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Investigación

Synthesis of Miconazole and Analogs Through a Carbenoid Intermediate

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Abstract. An alternative synthesis for the preparation of miconazole, enilconazole and econazole is described. The process involves the intermolecular insertion of a carbenoid species to imidazole from α -diazoketones with copper acetylacetonate as the key reaction of the synthesis route.

Keywords: Imidazole, carbenoid, miconazole.

Resumen. Se describe una síntesis alternativa para la obtención de miconazol, enilconazol y econazol. El proceso involucra la inserción intermolecular de una especie carbenoide a imidazol a partir de α -diazocetonas con acetilacetato de cobre como reacción clave de la ruta de síntesis.

Palabras clave: Imidazol, carbenoide, miconazol.

Introduction

The carbenoids derived from diazoketones have been effective intermediates in organic syntheses, specially the reaction of carbenoids over rich-electron heterocyclic compounds in the synthesis of polyenes from furans [1], and in the indolizine alkaloids synthesis from pyrroles [2]. Additionally carbenoid intermolecular and intramolecular insertions have been reported in thiophene [3], indole [4] and benzofuran [5].

In contrast, two-heteroatom five membered rings have been less studied in this area. Thiazoline ring in some penicillin derivatives reacted with an excess of ethyl diazoacetate in the presence of catalytic copper acetylacetonate to give [3+2] cycloaddition adducts [6]. On the other hand, an intramolecular cyclization through a carbenoid insertion occurred when 3-isoxalyl diazobutanone reacted with catalytic of rhodium (II) acetate [7].

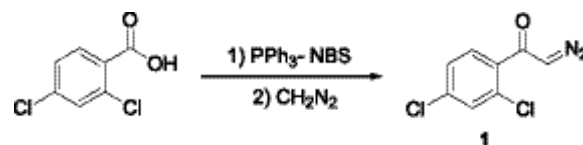
At the moment, few studies on carbenoid insertions on imidazoles have been done. Pellicciari and coworkers [8] reported the imidazole alkylation from α -diazocarbonyl compounds and copper bronze in moderate yields, however, they demonstrated that carbenoid insertions on imidazoles are feasible processes and that could be used in the synthesis of some imidazole pharmaceutical known products.

For example, miconazole (**6**) has a broad-spectrum antifungal activity *in vitro* and its therapeutic use in the treatment of dermatophytic infections is well known [9]. A number of publications for the miconazole synthesis has been reported [10-12].

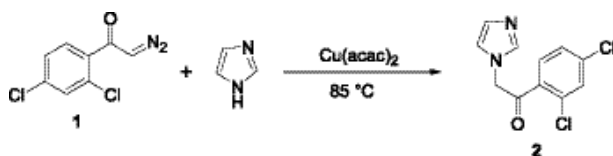
These elements motivated us to develop an alternative synthetic route to prepare miconazole where the key step could be a carbenoid insertion to imidazole.

Results and discussion

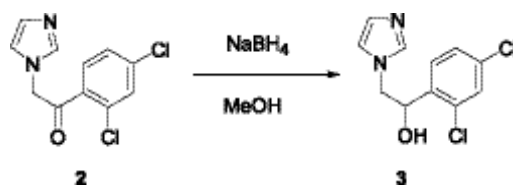
Initially, we attempted to prepare the 2,4-dichlorodiazoacetophenone **1** from 2,4-dichlorobenzoic acid using a novel technology that involves the use of acyloxyphosphonium salts [13]. Thus, the treatment of equimolar amounts of 2,4-dichlorobenzoic acid, triphenylphosphine and a slight excess of *N*-bromosuccinimide in THF at 0 °C during 15 min, and the subsequent addition of a excess of ethereal diazomethane (5:1) gave the corresponding diazoketone **1** in 76 % yield.



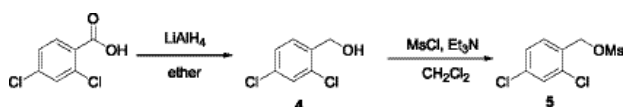
Diazoketone **1** was reacted with imidazole and a catalytic amount of copper (II) acetylacetonate (10% mol) in toluene at 85 °C, in a modification of the procedures described by the Sweeney [14] and West's [15] groups, to obtain the imidazolyl ketone **2** in 46 % yield. Although copper bronzes were used in the carbenoid insertions on imidazoles, other copper salts have not been studied yet. The use of Cu(acac)₂ decreases the temperature reaction and optimizes the process, other products are not detected while this procedure occurs in mild conditions and it is broad in scope.



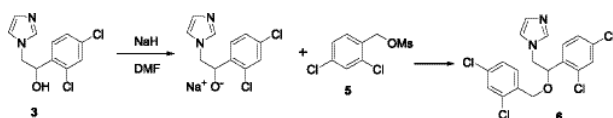
The imidazolyl ketone **2** was reduced to alcohol **3** using sodium borohydride in methanol, this reaction has been reported by Godefroi *et al* [10].



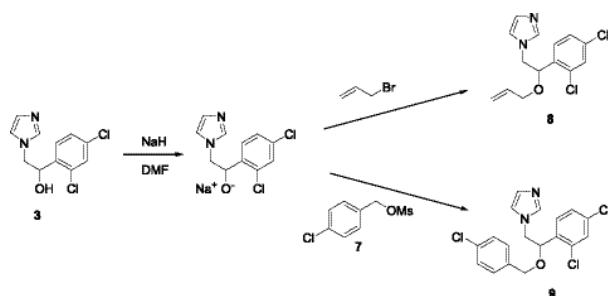
On the other hand, 2,4-dichlorobenzoic acid was treated with lithium aluminum hydride to obtain the benzyl alcohol **4** which in turn was reacted with methanesulfonyl chloride to obtain the mesylate **5**.



Finally, the sodium salt from alcohol **3** was mixed with the crude mesylate **5** in DMF at room temperature, and after work up, miconazole (**6**) was obtained in 70 % yield.



Using similar conditions, we prepared enilconazole **8** [16] and econazole **9** from the sodium salt of alcohol **3** with allyl bromide and the mesylate **7** respectively.



In summary, miconazole, econazole and enilconazole were prepared using α -diazocarbonyl compounds as departure materials. Novel imidazoles with antifungal activity can be obtained by this procedure. The carbenoid insertions are an excellent alternative route to prepare *N*-alkylated imidazoles, and some examples of their synthetic versatility were presented here. We hope to extend this method to the synthesis of other important imidazole products.

Experimental

General procedures were described previously [17].

2-Diazo-1-(2,4-dichlorophenyl)-ethanone (1). To a solution of PPh_3 (0.262 g, 1 mmol) and 2,4-dichlorobenzoic acid (0.191 g, 1 mmol) in anhydrous THF (1 mL) at 0 °C, NBS (0.182 g, 1.1 mmol) in THF (5 mL) was added dropwise over a 10 min period under a nitrogen atmosphere. The resulting reaction mixture was allowed to warm to room temperature continuing the stirring for an additional 15 min. The mixture was cooled to 0 °C again. Then, an ether solution of diazomethane (5 mmol) from *N*-methyl-*N*-nitroso-4-toluenesulfonamide (7.15 mmol) was added. A vigorous evolution of nitrogen occurred, and the mixture was allowed to warm to room temperature overnight. The solvent was removed *in vacuo* and the product was purified by flash column chromatography (SiO_2 , hexane/ethyl acetate 9:1) to afford the compound **1** as a yellow oil (0.163 g, 76%). IR (CHCl_3) ν_{max} 2110, 1620, 1354 cm^{-1} ; ^1H NMR (CDCl_3 , 200 MHz) δ 5.82 (s, 1H), 7.40-7.85 (m, 3H); ^{13}C NMR (CDCl_3 , 50 MHz) δ 57.5, 126.9, 129.2, 131.4, 135.3, 136.4, 139.6, 194.7; MS [EI^+] m/z (%): 215 [M^+] (85), 187 [$\text{M} - \text{N}_2$] $^+$ (38), 174 [$\text{M} - \text{CHN}_2$] $^+$ (55), 146 [$\text{M} - \text{COCHN}_2$] $^+$ (100).

1-(2,4-Dichlorophenyl)-2-imidazol-1-ylethanone (2). To a stirring solution of imidazole (0.136 g, 2 mmol) and $\text{Cu}(\text{acac})_2$ (0.048 g, 0.2 mmol) in toluene (2 mL) at 85 °C was added a solution of diazoketone **1** (0.45 g, 1.05 mmol) in toluene (8 mL) via syringe pump over 1 h under a nitrogen atmosphere. The resulting mixture was allowed to cool to room temperature continuing the stirring for additional 1 h. The solvent was removed *in vacuo* and the product was purified by flash column chromatography (SiO_2 , CH_2Cl_2 /methanol 95:5) to afford the compound **2** as a white solid (0.234 g, 46%), mp 169-170 °C; IR (CHCl_3) ν_{max} 2929, 1715, 1584 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$, 200 MHz) δ 5.03 (s, 2H), 6.92 (s, 1H), 7.04 (s, 1H), 7.30 (m, 1H), 7.43 (m, 1H), 7.49 (s, 1H), 7.78 (m, 1H); ^{13}C NMR ($\text{DMSO}-d_6$, 50 MHz) δ 58.3, 122.6, 125.9, 126.9, 129.2, 131.4, 135.3, 139.6, 139.8, 194.7; MS [FAB^+] m/z (%): 255 [$\text{M} + 1$] $^+$ (86).

1-(2,4-Dichlorophenyl)-2-imidazol-1-ylethanol (3). To a suspension of sodium borohydride (0.045 g, 1.1 mmol) in anhydrous methanol (50 mL) was added a solution of compound **2** (0.284 g, 1.1 mmol) in methanol (5 mL) maintaining

the temperature below 5 °C under a nitrogen atmosphere. The resulting mixture was stirred at room temperature for 1 h and thereafter was heated at 50 °C for 1 h. The reaction was cooled to room temperature and the solvent was removed *in vacuo*. Water (10 mL) was added and the product was extracted with ethyl acetate (3 × 5 mL), the organic phase was dried over Na₂SO₄ and the solvent was removed *in vacuo* to yield a white solid (0.172g, 60%) which was purified by crystallization, mp 131-133 °C; IR (CHCl₃) ν_{\max} 3318, 2927, 1588 cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) δ 3.92 (dd, 1H; J_{AB} = 15 Hz and J_{AX} = 9 Hz), 4.24 (dd, 1H, J_{BA} = 15 Hz and J_{BX} = 5 Hz), 5.24 (dd, 1H, J_{XA} = 9 Hz and J_{XB} = 5 Hz), 5.83 (s, 1H), 6.88-7.86 (m, 6H); ¹³C NMR (CDCl₃, 50 MHz) δ 57.6, 67.6, 120.3, 127.8, 128.8, 130.0, 130.1, 131.6, 133.5, 138.7, 139.8; MS [FAB+] m/z (%): 257 [M + 1]⁺ (30).

2,4-Dichlorophenylmethanol (4). To a solution of 2,4-dichlorobenzoic acid (0.5 g, 2.6 mmol) in anhydrous ether (5 mL) was added dropwise a suspension of lithium aluminum hydride (0.124 g, 3.2 mmol) in ether (10 mL) at 0 °C under a nitrogen atmosphere. The resulting mixture was heated at reflux temperature during 50 min. The reaction was cooled to 0 °C, water (5 mL) was added and the mixture was acidified to pH = 4 with 10% HCl solution. The product was extracted with CH₂Cl₂ (3 × 25 mL), the organic phase was dried over Na₂SO₄ and the solvent was removed *in vacuo* to afford the compound **4** in quantitative yield as a colorless oil which was used without purification. IR (CHCl₃) ν_{\max} 3235, 2919, 1591 cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) δ 4.74 (s, 2H), 7.24 (dd, 1H, J_{ortho} = 8.2 Hz, J_{meta} = 2.0 Hz), 7.37 (d, 1H, J_{meta} = 2 Hz), 7.43 (d, 1H, J_{ortho} = 8.2 Hz); ¹³C NMR (CDCl₃, 50 MHz) δ 62.1, 127.2, 129.1, 129.3, 133.1, 133.6, 136.7; MS [FAB+] m/z (%): 177 [M + 1]⁺ (15).

Preparation of Miconazole, 1-[2-(2,4-dichlorobenzoyloxy)-2-(2,4-dichlorophenyl)ethyl]imidazole (6). 2,4-dichlorophenylmethanol **4** (0.212 g, 1.2 mmol) was dissolved in CH₂Cl₂ (10 mL) and cooled at 0 °C. Freshly distilled Et₃N (0.17 mL, 1.2 mmol) was added to this solution, followed by dropwise addition of methanesulfonyl chloride (0.094 mL, 1.2 mmol). After addition was complete, stirring was continued at 0 °C under a nitrogen atmosphere for an additional 90 min and the solvent was removed *in vacuo*.

In a separate flask, a suspension of sodium hydride (0.040 g, 1.1 mmol) in DMF (5 mL) was treated with a solution of alcohol **3** (0.256 g, 1 mmol) in DMF (10 mL) at 0 °C, the resulting mixture was stirred under a nitrogen atmosphere at room temperature for 1 h. The mixture was cooled at 0 °C and a solution of the crude mesylate in DMF (5 mL) was added. The resulting mixture was stirred for 1 h at room temperature. The reaction was quenched by addition of water (150 mL). The aqueous phase was extracted with ethyl acetate (3 × 25 mL), the organic phase was washed with water (150 mL), dried over Na₂SO₄ and the solvent was removed *in vacuo*. Purification by column chromatography (SiO₂, hexane/ethyl

acetate 7:3) yielded a white solid (0.28 g, 70%), mp 184-185 °C; IR (CHCl₃) ν_{\max} 2968, 1590 cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) δ 4.01 (m, 2H), 4.09 (dd, 1H, J_{AB} = 14 Hz y J_{AX} = 8 Hz), 4.29 (dd, 1H, J_{BA} = 14 Hz y J_{BX} = 5 Hz), 4.82 (dd, 1H, J_{XA} = 8 Hz y J_{XB} = 5 Hz), 6.77 (m, 2H), 7.12 (m, 6H), 7.32 (m, 1H); ¹³C NMR (CDCl₃, 50 MHz) δ 57.6, 62.1, 67.6, 120.3, 127.2, 127.8, 128.8, 129.1, 129.3, 130.0, 130.1, 131.6, 133.1, 133.5, 133.6, 136.6, 138.7, 139.8; MS [FAB+] m/z (%): 415 [M + 1]⁺ (20).

Preparation of Enilconazole, 1-[2-allyloxy-2-(2,4-dichlorophenyl)ethyl]imidazole (8). A suspension of sodium hydride (0.040 g, 1.1 mmol) in DMF (5 mL) was treated with a solution of alcohol **3** (0.256 g, 1 mmol) in DMF (10 mL) at 0 °C. The resulting mixture was stirred under a nitrogen atmosphere at room temperature for 1 h. The mixture was cooled at 0 °C and allyl bromide (0.1 mL, 1.2 mmol) was added. The resulting mixture was stirred for 1 h at room temperature. The reaction was quenched by addition of water (150 mL). The aqueous phase was extracted with ethyl acetate (3 × 25 mL), the organic phase was washed with water (150 mL), dried over Na₂SO₄ and the solvent was removed *in vacuo*. Purification by column chromatography (SiO₂, hexane/ethyl acetate 7:3) afforded a colorless oil (0.24 g, 81%); IR (film) ν_{\max} 3083, 1646, 1588 cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) δ 3.97 (m, 2H), 4.05 (dd, 1H, J_{AB} = 16 Hz and J_{AX} = 8 Hz), 4.25 (dd, 1H, J_{BA} = 16 Hz and J_{BX} = 4 Hz), 4.93 (m, 2H), 5.19 (dd, 1H, J_{XA} = 8 Hz and J_{XB} = 4 Hz), 5.66-5.82 (m, 1H), 7.03-7.81 (m, 3H); MS [FAB+] m/z (%): 297 [M + 1]⁺ (26).

4-Chlorophenylmethanol. The procedure was similar to that used in the preparation of 2,4-dichlorophenyl methanol (**4**) affording a colorless oil (98%); IR (CHCl₃) ν_{\max} 3230, 2919, 1590 cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) δ 4.59, 7.18 (d, 2H), 7.36 (d, 1H); MS [FAB+] m/z (%): 143 [M + 1]⁺ (25).

Preparation of econazole, 1-[2-(4-chlorobenzoyloxy)-2-(2,4-dichlorophenyl)imidazole (9). The procedure was similar to that used in the preparation of miconazole, yielding a white solid (75 %), mp 166 °C; IR (CHCl₃) ν_{\max} 3067, 2969, 1594 cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) δ 4.05 (m, 2H), 4.15 (dd, 1H, J_{AB} = 14 Hz y J_{AX} = 8 Hz), 4.35 (dd, 1H, J_{BA} = 14 Hz y J_{BX} = 5 Hz), 4.88 (dd, 1H, J_{XA} = 8 Hz y J_{XB} = 5 Hz), 6.89 (m, 2H), 7.18 (m, 5H), 7.36 (m, 2H); MS [FAB+] m/z (%): 381 [M + 1]⁺ (5).

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