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Remote functionalisation *via* sodium alkylamidozincate intermediates: access to unusual fluorenone and pyridyl ketone reactivity patterns†

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Treating fluorenone or 2-benzoylpyridine with the sodium zincate [(TMEDA)·Na(μ-^tBu)(μ-TMP)Zn(^tBu)] in hexane solution, gives efficient ^tBu addition across the respective organic substrate in a highly unusual 1,6-fashion, producing isolable organometallic intermediates which can be quenched and aerobically oxidised to give 3-*tert*-butyl-9*H*-fluoren-9-one and 2-benzoyl-5-*tert*-butylpyridine respectively.

Fluorenone and its derivatives are currently attracting widespread interest due to their utilization in several diverse fields. For instance, because of their attractive luminescent properties, fluorenone-based materials are employed as photochemical sensitizers, organic and polymer light-emitting diodes, as well as bulk heterojunction solar cells. In addition, fluorenones are of high pharmacological importance and are key building blocks of many natural products. The synthesis of substituted fluorenones is therefore an important topic for synthetic chemists. Various methods have been developed for this purpose. For example, one approach has involved intramolecular Friedel–Crafts acylation of biaryls.¹ Using alternative directed metallation methodologies; Snieckus and co-workers have prepared a range of substituted fluorenones.² Langer *et al.*, have recently reported the synthesis of fluorenones using a [3+3] cyclisation/Suzuki cross-coupling/Friedel–Crafts acylation route starting from a 1,3-bis-silyl enol ether and a silyloxy-pentenone.³ In contrast, the synthesis of substituted fluorenones (particularly alkyl-substituted examples) from the parent fluorenone is more unusual. To the best of our knowledge, thus far it has not been possible to synthesize alkyl-substituted fluorenones directly from fluorenone. When fluorenone is treated with ⁿBuLi in THF at ambient temperature, the product, as expected, is the 1,2-nucleophilic addition complex, 9-*n*-butyl-9*H*-fluoren-9-ol which is formed (after aqueous

work up) in 51% yield.⁴ The selective functionalisation of pyridines has and continues to attract a great deal of interest, as the resultant *N*-heterocycles have a high pharmacological importance.⁵ Pertinent to the work presented herein, Maron and Okuda have recently highlighted that by utilizing a calcium bis(allyl) complex, 1,4-dihydropyridines can be regioselectively prepared⁶ and Hill has reduced pyridine to dihydropyridide anions using a well-defined magnesium hydride complex.⁷

Alkali metal zincates have recently come to the fore as efficient synthetic reagents. Of particular note, Mulvey has recently exploited the sodium amidodialkylzincate [(TMEDA)·Na(μ-^tBu)(μ-TMP)Zn(^tBu)], **1** (where TMEDA is *N,N,N',N'*-tetramethylethylenediamine and TMP is 2,2,6,6-tetramethylpiperidine) in a range of regioselective sodium-mediated zincation reactions (towards arenes⁸ and heterocycles⁹). In one study this zincate behaved anomalously, resulting in addition to benzophenone in a novel 1,6-manner.¹⁰ To investigate whether this surprising one-off reactivity could be extended to other systems, we have probed the reaction of this zincate with fluorenone and 2-benzoylpyridine. Could this represent a new synthetic method for the preparation of alkyl-substituted fluorenones and carbonyl-substituted pyridines?

Utilising **1** in a 1 : 1 stoichiometric reaction with fluorenone in hexane solution gave the selective 1,6-addition of a ^tBu group across the tricyclic ketone (Scheme 1).§ The resultant yellow, crystalline organometallic complex, [(TMEDA)·Na(μ-OC₁₃H₈-3-^tBu)(μ-TMP)Zn(^tBu)], **2** contains a 3-(*tert*-butyl)-3*H*-fluoren-9-olate anion, whereby one of the aromatic rings of fluorenone has been concomitantly dearomatized on ^tBu addition. The unit cell of **2** contains two crystallographically unique molecules, with essentially identical connectivities; however, one molecule contains a disordered TMP group. Structural discussions will focus on the non-disordered molecule. The molecular structure of **2** (Fig. 1) consists of a NaN₂ZnO four-atom four-element ring and retains the majority of the structural integrity of **1**, except that the ^tBu 'bridge' in **1** has been replaced by the aforementioned enolate anion. The Na centre in **2** adopts a distorted tetrahedral (N₃O) geometry (mean angle around Na atom, 107.96 Å) binding to one TMP and two TMEDA-*N* atoms, and the enolato-*O* atom. The four-atom four-element Na–N–Zn–O ring is effectively planar and the carbon skeleton of the substituted fluorenone

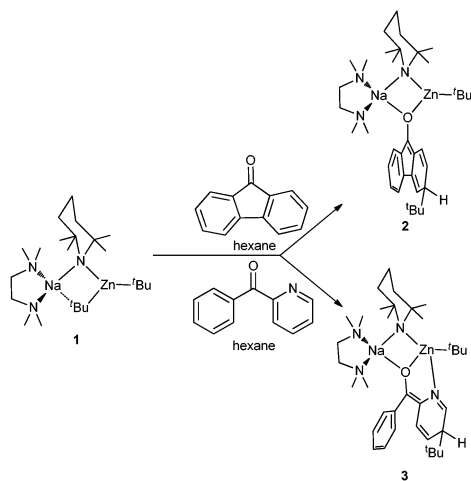
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† Electronic supplementary information (ESI) available: X-ray data, full experimental details, NMR spectra. CCDC 807682–3 (**2** and **3**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1cc10193e

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Scheme 1 Synthesis of **2** and **3**.

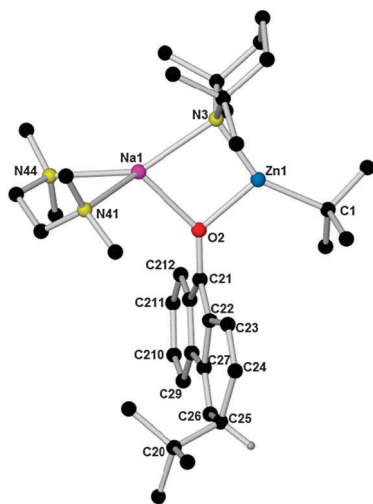


Fig. 1 Molecular structure of **2**.[†]

fragment does not deviate far from planarity [deviations of C23, C24, C25 and C26 from the plane defined by the five C atoms of the central ring are 0.168(6), 0.183(7), $-0.089(7)$ and $-0.014(6)$ Å respectively]. This enforced planarity has structural implications when it is compared to its benzophenone analogue. For instance, the plane of the fluorenyl ligand in **2** adopts a perpendicular stance between the two metal centres [dihedral angle between NaZnO ring plane and that of the 5-membered ring is $82.95(9)^\circ$], thus not favouring one metal over the other. This is in stark contrast to the situation in the benzophenone complex, where the aromatic and substituted rings are not constrained. Instead, the ^tBu-substituted ring lies towards the zinc and the unsubstituted less-sterically demanding phenyl ring favours the Na centre. Returning to **2**, the ^tBu group protrudes from its adjoining sp^3 carbon on the sodium side of the molecule and the loss of aromaticity in the six-atom ring is the evident due to the alternate short and long bond distances [C21–C22, 1.375(4); C22–C23, 1.442(4); C23–C24, 1.353(4); C24–C25, 1.523(5); C25–C26, 1.516(5); C26–C27, 1.335(4); C27–C28, 1.473(4) Å] consistent with localized C–C bonding. The unsubstituted ring of fluorenone remains aromatic as gauged by the similarity of the C29–C210,

C210–C211 and C211–C212 bond distances [range, 1.377(4)–1.386(4) Å].

Realising that the sodium alkylzincate-induced 1,6-addition could be applied to other ketones, we decided to design an approach to prepare further molecules which are not easily obtainable using conventional methods of synthesis. Our molecule of choice was 2-benzoylpyridine. Again we hoped to induce a 1,6-addition with respect to the carbonyl functional group; however, even more interestingly, if the addition occurred on the pyridine ring, this would amount to a C-3 addition with respect to its nitrogen atom. To elaborate, in ‘normal’ nucleophilic additions to pyridine rings, the nucleophile will generally add to the C-2 or C-4 positions [as C-3 (or C-5) addition is not favoured since the negative charge on the intermediate cannot be delocalized onto the electronegative nitrogen atom]. Addition at the C-3 position is generally only accomplished when this carbon carries a good leaving group. In our system, we can dupe the ligand into conducting a C-3 pyridyl addition since we generate an enolate anion—that is a canonical form where the negative charge still resides on an electronegative atom, this time an O atom. As now described, selective addition to C-3 was easily accomplished using this strategy. In the reaction, **1** was treated with 2-benzoylpyridine in a 1:1 molar ratio. The yellow crystalline product was characterised by X-ray crystallography as $[(\text{TMEDA})\cdot\text{Na}\{\mu\text{-O}(\text{Ph})\text{-2-C}_5\text{H}_4\text{N-4-}^t\text{Bu}\}(\mu\text{-TMP})\text{Zn}(^t\text{Bu})]$, **3** (Fig. 2). These data revealed that the branched alkyl group had indeed added across the pyridyl ring of the ligand, leaving the phenyl ring untouched.

Complex **3** was isolated in moderate to good yield (non-optimized yield, 56%). The added ^tBu-group is positioned β - to the pyridyl-*N* atom and *para*- to the COPh group. In keeping with the previous two examples of this 1,6-carbonyl addition, loss of aromaticity in the six-membered pyridyl ring is evident due to alternating short and long bonds (and in this case also C–N bonds). Both the Na and Zn atoms in **3** adopt a distorted tetrahedral geometry (sum of angles around the metal, 663.26 and 640.48° respectively). The zinc has undergone a coordination expansion with respect to that in **2** due to the additional dative pyridyl-*N* interaction which is possible with 2-benzoylpyridine. The facile syntheses of **2** and **3** are a significant advance showing that the selective 1,6-addition reaction can be extended to different arenes and heteroarenes. To investigate whether these complexes could be used to

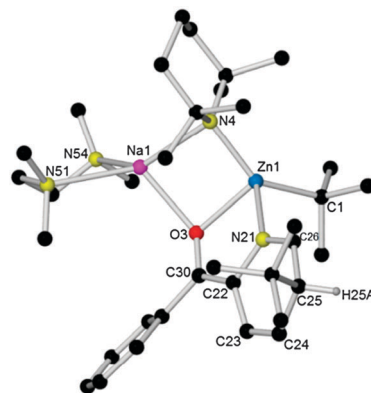


Fig. 2 Molecular structure of **3**.[†]

prepare their respective enol and ketone, we subjected **2** and **3** to a NMR spectroscopic study in d_6 -benzene solution. The respective ^1H NMR spectra show the expected resonances for the enolate complexes, the most indicative features being the presence of vinyl and allyl protons due to dearomatization of the aryl/pyridyl rings.† Solutions of **2** and **3** in d_6 -benzene were reacted with D_2O to give the respective D-enol product which was subsequently oxidized in air¹¹ to produce the 3-*tert*-butyl-9*H*-fluoren-9-one and 2-benzoyl-5-*tert*-butylpyridine in essentially quantitative yield (as measured by NMR spectroscopic analysis). Full NMR spectroscopic analyses of **2** and **3**, and their subsequent enol and ketone products are given in the ESI.† To the best of our knowledge, 3-*tert*-butyl-9*H*-fluoren-9-one has not previously been prepared directly from fluorenone. Longer syntheses involving indirect methods are known including the non-selective *tert*-butylation of fluorene using a Friedel–Crafts alkylation procedure, followed by oxidation,¹² and, a six-step process starting from 2-bromo-4-*tert*-butyltoluene.¹³ As far as we can ascertain, 2-benzoyl-5-*tert*-butylpyridine is a new compound never previously prepared. Its methyl-homologue was prepared (in 60% yield) by C-6 metallation of 3-picoline using BuLi – LiDMAE (DMAE, dimethylaminoethoxide) followed by electrophilic quenching with Me_2NCOPh .¹⁴

In summary, we have shown that sodium zincate mediated 1,6-addition is a viable methodology for the preparation of substituted fluorenones and pyridyl ketones. Future studies will determine the scope of this work in terms of screening new substrates, nucleophiles and other reagents such as alkali metal magnesiate.¹⁵ We would like to thank EPSRC (doctoral training grant, BJJ) and AstraZeneca (summer placement, SAO) for funding this work, and Prof. Robert Mulvey and Dr Eva Hevia for insightful discussions.

Notes and references

§ All reactions were carried out under a protective argon atmosphere. Synthesis of $[(\text{TMEDA})\cdot\text{Na}(\mu\text{-OC}_{13}\text{H}_8\text{-3-}^t\text{Bu})(\mu\text{-TMP})\text{Zn}(^t\text{Bu})]$ (**2**): a solution of $^t\text{Bu}_2\text{Zn}$ (0.36 g, 2 mmol) in hexane (10 mL) was transferred by cannula to a suspension of NaTMP in hexane [prepared *in situ* by reaction of $^t\text{BuNa}$ (0.16 g, 2 mmol) with TMP(H) (0.34 mL, 2 mmol)]. TMEDA (0.30 mL, 2 mmol) was then added. The resultant suspension was gently heated to produce a homogenous yellow solution to yield an *in situ* mixture of **1**. Fluorenone (0.36 g, 2 mmol) was added to the solution and the reaction mixture was allowed to stir at ambient temperature for 30 min. The resulting deep red solution was placed in a freezer (-28°C). Large yellow crystals of **2** were formed after 24 h (0.84 g, 66%). Full spectroscopic analysis is provided in the ESI.†

Synthesis of $[(\text{TMEDA})\cdot\text{Na}\{\mu\text{-O(Ph)-2-C}_5\text{H}_4\text{N-4-}^t\text{Bu}\}(\mu\text{-TMP})\text{Zn}(^t\text{Bu})]$ (**3**): A solution of $^t\text{Bu}_2\text{Zn}$ (0.36 g, 2 mmol) in hexane (10 mL) was transferred by cannula to a suspension of NaTMP in hexane [prepared *in situ* by reaction of $^t\text{BuNa}$ (0.16 g, 2 mmol) with TMP(H) (0.34 mL, 2 mmol)]. TMEDA (0.30 mL, 2 mmol) was then added. The resultant suspension was gently heated to produce a homogenous yellow solution to yield an *in situ* mixture of **1**. 2-Benzoylpyridine (0.37 g, 2 mmol) was added to the solution and the reaction mixture was allowed to stir at ambient temperature for 30 min. The resulting green solution was placed in a freezer (-28°C). Yellow crystals of **3** were formed after 24 h (0.72 g, 56%). Full spectroscopic analysis is provided in the ESI.

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