The Pyrethrins and Related Compounds. Part XVIII.[1] Insecticidal 2,2-Dimethylcyclopropanecarboxylates with New Unsaturated 3-Substituents

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Fifty new esters related to the insecticide bioresmethrin [5-benzyl-3-furylmethyl (1*R*,3*R*)-2,2-dimethyl-3-(2-methylprop-1-enyl) cyclopropanecarboxylate], having various groups in place of the 2-methylprop-1-enyl side chain, have been synthesised. *cis*- and *trans*-3-Formyl-2,2-dimethylcyclopropanecarboxylic esters are obtained by ozonolysis of the corresponding chrysanthemates. Wittig and other reactions with these esters then give the required products. 5-Benzyl-3-furylmethyl esters are obtained by transesterification or *via* acids obtained by cleavage of t-butyl esters under mild conditions.

THE insecticidal activity of compounds related to the synthetic pyrethroid bioresmethrin [5-benzyl-3-furylmethyl (1*R*,*trans*)-chrysanthemate † (1d)] depends on the nature and stereochemical disposition of the substituent at C-3 on the cyclopropane ring.[3-7] We report here syntheses of compounds required to examine this effect. The biological activity of the new esters has been summarised [5,8,9] and will be reported in detail elsewhere.

† The sequence rule [2] applied to this group of compounds gives opposite specifications for compounds of the same stereochemical series. Thus, natural (+)-*trans*-chrysanthemic acid [(1*R*,3*R*)-2,2-dimethyl-3-isobutenylcyclopropanecarboxylic acid] gives, by the route described here, an acid formally named (1*R*,3*S*)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylic acid. For clarity, the compounds are specified here by naming, for example, isomeric forms of chrysanthemic acid as (1*R*,*trans*)-[≡(+)-*trans*] and (1*S*,*cis*)[≡(−)-*cis*] and so on.

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The two (1*R*)-isomers of chrysanthemic acid [10,11] [(+)-*trans* (1c) and (+)-*cis* (10c; $R^2 = R^3 = Me$)] give esters with much greater insecticidal activity than the (1*S*)-forms [(−)-*trans* and (−)-*cis*], so to simplify interpretation of biological data, only esters with 1*R* stereochemistry were examined.

The compounds were prepared following the route used by Crombie *et al.*[12] to synthesise ^{14}C-labelled methyl (±)-*trans*-chrysanthemate and three related esters from the (±)-ester-aldehyde [(3a); (±)-form], but the (+)-*trans*- and (+)-*cis*-(1*R*,*trans*- and 1*R*,*cis*-) chrysanthemic acids, now synthesised commercially,[13] were used. The aldehydes (3a), (3b), (9a), and (9b) were generated by ozonolysis, following Martel;[14] this is more convenient than using osmium tetraoxide (or potassium permanganate[15]) and periodate.[12] Similar Wittig reactions introduce other substituents at position 3.[16,17]

3-Substituted 2,2-dimethylcyclopropanecarboxylic esters

Compound no.	Structure: Formula	R^2	R^3	Method of preparation [a]	*Z*-Isomer produced (%)	Method [a] of synthesis of final ester (5d) or (8d)	Final ester no.
17	(5a)	H	H	(3a), A		C	66
18	(5a)	H	Me	(3a), A + P [b]	90	C	67
19	(5a)	Me	H			C	68
20	(5a)	H	Et	(3a), A	>90	C	69
21	(5a)	H	Pr^n	(3a), A	>90	C	70
22	(5a)	H	Bu^n	(3a), A	>90	C	71
23	(5a)	H	CH_2=CH	(3a), A + P	60	C	72
24	(5a)	CH_2=CH	H			C	73
25	(5a)	H	MeCH=CH	(3a), A + P	50	C	74
26	(5a)	MeCH=CH	H			C	75
27	(5a)	H	Me_2C=CH	(3a), A + P	50	C	76
28	(5a)	Me_2C=CH	H			C	77
29	(5a)	CH_2=C(Me) and H		(3a), A	30	C	78
30	(5a)	CH_2=CH	Me	(4a), A		C	79
31	(5a)	MeCH=CH	Me	(4a), A		C	80
32	(5a)	Et and Me		(3a), special	50	C	81
33	(5b)	Cl and H		(3b), special	20	D	82
34	(5b)	Ac	H	(3b), B	<10	D	83
35	(5b)	CO_2Me	H	(3b), B	<10	D	84
36	(5b)	CO_2Et	H	(3b), B	<10	D	85
37	(5b)	CO_2Pr^n	H	(3b), B	<10	D	86
38	(5b)	CO_2Et	Me	(3b), B	<10	D	87
39	(5b)	CO_2Pr^n	Me	(3b), B	<10	D	88
40	(5b)	CO_2Me	Et	(3b), B	<10	D	89
41	(5b)	CO_2Et	Et	(3b), B	<10	D	90
42	(5b)	CO_2Pr^n	Et	(3b), B	<10	D	91
43	(5b)	CO_2Me	Cl	(3b), B	70	D	92
44	(5b)	CO_2Et	Cl	(3b), B	70	D	93
45	(5b)	CO_2Pr^n	Cl	(3b), B	80	D	94
46	(5b)	CO_2Et	Br	(3b), B	80	D	95
47	(5b)	Cl	Cl	(3b), special		D	96
48	(5b)	Br	Br	(3b), special		D	97
49	(8a) [c]	H	H	(7), A		C	98
50	(8a) [c]	H and Me		(7), A	40	C	99
51	(8a) [c]	H and Et		(7), A	80	C	100
52	(8a) [c]	H and Pr^n		(7), A	>90	C	101
53	(8a) [c]	H and CH=CH_2		(7), A		C	102
54	(11a)	X = O		(3a), special		C	103
55	(11a)	X = S		(3a), special		C	104
56	(5b)	CN	CN	(3b), special		D	105
57	(5b)	CN,CO_2Et		(3b), special		D	106
58	(12b)	R^6 = Me		(3b), special	50	D	107
59	(12b)	R^6 = Et		(3b), special	70/30	D	108
60	(12b)	R^6 = Pr^n		(3b), special	50	D	109
61	(12b)	R^6 = CH_2CH=CH_2		(3b), special	50	D	110
62	(14a)			(13a), special		C	111
63	(16a)			(15a), A		C	112
64	(10b)	H,Me_2C=CH		(9b), A			
65	(10b)	Br	Br	(9b), special		C	113

Methods A—D are described in the Experimental section, and special methods in the Supplementary Publication. [b] P = preparative g.l.c. [c] (8a) = ethyl ester.

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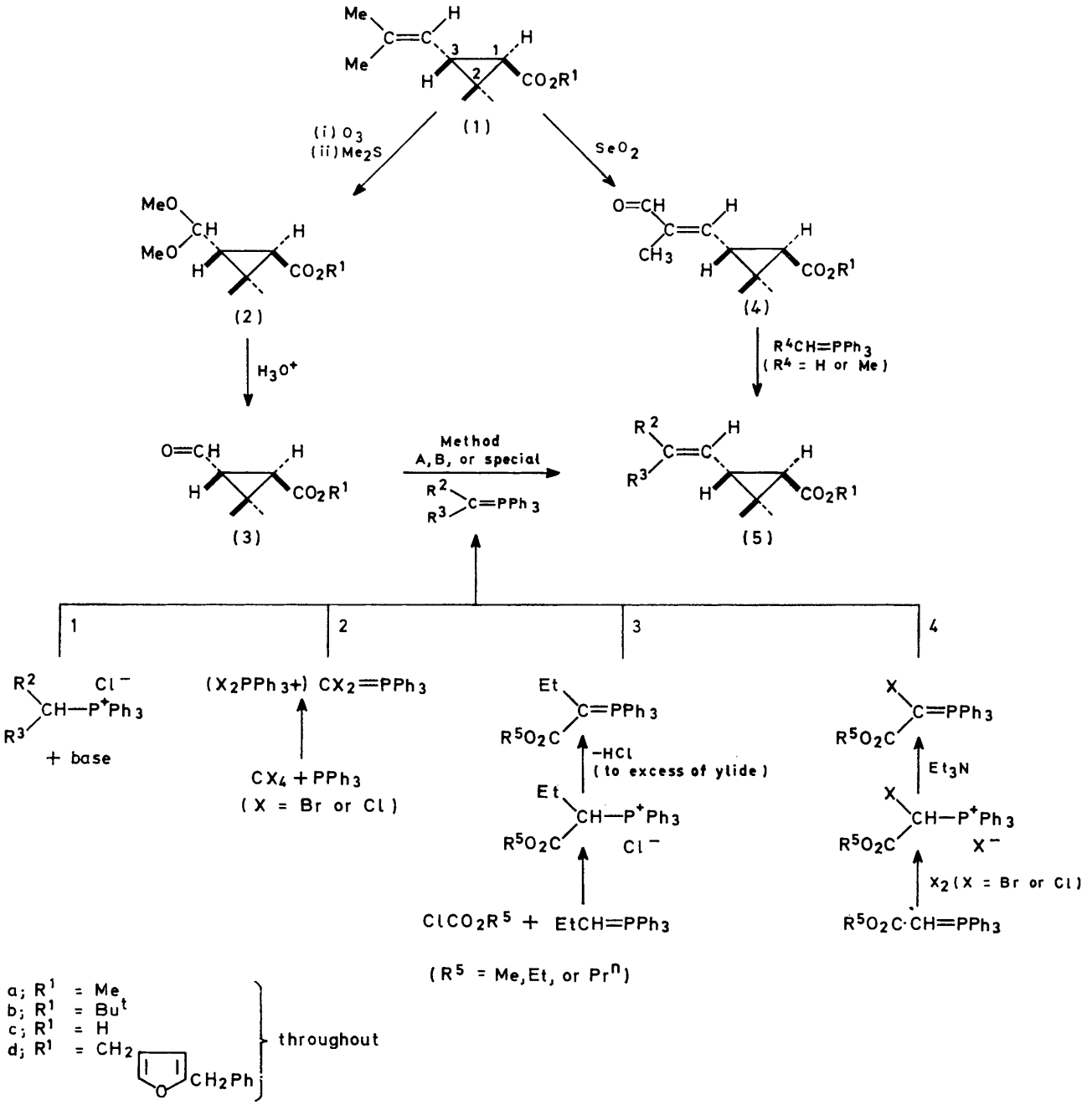
The Scheme indicates the main synthetic paths used (routes 1—4); the experimental conditions for the condensations are described in general (methods A and B) in the Experimental section and individually in Supplementary Publication No. SUP 21131 (16 pp., 1 microfiche).* Route 1, method A was applicable when large, the product was predominantly *cis* (*Z*), but with R^3 = Me, up to 10% of the isomer *trans* (*E*) about the C(1′)–C(2′) bond was formed, and separated by preparative g.l.c. Relative stereochemistries were established by n.m.r. [$J_{1',2'}$ 11 (*Z*) and 15 Hz (*E*)]. With R^3 = Et, no *trans* (*E*) isomer was detected (by g.l.c. or n.m.r.) but

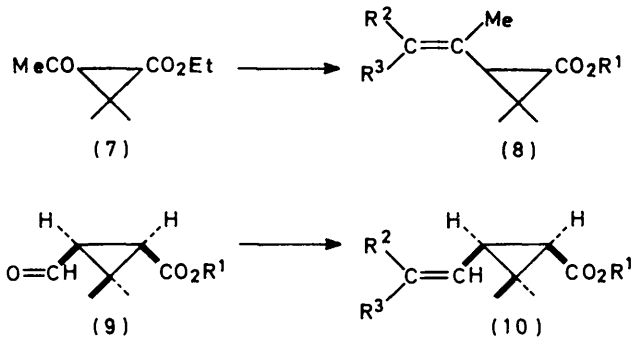


SCHEME

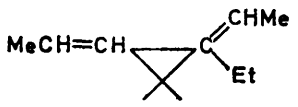
R^2 = H and R^3 = H, alkyl, or alkenyl (compounds 17—19, Table). Compounds 49—53 were prepared similarly from the ester-ketone (7). When R^2 was H and R^3 was using compounds in which R^2 = alkenyl, the reaction was less stereospecific, and both *E*- and *Z*-isomers were obtained, separated by g.l.c., and characterised (n.m.r.). A side-product, the hydrocarbon (6), formed by dual attack at the oxo-functions was detected in a large scale

* For details, see Notice to Authors No. 7 in *J.C.S. Perkin I*, 1973, Index issue.

reaction of the ester-aldehyde (3a) with ethylidenetriphenylphosphorane, and was isolated by preparative g.l.c. and characterised by n.m.r. and mass spectrometry.



5-Benzyl-3-furylmethyl esters [(5d), compounds 66—81 and 98—102] were obtained by alkali-catalysed transesterifications (method C) of the methyl and ethyl esters



[(5a), 17—32; (8), 49—53] and were characterised by n.m.r., mass spectrometry, and g.l.c. These products were directly suitable for bioassay.[5]

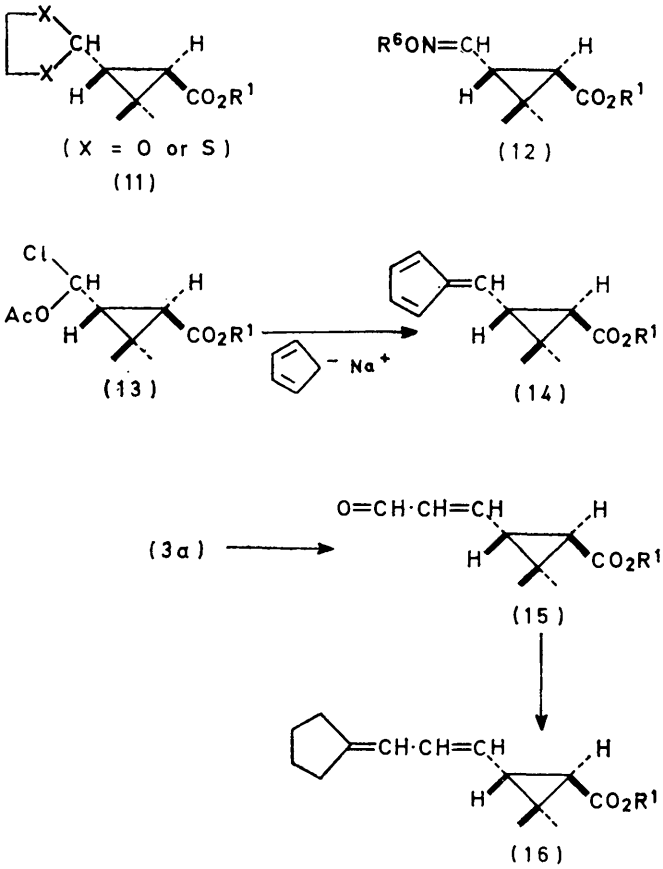
The above procedure (method A) gave only a poor yield from the secondary halide (R^2 = Me, R^3 = Et), so in this case the phosphorane was generated with sodium methylsulphinylmethanide in dimethyl sulphoxide (*cf.* ref. 12).

Transesterification (method C) was precluded in compounds with side chains sensitive to basic conditions. Ozonolysis of 5-benzyl-3-furylmethyl (1*R*,*trans*)-chrysanthemate failed to give the corresponding cyclopropane aldehyde (3d). An alternative route was therefore used, in which the ester-aldehyde (3b) obtained from t-butyl (1*R*,*trans*)-chrysanthemate by careful hydrolysis of the intermediate acetal (see Experimental section) gave 3-substituted t-butyl esters (5b). Heating with toluene-4-sulphonic acid generated the acids (5c), from which the 5-benzyl-3-furylmethyl esters were obtained *via* the acid chloride (method D). This procedure gave esters with oxo or ester functions (compounds 34—42) or bearing halogen (compounds 43—46). Phosphoranes with ester substituents were either obtained directly from the bromoacetates or bromopropionates (Route 1) or by alkoxycarbonylation with a chloroformate of the phosphonate from propyl bromide (Route 3). These stabilised phosphoranes gave *trans* (*E*) products stereospecifically (see the Table, compounds 34—42).

The monochlorovinyl compound (33) was obtained from the phosphorane by the method of Koebrich *et al.*[18] For dihalogenophosphoranes, the tetrahalide (CCl_4 or CBr_4) was treated with triphenylphosphine in the presence of the t-butyl formyl ester (3b) (Route 2), the phosphorane reacting as it was generated.[19,20] A satisfactory yield of the 3-(2,2-dibromovinyl)-ester (48) was obtained, but the corresponding 3-(2,2-dichlorovinyl) product (5b; $R^2 = R^3$ = Cl) was contaminated with the 3-dichloromethyl-ester formed from the Ph_3PCl_2 also generated,[19] and further purification was necessary. Halogenated ester side chains were obtained (Route 4) by halogenating alkoxycarbonylphosphoranes, followed by removal of hydrogen halide with triethylamine (compounds 43—45) (*cf.* ref. 21).

An extended conjugated system was generated (in compounds 30 and 31) from the aldehyde (4a) obtained[22] by selenium dioxide oxidation of methyl (1*R*,*trans*)-chrysanthemate.

Other 3-substituents were introduced by acid-catalysed condensation of the formyl ester (3a) with ethylene glycol



or ethanedithiol to give (11a; X = O or S). Condensation of the aldehyde (3b) with cyanoacetic ester or with malononitrile rapidly gave the esters (5b; $R^2 = R^3$ =CN or R^2,R^3 = CN,CO_2Et) from which the 5-benzyl-3-furylmethyl esters were prepared.

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[19] R. Rabinowitz and R. Marcus, *J. Amer. Chem. Soc.*, 1962, **84**, 1312.
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Alkyloximes (12b) were obtained either directly from (3b) with methoxylamine hydrochloride (R^6 = Me) or by alkylating the oxime (12b; R^6 = H) to give further analogues (12b; R^6 = Et, Pr^n, or $CH_2{\cdot}CH{:}CH_2$).

The α-chloroacetyl derivative (13a), made by the method of Kyburz *et al.*[23] from the aldehyde (3a) reacted with sodium cyclopentadienide to form the fulvene-ester (14a), which was transesterified to (14d).

The phosphorane from chloroacetaldehyde with (3a) smoothly yielded the αβ-unsaturated aldehyde (15a), an intermediate for conjugated derivatives. For example, (15a) with the phosphorane from cyclopentyl iodide gave the diene-ester (16a), and thence (16d).

The biological activities of the 5-benzyl-3-furylmethyl esters described here gave conclusions that led to the development of a pyrethroid with considerably greater photostability than previous members of this class [3-phenoxybenzyl 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate] [5] and another [(—)-(*S*)-α-cyano-3-phenoxybenzyl (1*R*,*cis*)-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropanecarboxylate] [9] with insecticidal activity (against at least five species) exceeding that of any previously described compound.

EXPERIMENTAL

N.m.r. spectra were determined with a Perkin-Elmer R10 spectrometer for dilute solutions in carbon tetrachloride, and mass spectra with a Perkin-Elmer–Hitachi RMU6E double-focusing spectrometer. For analysis by g.l.c. a 5 ft × $\frac{1}{8}$ in column of 5% QF1 or SE30 on Chromosorb W at 130—230°, with a flame ionisation detector in an Aerograph 1200 instrument was used, and for preparative g.l.c., a Pye 105 instrument, with a 30 ft × $\frac{3}{8}$ in column of 25% SE30 on Diatomite C at 180—230°. Fractions were collected at −10° (usually with a total efficiency >50%) and analysed by g.l.c. and n.m.r.

General Methods.—Method A. The phosphonium salt (17 mmol) was added in portions to a stirred solution of sodamide, from sodium (0·7 g, 30 mmol) in liquid ammonia (130 ml) at −33°. After 30 min, the ammonia was allowed to evaporate from the coloured solution, benzene (130 ml) was added, and the solution was refluxed to remove final traces of ammonia. The resulting solution was added to the carbonyl compound [(3a),[14] (4a),[22] or (7) [24]] (6·5 mmol) in benzene (15 ml) at 20° during 30 min. The reaction mixture was evaporated to dryness, treated with water and ether, and the organic phase was separated and evaporated to dryness. The product, with some triphenylphosphine oxide, was extracted into hexane (75 ml), then distilled, usually giving a 50—70% yield of product. Mixtures of stereoisomers were separated by preparative g.l.c., *Z* isomers being eluted before *E*.

Method B (for stabilised phosphoranes). t-Butyl (1*R*,*trans*)-chrysanthemate (1b) (19·5 g) was ozonised as for the corresponding methyl ester (1a).[14] The ozonolysis product was reduced with dimethyl sulphide (16·0 g) to give the crude dimethyl acetal (2b), which was hydrolysed with acetic acid (60 ml) in acetone (80 ml) and water (140 ml) at 20° for 1 h. Water (500 ml) and ether (400 ml) were added, and the organic layer was washed thoroughly with saturated sodium carbonate solution (traces of acid cause the acetal to re-form on standing). After drying (Na_2SO_4) and evaporation, distillation gave the product (14·6 g, 84%), b.p. 78—81° at 0·2 mmHg, n_D^{20} 1·4505, n.m.r. spectrum as recorded for the (±)-isomer.[17] This aldehyde (3b) (6·1 mmol) and the phosphorane (7·2 mmol) in dichloromethane (50 ml) were stirred at 20° overnight or at 60° for 2 h, and the mixture was then evaporated to dryness and extracted with hexane. The solution was washed, dried, and distilled to give the product, *ca.* 60%.

Method C (transesterification). The alkyl ester [*e.g.* (5a) or (8a)] (0·1 g) in toluene (1 ml) was passed through alumina (0·5 g; Hopkin and Williams neutral), then added to a portion (2·5 ml) of a solution prepared by treating sodium (0·02 g) with 5-benzyl-3-furylmethyl alcohol (1·0 g) in toluene (10 ml) under nitrogen. The mixture was heated at 110° for 30 min under nitrogen, then chromatographed on alumina (8·0 g; as above), eluting with benzene. The 5-benzyl-3-furylmethyl ester was obtained, usually without any detectable trace of 5-benzyl-3-furylmethyl alcohol and <10% of unchanged alkyl ester, by evaporating the eluate, finally at 0·1 mmHg.

Method D (pyrolysis, then esterification). The t-butyl ester [*e.g.* (5b)] (0·16 mmol) and toluene-4-sulphonic acid (46 mg) were heated in benzene (12 ml) until no more isobutene was evolved (n.m.r. control). The product was cooled, and treated with pyridine (0·16 mmol) and thionyl chloride (0·16 mmol) at 20° for 3 h. Then 5-benzyl-3-furylmethyl alcohol (0·17 mmol) and pyridine (0·16 mmol) in benzene (5 ml) were added, and after 12 h at 20°, the product was purified by chromatography on alumina as described above.

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