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Tetrahedron
Tetrahedron 60 (2004) 9391–9396

# Copper carbenoid mediated *N*-alkylation of imidazoles and its use in a novel synthesis of bifonazole

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Received 10 June 2004; revised 5 August 2004; accepted 5 August 2004

Available online 3 September 2004

**Abstract**—1*H*-Imidazoles are readily *N*-alkylated by a $Cu(acac)_2$ mediated reaction with α-diazocarbonyl compounds or with diazoalkanes generated in situ from the corresponding *p*-toluensulfonyl hydrazones. The antifungal agent bifonazole was prepared by the latter method.


## 1. Introduction

Whereas the reactions of α-diazocarbonyl derived carbenoids with monoheteroatomic aromatic systems including for example, furans,[1] pyrroles,[2] thiophenes,[3] indoles,[4] and benzofurans,[5] have been studied in some detail, those with diheteroatomic aromatic systems have been less frequently examined. One instance of an intermolecular reaction of a rhodium α-ketocarbenoid with an isoxazole has been reported,[6] and Pellicciari, et al. have described the *N*-alkylation of imidazoles and benzimidazoles with α-diazocarbonyl compounds through the copper–bronze catalyzed[7] or the photolytically generated α-ketocarbenoids.[8]

Given the frequent occurrence of the imidazole moiety in compounds of medicinal importance, especially in many broad spectrum antifungal agents,[9] we decided to take another look at the carbenoid mediated *N*-alkylation reactions of imidazoles. The ultimate intention of this study was to attempt to use such methodology to prepare some of the more common imidazole containing antifungal agents, for example, bifonazole, for which several syntheses have already been reported.[10]

Our intitial studies, which were carried out on ethyl diazoacetate and imidazole using catalytic rhodium(II) acetate[11] under various conditions, consistently failed to provide any *N*-alkylated imidazole, even though the diazo compound was consumed. In contrast, copper(II) acetylacetonate, which has been utilized to generate ammonium ylides from α-diazocarbonyl compounds,[12,13] immediately showed promise.

After some experimentation, the following protocol was found to be particularly effective for the generation of ethyl *N*-imidazole acetate **1**. A toluene solution of ethyl diazoacetate (1.2 equiv) was added dropwise (1 h) to a mixture of imidazole and $Cu(acac)_2$ (10 mol%) in toluene at 85 °C. The mixture was heated to reflux for 1 h, the solvent was removed in vacuo, and following chromatographic purification on silica gel, the *N*-alkylated imidazole **1** was obtained in 60% yield. In the same way, imidazole, substituted imidazoles, and benzimidazole, all were readily *N*-akylated, not only with ethyl diazoacetate, but with various α-diazoketones as well (Table 1). The noteworthy features of this process are its generality, and the economy in the use of both reagents.

The combination of in situ generation of diazoalkanes, from aldehyde or ketone *p*-toluenesulfonylhydrazones, with transition metal catalyzed processes, has recently been successfully utilized by several groups of investigators.[14] We have devised an adaptation of these procedures to the synthesis of *N*-alkylimidazoles (see Scheme 1). Thus, tetrahydrofuran solutions of various *p*-toluenesulfonylhydrazones were converted into the sodium salts with sodium hydride, and then tetra-*n*-butylammonium bromide (0.125 equiv), imidazole (1 equiv), $Cu(acac)_2$, and toluene (to allow for a 15 mL/mmol solution of the diazo compound) were added, and the mixture was stirred at 85 °C for 24 h. In this way, imidazole, substituted

*Keywords*: Copper; Carbenoid; Imidazole; Bifonazole.
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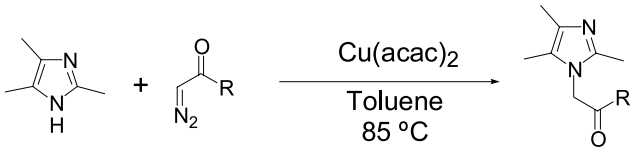
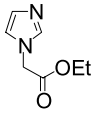
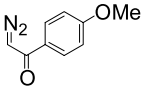
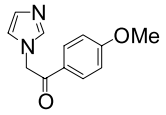
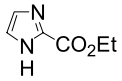
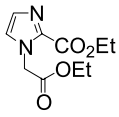
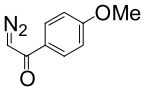
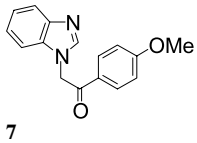
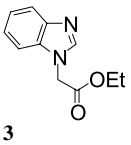
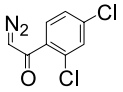
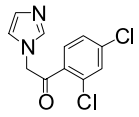
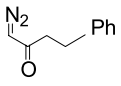
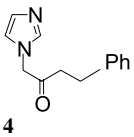
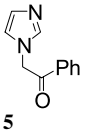
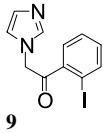
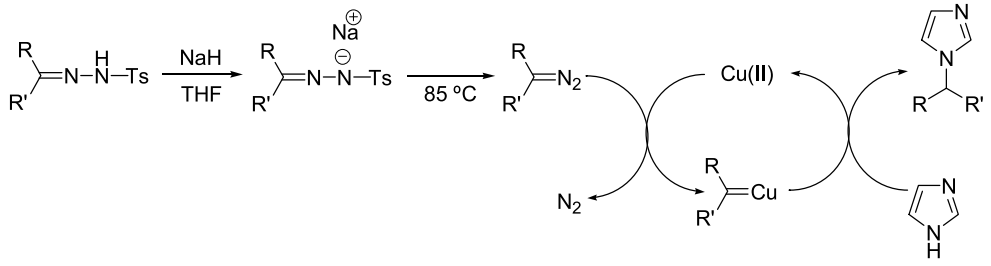
doi:10.1016/j.tet.2004.08.009

**Table 1.** *N*-alkylation products from α-diazo compounds, copper(II) acetylacetonate and diverse imidazoles




| Imidazole | Diazo-compound | Product | Yield (%) | Imidazole | Diazocompound | Product | Yield (%) |
|---|---|---|---|---|---|---|---|
|  |  |  **1** | 71 |  |  |  **6** | 58 |
|  |  |  **2** | 78 |  |  |  **7** | 78 |
|  |  |  **3** | 55 |  |  |  **8** | 46 |
|  |  |  **4** | 45 | | | | |
|  |  |  **5** | 40 |  |  |  **9** | 42 |




**Scheme 1.** General representation of imidazole alkylation with copper carbenoids derived from *p*-toluenesulfonylhydrazone salts.

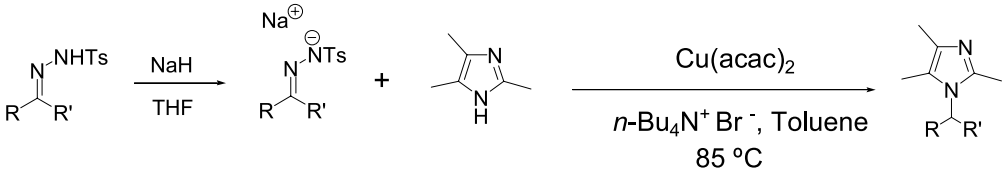
imidazoles, and benzimidazole were *N*-alkylated with mono- and diaryldiazomethanes, and diazocyclohexane (50–80% yields; Table 2). The antifungal agent Bifonazole **22** was also prepared in this manner (52% yield).

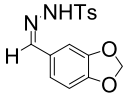
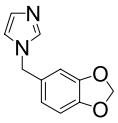
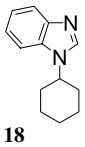
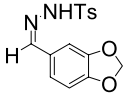
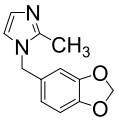
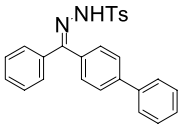
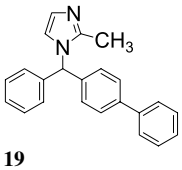
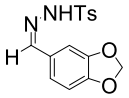
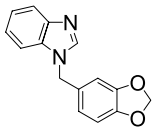
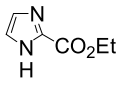
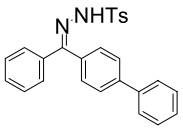
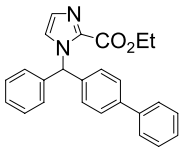
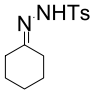
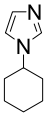
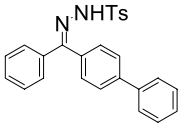
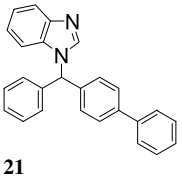
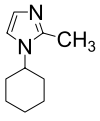
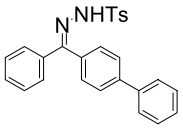
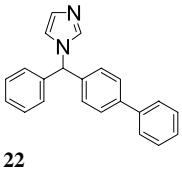
In summary, imidazoles, and benzimidazole are readily *N*-alkylated by a copper(acac)$_2$ catalyzed reaction with α-diazocarbonyl compounds or by diazoalkanes generated in situ from aldehyde or ketone *p*-touenesulfonylhydrazones. The latter one-pot procedure eliminates the need to isolate these potentially hazardous diazoalkanes. Both of the above processes make many *N*-substituted imidazoles easily available, and they represent a clearly viable alternative routes to the usual method of generation of these substances by alkylation of the imidazolyl anions with alkyl halides.

## 2. Experimental

The starting materials were purchased from Aldrich Chemical Co. and were used without further purification. Diazoketones were prepared from the corresponding acid

**Table 2.** *N*-alkylation products from *p*-toluenesulfonylhydrazones, copper(II) cetylacetonate and diverse imidazoles




| Imidazole | Tosythydrazone | Product | Yield (%) | Imidazole | Tosythydrazone | Product | Yield (%) |
|---|---|---|---|---|---|---|---|
|  |  |  | 65 |  |  |  | 58 |
| | **10** | **13** | | | | **18** | |
|  |  |  | 75 |  |  |  | 64 |
| | **14** | | | | **12** | **19** | |
|  |  |  | 80 |  |  |  | 67 |
| | **15** | | | | | **20** | |
|  |  |  | 55 |  |  |  | 76 |
| | **11** | **16** | | | | **21** | |
|  |  |  | 50 |  |  |  | 52 |
| | **17** | | | | | **22** | |

chlorides and excess ethereal diazomethane[15] or from carboxylic acids with triphenylphosphine, NBS and excess ethereal diazomethane.[16] Solvents were distilled before use; ether and tetrahydrofuran (THF) were dried over sodium using benzophenone as indicator. Diazomethane was prepared from *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (Diazald®) using a minimun amount of water and ethanol as cosolvent, and dried over KOH pellets before use. Silica gel (230–400 mesh) and neutral alumina were purchased from Merck. Silica plates of 0.20 mm thickness were used for thin layer chromatography. Melting points were determined with a Fisher–Johns melting point apparatus and they are uncorrected. $^1$H and $^{13}$C NMR spectra were recorded using a Varian Gemini 200, the chemical shifts ($\delta$) are given in ppm relative to TMS as internal standard (0.00). For analytical purposes the mass spectra were recorded on a JEOL JMS-5X 10217 in the EI mode, 70 eV, 200 °C via direct inlet probe. Only the molecular and parent ions (*m*/*z*) are reported. IR spectra were recorded on a Nicolet Magna 55-X FT instrument.

### 2.1. Insertion of α-diazoketones to imidazoles

*Typical procedure*. To a solution of imidazole (1 mmol) and $Cu(acac)_2$ (0.026 g, 0.1 mmol) in toluene (5 mL) at 85 °C under a nitrogen atmosphere was added a solution of diazoketone (1.2 mmol) in toluene (8 mL) via syringe pump over 1 h and the mixture was heated at 85 °C for additional 2 h. The mixture was allowed to cool to room temperature. The solvent was removed in vacuo and the product was purified by column chromatography ($Al_2O_3$ activity III, hexane/AcOEt 9:1).

**2.1.1. Imidazol-1-yl acetic acid ethyl ester (1).** Colorless oil[17] (71%). IR (film, cm$^{-1}$) 2979, 1745, 1507; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 1.29 (t, 3H), 4.24 (q, 2H), 4.70 (s, 2H),

6.96 (d, 1H), 7.10 (d, 1H), 7.52 (s, 1H); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ 14.1, 48.0, 62.3, 119.1, 129.4, 137.3, 167.3; MS [EI+] *m/z* (RI%): 154 $[M]^+$ (65), 81 $[M-CO_2Et]^+$ (100).

**2.1.2. 1-Ethoxycarbonylmethylimidazole-2-carboxylic acid ethyl ester (2).** Colorless oil (68%). IR (film, $cm^{-1}$) 2975, 1747, 1713; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 1.14 (t, 3H), 1.28 (t, 3H), 4.25 (q, 2H), 4.39 (q, 2H), 5.13 (s, 2H), 7.07 (d, 1H), 7.22 (d, 1H,); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ 14.1, 14.4, 49.8, 59.2, 61.6, 115.0, 126.6, 142.7, 160.6, 167.3; MS [EI+] *m/z* (RI%): 226 $[M]^+$ (46), 82 $[M-C_6H_8O_4]^+$ (100); HRMS ($FAB^+$): for $C_{10}H_{15}N_2O_4$ calcd 227.1032, found 227.1039.

**2.1.3. Benzoimidazol-1-yl acetic acid ethyl ester (3).** White solid (55%), mp 61–62 °C (lit. 61–63 °C).[18] IR (film, $cm^{-1}$) 2977, 1743; $^1$H NMR (DMSO-$d_6$, 200 MHz) $\delta$ 1.21 (t, 3H), 4.17 (q, 2H), 5.25 (s, 2H), 7.25 (m, 2H), 7.6 (m, 2H), 8.21 (s, 1H); $^{13}$C NMR (DMSO-$d_6$, 50 MHz) $\delta$ 14.1, 45.8, 61.8, 110.4, 119.6, 121.6, 122.4, 143.5, 144.6, 168.5; MS [EI+] *m/z* (RI%): 204 $[M]^+$ (27), 131 $[M-CO_2Et]^+$ (100).

**2.1.4. 1-Imidazol-1-yl-4-phenylbutan-2-one (4).** Colorless oil (45%). IR ($CHCl_3$, $cm^{-1}$) 2966, 1738; $^1$H NMR (DMSO-$d_6$, 200 MHz) $\delta$ 2.81 (s, 4H), 5.01 (s, 2H), 6.89 (s, 1H), 7.05 (s, 1H), 7.24 (m, 5H), 7.50 (s, 1H); $^{13}$C NMR (DMSO-$d_6$, 50 MHz) $\delta$ 28.5, 54.6, 120.6, 125.9, 128.1, 128.3, 138.0, 140.8, 203.8; MS [FAB+] *m/z* (RI%): 215 $[M+1]^+$ (100); HRMS ($FAB^+$): for $C_{13}H_{15}N_2O$ calcd 215.1184, found 215.1189.

**2.1.5. 2-Imidazol-1-yl-1-phenylethanone (5).** White solid (40%), mp 118 °C (lit. 117–118 °C).[19] IR ($CHCl_3$, $cm^{-1}$) 2962, 1707; $^1$H NMR (DMSO-$d_6$, 200 MHz) $\delta$ 5.74 (s, 2H), 6.92 (s, 1H), 7.12 (s, 1H), 7.54 (m, 5H), 8.04 (s, 1H); $^{13}$C NMR (DMSO-$d_6$, 50 MHz) $\delta$ 52.5, 120.8, 127.95, 128.9, 133.9, 134.4, 138.4, 193.5; MS [EI+] *m/z* (RI%): 186 $[M]^+$ (22), 105 $[C_6H_5CO]^+$ (100).

**2.1.6. 2-Imidazol-1-yl-1-(4-methoxyphenyl)ethanone (6).** (58%), mp 120–121 °C. IR ($CHCl_3$, $cm^{-1}$) 2968, 1697; $^1$H NMR (DMSO-$d_6$, 200 MHz) $\delta$ 3.90 (s, 3H), 5.44 (s, 2H), 6.84 (d, 1H), 7.0 (d, 2H), 7.20 (d, 1H), 7.58 (s, 1H), 7.97 (d, 2H); $^{13}$C NMR (DMSO-$d_6$, 50 MHz) $\delta$ 51.7, 55.1, 113.3, 113.7, 126.7, 129.8, 163.8, 189.8; MS [FAB+] *m/z* (RI%): 217 $[M+1]^+$ (100); HRMS ($FAB^+$): for $C_{12}H_{13}N_2O_2$ calcd 217.0977, found 217.0981.

**2.1.7. 2-Benzimidazol-1-yl-1-(4-methoxyphenyl)ethanone (7).** White solid (78%), mp 133–135 °C. IR ($CHCl_3$, $cm^{-1}$) 2970, 1696; $^1$H NMR (DMSO-$d_6$, 200 MHz) $\delta$ 3.91 (s, 3H), 5.95 (s, 2H), 7.14 (d, 2H), 7.21 (m, 2H), 7.49 (m, 1H), 7.68 (m, 1H), 8.09 (d, 2H), 8.17 (s, 1H); $^{13}$C NMR (DMSO-$d_6$, 50 MHz) $\delta$ 50.3, 55.6, 110.4, 114.1, 119.2, 121.3, 122.1, 127.3, 130.46, 134.5, 143.1, 144.9, 163.7, 191.5; MS [FAB+] *m/z* (RI%): 267 $[M+1]^+$ (75); HRMS ($FAB^+$): for $C_{16}H_{15}N_2O_2$ calcd 267.1134, found 267.1139.

**2.1.8. 1-(2,4-Dichlorophenyl)-2-imidazol-1-ylethanone (8).** White solid (46%), mp 169–170 °C. IR ($CHCl_3$, $cm^{-1}$) 2929, 1715; $^1$H NMR (DMSO-$d_6$, 200 MHz) $\delta$ 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 (DMSO-$d_6$, 50 MHz) $\delta$ 58.3, 122.6, 125.9, 126.9, 129.2, 131.4, 135.3, 139.6, 139.8, 194.7; MS [FAB+] *m/z* (RI%): 255 $[M+1]^+$ (15); HRMS ($FAB^+$): for $C_{11}H_9Cl_2N_2O$ calcd 255.0092, found 255.0998.

**2.1.9. 2-Imidazol-1-yl-1-(2-iodophenyl)ethanone (9).** White solid (42%), mp 142–143 °C. IR (film, $cm^{-1}$) 2961, 1687; $^1$H NMR (DMSO-$d_6$, 200 MHz) 5.56 (s,2H), 7.32 (m, 2H), 7.57 (m, 2H), 7.84 (m, 2H), 8.03 (m, 1H); $^{13}$C NMR (DMSO-$d_6$, 50 MHz) $\delta$ 54.1, 92.6, 128.3, 128.9, 131.3, 133.0, 138.6, 138.8, 140.2, 140.7, 197.5; MS [FAB+] *m/z* (RI%): 313 $[M+1]^+$ (100); HRMS ($FAB^+$): for $C_{11}H_{10}IN_2O$ calcd 312.9838, found 312.9841.

### 2.2. Preparation of *p*-toluenesulfonylhydrazones

*Typical procedure*. A solution of the *p*-toluenesulfonhydrazide (4.46 g, 24 mmol) and the appropriate carbonyl compound (20 mmol) in Me OH (50 mL) and 10% HCl (0.1 mL) was heated at reflux for 24 h. The reaction mixture was cooled to room temperature, the final product was filtered and purified by crystallization.

**2.2.1. *p*-Toluenesulfonylhydrazone of benzo[1,3]dioxole-5-carbaldehyde (10).** White solid (95%), mp 143–145 °C. IR (film, $cm^{-1}$) 3195, 2989, 1597, 1163; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 2.37 (s, 3H), 5.95 (s, 2H), 6.69 (m, 1H), 6.89 (m, 1H), 7.15, (m, 1H), 7.29 (d, 2H), 7.70 (s, 1H), 7.86 (d, 2H); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ 21.5, 101.4, 105.6, 108.0, 123.7, 127.7, 127.8, 129.6, 135.2, 144.0, 148.0, 148.1, 149.6; MS [EI+] *m/z* (RI%): 318 $[M]^+$ (40), 91 $[C_6H_4CH_3]^+$ (100); HRMS ($FAB^+$): for $C_{15}H_{15}N_2O_4S$ calcd 319.0753, found 319.0755.

**2.2.2. *p*-Toluenesulfonylhydrazone of -cyclohexanone (11).** White solid (97%), mp 161–162 °C (lit. 156 °C).[20] IR ($CHCl_3$, $cm^{-1}$) 3302, 2942, 1639, 1162; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 1.57 (m, 2H),1.77 (m, 4H), 2.22 (m, 4H), 2.42 (s, 3H), 7.31 (d, 2H), 7.85 (d, 2H); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ 21.5, 25.2, 25.6, 26.6, 26.6, 35.1, 128.0, 129.4, 135.4, 143.7, 163.2; MS [FAB+] *m/z* (RI%): 267 $[M+1]^+$ (100); HRMS ($FAB^+$): for $C_{13}H_{19}N_2O_2S$ calcd 267.1167, found 267.1163.

**2.2.3. *p*-Toluenesulfonylhydrazone of biphenyl-4-yl-phenyl methanone (12).** White solid (89%), mp 158–160 °C. IR ($CHCl_3$, $cm^{-1}$) 3276, 2926, 1599, 1164; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 2.42 (s, 3H), 7.13–7.24 (m, 2H), 7.32–7.72 (m, 14H), 7.86–7.88 (m, 2H); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ 21.5, 126.8, 126.9, 127.1, 127.6, 127.7, 127.8, 127.9, 128.2, 128.3, 128.8, 128.9, 129.6, 129.8, 130.1, 131.0, 135.3, 135.5, 136.4, 139.8, 140.1, 142,5, 143.0, 144.1, 153.9, 154.0; MS [FAB+] *m/z* (RI%): 427 $[M+1]^+$ (100); HRMS ($FAB^+$): for $C_{26}H_{23}N_2O_2S$ calcd 427.1480, found 427.1469.

### 2.3. Insertion of in situ generated diazoalkanes to imidazoles

*Typical procedure*. To a suspension of 60% NaH (0.063 g, 2.64 mmol) in THF (20 mL) was added the *p*-toluenesulfonylhydrazone (2.2 mmol). The mixture was stirred at

room temperature under a nitrogen atmosphere for 1 h and the solvent was removed in vacuo. Toluene (25 mL) was added and the suspension was treated successively with tetrabutylammonium bromide (0.080 g, 25 mmol), $Cu(acac)_2$ (0.052 g, 0.2 mmol) and the appropriate imidazole (2 mmol). The mixture was heated at 85 °C under a nitrogen atmosphere for 36 h. Then, the reaction mixture was allowed to cool to room temperature. The solvent was removed in vacuo and the product was purified by column chromatography ($SiO_2$, hexane/AcOEt 8:2).

**2.3.1. 1-Benzo[1,3]dioxol-5-ylmethylimidazole (13).** White solid (65%), mp 194–195 °C (lit. 198 °C).[21] IR (film, $cm^{-1}$) 2909, 1604; $^1H$ NMR ($CDCl_3$, 200 MHz) $\delta$ 5.14 (s, 2H), 6.08 (s, 2H), 6.84 (m, 1H), 7.07 (s, 1H), 7.20 (m, 1H), 7.25 (s, 1H), 7.44, (m, 1H), 7.59 (s, 1H); $^{13}C$ NMR ($CDCl_3$, 50 MHz) $\delta$ 51.5, 102.0, 106.8, 108.3, 119.3, 125.4, 128.6, 131.8, 137.8, 148.0, 148.3; MS [FAB+] *m/z* (RI%): 203 $[M+1]^+$ (50).

**2.3.2. 1-Benzo[1,3]dioxol-5-ylmethyl-2-methylimidazole (14).** White solid (75%), mp 200 °C (dec). IR (film, $cm^{-1}$) 2911, 1604; $^1H$ NMR ($CDCl_3$, 200 MHz) $\delta$ 2.41 (s, 3H), 5.14 (s, 2H), 6.07 (s, 2H), 6.84 (m, 1H), 7.05 (s, 1H), 7.17 (m, 1H), 7.25 (s, 1H), 7.45, (m, 1H); $^{13}C$ NMR ($CDCl_3$, 50 MHz) $\delta$ 23.8, 52.0, 102.0, 106.9, 108.2, 123.4, 125.4, 128.5, 131.8, 134.2, 148.6, 153.0; MS [FAB+] *m/z* (RI%): 217 $[M+1]^+$ (70); HRMS ($FAB^+$): for $C_{12}H_{13}N_2O_2$ calcd 217.0977, found 217.0974.

**2.3.3. 1-Benzo[1,3]dioxol-5-ylmethylbenzimidazole (15).** White solid (80%), mp 180–181 °C. IR (film, $cm^{-1}$) 2917, 1602; $^1H$ NMR ($CDCl_3$, 200 MHz) $\delta$ 5.09 (s, 2H), 5.99 (s, 2H), 6.94 (m, 1H), 7.20–7.34 (m, 3H), 7.45, (m, 1H), 7.53 (m, 2H); $^{13}C$ NMR ($CDCl_3$, 50 MHz) $\delta$ 47.9, 101.2, 106.8, 108.3, 110.8, 121.5, 124.6, 125.2, 128.5, 129.5, 131.8, 135.0, 144.6, 147.7.0, 148.0; MS [FAB+] *m/z* (RI%): 253 $[M+1]^+$ (30); HRMS ($FAB^+$): for $C_{15}H_{13}N_2O_2S$ calcd 253.0977, found 253.0978.

**2.3.4. 1-Cyclohexylimidazole (16).** Colorless oil (55%). IR (film, $cm^{-1}$) 2934, 2863; $^1H$ NMR ($CDCl_3$, 200 MHz) $\delta$ 1.59 (m, 2H), 1.74 (m, 4H), 1.86 (m, 4H), 3.66 (m, 1H), 6.99 (s, 1H), 7.12 (s, 1H), 7.56 (s, 1H); $^{13}C$ NMR ($CDCl_3$, 50 MHz) $\delta$ 21.4, 24.8, 24.8, 26.9, 26.9, 35.1, 51.4, 120.0, 129.9, 137.6; MS [EI+] *m/z* (RI%): 150 $[M]^+$ (65), 67 $[M-C_6H_{11}]^+$ (100); HRMS ($FAB^+$): for $C_9H_{15}N_2$ calcd 151.1235, found 151.1238.

**2.3.5. 1-Cyclohexyl-2-methylimidazole (17).** White solid (50%), mp 66–68 °C. IR (film, $cm^{-1}$) 2936, 2862; $^1H$ NMR ($CDCl_3$, 200 MHz) $\delta$ 1.55 (m, 2H), 1.72 (m, 4H), 1.85 (m, 4H), 2.40 (s, 3H), 3.63 (m, 1H), 6.97 (d, 1H), 7.10 (d, 1H); $^{13}C$ NMR ($CDCl_3$, 50 MHz) $\delta$ 21.3, 21.8, 25.1, 25.1, 26.6, 26.6, 50.8, 119.4, 128.8, 136.2; MS [EI+] *m/z* (RI%): 164 $[M]^+$ (30), 81 $[M-C_6H_{11}]^+$ (100); HRMS ($FAB^+$): for $C_{10}H_{17}N_2$ calcd 165.1392, found 165.1391.

**2.3.6. 1-Cyclohexylbenzimidazole (18).** White solid (58%), mp 74–75 °C. IR (film, $cm^{-1}$) 2934, 2863; $^1H$ NMR ($CDCl_3$, 200 MHz) $\delta$ 1.49 (m, 2H), 1.65 (m, 4H), 1.78 (m, 4H), 2.33 (s, 3H), 3.62 (m, 1H), 7.21 (m, 2H), 7.50 (m, 1H), 7.68 (m, 1H), 8.18 (s, 1H); $^{13}C$ NMR ($CDCl_3$, 50 MHz) $\delta$ 20.9, 25.3, 25.3, 26.5, 26.5, 50.8, 125.4, 125.6, 127.3, 128.0, 128.8, 136.2, 142.5; MS [EI+] *m/z* (RI%): 200 $[M]^+$ (40), 117 $[M-C_6H_{11}]^+$ (100); HRMS ($FAB^+$): for $C_{13}H_{17}N_2$ calcd 201.1392, found 201.1396.

**2.3.7. 1-(Biphenyl-4-ylphenylmethyl)-2-methylimidazole (19).** White solid (64%), mp 143–145 °C. IR (film, $cm^{-1}$) 3038, 2935; $^1H$ NMR ($CDCl_3$, 200 MHz) $\delta$ 1.46 (s, 3H), 4.94 (s, 1H), 7.15–7.52 (m, 16H); $^{13}C$ NMR ($CDCl_3$, 50 MHz) $\delta$ 21.8, 58.5, 109.5, 126. 4, 126.6, 126.7, 126.8, 127.0, 127.8, 128.5, 128.6, 128.8, 129.8, 130.2, 138.3, 139.2, 139.3, 140.7, 156.2; MS [FAB+] *m/z* (RI%): 325 $[M+1]^+$ (10); HRMS ($FAB^+$): for $C_{23}H_{21}N_2$ calcd 325.1705, found 325.1700.

**2.3.8. 1-(Biphenyl-4-ylphenylmethyl)imidazole-2-carboxylic acid ethyl ester (20).** White solid (64%), mp 33–34 °C. IR (film, $cm^{-1}$) 2981, 1710; $^1H$ NMR ($CDCl_3$, 200 MHz) $\delta$ 1.34 (t, 3H), 4.33 (q, 2H), 5.20 (s, 1H), 6.91 (d, 1H), 7.08–7.17 (m, 5H), 7.29–7.42 (m, 6H), 7.52–7.56 8m, 4H); $^{13}C$ NMR ($CDCl_3$, 50 MHz) $\delta$ 13.9, 61.2, 64.0, 124.0, 126.7, 127.1, 127.3, 127.9, 128.3, 128.5, 129.0, 136.4, 137.9, 138.9, 139.9, 140.7, 158.7; MS [FAB+] *m/z* (RI%): 383 $[M+1]^+$ (30); HRMS ($FAB^+$): for $C_{25}H_{23}N_2O_2$ calcd 383.1760, found 383.1750.

**2.3.9. 1-(Biphenyl-4-ylphenylmethyl)benzimidazole (21).** White solid (76%), mp 199–200 °C. IR (film, $cm^{-1}$) 3036, 2968; $^1H$ NMR ($CDCl_3$, 200 MHz) $\delta$ 5.23 (s, 1H), 6.77 (s, 1H), 7.17–7.57 (m, 17H), 7.86 (d, 1H); $^{13}C$ NMR ($CDCl_3$, 50 MHz) $\delta$ 63.2, 120.2, 122.4, 122.9, 126.8, 126.9, 127.1, 127.2, 127.5, 127.7, 127.7, 127.8, 128.1, 128.2, 128.5, 128.6, 128.7, 128.8, 128.9, 129.1, 129.2, 129.8, 130.2, 136.8, 137.8, 139.9, 141.2, 142.4, 143.8; MS [FAB+] *m/z* (RI%): 361 $[M+1]^+$ (40); HRMS ($FAB^+$): for $C_{26}H_{21}N_2$ calcd 361.1705, found 361.1706.

**2.3.10. Bifonazole, 1-(biphenyl-4-ylphenylmethyl)imidazole (22).** White solid (52%), mp 140–141 °C. IR (film, $cm^{-1}$) 3028, 2924; $^1H$ NMR ($CDCl_3$, 200 MHz) $\delta$ 5.29 (s, 1H), 6.93 (s, 1H), 7.13–7.60 (m, 16H); $^{13}C$ NMR ($CDCl_3$, 50 MHz) $\delta$ 52.3, 126. 4, 126.6, 126.7, 126.8, 127.0, 127.8, 128.5, 128.6, 128.8, 129.8, 130.2, 138.3, 139.2, 139.3, 140.7, 156.2; MS [FAB+] *m/z* (RI%): 311 $[M+1]^+$ (10); HRMS ($FAB^+$): for $C_{22}H_{18}N_2$ calcd 311.1548, found 311.1550.

## Acknowledgements

Financial support from CONACyT (no. 37312-E) is gratefully acknowledged. The authors would like to thank E. García, R. Patiño, A. Peña, E. Huerta, N. Zavala, J. Pérez and L. Velasco for the technical support.

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