KO$^t$Bu-mediated annulation of acetonitrile with aldehyde: synthesis of substituted dihydropyridin-2(1H)-ones, pyridin-2(1H)-ones, and thiopyridin-2(1H)-ones†

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The KO$^t$Bu-mediated annulation of acetonitrile with aldehyde was observed, in which the cleavage of four C(sp$^3$)–H bonds occurred and a total of eight new bonds were formed during the synthesis of substituted dihydropyridinones in the presence of peroxide. Furthermore, dihydropyridinones have been transformed into pyridinones using KO$^t$Bu in DMSO.

Annulation by the condensation of readily available substrates, in which the formation of several new bonds occurred by the coupling of C–H bonds in a single pot, is seen as an attractive approach for the preparation of heterocycles. This strategy avoids prefunctionalized coupling partners, particularly, halo-functionalized substrates, which generates H$_2$O as waste, and expands the substrate scope.

Heterocycles, particularly, N-containing, such as dihydropyridin-2(1H)-ones, pyridin-2(1H)-ones, and substituted pyridines, are privileged structures with various biological and medicinal properties. Dihydropyridin-2(1H)-one analogues are being used as hypertensive drugs for calcium channel blockage and for the treatment of diabetes, obesity, and neuropeptide. In addition, dihydropyridin-2(1H)-one core is present in the natural products such as homoclausenamide, batzelladine, and caramine alkaloids, which possess HIV-gp120CD4 inhibition and selective $\alpha_{1a}$ receptor antagonist activities.

In view of their biological importance, several synthetic methods have been presented in the literature (eqn (1), Scheme 1). The coupling of $\alpha$-$\beta$-unsaturated acid chloride and ester with enamino-nitrile and sodium cyanomethanide, respectively, have been studied for the synthesis of dihydropyridinones. Dihydropyridinones and substituted pyridines, are either expensive or difficult to handle. The use of prefunctionalized substrates in the coupling reactions restricts the substrate scope because of the difficulty in their synthesis and also due to their incompatibility with another coupling partner.

TM-free KO$^t$Bu-mediated C–C and C–X coupling reactions between C–H and C–X (X, halogens) bonds and cross coupling between two C–H bonds have been studied by us and others. Herein, we present a KO$^t$Bu base-mediated coupling reaction between aldehyde and acetonitrile for the synthesis of dihydropyridin-2(1H)-ones without employing prefunctionalized substrates (eqn (2)). In this coupling reaction, the cleavage of four sp$^3$–C–H bonds was observed, and total eight new bonds formed. Furthermore, synthesized dihydropyridin-2(1H)-ones have been oxidized into pyridin-2(1H)-ones using the novel approach of KO$^t$Bu in DMSO.

After the screening of various bases and additives for the coupling of acetonitrile with the aldehyde at 110 °C in a sealed tube (see ESI† pages S2–S4, for optimization), we chose one mmol of aldehyde, four mmol of KO$^t$Bu base and one mmol of aq. H$_2$O$_2$ in excess of CH$_3$CN (four mL) for the preparation of dihydropyridin-2(1H)-ones. The results are summarized in Scheme 2.
Dihydropyridin-2(1H)-one 1 was obtained in 70% yield by the condensation of benzaldehyde with acetonitrile. The formation of 4-phenyl-pyridine 2 was also observed as a minor product and could only be confirmed by mass analysis (see ESI† page S3). After the synthesis of 1, halogen-substituted benzaldehydes were subjected to the coupling reaction. Fluoro, difluoro, chloro, and bromo substituted benzaldehydes are well tolerated under the optimized reaction conditions and halogen-substituted dihydropyridin-2(1H)-ones 3–7 were obtained in 55–67% yields. Electron-donating substituents, such as CH$_3$, mono, di, and tri-OCH$_3$, SCH$_3$, and N(CH$_3$)$_2$ on benzaldehyde, have also shown compatibility under the reaction conditions and produced respective dihydropyridin-2(1H)-ones 9–17 in 48–70% yields. Interestingly, benzaldehyde-containing acidic OH protons also reacted with acetonitrile and formed hydroxy substituted dihydropyridin-2(1H)-ones 18–24. Various other aromatic aldehydes, such as naphthyl, furanyl, thiophenyl, and pyridyl aldehydes, also underwent coupling reactions with acetonitrile to provide naphthyl and heteroaryl dihydropyridin-2(1H)-ones 25–32 in 34–65% yields.

Alkyl aldehydes were then subjected to the coupling reaction with acetonitrile (Scheme 3). Indeed, alkyl aldehydes provided 4-alkyl substituted dihydropyridin-2(1H)-ones, such as methyl, n-butyl, n-decyl, iso-propyl, and cyclohexyl dihydropyridin-2(1H)-ones 33–40, in moderate yields, although a high temperature (130 °C) is required to accomplish the annulation (please see ESI† page S18).

Synthesized dihydro- and pyridin-2(1H)-ones 1, 5, 16 and 42 were also characterized by single crystal X-ray structural study (Fig. 1; for details, see ESI† pages S32–S77). Under optimized conditions, when ferrocene aldehyde was subjected for coupling with acetonitrile, 4-ferrocene substituted pyridine 41 was obtained in 76% yield instead of the expected ferrocenyl dihydropyridin-2(1H)-one (Scheme 4). The structure of 41 is established by single-crystal X-ray study.
Further utilities of synthesized dihydropyridin-2(1H)-ones were explored (Scheme 5). The addition of KOtBu to dihydropyridin-2(1H)-ones in DMSO provided selective oxidation of C–H bonds leading to pyridin-2(1H)-ones 42–47 in 35–80% yields. It appears that DMSO not only acts as a solvent but also as an oxidizing agent. The oxidation of dihydropyridin-2(1H)-ones into pyridin-2(1H)-ones could not be achieved in acetonitrile even in the presence of excess KOtBu and oxidant H2O2, and an excess of KOtBu led to the self-coupling of acetonitrile (see ESI,† page S29).

Synthesized 3,4-dihydropyridin-2(1H)-ones were then transformed into dihydropyridine-2(1H)-thiones (Scheme 5), which exhibit vasodilator, cardiotonic, and antitumor biological activities and also show enriched coordination chemistry as ligands.8,19 The addition of Lawesson’s reagent to dihydropyridin-2(1H)-ones gave respective thio analogues 48–50 in 87–90% yields.

Deuterated acetonitrile was then made to react with the benzaldehyde to gain mechanistic insight (Scheme 6). The obtained heterocycle 51 shows the incorporation of five deuterium atoms as studied by mass spectrometry. A deuterium–hydrogen exchange at the first and sixth positions of 3 was also observed and could be rationalized by mechanistic understanding (vide infra). When reaction was performed on (E/Z)-but-2-enal substrate under optimized conditions, dihydropyridin-2(1H)-one 33 was obtained, which was also formed by the reaction of acetaldheyde with acetonitrile (Scheme 3, vide supra).

In the tentative mechanism (Scheme 7), the deprotonation of acetonitrile in the presence of KOtBu would lead to cyanomethanide, which adds to the second molecule of CH3CN, forming (1-cyanopropan-2-ylidene)amide 1. This may form carbanion II via proton transfer, which then adds to aldehyde followed by H2O removal, providing (3-cyanobut-3-en-2-ylidene)amide III. This may react with the third CH3CN molecule to generate intermediate IV, which may convert into carbanion V by a 1,3-proton transfer. An intramolecular attack of carbanion V to the benzaldehyde would furnish the cyclized carbanion VI, which would undergo resonance, forming VII. Intermediate VII may be hydrolyzed to yield 3,4-dihydropyridin-2(1H)-one 1. Although the exact role of H2O2 is not known in the reaction, the formation of ammonia and the improved yield of 1 was observed in the presence of H2O2. This suggests that H2O2 facilitates NH hydrolysis into the C–O group.

In summary, we have shown that substituted dihydropyridin-2(1H)-ones can be synthesized from simple aldehyde and acetonitrile by employing KOtBu base without the use of prefunctionalized substrates. A wide range of aldehydes, including aliphatic; diversely substituted aromatics, including naphthalenes; and heteroaromatics, such as thiophenes, pyridines, and furans; coupled with the three molecules of acetonitrile. Moreover, dihydropyridin-2(1H)-ones have been oxidized into pyridin-2(1H)-ones through a novel method using KOtBu in DMSO. We are currently exploring the scope of the coupling reaction, particularly, for the synthesis of substituted pyridines from readily available substrates utilizing the KOtBu base.
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Notes and references


6 Single crystals were obtained by slow evaporation of CH3Cl2 solution, 5 crystallized in chiral P212121 space group.

7 On the suggestion of one of the reviewer, reaction mixture of PhCHO (1 equiv.), CH3CN, KOtBu (4 equiv.), and H2O2 (1 equiv.) was monitored by EPR spectroscopy. The formation of radical species could not be confirmed by EPR in the reaction mixture which suggests that reaction may not proceed via radical pathway.