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Potassium Iodide/*tert*-Butyl Hydroperoxide-Mediated Oxidative Annulation for the Selective Synthesis of *N*-Substituted 1,2,3-Benzotriazine-4(3*H*)-ones Using Nitromethane as the Nitrogen Synthon

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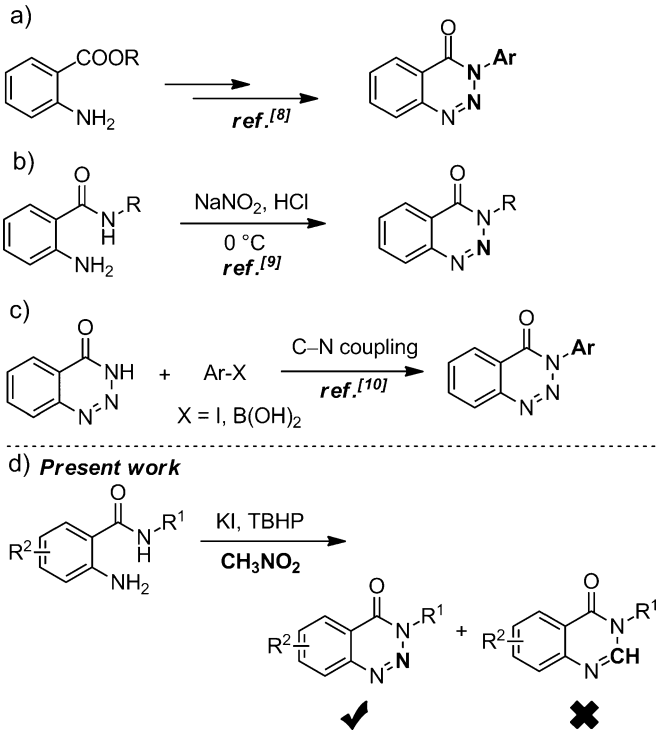
Abstract: A novel and efficient oxidative annulation of 2-aminobenzamides with nitromethane has been developed for the chemoselective synthesis of *N*-substituted 1,2,3-benzotriazine-4(3*H*)-ones in moderate to excellent yields under transition metal-free conditions. Two N–N bonds were constructed in one pot *via* C–N cleavage of nitromethane, which was selectively employed as the nitrogen synthon. The preliminary mechanistic studies revealed that this protocol proceeded under hypoiodite catalysis generated *in situ*.

Keywords: 1,2,3-benzotriazine-4(3*H*)-ones; C–N cleavage; hypoiodite catalysis; nitromethane; oxidation

1,2,3-Benzotriazine-4(3*H*)-ones represent an important class of nitrogen-containing heterocycles and have attracted much attention in the fields of bioorganic and medicinal chemistry.[1] For example, many pharmacological properties for this class of compounds have been reported, including drugs having sedative,[2] diuretic,[3] anesthetic,[4] antiarthritic,[5] antitumor[6] and antitubercular activities.[7] Traditionally, 1,2,3-benzotriazine.-4(3*H*)-ones were synthesized from methyl anthranilates *via* a multi-step process (Scheme 1a).[8] The diazotization of 2-aminobenzamides as an alternative general method also afforded 1,2,3-benzotriazine-4(3*H*)-ones in the presence of a strong acid and sodium nitrite (Scheme 1b).[9] Recently, a copper-catalyzed Ullmann-type coupling reaction between 1,2,3-benzotriazine-4(3*H*)-ones and aryl iodide (or arylboronic acids) has been used for the synthesis of 3-aryl-1,2,3-benzotriazine-4(3*H*)-ones (Scheme 1c).[7,10] However, these methods require tedious steps or transition metal catalysts, and they generally give low yields and have a limited substrate



Scheme 1. Approaches for the construction of 1,2,3-benzotriazine-4(3*H*)-ones.

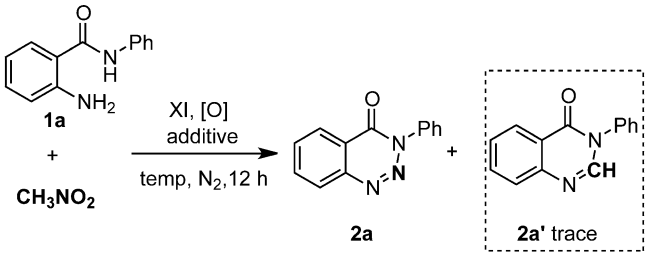
scope. Therefore, the development of a transition metal-free and efficient protocol for the synthesis of 1,2,3-benzotriazine-4(3*H*)-ones using readily available starting materials is highly desirable.

Nitromethane has emerged as a useful nucleophilic carbon synthon in organic reactions such as Henry reactions,[11] Michael additions,[12] cross dehydrogenation coupling (CDC) reactions[13] and multicomponent reactions (MCRs)[14] as well as being a common solvent. Moreover, it is well-known that nitromethane can be decomposed to a carbon synthon (HCHO) and a nitrogen synthon (HNO) *via* a Nef reaction.[15] Therefore, nitromethane can likely be employed as a carbon or nitrogen source for the synthesis of heterocycles. Recently, Zhang reported an interesting radical approach to the synthesis of 3-(trifluoromethyl)quinoxalines from *N*-arylenamines with nitromethane as an additional nitrogen source.[16] As part of our efforts in developing new carbon and nitrogen synthons for the transition metal-free synthesis of heterocycles,[17] herein we demonstrate an efficient potassium iodide/*tert*-butyl hydroperoxide-mediated oxidative annulation of 2-aminobenzamides with nitromethane by C–N bond cleavage and N–N bond formation, which represents a simple and general approach for the construction of 1,2,3-benzotriazine-4(3*H*)-ones in moderate to excellent yields under transition metal-free conditions (Scheme 1d). Notably, nitromethane was selectively used as a nitrogen synthon rather than a carbon synthon in this reaction.

We began our study with the reaction of 2-amino-*N*-phenylbenzamide (**1a**, 0.2 mmol) in the presence of potassium iodide (KI, 10 mol%) as a catalyst and *tert*-butyl hydroperoxide (TBHP, 70% in water, 2.5 equiv.) as an oxidant. When the reaction mixture was heated in 2 mL of nitromethane at 120 °C for 12 h, 3-phenylbenzo[*d*][1,2,3]triazin-4(3*H*)-one (**2a**) was obtained in 30% isolated yield, whereas a trace amount of 3-phenylquinazolin-4(3*H*)-one (**2a′**) was detected (Table 1, entry 1). To improve the yield of this reaction, 2 equiv. of HOAc were used in the reaction as an additive, affording **2a** in moderate 50% yield (Table 1, entry 2). When 2 equiv. of Cs_2CO_3 or CsOAc were added, the reaction gave **2a** in a 70% or 74% yield, respectively (Table 1, entries 3 and 4). This result indicated that both acids and bases could promote the reaction. Thus, we tried to use 1 equiv. of Cs_2CO_3 and 2 equiv. of HOAc as combined additives. To our delight, **2a** was obtained almost quantitatively (Table 1, entry 5) because Cs_2CO_3 could promote the decomposition of nitromethane to generate the NO anion; then, HOAc could regulate the pH value of the reaction system to generate HNO. When various iodine reagents, such as tetrabutylammonium iodide (TBAI) and iodine, were used as catalysts, **2a** was isolated in lower yields than with KI (Table 1, entries 6 and 7). Subsequently, examination of various peroxides, such as di-*tert*-butyl peroxide (DTBP) and H_2O_2 (30% in water), did not give better results (Table 1, entries 8 and 9). However, **2a** was not detected in the absence of oxidant, which indicated that an oxidant is essential for this reaction (Table 1, entry 10). When the reaction temperature was decreased from 120 °C to 100 °C or 80 °C, the reaction proceeded with a poor yield (Table 1, entries 11 and 12). Moreover, reducing the loading of KI to 5% decreased the yield of **2a** to 82% (Table 1, entry 13). Unexpectedly, **2a** was also obtained in a 65% yield in the absence of KI (Table 1, entry 14). When the loading of CH_3NO_2 was decreased from 2 mL to 2 equiv., only a 43% yield of **2a** was obtained (Table 1, entry 15). Thus, the optimal set of conditions was determined as described in entry 5.

Under these optimized reaction conditions, the scope of substrates that could be used and the versa-

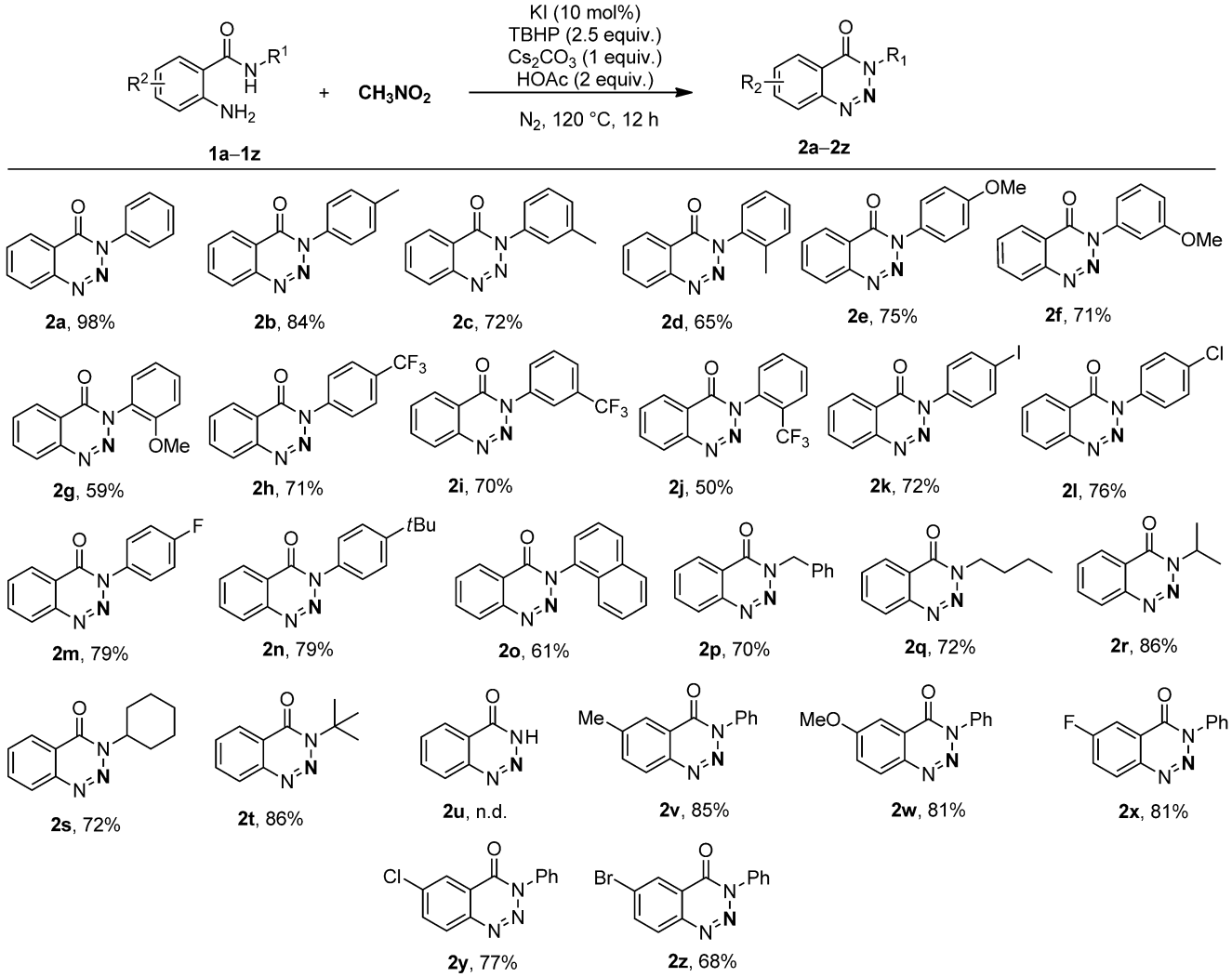
Table 1. Optimization of reaction conditions[a]



Entry	XI	Oxidant	Additive	Temp. [°C]	Yield [%][b]
1	KI	TBHP	None	120	30
2	KI	TBHP	HOAc	120	50
3	KI	TBHP	Cs_2CO_3	120	70
4	KI	TBHP	CsOAc	120	74
5[c]	**KI**	**TBHP**	**Cs_2CO_3/HOAc**	**120**	**98**
6	TBAI	TBHP	Cs_2CO_3/HOAc	120	75
7	I_2	TBHP	Cs_2CO_3/HOAc	120	71
8	KI	DTBP	Cs_2CO_3/HOAc	120	75
9	KI	H_2O_2	Cs_2CO_3/HOAc	120	80
10	KI	None	Cs_2CO_3/HOAc	120	n.d.
11	KI	TBHP	Cs_2CO_3/HOAc	100	10
12	KI	TBHP	Cs_2CO_3/HOAc	80	5
13[d]	KI	TBHP	Cs_2CO_3/HOAc	120	82
14	none	TBHP	Cs_2CO_3/HOAc	120	68
15[e]	KI	TBHP	Cs_2CO_3/HOAc	120	43

[a] *Reaction conditions:* **1a** (0.2 mmol), XI (0.02 mmol), oxidant (0.5 mmol), additive (0.4 mmol), CH_3NO_2 (2 mL), N_2, 12 h.
[b] Isolated yield.
[c] Cs_2CO_3 (0.2 mmol) and HOAc (0.4 mmol) were used.
[d] KI (0.01 mmol) was used.
[e] 2 equiv. of CH_3NO_2 in CH_3CN (2 mL).

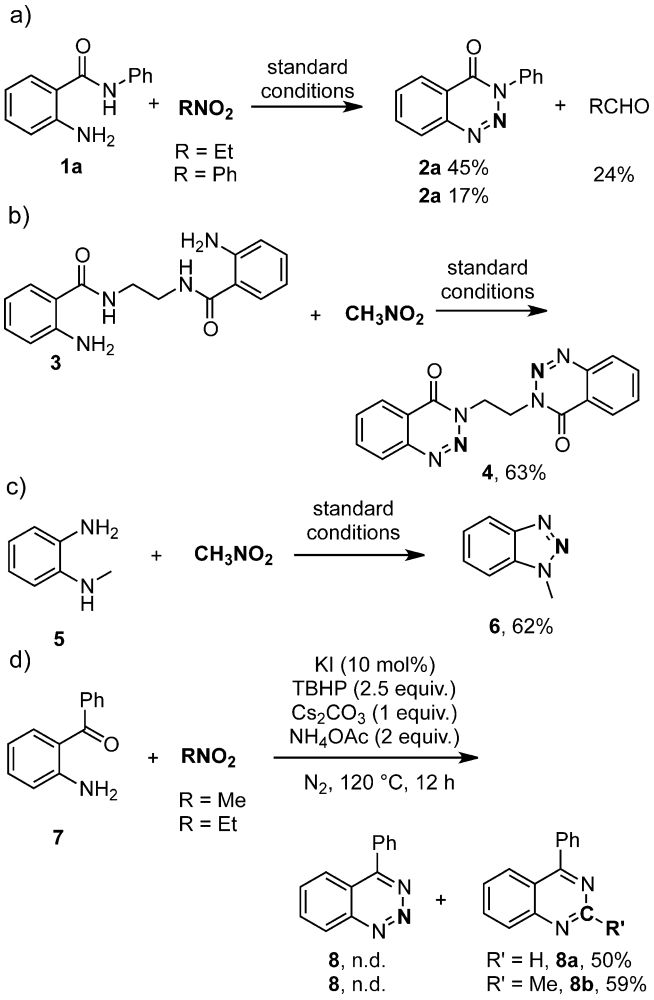
Table 2. Scope of 2-aminobenzamide substrates[a]



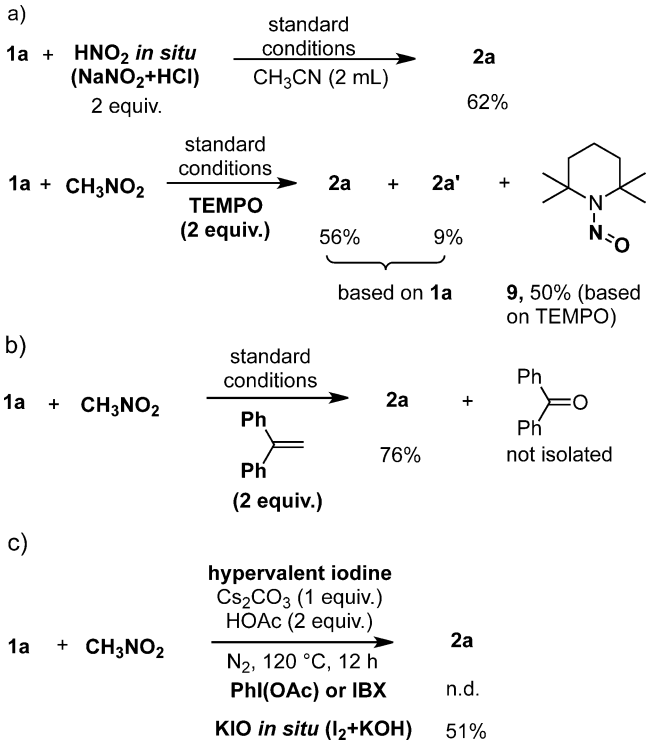
[a] *Reaction conditions:* **1** (0.2 mmol), KI (0.02 mmol), TBHP (0.5 mmol), Cs_2CO_3 (0.2 mmol), HOAc (0.4 mmol), CH_3NO_2 (2 mL), 120 °C, N_2, 12 h.

tility of the reaction were investigated. As shown in Table 2, various 2-aminobenzamides (**1a–1z**) were employed in this reaction to synthesize a variety of 1,2,3-benzotriazine-4(3*H*)-ones in good yields. First, when R^1 was an aromatic substituent, all of the desired products (**2a–2n**) were obtained in moderate to good yields. Notably, the reactions of 2-amino-*N*-arylbenzamides bearing electron-donating groups (4-Me, 4-OMe or 4-*t*-Bu) on the phenyl ring of R^1 gave higher yields than those of the substrates bearing electron-withdrawing groups (4-CF_3) on the phenyl ring. Moreover, the substrates bearing methyl, methoxy or trifluoromethyl groups at the *ortho*-position of the phenyl ring of R^1 gave lower yields compared with the *para*- or *meta*-substituted reactants, perhaps due to steric hindrance. When R^1 was a 1-naphthyl substituent, product **2o** was obtained in a 61% isolated yield. Subsequently, substrates with aliphatic groups, such as benzyl, *n*-butyl, isopropyl, cyclohexyl and *tert*-butyl as R^1 substituents could also be employed to give the corresponding products **2p–2t** in 70–86% yields. Unfortunately, 2-aminobenzamide (**2u**) did not give the desired product. Finally, 2-aminobenzanilides with various R^2 substituents such as methyl, methoxy, fluoro, chloro and bromo were also employed in this reaction, giving the desired products **2v–2z** in 68–85% yields. Among these reactions, substrates with electron-rich substituents (**1v** or **1w**) gave higher yields than those with electron-deficient ones (**1x**, **1y** or **1z**) because of the differences in amino nucleophilicity.

Next, we examined using this novel approach for the synthesis of other 1,2,3-benzotriazines (Scheme 2). First, when nitroethane was used instead of nitromethane, the reaction of **1a** afforded the product **2a** in a 45% yield, and no product with nitroethane as a carbon source was detected. When (nitromethyl)-



Scheme 2. Syntheses of other 1,2,3-benzotriazines.

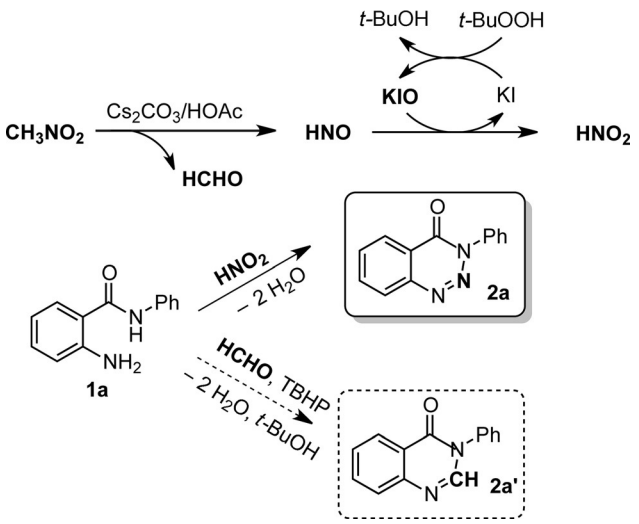


Scheme 3. Control experiments for mechanistic studies.

benzene was employed instead of nitromethane, the reaction of **1a** afforded the product **2a** in a 17% yield. Meanwhile, a 24% yield of benzaldehyde was obtained (Scheme 2a). Subsequently, when 1,2-bis[(2-aminobenzoyl)amino]ethane (**3**) was used as the substrate, the desired product 1,2-bis(4-oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl)ethane (**4**) containing two symmetrical 1,2,3-benzotriazine rings was obtained in a 63% yield (Scheme 2b). In addition, the reaction of *N*-methylbenzene-1,2-diamine (**5**) under standard conditions also gave the desired 1-methyl-1*H*-benzo[*d*][1,2,3]triazole (**6**) in a 62% isolated yield (Scheme 2c). However, 4-phenylbenzo[*d*][1,2,3]triazine (**8**) was not observed, and a 50% yield of 4-phenylquinazoline (**8a**) was obtained when 2-aminobenzophenone (**7**) was employed as the substrate. Similarly, when nitroethane was used instead of nitromethane, the reaction of **7** gave 2-methyl-4-phenylquinazoline (**8b**) with a 59% yield (Scheme 2d). These two results indicated that nitromethane and nitroethane were selectively used as carbon synthons in this reaction. When 2-amino-*N*-methyl-*N*-phenylbenzamide or 2-aminobenzenesulfonamide was used instead of 2-amino-*N*-phenylbenzamide, no desired product was observed when nitromethane is used as the nitrogen source. To extend the scope of substrates that could be used in this reaction, 2-amino-*N*-phenylacetamide containing an aliphatic amino group was used as the substrate; however, no corresponding product was detected.

To gain insight into the reaction mechanism, several control experiments were conducted (Scheme 3). First, the reaction of **1a** with 2 equiv. of HNO_2, generated *in situ* from $NaNO_2$ and HCl, gave **2a** in a 62% yield, which indicated that HNO_2 was probably the intermediate of this reaction (Scheme 3a). Subsequently, radical trapping experiments were performed (Scheme 3b). We observed that the reaction was not completely inhibited in the presence of 2,2,6,6-tetramethylpiperidinyl 1-oxyl (TEMPO) or 1,1-diphenylethylene. This observation implies that the reaction may not proceed *via* a radical pathway. Moreover, the effect of iodine was also investigated (Scheme 3c). When 2 equiv. of $PhI(OAc)_2$ or IBX were employed instead of our catalytic system, no **2a** was obtained. In contrast, when KIO generated *in situ* from I_2 and KOH was used, the reaction gave **2a** in a 51% yield. This result indicates that hypoiodite plays an important role in the reaction process.

On the basis of the results described above and previous reports, a plausible mechanism is proposed (Scheme 4). Initially, the Nef reaction of CH_3NO_2



Scheme 4. A plausible mechanism.

generates HCHO and HNO in the presence of Cs_2CO_3 and HOAc.[15,16] Then, HNO can be further oxidized to HNO_2 by KIO generated *in situ* from KI and TBHP.[18] Finally, the direct condensation of **1a** with HNO_2 affords the desired product **2a** by removal of two H_2O molecules.[9] As a minor pathway, **2a′** can be obtained *via* a tandem condensation-addition-oxidation process of **1a** with HCHO.[19] It is noteworthy that the I^-/IO^- catalytic cycle plays an important role in the reaction.

In summary, we have developed a transition metal-free oxidative annulation for the chemoselective synthesis of *N*-substituted 1,2,3-benzotriazine-4(3*H*)-ones and 1-methyl-1*H*-benzo[*d*][1,2,3]triazole using nitromethane as the nitrogen synthon. This novel protocol features transition metal-free conditions, high chemoselectivity, operational simplicity, easily accessible substrates and good functional group tolerance. Further studies are ongoing to expand the synthetic utility of this versatile catalytic system.

Experimental Section

General Procedure

Substrates **1** (0.2 mmol), KI (3.3 mg, 0.02 mol), Cs_2CO_3 (65.2 mg, 0.2 mmol), TBHP (75 μL, 0.5 mmol), HOAc (23 μL, 0.4 mmol) and CH_3NO_2 (2.0 mL) were successively added to a 10-mL Schlenk tube. After nitrogen displacement, the mixture was stirred at 120 °C for 12 h. The solution was then cooled to room temperature, quenched by aqueous Na_2SO_3 solution and extracted with EtOAc (3× 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated under vacuum. The residue was purified by column chromatography on silica gel to afford the desired products **2**.

Acknowledgements

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