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SYNTHESIS AND STRUCTURAL ELUCIDATION OF NOVEL HETEROCYCLIC COMPOUNDS FROM BENZIMIDAZOL-2-ONE

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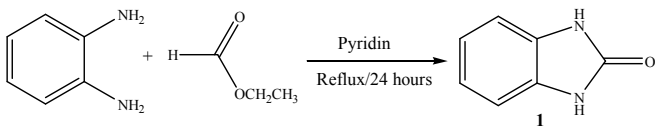
ABSTRACT
Novel potentially bioactive heterocyclic derivatives incorporating benzimidazol-2-one substructure were prepared in excellent yields by the monoalkylation of 1H-benzo[d]imiazol-2(3H)-one (**1**) with allyle and propargyle bromides, as well as benzyle bromides. Subsequent treatment of the three N-benzyle monoalkylated derivatives with allyle bromide afforded the corresponding N,N-disubstituted derivatives with excellent yields.

KEYWORDS: benzimidazol-2-one, N-alkylation, PTC, N,N- disubstituted benzimidazol-2-ones.

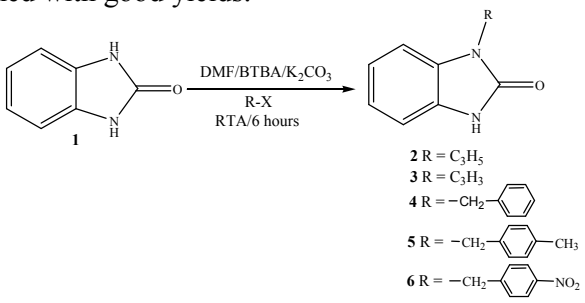
1. INTRODUCTION
Benzimidazole derivatives in general and benzimidazol-2-ones in particular have attracted much interest in the past few years due to their applications in various domains including pharmacological and industrial fields.[I-IV] In fact, these substances have been reported to exhibit a wide range of biological activities including antibacterial and antifungal,[V-VII] as well as anticancer activities.[VIII] Furthermore derivatives resulting from the chemical modifications of benzimidazol-2-one substructure have shown more diversified biological activities profile.[III-VII, IX] These are possible due to the presence of reactive sites which are likely to undergo alkylation, amination, chlorination, sulfonylation and even 1,3-dipolar cycloaddition.

2. RESULTS AND DISCUSSION
Several methods for the preparation of benzimidazol-2-ones have been reported in the literature since the 19th century.[X,XI] The method utilizing o-phenylenediamine remains sofar the most general.[XII] Thus, the condensation of o-phenylenediamine with ethyle chloroformiate in refluxing pyridine for 24 hours led to the formation of 1H-benzo[d]imidazol-2(3H)-one (**1**).



Scheme 1

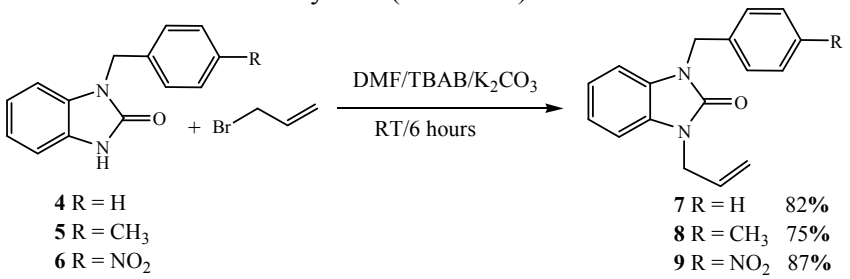
Compound **1**, which could be considered as a heterocyclic urea, was involved in different alkylation reactions likely to implicate the nitrogen atoms at position 1,3 in the bicyclic system, under a liquid-solid transfer phase catalytic conditions. DMF was used as solvent, K_2CO_3 as base and tetrabutylammonium bromide (TBAB) as catalyst. The reactions were carried out at room temperature. Allyl and propargyl bromides, and benzyl bromides were used as alkylating reagents. In all the cases, monosubstituted benzimidazol-2-ones (scheme 2) were obtained with good yields.



Scheme 2

The structures of compounds **2-6** were established on the basis of spectral (^{1}H-NMR, ^{13}C-NMR and MS) data.

The synthesized compounds are likely to be used as starting materials for the preparation of new derivatives of benzimidazol-2-one with various substitutions patterns on the nitrogen atoms of the bicyclic system. Thus, reacting allyl bromide respectively with the monosubstituted compounds **4-6** in similar phase transfer catalytic conditions, permitted to obtain compounds **7-9** with excellent yields (Scheme 3).



Scheme 3

The structures of compounds **7-9** were established on the basis of spectral (^{1}H-NMR, ^{13}C-NMR and MS) data.

3. EXPERIMENTAL

Uncorrected melting points were measured with a Buchi apparatus. The NMR spectra were recorded on a Brucker AC300-instrument. The chemical shifts are given in parts per million with reference to tetramethylsilane (TMS) used as internal reference, with a precision of ± 0,1

for the ^{13}C-N MR and ± 0,05 for the ^{1}H-NMR. The mass spectra were recorded on a Nermag R10-10C instrument.

1H-benzo[d]imidazol-2(3H)-one (**1**)*:*

To a solution of 4 g (0.037 mol) of o-phenylenediamine in 50 ml of pyridin, is added dropwise 0.044 mol of ethyl chloroformiate under magnetic stirring at 0 °C over a 15 minutes period; the reaction mixture is then refluxed for 24 hours and evaporated to dryness on a rotavapor. The residue obtained is washed with water, filtered and crystallized from methanol to afford a white powder. Yield = 89%, mp (°C) = 282 (from methanol); ^{1}H-RMN (DMSO-d_6, 300 MHz) δ ppm: 10.58 (s, 2H, NH); 6.91-6.98 (m, 4H, H_{Ar}); ^{13}C-RMN (DMSO-d_6, 75 MHz) δ ppm: 154.68 (C=O); 136.39, 129.27(Cq); 128.85, 127.54, 121.57, 108.53 (CH_{Ar}).

General procedure for the preparation of compounds 2-6 :

To a solution of 0.2 g ($1.49.10^{-3}$ mole) of 1H-benzo[d]imidazol-2(3H)-one in 25 ml of DMF, is added 0.41 g ($2.98.10^{-3}$ mole) of K_2CO_3, 0.04 g ($0.15.10^{-3}$ mole) of TBAB and $1.79.10^{-3}$ mole of the alkylating agent. The mixture is stirred at room temperature for 6 to 8 hours. After eliminating the salts by filtration, the excess DMF was evaporated under reduced pressure. The so obtained residual mixture was chromatographed on silica gel column with hexane/ethyl acetate (8/2) as eluent.

1-(prop-2-en-1-yl)-1H-benzo[d]imidazol-2(3H)-one (**2**)**:**

White powder, yield (%) = 80, mp (°C) = 87 (from methanol), ^{1}H-NMR ($CDCl_3$, 300 MHz) δ ppm: 10.19 (s, 1H, NH); 7.17-6.99 (m, 4H, H_{Ar}); 6.02-5.89 (m, 1H, H_{all}); 5.28-5.21 (m, 2H, CH_2); 4.57-4.54 (m, 2H, CH_2, J = 5 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δppm: 155.47 (C=O); 131.85 (CH_{All}); 130.19; 127.98 (Cq); 121.68, 121.33, 109.76, 108.46 (CH_{Ar}); 117.52 (CH_{2all}); 43.14 (CH_{2all}). MS (IE): m/z = 174 [$M^{+.}$].

1-(prop-2-ynyl)- 1H-benzo[d]imidazol-2(3H)-one (**3**)**:**

White powder, yield (%) = 85, mp (°C) = 68 (from methanol); ^{1}H-NMR ($CDCl_3$, 300 MHz) δppm: 7,21-7,11 (m, 4 H, H_{Ar}); 4.67 (s, 2H, CH_2); 2.28 (s, 1H, CH); ^{13}C-NMR ($CDCl_3$, 75 MHz) δppm: 155.63 (C=O); 130.29, 128.38 (Cq); 121.58, 121.34, 110.32, 108.26 (CH_{Ar}); 63.14 (Cq_{prop}); 47.45 (CH_{prop}); 28.62 (CH_{2prop}).

1-benzyl-1H-benzo[d]imidazol-2(3H)-one (**4**)**:**

White powder, yield (%) = 86, mp (°C) = 154 (from methanol); ^{1}H-NMR ($CDCl_3$, 300 MHz) δppm : 10,13 (s,1H, NH); 7.21-6.90 (m, 9H, CH_{Ar}); 5.15 (s, 2H, CH_2); ^{13}C-NMR ($CDCl_3$, 75 MHz) δppm: 154.68 (C=O); 136.39 (Cq); 128.85, 129.27 (C_q); 108.73-127.79 (CH_{Ar}); 45.01 (CH_2). MS (IE): m/z = 224[$M^{+.}$].

1-(4-methylbenzyl)-1H-benzo[d]imidazol-2(3H)-one (**5**)**:**

White powder, yield (%) = 88, mp (°C) = 183 (from methanol); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ ppm: 10.06 (s, 1H, NH); 7.29-6.89 (m, 8H, H_{Ar}); 5.08 (s, 2H, CH_2); 2.32 (s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$, 75 MHz) δppm: 155.58 (C=O); 137.49, 132.96, 130.04 (Cq); 129.60,

129.47 (CH_{Ar}); 127.88 (Cq); 127.38, 127.32, 122.33, 122.09, 121.87, 121.56, 114.69, 109.91, 109.70, 108.70, 108.39 (CH_{Ar}); 44.41 (CH_2); 21.11(CH_3). MS (IE): m/z = 237[$M^{+\cdot}$].

1-(4-nitrobenzyl)-1H-benzo[d]imidazol-2(3H)-one (**6**)**:**
White powder, yield (%) = 85, mp (°C) = 186 (from methanol); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ ppm: 9.90 (s, 1H, NH); 7.02-8.23 (m, 8H, H_{Ar}); 5.24 (s, 2H, CH_2), ^{13}C-NMR ($CDCl_3$, 75 MHz) δ ppm: 154.25 (C=O); 147.66, 143.29 (Cq); 128.04 (Cq); 124.40-108.33 (CH_{Ar}); 44.46 (CH_2).

General procedure for the preparation of compounds 7-9:

The same reaction conditions as above for the preparation of compounds **2-6**, were applied for the preparation of compounds **7-9**, whereby $1.79.10^{-3}$ mole of allyle bromide were added to compounds **4-6** respectively. The materials were isolated from the respective residual reactions' mixtures by triturating with dichloromethane/hexane mixture.

1-allyl-3-benzyl-1H-benzo[d]imidazol-2(3H)-one (**7**):
White powder, yield (%) = 87, mp (°C) = 152 (from methanol); ^{1}H-NMR ($CDCl_3$, 300 MHz) δppm : 7.33-6.87 (m, 9H, H_{ar}); 5.88-6.00 (m, 1H, CH_{all}); 5.27-5.21 (d, 2H, =CH_{2all}, J = 6.1 Hz); 5.10 (s, 2H, CH_2); 4.58-4.65 (dd, 2H, CH_{2all}, J = 3.8 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δppm: 171.02 (C=O); 136.29 (Cq); 132.01 (CH_{all}); 129.33-129.21 (Cq); 127.45-127.68 (CH_{ar}); 117.59 (CH_{2all}); 108.35,108.32 (CH_{ar}); 65.22 (CH_2). MS (IE): m/z = 264[$M^{+\cdot}$].

1-(4-methylbenzyl)-3-allyl-1H-benzo[d]imidazol-2(3H)-one (**8**):
White powder, yield (%) = 84, mp (°C) = 70 (from methanol); ^{1}H-NMR ($CDCl_3$, 300 MHz) δppm: 7.23-6.81 (m, 9H, H_{ar}); 5.74-5.66 (m, 1H, CH_{all}); 5.01-4.96 (d, 2H, =CH_{2all}, J = 4.9 Hz); 4.8 (s, 2H, CH_2); 4.65-4.57 (dd, 2H, CH_{2all}); ^{13}C-NMR ($CDCl_3$, 75 MHz) δppm: 136.16 (Cq); 132.21 (CH_{all}); 129.33-129.18 (Cq); 127.45-127.68 (CH_{ar}); 117.38 (CH_{2all}); 108.45,108.22 (CH_{ar}); 63.01 (CH_2).

1-(4-nitrobenzyl)-3 -allyl-1H-benzo[d]imidazol-2(3H)-one (**9**):
White powder, yield (%) = 89, mp (°C) = 95 (from methanol); ^{1}H-NMR ($CDCl_3$, 300 MHz) δppm: 8.19-8.15 (m, 2H, H_{ar}); 7.47 (d, 2H, H_{ar}, J = 8.7 Hz); 7.12-7.00 (m, 3H, H_{ar}); 6.86-6.83 (m, 1H, H_{ar}); 6.01-5.88 (m, 1H, H_{all}); 5.29-5.22 (m, 2H, CH_2); 5.19 (s, 2H, CH_2, J = 5.4 Hz); 4.59-4.56 (m, 2H, CH_2); ^{13}C-NMR ($CDCl_3$, 75 MHz) δppm: 43.71 (CH_2); 44.24 (CH_2); 107.90, 108.60 (CH_{ar}); 117.82 (CH_{2All}); 121.58, 121.89 (CH); 124.06, 128.17 (CH), 128.75, 129.41 (Cq); 143.73, 147.53 (Cq); 154(C=O). MS (IE): m/z = 309[$M^{+\cdot}$].

4. CONCLUSION

In this work, the high reactivity of benzimidazole was advantageously exploited in the implementation of a series of alkylation reactions under phase transfer catalytic conditions, which led to the preparation of new N-monosubstituted and N,N'-disubstituted benzimidazol-

2-ones. These compounds will be tested for antibacterial, antituberculosis and antifungal activity. The analyses are in progress and the results will be published in due course.

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