A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

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Accepted Article

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.202104503

Link to VoR: https://doi.org/10.1002/anie.202104503

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10.1002/anie.202104503

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RESEARCH ARTICLE

KIO_4-mediated selective hydroxymethylation /methylenation of imidazo-heteroarenes: a greener approach

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Abstract: Herein, we report a KIO_4-mediated, sustainable and chemoselective approach for the one-pot C3(sp^2)-H bond hydroxymethylation or methylenation of imidazo-heteroarenes with formaldehyde, generated *in situ* via the oxidative cleavage of ethylene glycol or glycerol (renewable reagents) through the Malaprade reaction. In the presence of ethylene glycol, a series of 3-hydroxymethyl-imidazo-heteroarenes was obtained in good to excellent yields. These compounds are important intermediates to access pharmaceutical drugs, *e.g.,* Zolpidem. Furthermore, by using glycerol, bis(imidazo[1,2-*a*]pyridin-3-yl)methane derivatives were selectively obtained in good to excellent yields.

Introduction

N-heteroarenes are of great pharmacological, economic and industrial importance.[1] In particular, imidazo[1,2-*a*]pyridines (IPs), which are comprised of a typical and privileged scaffold, are widely used in the pharmaceutical industry due to their diverse biological properties.[2] Furthermore, a large number of commercially available pharmaceutical drugs have IP derivatives as an active ingredient, *e.g.*, Zolpidem (sedative and hypnotic), Necopidem (anesthetic), Saripidem (anxiolytic), Minodronic acid (for the treatment of osteoporosis), SCH28080 (H^+,K^+-ATPase inhibitor) and GSK812397 (potential activity for treating HIV infections) (Figure 1). [3-5] Also, IP derivatives can be applied as charge transporters in optoelectronics and material sciences.[6] Therefore synthesis and functionalization of the IP core has gained a raising attention.[2, 7-8]

On the other hand, reactions involving hydroxymethylation are among the most important approaches in synthetic organic chemistry, and are widely applied in the synthesis of many natural products, pharmaceuticals and biologically active compounds.[9] Moreover, the hydroxymethyl group (-CH_2OH) is among the most widely used intermediates to access attractive target/lead compounds.

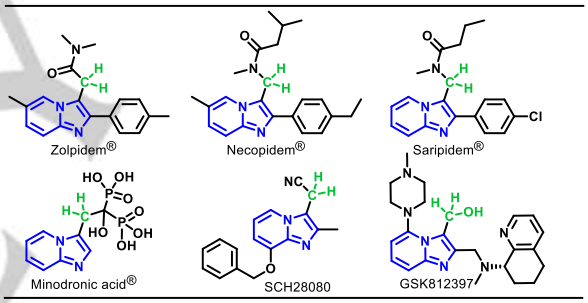

Figure 1. IP-based commercial drugs and biologically active compounds.

Traditionally, hydroxymethylation reactions involve the addition of nucleophilic carbon-centered radicals, generated from methanol, to protonated *N*-heteroarenes via the Minisci reaction[10] or the via nucleophilic addition of organometallic species (organolithium or Grignard reagents) to formaldehyde or paraformaldehyde.[11] Alternatively, the reduction of carbonyl groups, such as aldehydes, esters or carboxylic acids, also leads to this functionality.[12-13] In addition, there are a few reports of studies involving photoredox catalysis or the use of transition metal catalysts.[14-15]

Despite the biological and pharmaceutical importance of the IP core and hydroxymethylation reactions, to the best of our knowledge, there are only two methods in the literature which describe the hydroxymethylation of IPs: (i) the first approach involves Vilsmeier-Haack formylation followed by reduction of the formyl group to provide the corresponding alcohol (Scheme 1, eq. I),[16a] and (ii) the second approach involves the reaction of IP with excess formalin (aqueous formaldehyde solution) in a solution of acetic acid and sodium acetate (Scheme 1, eq. II).[16b]

Both of these methodologies are of great interest. However, a simple and straightforward approach that could be applied to a broad range of substrates which makes use of stable bench reagents is highly desirable.

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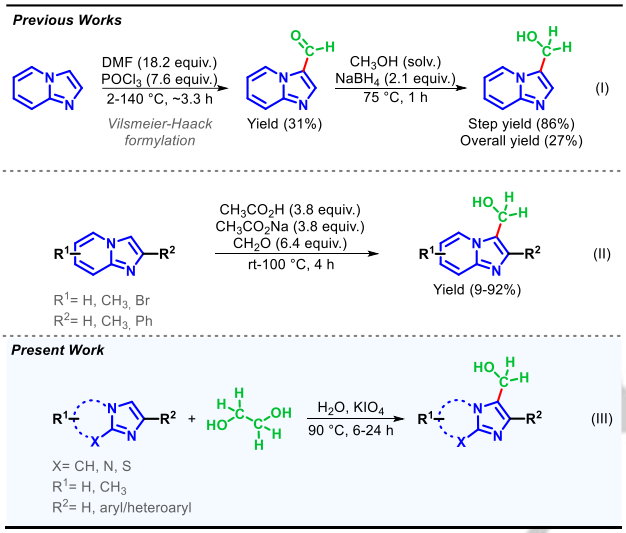
As part of our research interest in designing and developing sustainable processes, as well as the C(sp^2)-H functionalization of biologically-relevant heteroarenes,[17-18] herein, we describe, for the first time, a chemoselective and environmentally benign protocol for the hydroxymethylation of imidazo-heteroarenes via Malaprade oxidation. The reaction involves the use of IPs and ethylene glycol as substrates and KIO_4 as the oxidant, in water. In addition, the reaction has been successfully applied to other imidazo-heteroarenes (Scheme 1, eq. III). Furthermore, the use of glycerol instead of ethylene glycol results in another interesting class of compounds, bis(imidazo[1,2-*a*]pyridin-3-yl)methane (dimeric product). In view of this, we optimized a new, more efficient, sustainable and transition metal-free methodology for the methylenation of IPs.



Scheme 1. Methods for hydroxymethylation of imidazo-heteroarenes.

Results and Discussion

For the optimization of the hydroxymethylation of imidazo-heteroarenes, 2-phenylimidazo[1,2-*a*]pyridine (**1a**, 0.3 mmol) and ethylene glycol (**2a**, 1.0 molar equiv., a renewable reagent)[19] were employed as model substrates and 0.5 mL of water was used as a solvent.[20] Initially, the reaction was carried out at 50 °C for a duration of 1 h in the presence of 1.0 molar equiv. oxidant ($NaIO_4$, KIO_4, $NaIO_3$ and KIO_3, Table S1-ESI, entries 1-4). $NaIO_4$ and KIO_4 presented almost similar results, however we selected KIO_4 for further studies, considering its effectiveness, such as, ease of handling.

In the next step, the reaction temperature was optimized (entries 5-10) and 90 °C was found to be ideal for this transformation, affording hydroxymethylated product **3a** in 67% isolated yield (entry 8). Increasing the temperature above 90 °C resulted in a decrease in the yield of **3a** and the formation of bis(2-phenylimidazo[1,2-*a*]pyridin-3-yl)methane **4a** in 9% yield (entry 4). The formation of product **4a** can be attributed to the condensation of product **3a** with substrate **1a** at higher temperature.

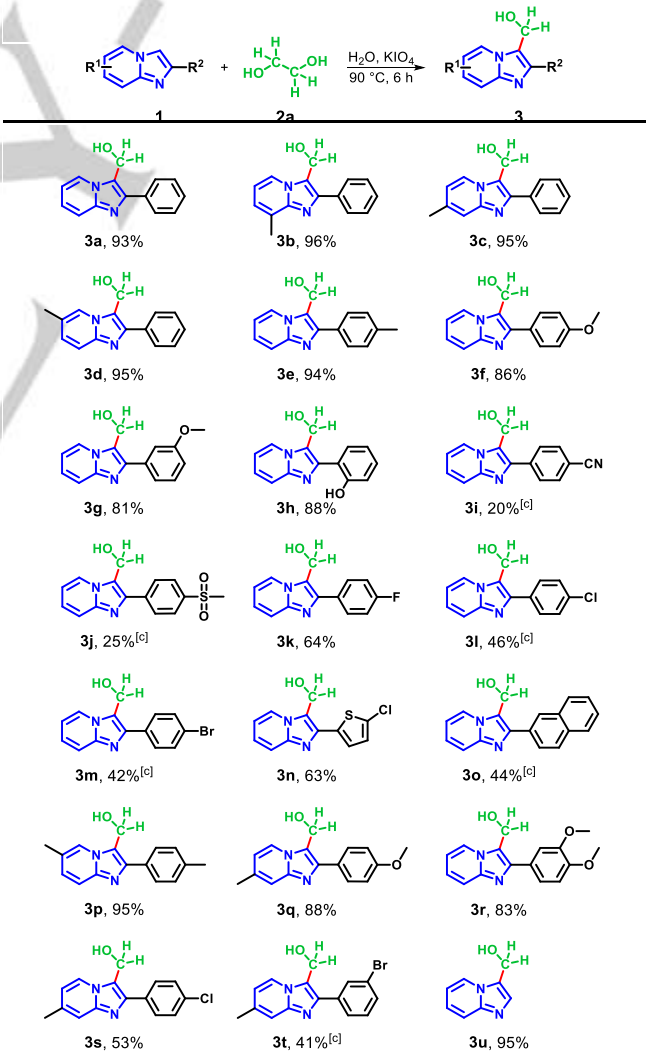
The influence of the reaction time applied in this transformation was then monitored (entries 11-16), and the optimized reaction time was found to be 6 h (entry 15) for the hydroxymethylation of **1a**.

Lastly, the use of stochiometric amounts of **2a** and KIO_4 was evaluated. In the absence of **2a** or KIO_4, no product was formed (entries 17 and 18). Decreasing the amounts of **2a** and KIO_4 resulted in **3a** in only 59% yield (entry 19). An increase in the stochiometric quantity of the reagents did not result in any improvement in the yield of **3a** (entry 20 *vs* 15).

With the best reaction parameters in hand (Table S1-ESI, Pg S3), entry 15), the generality and scope of the hydroxymethylation of IPs **2** were investigated (Table 1).

Initially, the *mono*-substituted IPs **1** with electron-donating groups (EDGs) on the pyridyl ring as well as on the C2 aryl ring were tested, where the corresponding hydroxymethylated products (**3a**-**h**) were obtained in good to excellent yields (81-96%). In the case of electron-withdrawing groups (EWGs) on the C2 aryl ring (cyano and sulfonyl groups), the corresponding products (**3i** and **j**) were obtained in low yields (20% and 25%, respectively), while halogen-substituted IPs **1** resulted in the respective products (**3k**-**m**) in moderate to good yields (42-64%). In the case of IP where C2 was substituted with a heteroaryl group, the desired product **3n** was obtained with 63% yield while IP with 2-naphthyl group, resulted in the product **3o** with 44% yield. When *di*-substituted IPs **1** (substituent on the C2 aryl ring and pyridine ring) were tested, a similar trend was observed.

Table 1. Synthesis of imidazo[1,2-*a*]pyridin-3-yl)methanol derivatives.[a, b]



[a] Reaction conditions: **1** (0.3 mmol), **2a** (1.0 molar equiv.), KIO_4 (1.0 molar equiv.), distilled water (H_2O, 0.5 mL), 90 °C, 6 h. [b] Isolated yield based on **1**. [c] Reaction time: 24 h.

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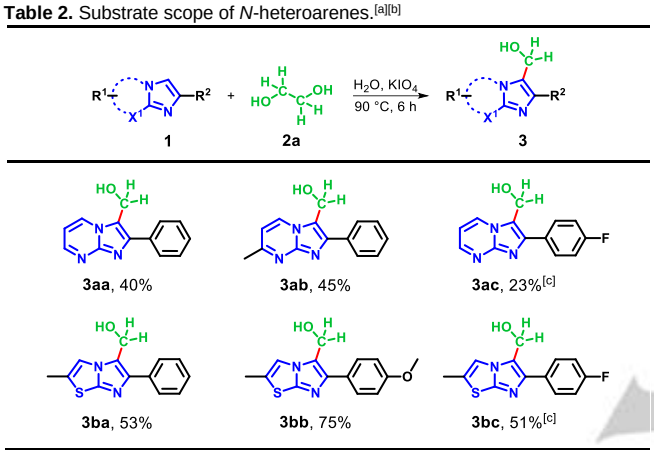
In the case of EDGs, the corresponding products (**3p**-**3r**) were obtained in good to excellent yields (83-95%), while **3s-t** were obtained in moderate yields in the case of EWG groups. Finally, with unsubstituted IP, the desired product **3u** was isolated in excellent yield.

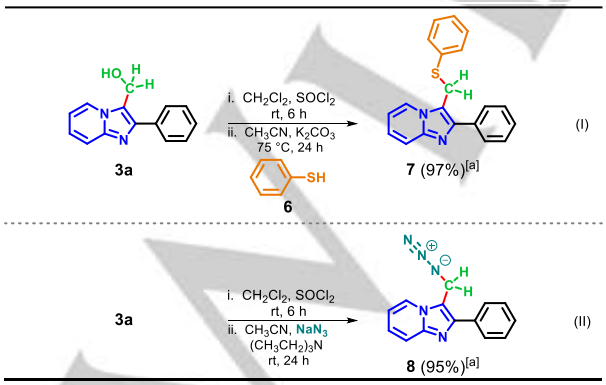
To verify the synthetic versatility of this methodology, the reaction scope was further extended to structurally different *N*-heteroarene compounds, *i.e.*, substituted imidazo[1,2-*a*]pyrimidines and imidazo[2,1-*b*]thiazoles (Table 2), under the optimized reaction conditions. The use of imidazo[1,2-*a*]pyrimidines resulted in the corresponding hydroxymethylated products **3aa**-**3ac** in yields of 23-45%, while imidazo[2,1-*b*]thiazoles afforded **3ba**-**3bc** in moderate to good yields (51-75%).

Table 2. Substrate scope of *N*-heteroarenes.[a][b]



[a] Reaction conditions: **1** (0.3 mmol), **2a** (1.0 molar equiv.), KIO_4 (1.0 molar equiv.), distilled water (H_2O, 0.5 mL), 90 °C, 6 h. [b] Isolated yield based on **1**. [c] Reaction time: 24 h.

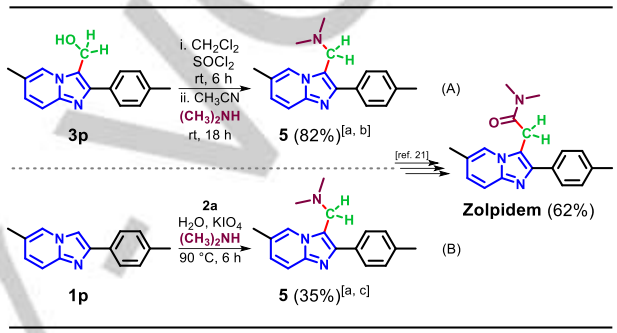
The hydroxymethylated product could be used in the synthesis of a number of interesting structures. To illustrate the synthetic utility of hydroxymethylated IPs, **3a** was used in the formation of a sulfenylated product in a one-pot approach, resulting in **7** with 97% yield (Scheme 2, eq. I). This approach motivated us to synthesize the azide-containing product, leading to **8** with 95% yield (Scheme 2, eq. II). Subsequently, compound **8** was used in the azide-alkyne cycloaddition (CuAAC) click reaction (with phenyl acetylene **9**) to obtain triazole **10** with 66% yield (Scheme S9-ESI, Pg S13).



Reaction conditions: (I) i: **3a** (0.2 mmol), CH_2Cl_2 (2 mL), $SOCl_2$ (2.0 molar equiv.), room temperature, 6 h. ii: CH_3CN (2 mL), **6** (2.0 molar equiv.), 75 °C, 24 h. (II) i: **3a** (1 mmol), CH_2Cl_2 (5 mL), $SOCl_2$ (2.0 molar equiv.), room temperature, 6 h. ii: CH_3CN (5 mL), $(CH_3CH_2)_3N$ (2.1 molar equiv.), NaN_3 (2.0 molar equiv.), room temperature, 24 h. [a] Isolated yield based on **3a**.

Scheme 2. Synthetic applications for hydroxymethylation products.

To further demonstrate the synthetic application of the hydroxymethylated product, we propose the formal synthesis of Zolpidem (commercial drug; sedative and hypnotic),[3a] Scheme 3A. This one-pot approach involves *in situ* transformation of the hydroxymethylated IP **3p** to the respective chloride from the reaction with thionyl chloride ($SOCl_2$), and subsequent reaction with dimethylamine to give the aminomethylated IP **5** with very good yield (82%). Compound **5** is the key intermediate in Zolpidem synthesis, as reported by Padi and collaborators,[21] thus, we performed its direct synthesis from IP **1p**, without the need for the preparation of **3p**. In this procedure, IP **1p** was reacted with *N,N*-dimethyl amine under the standard conditions (Scheme 3B). Despite omitting one step, we could obtain the key intermediate **5** by this direct approach, although in lower yield.



[a] Reaction conditions: (A) **3p** (0.2 mmol), CH_2Cl_2 (2 mL), $SOCl_2$ (2.0 molar equiv.), room temperature, 6 h. (II) CH_3CN (2 mL), $(CH_3)_2NH$ (30% w/v aqueous solution, 1 mL), room temperature, 18 h. (B) **1p** (0.3 mmol), **2a** (1.0 molar equiv.), KIO_4 (1.0 molar equiv.), $(CH_3)_2NH$ (30% w/v aqueous solution, 5.0 molar equiv.), distilled water (H_2O, 0.5 mL), 90 °C, 6 h. [b] Isolated yield based on **3p**. [c] Isolated yield based on **1p**.

Scheme 3. Formal synthesis of Zolpidem.

Following the success of the KIO_4-mediated hydroxymethylation of imidazoheteroarenes, we tested different sources of hydroxymethyl groups **2b-f** (Table S2-ESI, Pg S4).

Reactions with methanol **2b** or polyethylene glycol **2f** produced a mixture of products **3a** and **4a**, which were obtained in low yields (Table S2-ESI, Pg S4, entries 1 and 5). Surprisingly, when glycerol **2c** was used, the product bis(2-phenylimidazo[1,2-*a*]pyridin-3-yl)methane **4a** was obtained with 85% yield, while the hydroxymethylated product **3a** was obtained with 7% yield (entry 2). In the case of sucrose **2d** or paraformaldehyde **2e**, there was no formation of products **3a** or **4a** (entries 3 and 4).

This finding was of interest since, in the recent literature, there are only a few reports that describe the synthesis of bis(imidazo[1,2-*a*]pyridin-3-yl)methane **4** via methylenation of the IP core.[22] Despite their good features, some of these methods have limitations in terms of sustainability, such as the non-renewable methylene sources (*e.g.*, DMSO and DMA), use of organic solvents, low atom economy, very high temperature and use of a transition metal catalyst.

The results obtained (Table S2-ESI, Pg S4), entry 2) motivated us to further explore this more sustainable approach to the methylenation of IP derivatives **1** using 0.5 molar equiv. of glycerol **2c** (a renewable reagent)[23] as a methylene source in water (0.5 mL), as seen in Table S3-ESI, Pg S5. For this transformation, we selected **1a** as the standard substrate.

Initially, we varied the temperature (Table S3-ESI, Pg S5, entries 1-3) and found that 100 °C was most appropriate for this transformation, resulting only in product **4a**, with 91% yield (entry

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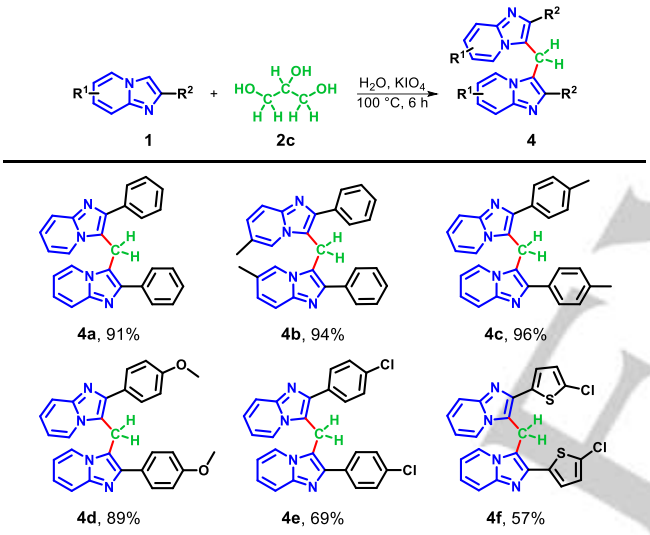
2). Subsequently, reducing the reaction time was evaluated (entries 4 and 5). However, with a shorter reaction time, a mixture of products **3a** and **4a** were obtained, with **4a** in lower yields.

The stoichiometry of the reagents, *i.e.*, glycerol and potassium periodate, was then evaluated (entries 6-8). It was observed that increasing the amounts of **2c** and KIO_4 resulted with **4a**, in 63% yield, as well as **3a**, with 11% yield (entry 6). In the absence of reagents **2c** or KIO_4 there was no reaction (entries 7 and 8).

After ascertaining the best reaction parameters (Table S3-ESI, Pg S5, entry 2), the generality and scope of this reaction in the synthesis of bis(imidazo[1,2-*a*]pyridin-3-yl)methanes derivatives **4** from IPs **1** and glycerol **2c** were investigated (Table 3). There was some influence of the electronic effect on the reaction. In general, IPs **1** with an EDG (*e.g.*, $-CH_3$ and $-OCH_3$) afforded the desired products in excellent yields compared to the EWG substituent. Furthermore, we also tested the heteroaryl substituted IP; to our delight, the reaction resulted in the product **4f** with 57% yield.

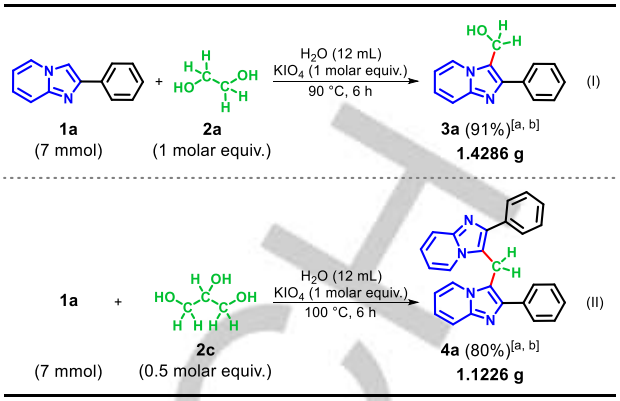
Table 3. Synthesis of bis(imidazo[1,2-*a*]pyridin-3-yl)methane derivatives.[a, b]



[a] Reaction conditions: **1a** (0.3 mmol), **2c** (0.5 molar equiv.), KIO_4 (1.0 molar equiv.), distilled water (0.5 mL), 100 °C, 6 h. [b] Isolated yield based on **1**.

The industrial importance and potential applications of these greener protocols were investigated in scale-up reactions at the gram scale (Scheme 4), using IP **1a** as the reagent under the optimized conditions. In the case of ethylene glycol, the desired product **3a** was isolated with no significant decrease in yield (Scheme 4, eq. I). Similarly, in the case of glycerol, the bis(imidazo[1,2-*a*]pyridin-3-yl)methane was obtained with 80% isolated yield (eq. II). Thus, these protocols can be used as robust methodologies for the gram-scale synthesis of the respective products, which are precursors for important bioactive molecules.

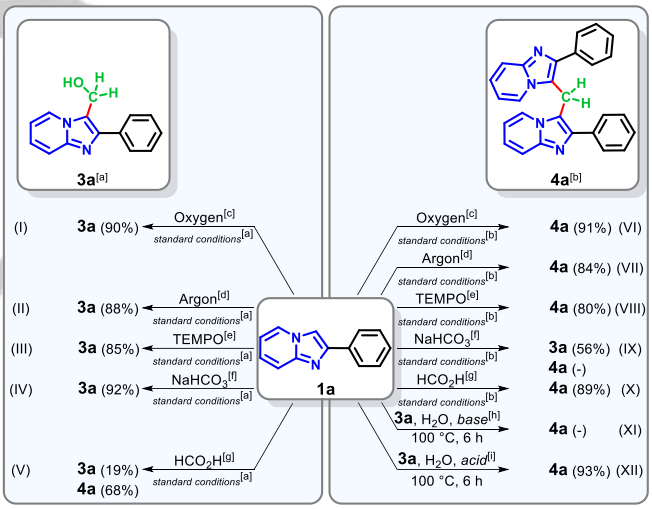
Considering the interesting features of these new coupling reactions, a number of control experiments were conducted (Scheme 5), aimed at better understanding the mechanism involved in the KIO_4-mediated C(sp^2)-H functionalization of imidazoheteroarenes.



[a] Reaction conditions: (I) **1a** (7 mmol), **2a** (1.0 molar equiv.), KIO_4 (1.0 molar equiv.), distilled water (H_2O, 12 mL), 90 °C, 6 h; (II) **1a** (7 mmol), **2c** (0.5 molar equiv.), KIO_4 (1.0 molar equiv.), distilled water (12 mL), 100 °C, 6 h. [b] Isolated yield based on **1a**.

Scheme 4. Schematic of the gram-scalable reaction.

Initially, we focused on the hydroxymethylation reaction (Scheme 5, eq. I-V) and there was no negative effect when the standard reaction was performed under oxygen or argon atmosphere (Scheme 5, eqs. I and II). The results obtained indicate that atmospheric oxygen does not actively contribute to this transformation. A radical inhibitor did not hamper the reaction and **3a** was obtained with 85% yield (Scheme 5, eq. III). Thus, the possibility of a radical pathway was disregarded.



[a] Reaction conditions: **1a** (0.3 mmol), **2a** (1.0 molar equiv.), KIO_4 (1 .0 molar equiv.), distilled water (0.5 mL), 90 °C, 6 h. [b] **1a** (0.3 mmol), **2c** (0.5. molar equiv.), KIO_4 (1.0 molar equiv.), distilled water (0.5 mL), 100 °C, 6 h. [c] Oxygen atmosphere. [d] Argon atmosphere. [e] TEMPO (2.0 molar equiv.). [f] $NaHCO_3$ (1.0 molar equiv.). [g] HCO_2H (1.0 molar equiv.). [h] **1a** (0.15 mmol), **3a** (1.0 molar equiv.), base ($NaHCO_3$, 1.0 molar equiv.), distilled water (0.5 mL), 100 °C, 6 h. [i] **1a** (0.15 mmol), **3a** (1.0 molar equiv.), acid (HCO_2H, 1.0 molar equiv.), distilled water (0.5 mL), 100 °C, 6 h. -: No product detected.

Scheme 5. Control experiments.

When the standard reaction was performed in the presence of $NaHCO_3$ as a base (Scheme 5, eq. IV), the reaction showed complete tolerance. Thus, the possibility of any acidic species being involved in this transformation can be neglected. However, when the reaction was carried out in the presence of formic acid, the product **3a** was obtained with only 19% yield. Interestingly, in this case, the dimeric product **4a** was isolated with 68% yield (Scheme 5, eq. V), indicating that the formation of **4a** is favored

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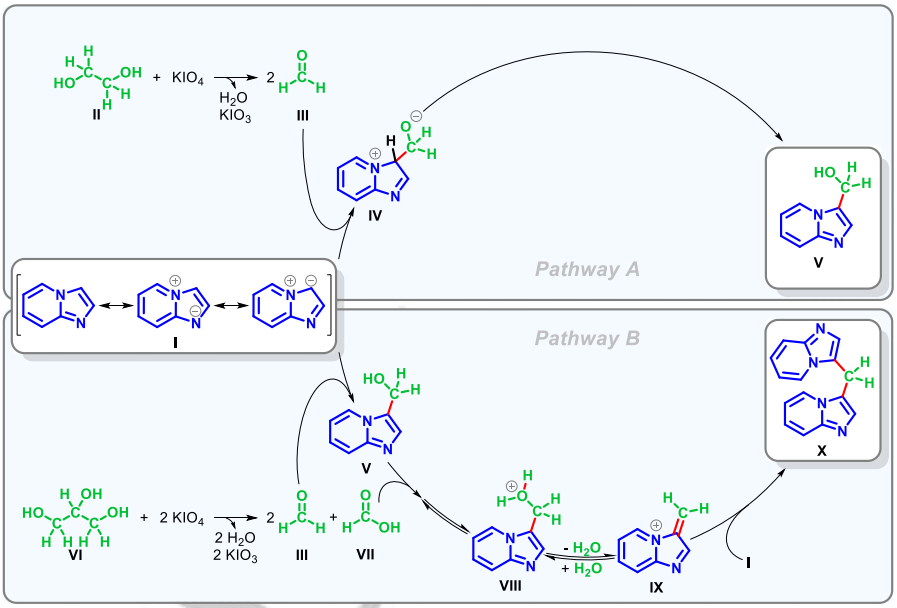
under acidic conditions. Subsequently, similar control experiments were conducted for the methylenation reaction (Scheme 5, eq. VI-XII). In the presence of an oxygen atmosphere or under inert conditions, there was no significant effect (Scheme 5, eq. VI and VII), highlighting the non-relevance of atmospheric oxygen. Similarly, the reaction proceeded normally in the presence of TEMPO, affording the product **4a** with 80% yield (eq. VIII), indicating an ionic pathway for the reaction. Surprisingly, when the standard reaction was carried out in the presence of 1 molar equiv. of base $NaHCO_3$, there was complete inhibition of the formation of product **4a**; however, in this case, compound **3a** was obtained with 56% yield (eq. IX). When the standard reaction was subsequently performed together with 1.0 molar equiv. of formic acid, the dimeric product **4a** was isolated with no significant variation in the yield (Scheme 5, eq. X). Both these results demonstrate that the formation of product **4a** is dependent on acidic conditions. In order to observe the role of the hydoxymethylated product in the dimerization reaction, we performed a standard reaction using 1 molar equiv. of **3a** in the presence of 1 molar equiv. of **1a** under both basic and acidic conditions. In the case of basic conditions ($NaHCO_3$), there was no formation of product **4a** (eq. XI). However, when formic acid was used, product **4a** was obtained with 93% yield (eq. XII). The results of these experiments demonstrate the importance of formic acid in this transformation.

Based on the results of the control experiments (Scheme 5), plausible mechanistic pathways for the hydroxymethylation and methylenation of imidazoheteroarenes could be proposed (Scheme 6). In the case of the hydroxymethylation of imidazoheteroarenes (Scheme 6, Pathway A), initially, oxidative cleavage of ethylene glycol (**II**) by KIO_4 results in the formation of formaldehyde (**III**). Subsequently, nucleophilic attack of IP (**I**) to formaldehyde (**III**) leads to species **IV**, the hydroxymethylated product (**V**) is obtained through intramolecular proton transfer (IPT).

In the methylenation reaction (Scheme 6, Pathway B), formaldehyde (**III**) and formic acid (**VII**) are generated *in situ* via oxidative cleavage of glycerol (**VI**) by KIO_4. The addition of IP (**I**) to formaldehyde (**III**) forms the hydroxymethylated product (**V**). Next, the reaction of the hydroxymethylated IP (**V**) with formic acid (**VII**) results in the formation of the species **VIII**, which generates species **IX**, detected during MS analysis.[24] Subsequently, the nucleophilic attack of C3 of another IP (**I**) to the intermediate (**IX**), results in the bis(imidazo[1,2-*a*]pyridin-3-yl)methane (**X**).



Scheme 6. Proposed mechanisms.

Conclusions

In summary, we developed synthetically attractive, robust, sustainable and chemoselective procedures for the hydroxymethylation and methylenation of imidazo-heteroarenes, providing useful products in good to excellent yields. Our synthetic protocols involve the use of renewable reagents (ethylene glycol and glycerol) and KIO_4, which generates formaldehyde (*in situ* via the Malaprade oxidation reaction) as C1 the building block. The reactions were carried out in an air atmosphere, using water as a solvent and easily accessible reagents. In the presence of ethylene glycol, hydroxymethylated products were obtained. Interestingly, the same reaction carried out with the additional presence of dimethylamine led to the most advanced intermediate of the drug Zolpidem, while the use of glycerol in the reaction resulted in the methylenated products. For the methylenation reaction, the presence of formic acid, formed during the oxidative cleavage of glycerol catalyzes this transformation. Furthermore, both methods could be applied for large-scale synthesis. These new sustainable methods for the *in situ* generation of formaldehyde have the potential to be applied as a C1 building block in different transformations, including MCR. Thus, the current report is an important contribution to the field, considering the potential synthetic, therapeutic and industrial application of these compounds.

Acknowledgements

We gratefully acknowledge CAPES (001), CNPq, CERSusChem GSK/FAPESP (grant 2014/50249-8) and INCT-Catálise for

financial support. M.S.F would like to acknowledge CNPq for a doctoral fellowship. CAPES–PrInt Project number 88887.310569/2018-00 is also acknowledged. J.R. is grateful to CNPq for funding (433896/2018-3 and 315399/2020-1). The authors also acknowledge CEBIME for the HRMS analysis.

Keywords: imidazo-heteroarenes • KIO_4 • hydroxymethylation • C(sp^2)-H functionalization • green chemistry

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[20] Optimization table and detailed discussion are available in ESI, Table S1 ESI, Pg. S3.

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[24] The species **IX** was detected in HRMS analysis of the reaction, Figure S3 ESI, Pg. 14.

10.1002/anie.202104503

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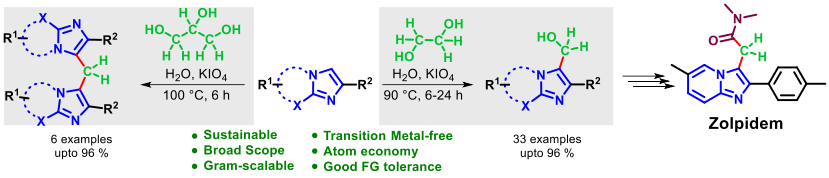

KIO_4-mediated selective hydroxymethylation /methylenation: An efficient, sustainable and chemoselective procedures for the C(sp^2)-H bond hydroxymethylation and methylenation of imidazo-heteroarenes, using KIO_4 has been developed. In the presence of ethylene glycol, hydroxymethylated products were obtained in excellent yields, while the use of glycerol in the reaction resulted in the methylenated products. The reaction allows to access the most advanced intermediate of the drug Zolpidem

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