ChemPubSoc Europe

DOI: 10.1002/ejoc.201700357

EurJOC European Journal of Organic Chemistry
Communication

Multicomponent Reactions

A Benzoquinone Imine Assisted Ring-Opening/Ring-Closing Strategy of the RCOCHN^{1}N^2 System: Dinitrogen Extrusion Reaction to Benzimidazoles[‡]

Atul Kumar[a,b] and Qazi Naveed Ahmed*[a,b]

Abstract: A mild, three-component dinitrogen extrusion reaction proceeding at room temperature to give different 1,2-disubstituted benzimidazoles from 2-oxoaldehydes, 4-azidophenol, and benzotriazoles was successfully developed. Mechanistically, this transformation occurs through the benzoquinone imine assisted ring opening/ring closing of a highly unstable RCOCHN^{1}N^2 system.

Introduction

1,2-Disubstituted benzimidazoles are an important class of heterocyclic compounds and are found in a diverse range of natural products and biologically active compounds.[1] The significance of these structures can be demonstrated by the profusion of drug leads/pharmaceutical products, including hepatitis C virus polymerase inhibitor **1**,[1c,1e,2] agonist **2** against the γ-aminobutyric acid A receptor ($GABA_A$),[3] telmisartan (the antihypertensive Micardis),[4] candesartan (Atacand),[5] and bilastine (Bilaxten)[6] (Figure 1). Besides, 1,2-disubstituted benzimidazoles are represented as intermediates to different dyes and polymers[7] and have been used as ligands.[8] Consequently, ample efforts have been dedicated to developing efficient methods to assemble this construct.[9] Whereas the number of procedures for the preparation of 1- or 2-substituted benzimidazoles has increased greatly during the last years,[10] the assembly of 1,2-disubstituted benzimidazoles is still a challenge (Scheme 1).[11] Reported strategies often require additional steps to prepare either the precursors or involve the use of expensive substrates/reagents.[12] Thus, designing new strategies for the construction of the benzimidazole backbones is highly desirable.

In the past, the Katritzky group produced several important heterocycles by using benzotriazoles as synthetic auxiliaries.[13] Benzotriazoles (BTZs), owing to their diverse roles in chemical transformations and in the discovery of bioactive scaffolds, have proven to be intriguing substrates.[14] However, owing to their innate tendency to exist as diazonium salts and to their high structural stability, the ring-opening chemistry of benzotriazoles has not been well studied.[15] Recently, our group established a novel route for the synthesis of 6-aminophenanthridines through a 2-oxo driven N_2 elimination induced decarbonylative cyclization strategy. This reaction presented a creative way to extrude N_2 from benzotriazoles.[16] Later, the same concept involving the RCOCHN^{1}N^2 system was extended to the synthesis of 2-oxoacetamidines.[17] In continuation, we recently established the divergent behavior of 2-oxo aldehydes (OAs) towards amino acid alkyl ester hydrochlorides. Therein, selenium dioxide was found to play a crucial role in promoting the regioselective synthesis of imidazoles through the in situ generated RCOCHN^{1}N^2 system.[18] An imperative feature of the RCOCHN^{1}N^2 system in this case was the presence of an adjacent electrophilic carbonyl group, which helped to fix two nitrogen atoms from the same amino acid. This observation led us to establish a reaction between 2-oxo aldehdyes, benzotriazoles, and 4-azidophenols. 4-Azidophenols have the innate tendency

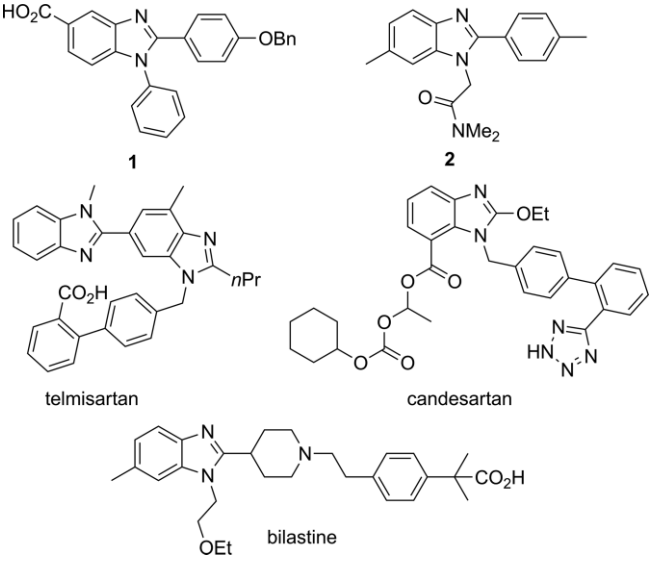
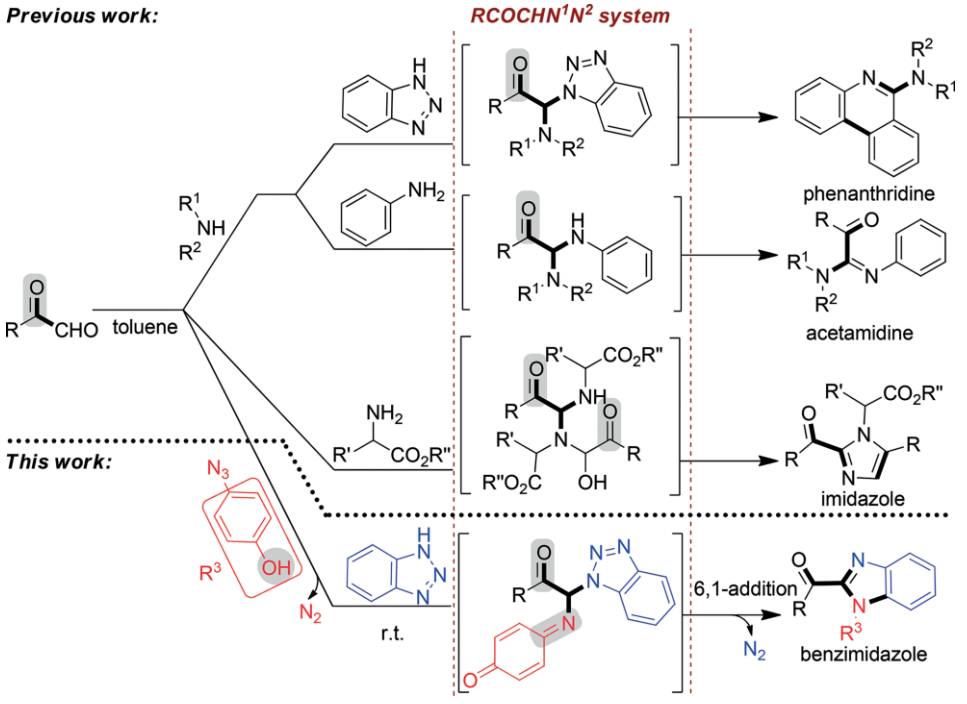


Figure 1. Structures of pharmacologically active benzimidazoles.

[‡] IIIM communication no. IIIM/2027/2017

[a] *Medicinal Chemistry Division, Indian Institute of Integrative Medicine (IIIM), Canal Road, Jammu, Jammu & Kashmir, 180001, India*
E-mail: naqazi@iiim.ac.in
http://www.iiim.res.in/People/CV/cv_naveed.php
[b] *Academy of Scientific and Innovative Research (AcSIR), Indian Institute of Integrative Medicine (IIIM), Canal Road, Jammu, Jammu & Kashmir, 180001, India*

Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under https://doi.org/10.1002/ejoc.201700357.



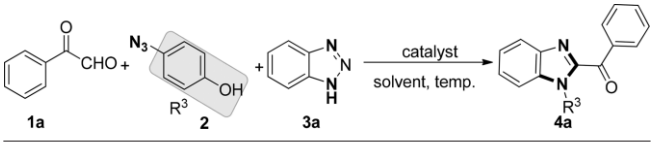
Scheme 1. Summary of this work.

to promote reactions through the benzoquinone imine system and have proven helpful in establishing a novel approach to 1,2-benzimidazoles given that the in situ generated RCOCHN^{1}N^2 system has an electrophilic nitrogen atom. The present method represents a complementary dinitrogen-extrusion/ring-opening/ring-closing strategy that is perhaps driven by two directing groups. This method once again justifies the role of the 2-oxo group in promoting the ring-opening/N_2-elimination reaction in benzotriazoles through a push–pull mechanism.

Results and Discussion

We started our study by investigating the nature of the product acquired upon mixing phenylglyoxal (**1a**; 1 mmol), 4-azidophenol (**2**; 1 mmol), and 1*H*-benzotriazole (**3a**; 1 mmol) in toluene at 80 °C (Table 1, Entry 1). To our delight, the reaction produced unanticipated product **4a** in 32 % yield. The structure of **4a** was established by HRMS, LC–MS (ESI), IR spectroscopy, and NMR spectroscopy (for details, see the Supporting Information). Following this promising outcome, the reaction conditions, particularly the concentrations and temperature along with the effects of copper salts, were thoroughly investigated (Table 1, Entries 2–15). Primarily, a survey of the concentrations of **2** and **3a** (Table 1, Entries 2–5) intimated that an improved yield of **4a** could be obtained at loadings of 1.1 mmol for **2** and 1.1 mmol for **3a** (Table 1, Entry 4). Later, the same reaction was performed at different temperatures (Table 1, Entries 6–9). The best yield was obtained at room temperature (Table 1, Entry 9). To improve the yield, we screened the reaction in the presence of different copper salts (Table 1, Entries 10–15). $Cu(OAc)_2$ (10 mol-%) was found to be the catalyst of choice for the generation of **4a** (79 % yield; Table 1, Entry 11). After these studies, we learned that the optimized conditions for the reaction involved treatment of **1a** (1 mmol) with **2** (1.1 mmol), **3a** (1.1 mmol), and $Cu(OAc)_2$ (10 mol-%) in toluene at room temperature (Table 1, Entry 11).

Table 1. Optimization of the reaction conditions.[a]



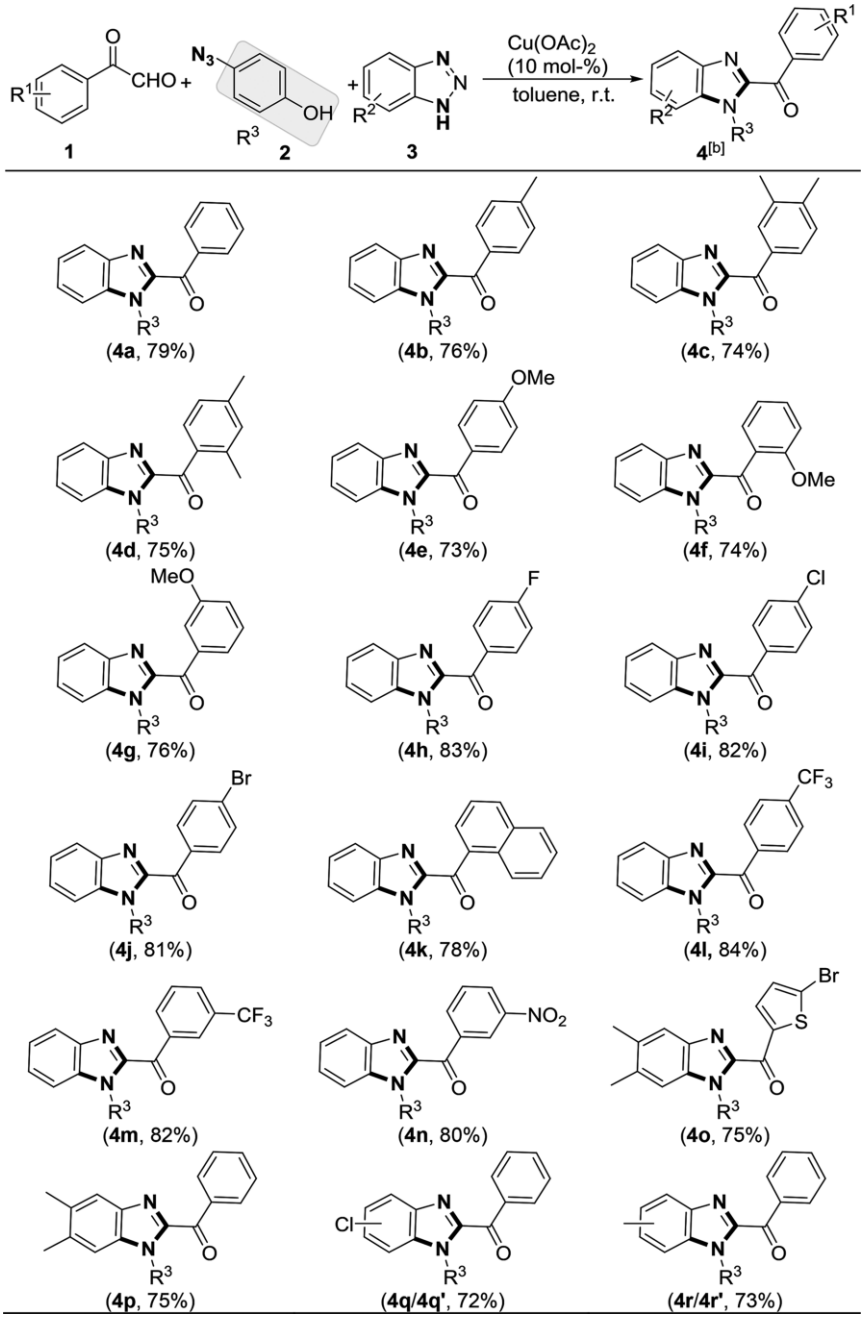
Entry	**2a** [mmol]	**3a** [mmol]	Catalyst (mol-%)	Temp. [°C]	Yield [%][b]
1	1	1	–	80	32
2	1.1	1	–	80	39
3	1.2	1	–	80	41
4	1.1	1.1	–	80	56
5	1.1	1.2	–	80	55
6	1.1	1.1	–	60	61
7	1.1	1.1	–	50	64
8	1.1	1.1	–	40	66
9	1.1	1.1	–	r.t.	68
10	1.1	1.1	$Cu(OAc)_2$ (5)	r.t.	71
11	1.1	1.1	$Cu(OAc)_2$ (10)	r.t.	79
12	1.1	1.1	$Cu(OAc)_2$ (20)	r.t.	81
13	1.1	1.1	CuBr (10)	r.t.	63
14	1.1	1.1	$CuBr_2$ (10)	r.t.	73
15	1.1	1.1	CuI (10)	r.t.	60

[a] Reaction conditions: 2-oxo aldehyde **1a** (1 mmol), 4-azidophenol (**2**; 1.1 mmol), and 1*H*-benzotriazole (**3a**; 1.1 mmol) in toluene (3 mL). [b] Yield of isolated product.

Having observed that 4-azidophenol (**2**) assisted the addition of 1*H*-benzotriazole (**3a**) with 2-oxo aldehyde **1a** under the above-optimized conditions, we decided to study the substrate

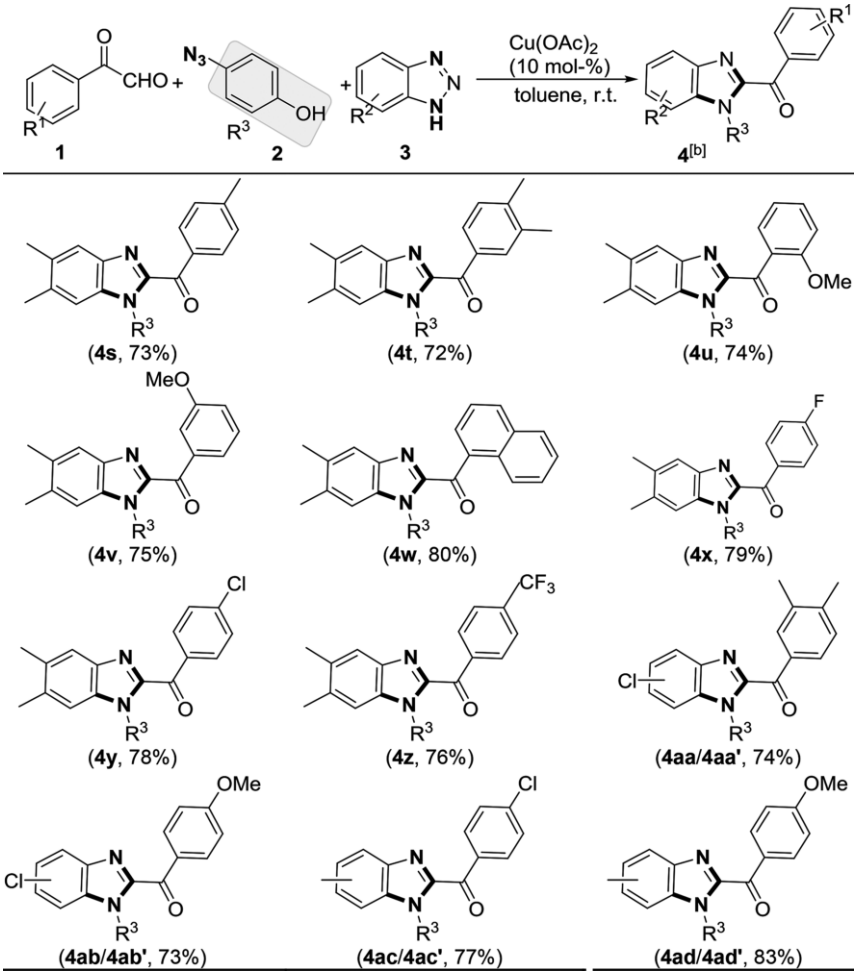
scope of this method. As compiled in Table 2, a variety of 2-oxo aldehydes **1** were tested against different benzotriazoles **3** with diverse electronic and steric properties (see products **4a**–**r**). We were pleased to find that the desired products **4** were produced in good yields in all of the tested reactions (72–84 % yield). In one set of experiments, different reactions were performed between diverse 2-oxo aldehydes **1**, 4-azidophenol (**2**), and 1*H*-benzotriazole (**3a**) (see products **4a**–**o**). Both electron-rich and electron-deficient OAs could be smoothly transformed into the desired products. However, the electronic environment of the phenyl ring in the OA had a slight effect on the yield of the product. On the basis of our observations, OAs bearing halogen/electron-withdrawing groups, for example, F (see **4h**), Cl (see **4i**), Br (see **4j**), CF_3 (see **4l** and **4m**), and NO_2 (see **4n**), afforded slightly higher yields than an unsubstituted 2-oxo aldehyde (see **4a**) and 2-oxo aldehydes containing electron-donating groups such as CH_3 (see **4b**–**d**) and OMe (see **4e**–**g**). The same reaction with naphthylglyoxal and a heterocyclic substrate produced good yields of products **4k** and **4o**. Furthermore, the reaction of phenylglyoxal (**1a**) and 4-azidophenol (**2**)

Table 2. Scope of the reaction with respect to **1** and **3**.[a]



[a] Reaction conditions: 2-oxo aldehyde **1** (1 mmol), 4-azidophenol (**2**, 1.1 mmol), benzotriazole **3** (1.1 mmol), and $Cu(OAc)_2$ (10 mol-%) in toluene (3 mL) at room temperature. [b] Yields of the isolated products are given.

Table 3. General substrate scope of the reaction.[a]



[a] Reaction conditions: 2-oxo aldehyde **1** (1 mmol), 4-azidophenol (**2**, 1.1 mmol), benzotriazole **3** (1.1 mmol), and $Cu(OAc)_2$ (10 mol-%) in toluene (3 mL) at room temperature. [b] Yields of the isolated products are given.

with other benzotriazoles, namely, 5,6-dimethylbenzotriazole, 5-chlorobenzotriazole, and 5-methylbenzotriazole, proceeded smoothly and gave analogous yields of the desired products **4p**, **4q**, and **4r**, respectively. However, as expected, reactions with 5-substituted BTZs produced regioisomers (see **4q**/**4q′** and **4r**/**4r′** in the Supporting Information).

In continuation, another set of experiments was performed between different OAs, BTZs, and 4-azidophenol to check the substrate scope (Table 3). In general, substituents at different positions of the arene group of the OA and their electronic nature did not affect the effectiveness of the reaction (see **4s**–**ad**). However, variations in the BTZ affected the overall yields to some extent.

To gain insight into the mechanism of this reaction and to establish the significance of different groups/reagents, several control experiments were performed (Figure 2). In Experiment (1), the failure of phenylglyoxal (**1a**; 1 mmol) to react with **3a** (1.1 mmol) under the optimized conditions directly confirmed the nonparticipation of the BTZ with the OA in the initial step. Further, upon performing four different reactions between 2-oxo aldehydes **1** (1 mmol) and 4-azidophenol [**2**; 1.1 mmol; Experiment (2)], we isolated the respective keto amides in high yields. This in fact is a new approach to hydroxy-substituted α-keto amides. This experiment indeed pointed towards the involvement of an α-keto amide as an intermediate for the generation of product **4**. To investigate this possibility, we performed a reaction between keto amide **5a** (1 mmol) and **3a** (1.1 mmol) under the optimized conditions [Experiment (3)]. The absence of any reaction proved the non-engagement of a keto amide in the reaction. Experiments (1)–(3) proved that a reaction intermediate is first generated from **1** and **2**, and it reacts in an unprecedented manner with **3** to give the desired product **4**. Furthermore, failure of phenylglyoxal (**1a**) to react with phenyl azide and **3a** certainly indicated the crucial role of 4-azidophenol in facilitating attack of the BTZ [Experiment (4)]. In continuation, two different reactions [Experiments (5) and (6)] were performed with 2-/3-azidophenol under the same conditions. However, in both reactions, no product was generated, which thus indicated the important role of the *para*-hydroxy group in **2** in promoting the reaction through a benzoquinone imine system. In addition, the reaction of benzaldehyde (1 mmol) with **2** and **3a** failed to produce any product, which thereby once

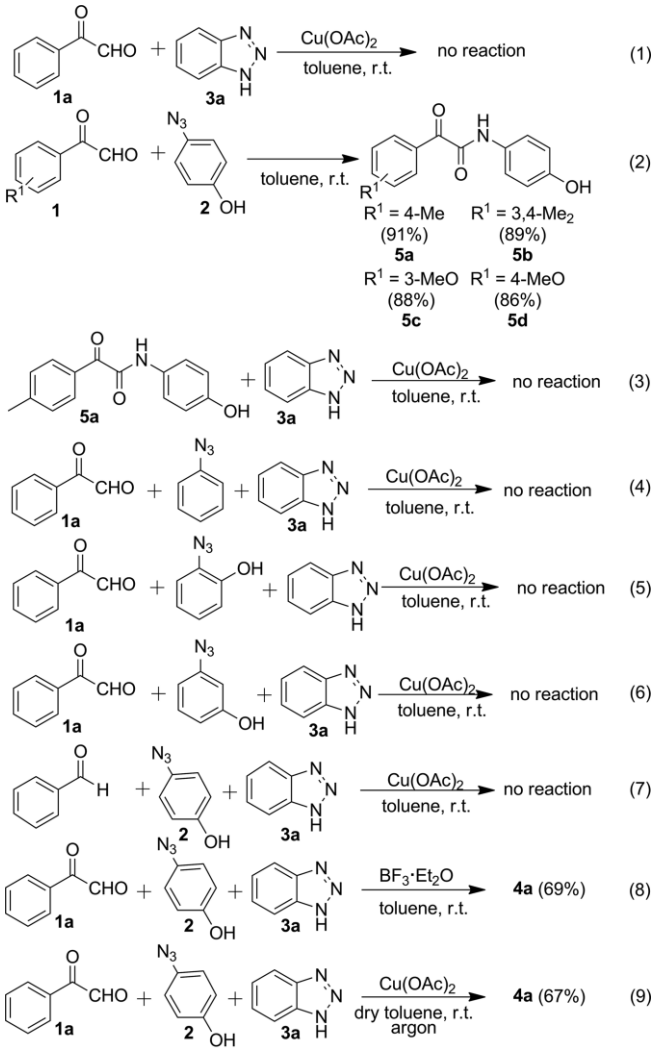


Figure 2. Control experiments.

again proved the role of the 2-oxo group in facilitating the reaction [Experiment (7)]. Furthermore, we performed the optimized reaction in the presence of BF_3·OEt_2 [Experiment (8)] and found a slight increase in the yield of **4a**. However, upon performing the optimized reaction in the presence of $Cu(OAc)_2$ (10 mol-%) under argon, the yield was not improved [Experiment (9)]. Both of these experiments indicate that copper, besides acting as a Lewis acid, increases the nucleophilicity of the BTZ through the assistance of air, which ultimately enhances the overall yield of the reaction.

On the basis of our understanding of activation through the RCOCHN^{1}N^2 system,[16–18] literature reports on the activation of copper,[19] and the above-mentioned results, we propose a mechanism for this reaction (Figure 3). The preliminary step involves the reaction of 2-oxo aldehyde **1** with 4-azidophenol (**2**) to form intermediate **A**. Intermediate **A** reacts at room temperature through the assistance of the *para*-hydroxy group and extrudes nitrogen to give intermediate **B**. On the one hand, intermediate **B** can undergo tautomerism followed by rearrangement to **C**, which ultimately generates α-keto amide **5**. On the other hand, in the presence of **3**, intermediate **B** reacts through an air-assisted, copper-catalyzed cycle to produce a novel RCOCHN^{1}N^2 system (intermediate **D**) having an electrophilic benzoquinone imine group. This intermediate perhaps generates intermediate **E**, which loses nitrogen (as a result of conjugation) and undergoes the expected 6,1-addition[20] to give product **4**.

Conclusions

We established a new concept around the benzoquinone imine assisted ring-opening/ring-closing strategy of the RCOCHN^{1}N^2 system and successfully applied it to the generation of different 1,2-disubtituted benzimidazoles from readily available substrates. Further studies related to the applications of this system in terms of different electrophiles are in progress.

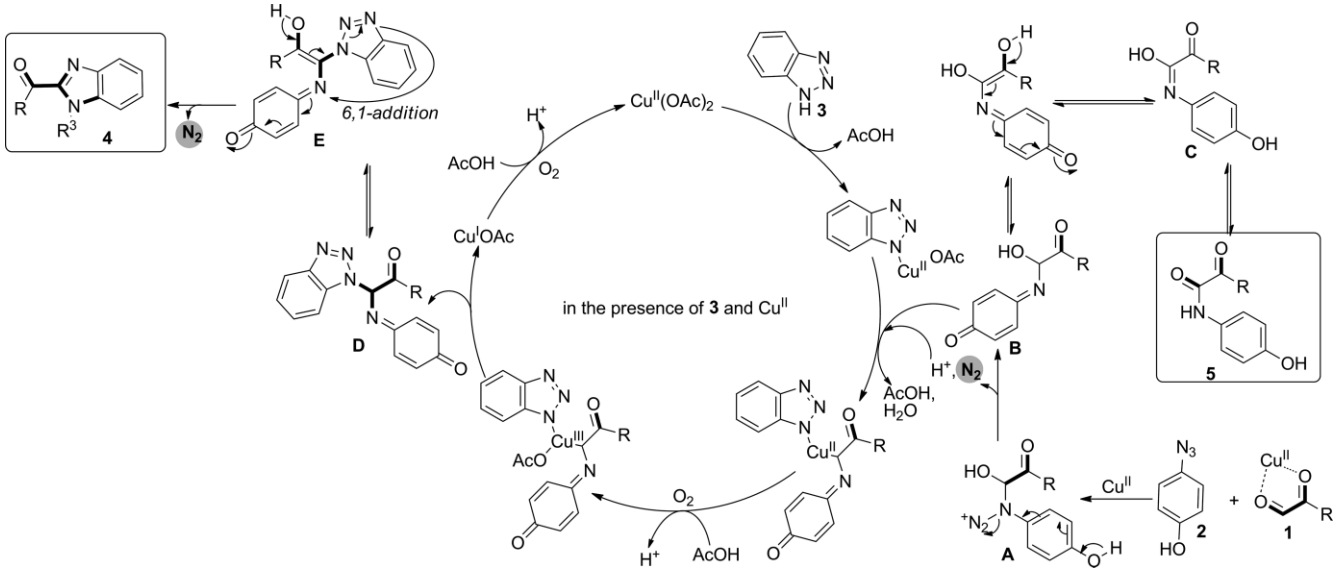


Figure 3. Plausible mechanism.

Experimental Section

General Procedure for the Synthesis of 4a–ad: A reaction vessel was charged with 2-oxo aldehyde **1** (1 mmol), 4-azidophenol (**2**; 1.1 mmol) and benzotriazole **3** (1.1 mmol) in toluene (3 mL). The mixture was stirred at room temperature for 12 h. Upon completion of the reaction, the solvent was removed under reduced pressure. The crude mixture was purified by column chromatography (100–200 # silica gel; CH_2Cl_2/MeOH, 9:1) to afford product **4** in good yield (72–84 %).

Acknowledgments

A. K. thanks the University Grants Commission (UGC) for the award of a JRF. Q. N. A. also thanks the analytical department of the Indian Institute of Integrative Medicine (IIIM). Finally, the authors are grateful to the Council of Scientific and Industrial Research (CSIR) network project (BSC-0108) for funding this work.

Keywords: Aldehydes · Copper · Nitrogen · Nitrogen heterocycles · Multicomponent reactions

[1] a) J. A. Asensio, E. M. Sanchez, P. Gomez-Romero, *Chem. Soc. Rev.* **2010**, *39*, 3210–3239; b) J. B. Wright, *Chem. Rev.* **1951**, *48*, 397–541; c) P. Naik, P. Murumkar, R. Giridhar, M. Yadav, *Bioorg. Med. Chem.* **2010**, *18*, 8418–8456; d) V. K. Vyas, M. Ghate, *Mini-Rev. Med. Chem.* **2010**, *10*, 1366–1384; e) T. Ishida, T. Suzuki, S. Hirashima, K. Mizutani, A. Yoshida, I. Ando, S. Ikeda, T. Adachi, H. Hashimoto, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1859–1863; f) Q. Dang, S. Kasibhatla, W. Xiao, Y. Liu, J. Dare, F. Taplin, K. Reddy, G. Scarlato, T. Gibson, P. van Poelje, S. Potter, M. Erion, *J. Med. Chem.* **2010**, *53*, 441–451; g) L. Bielory, K. Lien, S. Bigelsen, *Drugs* **2005**, *65*, 215–228; h) M. Gaba, D. Singh, S. Singh, V. Sharma, P. Gaba, *Eur. J. Med. Chem.* **2010**, *45*, 2245–2249; i) J. F. Miller, E. M. Turner, K. S. Gudmundsson, S. Jenkinson, A. Spaltenstein, M. Thomson, P. Wheelan, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2125–2128; j) M. Boiani, M. Gonzalez, *Mini-Rev. Med. Chem.* **2005**, *5*, 409–424; k) C. Chen, J. Yu, C. Bi, Y. Zhang, J. Q. Xu, J. X. Wang, M. G. Zhou, *Phytopathology* **2009**, *99*, 1403–1411.

[2] V. K. Vyas, M. Ghate, *Mini-Rev. Med. Chem.* **2010**, *10*, 1366–1384.

[3] a) L. Richter, C. de Graaf, W. Sieghart, Z. Varagic, M. Mörzinger, I. J. de Esch, G. F. Ecker, M. Ernst, *Nat. Chem. Biol.* **2004**, *8*, 455–464; b) V. Campagna-Slater, D. F. Weaver, *Mol. Graph. Model.* **2007**, *25*, 721–730.

[4] a) S. C. Benson, H. Pershadsingh, C. Ho, A. Chittiboyina, P. Desai, M. Pravenec, N. Qi, J. Wang, M. Avery, T. W. Kurtz, *Hypertension* **2004**, *43*, 993–1002; b) F. Sanchis-Gomar, G. Lippi, *J. Strength Conditioning Res.* **2011**, *26*, 1.

[5] a) M. Pfeffer, K. Swedberg, C. Granger, P. Held, J. McMurray, E. Michelson, B. Olofsson, J. Ostergren, S. Yusuf, S. Pocock, *Lancet* **2003**, *362*, 759–66; b) S. Julius, S. D. Nesbitt, B. M. Egan, M. A. Weber, E. L. Michelson, N. Kaciroti, H. R. Black, R. H. Grimm, Jr., F.-H. Messerli, S. Oparil, M. A. Schork, *New Engl. J. Med.* **2006**, *354*, 1685–97.

[6] a) R. Corcóstegui, L. Labeaga, A. Innerárity, A. Berisa, A. Orjales, *Drugs R& D* **2005**, *6*, 371–84; b) Cumulative Nce introduction index, 1983–2010, *Ann. Rep. Med. Chem.* **2011**, *46*, 531.

[7] M. J. Plater, P. Barnes, L. K. McDonald, S. Wallace, N. Archer, T. Gelbrich, P. N. Horton, M. B. Hursthouse, *Org. Biomol. Chem.* **2009**, *7*, 1633–1641.

[8] S. Harkal, F. Rataboul, A. Zapf, C. Fuhrmann, T. Riermeier, A. Monsees, M. Beller, *Adv. Synth. Catal.* **2004**, *346*, 1742–1748.

[9] a) M. Shen, T. G. Driver, *Org. Lett.* **2008**, *10*, 3367–3370; b) K. Hirano, A. T. Biju, F. Gloriua, *J. Org. Chem.* **2009**, *74*, 9570–9572.

[10] a) G. Brasche, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2008**, *47*, 1932–1934; *Angew. Chem.* **2008**, *120*, 1958–1960; b) B. Zou, Q. Yuan, D. Ma, *Angew. Chem. Int. Ed.* **2007**, *46*, 2598–2601; *Angew. Chem.* **2007**, *119*, 2652–2655; c) N. Zheng, K. W. Anderson, X. Huang, H. Nguyen, S. Buchwald, *Angew. Chem. Int. Ed.* **2007**, *46*, 7509–7512; *Angew. Chem.* **2007**, *119*, 7653–7656; d) C. Gil, S. Bräse, *J. Comb. Chem.* **2009**, *11*, 175–197.

[11] P. Wang, G. Zheng, Y. Wang, X. Wang, Y. Li, W. Xiang, *Tetrahedron* **2010**, *66*, 5402–5406.

[12] a) H. Jin, X. Xu, J. Gao, J. Zhong, Y. Wang, *Adv. Synth. Catal.* **2010**, *352*, 347–350; b) T. Ramana, T. Punniyamurthy, *Chem. Eur. J.* **2012**, *18*, 13279–13283; c) R. Chebolu, D. N. Kommi, D. Kumar, N. Bollineni, A. K. Chakraborti, *J. Org. Chem.* **2012**, *77*, 10158–10167; d) M. Pizzetti, E. De Luca, E. Petricci, A. Porcheddu, M. Taddei, *Adv. Synth. Catal.* **2012**, *354*, 2453–2464; e) L. Hao, Y. Zhao, B. Yu, H. Zhang, H. Xu, Z. Liu, *Green Chem.* **2014**, *16*, 3039–3044; f) S. Samanta, S. Das, P. Biswas, *J. Org. Chem.* **2013**, *78*, 11184–11193; g) M. S. Mayo, X. Yu, X. Zhou, X. Feng, Y. Yamamoto, M. Bao, *Org. Lett.* **2014**, *16*, 764–767; h) C. R. Carvalho, E. Fernandes, M. Manuel, B. Marques, *Chem. Eur. J.* **2011**, *17*, 12544–12555; i) Y. Kim, M. R. Kumar, N. Park, Y. Heo, S. J. Lee, *Org. Chem.* **2011**, *76*, 9577; j) H. Baars, A. Beyer, S. V. Kohlhepp, C. Bolm, *Org. Lett.* **2014**, *16*, 536; k) D. Mahesh, P. Sadhu, T. Punniyamurthy, *J. Org. Chem.* **2016**, *81*, 3227.

[13] a) A. R. Katritzky, S. Rachwal, *Chem. Rev.* **2010**, *110*, 1564–1610; b) A. R. Katritzky, S. Rachwal, *Chem. Rev.* **2011**, *111*, 7063–7120; c) A. R. Katritzky, X. Lan, J. Z. Yang, O. V. Denisko, *Chem. Rev.* **1998**, *98*, 409–548.

[14] a) A. R. Katritzky, B. Yang, *J. Org. Chem.* **1998**, *63*, 1467–1472; b) A. R. Katritzky, W. Du, Y. Mastukawa, I. Ghiviriga, S. N. Denisenko, *J. Heterocycl. Chem.* **1999**, *36*, 927–932; c) Y. Su, J. L. Petersen, T. L. Gregg, X. Shi, *Org. Lett.* **2015**, *17*, 1208–1211; d) T. Kim, K. Kim, *Tetrahedron Lett.* **2010**, *51*, 868–871; e) D. Kumar, B. B. Mishra, V. K. Tiwari, *J. Org. Chem.* **2014**, *79*, 251–266.

[15] a) N. A. Al-Jalal, M. R. Ibrahim, N. A. Al-Awadi, M. H. Elnagdi, Y. A. Ibrahim, *Molecules* **2014**, *19*, 20695–20708; b) J. K. Dutton, D. P. M. Pleynet, A. P. Johnson, *Tetrahedron* **1999**, *55*, 11927–11942; c) H. Al-Awadi, M. R. Ibrahim, N. A. Al-Awadi, Y. A. Ibrahim, *J. Heterocycl. Chem.* **2008**, *45*, 723–727; d) N. A. Al-Awadi, B. J. George, H. H. Dib, M. R. Ibrahim, Y. A. Ibrahim, O. M. E. El-Dusouqui, *Tetrahedron* **2005**, *61*, 8257–8263; e) R. A. Aitken, I. M. Fairhurst, A. Ford, P. E. Y. Milne, D. W. Russell, M. Whittaker, *J. Chem. Soc. Perkin Trans. 1* **1997**, 3107–3112; f) S. J. Barker, R. C. Storr, *J. Chem. Soc. Perkin Trans. 1* **1990**, 485–488.

[16] S. Battula, A. Kumar, A. P. Gupta, Q. N. Ahmed, *Org. Lett.* **2015**, *17*, 5562–5565.

[17] A. Kumar, N. Battini, R. R. Kumar, S. Athimoolam, Q. N. Ahmed, *Eur. J. Org. Chem.* **2016**, 3344–3348.

[18] A. K. Padala, R. R. Kumar, S. Athimoolam, Q. N. Ahmed, *Org. Lett.* **2016**, *18*, 96–99.

[19] a) F. Monnier, M. Taillefer, *Angew. Chem. Int. Ed.* **2009**, *48*, 6954–6971; *Angew. Chem.* **2009**, *121*, 7088–7105; b) I. P. Beletskaya, A. V. Cheprakov, *Organometallics* **2012**, *31*, 7753–7808; c) C. Sambiagio, S. P. Marsden, A. J. Blacker, P. C. McGowan, *Chem. Soc. Rev.* **2014**, *43*, 3525–3550.

[20] S. A. Konovalova, A. P. Avdeenko, I. L. Marchenko, *Russ. J. Org. Chem.* **2014**, *50*, 973–985.

Received: March 10, 2017

