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KI Catalyzed Nitrogenation of Aldehydes and Alcohols: Direct Synthesis of Carbamoyl Azides and Ureas

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An efficient KI catalyzed nitrogenation of aldehydes and alcohols for the direct synthesis of carbamoyl azides and ureas via a radical process has been developed. The simple operating procedures, the readily available starting materials including aldehydes, alcohols and amines, as well as the utility of the products all make this strategy very attractive.

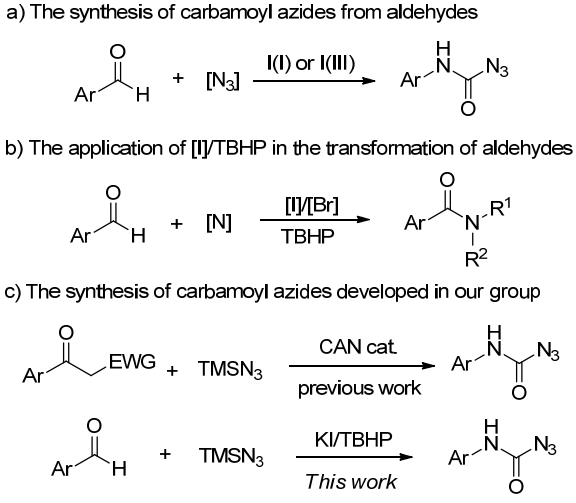
Keywords nitrogenation, aldehydes, carbamoyl azides, ureas, KI, TBHP

Introduction

Aldehydes are common and fundamental organic units, and are conveniently transformed to various value-added chemicals.[1] Among them, the oxidative coupling of aldehydes for the synthesis of other functional compounds has attracted considerable attentions.[2] By the employment of hypervalent iodine(III) reagents[3] or transition-metal catalysts,[4] some novel oxidative transformations of aldehydes have been developed. Carbamoyl azides are versatile intermediates and building blocks in organic synthesis.[5] Several groups reported the synthesis of carbamoyl azides from aldehydes with the employment of iodine(I) or iodine(III) reagents which were unstable or air sensitive (Scheme 1a).[6] Thus, it is highly desirable to develop a practical approach to realize the transformation of aldehydes to carbamoyl azides.

Recently, Wan[7] and Barbas III[8] groups reported the transformation of aldehydes to amides catalyzed by iodine/*tert*-butyl hydroperoxide (TBHP) system (Scheme 1b). With a new coupling partner, the effective strategy expands the application of iodine/TBHP system[9] in C—H functionalization of aldehydes. We previously reported a simple ceric ammonium nitrate (CAN) catalyzed functionalization of ketones through double C—C bond cleavage strategy for the synthesis of carbamoyl azides (Scheme 1c).[10] Inspired by the above results and our previous nitrogenation reactions,[11] herein, we tried to introduce the iodine/TBHP system into the nitrogenation chemistry of aldehydes and azides. The generated acyl azides by aldehydes and azides could be easily converted into isocyanates in situ via Curtius rearrangement.[12] The subsequent addition of hydrazoic acids to isocyanates would generate carbamoyl azides (Scheme 1c). In our assumption, the utility of aldehyde cross-coupling method will be further expanded to alcohols.

Scheme 1 The synthesis of carbamoyl azides



Experimental

A dry flask with stir bar was charged with benzaldehyde (0.3 mmol, 31.8 mg) and KI (0.06 mmol, 9.96 mg).

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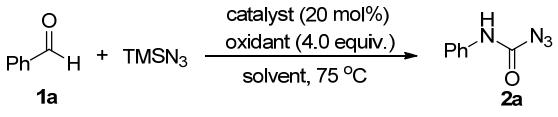
In Memory of Professor Enze Min.

Then $TMSN_3$ (1.2 mmol, 138 mg) and TBHP (1.2 mmol, 219 μL) in EtOAc (1 mL) was added to the flask at room temperature. The solution was stirred at 75 ℃ under air for 24 h. After being cooled down to room temperature, the resulting mixture was filtered and concentrated. The residue was purified by flash chromatography on silica gel (eluent: *V*(petroleum ether)/*V*(ethylacetate)=20∶1) to afford the product.

Results and Discussion

We commenced our hypothesis by investigating the reaction of benzaldehyde (**1a**) with trimethylsilylazide ($TMSN_3$) (Table 1). Firstly, a series of catalysts with TBHP as oxidant were tested. When TBAI was employed as the catalyst, the desired product **2a** was isolated in 17% yield (entry 1). Subsequent research of catalysts showed that KI was the best choice for this transformation (entries 1—3). The other solvents including THF, DMF, and dioxane decreased the efficiency of this reaction strongly (entries 4—6). The other oxidants such as *m*-CPBA or $K_2S_2O_8$ could not promote this reaction (entries 7—10). Elevating the reaction temperature to 100 ℃ had a slight positive effect on the yield (cf. entries 2 and 10). Only trace amount of the desired product was obtained when sodium azide (NaN_3) was used as the azide source (entry 11). The concentration of the reaction played an important role in this process. When the solvent was reduced to 1 mL, the desired product was isolated in 75% yield (entry 12).

Table 1 Optimization of the reaction conditions[a]



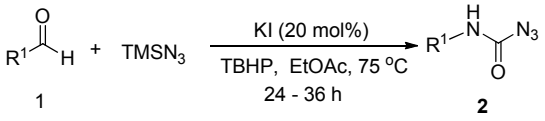
1a **2a**

Entry	Catalyst	Oxidant	Solvent	Yield[b]/%
1	TBAI	TBHP	EtOAc	17
2	KI	TBHP	EtOAc	50
3	I_2	TBHP	EtOAc	25
4	KI	TBHP	DMF	0
5	KI	TBHP	Dioxane	0
6	KI	TBHP	THF	trace
7	KI	*m*-CPBA	EtOAc	trace
8[c]	KI	TBHP(aq.)	EtOAc	44
9	KI	$K_2S_2O_8$	EtOAc	0
10[d]	KI	TBHP	EtOAc	56
11[e]	KI	TBHP	EtOAc	trace
12[f]	**KI**	**TBHP**	**EtOAc**	**75**

[a] Reaction conditions: The reaction mixture of **1a** (0.3 mmol), $TMSN_3$ (4.0 equiv.), catalyst (20 mol%), and oxidant (4.0 equiv.) in solvent (2.0 mL) was stirred under air for 48 h. [b] Isolated yields. [c] TBHP (70% aqueous solution). [d] At 100 ℃. [e] Sodium azide was used instead of $TMSN_3$. [f] The solvent was 1 mL and reaction time was 24 h.

With the optimized conditions in hand, a variety of substituted aryl aldehydes were subjected to this transformation (Table 2). The results showed that aryl aldehydes with electron-donating groups were well tolerated and gave the desired products in moderate to good yields (entries 1—4, 8—9). The electron-withdrawing group substituted aldehydes were also tolerated, but the efficiency decreased slightly (entries 5—7). Steric hindrance also showed an effect in the process. For example, the reaction of 2-methylbenzaldeyde (**1i**) with $TMSN_3$, produced the product **2i** in 50% yield (cf. entries 2 and 9). Moreover, heteroaryl aldehyde such as thiophene was tolerated in this transformation and provided the corresponding product **2l** in moderate yield (entry 12). Unfortunately, the aliphatic aldehydes are not compatible under standard reaction conditions.

Table 2 The scope of benzaldehydes[a]



1 **2**

Entry	R^1	Product	Yield[b]/%
1	C_6H_5	**2a**	75
2	4-Me-C_6H_4	**2b**	76
3	4-^{t}Bu-C_6H_4	**2c**	76
4	3,4-$(Me)_2$-C_6H_3	**2d**	70
5	4-F-C_6H_4	**2e**	61
6	4-Cl-C_6H_4	**2f**	57
7	4-Br-C_6H_4	**2g**	55
8	4-MeO-C_6H_4	**2h**	72
9	2-Me-C_6H_4	**2i**	50
10	4-EtO-C_6H_4	**2j**	63
11[c]	2-naphthyl	**2k**	61
12	3-thienyl	**2l**	49

[a] Reaction conditions: see Table 1, entry 12. [b] Isolated yields. [c] EtOAc (3 mL) was used.

We speculated that benzylamine, phenylacetaldehyde, and benzyl alcohol could also be converted to carbamoyl azide because they are easily oxidized to benzaldehyde under oxidative conditions. As we expected, when catalyzed by KI in the presence of TBHP at 75 ℃, the reaction of $TMSN_3$ with benzylamine, phenylacetaldehyde, or benzyl alcohol produced carbamoyl azide **2a** with lower efficiencies compared to that of benzaldehyde (Table 3). To our delight, carbamoyl azides (**2a**, **2b**, **2g**, **2f**) were obtained in moderate yields when the reaction of $TMSN_3$ and benzyl alcohol was catalyzed by 20 mol% I_2 in the presence of NaOH (entries 3—6). These results indicate that a cascade oxidative aldehyde generation through C—N or C—C cleavage and the subsequent nitrogenation of aldehyde via C—H bond cleavage, is involved in this process.

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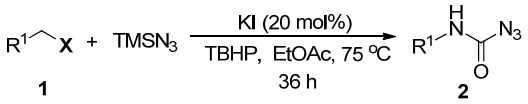
Table 3 The nitrogenation of benzylamine, phenylacetaldehyde, and benzyl alcohol[a]



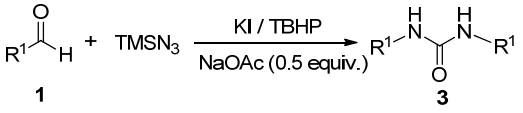
1 2

Entry	R^1	X	Product	Yield[b]/%
1	C_6H_5	NH_2	**2a**	23
2	C_6H_5	CHO	**2a**	19
3[c]	C_6H_5	OH	**2a**	50
4[c]	4-MeC_6H_4	OH	**2b**	52
5[c]	4-BrC_6H_4	OH	**2g**	42
6[c]	4-ClC_6H_4	OH	**2f**	46

[a] Reaction conditions: see Table 1, entry 12. [b] Isolated yields. [c] I_2 (20 mol%) was used instead of KI, NaOH (20 mol%) was added.

Carbamoyl azides are easily converted to symmetrical ureas under basic condition. Thus, we speculate that the aldehydes could be directly converted to ureas if NaOAc was added to the optimal conditions. As expected, symmetrical ureas could be directly prepared from the reaction of aryl aldehyde with azide in the presence of 0.5 equiv. of NaOAc catalyzed by KI (Table 4).

Table 4 The synthesis of symmetrical ureas from aldehyde[a]



1 3

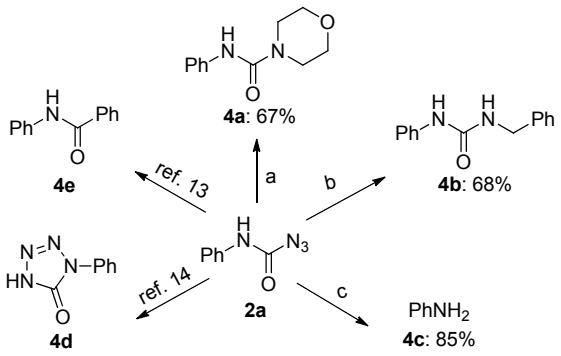
Entry	R^1	Product	Yield[b]/%
1	C_6H_5	**3a**	65
2	4-Me-C_6H_4	**3b**	70
3	4-^{t}Bu-C_6H_4	**3c**	69
4	3,4-$(Me)_2C_6H_3$	**3d**	60
5	4-F-C_6H_4	**3e**	63

[a] Reaction conditions: The reaction mixture of **1** (0.2 mmol), $TMSN_3$ (4.0 equiv.), KI (20 mol%), TBHP (4.0 equiv.), and NaOAc (0.5 equiv.) in EtOAc (1 mL) was stirred under air at 75 ℃ for 36 h. [b] Isolated yields.

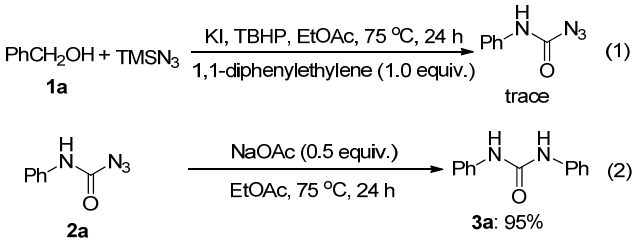
Carbamoyl azide could be transformed to various kinds of ureas via the reaction with amine nucleophiles. Moreover, under basic environment, carbamoyl azides would decompose to aniline. The amide would be obtained by the nucleophilic attack of Grignard reagent to carbamoyl azide.[13] Besides, it is noteworthy that carbamoyl azides could undergo a cyclization process to provide tetrazole, which is an useful building block and common biological active molecule.[14]

When 1,1-diphenyethylene (a radical scavenger) was added under the standard conditions, the yield of carbamoyl azide (**2a**) decreased dramatically, which indicated that a radical path may be involved in the azidation process (Eq. 1). When the carbamoyl azide was treated with 0.5 equiv. of NaOAc, the 1,3-diphenylurea (**3a**) could be obtained in 95% yield, which suggested that carbamoyl azide was the intermediate in the synthesis of diphenylurea (Eq. 2).[15]

Scheme 2 Transformations of phenylcarbamoyl azide



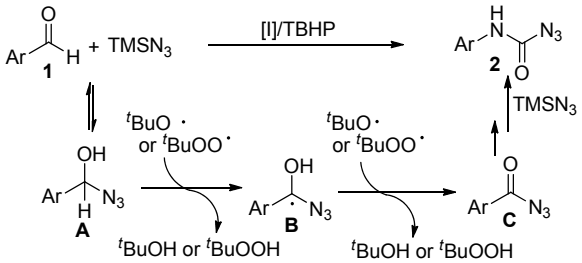
Reaction conditions: (a) **2a** (0.2 mmol), morpholine (0.4 mmol), EtOAc (1 mL), 75 ℃, 12 h. (b) **2a** (0.2 mmol), benzylamine (0.4 mmol), EtOAc (2 mL), 75 ℃, 12 h. (c) **2a** (0.4 mmol), NaOH (1.0 mL, 2 mol/L), dioxane (1.0 mL), r.t., 30 min. Then HCl (1.0 mL, 6 mol/L) was added, r.t., 30 min.



1a 2a

On the basis of the above experiments and previous studies, a proposed mechanism is shown in Scheme 3. Firstly, *tert*-butoxyl radical is generated from TBHP through the catalytic cycle, where I_2 plays a role as the catalyst.[16] Meanwhile, the substrate is attacked by the azide to produce the intermediate **A**. Secondly, *tert*-butoxyl radical abstracts two hydrogen atoms from the intermediate to generate acyl azide **C**.[17] The acyl azide will undergo Curtius rearrangement[12] to generate aryl isocyanate, which reacts with another azide to produce carbamoyl azide.

Scheme 3 Possible mechanism



Conclusions

In conclusion, an efficient KI catalyzed direct azida-

tion of aldehyde for the direct synthesis of carbamoyl azide and ureas via a radical process has been developed. The simple operating procedures, the readily availability of the starting materials, and the utility of the products all make the strategy attractive. Further application of this method and studies about the mechanism are ongoing in our laboratory.

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