Structurally-defined potassium-mediated regioselective zincation of amino- and alkoxy-substituted pyridines†

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The new synergic base [PMDETA·K(TMP)(Et)Zn(Et)] selectively zincates 4-(dimethylamino)pyridine at the 2-position and 4-methoxypyridine at the 3-position, to afford bimetallic potassium pyridylzinc complexes each displaying a novel, but remarkably different, structure.

A senior citizen of the organometallic world, potassium zincate chemistry first emerged 150 years ago through Wanklyn's epochal report of the synthesis of "potassium ethyl", (KZnEt₃), and its sodium congener.[1,2] The first structural determination of a potassium zincate, a powder diffraction study of the tetraethynyl zincate salt, [K₂Zn(C≡CH)₄], by Weiss and Wolfrum, also appeared early in the history of organometallic structural chemistry in 1968.[3] Surprisingly, in the intervening years to the present, conspicuously few potassium zincates have been crystallographically characterised.[4] Underlining this underdevelopment, potassium cyclopentadienylzincate, [KZn(C₅H₅)₃], which one might have thought (erroneously) was a known, classical zincate compound was actually only synthesised and its crystal structure elucidated as recently as 2007.[5]
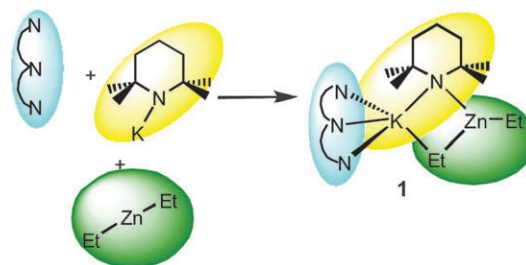
In this paper we have embarked on a study to steer potassium zincate chemistry onto a new course. To the best of our knowledge, the idea that such compounds could be utilised as reagents for executing direct zincation of C–H bonds within a range of aromatic substrates has hitherto never been explicitly proposed. However, some studies have certainly hinted at the prospect. Purdy and George's observation[6] that synthesising the trialkylzincate [KZn(CH₂SiMe₃)₃] in benzene solution also affords the byproduct [KZn(CH₂SiMe₃)₂Ph] through metallation of the solvent comes into this category. Our own report[7] that the triamidozincate [KZn(HMDS)₃] (HMDS = hexamethyldisilazide) can deprotonate toluene to form the benzyl product [{KZn(HMDS)₂(CH₂Ph)}∞] provides another example of an unintentional zincation. Here, inspired by recent advances in lithium- and sodium-mediated zincation,[8] we reveal the successful development of a rational potassium-mediated zincation methodology that creates novel potassium-functionalised pyridylzincate complexes.

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Applying a simple interlocking co-complexation strategy, we prepared our target zincating reagent [PMDETA·K(TMP)(Et)Zn(Et)] **1** (PMDETA = N,N,N',N'',N''-pentamethylethylenediamine; TMPH = 2,2,6,6-tetramethylpiperidine) by mixing together its three component chemicals (Scheme 1). KTMP is best introduced via KCH₂SiMe₃ and TMPH in a prior step, with two equivalents of PMDETA required for dissolution purposes. Colourless crystalline **1** was characterised by NMR spectroscopy and structurally defined by X-ray crystallography.†‡ Its molecular structure (Fig. 1) has the template design of lithium- and sodium-alkylamidozincate bases.[9] Possessing one terminal Et ligand, the trigonal Zn centre presents a mixed amido-N, alkyl-C edge to the K⁺ cation, generating a four (distinct)-atom (KNZnC) ring, with three PMDETA N atoms completing the five-coordinate environment of the alkali metal. The contrast with solvent-free [{KZn(CH₂SiMe₃)₂Ph}∞],[6] which has a polymeric lattice structure, highlights the aggregation-blocking role of PMDETA. Although the molecular connectivity of **1** is definite, its relatively poor accuracy devalues any discussion of bond dimensions.

To assess the direct zincating ability of **1** we reacted it with 4-(dimethylamino)pyridine (DMAP) (Scheme 2). DMAP was chosen due to its importance as an acylation catalyst, and since recent lithiation studies of it for "chemical tuning" purposes are available for comparison.[10] Zincation was confirmed through the isolation and NMR spectroscopic and X-ray crystallographic characterisation of the product [{PMDETA·K[2-Zn(Et)₂-4-Me₂N-C₅H₃N]}₂],†‡ **2**, obtained in a crystalline yield of 53%. Zinc has replaced the hydrogen regioselectively at the 2-position of the pyridyl ring. Earlier PM3 calculations on DMAP[10] point to C3 being the most acidic site, and this is where the superbasic Me₃SiCH₂Li–LiDMAE [LiDMAE = Me₂N(CH₂)₂OLi] combination selectively

**Scheme 1** "Interlocking co-complexation" synthesis of new synergic base **1**.

Fig. 1 Molecular structure of **1** with hydrogen atoms omitted for clarity. Selected dimensions (Å and °): K1–C3, 3.101(7); K1–N1, 2.834(5); K1–N2, 2.877(6); K1–N3, 2.903(6); K1–N4, 2.914(6); Zn1–C1, 2.049(8); Zn1–C3, 2.044(7); Zn1–N1, 2.016(5); N1–K1–N2, 127.20(16); N1–Zn1–C1, 124.7(3); N1–Zn1–C3, 115.9(2); C1–Zn1–C3, 119.3(3).

deprotonates in hexane–THF solution. In contrast BuLi–LiDMAE was found to give exclusive C2 lithiation. The distinction was attributed to an electronically-driven deprotonation in the former case and a pyridyl N atom assisted deprotonation in the latter case.[11] Extrapolating these ideas to **2** suggests that new base **1** might operate through a precoordination step with a pyridyl N–metal bond, followed by elimination of TMPH and concomitant formation of a C2–Zn bond.

The synergic (bimetallic) origin of this direct zincation reaction was established by the failure of either a Et_2Zn–2PMDETA mixture or a KTMP–2PMDETA mixture to metallate DMAP. Possessing C_i symmetry, the molecular structure of **2** (Fig. 2) is dimeric and could be regarded inexactly as a bipotassium-capped heterocyclic 9,10-dihydroanthracene derivative with a central diazadicarbadizinca ring. This central $(N1C1Zn1)_2$ ring is essentially planar and lies coplanar (1.0(8)°) with the two pyridine rings. The monomeric unit of the dianionic moiety consists of a DMAP molecule substituted at the 2-position by a diethylzinc fragment, with the dimerisation junction being antiparallel (head to tail) dative Zn–N(pyr) bonds. Overall this places Zn in a modestly distorted tetrahedral (mean bond angle, 109.30°) C_3N environment. The coordination geometry of K involves eight atoms, comprising two non-equivalent η^2-N,C interactions with the pyr rings

Scheme 2 Zincation reactions of amino (right) and alkoxy (top)-substituted pyridines.

Fig. 2 Molecular structure of **2** with hydrogen atoms omitted for clarity. Selected dimensions (Å and °): K1–C1, 3.2791(15); K1–C1'1, 3.1139(16); K1–C17, 3.2012(17); K1–C19'1, 3.3896(17); K1–N1, 3.2905(13); K1–N3, 2.8422(14); K1–N4, 3.0355(14); K1–N5, 2.8719(14); Zn1–C1, 2.0809(15); Zn1–C17, 2.0678(16); Zn1–C19, 2.0639(17); C1–Zn1–C17, 113.43(6); C1–Zn1–C19, 115.71(7); C17–Zn1–C19, 110.56(7); K1–C1–Zn1, 70.70(4).

leading to an unsymmetrically-bound tridentate PMDETA ligand, and the α-C of one Et ligand. Selected bond lengths and bond angles are in the legend to Fig. 2. The three distinct Zn–C "anionic" bonds have essentially the same length (mean, 2.070 Å), some 0.1178 Å shorter than the Zn–N dative bond. PMDETA provides the shortest bonds to K through its outer N atoms [mean, 2.857 Å; *cf.* 3.0355(14) Å to the central N], while one K–N(pyr) bond [3.0361(13) Å] and its adjacent K–C(pyr) bond [3.1139(16) Å] are significantly shorter than those in the other K-η^2-N, C interaction [3.2905(13) Å and 3.2791(15) Å, respectively]. Note that the Me_2N function is not perfectly coplanar with the pyridyl ring plane making a small dihedral angle of 20.6(2)° with it.

Representing the first zincated DMAP molecule, the structure of **2** appears to be unique for any metallated pyridine derivative. Made by salt metathesis and not direct metallation, there is only one example of a pyridylzinc structure in the simple ring dimer [{$(Me_2N)_2Si(NH^tBu)(N^tBu)2-ZnC_5H_4N$}$_2$].[12] Metallated DMAP structures are limited to two Al complexes[13] also displaying dihydroanthracene-type structures, but being non-ate, neutral compounds their flattened-chair $(NCAl)_2$ faces are vacant. Dimethyl-aluminium and -gallium complexes of unsubstituted pyridine [Me_2NE-(μ-pyr)]$_2$ (E = Al or Ga), with central $(NCE)_2$ shallow boat rings also made *via* salt metathesis, are known,[14] though again face capping is absent.

Next, we reacted **1** with 4-methoxypyridine to produce [*catena*-{PMDETA·K[3-Zn(Et)$_2$-4-MeO-C_5H_3N]}$_\infty$], **3**, in a crystalline yield of 52% (Scheme 2). Here zinc–hydrogen exchange has occurred regioselectively at the 3-position (with loss of TMPH) as determined from NMR spectroscopic and X-ray crystallographic studies.†‡ Previously reported lithiation–electrophilic quenching sequences of 4-methoxypyridine by phenyl- or mesityl-lithium and various electrophiles also

showed this regioselectivity predominately though no information was obtained on the lithiopyridine intermediates involved.[15–17] This contrast with the 2-zincation of DMAP can be ascribed to the greater D*o*M (directed *ortho*-metallation) ability of MeO⁻ over isoelectronic Me₂N⁻, which in part reflects accessibility of the O lone pairs and inaccessibility of the Me₂N lone pair due to its conjugation with the aromatic π-system. The structure of **3** is remarkably different to that of **2**. In the asymmetric unit (Fig. 3), Zn occupies a trigonal planar C₃ environment comprising two Et and one 3-pyr ligands, and lying above the pyr ring plane (2.364(7) Å out of the plane) K occupies an irregular N₃O polyhedron comprising a MeO group and a PMDETA ligand. Through an intermolecular K–N(pyr) bond (making K 5-coordinate overall, excluding some long contacts to C atoms), with K coplanar to this adjacent pyr ligand, the asymmetric unit propagates to form an infinite stepladder structure (Fig. 4). Curiously there are no Zn–N(pyr) bonds in **3** making Zn coordinatively-deficient in comparison to the four-coordinate Zn in **2** which forms dimerisation-defining Zn–N(pyr) bonds. Interestingly, therefore, substituting the Me₂N substituent for MeO, not only redirects the orientation of the zincation reaction, it also reprograms the pyridine to function as a nitrogen σ-donor towards potassium, rebuffing zinc. Selected dimensions in **3** are listed in the legend to Fig. 3. The shortening of the Zn–C bonds (mean, 2.036 Å) compared to those in **2** (2.070 Å) is not pronounced given the lower Zn coordination number involved. Also, situated far from the anionic pyr C atom [3.404(4) Å; *cf.* 3.1139(16) Å in **2**], K has a coordination sphere primarily involving dative bonding. A search of the Cambridge Crystallographic Database[18] found no example of a metallated methoxypyridine structure with which to compare with **3**.

In summary, this work has demonstrated the feasibility of potassium-mediated zincation. Zinc can be delivered either to the 2- or 3-position of a 4-substituted pyr ring depending on the substituent. Replacing lithium by zinc on pyridyl frameworks, especially alkali metal-stabilised ones, should lead to more robust pyridylmetal complexes less susceptible to isomerisation or thermal decomposition. Another benefit of this new methodology is its capacity to construct novel molecular or supramolecular architectures.
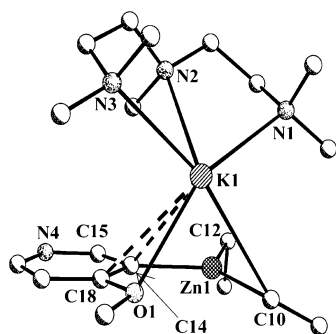
Fig. 3 Asymmetric unit of **3** with hydrogen atoms omitted for clarity. Selected dimensions (Å and °): K1–C14, 3.404(4); K1–C18, 3.334(4); K1–O1, 2.796(3); K1–N1, 2.913(4); K1–N2, 2.926(4); K1–N3, 2.884(4); Zn1–C10, 2.025(5); Zn1–C12, 2.023(5); Zn1–C14, 2.062(4); C10–Zn1–C12, 123.5(2); C10–Zn1–C14, 121.85(18); C12–Zn1–C14, 114.67(19); K1–C14–Zn1, 70.76(12).
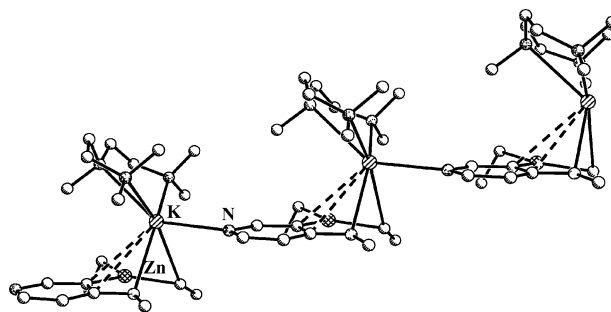
Fig. 4 Section of the infinite stepladder structure of **3**.

Notes and references

‡ Crystal data for **1**: C₂₂H₅₁KN₄Zn, M = 476.14, orthorhombic, space group $P2_12_12_1$, a = 8.0619(2), b = 15.9886(4), c = 21.2669(6) Å, V = 2741.27(12) Å³, Z = 4, λ = 0.71073 Å, μ = 1.061 mm⁻¹, T = 123 K; final refinement to convergence on F^2 gave R = 0.0764 (F, 4132 obs. data only) and R_w = 0.1607 (F^2, 4780 unique data), GOF = 1.121. Crystal data for **2**: C₄₀H₈₄K₂N₁₀Zn₂, M = 914.11, monoclinic, space group $C2/c$, a = 28.3709(8), b = 12.1545(3), c = 18.5001(5) Å, β = 128.617(1)°, V = 4984.5(2) Å³, Z = 4, λ = 0.71073 Å, μ = 1.218 mm⁻¹, T = 123 K; final refinement to convergence on F^2 gave R = 0.0274 (F, 4762 obs. data only) and R_w = 0.0672 (F^2, 5679 unique data), GOF = 1.062. Crystal data for **3**: C₁₉H₃₉KN₄OZn, M = 444.01, orthorhombic, space group $Pna2_1$, a = 19.3708(11), b = 7.6797(4), c = 16.2156(9) Å, V = 2412.3(2) Å³, Z = 4, λ = 0.71073 Å, μ = 1.204 mm⁻¹, T = 123 K; final refinement to convergence on F^2 gave R = 0.0529 (F, 3704 obs. data only) and R_w = 0.1037 (F^2, 5218 unique data), GOF = 1.050. CCDC reference numbers 683512–683514.

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