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A versatile access to pyridazines with tethered imidazolium groups—new precursors for mono- and binucleating NHC/pyridazine hybrid ligands

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Abstract—One or two imidazolium groups have been attached to the 3- and 6-positions of the pyridazine heterocycle, providing valuable precursors for mono- and binucleating NHC/pyridazine hybrid ligands. For *N*-methyl imidazole with specific backbone substituents an unexpected methyl group transfer is observed, which defines the scope of the synthetic procedure. H-Bonding patterns in the solid state are elucidated by X-ray crystallography for seven chloride or PF_6^- salts of the new compounds.

1. Introduction

Compounds containing N-heterocyclic carbenes (NHCs) have attracted a lot of attention as ligands towards transition metals,[1–3] mainly sparked by the discovery of a first stable NHC by Arduengo et al. in 1991.[4] The original and most commonly used NHCs usually bear two identical bulky hydrocarbon groups at the nitrogen atoms of the imidazole ring, since the required symmetric imidazolium salts that serve as precursors for such NHCs are conveniently accessible via standard preparation procedures.[5] Their availability and versatile usability make them a preferred class in NHC chemistry, for example, in Grubbs-type catalyst.[6] Over the last years, manifold variations have been introduced into this chemistry, like substitutions at the backbone of the imidazole or NHCs having different groups in the periphery,[7–9] including linkers to connect several NHCs within one ligand molecule and/or side arms containing additional heteroatoms as potential donor atoms in pincer complexes.[10,11] In a further elaboration, rigid scaffolds with several imidazolium groups and a central bridging unit may support the formation of preorganized NHC-based bimetallic complexes.[12–14] However, the latter type of complex is still quite rare, largely because of the paucity of versatile synthetic approaches to the required binucleating NHC-containing ligands.

Pyridazines are well established as potential bridging units in binuclear complexes since they are capable of spanning two metal ions via their two N atoms.[15–17] We therefore set out to attach different imidazolium groups to the 3,6-positions of the pyridazine heterocycle in order to provide a multifunctional ligand framework for binuclear NHC complexes.[13] The synthesis of such pyridazine/imidazolium hybrid ligands **2** turned out to strongly depend on the substitution pattern of the imidazoles, and in some cases reactions took an unexpected course. The scope and limitations of the synthetic approach for this type of ligands and closely related type **3**, **4** and **5** compounds are reported in this contribution (Fig. 1).

2. Results

A few 3,6-bis(imidazolium-3-yl)pyridazines have already been published.[12,13] The general synthetic route is depicted in Scheme 1. The substituted imidazoles employed in this work are listed in Table 1.

All reactions were performed in a melt of the neat reactants, that is, without any solvent, because even in high boiling solvents such as chlorobenzene or xylene no product formation was observed and only unreacted starting materials could be recovered. Stoichiometry

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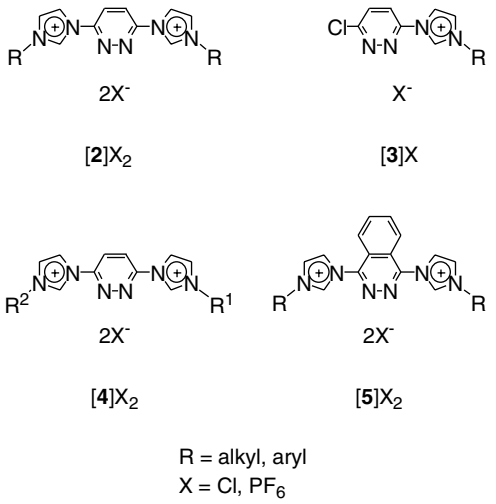


Figure 1. General scheme of compounds **2–5**.

has a major impact on the reaction: using a ratio 3,6-dichloropyridazine to substituted imidazole of approx. 1:6 almost exclusively gives the desired [**2**]Cl_2. An inverted ratio yields [**3**]Cl, in some cases accompanied by traces of the respective [**2**]Cl_2. The excess of 3,6-dichloropyridazine or substituted imidazole can usually be recovered almost quantitatively. When equimolar amounts are used, that is, when none of the reactants is present in significant excess, overall yields are quite low and/or mixtures are obtained. Products [**2**]Cl_2 and [**3**]Cl are soluble only in methanol and water. Subsequent salt metathesis with NH_4PF_6 gives [**2**]$(PF_6)_2$ and [**3**]PF_6 (Scheme 1), which are soluble in aprotic solvents such as acetonitrile or acetone. In addition, the anion exchange step is beneficial for purification: reactants **1** with aliphatic substituents usually are hygroscopic but can easily be separated this way. Additionally, traces of byproducts or decomposition products that in some cases are formed under the reaction conditions can be removed via the salt metathesis.

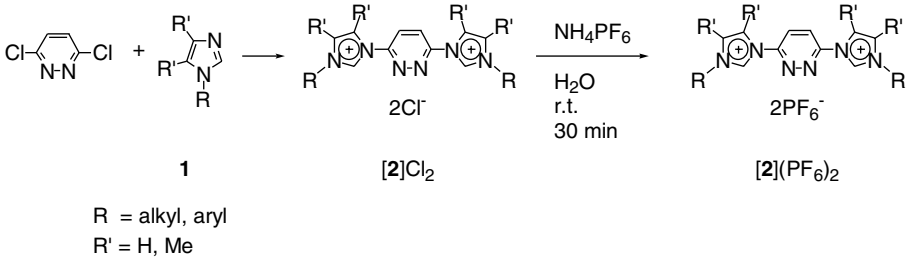
Table 1. Imidazole derivatives used and products obtained

	R	R′	Product(s)
1a	$C_6H_3Me_2$-2,6	H	**2a**, **3a**, **4ah**
1b	C_6H_3iPr-2-Me-6	H	**2b**
1c	C_6H_3iPr-2,6	H	**5c**
1d	$C_6H_4CF_3$-2	H	**2d**, **3d**
1e	C_6F_5	H	**3e**
1f	$C_6H_4OCH_3$-4	H	**3f**
1g	$C_6H_4NO_2$-4	H	**3g**
1h	*tert*-Bu	H	**3h**, **4ah**
1i	Me	Me	**2i**
1j	Me	Cl	**6j**, **7j**, **8j**
1k[a]	Me		**2k**, **6k**, **7k**

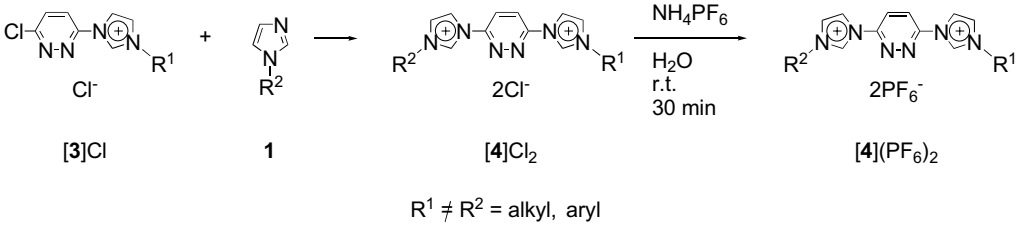
[a] 1-Methylbenzimidazole, R′–R′ = C_4H_4.

Apart from the ratio of reactants, the nature of the substituents on the imidazole plays an important role. Reactions with aliphatic or electron rich aromatic residues on the imidazole nitrogen atom run smoothly (at 110 °C to 160 °C),[13] which was confirmed here for the new compounds [**2a**]Cl_2 and [**2b**]Cl_2 obtained from **1a** and **1b**, respectively. However, it appears difficult to introduce imidazoles with less electron rich residues (**1d**–**1g**), which is likely due to their reduced reactivity in the nucleophilic aromatic substitution. Harsher conditions, that is, even higher temperatures, just lead to decomposition. Products [**2**]Cl_2 therefore could not be obtained for all but one of the reactants **1d**–**1g**, but products [**3**]Cl are conveniently accessible in all cases.

We found that the single-armed [**3**]Cl can be reacted further with another differently substituted imidazole **1** (Scheme 2), but neither the first nor the second imidaz-



Scheme 1. Synthesis of [**2**]Cl_2 and [**2**]$(PF_6)_2$.



Scheme 2. Synthesis of unsymmetrical [**4**]Cl_2 and [**4**]$(PF_6)_2$.

ole attached to the pyridazine may have electron poor aromatic substituents. Reaction conditions have to be set with care in these procedures, since deviation from the ideal parameters (temperature, reaction time) can lead to a scrambling of imidazole substituents leading to the 'normal' symmetrical products [**2**]Cl_2. As a representative example the 'mixed' unsymmetrical product derived from **1a** and **1h** was fully characterized. Either of the imidazole side arms can be introduced first or last.

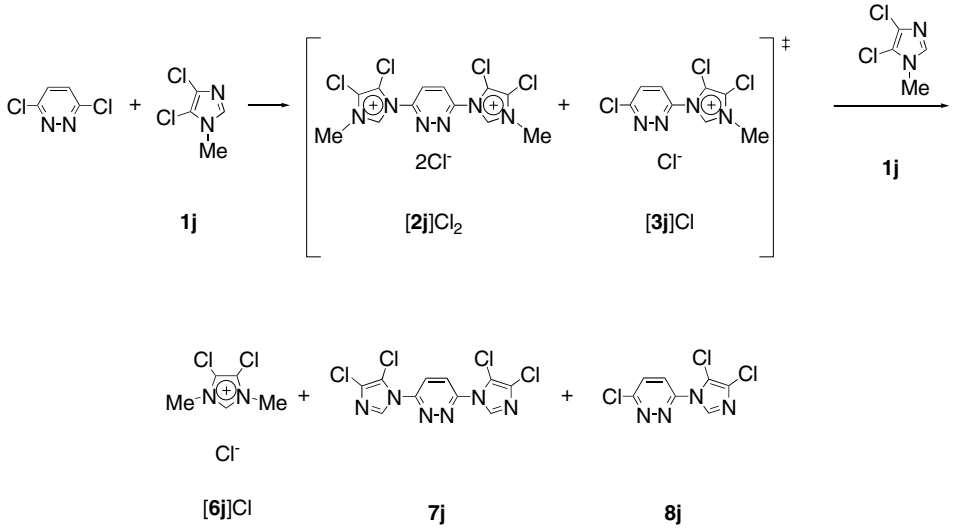
Variations of the imidazole-N substituents are desirable, as electronic and/or steric characteristics should have a pronounced effect on the ligating properties of the resulting NHC.[18] The same holds true for modifications at the NHC backbone, and selected examples of C^4/C^5-substituted imidazoles have thus been used. 1,4,5-Trimethylimidazole (**1i**) gave the expected product [**2i**]Cl_2, but reactions with 4,5-dichloro-1-methylimidazole (**1j**) and 1-methylbenzimidazole (**1k**) followed an unexpected course (Scheme 3).

These latter reactions were examined in some detail to identify the mechanism and the products obtained. Treatment of **1j** with 3,6-dichloropyridazine gave 4,5-dichloro-1,3-dimethylimidazolium chloride [**6j**]Cl as the main product, which was unambiguously identified and characterized crystallographically (see below). When identical conditions were applied to pure **1j** only, no [**6j**]Cl was formed, confirming that the presence of 3,6-dichloropyridazine is essential. During work-up, [**6j**]Cl was separated from a residue mainly composed of excess **1j**. Column chromatography of this residue allowed for the isolation of two more substances (**7j**, **8j**) that were identified by means of NMR spectroscopy and MS data. Their formation can be rationalized by assuming initial formation of intermediates [**2j**]Cl_2 and [**3j**]Cl via the anticipated nucleophilic aromatic substitution, followed by subsequent transfer of the methyl group(s) to excess **1j** (Scheme 3). Neither [**2j**]Cl_2 nor [**3j**]Cl have been directly detected, even when altering the reaction conditions (temperature, reaction time). In order to corroborate the mechanistic assumptions and to ascertain that the methyl groups in [**6j**]Cl do not originate from methanol used in the work-up process, ethanol or deuterated methanol was used instead. According to spectroscopic data (NMR and MS), [**6j**]Cl is again formed, and neither ethyl nor deutero-methyl groups are incorporated.

Temperature has little effect on the reaction of **1j** and 3,6-dichloropyridazine. This is somewhat different for 1-methylbenzimidazole (**1k**). When this reaction is run at high temperature (160 °C), 1,3-dimethylbenzimidazolium chloride [**6k**]Cl is found as the major product whereas at lower temperature (110 °C) mainly [**2k**]Cl_2 is obtained. Formation of [**6k**]Cl is accompanied by the formation of **7k**, but separation of the different products and the excess reactant by column chromatography proved to be difficult. Therefore, this approach cannot be considered as synthetically useful. Preparation of compounds [**6j**]Cl/[**6k**]Cl from the corresponding imidazole **1j**/**1k** and methyl iodide is a more efficient method. A convenient synthesis for compounds of types **7** and **8** from alkali metal hydrides, **1** and 3,6-dichloropyridazine has been described previously.[19]

Modifications of these potential pyridazine/NHC hybrid ligands are possible not only by changing the substituents on the imidazole, but also by varying the central bridging part. To illustrate this, related compounds ([**5c**]Cl_2 and [**5c**]$(PF_6)_2$) based on 1,4-dichlorophthalazine instead of 3,6-dichlororpyridazine have been prepared by analogous reactions.

Crystals of several of the new compounds were grown from diethyl ether diffusion into solutions of the respective compound in methanol ([**2a**]Cl_2, [**2d**]Cl_2, [**3a**]Cl, [**3h**]Cl, [**6j**]Cl), methanol/water (1:1) ([**3g**]Cl) or acetonitrile ([**4ah**]$(PF_6)_2$) and were analyzed by X-ray crystallography. Molecular structures of the unsymmetrically substituted cation $[\mathbf{4ah}]^{2+}$ and of [**6j**]Cl are shown as examples in Figures 2 and 3, respectively. Molecular structures for the other compounds are provided in Figures S1–S5 ([**2a**]Cl_2, [**2d**]Cl_2, [**3a**]Cl, [**3h**]Cl, [**3g**]Cl).



Scheme 3. Reaction of **1j** with 3,6-dichloropyridazine.

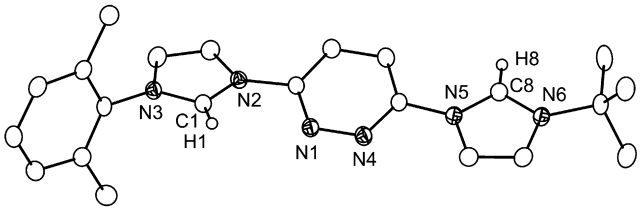


Figure 2. Plot (30% probability thermal ellipsoids) of the molecular structure of [**4ah**]$^{2+}$. For the sake of clarity most hydrogen atoms and the solvent molecules have been omitted.

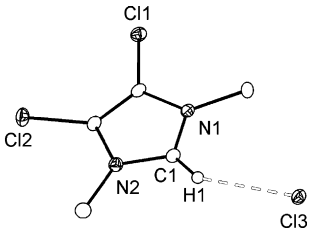


Figure 3. Plot (30% probability thermal ellipsoids) of the molecular structure of [**6j**]Cl emphasizing the hydrogen bonding (dashed lines). For the sake of clarity hydrogen atoms of the methyl groups have been omitted. Selected bond lengths (Å) and angles (°): C1···Cl3 3.390(2); C1–H1···Cl3 149(2).

Crystal data and details of the data collections for all seven compounds are given in Table S2 (Supplementary data).

All of the parameters found (orientation of the imidazolium–C^2H group(s) relative to the pyridazine, C–H···Cl^- and C–H···FPF_5^- distances and angles, etc.) lie within the expected range.[13] Pyridazine- and imidazolium planes are tilted relative to each other by 4–25°, and planes of the two dangling imidazolium rings in type [**2**]X_2 compounds are twisted by 2–51°. The imidazolium C^2H-group(s) are usually directed away from the pyridazine-N atoms, only in one case ([**3h**]Cl) the opposite arrangement is found, and in [**2d**]Cl_2 and [**4ah**]$(PF_6)_2$ the two groups point in different directions. The orientation for individual systems cannot be predicted, since both situations seem to be energetically fairly similar and easy rotation around the imidazole-pyridazine linkage can be assumed. The C–H···Cl^- interactions in the chloride salts are between 3.27 Å and 3.39 Å, angles range from 149° to 176°. Deviations are found in [**3a**]Cl and [**3h**]Cl: crystals of the former include methanol, which forms O–H···Cl^- hydrogen bonds and simultaneously weakens the C–H···Cl^- contact (3.55 Å, 165°); in the case of [**3h**]Cl hydrogen bonds from C1 to Cl1 were not found. Distances and angles for the C–H···FPF_5^- interactions in [**4ah**]$(PF_6)_2$ are well within the usual limits.[13]

3. Conclusions

Products **2**–**5** can be expected to serve as versatile building blocks for the synthesis of mono- and bimetallic NHC complexes, as has been demonstrated recently for the first few related cases. Several new pyridazines with tethered imidazolium groups and with different substitution pattern as well as a related imidazolium/phthalazine compound are now accessible via a straightforward synthetic procedure, also including the first unsymmetrical derivatives with two different imidazolium side arms. Variations of the imidazole substituents have revealed the scope of obtainable products and limitations of the synthetic approach. *Inter alia*, an unexpected methyl group transfer takes place in the case of 4,5-dichloro-1-methylimidazole and 1-methylbenzimidazole. The new imidazolium/pyridazine hybrid compounds are anticipated to find use as ligand scaffolds in bimetallic NHC coordination chemistry and catalysis.

Acknowledgement

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Supplementary data

CCDC 651177, 651178, 651179, 651180, 651181, 651182 and 651183 contain the supplementary crystallographic data for [**2a**]Cl_2, [**2d**]Cl_2, [**3a**]Cl, [**3g**]Cl, [**3h**]Cl, [**4ah**]$(PF_6)_2$ and [**6j**]Cl. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk. Supplementary data (preparatory, analytical and crystallographic data) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.09.099.

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