DOI: http://dx.doi.org/10.32571/ijct.1130734 **E-ISSN: 2602-277X**

International Journal of Chemistry and Technology

http://dergipark.org.tr/ijct

Research Article

Copper catalyzed C–N bond formation and synthesis of imidazopyridinone derivatives

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Received: 14 June 2022; Revised: 21 June 2022; Accepted: 30 June 2022

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Citation: Doğan, Ş. D.; Ongun, M. *Int. J. Chem. Technol.* **2022**, 6 (1), 61-65.

ABSTRACT

The formation of the C–N bond is critical because it allows for the incorporation of nitrogen into organic molecules. Despite significant advances in this area, the formation of the C–N bond continues to be a challenge for organic chemists owing to the need of severe reaction conditions or costly catalysts in many cases. As a result, developing alternate, milder, and less expensive C–N bonding techniques is a challenge. Herein, a series of novel imidazopyridinone derivatives (**8a-8e**) were synthesized via copper-mediated C–N bond-forming reaction. This reaction takes place under mild conditions with high efficiency, step economy, and tolerance for a wide range of functional groups. All synthesized new compounds were analyzed by ^{1}H NMR, ^{13}C NMR and mass spectrometry.

Keywords: Synthesis, imidazopyridinones, Copper-catalyzed, C–N bond formation, urea.

Bakır katalizörlüğünde C–N bağı oluşumu ve imidazopiridinon türevlerinin sentezi

ÖZ

C–N bağının oluşumu, azot atomunun organik moleküllere katılmasında açısından oldukça önemlidir. C–N bağı oluşumu ile ilgili önemli gelişmeler kaydedilmesine rağmen zorlayıcı reaksiyon koşulları veya pahalı katalizörlere ihtiyaç duyulmasından dolayı organik kimyacılar için bu alan güncelliğini korumaktadır. Sonuç olarak alternatif olabilecek daha kolay ve daha ucuz yollu C–N bağı oluşturma tekniklerinin geliştirilmesi çalışmaları güncelliğini korumaktadır. Bu çalışmada imidazopiridinon türevleri (**8a-8e**) bakır katalizörlüğünde C–N bağı oluşturma reaksiyonu kullanılarak sentezlenmiştir. Bu C–N bağı oluşumu reaksiyonu oldukça kolay uygulanabilir koşullarda, yüksek verimlerle ve az basamaklı olarak farklı türevlerin sentezine uygulanabilmiştir. Sentezlenen yeni bileşiklerin yapı tayininde ^{1}H NMR, ^{13}C NMR ve kütle spektrumları kullanılmıştır.

Anahtar Kelimeler: Sentez, imidazopiridinon, bakır katalizörlüğü, C–N bağı oluşumu, üre.

1. INTRODUCTION

Imidazopyridinones (**1**) with a pyrido-fused cyclic urea framework are useful heterocyclic building blocks which are common structural element of compounds with a wide range of intriguing biochemical and pharmacological properties.[1,2] Imidazopyridinones and related cyclic urea derivatives were revealed to have antipyretic, antiulcer, antiviral, cytostatic, antimicrobial, cardiovascular properties, p38 MAPK and TNF-α inhibitory activities (Figure 1).[3,4]

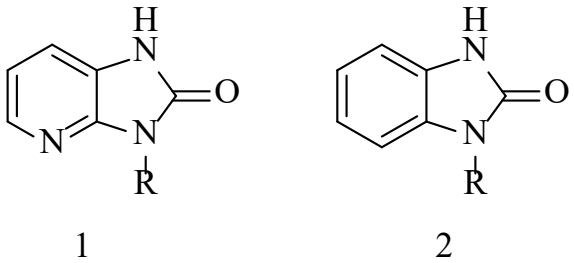

Figure 1. Important cyclic urea containing compounds

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As a consequence, the development of effective methods for the preparation of imidazopyridinones and formation of cyclic urea frame have received much attention. Due to the high demand, numerous synthetic routes to these interesting compounds have been developed, the most of which include 1,2-diaminopyridine as key intermediates.[5-7] Because their cyclization reactions have involved toxic chemicals such as phosgene, triphosgene and carbonyldiimidazole, limited availability of diversely substituted 1,2-diaminopyridine and harsh reaction condition, alternative protocols such as transition-metal-catalyzed intramolecular C−N bond formation have been developed.

Transition-metal-catalyzed C-N bond-forming reactions are of continuing interest. Several studies have revealed the generation of C-N bond formation by nitrogen nucleophilic displacement of aryl halogen catalyzed by transition metals.[8, 9] The transition-metal-catalyzed C−N cross-coupling methodologies for the synthesis of benzimidazole derivatives have also been reported.[8, 10] Liu and coworkers synthesized via a copper-catalyzed one-pot process N-substituted 1,3-dihydrobenzimidazol-2-ones (**2**) from N′-substituted N-(2-halophenyl)ureas under microwave heating.[11] But there are limited studies on its application to the synthesis of imidazopyridinones derivatives. Using the copper as a transition metal for the formation of C-N bond formation has received significant interest in the past two decades due to their effectiveness, low cost and more environmentally friendly compared to other metals.[12, 13]

In light of these considerations, we reported the protocol for the synthesis of imidazopyridinones, from *N*-(4-phenyl)-*N*'-(2-bromo-3-pyridinyl)-urea derivatives, via a copper (I)-catalyzed intramolecular cyclization process from N′-substituted N-(2-halopyridinyl)ureas using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as base in dimethyl sulfoxide (DMSO) under microwave heating.

2. MATERIALS AND METHODS

2.1. General procedure for the synthesis of urea derivatives 7a-7e

7a-7e were synthesized according to the reported literature procedure. Briefly, they are obtained by the reaction of refluxing the acyl azide **6** in dry benzene with corresponding amine to produce the urea derivatives. The resulting residue obtained upon the completion of the reaction was purified by crystallization from ethanol to afford the compounds **7a-7e**.[14, 15]

2.2. General procedure for the synthesis of imidazopyridinones derivatives (8a-8e)

A mixture of urea derivative **7a-7e** in 1 mL DMSO, CuI (0.2 equiv) and DBU (2 equiv) were taken in a glass vial and heated under microwave at a power of 60 W for 30 min (TLC). After completion of the reaction monitored by TLC, the reaction mixture was extracted with EtOAc (3x25 mL). The combined EtOAc layers were then dried over anhydrous $MgSO_4$ and removed under reduced pressure. The crude product was purified by column chromatography to afford pure compounds **8a-8e.**

2.2.1. 3-Phenyl- 1,3-dihydro- 2H-imidazo [4,5-b] pyridin-2-one (8a)

Brown solid, yield: 53%. mp 233-234 °C; R_f (50% Hexane/EtOAc):0.23; IR (ATR) 3662, 2987, 2900, 1686, 1594, 1393, 1229, 1065. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.41 (s, 1H, -NH), 7.92 (dd, J = 5.2, 1.5 Hz, 1H), 7.66 – 7.62 (m, 2H), 7.52 (t, J = 7.9 Hz, 2H), 7.43 – 7.37 (m, 2H), 7.09 (dd, J = 7.7, 5.1 Hz, 1H). ^{13}C NMR (100 MHz, DMSO) δ 153.06, 144.23, 140.28, 133.91, 129.25, 127.67, 126.65, 123.24, 118.52, 115.90. HRMS (EI): $[M+H]^+$, found 212.0835. $C_{12}H_{10}N_3O$ calculated 212.0824.

2.2.2. 3-(4-Methoxyphenyl)- 1,3-dihydro- 2H-imidazo[4,5-b] pyridin-2-one (8b)

White solid, yield: 50%. mp 252-254 °C; R_f (50% Hexane/EtOAc):0.14; IR (ATR) 3663, 2988, 2906, 1708, 1623, 1517, 1386, 1231, 1066. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.35 (s, 1H), 7.90 (d, J = 5.2 Hz, 1H), 7.49 (d, J = 8.6 Hz, 2H), 7.37 (d, J = 7.7 Hz, 1H), 7.17 – 6.97 (m,3H), 3.80 (s, 3H). ^{13}C NMR (100 MHz, DMSO) δ 158.69, 153.31, 144.55, 140.28, 128.26, 126.48, 123.15, 118.30, 115.77, 114.52, 55.84. HRMS (EI): $[M+H]^+$, found 242.0925. $C_{13}H_{12}N_3O_2$ calculated 242.0930

2.2.3. 3-(4-Chlorophenyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (8c)

White solid, yield: 67%. mp 225-226 °C; R_f (50% Hexane/EtOAc):0.28; IR (ATR) 3662, 2985, 2887, 1713, 1496, 1384, 1229, 1066, 891. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.46 (s, 1H, -NH), 7.94 (dd, J = 5.3, 1.5 Hz, 1H), 7.74 (dd, J = 9.1, 2.5 Hz, 2H), 7.64 – 7.55 (m, 2H), 7.41 (dd, J = 7.7, 1.4 Hz, 1H), 7.11 (dd, J = 7.7, 5.2 Hz, 1H). ^{13}C NMR (100 MHz, DMSO) δ 152.85, 143.90, 140.29, 132.89, 131.76, 129.23, 128.04, 123.30, 118.75, 116.09. HRMS (EI): $[M+H]^+$, found 246.0431. $C_{12}H_9ClN_3O$ calculated 246.0434.

2.2.4. 3-(4-Nitrophenyl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one (8d)

Yelow solid, yield: 31%. mp decomposition above 290°C; R_f (50% Hexane/EtOAc):0.26; IR (ATR) 366, 2987, 2875, 1729, 1592, 1504, 1383, 1348, 1229, 1066. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.44-11.03 (brs, 1H, -NH), 8.40 (d, J = 8.5 Hz, 2H), 8.16 (d, J = 8.8 Hz, 2H), 8.01 (d, J = 5.2 Hz, 1H), 7.46 (d, J = 7.7 Hz, 1H), 7.25 – 7.13 (m, 1H). ^{13}C NMR (100 MHz, DMSO) δ 152.54, 145.45, 143.38, 140.36, 140.18, 125.90, 124.67, 123.57,

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119.42, 116.55. HRMS (EI): $[M+H]^+$, found 257.0662. $C_{12}H_9N_4O3$ calculated 257.0675.

2.2.5. 3-(2-Aminophenyl)-1,3- dihydro- 2H-imidazo [4,5-b]pyridin-2-one (8e)

Brown solid, yield: 33%. mp 248-250°C; R_f (50% Hexane/EtOAc):0.34; IR (ATR). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.20 (s, 1H, -NH), 7.82 (d, J = 5.2 Hz, 1H), 7.32 (dd, J = 7.7, 1.6 Hz, 1H), 7.19 – 7.10 (m, 1H), 7.01 (dd, J = 7.6, 5.3 Hz, 2H), 6.84 – 6.78 (m, 1H), 6.66 – 6.54 (m, 1H), 5.03 (s, 2H). ^{13}C NMR (100 MHz, DMSO) δ 153.33, 146.47, 145.11, 139.98, 130.31, 129.76, 123.94, 120.89, 117.81, 116.28, 115.26, 108.95. HRMS (EI): $[M+H]^+$, found 227.0933. $C_{12}H_{11}N_4O$ calculated 227.0923.

3. RESULTS AND DISCUSSION

In order to apply the C-N bond formation procedure and synthesis of imidazopyridinones derivatives, corresponding N-(4-phenyl)-N'-(2-bromo-3-pyridinyl)-urea derivatives (**7a-7e**) were synthesized as a starting compounds (Figure 2). The starting scaffold N-(4-phenyl)-N'-(2-bromo-3-pyridinyl)-urea derivatives (**7**) was obtained in accordance with previously published protocols. The bromination reaction of **3** was performed in hydrobromic acid at °0 C, gave the bromination product **4**. [16] The oxidation of bromination product **4** to 2-bromonicotinic acid (**5**) was carried out in water using $KMnO_4$.[17] Urea derivatives **(7a-7e)** were achieved from corresponding acyl azides **6** which were obtained by the treatment of 2-bromonicotinic acid (**5**) with ethyl chloroformate in the presence of Et_3N followed by the addition of NaN_3 aqueous solution. Refluxing the acyl azide in dry aprotic solvent (benzene) initiated rearrangement (Curtius rearrangement) to the corresponding isocyanate which was then reacted with corresponding amine to produce the urea derivatives.[14] In order to reveal the effects of electron donating and electron withdrawing substituents in the C-N bond formation procedure, five different urea derivatives (**7a-7e**) were synthesized.

For the synthesis of imidazopyridinones derivatives via C-N bond formation, we adapted the procedure applied to the synthesis of dihydrobenzimidazol-2-one derivatives known in the literature to our own system [11]. The target compounds, imidazopyridinones derivatives **8a-8e**, were synthesized via C-N bond formation using copper iodide as catalyst and DBU as a base. Treatment of **7** with CuI in DMSO in the presence of DBU afforded the desired cyclized compound **8a-8e** (Figure 3) via intramolecular C-N bond formation reaction but in a modest yield (31-67%). In all cases, the final products were purified by silica gel chromatography.

Postulated structures of the newly synthesized imidazopyridinones derivatives (**8a-8e**) were in full agreement with their spectral data. Although ^{1}H NMR spectra of pyridine derivatives (**7a-7e**) revealed the presence of two D_2O exchangeable singlet signals attributable to the -NH groups of the urea group in the regions δ 10.30 – 8.39 and 8.54 – 8.29 ppm, imidazopyridinones derivatives (**8a-8e**) showed only one D_2O exchangeable singlet signals attributable to the -NH groups of the cyclic urea group in the regions δ 12.44 – 11.03 ppm. On the other hand, ^{13}C-NMR spectra of compounds **8a-8e** confirmed with presence of C=O peak of cyclic urea motif at 158.69 – 152.54 ppm. The experimental and supplementary information sections require a detailed procedures and spectral data for the target compounds.

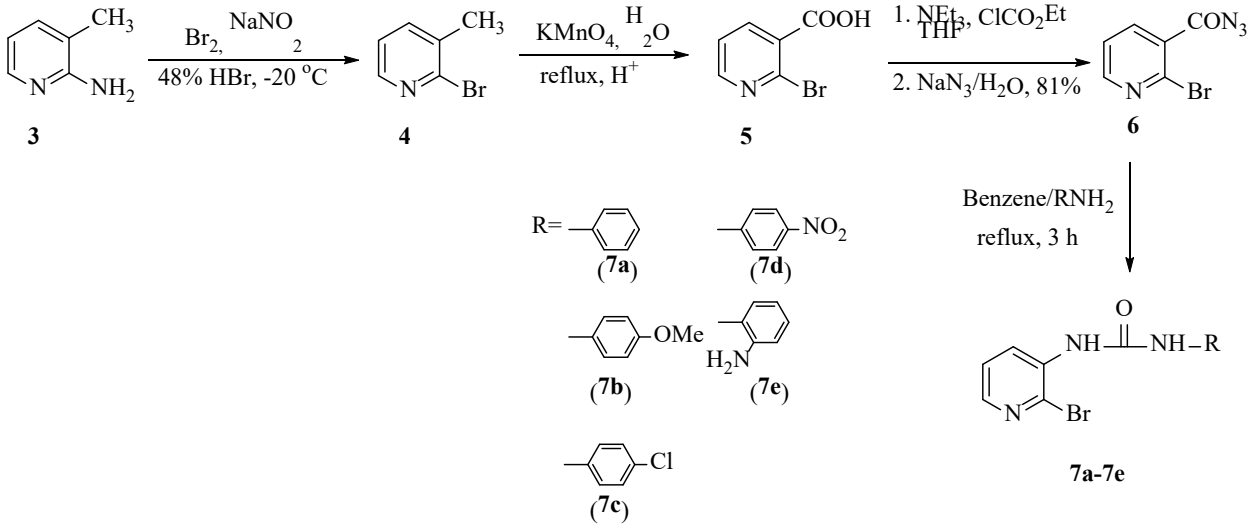

Figure 2. Synthesis of starting compound **7a-7e**

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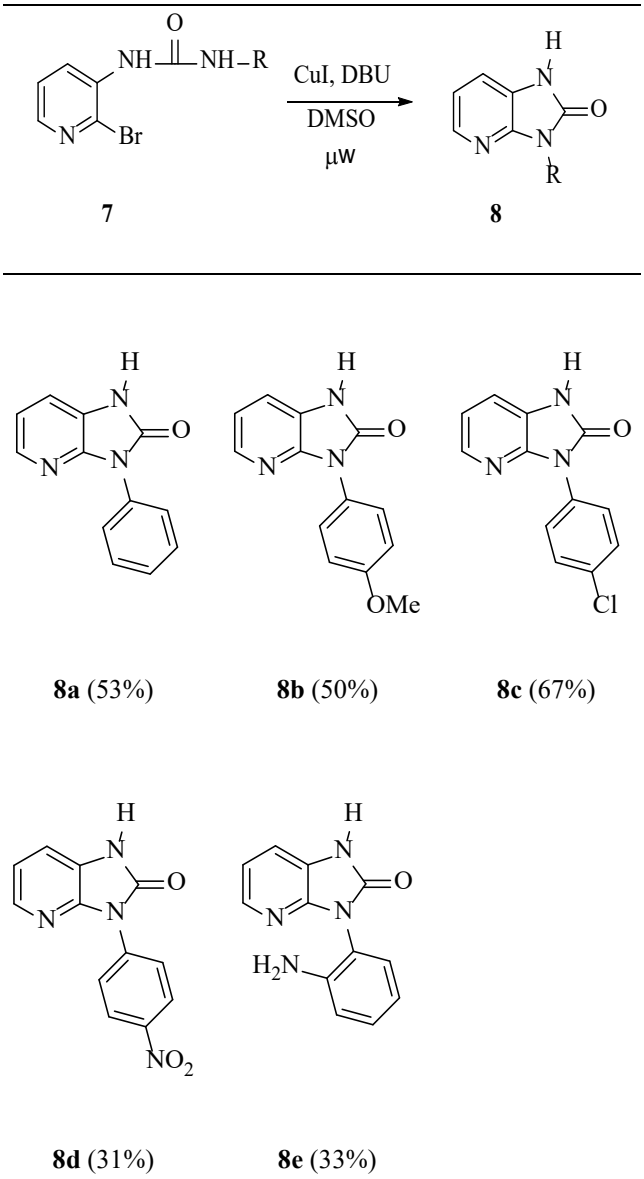

Figure 3. Synthesis of imidazopyridinones derivatives **8a-8e**

4. CONCLUSIONS

In this paper, a new series of imidazopyridinone compounds has been successfully designed and synthesized (**8a-8e**) via Cu(I)-mediated/MW-assisted C-N bond formation of N-(4-phenyl)-N'-(2-bromo-3-pyridinyl)-urea derivatives **7a-7e**. This synthetic strategy allows the synthesis of libraries rich in biological active compounds.

ACKNOWLEDGEMENTS

The author is indebted to the Faculty of Pharmacy at Erciyes University for the use of faculty facilities. This study was published as Melike Ongun's graduation project thesis (2018).

Conflict of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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