Chemical Papers
https://doi.org/10.1007/s11696-021-01785-7

ORIGINAL PAPER

Nitroarenes as versatile building blocks for the synthesis of unsymmetrical urea derivatives and N-Arylmethyl-2-substituted benzimidazoles

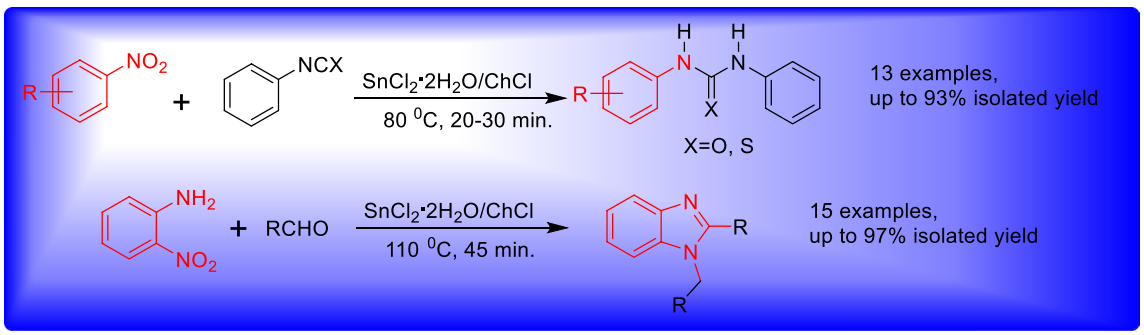
Paula A. Rodríguez-Huerto[1] · Diana Peña-Solórzano[1] · Cristian Ochoa-Puentes[1]

Received: 29 March 2021 / Accepted: 6 July 2021

Abstract

In this contribution, a fast and simple method for the synthesis of unsymmetrical urea derivatives and N-arylmethyl-2-substituted benzimidazoles was developed starting from nitroarenes. The reaction of nitroarenes and phenyl isocyanate or phenyl isothiocyanate in tin (II) chloride dihydrate/choline chloride eutectic mixture afforded the expected urea and thiourea derivatives, while the reaction of different aldehydes with o-nitroaniline or 4-methoxy-2-nitroaniline shows a markedly high preference for the obtention of N-arylmethyl-2-substituted benzimidazoles over the 2-substituted analogues. This method offers a straightforward alternative to obtain the target compounds in good to excellent yields with short reaction times employing an operationally simple experimental set-up.

Graphic abstract



A series of unsymmetrical urea and thiourea derivatives together with 1,2-disubstituted benzimidazoles are easily obtained in good yields starting from nitroarenes employing the eutectic mixture tin (II) chloride dihydrate/choline chloride as reductive reaction media.

Keywords Benzimidazoles · Deep eutectic solvents · Nitroarenes · Redox solvent · Urea derivatives

Introduction

Urea derivatives are widely found in diverse synthetic molecules and natural products. Several bioactive compounds and marketed drugs have the urea functionality in the structure which, in many cases is responsible for the marked biological activity due to the capability of this subunit to form stable multiple hydrogen bonds with receptors such as proteins. The enhanced affinity of the urea fragment with different

✉ Cristian Ochoa-Puentes
cochoapu@unal.edu.co

[1] Laboratorio de Síntesis Orgánica Sostenible, Departamento de Química, Universidad Nacional de Colombia–Sede Bogotá, Carrera 45 # 26–85, A.A. 5997, Bogotá, Colombia

Published online: 21 July 2021

receptors is fundamental for drug development, and considering this, compounds with antiviral, anti-inflammatory, antimicrobial, anticonvulsant, anti-ulcerogenic and antitrypanosomal activities together with derivatives with potential use in the treatment of pain and nervous system disorders have been reported (Jagtap et al. 2017; Patil et al. 2019). In addition, drugs for the treatment of different types of cancer, HIV, Parkinson's disease, schizophrenia and bipolar disorders, migraine, allergic and inflammatory states have been developed and approved by the FDA (Fig. 1) (Ghosh and Brindisi 2020).

Urea derivatives also play a fundamental role in the construction of several urea-based receptors used for the molecular recognition of anions, (Amendola et al. 2010) and as versatile organocatalysts, (Zhang and Schreiner 2009; Atashkar et al. 2018) where the use of chiral ureas have been the platform to develop the asymmetric synthesis (Connon 2006; Limnios and Kokotos 2016).

Considering the importance of this scaffold in different areas, several approaches for the obtention of unsymmetrical ureas have been developed including the direct carbonylation of primary amines using carbon monoxide, (McCusker et al. 2000; Zhao et al. 2016) addition of amines to carbonyldiimidazole, (Padiya et al. 2012) transition-metal-catalyzed reactions, (Kim and Hong 2016; Vinogradova et al. 2012; Guan et al. 2012) direct conversion of ketones to urea, (Sribalan et al. 2017) rearrangement of N-fluoro-N-(phenylsulfonyl) benzamides, (Zhao et al. 2020) among others. However, conventional methods such as the reaction of amines with commercially available or generated in situ isocyanates remains as one of the most simple and accessible method for the obtention of the desired molecules (Singh et al. 2019; Kulkarni et al. 2017).

1,2-Disubstituted benzimidazoles are of immense importance in medicinal chemistry due to their diverse range of biological and pharmacological properties (Keri et al. 2015; Wang et al. 2015). Recognized marketed drugs such as astemizole, tecastemizole, mizolastine (antihistamine drugs) and candesartan, telmisartan (antihypertensives drugs) possess in their structure this heterocyclic skeleton (Fig. 2) (Bansal and Silakari 2012).

Classical methods for the obtention of 1,2-disubstituted benzimidazoles involve the N-alkylation of 2-substituted benzimidazoles; (Hérault et al. 2007; Chakraborty et al. 2018) and the condensation of *o*-phenylenediamine with aldehydes employing different catalysts.

Although 2-substituted and 1,2-disubstituted benzimidazole derivatives can be obtained in this reaction, good selectivity towards the 1,2-disubstituted analogue is usually reported modulating the reaction conditions (Bahrami et al. 2010; Majumdar et al. 2015; Jin et al. 2014; Kokare et al. 2007; Herrera Cano et al. 2016). Other modern and alternative methods include the dehydrogenative coupling of *ortho*-phenylenediamine and benzylic alcohols, (Das et al. 2018) di N-alkylation oxidation-cyclization sequence, (Sharma et al. 2019) reaction of mono-N-alkyl-ortho-phenylenediamines and carboxylic acids or aldehydes, (Blatch et al. 2006) metal-catalyzed intramolecular amination/cyclization of amidines, (Carvalho et al. 2011) intramolecular C(sp3) – H imination (Bose et al. 2019), iron-catalyzed oxidative

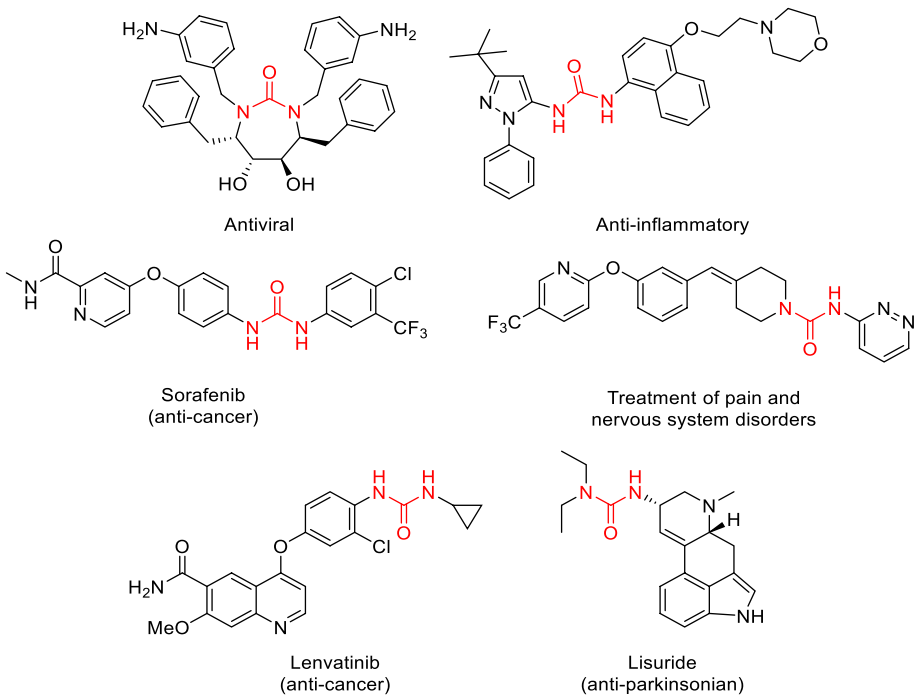


Fig. 1 Biologically active unsymmetrical urea derivatives

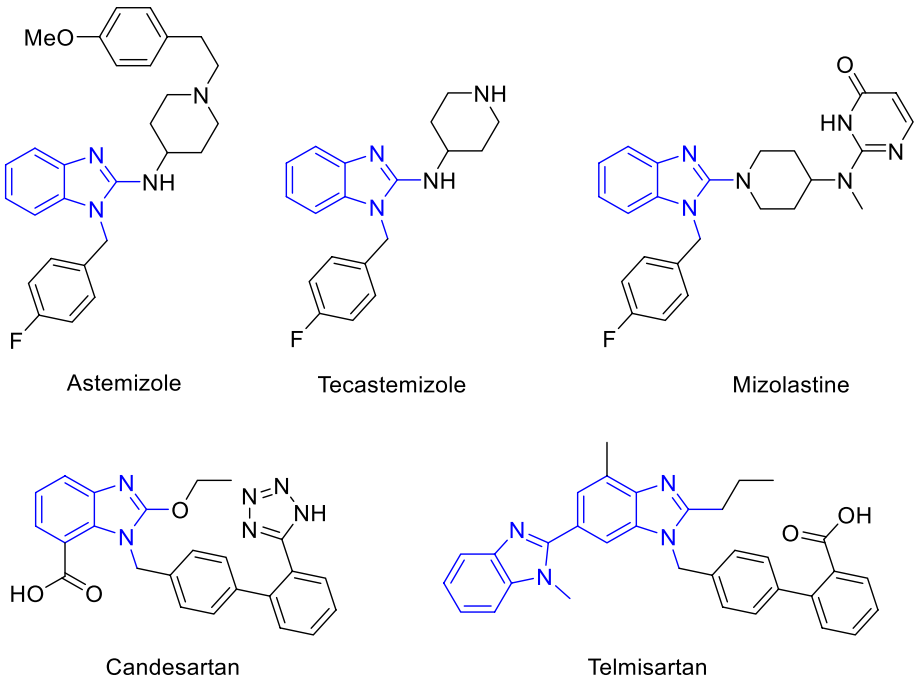
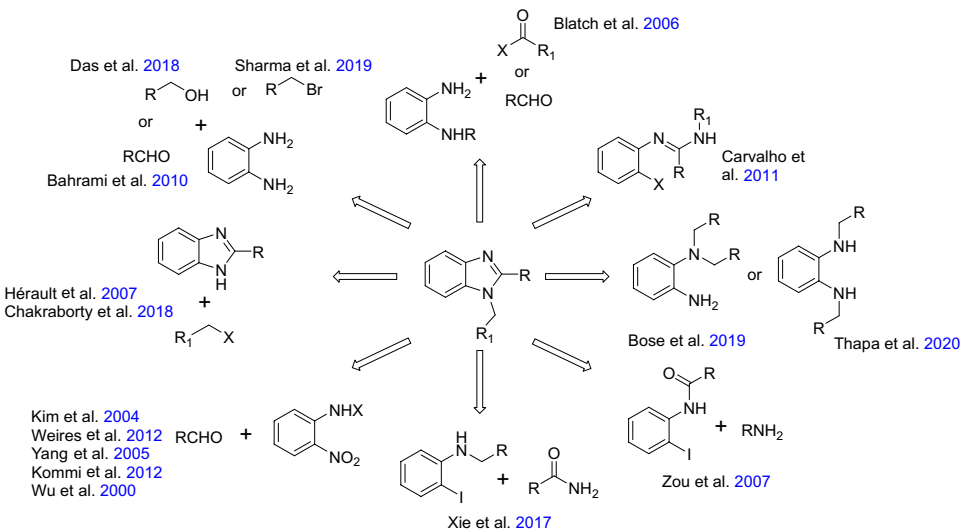


Fig. 2 Structure of marketed drugs containing the 1,2-disubstituted benzimidazole core

coupling of di-substituted ortho-phenylenediamines, (Thapa et al. 2020) cascade arylamination/condensation of *o*-bromo- or *o*-chloro-acetanilides, (Zou et al. 2007) N-arylation/condensation of benzamides (Xie et al. 2017) and the reductive intermolecular coupling/heterocyclization between 2-nitroaniline derivatives and aromatic aldehydes (Kim et al. 2002; Kim et al. 2004; Weires et al. 2012; Yang et al. 2005; Kommi et al. 2012; Wu et al. 2000) (Scheme 1).

Deep eutectic solvents have emerged as a new platform to perform several organic transformations in which the eutectic mixture can play a role as catalyst, solvent and starting material (Shahabi and Tavakol 2018; Abtahi and Tavakol 2020; Keshavarzipour and Tavakol 2016; Shahabi and Tavakol 2017). The low cost of the reagents, easy preparation, storage and the reusability are some fundamental characteristics of DES that have promoted their wide application in synthetic chemistry and allowed the construction of diverse molecular structures including biological active compounds (Ghosh and Nagarajan 2016; Higuera et al. 2019; Massolo et al. 2016; Peña-Solóorzano et al. 2019).

Considering the benefits of using DES in organic chemistry, the broad spectrum of applications of urea derivatives and benzimidazoles together with the easy access and large number of commercially available nitroarenes, in this contribution we report the use of nitroaromatic compounds as starting materials for the synthesis of unsymmetrical urea



Scheme 1 Common strategies for the synthesis of 1,2-disubstituted benzimidazoles

derivatives and benzimidazoles employing tin (II) chloride dihydrate/choline chloride deep eutectic solvent (DES) as reductive reaction medium (Scheme 2).

Experimental section

Chemistry

All the chemicals and solvents were purchased from commercial suppliers (Aldrich, Merck). Melting points, reported without correction, were measured using a Stuart SMP10 apparatus. The FT-IR spectra were obtained with a Shimadzu IR prestige 21 spectrophotometer (Columbia, MD, USA). ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AVANCE III system operating at 400 MHz, using residual and deuterated solvent peaks of $CDCl_3$ (δH 7.26; δC 77.0) and DMSO (δH 2.50; δC 39.5) as reference standards.

2.1.1 $SnCl_2{\cdot}2H_2O$/ChCl (2:1 molar ratio) DES Preparation. A mixture of $SnCl_2{\cdot}2H_2O$ (1451 mg, 6.43 mmol) and ChCl (449 mg, 3.215 mmol) was poured in a glass vial. The mixture was stirred and heated up to 80 °C until a homogeneous colourless liquid was obtained.

General experimental procedure for the synthesis of unsymmetrical urea and thiourea derivatives *1–13*

To an open headspace vial equipped with a magnetic stir bar, the nitroarene (1.0 mmol) and 1.9 g of $SnCl_2{\cdot}2H_2O$/ChCl (2:1 molar ratio) DES were added, and the resulting solution was then stirred and heated at 80 °C. After complete reduction in the nitroarene (5 min, TLC), phenyl isocyanate (1.2 mmol) was added, and heating was continued until the reaction was complete (15–25 min, TLC analysis). Next, the mixture was cooled to room temperature, neutralized (pH 7) with aqueous NaOH (10% NaOH) and extracted with AcOEt (5 X 2 mL), the organic layer was separated and dried over anhydrous Na_2SO_4. After evaporating the solvent under reduced pressure, the desired product was obtained in high purity without further purification.

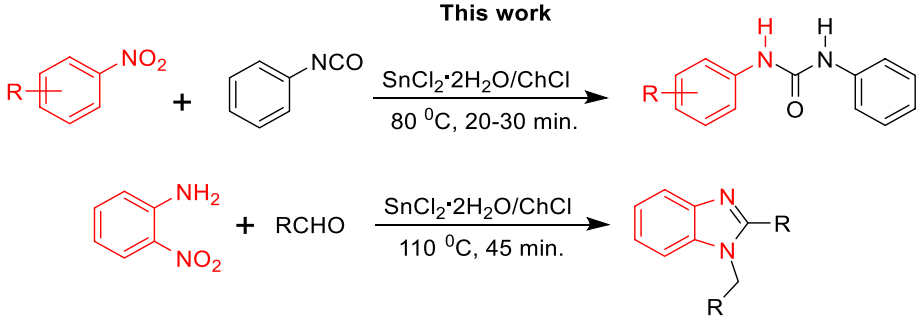
General experimental procedure for the synthesis of N-arylmethyl-2-substituted benzimidazoles *14–21* and *22,22a-28,28a*

To an open headspace vial equipped with a magnetic stir bar, *o*-nitroaniline or 2-nitro-4-methoxyaniline (1.0 mmol), the corresponding aldehyde (3 mmol) and 1.9 g of $SnCl_2{\cdot}2H_2O$/ChCl (2:1 molar ratio) DES were added, and the resulting solution was then stirred and heated at 110 °C. After running the reaction to an appropriate time (45 min, TLC analysis), the mixture was cooled to room temperature, neutralized (pH 7) with aqueous NaOH (10% NaOH) and extracted with AcOEt (3 × 10 mL). After drying over anhydrous Na_2SO_4 and evaporating the solvent under reduced pressure, the crude material was purified by column chromatography on silica gel to afford the desired product.

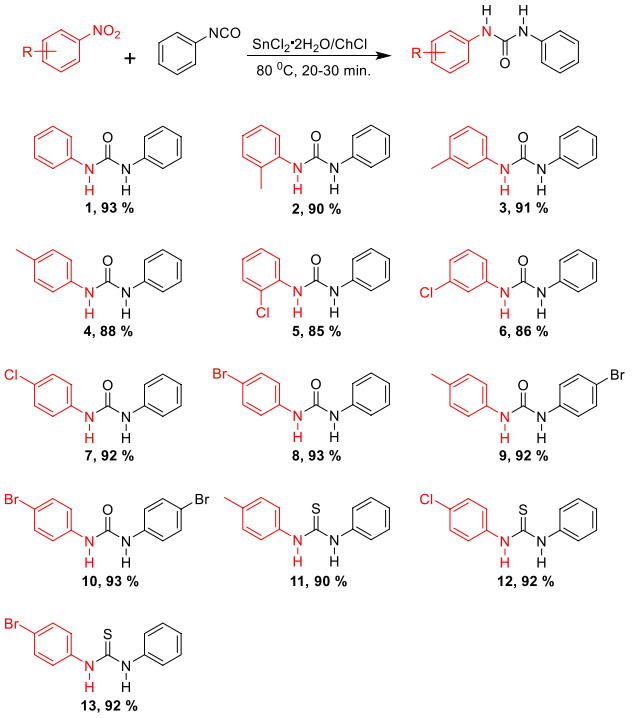
Results and discussion

Recently, we have reported the redox capability of tin (II) chloride dihydrate/choline chloride eutectic mixture in the conversion of several nitroarenes into the corresponding aromatic amines, N-arylacetamides and quinoxalines (Trujillo et al. 2020). Our initial studies showed that nitrobenzene and its analogues bearing electron donating and electron withdrawing groups are easily reduced by the DES affording the corresponding anilines in short reaction times with excellent yields (Trujillo et al. 2020). Considering this, in this work our initial efforts were directed at studying the reaction of phenyl isocyanate and nitroarenes to afford unsymmetrical urea derivatives employing the DES. Initially, nitrobenzene was poured into the DES, and after its conversion to aniline (5 min, TLC), phenyl isocyanate was added obtaining the desired urea **1** in 93% isolated yield after 20 min. With these interesting results in our hands, the reactivity of different substituted nitroarenes in this reaction was also evaluated. Results are depicted in Scheme 3.

As seen in Scheme 3, nitroarenes bearing electron donating and electron withdrawing groups (methyl-, chloro- and bromo-, respectively) afforded the target urea derivatives **2–8** in 85–93% yield. In addition, 4-bromophenyl isocyanide



Scheme 2 Nitroarenes in the synthesis of unsymmetrical urea and benzimidazole derivatives



Scheme 3 One-pot synthesis of unsymmetrical urea and thiourea derivatives

and phenyl isothiocyanate also reacted smoothly yielding the urea (**9** and **10**) and thiourea (**11**–**13**) derivatives in excellent yields (Scheme 3). No clear tendency on the reactivity was observed regarding the different substituents located at the nitroarene or the phenyl isocyanate derivative.

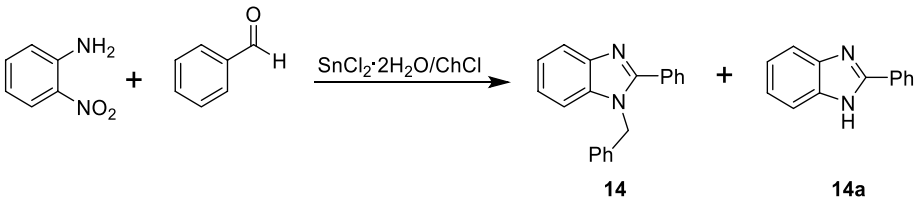
Next, we focused our efforts on the synthesis of 2-arylbenzimidazoles by reacting o-nitroaniline with different aldehydes; and for this, benzaldehyde was selected as starting material in the model reaction (Table 1).

To our surprise, after running the reaction with 1 equiv. of *o*-nitroaniline and 1 equiv. of benzaldehyde we found that the desired 2-phenylbenzimidazole **14a** was obtained in 22% and the disubstituted analogue **14** was obtained in 66% yield (Table 1 entry 1).

This result prompted us to redirect our synthesis towards the access to the disubstituted analogue **14**; and for this, the equivalents of benzaldehyde were increased in 2, 2.5 and 3 folds (Table 1, entries 2 to 4). It was observed that the amount of isolated benzimidazole **14a** decreases with the increase in benzaldehyde, and the reaction is selective towards the obtention of the disubstituted analogue **14** when 3 equiv. of benzaldehyde are employed (Table 1, entry 4).

In addition, reactions performed at low temperatures or prolonged reaction times did not improve the yield of the reaction (Table 1, entries 5 and 6). A review of literature reveals that some authors also have studied the same transformation starting from o-nitroaniline. Kim and collaborators(Kim et al. 2002, 2004) found that this

Table 1 Optimization studies for the reaction of *o*-nitroaniline and benzaldehyde[a]



Entry	Conditions: ratio amine/aldehyde, T (°C), t (min)	Yield[b]	
		14	14a
1	1:1, 110 °C, 45 min	6[c]	22[c]
2	1:2, 110 °C, 45 min	74[d]	9[d]
3	1:2.5, 110 °C, 45 min	77[d]	5[d]
4	1:3, 110 °C, 45 min	85[d]	0[d]
5	1:3, 80 °C, 45 min	72[d]	0[d]
6	1:3, 110 °C, 75 min	85[d]	0[d]
7	1:2, Zn (10 equiv.), BNP (2 equiv.), MeOH/DCM (1/1), rt, 10 h(Kim et al. 2002)	33	57
8	1:2, In (5 equiv.), BNP (4 equiv.), MeOH/H_2O (2/1), rt, 5 h(Kim et al. 2004)	70	10
9	1:2, NH_4HCO_2 (3.3 equiv.), Pd/C (0.05 mmol Pd), mont. K-10, toluene, reflux, 16 h(Weires et al. 2012)	43	43

[a] All reactions were performed in 1.9 g of tin (II) chloride dihydrate/choline chloride ($SnCl_2{\cdot}2H_2O$/ChCl, 2:1 molar ratio) DES. [b] Isolated yield. [c] Yields based on the amount of benzaldehyde. [d] Yields based on the amount of *o*-nitroaniline

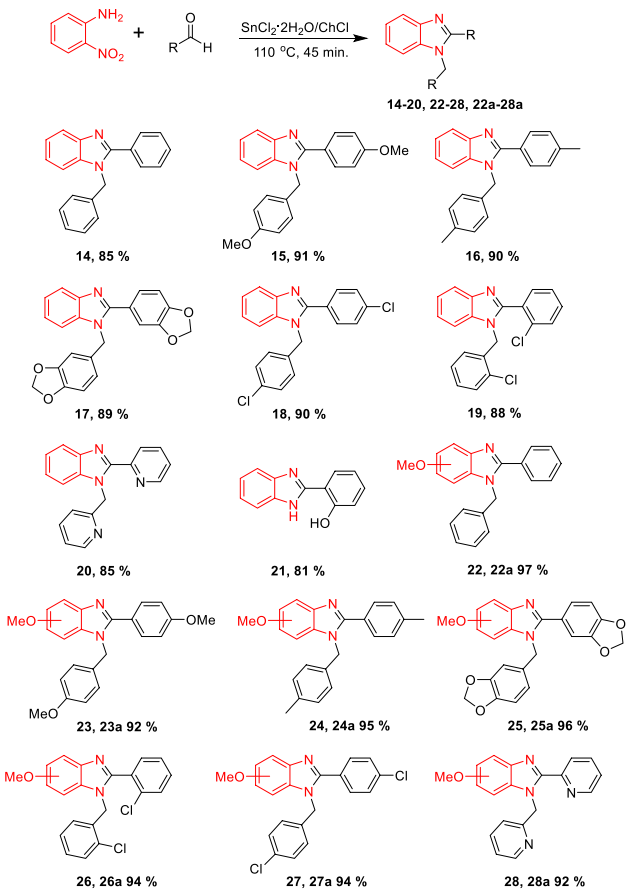
reductive intermolecular coupling/heterocyclization reaction can be accomplished in the presence of Zn or In and 2-bromo-2-nitropropane (BNP); however a poor selectivity is obtained when zinc is employed, and 2-phenylbenzimidazole **14a** is obtained as major product when indium is used (Table 1, entries 7 and 8). On the other hand, Weires et al. (Weires et al. 2012) employed a mixture of two heterogeneous catalysts (montmorillonite-K10 and Pd/C), but this strategy afforded an equimolar mixture of benzimidazoles **14** and **14a**. (Table 1, entry 9). The poor selectivity towards the disubstituted benzimidazole **14**, low yields and long reaction times found in the aforementioned procedures highlight the novelty of our method. The scope and limitations of this synthetic procedure was further studied in the reaction of different aldehydes and *o*-nitroaniline. Results are illustrated in Scheme 4.

As shown in Scheme 4, the electronic nature of the aromatic aldehydes does not influence the outcome of the reaction: aldehydes with electron donating groups (methoxy, methyl, and methylenedioxy) afforded the target N-arylmethyl-2-substituted benzimidazoles **15**–**17** in 91, 90 and 89% yield, while aldehydes with electron withdrawing groups (*o*-chloro and *p*-chloro) yielded compounds **18** and **19** in 90 and 88%, respectively.

In addition, heterocyclic aldehydes such as 2-pyridinecarboxyaldehyde afforded the compound **20** in good yield, but aliphatic (*n*-decanal) and masked aldehydes (2,3-dihydrofuran and 2,3-dihydropyran) give a complex mixture of products probably due to the enolizable character of these aldehydes. Interestingly, when 2-hydroxybenzaldehyde was employed in the reaction, only 2-arylbenzimidazole **21** was obtained, which is most likely formed through an imine intermediate where an intramolecular hydrogen bond stabilizes the structure and promotes the nucleophilic attack of the second nitrogen atom (see supporting information).

To further expand the scope of our method, and to evaluate the regioselectivity of this reaction, 2-nitro-4-methoxyaniline was also employed as starting material. As depicted in Scheme 4, this nitroaniline also reacted smoothly with all aldehydes affording the corresponding derivatives; however a preference for the obtention of one regioisomer was not observed and an equimolar mixture of both isomers was obtained according to ^{1}H-NMR. Different attempts to separate such isomers by column chromatography were unsuccessful.

The efficiency and synthetic utility of this method was next evaluated by performing a gram scale experiment. According to this, o-nitroaniline (10 mmol) and benzaldehyde (30 mmol) were poured into the DES and the reaction mixture was run for 45 min at 110 °C. After the proper work-up and purification, the compound **14** was obtained in 78% yield.

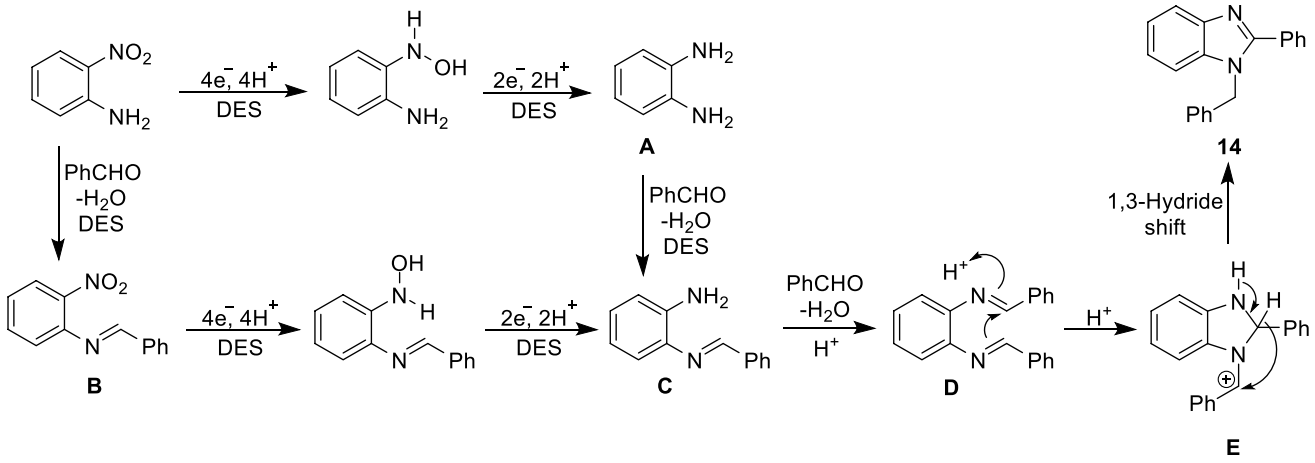


Scheme 4 One-pot synthesis of N-arylmethyl-2-substituted benzimidazoles. Products **22**–**28** are 1:1 mixture of the 5- and 6-isomers

To get insights into the reaction mechanism, we decided to perform two reactions starting from o-phenylenediamine (see supporting information).

For the first reaction, *o*-phenylenediamine (1 equiv.) was reacted with benzaldehyde (3 equiv.) employing the DES as solvent obtaining the compound **14a** in 25% yield. Interestingly compound **14** was not observed in this reaction. The second reaction was achieved with the same starting materials employing HCl (drops) in ethanol at reflux, and under these conditions, the 1,2-disubstituted benzimidazole **14** was obtained in 68% yield. The results obtained in these reactions indicate that the DES do not catalyze the cyclocondensation to afford **14**, and instead of this, HCl is capable of promoting the desired transformation. With this information, a plausible reaction mechanism is proposed in Scheme 5.

According to the mechanism, the reaction might follow two paths for the first: *o*-nitroaniline can be reduced by the DES affording *o*-phenylenediamine **A**, which reacts with benzaldehyde yielding the imine **C**. Alternatively, the

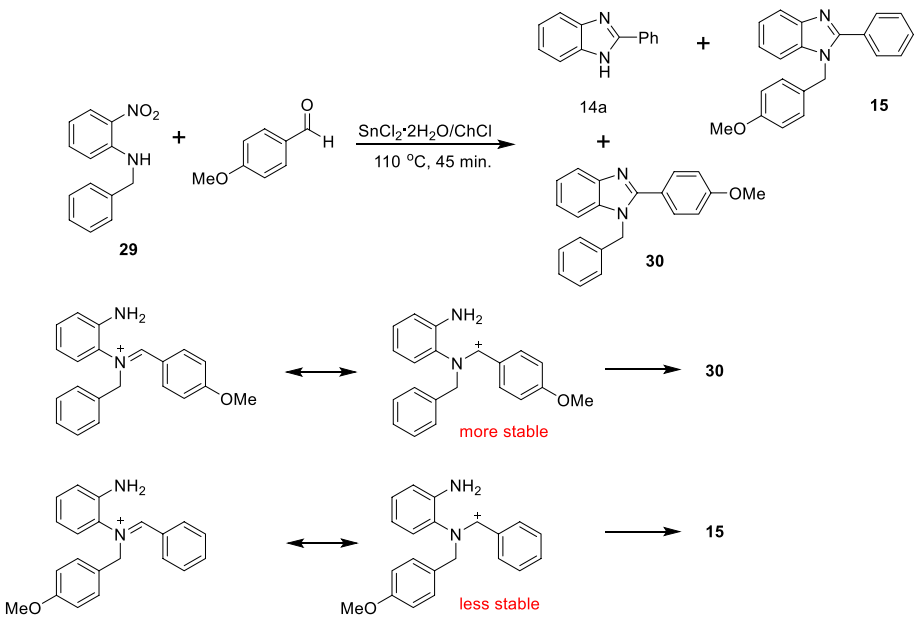


Scheme 5 Plausible reaction mechanism for the synthesis of N-arylmethyl-2-substituted benzimidazoles in $SnCl_2{\cdot}2H_2O$/ChCl DES

second path involves the condensation of *o*-nitroaniline with benzaldehyde forming the azomethine **B** which is reduced by the DES affording the compound **C**. Next, compound **C**, which is responsible for the formation of **14a**, react with a second equivalent of benzaldehyde in acidic media (HCl, which is formed during the reduction in *o*-nitroaniline and compound **B**) yielding the bis imine **D** that undergoes an intramolecular cyclization affording the intermediate **E**. Finally, isomerization of **E** through a 1,3-hydride shift yields the corresponding 1,2-disubstituted benzimidazole **14**.

Finally, although this novel methodology allows the access to N-arylmethyl-2-substituted benzimidazoles having identical aromatic rings at positions 1 and 2, we also explored the synthesis of derivatives with different substituents at the same positions, and thus increase the structural diversity of such derivatives. To accomplish this, compound **29** was synthesized (Siddiqui et al. 2006) and it was reacted with *p*-anisaldehyde; however a complex mixture was obtained where compounds **14a**, **15** and **30** were identified and obtained in a ratio of 1:1.3:2.5, respectively, according to GCMS analysis (Scheme 6). The origin of regioselectivity for compounds **15** and **30** could be explained in terms of relative stability of benzylic carbocations where the more electron rich the arene afford the more stable carbocation. Thus, after cyclization the corresponding benzimidazole **30** can be generated as the major isomer (Bose et al. 2019).

Scheme 6 Identified compounds in the reaction of compound **29** and *p*-anisaldehyde in $SnCl_2{\cdot}2H_2O$/ChCl DES



Conclusion

In conclusion, we have developed a simple and straightforward method for the synthesis of unsymmetrical urea and thiourea derivatives together with 1,2-disubstituted benzimidazoles starting from nitroarenes. Different nitroaromatic compounds are effectively reduced employing the $SnCl_2{\cdot}2H_2O$/ChCl DES, and the formed anilines reacted smoothly with phenyl isocyanate or phenyl isothiocyanate affording the corresponding ureas or thioureas in good yields. Similarly, the reaction of *o*-nitroaniline or 2-nitro-4-methoxyaniline with several aromatic and heteroaromatic aldehydes employing the same DES as a reductive reaction medium yielded 1,2-disubstituted benzimidazole derivatives in good yields; however, no regioselectivity was observed when 2-nitro-4-methoxyaniline was used.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11696-021-01785-7.

Acknowledgements We gratefully acknowledge the financial support from Universidad Nacional de Colombia. C. O-P. We sincerely thank Prof. Humberto Zamora for providing some infrastructure facilities.

Declarations

Conflict of interest 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.

References

Abtahi B, Tavakol H (2020) Choline chloride-urea deep eutectic solvent as an efficient media for the synthesis of propargylamines via organocuprate intermediate. Appl Organomet Chem 34(11):e5895. https://doi.org/10.1002/aoc.5895

Amendola V, Fabbrizzi L, Mosca L (2010) Anion recognition by hydrogen bonding: urea-based receptors. Chem Soc Rev 39(10):3889–3915. https://doi.org/10.1039/B822552B

Atashkar B, Zolfigol MA, Mallakpour S (2018) Applications of biological urea-based catalysts in chemical processes. Mol Catal 452:192–246. https://doi.org/10.1016/j.mcat.2018.03.009

Bahrami K, Khodaei MM, Nejati A (2010) Synthesis of 1,2-disubstituted benzimidazoles, 2-substituted benzimidazoles and 2-substituted benzothiazoles in SDS micelles. Green Chem 12(7):1237–1241. https://doi.org/10.1039/C000047G

Bansal Y, Silakari O (2012) The therapeutic journey of benzimidazoles: a review. Bioorg Med Chem 20(21):6208–6236. https://doi.org/10.1016/j.bmc.2012.09.013

Blatch AJ, Chetina OV, Howard JAK, Patrick LGF, Smethurst CA, Whiting A (2006) Synthesis and structure of bifunctional N-alkylbenzimidazole phenylboronate derivatives. Org Biomol Chem 4(17):3297–3302. https://doi.org/10.1039/B607127A

Bose A, Maiti S, Sau S, Mal P (2019) An intramolecular C(sp3)–H imination using PhI–mCPBA. Chem Commun 55(14):2066–2069. https://doi.org/10.1039/C8CC09100E

Carvalho LCR, Fernandes E, Marques MMB (2011) Developments towards regioselective synthesis of 1,2-Disubstituted benzimidazoles. Chem - Eur J 17(45):12544–12555. https://doi.org/10.1002/chem.201101508

Chakraborty A, Debnath S, Ghosh T, Maiti DK, Majumdar S (2018) An efficient strategy for N-alkylation of benzimidazoles/imidazoles in SDS-aqueous basic medium and N-alkylation induced ring opening of benzimidazoles. Tetrahedron 74(40):5932–5941. https://doi.org/10.1016/j.tet.2018.08.029

Connon SJ (2006) Organocatalysis mediated by (thio)urea derivatives. Chem - Eur J 12(21):5418–5427. https://doi.org/10.1002/chem.200501076

Das K, Mondal A, Srimani D (2018) Selective synthesis of 2-substituted and 1,2-disubstituted benzimidazoles directly from aromatic diamines and alcohols catalyzed by molecularly defined nonphosphine manganese(I) complex. J Org Chem 83(16):9553–9560. https://doi.org/10.1021/acs.joc.8b01316

Ghosh AK, Brindisi M (2020) Urea derivatives in modern drug discovery and medicinal chemistry. J Med Chem 63(6):2751–2788. https://doi.org/10.1021/acs.jmedchem.9b01541

Ghosh SK, Nagarajan R (2016) Deep eutectic solvent mediated synthesis of quinazolinones and dihydroquinazolinones: synthesis of natural products and drugs. RSC Adv 6(33):27378–27387. https://doi.org/10.1039/C6RA00855K

Guan Z-H, Lei H, Chen M, Ren Z-H, Bai Y, Wang Y-Y (2012) Palladium-catalyzed carbonylation of amines: switchable approaches to carbamates and N, N′-disubstituted ureas. Adv Synth Catal 354(2–3):489–496. https://doi.org/10.1002/adsc.201100545

Hérault D, Aelvoet K, Blatch AJ, Al-Majid A, Smethurst CA, Whiting A (2007) Benzimidazole nitrogen-directed, regiocontrolled, lithiation of ferrocenyl- and phenyl-N-n-butylbenzimidazoles. J Org Chem 72(1):71–75. https://doi.org/10.1021/jo061639+

Herrera Cano N, Uranga JG, Nardi M, Procopio A, Wunderlin DA, Santiago AN (2016) Selective and eco-friendly procedures for the synthesis of benzimidazole derivatives. The role of the $Er(OTf)_3$ catalyst in the reaction selectivity. Beilstein J Org Chem 12:2410–2419. https://doi.org/10.3762/bjoc.12.235

Higuera NL, Pemña-Solóorzano D, Ochoa-Puentes C (2019) Urea–zinc chloride eutectic mixture-mediated one-pot synthesis of imidazoles: efficient and ecofriendly access to trifenagrel. Synlett 30(2):225–229. https://doi.org/10.1055/s-0037-1610679

Jagtap AD, Kondekar NB, Sadani AA, Chern J-W (2017) Ureas: applications in drug design. Curr Med Chem 24(6):622–651. https://doi.org/10.2174/0929867323666161129124915

Jin M, Song G, Li Z, Zhou F, Fan B, Ouyang P (2014) Efficient synthesis of 2-aryl-1-arylmethyl-1H-benzimidazoles in ball mill without solvent. J Heterocyclic Chem 51(6):1838–1843. https://doi.org/10.1002/jhet.1113

Keri RS, Hiremathad A, Budagumpi S, Nagaraja BM (2015) Comprehensive review in current developments of benzimidazole-based medicinal chemistry. Chem Biol Drug Des 86(1):19–65. https://doi.org/10.1111/cbdd.12462

Keshavarzipour F, Tavakol H (2016) The synthesis of coumarin derivatives using choline chloride/zinc chloride as a deep eutectic solvent. J Iran Chem Soc 13(1):149–153. https://doi.org/10.1007/s13738-015-0722-9

Kim BH, Han R, Han TH, Jun YM, Baik W, Lee BM (2002) Heterocyclizations towards 2-arylbenzimidazoles via intermolecular coupling of 2-nitroanilines and aryl aldehydes. Heterocycles 57(1):5–10. https://doi.org/10.3987/COM-01-9381

Kim BH, Han R, Kim JS, Jun YM, Baik W, Lee BM (2004) Indium-mediated reductive inter-molecular coupling reaction of 2-nitroaniline with aromatic aldehydes to benzimidazoles. Heterocycles 63(1):41–54. https://doi.org/10.3987/COM-03-9903

Kim SH, Hong SH (2016) Ruthenium-catalyzed urea synthesis using methanol as the C1 source. Org Lett 18(2):212–215. https://doi.org/10.1021/acs.orglett.5b03328

Kokare ND, Sangshetti JN (2007) Shinde DB (2007) One-pot efficient synthesis of 2-aryl-1-arylmethyl-1H-benzimidazoles and 2,4,5-triaryl-1H-imidazoles using oxalic acid catalyst. Synthesis 18:2829–2834. https://doi.org/10.1055/s-2007-983872

Kommi DN, Kumar D, Bansal R, Chebolu R, Chakraborti AK (2012) "All-water" chemistry of tandem N-alkylation–reduction–condensation for synthesis of N-arylmethyl-2-substituted benzimidazoles. Green Chem 14(12):3329–3335. https://doi.org/10.1039/C2GC36377A

Kulkarni AR, Garai S, Thakur GA (2017) Scalable, one-pot, microwave-accelerated tandem synthesis of unsymmetrical urea derivatives. J Org Chem 82(2):992–999. https://doi.org/10.1021/acs.joc.6b02521

Limnios D, Kokotos CG (2016) Chapter 19 Ureas and thioureas as asymmetric organocatalysts In Sustainable catalysis: without metals or other endangered elements. Part 2.The Royal Society of Chemistry, Cambridge. https://doi.org/10.1039/9781782626435-00196

Majumdar S, Chakraborty M, Pramanik N, Maiti DK (2015) Grindstone chemistry: protic ionic liquid-substrate tuned green synthesis of 1,2-disubstituted and 2-substituted benzimidazoles with outstanding selectivity. RSC Adv 5(63):51012–51018. https://doi.org/10.1039/C5RA08183A

Massolo E, Palmieri S, Benaglia M, Capriatu V, Perna FM (2016) Stereoselective organocatalysed reactions in deep eutectic solvents: highly tunable and biorenewable reaction media for sustainable organic synthesis. Green Chem 18(3):792–797. https://doi.org/10.1039/C5GC01855B

McCusker JE, Main AD, Johnson KS, Grasso CA, McElwee-White L (2000) W(CO)6 Catalyzed oxidative carbonylation of primary amines to N, N'disubstituted ureas in single or biphasic solvent systems Optimization and functional group compatibility studies. J Org Chem 65(17):5216–5222. https://doi.org/10.1021/jo000364

Padiya KJ, Gavade S, Kardile B, Tiwari M, Bajare S, Mane M, Gaware V, Varghese S, Harel D, Kurhade S (2012) Unprecedented "in water" imidazole carbonylation: paradigm shift for preparation of urea and carbamate. Org Lett 14(11):2814–2817. https://doi.org/10.1021/ol301009d

Patil M, Noonikara-Poyil A, Joshi SD, Patil SA, Patil SA, Bugarin A (2019) New urea derivatives as potential antimicrobial agents: synthesis, biological evaluation, and molecular docking studies. Antibiotics 8(4):178. https://doi.org/10.3390/antibiotics8040178

Peña-Solóorzano D, Gonzáalez Guilombo CE, Ochoa-Puentes C (2019) Rapid and eco-friendly high yield synthesis of dihydroquinazolinones mediated by urea/zinc chloride eutectic mixture. Sustain Chem Pharm 14(2019):100167. https://doi.org/10.1016/j.scp.2019.100167

Shahabi D, Tavako H (2018) High catalytic ability of Fe_3O_4/EDTA magnetic nanocatalyst in comparison with various deep eutectic solvents for one-pot synthesis of 4H-pyrans. J Nanoanal 5(1):49–57. https://doi.org/10.22034/JNA.2018.541849

Shahabi D, Tavako H (2017) Synthesis of 14H-dibenzo xanthene derivatives using choline chloride/tin(II) chloride deep eutectic solvent and Fe3O4/ϰ-carrageenan/Zn(II). J Iran Chem Soc 14(1):135–142. https://doi.org/10.1007/s13738-016-0965-0

Sharma R, Sofi FA, Rana P, Bharatam PV (2019) Bimetallic Cu–Mn B spinel oxide catalyzed oxidative synthesis of 1,2-disubstituted benzimidazoles from benzyl bromides. New J Chem 43(10):4013–4016. https://doi.org/10.1039/C8NJ05504A

Siddiqui MA, Mansoor UF, Reddy PA, Madison VS (2006) Compounds for the treatment of inflammatory disorders. US Patent, US2006178366A1, Aug 10, 2006

Singh AS, Agrahari AK, Singh SK, Yadav MS, Tiwari VK (2019) An improved synthesis of urea derivatives from N-acylbenzotriazole via curtius rearrangement. Synthesis 51(18):3443–3450. https://doi.org/10.1055/s-0039-1689937

Sribalan R, Sangili A, Banuppriya G, Padmini V (2017) An efficient synthesis of nitrile, tetrazole and urea from carbonyl compounds. New J Chem 41(9):3414–3421. https://doi.org/10.1039/C6NJ03860C

Thapa P, Palacios PM, Tran T, Pierce BS, Foss FW (2020) 1,2-Disubstituted benzimidazoles by the iron catalyzed cross-dehydrogenative coupling of isomeric o-phenylenediamine substrates. J Org Chem 85(4):1991–2009. https://doi.org/10.1021/acs.joc.9b02714

Trujillo SA, Peña-Solórzano D, Bejarano OR, Ochoa-Puentes C (2020) Tin(II) chloride dihydrate/choline chloride deep eutectic solvent: redox properties in the fast synthesis of N-arylacetamides and indolo(pyrrolo)[1,2-a]quinoxalines. RSC Adv 10(66):40552–40561. https://doi.org/10.1039/D0RA06871C

Vinogradova EV, Fors BP, Buchwald SL (2012) Palladium-catalyzed cross-coupling of aryl chlorides and triflates with sodium cyanate: a practical synthesis of unsymmetrical ureas. J Am Chem Soc 134(27):11132–11135. https://doi.org/10.1021/ja305212v

Wang M, Han X, Zhou Z (2015) New substituted benzimidazole derivatives: a patent review (2013–2014). Expert Opin Ther Pat 25(5):595–612. https://doi.org/10.1517/13543776.2015.1015987

Weires NA, Boster J (2012) Magolan J (2012) Combined Pd/C and montmorillonite catalysis for one-pot synthesis of benzimidazoles. Eur J Org Chem 33:6508–6512. https://doi.org/10.1002/ejoc.201201101

Wu Z, Rea P, Wickham G (2000) 'One-pot' nitro reduction–cyclisation solid phase route to benzimidazoles. Tetrahedron Lett 41(50):9871–9874. https://doi.org/10.1016/S0040-4039(00)01732-9

Xie C, Han X, Gong J, Li D, Ma C (2017) One-pot strategy of copper-catalyzed synthesis of 1,2-disubstituted benzimidazoles. Org Biomol Chem 15(27):5811–5819. https://doi.org/10.1039/C7OB00945C

Yang D, Fokas D, Li J, Yu L (2005) Baldino CM (2005) A versatile method for the synthesis of benzimidazoles from o-nitroanilines and aldehydes in one step via a reductive cyclization. Synthesis 1:47–56. https://doi.org/10.1055/s-2004-834926

Zhang Z, Schreiner PR (2009) (Thio)urea organocatalysis—What can be learnt from anion recognition? Chem Soc Rev 38(4):1187–1198. https://doi.org/10.1039/B801793J

Zhao J, Li Z, Yan S, Xu S, Wang M-A, Fu B, Zhang Z (2016) Pd/C catalyzed carbonylation of azides in the presence of amines. Org Lett 18(8):1736–1739. https://doi.org/10.1021/acs.orglett.6b00381

Zhao Y-X, Xie T, Yang S-K (2020) Yang X-J (2020) A novel C-N migration rearrangement based on N–F compounds for the synthesis of N-alkyl diaryl ureas. Eur J Org Chem 4:437–445. https://doi.org/10.1002/ejoc.201901602

Zou B, Yuan Q, Ma D (2007) Synthesis of 1,2-disubstituted benzimidazoles by a Cu-catalyzed cascade aryl amination/condensation process. Angew Chem, Int Ed Engl 46(15):2598–2601. https://doi.org/10.1002/anie.200700071