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

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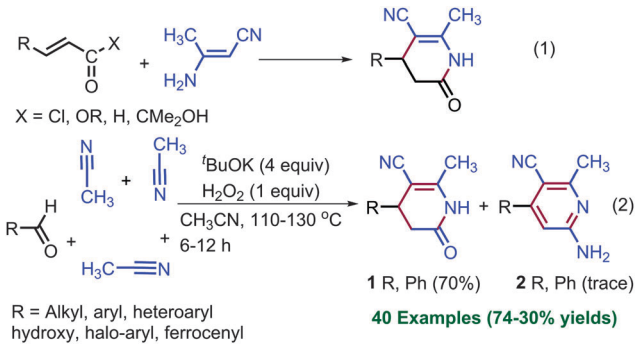
The KO^{t}Bu-mediated annulation of acetonitrile with aldehyde was observed, in which the cleavage of four C(sp^3)–H bonds occurred and a total of eight new bonds were formed during the synthesis of substituted dihydropyridinones in the presence of peroxide. Furthermore, dihydropyridinones have been 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.[1] This strategy avoids prefunctionalized coupling partners, particularly, halogenated substrates, which generates H_2O as waste, and expands the substrate scope.

Heterocycles, particularly, N-containing, such as dihydropyridin-2(1*H*)-ones, pyridin-2(1*H*)-ones, and substituted pyridines, are privileged structures with various biological and medicinal properties.[2,3] Dihydropyridin-2(1*H*)-one analogues are being used as hypertensive drugs for calcium channel blockage and for the treatment of diabetes, obesity, and neuropeptide.[3] In addition, dihydropyridin-2(1*H*)-one core is present in the natural products such as homoclausenamide, batzelladine, and carambine alkaloids, which possess HIV-gp-120CD4 inhibition and selective α_{1a} receptor antagonist activities.[4]

In view of their biological importance, several synthetic methods have been presented in the literature (eqn (1), Scheme 1).[5–13] The coupling of α,β-unsaturated acid chloride and ester with enaminonitrile and sodium cyanomethanide, respectively, have been studied for the synthesis of dihydropyridinones.[5–8,11,12] Bode *et al.* and Biju *et al.* synthesized dihydropyridinones enantioselectively by the coupling of α,β-unsaturated aldehydes with various imine derivatives catalysed by N-heterocyclic carbene.[10]



Scheme 1 Synthesis of dihydropyridin-2(1*H*)-ones.

Nonetheless, these methods required prefunctionalized substrates to obtain dihydropyridin-2(1*H*)-ones and pyridin-2(1*H*)-ones. Prefunctionalized substrates, such as α,β-unsaturated acyl chloride, esters, sodium cyanomethanide, and β-aminonitrile, 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.[14–17] Herein, we present a KO^{t}Bu base-mediated coupling reaction between aldehyde and acetonitrile for the synthesis of dihydropyridin-2(1*H*)-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(1*H*)-ones have been oxidized into pyridin-2(1*H*)-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_2O_2 in excess of CH_3CN (four mL) for the preparation of dihydropyridin-2(1*H*)-ones. The results are summarized in Scheme 2.

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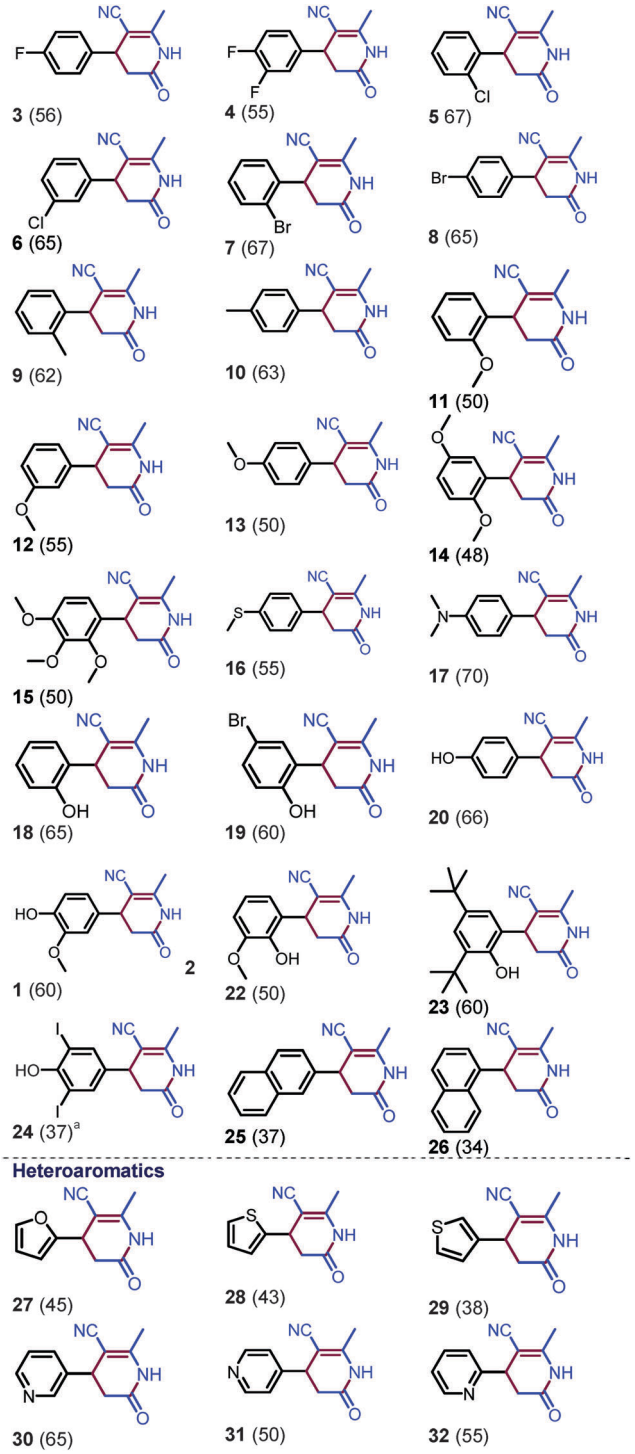
† Electronic supplementary information (ESI) available: Experimental procedure, spectra, crystal data. CCDC 1038679 (**1**), 1038680 (**5**), 1057417 (**16**), 1057418 (**41**), 1038678 (**42**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5cc02964c



Scheme 2 Substrate scope with regard to aromatic aldehydes. Reaction was carried by heating aldehyde (1 mmol), KO^{t}Bu (4 mmol), and H_2O_2 (1 mmol, 30% aq. solution), and CH_3CN (4 mL) in a sealed tube at 110 °C. Yields were reported with respect to aryl aldehyde. [a] Heated at 130 °C.

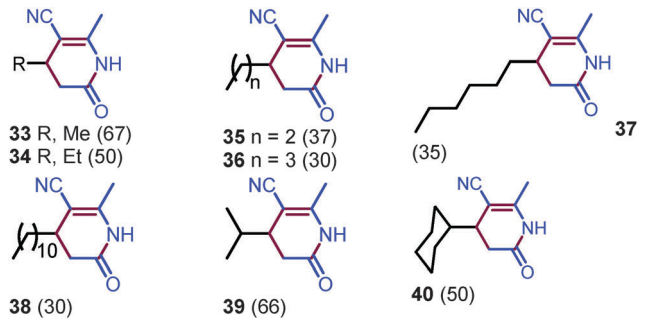
Dihydropyridin-2(1*H*)-one **1** was obtained in 70% yield by the condensation of benzaldehyde with acetonitrile.

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(1*H*)-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(1*H*)-ones **9–17** in 48–70% yields. Interestingly, benzaldehyde-containing acidic O*H* protons also reacted with acetonitrile and formed hydroxy substituted dihydropyridin-2(1*H*)-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(1*H*)-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(1*H*)-ones, such as methyl, *n*-butyl, *n*-decyl, iso-propyl, and cyclohexyl dihydropyridin-2(1*H*)-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(1*H*)-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).[18]

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(1*H*)-one (Scheme 4). The structure of **41** is established by single-crystal X-ray study.



Scheme 3 Substrate scope with regards to alkyl aldehydes.

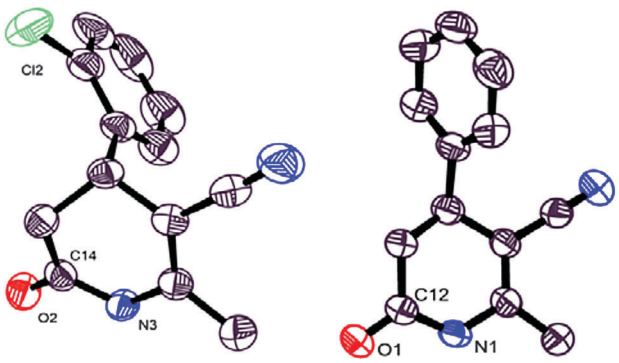
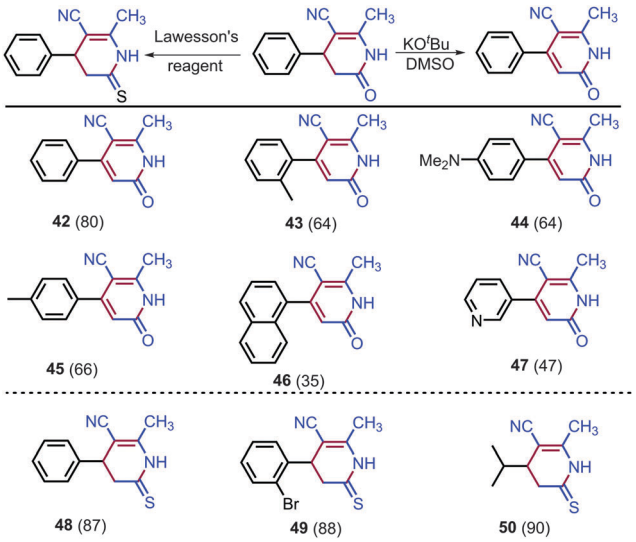
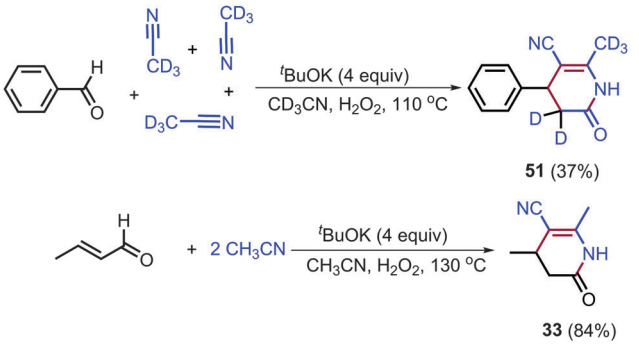


Fig. 1 Crystalline structures of dihydro- and pyridin-2(1*H*)-ones **5** and **42**.

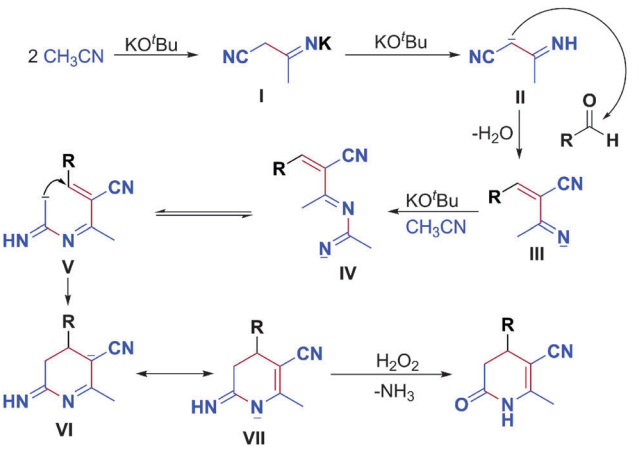
Scheme 4 Synthesis of 4-ferrocenyl pyridine under optimized conditions.



Scheme 5 Conversion of dihydropyridin-2(1*H*)-ones into pyridin-2(1*H*)-ones and thio analogues.



Scheme 6 Control reactions with CD_3CN and with 2-alkene aldehyde.



Scheme 7 Proposed mechanism for the coupling of CH_3CN.[20]

Further utilities of synthesized dihydropyridin-2(1*H*)-ones were explored (Scheme 5). The addition of KO^{t}Bu to dihydropyridin-2(1*H*)-ones in DMSO provided selective oxidation of C–H bonds leading to pyridin-2(1*H*)-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(1*H*)-ones into pyridin-2(1*H*)-ones could not be achieved in acetonitrile even in the presence of excess KO^{t}Bu and oxidant H_2O_2, and an excess of KO^{t}Bu led to the self-coupling of acetonitrile (see ESI,† page S29).

Synthesized 3,4-dihydropyridin-2(1*H*)-ones were then transformed into dihydropyridine-2(1*H*)-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(1*H*)-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(1*H*)-one **33** was obtained, which was also formed by the reaction of acetaldehyde with acetonitrile (Scheme 3, *vide supra*).

In the tentative mechanism (Scheme 7), the deprotonation of acetonitrile in the presence of KO^{t}Bu would lead to cyanomethanide, which adds to the second molecule of CH_3CN, forming (1-cyanopropan-2-ylidene)amide **I**.[21] This may form carbanion **II** *via* proton transfer, which then adds to aldehyde followed by H_2O removal, providing (3-cyanobut-3-en-2-ylidene)amide **III**. This may react with the third CH_3CN 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 benzylic carbon would furnish the cyclized carbanion **VI**, which would undergo resonance, forming **VII**. Intermediate **VII** may be hydrolyzed to yield 3,4-dihydropyridin-2(1*H*)-one **1**. Although the exact role of H_2O_2 is not known in the reaction, the formation of ammonia and the improved yield of **1** was observed in the presence of H_2O_2. This suggests that H_2O_2 facilitates NH hydrolysis into the C=O group.

In summary, we have shown that substituted dihydropyridin-2(1*H*)-ones can be synthesized from simple aldehyde and acetonitrile by employing KO^{t}Bu 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(1*H*)-ones have been oxidized into pyridin-2(1*H*)-ones through a novel method using KO^{t}Bu 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 KO^{t}Bu base.

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