Green Synthesis: A Novel Method for Bromination of 7-Amino-Phthalide

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Abstract: A novel method for preparing a bromo substituted 7-Amino-phthalides and 7-Amino-3-hydroxy-phthalides via the bromonium ion intermediate under acidic conditions at higher temperature were developed. The results will illustrate the potential utility of this method as an environment-friendly process for synthesis of bromo substituted aryl amines, along with conservation of half mole equivalent of halides.

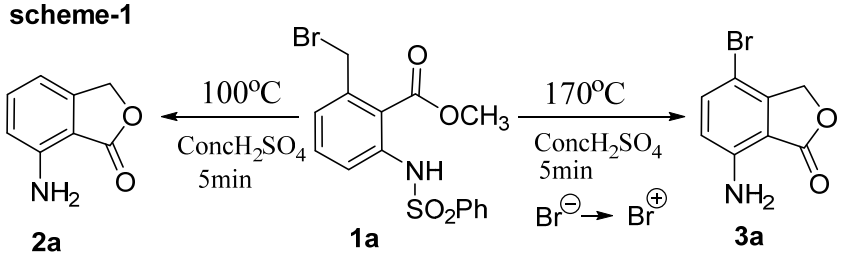
Key words: 7-Amino-phthalide, bromonium ion, desulfonation, green chemistry,

Introduction: Much attention has been given in recent years to the preparation of halide substituted phthalide[1,2] because such molecules occur widely in natural products[3-5] which display a wide variety of significant biological activity. They have also been employed as key intermediate for the synthesis of natural products[6] and useful pharmaceuticals value products namely citralophram[7] 2-phenylbenzimidazole-4-carboxamide[8] and Remoxipride analogues[9] Phthalides are transformed into number of other functional groups, namely Isoquinazoline,[10] furan derivatives,[11] phthalzine,[12] phtlimide,[13] and phthalide-3-OH derivatives,[14] indeed the phthalides-3-OH groups are converted into biological active molecules for studies in 5-HTR receptors,[15] antileishmanial[16], in Alzheimer therapy,[17] topoisomerase,[18,19] antidiabetic agents,[20] PARP inihibitors[21], Leukotriene receptors agonst[22] and antiproliferative activity.[23] A

variety of efficient synthetic methods have been reported on the synthesis of phthalides.[24 25] However, while these are of great value, there is still a need for new method which would allow us to obtain phthalides, particularly bromo substituted 7-Amino phthalides in an environment-friendly manner, where there is no single procedure is reported. The development of new methods that to with green chemistry protocols therefore continues to be an important area of research. The purpose of this paper is to describe the novel method for synthesis of bromo substituted 7-Amino phthalides and 7-Amino hydroxy-phthalide in an environment eco-friendly manner with conserve the half mole equivalent of halides.

Present Work: Methyl 2-N-methyl- 2-N-tosyl-6-nitroanthranilate on treatment with concentrated sulfuric acid (3 mL) heated at 100°C for 30 minutes gives free amine by desulfonation are well documented[26]. In another reported methods[27], 4-nitrophthalide is formed from methyl-2-bromomethyl-4-nitro-benzoate by using concentrated sulfuric acid (at 100°C) under distillation conditions.

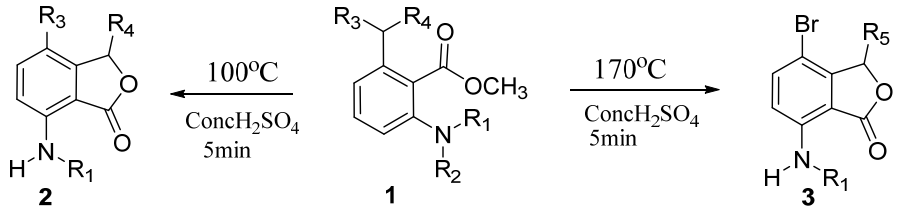
scheme-1



After observing these two reactions, we treated compounds **1a** (scheme-1) having benzylic bromo and sulfonamide group treated under similar condition, as expected we isolated the 2a. It is understood that phthalide ring is formed, due of hydrolysis of methyl ester, the *in situ* generated carboxylic ion on nucleophilic attack on bromo bearing benzylic carbon, leaving the bromide ion, and followed by desulfonation to obtained 7-Amino-3H-isobenzofuran-1-one (**2a**). To utilize the oxidation potentials of bromine and iodine in reducing the sulfuric acid, we done a series of reaction with variation in temperature. To our surprise, when the temperature

at 170°C, we isolated the 7-Amino-4-Bromo-3H-isobenzofuran-1-one (**3a**). it proved 170°C, its critical temperature where the liberated bromide ion act as reducing agent[28] to reduce the sulfuric acid and itself oxidized to bromine/*bromonium ion*, which undergoes electrophilic bromination on 7-Aminophthalide (**2a)** to give product **3a**. In this protocol, resulting in a no bromine content in the wastewater and also avoiding the sulfonated products as impurities[29].

table-1

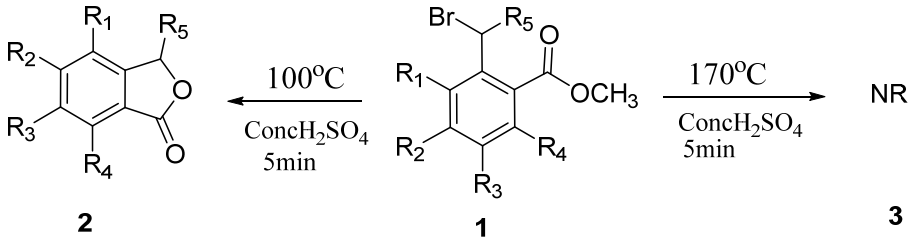


Entry	Substrate	R_1	R_2	R_3	R_4	R_5	100°C Yield (%)	170°C Yield (%)
1	1a	H	SO_2Ph	Br	H	H	2a, 90	3a, 93
2	1b	H	SO_2Ph	I	H	H	2a, 87	3b, 05
3	1c	H	SO_2Ph-4CH_2Br	Br	H	H	2a, 89	3a, 91
4	1d	H	SO_2Ph-4NO_2	Br	H	H	2a, 90	3a, 90
5	1e	CH_3	SO_2Ph	Br	H	H	2e, 91	3e, 91
6	1f	CH_3	SO_2Ph	Cl	H	H	2e, 89	NR
7	1g	CH_3	SO_2Ph-4CH_2Br	Br	H	H	2e, 90	3e, 90
8	1h	CH_3	SO_2Ph-4NO_2	Br	H	H	2e, 91	3e, 90
9	1i	CH_3	SO_2Ph	OCH_3	H	H	2e, 81	NR
10	1j	H	SO_2Ph	Br	Br	OH	2j, 91	3j, 85

Encouraged by this result, we investigated these procedures with a variety of benzyl halides (table 1) to explore the generality of this system (see table 1). At 100°C all substrates (1a-1j) given the phthalide (**2a** and **2e**) in excellent yield, whereas at higher temperature, the benzyl bromo gives excellent yield of bromo substituted 7-Aminophthalides (**3a** and **3e**). The structures (**3a** and **3e**) was proved by single crystals data. In case of Benzyliodo (**1b**), gives iodo substituted 7-Aminophthalide (**3b**) but yield is poor (5%). It can be explained as, even though Iodide ion is oxidized to iodine/iodonium ion in sulfuric acicd, due to higher temperature it sublimes before it reacts with 7-amino phthalide (**2a**). In case of chloro substrate (**1f**), the liberated chloride ion form HCl, due to inability of sulfuric acid to oxidize

the chloride ion to chloronium ion (or chlorine gas). The CBZ protected aniline with methoxy group[30] (**1i**) does not given any corresponding anisole derivatives, even prolong the reaction time at higher temperature. Substituted on benzene sulfonate group (**1c,1d,** and **1f,1g**) are also giving the same results (**2a** and **2e**). When dibromo substrate[31] (**1j**) under these conditions gives **2j** (not isolated) and **3j,** respectively. During the formation of **3j**, it is understood that 3-bromo phthalide is first formed, followed by hydrolysis to give the 3-hydroxy-7-Aminophthalide. This study clearly shows that other halogens, chlorine (sulfuric acid unable to oxidize) and iodine (sublime properties) are not effective as bromine. Finally, the temperature factor is significant since at 100°C, irrespective of halogenated substrates, the intermediate phthalides **2a, 2e** and **2j** (not isolated) is formed, and whereas at 170°C, formation of halide substituted 7-amino phthalide is depends on halogenated substrate.

table-2



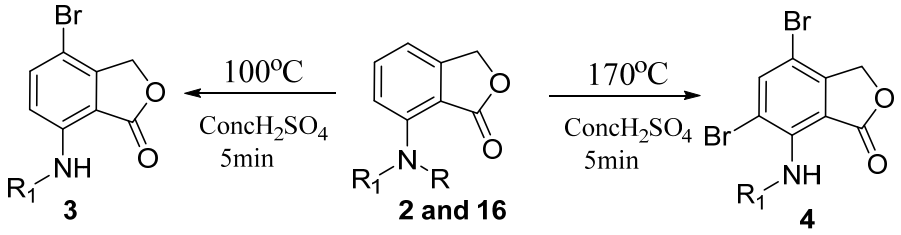
2 **1** **3**

Entry	Substrate	R_1	R_2	R_3	R_4	R_5	100°C Yield (%)	170°C Yield (%)
1	1k	H	H	H	H	Br (OH)	2k, 91	mix
2	1l	H	H	H	H	H	2l, 93	mix
3	1m	H	H	H	NO_2	H	2m, 85	NR
4	1n	H	H	NO_2	H	H	2n, 89	NR
5	1o	NO_2	H	H	H	H	2o, 91	NR
6	1p	H	NO_2	H	H	H	2p, 88	NR

When unsubstituted benzyl dibromo (**ik**) and benzyl bromo (**1l**) (table-2), treated under similar condition, as expected the 3-OH phthalide (**2k**) and phthalide (**2l**) are formed 100°C, but when on heating at 170°C, inseparable mixture of product is formed. In case of nitro substituted benzyl bromides (**1m**,**1n** and **1o**), only nitro-phthalides (**2m**,**2n** and **2o**) are formed at 100°C, whereas no brominated nitro-phthalides were isolated at 170°C. it clearly

shows neither nucleophilic bromination at 100°C and nor electrophilic bromination at 170°C occurs.

table-3



Entry	Substrate	R	R_1	Yield (%)	Yield (%)
1	2a	H	H	3a, 91	4a, 92
2	2e	H	CH_3	3e, 90	4e, 91
3	16	SO_2Ph	CH_3	3e, 89	4e, 90

Bromine as external source: Independently, the 7-Amino phthalide (**2a** and **2e**), and its sulfonated substrate (**16**) on treatment (table-3) with 1.0 eq of bromine in conc sulfuric acid at 100°C obtains the mono brominated 7-Aminophthalides (**3a** and **3e),** this is due to availability of bromonium ion by cleavage of bromine molecules, whereas at 170°C as expected we isolated the dibromo derivatives **4a** and **4e** respectively. These products (**4a** and **4e**) formation further suggest bromide ion is oxidized to bromine/bromonium ion in conc sulfuric acid at 170°C and facilitate electrophilic bromination. Further the **4a** is proved by single crystals data. When 4-aminopthalide (**17**) is under these conditions gives inseparable mixture, due to mismatching effect of amine/carbonyl groups on the incoming group. The bromo derivatives 4-aminophthalide **17** preparation was attempted, (shown in experimental part) but during the bromination stage, instead of benzylic bromide **20**, it gives substituted on 4-bromo-sulfonamide compound **21**, whereas with mesylate **22**, no reaction occurs.

The reaction is exceptionally clean and easy workup is required to obtained spectrally pure substances. No side products were isolated from any reaction. However, despite its utility and simplicity, limitations are sometimes encountered, particularly with acid sensitive benzyl bromide substrates, which are cleaved in acidic medium.

In conclusion, we have found a novel method for preparing a bromo substituted 7-amino phthalide and its 3-hydroxy derivatives via the bromonium ion intermediate under acidic conditions. The results illustrate the potential utility of this method as an environment-friendly process with conserve the half mole equivalent of halide. The obtained products were useful in fluorescence probe study to modify the cysteine and its application to protein modifications[32].

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■ **Competing interests:** There is no Competing Interests pending

Data and materials availability: Crystallographic model data is available through the CCDC under identifier 2004667 (2-Bromomethyl-6-[methyl-(4-nitro-benzenesulfonyl)-amino]-benzoic acid methyl ester, **1h**), 1990752 (2-Benzenesulfonylamino-6-dibromomethyl-benzoic acid methyl ester, **1j**), 2004106 (isobenzofuran-1(3H)-one, **2l**), 1990762 (7-Amino-4-bromo-3H-isobenzofuran-1-one, **3a**), 1990754 (4-Bromo-7-methylamino-3H-isobenzofuran-1-one, **3e**),

1990759 (7-Amino-4,6-dibromo-3H-isobenzofuran-1-one, **4a**), 2004668 (2-(Benzenesulfonylmethylamino)-6-methyl-benzoic acid methyl ester, **10**), 2004669 (2-Methyl-6-[methyl-(4-nitro-benzenesulfonyl)-amino]-benzoic acid methyl ester, **12**) and 1990780, VABSAW, N-Methyl-N-(3-oxo-1,3-dihydro-isobenzofuran-4-yl)-benzenesulfonamide **(16).**

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