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Simple Synthesis of 4-Substituted 1(2*H*)-Isoquinolinones via Electrophilic Trapping of Lithiated Mono- and Dianion Precursors

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Abstract: Synthetic routes have been developed to access 4-substituted 1(2*H*)-isoquinolinones from readily available precursors. This is achieved via electrophilic trapping of di- and monolithium anions derived from alkyllithium exchange of 4-bromo-1(2*H*)-isoquinolinones and corresponding 4-bromo-1-methoxyisoquinolines, respectively. Products derived from the latter are then hydrolyzed to the target 4-substituted 1(2*H*)-isoquinolinones. The methodology has potential application to access 4-substituted 1(2*H*)-isoquinolinones with additional substituents in either ring.

Keywords: alkyllithium–halogen exchange, poly(ADP-ribose)polymerase inhibitors, 4-substituted 1(2*H*)-isoquinolinones

INTRODUCTION

As part of a program directed toward the synthesis of 1(2*H*)-isoquinolinones as inhibitors of the nuclear DNA-binding protein poly(ADP-ribose)polymerase-1 (PARP-1),[1] structure–activity studies showed that potency was increased by selected monosubstitution on the 4- or 5-position of the ring system and markedly enhanced by 4,5-disubstitution, whereas alkyl

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substitution on the N-2 position abolished activity.[2] In this article, we outline short, convenient routes to synthesize 2-unsubstituted-1(2*H*)-isoquinolinones bearing two of the favorable substitution patterns.

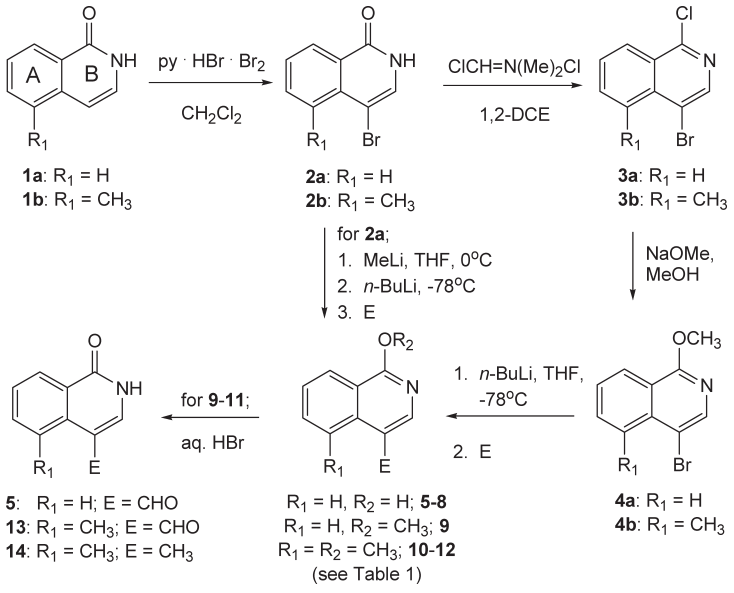
Because of the commercial availability of certain 2-unsubstituted-1(2*H*)-isoquinolinones and the ease of synthesis of various A-ring analogs,[3] we were interested in utilizing these as precursors for selective functionalization of the 4-position. Recent reviews[4] and earlier studies[5] revealed that direct nitration, Friedel–Crafts type acylation, and Vilsmeier–Haack formylation of 1(2*H*)-isoquinolinone (isocarbostyril) either does not occur or does so inefficiently, although direct bromination takes places essentially quantitatively. In contrast, a variety of electrophilic substitution reactions occur readily and in good yield on 2-alkyl congeners.[5,6] This, coupled with a report[7] wherein 2-methyl-1(2*H*)-isoquinolinone was converted in one step to 1-chloro-1(2*H*)-isoquinolinone in reasonable yield (69%), presented a potential alternative route to our target compounds. Finally, there have been sparse reports of the introduction of C-4 substitutents from 4-bromo or iodo precursors via palladium-catalyzed chemistry (Suzuki and Stille reactions).[8] There are no reports in which such functionalization has been carried out via simple carbanion chemistry. Thus, we embarked on a study of the reaction of lithiated species, derived from alkyllithium exchange of 4-bromo-1(2*H*)-isoquinolinones (and corresponding 4-bromo-1-methoxyisoquinolines), with representative common electrophiles.

RESULTS AND DISCUSSION

The routes utilized to generate our targeted 4-substituted 1(2*H*)-isoquinolinones are shown in Scheme 1.

Initial studies to develop our chemistry were carried out on isocarbostyril (**1a**). Reaction of this with pyridinium bromide perbromide cleanly gave the 4-bromo adduct (**2a**)[2,5,9] in 80% yield. The generation of the lithiated dianion of **2a** was evaluated under a number of conditions. Initially, we encountered difficulties in generating a clean dianion at -78°C in THF (as determined by quenching experiments) when utilizing 2.2 eq of *n*-butyllithium. This suggested that the rate of metal–halogen exchange was competitive with that of lactam proton abstraction, leading to self-quenching. Thus, we carried out a stepwise addition of first 1 equivalent of methyllithium to selectively deprotonate the lactam, followed by two equivalents of *n*-butyllithium for metal–halogen exchange. Trapping the resultant dilithiated species with representative common electrophiles followed by standard workup provided the 4-substituted products in good to excellent isolated yields (Table 1; compounds **5**–**8**). It was important in this and subsequent studies that the THF utilized in all anion chemistry be scrupulously dry.

An attempt was then made to extend the dianion methodology to an A-ring substituted 1(2*H*)-isoquinolinone. Thus, 4-bromo-5-methyl-1



Scheme 1.

(2*H*)-isoquinolinone (**2b**), synthesized from **1b**[3] as described previously, was treated under a variety of lithiation conditions (methyllithium and then *n*-butyl- or *t*-butyllithium) followed by treatment with DMF or iodomethane. This resulted in substantial amounts of quenched anion after workup (i.e., Br exchanges for H in **2b**). To address this problem, we decided to utilize a workaround strategy by masking the lactam function as a lactim so that less challenging monolithiation could be achieved. Accordingly, conversion of **2b** to the 1-methoxy ether **4b** was carried out in a standard two-step process in 68% yield. Treatment of **4b** with *n*-butyllithium resulted in clean

Table 1. Products of electrophilic trapping of lithiated mono- and di-anions

Starting material	Electrophile	Product	E	Yield (%)
2a	DMF	**5**	CHO	82
2a	CO_2	**6**	CO_2H	52
2a	CH_3I	**7**	CH_3	73
2a	$(CH_3S)_2$	**8**	SCH_3	56
4a	$PhN(CH_3)CHO$	**9**	CHO	66
4b	DMF	**10**	CHO	86
4b	CH_3I	**11**	CH_3	79
4b	$(CH_3S)_2$	**12**	SCH_3	35

lithium–halogen exchange to give the mono anion. Reaction of this was carried out with representative electrophiles to provide products in moderate to excellent isolated yields (compounds **10**–**12** in Table 1). This methodology was also applied to a single example of a 5-unsubstituted lactim (compound **9**, Table 1). Aqueous HBr hydrolysis of representative lactims (compounds **9**–**11** of Table 1) provided target 4-substituted 1(2*H*)-isoquinolinones (**5**, **13**, **14**, respectively, of Scheme 1) in 52–88% yields.

When tested in vitro in an assay utilizing PARP prepared from calf thymus,[10] the 4- and 4,5-substituted 1(2*H*)-isoquinolinones reported in this article were found to be potent inhibitors of the enzyme with $IC_{50} = 0.02–0.31$ μM.

In conclusion, we have developed simple routes to 4-substituted 1(2*H*)-isoquinolinones from readily available precursors. Yields ranged from modest to excellent for the electrophilic trapping of mono- and dilithium carbanions. Yields have not been optimized except for representative examples from both routes that were developed to a modest scale. The methodology has potential application to access 4-substituted 1(2*H*)-isoquinolinones with additional substituents in either ring.

EXPERIMENTAL

Melting points were taken on a Thomas-Hoover Unimelt capillary melting-point apparatus and are uncorrected. NMR spectra were obtained on a Bruker AM-250 spectrometer (^{1}H) and a Varian Unity 400 spectrometer (^{1}H, ^{13}C). Chemical shifts are reported as δ (ppm) values downfield from internal TMS. The following abbreviations are used to describe peak patterns when appropriate: br = broad, s = singlet, d = doublet, t = triplet. Combustion analyses were determined on a CEC 440 elemental analyzer or by Robertson Microlit Laboratories, Inc., Madison, N.J. Column chromatography was carried out in the flash mode utilizing Merck 230–400-mesh SiO_2. Analytical thin-layer chromatography (TLC) was carried out on Merck (Kiesegel 60F-254) silica-gel plates with detection by UV light. All reaction solvents were reagent grade or distilled in glass. THF utilized in lithiation reactions was freshly distilled over lithium aluminium hydride (LAH). Following normal workup procedures, organic extracts were dried over anhydrous $MgSO_4$ or Na_2SO_4 prior to concentration. All lithiation reactions were run under a positive pressure of dry N_2.

General Procedure

4-Bromo-1(2*H*)-isoquinolinone (**2a**)

A stirred mixture of 50 g (334 mmol) of isocarbostyril (**1a**) in 1 L of dichloromethane at 25°C was treated with 121. 4 g (342 mmol) of 90% pyridinium

bromide perbromide. After ca. 20 min, a suspension began to form, and after 3 h, TLC (SiO_2; 6:5 EtOAc–cyclohexane) showed complete reaction. The suspension was filtered, and the solids were washed with CH_2Cl_2. The filtrate was diluted carefully with 5% aqueous $NaHCO_3$ saturated with Na_2SO_3, which caused immediate precipitation of additional solids. The solids were filtered off, combined with the others, and recrystallized from DMF to provide 61.2 g (80%) of analytically pure **2a**, mp 247–249°C (lit.[2] 245–250°C; lit.[5] 247–248°C; lit.[9] 248–249°C), in two crops. The ^{1}H NMR was the same as previously reported.[5]

4-Bromo-5-methyl-1(2*H*)-isoquinolinone (**2b**)

Reaction was performed on 20 g (126 mmol) of 5-methyl-1(2*H*)-isoquinolinone (**1b**)[3] and 60 g (169 mmol) of 90% pyridinium bromide perbromide overnight followed by workup as described previously to give 17.8 g (59%) of **2b**, mp 207–209°C, in two crops. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.59 (br s, 1H, D_2O exchangeable), 8.21 (dd, $J = 8$ Hz, 1 Hz, 1H), 7.61 (dd, $J = 8$ Hz, 1 Hz, 1H), 7.48 (s, 1H), 7.45 (t, $J = 7.6$ Hz, 1H), 2.89 (s, 3H). Anal. calcd. for $C_{10}H_8BrNO$: C, 50.45; H, 3.39; N, 5.88. Found: C, 50.60; H, 3.43; N, 5.93.

4-Bromo-1-chloroisoquinoline (**3a**)

Fresh Vilsmeier's reagent was prepared as follows: A 0°C solution of 47 mL (604 mmol) of DMF in 350 mL of 1,2-dichloroethane was treated dropwise over 1 h with 52.7 mL (604 mmol) of oxalyl chloride. The viscous suspension was stirred at 25°C for 10 min, and then 61.2 g (273 mmol) of 4-bromo-1(2*H*)-isoquinolinone (**2a**) was added to the reagent as a solid. The suspension was heated at 80°C for 1 h, cooled, and diluted with CH_2Cl_2. The solution was washed with H_2O, dried, and concentrated to afford 65.4 g (99%) of a pale yellow solid, mp 95–98°C. A small sample was crystallized from isopropyl ether to give an analytical sample of **3a**, mp 97–98°C. The ^{1}H NMR was identical to that previously reported.[11] Anal. calcd. for C_9H_5NBrCl: C, 44.58; H, 2.08; N, 5.78; Br, 32.95; Cl, 14.62. Found: C, 44.54; H, 1.72; N, 5.64; Br, 32.74; Cl, 14.53.

4-Bromo-1-chloro-5-methyl-isoquinoline (**3b**)

Reaction of 38.7 g (163 mmol) of 4-bromo-5-methyl-1(2*H*)-isoquinolinone (**2b**) with Vilsmeier's reagent for 3 h followed by workup as described previously gave 32.2 g (77%) of **3b**, mp 128–131°C, following trituration from 1:1 diethyl ether–petroleum ether. The product was used directly in the next step.

4-Bromo-1-methoxyisoquinoline (**4a**)

A mixture of 65.4 g (270 mmol) of 4-bromo-1-chloroisoquinoline (**3a**), 27.75 g (488 mmol) of 95% NaOMe, and 550 mL of anhydrous MeOH was stirred at reflux for 16 h at which time TLC (three elutions with 10:1 ether–hexanes) showed no starting material. The suspension was concentrated to a residue that was diluted with H_2O and extracted with $CHCl_3$. The combined organic extracts were dried and concentrated to a viscous oil that solidified upon standing. Crystallization from EtOH afforded 59 g (92%) of **4a**, mp 53–55°C, in four crops. The ^{1}H NMR spectrum was identical to that previously reported.[12] Anal. calcd. for $C_{10}H_8NOBr$: C, 50.45; H, 3.39; N, 5.88; Br, 33.56. Found: C, 50.43; H, 3.30; N, 5.70; Br, 33.54.

4-Bromo-1-methoxy-5-methylisoquinoline (**4b**)

Reaction of 46.5 g (181 mmol) of 4-bromo-1-chloro-5-methylisoquinoline (**3b**) with 2.5 equiv. of NaOMe for 3 h followed by workup as described previosly gave a viscous oil that slowly crystallized. Filtration of the solids followed by washing with cold isopropyl ether gave 40.4 g (88%) of **4b**, mp 55–58°C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 8.28–8.13 (m, 2H), 7.58–7.38 (m, 2H), 4.09 (s, 3H), 3.05 (s, 3H). Anal. calcd. for $C_{11}H_{10}NOBr$: C, 52.41; H, 4.00; N, 5.56; Br, 31.70. Found: C, 52.80; H, 4.06; N, 5.68; Br, 31.76.

4-Substituted 1(2*H*)-Isoquinolinones via Lithiated Dianions (General Procedure)

1,2-Dihydro-1-oxo-4-isoquinolinecarboxaldehyde (**5**)

A 0°C suspension of 15 g (67 mmol) of 4-bromo-1(2*H*)-isoquinolinone (**2a**) in 600 mL of THF was charged with 54 mL (75.6 mmol, 1.13 equiv) of MeLi (1.4 M in diethyl ether). The resultant solution was stirred for 10 min, cooled to −78°C, and treated with 85.5 mL (136.8 mmol, 2 equiv) of *n*-BuLi (1.6 M in hexanes). After stirring for 30 min, the solution was treated with 15 mL (194 mmol, 2.9 equiv) of DMF. The solution was maintained at −78 0°C for 1 h and then quenched with sat. aqueous NH_4Cl. The mixture was slowly warmed to 25°C, diluted with H_2O, and extracted with CH_2Cl_2 (3×). The combined extracts were washed with H_2O, dried, and concentrated to a solid that was crystallized from EtOH to provide 9.55 g (82%) of **5**, mp 235–238°C (lit.[13] 222–223°C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.25 (br s, 1H, D_2O exchangeable), 9.78 (s, 1H), 8.97 (d, $J = 8.2$ Hz, 1H), 8.27 (d, $J = 8.0$ Hz, 1H), 8.17 (s, 1H), 7.85 (t, $J = 7.7$ Hz, 1H), 7.62 (t, $J = 8.1$ Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 190.3, 162.2, 147.4, 134.1, 133.8, 128.0, 127.5, 125.1, 124.6, 114.1. Anal. calcd. for $C_{10}H_7NO_2$: C, 69.36; H, 4.07; N, 8.09. Found: C, 69.22; H, 4.00; N, 8.00.

1,2-Dihydro-1-oxo-4-isoquinolinecarboxylic acid (**6**)

Reaction of the dianion formed from 223 mg (1 mmol) of **2a** as discussed previously was followed by trapping with excess dry CO_2. Following the NH_4Cl quench and dilution with H_2O, the aqueous layer was extracted with $CHCl_3$ to remove organic impurities and then acidified to pH 2 with aqueous HCl. The formed precipitate was collected by filtration, washed with H_2O, and dried to leave 146 mg (73%) of **6**, mp $> 250^\circ$C (lit.[14] 296–297°C dec). ^{1}H NMR (DMSO-d_6, 250 MHz): δ 12.68 (br s, 1H, D_2O exchangeable), δ 11.85 (br s, 1H, D_2O exchangeable), 8.83 (d, $J = 8.3$ Hz, 1H), 8.23 (d, $J = 7.8$ Hz, 1H), 8.04 (s, 1H), 7.76 (t, $J = 7.5$ Hz, 1H), 7.52 (t, $J = 7.5$ Hz, 1H). Anal. calcd. for $C_{10}H_7NO_3 \cdot 0.6H_2O$: C, 60.06; H, 4.13; N, 7.00. Found: C, 59.66; H, 3.76; N, 7.25.

4-Methyl-1(2*H*)-isoquinolinone (**7**)

Following the general procedure, reaction of 223 mg (1 mmol) of **2a** with 3 equiv. of CH_3I provided 84 mg (52%) of **7**, mp 170–172°C, following crystallization from EtOAc–hexanes. The ^{1}H NMR was identical to that previously reported.[15] Anal. calcd. for $C_{10}H_9NO \cdot 0.1\ H_2O$: C, 74.61; H, 5.76; N, 8.70. Found: C, 74.68; H, 5.53; N, 8.74.

4-(Methylthio)-1(2*H*)-isoquinolinone (**8**)

Following the general procedure, reaction of 223 mg (1 mmol) of **2a** provided 107 mg (56%) of **8**, mp 170–172°C, following trituration from 2-PrOH. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 11.45 (br s, 1H, D_2O exchangeable), 8.42 (d, $J = 8.0$ Hz, 1H), 8.12 (d, $J = 8.0$ Hz, 1H), 7.85–7.73 (m, 1H), 7.61–7.48 (m, 1H), 7.46 (s, 1H), 2.33 (s, 1H). Anal. calcd. for $C_{10}H_9NOS$: C, 62.80; H, 4.74; N, 7.32. Found: C, 63.06; H, 4.61; N, 6.93.

4-Substituted 1-Methoxyisoquinolinones via Lithiated monoanions (General Procedure)

1-Methoxy-4-isoquinolinecarboxaldehyde (**9**)

A -78°C solution of 30 g (126 mmol) of 4-bromo-1-methoxyisoquinoline (**4a**) in 230 mL of THF was charged slowly with 86.6 mL (139 mmol, 1.1 equiv) of *n*-BuLi (1.6 M in hexanes). The resultant yellow suspension was stirred for 35 min and then treated with 15.7 mL (127 mmol) of *N*-methylformanilide. After stirring for 30 min at -78°C, the cold mixture was quenched with 80 mL of H_2O. The mixture was concentrated and extracted with $CHCl_3$ (3×). The combined extracts were washed with H_2O, dried, and concentrated to a yellow oil that solidified on standing. Crystallization from isopropyl ether

afforded 15.6 g (66%) of **9**, mp 83–85°C. A small sample was sublimed at 65°C/0.01 mm to provide analytical material, mp 87–89°C. ^{1}H NMR (DMSO-d_6, 250 MHz): δ 10.18 (s, 1H), 9.05 (d, $J = 8.4$ Hz, 1H), 8.67 (s, 1H), 8.26 (d, $J = 8.0$ Hz, 1H), 7.94 (dt, $J = 7.5$ Hz, 1.1 Hz, 1H), 7.74 (t, $J = 7.5$ Hz, 1H), 4.18 (s, 3H). Anal. calcd. for $C_{11}H_9NO_2$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.50; H, 4.80; N, 7.44.

1-Methoxy-5-methyl-4-isoquinolinecarboxaldehyde (**10**)

Following the general procedure, 12.6 g (50 mmol) of 4-bromo-1-methoxy-5-methylisoquinoline (**4b**) in 250 mL of THF was with treated with 1.2 equiv. of *n*-BuLi and then 2.4 equiv. of DMF. After slowly warming to 10°C over 1 h, the mixture was cooled to −50°C and further processed as described previously to leave an oil that solidified. Crystallization from isopropyl ether gave 8.7 g (86%) of **10**, mp 87–89°C. A small sample was sublimed at 60°C/0.5 mm to provide analytical material, mp 93–95°C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 10.67 (s, 1H), 8.51 (s, 1H), 8.24 (d, $J = 5.0$ Hz, 1H), 7.63 (d, $J = 6.8$ Hz, 1H), 7.52 (t, $J = 7.7$ Hz, 1H), 4.20 (s, 3H), 2.76 (s, 3H). Anal. calcd. for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.66; H, 5.48; N, 7.01.

4,5-Dimethyl-1-methoxyisoquinoline (**11**)

Following the general procedure, the anion derived from 2 g (7.9 mmol) of **4b** was treated with 3 equiv. of CH_3I. Further processing as described previously left a brown oil that was purified by column chromatography eluting with hexanes–EtOAc (97:3). Concentration of product fractions followed by molecular distillation afforded 1.18 g (79%) of **11**, bp 70°C/0.1 mm. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 8.17 (d, $J = 8.0$ Hz, 1H), 7.75 (s, 1H), 7.53–7.28 (m, 2H), 4.08 (s, 3H), 2.87 (s, 3H), 2.71 (s, 3H). Anal. calcd. for $C_{12}H_{13}NO \cdot 0.1H_2O$: C, 76.24; H, 7.04; N, 7.41. Found: C, 76.13; H, 7.03; N, 7.57.

1-Methoxy-5-methyl-4-(methylthio)isoquinoline (**12**)

Following the general procedure, the anion derived from 3 g (11.9 mmol) of **4b** was treated with 2.5 equiv. of methyl disulfide. Workup and chromatography as discussed previously gave an oil that solidified on standing. Trituration in isopropyl ether afforded 921 mg (35%) of **12**, mp 39–41°C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 8.19 (d, $J = 8.0$ Hz, 1H), 8.08 (s, 1H), 7.53–7.35 (m, 2H), 4.10 (s, 3H), 3.09 (s, 3H), 2.44 (s, 3H). Anal. calcd. for $C_{12}H_{13}NOS$: C, 65.72; H, 5.97; N, 6.39; S, 14.62. Found: C, 65.59; H, 5.97; N, 6.38; S, 14.78.

Hydrolysis of 4-Substituted 1-Methoxyisoquinolines (General Procedure)

1,2-Dihydro-5-methyl-1-oxo-4-isoquinolinecarboxaldehyde (**13**)

A suspension of 23.85 g (118.5 mmol) of 1-methoxy-5-methyl-4-isoquinolinecarboxaldehyde (**10**) and 150 mL of 20% HBr was stirred at 25°C overnight, and then poured into 780 mL of cold H_2O. After stirring for 3 h, the solids were collected and then washed successively with H_2O, MeOH, and diethyl ether. Crystallization from MeOH afforded 12.6 g (55%) of **13**, mp 231–233°C. ^{1}H NMR (DMSO-d_6, 250 MHz): δ 12.13 (br s, 1H, D_2O exchangeable), 9.98 (s, 1H), 8.14 (d, $J = 7.7$ Hz, 1H), 8.00 (s, 1H), 7.66 (d, $J = 7.3$ Hz, 1H), 7.51 (t, $J = 7.5$ Hz, 1H), 2.54 (s, 3H). Anal. calcd. for $C_{11}H_9NO_2 \cdot 0.3\ H_2O$: C, 68.60; H, 5.02; N, 7.27. Found: C, 68.56; H, 4.66; N, 7.27.

4,5-Dimethyl-1(2*H*)-isoquinolinone (**14**)

Reaction of 5.6 g (30 mmol) of 4,5-dimethyl-1-methoxy-4,5-isoquinoline (**11**) with 40 mL of 48% HBr for 6 h at 80°C followed by workup as described previously and crystallization from EtOH gave 2.7 g (52%) of **14**, mp 237–239°C. ^{1}H NMR ($CDCl_3$ + DMSO-d_6, 250 MHz): δ 10.88 (br s, 1H, D_2O exchangeable), 8.36 (d, $J = 7.8$ Hz, 1H), 7.45 (d, $J = 7.0$ Hz, 1H), 7.42–7.31 (m, 1H), 6.84 (s, 1H), 2.79 (s, 3H), 2.50 (s, 3H). Anal. calcd. for $C_{11}H_{11}NO$: C, 76.28; H, 6.40; N, 8.09. Found: C, 76.58; H, 6.63; N, 7.87.

1,2-Dihydro-1-oxo-4-isoquinolinecarboxaldehyde (**5**)

Reaction of 5 g (26.7 mmol) of 1-methoxy-4-isoquinolinecarboxaldehyde (**9**) and 50 mL of 48% HBr for 16 h at 25°C followed by workup as described previously provided solids that were boiled in 100 mL of H_2O for 4 h. The solids were collected and dried to leave 4.1 g (88%) of **5**, identical to that reported previously.

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