CHAPTER – I I

STUDIES WITH PHOSPHINE-
AND
PTC- FREE HECK REACTION

CHAPTER – II

STUDIES WITH PHOSPHINE- AND PTC- FREE HECK REACTION

INTRODUCTION :

Heck reaction occupies a special place in the palladium catalysed reactions which have become indispensable tools in organic synthesis. Phosphine- assisted Heck reaction is well established and various aspects of the mechanism have been discussed in Chapter-I. As it is evident by now, none of the steps in the general Heck cycle requires the presence of a phosphine ligand nor any other strongly bound ligand in the coordination shell of palladium. The oxidative addition, migratory insertion and hydride elimination do not require the assistance of specific ancillary ligands. The inherent reactivity of nonligated palladium is sufficient for oxidative addition to most kinds of C-X bonds. On the other hand, phosphine-free process could lead to huge catalytic activity and the possibility of performing catalytic transformations in the cases of high steric demands.

The most serious drawback of phosphine-free systems is the inherent instability of catalytic cycles driven by palladium complexes with an undefined coordination shell. Mismatch of reaction rates of individual stages leading to the deactivation of catalyst can be caused by many factors including temperature, variation of concentration, change of the composition of reaction mixture in the course of reaction, etc. Phosphine-free systems thus ought to be specifically and separately tailored to each reaction. Often success is a matter of chance. Nevertheless, more and more data is being obtained which reveal the potential of such systems.

Due to the lack of strongly bound neutral ligands, phosphine-free systems are bound to proceed via the cationic route via the delegation of anionic ligands.

Therefore, phosphine-free systems are realized in polar solvents (DMF and the like) particularly in aqueous media.

In the seminal work by Spencer[1], a phosphine-free system has been shown to be quite suitable for the reactions with activated bromoarenes showing almost identical yields to the system supported by 4 equivalent of PPh_3 ligand, though inferior to the $P(o\text{-}Tol)_3$ – assisted system. Further development of phosphine-free protocol is associated with the introduction of phase-transfer agents, halide salt promoters, and aqueous systems.[2]

The reasons for considering phosphine-free Heck reactions are both economical and chemical. Phosphine ligands are expensive, toxic and unrecoverable. In large scale applications on industrial and semi-industrial scale, the phosphines might be a serious economical burden than even palladium itself, which can be recovered at any stage of production or from wastes. The chemical reason is lower reactivity of fully ligated complexes of palladium, the main result of which is the need for higher loads of catalyst to achieve appropriate rates of reaction and therefore, further increase of procedure cost.

Both underligated and phosphine-free catalysis are opposite to the phosphine-assisted conservative methodology. It relies not on the intrinsic stability of properly ligated isolable complexes, but rather on making zerovalent palladium species run for life within the Heck catalytic cycle or get inactivated as black sediments. Underligated Pd(0) species (the term underligated means that a given palladium complex bears less strongly bonded ligands than is required to form a stable complex) are intrinsically unstable to survive outside of the cycle but are likely to have higher reactivity, therefore, their stationary concentration in a catalytic system is much lower. It is with a hope that some helpful trends could be

evaluated and used to refine the procedures. The advantages would be high catalytic efficiency and economic feasibility of processes.

Aqueous Heck Chemistry

Palladium-catalysed processes including the Heck reaction, Suzuki and Stille cross-coupling, Sonogashira reaction, carbonylation, hydrogenation, hydrogenolysis, and Wacker-type oxidation can be run in the presence of water or in mainly aqueous environments[3]. The use of aqueous solvents pursues such utilitarian goals as the development of environmentally and technologically safe processes but also brings a new dimension into the chemistry of palladium-catalysed reactions.

Water is one of the most polar solvents known. As such it must have an accelerating influence on the Heck reaction as it promotes the migratory insertion to follow the cationic mechanism. Therefore, the effect of water must be more pronounced for underligated and phosphine-free systems. However, nothing is known so far about the influence of water on the oxidative addition reaction.

Water is a good ligand for palladium – strongly bonded but kinetically labile. Brown has estimated a stability constant for the hydration equilibrium as $500 \ M^{-1}$. Water is thus a good placeholder ligand, particularly effective in phosphine-free reactions. Due to the high concentration in aqueous solvents (water is often 5-10 vol % amounts, which corresponds to 3-6 M concentrations giving a huge excess over the palladium catalyst), water is able to displace other labile ligands from the coordination shell of palladium, particularly iodide which poisons the catalyst and blocks the cationic path. Water literally washes iodide and other interfering ligands out of the coordination shell. Again, this is not always good as water equally well washes off some helpful ligands, for example,

acetate. Jeffery noted a negative influence of water on the reactions in which acetates of hydrocarbonates were used as bases[5].

Moreover, the aqueous environment has an effect similar to the effect of high pressure as hydrophobic interactions make more compact transition states more favourable. Therefore, highly aqueous media must exert an influence on the rates and regioselectivities of Heck reactions, particularly intramolecular cyclizations, in a way similar to well-known effect of water on Diels-Alder reactions, Claisen rearrangement, etc.[3] Indeed, a positive effect of water on the intramolecular Heck reaction has been noticed and exploited.

Water has been allowed to enter Heck chemistry only relatively recently. The traditional technique for carrying out the Heck reaction has been to use anhydrous polar solvents (DMF and MeCN are most frequently used) and tertiary amines are bases.

First, it was shown that the Heck reaction can be accomplished under phase transfer catalyst conditions[6] with inorganic carbonates as bases under very mild conditions even at room temperature. The reactions were carried out in a liquid-liquid system. As the reaction in such systems actually runs in the nonaqueous phase formed by organic reagents, this case cannot be regarded as a true aqueous Heck process.

Water and aqueous organic solvents can be successfully used for carrying out the Heck reaction in the aqueous phase catalysed by simple palladium salts in the presence of inorganic bases K_2CO_3, Na_2CO_3, $NaHCO_3$ or KOH[7]. The reaction of water soluble acrylic acid with aryliodides and bromides with both electron-donating and electron-withdrawing substituents can be easily carried out in DMF-

H_2O or $HMPA-H_2O$ mixtures with a water content from 10% to 80% (v/v) at 70-100°C in the presence of $Pd(OAc)_2$ as catalyst precursor and K_2CO_3 as base.

PRESENT WORK

It is clear from the foregoing discussion that the Heck reaction can be carried out without the use of phosphines and phase-transfer catalyst (PTC). This would make the Heck reaction environmentally friendly (Green chemistry approach). Phosphine-free systems ought to be specifically and separately tailored to each reaction as there is inherent instability of the catalytic cycle due to variation of many factors including temperature, concentration, change of composition of reaction mixture in the course of reaction. We present here our work on Heck reaction under phosphine –free and phase transfer catalyst-free conditions.

Heck reaction of p-iodoanisole (1.3) with styrene (1.4) was carried out in aqueous DMF using palladium chloride and potassium carbonate to yield 4'-methoxystilbene (1.5) in high yield. The m.p. of the product matched with the reported one. The structure of the product was confirmed by spectroscopic data.

The I.R. spectrum (Fig.1) exhibited peaks at 3019, 1605, 1512, 1216, 689, 669 cm^{-1} indicating presence of aromatic ring and double bond.

The P.M.R. spectrum (Fig.2) showed a singlet for the methoxy group at 3.85 and a multiplet for the nine aromatic protons and two vinylic protons between 6.85 and 7.65. The ^{13}C-NMR (Fig.3) showed a singlet for the methoxy group at 55.00, a strong peak for the vinylic carbons at 113.87 and aromatic carbons at 125.99 (strong), 126.15, 127.21, 127.45 (strong), 128.05 and 128.37. The mass spectrum (Fig.4) exhibited a strong molecular ion peak at (m/z) 210.

CHART – I

Scheme - 1

$$\underset{1}{H_3CO-\!\!\!-\!\!\!-NH_2} \xrightarrow[0-5^\circ C]{NaNH_2 / HCl} \underset{2}{H_3CO-\!\!\!-\!\!\!-\overset{\oplus}{N}\equiv N\ \overset{\ominus}{Cl}} \xrightarrow{KI} \underset{3}{H_3CO-\!\!\!-\!\!\!-I}$$
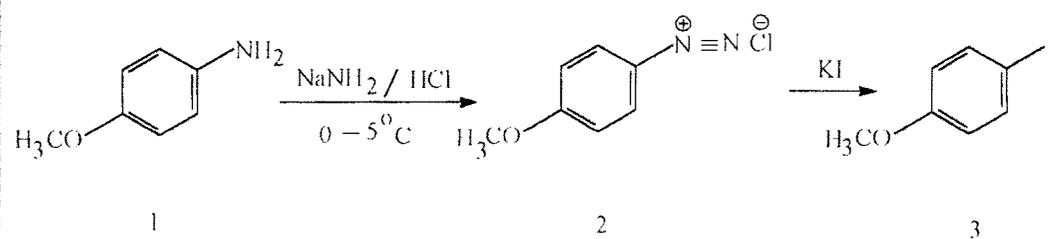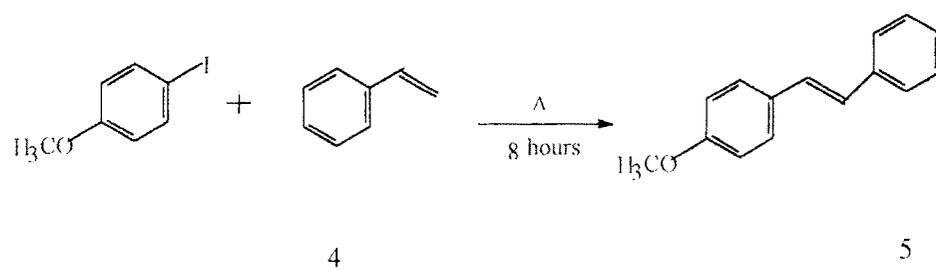
Scheme - 2

Scheme - 3
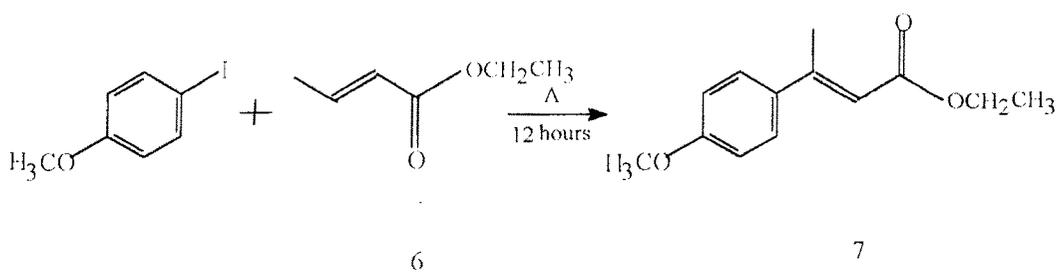
A : PdCl$_2$(0.00002 mol), K$_2$CO$_3$ (0.002 mol), DMF-H$_2$O.

The peaks at 195 (M-15, loss of methyl), 179 (M-31, loss of OCH_3), 165, 115, 77 (phenyl cation) agreed with the structure.

The Heck reactions of p-iodotoluene (2.3) with styrene (2.4) under the same condition yielded 4'-methylstilbene (2.5) m.p. 119-120°C (Lit.[9] m.p. 120°C).

Similarly the Heck reaction of bromobenzene (3.1) with styrene (3.2) yielded stilbene (3.3), m.p. 124-125°C (Lit.[10] m.p. 122-124°C).

The Heck reaction of p-iodotoluene (2.3) with methyl crotonate (2.6) using $PdCl_2$, K_2CO_3 and DMF-H_2O yielded methyl 3- (4'-methylphenyl)-3-methylacrylate (2.7) in good yield. This compound has been prepared earlier by Reformatsky reaction of methyl 2-bromoacetate on p-methylacetophenone followed by dehydration and has been converted into ar-turmerone, the natural product from *Curcuma longa* Linn. The structure of this product has been established by following spectral data. The I.R. spectrum (Fig.5), indicated a strong carbonyl absorption for the conjugated ester group at 1720, a double bond absorption at 1615 and 1600 and other peaks at 1230, 1150, 800 cm^{-1}.

The P.M.R. spectrum (Fig.6) exhibited a singlet at 2.35 for the aromatic methyl, a singlet at 2.56 for the vinylic-methyl deshielded due to the ester carbonyl group, a singlet at 3.74 for the methoxy group, a singlet at 6.13 for the vinylic-proton, a doublet at 7.16 with a ortho coupling constant of 8 Hz for the two aromatic protons meta to methyl group and a doublet for the remaining protons at 7.37 with a ortho coupling constant of 8 Hz.

The Heck reaction of p-iodoanisole (1.3) with ethyl crotonate under the above condition yielded ethyl 3-(4'-methoxyphenyl)-3-methylacrylate (1.4) in good yield. The I.R. spectrum (Fig.7) of the product showed strong carbonyl absorption for the conjugated ester group at 1720 cm^{-1}. The P.M.R. spectrum

CHART – II

Scheme - 4

Aniline derivative **1** + NaNO₂/HCl at 0–5°C → diazonium salt **2** → iodo compound **3**

$$\text{1} \xrightarrow[0-5^{\circ}C]{NaNO_2/HCl} \text{2} \longrightarrow \text{3}$$

Scheme -5

$$\text{4} \xrightarrow[8 \text{ hours}]{A} \text{5}$$

Scheme -6

$$\text{6} \xrightarrow[12 \text{ hours}]{A} \text{7}$$
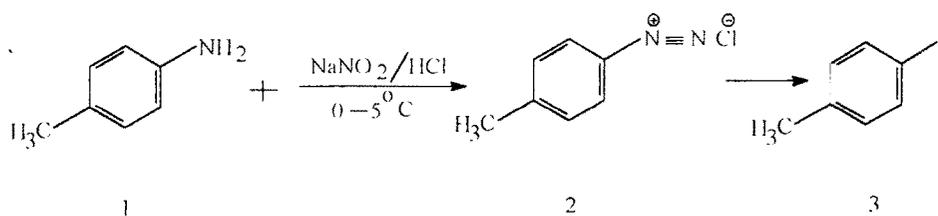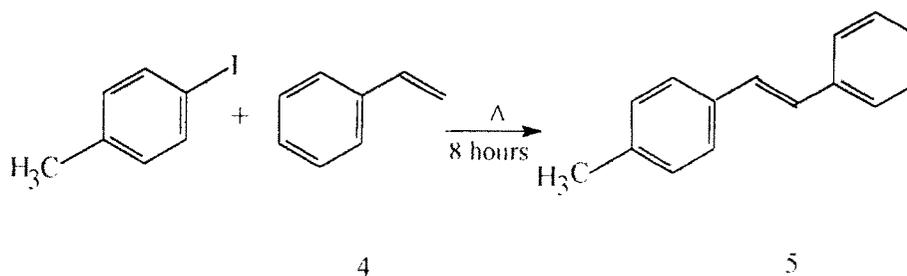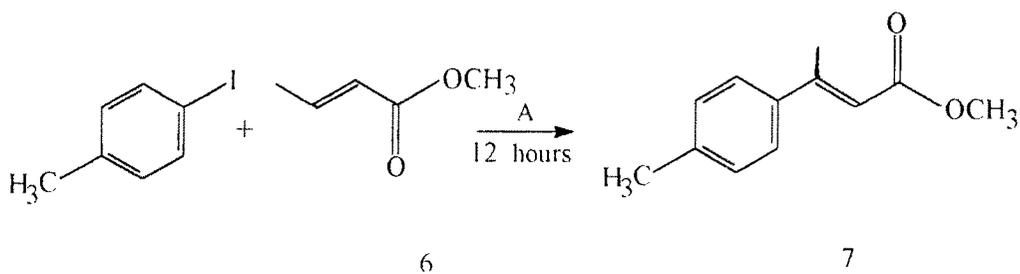
A : PdCl₂ (0.000025 mol), K₂CO₃ (0.0025 mol), DMF-H₂O

(Fig.8) displayed a triplet for the ester methyl group at 1.31, a singlet for the vinylic-methyl group at 2.56, a singlet for the methoxy group at 3.81, a quartet for the methylene group at 4.20, a multiplet for the vinylic proton at 6.11, a doublet for the aromatic protons ortho to methoxy group at 6.88 with a coupling constant of 8 Hz and another doublet for the remaining aromatic protons at 7.45 with a ortho coupling constant of 8 Hz.

The Heck reaction conditions developed above have been successfully applied to the synthesis of cinnamic acid (3.6) by reaction of bromobenzene (3.4) and acrylic acid (3.5).

Conclusion :

Heck reaction can be performed in the absence of phosphine and phase-transfer catalyst in DMF-H_2O to give good yields of the products. This is an environmentally friendly (Green chemistry) approach to Heck reaction.

CHART – III

Scheme - 7

1   2   3

Scheme - 8

4   5
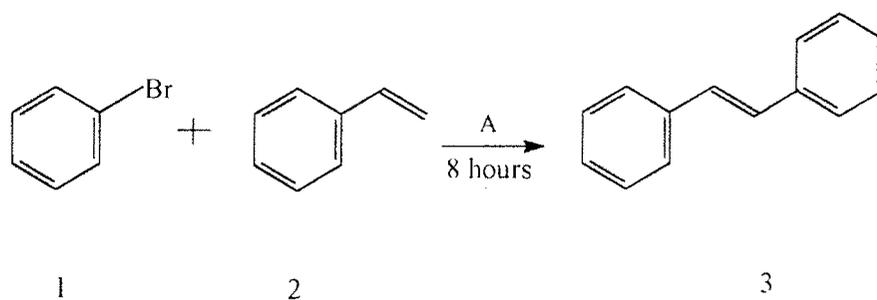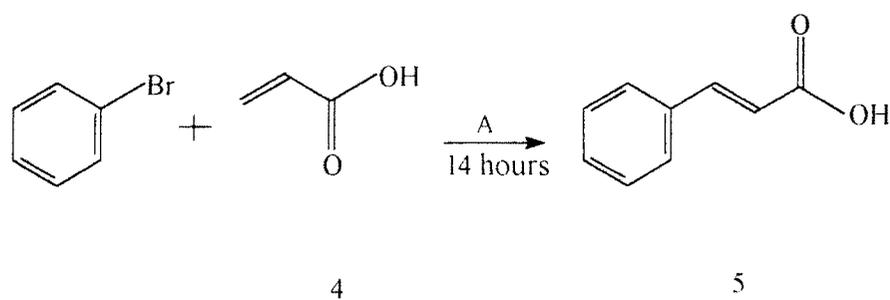
A : $PdCl_2$(0.00003 mol), K_2CO_3 (0.003 mol), $DMF-H_2O$.

44

WAVENUMBER (CM^{-1})

FIG. 1

TRANSMITTANCE (%)

FIG. 2

F I G . 3

47
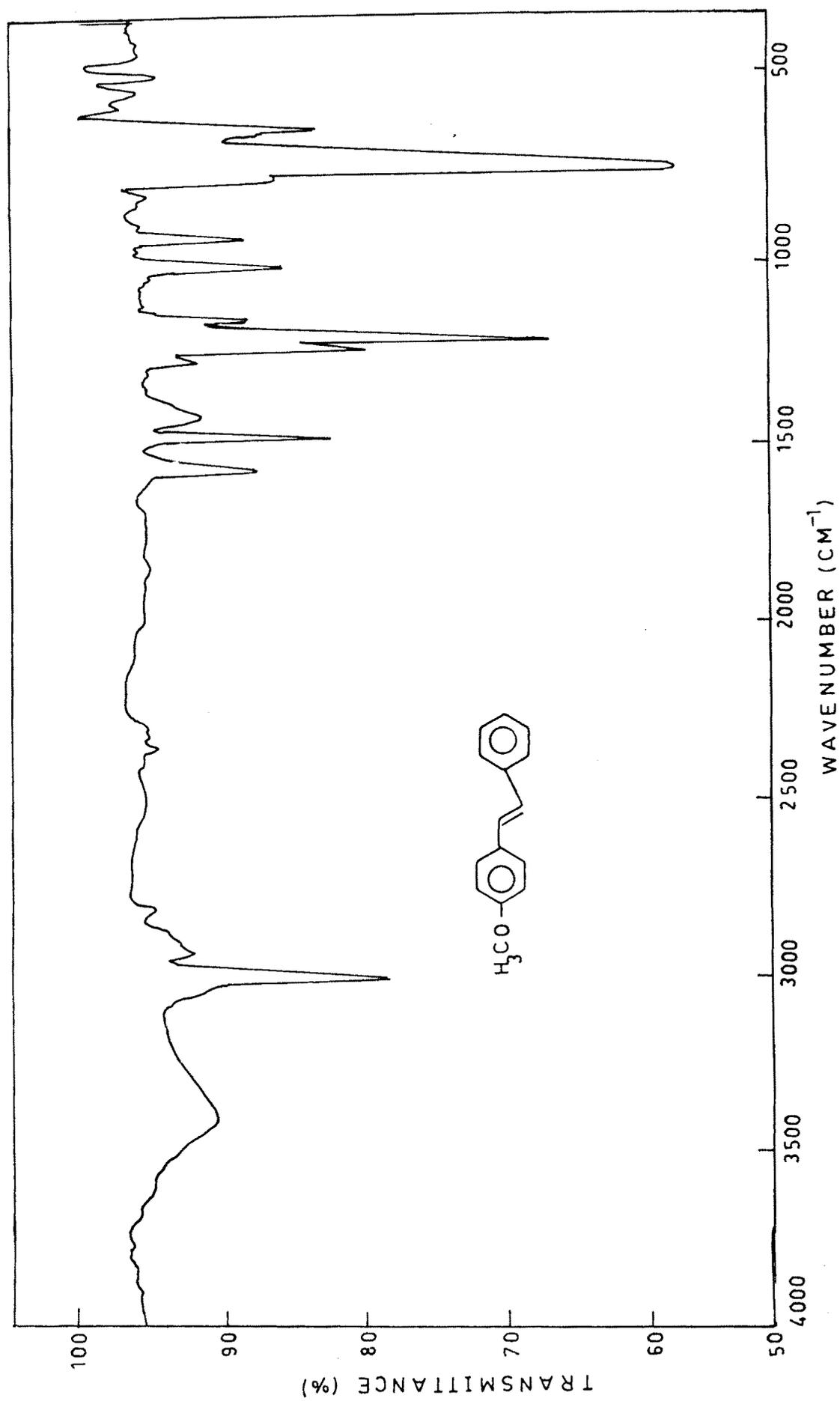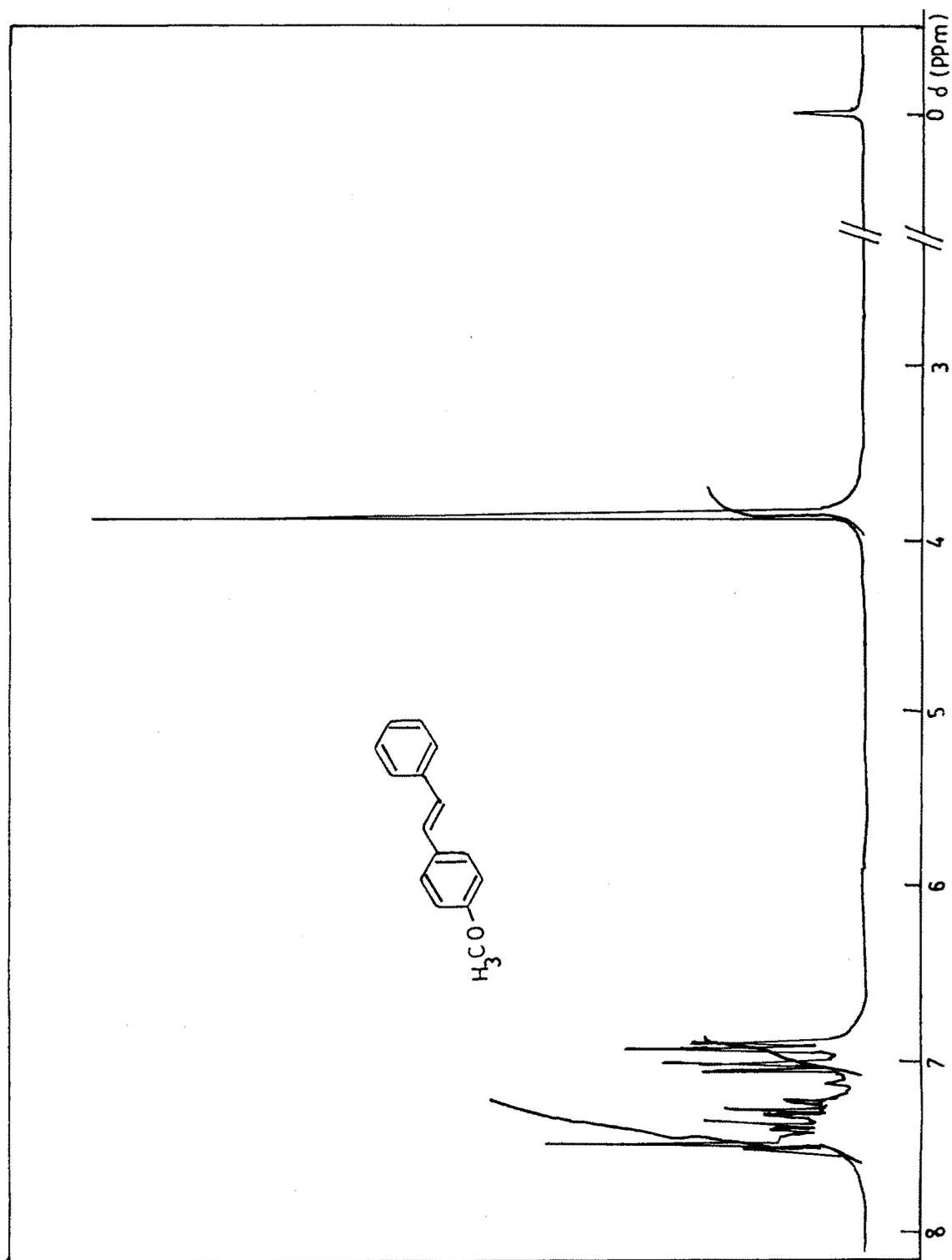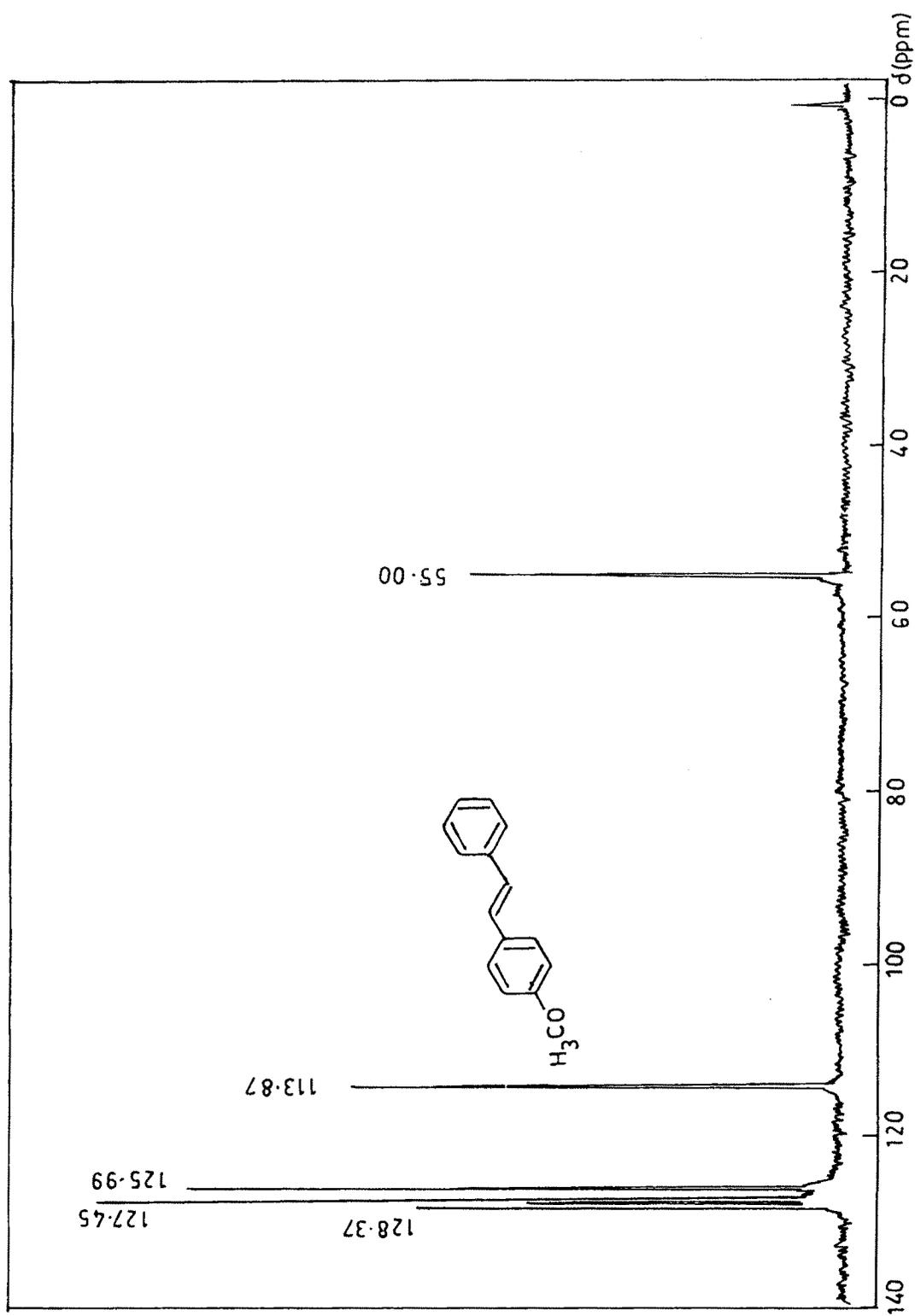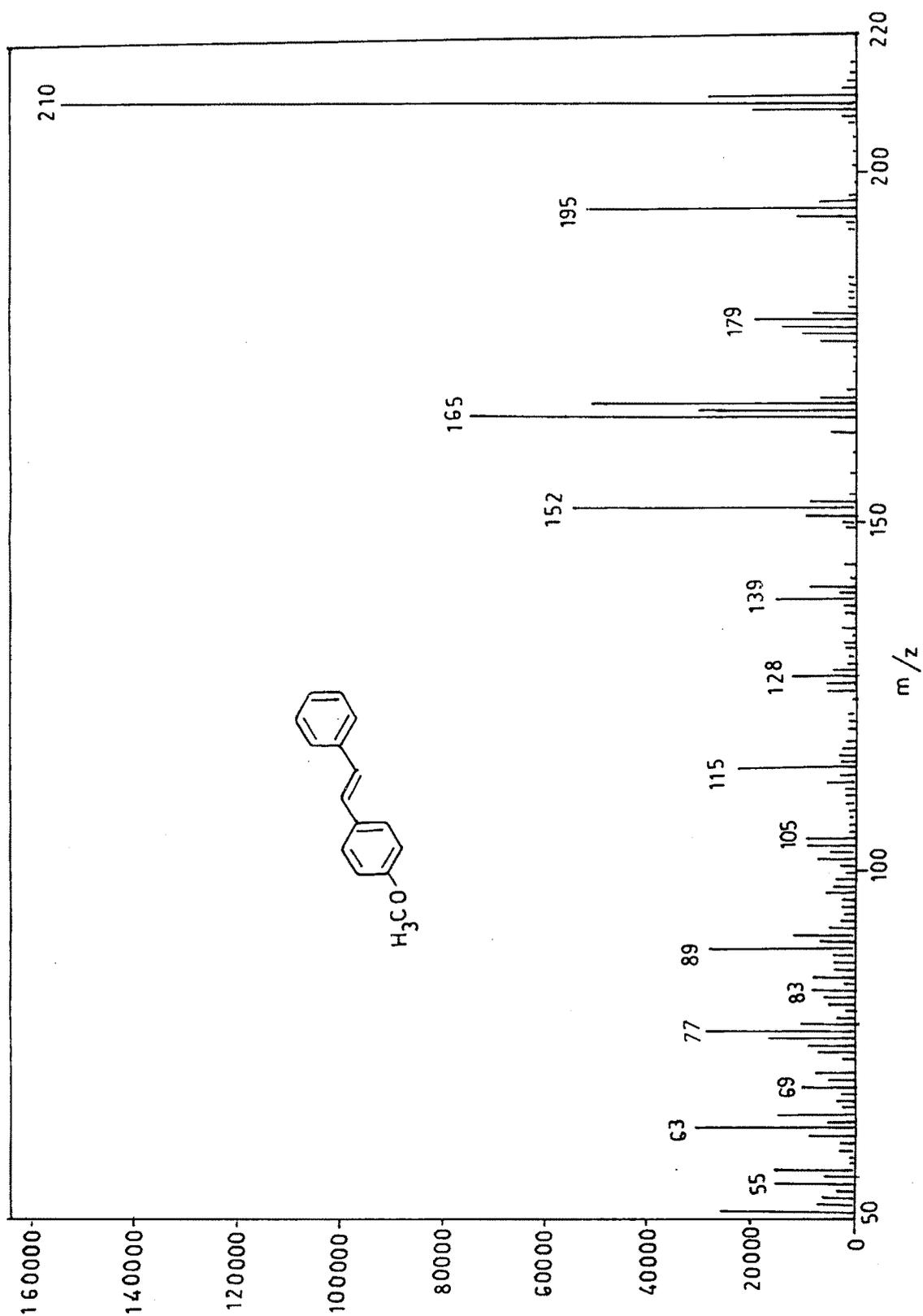
FIG.4
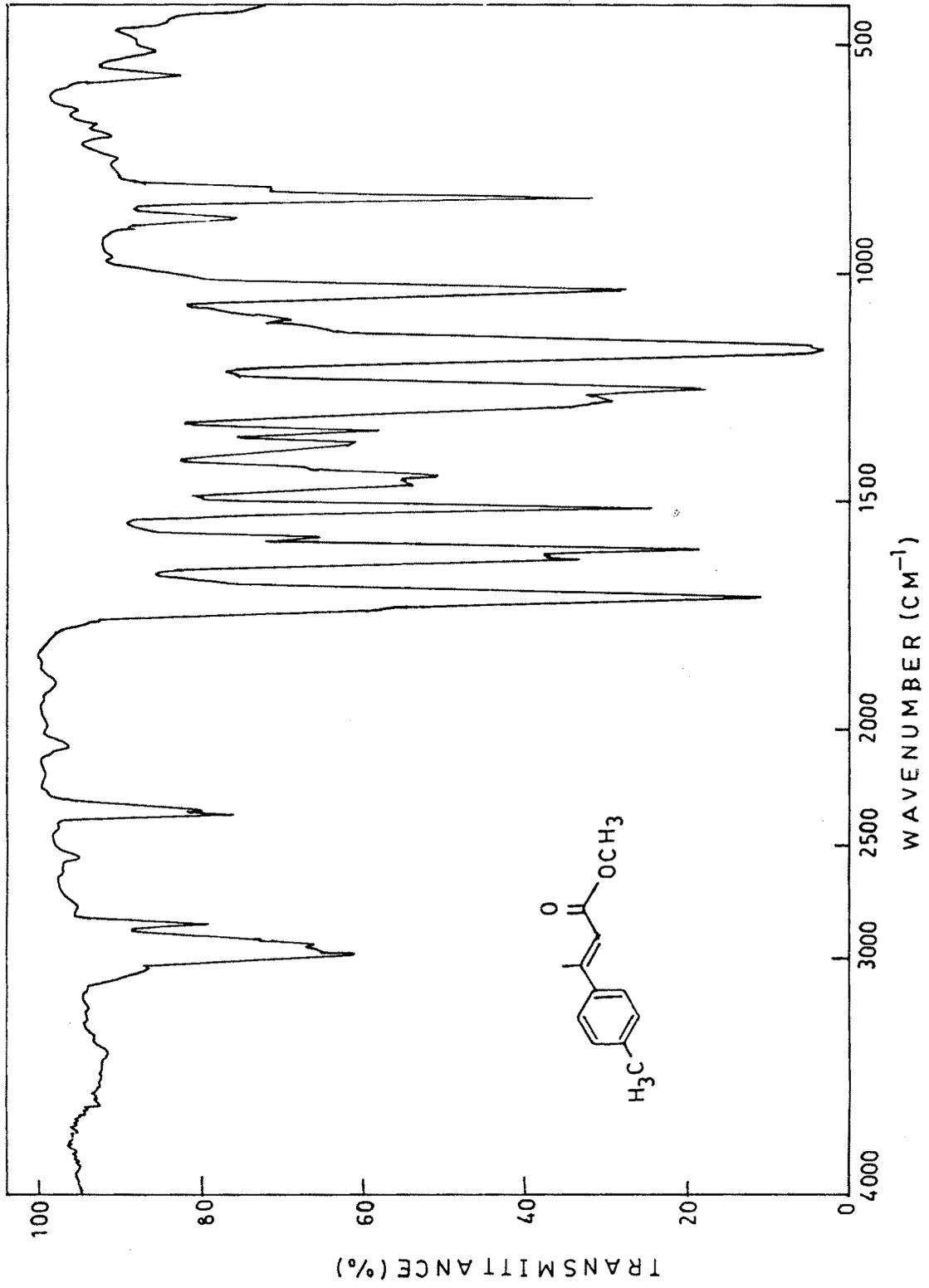
FIG. 5
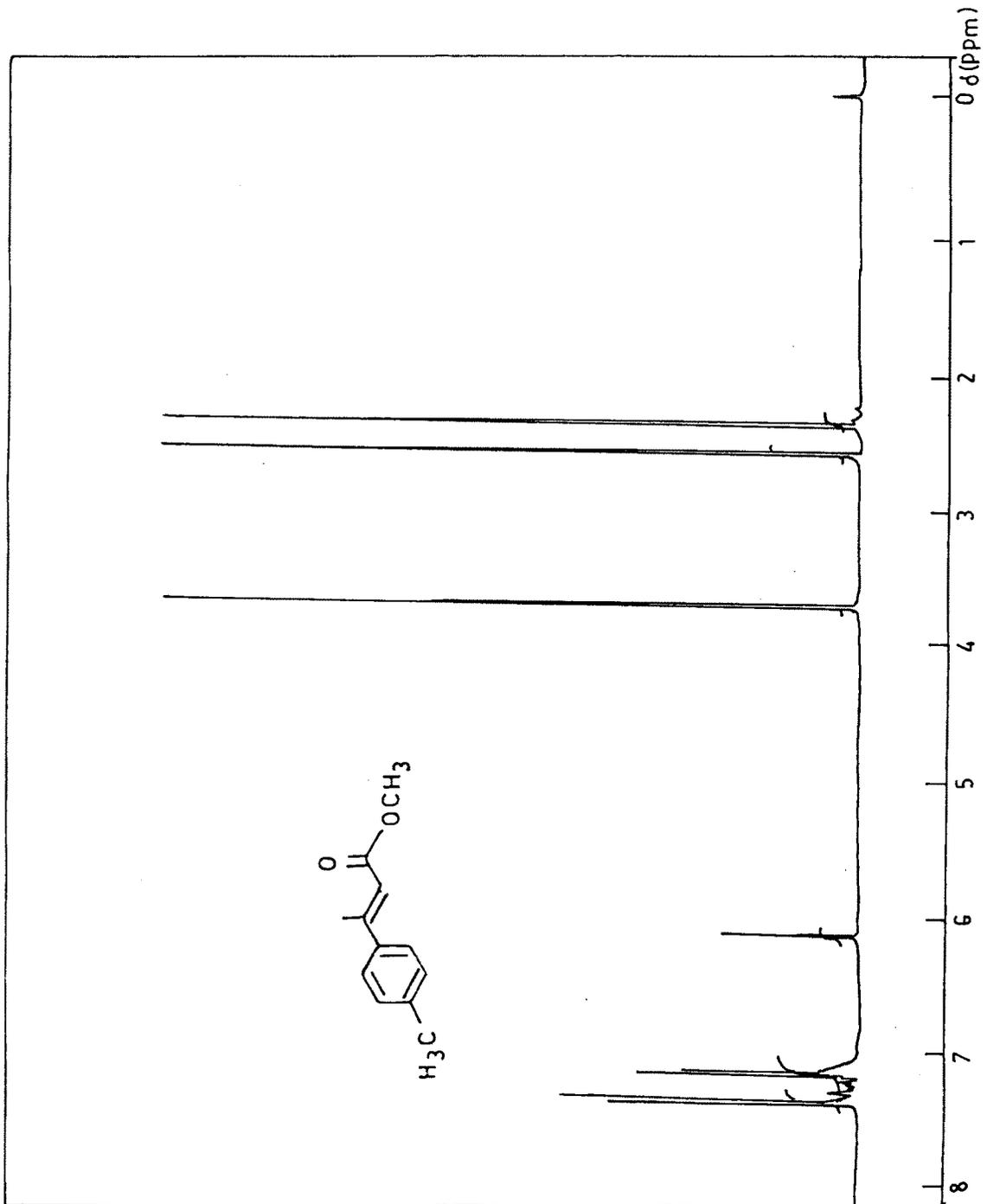
FIG. 6
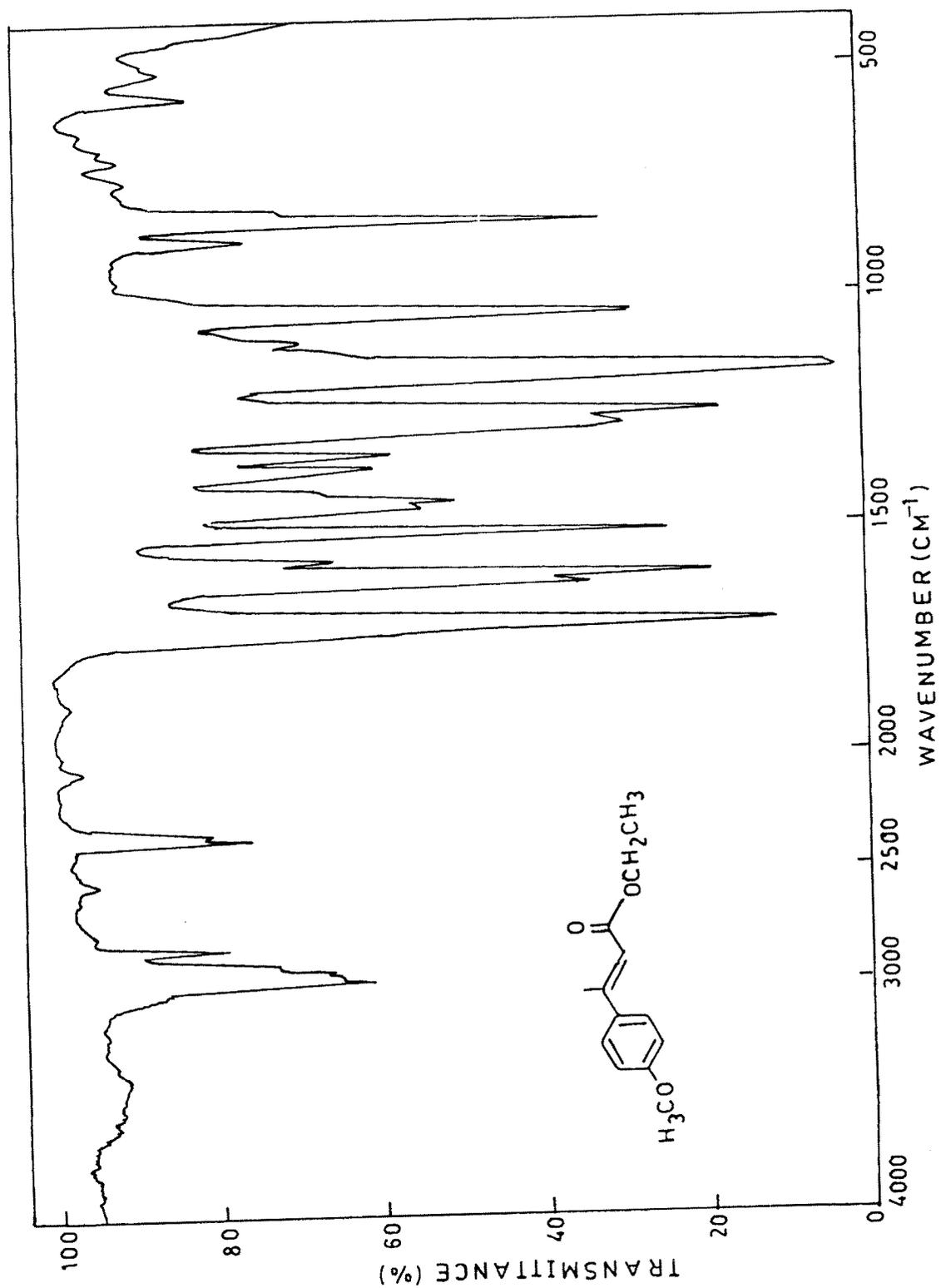
FIG. 7
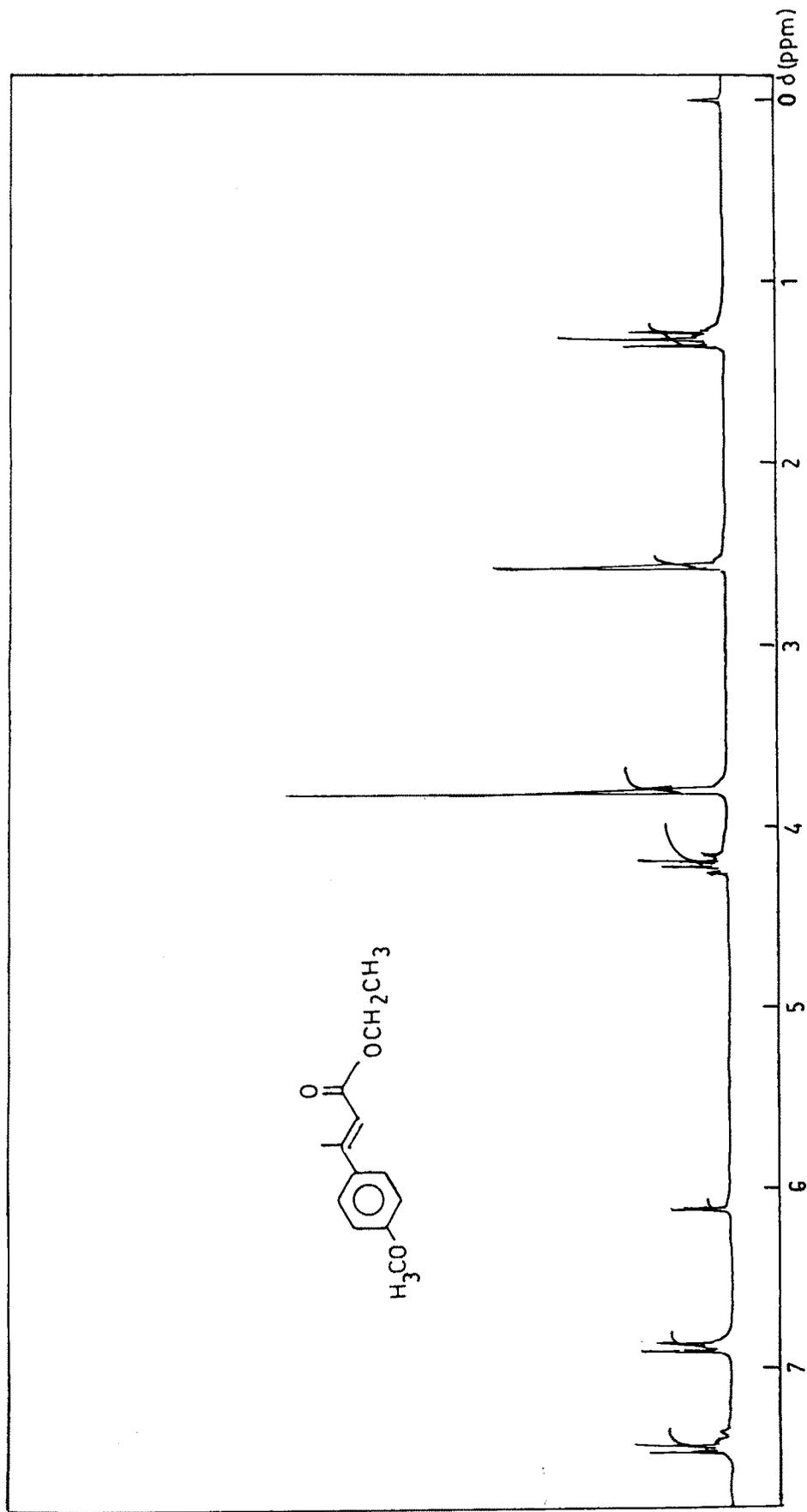
FIG. 8

EXPERIMENTAL

General remark :

The structures are indicated by a double number, the first part of which indicates the chart in which it occurs and the second part indicates the serial number of structures.

All boiling points and melting points are uncorrected.

Distilled solvents have been used in all cases. Pet. ether refers to the petroleum fraction boiling between 60-80°C.

All liquid reagents were distilled and stored under anhydrous conditions. Silica gel used for TLC was of greater than 200 mesh.

The I.R. spectra were recorded on a Perkin-Elmer-783 spectrometer. The I.R. data are presented in wavenumbers. The P.M.R. spectra were recorded on AC 200 (MHz) model with TMS as an internal standard.

The P.M.R. data using standard notations are presented in the following order : chemical shift in δ units in ppm / No. of protons / splitting pattern / coupling constant / assignments.

Preparation of p-iodoanisole[8] (1.3) :

p-Anisidine (31.0 g 0.25 mol) was dissolved in conc. HCl (72 ml) and water (72 ml). The solution was cooled with stirring at 0-5°C. It was diazotised by the gradual addition of ice-cold solution of sodium nitrite (18.6 g 0.27 mol) in water (48 ml). After the diazotisation, a solution of potassium iodide (45.9 g 0.27 mol) in water (48 ml) was added with constant stirring. The mixture was allowed to stand for 1 hr. at room temperature and then heated on water-bath until the evolution of nitrogen ceased. It was cooled when the crude p-iodoanisole was formed at the bottom. The aqueous layer was removed and sodium metabisulphite (3.0 g) was added to remove the dark colour of solution. The crude p-iodoanisole was then treated with 10% NaOH solution in order to remove p-methoxy phenol, which may be formed. The crude p-iodoanisole was separated by steam distillation. It was recrystallised from ethanol to yield 48.0 g (76%) of pure product (1.3), m.p. 63-64°C (Lit.[8] m.p. 63-64°C).

Preparation of 4'-methoxy stilbene (1.5) :

A mixture of p-iodoanisole (0.500 g, 0.0020 mol), K_2CO_3 (0.280 g, 0.0020 mol), styrene (0.208 g, 0.0020 mol) and palladium chloride (0.004 g, 0.00002 mol) in DMF (5 ml) and water (0.5 ml) was heated at 100°C on an oil bath for 8 hrs with stirring. The completion of reaction was monitored by TLC using pet. ether and ethyl acetate (90:10) as solvent system. The reaction mixture was cooled, diluted with water (10 ml) and extracted with ether (3x10 ml). The ether layer was washed with water and dried over anhydrous sodium sulphate. Removal of ether by distillation gave crude 4'-methoxy stilbene (1.5) which was purified by

recrystallised from chloroform and pet. ether. Yield 0.361 g (86%) m.p. 135-136°C (Lit.[9b] m.p. 135-136°C).

I.R. (Fig.1) : 3019, 1605, 1512, 1216, 689, 669 cm^{-1}

P.M.R. (Fig.2) : 3.85 (3H, s, OCH$_3$), 6.85 to 7.65 (11H, m, Ar-H and vinylic-H).

^{13}C N.M.R. (Fig.3) : 55.00, 113.87, 125.99 (strong), 126.15, 127.21,

127.45 (strong), 128.05 and 128.37.

Mass (Fig.4) : (m/z) 210 (M$^+$), 195 (M-15), 179 (M-31), 165, 115 and 77 (C$_6$H$_5^+$).

Preparation of p-iodotoluene[8] (2.3) :

p-Toludine (27.0 g, 0.25 mol) was dissolved in conc. HCl(63 ml) and water (63 ml). The solution was cooled with stirring at 0-5°C. It was diazotised by the gradual addition of ice-cold solution of sodium nitrite (18.6 g 0.27 mol) in water (48 ml). After the diazotisation, a solution of potassium iodide (45.9 g 0.27 mol) in water (48 ml) was added with constant stirring. The mixture was allowed to stand for 1 hr. at room temperature and then heated on water-bath until the evolution of nitrogen ceased. It was cooled, when the crude p-iodotoluene was formed at the bottom. The aqueous layer was removed and sodium metabisulphite (3.0 g) was added to remove the dark colour of solution. The crude p-iodotoluene was then treated with 10% NaOH solution in order to remove any cresol, which may be formed. The crude p-iodotoluene was separated by steam distillation. It was recrystallised from ethanol to yield 34.1 g (62%) of pure product (2.3). m.p. 34-36°C (Lit.[8] m.p. 34-36°C).

Preparation of 4'-methyl stilbene (2.5) :

A mixture of p-iodotoluene (0.550 g 0.0025 mol), K$_2$CO$_3$ (0.345 g 0.0025 mol), styrene (0.260 g 0.0025 mol) and palladium chloride (0.004 g 0.00002 mol)

in DMF (5 ml) and water (0.5 ml) was heated at 100°C on an oil bath for 8 hrs with stirring. The completion of reaction was monitored by TLC using pet. ether and ethylacetate (90:10) as solvent system. The reaction mixture was cooled, diluted with water (10 ml) and extracted with ether (3x10 ml). The ether layer was washed with water and dried over anhydrous sodium sulphate. Removal of ether by distillation gave crude 4'-methyl stilbene (2.5) which was purified by recrystallised from chloroform and pet. ether. Yield 0.395 g (87%). m.p. 119-120°C (Lit.[9] m.p. 120°C).

Preparation of Stilbene (3.3) :

A mixture of bromobenzene (0.470 g 0.003 mol), K_2CO_3 (0.415 g, 0.003 mol), styrene (0.310 g, 0.003 mol) and palladium chloride (0.004 g, 0.00003 mol) in DMF (5 ml) and water (0.5 ml) was heated at 100°C on an oil bath for 10 hrs with stirring. The completion of reaction was monitored by TLC using pet. ether and ethyl acetate (90:10) as solvent system. The reaction mixture was cooled, diluted with water (10 ml) and extracted with ether (3x10 ml). The ether layer was washed with water and dried over anhydrous sodium sulphate. Removal of ether by distillation gave crude stilbene (3.3) which was purified by recrystallised from chloroform and pet. ether. Yield 0.437 g (81%) m.p. 123-124°C (lit.[9d] m.p. 122-124°C).

Preparation of methyl 3-(4'- methylphenyl)-3-methyl acrylate (2.7) :

A mixture of p-iodotoluene (0.550 g, 0.0025 mol), K_2CO_3 (0.345 g 0.0025 mol), methyl crotonate (0.230 g 0.0025 mol) and palladium chloride (0.004 g 0.00002 mol) in DMF (5 ml) and water (0.5 ml) was heated at 100°C on an oil bath for 12 hrs with stirring. The completion of reaction was monitored by TLC using pet. ether and ethyl acetate (90:10) as solvent system. The reaction mixture

was cooled, diluted with water (10 ml) and extracted with ether (3x10 ml). The ether layer was washed with water and dried over anhydrous sodium sulphate. Removal of ether by distillation gave crude methyl 3-(4'-methylphenyl)-3-methyl acrylate (2.7). It was purified by short-path distillation to yield 0.310 g (69%) of product. b.p. 275°C (Lit[10] b.p. 275°C).

I.R. (Fig.5)   : 1720, 1615, 1600, 1230, 1150, 800 cm^{-1}.

P.M.R. (Fig. 6) : 2.35 (3H, s, Ar-CH$_3$), 2.56 (3H, s, vinylic-CH$_3$),

3.74 (3H, s, OCH$_3$), 6.13 (1H, s, vinylic-H),

7.16 (2H, d, J=8 Hz, Ar-H ortho to OCH$_3$)

7.37 (2H, d, J=8 Hz Ar-H meta to OCH$_3$)

Preparation of ethyl 3-(4'-methoxyphenyl)-3-methyl acrylate (1.7) :

A mixture of p-iodoanisole (0.500 g 0.0020 mol), K$_2$CO$_3$ (0.280 g 0.0020 mol), ethyl crotonate (0.350 g 0.0020 mol) and palladium chloride (0.004 g 0.00002 mol) in DMF (5 ml) and water (0.5 ml) was heated on an oil bath for 12 hrs with stirring. The completion of reaction was monitored by TLC using pet. ether and ethyl acetate (90:10) as solvent system. The reaction mixture was cooled and diluted with water (10 ml) and extracted with ether (3x10 ml). The ether layer was washed with water and dried over anhydrous sodium sulphate. Removal of ether by distillation gave the crude ethyl 3-(4'-methoxyphenyl)-3-methyl acrylate (1.7). It was purified by short-path distillation to yield 0.352 g (62%) of product. b.p. 255-257°C (Lit.[11,12] b.p. 257°C.

I.R. (Fig. 7)   : 1720 cm^{-1}

P.M.R. (Fig. 8) : 1.31 (3H, t, J=7 Hz CH$_3$), 2.56 (3H, s, vinylic CH$_3$),

3.81 (3H, s, OCH$_3$) 4.20 (2H, q, J=7 Hz, OCH$_2$),

6.11 (1H, m, vinylic-H), 6.88 (2H, d, J=8 Hz Ar-H ortho to OCH$_3$),

7.45 (1H, d, J=8 Hz, Ar-H meta to OCH$_3$).

Preparation of cinnamic acid (3.5) :

A mixture of bromobenzene (0.470 g 0.003 mol), K$_2$CO$_3$ (0.415 g 0.003 mol), acrylic acid (0.220 g 0.003 mol) and palladium chloride (0.004 g 0.00003 mol) in DMF (5 ml) and water (0.5 ml) was heated on an oil bath for 14 hrs. The completion of reaction was monitored by TLC using pet. ether and ethylacetate (90:10) as solvent system. The reaction mixture was cooled and acidified with ice-cold dil. HCl and extracted with ether (3x10 ml). The ether layer was washed with water and dried over anhydrous sodium sulphate. Removal of ether gave crude cinnamic acid (3.5) which was purified by recrystallised from hot water. Yield 0.345 g (78%) m.p. 133-134°C (Lit.[8] m.p. 133-134°C).

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