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Transamination at the Crossroad of the One-Pot Synthesis of N-Substituted Quinonediimines and C-Substituted Benzobisimidazoles

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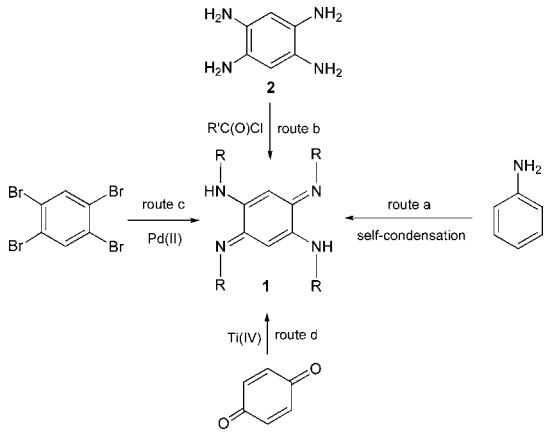
Supporting Information

ABSTRACT: A green and very efficient synthesis of N-substituted benzoquinonediimines or C-substituted benzo-bis(imidazole) derivatives is described under similar conditions. The different reaction pathway is only controlled by the nature of the primary amines, which tunes the reactivity of the intermediates.

Quinoid compounds are attracting considerable attention because of their specific properties and their numerous applications in a wide spectrum of science.[1−4] More specifically, benzoquinonediimines (BQI) of type **1** (R = alkyl or aryl) have been extensively investigated because of their remarkable fundamental and applied aspects. The former results from the unique distribution of their overall 12-π electrons system, which is best described as constituted by two 6-π electron subunits chemically connected through two C−C single bonds, but electronically not conjugated (i.e., the so-called "coupling principle"),[5] giving rise to fascinating optical properties.[6] The applied aspects correspond to the use of BQI of type **1** as reagents in three main axis: (i) in organic chemistry as precursors of benzobisimidazole derivatives,[7−9] (ii) in analytical chemistry as unusual proton sensors,[6,10] and (iii) in coordination chemistry as new ligands for the preparation of complexes that recently revealed unprecedented properties for many technological sectors,[11−17] highlighting the crucial role of the metal center but also, and importantly, of the N-substituents.

As such, different synthetic strategies giving access to N-substituted BQI **1** have been reported. In 1875, Kimish reported the first preparation by self-condensation of aniline affording **1** with R = phenyl exclusively (i.e., azophenine, route a, Scheme 1).[18] In order to extend the nature of the N-substituents, we described in 2000 a stepwise procedure from tetraaminobenzene **2**·4HCl, which required the need for highly reactive acid chlorides R′C(O)Cl and the use of metallic and strong reducing agents.[6,19] In addition, this approach affords exclusively *N*-methylenic molecules **1** (N−CH_2−R′), limiting the tuning of R (route b, Scheme 1). To overcome this limitation, Harlan et al. reported in 2004 an efficient alternative based on the Pd-catalyzed aryl amination of the 1,2,4,5-tetra-

Scheme 1. Syntheses of 1 (Limiting Factors on the Arrows)



bromobenzene (Buchwald−Hartwig coupling reaction, see route c, Scheme 1).[20,21] This route allows the use of primary amines with highly versatile R groups, but requires, however, Pd(II) catalyst, which is not environmentally friendly. Finally, Harvey et al. described more recently (2014) another metal-based strategy from benzoquinone and a primary amine catalyzed by $TiCl_4$.[22]

Therefore, elaborating a new synthesis of molecules **1** that would be simultaneously versatile (to overcome route a, b, and d) and metal-free (to overcome routes b, c, and d) is objectively of major importance in quinoid chemistry. During the course of this work, we developed, by serendipity, a new preparation of C-substituted benzobisimidazoles **3**, which have recently

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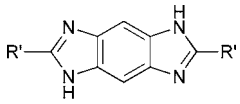
attracted major interests in numerous applications ranging from photonic[8,9,23] and sensing[24−27] to coordination chemistry[28,29] and materials science.[30] Molecules **3** have been prepared previously by using three different strategies that revealed drawbacks such as the need of a metal center[31] and/or of an electrophile of type R′C(O)X (X = H or Cl)[8,9,23−27] that limits the nature of R′.



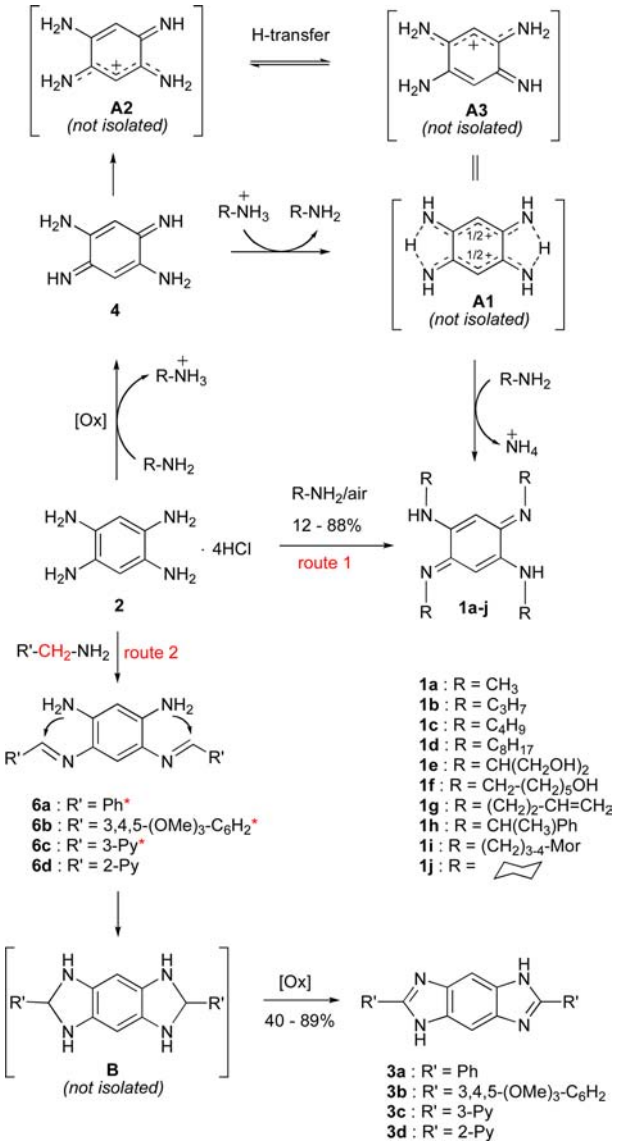
3

Herein, we report a new and efficient metal-free preparation of N-substituted BQI **1** in MeOH for which the *N*-alkyl substituents (i.e., the properties) can be easily varied by using a transamination reaction on a key intermediate **A1**. When the same reaction was conducted with primary amines of type R′−CH_2−NH_2 (R′ = aryl), the formation of unexpected benzobisimidazoles **3** could be observed in good yields.

Compound **2**·4HCl reacted with a large excess of various aliphatic primary amines RNH_2 in MeOH at room temperature under air to form a precipitate that could be isolated by filtration affording BQI **1a−j** in 12−88% yield depending on the nature of R (Scheme 2, route 1). Their ^{1}H NMR spectra showed in solution a structure of high symmetry in agreement with a fast intramolecular double proton transfer involving two degenerate tautomers (see Supporting Information (SI)).[6,32] A single crystal X-ray analysis of new **1c** confirmed the presence of four alkyl groups and established its *p*-benzoquinonediimine form (Figure 1). Examination of the bond distances within the N(1)−C(2)−C(1)−C(3)−N(2) moiety of **1c** reveals a localized π system and a C(2)−C(3) distance of 1.502(4) Å corresponding to a single bond as already observed for this class of 12-π electrons quinones.[6]

The one-pot formation of the BQI **1a−j** can be explained by (i) deprotonation of **2**·4HCl in the presence of amines RNH_2 generating RNH_3^+, (ii) air oxidation of **2** to afford intermediate **4**, which, being more basic than RNH_2, can deprotonate in turn RNH_3^+ and form a monocation **A1** that underwent (iii) a transamination reaction by nucleophilic attack of RNH_2 to give the target compounds of type **1**. In order to demonstrate the key role of **A1**, the synthesis of BQI **1a−j** was also carried out directly from **4**[33] in the presence of acid HCl, generating in situ the monoprotonated species **A1** for which the positive charge is shared between the lower (form **A2**) and upper (form **A3**) parts of the molecule (i.e., average structure (**A1**) in solution resulting from the two tautomers **A2** and **A3** in equilibrium in solution).[6] Interestingly, the reaction from **4** does not proceed in absence of acid supporting the crucial role of the iminium functions in **A1** (Scheme 2). This behavior parallels the case of zwitterionic quinoneimines for which transamination reaction occurs on the positively charged subunit.[34,35] Reaction with bulky primary amines (for which the amino function is attached to a secondary carbon) could also proceed to give **1e**, **1h**, and **1j**. Furthermore, this efficient synthesis allows the preparation of BQI **1** with interesting functionalities such as OH (**1e** and **1f**) or a C=C double bond (**1h**) that might be a precursor of choice for polymerization processes. At this stage, three additional remarks can be made: (i) depending on the nature of the primary amine (i.e., its acido-basic character), transamination reactions on the diprotonated species of **4** can not be excluded; (ii) in contrast to the related amino *p*-quinones,[36] partly transaminated compounds could not be isolated owing

Scheme 2. Syntheses of 1 and 3



*Not isolated.

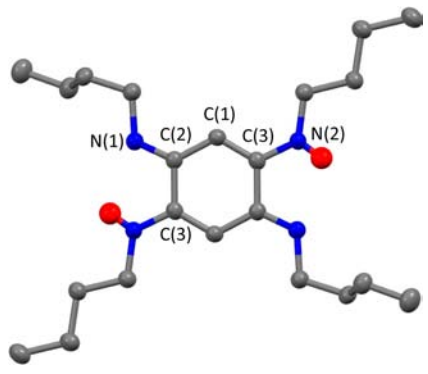


Figure 1. X-ray structure of **1c**.

the need of primary amine RNH_2 in excess and the difficult purification of the mixture (only tetra-N-substituted QDIs precipated in solution); and (iii) the use of aromatic primary amines did not succeed even under high temperatures and

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longer time reactions probably due to a weaker nucleophilic character of the amine precursors.

Remarkably, when the same reaction was carried out under similar conditions with primary amines of type $R'CH_2NH_2$ (R′ = aryl instead of alkyl group), we now observed the unexpected formation of fluorescent benzobisimidazoles **3a–d** in 40–89% yields (Scheme 2, route 2). The latter could be fully characterized (see SI) including by X-ray diffraction for **3a**, which showed am anti-NH configuration (Figure 2). This observation contrasts with the syn-NH isomer of **3a**, which was previously determined resulting from a different packing in the solid state.[30]

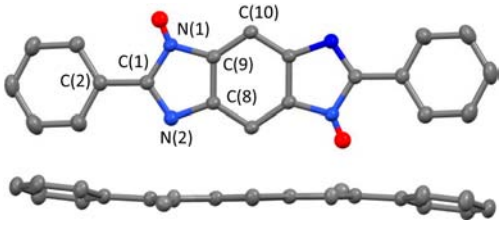
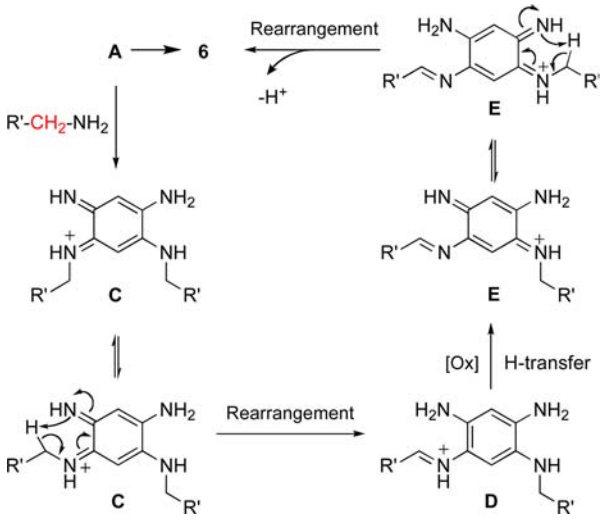


Figure 2. Molecular structure of **3a**.

The formation of compounds **3a–d** proceeds probably also by transamination reaction from intermediate **A** leading to **C**, which would be then rearranged into **D** because of the presence of the aryl group that stabilizes the intermediate by conjugation (Scheme 3). **D** would then be oxidized into **E** that underwent a similar rearrangement providing intermediates of type **6** that could be isolated in the case of **6d** (see SI).

Scheme 3. Mechanism for the Formation of Intermediates 6



When **2**·4HCl was reacted simultaneously with equimolar quantities of methylamine and benzylamine under similar conditions, we observed the formation of a complex mixture of products that could not be separated. This observation suggests similar relative reaction rates between the two primary amines.

To the best of our knowledge, the isolation of this class of compounds (**6**) is very seldom reported despite its potential in organic synthesis as 1,3-diaminobenzene precursors (only one example reported in the literature).[37] Intramolecular cyclization of **6a–d** in alcohol gives intermediates **B**, which are readily oxidized under air to afford the C-substituted benzobisimidazoles **3a–d** (Scheme 2). The ^{1}H NMR spectrum of **6d** showed the presence of two characteristic resonances at 5.66 and 8.72 ppm corresponding to the amine (NH_2) and imine (H–C=N) protons, respectively. Intramolecular cyclization of **6d** in EtOH could be followed by absorption (Figure 3) and emission

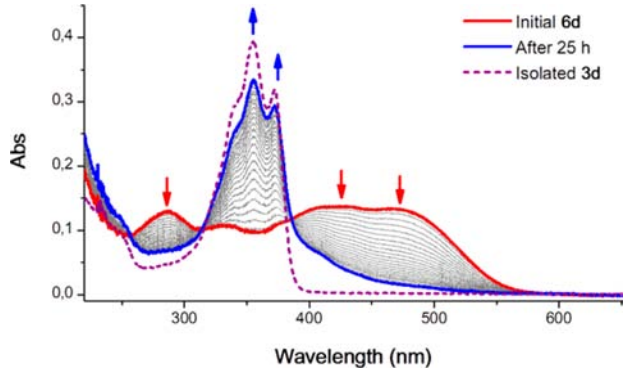


Figure 3. Intramolecular cyclization of **6d** into **3d** (EtOH at rt).

spectroscopy (Figure S17, see SI), which clearly demonstrated its full conversion into **3d** at room temperature (rt). It is noteworthy that this conversion is much faster in the presence of water and/or acid.

In conclusion, we described a new synthesis of two major classes of conjugated π-systems from the commercially available tetraaminobenzene **2**. (1) N-substituted BQI **1a–j** could be isolated through a transamination reaction on a key cationic intermediate **A1**. Unlike all the previous routes, our approach is simultaneously versatile and environmentally friendly because it allows the introduction of new functionalities, hitherto unknown, and it proceeds one-pot with no heat and no metal. (2) Benzobisimidazoles **3a–d** were also obtained in good yields by using primary amines of type $R'CH_2NH_2$ bearing an aromatic unit (R′) that modulates the reactivity (route 1 vs route 2). The versatility and simplicity of these "green" approaches pave the way for new perspectives in quinoid chemistry and photonic (benzobisimidazole-based fluorophores).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02640.

Experimental details and characterization data (PDF)
CCDC 1496322, **3a** (CIF)
CCDC 1496323, **1c** (CIF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Pataï, S.; Rappoport, Z. *The Chemistry of the Quinonoid Compounds*; Wiley: New York, 1988; Vol. *1*.
(2) Hettegger, H.; Hosoya, T.; Rosenau, T. *Curr. Org. Synth.* **2016**, *13*, 86.
(3) Lopez, J.; de la Cruz, F.; Alcaraz, Y.; Delgado, F.; Vazquez, M. A. *Med. Chem. Res.* **2015**, *24*, 3599.
(4) Moussa, J.; Amouri, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 1372.
(5) Dähne, S.; Leupold, D. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 984.
(6) Siri, O.; Braunstein, P.; Rohmer, M.-M.; Bénard, M.; Welter, R. *J. Am. Chem. Soc.* **2003**, *125*, 13793.
(7) Boydston, A. J.; Khramov, D. M.; Bielawski, C. *Tetrahedron Lett.* **2006**, *47*, 5123.
(8) Tasior, M.; Hugues, V.; Blanchard-Desce, M.; Gryko, D. *Chem. - Asian J.* **2012**, *7*, 2656.
(9) Shilova, E. A.; Heynderickx, A.; Siri, O. *J. Org. Chem.* **2010**, *75*, 1855.
(10) Elhabiri, M.; Siri, O.; Sornosa-Tent, A.; Albrecht-Gary, A.-M.; Braunstein, P. *Chem. - Eur. J.* **2004**, *10*, 134.
(11) Sarkar, B.; Schweinfurth, D.; Deibel, N.; Weisser, F. *Coord. Chem. Rev.* **2015**, *293−294*, 250.
(12) Jeon, I.-R.; Park, J. G.; Xiao, D. J.; Harris, T. D. *J. Am. Chem. Soc.* **2013**, *135*, 16845.
(13) Schweinfurth, D.; Khusniyarov, M. M.; Bubrin, D.; Hohloch, S.; Su, C.-Y.; Sarkar, B. *Inorg. Chem.* **2013**, *52*, 10332.
(14) Krupski, S.; Dickschat, J. V.; Hepp, A.; Pape, T.; Hahn, F. E. *Organometallics* **2012**, *31*, 2078.
(15) Deibel, N.; Sommer, M. G.; Hohloch, S.; Schwann, J.; Schweinfurth, D.; Ehret, F.; Sarkar, B. *Organometallics* **2014**, *33*, 4756.
(16) Ohno, K.; Nagasawa, A.; Fujihara, T. *Dalton T.* **2015**, *44*, 368.
(17) Su, Y.; Zhao, Y.; Gao, J.; Dong, Q.; Wu, B.; Yang, X.-J. *Inorg. Chem.* **2012**, *51*, 5889.
(18) Kimich, C. *Ber. Dtsch. Chem. Ges.* **1875**, *8*, 1026.
(19) Siri, O.; Braunstein, P. *Chem. Commun.* **2000**, 2223.
(20) Wenderski, T.; Light, K. M.; Ogrin, D.; Bott, S. G.; Harlan, C. J. *Tetrahedron Lett.* **2004**, *45*, 6851.
(21) Khramov, D. M.; Boydston, A. J.; Bielawski, C. *Org. Lett.* **2006**, *8*, 1831.
(22) Abdelhameed, M.; Langlois, A.; Fortin, D.; Karsentia, P.-L.; Harvey, P. D. *Chem. Commun.* **2014**, *50*, 11214.
(23) Boydston, A. J.; Vu, P. D.; Dykhno, O. L.; Chang, V.; Wyatt, A. R., II; Stockett, A. S.; Ritschdorff, E. T.; Shear, J. B.; Bielawski, C. W. *J. Am. Chem. Soc.* **2008**, *130*, 3143.
(24) Zapata, F.; Caballero, A.; Trraga, A.; Molina, P. *J. Org. Chem.* **2010**, *75*, 162.
(25) Zapata, F.; Caballero, A.; Espinoza, A.; Trraga, A.; Molina, P. *Dalton T.* **2010**, *39*, 5429.
(26) Jain, A. K.; Bhattacharya, S. *Bioconjugate Chem.* **2011**, *22*, 2355.
(27) Huang, J.; Li, G.; Wu, Z.; Song, Z.; Zhou, Y.; Shuai, L.; Weng, X.; Zhou, X.; Yang, G. *Chem. Commun.* **2009**, 902.
(28) Yoshimura, A.; Nozaki, K.; Ikeda, N.; Ohno, T. *J. Am. Chem. Soc.* **1993**, *115*, 7521.
(29) Ohno, T.; Nozaki, K.; Haga, M. *Inorg. Chem.* **1992**, *31*, 4256.
(30) Tomlin, D. W.; Fratini, A. V.; Hunsaker, M.; Adams, W. W. *Polymer* **2000**, *41*, 9003.
(31) Zhao, D.; Hu, J.; Wu, N.; Huang, X.; Qin, X.; Lan, J.; You, J. *Org. Lett.* **2011**, *13*, 6516.
(32) Rumpel, H.; Limbach, H.-H. *J. Am. Chem. Soc.* **1989**, *111*, 5429.
(33) Audi, H.; Chen, Z.; Charaf-Eddin, A.; D'Aléo, A.; Canard, G.; Jacquemin, D.; Siri, O. *Chem. Commun.* **2014**, *50*, 15140.
(34) Siri, O.; Braunstein, P. *Chem. Commun.* **2002**, 208.
(35) Braunstein, P.; Siri, O.; Taquet, J.-p.; Rohmer, M.-M.; Bénard, M.; Welter, R. *J. Am. Chem. Soc.* **2003**, *125*, 12246.
(36) Das, H. S.; Weisser, F.; Schweinfurth, D.; Su, C.-Y.; Bogani, L.; Fiedler, J.; Sarkar, B. *Chem. - Eur. J.* **2010**, *16*, 2977.
(37) Escudero-Adán, E. C.; Martínez Belmonte, M.; Martin, E.; Salassa, G.; Benet-Buchholz, J.; Kleij, A. W. *J. Org. Chem.* **2011**, *76*, 5404.

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