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Aerobic α,β-C(sp^3)−H Bond Difunctionalization and C−N Bond Cleavage of Triethylamine: Difunctional Ammonium Iodide Enabling the Regioselective Synthesis of 4-Arylpyrimido[1,2-*b*]indazoles

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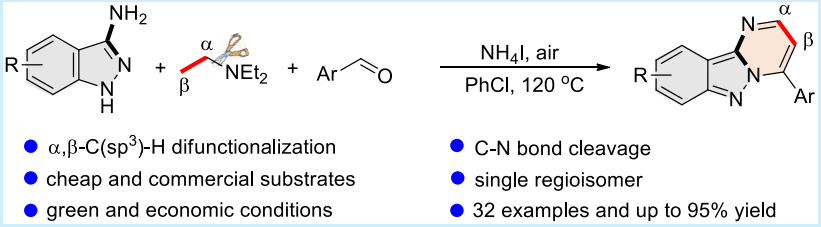
Supporting Information



ABSTRACT: A novel method for the regioselective synthesis of 4-arylpyrimido[1,2-*b*]indazoles has been developed via the dual C(sp^3)−H bond functionalization and C−N bond cleavage of triethylamine. The elusive acyclic enamine intermediates are effectively in situ generated and captured by aromatic aldehydes to form a wide array of tricyclic products from 3-aminoindazoles under the NH_4I-mediated aerobic oxidative conditions. This reaction features easily available feedstock, green and economic conditions, and valuable products.

Fused nitrogen tricyclic skeletons occur widely in natural products and synthetic drugs.[1] Among them, pyrimido[1,2-*b*]indazole derivatives have shown prominent biological properties, such as anticancer activity by inhibition of topoisomerase II*α*, anti-infective activity of hepatitis C virus, and protein kinase inhibiting activity.[2] Unfortunately, despite their importance and utility, little attention has been focused toward constructing tricyclic pyrimido-fused indazole derivatives. Recently, it was found that condensation of 1*H*-indazol-3-amines with carbonyl compounds was the frequent and efficient strategy toward a diverse range of substituted pyrimido[1,2-*b*]indazoles.[3] Generally, the free primary NH_2 group in 3-aminoindazoles was reacted with the carbonyl compounds preferentially and then the cyclization reactions took place. We have thus investigated the possibility of the formation of a C−N bond from the carbonyl group with the N2 in 3-aminoindazoles to furnish the annulation products in a selective manner. The key to realize this transformation might be the ability to adjust the interaction mode of the substrates. Herein, we report that ammonium iodide is able to perform regioselective synthesis of 4-arylpyrimido[1,2-*b*]indazoles via *α*,*β*-difunctionalization and C−N bond cleavage of triethylamine.

In recent years, transition-metal-catalyzed cleavage of the C−N single bond in inactivated amines has been developed into a convenient nitrogen and carbon source to construct useful molecules.[4] However, the high C−N bond dissociation energy and requirement for site selective functionalization makes this process extremely challenging.[5] Also, over the past few years, considerable effort has been dedicated to the development of methods for the tertiary amine *α*-C(sp^3)−H bonds functionalization via reactive intermediates such as iminium ions, *α*-amino organometallics, and *α*-amino radicals, and this has enhanced their functional-group diversity.[6] In stark contrast, the direct *β*-functionalization of tertiary amines is less established.[7] Importantly, some pioneering examples of the selective transformation of the inert aliphatic *β*-C−H bonds of ethyl tertiary amines have been reported. In 2015, the Pan group reported a Cu-catalyzed regioselective *β*-functionalization of aliphatic tertiary amines with thiophenols through a radical pathway to obtain a series of *α*,*α*-disulfenylated aldehydes, in which the yields of aldehydes decreased as the carbon chain length increased on the tertiary amines [Scheme 1a(i)].[8] Subsequently, Yuan et al. established an interesting route for the selective synthesis of *β*-arylsulfonyl enamines from sodium sulfinate and Et_3N, and DMSO could promote the *β*-C−H bond cleavage of the iminium ions for the in situ generation of reactive enamines [Scheme 1a(ii)].[9] Later on, Zhou described a Cu-catalyzed oxidative *β*-functionalization of acyclic *N*,*N*-diethyl anilines with *N*-tosylaldimines as electrophiles to produce 1,3-diamines [Scheme 1a(iii)].[10] Most recently, Ma and co-workers found the $B(C_6F_5)_3$-catalyzed borrowing hydrogen strategy to be able to accomplish the

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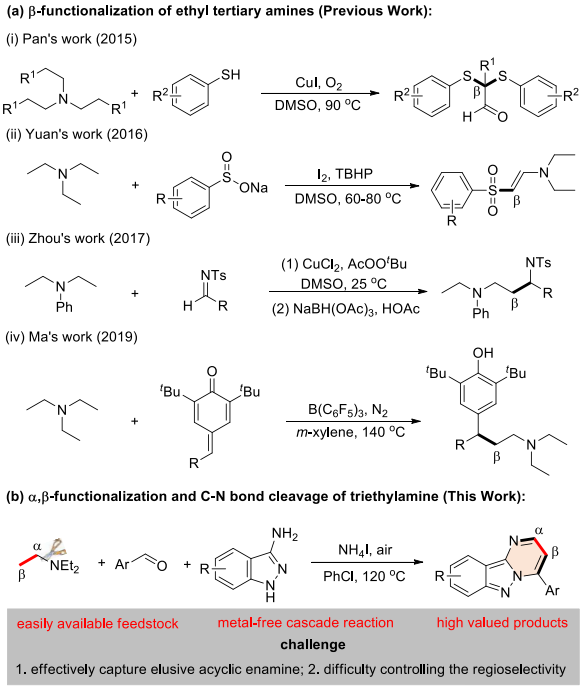
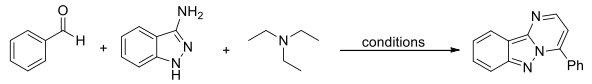
Scheme 1. Previous Overviews and New Challenge



functionalization of the C(sp^3)−H bond at the *β*-position of Et_3N via conjugate addition to *para*-quinone methides [Scheme 1a(iv)].[11] Among these transformations, converting the inert *β*-position of saturated amines to an active nucleophilic position via deprotonation process to form enamine intermediates was a crucial process. Thus, based on this new variant of these transformations, we recognized an opportunity to enable the *α*,*β*-difunctionalization of amines via transient enamines under appropriate conditions. In this paper, we disclose an appealing strategy for the realization of simultaneous C(sp^3)−H bond difunctionalization and C−N bond cleavage of Et_3N to produce pyrimido-fused indazoles under the mild and metal-free conditions (Scheme 1b).

We initiated this novel sequential reaction of commercial benzaldehyde (**1a**) with 1*H*-indazol-3-amine (**2a**) and triethylamine (**3a**) in the presence of NIS and DTBP (di-*tert*-butyl peroxide) in chlorobenzene at 130 °C for 18 h (Table 1). To our delight, the desired 4-phenylpyrimido[1,2-*b*]indazole (**4aa**) was obtained in 21% yield (entry 1). On the basis of this encouraging result, different kinds of iodine reagents such as NH_4I, elemental iodine, KI, and TBAI were observed (entry 2−5), which showed that NH_4I enhanced the yield of **4aa** and TBAI quenched the desired transformation. To improve the reaction efficiency, by replacing DTBP with BPO (benzoyl peroxide), TBPB (*tert*-butyl peroxybenzoate), DMSO, or dioxygen, the desired product was isolated in 63%, 66%, 75%, and 83% yields, respectively, and other peroxide oxidants were unsuitable for the reaction (entries 6−14). Gratifyingly, the air atmosphere also worked most efficiently (entry 15). Next, we screened the solvent effects on this transformation (entries 16−22), and it turned out chlorobenzene was still the best choice. Then, the temperature was tested (entries 23−25), which revealed that the reaction could proceed successfully as well at 120 °C (entry 24), and a dramatic decrease in yield was observed when the temperature was reduced to 110 °C (entry 25). In addition, only 67% yield of **4aa** was obtained when 0.2 equiv (catalytic amount) of NH_4I was used (entry 26).

Table 1. Optimization of the Reaction Conditions[a]



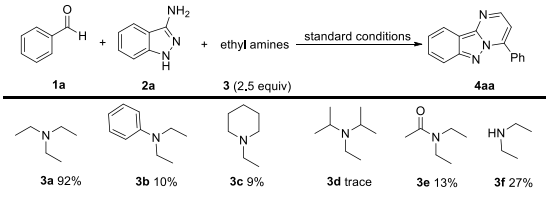
entry	[I]	oxidant	solvent	temp (°C)	yield (%)[b]
1	NIS	DTBP	PhCl	130	21
2	NH_4I	DTBP	PhCl	130	54
3	I_2	DTBP	PhCl	130	14
4	KI	DTBP	PhCl	130	9
5	TBAI	DTBP	PhCl	130	trace
6	NH_4I	TBHP	PhCl	130	31
7	NH_4I	DPO	PhCl	130	43
8	NH_4I	BPO	PhCl	130	63
9	NH_4I	TBPB	PhCl	130	66
10	NH_4I	CHP	PhCl	130	trace
11	NH_4I	H_2O_2	PhCl	130	23
12	NH_4I	DMSO	PhCl	130	75
13	NH_4I	$K_2S_2O_8$	PhCl	130	37
14	NH_4I	O_2	PhCl	130	83
15	NH_4I	air	PhCl	130	82
16	NH_4I	air	toluene	130	80
17	NH_4I	air	dioxane	130	65
18	NH_4I	air	CH_3CN	130	78
19	NH_4I	air	NMP	130	43
20	NH_4I	air	DCE	130	21
21	NH_4I	air	DMF	130	41
22	NH_4I	air	DMSO	130	17
23	NH_4I	air	PhCl	150	84
24	NH_4I	air	PhCl	120	82
25	NH_4I	air	PhCl	110	62
26[c]	NH_4I	air	PhCl	120	67
27[d]	NH_4I	air	PhCl	120	92
28[e]	**NH_4I**	**air**	**PhCl**	**120**	**92(78)**[g]
29[f]	NH_4I	air	PhCl	120	63

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), **3a** (2.0 mmol), [I] (0.5 mmol), oxidant (1.5 mmol), solvent (2 mL) for 18 h. [b]Isolated yields. [c]NH_4I (0.1 mmol). [d]NH_4I (0.75 mmol). [e]**3a** (1.25 mmol), NH_4I (0.75 mmol). [f]**3a** (0.5 mmol), NH_4I (0.75 mmol). [g]**1a** (5 mmol), **2a** (5 mmol), **3a** (12.5 mmol).

Surprisingly, the yield of **4aa** was improved to 92% when increasing the amount of NH_4I to 1.5 equiv (entry 27). To our delight, the yield of **4aa** has no distinct influence when we used 2.5 equiv of Et_3N (entry 28).

Based on the optimized conditions described above, we further examined another variety of ethyl amines (**3b**−**f**) as the carbon source to react with benzaldehyde (**1a**) and 1*H*-indazol-3-amine (**2a**) for the construction of tricyclic pyrimido-fused indazoles. As shown in Scheme 2, only diethylamine (**3f**) gave **4aa** in only 27% yield, and other tertiary ethyl amines were ineffective. These results clearly

Scheme 2. Representative Ethyl Amines



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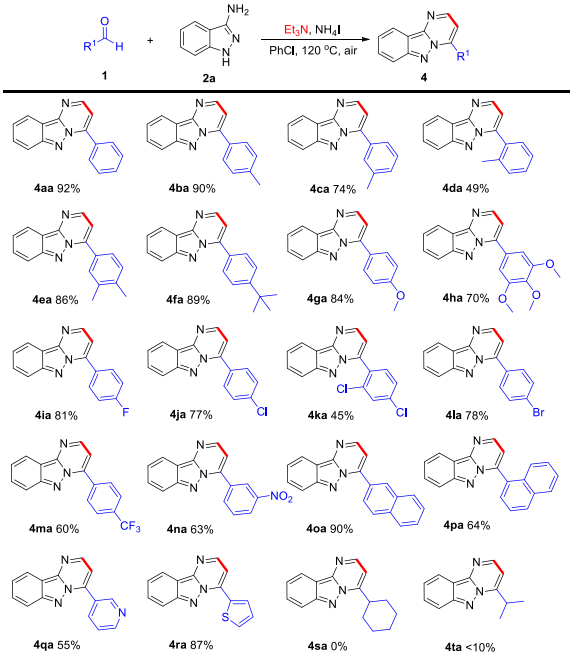
show that the choice of amines is crucial for this cascade process.

Subsequently, we explored the generality and scope of this aerobic NH_4I-mediated three-component [3 + 2 + 1] annulation under the optimized reaction conditions. A wide range of aromatic aldehydes were found to display comparable reactivities to benzaldehyde (Scheme 3). The benzaldehydes

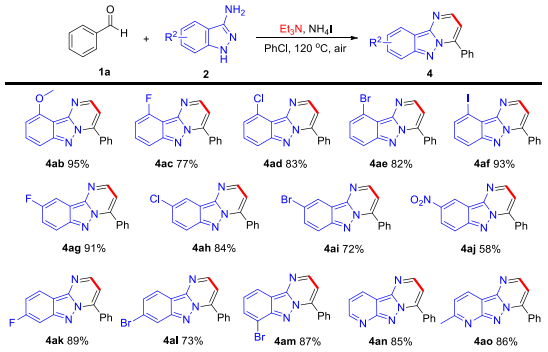
Scheme 3. Substrate Scope of Aldehydes



with electron-neutral and electron-donating groups on the aromatic rings such as methyl, tertiary butyl, and methoxyl delivered to the corresponding pyrimido[1,2-*b*]indazoles in moderate to good yields (49−90%; **4ba**−**ha**). Notably, the halo groups including fluoro-, chloro-, bromo-, and trifluoromethyl could be incorporated into the phenyl ring of 4-phenylpyrimido[1,2-*b*]indazoles, and products **4ia**−**ma** are obtained in 45−81% yields. In particular, these biologically relevant functionalities such as methyl, methoxyl, and trifluoromethyl highlighted the potential medicinal use of the products. These results indicated the steric effect played a role in the reaction (**4db** and **4ka**), and multisubstituted aldehydes effciently reacted as well (**4ea**, **4ha**, and **4ka**). Meanwhile, the benzaldehydes with the strongly electron-withdrawing group nitro could be accessed through this route to generate the targeted products in acceptable yield (63%; **4na**). Moreover, the reactions with 2-naphthaldehyde (**1o**), 1-naphthaldehyde (**1p**), nicotinaldehyde (**1q**), and thiophene-2-carbaldehyde (**1r**) also reacted smoothly to afford **4oa**−**4ra** in 55−90% yields, respectively. In the case of substrate (**1s**), no annulation product (**4sa**) can be detected under the standard conditions. We attribute the poor reaction efficiency to alkyl aldehyde. In addition, the structure of **4ja** was unambiguously confirmed by single-crystal X-ray diffraction (CCDC 1923241).

We next focused on the scope with respect to the representative 3-aminoindazoles in this dehydrogenative reaction. A series of 3-aminoindazoles bearing various groups at all positions of the phenyl rings were proven to be good candidates (Scheme 4). For instance, 3-aminoindazoles substituted with a variety of functional groups such as

Scheme 4. Substrate Scope of 3-Aminoindazoles



methoxy, fluoro, chloro, bromo, and iodo at the C-4 position showed good reactivity in this transformation, leading to the corresponding products (**4ab**−**af**) in 77−95% yields. Similarly, 3-aminoindazoles halo-substituted at the C-5, C6, and C7 positions were also found to be effectual for generating pyrimido[1,2-*b*]indazole derivatives in moderate yields (72−91%; **4ag**−**ai**, **4ak**−**am**). Notably, halogen atoms, including F, Cl, Br, and I, provided a convenient handle for further synthetic elaboration of products. Furthermore, a strong electron-withdrawing group (5-NO_2) rendered moderately lower yields presumably because of the lowered nucleophilicity. Compared with 3-aminoindazoles, 1*H*-pyrazolo[3,4-*b*]pyridin-3-amines **2n** and **2o** remained unaffected under these reaction conditions to produce **4an** and **4ao** in 85% and 86% yields, respectively.

With the scope of the method established, preliminary mechanistic investigations were carried out. The addition of commonly used radical scavengers TEMPO or BHT did not dramatically affect the yields of **4aa** under the standard conditions. This means a nonradical pathway might not be involved in the process (Scheme 5a). A reaction performed with cinnamic aldehyde (**5**) and 3-aminoindazole (**2a**) could provide the pyrimido[1,2-*b*]indazole product in 41% yield (Scheme 5b). Since it is known that triethylamine generates the acetaldehyde[12] or *N*,*N*-diethylethenamine,[13] it is possible that they might be the intermediates in this reaction. However, no conversion occurred when Et_3N was replaced by metaldehyde and enamine (**6**) (Scheme 5c and 5d). These results strongly demonstrated that the imine intermediate from Et_3N was preferentially captured by 3-aminoindazoles and prevented from converting to its enamine form under the NH_4I-mediated aerobic oxidative conditions.[14] Based on the blank experiments, it was confirmed that NH_4I and molecular oxygen were indispensable for this transformation (Scheme 5e and 5f). Moreover, the speculation that the α-C and β-C of triethylamine was integrated into the final tricyclic pyrimidines has been demonstrated when **3a**-d_{15} was used under the standard conditions (Scheme 5g).

Nevertheless, a similar ammonium salt NH_4Br or NH_4Cl resulted in a lower yield and NH_4OAc gave **4aa** in 47% yield (Scheme 6a). In comparison, this transformation led to the formation of **4aa** only in 26% yield in the presence of HOAc. It still remains unclear, however, why NH_4I plays such a critical role in this oxidative annulation reaction. We believe that HI and I_2 are the real forms of NH_4I that participated in this reaction. Compared to I_2, **4aa** was produced in a higher yield when the reaction was run with HI. Additionally, different ratios of HI and I_2 have a great effect on this reaction (Scheme

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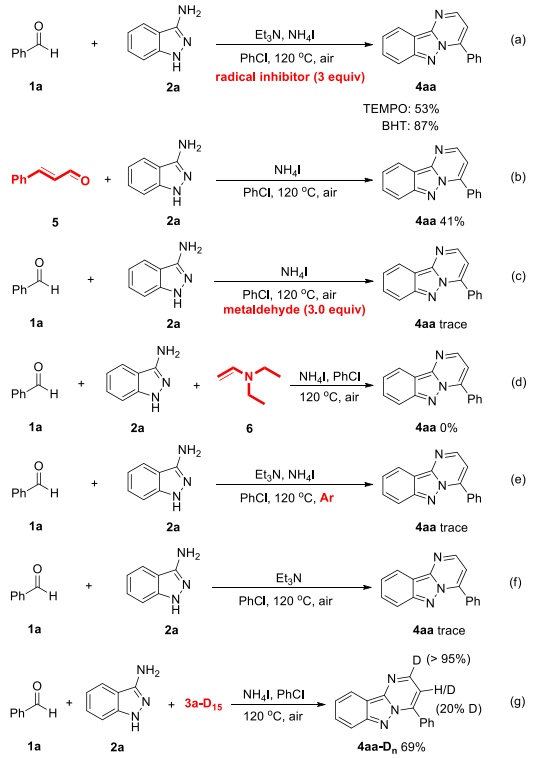
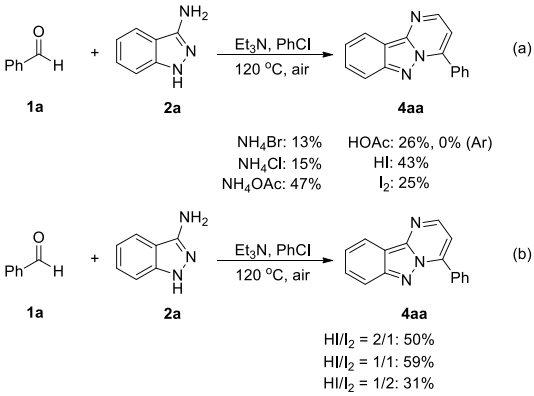
Scheme 5. Control Experiments



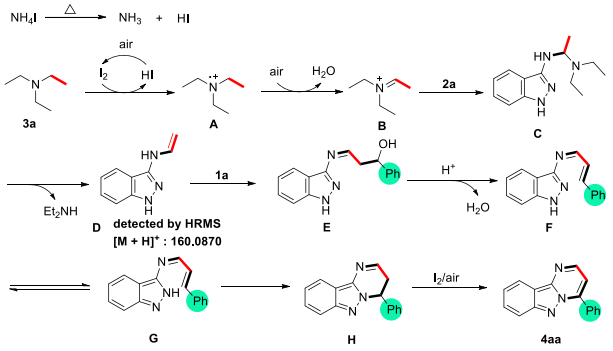
Scheme 6. Control Experiments



6b). These results suggested the concentration of HI was well controlled in the case of NH_4I since its decomposition was a reversible process.[15]

On the basis of the above observations and previous reports,[10,11,16] a plausible mechanism for the formation of pyrimido[1,2-*b*]indazoles is illustrated in Scheme 7. First, heat splits NH_4I into NH_3 and HI, and HI is further oxidized by air to produce I_2. Subsequently, the oxidations of **3a** with I_2 and air would form the imine-type intermediate **B**, which reacts with the nucleophilic 3-aminoindazole to provide the intermediate **C**. Elimination of Et_2NH from **C** generates the key enamine intermediate **D** in situ. Then, nucleophilic addition of **D** to the aldehyde and dehydration affords the intermediate **F**, which isomerizes to the intermediate **G**. Finally, intramolecular Michael addition of **G** renders the intermediate **H** followed by oxidative aromatization to furnish the desired product **4aa**.

Scheme 7. Plausible Mechanism



In summary, we have developed an appealing and versatile strategy for the regioselective synthesis of pyrimido[1,2-*b*]indazole derivatives from readily available building blocks under air conditions. The key success of this reaction is the generation of the elusive acyclic enamine enabled by the cleavage of the C(sp^3)−H bond and C−N bond in triethylamine. Significantly, NH_4I plays a dual-function role in this sequential process, serving as an iodine source to enable the oxidation reaction and as an acid to facilitate the condensation reaction.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02218.

General experimental procedures and spectroscopic data for the corresponding products (PDF)

Accession Codes

CCDC 1923241 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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