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I. Basnak [a], K. Jurkovic [a] & G. Basnakova [b]
[a] Institute of Biotechnology, Faculty of Chemical Technology, Slovak Technical University, Kollarovo nam. 9, 81237, Bratislava, CZECHOSLOVAKIA
[b] Research Institute of Irrigation Management, Vrakunska 29, 82563, Bratislava, CZECHOSLOVAKIA

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THE SYNTHESIS OF METHYL CYCLOPROPYLACETATE BY PALLADIUM(II) ACETATE CATALYSED REACTION OF DIAZOMETHANE WITH VINYL GROUP

I. Basnak* and K. Jurkovic

Institute of Biotechnology, Faculty of Chemical Technology, Slovak Technical University, Kollarovo nam.9, 81237 Bratislava, CZECHOSLOVAKIA

G. Basnakova

Research Institute of Irrigation Management, Vrakunska 29, 82563 Bratislava, CZECHOSLOVAKIA

ABSTRACT: The methyl cyclopropylacetate was prepared in high yield by Palladium(II) acetate catalysed reaction of vinyl acetic acid with an excess of diazomethane. The cyclopropylacetonitrile was prepared from allyl cyanide by the same method.

The incorporation of the cyclopropyl group into complex molecules is often complicated or laborious. In this connection we were limited in preparation of the desired amount of methyl cyclopropylacetate (III)[1], the key intermediate in the synthesis of 5-cyclopropyl2'-deoxyuridine[2]. Therefore we searched

* To whom correspondence should be addressed (New address: The School of Chemistry, University of Birmingham, P.O. Box 363, Birmingham B15 2TT, UK.)

for a more convenient and reproducible synthesis of the ester III or a suitable precursor.

$R\text{-}CH_2\text{-}Y$

	R	Y
I.	CH_2=CH-	$-CO_2H$
II.	c-C_3H_5-	-CN
III.	c-C_3H_5-	$-CO_2CH_3$

According to the literature the ester III or its ethyl analogue, as well as free cyclopropylacetic acid were prepared by several different methods. The most promising methods were Wolf rearrangement of suitable diazomethylketones[3-8] and Simmons Smith synthesis from vinylacetic acid (I) or its esters[9-17] with predominantly good yields but without satisfactory reproducibility and complicated purification in some cases. The cyclopropylacetic acid was also prepared by the Grignard reaction[18,19], from cyclopropyllithium[20,21], from cyclopropylmethylene-triphenylphosphorane[22] or from cyclopropylmethyl ketone by the Willgerodt reaction[23]. All these methods are either very complicated or give low yields so that

they cannot be taken as the methods of choice. The cyclopropylacetic acid was also prepared in good yield by the alkaline hydrolysis of cyclopropylacetonitrile, which had been obtained by the reaction of cyclopropylcarbinyl bromide with natrium cyanide[24,25].

Cyclopropanation of vinyl group by diazomethane, catalyzed by Palladium(II) acetate, is an interesting alternative to the Simmons Smith reaction and was succesfully used for cyclopropanation of styrene[26], α,β-unsaturated carbonyl compounds[27,28], allyl compounds[29] and cinnamic esters[30]. Recently this method was successfully used for the synthesis of C(3)-cyclopropyl cephems and carbacephems from their C(3)-vinyl precursors[31]. These results prompted us to use this reaction for the synthesis of the ester III from suitable vinyl substrates. Pd(II) acetate catalyzed cyclopropanation of allyl cyanide was performed with varying ratios of diazomethane. The results of four experiments in Table 1 clearly show that a 6-times molar excess of diazomethane to allyl cyanide is the optimum ratio of reagents.Under these conditions the reaction yielded ca 88% of the crude cyclopropylacetonitrile with not more than 1% of unreacted allyl cyanide. The fractional distillation caused a loss of the product without any improvement

Tab.1: The results of cyclopropanation of allyl cyanide with different ratios of diazomethane to allyl cyanide.

No. of Exp.	Substrate/ /Diazomethane (mol/mol)	Resulting reaction mixture (%)	
		Nitrile II	Allyl cyanide
1	1 : 3	83	9
2	1 : 5.3	84	1.5
3	1 : 6	88	1
4	1 : 6	87	1

of its purity. The alcaline hydrolysis of the nitrile II at higher temperature and subsequent esterification of the crude cyclopropylacetic acid with diazomethane gave 69% yield of the distilled ester III which was of the same purity as the substrate II.

Vinylacetic acid proved to be a much better substrate for the synthesis of the ester III than allyl cyanide. Using the same methodology, but with a 7-times molar excess of diazomethane, vinylacetic acid was cyclopropanated with concommitant esterification to give the methyl cyclopropylacetate(III) in nearly quantitative yield(97%).

The identity of the ester III was finaly confirmed by the synthesis of 5-cyclopropyl-2-thiouracil with the result fully comparable with that published in the literature[1].

EXPERIMENTAL

GC analyses were performed on a CHROM 42 instrument (Laboratorni Pristroje, CSFR) with a flame ionization detector, 5% SE on Chromosorb W (2,4m glass column). ^{1}H NMR spectra were recorded at 60 MHz in $CDCl_3$ on a TESLA BS 467 spectrometer (CSFR) using tetramethylsilane as an internal standard, chemical shifts in ppm. Diazomethane was prepared from N-methyl-N-nitroso-p-toluenesulphonamide (Diazald) according to Hudlicky[32]. The concentration of diazomethane in dry ether was 0,48 mol/l. Allyl cyanide was of 98% purity (FLUKA) and Palladium(II) acetate was of 98% purity (FLUKA).

Vinylacetic acid (I)

Vinylacetic acid was prepared by the hydrolysis of 100g of allyl cyanide according to the literature[33]. The product was purified by fractional distillation on the Fisher Spaltrohr System apparatus at 39-41°C/133kPa. The pure product (54g, 42%) was obtained in 98% purity (GC). ^{1}H NMR,δ:11,45(s,-CO_2H),

5,55-6,30(m,-CH=), 4,92-5,20(m,=CH_2), 3,07 (d,J=7Hz, -CH_2-).

Cyclopropylacetonitrile (II)

To the magnetically stirred solution of 1,34g (20mmol) of allyl cyanide in 10ml of dry ether at 0°C was added diazomethane and subsequently 70mg (0,312mmol) of Palladium(II) acetate in 50ml of dry ether. After 10 minutes the evolution of N_2 ceased and the reaction mixture became colourless, with a fine brown precipitate of the catalyst. The ether was distilled off to the reduced volume of the reaction mixture ca 10ml. The precipitate was filtered off on a fritted glass funnel and the filtrate analysed by GC. Four experiments were repeated with the same amount of allyl cyanide and the catalyst but different amounts of diazomethane (Tab.1). The filtrates from the experiments No.2-4 were combined and fractionally distilled at normal pressure yielding 2,2g (45%) of II (142-148°C). The product was of 85% purity (GC) with several impurities (not identified). ^{1}H NMR,δ: 2,31(d,J=6Hz,-CH_2-), 0,12-1,30(m,-c-C_3H_5).

Methyl cyclopropylacetate (III) from II

The mixture of II (1,2g) and 10ml of aqueous sodium hydroxide (25%) was stirred at 130-140°C for 7hrs. The reaction mixture was cooled with ice and neutralized with aqueous sulphuric acid (25%) to pH 1.

The organic layer was separated and the aqueous layer was extracted with ether (5x10ml). The organic layer was combined with the extracts and treated with natrium sulphate. The solution was decanted and esterified with diazomethane to a slightly yellow colour. The excess of diazomethane and ether was distilled off and the crude product was distilled at normal pressure yielding 1,1g(69%) of III boiling at 129-134°C, 85% purity (GC). ^{1}H NMR,δ: 3,52(s,-OCH_3), 2,05(d,J=6,5Hz,-CH_2-), 0,01-1,30(m,-c-C_3H_5).

Methyl cyclopropylacetate (III) from I

Diazomethane (6,17g, 147mmol) was added dropwise to 1,8g(21mmol) of vinylacetic acid (I) in 10ml of dry ether with intensive stirring at 0°C. Then 70mg (0,312mmol) of Palladium(II) acetate in 50ml of dry ether was added all at once. Then stirring at 0°C continued until the evolution of N_2 ceased (10min.). The reaction mixture was worked up as in the cyclopropylacetonitrile preparation. The crude product contained 97% of III (GC). The distillation at normal pressure gave 1,7g(75%) of III boiling at 130-136°C (lit.[1]: b.p.128-134°C). ^{1}H NMR: identical with that of the product prepared from cyclopropylacetonitrile, without impurities.

5-Cyclopropyl-2-thiouracil

5-Cyclopropyl-2-thiouracil (256mg, 18%) was prepared from 1,14g of III (97% purity) according to the literature[1], m.p.209-211°C (lit.[1]: m.p.211-212°C, yield 21%). The identity and purity of the product was further confirmed by TLC, UV and ^{1}H NMR spectra (lit.[1]).

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