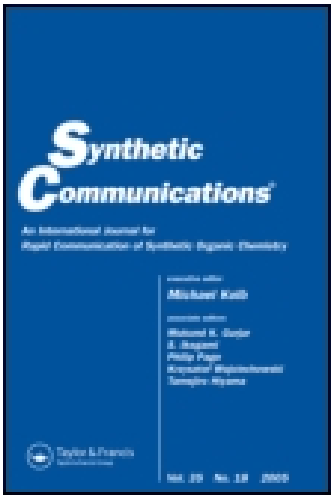

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Novel Approach to 3-Methyl-1H-quinoxalin-2-ones

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Abstract: A novel approach to the synthesis of 3-methyl-1H-quinoxalin-2-ones has been described. These compounds were regioselectively prepared by starting from substituted phenylamines and α-chloropropionyl chloride through the efficient procedures of acylation, nitration, reduction, intramolecular alkylation, and oxidation.

Keywords: α-Chloropropionyl chloride, 3-methyl-1H-quinoxalin-2-ones, regioselective synthesis, substituted phenylamine

3-Methyl-1H-quinoxalin-2-ones have been postulated as important intermediates for the synthesis of various useful heterocyclic compounds.[1−3]Hence, preparation of 3-methyl-1H-quinoxalin-2-ones **6** has attracted considerable attention in recent years.

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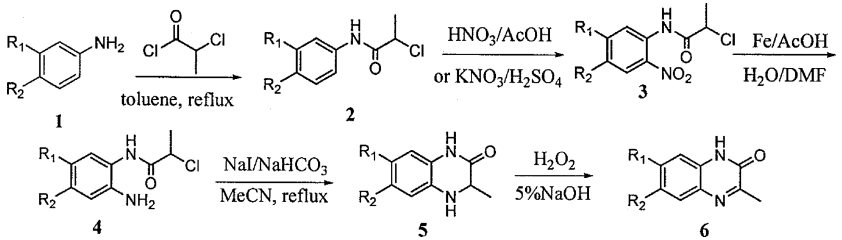
These compounds are generally prepared by the condensation of *o*-phenylene-diamine with pyruvic acid, but multiple of by-products are obtained when asymmetrical diamines were used as starting materials.[4] in addition, these compounds also can be obtained by some other regioselective methods,[5–7] however, there are issues associated with each approach.

Makino et al. reported the synthesis of 3-methyl-quinoxalin-2-ones **6** in 1985, which involved C-methylation of quinoxalin-2-ones to give the target compound.[5]

Van Dusen and Schultz [6] reported the synthesis of 3-methyl-6- and -7-bromo-2-quinoxalinols, which involved condensation of *dl*-α-alanine with 2,5-dibromonitrobenzene, followed by reductive cyclization with alcoholic hydrochloric acid and iron in the presence of a Raney nickel catalyst, and subsequent oxidation with basic hydrogen peroxide solution gave the desired product. Yet these reactions either had long tedious routes, and low yields or were not easily executed, which limited their applications. Therefore, alternative regioselective methods need to be developed for the preparation of a wide variety of the 3-methyl-1H-quinoxalin-2-one derivatives. However, a review of the literature revealed that no effectively regioselective synthesis of 3-methyl-quinoxalin-2-ones **6** or its substituted analogue has been published.

We have reported our preliminary investigation concerning the syntheses of 6,7-disubstituted-1H-quinoxalin-2-ones.[8] We expected to expand its application to an efficient and practical route for the synthesis of 3-methyl-1H-quinoxalin-2-ones **6**. We chose commercially available substituted phenylamines and α-chloropropionyl chloride as the starting materials for efficient procedures of acylation, nitration, reduction, intramolecular alkylation, and oxidation (see Scheme 1). Compared with the other reactions, the conditions of these reactions were mild, easily executed, and more regioselective.

Reaction of substituted phenylamines with α-chloropropionyl chloride in toluene under refluxing afforded acetamide **2** in almost quantitative yield and the hydrogen chloride generated in the reaction was absorbed in another flask containing sodium hydroxide solution. Acetamide **2** was nitrated by KNO_3/H_2SO_4 or mild nitrating reagent HNO_3/CH_3COOH according to the substituted groups of benzene ring to give single o-nitroacetamide 3 in 80–93%



Scheme 1.

yield. **3** was quantitatively transferred to **4** within 15 min by ferrous powder reduction in 50–70% yield. Other reductive methods such as hydrazine hydrate in the presence of an iron oxide/hydroxide catalyst,[9] Zn/NH_4Cl,[10] Pd-C/H_2,[11] $SnCI_2$,[12] and so on were less efficient. The optimum experimental conditions have been developed, and N,N-dimethylformamide was chosen as solvent to improve dissolution of **3** in a ferrous powder reductive suspension, which could increase reaction efficiency. In addition, mild reaction temperature was used to decrease the dechlorinating by-products. Subsequent intramolecular cyclization of **4** in the presence of sodium iodide and sodium bicarbonate gave substituted 3-methyl-3,4-dihydro-lH-quinoxalin-2-one **5** in 51–62% yield separated by column chromatography on silica gel. Sodium iodide was used as a catalyst to promote the nucleophilic substitution reaction. **5** was readily transformed to the corresponding 3-methyl-lH-quinoxalin-2-ones **6** by treatment with hydrogen peroxide in 5% NaOH solution in 51–86% yield. The desired compounds have been fully characterized by IR, ^{1}H NMR, MS, and elemental analysis and the analytical results are shown in Table 1 and Table 2.

In summary, we have developed an efficient five-step synthesis of 3-methyl-1H-quinoxalin-2-ones **6** from substituted phenylamines, which overcomes the limitations of previous syntheses. Moreover, the new procedure is simple, inexpensive, and regioselective, and gives good yield. This convenient method can be a useful method to obtain more series of such compounds.

EXPERIMENTAL

Melting points were determined on an X-6 type digital apparatus, and are uncorrected. Elemental analyses were carried out on a Perkin-Elmer

Table 1. Synthesis of 3-methyl-1H-quinoxalin-2-ones

Product	R_1	R_2	Mp (°C)	Total yield (%)
6a	H	CH_3	257–258	34
6b	H	C_4H_9	162–163	27
6c	H	CH_3O	253–254	31
6d	H	C_2H_5O	237–238	28
6e	Me	Me	276–277	39
6f	H	Cl	263–264	24
6g	H	Br	256–257	33
6h	H	F	273–274	37
6i	Cl	CH_3	292–293 dec.	12
6j	Cl	F	328–329 dec.	39
6k	F	F	318–319 dec.	41

Note: **6a**–**6e**: nitrated with HNO_3/AcOH; **6f**–**6k**: nitrated with KNO_3/H_2SO_4.

Table 2. Characteriztion of substituted 3-methyl-1H-quinoxalin-2-ones, **6a–k** prepared

No.	Molecular formula	Elemental analysis (C% H% N%) calculated; found	ESI-MS (m/z)	IR (KBr, cm^{-1})	HPLC (%)	^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm)
6a	$C_{10}H_{10}N_2O$ (174)	68.97, 5.75, 16.09; 68.91, 5.89, 16.26	173.8 $[M-H]^+$	1668.2 (CO) 1504.6 (CN) 588.6 (CH)	99.6	2.35 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 7.16 (d, 1H, $J = 8.4$, ArH), 7.27–7.29 (m, 1H, ArH), 7.48 (s, 1H, ArH), 12.19 (s, 1H, NH).
6b	$C_{13}H_{16}N_2O$ (216)	72.22, 7.41, 12.96; 72.00, 7.50, 13.08	216.2 $[M-H]^+$	1663.4 (CO) 1499.6 (CN) 590.5 (CH)	98.3	0.86–0.90 (m, 3H, CH_3), 1.24–1.33 (m, 2H, CH_2), 1.52–1.59 (m, 2H, CH_2), 2.37 (s, 3H, CH_3), 2.50–2.64 (m, 2H, CH_2), 7.17 (d, 1H, $J = 8.4$, ArH), 7.28–7.30 (m, 1H, ArH), 7.47 (d, 1H, $J = 1.2$, ArH), 12.20 (s, 1H, NH).
6c	$C_{10}H_{10}N_2O_2$ (190)	63.16, 5.26, 14.74; 2.92, 5.64, 14.91	189.7 $[M-H]^+$	1667.8 (CO) 1490.2 (CN) 593.6 (CH)	95.8	2.38 (s, 3H, CH_3), 3.79 (s, 3H, CH_3), 7.09–7.12 (m, 1H, ArH), 7.18–7.21 (m, 2H, ArH), 12.17 (s, 1H, NH).
6d	$C_{11}H_{12}N_2O_2$ (204)	64.71, 5.88, 13.73; 64.99, 5.81, 13.60	204.1 $[M-H]^+$	1669.9 (CO) 1506.1 (CN) 593.6 (CH)	96.9	1.31–1.34 (m, 3H, CH_3), 2.38 (s, 3H, CH_3), 4.02–4.07 (m, 2H, CH_2), 7.08–7.10 (m, 1H, ArH), 7.17–7.19 (m, 2H, ArH), 12.16 (s, 1H, NH).

6e	$C_{11}H_{12}N_2O$ (188)	70.21, 13.64, 14.89; 70.37, 13.49, 14.91	188.4 $[M-H]^+$	1659.6 (CO) 1559.8 (CN) 592.7 (CH)	98.6	2.26–2.30 (m, 6H, CH_3), 2.35 (s, 3H, CH_3), 7.01 (s, 1H, ArH), 7.45 (s, 1H, ArH), 12.33 (s, 1H, NH).
6f	$C_9H_7N_2OCl$ (194.5)	55.53, 3.60, 14.40; 55.66, 3.65, 14.29	195.3 $[M-H]^+$	1664.9 (CO) 1492.2 (CN) 590.6 (CH)	99.3	2.37 (s, 3H, CH_3), 7.23 (d, $J = 9.2$ Hz, 1H, ArH), 7.44–7.47 (m, 1H, ArH), 7.65 (d, $J = 2.4$ Hz, 1H, ArH), 12.33 (s, 1H, NH).
6g	$C_9H_7N_2OBr$ (239)	45.19, 2.93, 11.72; 45.30, 2.89, 11.71	239.3 $[M-H]^+$	1664.6 (CO) 1496.2 (CN) 587.5 (CH)	99.1	2.40 (s, 3H, CH_3), 7.21 (d, $J = 8.8$ Hz, 1H, ArH), 7.60–7.63 (m, 1H, ArH), 7.86 (d, $J = 2.4$ Hz, 1H, ArH), 12.37 (s, 1H, NH).
6h	$C_9H_7N_2OF$ (178)	60.67, 3.93, 15.73; 60.55, 3.99, 15.86	177.8 $[M-H]^+$	1676.1 (CO) 1490.7 (CN) 593.6 (CH)	96.4	2.38 (s, 3H, CH_3), 7.26–7.37 (m, 2H, ArH), 7.48 (d, $J = 9.2$ Hz, 1H, ArH), 12.34 (s, 1H, NH).
6i	$C_9H_6N_2OF_2$ (196)	55.10, 3.06, 14.29; 55.28, 3.15, 14.19	196.1 $[M-H]^+$	1668.9 (CO) 1488.7 (CN) 595.7 (CH)	95.7	2.34 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 7.24 (s, 1H, ArH), 7.63 (s, 1H, ArH), 12.19 (s, 1H, NH).
6j	$C_9H_6N_2$-OFCl (212.5)	50.82, 2.82, 13.18; 50.68, 3.09, 13.35	212.8 $[M-H]^+$	1666.9 (CO) 1486.6 (CN) 588.6 (CH)	97.4	2.38 (s, 3H, CH_3), 7.33 (d, $J = 6.8$ Hz, 1H, ArH), 7.71 (d, $J = 9.6$ Hz, 1H, ArH), 12.34 (s, 1H, NH).
6k	$C_{10}H_9N_2OCl$ (208.5)	57.55, 4.32, 13.43; 57.74, 4.41, 13.28	208.9 $[M-H]^+$	1672.7 (CO) 1514.7 (CN) 592.1 (CH)	98.9	2.38 (s, 3H, CH_3), 7.12–7.16 (q, 1H, ArH), 7.72–7.77 (q, 1H, ArH), 12.34 (s, 1H, NH).

C, H, and N elemental analyzer. Low-resolution electron-ionization (EI) mass spectra were obtained from an API4000 instrument using fast atom bombardment (FAB) as ionization mode with meta-nitrobenzyl alcohol (NBA) as a matrix support. Infrared spectra (IR) were measured on Nicolet Nexus 470 FT infrared spectrophotometer in the range of 4000–400 cm^{-1}, and the solid products and were palletized in KBr. All ^1H NMR spectra were recorded on a Bruker AMX-400 spectrometer and were referenced to TMS (Me_4Si) as an internal standard; chemical shifts (δ) are listed in ppm against deuterated solvent peaks as an internal reference. Coupling constants (J) are reported in hertz, and the abbreviations for splitting include the following: s, single; d, doublet; t, triplet; q, quartet; m, multiplet. The purity of compounds was >95% as determined by HPLC analysis using an analytical C_{18} reversed-phase column. Flash chromatography was performed using 200–300-mesh silica gel and the solvent system indicated in the procedure. All reactions except those in aqueous media were carried out by standard techniques for the exclusion of moisture. Reaction courses and product mixtures were routinely monitored by thin-layer chromatography (TLC) on silica gel (precoated GF254 plates). Visualization on TLC was achieved using UV light, iodine vapor, $KMnO_4$, triketohydrindene hydrate, and/or 5% phosphomolybdic acid in 95% ethanol. Toluene and tetrahydrofuran were used freshly distilled from sodium benzophenone. Other chemicals and solvents purchased commercially were reagent grade and were purified according to the standard procedures before use.

Typical procedures for the synthesis of 6-chloro-3-methylquinoxalin-2(1H)-one (**6f**) was as follows.

2-Chloro-N-(4-chlorophenyl)acetamide (2f): A stirred solution of p-chloroaniline (l0 mmol) in toluene (20 mL) was treated with α-chloropropionyl chloride (12 mmol). After refluxing for 1 h, the reaction mixture was allowed to cool down to room temperature. The solvent was removed under vacuum and the residue was recrystallized from an ethyl acetate–petroleum ether (1:2) mixture to afford the product as white crystal. Yield 99%, mp 175–176°C. ^1H NMR (DMSO-d_6) δ 3.28 (s, 3H, CH_3), 4.24 (m, 1H, CH), 7.38 (d, 2H, $J = 8.8$Hz, ArH), 7.61 (d, 2H, $J = 8.8$ Hz, ArH), 10.39 (s, 1H, NH). Elemental analyses calculated for $C_8H_7NOCl_2$: C, 47.06; H, 3.43; N, 6.86. Found: C, 47.87; H, 2.99; N, 6.93. ESI-MS: m/z (rel intensity) 203.3 $[M\text{-}H]^+$.

2-Chloro-N-(4-chloro-2-nitrophenyl)propanamide (3f): Concentrated nitric acid (1 mL) was added to the solution of **2f**(4.2-mmol) in acetic acid (5 mL) and water (2 mL) (or a stirred solution of **2f** in concentrated sulfuric acid was treated with 1.05 equiv of potassium nitrate). About 5 min later, concentrated sulfuric acid (6.3 mmol) was added dropwise within 20 min at 0°C, and then stirred for another 1 h at room temperature. The resulting yellow-brown solution was poured into crushed ice (50 g). The resultant solid was collected

by filtration and then washed successively with water (3 × 10 mL) to afford the crude product **3f** as a pale yellow solid, which was purified by recrystallization from methanol and dried under vacuum. Yield 86%, mp 137–138°C. ^{1}H NMR (DMSO-d_6) δ 2.09 (s, 3H, CH_3), 4.53 (m, 1H, CH), 7.77–7.83 (m, 2H, ArH), 8.09 (d, 1H, J = 2.0 Hz, ArH), 10.72 (s, 1H, NH). Elemental analyses calculated for $C_8H_6N_2O_3Cl_2$: C, 38.55; H, 2.41; N, 11.24. Found: C, 39.46; H, 2.52; N, 10.66. ESI-MS: m/z (rel intensity) 248.1 $[M-H]^+$.

N-(2-Amino-4-chlorophenyl)-2-chloropropanamide (4f): A mixture of reductive ferrous powder (2.0 g, 35.7 mmo1), ammonium chloride (0.1 g, 1.9 mmol), and acetic acid (0.5 mL, 8.7 mmol) in water (30 mL) was vigorously stirred with a mechanical stirrer at 50°C for 10–15 min. To this reaction mixture, a solution of **3f** (4 mmol) in dimethylformamide (10 mL) was added. After the reaction was over (monitored by TLC, about 15 min), the mixture was basified to pH = 8–9 by the addition of 10% aqueous sodium carbonate. The resulting slurry was filtered, and the residue was washed with water (2 × 20 mL) and ethyl acetate (2 × 30 mL) successively. After the washings, the organic materials were separated and the aqueous phase was extracted three times with ethyl acetate (3 × 10 mL). The combined organic extracts were washed successively with water (3 × 25 mL) and brine (25 mL), and dried over anhydrous sodium sulfate. After removal of the solvent, the crude product was dried under reduced pressure and purified by flash chromatograsphy (ethyl acetate–petroleum ether = 2:3 to 3:2, v/v) to give **4f** as brown solid. It is noteworthy that the amino product is sensitive to oxygen in open air, so it should be used immediately for the next procedure after purification. Yield 56%, mp 157–158°C. ^{1}H NMR (DMSO-d_6) δ 1.07 (s, 3H, CH_3), 2.34 (m, 1H, CH), 5.29 (s, 2H, CH_2), 6.89 (s, 1H, ArH), 7.33 (s, 1H, ArH), 7.54 (s, 1H, ArH), 9.02 (s, 1H, NH). Elemental analyses calculated for $C_8H_8N_2OCl_2$: C, 43.84; H, 3.65; N, 12.79. Found: C, 44.35; H, 3.09; N, 12.14. ESI-MS: m/z (rel intensity) 218.3 $[M-H]^+$.

6-Chloro-3-methyl-3,4-dihydroquinoxalin-2(1H)-one (5f): Sodium iodide dihydrate (1.6 mmol) and sodium bicarbonate (6.5 mmol) were added to a acetonitrile under nitrogen atmosphere. The resulting solution was allowed to reflux until completion while the reaction was monitored by TLC. After cooling to room temperature, the solvent was removed under reduced pressure. The residue was treated with water (100 mL) and was stirred at room temperature for l0 min, and acidified by the addition of 2N hydrochloric acid to pH = 5–6. The pale gray solid was collected by filtration and washed with water (2 × 20 mL), dried in vacuum to afford the crude product **5f**, ether = 2:3 v/v). Yield 60%, mp 217–218°C. ^{1}HNMR (DMSO-d_6) δ 2.49 (s, 3H, CH_3), 3.73 (m, 1H, CH), 6.21 (s, 1H, NH), 6.56 (m, 1H, ArH), 6.68 (s, 2H, ArH), 10.33 (s, 1H, NH). Elemental analyses calculated for $C_9H_9N_2OCl$: C, 54.96; H, 4.58; N, 14.25. Found: C, 54.03; H, 4.66; N, 15.02. ESI-MS: m/z (rel intensity) 195.1 $[M-H]^+$.

6-Chloro-3-methylquinoxalin-2(1H)-one (6f): To a 5% sodium hydroxide solution (10 mL) of **5f** (1 mmol) was sequentially added 30% hydrogen peroxide (1 mL) and water (2 mL). The solution was stirred at 60°C for 6 h, then allowed to cool down to room temperature. The precipitate was filtered and washed with water (5 mL), and dried under reduced pressure to afford the crude product **6f**, which was purified by flash-column chromatography (ethyl acetate–petroleum ether = 2:3 to 3:2 v/v) as silvery white solid. Yield 83%, mp 263–264°C.

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