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C–H Functionalization

Dioxygen-Mediated Decarbonylative C–H Alkylation of Heteroaromatic Bases with Aldehydes

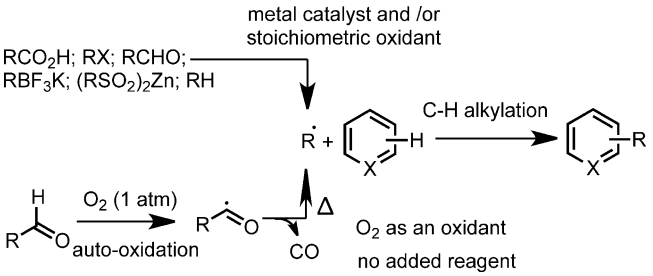
Subhasis Paul and Joyram Guin*[a]

Abstract: An operationally simple and economical method for the direct alkylation of heteroaromatic bases employing readily available aldehydes as alkyl radical precursors and molecular oxygen as a reagent is presented. This simple transformation demonstrates a broad substrate scope with respect to aldehydes and nitrogen heterocycles, enabling the introduction of several medicinally important yet challenging alkyl moieties, such as ethyl, isopropyl, *tert*-butyl, and cyclohexyl to the different classes of heterocyclic bases in good to excellent yields.

Alkyl-substituted nitrogen-containing heterocyclic compounds are extremely important molecules because these structural motifs are found in a broad range of highly potent drug molecules[1] and in many biologically relevant compounds.[2] Although diverse synthetic strategies, including transition-metal-catalyzed cross-coupling with functionalized substrates[3] and hydroheteroarylation of olefins,[4] have been developed, the direct C–H alkylation through homolytic aromatic substitution (HAS)[5] of alkyl radicals with electron-deficient nitrogen heterocycles (Minisci reaction) remains the most straightforward approach to such compounds.[6] However, a major drawback of this process is the limited access to alkyl radicals. Initially, alkylation of nitrogen heterocycles was accomplished with alkyl radicals derived from alkyl carboxylic acids[7] or halides.[8] Later, alkyl boron compounds,[9] zinc bis(alkanesulfinate) salts,[10] peroxides,[11] and hydrocarbons[12] were used as the sources of alkyl radicals for electrophilic nitrogen heterocycle functionalization. Despite all of these developments, the existing methods often require expensive starting materials or catalysts in combination with stoichiometric amounts of metallic or nonmetallic oxidants.

Aldehydes, however, are readily available and inexpensive bulk chemicals that have been utilized as a source of acyl radicals, which are known to deliver the corresponding alkyl radicals through decarbonylation under suitable reaction conditions.[13,14] Although there have been few reports on the decarbonylative C–H alkylation of heteroaromatic bases employing aldehydes as alkyl radical precursors, these methods however suffer several disadvantages such as the use of overstoichiometric amount of peroxide as initiator and oxidant,[15] metal salt as additive,[16] or UV light irradiation.[17] In view of the growing environmental concern with regard to waste management, the development of a general, efficient and metal-free method for the direct alkylation of nitrogen heterocycles with aldehydes avoiding the use of stoichiometric amount of reagent would be highly desirable.

We therefore envisioned that the well-investigated auto-oxidation of aldehyde,[18] which allows mild and selective generation of acyl radical by using O_2 as a reagent, could lead to the formation of alkyl radical by decarbonylation under suitable reaction conditions. The generated alkyl radical is expected to combine with the electrophilic nitrogen heterocycles to afford the corresponding alkylated products (Scheme 1). Although



Scheme 1. Aerobic C–H alkylation of nitrogen heterocycles with aldehydes.

the auto-oxidation of aldehyde has been utilized in aerobic hydroacylation[19] and epoxidation[20] of olefins, this approach remains unexplored for the direct alkylation of heteroaromatic bases. Herein, a successful implementation of this strategy to the C–H alkylation of nitrogen heterocycles with inexpensive aldehydes in the presence of O_2 is described. This method does not require any additional reagent or catalyst.

In accordance to the concept presented in Scheme 1, we began our study with the reaction of aldehyde **1a** with protonated isoquinoline under various reaction conditions in the presence of O_2 (see the Supporting Information). After having optimized procedure in hand, the scope of this transformation was evaluated with structurally different aldehydes (Table 1). The α-branched aldehydes **1a–d** furnished the corresponding alkylated products **2a–d** in good yields (60–82%, isolated products; Table 1, entries 1–4) with no detectable amount of the acylated products **3a–d**. Although a small amount of the

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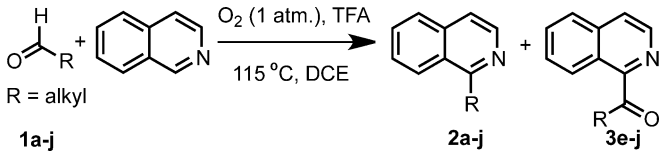
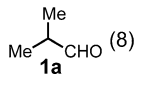
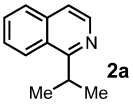
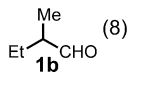
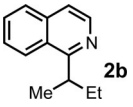
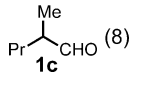
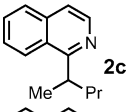
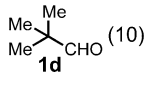
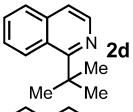
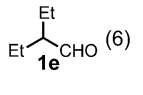
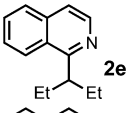
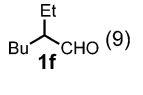
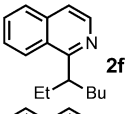
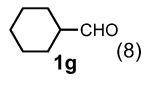
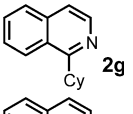
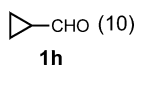
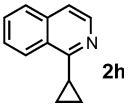
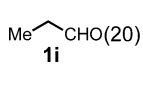
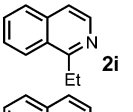
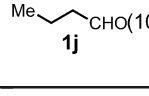
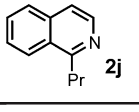
Table 1. Aldehyde substrate scope with isoquinoline.[a]



Entry	Aldehyde (equiv)	Alkylated product	*t* [h]	Yield [%]	Selectivity[b] [%]
1[c]	 (8)	 **2a**	12	82	>99
2	 (8)	 **2b**	12	66	>99
3	 (8)	 **2c**	16	60	>99
4	 (10)	 **2d**	12	76	>99
5	 (6)	 **2e**	12	78	88
6	 (9)	 **2f**	12	60	90
7	 (8)	 **2g**	12	58	90
8[c]	 (10)	 **2h**	21	32	31
9[c]	 (20)	 **2i**	25	71	45
10[c]	 (10)	 **2j**	20	75	40

[a] Reaction conditions (unless otherwise stated): Isoquinoline (1.0 equiv), trifluoroacetic acid (TFA; 1.5 equiv), aldehyde (6–20 equiv), 1,2-dichloroethane (DCE; 1.5 M solution of isoquinoline); combined yields of the isolated materials; [b] selectivity refers to the ratio between alkylated and acylated products, determined by ^{1}H NMR spectroscopic analysis of the crude mixture and by GCMS analysis for entries 1–4; [c] conc. = 0.15 M.

acylated isoquinolines **3e**–**g** were formed from aldehydes **1e**–**g**, the corresponding alkylated isoquinolines **2e**–**g** were isolated as major products (Table 1, entries 5–7). Surprisingly, cyclopropanecarboxaldehyde (**1h**) was found to be less reactive, furnishing the alkylated product **2h** in a much lower yield and selectivity (Table 1, entry 8). The linear aldehydes **1i** and **1j** could be included in this procedure. Accordingly, ethyl- and *n*-propyl-substituted isoquinolines **2i** and **2j** were isolated along with the acylated products **3i** and **3j** in good combined yields (Table 1, entries 9 and 10). The selectivity for alkylation over acylation was significantly reduced with linear aldehydes. This could be attributed to the fact that the formation of primary alkyl radical by decarbonylation of the corresponding acyl radical is unfavorable.[14e]

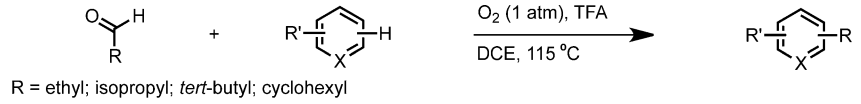
Having explored variation of aldehydes, the scope of this transformation was evaluated on a broad range of nitrogen heterocyclic compounds. The title reaction allowed incorporation of the challenging isopropyl moiety to a wide range of different classes of heterocyclic bases with various substituents (Table 2). The products **4**–**40** were isolated in yields ranging from 31 to 97%, with predominant regioselectivity at the 2- and 4-positions of the heterocycles. Where more than one active site was present, both the mono- and bis-alkylated products were formed.[21] Pyridine moieties having cyano, acetyl, 2,4-difluorophenyl, *tert*-butyl, methyl, phenyl, and *p*-methoxyphenyl groups rendered the corresponding alkylated products **4**–**12** in good isolated yields. 4,4′-Di-*tert*-butyl-2,2′-bipyridine could be converted to the desired product **13** in 83% yield. Quinoline and its derivatives were alkylated smoothly with this procedure (**14**–**16**). The incorporation of ethyl, isopropyl, and cyclohexyl moieties to lepidine delivered the medicinally important compounds **17**–**19**. Notably, the products **18** and **19** have been reported to exhibit tuberculosis inhibitory activity.[1a] The isopropyl-substituted acridine **20** was synthesized in 43% yield. Isoquinolines bearing nitro and bromo functionality furnished the corresponding alkylated products **21** and **22**, respectively. The reaction proved scalable, with isoquinoline performing well on gram scale, delivering the alkylated product **2a** in 72% yield. The quinoxaline derivative, quinazoline, phthalazine, 4-hydroxyquinazoline, benzimidazole, and benzothiazole were all alkylated by this method (**23**–**28**; 38–97%). The isopropyl, *tert*-butyl, and cyclohexyl-substituted thiazoles **29**–**31** were also synthesized in good yields.

The substrate scope study was continued with naturally occurring nitrogen heterocycles (Table 2). With this simple procedure, the introduction of hindered isopropyl, *tert*-butyl, and cyclohexyl moieties were accomplished selectively at the C6 position of nicotine, giving access to the alkylated products **32**–**34** (51–81%). Likewise, biologically important purine bases, such as caffeine and theophylline, were easily converted into the corresponding alkylated derivatives **35**–**40** in good yields (40–65%). Notably, the direct introduction of isopropyl group to caffeine, which is an otherwise challenging reaction,[7c,10a,17,22] could be performed on gram scale.

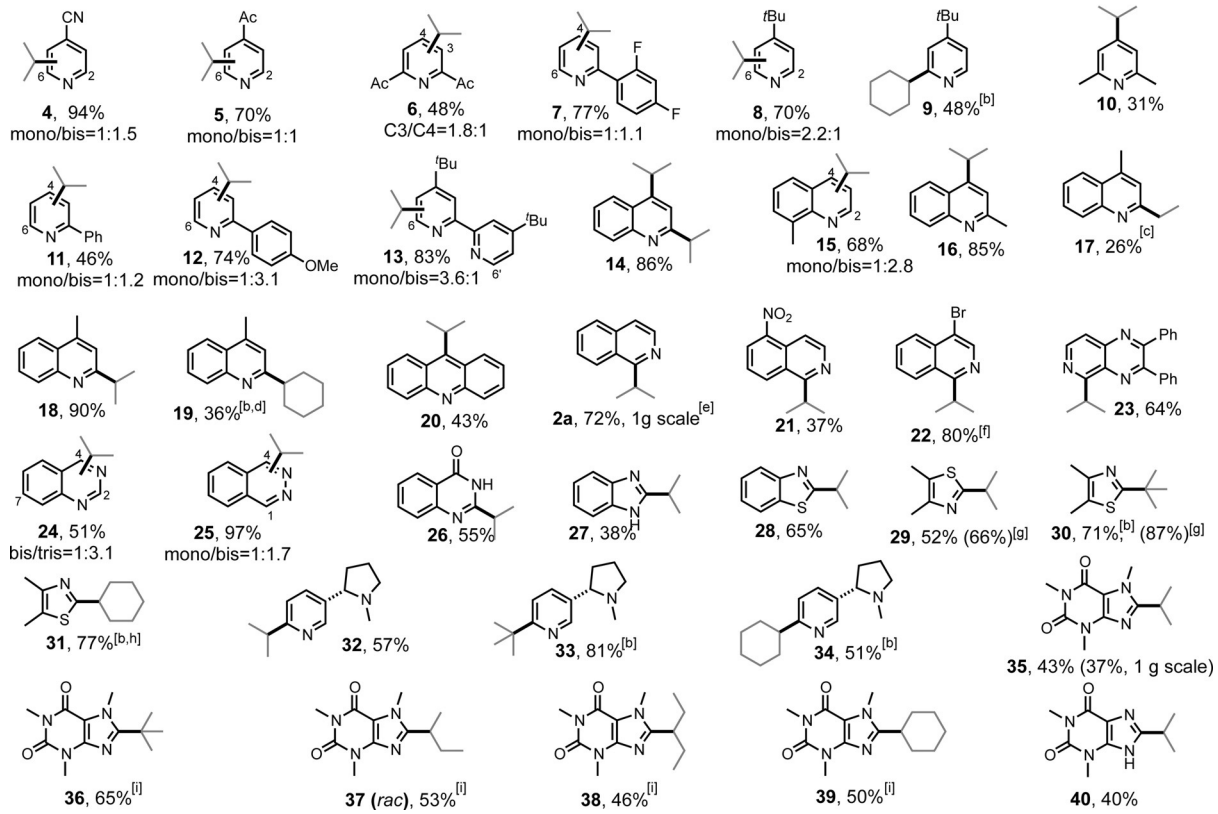
To further test the versatility of this transformation, a one-pot sequential C–H alkylation of a given nitrogen heterocycle was performed with two different aldehydes (Scheme 2). Accordingly, when 4-acetylpyridine was allowed to react with aldehydes **1d** and **1a** successively, the desired trifunctionalized pyridine **41** was isolated in 24% yield.

A proposed reaction mechanism that reconciles our experimental results with literature precedents is depicted in Scheme 3. The auto-oxidation of aldehyde has been shown to involve acyl radical **42**, which delivers the carboxylic acid **44**

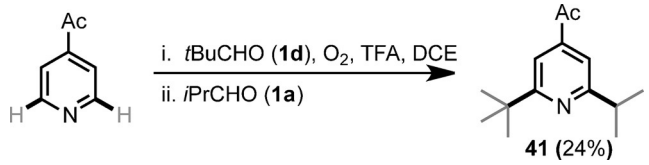
Table 2. Nitrogen heterocycle substrate scope.[a]



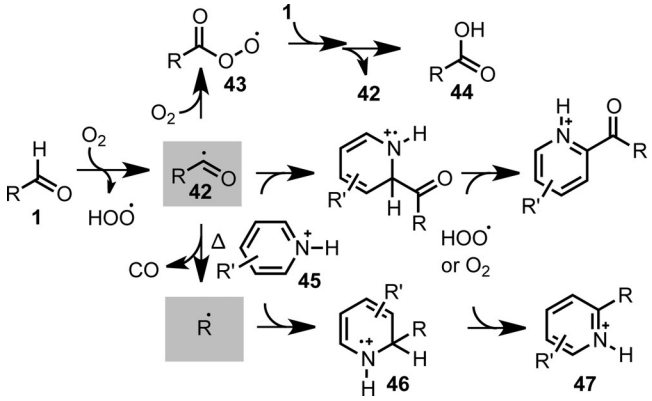
R = ethyl; isopropyl; *tert*-butyl; cyclohexyl



[a] Reaction conditions (unless otherwise stated): Heterocycle (1.0 equiv), TFA (1.5–4.5 equiv), aldehyde (6–20 equiv), DCE (1.5 M solution of heterocycle), 12–65 h; yields refer to isolated products; [b] conc. = 1.5 M; [c] 25% acylated product was formed; [d] 6% bis-alkylated product at C2 and C8 positions was isolated; [e] 3% acylated product was formed; [f] 5% acylated product was formed; [g] yields indicated in parentheses determined by ^{1}H NMR spectroscopic analysis of the crude mixture using mesitylene as internal standard; [h] 12% acylated product was formed; [i] conc. = 0.75 M.



Scheme 2. One-pot differential C–H alkylations of 4-acetylpyridine with **1d** and **1a**.



Scheme 3. Proposed reaction mechanism.

through a peracyl radical **43**.[19e] The acyl radical **42** is thus expected to deliver the corresponding alkyl radical through decarbonylation under the optimized reaction conditions. It is probable that this alkyl radical reacts with the protonated heterocycle **45** to form the radical cation **46**, which furnishes the alkylated product **47** after rearomatization with O_2 or hydroperoxide radical. Presumably, the minor acylated product resulted, in some cases, from the addition of acyl radical **42** to heterocycle **45**.[23] It is important to note that this reaction in air gave moderate yield of the desired product. In addition, a trace amount of the desire product was realized when the reaction was performed without using O_2 or acid (see the Supporting Information).

In conclusion, we have developed a metal-free, scalable, and operationally simple protocol for the direct alkylation of nitrogen heterocycles employing inexpensive aldehydes as alkyl radical precursors and molecular oxygen as a reagent. The methodology enables the incorporation of various structurally diverse and medicinally important alkyl moieties to the different classes of biologically relevant nitrogen-rich heterocycles in good yields. Many of the products reported herein are new chemical entities that could be valuable building blocks for drug discovery. Exploration of this simple and reagent-free methodology for the generation of alkyl radicals from aldehydes towards alkylation of other potential radical acceptors is the current research interest of our group.

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Keywords: auto-oxidation · C–H functionalization · heterocycles · oxygen · radical reactions

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