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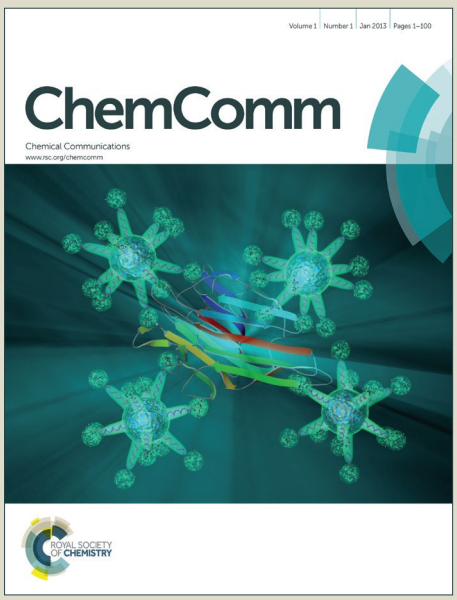

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COMMUNICATION

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

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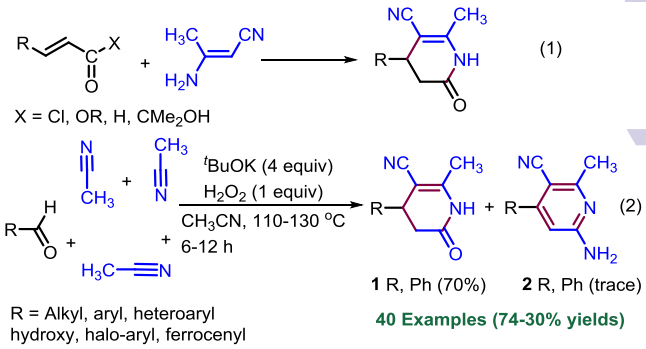
KO^{t}Bu-Mediated annulation of acetonitrile with aldehyde was observed in which cleavage of four C(sp^3)-H bonds occurred, and total eight new bonds formed during the synthesis of substituted dihydropyridinones in the presence of peroxide. Furthermore, dihydropyridinones have been transformed into pyridinones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

Annulation by the condensation of readily available substrates, in which formation of several new bonds occurred by the coupling of C-H bonds in a single pot, is as an attractive approach for the preparation of heterocycles.[1] This strategy avoids prefunctionalized coupling partners, particularly, halogenated substrates, 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 privilege structures with various biological and medicinal properties.[2,3] Dihydropyridin-2(1*H*)-one analogues are being used as hypertensive drugs for the blockage of calcium channel, for the treatment of diabetes, obesity, and neuropeptide.[3] Also 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 antagonists activities.[4]

In view of their biological importance, several synthetic methods have been presented in the literatures (eq 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.* have synthesized dihydropyridinones enantioselectively by the coupling of α,β-unsaturated aldehydes with various imine derivatives catalysed by N-heterocyclic carbene.[10] Nonetheless, these methods required prefunctionalized substrates to obtain

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



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-aminonitriles are either expensive or difficult to handle. The use of prefunctionalized substrates in the coupling reactions restricts the substrate scope because of 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 have been studied between C-H and C-X (X, halogens) bonds, and cross coupling between two C-H bonds by us and others.[14-] Here; 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 (eq 2). In this coupling reaction, 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 novel approach KO^{t}Bu in DMSO.

After screening of various bases and additives for the coupling of acetonitrile with the aldehyde at 110 °C in a sealed tube (see SI, page 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 the excess of CH_3CN (four mL) for the preparation of dihydropyridin-2(1*H*)-ones. The results are summarized

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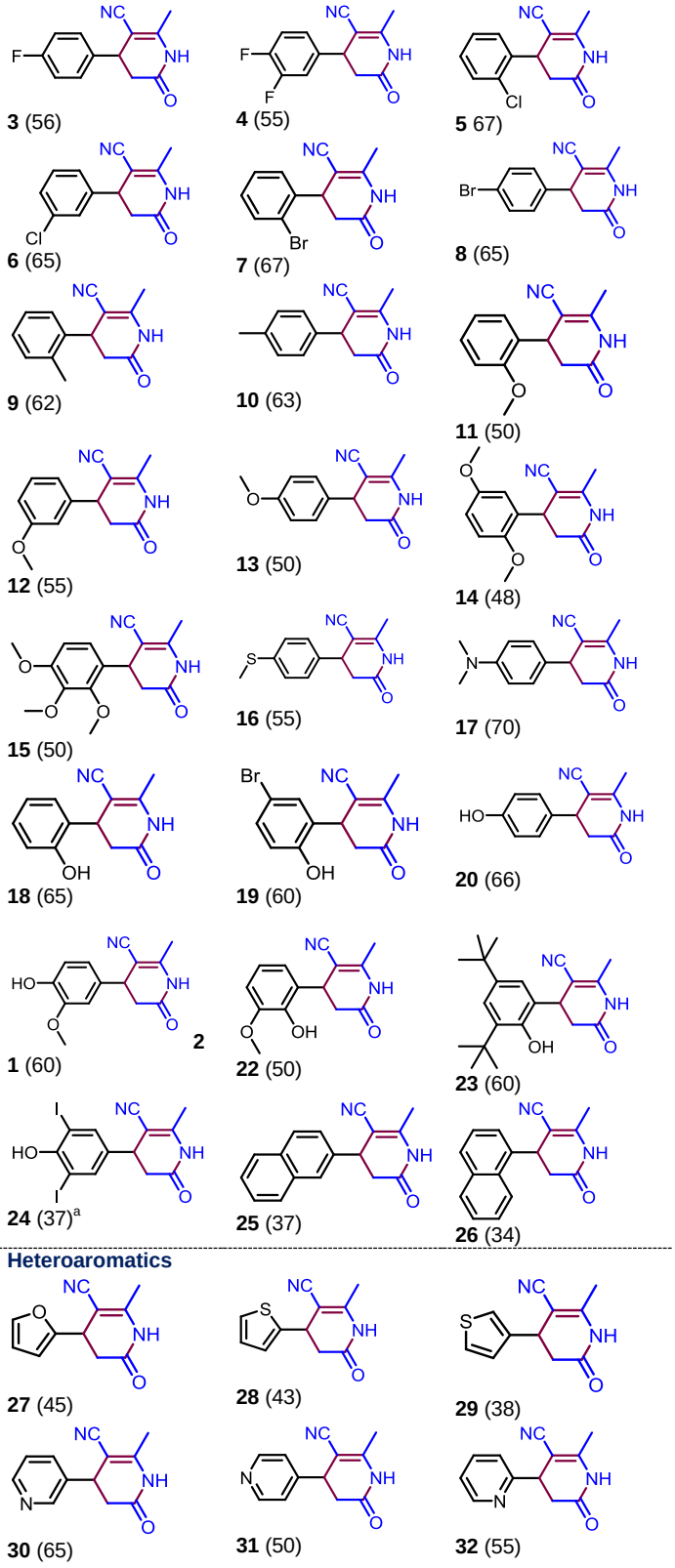
† Electronic Supplementary Information (ESI) available: [experimental procedure, spectra, crystal data CCDC No. 1038678 (**1**), 1038680 (**5**), 1057417 (**16**), 1057418 (**41**), 1038679 (**42**)]. See DOI: 10.1039/x0xx00000x

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

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

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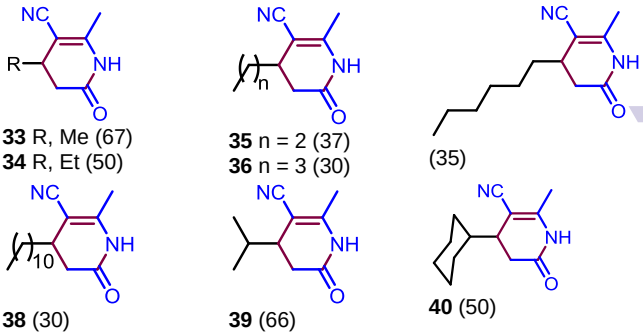
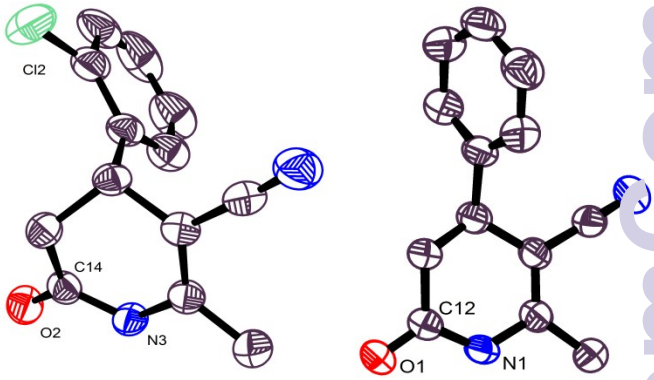
The formation of 4-phenyl-pyridine **2** was also observed as a minor product and could only be confirmed by mass analysis (See, SI page S3). After synthesis of **1**, halogen substituted benzaldehyde were subjected to the coupling reaction. Fluoro, difluoro, chloro, bromo and even iodo are well tolerated under the optimized reaction conditions and halogen substituted dihydropyridin-2(1*H*)-ones **2**-**7** were obtained in 55-67% yields. Electron donating substituents such as CH_3, mono, di, and tri OCH_3, SCH_3, $N(CH_3)_2$ on benzaldehyde have also shown the compatibility under the reaction conditions and produced respective dihydropyridin-2(1*H*)-ones **9-17** in 48-70% yields. Interestingly, benzaldehyde containing acidic OH proton also reacted with acetonitrile and formed hydroxy substituted dihydropyridin-2(1*H*)-ones **18**-**24**. Various other aromatic aldehydes such as naphthyl, furanyl, thiophenyl, pyridyl aldehydes also underwent coupling reaction with acetonitrile to provide the naphthyl, heteroaryl dihydropyridin-2(1*H*)-ones **25**-**32** in 37-65% yields.

Scheme 3. Substrate scope with regards to alkyl aldehydes



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

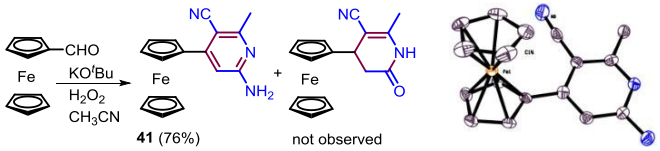
Fig. 1. Crystal structures of dihydro and pyridin-2(1*H*)-ones **5** and **42**



Synthesized dihydro and pyridin-2(1*H*)-ones **1**, **5**, **16** and **42** were also characterized by single crystal X-ray structure study (Fig. 1, for details see SI, pages S32-S77).[18]

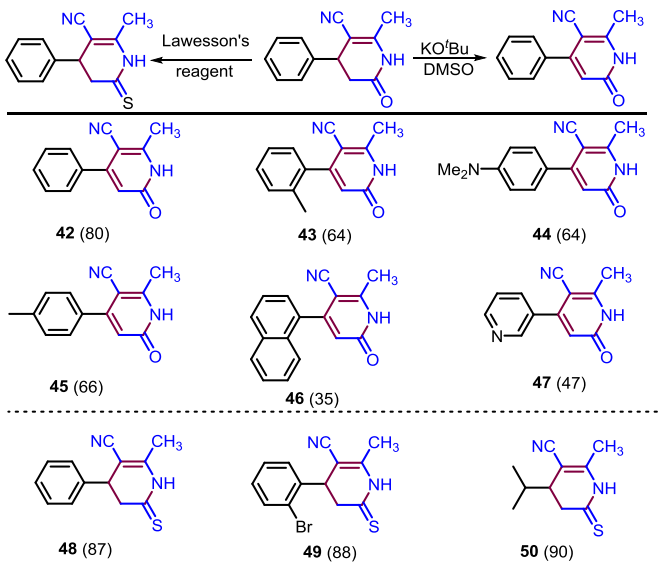
Under the optimized conditions, when ferrocene aldehyde was subjected for coupling with acetonitrile, 4-ferrocene substituted pyridine **41** was obtained in 76% yield instead of expected ferrocenyl dihydropyridin-2(1*H*)-one (Scheme 4). Structure of **41** is established by single crystal X-ray study.

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



Further utilities of synthesized dihydropyridin-2(1*H*)-ones were explored (Scheme 5). 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 seems DMSO not only acts as a solvent but also oxidizing agent. Oxidation of dihydropyridin-2(1*H*)-ones into pyridin-2(1H)-ones could not be achieved in acetonitrile even in the presence of excess KO^{t}Bu and oxidant H_2O_2 and excess of KO^{t}Bu led to self-coupling of acetonitrile (see SI page S29).

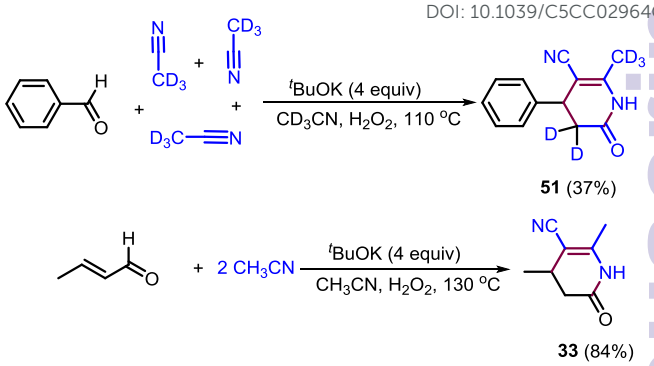
Scheme 5. Conversion dihydropyridin-2(1*H*)-ones into pyridin-2(1*H*)-ones and thio analogues



Next, synthesized 3,4-dihydropyridin-2(1*H*)-ones were 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] Dihydropyridine-2(1*H*)-thiones Addition of Lawesson's reagent to the dihydropyridine-2(1*H*)-thiones gave respective thio analogues **48**-**50** in 87-90% yields.

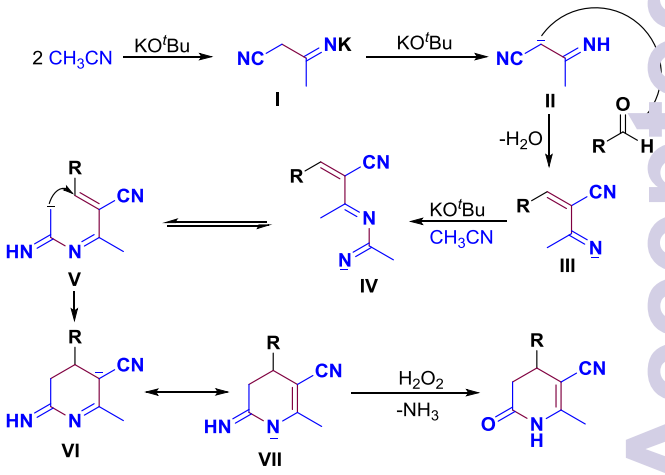
Next, deutrated acetonitrile was reacted with the benzaldehyde to gain mechanistic insight (Scheme 6). The obtained heterocycle **51** shows incorporation of five deuterium atoms as studied by mass spectrometry. Deuterium-hydrogen exchange at first and sixth position of **3**

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



was also observed and could be rationalized by mechanistic understanding (*vide infra*). When reaction was performed on (*E/Z*)-but-2-enal substrate under the optimized condition dihydropyridin-2(1H)-one **33** was obtained, which also formed by the reaction of acetaldehyde with acetonitrile (Scheme 5, *vide supra*).

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



In the tentative mechanism (Scheme 7), deprotonation of acetonitrile in the presence of KO^{t}Bu would led 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, would give (3-cyanobut-3-en-1-ylidene)amide **III**. This may react with the third CH_3CN molecule to generate intermediate **IV** which may convert into carbanion **V** by 1,3-proton transfer. Intramolecular attack of carbanion **V** to the benzylic carbon would furnish the cyclized carbanion **VI**. This cyclized carbanion **VI** would undergo resonance forming **VII**. Intermediate **VII** may be hydrolized to yield 3,4-dihydropyridin-2(1*H*)-one **1**. Although, exact role of H_2O_2 is not known in the reaction, however, formation of ammonia and better yield of **1** was observed in the presence of H_2O_2. This suggests that H_2O_2 facilitate the hydrolysis of NH into C=O group.

In summary, we have shown that substituted dihydropyridin-2(1*H*)-ones, can be synthesized from simple aldehyde and

acetonitrile employing KO^{t}Bu base without using prefunctionalized substrates. A wide range of aldehydes, including aliphatic, diversely substituted aromatic including naphthalenes and heteroaromatics such as thiophenes, pyridines, and furan coupled with the three molecules of acetonitrile. Moreover, dihydropyridin-2(1*H*)-ones has been oxidized into pyridin-2(1*H*)-ones by novel method using KO^{t}Bu in DMSO. Currently, we are exploring the scope of the coupling reaction, particularly, for the synthesis of substituted pyridines, from readily available substrates utilizing KO^{t}Bu base.

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