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$NaNO_2/I_2$ as an Alternative Reagent for the Synthesis of 1,2,3-Benzotriazin-4(3*H*)-ones from 2-Aminobenzamides

Dinesh S. Barak[a], Sushobhan Mukhopadhyay [a], Dipak J. Dahatonde [a], Sanjay Batra * [a,b]

[a] *Medicinal and Process Chemistry Division, CSIR-Central Drug Research Instirtute, Sector 10, Jankipuram Extension, Sitapur Road, Lucknow-226031, Uttar Pradesh, India.*
[b] *Academy of Scientific and Innovative Research, New Delhi 110025, India.*

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* Corresponding author. Tel.: +91-522-2772450/2772550 xtn 4705/4706/4732; e-mail: batra_san@yahoo.co.uk, s_batra@cdri.res.in

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ABSTRACT

An efficient transformation of 2-aminobenzamides to 1,2,3-benzotriazin-4(3*H*)-ones in the presence of sodium nitrite ($NaNO_2$) and Iodine (I_2) is described. The reaction is proposed to proceed via formation of nitrosyl halide that induces nitrosylation of the amino group of 2-aminobenzamide leading to diazotization followed by intramolecular cyclization.

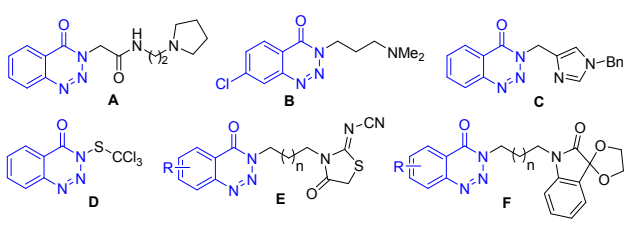
1. Introduction

1,2,3-Benzotriazin-4(3*H*)-one is considered to be an important heterocyclic core in the realms of medicinal and agricultural chemistry.[1] Compounds bearing this scaffold are endowed with diverse pharmacological properties which include sedative, antitumor, antitubercular, anaesthetic, antiarthritic, diuretic and LTA4H aminopeptidase inhibitors (Fig. 1).[2] This class of compounds are also reported as nematicidal and herbicidal agents for use in agriculture.[3] Beside differently substituted 1,2,3-benzotriazin-4(3*H*)-ones are useful precursors for synthesizing various azaheterocycles via metal-catalyzed denitrogenative transannulation reactions.[4] Classical synthesis of 1,2,3-benzotriazin-4(3*H*)-one is a multistep procedure originating from methyl anthranilate.[5] But the more general method of synthesis of this heterocycle involves diazotization of 2-aminobenzamide in the presence of $NaNO_2$ and strong acid.[6] Alternatively, reports of diazotization using *t*-BuONO as the nitrogen source either in the presence of TBAI or saccharin or AcOH exist.[7] Moreover, Yan et al. reported nitromethane as the nitrogen source to access 1,2,3-benzotriazin-4(3*H*)-one from 2-aminobenzamide in the presence of KI/TBHP.[8] Besides, several new approaches for the synthesis of this core have been reported recently. A copper-catalyzed Ullman type coupling reaction of 1,2,3-benzotriazin-4(3*H*)-one with aryl iodide or aryl boronic acid for preparing 3-aryl-1,2,3-benzotriazin-4(3*H*)-one was developed.[2e] Recently, Hemmings et al. discovered that attempted *N*-arylation of *N*-(2-azidoaryl)-sulfonyl prolinol with 5-bromopent-1-ene produced a separable

Figure 1. A few bioactive compounds bearing the 1,2,3-Benzotriazin-4(3*H*)-one core

mixture (1:1) of 1,2,3-benzotriazin-4(3*H*)-one and quinazolin-4-one.[9] Chandrasekhar and Sankararaman disclosed that 1,3-diaryltriazines via Pd(0)-catalyzed annulation reaction provided 3-aryl-1,2,3-arylbenzotriazin-4(3*H*)-ones.[10] More recently, Song et al. reported the first oxidative rearrangement of 3-aminoindazole to 1,2,3-benzotriazine-4(3*H*)-ones in the presence of 1,3-dibromo-5,5-dimethylhydantoin and CAN.[11] These methods are efficient, but involve use of acid, oxidants or metal catalysts and are successful mostly with 2-amino-*N*-substituted benzamides. Therefore, a simpler method using cheap reagents under mild condition with broad substrate scope would be a useful addition to the repertoire.

We have been investigating the synthetic potential of $NaNO_2$/ I_2 for preparing useful products.[12] In this context, we recently reported direct transformation of arylamine to aryl halide in the presence of $NaNO_2$/ NXS.[13] The reaction was proposed to proceed via nitrosylation of the aromatic amino group leading to diazo intermediate which undergoes nucleophilic halogenation to afford the aryl halide. During the course of this study it was discovered that the 2-amino-*N*-phenylbenzamide when treated with $NaNO_2$/ NIS in DMF at room temperature afforded 1,2,3-benzotriazin-4-one in minor quantity instead of the anticipated 2-iodobenzamide. Probing the reaction under heating increased to the yield of 1,2,3-benzotriazin-4(3*H*)-one to 35% together with recovery of the starting material. Given the importance of 1,2,3-benzotriazin-4(3*H*)-one, we considered optimizing the reaction and we have now found that treating 2-aminobenzamides with $NaNO_2$/ I_2 in MeCN as medium produced the desired product exclusively in excellent yields. The details of this study are presented herein.

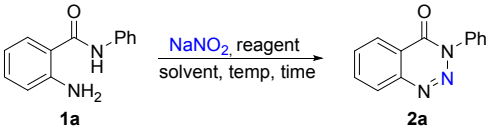


2. Results and Discussion

Initially we observed that treating 2-amino-*N*-phenylbenzamide **1a** with $NaNO_2$ (1.5 equiv) and NIS (1.0 equiv) in DMF as medium at

room temperature afforded 3-phenyl-1,2,3-benzotriazin-4(3*H*)-one **2a** instead of the expected 2-iodo-*N*-phenylbenzamide in 8% yield together with recovery of the starting material (entry 1, Table 1). However, heating the identical reaction at 100 °C led to isolation of **2a** in 35% yield in 5 h (entry 2). To drive reaction to completion, first the amount of $NaNO_2$ was increased to 3.0 equiv, which produced **2a** in 53% yield (entry 3). Changing the solvent from DMF to MeCN and temperature to 80 °C gave **2a** in 56% yield (entry 4). Increasing the amount of NIS to 2.0 equiv resulted in complete reaction in 5 h to afford **2a** in 80% yield (entry 5). Alternating the iodine source from NIS (2.0 equiv) to molecular I_2 (1.0 equiv) gratifyingly expedited the reaction to be completed in 3.0 h to furnish 2a in superior yield of 83% (entry 6). Reducing the amount of I_2 to 0.5 equiv however, gave **2a** in 58% isolated yield after 5 h of reaction time (entry 7). We also investigated NBS and NCS for the protocol and we discovered that they furnished **2a** in 21 and 13% yield, respectively (entries 8 and 9). Thus, the optimized condition that worked best in our hand is 2-amino-

Table 1. Results of the optimization study for transforming **1a** to **2a**[a]



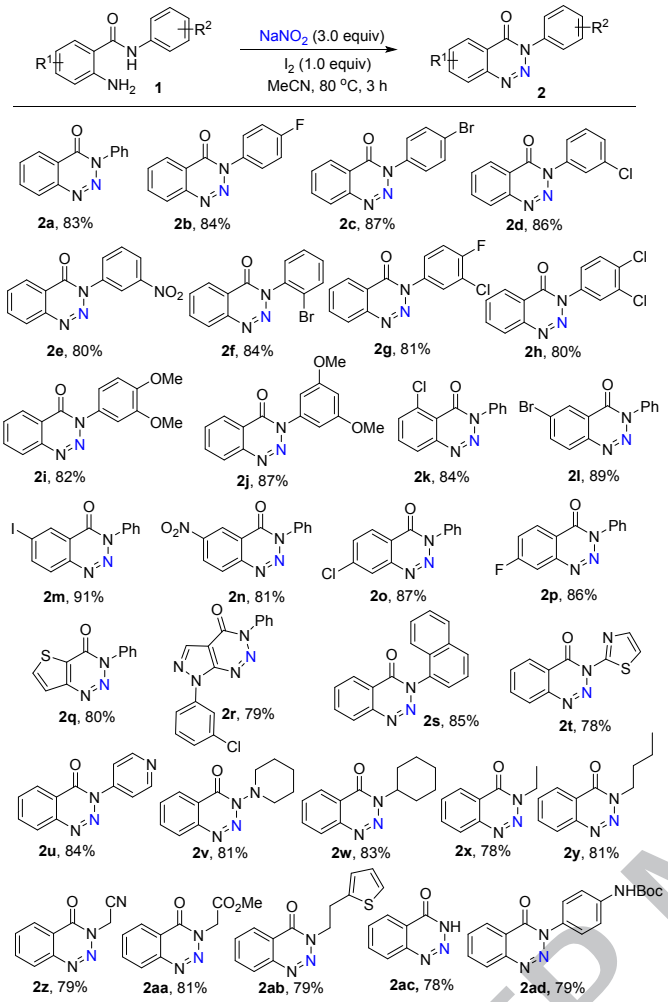
1a **2a**

entry	$NaNO_2$ (equiv)	reagent (equiv)	solvent	temp (°C)	time (h)	yield[b] (%) of **2a**
1[c]	1.5	NIS (1.0)	DMF	rt	5	8
2[c]	1.5	NIS (1.0)	DMF	100	5	35
3[c]	3.0	NIS (1.0)	DMF	100	5	53
4[c]	3.0	NIS (1.0)	MeCN	80	5	56
5	3.0	NIS (2.0)	MeCN	80	5	80
6	**3.0**	**I_2 (1.0)**	**MeCN**	**80**	**3**	**83**
7	3.0	I_2 (0.5)	MeCN	80	5	58
8[d]	3.0	NBS (2.0)	MeCN	80	3	21
9[d]	3.0	NCS (2.0)	MeCN	80	3	13

[a]All the reactions were carried out using **1a** (0.2 g, 0.94 mmol), $NaNO_2$, solvent (5 mL) under heating for indicated time. [b]Isolated yields after purification. [c]Unreacted starting material recovered too. [d]Several inseparable side products were observed.

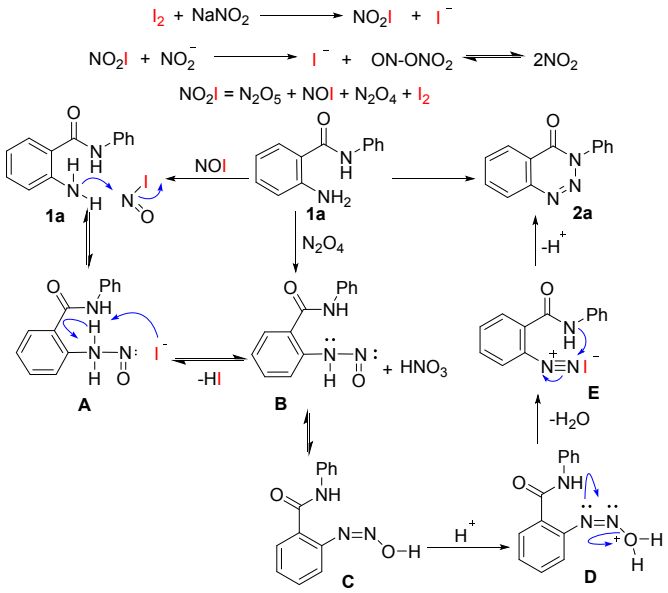
N-phenylbenzamide (1.0 equiv), $NaNO_2$ (3.0 equiv) and I_2 (1.0 equiv) under MeCN as the medium at 80 °C for 3h.

With optimized conditions identified, we explored the scope of the protocol with diverse 2-aminobenzamides. In the first set, reactions of substrates **1a-j** bearing different substitutions on the *N*-phenyl ring were investigated and all the substrates smoothly afforded the corresponding products **2a-j** in 80-87% yields (Scheme 1). The reaction tolerated both electron donating and electron withdrawing substitutions on the phenyl ring. In the next set, substrates **1k-p** bearing different substitutions on the phenyl ring carrying the amino group were investigated and the corresponding products **2k-p** were isolated in 81-91% yields. The

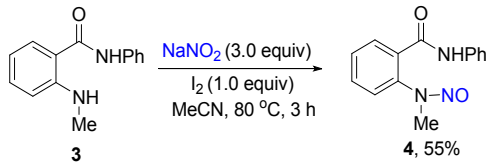


Scheme 1. Scope of the synthesis of 1,2,3-Benzotriazin-4(3*H*)-ones from 2-aminobenzamides. All reactions were performed at 0.2 g scale

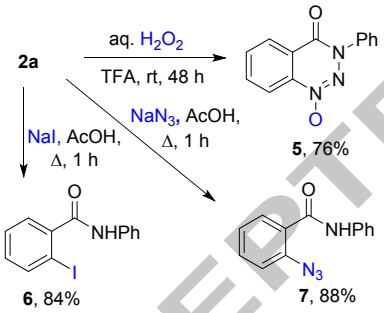
heterocyclic substrates **1q** and **1r** also afforded the benzotriazin-4(3*H*)-ones **2q** and **2r**, respectively in 79-80% yields. Subsequently, the *N*-phenyl ring was replaced by naphthyl, thiazolyl and pyridyl ring to generate substrates **1s-1u** and here too corresponding products **2s-2u** were formed satisfactorily. The amide **1v** bearing *N*-aminopiperidine was compatible to the protocol to give **2v** in 81% yield. Next the scope was evaluated with substrates bearing *N*-aliphatic chain instead of the aryl unit as represented by compounds **1w-1ab** and pleasingly the respective products **2w-2ab** were isolated in 78-83% yields. Finally, subjecting simple 2-aminobenzamide **1ac** to the reaction resulted in the formation of **2ac** (78%).



Scheme 2. A plausible mechanism for the formation of 1,2,3-benzotriazine-4(3*H*)-one



Scheme 3 Formation of nitrosylated derivative from 2-(methylamino)-*N*-phenylbenzamide



Scheme 4. Transformations of 1,2,3-benzotriazin-4(3*H*)-ones

A plausible mechanism for the formation of benzotriazin-4(3*H*)-one is outlined in Scheme 2. It is presumed that the nitrosylation of the amino group followed by dehydration to offer the diazo intermediate occur as reported earlier.[13] The diazo intermediate is attacked by the NH group of the amide followed by loss of the proton to result into the observed product. Based on the suggested mechanism, it is expected that treating 2-(methylamino)-*N*-phenylbenzamide with $NaNO_2$ and I_2 would afford nitrosylated product, and indeed reaction of **3** under the optimized conditions furnished **4** albeit in 55% yield (Scheme 3). Further, as the acid is liberated in situ during the reaction, we investigated the fate of a Boc-protected 2-aminobenzamide **(1ad)** in the protocol. We were delighted to discover that product **2ad** was isolated in 79% yield suggesting the utility of the methodology for the substrates bearing acid-labile Boc-group.

Finally, to ascertain the formation of 1,2,3-benzotriazin-4(3*H*)-ones chemically, a few reported transformations of this scaffold were performed. Treating **2a** with H_2O_2 in the presence of TFA at room temperature for 48 h afforded the N-oxide **5** in 76% yield (Scheme 4).[14] Heating **2a** with NaI or NaN_3 in AcOH at reflux temperature gave the 2-iodo-*N*-phenylbenzamide **6** and 2-azido-*N*-phenylbenzamide **7** in 84% and 88% yield, respectively.[15-16]

In summary, we have developed a mild and efficient alternative route to acid-free synthesis of 1,2,3-benzotriazin-4(3*H*)-ones from 2-aminobenzamides using $NaNO_2$/ I_2 as the nitrosylating agent. This protocol has broad substrate scope and accommodates even the unsubstituted amide and substrate bearing acid-labile group. The present approach adds on to the utility of the $NaNO_2$/ I_2 system for preparing useful heterocyclic system.

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Supplementary Material

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Graphical Abstract

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$NaNO_2/I_2$ as an alternative reagent for the synthesis of 1,2,3-benzotriazin-4(3*H*)-ones from 2-aminobenzamides

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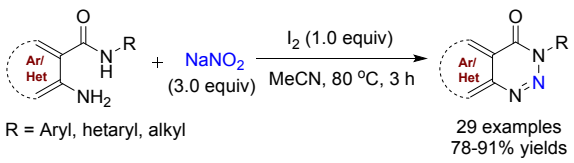

R = Aryl, hetaryl, alkyl

29 examples
78-91% yields

Highlights

- $NaNO_2$/ Iodine mediated transformation of 2-Aminobenzamides to 1,2,3-benzotriazine-4(3*H*)-ones

- Acid-free efficient method with broad substrate scope
- Accommodates unsubstituted 2-Aminobenzamides and substrate bearing acid-labile Boc-group
- Ionic mechanism via nitrosylation of amino group