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Molecular Iodine-Mediated Domino Reaction for the Synthesis of Benzamides, 2,2-Diazidobenzofuran-3(2*H*)-ones and Benzoxazolones

K. Rajendar,[a] Ruchir Kant,[b] and T. Narender[a,*]

[a] Medicinal and Process Chemistry Division, CSIR – Central Drug Research Institute, Lucknow – 226031, U.P., India
E-mail: t_narendra@cdri.res.in
[b] Molecular and Structural Biology Division, CSIR – Central Drug Research Institute, Lucknow – 226051, U.P., India

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Abstract: A simple and efficient domino protocol has been developed for the preparation of biologically important benzamides, 2,2-diazidobenzofuran-3(2*H*)-ones and benzoxazolones from various structurally and electronically divergent acetophenones and *ortho*-hydroxyacetophenones in the presence of molecular iodine, sodium azide and sodium bicarbonate at 100 °C in good to excellent yields.

Keywords: benzamides; benzoxazolones; Curtius rearrangement; 2,2-diazidobenzofuran-3(2*H*)-ones; Haller–Bauer reaction; iodine; sodium azide

Benzamides and benzoxazolones are privileged scaffolds in the pharmaceutical industry, natural products,[1] agrochemical products,[2] and constitute excellent intermediates and raw materials for synthetic organic chemistry and medicinal chemistry.[3] They have a broad spectrum of biological activities due to their ability to act as a metabolically stable mimic of phenols, catechol, coumarin, and related compounds, as a result, some of them are in clinical use[4] (Figure 1). 2-Benzoxazolones have also been used as chiral templates for enantioselective Diels–Alder reactions.[5]

Classical approaches for the synthesis of benzamides are the addition of amines to carboxylic acid derivatives (acids, acyl halides, mixed anhydrides, esters, aldehydes), reduction of acyl azides and acyl hydrazides,[6] direct transformation of methyl ketones to primary amides using aqueous ammonia,[7] hydration of nitriles to the corresponding primary amides in the presence of acids, bases and transition metal catalysts,[8] rearrangement of aldoximes to primary amides using transition metal catalysts,[9] metalloporphyrins-catalyzed oxidation of terminal alkynes,[10] ruthenium-catalyzed dehydrogenative coupling of primary alcohols with amines,[11] etc.

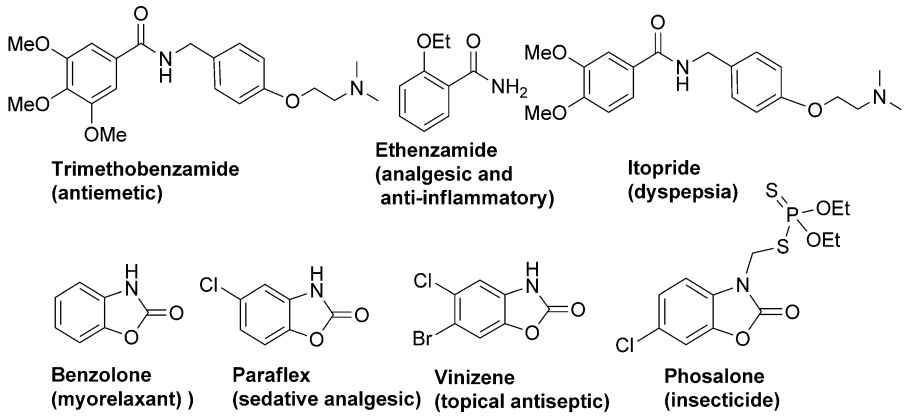
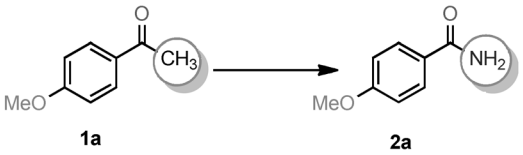


Figure 1. Marketed drugs with benzamide and benzoxazolone skeletons.



Scheme 1. Model domino reaction for the synthesis of benzamides from aromatic ketones.

Most of the benzoxazolone derivatives have been prepared from 2-aminophenols,[12] for example, metal or metal-free catalyzed reductive carbonylation of 2-nitrophenol.[13] The other methods include processes starting from nitroarenes, aryl halides,[14] the iodosylbenzene-induced intramolecular Hofmann rearrangement of amides,[15] the reaction between phosgene and 2-aminophenol. All these existing methods for the synthesis of benzamides and benzoxazolones have a few demerits such as multistep synthesis, use of hazardous reagents and solvents, and generation of wastes that not only reduce process efficiency but also pose environmental problems.

In continuation of our synthetic program, we have developed a common protocol to synthesize benzamides, 2,2-diazidobenzofuran-3(2*H*)-ones and benzoxazolones in one-pot, which is novel, user-friendly and addresses the disadvantages of the existing methods. We started our investigation on *para*-methoxyacetophenone (**1a**) with iodine, sodium azide and sodium bicarbonate in the presence of water, which resulted in the formation of benzamide (**2a**) in moderate yields (Scheme 1).

We further explored this reaction to find out the optimized conditions such as temperature, molar ratio of reagents and solvents to improve the yields (Table 1). The yields varied upon changing the reaction temperature (entries 1–7). When we lowered the temperature from 60 °C to room temperature, the yields decreased and reaction time increased (entries 6 and 7). On increasing the equivalents of iodine, the yield percentage also decreased (entries 8–10). The number of equivalents of NaN_3 also has an influence on the isolated yields of the reaction (entries 11–13). $NaHCO_3$ gave good results among other bases such as K_2CO_3 and Cs_2CO_3 (entries 16–18). The effect of solvents was also investigated. It was found that the protic solvent water was superior to other aprotic solvents such as DMF and CH_3CN (entries 19 and 20) in the synthesis of benzamides. Finally we were delighted to find a good yield of this model reaction, when the aryl ketone **1a** was treated with I_2 (6 equiv.), NaN_3 (7 equiv.) and $NaHCO_3$ (10 equiv.) in water at 100 °C (entry 16), which resulted in the formation of benzamide (**2a**) in 90% yield without any side product such as from a Schimdt[16] or Curtius rearrangement.[17]

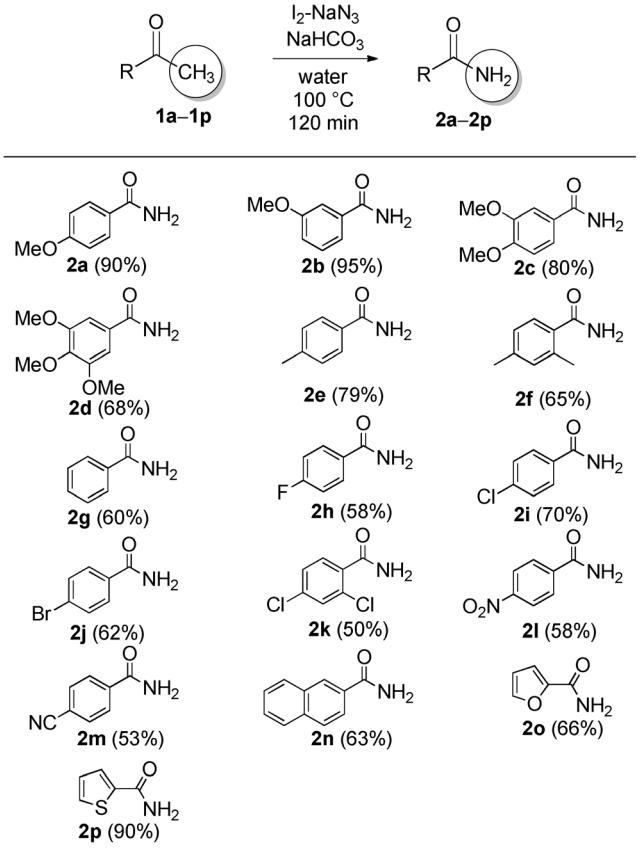
To understand the substituent effect on this reaction, a wide range of aryl (**1a–1n**) and heteroaryl ketones (**1o** and **1p**) were reacted under the optimized reaction conditions (Table 2), which gave good to ex-

Table 1. Optimization of the one-pot synthesis of *para*-methoxybenzamide from *para*-methoxyacetophenone.

Entry	I_2 (equiv.)	NaN_3 (equiv.)	$NaHCO_3$ (equiv.)	Temperature[a]	Time[b]	Solvent	Yield [%]
1	5	5	5	60	6	water	58
2	5	5	5	80	4	water	60
3	5	5	5	100	2	water	63
4	5	5	5	120	1.5	water	40
5	5	5	5	140	1	water	35
6	5	5	5	40	24	water	30
7	5	5	5	r.t.	50	water	30
8	6	5	5	100	2	water	70
9	9	5	5	100	2	water	65
10	10	5	5	100	2	water	62
11	6	7	5	100	2	water	70
12	6	9	5	100	2	water	68
13	6	10	5	100	2	water	65
14	6	7	7	100	2	water	75
15	6	7	9	100	2	water	88
16	6	7	10	100	2	water	90
17	6	7	10[c]	120	2	water	65
18	6	7	10[d]	140	2	water	67
19	6	7	10	100	2	DMF	55
20	6	7	10	100	3	CH_3CN	22

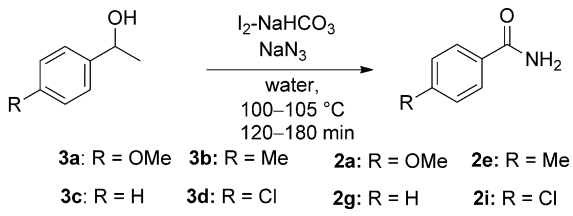
[a] Temperature in degrees centigrade.
[b] Time in hours.
[c] K_2CO_3 was used instead of $NaHCO_3$.
[d] Cs_2CO_3 was used instead of $NaHCO_3$.

Table 2. One pot synthesis of benzamides (**2a–2p**) under the optimized conditions.



cellent yields of benzamides (**2a–2p**). Substrates in which the benzene ring contained various electron-donating and electron-withdrawing substituents reacted smoothly to give the desired product in good yields. The position of the substituents on the aromatic ring affected the reaction yields slightly. Moderate yields were obtained for **2n**–**2p**, when the same reaction conditions were applied on 1-acetylnaphthalene (**1n**) and heterocyclic aryl compounds **1o** and **1p**.

We also attempted to convert methyl carbinols into amides using the similar reaction conditions (Scheme 2). Interestingly carbinols (**3a–3d**) also gave the respective benzamides (**2a**, **2e**, **2g** and **2i**) in good yields similar to aryl ketones. In this reaction carbinols might have been oxidized to ketones by iodine[18]

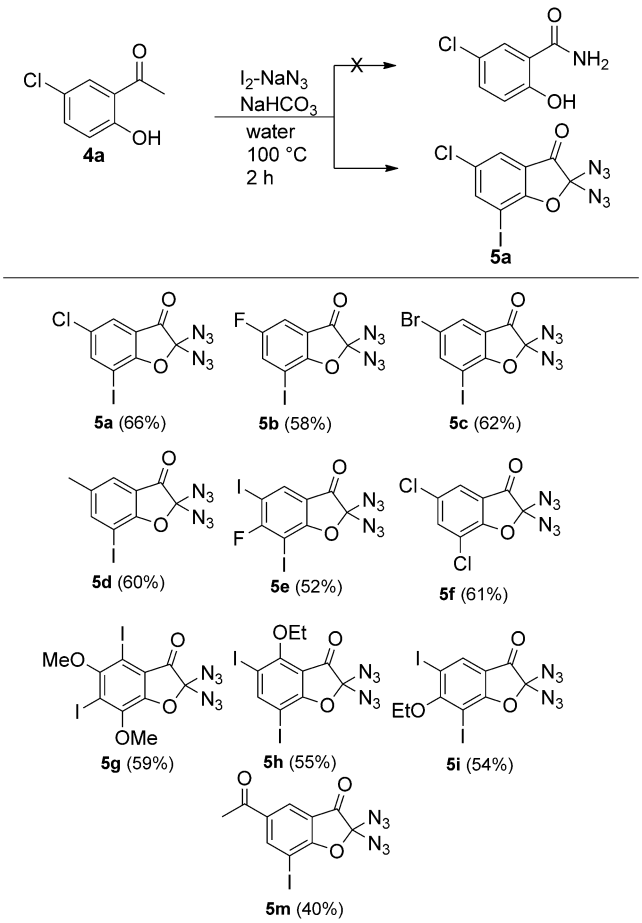


Scheme 2. Synthesis of benzamides from carbinols.

prior to progression of the reaction towards benzamide formation.

On achieving the successful synthesis of benzamides from aromatic ketones and carbinols, the optimized conditions were then applied to *ortho*-hydroxyacetophenone (**4a**) to afford the desired *ortho*-hydroxybenzamide, however, surprisingly we obtained a 2,2-diazidobenzofuran-3(2*H*)-one derivative (**5a**) instead of the anticipated *ortho*-hydroxybenzamide (Scheme 3), Different substituted *o*-hydroxyactophenones (**4a–4i** and **4m**) were also tested, and gave the respective 2,2-diazidobenzofuran-3(2*H*)-ones (**5a–5i** and **5m**) in good yields. The unusual chemical structure of the 2,2-diazidobenzofuran-3(2*H*)-one skeleton was confirmed by the single crystal X ray data of **5f** (Figure 2). CCDC 952346 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

In a further attempt to synthesize hydroxybenzamides, we focused on a change of the solvent with



Scheme 3. One-pot synthesis of 2,2-diazidobenzofuran-3(2*H*)-ones (**5a–5i** and **5m**) in water from *ortho*-hydroxyacetophenones (**4a–4i** and **4m**).

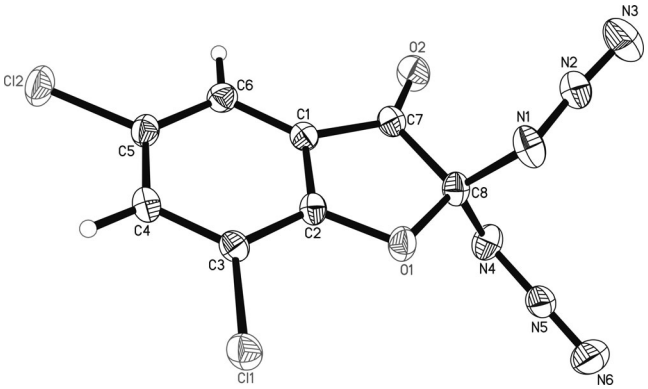
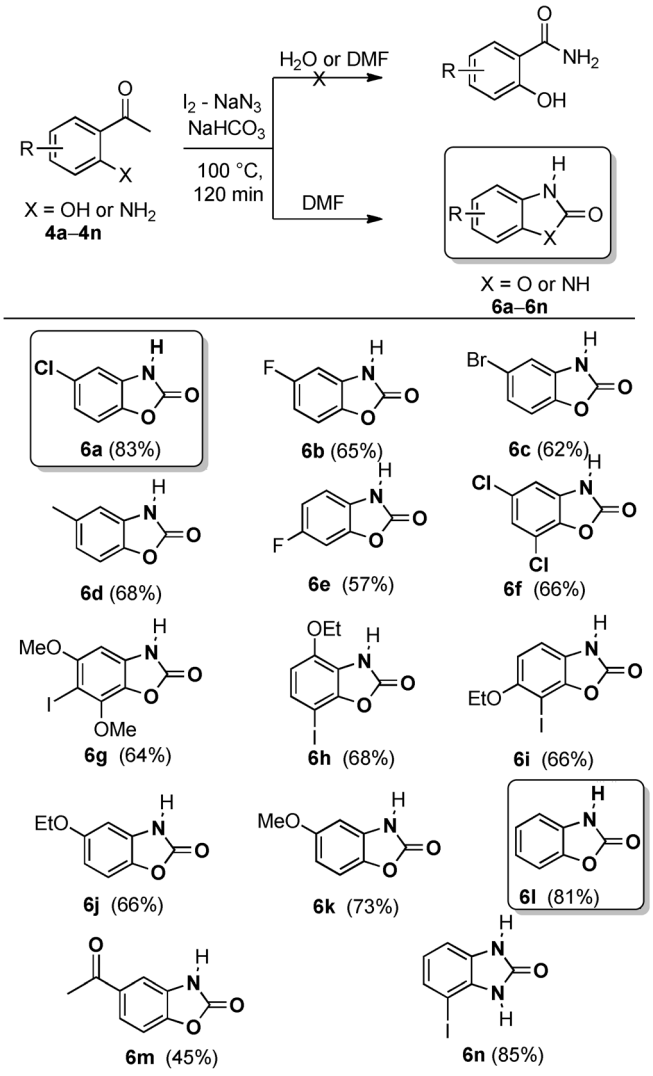


Figure 2. ORTEP diagram drawn with 30% ellipsoid probability for non-H atoms of the asymmetric unit of the crystal structure of compound **5f** determined at 293 K.

otherwise the same reaction conditions. Interestingly treatment of *ortho*-hydroxyacetophenone (**4a**) with I_2, NaN_3 and $NaHCO_3$ in the aprotic solvent DMF afforded benzoxazolone (**6a**) in excellent yield instead of *ortho*-hydroxybenzamide or 2,2-diazidobenzofuran-3(2*H*)-one (Scheme 4). Various substituted *ortho*-hydroxyacetophenones **4b–4l** were also tested with DMF as solvent and in all cases the respective bezoxazolones **6b–6l** were obtained in good to excellent yields. We further carried out a reaction with **4m** [1,1′-(4-hydroxy-1,3-phenylene)diethanone], which resulted in the formation of benzoxazolone (**6m**) regioselectively. When an amine group instead of a hydroxy group as in **4n** was at the *ortho* position, the reaction under similar conditions afforded the cyclic benzimidazolone (**6n**) in 85% yield.

It is remarkable to mention here that we could synthesize the marketed sedative and analgesic drug paraflex (**6a**), myorelaxant, benzolone (**6l**) and their analogues (Figure 1) in one-pot with readily available starting materials, whereas the industrial methods to produce these compounds involve the preparation of starting materials as well as special reagents.

The possible reaction mechanism (Figure 3) for the formation of benzamides and benzoxazolones appears to be three sequential α-halogenations of acetophenone to afford the key intermediate, α,α,α-triiodomethyl ketone (**II**).[19] This key intermediate might have converted into benzamide (**VI**) by way of a Haller–Bauer reaction in the presence of water or DMF due to attack of azide as a nucleophile on the carbonyl group,[20] accompanied by the cleavage of carbon-carbon bond leading to keto azide (**IV**) and conversion of resultant keto azide (**IV**) into benzamide (**VI**) due to loss of molecular nitrogen. In the case of 2-hydroxyaryl ketones the azide (**IV**) might have further transformed into benzoxazolones (**VII**) by way of an intramolecular Curtius rearrangement[21] (Figure 3) due to a solvent effect (DMF), whereas in 2,2-diazidobenzofuran-3(2*H*)-one formation the key



Scheme 4. One-pot synthesis of benzoxazolones (**6a–6m**) and benzimidazolone (**6n**).

intermediate **II** with a 2-hydroxy (chelated hydroxy) group might have undergone a substitution reaction with azide in the presence of water to give diiodoazide intermediate **VIII** instead of **III**, since water can form hydrogen bonds and tends to decrease the reactivity of the nucleophile (azide). The attack of oxygen's lone pair electrons (hydroxy) on the azide attached carbon might have led to a five-membered ring compound **IX** and subsequent attack of a second sodium azide molecule might provide 2,2-diazidobenzofuran-3(2*H*)-one derivative (**X**) (Figure 3). Further studies, however, are required to confirm the exact reaction mechanism.

In summary, we have developed a novel, convenient and user-friendly one-pot domino synthetic method for the preparation of benzamides, 2,2-diazidobenzofuran-3(2*H*)-ones, benzimidazolone and benzoxazolones from aryl ketones and heteroaryl ketones in aqueous/DMF medium using I_2, NaN_3 and

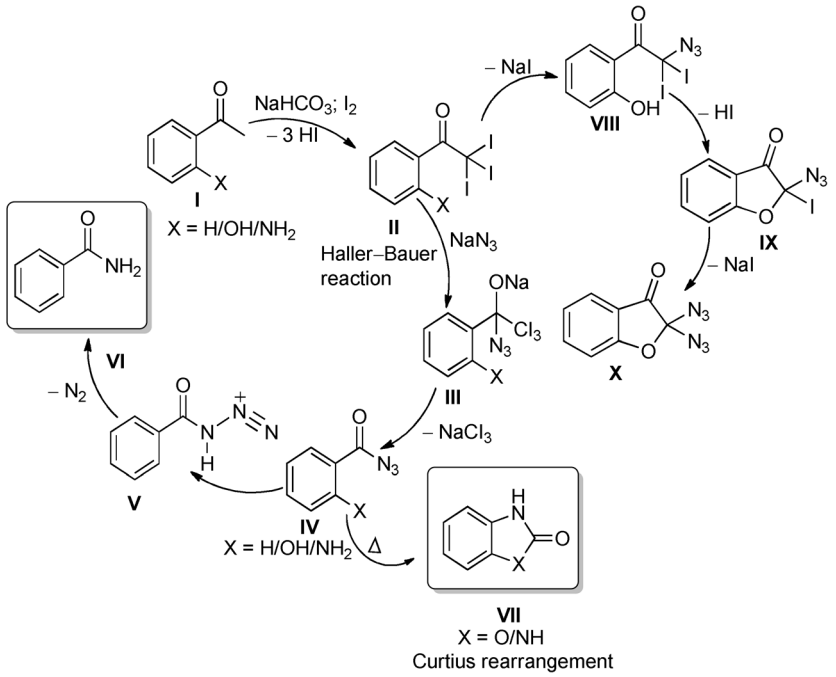


Figure 3. Proposed tandem mechanism for the transformation of aromatic ketone to primary amides, 2,2-diazidobenzofuran-3(2*H*)-ones and benzoxazolones.

$NaHCO_3$. During this work we also synthesized a few marketed drugs such as paraflex **6a** (sedative, analgesic), benzolone **6l** (myorelaxant) and several analogues of these drugs in the shortest route with good to excellent yields. Our method has wide application in industry for the preparation of intermediates and pharmaceuticals for drug discovery.

Experimental Section

General Procedure for Preparation of Benzamides (2a–2p) and 2,2-Diazidobenzofuran-3(2*H*)-one (5a–5n)

A 50-mL, single-neck, round-bottom flask was charged with acetophenone (1 equiv.), iodine (6 equiv.), sodium azide (7 equiv.), sodium bicarbonate (10 equiv.) and 4 mL of normal tap water at 100 °C. After being stirred for 120 min, the reaction mixture was allowed to cool to room temperature and was quenched with sodium thiosulphate ($Na_2S_2O_3$). The residue was dissolved in water and extracted with ethyl acetate (3×25 mL), dried (Na_2SO_4) and evaporated to give a residue, that was purified by silica gel column chromatography using hexane and ethyl acetate.

General Procedure for Preparation of Benzoxazol-2(3*H*)-ones (6a–6n)

A 50-mL, single-neck, round-bottom flask was charged with *ortho*-hydroxyacetophenone (1 equiv.), iodine (6 equiv.), sodium azide (7 equiv.), sodium bicarbonate (10 equiv.) and 4 mL of DMF at 100 °C. After being stirred for 120 min, the reaction mixture was allowed to cool to room temperature and was quenched with sodium thiosulphate ($Na_2S_2O_3$). The residue was dissolved in water and extracted with ethyl acetate (3×25 mL), dried (Na_2SO_4) and evaporated to give a residue, that was purified by silica gel column chromatography using hexane and ethyl acetate.

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