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Synthesis of 3-Aryl-4(3*H*)-quinazolinones from Anthranilic Acids and Triethyl Orthoformate

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Abstract: A one-step, convenient approach to the synthesis of 3-aryl-4(3*H*)-quinazolinones by the reaction of anthranilic acid with triethyl orthoformate in the presence of a catalytic amount of concentrated sulfuric acid has been developed. The possible reaction pathway was proposed.

Keywords: 2-Amino-5-methylbenzoic acid; Anthranilic acid; 3-Aryl-4(3*H*)-quinazolinone; Heterocyclization; Triethyl orthoformate

INTRODUCTION

4(3*H*)-Quinazolinones bearing substituents on either C-2 or N-3 or both C-2 and N-3 display a wide range of biological activities such as antitumor,[1] anti-inflammatory,[2] antibacterial,[3] anticonvulsive,[4] and antihypertensive activities.[5] Therefore, many methods for the synthesis of 4(3*H*)-quinazolinones have been developed and reported in the literature, which had been reviewed recently by Connolly et al.[6] As for N-3-substituted 4(3*H*)-quinazolinones, the most popular synthetic approach involves the amidation of (4*H*)-3,1-benzoxazin-4-ones with alkyl or aryl amines.[7] Recently, Majo and Perumal described a novel dimerization reaction by treating 5-substitued-2-aminobenzoic acid with Vilsmeier

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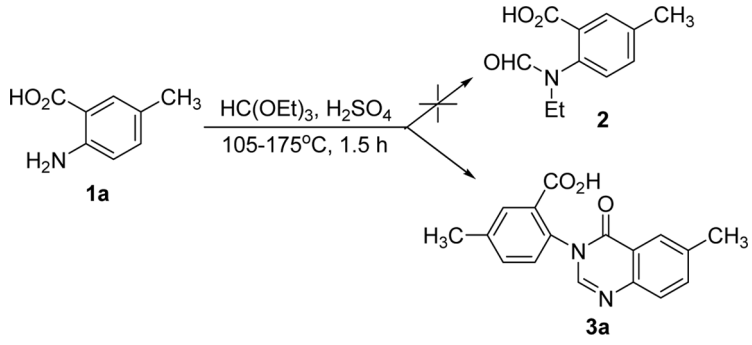
reagent, a combination of N, N-dimethylformamide (DMF) and $POCl_3$, to furnish 3-substitued-4(3*H*)-quinazolinones.[8]

In our attempt to prepare pure *N*-monoalkylated derivatives of 2-amino-5-methylbenzoic acid **1a**, such as 5-methyl-2-(methylamino)benzoic acid, and 2-(ethylamino)-5-methylbenzoic acid, which would be used as starting material for the synthesis of N-1 substituted 4(3*H*)-quinazolinones, a dimerization of **1a** forming 3-aryl-4(3*H*)-quinazolinone was observed. We report here this unexpected reaction and its application.

RESULTS AND DISCUSSION

Heating 3-methylaniline with triethyl orthoformate in the presence of a catalytic amount of concentrated sulfuric acid, while removing ethanol formed by distillation, affords *N*-ethyl-*N*-formyl-3-methylaniline, which followed by acidic hydrolysis gives pure *N*-ethyl-3-methylaniline.[9] However, the reaction of 2-amino-5-methylbenzoic acid **1a** under the same condition did not yield the desired compound **2**, but rather **3a** (Scheme 1). Interestingly, treating **1a** with trimethyl orthoformate gave the same product **3a**. The structure of **3a** was confirmed by means of ^{1}H NMR, electrospray ionization mass spectrum (ESI-MS), and elemental analysis. Furthermore, a single crystal of **3a** was obtained and its structure was solved by X-ray diffraction (Figure 1).

[X-ray crystal data for **3a**: CCDC deposit no. 642545; empirical formula: $C_{17}H_{14}N_2O_3$; formula weight: 294.30; T = 293(2) K; $\lambda = 0.71073$ Å; crystal system = monoclinic; space group: *P*2(1)/n; unit cell dimensions: $a = 9.841(2)$, $b = 10.901(2)$, $c = 13.791(3)$ Å, $\alpha = 90.00$, $\beta = 95.17(3)$, $\gamma = 90.00$ °; $V = 1473.5(5)$ Å^3; $Z = 4$; $D_{cal} = 1.327$ g cm^{-3}; $\mu = 0.093$ mm^{-1}; θ range for data collection: 2.39–25.02 °; reflections



Scheme 1. The unexpected reation of 1a.

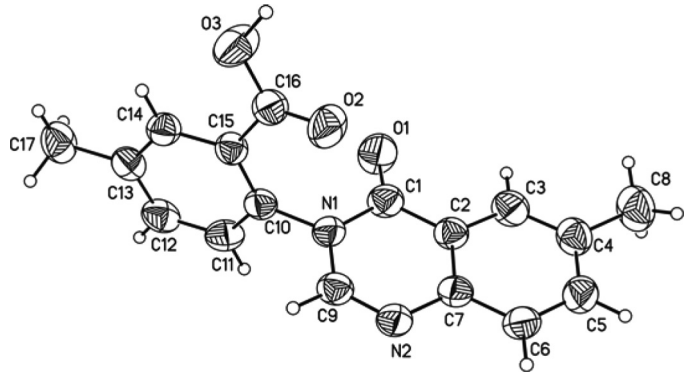
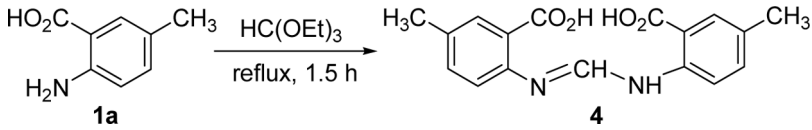


Figure 1. Molecular structure of 5-methyl-2-(6-methyl-4-oxoquinazolin-3(4H)-yl)benzoic acid 3a.

used: 9408; independent reflections: 2602 [R(int) = 0.0364]; refinement method: full-matrix least-squares on F^2; $R_1 = 0.0650$, $wR_2 = 0.1048$ [$I > 2\sigma$ (I)]. Structure solution and refinement were achieved using SHELXS98 and SHELXL98[10]].

To investigate whether the formation of **3a** involves the heterocyclization of 2-amino-5-methylbenzoic acid **1a** with triethyl orthoformate, and amidation of resultant 6-methyl-4*H*-3,1-benzoxazin-4-one with unreacted **1a**, **1a** was heated with triethyl orthoformate (molar ratio = 1:2) under reflux for 1.5 h, without distilling to remove the low boiling-point substances that formed. Consequently, the intermediate amidine **4** instead of 6-methyl-4*H*-3,1-benzoxazin-4-one as described in literature[11,12] was obtained (Scheme 2), which may cyclodehydrate to provide the final product **3a**. In fact, adding 2 drops of concentrated sulfuric acid into the mixture after treating **1a** with triethyl orthoformate under reflux for 1.5 h and refluxing for 1 h further afforded **3a** eventually. Therefore, the presence of concentrated sulfuric acid could promote the formation of imidic ester, the precursor of amidine **4**, as well as the cyclodehydration of **4** to give **3a**.

For optimizing the reaction conditions, acid, solvent, and the relative molar ratio of **1a** to triethyl orthoformate were varied, and the results are



Scheme 2. Reaction of 1a with triethyl orthoformate in the absence of concentrated H_2SO_4.

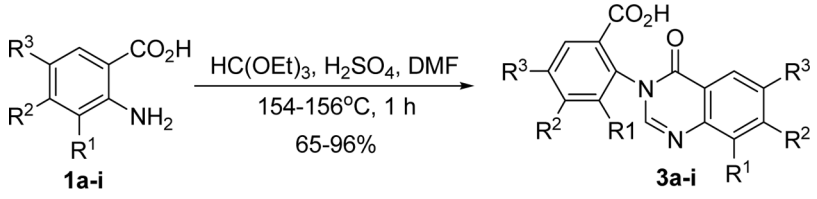
Table 1. Yields of **3a** in the reaction of **1a** with $HC(OEt)_3$ under various conditions after 1 h at 154–156 °C[a]

Entry	Acid	Solvent	Molar ratio [**1a**/$HC(OEt)_3$]	Yield of **3a** (%)[b]
1	H_2SO_4	Solvent-free	1:1	69
2	H_2SO_4	Solvent-free	1:1.5	65
3	H_2SO_4	DMF	1:1	73
4	H_2SO_4	DMF	1:1.25	76
5	H_2SO_4	DMF	1:1.5	91
6	H_2SO_4	DMF	1:1.75	79
7	H_2SO_4	DMF	1:2	27
8	TsOH	DMF	1:1.5	45

[a]The low boiling-point substance formed was removed by distillation.
[b]Yields of pure isolated products.

listed in Table 1. Although the reaction under solvent-free conditions could give **3a** in moderate yield, the use of DMF as solvent, especially increasing the molar ratio of **1a** to triethyl orthoformate, could obviously improve the yield. Nevertheless, when the molar ratio of **1a** to triethyl orthoformate was more than 1:1.5, the yield decreased drastically. Moreover, the replacement of concentrated sulfuric acid with 4-methylbenzenesulfonic acid (TsOH) decreased the yield from 91% to 45%.

Under the optimized conditions, a range of anthranilic acids with various substituents (**1a–j**) were treated with triethyl orthoformate, providing 3-aryl-4(3*H*)-quinazolinons **3a–i** (Scheme 3 and Table 2). As seen from Table 2, most anthranilic acids with electron-donating substituents underwent the reaction in fairly high yields, whereas the anthranilic acid **1i** with electron-withdrawing substituent (4-carboxyl) converted into **3i** only in 65% yield. In the case of 2-amino-5-nitrobenzoic acid **1j**, the expected product was not obtained, but imidic ester **5** was isolated in 39% yield instead (Scheme 4).



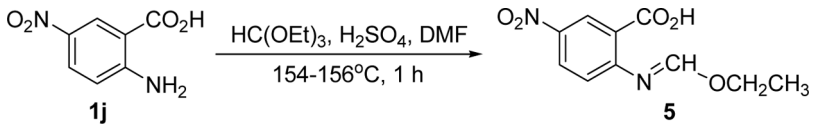
Scheme 3. For R^1, R^2 and R^3, see Table 2.

Table 2. Synthesis of 3-aryl-4(3*H*)-quinazolinone **3a–i**

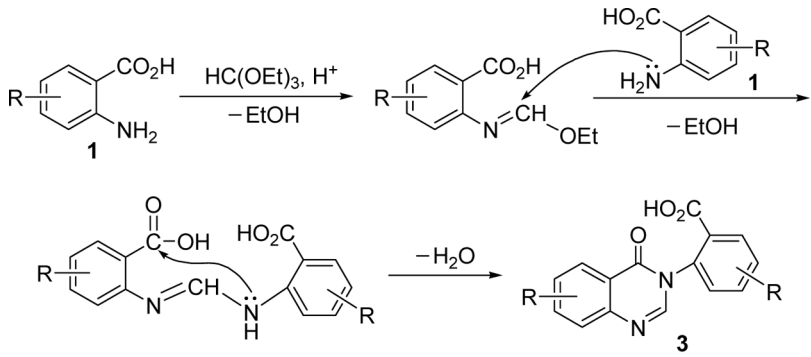
Entry	3	R^1	R^2	R^3	Yield (%)[a]
1	**3a**	H	H	Me	91
2	**3b**	Me	H	H	85
3	**3c**	H	H	OH	96
4	**3d**	H	H	Cl	80
5	**3e**	H	Cl	H	92
6	**3f**	H	H	Br	78
7	**3g**	H	H	AcNH	67
8	**3h**	H	H	H	85
9	**3i**	H	CO_2H	H	65

[a]Yields of isolated products.

Although the reaction of 2-amino-5-nitrobenzoic acid **1j** with triethyl orthoformate could not yield the heterocyclized product, the isolated intermediate imidic ester **5** is helpful in outlining the possible reaction pathway. Rad-Moghadam and Mohseni[13] reported that the reaction of anthranilic acid and orthoesters in the presence of ammonium acetate under microwave conditions produced 2-substituted quinazolin-4(3*H*)-ones, and the reaction was thought to proceed through the intermediate amidine. Considering together with the intermediate amidine **4** obtained in the reaction of **1a** with triethyl orthoformate, we supposed that the whole reaction proceeded in three steps: condensation of anthranilic acids with triethyl orthoformate promoted by sulfuric acid gave imidic ester (for example, **5**); the intermediate imidic ester undergoes necleophilic attack by the amino group in remaining anthranilic acid to produce amidine (for example, **4**); and cyclization of amidine through the elimination of a molecule of H_2O to form the final product 3-aryl-4(3*H*)-quinazolinones (Scheme 5). Thus, anthranilic acids with electron-donating substituents underwent the reaction smoothly in each step, whereas those with electron-withdrawing groups (for instance **1i**) could not efficiently attack the intermediate imidic ester because of the poor necleophility of amino group, so the yield was relatively low (65%). As for anthranilic acid **1j** with strong electron-withdrawing nitro group, the reaction rested on



Scheme 4. Reaction of 1j with triethyl orthoformate in the presence of concentrated H_2SO_4.



Scheme 5.

the stage of imidic ester **5**, and neither heterocyclized product nor amidine intermediate was obtained.

In summary, we have described a simple and efficient synthesis of 3-aryl-4(3*H*)-quinazolinones from anthranilic acids. The methodology was suitable for a range of substituted anthranilic acids except for 5-nitro anthranilic acid, which gave the intermediate imidic ester. The structures of the final products and the intermediates isolated have been confirmed by MS, ^{1}H NMR, elemental analysis, or HRMS, which enabled us to elaborate the possible reaction pathway.

EXPERIMENTAL

Melting points were determined on an X-6 microscopic melting-point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AC-200P spectrometer at 200 MHz using tetramethylsilane (TMS) as internal standard. Chemical ionization (CI) mass spectrum was recorded on a Finnigan Trace DSQ mass spectrometer. Low-resolution electrospray ionization (ESI) mass spectra were recorded on a Bruker Daltonics Esquire-LC 00136 mass spectrometer, and high-resolution electrospray ionization (HR-ESI) mass spectra were recorded on a Bruker Apex II FT-ICR mass spectrometer. High-resolution electron impact (HR-EI) mass spectrum was recorded on a Micromass GCT mass spectrometer. Elemental analyses were performed by the Institute of Chemistry, Chinese Academy of Science, on a Flash EA 1112 elemental analyzer. Column chromatography was carried out on silica gel (200–300 mesh). 2-Amino-5-methylbenzoic acid was prepared according to the reported method.[14] Triethyl orthoformate was distilled before using, and other commercially available reagents were used without further purification.

Selected Data for Compound 4

Mp: 266–267 °C; ^{1}H NMR (200 MHz, DMSO-d_6): δ = 2.32 (s, 6 H, CH_3), 7.43 (d, J = 8.1 Hz, 2 H, Ar-H), 7.68 (d, J = 8.1 Hz, 2 H, Ar-H), 7.80 (s, 2 H, Ar-H), 8.84 (s, 1 H, CH=N); ESI-MS: m/z = 313 $[M+H]^+$. HRMS (ESI): m/z calcd. for $C_{17}H_{16}N_2O_4$: 311.1037 $[M-H]^-$; found: 311.1036.

General Procedure for the Preparation of 3-Aryl-4(3*H*)-quinazolinones 3a–i

To a stirred solution of triethyl orthoformate (1.48 g, 10 mmol), concentrated H_2SO_4 (2 drops) in DMF (5 mL) was added along with anthranilic acid **1** (6.67 mmol), and the mixture was heated carefully. As the temperature rose, some low-boiling-point substances formed, which were removed by distillation. After the temperature rose to 154 °C, the reaction mixture was stirred at 154–156 °C for another 1 h. The mixture was cooled to room temperature and poured into ice water (20 mL) under stirring. The separated solid was collected by filtration and was recrystallized from DMF-H_2O to give 3-aryl-4(3*H*)-quinazolinones **3a–i** (Table 1).

Data

Compound **3a**: 5-Methyl-2-(6-methyl-4-oxoquinazolin-3(4*H*)-yl)benzoic acid, mp: 269–270 °C; ^{1}H NMR (200 MHz, DMSO-d_6): δ = 2.45 (s, 3 H, CH_3), 2.46 (s, 3 H, CH_3), 7.45 (d, J = 8.0 Hz, 1 H, Ar-H), 7.60 (d, J = 7.9 Hz, 1 H, Ar-H), 7.69 (m, 2 H, Ar-H), 7.89 (s, 1 H, Ar-H), 7.96 (s, 1 H, Ar-H), 8.21 (s, 1 H, Ar-H); ESI-MS: m/z = 295 $[M+H]^+$. Anal. calcd for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.79; N, 9.52. Found: C, 69.28; H, 4.83; N, 9.33.

Compound **3b**: 3-Methyl-2-(8-methyl-4-oxoquinazolin-3(4*H*)-yl)benzoic acid, mp: 254–255 °C; ^{1}H NMR (200 MHz, DMSO-d_6): δ = 2.13 (s, 3 H, CH_3), 2.60 (s, 3 H, CH_3), 7.48 (t, J = 7.6 Hz, 1 H, Ar-H), 7.59 (t, J = 7.7 Hz, 1 H, Ar-H), 7.73 (d, J = 7.2 Hz, 1 H, Ar-H), 7.77 (d, J = 7.1 Hz, 1 H, Ar-H), 7.96 (d, J = 7.6 Hz, 1 H, Ar-H), 8.03 (d, J = 8.0 Hz, 1 H, Ar-H), 8.25 (s, 1 H, Ar-H); ESI-MS: m/z = 295 $[M+H]^+$. Anal. Calcd. for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.79; N, 9.52. Found: C, 69.14; H, 4.83; N, 9.58.

Compound **3c**: 5-Hydroxy-2-(6-hydroxy-4-oxoquinazolin-3(4*H*)-yl)benzoic acid, mp: >300 °C; ^{1}H NMR (200 MHz, DMSO-d_6): δ = 7.10 (dd, J = 8.5, 2.7 Hz, 1 H, Ar-H), 7.32 (m, 2 H, Ar-H), 7.44

(m, 2 H, Ar-H), 7.60 (d, $J = 8.7$ Hz, 1 H, Ar-H), 8.03 (s, 1 H, Ar-H); ESI-MS: $m/z = 299$ $[M + H]^+$, Anal. Calcd. for $C_{15}H_{10}N_2O_5 \cdot H_2O$: C, 56.96; H, 3.82; N, 8.86. Found: C, 57.23; H, 3.76; N, 8.59.

Compound **3d**: 5-Chloro-2-(6-chloro-4-oxoquinazolin-3(4*H*)-yl)benzoic acid, mp: >300 °C; ^{1}H NMR (200 MHz, DMSO-d_6): $\delta = 7.70$ (d, $J = 8.4$ Hz, 1 H, Ar-H), 7.79 (d, $J = 8.7$ Hz, 1 H, Ar-H), 7.89–7.96 (m, 2 H, Ar-H), 8.06 (d, $J = 2.3$ Hz, 1 H, Ar-H), 8.11 (d, $J = 2.1$ Hz, 1 H, Ar-H), 8.38 (s, 1 H, Ar-H), 13.52 (br s, 1 H, OH); CI-MS: $m/z = 355$ $[M + H]^+$. Anal. Calcd. for $C_{15}H_8Cl_2N_2O_3$: C, 53.76; H, 2.41; N, 8.36. Found: C, 53.47; H, 2.52; N, 8.20.

Compound **3e**: 4-Chloro-2-(7-chloro-4-oxoquinazolin-3(4*H*)-yl)benzoic acid, mp: >300 °C (lit.: 298 °C)[15]; ^{1}H NMR (200 MHz, DMSO-d_6): $\delta = 7.65$ (dd, $J = 8.5$, 2.0 Hz, 1 H, Ar-H), 7.78 (dd, $J = 8.4$, 2.1 Hz, 1 H, Ar-H), 7.84 (d, $J = 2.0$ Hz, 1 H, Ar-H), 7.88 (d, $J = 2.1$ Hz, 1 H, Ar-H), 8.10 (d, $J = 8.4$ Hz, 1 H, Ar-H), 8.17 (d, $J = 8.5$ Hz, 1 H, Ar-H), 8.42 (s, 1 H, Ar-H); ESI-MS: $m/z = 335$ $[M + H]^+$. Anal. Calcd. for $C_{15}H_8Cl_2N_2O_3$: C, 53.76; H, 2.41; N, 8.36. Found: C, 53.81; H, 2.53; N, 8.46.

Compound **3f**: 5-Bromo-2-(6-bromo-4-oxoquinazolin-3(4*H*)-yl)benzoic acid, mp: >300 °C; ^{1}H NMR (200 MHz, DMSO-d_6): $\delta = 7.38$ (d, $J = 8.4$ Hz, 1 H, Ar-H), 7.67 (d, $J = 8.7$ Hz, 1 H, Ar-H), 7.73 (dd, $J = 8.4$, 2.0 Hz, 1 H, Ar-H), 7.95 (s, 1 H, Ar-H), 8.01 (dd, $J = 8.7$, 2.3 Hz, 1 H, Ar-H), 8.18 (s, 1 H, Ar-H), 8.22 (d, $J = 2.3$ Hz, 1 H, Ar-H); ESI-MS: $m/z = 423$ $[M + H]^+$; HRMS (ESI): m/z calcd. for $C_{15}H_8Br_2N_2O_3$: 420.8829 $[M - H]^-$; found: 420.8825.

Compound **3g**: 5-Acetamido-2-(6-acetamido-4-oxoquinazolin-3(4*H*)-yl)benzoic acid, mp: 246–248 °C; ^{1}H NMR (200 MHz, DMSO-d_6): $\delta = 2.11$ (s, 3 H, $COCH_3$), 2.12 (s, 3 H, $COCH_3$), 7.51 (d, $J = 8.6$ Hz, 1 H, Ar-H), 7.72 (m, 2 H, Ar-H), 7.99 (m, 2 H), 8.21 (s, 1 H, Ar-H), 8.32 (d, $J = 2.5$ Hz, 1 H, Ar-H), 8.45 (m, 2 H); ESI-MS: $m/z = 381$ $[M + H]^+$. Anal. Calcd. for $C_{19}H_{16}N_4O_5 \cdot H_2O$: C, 57.28; H, 4.55; N, 14.06. Found: C, 57.32; H, 4.55; N, 13.72.

Compound **3h**: 2-(4-Oxoquinazolin-3(4*H*)-yl)benzoic acid, mp: 287–288 °C (lit.: 283 °C)[15]; ^{1}H NMR (200 MHz, DMSO-d_6): $\delta = 7.55$–7.93 (m, 6 H, Ar-H), 8.08 (dd, $J = 7.6$, 1.4 Hz, 1 H, Ar-H), 8.17 (dd, $J = 7.9$, 1.0 Hz, 1 H, Ar-H), 8.32 (s, 1 H, Ar-H); ESI-MS: $m/z = 267$ $[M + H]^+$. Anal. Calcd. for $C_{15}H_{10}N_2O_3$: C, 67.67; H, 3.79; N, 10.52. Found: C, 67.32; H, 3.89; N, 10.49.

Compound **3i**: 2-(7-Carboxy-4-oxoquinazolin-3(4*H*)-yl)benzene-1,4-dioic acid, mp: >300 °C; ^{1}H NMR (200 MHz, DMSO-d_6): $\delta = 7.95$–8.29 (m, 6 H, Ar-H), 8.40 (s, 1 H, Ar-H); ESI-MS: $m/z = 355$ $[M + H]^+$, HRMS (EI): m/z calcd. for $C_{17}H_{10}N_2O_7$: 354.0488 $[M^+]$; found: 354.0490.

The reaction of 5-nitro-2-aminobenzoic acid **1j** was carried out according to this general procedure. Column chromatography (eluent: petroleum ether-AcOEt, 3:2) of the product gave 2-(*N*-ethoxymethylene-amino)-5-nitrobenzoic acid **5** as a yellow solid, yield: 39%, mp: 100–102 °C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.48$ (t, $J = 7.1$ Hz, 3 H, OCH_2CH_3), 4.48 (q, $J = 7.1$ Hz, 2 H, OCH_2CH_3), 8.39 (dd, $J = 9.3$, 2.7 Hz, 1 H, Ar-H), 8.62 (s, 1 H, N=CH), 8.94 (m, 2 H, Ar-H), 11.39 (br s, 1 H, OH); ESI-MS: $m/z = 239$ $[M + H]^+$, Anal. Calcd. for $C_{10}H_{10}N_2O_5$: C, 50.42; H, 4.23; N, 11.76. Found: C, 50.74; H, 4.38; N, 12.12.

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