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FULL PAPER

Synthesis of Novel Phthalazino[1,2-*b*]quinazolinedione Derivatives: Efficient and Practical Reaction of 2-Amino-*N*′-Arylbenzohydrazides and 2-Formylbenzoic Acids

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This work reported the synthesis of novel phthalazino[1,2-*b*]quinazolinedione derivatives through the reaction of 2-amino-*N*′-arylbenzohydrazides and 2-formylbenzoic acids in the presence of TsOH in EtOH under reflux conditions.

Keywords: 2-Amino-*N*′-arylbenzohydrazides, Isatoic anhydride, 2-Formylbenzoic acids, Phthalazino[1,2-*b*]quinazolinedione, Hydrazines.

Introduction

It is well-known that choosing the most suitable starting material is a key step for planning a synthesis of organic compounds. In this regard, isatoic anhydride is a versatile starting material and its ring-opening reaction with different amines yields bident nucleophiles [1], which is potent to react with various electrophiles, such as dimethyl acetylenedicarboxylate [2], aldehydes [3 – 5], *Vilsmeier* reagent [6], boronic acids [7], carbon disulfide and anthranilic acids [8], and *N*,*N*′-dialkylcarbodiimides [9]. Isatoic anhydride has been considered especially for the synthesis of various functionalized quinazolinones. As quinazolinones are an important class of heterocycles due to a wide range of medicinal properties, they have been the center of our research group's attention. Quinazolinones and fused derivatives [10] have attracted a lot of attention owing to their antimycobacterial [11], angiotensin-converting enzyme (ACE) inhibitory [12], antituberculosis [13], monoamine oxidase (MAO) inhibitory [14], and anti-leishmania [15] activities. Phthalazinone derivatives are also significant pharmacophores in drug discovery developments which have been broadly examined [16]. It seems that fused quinazolinone-phthalazinone derivatives provide versatile biological activities which have not been investigated in the literature.

Ring opening of isatoic anhydride using phenylhydrazines affords 2-amino-*N*′-arylbenzohydrazides which has been used for the formation of novel heterocycles [17]. Synthesis of benzisoxazoles and benzisothiazoles was developed through $PhI(OAc)_2$-mediated oxidation followed by intramolecular oxidative O–N/S–N bond formation of 2-amino-*N*′-arylbenzohydrazides [17a]. Also, indazolo[3,2-*b*]quinazolinones were efficiently prepared *via* a Pd-catalyzed cascade reaction of 2-amino-*N*′-arylbenzohydrazides with triethyl orthobenzoates [17b]. Herein, we report the synthesis of novel phthalazino[1,2-*b*]quinazolinediones **5** through TsOH-mediated reaction of 2-amino-*N*′-arylbenzohydrazides **3** and 2-formylbenzoic acids **4** in refluxing EtOH [2 – 9] (*Scheme 1*).

Results and Discussion

All required 2-amino-*N*′-arylbenzohydrazides **3** were prepared by the reaction of isatoic anhydride (**1**) and different phenylhydrazines **2** in H_2O at room temperature for 4 h. By choosing 2-amino-*N*′-phenylbenzohydrazide (**3a**) as a model substrate, we investigated its reaction with 2-formyl benzoic acid (**4a**). The reaction of **3a** and 2-formyl benzoic acid (**4a**) was conducted in various solvents and temperatures in the presence of conventional acidic reagent (*Table 1*). It should be noted that the basic reagent did not work efficiently, which is probably related to the formation of a carboxylate anion. Hence, AcOH, sulfamic acid, and TsOH were examined. As demonstrated in *Table 1*, using 1,4-dioxane, toluene, DMF, and CH_2Cl_2 did not lead to the formation of the corresponding product **5a** in good yield. It was revealed that the reaction proceeded smoothly in EtOH to afford the desired

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Scheme 1. Synthesis of novel phthalazino[1,2-*b*]quinazolinediones **5**.

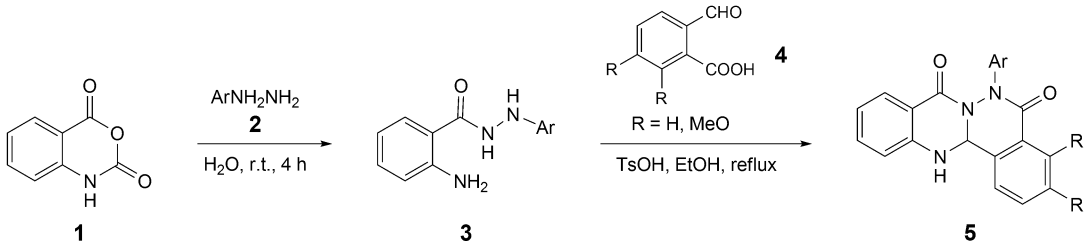


Table 1. Optimization of reaction conditions for the synthesis of **5a**[a])

Entry	Reagent	Solvent	Condition	Yield [%][b])
1	TsOH	EtOH	r.t.	20
2	TsOH	EtOH	Reflux	85
3	TsOH	1,4-Dioxane	Reflux	30
4	TsOH	CH_2Cl_2	Reflux	25
5	TsOH	Toluene	Reflux	20
6	TsOH	DMF	r.t.	–
7	TsOH	DMF	Reflux	35
8	AcOH	EtOH	Reflux	30
9	Sulfamic acid	EtOH	Reflux	40
10	Sulfamic acid	1,4-Dioxane	Reflux	15

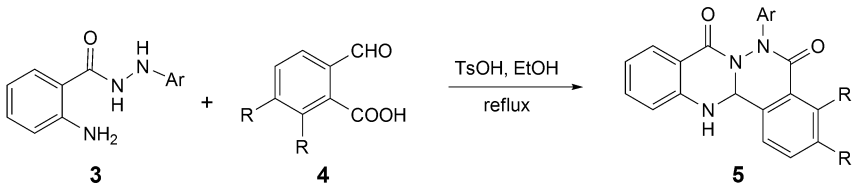
[a]) The model reaction was conducted using 2-amino-*N*′-phenylbenzohydrazide (**3a**, 2 mmol) and 2-formylbenzoic acid (**4a**, 2 mmol) in a solvent (8 ml) in the presence of selected reagent (0.4 mmol) for 2 h. [b]) Yield of isolated product.

product. Also, temperature screening showed that performing the model reaction under reflux conditions gave the product in good yield.

Obtaining the optimized conditions led us to investigate the generality of our reaction with different 2-amino-*N*′-arylbenzohydrazides **3** and 2-formylbenzoic acid/6-formyl-2,3-dimethoxybenzoic acid **4** to afford novel phthalazino[1,2-*b*]quinazolinediones **5** (*Table 2*).

The reaction sequence for the formation of product **5** has been illustrated in *Scheme 2*. First, reaction of 2-amino-*N*′-arylbenzohydrazides **3** and TsOH-activated aldehyde **4** led to the formation of *N*-benzylidene-2-(2-arylhydrazine-1-carbonyl)benzenaminium **6**, which tolerated intramolecular nucleophilic substitution reaction to afford **7**. Further intramolecular reaction of the NH group and the C=O group of the carboxylic acid gave the corresponding product **5**.

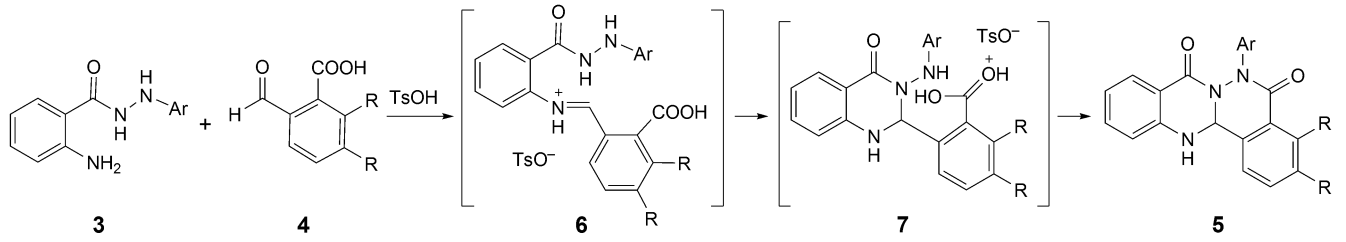
Table 2. Synthesis of phthalazino[1,2-*b*]quinazolinediones **5**



Entry	R	Ar	Product **5**	Yield [%][a])
1	H	Ph	**5a**	85
2	MeO	Ph	**5b**	80
3	H	4-F–C_6H_4	**5c**	70
4	MeO	4-F–C_6H_4	**5d**	75
5	H	4-Br–C_6H_4	**5e**	60
6	MeO	4-Br–C_6H_4	**5f**	65
7	H	4-MeO–C_6H_4	**5g**	60
8	MeO	4-MeO–C_6H_4	**5h**	75

[a]) Yield of isolated product.

Scheme 2. Reaction sequence for the formation of phthalazino[1,2-*b*]quinazolinediones **5**.



Conclusion

In conclusion, we successfully reported the synthesis of novel phthalazino[1,2-*b*]quinazolinedione derivatives through a TsOH-mediated reaction of 2-amino-*N*′-arylbenzohydrazides and 2-formylbenzoic acids in refluxing EtOH. As the synthesis of fused phthalazinoquinazolinedione heterocycles has not been broadly investigated in the literature, it may attract the attention of organic and medicinal chemists.

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Experimental Part

General

M.p.: *Kofler* hot stage apparatus (Austria). IR Spectra: *Nicolet Magna FTIR 550* spectrophotometer (USA; in KBr); $\tilde{\nu}$ in cm^{-1}. ^{1}H- and ^{13}C-NMR spectra: *Bruker FT-500* (Germany); δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. MS: *Agilent-Technology* (*HP*) mass spectrometer (USA), ionization potential 70 eV; in *m*/*z*. Elemental analysis: *VarioEL CHNS* mode (*Elementar Analyses System GmbH*, Hanau, Germany).

Synthesis of Phthalazino[1,2-b]quinazolinones **5**. *General Procedure*. All 2-amino-*N*′-arylbenzohydrazides **3** were prepared *via* the reaction of equiv. amounts of isatoic anhydride (**1**) and different phenylhydrazine derivatives **2** in H_2O at r.t. for 4 h. After completion of reaction, the precipitated product **3** was filtered off, dried at 50 – 60 °C, and used for next reactions without purification. Then, a mixture of compound **3** (1 mmol), 2-formylbenzoic acid derivative **4** (1 mmol), and TsOH (0.4 mmol) in EtOH (8 ml) was heated under reflux for 2 – 8 h. After completion of the reaction (checked by TLC), the mixture was poured into the crushed ice, the precipitated product was filtered off, and recrystallized from AcOEt/petroleum ether (1:4) to afford pure product **5**.

13,13a-Dihydro-6-phenyl-6*H*-phthalazino[1,2-*b*]quinazoline-5,8-dione (**5a**). Yield: 0.29 g (85%). Colorless crystals. M.p. 188 – 190 °C. IR: 3295, 3102, 3038, 1718, 1683, 1599. ^{1}H-NMR: 6.33 (*s*, 1 H, CH); 6.56 – 7.02 (*m*, 6 H, Ph, NH); 7.32 (*t*, *J* = 7.5, H–C(10)); 7.42 (*t*, *J* = 8.0, H–C(3)); 7.55 (*t*, *J* = 8.0, H–C(2)); 7.69 (*t*, *J* = 7.5, H–C(11)); 7.84 (*d*, *J* = 7.5, H–C(12)); 7.98 (*d*, *J* = 8.0, H–C(4)); 8.13 (*d*, *J* = 8.0, H–C(1)); 8.24 (*d*, *J* = 7.5, H–C(9)). ^{13}C-NMR: 73.1; 114.4; 120.4; 121.9; 124.4; 125.3; 126.7; 128.9; 129.2; 130.4; 132.0; 133.1; 134.3; 137.9; 139.0; 142.0; 147.5; 155.0; 164.0. MS: 341 (55), 235 (100), 207 (61), 179 (30), 152 (30), 120 (30), 77 (70). Anal. calc. for $C_{21}H_{15}N_3O_2$ (341.12): C 73.89, H 4.43, N 12.31; found: C 73.67, H 4.28, N 12.48.

13,13a-Dihydro-3,4-dimethoxy-6-phenyl-6*H*-phthalazino[1,2-*b*]quinazoline-5,8-dione (**5b**). Yield: 0.32 g (80%). Colorless crystals. M.p. 252 – 254 °C. IR: 3280, 3011, 2937, 2837, 1710, 1681, 1601. ^{1}H-NMR: 3.86 (*s*, MeO); 4.13 (*s*, MeO); 6.22 (*s*, 1 H, CH); 6.61 – 7.07 (*m*, 6 H, Ph, NH); 7.30 – 7.33 (*m*, H–C(2,10)); 7.50 (*d*, *J* = 7.5, H–C(12)); 7.67 (*t*, *J* = 7.5, H–C(11)); 8.11 (*d*, *J* = 8.0, H–C(1)); 8.22 (*d*, *J* = 7.5, H–C(9)). ^{13}C-NMR: 56.5; 62.5; 72.1; 114.5; 114.6; 115.2; 117.3; 120.6; 121.9; 122.1; 124.0; 124.1; 125.2; 129.0; 134.2; 135.5; 143.1; 154.7; 155.1; 155.0; 164.1. Anal. calc. for $C_{23}H_{19}N_3O_4$ (401.14): C 68.82, H 4.77, N 10.47; found: C 68.69, H 4.59, N 10.61.

6-(4-Fluorophenyl)-13,13a-dihydro-6*H*-phthalazino[1,2-*b*]quinazoline-5,8-dione (**5c**). Yield: 0.25 g (70%). Colorless crystals. M.p. 196 – 198 °C. IR: 3264, 1728, 1674, 1602. ^{1}H-NMR: 6.35 (*s*, 1 H, CH); 6.51 – 6.53 (*m*, H–C(3′,5′)); 6.73 – 6.75 (*m*, H–C(2′,6′)); 7.22 (br. *s*, 1 H, NH); 7.34 (*t*, *J* = 7.5, H–C(10)); 7.49 (*t*, *J* = 7.5, H–C(3)); 7.57 (*t*, *J* = 7.5, H–C(2)); 7.70 (*t*, *J* = 7.5, H–C(11)); 7.84 (*d*, *J* = 7.5, H–C(12)); 7.99 (*d*, *J* = 7.5, H–C(4)); 8.11 (*d*, *J* = 7.5, H–C(1)); 8.23 (*d*, *J* = 7.5, H–C(9)). ^{13}C-NMR: 73.1; 115.1; 115.6 (*d*, *J*(C,F) = 27.5); 118.8; 120.6; 124.5; 125.4; 126.7; 129.2; 129.4; 130.6; 132.0; 133.2; 134.6; 138.6; 145.8; 155.1; 158.2 (*d*, *J*(C,F) = 245.0); 166.0. Anal. calc. for $C_{21}H_{14}FN_3O_2$ (359.11): C 70.19, H 3.93, N 11.69; found: C 70.33, H 4.15, N 11.51.

6-(4-Fluorophenyl)-13,13a-dihydro-3,4-dimethoxy-6*H*-phthalazino[1,2-*b*]quinazoline-5,8-dione (**5d**). Yield: 0.31 g (75%). Colorless crystals. M.p. 236 – 238 °C. IR: 3272, 3014, 1708, 1682, 1603. ^{1}H-NMR: 3.69 (*s*, MeO); 4.13 (*s*, MeO); 6.22 (*s*, 1 H, CH); 6.56 – 6.57 (*m*, H–C(3′,5′)); 6.74 – 6.77 (*m*, H–C(2′,6′)); 6.98 (br. *s*, 1 H, NH); 7.30 – 7.33 (*m*, H–C(2,10)); 7.48 (*d*, *J* = 8.0, H–C(12)); 7.67 (*t*, *J* = 8.0, H–C(11)); 8.10 (*d*, *J* = 8.0, H–C(1)); 8.21 (*d*, *J* = 8.0, H–C(9)). ^{13}C-NMR: 56.5; 62.5; 72.0; 115.5; 115.7 (*d*, *J*(C,F) = 22.5); 117.2; 118.8; 120.6; 122.1; 123.9; 125.2; 129.1; 131.1; 134.3; 137.6; 143.8; 154.1; 154.2; 155.5; 158.3 (*d*, *J*(C,F) = 245.0); 164.0. Anal. calc. for $C_{23}H_{18}FN_3O_4$ (419.13): C 65.87, H 4.33, N 10.02; found: C 65.69, H 4.50, N 10.18.

6-(4-Bromophenyl)-13,13a-dihydro-6*H*-phthalazino[1,2-*b*]quinazoline-5,8-dione (**5e**). Yield: 0.25 g (60%). Colorless crystals. M.p. 220 – 222 °C. IR: 3261, 1727, 1673, 1599. ^{1}H-NMR: 6.31 (*s*, 1 H, CH); 6.44 (*d*, *J* = 7.5, H–C(3′,5′))); 6.83 (br. *s*, 1 H, NH); 7.12 (*d*, *J* = 7.5, H–C(2′,6′))); 7.33 (*t*, *J* = 7.5, H–C(10)); 7.48 (*t*, *J* = 7.5, H–C(3)); 7.57 (*t*, *J* = 7.5, H–C(2)); 7.69 (*t*, *J* = 7.5, H–C(11)); 7.81 (*d*, *J* = 7.5, H–C(12)); 8.00 (*d*, *J* = 7.5, H–C(4)); 8.11 (*dd*, *J* = 7.5, 1.5, H–C(1)); 8.23 (*d*, *J* = 7.5, H–C(9)). ^{13}C-NMR: 73.1; 114.2; 116.1; 118.4; 120.5; 124.5; 125.4; 126.5; 129.2; 130.6; 131.8; 132.0; 133.2; 134.5; 137.4; 138.5; 146.6; 155.2; 165.7. Anal. calc. for $C_{21}H_{14}BrN_3O_2$ (419.03): C 60.02, H 3.36, N 10.00; found: C 59.84, H 3.48, N 10.21.

6-(4-Bromophenyl)-13,13a-dihydro-3,4-dimethoxy-6*H*-phthalazino[1,2-*b*]quinazoline-5,8-dione (**5f**). Yield: 0.31 g (65%). Colorless crystals. M.p. 245 – 247 °C. IR: 3267, 3092, 2939, 2837, 1710, 1683. ^{1}H-NMR: 3.87 (*s*, MeO); 4.12 (*s*, MeO); 6.20 (*s*, 1 H, CH); 6.49 (*d*, *J* = 7.5, H–C(3′,5′))); 6.98 (br. *s*, 1 H, NH); 7.16 (*d*, *J* = 7.5, H–C

(2′,6′))); 7.26 – 7.32 (*m*, H–C(2,10)); 7.45 (*d*, *J* = 7.5, H–C (12)); 7.66 (*t*, *J* = 7.5, H–C(11)); 8.11 (*d*, *J* = 8.0, H–C(1)); 8.21 (*d*, *J* = 7.5, H–C(9)). ^{13}C-NMR: 56.5; 62.5; 72.1; 114.1; 116.1; 117.3; 120.6; 121.9; 123.9; 125.2; 129.1; 130.9; 131.8; 134.4; 136.5; 146.8; 147.9; 154.3; 154.6; 155.1; 163.9. Anal. calc. for $C_{23}H_{18}BrN_3O_4$ (479.05): C 57.51, H 3.78, N 8.75; found: C 57.68, H 3.86, N 8.61.

13,13a-Dihydro-6-(4-methoxyphenyl)-6*H*-phthalazino[1,2-*b*]quinazoline-5,8-dione (**5g**). Yield: 0.22 g (60%). Colorless crystals. M.p. 195 – 197 °C. IR: 3263, 2916, 2834, 1725, 1676, 1599. ^{1}H-NMR: 3.68 (*s*, MeO); 6.33 (*s*, 1 H, CH); 6.52 – 6.71 (*m*, 5 H, H–C(2′,3′,5′,6′), NH); 7.31 (*t*, *J* = 7.5, H–C(10)); 7.48 (*t*, *J* = 7.5, H–C(3)); 7.56 (*t*, *J* = 7.5, H–C(2)); 7.66 (*td*, *J* = 7.5, 1.5, H–C(11)); 7.87 (*d*, *J* = 7.5, H–C(12)); 7.98 (*d*, *J* = 7.5, H–C(4)); 8.12 (*dd*, *J* = 7.5, 1.0, H–C(1)); 8.23 (*d*, *J* = 7.5, H–C(9)). ^{13}C-NMR: 55.5; 73.1; 114.4; 116.0; 120.4; 124.3; 125.3; 126.9; 129.1; 130.4; 132.0; 133.1; 134.3; 137.5; 138.9; 140.7; 154.3; 155.1; 155.2; 165.8. Anal. calc. for $C_{22}H_{17}N_3O_3$ (371.13): C 71.15, H 4.61, N 11.31; found: C 71.32, H 4.48, N 11.50.

13,13a-Dihydro-3,4-dimethoxy-6-(4-methoxyphenyl)-6*H*-phthalazino[1,2-*b*]quinazoline-5,8-dione (**5h**). Yield: 0.28 g (65%). Colorless crystals. M.p. 245 – 247 °C. IR: 3270, 3004, 2938, 2835, 1711, 1682. ^{1}H-NMR: 3.68 (*s*, MeO); 3.87 (*s*, MeO); 4.13 (*s*, MeO); 6.22 (*s*, 1 H, CH); 6.57 – 6.64 (*m*, H–C(2′,3′,5′,6′)); 7.00 (br. *s*, 1 H, NH); 7.26 – 7.32 (*m*, H–C(2,10)); 7.53 (*d*, *J* = 8.0, H–C(12)); 7.66 (*td*, *J* = 8.0, 1.5, H–C(11)); 8.11 (*d*, *J* = 7.5, H–C(1)); 8.22 (*d*, *J* = 8.0, H–C(9)). ^{13}C-NMR: 55.5; 56.5; 62.5; 72.0; 114.4; 116.0; 117.2; 120.5; 122.3; 124.1; 125.2; 126.0; 129.1; 131.3; 131.5; 134.2; 137.3; 142.1; 154.1; 155.1; 155.3; 165.0. Anal. calc. for $C_{24}H_{21}N_3O_5$ (431.15): C 66.81, H 4.91, N 9.74; found: C 66.62, H 5.14, N 9.86.

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