Heterocyclic Letters
Vol. 10|No.3|383-388|May-July|2020
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

PREPARATION ANDQUANTITATIVE STRUCTURE-ACTIVITY RELATIONSHIPS PROPERTIES OF PRECURSORS FOR THE SYNTHESIS OF IMIDAZOLIUM SALTS USED AS LIGANDS FOR THE ENANTIOSELECTIVE SYNTHESIS OF HETEROSTEROIDS COMPOUNDS

MessaoudGuerri[a,b], Oumelkheir Rahim[b*] and SoulefBenabdesselam[c]

[a]Laboratoire de Synthèse Totale et de Réactivité Organique. Université Aix-Marseille III, Stéréo UMR 6263, France.
[b] Department of Chemistry,Faculty of mathematics and Matter sciences, Pollution & Waste Treatment Laboratory, Kasdi Merbah University, Ouargla, Algeria.*
[c] Department of Process Engineering ,Faculty of applied sciences, Laboratory of Engineering of Water and Environment in Saharan Environment, Kasdi Merbah University, Ouargla, Algeria*
E-mail: romolkheir1@gmail.com

ABSTRACT
1-phenyl-1H-imidazole **(3)** and 2-(1H-imidazol-1-yl)pyridine**(5),**have respectively beenprepared by the reaction of 1-bromobenzene (**1)** and 2-bromopyridine **(4)** with imidazole (**2)** in DMF. While, 1-mesityl-1H-imidazole (**7)** and2-(1H-imidazol-1-yl) pyrimidine (**9)** have been respectively prepared by the reaction of 2-iodo mesitylene **6** and2-chloropyrimidine (**8)** with imidazole (**2)** in DMF. The purity of these compounds was confirmed by spectroscopic data. The NMR spectra showed all the signals and the structures were confirmed by HRMS. Quantitative structure-activity relationships properties of the fourth compounds;octanol/water partition coefficient, hydration energy, molar polarisability, molar refractivity, molar volume, molar weight and surface grid calculated.

KEYWORDS:*I*midazolium salts;***S***ynthesis;*L*igands;*E*nantioselective;*H*eterosteroids;*Q*SAR

INTRODUCTION
N-Arylimidazoles compounds have received great attention in a variety of fields throughout the chemical, pharmaceutical, and material sciences [i-vi]. Traditionally, these N-arylazoles have been synthesized via S_NAr (nucleophilic aromatic substitution) of N-containing heterocycles with electron-deficient aryl halides [vii-x] or via the classical Ulmann-type coupling with aryl halides [xi-xiii].These well-known reactions, however, generally suffer from several limitations : (i) high reaction temperatures (Often 120 °C), (ii) the use of stoichiometric amounts of sopper reagents, (iii) moderate yields, and (iv) poor substrate generality.

Despite significant progress in the Cu-catalyzed N-arylation of nitrogen heterocycles with aryl halides, only a few reports have appeared describing the couplings of imidazoles with aryl brimides or of functional substrates or of hindered substrates [xiv-xxxvii]. After optimizing of the conditions, we explored the scope of the coupling reactions of aryl and heteroaryl halides with imidazole in the presence of 20 % of CuI and 2 equiv of Cs_2CO_3 in DMF at 120 °C under Argon, and the results are summarized in the Scheme 1.

EXPERIMENTAL

Synthesis

Preparation of 1-phenyl-1H-imidazole (3)

To a flame-dried Schlenk test tube with a magnetic stirring bar was charged with CuI (0.76 g, 4.0 mmol, 0.2 equiv), Cs_2CO_3 (13.00 g, 40.0 mmol, 2.0 equiv), Imidazole (1.90 g, 28.0 mmol, 1.4 equiv), 1-bromobenzene (2.10 g, 20.0 mmol, 1.0 equiv) and DMF (40 mL) under argon. A rubber septum was replaced with a glass stopper, and the system was then evacuated twice and back filled with argon. The reaction mixture was stirred for 30 min at room temperature, and then heated at 120 ℃ for 24 hours. The reaction mixture was then cooled to ambient temperature, diluted with (20 mL) of ethyl acetate, filtred throught a plug of silica gel, and washed with ethyl acetate(100 mL). The combined organic extracts were concentrated and the resulting residue was purified by column chromatography on silica gel (Petroleum ether/EtOAc = 20:80)to yield 1-phenyl-1H-imidazole as a yellow oil (2.30 g, 80 % yield).

^{1}H NMR (300 MHz, $CDCl_3$): δ=7.20 (s, 1H), 7.23-7.30 (m, 1H), 7.31-7.42 (m, 3H), 7.43-7.55 (m, 2H), 7.84 (s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=118.1, 121.4, 127.3, 129.8, 130.3, 135.5, 137.3 ppm.

HRMS (ESI) Calcd for $C_9H_8N_2$ $[M+H]^+$: 145.0760. Found : 145.0760.

Preparation of 2-(1H-imidazol-1-yl) pyridine(5)

To a flame-dried Schlenk test tube with a magnetic stirring bar was charged with CuI (0.76 g, 4.0 mmol, 0.2 equiv), Cs_2CO_3 (13.00 g, 40.0 mmol, 2.0 equiv), Imidazole (1.90 g, 28.0 mmol, 1.4 equiv), 2-bromopyridine (1.9 mL, 20.0 mmol, 1.0 equiv) and DMF (40 mL) under argon. A rubber septum was replaced with a glass stopper, and the system was then evacuated twice and back filled with argon. The reaction mixture was stirred for 30 min at room temperature, and then heated at 120 ℃ for 40 hours. The reaction mixture was then cooled to ambient temperature, diluted with 20 mL of ethyl acetate, filtred throught a plug of silica gel, and washed with 100 mL of ethyl acetate. The combined organic extracts were concentrated and the resulting residue was purified by column chromatography on silica gel (Petroleum ether/EtOAc = 2:8)to yield 2-(1H-imidazol-1-yl)pyridine as a clear yellow solid (1.98 g, 68 % yield) m.p : 36 – 38 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ=7.14 (bs,1H), 7.17 (ddd, ^3J = 7.5 Hz, ^3J = 4.9 Hz, ^4J = 0.9 Hz, 1H), 7.29 (dt, ^3J = 8.2 Hz, ^4J = 0.9 Hz, 1H), 7.59 (bs, 1H), 7.75 (ddd, ^3J = 8.2 Hz, ^3J = 7.5 Hz, ^4J = 1.9 Hz, 1H), 8.29 (bs, 1H), 8.41 (ddd, ^3J = 4.9 Hz, ^4J = 1.8 Hz, ^5J = 0.8 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=112.3, 116.1, 121.5, 122.0, 130.6, 135.0, 139.0, 149.1 ppm.

Preparation of 1-mesityl-1H-imidazole (7)

To a flame-dried Schlenk test tube with a magnetic stirring bar was chareged with CuI (0.38 g, 2.0 mmol, 0.1 equiv), Cs_2CO_3 (13.70 g, 42.0 mmol, 2.1 equiv), Imidazole (1.63 g, 24.0 mmol, 1.2 equiv), 2-iodo mesitylene (4.92 g, 20.0 mmol, 1.0 equiv), *N,N'*-dimethylethylenediamine (0.9 mL, 8.0 mmol, 0.4 equiv) and DMF (20 mL) under argon. A rubber septum was replaced with a glass stopper, and the system was then evacuated twice and back filled with argon. The reaction mixture was stirred for 30 min at room temperature, and then heated at 170 °C for 48 hours. The reaction mixture was then cooled to ambient

temperature, diluted with 20 mL of ethyl acetate, filtred throught a plug of silica gel, and washed with 100 mL of ethyl acetate. The combined organic extracts were concentrared and the resulting residue was purified by column chromatography on silica gel (Petroleum ether/EtoAc = 2:8)to yield 1-mesityl-1H-imidazole as a clear yellow solid (1.2 g, 33 % yield) m.p : 115 – 116 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ=1.97 (s, 6H), 2.32 (s, 3H), 6.87 (s, 1H), 6.95 (s, 2H), 7.21 (s, 1H), 7.42 (s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=17.2, 20.9, 120.0, 128.9, 129.4, 133.3, 135.3, 137.4, 138.7 ppm.

HRMS (ESI) Calcd for $C_{12}H_{14}N_2$ $[M+H]^+$: 187.1230. Found : 187.1234.

Preparation of 2-(1H-imidazol-1-yl) pyrimidine (9)

To a flame-dried Schlenk test tube with a magnetic stirring bar was charged with CuI (0.76 g, 4.0 mmol, 0.2 equiv), Cs_2CO_3 (13.00 g, 40.0 mmol, 2.0 equiv), imidazole (1.90 g, 28.0 mmol, 1.4 equiv), 2-chloropyrimidine (2.28 g, 20.0 mmol, 1.0 equiv) and DMF (40 mL) under argon. A rubber septum was replaced with a glass stopper, and the system was then evacuated twice and back filled with argon. The reaction mixture was stirred for 30 min at room temperature, and then heated at 120 °C for 40 hours. The reaction mixture was then cooled to ambient temperature, diluted with (20 mL) of ethyl acetate, filtred throught a plug of silica gel, and washed with ethyl acetate (100 mL). The combined organic extracts were concentrated and the resulting residue was purified by column chromatography on silica gel (Petroleum ether/EtOAc = 20:80)to yield 2-(1H-imidazol-1-yl)pyrimidine as a white solid (2.29 g, 78 % yield) m.p : 128-129 °C .

^{1}H NMR (300 MHz, $CDCl_3$): δ=7.12 (s,1H), 7.16 (t, ^{3}J = 4.9 Hz, 1H), 7.85 (t, ^{4}J = 1.3 Hz, 1H), 8.58 (s, 1H), 8.65 (d, ^{3}J = 4.9 Hz, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=116.4, 118.8, 130.6, 136.0, 158.6 ppm.

Ms (ESI) for $C_7H_6N_4$ $[M+Na]^+$: 168.7.

HRMS (ESI) Calcd for $C_7H_6N_4$ $[M+H]^+$: 147.0665. Found : 147.0666.

Anal. Calcd for $C_7H_6N_4$ (146.15) : C, 57.53; H, 4.4; N, 38.34 %.

Found : C, 57.61; H, 4.12; N, 38.09 %.

QSAR's properties study

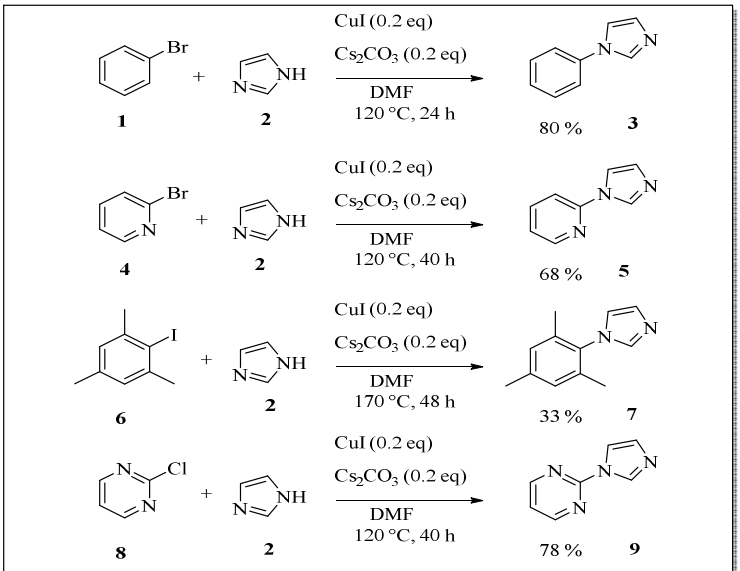
The four prepared molecules have been pre-optimized using the Molecular Mechanics (MM^+) force field included in HyperChem version 8.0.3.

HyperChem's QSAR property module was used to calculate: molar weight (MW),molarpolarisability (Pol), molar refractivity (MR), octanol/water partition coefficient (logP), hydration energy (HE), molar volume (MV), surface grid (SAG) and Surface Area Approx (SAA).

RESULTS AND DISCUSSION

Synthesis

We were delighted to find that the catalytic system was able to tolerate a broad range of aryl bromides such as 1-bromobenzene (**1)** and 2-bromopyridine (**4)** to afford respectively the corresponding N-arylimidazoles such as 1-phenyl-1H-imidazole (**3)** and 2-(1H-imidazol-1-yl)pyridine (**5)**. In addition, Ullmann-type condensations are generally sensitive to steric hindrance near the halogen atom, and there are rare examples descibing the Cu-catalyzed couplings of imidazoles with sterically hindered aryl halides. Our catalytic system could be applied to N-arylation of imidazole with ortho, metha and para subsutituted aryl iodide such as 2-iodo mesitylene (**6)** to afford 1-mesityl-1H-imidazole (**7**). Preliminary results suggest that the current system could be applicable to aryl chlorides such as 2-chloropyrimidine (**8)** to yeild 2-(1H-imidazol-1-yl)pyrimidine (**9)**. Scheme 1 presents the catalytic N-arylation of imidazole with aryl and heteroaryl halides



Scheme 1: Catalytic N-arylation of imidazole with aryl and Heteroaryl halides

Relationship structure-activity (SAR)

We studied 8 physico-chemical properties of series of 4 imidazole derivatives (3, 5, 7 and 9), using HyperChem software. QSAR properties such as van der Waals surface, molecular volume (MV), Surface Area Grid (SAG) and Surface Area Approx (SAA), octanol-water partition coefficient (log P), molar refractivity (MR), polarisability (Pol), molecular volume and molecular weight (MW) accessible to solvents and bound to the surface were studied and are gathered in the table 1.

Table 1. QSAR Properties

Compounds	(MW) amu	(Pol) Cm^3	(MR) Cm^3	(log P)	(HE) kcal/mol	(MV) Cm^3	(SAG) Cm^2	(SAA) Cm^2
3	**144.176**	**17.258**	**49.598**	**-5.231**	**-5.231**	**476.417**	**316.670**	**250.423**
5	**145.164**	**16.549**	**45.468**	**-0.039**	**-6.003**	**465.197**	**316.537**	**237.158**
7	**186.257**	**22.763**	**62.444**	**0.202**	**-1.914**	**615.663**	**382.014**	**334.140**
9	**146.151**	**15.840**	**42.581**	**-0.475**	**-6.853**	**455.423**	**313.700**	**224.068**

CONCLUSION

In conclusion, we have developed relatively mild and highly efficient CuI-catalized N-arylation procedures for nitrogen containing heterocycles with aryl and heteroaryl halides. The system is effective for aryl bromides and aryl chlorides, but to a less extent, for aryl iodides. In addition, the procedures could be performed easily. This work should find wide application for synthesis of imidazolium salts used as ligands for the enantioselective synthesis of Heterosteroids compounds.

REFERENCES

[i]. Craig, P. N; In *Comprehensive Medicinal Chemistry*; Drayton, C. J., Ed.; Pergamon Press: New York, 1991; **Vol. 8**.

[ii]. Cozzi, P.; Carganico, G.; Fusar, D.; Grossoni, M.; Menichincheri, M.; Pinciroli, V.; Tonani, R.; Vaghi, F.; Salvati, P. *J. Med. Chem.* **1993**, *36*, 2964.

[iii]. Negwer, M. In *Organic-Chemical Drugs and their Synonyms: An InternationalSurVey*, 7th ed.; AkademieVerlag GmbH: Berlin, Germany, 1994.

[iv]. Kundu, N. G.; Mahanty, J. S.; Chowdhurry, C.; Dasgupta, S. K.; Das, B.; Spears, C. P.; Balzarini, J.; De Clercq, E. *Eur. J. Med. Chem.* **1999**, *34*, 389.
[v]. Kunz, K.; Scholtz, U.; Ganzer, D. *Synlett***2003**, *15*, 2428.
[vi]. Herrmann, W. A. *Angew. Chem., Int. Ed*. **2002**, *41*, 1290.
[vii]. Bambal, R.; Haznlik, R. P. *J. Org. Chem.* **1994**, *59*, 729.
[viii]. Venuti, M. C.; Stephenson, R. A.; Alvarez, R.; Bruno, J. J.; Strosberg, A. M.*J. Med.Chem.* **1988**, *31*, 2136.
[ix]. Qiao, J. X.; Cheng, X.; Modi, D. P.; Rossi, K. A.; Luettgen, J. M.; Knabb, R. M.;Jadhav, P. K.; Wexler, R. R. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 29.
[x]. Gu¨ngo¨r, T.; Fouquet, A.; Teulon, J.-M.; Provost, D.; Cazes, M.; Cloarec, A. *J. Med. Chem*. **1992**, *35*, 4455.
[xi]. Jacobs, C.; Frotscher, M.; Dannhardt, G.; Hartmann, R. W. *J. Med. Chem.* **2000**, *43*, 1841.
[xii]. Fan, J.; Sun, W.; Okamura, T.; Tang, W.;Ueyama, N. *Inorg. Chem.* **2003**, *42*, 3168.
[xiii]. Martinez, G. R.; Walker, K.A. M.; Hirschfeld, D. R.; Bruno, J. J.; Yang, D. S.; Maloney, P. J. *J. Med. Chem.* **1992**, *35*, 620.
[xiv]. Cristau, H. J.; Cellier, P. P.; Spindler, J. F.; Taillefer, M. *Eur. J. Org. Chem.* **2004**,695.
[xv] Taillefer, M.; Cristau, H. J.; Cellier, P. P.;Spindler, J. F. FR 0116547, 2001.
[xvi]. Cristau, H. J.; Cellier, P. P.; Spindler,J. F.; Taillefer, M. *Chem.*s*Eur. J.* **2004**, *10*, 5607.
[xvii]. Ma, D.; Cai, Q. *Synlett***2004**, 128.
[xviii]. Zhang, H.; Cai, Q.; Ma, D. *J. Org. Chem.* **2005**, *70*, 5164.
[xix]. Lv, X.; Wang, Z.; Bao, W. *Tetrahedron***2006**, *62*, 4756.
[xx]. Alcalde, E.; Dinare`s, I.; Rodrı´guez, S.; de Miguel, C. G. *Eur. J. Org. Chem.* **2005**,1637.
[xxi]. Kuil, M.; Bekedam, E. K.; Visser, G. M.; van den Hoogenband, A.; Terpstra, J. W.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; van Strijdonck, G. P. F. *Tetrahedron Lett.* **2005**, *46*, 2405.
[xxii]. Jerphagnon, T.; van Klink, G. P. M.; de Vries, J. G.; van Koten, G. *Org. Lett.* **2005**, *7*,5241.
[xxiii]. Xu, L.; Zhu, D.; Wu, F.; Wang, R.; Wan, B. *Tetrahedron* **2005**, *61*, 6553.
[xxiv]. Rao, H.; Jin, Y.; Fu, H.; Jiang, Y.; Zhao, Y. *Chem.*s*Eur. J.* **2006**, *12*, 3636.
[xxv]. Zhang, Z.; Mao, J.; Zhu, D.; Wu, F.; Chen, H.; Wan, B. *Tetrahedron* **2006**, *62*, 4435.
[xxvi]. Xie, Y.; Pi, S.; Wang, J.; Yin, D.; Li, J. *J. Org. Chem.* **2006**, *71*, 8324.
[xxvii]. Liu, L.; Frohn, M.; Xi, N.; Dominguez, C.; Hungate, R.; Reider, P. J. *J. Org. Chem.***2005**, *70*, 10135.
[xxviii]. Guo, X.; Rao, H.; Fu, H.; Jiang, Y.; Zhao, Y. *Ad*V.*Synth. Catal.***2006**, *348*, 2197.
[xxix]. Lv, X.; Bao, W. L. *J. Org. Chem.* **2007**, *72*, 3863.
[xxx]. Altman, R. A.; Buchwald, S. L. *Org. Lett.* **2006**, *8*, 2779.
[xxxi]. Chang, J. W. W.; Xu, X.; Chan, P. W. H. *Tetrahedron Lett.* **2007**, *48*, 245.
[xxxii]. Vargas, V. C.; Rubio, R. J.; Hollis, T. K.; Salcido, M. E. *Org. Lett.***2003**, *5*, 4847.
[xxxiii]. Wu, Q.; Hook, A.; Wang, S. *Angew. Chem., Int. Ed.***2000**, *39*, 3933.
[xxxiv]. Choudary, B. M.; Sridhar, C.; Kantam, M. L.; Venkanna, G. T.; Sreedhar, B. *J. Am. Chem. Soc.* **2005**, *127*, 9948.

[xxxv]. Taillefer, M.; Xia, N.; Ouali, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 934.
[xxxvi]. Altman, R. A.; Koval, E. D.; Buchwald, S. L. *J. Org. Chem.* **2007**, *72*, 6190.
[xxxvii]. Zhu, L.; Cheng, L.; Zhang, Y.; Xie, R.; You, J. *J. Org. Chem.* **2007**, *72*, 2737.

Received on May 29, 2020