STUDY OF THE ALKYLATION REACTIONS OF 5-NITROBENZIMIDAZOL-2-ONE BY VARIOUS ALKYLATING AGENTS IN LIQUID-SOLID PHASE TRANSFER CATALYSIS CONDITIONS

Younes Ouzidan\textsuperscript{a}, Youssef Kandri Rodi\textsuperscript{b}\textsuperscript{*}, Fouad Ouazzani Chahdi\textsuperscript{b}, Said Chakroune\textsuperscript{b} and El Mokhtar Essassi\textsuperscript{c}

\textsuperscript{a}Laboratoire de Chimie-Physique et Biotechnologie des Biomolécules et Matériaux, Faculté des Sciences et Techniques, Université Hassan II, BP 146, Mohammedia 28800, Morocco
\textsuperscript{b}Laboratory of Applied Organic Chemistry, Faculty of Science and Technology, Sidi Mohamed Ben Abdellah University, BP 2202, Fez, Morocco
\textsuperscript{c}Laboratory of Heterocyclic Organic Chemistry URAC21, Faculty of Sciences, University of Mohamed V, Rabat, Morocco

Corresponding author: youssef_kandri_rodi@yahoo.fr

Received: 01/06/2022; Accepted: 03/10/2022

Abstract

The alkylation reactions of 5-nitrobenzimidazol-2-one have been carried out using benzyl chloride, picolyl chloride, N-3-(bromopropyl)phtalimide, cinnamyl bromide, allyl bromide, propargyl bromide as alkylating agents in liquid-solid phase transfer catalysis (PTC) conditions. The structures of the obtained dialkylated benzimidazolones have been elucidated on the basis of spectral data and confirmed by a single-crystal X-ray diffraction studies.

Key words: 5-nitrobenzimidazol-2-one, alkylation, PTC, spectroscopy, X-ray diffraction.

Introduction

Benzimidazole derivatives play an important role as progesterone receptor antagonist I, II [1,2]. Also, compound III is known as selective antagonist of vasopression receptors [3]. The benzimidazole IV is used as farmesyl transferase selective inhibitor. Compound V [4] possess an activation of the K+ chanels [5,6] Figure 1.

In continuation of our research works on the synthesis, reactivity and structures of benzimidazole derivatives [6-16] we report in this current work the alkylation reaction of 5-nitrobenzimidazol-2-one 1 with various alkylating agents under liquid-solid phase transfer catalysis conditions.
Results and discussion

The alkylation reaction of benzimidazole derivatives have been described by several works using various conditions. In our part we interested in the alkylation of 5-nitro-benzimidazol-2-one under liquid-solid phase transfer catalysis (PTC) conditions in the presence on an excess of the alkylation agent, potassium carbonate ($K_2CO_3$) and tetra n-butylammonium bromide (TBAB) as catalyst in N,N–dimethylformamide (DMF) for six hours at room temperature (Scheme 1).

Scheme 1: Alkylation reactions of 5-nitrobenzimidazol-2-one under (PTC) conditions.
It is worthy to note that when 2-picoly chloride was employed as an alkylating agent, 1,3-
 picoly-5-nitrobenzimidazol-2-one has been isolated after heating the reaction mixture at 70°C
 for 24 hours (Scheme 2).

Scheme 2: Synthesis of 5-nitro-1,3-dipicolylbenzimidazol-2-one in PTC condition at 70°C for
24 hours.

All the structures of benzimidazolic compounds 2a-f obtained have been elucidated on the
basis of spectral data (1H NMR, 13C NMR) and confirmed in case of 2e by a single crystal X-
ray diffraction study [16].

Figure 1: The molecular structure of compound 2e with 50% probability displacement
ellipsoids (molecule I, left; molecule II, right).

Experimental
The characterization of the prepared compound by NMR spectra was acquired on a Bruker
Avance DR-300 spectrometer using CDCl₃ as solvent. All the chemicals and reagents were of
analytical grade and used without further purification. Column chromatography and TLC
(thin-layer chromatography) were performed using silica gel and silica plates, respectively.
Chemical synthesis of 2a-e
To a solution of 5-nitro-1H-benzimidazol-2(3H)-one (0.2 g, 1.11 mmol), potassium carbonate (0.34 g, 2.45 mmol) and tetra-n-butylammonium bromide (0.03 g, 0.1 mmol) in DMF (20 mL) were added 2.45 mmol of the alkylating agent. The reaction mixture was stirred for 6 h at room temperature. After the completion of the reaction (as monitored by TLC), the inorganic material salt was filtered and the solvent was removed under reduced pressure. The obtained residue was purified by column chromatography on silica gel by using (ethyl acetate/hexane: 1/2) as eluent.

**Compound 2a:** Yield (%) = 84%, mp (°C) = 223, \(^1\)H NMR (CDCl\(_3\), 300 MHz) δ ppm: 8.01 (dd, 1H, H\(_{Ar}\), J\(_1\) = 8.7 Hz, J\(_2\) = 2.1 Hz); 7.81 (d, 1H, H\(_{Ar}\), J = 2.1 Hz); 7.41-7.33 (d, 1H, H\(_{Ar}\), J = 8.7 Hz); 5.19 (s, 2H, CH\(_2\)); 5.19 (s, 2H, CH\(_2\)). \(^1^3\)C NMR (CDCl\(_3\), 75 MHz) δ ppm: 154.78 (C=O); 142.72, 135.16, 135.12, 134.34, 129.24 (Cq); 129.12, 129.09, 129.02, 128.3, 128.29, 127.61, 127.50, 118.55, 107.54, 104.03 (CH\(_{Ar}\)); 45.47, 45.43 (C, CH\(_2\)).

**Compound 2b:** Yield (%) = 79%, mp (°C) = 223, \(^1\)H NMR (CDCl\(_3\), 300 MHz) δ ppm: 8.01 (dd, 1H, H\(_{Ar}\), J\(_1\) = 8.7 Hz, J\(_2\) = 2.1); 7.82-7.78 (m, 5H, H\(_{Ar}\)); 7.10-7.02 (m, 4H, H\(_{Ar}\)); 5.19 (s, 2H, CH\(_2\)); 3.80-3.75 (m, 4H, N-CH\(_2\)); 2.23-2.15 (m, 4H, CH\(_2\)). \(^1^3\)C NMR (CDCl\(_3\), 75 MHz) δ ppm: 168.22, 168.18 (2C=O); 154.16 (C=O); 142.55, 134.30 (Cq); 131.94, 131.90 (CH\(_{Ar}\)); 131.84, 131.80 (C, -CH=); 118.45, 118.41, 104.02 (C, CH\(_{Ar}\)); 39.51, 39.42, 35.48, 35.46 (N-CH\(_2\)); 27.13, 27.10 (CH\(_2\)).

**Compound 2c:** Yield (%) = 70, mp (°C) = 74, \(^1\)H NMR (CDCl\(_3\), 300 MHz) δ ppm: 8.10 (dd, 1H, H\(_{Ar}\), J\(_1\) = 8.7 Hz, J\(_2\) = 2.1 Hz); 7.98 (d, 1H, H\(_{Ar}\), J = 2.1 Hz); 7.14 (d, 1H, H\(_{Ar}\), J = 8.7); 6.77-6.67 (m, 2H, CH=); 6.35-6.26 (m, 2H, CH=); 4.80-4.78 (m, 4H, CH\(_2\)). \(^1^3\)C NMR (CDCl\(_3\), 75 MHz) δ ppm: 153.96 (C=O); 142.64, 134.39, 129.20 (Cq); 118.41, 118.45, 118.45 (CH\(_2\)); 43.87, 43.91 (N-CH\(_2\)).

**Compound 2d:** Yield (%) = 68, mp (°C) = 74, \(^1\)H NMR (CDCl\(_3\), 300 MHz) δ ppm: 8.06 (dd, 1H, H\(_{Ar}\), J\(_1\) = 8.68 Hz, J\(_2\) = 2.15 Hz); 7.87 (d, 1H, H\(_{Ar}\), J = 2.14 Hz); 7.04 (d, 1H, H\(_{Ar}\), J = 8.68 Hz); 5.86-5.96 (m, 2H, CH=); 5.20-5.32 (m, 4H, CH=); 4.56-4.59 (m, 4H, N-CH\(_2\)). \(^1^3\)C NMR (CDCl\(_3\), 75 MHz) δ ppm: 153.96 (C=O); 142.64, 134.39, 129.20 (Cq); 118.41, 107.45, 104.04 (C, CH\(_{Ar}\)); 130.94, 118.45, 118.54 (CH\(_2\)); 43.87, 43.91 (N-CH\(_2\)).

**Compound 2e:** Yield (%) = 82, mp (°C) = 144, \(^1\)H NMR (CDCl\(_3\), 300 MHz) δ ppm: 8.17 (dd, 1H, H arom, J\(_1\) = 8.64 Hz, J\(_2\) = 2.15 Hz); 7.98 (d, 1H, H arom, J = 2.07 Hz); 5.86-5.96 (m, 2H, CH=); 5.20-5.32 (m, 4H, CH=); 4.56-4.59 (m, 4H, N-CH\(_2\)). \(^1^3\)C NMR (CDCl\(_3\), 75 MHz) δ ppm: 152.72 (C=O); 143.16, 133.47, 128.47 (Cq); 75.77 (2Cq, -CH=); 118.94, 108.01, 104.53 (CH arom); 73.96, 74.07 (CH=); 31.05 (CH2).

Chemical synthesis of 2f
To a solution of 5-nitro-1H-benzimidazol-2(3H)-one (0.5 g, 2.79 mmol), potassium carbonate (0.61 g, 4.46 mmol) and tetra-n-butylammonium bromide (0.072 g, 0.2 mmol) in DMF (20 mL) was added (0.5 g, 3 mmol) of 2-picoly chloroform-hydrochloride. The mixture was heated for 24 h. After the completion of the reaction (as monitored by TLC), the inorganic material salt was filtered and the solvent was removed under reduced pressure. The obtained residue was purified by column chromatography on silica gel by using (ethyle acetate/hexane: 1/1) as eluent.

**Compound 2f:** Yield (%) = 76, mp (°C) = 175, \(^1\)H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ ppm: 8.47-8.50 (m, 2H, 2CH Pyr (=N-CH=)); 8.05-7.99 (m, 2H, CH\(_{Ar}\) + CH Pyr); 7.83-7.77 (m, 2H, CH...
Conclusion

In this work, we have synthesized a various highly substituted benzimidazol-2-ones 2a-f with potent biological and pharmacological properties. As synthetic route, we have used liquid-solid phase transfer catalysis (PTC) in two different reaction conditions. The structures of compounds obtained have been elucidated on the basis of spectral data ($^1$H NMR, $^{13}$C NMR) and confirmed by a single crystal X-ray diffraction study in the case of compound 2f.

References