six-membered heterocyclic compounds, e.g., isoxazoles,[7] pyrazoles[10] and pyrimidinones.[11]

The aim of this work is to report an improved one-pot synthesis procedure of (5)3-ethoxycarbonylpyrazoles **2a–e**, by the reaction of β-alkoxyvinyl trichloromethyl ketones **1a–e**, with hydrazine hydrochloride in ethanol (Scheme).



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

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

Scheme

The cyclocondensation of **1a–e** with hydrazine hydrochloride was carried out in a molar ratio 1:1.2 using 96% grade ethanol as the solvent. The use of a small excess of hydrazine hydrochloride 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 4 hours. Thus, all reaction mixtures were stirred under reflux for 4 hours (78 °C), then excess hydrazine hydro-

Table. Selected Physical and Spectral Data of **2a–e**

Product	Yield[a] (%)	mp (°C) found	mp (°C) reported[5]	^{1}H NMR ($CDCl_3$/TMS) δ, J (Hz)	^{13}C NMR ($CDCl_3$/TMS) δ
2a	80	155–157	156–158	7.74 (d, 1H, J = 2.0, H3), 6.73 (d, 1H, J = 2.0, H4), 13.49 (s, 1H, NH)	132.0 (C3), 107.7 (C4), 142.0 (C5), 162.2 (C=O)
2b	77	81–83	83	2.34 (d, 3H, J = 0.6, CH_3), 6.54 (q, 1H, J = 0.6, H4), 12.18 (s, 1H, NH)	141.6 (C3), 106.6 (C4), 142.2 (C5), 162.1 (C=O)
2c	70	155–157	157–158	7.54 (q, 1H, J = < 0.5, H3), 2.31 (d, 3H, J = < 0.5, CH_3), 10.40 (s, 1H, NH)	134.5 (C3), 120.0 (C4), 136.9 (C5), 162.1 (C=O)
2d	91	138–140	140	7.21–7.74 (m, 5H, Arom), 6.94 (s, 1H, H4), 12.86 (s, 1H, NH)	132.5 (C3), 105.0 (C4), 140.5 (C5), 161.1 (C=O)
2e[b]	81	92	106–107	1.62–2.00 (m, 4H, $CH_2\underline{CH_2CH_2}CH_2$), 2.63–3.00 (m, 4H, $\underline{CH_2}CH_2CH_2\underline{CH_2}$), 11.81 (s, 1H, NH)	135.6 (C3), 119.3 (C4), 144.8 (C5), 161.9 (C=O)

[a] Yields of isolated compounds.
[b] GC/MS: m/z = 195 (M^+ + H, 100), 165 (18), 149 (12), 121 (28), 94 (10), 81 (3).

chloride was filtered off and the solvent was evaporated under reduced pressure. The product was taken up in dichloromethane and recrystallized from a mixture of hexane and ethyl acetate (1 : 1). The analytically pure 3(5)-ethoxycarbonylpyrazoles **2a–e** were obtained in 70–91 % yield (Table).

Finally, the advantages of our method are an improved one-pot procedure, ready access to the precursors, high yields, and the relatively short reaction time.

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. ^1H and ^{13}C NMR spectra were recorded on a BRUKER AC-80 spectrometer (^1H at 80 MHz and ^{13}C at 20 MHz) in $CDCl_3$/TMS.

3(5)-Ethoxycarbonylpyrazoles 2a–e; General Procedure:
To a stirred solution of $NH_2NH_2 \cdot HCl$ (0.82 g, 12 mmol) in EtOH (10 mL) was added the appropriate β-alkoxyvinyl trichloromethyl ketone **1** (10 mmol) rapidly at r.t. The mixture was stirred under reflux for 4 h (78 °C). The excess of $NH_2NH_2 \cdot HCl$ was filtered off, and the solvent was evaporated under reduced pressure. The product was taken up in CH_2Cl_2, and the solution was washed with 0.1 N HCl (3 × 15 mL), then with H_2O (15 mL) and dried overnight (Na_2CO_3). After removal of the solvent under reduced pressure, the residue was recrystallized from a mixture of hexane/EtOAc (1 : 1) (Table).

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