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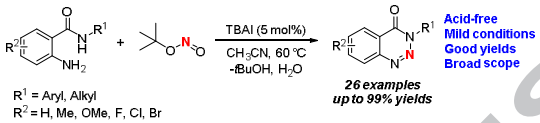

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Mild and efficient TBAI-catalyzed synthesis of 1,2,3-benzotriazine-4-(*3H*)-ones from *tert*-butyl nitrite and 2-aminobenzamides under acid-free conditions

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ABSTRACT

A facile and efficient annulation of 2-aminobenzamides and *tert*-butyl nitrite was developed, affording 1,2,3-benzotriazine-4-(*3H*)-ones in good yields under mild conditions. Notably, the reaction was carried out in the absence of strong acid and *tert*-butyl nitrite was employed as the nitrogen source.

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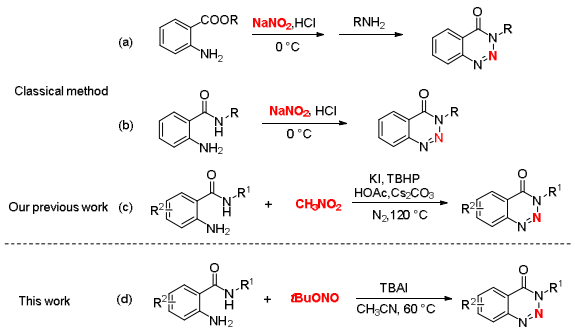
1,2,3-Benzotriazine-4-(*3H*)-ones have attracted considerable attention because of potential pharmacological properties, such as sedative, diuretic, anesthetic, antiarthritic, antitumor and antitubercular activities in the field of bioorganic and medicinal chemistry.[1,2] Traditionally, 1,2,3-benzotriazine-4-(*3H*)-ones were formed from methyl anthranilates[3] or 2-aminobenzamides[4] via diazotization in the presence of strong acid (HCl or H_2SO_4) and $NaNO_2$ at 0°C (Scheme 1a and 1b). However, strong acid and low temperature were required and substrate scope was limited, giving the products in moderate yields. Recently, we have developed an efficient KI/TBHP-mediated oxidative annulation of 2-aminobenzamides with nitromethane via C–N cleavage and N–N bond formation, affording 1,2,3-benzotriazine-4-(*3H*)-ones in moderate to excellent yields under transition-metal-free conditions (Scheme 1c).[5] In this protocol, nitromethane was used as the nitrogen synthon. Although the yield of product was good and the substrate scope was broad, acid (HOAc) and high temperature (120°C) remained required, which limited further applications in organic synthetic industry. Therefore, the development of mild and efficient protocol for the synthesis of 1,2,3-benzotriazine-4-(*3H*)-ones in the absence of acid is highly desirable.

Recently, *tert*-butyl nitrite (TBN) has emerged as a useful nitrogen synthon in organic synthesis.[6] Especially, TBN has been widely used for efficient synthesis of nitrogen containing heterocycles under mild conditions.[7] Inspired by these reports, herein we demonstrate a mild and efficient TBAI-catalyzed



Scheme 1. Synthetic routes to 1,2,3-benzotriazine-4-(*3H*)-ones

synthesis of 1,2,3-benzotriazine-4-(*3H*)-ones from *tert*-butyl nitrite and 2-aminobenzamides under acid-free conditions (Scheme 1d)

We began our study with the reaction of 2-amino-N-phenylbenzamide (**1a**, 0.2 mmol) and *tert*-butyl nitrite (**2**, 0.6 mmol) in the presence of tetrabutylammonium iodide (TBAI, 10 mol%) as the catalyst. After the reaction mixture was heated in 2 mL of CH_3CN at 60 °C for 12 h, 3-phenylbenzo[*d*][1,2,3]triazin-4(*3H*)-one (**3a**) was obtained in almost quantitative yield (Table 1, entry 1). When tetrabutylammonium bromide (TBAB) and tetrabutylammonium chloride (TBAC) were used as the catalyst, the reaction yields slightly decreased (Table 1, entries 2 and 3). When lowering reaction temperature from 60 °C to 50 °C or 40

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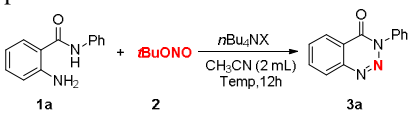
°C, the reaction yield obviously decreased (Table 1, entries 4 and 5), Moreover, reducing the amount of TBAI to 5 mol% didn't decrease the yield of **3a** (Table 1, entry 6). However, **3a** was obtained in only 68% yield in absence of TBAI, which indicated that TBAI played an important role in the transformation (Table 1, entry 7). In addition, the yield of **3a** decreased gradually with reducing the amount of *tert*-butyl nitrite (Table 1, entries 8 and 9). Expectedly, no desired **3a** was observed in the absence of *tert*-butyl nitrite. This result revealed that the additional nitrogen atom of product **3a** was derived from *tert*-butyl nitrite (Table 1, entry 10). Thus, an optimal set of conditions were determined as described in entry 6.

Table 1. Optimization of reaction conditions[a]



Entry	Catalyst	TBN(equiv)	Temp(°C)	Yield[b](%)
1	TBAI	3	60	99
2	TBAB	3	60	95
3	TBAC	3	60	90
4	TBAI	3	50	85
5	TBAI	3	40	75
6[c]	**TBAI**	**3**	**60**	**99**
7	None	3	60	68
8	TBAI	2	60	85
9	TBAI	1	60	43
10	TBAI	0	60	ND

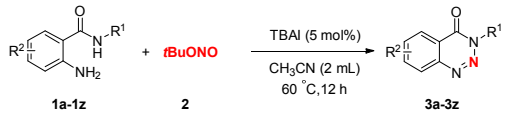
[a] Reaction conditions: 1a (0.2 mmol), 2 (0.6 mmol), nBu$_4$NX (10 mol%, 0.02mmol), CH$_3$CN (2 mL), 60 °C, 12 h.

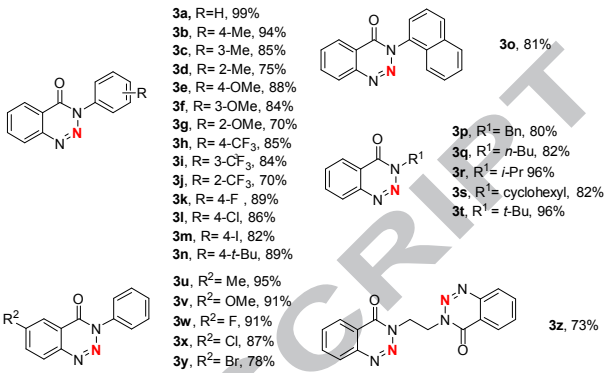
[b] Isolated yield

[c] 5 mol% of TBAI

With suitable reaction conditions in hand, we next explored the generality of these reaction conditions for variously substituted 2-aminobenzamides (Table 2). Various 2-aminobenzamides (**1a-1z**) were employed in this reaction for the synthesis of a variety of 1,2,3-benzotriazine-4-(*3H*)-ones in good yields. First, 2-amino-N-arylbenzamides (**1a-1n**) with common substituents such as Me, OMe, CF$_3$, F, Cl, Br and *t*-Bu on phenyl ring readily reacted with *tert*-butyl nitrite to give the corresponding N-aryl-1,2,3-benzotriazine-4-(*3H*)-ones in good isolated yields (Table 2, entries **3a–3n**). It is noted that the reaction of 2-amino-N-arylbenzamides bearing electron-donating groups (4-Me, 4-OMe or 4-*t*Bu) on the phenyl ring gave higher yields than that of electron-withdrawing groups (4-CF$_3$) on the phenyl ring. In addition, 2-amino-N-arylbenzamides bearing Me, OMe or CF$_3$ on *ortho*-position of phenyl ring gave lower yields compared to *para*-position because of steric effect. This synthesis was also applicable for the reaction of 2-amino-N-(naphthalen-1-yl)benzamide with *tert*-butyl nitrite to produce **3o** in 81% yield (Table 2, entry **3o**). Subsequently, substrates with aliphatic groups as R^1 substituent, such as Bn, *n*-Bu, *i*-Pr, cyclohexyl and *t*-Bu, could also be employed to give the corresponding products **3p-3t** in excellent yields (Table 2, entries **3p–3t**). Furthermore, 2-aminobenzanilides with various R^2 substituents such as Me, OMe, F, Cl and Br were also employed in this reaction, giving the desired products in good to excellent yields (Table 2, entries **3u–3y**). Finally, to extend the applicability of this method in

Table 2. 1,2,3-benzotriazine-4-(*3H*)-ones from various 2-aminobenzamides[a]

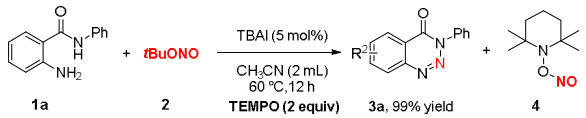




a Reaction conditions: 1a-1z (0.2 mmol), 2 (0.6 mmol), nBu$_4$NI (5 mol%, 0.01mmol), CH$_3$CN (2 mL), 60 °C, 12 h.

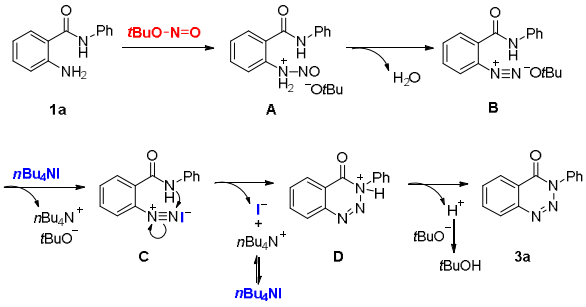
more complicated molecules, we tested this methodology for 2-bis-{(2-aminobenzoyl-)amino}ethane (**1z**). Thus, the desired product 1,2-bis-(4-oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl)ethane (**3z**) containing two symmetrical 1,2,3-benzotriazine rings was efficiently obtained in 73% yield (Table 2, entry **3z**).

According to previous reports on *tert*-butyl nitrite as the nitrogen source, a radical intermediate, such as NO radical, may be generated via the decomposition of TBN.[6,7] To gain insight into the mechanism, a radical trappling experiments was performed (Scheme 2). The reaction was not obviously inhibited in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and the expected trapping product **4** was also not detected. This observation implies that the reaction may not undergo a radical pathway, similar to our previous report. Moreover, when the reaction was completed, *t*BuOH was detected as a main byproduct by GC-MS anaylsis (See SI for details).



Scheme 2. Radical trapping experiment

On the basis of results described above and previous reports[6,7], a plausible mechanism is proposed (Scheme 3). Initially, the reaction of 2-aminobenzamide with *tert*-butyl nitrite generates a unstable cation intermediate **A** via the nitrosation of primary amino. Then **A** can be transformed to a diazonium salt **B** through the dehydration, which generates a diazonium iodide **C** via the anion exchange in the presence of TBAI. Finally, the direct



Scheme 3. A proposed mechanism

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intramolecular substitution affords the intermediate D, which further gives **3a** by removing hydrogen ion. Notably, the residual iodine anion regenerate the catalyst TBAI and hydrogen cation with *tert*-butoxyl anion gives the byproduct *tert*-butyl alcohol.[6b-d,7a-b]

In summary, a diverse array of 1,2,3-benzotriazine-4-(*3H*)-ones were prepared from 2-aminobenzamides and *tert*-butyl nitrite in good to excellent yields. Compared to previous reports, this novel protocol is distinguished by (1) acid-free and mild conditions, (2) operational simplicity, (3) high yields, (4) broad substrate scope and (5) water and *tert*-butyl alcohol as green byproducts. Further developments of *tert*-butyl nitrite based novel synthesis of N-heterocycles are currently in progress in our laboratory.

Acknowledgments

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Supplementary data

Experimental procedures, compound characterization data and copies of NMR spectra for all products are included in Supplementary data. Supplementary data associated with this article can be found in the online version.

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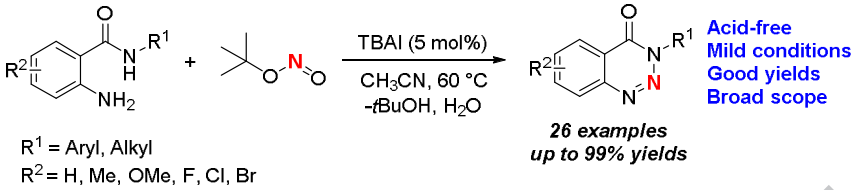

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Highlights

- 1,2,3-benzotriazine-4-(*3H*)-ones was firstly synthesized from *tert*-butyl nitrite
- The reaction was carried out under mild conditions in the absence of strong acid
- *tert*-Butyl nitrite was employed as the nitrogen source of the products
- A plausible mechanism is proposed based on control experiment and GC-MS analysis

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