Chinese Chemical Letters Vol. 15, No. 12, pp 1400-1402, 2004
http://www.imm.ac.cn/journal/ccl.html

An Efficient Approach to 6, 7-Disubstituted-1*H*-quinoxalin-2-ones

Xun LI[1], Qing Ping HU[1], Xue Gui CUI[1], Dong Hua WANG[2]*

[1]College of Pharmacy, Shandong University, Jinan 250100
[2]College of Pharmaceuticals and Biotechnology, Tianjin University, Tianjin 300072

Abstract: A novel approach to the synthesis of 6, 7-disubstituted-1*H*-quinoxalin-2-ones is described. The title compounds were regioselectively prepared by starting from substituted phenylamines and chloroacetyl chloride through the efficient sequence of acylation, nitration, reduction, intramolecular alkylation, and oxidation.

Keywords: 6, 7-Disubstituted-1*H*-quinoxalin-2-ones, regioselective, substituted phenylamine.

6, 7-Disubstituted-1*H*-quinoxalin-2-ones are important precursors for the synthesis of many pharmaceuticals and pesticides[1~3]. Many of them can be prepared by the condensation of *o*-phenylenediamines and glyoxalic acid, but regioisomeric mixtures are often obtained when unsymmetrical diamines are used[4]. Tennant[5] has reported a regioselective method for preparing 6-chloro-1*H*-quinoxalin-2-one, which is the key intermediate of pesticide quizalofop, starting from 4-chloro-2-nitrophenylamine and diketene. But the regioselective synthesis of other substituted quinoxalin-2-ones except 6-substituted compounds has not been mentioned in these literatures[6~8]. It is desirable to develop an alternative method for the regiospecific preparation of the related unsymmetric compounds. Herein, we report a simple approach to 6, 7-disubstituted-1-*H*-quinoxalin-2-ones, starting from the substituted phenylamines and chloroacetyl chloride through the sequence of acylation, nitration, reduction, intramolecular alkylation, and oxidation steps.

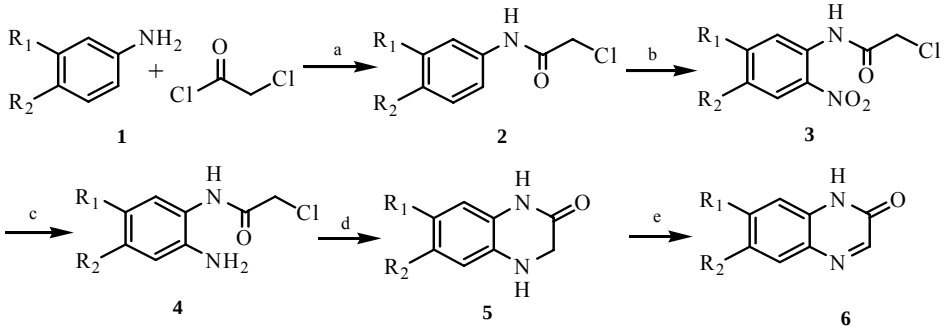
Treatment of substituted phenylamines with chloroacetyl chloride (molar ratio 1: 1.1) in toluene at refluxing temperature for 1h afforded acetamides **2** in high yield (95.0~99.3%) and **2** can be nitrated by HNO_3/AcOH or KNO_3/H_2SO_4 at room temperature for 1 h to give *o*-nitro acetamide **3** (82.6~94.0%). The reduction of **3** by using iron powder in water at 50℃ for 15 minute gave compound **4** in 88.0~93.0% yield. Subsequent intramolecular cyclization of **4** in acetonitrile at refluxing temperature produced substituted 3, 4-dihydro-1*H*-quinoxalin-2-ones **5** (48.0~77.4%).

Treatment of **5** with H_2O_2 in 5% NaOH/H_2O solution at 60℃ for 6 h obtained final product 6, 7-disubstituted-1*H*-quinoxalin-2-ones **6** in 52.9~92.6% yield. The structure of the target compounds was confirmed by ^{1}H-NMR and mass spectrum[9].

The results, summarized in **Table 1**, showed the isolated yield of 6, 7-disubstituted-1*H*-quinoxalin-2-ones from substituted phenylamines.

* E-mail: wdh0221@yahoo.com.cn

Scheme 1



Reagents and conditions: (a) PhMe, 120℃, 1h; (b) HNO_3/AcOH or KNO_3/H_2SO_4, 0℃~r.t., 4h; (c) Fe, H_2O, DMF, AcOH, 50℃,15 min; (d) NaI/$NaHCO_3$, MeCN, reflux, 8h; (e) H_2O_2, 5%NaOH, 60 ℃, 6h.

Table 1 Synthesis of 6, 7-disubstituted-1*H*-quinoxalin-2-ones

[b]Product	R_1	R_2	Yield[a] (%)
6a	H	CH_3	44.7
6b	H	C_4H_9	31.5
6c	H	CH_3O	31.3
6d	H	C_2H_5O	32.9
6e	H	Cl	51.2
6f	H	Br	47.3
6g	H	F	54.5
6h	Cl	CH_3	40.6
6i	Cl	F	43.8
6j	F	F	42.2

a. Isolated yield from substituted phenylamine

b. **6a~6d**: nitrated with HNO3/ AcOH, **6e~6j**: nitrated with KNO3/H2SO4

Compounds **2** were prepared at refluxing temperature from substituted phenylamines, the generated hydrogen chloride was absorbed by sodium hydroxide solution in another flask. The hydrogen chloride salts of substituted phenylamines formed at low temperature can be decomposed at refluxing temperature. Pure compounds **2** could be obtained by this method in almost quantitative yield when solvent was removed by vacuum distillation.

It is important to select nitration reagent when compound **2** was nitrated. When R_1 or R_2 was electron-withdrawing group, KNO_3/H_2SO_4 was selected as a nitration reagent (entries **6e~j**). When R_1 and R_2 were electron-donating groups or more hydrogen, several by-products appeared under the same nitration conditions. So mild nitration condition such as HNO_3/AcOH was selected **6a**~**d** (entries **6e~j**).

The influence of reductive catalyst on this reaction was studied. H_2/Pt/C, $SnCl_2$, iron powder *etc.* as reductants gave dechlorinating by-products, but only iron powder reduction could gave satisfactory result by optimizing reaction conditions. In this case, compound **4** could be obtained in high selectivity and high yield.

In conclusion, a facile method was developed for the preparation of 6, 7-disubstituted-1H-quinoxalin-2-ones, and a series of such compounds were synthesized by this method.

Acknowledgments

We thank the supports from the National Young Scholar Award of the NNSFC (#30125043), from the Basic Research Project (#2002CCA01500) of the MOST, and from the Natural Science Foundation of Shandong (#Y2002B14).

References and Notes

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9. Spectral data: **6a**: ^{1}HNMR (400 MHz, DMSO-d_6, δ ppm): 2.37 (s, 3H, CH_3), 7.20 (d, 1H, *J*=8.0, ArH), 7.35～7.38 (m, 1H, ArH), 7.57 (s, 1H, ArH), 8.12 (s, 1H, =CH), 12.29 (s, 1H, NH); MS (*m/z*): 160(M^+), 131, 104. **6b**: ^{1}HNMR (400 MHz, DMSO-d_6, δ ppm): 0.88～0.92 (m, 3H, CH_3), 1.29～1.34 (m, 2H, CH_2), 1.55～1.62 (m, 2H, CH_2), 2.64～2.68(m, 2H, CH_2), 7.23 (d, 1H, *J*=8.4, ArH), 7.38～7.41 (m, 1H, ArH), 7.58 (d, 1H, *J*=1.6, ArH), 8.14 (s, 1H, =CH), 12.31(s, 1H, NH); MS (*m/z*): 202(M^+), 159, 131. **6c**: ^{1}HNMR (400 MHz, DMSO-d_6, δ ppm): 3.83 (s, 3H, CH_3), 7.20～7.29 (m, 3H, ArH), 8.16 (s, 1H, =CH), 12.29 (s, 1H, NH); MS (*m/z*): 176(M^+), 161, 133. **6d**: ^{1}HNMR (400 MHz, DMSO-d_6, δ ppm): 1.33～1.37 (m, 3H, CH_3), 4.06～4.11 (m, 2H, CH_2), 7.19～7.27 (m, 3H, ArH), 8.15 (s, 1H, =CH), 12.27(s, 1H, NH); MS (*m/z*): 190(M^+), 134, 105. **6e**: ^{1}HNMR (400 MHz, DMSO-d_6, δ ppm): 7.30 (d, 1H, *J*=8.8Hz, ArH), 7.59~7.62 (m, 1H, ArH), 7.84 (d, 1H, *J*=2.0Hz, ArH), 8.21 (s, 1H, =CH), 12.54 (s, 1H, NH); MS (*m/z*): 180(M^+), 152, 125. **6f**: ^{1}HNMR (400 MHz, DMSO-d_6, δ ppm): 7.25 (d, *J*=8.8Hz, 1H, ArH), 7.70(d, 1H, *J*=8.4Hz, ArH), 7.95(s, 1H, ArH), 8.18 (s, 1H, =CH), 12.48 (s, 1H, NH); MS (*m/z*): 224(M^+), 196, 117. **6g**: ^{1}HNMR (400 MHz, DMSO-d_6, δ ppm): 7.30～7.34 (m, 1H, ArH), 7.44～7.50 (m, 1H, ArH), 7.60～7.63 (m, 1H, ArH), 8.21 (s, 1H, =CH), 12.46 (s, 1H, NH); MS (*m/z*): 164(M^+), 136, 82. **5h**: ^{1}HNMR (400 MHz, DMSO-d_6, δ ppm): 2.13 (s, 3H, CH_3), 3.69 (s, 2H, CH_2), 5.99 (s, 1H, NH), 6.56 (s, 1H, ArH), 6.71 (s, 1H, ArH), 10.21 (s, 1H, NH). **6h**: ^{1}HNMR (400 MHz, DMSO-d_6, δ ppm): 2.37 (s, 3H, CH_3), 7.30 (s, 1H, ArH), 7.76 (s, 1H, ArH), 8.14 (s, 1H, =CH), 12.37 (s, 1H, NH); MS (*m/z*): 194(M^+), 165, 131. **5i**: ^{1}HNMR (400 MHz, DMSO-d_6, δ ppm): 3.76 (s, 2H, CH_2), 6.35 (s, 1H, NH), 6.59 (d, 1H, *J*=10.8Hz, ArH), 6.75 (d, 1H, *J*=7.2Hz, ArH), 10.31 (s, 1H, NH). **6i**: ^{1}HNMR (400 MHz, DMSO-d_6, δ ppm): 7.36 (d, 1H, *J*=6.8Hz, ArH), 7.83 (d, 1H, *J*=9.6Hz, ArH), 8.20 (s, 1H, =CH), 10.31 (s, 1H, NH); MS (*m/z*): 198(M^+), 170, 143. **5j**: ^{1}HNMR (400 MHz, DMSO-d_6, δ ppm): 3.70 (d, 2H, *J*=1.6Hz, CH_2), 6.07 (s, 1H, NH), 6.60～6.71 (m, 2H, ArH), 10.25 (s, 1H, NH). **6j**: ^{1}HNMR (400 MHz, DMSO-d_6, δ ppm): 7.21～7.25 (m, 1H, ArH), 7.89～7.94 (m, 1H, ArH), 8.18 (s, 1H, =CH), 12.51 (s, 1H, NH); MS (*m/z*): 182(M^+), 154, 127.

Received 27 October, 2003