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STEREOCHEMICAL COURSE OF THE PALLADIUM-CATALYSED ARYLATION OF DISUBSTITUTED ACTIVATED ALKENES WITH BENZOYL CHLORIDE

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Summary

The palladium-catalysed arylation of ten 1,1- and 1,2-disubstituted activated alkenes with benzoyl chloride was studied. In most cases, more than one product was formed. The stereochemical course of the arylation appears to be controlled by the polarity of the double bond, the tendency to *cis* (suprafacial) alkene insertion and subsequent re-elimination, steric hindrance in the alkylpalladium(II) species formed on alkene insertion, and the reversible nature of the alkene elimination.

Introduction

We have recently reported the alkylation of simple activated alkenes by aroyl chlorides, catalysed by palladium acetate, to give cinnamic acid and stilbene derivatives [1].

$$C_6H_5COCl + CH_2{=}CHX \xrightarrow[\text{Base}]{Pd(OAc)_2} C_6H_5CH{=}CHX + CO + HCl$$

($X = CO_2Et$, $CONMe_2$, CN, C_6H_5 etc.)

The alkenes studied lead exclusively to the formation of the *E*-isomer of the resulting product, except for acrylonitrile where a small amount of the *Z*-isomer was formed. In order to study further the stereochemistry of the reaction, we have investigated the arylation of disubstituted alkenes using benzoyl chloride. The arylation with aryl bromides or iodides of some of the alkenes used here has been reported previously by Heck et al. [2–6].

Results

All reactions were carried out at 130°C in *p*-xylene as solvent. *N*-Benzyldimethylamine was used as base. The disubstituted alkenes reacted significantly more slowly than those previously studied, necessitating a relatively high catalyst concentration.

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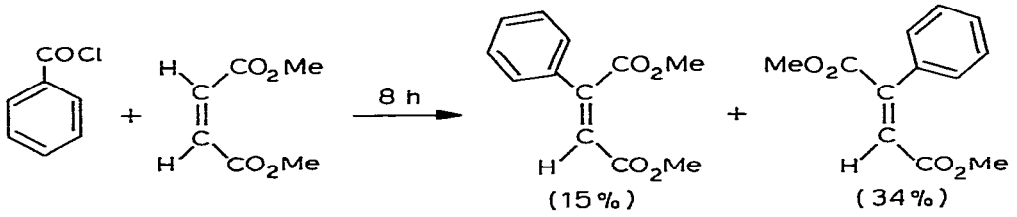
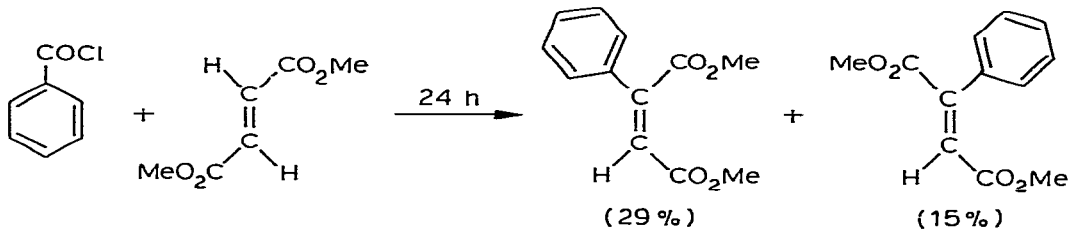
Palladium acetate was used throughout at 1 mol% relative to benzoyl chloride. In the arylation of dimethyl maleate both isomers of the expected product were formed.



After 8 h the yield of dimethyl fumarate is only 0.2% based on the dimethyl maleate used and at this point arylation has virtually ceased. Even after 24 h only 1% of dimethyl fumarate had been formed.

In order to check whether the isomer distribution was dependent on the choise of base, the reaction was repeated using tri-n-butylamine and *N*-ethylmorpholine which represent a p*K* range of about three units. The results are given in Table 1. The small difference between tri-n-butylamine and the other two bases appears to be just significant compared with the error in their determination (gas chromatography), but the main effect is on the yield rather than the selectivity. As previously reported, tri-n-butylamine reacts slowly with benzoyl chloride and is therefore poorly suited to cases where the arylation itself is slow [1]. No significant change in the *E*/*Z* ratio occurred during the reactions. The following experiments were all carried out using *N*-benzyldimethylamine.

Dimethyl fumarate reacted in a manner analogous to dimethyl maleate, the main product again having the opposite arrangement of the ester groups to the starting alkene.



Although the reaction proceeds at about the same rate as with dimethyl maleate it was allowed to continue for 24 h, without change in the *E*/*Z* ratio.

TABLE 1

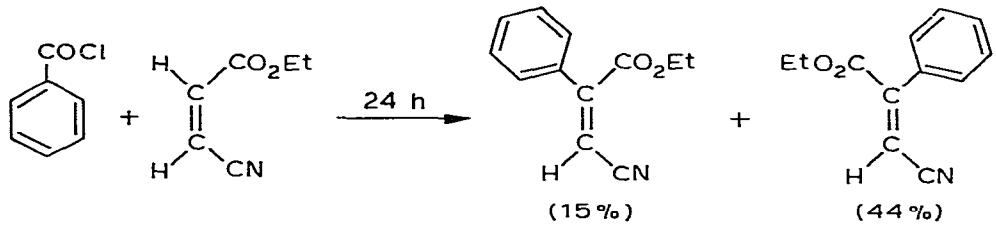
EFFECT OF BASE STRENGTH ON THE ARYLATION OF DIMETHYL MALEATE WITH BENZOYL CHLORIDE[a]

Base	p*K*	Isomer ratio (*E*/*Z*)	Yield (%)
N-Ethylmorpholine	7.80	71/29	48
N-Benzyldimethylamine	9.03	70/30	49
Tri-n-butylamine	10.89	76/24	19

[a] Conditions as in experimental.

The olefinic protons of the two products occur in the NMR spectrum at 6.33 and 7.03 ppm. From the reaction of benzoyl chloride with diethyl maleate a pure sample of the major product was isolated. The ^{13}C NMR spectrum shows a coupling constant of 7 Hz between the vinyl proton and the carbonyl carbon of the non-geminal ester group, indicating that this is *cis* to the proton [7]. Thus the major isomer here has the *E* configuration with the vinyl proton at 7.03 ppm in the ^{1}H spectrum of the dimethyl ester (ethyl ester 6.97 ppm).

Ethyl (*Z*)-3-cyanoacrylate also gives two main products.



The structural assignment is again based on the ^{13}C spectrum where the coupling constant (6 Hz) of the olefinic proton to the carbonyl carbon in the major isomer indicates again the *E* configuration. These appear to be new compounds. ^{1}H NMR spectra for new compounds are given in Table 2. Gas chromatography shows two other products are formed to the extent of 3 and 4% only. Their ^{1}H NMR spectra show singlets at 6.88 and 7.26 ppm which suggests that these two products are the *E* and *Z* isomers of ethyl 3-cyanocinnamate.

In order to investigate further the directing effect of the activating group on the arylation, ethyl (*E*)-cinnamate and (*E*)-cinnamonitrile were studied.

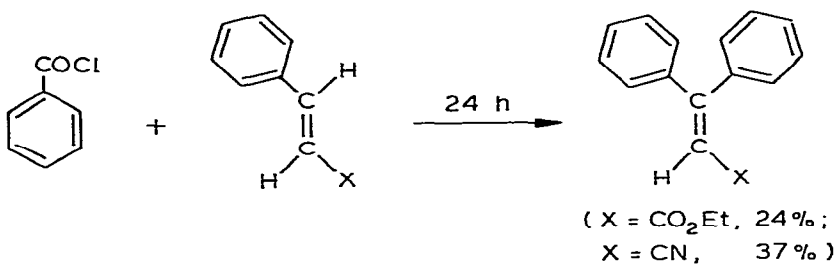


TABLE 2

^{1}H NMR SPECTRA OF NEW PRODUCTS[a]

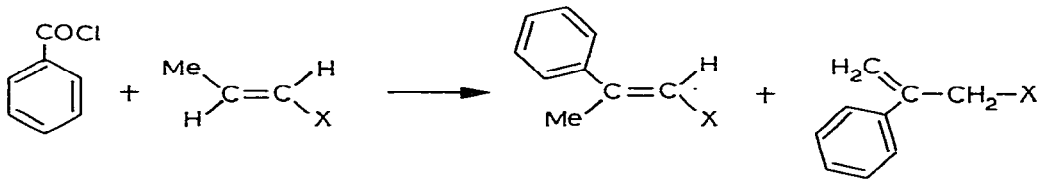
(*E*)-3-Ethoxycarbonylcinnamonitrile	7.42–7.58 (m, 5H), 6.52 (s, 1H), 4.33 (q *J* 7 Hz, 2H), 1.32 (t, *J* 7 Hz, 3H).
(*Z*)-3-Ethoxycarbonylcinnamonitrile	7.42–7.58 (m, 5H), 5.94 (s, 1H), 4.46 (q *J* 7 Hz, 2H), 1.43 (t *J* 7 Hz, 3H).
Methyl 3-phenyl-but-3-enoate	7.2–7.5 (m, 5H), 5.56 (bs, 1H), 5.24 (bs, 1H), 3.67 (s, 3H), 3.54 (bs, 2H).
Methyl 2-benzylcinnamate	7.94 (s, 1H), 7.18–7.42 (m, 10H), 3.96 (s, 2H), 3.75 (s, 3H).
2-Benzylacrylonitrile	7.25–7.45 (m, 5H), 5.67 (bs, 1H), 5.92 (bs, 1H), 3.56 (bs, 2H).

[a] Chemical shifts in ppm.

In both cases only the 3,3-diphenyl derivatives were formed. The assignment as the 3,3-diphenyl derivatives is based on the chemical shifts of the olefinic protons which are 6.36 ($X = CO_2Et$) and 5.74 ppm ($X = CN$), in agreement with the literature values [8, 9]. The directing effect towards arylation at the carbon atom β to the activating group is thus $CN > CO_2Et > C_6H_5$.

Benzoyl chloride was caused to react in a competition experiment with one third of its amount of the three alkenes, acrylonitrile, ethyl acrylate and styrene, again with *N*-benzyldimethylamine as base. The results are given in Table 3. The experiment was carried out at 0.04 mol% palladium acetate to reduce the rate to one that could be readily followed. The order of the initial rates, as measured by the catalytic activity, is the same as that for the directing effect of these groups given above.

In the arylation of methyl (*E*)-but-2-enoate and (*E*)-1-phenyl-1-propene, only the *E* isomers of the expected products were observed, in addition to the isomerised products, methyl 3-phenylbut-3-enoate and 2,3-diphenyl-1-propene.



(X = CO_2Me, 46%; 16% (26 h);
X = C_6H_5, 13% 7% (31 h))

Although both these latter products are styrene derivatives no further arylation was observed in these cases (see below). For the major products, the vinylic protons occur at 6.08 ppm for methyl (*E*)-3-phenylbut-2-enoate and at 6.83 ppm for (*E*)-1,2-diphenyl-1-propene. 2,3-Diphenyl-1-propene shows the two vinyl protons at 5.01 and 5.50 ppm with the methylene group at 3.84 ppm. All three spectra have been reported previously [10–12]. Methyl 3-phenylbut-3-enoate appears to be a new compound.

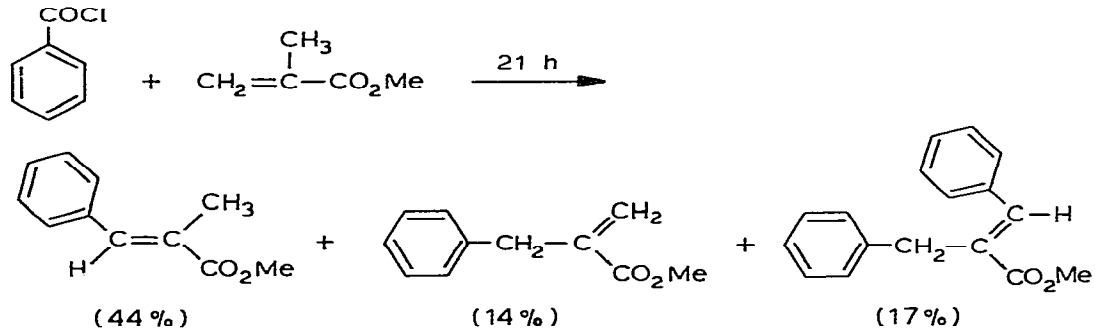
Methyl methacrylate reacted with benzoyl chloride to give three products.

TABLE 3

COMPETITIVE ARYLATION OF ACRYLONITRILE, ETHYL ACRYLATE AND STYRENE WITH BENZOYL CHLORIDE

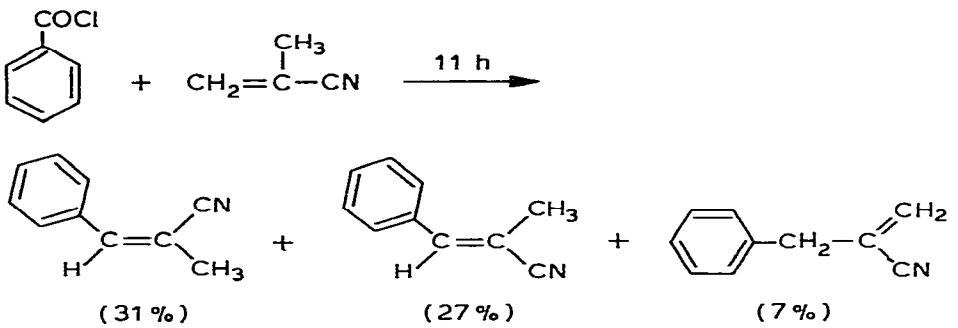
	Initial activity (min^{-1}) [a]	Final yield (%) [b]	Reaction time (min) [c]
$C_6H_5CH{=}CHCN$	192	89	60
$C_6H_5CH{=}CHCO_2Et$	105	74	30
$C_6H_5CH{=}CHC_6H_5$	38	62	60

[a] Mol product/mol catalyst/min. [b] Based on alkene. [c] Time to maximum yield. Benzoyl chloride 0.12 mol, acrylonitrile 0.04 mol, ethyl acrylate 0.04 mol, styrene 0.04 mol, *N*-benzyldimethylamine 0.12 mol, palladium acetate 0.048 mmol, *p*-xylene 240 ml, n-eicosane 4g (GC standard), 130°C.

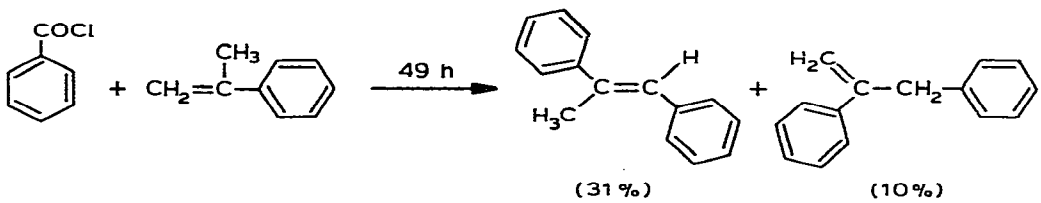


This was the only case in which a second arylation of the isomerised alkene was observed. The *Z*-isomer of the main product was not detected. Methyl 2-methylcinnamate shows the vinyl proton at 7.65 ppm indicating the *E*-isomer [10]. Methyl 2-benzylacrylate shows vinyl protons at 6.43 and 5.46 ppm and the methylene protons at 3.64 ppm. The compound has been reported previously by Heck [5]. Methyl 2-benzylcinnamate shows the vinyl resonance at 7.94 ppm. By analogy with methyl 2-methylcinnamate, it should be the *E*-isomer as expected. Although the ester appears again to be a new compound, 2-benzylcinnamic acid is reported to show a vinyl resonance at 7.97 ppm [13]. The stereochemistry was not described, but this would again appear to be the *E* isomer.

Both *E* and *Z* isomers of the expected product are obtained in the arylation of methacrylonitrile, together with the isomerised alkene.

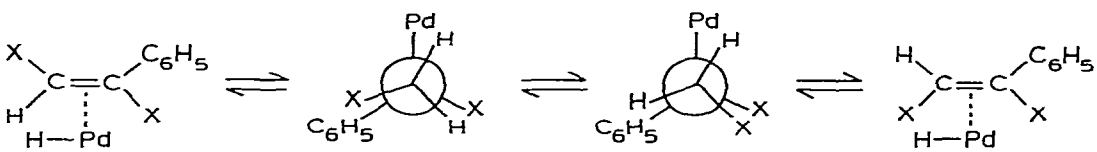


A diarylation product was not formed. The *E* and *Z* isomers exhibit vinyl resonances at 7.21 and 6.92 ppm, respectively. Both have been reported previously [14]. 2-Benzylacrylonitrile appears to be a new compound. The arylation of 2-phenyl-1-propene leads to the same two products as were obtained with (*E*)-1-phenyl-1-propene, but in improved yields. Again, no diarylation products were observed.



Discussion

From the results of the arylation of these alkenes, conclusions can be drawn regarding the stereochemistry of the reaction. These are based on the proposed mechanism [1]. The relevant steps are the insertion of the alkene into the palladium–phenyl bond, the elimination of a palladium hydride species and the subsequent behaviour of the hydride. It has been shown that the insertion of an alkene into a palladium(II)–phenyl bond occurs in a *cis* (suprafacial) manner [15]. For three of the (*E*)-alkenes (dimethyl fumarate, methyl but-2-enoate, 1-phenyl-1-propene) and the two (*Z*)-alkenes (dimethyl maleate, ethyl 3-cyanoacrylate) the main product is in all cases that which would be obtained if the insertion was followed by a *cis*-elimination. Ethyl cinnamate and cinnamonitrile are to this end uninformative as in both cases 3,3-diphenyl derivatives are formed. Heck has observed a similar situation in the arylation of some of these alkenes with aryl bromides and iodides [2–4, 6]. In the case of dimethyl maleate and fumarate, and ethyl (*Z*)-3-cyanoacrylate both *E* and *Z* isomers of the product are formed. The extremely low concentration of dimethyl fumarate formed in the arylation of dimethyl maleate and the similar rates of arylation of these two alkenes, indicate that the minor isomers are not formed by a prior alkene isomerisation. The minor isomer corresponds to that which would be formed by a *trans* (antarafacial) elimination. The same isomer could also be obtained by a re-addition of the palladium hydride species in the reverse sense to the double bond and subsequent *cis*-elimination.

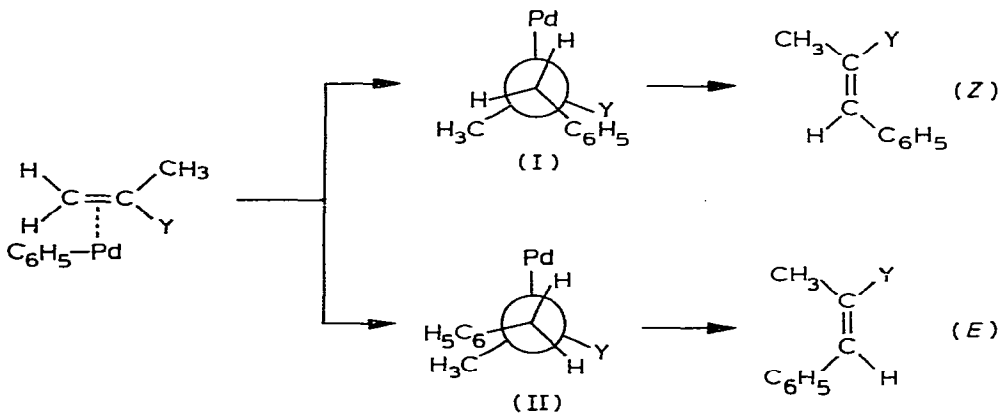


(X = CO_2Me)

If the palladium re-adds to the double bond in the original sense, only a *trans*-elimination can lead to alkene isomerisation.

If a base-catalysed *trans*-elimination does occur, its extent might reasonnably be expected to be dependent on the p*K* of the base. Heck has reported [6] that in the arylation of dimethyl maleate with iodobenzene more of the *Z* isomer of the product, which is that which would arise from a *trans*-elimination, is formed using triethylamine as base than with tri-n-butylamine. The p*K* difference here is very small, and it is perhaps better to draw no conclusion, especially as the literature is not unanimous as to which of these two bases is the stronger. The results in Table 3 clearly do not support the idea of a base-catalysed *trans*-elimination. It is well-known that *cis*-elimination of a hydride is a very facile process for alkyl-transition metal compounds [16], and also that *cis*-hydridoalkene complexes rapidly undergo the insertion–elimination sequence [17]. This suggests that the reverse re-addition plus *cis*-elimination mechanism is a more probable source of the minor isomers than a direct *trans*-elimination. The absence of any significant isomerisation of the starting alkene suggests that free palladium(II) hydride species do not exist in solution. Conceivably, the alkylpalladium(II) and alkenehydridopalladium(II) species persist

in a relatively labile equilibrium, leading to product isomerisation, until the hydride is destroyed by reaction with the base. The product distribution would therefore reflect the relative rates of the two modes of *cis*-addition of the hydride to the alkene double bond. With methyl (*E*)-but-2-enoate and (*E*)-1-phenyl-1-propene, the *Z* isomers of the products are not formed, the other products being methyl 3-phenyl-but-3-enoate and 2,3-diphenyl-1-propene. These products may again arise from the reverse re-addition process, with the final elimination involving a hydrogen of the methyl group. The alternative would be a 1,3-elimination of the palladium hydride species, which we regard as far less likely. For the three 1,1-disubstituted alkenes methyl methacrylate, methacrylonitrile and 2-phenyl-1-propene both *E* and *Z* isomers of the normal arylation products can be formed by *cis*- or *trans*-elimination. The product formation appears here to be determined by steric interactions in the intermediate alkylpalladium complexes.



(Y = CO_2Me, C_6H_5 , CN)

For $Y = CO_2Me$ and C_6H_5, only the *E* isomer of the product is formed. This suggests that the steric interaction of the phenyl group in I with Y is in these two cases sufficient to force the reaction to proceed solely via alkyl (II).

For methacrylonitrile the relevant interactions are phenyl-cyano (I) and phenyl-methyl (II) and the *E* and *Z* isomers are formed in almost equal amounts.

In these reactions the palladium adds to the carbon atom adjacent to the methyl group. This permits the direct formation of the methylene derivatives methyl 2-benzylacrylate, 2-benzylacrylonitrile and 2,3-diphenyl-1-propene as well as the expected products.

The directing effect of substituents as judged by the results with ethyl cinnamate, cinnamonitrile and ethyl 3-cyanoacrylate indicates that the phenyl group adds preferentially to the most positive carbon atom of the double bond. The presence of a methyl group on either olefinic carbon atom does not affect this. The main products formed here are not those which would be expected on steric grounds. It therefore appears probable that the production of cinnamic acid and stilbene derivatives in the arylation of monosubstituted activated alkenes [1] is also due to electronic rather than steric factors.

It is interesting that the initial rates observed in the competition experiment follow the same order as the directing effect of the three activating groups. The rate effect might simply reflect the relative coordinating ability of the three alkenes to

palladium. If it is an effect on the actual catalytic reaction, the explanation may be that the alkene insertion is the rate determining step, the more strongly polarised double bonds facilitating this process.

Experimental

Palladium acetate was obtained from Engelhard. Other chemicals were from Fluka. Benzoyl chloride was distilled before use. Alkenes were used as received. Ethyl (*Z*)-3-cyanoacrylate was prepared by the literature method [18]. For gas chromatography, a Varian 3700 chromatograph equipped with a Shimadzu Chromatopac E1A integrator was used. IR spectra were obtained using a Perkin–Elmer 157 instrument; ^{1}H NMR spectra (250 MHz) with a Bruker WM 250 and ^{13}C spectra using a Varian XL-100; and mass spectra with Varian CH 5 and CH 7 instruments. Chemical shifts are in ppm downfield from TMS. Elemental analyses were performed by the Microanalytical laboratory at Ciba-Geigy. Satisfactory analyses were obtained for all new compounds.

Alkene arylation. The following procedure was used. Reactions were carried out in a conventional reflux apparatus under argon. To *p*-xylene (100 ml) were added under argon palladium acetate (0.2244 g, 1 mmol), benzoyl chloride (11.62 ml, 100 mmol), alkene (100 mmol), and *N*-benzyldimethylamine (15.06 ml, 100 mmol). The reaction mixture was stirred at 130°C for the required time. After cooling to room temperature, the mixture was filtered and the precipitated amine salt washed with toluene (50–100 ml). The combined filtrate was extracted twice with 2 *M* hydrochloric acid (2 × 100 ml) and dried over magnesium sulphate. After removal of the solvents, the products were isolated by distillation, chromatography and recrystallisation. In most cases, *E* and *Z* isomers were isolated together.

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