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Electrophilic *N*-Amination of Two Quinazoline-2,4-diones Using Substituted (Nitrophenyl)hydroxylamines

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Abstract:

The preparation of a few (nitrophenyl)hydroxylamines and reaction with two quinazoline-2,4-diones is described. The electrophilic aminating agents were assessed in terms of yield for the N-amination of two quinazoline-2,4-diones and safety considerations for rapid scale-up. For the amination of the described system, the best yield and the highest onset temperature were found in the same aminating agent, specifically, (4-nitrophenyl)hydroxylamine.

Introduction

To rapidly supply material to support toxicological studies of novel antibacterial agents, we had a need to prepare 3-amino-quinazoline-2,4-diones **1** and **2** (Figure 1). This required the preparation of the corresponding imides **3** and **4** followed by N-amination. The aminating agent used by discovery chemistry[1] was *O*-(2,4-dinitrophenyl)hydroxylamine **5**.[2] Due to potential safety concerns surrounding this aminating agent, a sample was tested in our hazards evaluation lab, and (dinitrophenyl)hydroxylamine **5** was found to be quite energetic (vide infra; see Table 2).

More importantly the onset temperature was about 90 °C; chemistry that had been done in-house using (dinitrophenyl)-hydroxylamine **5** was reported to occur at 70−80 °C. These issues caused us to look into the preparation and use of other, readily available (nitrophenyl)hydroxylamines. We chose and limited ourselves to substituted (nitrophenyl)hydroxylamines as aminating agents because we thought that we could easily evaluate them and readily prepare enough aminating agent to fulfill the required immediate compound need. We chose precursors to the aminating agents based on the cost, commercial availability, and substrates that would produce less energetic aminating agents.

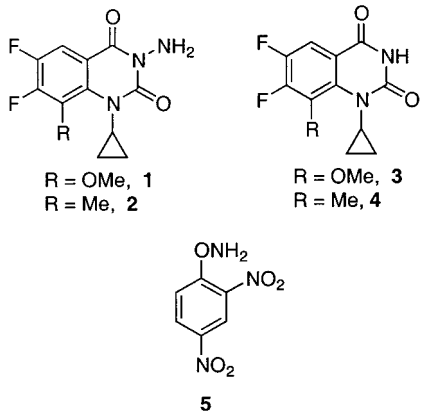
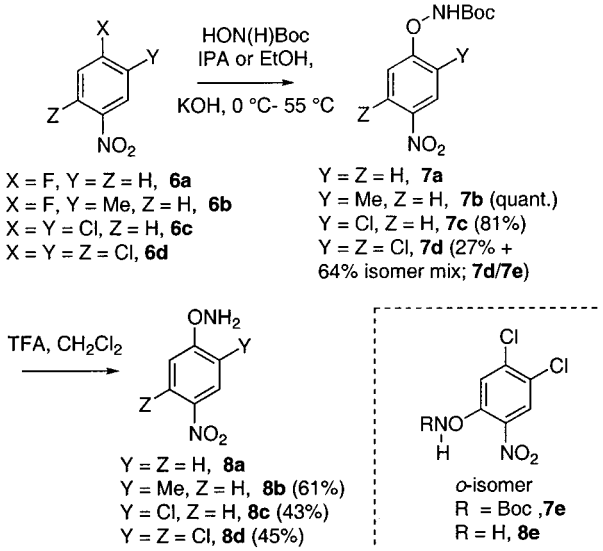


Figure 1.

Scheme 1



Synthesis. The route to the aminating agents is shown in Scheme 1. Although this is a known route to **8a** and **5**,[2] several other *N*-Boc precursors and subsequent (nitrophenyl)-hydroxylamines to our knowledge have not been reported. Preparation of the (nitrophenyl)hydroxylamines involved

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(1) Discovery Chemistry did not have any mishaps during the conduct of their work. See: Bird, P.; Ellsworth, E. L.; Nguyen, D. Q.; Sanchez, J. P.; Showalter, H. H. D.; Singh, R.; Stier, M. A.; Tran, T. P.; Watson, B. M.; Yip, J. (Warner-Lambert Co.). 3-Aminoquinazolin-2,4-diones Antibacterial Agents, WO 0153273, July 26, 2001. A detonation has been reported using **5** under basic conditions. See: Radhakrishna, A. S.; Loudon, G. M.; Miller, M. J. *J. Org. Chem*. **1979**, *44*, 4836.

(2) Sheradsky, T.; Salemnick, G.; Nir, Z. *Tetrahedron* **1972**, *28*, 3833. For a review on electrophilic aminations see: Tamura, Y.; Minamikawa, J.; Ikeda, M. *Synthesis* **1977**, 1.

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Scheme 2

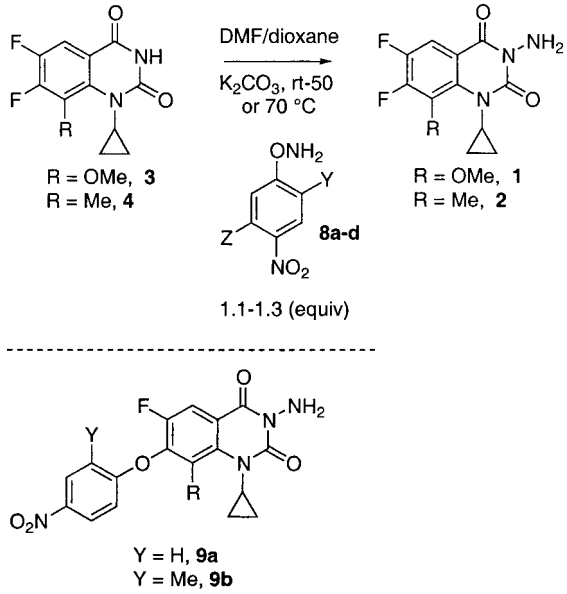

Table 1: **Amination of quinazolindiones 3 and 4**

aminating agent	substrates for amination: imide **3** temperature, time, yield	imide **4** temperature, time, yield
8a	72 °C, 2 h, 75%	72 °C, 2 h, 79%
8b	72 °C, 2 h, 74%	72 °C, 2 h, 62%
8c	50 °C, 3.5 h, 62%	50 °C, 3.5 h, 70%
8d	50 °C, 3 h, 47%	50 °C, 3 h, 51%
8d/8e (85:15)	−	50 °C, 3 h, 59%

nucleophilic aromatic substitution of an *N*-Boc hydroxylamine on the halonitro arene using KOH in EtOH or IPA. Boc cleavage using TFA then rapidly gave the desired phenylhydroxylamines **8a**−**e**. Other acids were tried for this deprotection including formic acid, methane sulfonic acid, and HCl in Et_2O but gave inferior yields (15−35%) to those using TFA.

Aminations were initially done using NaH in a 1:1 mixture of DMF[3] and dioxane or THF, but K_2CO_3 was found to be adequate for this reaction and was used in the amination survey with reagents **8a**−**e** on the quinazoline-2,4-diones **3** and **4**. A polar solvent like DMF, DMA, or NMP is necessary for the reaction to occur. Use of only dioxane or THF gave no desired amination products. The survey was conducted using 1 g of imide **3** or **4**, 1.1 equiv of aminating agent (**8a**−**e**), 1.5 equiv of K_2CO_3 in a 1:1 mixture of dioxane and DMF at the temperatures and times shown. The products were isolated by chromatography on SiO_2. Results from this survey are shown in Scheme 2 and Table 1.

The more reactive aminating agents allowed the reaction to occur at lower temperature but gave diminished yield. *O*-(4-Nitrophenyl)hydroxylamine (**8a**) was found to give the best yield; although, with the more reactive methoxy core **3**, a byproduct was generated in the 4−7% range (HPLC area%).[4] Byproduct **9a** is due to attack of the resulting phenoxide on the quinazoline-2,4-dione heterocycle (Scheme 2). Byproduct **9b** is also observed in the amination of **3** using *O*-(2-methyl-4-nitrophenyl)hydroxylamine (**8b**), albeit in lesser amounts. The 2-methyl and 2-chloro aminating agents **8b** and **8c** run a close second in yield. The reaction of the monochlorinated reagent went smoothly at 50 °C in 3.5 h, whereas the dichloro-aminating agent **8d** promoted amination in 2 h at that same temperature, but gave an inferior yield. The increase in reactivity due to the addition of electron-withdrawing substituents proved to also prevent the formation of phenoxide addition products to the methoxy core **3**; phenol addition byproducts (i.e., **9a,b**) were not observed using **8c,d**. A mixture of **8d/8e** (85:15) was also used as an aminating agent. Interestingly, examination of the crude reaction mixture showed that **8d** did the amination while **8e,** the ortho-substituted aminating agent, was left behind, unchanged.

Table 2: **DSC and ARC data on aminating agents**

aminating agent	onset temperature (ARC) (°C)	onset temperature (DSC) (°C)	energy (DSC)[b] (J/g)
5	90	110[a]	2308[c]
8a	120	−	1800[c]
8b	118	128	1262
8c	95	119	1291
8d	90	124	1663

[a] This is the temperature at which the test cell burst, destroying our DSC sensor. ARC measured ΔP_{max} readings in excess of 20 000 psi/min for some runs. [b] TNT is reported to have a measured decomposition energy of 4395 J/g with an onset temperature of 250 °C.[5] [c] Measured by ARC. This value is likely less than the actual value because the decompositions out-ran the calorimeter creating a nonadiabatic condition.

Hazards Evaluation. The first aminating agent, *O*-(2,4-dinitrophenyl)hydroxylamine (**5**) was initially subjected to DSC (differential scanning calorimetry) analysis; this resulted in the over-pressurization of the medium-pressure stainless steel cell with enough force to shatter the ceramic sensor and damage the surrounding oven. Testing was then conducted in the ARC (accelerating rate calorimetry) using very small sample sizes (0.25−0.5 g). All subsequent aminating agents were evaluated by DSC and ARC. Dinitrophenylhydroxylamine **5** was found not to be shock-sensitive at 200 kg-cm. No other aminating agents were tested for shock sensitivity. DSC and ARC data for these materials are presented in Table 2. All aminating reagents prepared were less energetic than *O*-(2,4-dinitrophenyl) hydroxylamine (**5**); we were able to obtain data without destruction of the instruments. Although the chloro-substituted phenyl hydroxylamines **8c** and **8d** were less energetic, their onset temperatures were decreased. The 2-methylnitro-arene **8b** proved to be the least energetic and had a comparable onset temperature to **8a**. Unfortunately, for all aminating agents tested, once reagent decomposition was initiated, a runaway-reaction-scenario was created. We thought it best to go with the *O*-(4-nitrophenyl)hydroxylamine (**8a**) because we could work at about 50 °C less than the ARC onset temperature. Nitrophenylhydroxylamine **8a** also had a lower cost of preparation in comparison to the other reagents, and we

(3) Mixtures of DMF and NaH have been reported to give spontaneous, uncontrollable exotherms. See: *Bretherick's Handbook of Reactive Chemical Hazards*, 6th ed.; Butterworth-Heinemann Ltd.: Oxford, 1999; Vol. 1, pp 1604−1605

(4) Byproduct **9a** was isolated, and NMR experiments proved adequate for structural elucidation.

(5) Kohler, J.; Meyer, R. *Explosives*, 4th ed.; VCH: Weinheim, 1993; pp 371−374

obtained a good yield of **1** and **2**. This reagent was used to prepare **1** and **2** on 0.5−0.75 mole scale without incident.

Conclusions

In conclusion, we have prepared and used a number of phenylhydroxylamines to *N*-aminate quinazoline-2,4-diones **3** and **4** in good yield. The thermal analysis of the phenyl hydroxylamines has been conducted to allow the determination of safe operating conditions for these aminating agents.

Experimental Section

The preparation of *N*-Boc(4-nitrophenyl)hydroxylamine (**7a**) and *O*-(4-nitrophenyl)-hydroxylamine (**8a**) have been previously reported.[2] NMR data was recorded on Varian Unity NMRs at 400 MHz. Mass spectra were recorded on micromass platform LC. IR were recorded on a Biorad FTS45 FTIR. CHN analyses were recorded on Lehman Labs 440. Melting points were recorded on a Thomas-Hoover melting point apparatus and are uncorrected. DSC were measured using sealed 120 uL medium-pressure stainless steel crucibles in a Mettler DSC 821 and Mettler STAR software. ARC data was measured using an A. D. Little ARC-2000 accelerating rate calorimeter with a 1 in. diameter, 0.25 in. neck titanium bomb. Drop-weight tests were performed using a Technoproducts ASTM standard drop-weight tester under ASTM standard methods. EIHRMS (electron impact high-resolution mass spectrum) were recorded on a VG 70−250-S.

General Procedure for the Preparation of Aminating Reagents: Nucleophilic Aromatic Substitution and *tert*-Butylcarbamate Cleavage. The *N*-Boc phenylhydroxylamines **7a**−**e** were either chromatographed or used crude in the deprotection step. The phenylhydroxylamines **8a**−**e** were purified by recrystallization. The preparation of *O*-(2-methyl-4-nitrophenyl)hydroxylamine (**8b**) is representative of the substitution and Boc cleavage.

***N*-Boc-(2-Methyl-4-nitrophenyl)hydroxylamine (7b).** A mixture of KOH pellets (88%, 42.8 g, 0.67 mol, 1.3 equiv) in EtOH (absolute, 875 mL) was prepared at room temperature and stirred until the KOH dissolved (15 min). *tert*-Butyl-*N*-hydroxy carbamate (106 g,0.80 mol, 1.6 equiv) was added portionwise to give a yellow solution. To this mixture was added a solution of 2-fluoro-5-nitrotoluene (**6b**, 79.9 g, 0.52 mol) in EtOH (absolute, 875 mL) rapidly. The resulting solution became intensely orange. The reaction was then warmed to 50 °C for 68 h (over weekend). The reaction mixture was allowed to cool and concentrated in vacuo. The resulting red oil was redissolved in EtOAc (800 mL) and washed with NH_4Cl solution (saturated, 800 mL). Phases were separated and the aqueous phase extracted with EtOAc (1 × 400 mL). The combined organic phases were washed with brine (1 × 500 mL), dried ($MgSO_4$), and filtered, and the filtrate was concentrated in vacuo to give a yellow solid which was dried (rt, 15 mmHg) to afford **7b** as yellow solid, 138 g, quantitative crude. This was used without purification in the subsequent step. For **7b**: ^{1}H NMR ($CDCl_3$) 8.2 (bs, 1H), 8.0 (dd, 1H, J = 2.5, 9 Hz), 7.9 (d, 1H, J = 2.5 Hz), 7.3 (d, 1H, J = 2.5 Hz), 2.3 (s, 3H), 1.5 (s, 9H); EIMS *m*/*e* (relative intensity) 267 (M^-, 40), 152 (100).

***N*-Boc-(2-chloro-4-nitrophenyl)hydroxylamine (7c).** Reaction of 1,2-dichloro-4-nitrobenzene (**6c**, 20 g, 104 mmol) in IPA with KOH and *tert*-butyl-*N*-hydroxy carbamate (16.1 g, 121 mmol, 1.2 equiv) gave after SiO_2 plug filtration (20% EtOAc/hexanes) 24.3 g, 81% yield of **7c** as a yellow solid. For **7c**: ^{1}H NMR ($CDCl_3$) 8.2 (d, 1H, J = 2.5 Hz), 8.1 (dd, 1H, J = 2.5, 9.2 Hz), 7.9 (bs, 1H), 7.3 (d, 1H, J = 9.2 Hz), 1.5 (s, 9H); EIMS *m*/*e* (relative intensity) 287 (M^-, 5), 172 (100).

***N*-Boc-(2,5-dichloro-4-nitrophenyl)hydroxylamine (7d).** Reaction of 1,2,5-trichloro-4-nitrobenzene (**6d**, 47.2 g, 208 mmol) in EtOH with KOH and *tert*-butyl-*N*-hydroxy carbamate (33.2 g, 226 mmol, 1.2 equiv) gave an 85:15 mixture of *p*:*o*-substituted isomers. A portion of (4-nitrophenyl)-hydroxylamine **7d** was isolated by SiO_2 chromatography (10% EtOAc/hexanes) 18.4 g, 27% yield of **7d** as a yellow solid. An additional 43 g of a mixture of *o*- and *p*-isomers 64% was obtained. For **7d**: ^{1}H NMR ($CDCl_3$) 8.1 (s, 1H), 7.8 (s, 1H), 7.7 (s, 1H), 1.5 (s, 9H); EIMS *m*/*e* (relative intensity) 321 (M^-, 80), 205 (100).

(2-Methyl-4-nitrophenyl)hydroxylamine (8b). A solution of crude **7b** (138 g, 0.52 mol) in CH_2Cl_2 (1.4 L) was cooled to 5 °C and treated with TFA (180 mL) in one portion. The resulting reaction mixture was allowed to warm to room temperature with stirring for 16 h. The reaction mixture was concentrated to give a dark, red oil. The oil was redissolved in CH_2Cl_2 (800 mL) and washed with 10% Na_2CO_3. The organic phase was dried ($MgSO_4$) and filtered, and the filtrate was concentrated in vacuo to give a beige solid. Recrystallization from TBMe (600 mL) and heptane (1.6 L) gave 87 g of **8b** as a beige solid; 61% yield. For **8b**: mp = 105−107 °C; ^{1}H NMR ($CDCl_3$) 8.1 (dd, 1H, J = 2.5, 9.0 Hz), 8.0 (d, 1H, J = 2.5 Hz), 7.6 (d, 1H, J = 9.0 Hz), 6.0 (bs, 2H), 2.2 (s, 3H); EIMS *m*/*e* (relative intensity) 169 (M^+, 97), 138 (100); IR (neat) υ_{max} 3325, 3259, 1587, 1492, 1480, 1336 cm^{-1}. Anal. Calcd for $C_7H_8N_2O_3$: C, 50.00; H, 4.80; N, 16.66. Found: C, 50.29; H, 4.73; N, 16.60.

(2-Chloro-4-nitrophenyl)hydroxylamine (8c). Reaction of *N*-Boc-2-chloro-4-nitrophenyl)hydroxylamine (**7c**, 11.3 g, 39 mmol) with TFA (14 mL) in CH_2Cl_2 (130 mL) gave after recrystallization from TBME/heptane 3.18 g, 43% yield, of **8c** as a light brown solid. For **8c**: mp = 120−121 °C; ^{1}H NMR (DMSO-d_6) 8.2 (m, 1H), 8.1 (m, 1H), 7.7 (d, 1H, J = 9.0 Hz), 7.6 (s, 2H); EIMS *m*/*e* (relative intensity) 187 (M^-, 97), 172 (100); IR (neat) υ_{max} 3340, 3106, 1583, 1510, 1468, 1336 cm^{-1}. Anal. Calcd for $C_6H_5ClN_2O_3$: C, 38.22; H, 2.67; N, 14.86. Found: C, 39.40; H, 2.95; N, 14.10. EIHRMS (*m*/*e*) 187.9992 (M^+) ($C_6H_5ClN_2O_3$ requires 187.9989; σ = 1.6 ppm)

(2,5-Dichloro-4-nitrophenyl)hydroxylamine (8d). Reaction of *N*-Boc-(2,5-dichloro-4-nitrophenyl)hydroxylamine (**8d**, 5.5 g, 17 mmol) with TFA (6 mL) in CH_2Cl_2 (55 mL) gave after recrystallization from TBME/heptane 1.69 g, 45% yield, of **8d** as a light brown solid. For **8d**: mp = 117−118 °C; ^{1}H NMR ($CDCl_3$) 8.1 (s, 1H), 8.0 (s, 1H), 6.2 (s, 2H); EIMS *m*/*e* (relative intensity) 206 (M^- − NH_2, 100); IR

(neat) υ_{max} 3340, 3106, 1583, 1510, 1468, 1336 cm^{-1}. Anal. Calcd for $C_6H_4Cl_2N_2O_3$: C, 32.31; H, 1.81; N, 12.56. Found: C, 32.62; H, 1.66; N, 12.39.

General Procedure for Amination of Quinazoline-2,4-diones 3 and 4 Using NaH and K_2CO_3. Preparation of Hydrazides 1 and 2. *3-Amino-1-cyclopropyl-6,7-difluoro-8-methoxy-1H-quinazoline-2,4-dione (**1**).* A slurry of cyclic imide **3** (150 g, 0.56 mol) in dioxane (1.3 L) and DMF (1.3 L) was cooled to 2 °C and treated portionwise with NaH (60% in oil, 24.8 g, 1.1 equiv; 6 portions). After gas evolution subsided, the reaction was warmed to room temperature then further warmed to 72 °C and held at that temperature for 1 h. *O*-(4-nitrophenyl)hydroxylamine (**8a**; 96.4 g, 0.63 mol, 1.1 equiv) was added in one portion (resulted in a 2 °C endotherm). After 4 h at 72 °C, additional aminating agent (17.6 g, 0.11 mol, 0.2 equiv) was introduced. After stirring for 20 h, the reaction was judged complete (TLC; 1:1 EtOAc/hexanes). The reaction mixture was concentrated in vacuo (remove dioxane and some DMF) then poured into water (950 mL) and crushed ice (950 mL) with vigorous stirring. The solid was collected and washed with water (1.5 L). The solid was reslurried in water (2 L) and filtered. The resulting solid was recrystallized from IPA (1.2 L) and heptane (1.4 L). The crystals were collected and dried to give 103 g, 65%. For **1**: mp 148−150 °C; ^{1}H NMR (DMSO-d_6) 7.7 (m, 1H), 5.5 (bs, 2H), 3.93 (s, 3H), 3.3 (m, 1H), 0.99 (m, 2H), 0.64 (m, 2H); ^{19}F NMR −141 (m), −145 (m); IR (KBr) ν_{max} 3359, 3251, 1729, 1658, 1482, 1407 cm^{-1}. Anal. Calcd for $C_{12}H_{11}F_2N_3O_3$: C, 50.89; H, 3.91; N, 14.84. Found: C, 51.40; H, 4.13; N, 14.61.

*3-Amino-1-cyclopropyl-6,7-difluoro-8-methyl-1H-quinazoline-2,4-dione (**2**).* A slurry of cyclic imide **4** (190 g, 0.754 mol) and K_2CO_3 (156 g, 1.13 mol, 1.5 equiv) in dioxane (2.1 L) and DMF (2.1 L) was warmed to 72 °C for 30 min then *O*-(4-nitrophenyl)hydroxylamine (**8a**, 122 g, 0.793 mol, 1.05 equiv) was added to the reaction mixture (an endotherm of 2 °C resulted). After 2 h at 72 °C an additional portion of aminating agent was added (12.3 g 0.08 mol, 0.1 equiv) and heating continued for 20 h at which time the reaction was judged complete (TLC, 50% EtOAc/hexanes). The reaction mixture was allowed to cool. The solids which formed were filtered and washed with THF (3 × 250 mL). The filtrate was concentrated to about 1/10 volume (ca. 500 mL) in vacuo. The concentrated solution was poured into ice (1 L) and water (1.4 L) with stirring. Crystallization of the gooey solid was initiated by adding 1 L of TBME to the mixture with continued stirring for about 15 min, which afforded a powdery beige solid. The solid was collected and washed with water (2 × 300 mL). The crude solid was recrystallized with IPA (1.5 L) and heptane (1.5 L), solid filtered off and dried (15 mmHg, rt) to give pure **2** as a light brown solid, 166 g, 83%. For **2**: mp = 163−164 °C; ^{1}H NMR (DMSO-d_6) 7.73 (t, 1H, J = 9.3 Hz), 5.4 (s, 2H), 3.4 (m, 1H), 2.6 (t, 3H, J = 3 Hz), 1.0 (m, 2H), 0.62 (m, 2H); ^{19}F NMR −129 (m), −143 (m); IR (KBr) ν_{max} 3333, 3244, 1716, 1637, 1474, 1410, 1308 cm^{-1}. Anal. Calcd for $C_{12}H_{11}F_2N_3O_2$: C, 53.93; H, 4.15; N, 15.72. Found: C, 53.72; H, 4.10; N, 15.57.

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