Tetrahedron Vol. 43, No. 22, pp. 5335 to 5340, 1987
Printed in Great Britain.

0040-4020/87 $3.00 + .00

TANDEM INTRAMOLECULAR WITTIG AND CLAISEN REARRANGEMENT REACTIONS IN THE THERMOLYSIS OF 2-METHYL-2-PHENOXY-PROPIONYL-CYANOMETHYLENETRIPHENYLPHOSPHORANES: SYNTHESIS OF SUBSTITUTED 2H-1-BENZOPYRANS AND BENZOFURANS

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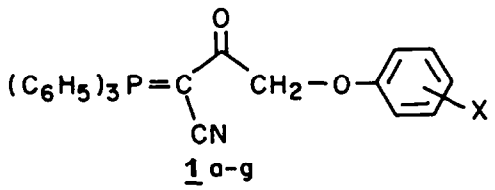
(*Received in UK* 9 *September* 1987)

Abstract - The preparation and thermolysis in vacuum of 2-methyl-2-phenoxy-propionyl-cyanomethylenetriphenylphosphorane and derivatives containing methyl-, methoxy- and chloro- substituents in the phenoxy ring is reported. The method merges the preparation of phenyl propargyl ethers by intramolecular Wittig reaction and their Claisen rearrangement into one step. The final products were the corresponding 2H-1-benzopyran or benzofuran or a mixture of both. The propargylic ether derived from the ylide containing 2-methylphenoxy-group gave not only 4-cyano-2,2,8-trimethyl-2H-1-benzopyran but also 7-cyano-6-isopropylideno-1-methyl-tricyclo[3.2.1.$0^{2,7}$]-oct-3-ene-8-one as a minor product.

The intramolecular Wittig reaction of substituted acylphosphoranes is a convenient method for the synthesis of some disubstituted acetylenes[1-4]. This thermally induced reaction could be merged with the Claisen rearrangement of substituted aryl propargyl ethers[5]. Previously we studied[6] the thermolysis of phenoxy-acetyl-cyanomethylenetriphenylphosphorane 1a and its derivatives 1b-g and found that phosphoranes 1a, 1f and 1g gave the corresponding acetylenic nitriles 2a, 2f and 2g as major product. Traces of 4-cyano-2H-1-benzopyran 3a was isolated from the decomposition of 1a. The rest of the ylides 1b-e gave the corresponding benzofuran 4b-e (see scheme 1). In the present study the decomposition of 2-methyl-2-phenoxy-propionyl-cyanomethylenetriphenylphosphorane 7a and its derivatives 7b-g was investigated. These phosphoranes are expected to give rise to ethers having a gem-dimethyl group on the propargylic carbon. This is expected to enhance the ease of 3,3-sigmatropic reaction[7]. Also the phosphoranes 7a-g can be prepared from cyanomethylenetriphenylphosphorane 5 and the corresponding acid chlorides 6a-g in over 80% yield skipping the transylidation step[3] (see scheme 2).

The phosphoranes 7a-g were decomposed in a short path distillation apparatus in vacuum. The maximum decomposition temperature for optimum yield was found to be in the range 260-270°. Above 270° the formation of the corresponding phenol as a side product reduced the yield of cyclised product(s). All the phosphoranes gave the corresponding 2H-1-benzopyran and/or benzofuran. The mechanism of Claisen rearrangement and also the formation of 2H-1-benzopyran system from phenyl propargyl ethers have been studied[7-9] and scheme 3 represents all the possible pathways leading to the formation of oxygen heterocycles. The paths A, B and C depict the different routes by which the precursors 11 and 13 for the 2H-1-benzopyran and benzofuran system respectively are formed. The following generalisations have also been made. (1) Electron donor and attracting groups favour the formation of 6- and 5-membered ring respectively[10]. (2) The presence of a base leads to furan ring system[11]. (3) In highly polar medium[12-16] the formation of 5-membered ring was observed. The experimental conditions employed by us for Claisen rearrangement are quite different from those normally used and the above generalisations may not be valid in cases

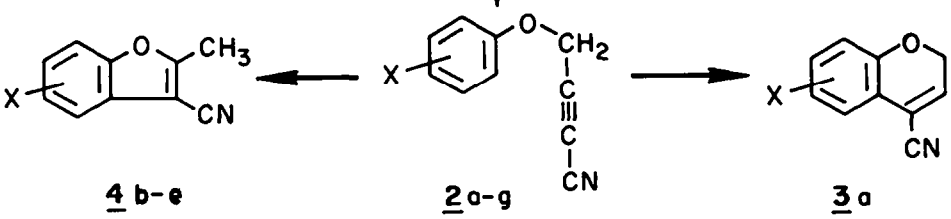
under study. The first reaction to take place should be an intramolecular Wittig reaction[1-4] to give an aryl propargyl ether derivative. Then 3,3-sigmatropic and other reactions follow.



1 a-g

a) X=H; b) X=4-OCH_3; c) X=2-OCH_3; d) X=4-Cl; e) X=2-Cl; f) X=4-CH_3; g) X=2-CH_3

250-260°/~2 Torr



4 b-e 2 a-g 3 a

b) X=5-OCH_3
c) X=7-OCH_3
d) X=5-Cl
e) X=7-Cl

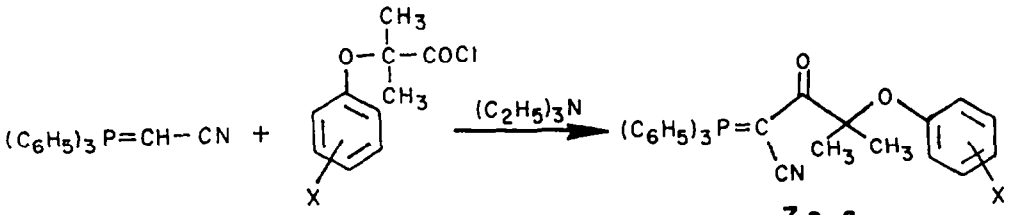
a) X=H
f) X=4-CH_3
g) X=2-CH_3

a) X=H

SCHEME 1

As has been predicted earlier[7], gem-dimethyl substitution of the propargyl carbon enhances the tendency to undergo 3,3-sigmatropic reaction. This is supported by our results obtained from the phosphoranes 7a-g as compared to those reported[6] previously for 1a-g by us. The formation of a 2H-1-benzopyran or benzofuran system or both was judged from ^{1}H-NMR analysis of the crude reaction mixture freed from triphenylphosphine oxide and phenolic impurities. The presence of a benzofuran system is inferred from the appearance of a distinct septet and a doublet for the isopropyl group in the region around δ 3.0 and 1.3 ppm respectively. The appearance of two singlet signals one each for lone olefinic hydrogen and gem-dimethyl group in the region around δ 6.0 and 1.3 ppm respectively are diagnostic for the 2H-1-benzopyran system. The gas chromatographic analysis showed a single peak in some cases though mixtures were present in the product as revealed by ^{1}H-NMR spectra. According to NMR data, phosphorane 7a, its ortho-methoxy 7c and the para-methyl derivative 7f gave the corresponding 2H-1-benzopyran system only. These were isolated in pure state[17]. The results from the rest of the ylides are examined below. The para-methoxy derivative 7b gave an inseparable mixture of 4-cyano-2,2-dimethyl-6-methoxy-2H-1-benzopyran 12b and 3-cyano-2-isopropyl-5-methoxy-benzofuran 14b. The ortho-chloro- derivative 7e also gave a mixture but the major product isolated in 50% yield was identified as 7-chloro-3-cyano-2-isopropyl-benbzofuran 14e. Its isomer 8-chloro-3-cyano-2,2-dimethyl-2H-1-benzopyran could not be obtained in pure state. The result obtained with the ortho-chloro- derivative 7e led us to repeat the experiments on the thermolysis of para-chloro- derivative 7d from which the isolation of a single compound namely 6-chloro-7-cyano-2,2-dimethyl-2H-1-benzopyran 12d was reported by us in a preliminary communication[5]. We found that our earlier observation was incorrect. ^{1}H-NMR analysis of the crude product showed signals assignable to 12d (two singlets at δ 1.28 and 5.73 ppm respectively) and 14d (a doublet at δ 1.25 ppm and a septet at δ 3.0 ppm). We failed to obtain either component in pure state by column chromatography on silica gel or alumina using different eluents.

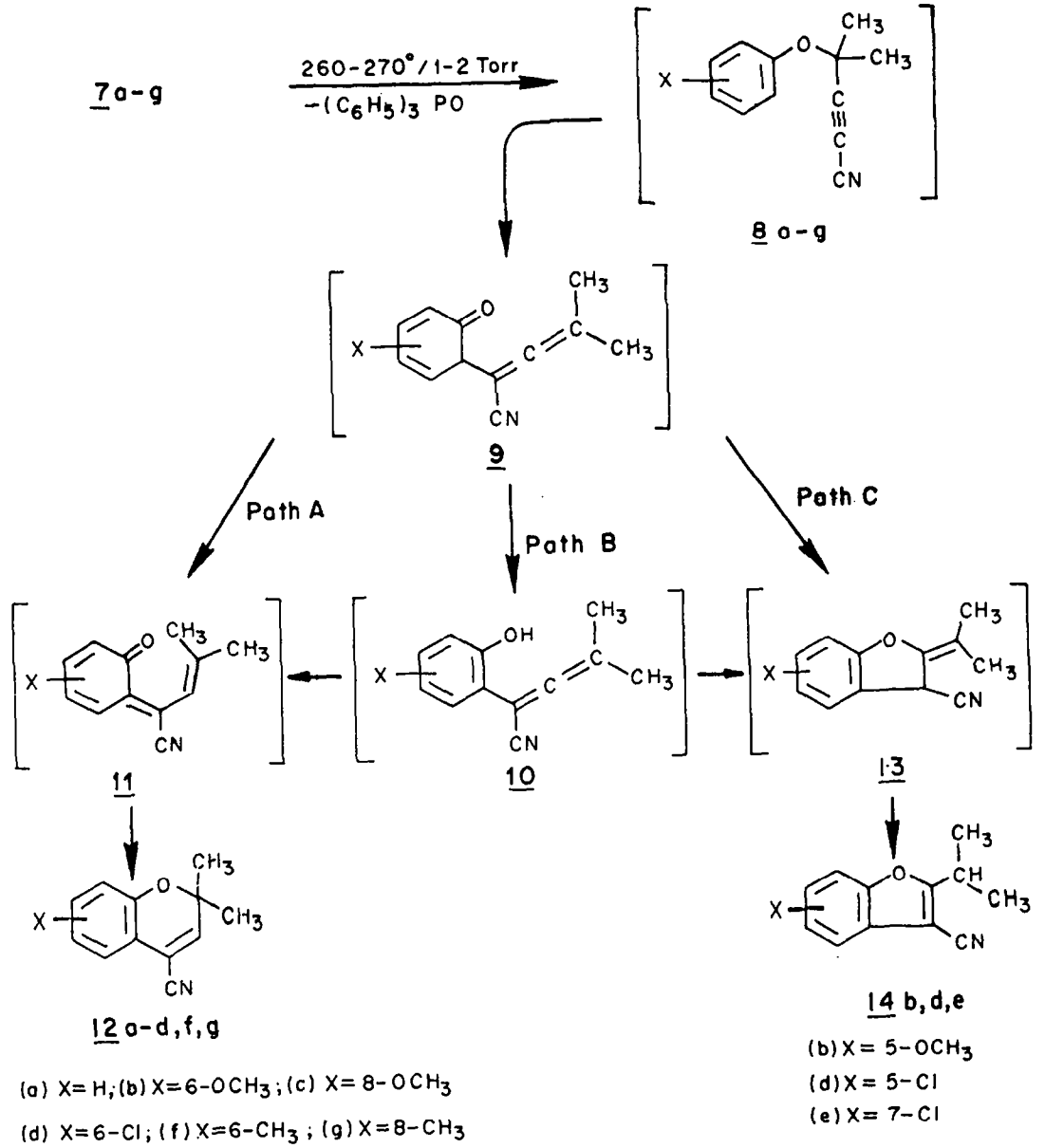
The 2-methyl derivative 8g needs a special mention. In this case two products were isolated. The major product obtained in 54% yield was identified as 4-cyano-2,2,6-trimethyl-2H-1-benzopyran 12g. The minor product isolated in 10% yield was found to be an isomer. The ^{1}H-NMR spectrum showed the three methyl groups to be chemically nonequivalent as revealed by the appearance of three singlets at



5 6 a-g 7 a-g

(a) X=H ; (b) X= 4-OCH_3 ; (c) X= 2-OCH_3 ; (d) X= 4-Cl;
(e) X= 2-Cl ; (f) X= 4-CH_3 ; (g) X= 2-CH_3

SCHEME 2

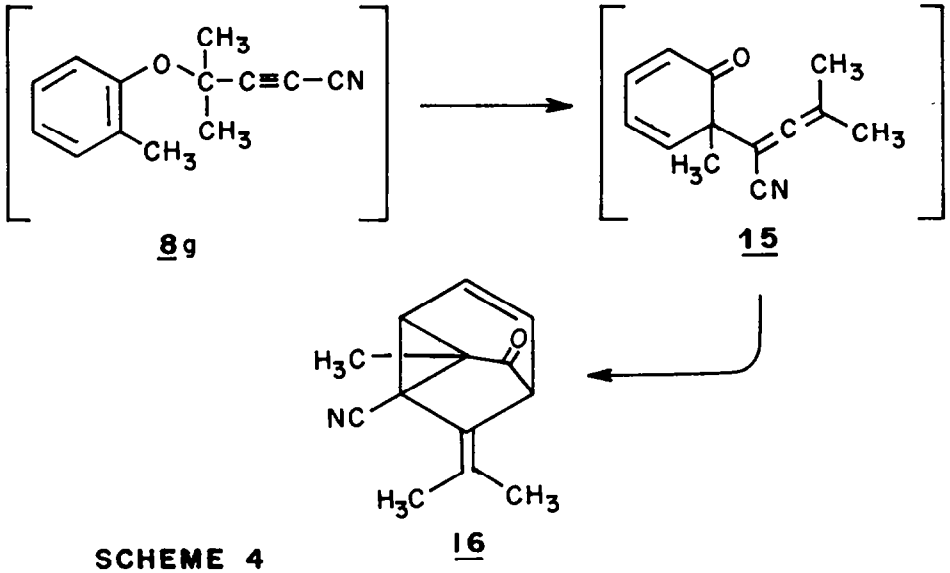


(a) X= H ; (b) X= 6-OCH_3 ; (c) X= 8-OCH_3
(d) X= 6-Cl ; (f) X= 6-CH_3 ; (g) X= 8-CH_3

14 b,d,e
(b) X= 5-OCH_3
(d) X= 5-Cl
(e) X= 7-Cl

SCHEME 3

δ 1.29, 1.51 and 1.87 ppm respectively. The aromatic hydrogens are absent but in their place two distinct quartets and a complex multiplet signal appear at δ 2.44 (1H) 3.09 (1H) and 5.22-5.6 ppm (2H) respectively. The coupling constant of the two distinct quartet signals and decoupling experiments have shown that these 4 hydrogens form an ABXY spin system with non-vicinal XY part. The data given above fit the tricyclic structure 16. The IR spectrum showed a strong absorption band at 1750 cm^{-1} assignable to the carbonyl group of the 5 membered ring. The formation of 16 can be traced to a 3,3-sigmatropic shift taking place in the direction of ortho-position already substituted with methyl group to give the intermediate 15. This having no option for the type of prototropic shift depicted earlier may undergo intramolecular Diels-Alder reaction to give the tricyclic isomer 16 (see scheme 4). Such a course of reaction has been postulated in the thermolysis of phenyl propargyl ether and its methyl derivatives[8,9,18,19].



SCHEME 4

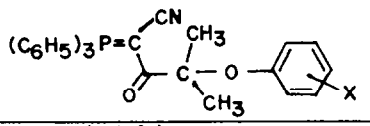
EXPERIMENTAL

The ^{1}H-NMR spectra were recorded on a Jeol FX-90A FT instrument in chloroform-d using TMS as internal standard. The mass spectra were recorded on a VG micromass 70-70H spectrometer. An HP 5880 gas chromatograph with 8' x 1/8" column packed with 10% OV-17 on chromosorb W (80-100 mesh) with temperature programming (100-15°/min-250°) was used for analysis. Melting points were determined on Mettler FP 51 (Neo-Pharma Instruments Corp.) and are not corrected.

2-METHYL-2-PHENOXY-PROPIONIC ACID AND ITS DERIVATIVES: The parent compound and its derivatives containing chloro-[20-23], methoxy-[22,24] and methyl-[25,26] substituents in the phenoxy ring were prepared by a known method by reaction of the corresponding phenol with acetone, NaOH and $CHCl_3$.

GENERAL METHOD OF PREPARATION OF YLIDES 7a-g: The reaction is carried out under anhydrous conditions. To a vigorously stirred suspension of 33.78 g (0.1 mole) cyanomethyltriphenylphosphonium chloride[3] in 200 ml dry toluene, 10.1 g (0.1 mole) triethylamine (distilled over CaH_2) was added dropwise and stirred for 4 hrs at ambient temperature. Then 0.1 mole 2-methyl-2-phenoxy-propionylchloride (freshly prepared from the corresponding acid and thionyl chloride) in 25 ml dry toluene and 10.1 g (0.1 mole) triethylamine were taken in two separate dropping funnels and were added dropwise simultaneously over a period of 1 hr. The mixture was stirred overnight at room temperature, the precipitate was filtered off, washed with water. The water insoluble ylide is further purified by recrystallisation from a solvent mixture containing ethyl acetate:ethanol:chloroform in volume ratio 4:2:1 and dried in vacuum. The physical constants are summarised in the table below.

TABLE: PHYSICAL DATA ON PHOSPHORANES 7a-g



Phosphorane	m.p.	% yield	IR ($CHCl_3$) ν_{CN} cm^{-1}	IR ($CHCl_3$) ν_{CO} cm^{-1}	Molecular peak at m/e
7a, X=H	218.5°	91	2170	1560	463
7b, X=4-Methoxy	161.5°	89	2175	1560	493
7c, X=2-Methoxy	178°	88	2170	1558	493*
7d, X=4-Chloro	181°	84	2175	1562	497*
7e, X=2-Chloro	177°	86	2170	1560	497
7f, X=4-Methyl	192°	94	2170	1560	477
7g, X=2-Methyl	182°	81	2175	1560	477

*The isotope peak for ^{37}Cl appeared at m/e 499.

GENERAL METHOD OF DECOMPOSITION OF YLIDES:

The apparatus consists of two 25 ml round-bottom flasks connected via a 9 cm long bent tube. About 6 g of the ylide was taken in one flask immersed in wood metal bath and the receiver cooled in a Dewar containing liquid nitrogen. Vacuum was applied at the receiver end and maintained between 1-2 Torr. The bath was heated gradually to 260-270°. The distillate was extracted with benzene and the extract washed with 10% NaOH. After the usual work up, the residue from the benzene extract was purified by column chromatography over silica gel using first hexane and progressively increasing the polarity of the eluent by addition of ethyl acetate up to 4%. Results from the individual phosphoranes are given below.

Thermolysis of 2-methyl-2-phenoxy-propionyl-cyanomethylenetriphenylphosphorane 7a:

4-Cyano-2,2-dimethyl-2H-1-benzopyran 12a was isolated. Oily liquid; yield:58%; IR($CHCl_3$): ν_{CN} 2230 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ ppm; 1.29 (s,6H gem-dimethyl), 5.69 (s, 1H, olefinic) 6.01-6.62 (4H, unresolved multiplets, aromatic protons). High resolution mass spectrum: $M^{\cdot+}$ at m/e 185.0837 (cald. for $C_{12}H_{11}NO$ 185.0841).

Thermolysis of 2-(4-methoxyphenoxy)-2-methyl-propionyl-cyanomethylenetriphenylphosphorane 7b:

An inseparable mixture of 4-cyano-2,2-dimethyl-6-methoxy-2H-1-benzopyran 12b and 3-cyano-2-isopropyl-5-methoxy-benzofuran 14b was isolated as oily liquid. The ^{1}H-NMR ($CDCl_3$) of the mixture showed signals at δ ppm; 1.35 (d,J=7 Hz), 1.41 (s), 3.0 (septet, J=7 Hz), 5.68 (s), 6.1-6.66 (unresolved multiplets).

Thermolysis of 2-(2-methoxyphenoxy)-2-methyl-propionyl-cyanomethylenetriphenylphosphorane 7c:

4-Cyano-2,2-dimethyl-8-methoxy-2H-1-benzopyran 12c was isolated, m.p. 72.5°; yield: 61%; IR($CHCl_3$): ν_{CN}: 2230 cm^{-1}, ^{1}H-NMR ($CDCl_3$) δ ppm: 1.38 (s, 6H, gem-dimethyl), 3.47 (s, 3H, OCH_3), 5.78 (s, 1H, olefinic), 6.15-6.45 (unresolved multiplets, 3H, aromatic). High resolution mass spectrum: $M^{\cdot+}$ at m/e 215.0946 (cald. for $C_{13}H_{13}NO_2$ 215.0946).

Thermolysis of 2-(4-chlorophenoxy)-2-methyl-propionyl-cyanomethylenetriphenylphosphorane 7d:

A mixture consisting of 6-chloro-4-cyano-2,2-dimethyl-2H-1-benzopyran 12d and 5-chloro-3-cyano-3-isopropyl-benzofuran 14d was isolated. ^{1}H-NMR ($CDCl_3$) spectrum showed signals at δ ppm: 1.25 (d, J=7 Hz), 1.28 (s), 3.0 (septet, J=7 Hz), 5.73 (s), 6.5-6.8 (unresolved multiplets).

Thermolysis of 2-(2-chlorophenoxy)-2-methyl-propionyl-cyanomethylenetriphenylphosphorane 7e:

7-Chloro-3-cyano-2-isopropyl-benzofuran 14e was isolated, m.p: 75.7°; yield: 50%; IR($CHCl_3$): ν_{CN} 2230 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ ppm: 1.22 (6H, d, J=7 Hz, methyls), 3.11 (1H, septet, J=7 Hz, methine); 6.53-6.84 (3H, unresolved multiplets, aromatic). High resolution mass spectrum: $M^{\cdot+}$ at m/e 219.0450 (cald. for $C_{12}H_{10}{}^{35}ClNO$ 219.0451).

Thermolysis of 2-methyl-2-(4-methylphenoxy)-propionyl-cyanomethylenetriphenylphosphorane 7f:

4-Cyano-2,2,6-trimethyl-2H-1-benzopyran 12f was isolated as oily liquid, yield: 54%; IR($CHCl_3$): ν_{CN} 2230 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ ppm: 1.32 (s, 6H, gem-dimethyl), 2.07 (s, CH_3 on aromatic ring), 5.73 (s, 1H, olefinic), 6.3-6.74 (3H, unresolved multiplets, aromatic). High resolution mass spectrum: $M^{\cdot+}$ at m/e 199.1012 (cald. for $C_{13}H_{13}NO$ 199.0997).

Thermolysis of 2-methyl-2-(2-methylphenoxy)-propionyl-cyanomethylenetriphenylphosphorane 7g:

4-Cyano-2,2,8-trimethyl-2H-1-benzopyran 12g eluted first. Oily liquid; yield: 54%; IR($CHCl_3$): ν_{CN} 2230 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ ppm: 1.38 (s, 6H, gem-dimethyl), 1.96 (s, CH_3 on aromatic ring), 5.69 (s, 1H, olefinic), 6.2-6.6 (3H, unresolved multiplets, aromatic). High resolution mass spectrum: $M^{\cdot+}$ at m/e 199.1006 (cald. for $C_{13}H_{13}NO$ 199.0997). 7-Cyano-6-isopropylideno-1-methyl-tricyclo[3.2.1.$0^{2,7}$]-oct-3-ene-8-one 16 was isolated as second component. Oily liquid, yield: 10%, IR($CHCl_3$): ν_{CN} 2225 cm^{-1}, ν_{CO} 1750 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ ppm: 1.29 (s, 3H), 1.51 (s, 3H), 1.87 (s, 3H), 2.44 (dd, J=3 Hz, J=5 Hz, 1H), 3.09 (dd, J=2 Hz, J=8 Hz, 1H), 5.22-5.60 (complex multiplet, 2H). High resolution mass spectrum: $M^{\cdot+}$ at m/e 199.0991 (cald. for $C_{13}H_{13}NO$ 199.0997).

Acknowledgement: The authors thank Dr A V Rama Rao, Director, Regional Research Laboratory, Hyderabad for providing facilities. HR thanks CSIR, New Delhi for a Senior Research Fellowship.

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