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Novel imidazole derivatives as potential agrochemicals: Synthetical and mechanistic studies

RAPHAEL I NGOCHINDO
Department of Chemistry, Federal University of Technology, P.M.B. 1526, Owerri, Nigeria

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Abstract. The importance of the imidazole nucleus is briefly outlined and some naturally occurring derivatives listed. The problem associated with direct alkylation on the imino nitrogen is discussed and synthesis of 1-alkyl derivatives by the thermal decarboxylation of 1-alkoxycarbonylimidazoles examined as a possible alternative. Spectroscopic investigation of this mechanism is reported. The fungal threat to plantains in the tropics by black sigatoka and the option of chemical control are discussed. Synthesis of potential fungicides are reported.

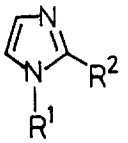
Keywords. Novel imidazole derivatives; agrochemicals; fungicides.

1. Introduction

The imidazole nucleus has remained the subject of much research as a result of its biological/pharmacological significance (Glasby 1976; Lednicer and Mitscher 1977; Hartley 1985). Antimicrobial and fungicidal activities have been associated with some simple derivatives, many of which possess simple structural features with varying substitution patterns. Imidazole derivatives occur naturally. Simple examples include azomycin, which is an antitrichomonal agent, histamine, which is responsible for several physiological actions, and caffeine and pilocarpine, which occur in tropical plants and possess physiological activities. The imidazole nucleus has also served as ligand and enzymic model (Haake *et al* 1971; Brown and Huguet 1980; Zimmerman and Cramer 1988; Vaira *et al* 1989).

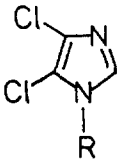
Synthesis of suitable derivatives has also been the subject of much study. The site of electrophilic substitution in imidazoles varies with the reaction conditions, the nature of the substrate, and the electrophile; substitution may occur at any one or all three nuclear carbon atoms. An alternative procedure is construction of the imidazole ring with in-built substituents. As imidazole is readily available commercially, electrophilic substitution remains a more viable option. Alkylation on the imino nitrogen, however, often leads to quarternisation on the azomethine nitrogen. 1-Alkyl derivatives have, therefore, been prepared in high yields by the thermal decarboxylation of 1-alkoxycarbonylimidazoles (Loozen *et al* 1975). The mechanism of this reaction is briefly examined by NMR spectroscopy through the syntheses of *inter alia* the

carboxylates (1)–(3).



(1) $R^1 = CO_2Et$, $R^2 = H$
(2) $R^1 = CO_2Me$, $R^2 = Me$
(3) $R^1 = CO_2CMe_3$, $R^2 = H$

Reports in the literature suggest that antimicrobial activity of the imidazole nucleus is associated with nitro derivatives while fungicidal activity is associated with chloro derivatives (Glasby 1976; Lednicer and Mitscher 1977, 1980; Hartley 1985). As part of a continuing interest in the fungicidal activity of imidazole derivatives (Ngochindo 1985) syntheses of chloro derivatives of 1-benzoylimidazole and N,N-dimethylimidazole-1-sulphonamide (DIS), (4)–(6), are here reported.



(4) $R = 4\text{-}Cl\text{-}C_6H_4\text{-}CO$
(5) $R = 2,6\text{-}Cl_2\text{-}C_6H_3\text{-}CO$
(6) $R = SO_2NMe_2$

2. Results and discussion

2.1 *Thermal decarboxylation*

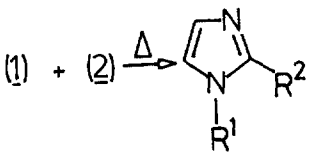
Decarboxylation of (1) by the procedure reported by Loozen's group gave 1-ethylimidazole in 35% yield (lit. value 68%, Loozen *et al* 1975). The product was, however, obtained by a modification of the reported procedure (see § 3) in 85% yield. The mechanism of the decarboxylation, as suggested by Loozen's group, is an O→N shift of the alkyl group, comparable to the rearrangement of diethyl *N*-(4-tolylsulphonyl)imidocarbonate (1) (Meyer 1963) and the conversion of alkylimido or arylimido esters into amides (the Chapman rearrangement) (2) (Schulenberg and Archer 1965).

$$Ts\text{–}N = C(OEt)_2 \xrightarrow{200°C} Ts\text{–}N(Et)\text{–}CO_2Et \tag{1}$$

$$R^1\text{–}C(OR^2) = NR^3 \xrightarrow{200°C} R^1\text{–}CO\text{–}NR^2R^3 \tag{2}$$

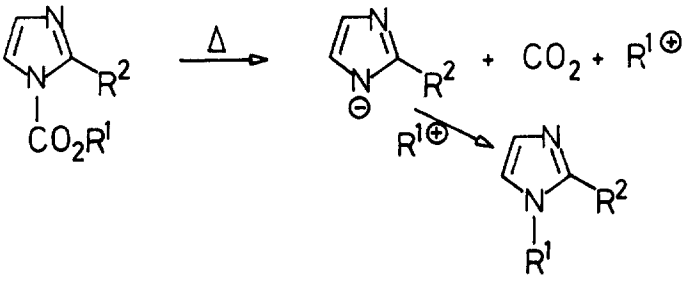
Since both reactions are intramolecular (Meyer 1963; Schulenberg and Archer 1965) their association with decarboxylation of carboxylates implies an intramolecular reaction. The squandering of substituents reported by Loozen's group, however, suggests formation of intermediates capable of intermolecular recombination. The mechanism of the decarboxylation process was, therefore, briefly examined.

A mixture of (1) and (2) was decarboxylated to give a mixture of products (3). 1-Methylimidazole and 1,2-dimethylimidazole were easily identified by their singlet



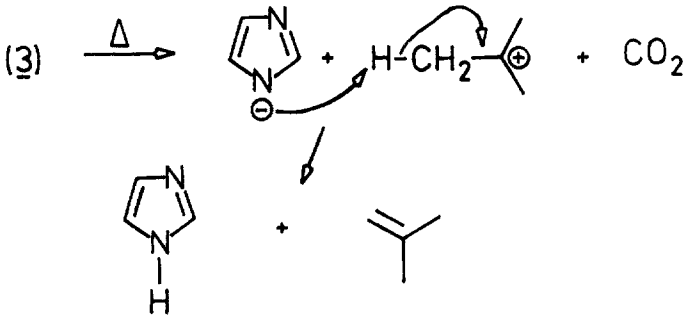
(7) $R^1 = Et$, $R^2 = H$
(8) $R^1 = Et$, $R^2 = Me$
(9) $R^1 = R^2 = Me$
(10) $R^1 = Me$, $R^2 = H$
ratio (8):(9):(10) = 1·0:1·6:1·5 (3)

NMR methyl resonances which increased in intensity on alternate additions of authentic samples of 1-methyl- and 1,2-dimethylimidazole. Addition of an authentic sample of 1,2-dimethylimidazole to the NMR sample also aided in the differentiation of the 2-methyl resonances due to 1-ethyl-2-methylimidazole and 1,2-dimethylimidazole. Two sets of resonances associated with 1-ethyl derivatives were identified and assigned to 1-ethylimidazole and 1-ethyl-2-methylimidazole. The ratio quoted in (3) for the last three products were based on the resonances due to the N-methyl groups (for 1-methyl- and 1,2-dimethylimidazole) and the 2-methyl groups (for 1,2-dimethyl- and 1-ethyl-2-methylimidazole).



Scheme 1.

Although further studies are necessary to determine the nature of the fragments involved in the reaction, there are reasons to believe that the products are formed by the recombination of ionic fragments (scheme 1). The squandering of substituents is probably a result of the attack of the imidazolide ions on the two possible carbenium ions (scheme 1; $R^1 = Me$, Et; $R^2 = H$, Me). The partial double bond character of the oxygen-phenyl bond in 1-carbophenoxy-2-ethylimidazole probably explains its inability to form imidazolide ions. The observation of decarboxylation of (2) at room temperature suggests that the process is probably catalysed by the imidazole. Preparation of 1-*t*-butylimidazole by decarboxylation of (3) was unsuccessful due to the facile formation of 2-methylpropene and imidazole (scheme 2).

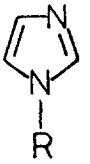


Scheme 2.

2.2 *Chloro imidazoles*

The fungicidal activity of chloro derivatives of heteroaromatic compounds is well documented in the patent literature (Hartley 1985). Of interest in the present study are those which are fungicidal against *Mycosphaerella fijiensis* (black sigatoka). The fungus attacks plantains (*Musa sp.*) and was reported in Nigeria in 1986 (Wilson and

Buddennhagen 1986; FDA 1987). It has been reported to have a devastating effect of epidemic proportions on banana plantations in Latin America (Wilson and Buddenhagen 1986). Chemical control of the fungus has often led to the observation of resistance to a particular chemical on continual application. Resistance is minimised by simultaneous use of different chemicals. A common feature of the heteroaromatic fungicides that have been employed is the presence of the halogen atom on the carbocylic moiety. Imidazolyl examples include imazalil (11), prochloraz (12), and climbazol (13) (Hartley 1985).



(11) R = 2,4-Cl_2-C_6H_3-CH($OCH_2CH=CH_2$)-CH_2
(12) R = 2,4,6-Cl_3-C_6H_2-O[CH_2]$_2$-N(Pr)-CO
(13) R = 4-Cl-C_6H_4-O-CH($COCMe_3$)

Syntheses of novel imidazoles which incorporate the halogen atoms in both the heterocyclic and carbocylic portions were thus considered potential complementary fungicides. Compounds (4) and (5) are presently the subject of mycological studies.

The reported biological activity of DIS (Ngochindo 1985) and the observed effect of nuclear chlorination of imidazoles helped in the synthesis of (6).

3. Experimental

Spectroscopic characterisation and procedures for solvent preparation have been described in earlier papers (Chadwick and Ngochindo 1984; Ngochindo 1990). NMR was recorded on a Perkin-Elmer R34 (220 MHz) spectrometer in deuterochloroform with tetramethylsilane as internal lock standard.

3.1 *1-Ethoxycarbonylimidazole* (1)

Ethyl chloroformate (50·2 mmol) was added to a mixture of imidazole (3·40 g, 49·9 mmol) and triethylamine (50·2 mmol) in benzene (100 ml) in an ice bath. The mixture was stirred at ambient temperature for 2·5 h, filtered and the precipitate washed with benzene (100 ml *in toto*). Evaporation of solvent gave the product (85%) which was purified by distillation, b.p. 37°C/0·1 mm Hg; δ_H 1·45 (3 H, *t*, *J* 7·3 Hz, CH_3), 4·50 (2 H, *q*, *J* 7·3 Hz, CH_2), 7·12 (1 H, *m*, imidazole 5-H), 7·48 (1 H, *m*, imidazole 4-H), and 8·20 (1 H, *m*, imidazole 2-H); ν_{max} ($CHCl_3$) 1760 cm^{-1}.

3.2 *1-Methoxycarbonyl-2-methylimidazole* (2)

Methyl chloroformate (29·8 mmol) was added with stirring to a mixture of 2-methylimidazole (2·0 g, 24·4 mmol) and triethylamine (28·7 mmol) in benzene (70 ml) in an ice bath. The mixture was stirred at room temperature for 14 h, filtered and the precipitate washed with benzene. Evaporation of solvent followed by distillation gave (2), (2·70 g, 79%), b.p. 55°C/0·35 mm Hg; δ_H 2·64 (3 H, *s*, Me), 3·98 (3 H, *s*, OMe),

6·86 (1 H, *d*, *J* 1·7 Hz, imidazole 5-H), and 7·35 (1 H, *d*, *J* 1·7 Hz, imidazole 4-H); ν_{max} (CCl_4) 1768 cm^{-1}; *m/z* 140 (M^+, 29%) and 82 (100).

3.3 *1-(t-Butoxycarbonyl) imidazole* (3)

Di-*t*-butyldicarbonate (4·6 mmol) in dry Et_2O (5 ml) was added to the sodium salt of imidazole (0·6 g, 5·8 mmol) in dry Et_2O (10 ml) at 0°C under an atmosphere of nitrogen. The mixture has stirred at room temperature for 3 h and H_2O (15 ml) was added. The ethereal solvent was evaporated and the aqueous solution extracted with EtOAc (10 ml × 4). Evaporation of solvent from the combined and dried ($MgSO_4$) solution gave the product as an oil (0·54 g, 70%), b.p. 54°C/0·25 mm Hg; δ_H 1·60 (9 H, *s*, Me_3), 7·07 (1 H, *m*, imidazole 5-H), 7·43 (1 H, *m*, imidazole 4-H), and 8·14 (1 H, *m*, imidazole 2-H); ν_{max} (CCl_4) 1756 cm^{-1}; *m/z* 168 (M^+, 13%) and 57 (100).

3.4 *Decarboxylation of a mixture of* (1) *and* (2)

A mixture of (1) (0·51 g, 3·6 mmol) and (2) (0·43 g, 3·1 mmol) was heated for 1 h at 148–180°C under an atmosphere of nitrogen to give 1-ethylimidazole, (7), 1-ethyl-2-methylimidazole (8), 1,2-dimethylimidazole, (9), and 1-methylimidazole, (10) (0·61 g, 95%).

3.5 *1-(4-Chlorobenzoyl)-4,5-dichloroimidazole* (4)

4-Chlorobenzoyl chloride (3·3 mmol) was added to 4,5-dichloroimidazole (0·4 g, 2·92 mmol) dissolved in tetrahydrofuran (THF) (35 ml) containing triethylamine (0·5 ml) at 0°C. The mixture was stirred at room temperature for 10 h, filtered, and solvent evaporated *in vacuo* from the filtrate. The resulting solid was taken into ethyl ethanoate and washed several times with saturated aqueous sodium hydrogen carbonate solution. The organic solution was dried ($MgSO_4$) and solvent evaporated *in vacuo* to obtain the product (0·90 g, 98%), m.p. 194–196°C; δ_H 7·56–7·66, 7·80–7·87, 8·12–8·16 (5 H, *m*, imidazole 2-H and C_6H_4Cl); *m/z* 274 (M^+, 2%) and 139 (100).

3.6 *1-(2,6-Dichlorobenzoyl)-4,5-dichloroimidazole* (5)

2,6-Dichlorobenzoyl chloride (3·39 mmol) was reacted with 4,5-dichloroimidazole as in the synthesis of (4) to obtain the product, (5) (1·02 g, 98%), m.p. 104–106°C, δ_H 7·48–7·70, 7·85–7·96 (4 H, *m*, imidazole 2-H and $C_6H_3Cl_2$); *m/z* 308 (M^+, 1%) and 173 (100).

3.7 *4,5-Dichloro-N,N-dimethylimidazole-1-sulphonamide* (6)

Dimethylsulphanoyl chloride (27·9 mmol) was added with stirring to a mixture of 4,5-dichloroimidazole (3·45 g, 25·2 mmol) and triethylamine (28·7 mmol) in benzene (80 ml). The mixture was stirred at room temperature for 10 h and filtered. The precipitate was washed with benzene and solvent evaporated from the combined filtrate to obtain the crude product. Chromatography on silica gel with 20% ethyl

ethanoate-petroleum ether (b.p. 40–60°C) as eluent gave the product (4·83 g, 79%), m.p. 69–72°C, δ_H 3·06 (6 H, *s*, Me_2) and 7·87 (1 H, *s*, imidazole 2-H).

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