Reliable Functionalization of 5,6-Fused Bicyclic N-Heterocycles Pyrazolopyrimidines and Imidazopyridazines via Zinc and Magnesium Organometallics

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Dedicated to our colleague Professor Anja Hoffmann-Röder on the occasion of her 50th birthday.

Abstract: DFT-calculations allow prediction of the reactivity of uncommon N-heterocyclic scaffolds of pyrazolo[1,5-a]pyrimidines and imidazo[1,2-b]pyridazines and considerably facilitate their functionalization. The derivatization of these N-heterocycles was realized using Grignard reagents for nucleophilic additions to 5-chloropyrazolo[1,5-a]pyrimidines and TMP₂Zn·2MgCl₂·2LiCl allowed regioselective zinccations. In the case of 6-chlorimidazo[1,2-b]pyridazine, bases such as TMP₂Zn·MgCl₂·2LiCl, in the presence or absence of BF₃·OEt₂, led to regioselective metalations at positions 3 or 8. Subsequent functionalizations were achieved with TMP₂MgCl·LiCl, producing various polysubstituted derivatives (up to penta-substitution). X-ray analysis confirmed the regioselectivity for key functional heterocycles.

Introduction

N-Heterocycles are key scaffolds for various applications, especially in pharmaceutical and agrochemical research.[3] Monocyclic N-heterocycles, including pyridines, pyrimidines, pyridazines, pyroles, imidazoles and pyrazoles, as well as benzo-derivatives of these skeletons such as indoles and quinolines, have found numerous applications.[2] The synthesis of new N-heterocyclic cores are being actively investigated; the interest being, triggered by their potential new physicochemical and medicinal properties and favorable pharmacokinetics.[3] Two promising isomeric N-heterocycles, containing three nitrogen atoms embedded in a [4.3.0]-ring system, are pyrazolo[1,5-a]pyrimidines (1a) and imidazo[1,2-b]pyridazines (2a). These systems have been chosen based on the potential high impact of the pyrazolo[1,5-a]pyrimidine scaffold for pharmaceutical applications.[3] Thus, pyrazolo[1,5-a]pyrimidines such as zaleplon (3), a sedative and hypnotic agent,[3] the pain regulator lortictatinib 4,[6] and the kinase inhibitor 5,[7] are representative biomolecules of this important class of bicyclic N-heterocycles.[8] The antiplasmodial imidazopyridazine 6[9] is also representative for this second class of bicyclic N-heterocycles (Figure 1).

The predictive decoration of these new heterocyclic scaffolds is an important synthetic challenge. The principle of predictive functionalization has been successfully applied to various N-heterocycles using theoretical computational methods such as molecular mechanics (MM) and density-functional theory (DFT).[10] Such approaches may allow a differentiation of all possible ring positions and an assessment of the electrophilicity of each carbon as well as the acidity of each ring proton. To facilitate such reactivity differences, we choose to start with the mono-chloro-substituted compounds 1b and 2b, assuming that the chlorine substituent can be readily replaced with various functional groups at a later stage.[11]

Herein, we report a range of selective functionalizations of the isomeric N-heterocycles 1b and 2b with the help of theoretical investigations. Remarkably, this study led to a new nucleophilic addition procedure on heterocycles derived from pyrazolo[1,5-a]pyrimidine (1a). This nucleophilic addition considerably expands the functionalization opportunities of scaffold 1a and complements metalations of 1a with TMP-bases (TMP = 2,2,6,6-tetramethylpiperidyl). In the case of N-heterocycles of type 2a, calculations showed that successive metalations should allow their full regioselective decoration. These successful functionalizations of 1b and 2b are described below.
Results and Discussion

We have initiated our investigations by calculating the pKₐ-values of all ring protons in compounds 1a, 1b, 2a and 2b as well as the BF₃-complex 2c using previously developed computational protocol[10e] (Figure 1). These pKₐ-values clearly indicated that position 7 of the pyrazolo[1,5-a]pyrimidines 1b is the most acidic and should be selectively metalated. On the other hand, in the case of the chlorinated imidazo[1,2-b]pyridazine 2b the predicted pKₐ-values of H3 and H8 were identical. Thus, thermodynamic considerations will not allow a differentiation of these positions. However, kinetic considerations involving the complex-induced proximity effect (CIPE) introduced by Snieckus and Beak[12] clearly favor position 8 for a first metalation due to the preferred coordination of the metallic base to the most basic N(1)-atom. We have also examined the coordination of a strong Lewis acid such as BF₃-OEt₂ to the nitrogen atoms of 2b in order to induce a pKₐ change and have explored the impact of this change on the metalation regioselectivity. Initial calculations indicated that the thermodynamically preferred site for Lewis acid coordination is N1 (see structure 2c, Figure 1).

This coordination lowered the pKₐ-values of all protons in the Lewis acid adduct. However, the position 3 was clearly most acidified, indicating that a regioselectivity switch of the metalation might be induced through a coordination with BF₃-OEt₂ before the addition of the TMP-base.[13] Finally, we have calculated the electrophilicity of the various ring positions by using methyl anion affinities (MAA)[14] as indicated in Figure 2. Thus, the MAA of various positions for 1b and 2b have been determined, showing that position 7 of 1b was highly activated towards a nucleophilic attack (MAA(C7)= 102.0 kJ/mol). On the other hand, for the imidazo[1,2-b]pyridazine 2b the corresponding position C8 was significantly less electrophilic (MAA(C8)= 80.3 kJ/mol). In summary, the pyrazolo[1,5-a]pyrimidine 1b is expected to coordinate metallic bases such as TMPMetX (Met=Zn, Mg; X=Hal), or organometallic reagents RMetX preferentially at N (1) allowing both metalations or nucleophilic addition via primary complexes A or B (Scheme 1).

After metalation or nucleophilic addition, the organometallic intermediate 7 or 8 should be obtained. Reaction with an electrophile (E-X) or oxidative workup would yield functionalized pyrazolo[1,5-a]pyrimidines of type 9 or 10. Concerning 6-chloroimidazo[1,2-b]pyridazine (2b), a complexation of either
TMPMetX or BF$_3$·OEt$_2$ at the most basic N(1)-nitrogen atom should provide the complexes C and D. This complex C will readily lead to the metalation of position 8 affording the organometallic species 11 which after reaction with an electrophile E–X will afford 8-functionalized 6-chloroimidazo[1,2-b]pyridazine of type 12. Alternatively, the complexation with BF$_3$·OEt$_2$ leading to the adduct D, will complex TMPMetX at the next basic nitrogen atom N(5), providing the complex E. By proximity, complex E will lead to a metalation at position 3 furnishing the organometallic species 13, which after subsequent quenching with an electrophile E–X will give 3-functionalized imidazopyridazines of type 14 (Scheme 2).

According to these predictions, we first investigated the metalation of the pyrazolo[1,5-a]pyrimidine 1b and have found that TMP$_2$Zn·2MgCl$_2$·2LiCl (15) in THF led to a selective zincation at the predicted 7-position at -40°C within 10 min, affording the diheteroarylzinc derivative 16. The use of TMPMgCl·LiCl (17) and other related bases were much less satisfactory. The quenching of the organozinc intermediate 16 with various electrophiles provided disubstituted pyrazolo[1,5-a]pyrimidines 18a–18f in 48–81% isolated yield.

Figure 2. Methyl anion affinity values (MAA, in kJ/mol) calculated at SMD-(DMSO)/B3LYP/6-311 + + G(3df,2pd) //B3LYP/6-31G(d,p) level of theory. [a] Addition of methyl anion leads to Cl elimination.

Scheme 1. Predicted reactivity of the 5,6-fused bicyclic heterocycle 5-chloropyrazolo[1,5-a]pyrimidine 1b. Met=Zn, Mg.

Scheme 2. Predicted reactivity of the 5,6-fused bicyclic heterocycle 6-chloroimidazo[1,2-b]pyridazine 2b. Met=Zn, Mg.
Thus, iodolysis of 16 gave the corresponding iodo-derivative 18a in 81% yield. Treatment of 16 with CuCN·2LiCl (50 mol%) followed by the addition of benzoyl chloride derivatives (25°C, 2 h) furnished the ketones 18b and 18c in 48–54% yield. Negishi cross-couplings [19] of the diheteroarylzinc derivative 16 with various aryl iodides in the presence of catalytic amounts of Pd(dba)2 (5 mol%; dba = dibenzylideneacetone) and tfp [20] (10 mol%; tfp = tri(2-furyl)phosphine, 40°C, 2 h) gave the arylated N-heterocycles 18d–18f in 65–79% isolated yield.

Although the nucleophilic addition to electron-deficient heterocycles was reported previously, only a few classes of N-heterocycles besides pyridines led to practical applications. In addition, most reported nucleophilic addition reactions to N-heterocycles required either very harsh conditions or a preactivation via ionic intermediates such as pyridinium ions. Based on the previously mentioned theoretical calculations (Figure 2), we treated pyrazolo[1,5-a]pyrimidine (1b) with various organometallics, of which organomagnesium halides complexed with lithium chloride of type 19 gave the best results (Scheme 3). Thus, iodolysis of 16 gave the corresponding iodo-derivative 18a in 81% yield. Treatment of 16 with CuCN·2LiCl (50 mol%) followed by the addition of benzoyl chloride derivatives (25°C, 2 h) furnished the ketones 18b and 18c in 48–54% yield. Negishi cross-couplings [19] of the diheteroarylzinc derivative 16 with various aryl iodides in the presence of catalytic amounts of Pd(dba)2 (5 mol%; dba = dibenzylideneacetone) and tfp [20] (10 mol%; tfp = tri(2-furyl)phosphine, 40°C, 2 h) gave the arylated N-heterocycles 18d–18f in 65–79% isolated yield.

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was then trapped with PhSO₂SMe\textsuperscript{(28)} (1.2 equiv., 25 °C, 1 h) leading to a single trans-diastereomer of type 20.\textsuperscript{(29)} These partially saturated heterocycles proved not to be bench-stable and decomposed slowly over time. Therefore, these compounds were directly oxidized with DDQ (DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, 1.2 equiv., 40 °C, 5–7 h) in THF, furnishing the tri-substituted pyrazolo[1,5-a]pyrimidine 21a in 65% overall yield. An addition of 19a to 1b followed by an aqueous work-up and DDQ-oxidation, gave the di-substituted N-heterocycle 21b in 48% yield. This reaction sequence was also extended to other electrophiles. Thus, the addition of ethyl cyanoformate (2.0 equiv., 25 °C, 3 h) gave the polyfunctional N-heterocycle 21c in 60% yield. Also, copper-mediated acylation with pivaloyl chloride furnished the ketone 21d in 47% yield. Other arylmagnesium reagents such as 4-chlorophenyl-magnesium bromide (19b) or 3,5-dimethylphenylmagnesium bromide (19c) gave the expected pyrazoloypyrimidine 21e and 21f in 54–67% yield after PhSO₂SMe quench and rearamORIZATION with DDQ. The nucleophilic addition of alkylmagnesium reagents was also possible, as demonstrated by use of iPrMgCl·LiCl. Various trapping reactions with PhSO₂SMe, PhCOCl and NCCO₂Et followed by a DDQ oxidation gave the expected products 21g–21i in 44–60% overall yield (Scheme 4).

As mentioned above, the partially reduced adducts of type 20 were moderately stable. However, we were able to isolate the 7,6-disubstituted product 20a, in 78% yield (Scheme 5). This compound could be stored at 0 °C for 2–3 d. Considerably better stabilities were observed for the fully reduced pyrimidine ring products obtained by treating compounds of type 20 with Na(CN)BH₄ (2.0 equiv., 1 M HCl, H₂O; MeOH, 25 °C, 2 h) providing fused N-heterocycle 22a and diastereomerically pure trans-22b in 41–56% isolated yield. Interestingly, the arylation of 1b with p-anisylzinc chloride\textsuperscript{(27)} (23, 1.5 equiv.) in the presence of 2.5% Pd(OAc)₂ and 5% SPhos\textsuperscript{(28)} (50 °C, 1.5 h) gave the fused heterocycle 24 in 70% yield (Scheme 6). This N-heterocycle 24 underwent the same sequence (nucleophilic addition, electrophilic quench and reduction) as outlined in Scheme 6, providing the bicyclic pyrazine 25 as a single diastereomer. The relative configuration was established using X-ray analysis\textsuperscript{(17)} by converting 25 into the corresponding benzamide 26 (PhCOCl, 1.1 equiv.) in 80% yield.

Furthermore, the post-functionalization of position 3 of the pyrazine ring of 26 was realized by iodination using NIS\textsuperscript{(29)} (1.0 equiv.) in acetonitrile (25 °C, 1 h), affording the iodo N-heterocycle 27 in 63% yield. This iodide was readily arylated by a Negishi cross-coupling\textsuperscript{(19)} with p-anisylzinc chloride 23 providing the 3-arylated heterocycle 28 in 51% yield (Scheme 6). Furthermore, we have derivatized tri-substituted heterocycles 21c and 21f in order to prepare highly functionalized derivatives. Thus, treatment of 21c with pyrrolidine at 25 °C for 2 h provided an addition-elimination reaction\textsuperscript{(30)} the aminated product 29 in 92% yield. Iodination of 29 as described above with NIS gave the 3-iodinated pyrazine derivative 30 which after Negishi cross-coupling\textsuperscript{(19)} provided the tetra-substituted pyrazolopyrimidine 31 in 58% yield. On another hand, formylation of 29 by a Vilsmeier–Haack reaction\textsuperscript{(31)} using POCl₃ in DMF gave the 4-substituted heterocycle 32 in 74% yield. The structure of 32 was confirmed by X-ray analysis.\textsuperscript{(17)} Conversion of 32 to the oxadiazole derivative 33 was achieved by a two-step sequence in an overall yield of 60% using benzoylhydrazide followed by oxidative cyclization.\textsuperscript{(31)} Also, the bromination of 21f with NBS\textsuperscript{(32)} gave the bromo-derivative 34 in 96% yield. Br/Mg-exchange of 34 with iPrMgCl·LiCl\textsuperscript{(33)} gave an intermediate magnesium reagent, which was cyanylated with TsCN\textsuperscript{(34)} affording the nitrile 35 in 59% yield (Scheme 7).

The carbon-chloride bond of 21c, 21d and 21f was further used to increase the complexity of these heterocycles by straightforward derivatization. Thus, Sonogashira cross-coupling of 21c with propargylic alcohol (36) using a dual copper-

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\textsuperscript{(17)} Conversion of 32 to the oxadiazole derivative 33 was achieved by a two-step sequence in an overall yield of 60% using benzoylhydrazide followed by oxidative cyclization.\textsuperscript{(31)} Also, the bromination of 21f with NBS\textsuperscript{(32)} gave the bromo-derivative 34 in 96% yield. Br/Mg-exchange of 34 with iPrMgCl·LiCl\textsuperscript{(33)} gave an intermediate magnesium reagent, which was cyanylated with TsCN\textsuperscript{(34)} affording the nitrile 35 in 59% yield (Scheme 7).
palladium catalysis\(^{[26]}\) provided the alkynylated product 37 in 59\% yield (Scheme 8).

Treatment of 21d with hydrazine hydrate\(^{[27]}\) provided the annulated heterocycle 38 in 62\% yield. Finally, Negishi cross-couplings\(^{[28]}\) of 21f with PhZnCl\(_2\)-LiCl furnished the phenylated product 39 in 66\% yield. We turned then our attention to the functionalization of 6-chlorimidazo[1,2-b]pyridazine (2b) according to the prediction depicted in Scheme 2. Thus, we have treated 6-chloroimidazo[1,2-b]pyridazine (2b) with TMPMgCl-LiCl (17)\(^{[29]}\) in THF which led to a selective magneisation at the predicted 8-position at -60\(^\circ\)C within 30 min, affording magnesiumated species of type 40. Thus, iodolysis of 40 afforded the corresponding iodo-derivative 41a in 73\% yield (Scheme 9). Treatment of 40 with electrophiles such as PhSO\(_2\)Me, PhSO\(_2\)SPh\(^{[30]}\) gave sulfides 41b, and 41c in 63–76\% yield whereas, treatment with commercially available TsCN gave cyano-compound 41d in 47\% yield. Unfortunately, direct Kumada cross-coupling\(^{[31]}\) of type 40 with aryl iodides gave an unsatisfactory result. We found that, iodide 41a was readily aryalted with different arylzinc derivatives (p-anisylzinc chloride 23, or p-carbethoxyphenylzinc chloride lithium chloride 42) via Negishi cross-coupling\(^{[32]}\) in the presence of catalytic amounts of Pd(dbah)\(_2\) (5 mol\%) and tfp\(^{[33]}\) (10 mol\%, 25\(^\circ\)C, 0.5 h) giving the aryalted N-heterocycles 43a-43b in 83–88\% isolated yield.

As described above in Scheme 2 a complexation of 2b with BF\(_3\)-OEt\(^{[34]}\) allowed a regioselectivity switch with TMPMgCl-LiCl (44) in THF at -20\(^\circ\)C within 20 min, affording zinicated N-heterocycle of type 45 (Scheme 10). The quenching of 45 with various electrophiles provided the 3,6-disubstituted imidazo[1,2-b]pyrazidines 46a-46e in 32–83\%.

Thus, iodolysis of 45 provided the corresponding iodo-derivative 46a in 83\% yield. Treatment of 45 with CuCN·2LiCl (20 mol\%)\(^{[35]}\) followed by addition of acyl chlorides, allyl bromide (25\(^\circ\)C, 2 h) furnished the ketones 46b, 46c and allylated N-heterocycle 46d. Negishi cross-couplings\(^{[36]}\) of the diheteroarylzinc derivative 45 with p-iodoanisole in the presence of catalytic amounts of Pd(PPh\(_3\))\(_2\) (5 mol\%, 40\(^\circ\)C, 2 h) gave the aryalted N-heterocycle 46e in 67\% isolated yield. The structure of 46c was confirmed by X-ray analysis\(^{[37]}\). A second metlation using TMPMgCl-LiCl (17) was also possible (Scheme 11). Treatment of 6-chloro-8-phenylthio-N-heterocycle 41c (from Scheme 9) with 17 (1.2 equiv., THF, -60\(^\circ\)C, 0.5 h) provided a full conversion to 3-magnesiated N-heterocycle 47.

This organometallic intermediate was successfully quenched with typical electrophiles providing 3,6-trisubstituted imidazo[1,2-b]pyrazidines 48a-48e.

Thus, iodolysis of 47 provided the corresponding iodo-derivative 48a in 69\% yield. Treatment of 47 with pivaloyl chloride, allyl bromide in the presence of CuCN·2LiCl (20 mol\%) or with benzoyl chloride (25\(^\circ\)C, 2 h) in the presence of Pd(PPh\(_3\))\(_2\) (5 mol\%)\(^{[38]}\) furnished the ketones 48b, 48c in 75–93\% yield and allyl compound 48d in 70\% yield. Whereas, quenching the

\[\text{Scheme 7. Post-functionalization of the pyrazine ring of heterocycles 21c and 21f leading to tetra-substituted pyrazolo[1,5-a]pyrimidines 31, 33 and } 35.\]

\[\text{Reagents and conditions: (i) Pyrrolidine (1.5 equiv.), THF, 25\(^\circ\)C, 2 h; (ii) NIS, MeCN, 25\(^\circ\)C, 1 h; (iii) 23, Pd(OAc)\(_2\) (2.5 mol\%), SPhos (5 mol\%), THF, 50\(^\circ\)C, 1.5 h; (iv) POCl\(_3\), DMF, 25\(^\circ\)C, 12 h; (v) PhCONHNHMe, MeOH, 25\(^\circ\)C, 1 h; (vi) K\(_2\)CO\(_3\), dioxane, 80\(^\circ\)C, 3 h; (vii) NBS, MeCN, 25\(^\circ\)C, 1 h; (viii) Pd(OAc)\(_2\) (2.5 mol\%), SPhos (5 mol\%), THF, 50\(^\circ\)C, 1.5 h; (ix) TsCN, MeCN, 25\(^\circ\)C, 30 min; (x) TsCN, 25\(^\circ\)C, 3 h.}\]

\[\text{Isolated yield of analytically pure compounds.}\]
intermediate 47 with TsCN (1.5 equiv., 25 °C, 3 h) gave cyano-derivative 48e in 77% yield.

A third functionalization of the imidazo[1,2-b]pyridazines skeleton was demonstrated on the ketone 48b (Scheme 12). Therefore, treating 48b with TMPMgCl·LiCl (17) in THF at −40 °C within 20 min afforded selectively 2-magnesiated species of type 49. The quenching of organomagnesium intermediates (49) with various electrophiles provided tetra-substituted imidazo[1,2-b]pyridazines 50a-50d. Thus, iodolysis of 49 furnished the corresponding iodo-derivative 50a in 83% yield. Treatment of 49 with TsCN (1.5 equiv., 25 °C, 2 h) gave cyano-derivative 50b in 75% yield. Magnesiated species of type 49...
underwent transmetalation with a 1 M THF solution of ZnCl₂ (1 equiv.) for 15 min giving a diheteroarylzinc species. The resulting zinc reagents were subjected to cross-coupling with various aryl iodides in the presence of catalytic amounts of Pd(OAc)₂ (5 mol%) and XantPhos (10 mol%), 40 °C, 4 h) to give the arylated N-heterocycles 48a-48e in 43–70% isolated yield.

Furthermore, oxidation of sulfide 50b with m-CPBA (1.5 equiv., 25 °C, 2 h) afforded the sulfoxide 51 as a pure compound in 85% yield. Reacting sulfoxide 51 with pyrrolidine (1.5 equiv., 0 °C, 20 min) led to a selective substitution of the sulfoxide moiety (and not a substitution of the chloride) giving amine 52 in 46% yield. The structure of 52 was confirmed by X-ray analysis.

In addition, magnesiation of sulfoxide 51 with TMPMgCl·LiCl (17) in THF (−60 °C, 1 min) led to a fast metalation at the 7-position 53 (Scheme 13). The iodolysis of 53 afforded an unstable iodo-derivative 54a which was characterized by mass spectrometry, but was too unstable to record full analytical data. Therefore, we quenched 53 with allyl bromide (2 equiv., 25 °C, 0.5 h) in the presence of CuCN·2LiCl (50 mol%) and in this case we were able to isolate fully substituted 54b in 58% yield. The structure of 54b was confirmed by X-ray analysis.

We suspected that the sulfoxide moiety was responsible for the instability of these heterocycles. We overcame this problem by in situ treatment of sulfoxides with pyrrolidine (5 equiv., 25 °C, 10 min) to give penta-substituted imidazo[1,2-b]pyridazines 55a-55d in 30–70%.

Conclusion

In summary, by using theoretical calculations of new N-heterocyclic scaffolds 1b and 2b, we were able to establish a reliable protocol for the functionalization of most positions of 5,6-fused bicyclic pyrazolopyrimidines of type 1b and imidazolopyridazines of type 2b combining nucleophilic addition of Grignard reagents (in the case of 1b) and successive metalations using various TMP-zinc and magnesium bases. This study allowed a straightforward and rational functionalization of the
two scaffolds of pyrazolo[1,5-α]pyrimidines (1a) and imidazo[1,2-b]pyridazines (2a). Further extensions of this approach with the help of theoretical calculations and consideration for organometallic functionalizations of other complex N-heterocycles are currently underway.

Experimental

Full details of materials, synthetic procedures and product analysis can be found in the Supporting Information.

Deposition Number(s) 2155748 (26), 2155751 (32), 2155749 (46c), 2155750 (52), 2155752 (54b) contain(s) the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

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Conflict of Interest

The authors declare no conflict of interest.

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Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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See Supporting Information.

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