Synthesis and insecticidal activity of some 1,3,4-oxadiazole derivatives containing phenoxyfluorophenyl group

TP Mohan1, B Vishalakshi2*, K S Bhat1, K S Rao1 & GN Kendappa1

1Department of Post Graduate Studies and Research in Chemistry, Mangalore University, Mangalagangothri 574 199, India
e mail: koodivishalash@yahoo.co.uk
2Rallis Research Centre, #21 & 22, PIA, Peenya II Phase, Bangalore 560 058, India

Received 22 May 2003; accepted (revised) 5 April 2004

The synthesis of a few 1,3,4-oxadiazoles 5a-e is described. 4-Fluoro-3-phenoxybenzoic acid 2 is prepared starting from 4-Fluoro-3-phenoxybenzaldehyde 1. Esterification of 2 with methanol in the presence of H2SO4 gives the corresponding ester 3. Hydrazinolysis of 3 with hydrazine hydrate results in acid hydrazide 4. Hydrazide on reaction with aryl acid chlorides in presence of POCl3 affords oxadiazoles 5a-e. The compounds 5b-e manifest low insecticidal activity against certain crop pests.

IPC: Int.CI. C 07D 271/10

Synthetic pyrethroids are compounds derived from natural pyrethrin1,2 and have been extensively exploited commercially as insecticides on various crops and as pest control agents in household applications3,4. Phenoxyphenyl group has been an essential moiety in the recent generation of synthetic pyrethroids5.

In recent past, it has been observed and reported that considerable antibacterial and antifungal activity has been exhibited by 1,3,4-oxadiazole derivatives suitably substituted at 2 and 5 positions6-9.

Prompted by the above observations, as a part of our work on the development of novel agrochemicals, we have attempted to explore the possibility of generation of insecticidal activity in oxadiazoles by the substitution of the phenoxyfluorophenyl group. We report herein the results of our studies on the insecticidal activity of a few new oxadiazole derivatives along with their synthesis as outlined in Scheme I. The formation and structure of the compounds have been established on the basis of the IR and NMR spectral data. The purity of the compounds have been checked by TLC and HPLC. The new compounds were tested for their insecticidal activity.

4-Fluoro-3-phenoxybenzoic acid 2 is obtained by the potassium permanganate oxidation of 4-fluoro-3-
phenoxymethanoldehyde 1. The methyl ester 3 is prepared by refluxing 2 in methanol with a catalytic amount of H$_2$SO$_4$, and is then converted to desired 4-fluoro-3-phenoxymethanoic acid hydrazide 4 by refluxing with excess hydrazine hydrate in methanol. Further treatment of 4 with different acid chlorides by refluxing with POCl$_3$ resulted in the formation of corresponding 2-(4′-fluoro-3′-phenoxymethyl)-1,3,4 oxadiazoles 5a-e. Characterization data of compounds are given in Table I.

The IR spectrum of 2 shows the absorption bands at 3500-3000 and 1693 cm$^{-1}$ for the carboxylic acid group. The $^1$H NMR spectrum of 2 showed a singlet at $\delta$ 13.2 characteristic of the acid proton. The formation of 2 is further supported by the absence of aldehydeic C-H stretching at 2831 and C=O stretching at 1703 cm$^{-1}$ respectively. The IR spectrum of ester 3 showed absorption at 1727 cm$^{-1}$ corresponding to the carbonyl group of the methyl ester. The formation of 3 was further evident from the appearance of a singlet at $\delta$ 4.1 integrating for 3 protons. The conversion of the ester 3 to the acid hydrazide 4 is supported by the IR absorption due to hydrazide carbonyl at 1600 and two bands at 3303 and 3202 cm$^{-1}$ corresponding to N-H stretching. In the $^1$H NMR of 4, three protons of the hydrazide group resonated at $\delta$ 4.3 and 9.3 integrating for two protons and one proton respectively.

The mass spectra of the compounds 2 and 4 showed molecular ion peak at m/z 232 and 246 which is consistent with their molecular formula C$_{10}$H$_{15}$FO$_3$ and C$_{10}$H$_{11}$FN$_2$O$_2$ respectively. The other prominent peak in the mass spectrum of compounds 2 and 4 was at m/z 215 corresponding to the fluorophenoxyacetyl residue.

The IR spectra of compounds 5a-e showed the characteristic absorption for C-O-C at 1217 - 1225 cm$^{-1}$ and typical absorption bands due to carbonyl and hydrazide moieties of 4 were absent. The $^1$H NMR spectrum of compound 5d showed singlet at $\delta$ 3.2 and multiplet at 7-8 corresponding to methoxy protons and aromatic protons respectively. The absence of peaks corresponding to protons of parental hydrazide supports the formation of cyclic structure.

IR spectra of all the compounds 2-5 showed absorption bands in region 3100-3000 (aromatic C-H stretch.), 1600-1400 (ring C=C/ C=N stretch.) cm$^{-1}$.

Further evidence for the proposed structures of 5a-e is obtained from the mass spectral data. As a typical example, the mass spectra of compound 5b showed the molecular ion peak 366 and 368 which corresponds to the molecular formula C$_{30}$H$_{13}$ClF$_2$N$_2$O$_2$ along with M+2 peak indicating the presence of chlorine. These molecular ions underwent fragmentation to produce ions at m/z 112,139,153 and 215 as base peak which corresponds to C$_{10}$H$_{14}$Cl, CIC$_{6}$H$_{5}$CO, C$_{9}$H$_{14}$NCO$^+$ and fluorophenoxyacetyl residue respectively.

Insecticidal activity

The compounds 5a-e were tested for their insecticidal activity against certain crop pests. Laboratory reared insects namely, the American bollworm, Helicoverpa armigera, tobacco leaf eating caterpillar, Spodoptera litura, bean aphid, Aphis craccivora, cabbage diamondback moth, Plutella xylostella, rice brown planthopper, Nilaparvata lugens, and red spider mite Tetramychus neocaledonicus were selected. The percentage mortality of the pests after 48 hr were recorded by leaf dipping and spray turntable methods. The new molecules were evaluated at 2500 and 5000 ppm against the above said insects. The results were compared with the standard compounds, namely, Imidacloprid 200SL, Cypermethrin 25% EC and Ethion 50% EC (Table II).

The results reveal that new compounds 5b-5e manifested low insecticidal activity against A craccivora and 5e showed similar effect against T. neocaledonicus, at relatively high concentrations (2500 and 5000 ppm) as compared to the standard. The insecticidal activity of the new compounds against the other crop pests were insignificant.

The insecticidal activities of the compounds are not highly encouraging. Hence, further improvement in the structures of these compounds is being attempted.

Experimental Section

Melting points were determined by open capillary tubes and are uncorrected. IR spectra were recorded on a Perkin-Elmer -882 IR spectrophotometer in KBr.
pellet forms. $^1$H NMR spectra were recorded on an AMX 400 NMR spectrometer (400 MHz) using DMSO-$d_6$ as solvent and TMS as internal standard. The mass spectra were recorded on a Jeol-JMS-D 300 mass spectrometer operating at 70 ev. The separation and purification of the compounds were carried on a Shimadzu LC 10 AVP HPLC system using the solvent mixture acetonitrile, water and acetic acid in the ratio 70:29:01. A UV detector operating at 254 nm was used for monitoring the elution. TLC was carried out on precoated silica gel plates using the solvent mixture ethyl acetate and hexane in the ratio 4:1 as eluent.

4-Fluoro-3-phenoxyl-benzaldehyde 1 is prepared according to the method reported earlier.$^{11,12}$

**Synthesis of 4-fluoro-3-phenoxylbenzoic acid 2.** A solution of 1 (0.1 mole) in 50 mL water was heated to 70-80°C and a saturated solution of potassium permanganate (0.13 mole) was added and refluxed for 2hr. The resulting mixture was filtered and the filtrate was acidified with dilute HCl to a pH of 4.5. The precipitated product was filtered, dried and purified by recrystallisation from toluene: IR (KBr): 3500-3000 (O-H strenght), 1693 (C=O strenght), 1595 cm$^{-1}$ (ring C=C strenght); $^1$H NMR: δ 13.2 (s, 1 H, OH), 7-8 (m, 8H, Ar-H); Mass: m/z 232 (M$^+$), 214 (C$_3$H$_4$FO$_2$)$^+$, 187 (C$_6$H$_4$FO$_3$)$^+$.

**Synthesis of 4-fluoro-3-phenoxylbenzoic acid methyl ester 3.** A mixture of 2 (0.1 mole), methanol (0.2 mole), dichloroethane (100 mL) and conc. H$_2$SO$_4$ (5 drops) was refluxed for 5 hr and then cooled to 5°C. The contents were poured to ice water (100 mL). The organic layer was separated and dichloroethane was distilled off to get the crude product which was recrystallised from methanol; IR (KBr): 3057 (aromatic C-H strenght), 1717 (C=O strenght), 1596 cm$^{-1}$ (ring C=C strenght); $^1$H NMR: δ 8.4 (s, 3H, CH$_3$), 7-8 (m, 8H, Ar-H).

**Synthesis of 4-fluoro-3-phenoxylbenzoic acid hydrazide 4.** To a boiling solution of 3 (0.1 mole) in methanol (30 mL), 99% hydrazine hydrate (7.5 g, 0.15 mole) was added and refluxed for 1hr. It was then cooled to 0°C. The precipitated 4 was filtered and dried; IR (KBr): 3303, 3202(NH strenght), 3022(aromatic C-H strenght), 1660(C-O strenght), 1622(N-H bending), 1595 cm$^{-1}$ (ring C=N strenght). $^1$H NMR: δ 4.3 (s, 2H, NH$_2$), 9.3 (s, 1H, NH), 7-8 (m, 8H, Ar-H); Mass: m/z 246 (M$^+$), 215 (C$_5$H$_4$FO$_2$)$^+$.

**Synthesis of 2-(4-fluoro-3-phenoxylphenyl)-5-(p-substituted phenyl)-1,3,4-oxadiazole 5a-e.** To a solution of 4-substituted benzoyl chloride (0.01 mole, 10 mL) and compound 4 (0.01 mole) in dichloroethane, phosphorous oxychloride (5 mL) was added and the mixture was refluxed for 8hr on an oil-bath. The solvent and excess of POCl$_3$ were distilled at reduced pressure. Reaction mass was cooled and poured onto crushed ice and left overnight. The precipitated product was filtered and recrystallised from methanol; IR (KBr): 3069(aromatic C-H strenght), 1220(C-O-C strenght), 1448-1599 cm$^{-1}$ (ring C=C and C=N strenght); 5b;
\[ ^1H \text{NMR: } \delta\ 7-8\ (m, 12\text{H, Ar-H});\ 
\text{Mass: } m/z\ 366\ (M^+),\ 
139\ (\text{CIC}_3\text{H}_{15}\text{CO}^+),\ 153\ (\text{C}_6\text{H}_{12}\text{CINO}^+),\ 111\ (\text{CIC}_6\text{H}_4^+).\]

Acknowledgement
Authors thank Dr M S Mithyantha, Vice President (R&D) and The Management, Rallis India Limited, Bangalore for providing facilities and constant encouragement.

References