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APPLICATION OF SCHOTTEN–BAUMANN AND GABRIEL- MICHAEL REACTION FOR SYNTHESIS OF NOVEL PHTHALAZINE DERIVATIVES

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Abstract:
A simple and convenient procedure has been developed for the synthesis of Novel 1-phthalazinone and 1, 4-phthalazinedione derivatives using Schotten–Baumann reaction and Gabriel- Michael reaction respectively. All compounds have been characterized by IR, NMR, and MASS spectroscopy.

Keywords:
1-Phthalazinone, 1, 4-Phthalazinedione, Schotten–Baumann reaction, Gabriel- Michael reaction

Introduction:

A number of phthalazine derivatives show high potency as biologically active molecules since the discovery of hydralazine and are widely used in the pharmaceutical industry. Consequently, much attention and extensive research have been focused on the synthesis of phthalazine derivatives.

This article describes the synthesis of 1-phthalazinone and 1, 4-phthalazine-dione derivatives. The phthalazine ring forming reaction has been discussed previously in the chemical literature[1]. Phthalazine have played a unique role in the design and synthesis of novel biologically active compounds serving as, anticonvulsant[2], antimicrobial[3], antifungal[4], vasorelaxant[5], anti HIV[6], anticancer activity[6], PDE3/PDE4 Inhibitory Agents[7], antiasthamatic[8], Leishmanicidal[9], antidiabetic[10], etc.

Phthalazine derivative has been synthesised by variety of reaction. We synthesised three phthalazine derivatives by Schotten–Baumann reaction [11, 12] and six derivatives by Gabriel-Michael reaction [13, 14, 15]. Schotten–Baumann reaction is used for preparation of amide from amine and acid choride.

Results and Discussion:

Several 2-substituted phthalazine-1, 4-diones, 2, 4-disubstituted 1-phthalazinone from phthallic anhydride has been synthesised and those compounds have been tested on several disease conditions.

The first step in the synthetic pathway **(Scheme 1)** consists of the reaction of one equimolecular amounts of phthalic anhydrides **1** with two equimolecular amount of hydrazine hydrate **2** in ethanol. By this method, 1, 4-Phthalazinedione **3** can be prepared easily [16, 17, 18, 19]. Compound 3 is then reacted with compound **4a-c** to form substituted 1, 4-Phthalazinedione **5a-c.** There are several reported methods for synthesis of 2-substituted 1, 4-Phthalazinedione [20, 21] but in our literature survey we did not find any article used Schotten–Baumann reaction for the synthesis of 1, 4-Phthalazinedione Uses of Schotten–Baumann reaction in synthesis give efficient and mild condition of reaction than reported process for synthesis of other 1, 4-phthalazine-dione derivatives [1]. Mechanism for scheme 1 is described in **figure 2** and **figure 3** for step1 and step2 respectively.

Figure 1: Scheme 1

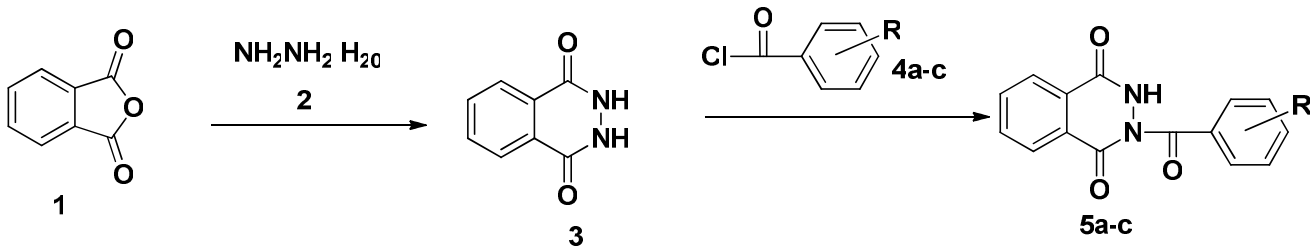


Table 1: Characterization of compound 5a-c

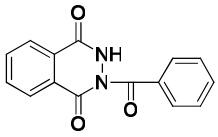
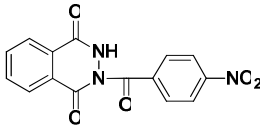
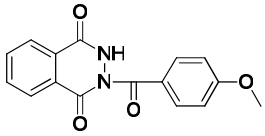
Compound no.	Compound structures	Yield	Melting point ^{o}C	Calculated % Found% C	H	N	Mass
5a		95%	230	67.67 67.26	3.79 3.82	10.52 10.29.	67.37
5b		89%	295	57.88 58.01	2.91 3.10	13.50 13.56	312.24
5c		72%	285	64.86 64.90	4.08 4.15	9.46 9.32	297.26

Figure 2: Mechanism for step - 1 of scheme 1

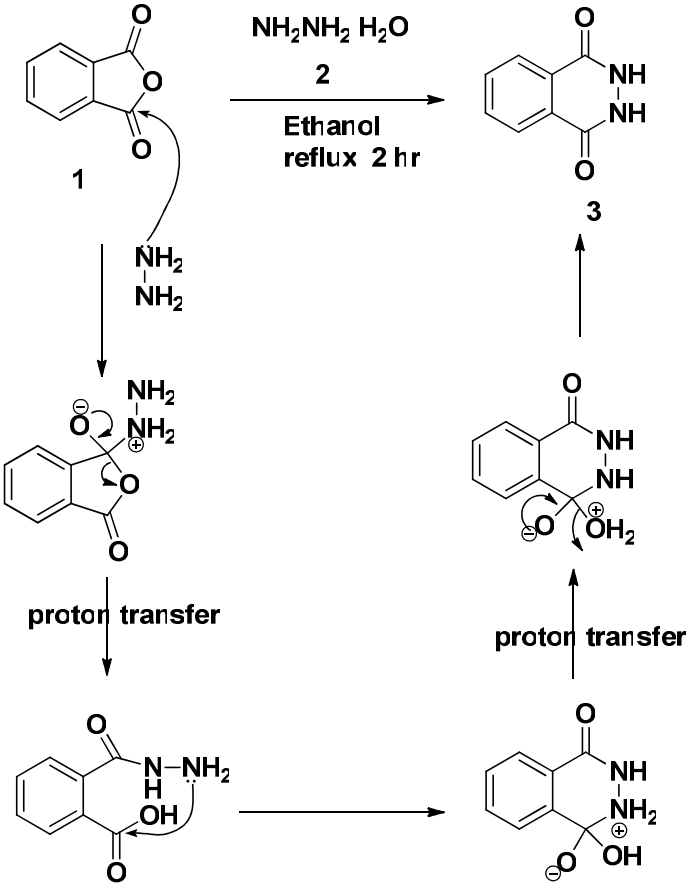
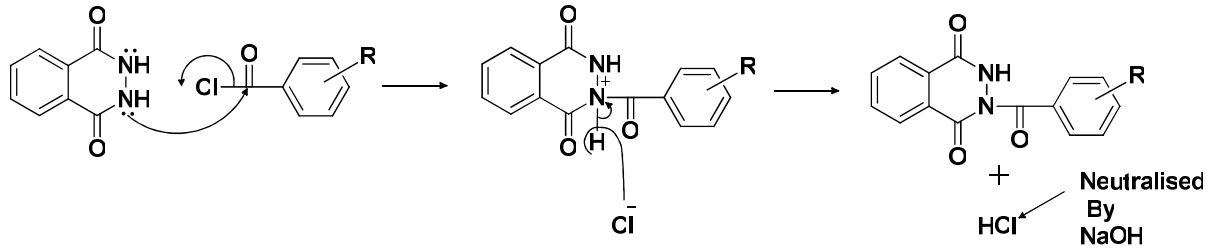


Figure 3:Mechanism for step - 2 of scheme 1



Addition of a base is required for schotten baumann reaction to abstract acidic proton, or to maintain the basicity of amine. Often, an aqueous solution of a base added to the reaction mixture. In Schotten-Baumann reaction mostly two-phase solvent system is used, consisting of water and an organic solvent. The base within the water phase neutralizes the acid, generated in the reaction, while the starting materials and product remain in the organic phase, often dichloromethane or diethylether are used as organic phase.

Scheme 2

The previously developed reaction conditions in literature were applied for synthesis of novel 2, 4- substituted 1-phthalazinone **9a-f** [22, 23] First step in synthetic pathway **(scheme 2)** was carried

out by Gabriel- Michael reaction. By our literature survey we found that Gabriel- Michael reaction was carried out with this type of conditions and regents [24, 25]. The probable mechanism for scheme 2 is described in **figure 5 and figure 6**. In Gabriel- Michael reaction, sodium acetate was used in catalytic amount while phthalic anhydride **1** and aryl acetic acid **6a-c** was used in equimolecular amount in benzene, heated at 240-260^{o} C produced benzalphtalide**7 a-c**. Benzalphtalide **7a-c** and hydrazine derivatives **8a-b** which are heated at 80 ^{o} C in ethanol to produce 2, 4- substituted 1-phthalazinone **9a-f.**

Figure 4: Scheme 2

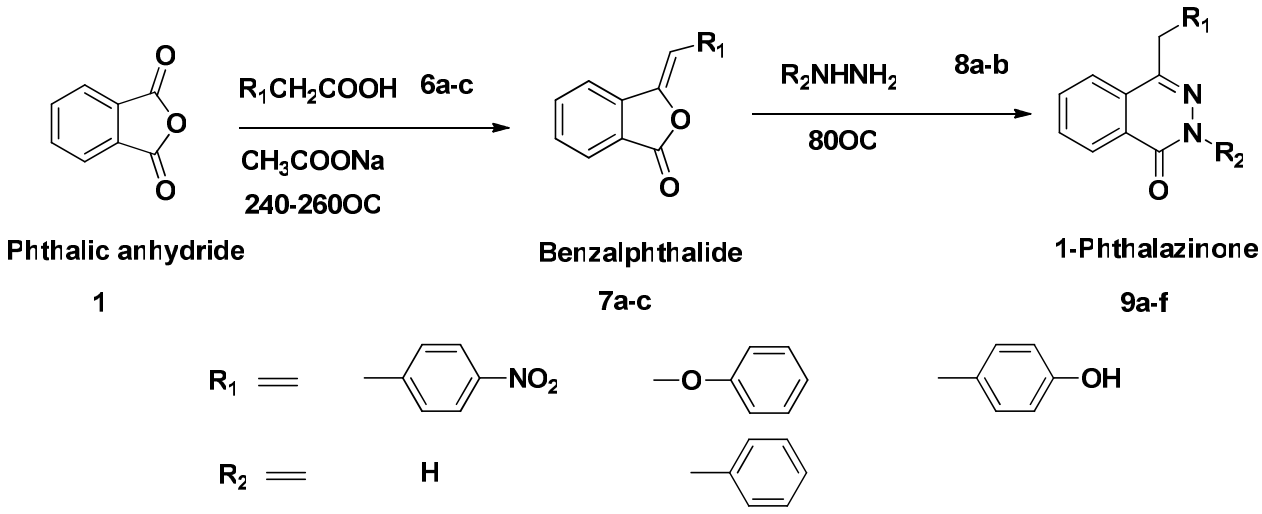
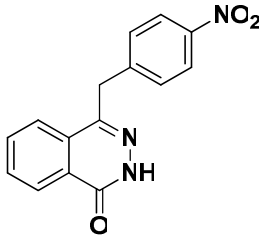
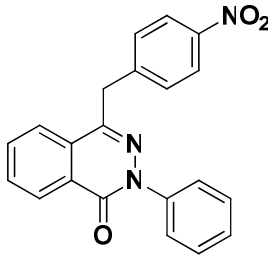


Table 2: Characterization of compound 9a-f

Compound no.	Compound structures	Yield	Melting point ^{o}C	Calculated % Found%			Mass
				C	H	N	
9a		64%	290	64.05 64.16	3.94 4.10	14.94 14.50	282.15
9b		45%	201	70.58 70.23	4.23 4.14	11.26 10.99	358.19

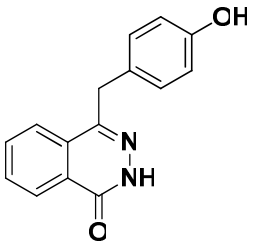
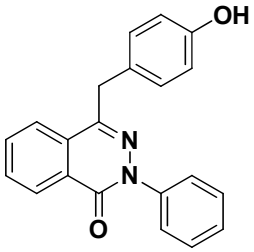
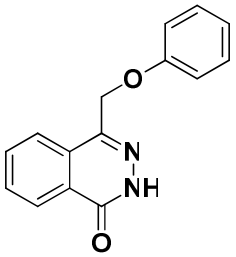
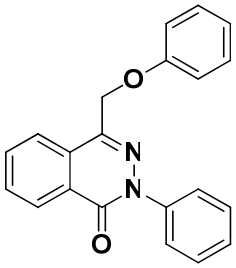
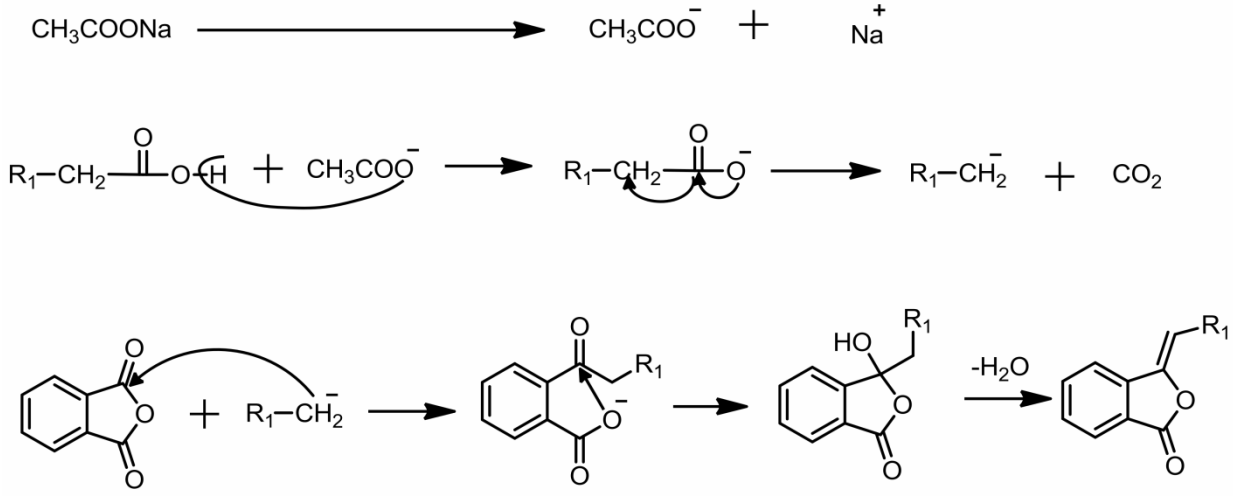
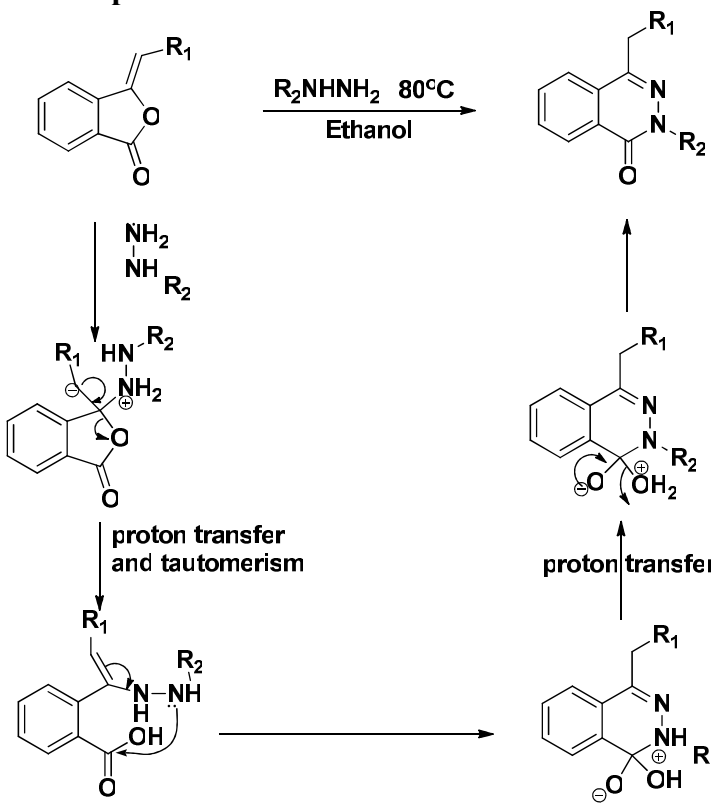
9c		78%	228	71.42 71.39	4.79 4.84	11.10 11.01	253.40
9d		32%	256	76.81 76.92	4.91 4.86	8.53 8.56	329.16
9e		58%	219	71.42 71.38	4.79 4.84	11.10 10.96	253.28
9f		47%	183	76.81 76.99	4.91 5.11	8.53 8.40	329.13

Figure 5: Mechanism for step - 1 of scheme 2



In first step of reaction acetate ion of the sodium acetate acts as base and abstract proton from aryl acetic acid and generate carboxylate ion of aryl acetic acid. In the second step transfer of electron from carboxylate ion to α carbon lead to the generation of carbanion with the loss the carbon dioxide. In the third step, this carbanion attack on carbonyl carbon and opened the five ring of phthalic anhydride. The carboxylate ion of opened ring attack on carbonyl carbon forming five member ring. In the next step dehydration occurs and water molecules were removed from reaction mixture by use of dean stark apparatus. Benzalphthalide was obtained after 8 hour heating.

Figure 6: Mechanism for step - 2 of scheme 2



Conclusion:

We have reported an efficient, convenient, and rapid synthesis of Novel 1-phthalazinone and 1, 4-phthalazinedione derivatives in excellent yield by making use of Schotten–Baumann reaction and Gabriel- Michel reaction respectively.

Experimental:

Melting points were determined using one end open capillary tubes with a Veego apparatus and are uncorrected. ^{1}H NMR spectra of synthesized compounds were recorded on "FTNMR VARIAN MERCURY YH-300" Spectrometer at 300 MHz Frequency in $CDCl_3$ using tetramethylsilane (TMS) as internal standard. FT-IR (KBr) spectra were recorded on "JASCO FT-IR V-460 plus" Spectrophotometer (Vmax in cm^{-1}). Mass spectra were determined LCMS were recorded on "2010EV LCMS Shimadzu" instrument by direct injection method. Elemental analysis was performed on FLASH EA 1112 Analyser series equipment by Thermoelectron

Corporation. Phthalic anhydride, hydrazine, benzoyl chloride derivatives, aryl acetic acid derivative, sodium acetate was procured from Merck and SD fine chemicals and used without further purification.

General procedure for scheme 1

Synthesis of 1, 4-phthalazine-dione (3)

A mixture of hydrazine (2 eqiv.) and phthalic anhydride (1 eqiv.) are stirred and heated at reflux for 2 hour in ethanol (30 ml). The product, which precipitates, is filtered and dried in vacuo.

Synthesis of 2-benzoyl 1, 4-phthalazine-dione (5a-c)

Synthesis of 2-benzyoyl 1, 4-phthalazine-dione done with help of Schotten–Baumann reaction. A mixture of 1, 4-phthalazine-dione (1 eqiv.) and benzoyl chloride (1.2 eqiv.)[16] derivative are taken in mixture of dichloromethane and 10-15% NaOH solution, stirred for 2-3 hours, neutralised with dil. HCl and precipitate is obtained, the reaction is monitored with TLC and purified with methanol so remaining benzoyl chloride become acid and wash with cold water.

Spectral Data for Selected Compounds:

1. 2-benzoyl-2,3-dihydrophthalazine-1,4-dione (5a)

IR (KBr, cm^{-1}): 1492, 1670, 1739(C=O), 3313(-NH), ^1H NMR ($CDCl_3$): 7.55-7.61 (m, 2H), 7.63-7.65(m, 1H), 7.70-7.76 (m, 2H), 7.82-7.90 (m, 2H), 8.26-8.30 (d, 2H), 10.32 (s, 1H).

2. 2-(4-nitrobenzoyl)-2,3-dihydrophthalazine-1,4-dione (5b)

IR (KBr, cm^{-1}): 1496, 1600, 1662(C=O), 3413 (-NH), ^1H NMR ($CDCl_3$): 7.72-7.78 (m, 2H), 7.80-7.83 (m, 2H), 8.50-8.56 (d, 2H), 8.86-8.90 (d, 2H), 10.32 (s, 1H).

3. 2-(4-methoxybenzoyl)-2,3-dihydrophthalazine-1,4-dione (5c)

IR (KBr, cm^{-1}): 1261(C-O), 1496, 1606, 1662,(C=O), 3428(-NH), ^1H NMR ($CDCl_3$): 3.45(s,3H),7.22-7.29 (d,2H),7.69-7.77(m,2H),7.82-7.86(m,2H), 8.20-8.25(d,2H), 10.40 (s,1H),

General procedure for scheme 2

Synthesis of benzalphthalide derivatives (7a-c) [17]

Phthalic anhydride(1 eqiv.) and phenyl acetic acid(1 eqiv.) is added to sodium acetate(0.05 eqiv.) and benzene in a round bottom flask attached to Dean-Stark apparatus and the reaction mixture is heated at 230–240^o C for 6 hr. The reaction is monitored by TLC. After completion of the reaction, the mixture is cooled to room temperature; precipitate is obtained, filtered, dried, and evaporated off. The precipitate is recrystallized with acetic acid.

Synthesis of 1-phthalazinone derivatives (9a-f)

Hydrazine (1 eqiv.) derivatives are added in Benzalphthlide (1 eqiv.) derivatives in ethanol and heated for 8 hours at 80°C. The completion of reaction is monitored by TLC. The mixture is cooled to room temperature. The precipitate obtained is filtered, dried in vacuo and recrystallized in methanol.

4. 4-(4-nitrobenzyl)phthalazin-1(2H)-one (9a)

IR (KBr, cm^{-1}): 1658(C=O), 3432(-NH). ^1H NMR ($CDCl_3$): 3.80(s, 2H), 7.30-7.34(d, 2H), 7.71-7.75(m, 2H), 8.45(s, 1H), 8.50-8.51(m, 2H), 8.86-8.90(d, 2H).

5. 4-(4-nitrobenzyl)-2-phenylphthalazin-1(2H)-one (9b)

IR (KBr, cm^{-1}): 1708(C=O). ^1H NMR ($CDCl_3$): 3.60(s, 2H), 7.38-7.44(m, 1H), 7.50-7.55(m, 2H), 7.78-7.85(m, 6H), 8.61-8.65(m, 2H), 8.80-8.86(d, 2H).

6. 4-(4-hydroxybenzyl)phthalazin-1(2H)-one (9c)

IR (KBr, cm^{-1}): 1649(C=O), 3313(-OH), 3494(-NH). ^1H NMR ($CDCl_3$): 3.66(s, 1H), 6.72-6.74(d, 2H), 7.14-7.18(d, 2H), 7.67-7.71(m, 2H), 8.30(s, 1H), 8.41-8.44(m, 2H).

7. 4-(4-hydroxybenzyl)-2-phenylphthalazin-1(2H)-one (9d)

IR (KBr, cm^{-1}): 1747(C=O), 3166(-OH). ^1H NMR ($CDCl_3$): 3.62(s,2H), 5.04(s.1H), 6.74-6.77(d,2H), 7.20-7.25(d,2H), 7.35-7.40(m,1H), 7.48-7.53(m,2H), 7.70-7.76(m,4H), 8.50-8.53(m,2H).

8. 4-(phenoxymethyl)phthalazin-1(2H)-one (9e)

IR (KBr, cm^{-1}): 1234(C-O),1670(C=O), 3482(-NH). ^1H NMR ($CDCl_3$): 5.01(s, 2H), 7.10-7.13(d, 2H), 7.42-7.45(m, 1H), 7.50-7.54(m, 2H), 7.71-7.74(m, 2H), 8.41(s, 1H), 8.43-8.47(m, 2H).

9. 4-(phenoxymethyl)-2-phenylphthalazin-1(2H)-one (9f)

IR (KBr, cm^{-1}): 1241(C-O),1670(C=O).^1H NMR ($CDCl_3$): 5.20(s, 2H), 6.85-6.92(d, 2H), 7.11-7.13(m, 1H), 7.20-7.24(m, 1H) 7.32-7.41(m, 4H), 7.42-7.46(m, 2H), 7.75-7.83(m, 4H), 8.51-8.54(m, 2H).

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