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Calculation-assisted regioselective functionalization of the imidazo[1,2-a]pyrazine scaffold via zinc and magnesium organometallic intermediates†

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Straightforward calculations such as determinations of pK_a values and N-basicities have allowed the development of a set of organometallic reactions for the regioselective functionalization of the underexplored fused N-heterocycle imidazo[1,2-a]pyrazine. Thus, regioselective metalations of 6-chloroimidazo[1,2-a]pyrazine using TMP-bases (TMP = 2,2,6,6-tetramethylpiperidyl) such as TMPMgCl·LiCl and TMP₂Zn·2MgCl₂·2LiCl provided Zn- and Mg-intermediates, that after quenching with various electrophiles gave access to polyfunctionalized imidazopyrazine heterocycles. Additionally, the use of TMP₂Zn·2MgCl₂·2LiCl as base for the first metalation allowed an alternative regioselective metalation. Nucleophilic additions at position 8 as well as selective Negishi cross-couplings complete the set of methods for selectively decorating this heterocycle of the future.

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Introduction

N-heterocycles are ubiquitous scaffolds in pharmaceutical and agrochemical research.1 They possess unique physicochemical and medicinal properties in addition to favorable pharmacokinetics, which make their efficient further functionalization an attractive research goal.2 Besides standard N-heterocycles such as pyridines, diazines and indoles for which functionalization methods are well established, there is a current trend to investigate less common N-heterocycles as pharmaceutical scaffolds.³ Recently, we have reported the decoration of a range of new fused N-heterocycles such as pyrazolo[1,5-a]pyrimidines (1) and imidazo[1,2-b]pyridazines (2).4 From these studies, we were anticipating useful properties of the imidazo[1,2-a]pyrazine ring system (3, Scheme 1a). This structural motif has already found pharmaceutical applications as the kinase inhibitor 45 and the AKT inhibitor 56 (Scheme 1a).7 However, most previous synthetic approaches towards

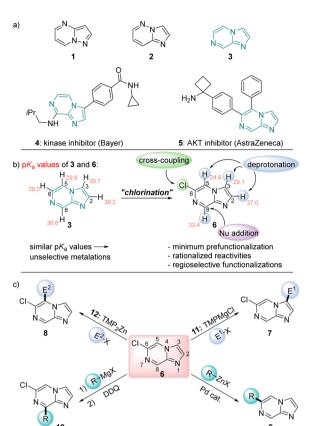
either electrophilic bromination,8 followed by Suzuki-Miyaura cross-couplings, or transition metal-catalyzed direct C-H arylations.9 As a result, there are significant limitations in scope for preparing more complex and multifunctionalized derivatives. Combining theoretical calculations and extensive experimental knowledge in the functionalization of N-heterocycles has now allowed us to develop a rational approach towards the decoration of this relatively underexplored heterocyclic scaffold. Thus, we calculated the pK_a values of all ring hydrogens of $3^{4a,b}$ in order to predict the metalation regioselectivity with TMP-bases (TMP = 2,2,6,6-tetramethylpiperidyl).10 We have found very similar pK_a values of position 3 and 5 as well as prohibitively high values for metalations in position 6 and 8 for the unsubstituted scaffold 3. In fact, metalation of 3 with TMPMgCl·LiCl (11) in THF (−60 °C, 0.5 h) produced after deuterolysis quench a 60:40 mixture of C3/C5 deuterated products. 11 This data let us consider the introduction of an electronegative substituent, which would lower all the pK_a values and introduce a larger pK_a difference between positions 3 and 5. A chlorine substituent at position 6 was an ideal solution to these problems since it can be readily removed or substituted.12 A web-search showed that 6-chloroimidazo[1,2-a]pyrazine (6) is easily prepared13 and commercially available. Calculations of the pKa values of 6 confirmed our hypothesis (Scheme 1b). Furthermore, thanks to extensive calculations, we were able to get a deeper and more accurate insight into the metalation regioselectivities of various

functionalization of the imidazo[1,2-a]pyrazine scaffold involve

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Scheme 1 (a) Heterocycles of the future 1, 2 and 3.3 (b) Calculated p K_a values indicated that a chlorination led to enhanced p K_a differences. (c) Reactivity pattern of 6 producing imidazo[1,2-a]pyrazines of type 7–10. Salts are omitted for clarity.

substituted imidazo[1,2-a]pyrazines of type 6. We realized that the relative energies of the organometallic intermediates and the inclusion of additives such as LiCl in the calculations provided a basis for the rationalization of observed regioselectivities.

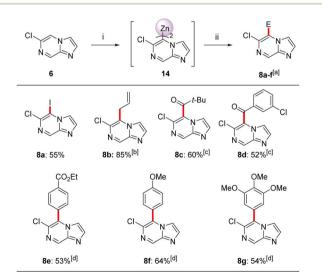
Herein, we report a versatile selective functionalization of this scaffold using regioselective metalations, nucleophilic additions and cross-couplings. As bases we have used TMP-bases¹⁰ of Mg¹⁴ and Zn¹⁵ such as TMPMgCl·LiCl^{14a} (11), and TMP₂Zn·2MgCl₂·2LiCl^{15a} (12, Scheme 1c).¹⁶

Results and discussion

Thus, we have found that the metalation of 6-chloroimidazo [1,2-a]pyrazine (6) with TMPMgCl·LiCl (11) in THF led to a selective magnesiation at position 3 at -60 °C within 30 min affording magnesium derivatives of type 13.¹⁷ The quenching of 13 with various electrophiles gave 3,6-disubstituted imidazo [1,2-a]pyrazines 7a-g in 40–78% yield (Scheme 2).¹⁸ Iodolysis of 13 gave the corresponding iodide 7a in 78% yield. Whereas, treatment of 13 with allyl bromide or acyl chlorides (25 °C, 2 h) in the presence of catalytic amounts of CuCN·2LiCl¹⁹ (20–50 mol%) furnished allylated derivative 7b in 56% yield and ketones 7c and 7d in 40–56% yield. The scope was further increased by treating Mg-intermediate 13 with commercially

Scheme 2 Regioselective magnesiation of 6-chloroimidazo[1,2-a] pyrazine (6) using TMPMgCl·LiCl (11) followed by quenching with electrophiles. Reagents and conditions: (i) TMPMgCl·LiCl (11, 1.2 equiv.), THF, -60 °C, 30 min; (ii) E-X, THF, 25 °C, 0.15-2 h; ^aisolated yield of analytically pure products; ^bthe allylation was mediated by CuCN·2LiCl (50 mol%), THF, 25 °C, 1.5 h; ^cthe acylation was mediated by CuCN·2LiCl (20–50 mol%), THF, 25 °C, 2 h.

available TsCN, ethyl cyanoformate or freshly prepared PhSO₂-SMe²⁰ affording cyano-derivative **7e**, ester derivative **7f** and thioether **7g** in 48–70% yield. The structure of **7a** was confirmed by single crystal X-ray diffraction.¹¹ DFT calculations confirmed the observed metalation regioselectivity at position 3 and clearly showed that the intermediate **13** was the most stable organometallic intermediate. In addition, we found that the NBO



Scheme 3 Regioselective zincation of 6-chloroimidazo[1,2-a]pyrazine (6) using TMP₂Zn·2MgCl₂·2LiCl (12) followed by quenching with electrophiles. Reagents and conditions: (i) TMP₂Zn·2MgCl₂·2LiCl (12, 0.6 equiv), THF, -20 °C, 15 min; (ii) E-X, THF, 25 °C, 2 h. ^aIsolated yield of analytically pure products; ^bthe allylation was mediated by CuCN·2LiCl (20 mol%), THF, 25 °C, 1.5 h; ^cthe acylation was mediated by CuCN·2LiCl (20 mol%), THF, 25 °C, 2 h. ^dPd(PPh₃)₄ (5 mol%), THF, 50 °C, 2 h.

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Scheme 4 Thermodynamically driven regioselectivity switch in the metalation of 6-chloroimidazo[1,2-a]pyrazine using either TMPMgCl-LiCl (11) or TMP $_2$ Zn-2MgCl $_2$ -2LiCl (12). Salts are omitted for clarity.

charge at C3 was the most negative among all carbon atoms in heterocycle ${\bf 6.}^{11}$

Interestingly, the treatment of 6-chloroimidazo[1,2-a]pyrazine (6) with $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (12) in THF led to a complete regioselectivity switch affording diheteroarylzinc derivatives of type 14 within 15 min at -20 °C. The Subjecting this intermediate to various electrophiles gave 5,6-disubstituted imidazo[1,2-a]pyrazine 8a-g in 52–85% isolated yield (Scheme 3).

Thus, iodolysis of **14** gave the corresponding iodide **8a** in 55% yield. Whereas, treatment of **14** with CuCN·2LiCl (20 mol%) followed by addition of allyl bromide or different acyl chlorides (25 °C, 1.5–2 h) furnished the allylated derivative **8b** in 85% yield and ketones **8c** and **8d** in 52–60%. Negishi crosscouplings²¹ of the diheteroarylzinc derivative **14** with aryl iodides in the presence of catalytic amounts of Pd(PPh₃)₄ (5 mol%, 50 °C, 2 h) gave the arylated N-heterocycles **8e–8g** in 53–64% isolated yield. The structure of **8b** was confirmed by single crystal X-ray diffraction.¹¹

The rationalization of these complementary regioselectivites may be tentatively done based on relative basicities. Thus, DFT calculations indicated that the C5-metalated intermediate 14 was preferred for thermochemical reasons, possibly due to attractive intramolecular CH···Cl interactions.11 The Zn-base 12 (bearing a N-Zn bond) is less reactive than the Mg-base 11 which is bearing a more ionic N-Mg bond. The temperatures -60 °C in the case of 13 and -20 °C in the case of 1 have been optimized to achieve the best yields.22 The observed regioselectivity reflects according to our calculations the relative stability of the produced organometallic intermediates 13 or 14 overcomes complex-inducing and proximity effects (Scheme 4).23

A second zincation of 3,6-disubstituted imidazo[1,2-*a*]pyrazine (7e) using TMP₂Zn·2MgCl₂·2LiCl (12) was also possible (Scheme 5). Thus, treatment of imidazo[1,2-*a*]pyrazine-3-carbonitrile (7e) with 12 (0.6 equiv., THF, -20 °C, 15 min) provided diheteroarylzinc intermediate 15, which was successfully quenched with electrophiles providing trisubstituted imidazo[1,2-*a*]pyrazines 16a-e in 33-72% yield. Thus, iodolysis of 15 afforded iodide 16a in 52% yield. Whereas, treatment of 15 with CuCN·2LiCl (20 mol%) followed by addition of allyl bromide or pivaloyl chloride (25 °C, 2 h) furnished allyl derivative 16b in 50% yield and ketone 16c in 33% yield. Negishi cross-couplings of the diheteroarylzinc derivative 15 with aryl iodides in the presence of catalytic amounts of Pd(PPh₃)₄ (5 mol%, 50 °C, 2 h) gave the arylated N-heterocycles 16d-e in

Scheme 5 Selective zincation of N-heterocycle 7e using TMP₂-Zn·2MgCl₂·2LiCl (12) followed by quenching with electrophiles affording trisubstituted N-heterocycles 16a–e. Reagents and conditions: (i) TMP₂Zn·2MgCl₂·2LiCl (12, 0.55 equiv.), THF, -20 °C, 15 min; (ii) E-X, THF, 25 °C, 2 h. alsolated yield of analytically pure products; the allylation was mediated by CuCN·2LiCl (20 mol%), THF, 25 °C, 1.5 h; the acylation was mediated by CuCN·2LiCl (20 mol%), THF, 25 °C, 2 h; d Pd(PPh₃)₄ (5 mol%), THF, 50 °C, 2 h.

55–72% yield. The metalation regioselectivity at position 2 of **7e** was investigated by DFT calculations showing that C2 metalated intermediate **15** was stabilized by the neighbouring LiCl and MgCl₂ *via* non-covalent interactions. In this case, we have also considered an equilibrium between various Zn-TMP bases which may contain TMP₂Zn as well as TMPZnCl. In addition, we have found that the cyano group was responsible for unfavourable steric effects onto the C5 position.¹¹

Scheme 6 Magnesiation of the trisubstituted imidazopyrazine 16e using TMPMgCl·LiCl (11) followed by various quenching reactions with electrophiles. Reagents and conditions: (i) TMPMgCl·LiCl (11, 1.2 equiv.), THF, -40 °C, 30 min; (ii) E-X, THF, 25 °C, 0.15-2 h. ^aIsolated yield of analytically pure products; ^btransmetalation with ZnCl₂ (1 M solution in THF, 1.2 equiv.), 15 min. ^cPd(PPh₃)₄ (5 mol%) THF, 50 °C, 2 h.

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A further magnesiation of 2,3-disubstituted 6-chloroimidazo [1,2-a]pyrazine derivative **16e** was possible (Scheme 6). Thus, treating the trisubstituted heterocycle 16e with TMPMgCl·LiCl (11) in THF at -40 °C within 30 min afforded the magnesiated species 17. This regioselectivity can be rationalized with calculations including LiCl, which formed the very stable mixed Li,Mg-intermediate 17 depicted in Scheme 6.11 Its quenching with electrophiles gave access to tetrasubstituted derivatives 18a-e in 39-69% yield. Thus, iodolysis of 17 provided the iodide 18a in 68% yield. Treatment of 17 with PhSO₂SMe afforded the desired sulfide 18b in 39% yield. After transmetalation with a solution of ZnCl₂ (1 M in THF, 1.2 equiv.) for 15 min the resulting heteroarylzinc species was subjected to Negishi crosscouplings with aryl iodides in the presence of catalytic amounts of Pd(PPh₃)₄ (5 mol%, THF, 50 °C, 2 h) giving the arvlated Nheterocycles 18c-e in 46-69% yield. The structure of 18a was confirmed by single crystal X-ray diffraction.11

Lithiation of the trisubstituted N-heterocycle 18e using TMPLi (19, 1.2 equiv.) at -40 °C, 10 min led to a regioselective lithiation at position 5 and subsequent trapping with iodine gave the fully functionalized N-heterocycle 20 in 40% yield (Scheme 6).24 The presence of chlorine- and iodine-substituents now opens the way for diverse further functionalizations. Concerning the replacement of the chlorine substituent, this was demonstrated by submitting 6-chloroimidazo[1,2-a]pyrazine (6) to cross-couplings with functionalized organozinc reagents of type 2125 in the presence of 5 mol% of Pd-PEPPSI-iPr26 or Pd-PEPPSI-iPent²⁷ affording functionalized 6-substituted imidazo [1,2-a]pyrazines 22a-e in up to 98% yield (Scheme 7). Thus, cross-coupling of 6 with arylzinc reagents 21a or 21b bearing a sensitive ester^{25c} or cyano^{25a} functionality led to 6-arylated imidazo[1,2-a]pyrazines 22a-b in 90-93% yield. Interestingly, alkylzinc reagents such as $21c^{25d}$ or $21d^{25d}$ showed superior results when the more sterically hindered catalyst Pd-PEPPSI-

Scheme 7 Palladium-catalyzed Negishi cross-couplings of 6 using functionalized aryl, alkyl and benzylic zinc reagents of type 21 leading to functionalized 6-substituted imidazo[1,2-a]pyrazines 22a-e. Reagents and conditions: X = Cl-MgICl-LiCl, Cl-MgBrCl-LiCl or $\text{Cl-MgCl}_2 \cdot \text{LiCl}$; R = Alk, Ar, Bz; R' = iPr or iPent. alsolated yield of analytically pure products; the cross-coupling was catalyzed by Pd-PEPPSI-iPr (5 mol%), THF, 25 °C, 5 h; the cross-coupling was catalyzed by Pd-PEPPSI-iPent (5 mol%), THF, 25 °C, 16 h.

Scheme 8 Nucleophilic addition of Grignard reagents of type 23 to 6-chloroimidazo[1,2-a]pyrazine (6). Reactions and conditions: (i) RMgX·LiCl (23, 1.2 equiv.), THF, 40 °C, 10 min; (ii) aq. workup or E-X (1.2 equiv.), THF, 25 °C, 2 h; (iii) DDQ (1.2 equiv.), THF, 25 °C, 16 h.

iPent (5 mol%)²⁷ was used resulting in the N-heterocycles **22c-d** in up to 98% yield. Finally, functionalized benzylic zinc reagent $21e^{25b}$ was an excellent substrate for this cross-coupling leading to the benzoylated heterocycle **22e** in 95% yield. Related Suzuki–Miyaura cross-couplings can be performed using **7e** and arylboronic acid esters in the presence of Pd(PPh₃)₄ (10 mol%), albeit in lower yields (up to 50% isolated yield) and under harsher reaction conditions (100 °C, 5 h).¹¹

In addition, based on previously described nucleophilic addition reactions to pyrazolo [1,5-a] pyrimidine $(1, Scheme 1)^{4c}$ we have examined the addition of Grignard reagents triggered by a coordination at the most basic nitrogen N1 (see 24). Thus, we have treated 6-chloroimidazo[1,2-a]pyrazine (6) with various organomagnesium halides complexed with lithium chloride of type 23²⁸ (Scheme 8). Indeed, the reaction of 6 with 4-methoxyphenylmagnesium bromide·lithium chloride (23a)28a gave an intermediate magnesium species 25 which after water quenching provided dihydroimidazo[1,2-a]pyrazine 26a in 63% yield. Due to instability of such partially saturated heterocycles, these compounds of type 26 were, after an aqueous work-up, directly oxidized with DDQ (DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone), furnishing 8-arylated imidazo[1,2-a]pyrazines 27a-c in 37-78% yield. This reaction sequence was also extended to the addition of alkylmagnesium reagents such as 23d-e resulting in the alkylated N-heterocycles 27d-e in 67-95% yield. Trapping of 25a with PhSO₂SPh followed by rearomatization with DDQ gave disubstituted imidazo[1,2-a]pyrazine 27f in 33% isolated yield.

Conclusions

In summary, with the help of theoretical calculations such as pK_a determinations, N-basicity evaluations, and thermochemical analysis of the various Zn or Mg organometallic intermediates, we were able to fully rationalize the observed metalation selectivities of the underexplored fused N-heterocycle scaffold **6**. Despite the general usefulness of pK_a values and N-basicities, we find the relative stabilities of the Zn- or Mg-intermediates

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were key be more helpful for the rationalization of experimental results. In addition, we found that the coordination of additives such as LiCl to the N1 position were crucial for directing the metalation to the C2 or C8 positions due to stabilizing chelating interactions as shown for intermediate 17 in Scheme 6. This "chelate"-effect is equally possible in zinc intermediate 15 (Scheme 5).11 We have successively metalated all positions of the 5,6-fused bicyclic N-heterocycle 6-chloroimidazo[1,2-a]pyrazine (6) using a combination of different bases such as TMPMgCl·LiCl (11) and/or TMP2Zn·2MgCl2·2LiCl (12) as well as TMPLi (19). The resulting metalated species were then quenched with different electrophiles giving access to a broad scope of functionalized imidazopyrazine derivatives. Furthermore, 6-chloroimidazo[1,2-a]pyrazine (6) underwent Pdcatalyzed cross-couplings using aryl, alkyl and benzylic zinc reagents allowing further functionalizations of this important heterocycle and a nucleophilic addition of Grignard reagents was also possible giving an access to partially saturated heterocycle (26a) with favorable solubilities. This calculationassisted functionalization of heterocyclic scaffolds should be applicable to further uncommon heterocycles of pharmaceutical (or agrochemical) interest and deserve further exploration.

Data availability

Crystallographic data for compounds 7a, 8b, 16a and 18a has been deposited at the CCDC under 2258909-2258912. The datasets supporting this article have been uploaded as part of the ESI.†

Author contributions

A. K., A. K., A. S., Y. C. G. and S. K. R. performed and analyzed the experiments. K. K. measured and analyzed X-ray crystal structures. V. K. and H. Z. performed DFT calculations. A. K., A. K. and P. K. designed the experiments. A. K., H. Z. and P. K. prepared the manuscript with contributions of all authors.

Conflicts of interest

There are no conflicts to declare.

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- 17 No organometallic intermediates have been isolated or characterized. Their structures are reasonable based on the obtained products and precedent in the literature as found in ref. 10.
- 18 Other regioisomers are, if any, formed in negligible amounts (less than 2%). However, these functionalized heterocycles

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