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SYNTHESES OF SOME ARYL-SUBSTITUTED DIHYDROFURYLESTERS

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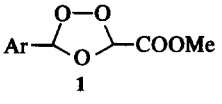
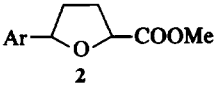
Abstract—Syntheses of the title compounds were achieved by rearrangement of the isomeric cyclopropyl-α-ketoesters using acid treated aluminium oxide in a chromatographic column. The cyclopropyl derivatives were obtained from copper catalyzed reaction of a diazoketoester to the properly substituted styrenes. On the basis of an observed substituent effect a mechanism is proposed involving a transition state incorporating both the styrene, the diazoketoester and the catalyst. The role of the latter is most likely exerted in the initiating step of the radical reaction invoked. *p*-Methoxy styrene also yielded the dihydrofuran directly.

In connection with our studies on the physical and spectroscopic properties of ozonides (1,2,4-trioxolanes) it would be of interest to compare the ozonides with 5-membered rings where some of the O atoms are replaced by the isoelectronic methylene group. We therefore wanted to compare the ozonides (**1**) formed from the ozonation of substituted cinnamic esters with the corresponding tetrahydrofurans (**2**). In order to simplify the syntheses of the isomeric tetrahydrofurans, we decided first to prepare the corresponding 2,3-dihydrofurans (**3**).



1



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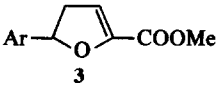
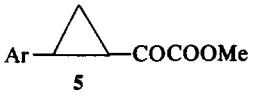


3

a: Ar = *p*-Cl-ϕ
b: Ar = ϕ
c: Ar = *p*-MeO-ϕ

In principle, a ketocarbene should be able to react in a 1,3-dipolar way[1] with olefins to give dihydrofurans, and, in fact, ketocarbenes generated from 4-substituted diazoacetophenones reacted with ketenacetals to give 5 - aryl - 2,3 - dihydrofurans.[2]

Methyl - 3 - diazo - 2 - oxopropionate (**4**) was found to react with 4-substituted styrenes using copper powder as catalyst and in absence of a solvent. The products were isolated using column chromatography or high vacuum distillation. Spectroscopic examination as described in the Experimental indicated that only from *p*-methoxy-styrene a dihydrofuran derivative (**3c**) was obtained, while from *p*-chloro and unsubstituted styrene cyclopropyl derivatives (**5**) were the sole products.

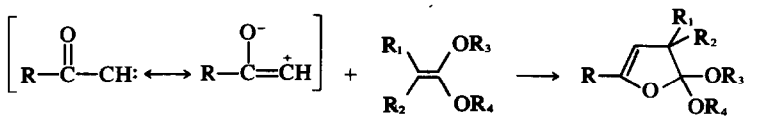


5

a: Ar = *p*-Cl-ϕ
b: Ar = ϕ
c: Ar = *p*-MeO-ϕ

The cyclopropyl derivatives can exist in two stereoisomeric forms, and, in fact, both stereoisomers were obtained. In Table 1 total yields and isomer distribution are listed.

The stereochemical assignments were based on oxidative decarbonylation of the α-keto esters to the corresponding aryl cyclopropyl acids whose mps agreed very well with those in the literature.[3] Although both **5a** (*cis*) and **5b** (*cis*) was isomerized to the corresponding *trans*-forms on prolonged treatment with excess alkali the short-time oxidative treatment of **5a** (*cis* or *trans*, respectively) in the weakly alkaline medium yielded pure isomers



SCHEME 1.

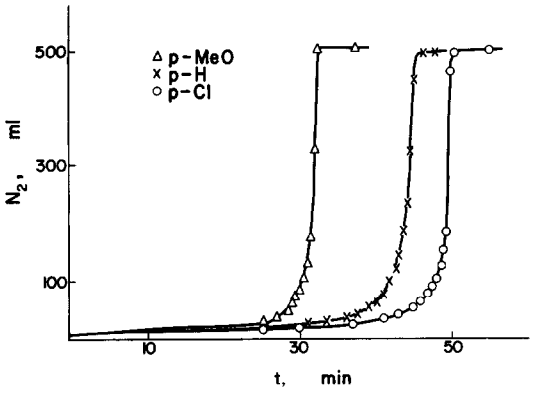


Fig 1.

Table 1.[a] Reaction of methyl 3 - diazo - 2 - oxo - propionate (4) with substituted styrenes (6)

6	3	5	*cis*-5/*trans* 5[b]
a	—	60	0·67
b	—	53	0·43
c	34	30	~0

[a] Yields of isolated products in per cent of theoretical.

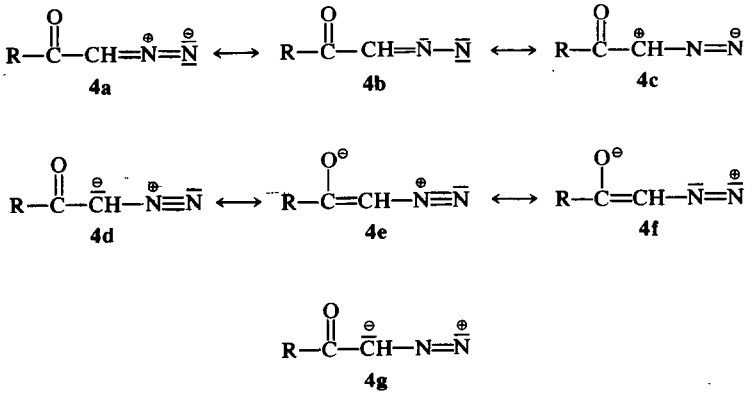
[b] Isomer distribution estimation by NMR using the integrated peak area of the ester methoxy groups. The figures are the average of several runs.

of the corresponding aryl cyclopropyl carboxylic acids.

A possible reaction mechanism must take into account the following experimental facts:

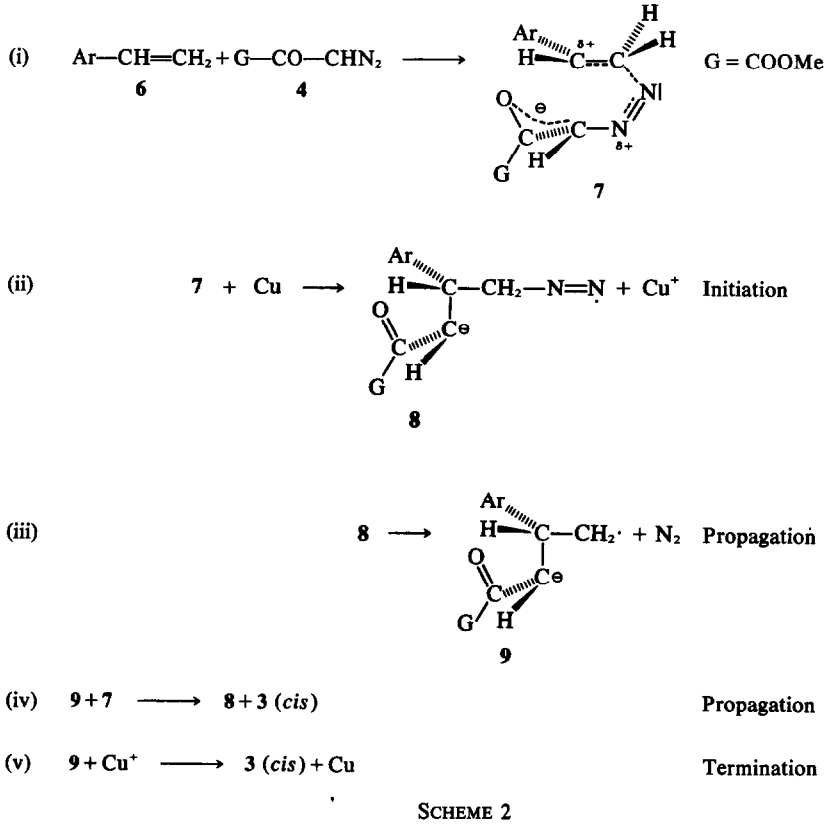
1. The product variation and their stereochemistry (Table 1).
2. The influence of substituents on reaction rate as measured by the nitrogen evolution (Fig 1).
3. On following the reaction (by NMR) between the diazoketoester and *p*-chlorostyrene it was disclosed that the cyclopropyl compounds were the only products formed, that kinetically their formation rather closely followed the nitrogen evolution and that no intermediate products were observed.

Diazoketones are considered to decompose thermally (in the presence of copper salts) to ketocarbenes[4] which subsequently react with multiple bonds to give the products. However, the substituent effect on the nitrogen evolution (Fig 1) does not seem to confirm such a view, at least not in the present case. The direction of this effect points to a somewhat electron deficient benzylic carbon in the transition state. Furthermore, the rate of reaction suggests a radical pathway where the substituents do not seem to play a dominant role, except in affecting the induction period. Thus, one may suggest a mechanism passing through a rate determining transition state incorporating both the diazoketoester **4** and the styrenes, and most likely also the copper catalyst. The nature of such a transition state is certainly dependent on the structure of the diazoketoester, which most likely must be very much like diazoketones. It is well known that diazoalkanes react with olefins to form Δ^1-pyrazolines. Huisgen[5] has compared the reactivities of several diazo compounds towards a strained olefin and found that diazoketones react several powers of ten slower than diazomethane, and indeed, NMR revealed that in the absence of copper our diazoketoester did not show detectable amounts of analogous Δ^1-pyrazolines (or any reaction at all) when heated in *p*-chlorostyrene solution for several hr at 70°. Huisgen's observation was interpreted to reflect an increased resonance stabilization in the ground state of the diazoketones and together with other experimental evidence this constituted the base for suggesting the 1,3-dipolar reactivity of diazo compounds. A closer look on the valence bond structures (**4a-g**) representing a diazoketone (or diazoketoester) may be useful in the understanding of both the reactivity and direction of attack on unsymmetrical olefins and thereby also the nature of the above mentioned transition state. Compound **4c** is most likely a high



energy structure since it has a positive charge on the carbon next to the CO group. **4b**, **4f** and **4g** are sextet structures and thus probably less significant. Since **4a** has the positive end of the nitrogen dipole next to the CO group, the most important contributing structures must be **4d** and **4e**. The dipole moments of ethyl diazoacetate, 2·03 D, and of diphenyldiazomethane, 1·42 D,[6] indicate a more extended conjugation in diazoketones than in diazoalkanes, thus weakening the tendency towards concerted 1,3-dipolar addition of the former diazo compounds. Keeping in mind the direction of the substituent effect a stepwise electrophilic addition of the nitrogen end of the diazoketone may lead to a transition state like **7** (Scheme 2).

A tentative mechanism for the total reaction is presented in Scheme 2.



SCHEME 2

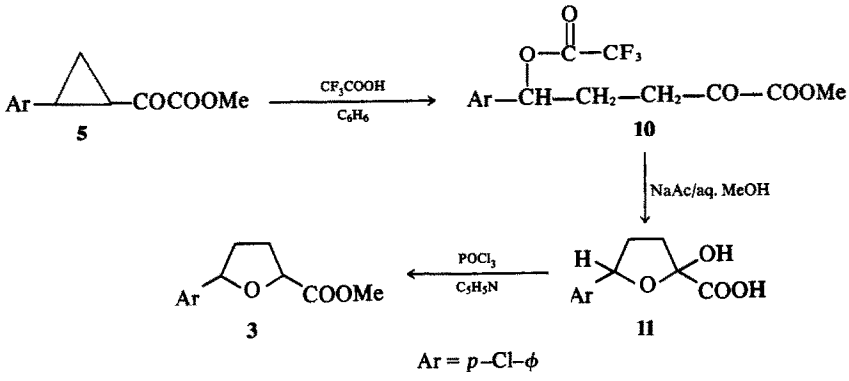
Two points concerning this mechanism must be discussed. Firstly, the variation of the products formed and, secondly, the stereochemistry of the cyclopropanes **3**. In the mechanism in Scheme 2 only cyclopropane formation is indicated. As seen in Table 1 a 2,3-dihydrofuran was obtained when *p*-methoxystyrene was used. A closer look on transition state **7** reveals that formation of this compound is possible through a reaction resembling O-alkylation of enolate ions. In general C-alkylation (here leading to cyclopropanes) is more likely when bond breaking in the alkyl halides is more important (S_N2-mechanism), while when bond breaking is less important (carbonium ions more stable) O-alkylation may compete favourably. Since build-up of a positive charge on the benzylic carbon in **7** is more energetic feasible having electron donating para-substituents, formation of the 2,3-dihydrofuran using *p*-methoxystyrene is reasonable.

The stereochemistry of the cyclopropanes (according to the above mechanism) is determined in the transformation **7**→**8**. Since the π-electrondensity of the aromatic ring is lowest having chlorine as substituent a possible charge-transfer interaction between the electronegative carbonyl oxygen and the π-system of the ring will be stronger in this case, leading to the highest yields of *cis* cyclopropane.

REARRANGEMENT TO DIHYDROFURANS

Thermal rearrangement of 1 - benzoyl - 1,2,2 - triphenyl cyclopropane to 2,2,4,5 - tetraphenyl - 2,3-dihydrofuran is described.[7] After 8 hr heating at 150°, no changes in the IR spectra of the cyclopropyl derivatives **5** was observed. Increasing the temperature to 190° led to extensive decomposi-

tion and no dihydrofurans could be identified. Rearrangement of 1-substituted cyclopropyl ketones using catalytic amounts of triphenyl phosphine gave 4,5-disubstituted dihydrofurans.[8] Similar treatment of our compounds did not result in rearrangement. Acid catalyzed ring enlargening was reported successful with 1 - benzoyl - 1,2,2 - triphenyl cyclopropane.[7] Similar attempts with our cyclopropanes led to ring opening. Thus, when methyl 2 - (4 - chlorophenyl) - cyclopropyl oxoacetate (**5a**) was heated with slight excess of trifluoroacetic acid in benzene solution good yields of **10** were obtained. Reactions outlined in Scheme 3 finally led to the title compound.



SCHEME 3

However the reaction way was tedious and the overall yields of conversion were not more than 40%.

Since acidic treatment must have involved a protonation of the molecule followed by attack of the poor nucleophile trifluoroacetic acid at the benzylic carbonium ion, the total absence of nucleophiles should enable the oxygen atom in the keto group (or of the enol hydroxyl group in the enol form of **5**) to attack nucleophilically at this carbon, thus forming the dihydrofurans. Using highly activated acid treated aluminium oxide in a chromatographic column, the ring interconversion was achieved in a simple way and with a total yield of around 65%.

EXPERIMENTAL

General. IR spectra were recorded on a Perkin-Elmer model 457 grating spectrophotometer. PMR spectra were recorded on a Varian A60A instrument using $CDCl_3$ as solvent and TMS as internal reference. Mass spectra were obtained on a AEI MS902 spectrometer. M. ps are not corrected.

Materials. Methyl 3 - diazo - 2 - oxo - propionate was prepared from 2 - methoxy - 2 - oxo - propionylchloride according to Ratusky and Sorm.[9] The styrenes used were commercially available and distilled prior to use.

Reaction between styrenes and methyl 3-diazo-2-oxo-propionate

(*A*) *p-Chlorostyrene.* The diazo compound **4** (2·56 g – 20 mM) was dissolved in *p*-chlorostyrene (10 ml), Cu powder (0·5 g) was added and the solution stirred at 70°. When the gas evolution ceased excess *p*-chlorostyrene was removed by distillation. High vacuum distillation of the residue gave **5a** (2·8 g – 60%), bp 102°/0·02 mm. The product was a mixture of the two possible stereoisomers, which could be separated by fractional crystallization from EtOH. M. ps and elemental analysis, Table 3.

(*B*) *Styrene.* The reaction was carried out as in (A), yield 53%, bp 92–94/0·05 mm. The product was a mixture of the stereoisomers. Fractional crystallization yielded only the *trans* isomer in pure state (Table 3).

(*C*) p-*Methoxystyrene.* The reaction was carried out as before. After distilling off *p*-methoxystyrene (bp 39–40°C/0·07 mm), NMR on the residue showed the presence of both **5c** and **3c**. It was therefore subjected to chromatography on a silica gel column. Elution with benzene/methylene chloride with increasing amounts of the latter solvent yielded pure *trans* form of **5c** in the first fractions (0% CH_2Cl_2) and the later fractions yielded pure **3c** (Tables 3 and 4).

Kinetic measurements. The styrenes were distilled prior to use to remove the stabilizer *p-t*-butylcatechol.

Table 2. Results of decarbonylation experiments

Compd.	Melting points Before decarb.	After decarb.	Lit. m.p.[3] (config)
5a (*trans*)	71–72°	115–117°	115·8–116·7° (*trans*)
5a (*cis*)	104–105°	129–130°	128·1–129·1° (*cis*)
5b	54–55°	90–91°	90·8–91·4° (*trans*)
5c	66–67°	113–114°	113·2–116·7° (*trans*)

Table 3. Physical and spectral properties of methyl 2-aryl-cyclopropyl oxoacetate (5)

	Mp	El. anal.	IR (KBr)	MS	NMR (δ in ppm)
5a	71–72°	C60·4, H4·6	1725 cm^{-1}	240 / 238 (M^+)	7·08–7·33 (m, 4H, Arom. H, AA' BB')
trans		Cl 15·1	1700 cm^{-1}		3·90 (s, 3H, CH_3O)
		Calc. for $C_{12}H_{11}ClO_3$	1015 cm^{-1}		2·8 (m, 2H, tert. prot.)
		C60·4, H4·7			
		Cl 14·9			1·7 (m, 2H, cycloprop.)
5a	104–105°	C60·4, H4·6	1725 cm^{-1}	240 / 238 (M^+)	7·22 (s, 4H, Arom H)
cis		Cl 15·1	1700 cm^{-1}		3·80 (s, 3H, CH_3O)
			1015 cm^{-1}		3·0 (m, 2H, tert. prot.)
					1·8 (m, 2H, cycloprop.)
5b	54–55°	C70·2, H5·9	1715 cm^{-1}	204 (m^+)	7·2 (m, 5H, Arom H)
trans		Calc. for	1690 cm^{-1}		3·88 (s, 3H, CH_3O)
		$C_{12}H_{12}O_3$	1010 cm^{-1}		2·9 (m, 2H, tert. prot.)
		C70·6, H5·9			1·7 (m, 2H, cycloprop.)
5c	66–67°	C66·5, H6·1	1735 cm^{-1}	234 (M^+)	6·85–7·12 (m, 4H, Arom. H, AA' BB')
trans		Calc. for	1710 cm^{-1}		3·88 (s, 3H, CH_3O)
		$C_{13}H_{14}O_4$	1020 cm^{-1}		3·80 (s, 3H, CH_3O)
		C66·7, H6·0			2·8 (m, 2H, tert. prot.)
					1·7 (m, 2H, cycloprop.)

Table 4. Physical and spectral properties of methyl 2-aryl-5-carbomethoxy-2,3-dihydrofurans (3)

	Bp.	El. anal.	IR (liq. film)	MS	NMR(δ in ppm)
3a	135/0·4	C 60·3, H 5·1	1725 cm^{-1}	240 / 238 (M^+)	7·33 (s, 4 H, Arom H)
		Calc. for	1620 cm^{-1}		5·98 (t, 1 H, Olef. H, J = 3hz)
		$C_{12}H_{11}ClO_3$			5·68 (1 H, X-proton in ABX-system, J_{AX} = 9·0, J_{BX} = 10·5hz)
		C 60·4, H 4·7			3·83 (s, 3 H, CH_3O)
					3·28 (1 H, B-proton in ABX-system, J_{AB} = 17·5hz, J_{BX} = 10·5hz)
					2·71 (1H, A-proton in ABX-system, J_{AB} = 17·5hz, J_{AX} = 9·0hz)
3b	125/0·1	C 70·4, H 6·0	1725 cm^{-1}	204 (M^+)	7·3 (m, 5 H, Arom H)
		Calc. for	1620 cm^{-1}		6·01 (t, 1 H, Olef. H, J = 3hz
		$C_{12}H_{12}O_3$			5·71 (1H, X-proton in ABX-system, J_{AX} = 9·0hz, J_{BX} = 10·5hz)
		C 70·6, H 5·9			3·84 (s, 3 H, CH_3O)
					3·28 (1 H, B-proton in ABX-system, J_{AB} = 17·5hz, J_{BX} = 10·5hz)
					2·76 (1 H, A-proton in ABX-system, J_{AB} = 17·5hz, J_{AX} = 9·0hz)
3c	134/0·06	C 66·8, H 6·0	1725 cm^{-1}	234 (M^+)	7·35–6·92 (m, 4 H, Arom H, AA' BB')
		Calc. for	1630 cm^{-1}		5·98 (t, 1 H, Olef. H, J = 3.0hz)
		$C_{13}H_{13}O_4$	1610 cm^{-1}		5·65 (1 H, X-proton in ABX-system, J_{AX} = 9·5hz, 5_{BX} = 10·5hz)
		C 66·7, H 6·0			3·84 (s, 3 H, CH_3O)
					3·82 (s, 3 H, CH_3O)
					3·24 (1H, B-proton in ABX-system, J_{AB} = 18·0hz, J_{BX} = 10·5hz)
					2·77 (1 H, A-proton in ABX-system, J_{AB} = 18·0hz, J_{AX} = 9·5hz)

Diazoketoester **4** (2·56 g – 20 mM), 0·5 g Cu powder and 10 ml of the proper styrene were mixed, stirred well, purged thoroughly with oxygen-free nitrogen and heated in an oilbath at 70°. The outlet gases were led into a gas burette and the evolution was measured against time. Nitrogen evolved: 500, 495, 505 ml for **5a**, **5b**, **5c** respectively. Calculated 496 ml (750 mm Hg, 25°). The results are plotted in Fig 1.

Configurational assignments

Decarbonylation. 150 mg **5a** (assumingly *trans*) was heated on a steambath with 10% H_2O_2 (4 ml) containing 30

mg NaOH. When gas evolution ceased (approx 0·5 hr) the soln was acidified and the ppt collected by filtration and dried. 100 mg. Mp 115–17°. (*Trans-p*-chlorophenyl cyclopropane carboxylic acid is reported to melt at 115·8–116·7°.[3]) When treated likewise the other cyclopropyl derivatives (**5**) gave compounds as shown in Table 2.

Alkaline treatment. 0·9 g **5a** (60% *trans* and 40% *cis* from NMR) was dissolved in MeOH (4 ml) and 1N NaOH (20 ml) was added. After standing overnight at room temp, the soln was acidified and extracted with ether. After treatment with diazomethane, 0·76 g **5a** was recovered (92% *trans* and 8% *cis* from NMR).

1 g **5b** (55% *trans*, 45% *cis*) gave on similar treatment 0·56 g **6b** (96% *trans*, 4% *cis*).

Ring interconversion

Acid aluminium oxide (15 g Woelm, activity I) was packed in a chromatography column, 1·5 cm ID. Cyclopropyl derivative (*cis* or *trans*) was dissolved in CCl_4 and introduced in the column. A yellow zone appeared at the top. Elution was started after 1 hr, using first CCl_4 and then $CHCl_3$ (MeOH for **5b**). The product (**3**) was then distilled, yields 65–67%, physical and spectral properties see Table 4.

Ring opening of cyclopropyl derivative **5a**. **5a** (5·5 g − 0·023 moles) was dissolved in benzene (10 ml) and trifluoroacetic acid (4·5 g − 0·04 moles) was added and refluxed for 4 hr. Solvent evaporated; residue distilled, bp 140/0·05; crystallized from ether/pentane, mp 67°, yield 6·5 g − 80%. Spectroscopy confirmed its identity as methyl 5 - (*p*- chlorophenyl) - 2 - oxo - 5 - trifluoroacetoxy - pentanate (**10**, Ar = *p*-chlorophenyl).

Ring closure of **10**. **10** (3·5 g − 0·01 mole) was added to aqueous MeOH (70 ml, 1:1) together with NaOAc (3 g) and the soln refluxed for 3 hr. MeOH was removed and the residue extracted with ether. The aqueous phase was acidified. White crystals, which could be recrystallized from chloroform, mp 123–125°C, yield 1·7 g − 65%. (Found C 54·9, H 4·6, Cl 14·6. Calc. for $C_{11}H_{11}ClO_4$: C54·6, H 4·6, Cl 14·6). Its identity was confirmed spectroscopically to be 2 - (4 - chlorophenyl) - 5 - hydroxy - 5 - carboxy tetrahydrofuran (**11**).

Dehydration of the methyl ester of **11**. **11** was converted to its ester with diazomethane, bp 122°/0·04. (Found: C 56·0, H 5·1. Calc. for $C_{12}H_{13}ClO_4$: C 56·2, H 5·1). This ester (1·0 g − 0·004 moles) was treated for 1/2 hr with $POCl_3$ (2 ml) in dry pyridin (7 ml) and afterwards poured on ice. After extracted with ether, evaporation of the ether left a dark oil which was distilled, bp 135°/0·4, yield 0·7 g (76%). Identified as **3a** by IR spectroscopy.

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