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- Bu)(µ-TMP)Zn(Bu)] in hexane solution, gives efficient µ-Bu 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-9H-fluoren-9-one and 2-benzoyl-5-tert-butylpyridine respectively.

Fluorenones 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 photo-chemical 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 silyloxypentene.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 BuLi in THF at ambient temperature, the product, as expected, is the 1,2-nucleophilic addition complex, 9-µ-buty1-9H-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 dihydropyridine 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 amidodialkyzincate [(TMEDA)-Na(µ-Bu)(µ-TMP)Zn(Bu)], 1 (where TMEDA is N,N,N’,N’-tetramethylethylendiamine and TMP is 2,2,6,6-tetramethylpiperide) in a range of regioselective sodium-mediated zinication reactions (towards arenes8 and heterocycles9). In one study this zinicate behaved anomalously, resulting in addition to benzo-phenone 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 zinicate 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 µ-Bu group across the tricyclic ketone (Scheme 1).6 The resultant yellow, crystalline organometallic complex, [(TMEDA)-Na(µ-OC13H8-3-µ-Bu)(µ-TMP)Zn(Bu)], 2 contains a 3-(tert-buty1)-3H-fluoren-9-olate anion, whereby one of the aromatic rings of fluorenone has been concomitantly deaeromatized on µ-Bu 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 NaNZnO four-atom four-element ring and retains the majority of the structural integrity of 1, except that the ‘Bu ‘bridge’ in 1 has been replaced by the aforementioned enolate anion. The Na centre in 2 adopts a distorted tetrahedral (N2O) 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.
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 NaNZnO ring plane and that of the 5-membered ring is 82.95(9), 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 sp3 carbon on the sodium side of the molecule and the loss of aromaticity in the six-atom ring is 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 [(TMEDA)Na{μ-O(Ph)-2-C5H4N-4-tBu)(μ-TMP)Zn(tBu)]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
prepare their respective enol and ketone, we subjected 2 and 3 to a NMR spectroscopic study in d<sub>6</sub>-benzene solution. The respective <sup>1</sup>H NMR spectra show the expected resonances for the enolate complexes, the most indicative features being the presence of vinyl and allyl protons due to deprotonation of the aryl/pyridyl rings. Solutions of 2 and 3 in d<sub>6</sub>-benzene were reacted with D<sub>2</sub>O to give the respective D-enol product which was subsequently oxidized in air<sup>11</sup> to produce the 3-tert-butyl-9H-fluoren-9-one and 2-benzoyl-5-tert-butylypyridine 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.<sup>1</sup>

The resulting green solution was placed in a freezer (<sup>2</sup>-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 deep red solution was placed in a freezer (<sup>1</sup>-NMR analysis). Full NMR spectroscopic analyses of 2 and 3 have been provided in the ESI.<sup>1</sup>

Longer syntheses involving indirect methods are known and, a six-step process starting from 2-bromo-4-tert-butylpyridine (<sup>15</sup>) is a new compound never previously prepared. Its methylamine derivative followed by electrophilic quenching with Me<sub>2</sub>NCOPh.<sup>14</sup>

In summary, we have shown that sodium zinicate mediated 1,6-addition is a viable methodology for the preparation of substituted fluorones 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 magnesiates.<sup>15</sup> We would like to thank EPSRC (doctoral training grant, BJF) and AstraZeneca (summer placement, SAO) for funding this work, and Prof. Robert Mulvey and Dr Eva Hevia for insightful discussions.

**Notes and references**

All syntheses were carried out under a protective argon atmosphere. Synthesis of [(TMEDA)<sub>2</sub>Na][μ-OC<sub>2</sub>H<sub>5</sub>-3-][Bu(μ-TMP)Zn(μ-Bu)] (2): a solution of Bu<sub>2</sub>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 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 <em>in situ</em> mixture of I. 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 (<sup>−28</sup>°C). Large yellow crystals of 2 were formed after 24 h (0.84 g, 66%). Full spectroscopic analysis is provided in the ESI.<sup>1</sup>

Synthesis of [(TMEDA)<sub>2</sub>Na(μ-O)(Ph)-2-C<sub>6</sub>H<sub>4</sub>N-4'-Bu(μ-TMP)-Zn(μ-Bu)] (3): A solution of Bu<sub>2</sub>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 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 <em>in situ</em> 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 (<sup>−28</sup>°C). Yellow crystals of 3 were formed after 24 h (0.72 g, 56%). Full spectroscopic analysis is provided in the ESI.