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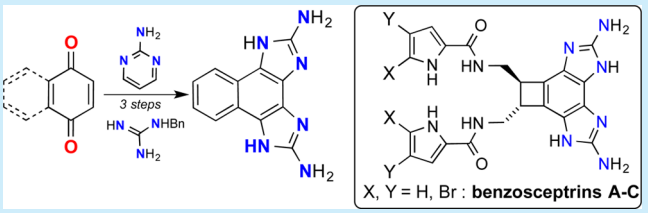
Reaction of Quinones and Guanidine Derivatives: Simple Access to Bis-2-aminobenzimidazole Moiety of Benzosceptrin and Other Benzazole Motifs

Minh Quan Tran, Ludmila Ermolenko, Pascal Retailleau, Thanh Binh Nguyen,* and Ali Al-Mourabit*

Centre de Recherche de Gif-sur-Yvette, Institut de Chimie des Substances Naturelles, CNRS, 91198 Gif-sur-Yvette Cedex, France.

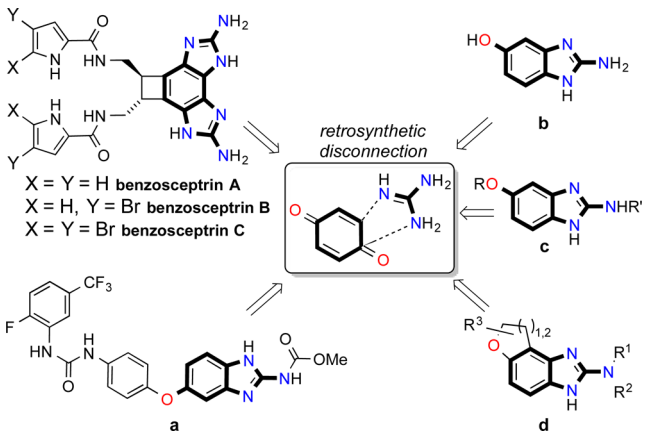
Supporting Information

ABSTRACT: A new strategy for the synthesis of 2-aminobenzimidazol-6-ols via a reaction of quinones with guanidine derivatives is reported. Sequential application of this methodology provided a simple access to the first benzosceptrin analogue bearing a bis-2-aminoimidazole moiety. A concomitant addition of two guanidines to the naphtho[1′,2′:4,5]-imidazo[1,2-*a*]pyrimidine-5,6-dione, which includes the redox neutral debenzylation and guanidine-assisted cleavage of the 2-aminopyrimidine part resulted in the synthesis of the free challenging contiguous bis-2-aminoimidazole moiety of benzosceprins in one step.



Benzimidazoles are one of the most important classes of heterocycles for drug and material development purposes.[1] Particularly intriguing is the challenging structure of the marine alkaloids benzosceptrins A and B (Scheme 1), a subgroup of

Scheme 1. Benzosceptrins and Other Bioactive 2-Aminobenzimidazoles with Possible Approach from Quinone and Guanidine



the pyrrole-2-aminoimidazole family that we have isolated from the sponges *Agelas* cf. *mauritiana* and *Phakellia* sp.[2] Interestingly, the benzimidazole substructure exists in numerous bioactive molecules such as **a** as inhibitors of VEGFR-2 and TIE-2 kinase receptors, both of which are implicated in angiogenesis,[3] simple benzimidazole **b** as inhibitors of urokinase,[4] 6-aryl/heteroalkyloxy benzimidazoles **c** as c-Met inhibitors,[5] and tricyclic **d** as inhibitors of microsomal prostaglandin E synthase-1 (mPGES-1) and therefore useful in the treatment of pain and/or inflammation from a variety of diseases or conditions such as asthma, osteoarthritis, rheumatoid arthritis, acute or chronic pain, and neurodegenerative diseases.[6]

In this context, we were eager to initiate a synthetic project of analogues of benzosceptrins and their biological activities. For this purpose and in view of the pharmacological relevance of the structures exemplified above, a simple and efficient approach to 2-aminobenzimidazoles is obviously of considerable importance in medicinal chemistry. The common methods for the synthesis of 2-aminobenzimidazoles are based on the condensation of *o*-phenylenediamines with cyanogen bromide[7] and related compounds,[8] with isonitriles under oxidizing conditions,[9] or using copper-catalyzed guanidination of 1,2-dihalobenzenes,[10] amination of 2-unsubstituted- or 2-halo-benzimidazoles,[11] cyclization of arylguanidines,[12] (2-aminophenyl)thioureas,[13] *N*-cyano-*N*′-arylhydrazines,[14] and propargylguanidine cyclization.[15]

Nevertheless, such methods suffer from difficulties in the preparation of readily oxidized *o*-phenylenediamines, the toxicity of cyanogen bromide, and the disagreeable smell of isocyanide.[16]

On several occasions, we have used oxidative addition of substituted guanidines including 2-aminopyrimidine as versatile bis-nucleophilic building blocks with olefins as in the synthesis of different target 2-aminoimidazole systems.[17] Generally, the addition−cyclization of 1,3-bis-nucleophiles such as enamines (Nenitzescu indole synthesis),[18] thioureas,[19] 2-aminothiazoles, 2-aminooxazoles and related 2-amino aza heterocycles,[20] and 2-aminopyridine[21] to benzoquinones is known to provide a benzazole bearing a hydroxy group in the benzo ring (possibly useful for further functionalization). On the basis of

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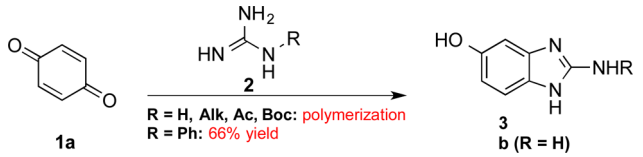
retrosynthetic disconnections for compounds presented in Scheme 1, we reasoned that the same reaction between a quinone and a guanidine derivative would constitute a straightforward approach to the desired 2-aminobenzimidazol-6-ols. Surprisingly, such reactions are only known for benzoquinone itself with 2′-deoxyguanosine as a guanidine analogue in low yields.[22]

We report herein our studies on the reaction between quinones with guanidine derivatives and their applications in the synthesis of several interesting 2-aminobenzimidazole systems.

To test our idea, we first examined the reaction of *p*-benzoquinone **1** with guanidine itself as free base or as carbonate salt at room temperature or lower in different solvents ranging from aprotic (DMF, DMSO, Et_2O) to protic (MeOH, H_2O) (Scheme 2).

Scheme 2. Reaction of Quinone 1a with Guanidines

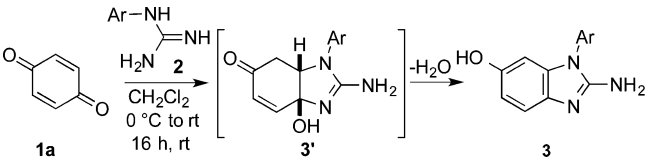


Unfortunately, contrary to our expectations, under these conditions, while guanidine remained unchanged, *p*-benzoquinone is transformed into an intractable mixture possibly due to strong base-promoted polymerization. Although unsubstituted guanidine itself is more nucleophilic than most ordinary amines,[23] this highly basic compound is capable of deprotonating water and other hydroxylic compounds (for example, the presumably formed product **b**) to yield a strongly resonance-stabilized and non-nucleophilic guanidinium cation and the corresponding oxygenated anion. The latter species, due to its sufficient basicity, can trigger a chain reaction of polymerization of *p*-benzoquinone **1a**. To overcome this problem, other guanidine derivatives with lower basicity should be used. While acetylguanidine and Boc-guanidine were shown to be unreactive in dichloromethane or toluene, they catalyzed the polymerization of the benzoquinone in methanol.

In time, we found that the reaction of phenylguanidine **2a** with benzoquinone smoothly afforded 2-aminobenzimidazole **3a** as a single regioisomer in good yield (Table 1, entry 1). The reaction of *p*-benzoquinone **1a** with various arylguanidines **2** was next investigated under the optimized conditions to yield 1-aryl-2-amino-6-hydroxybenzimidazoles **3**. The effects of substituent (methyl, methoxy, chloro) of arylguanidines **2** were then investigated. All tested arylguanidines **2** could react with *p*-benzoquinone **1a** and gave similar results, indicating that the substituent on the aromatic ring had little effects in this reaction. Careful analysis by ^{1}H NMR of the reaction mixture indicated that the primary adduct **3′** had been produced and was next dehydrated into **3** (see the Supporting Information).

To further broaden the scope of this reaction, we next extended the method to *N*,*N*′-diarylguanidines **4**. Gratifyingly, under similar conditions, this reaction worked efficiently and provided the dehydrated adduct **5** as a single regioisomer. Compared to the previous case (Table 1), the polymerization of *p*-benzoquinone **1a** in the present case (Table 2) is limited, possibly because **4** is less basic than **2**, thus resulting in better yields of **5**. In some trials, benzimidazole products **5** crystallized

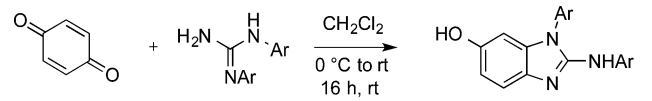
Table 1. Reaction of Quinone 1a with Arylguanidines 2[a]



entry	arylguanidine **2**	Ar	**3**, yield[b] (%)
1	**2a**	C_6H_5	**3a**, 66
2	**2b**	4-MeC_6H_4	**3b**, 61
3	**2c**	4-$MeOC_6H_4$	**3c**, 73
4	**2d**	4-ClC_6H_4	**3d**, 71
5	**2e**	2-MeC_6H_4	**3e**, 60
6	**2f**	3-MeC_6H_4	**3f**, 62
7	**2g**	3-$MeOC_6H_4$	**3g**, 58
8	**2h**	3,5-$Me_2C_6H_3$	**3h**, 62

[a]Reaction conditions: **1** (2.5 mmol), **2** (2 mmol) in CH_2Cl_2 (4 mL), 0 °C to rt then 16 h at rt. [b]Isolated yield.

Table 2. Reaction of Quinone 1 with *N*,*N*′-Diarylguanidines 4[a]



entry	diarylguanidine **4**	Ar	**5**, yield[b] (%)
1	**4a**	C_6H_5	**5a**, 93
2	**4b**	4-MeC_6H_4	**5b**, 66
3	**4c**	4-$MeOC_6H_4$	**5c**, 95
4	**4d**	4-ClC_6H_4	**5d**, 82
5	**4e**	2-MeC_6H_4	**5e**, 78
6	**4f**	3-MeC_6H_4	**5f**, 81
7	**4g**	3-$MeOC_6H_4$	**5g**, 79
8	**4h**	3,5-$Me_2C_6H_3$	**5h**, 85

[a]Reaction conditions: **1** (2.5 mmol), **2** (2 mmol) in CH_2Cl_2 (4 mL), 0 °C to rt then 16 h at rt. [b]Isolated yield.

out from the reaction mixture and could be isolated by simple filtration.

Initial mechanistic consideration suggested that various regioisomers of **3** and **5** in which the aryl groups located differently in three nitrogen atoms might be envisioned. This point was clarified unambiguously by X-ray crystallography (Figure 1) that confirmed that the formed 2-aminobenzimidazoles have structures **3** and **5**.

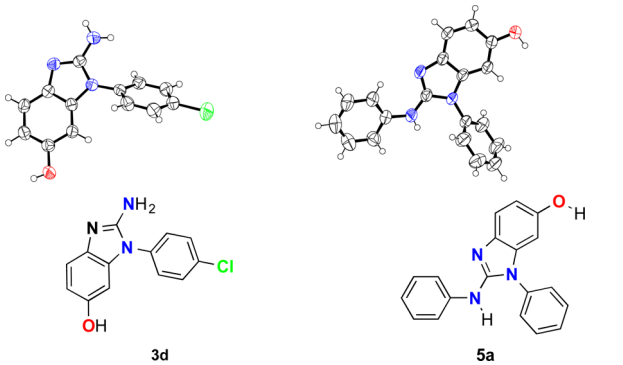


Figure 1. X-ray structure of **3d** and **5a**.

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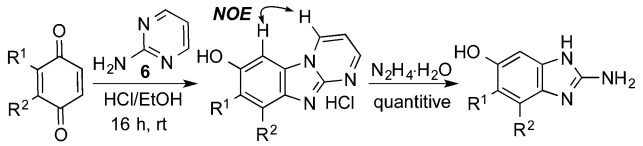
Finally, the feasibility of the reaction was also tested using 2-aminopyrimidine **6** as a weakly basic guanidine derivative (Scheme 3). In this case, the reaction with benzoquinone **1a**

Scheme 3. Fused Benzimidazole 7 from Quinone 1 and 2-Aminopyrimidine 6. Deprotection of 7 with N_2H_4



1a, $R^1 = R^2 = H$
1b, $R^1 = H$, $R^2 = Me$
1c, R^1-$R^2 = C_4H_4$

7a, $R^1 = R^2 = H$, 79%
7b, $R^1 = H$, $R^2 = Me$, 45%
7c, $R^1R^2 = C_4H_4$, 57%

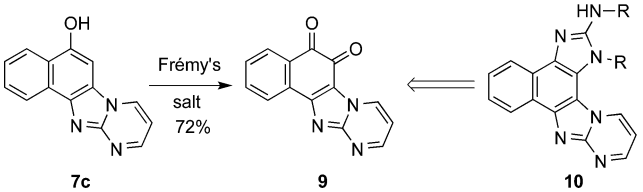
8a, $R^1 = R^2 = H$
8c, $R^1R^2 = C_4H_4$

and naphthoquinone **1b** required the presence of a strong acid (HCl) and gave good yields of fused 2-aminobenzimidazoles **7**. The regiochemistry of **7** was secured from a NOESY analysis. Deprotection[17b,24] of 2-aminobenzimidazole **7a,c** was effected efficiently by heating with hydrazine hydrate and afforded quantitatively the desired products **8a,c**.

We next turned our attention to the application of our quinone–guanidine methodology to a 2-fold reaction to provide the bis-2-aminoimidazole core of benzosceptrins. It is important to note that even if the total synthesis of benzosceptrins skeleton was not achieved, the Molinski and Romo groups described de novo synthesis of benzosceptrin C through the dimerization of oroidin using cell-free enzyme preparation.[25]

Having successfully obtained the fused condensed product **7c**, in which the benzo moiety could be considered as a disubstituted motif of the central benzene ring of benzosceptrins, we have chosen **7c** as a model substrate to investigate this idea. Oxidation of **7c** with Frémy's salt led to *o*-quinone (Scheme 4).[26] At this stage, the choice of guanidine derivative

Scheme 4. Possible Pathway for the Subsequent Reductive Guanidination of *o*-Quinone 9



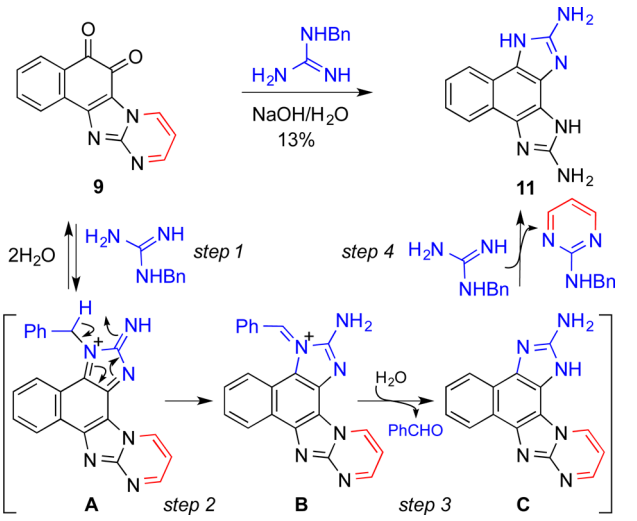
7c **9** **10**

plays a crucial role for the success of the guanidination because the final product of type **10** has a lower oxidation state than the theoretical quinone–guanidine adduct of type **A** (Scheme 5). Consequently, the condensation of **9** with a guanidine should be carried out under reducing conditions. We initially envisioned the use of an external reducing agent.

Attempted reductive guanidination using unsubstituted guanidine, methylguanidine, (di)phenylguanidines **2a** or **4a**, or 2-aminopyrimidine **6** in the presence of a reducing agent capable of promoting the well-known reaction of reductive amination such as $NaBH_3CN$ or $NaBH(AcO)_3$ did not lead to any satisfactory result.

To our delight, use of benzylguanidine as a guanidinating agent in a basic aqueous solution of NaOH[27] led to a surprisingly interesting formation of unprotected bis-guanidi-

Scheme 5. Approach to Benzosceptrin Analogue 11 from 9



9 **11**

A **B** **C**

nated naphthalene **11** as a result of a series of reactions where the reaction order is arbitrarily proposed (Scheme 5).

In fact, the addition occurred probably stepwise starting with the introduction (step 1) of the benzylguanidine moiety by an addition cyclization (**9** → **A**) giving the first adduct **A** where the bis-imidazolimine is highly electron demanding. This process is potentially reversible, but an intramolecular base-induced proton transfer (step 2) irreversibly gave the exocyclic iminium **B**. Interestingly, the outcome of this tautomerism is the reduction of the bis-imidazolimine moiety (**A** → **B**) rendered possible by the concomitant debenzylation via the oxidation of the benzyl group (step 3) generating the iminium salt. Hydrolysis of the iminium **B** gave benzaldehyde and 2-aminoimidazole derivative **C**. The reaction mixture had the distinctive odor of benzaldehyde that was identified by TLC analysis. The final result is redox-neutral, but the hydrolysis of the iminium resulted in the reduced species **C**. Finally, the interesting deprotection (step 4) of the aminopyrimidine moiety resulted in the transfer of the trimethine moiety on the free benzylguanidine (**C** → **11**). The outcome of this transfer is interesting in the sense that aminopyrimidine is regenerated. It is noteworthy that using an excess amount of NaOH was crucial, as the intramolecular redox process **A** → **B** required a base to deprotonate the α position of the benzyl group to trigger the tautomerism. The unoptimized low yield of the reaction could be explained by the formation of (1) byproducts (benzaldehyde, 2-benzylaminopyrimidine) and (2) side products issued from the degradation of quinone **9** and byproducts in a strongly basic reaction medium along with all the difficulties encountered during the column chromatography purification of highly polar and basic product **11**. One of the degradation products of quinone **9** was identified as sodium phthalate. When the reaction was performed without NaOH, the basic effect of the guanidine was not sufficient for transforming **9** into **11**. The starting material was mainly recovered with some degradation.

In summary, we have described a new simple and efficient one-step approach to a diverse range of 2-aminobenzimidazol-6-ols by the addition–cyclization reaction between quinones and guanidine derivatives. This finding is a new access to various interesting 2- aminobenzimidazole motifs. In addition to the total synthesis of benzosceptrin A that became conceivable using this approach, the prepared molecules such

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as **3**, **5**, **7**, **8**, and **11** are also to be considered as well suited for the quick preparation of a library of analogues of this biologically interesting 2-aminobenzazole derivatives. This has been successfully applied to accomplish a concise synthesis of the recently identified urokinase inhibitor **b** (**8a**) in two steps. The access in three steps to **11** that possess one of the essential features containing the bis imidazolylbenzen moiety core of the benzosceptrin skeleton is currently considered to envision the total synthesis of benzosceptrin A.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, product characterization, and copies of the ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: nguyen@icsn.cnrs-gif.fr.
*E-mail: ali.almourabit@icsn.cnrs-gif.fr.

Notes

The authors declare no competing financial interest.

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