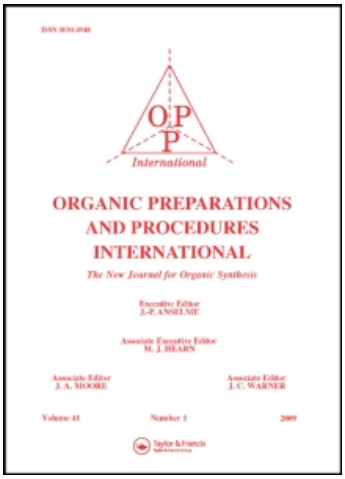

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AN IMPROVED PROCEDURE FOR THE PREPARATION OF 1,1,1-TRICHLORO-4-METHYL-3-PENTEN-2-YL DIAZOACETATE

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OPPI BRIEFS

AN IMPROVED PROCEDURE FOR THE PREPARATION OF 1,1,1-TRICHLORO-4-METHYL-3-PENTEN-2-YL DIAZOACETATE

Submitted by (09/09/88)

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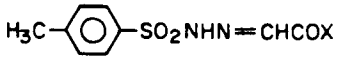
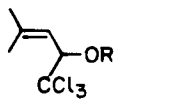
In connection with an ongoing project on pyrethroid synthesis,[1] 1,1,1-trichloro-4-methyl-3-penten-2-yl diazoacetate (2a) was required in large quantities. The use of triethylamine in the reaction of tosylhydrazone glyoxalyl chloride (1a) with 1,1,1-trichloro-4-methyl-3-pentenol (2b) resulted in the formation of diazoacetate 2a in only 48% yield.[2] This prompted us to attempt to improve the yield of 2a. The low yield of the desired diazo ester in a similar reaction was attributed to the formation of p-toluenesulfinate ester as a by-product, arising through rearrange-



1

a) X = Cl

b) X = O-CH(CCl3)-CH=CH2

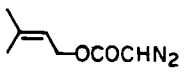


2

a) R = COCHN2

b) R = H

c) R = H3C-C6H4-SO



3

ment of an intermediate ketene. The formation of sulfinate ester could be suppressed by replacing triethylamine with N,N-dimethylaniline for the esterification step; the resulting tosylhydrazone ester was then decomposed with triethylamine to give the diazo ester in excellent yield.[3] However, adaptation of this modification to our reaction resulted in the formation of the sulfinate ester 2c in significant quantity, and gave a poor yield of 2a. We now report a modified procedure for the synthesis of 2a in high yield.

The reaction of allylic alcohol 2b with the tosylhydrazone glyoxalyl chloride (1a) in refluxing methylene chloride in the presence of anhydrous potassium carbonate afforded ester 1b. Treatment of the crude ester 1b with triethylamine or aqueous potassium carbonate-triethylbenzylammonium bromide furnished 2a in more than 90% yield. The spectral characteristics of this compound were identical with those reported.[2] The ester 2a can be used without further purification for the preparation of (±) cis-2,2-dimethyl-3-(2,2-dichlorovinyl)-cyclopropanecarboxylic acid, a key intermediate in pyrethroid synthesis. This procedure was used to prepare prenyl diazoacetate (3) in good yield.

EXPERIMENTAL SECTION

Mps were taken on Termonik M. P. apparatus and are uncorrected. Elemental analyses were carried out using empty tube combustion method. IR Spectra were determined on Perkin-Elmer 599B spectrophotometer. ^{1}H NMR Spectra were recorded on Varian T-60 and Bruker WH-90 spectrometer. NOTE ON SAFETY: Caution (use of a hood and safety shield) should be observed when working with diazo compounds.

1,1,1-Trichloro-4-methyl-3-penten-2-yl p-Toluenesulfonylhydrazone Glyoxylate (1b).- To a solution of acid chloride 1a[4] (52 g, 0.2 mol) in dry methylene chloride (300 ml), trichloropentenol (2b, 20.30 g, 0.1 mol) and anh. potassium carbonate (42 g, 0.3 mol) were added. The mixture was refluxed under stirring for 50 hrs. It was then filtered and the residue washed with methylene chloride. The filtrate was washed successively with water (3x50 ml), aqueous sodium carbonate (5%, 3x50 ml), water (3x50 ml) and dried (Na_2SO_4). This solution was used as such for the preparation of diazoacetate 2a. A small portion of this solution was concentrated to give solid 1b, which was crystallized from EtOAc-pet. ether (1:9) to give white needles, mp. 94-95°; IR: 3110, 1740, 1600, 1235, 1180 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$): δ 1.83 (s, 6H), 2.4 (s, 3H), 5.3 (d, J = 9 Hz, 1H), 6.0 (d, J = 9 Hz, 1H), 6.8 (s, 1H), 7.2 (d, J = 8 Hz, 2H), 7.7 (d, J = 8 Hz, 2H), 12.1 (br s, 1H).

Anal. Calcd. for $C_{15}H_{17}Cl_3N_2O_4S$: C, 42.12; H, 4.01; N, 6.55

Found : C, 42.45; H, 4.23; N, 6.88

1,1,1-Trichloro-4-methyl-3-penten-2-yl Diazoacetate (2a). Method A.- The above methylene chloride solution of 1b (400 ml) was treated with triethylamine (20.2 g, 0.2 mol) at 20° and stirred for 1 hr. It was then washed with water (2x75 ml), dil. HCl (2%, 2x100 ml) followed by water (3x75 ml) and dried (Na_2SO_4). Removal of solvent by distillation under reduced pressure (see note on safety above) furnished the diazoacetate 2a (24.95 g, 92% from 1b) as a pale yellow oil. IR: 2110, 1710, 1230, 1160, 1040 cm^{-1}; ^{1}H NMR (60 MHz, CCl_4): δ 1.90 (s, 6H), 4.83 (s 1H), 5.33 (br d, 1H), 6.03 (d, J = 9 Hz, 1H); Mass spectrum: m/z 270 (M^+), 235, 185, 166, 149, 85.

Anal. Calcd. for $C_8H_9Cl_3N_2O_2$: C, 35.38; H, 3.34; N, 10.32

Found : C, 35.03; H, 3.52; N, 10.14

Method B.- To a solution of hydrazone ester 1b (1 g, 2.34 mmol) in benzene (10 ml), a solution of potassium carbonate (0.5 g, 3.6 mmol) in water (10 ml) and triethylbenzylammonium bromide (0.01 g) was added. The reaction mixture was stirred at room temperature for 1 hr. The organic layer was separated and the aqueous layer extracted with benzene (2x10 ml). The combined organic extract was washed with water, dried (Na_2SO_4) and solvent was removed by distillation under reduced pressure (see note on safety above) to afford 2a as a pale yellow oil (0.62 g, 95%) having the same spectral characteristics as the material obtained in method A.

3-Methyl-2-butenyl Diazoacetate (3).- To a solution of acid chloride 1a (13.07 g, 0.05 mol) in dry methylene chloride (100 ml), prenyl alcohol (2.15 g, 0.025 mol) and anh. calcium carbonate (7.5 g, 0.075 mol) were added. The mixture was stirred at room temperature for 5 hrs. It was

then filtered and the residue washed with methylene chloride. The filtrate was washed successively with water (3x20 ml), aq. sodium carbonate (5%, 3x20 ml) and dried (Na_2SO_4). This methylene chloride solution was treated with triethylamine (5.05 g, 0.05 mol) at 20° and stirred for 1 hr. It was then washed with water (2x25 ml), dil. HCl (2%, 2x25 ml) followed by water (3x20 ml) and dried (Na_2SO_4). Removal of solvent by distillation under reduced pressure (see note on safety above) furnished the diazoacetate 3 (3.82 g, 90% based on prenyl alcohol). IR: 2120, 1710, 1240 cm^{-1}; ^1H NMR (60 MHz, CCl_4): δ 1.73 (s, 6H), 4.53 (d, J = 7 Hz, 2H), 4.56 (s, 1H), 5.26 (m, 1H).

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FACILE SYNTHESIS OF 2-METHOXYISOBUTYLISONITRILE

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2-Methoxyisobutylisonitrile is a key starting material for the preparation of Tc-99m hexakis (2-methoxyisobutylisonitrile) which appears to be clinically useful as a myocardial perfusion agent.[1] The synthesis of a number of isocyanides have been reported.[2] A new synthetic route to isocyanides which utilizes trichloromethyl chloroformate ("diphosgene") as a dehydrating agent has been reported recently.[3] We now report a procedure for the preparation of 2-methoxyisobutylisonitrile in a 26% overall yield from commercially available 2-hydroxyisobutyronitrile in only four steps. While our work was in progress, two independent syntheses were reported,[4,5] one involving six steps (no yields were reported)[4] and the applied for patent requiring a five-step process[5] with an overall yield of 8.1%.

Etherification of nitrile 1 was effected with anhydrous methanol and freshly fused zinc chloride to give ether 2 (51%), which was successfully reduced with lithium aluminum hydride to give 3 in good yield (82%) in about 8 hrs. N-Formylation of 3 with ethyl formate in the