Molecules **1996**, *1*, 37 – 40

A Facile Synthesis of Quinoxaline-2,3-diones as NMDA Receptor Antagonists

Shu-Kun Lin

Ciba-Geigy Limited, Pharmaceuticals Division, CH-4002 Basel, Switzerland
Present Address: Molecular Diversity Preservation International (MDPI), Saengergasse 25, CH-4054 Basel, Switzerland.
Tel.: +41 79 322 3379; Fax: +41 61 302 8918 (100700.1527@compuserve.com)

Received: 15 May 1996 / Accepted: 12 July 1996 / Published: 09 August 1996

Abstract

The rotary evaporation of 1,2-diamino aromatic compounds in diethyl oxalate at 50-80 °C and 20 mbar leads to the formation of quinoxalines-2,3-diones, as precipitates. Further purification is not necessary except for washing with ether.

Keywords: Quinoxaline-2,3-diones, diethyl oxalate, compound separation, purification

Introduction

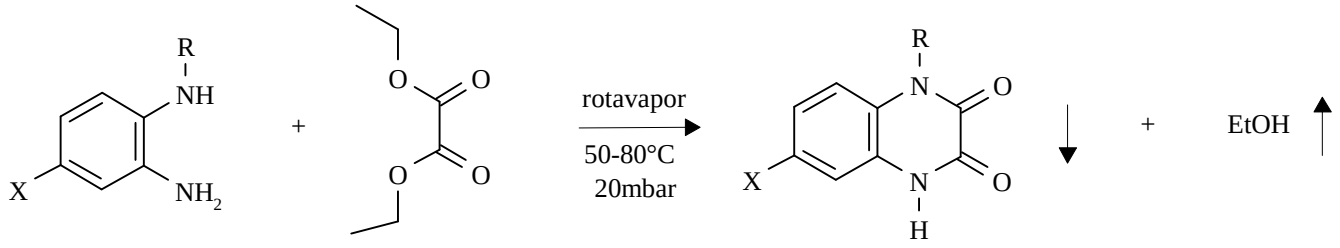
Experienced synthetic organic chemists will agree that the time normally spent in the laboratory on product isolation and purification is much more than the time spent on carrying out the reaction itself. Sometimes, an organic synthesis will fail if the target product cannot be isolated, even if conversion to the product is complete. In practice, a facile organic synthesis is a combination of both a satisfactory reaction and, more significantly, easy product isolation and purification. A simple organic synthesis has been designed to perform both the reaction and product isolation in one operation under reduced temperature and pressure (Scheme 1).

Moreover, we are interested in the synthesis of the compounds in the title because several publications recently indicated that certain quinoxaline-2,3-diones [1,2] and quinoxaline-2-ones [3] were highly potent NMDA receptor antagonists.

Results and Discussion

Quinoxaline-2,3-diones and quinoxaline-2-ones are mainly prepared by condensation of *o*-phenylenediamines with various ketoacid derivatives [4], although they can be prepared by other reactions, such as the photorearrangement of quinoxaline-1,4-dioxides [5]. Several general methods are available for preparing *o*-phenylenediamine derivatives [6]. The ring closure of an *o*-phenylenediamine with oxalate derivatives, used to form the six-member *para*diazine ring of a quinoxaline-2,3-dione, is usually the last and crucial step. Normally, this step is carried out using the method of Phillips [7] under the catalysis of strong acid [1] or at elevated or reflux (diethyl oxalate has a b.p. of 182-186 °C [4a]) temperatures [7,8]. Sometimes a solvent is also used [1,8].

With the structural modifications at other sites on 1,2-diaminobenzene completed in the previous steps, it is desirable to perform the ring closure in the synthesis of quinoxaline-2,3-dione under mild reaction conditions in order to avoid any side reactions. The general Phillips reaction carried out under harsh conditions, as commented by Piguet



Product	X	R
1	Cl	CH_2CH_2CN
2	CF_3	CH_2CH_2CN
3	H	C_6H_5
4	CH_3	H
5	Cl	H
6	H	H

Scheme 1

et al. [9], needs be modified for various reasons. If possible, catalysts and solvents should not be used, because any such substances are potential impurities in the final product. In our modified procedure, no other solvents and no catalysts have been employed. The reaction temperature is low, *ca.* 50-80 °C. Excess diethyl oxalate, a reactant, serves as a mild solvent and can be easily removed from the solid product by simply washing with ether. The results are shown in Scheme 1 [10].

The reactions on a rotary evaporator (rotavapor) or *in vacuo* may represent a general technique for syntheses where small molecules are released and a crystal product is formed. Generally, the lower temperature range reduces the reaction velocity and the reduced pressure leads to lower concentrations. However, the efficient separation due to crystallisation (facilitated by reduced temperature) and evaporation (facilitated by reduced pressure) may substantially shift the chemical equilibrium. Because the products are readily isolated, side reactions involving the products are eliminated. The strategy based on the rotavapor technique does not contradict well-established, conventional chemical kinetic theory and the thermodynamic theory of chemical equilibrium. As shown in Scheme 2, the optimum situation is that the two products (solid S and gas G) are separated from each other and also from the unreacted reactants and solvents in the liquid phase (L). In this strategy G can be any small molecules such as H_2O, a simple alcohol, an ether, acids (HX), bases (ammonia or simple amines), etc., which are not necessarily in a gaseous state at ambient conditions (their partial vapour pressures are less than 1 atm) [11]. Instead of evaporation on a rotary evaporator, the combined one-step procedure of reaction and separation described here can also be readily carried out by stirring *in vacuo.*

Regardless of their theoretical implications [12] and low yields [10], these reactions (Scheme 1) also indicate the special reactivity of alkyl oxalate derivatives towards amines [13].

Experimental Part

General

See also reference 14. Melting points were measured on a Thomas-Hoover melting point apparatus in open capillary tubes and are uncorrected. Routine ^{1}H-NMR spectra were obtained on a Varian-Gemini 300 M Hz spectrometer; chemical shifts δ in ppm relative to TMS, J in Hz. IR spectra were measured on a Perkin-Elmer 983 spectrometer as KBr pellet. Elemental analyses were performed by the Analytical Research Services, Ciba-Geigy Limited. FAB mass spectra were recorded on a ZAB HF instrument, with thioglycerin or nitrobenzyl alcohol as matrix. Diethyl oxalate is a Fluka product, purum, b.p. 182-186 °C.

*6-Chloro-1-(2'-cyanoethyl)-1,2,3,4-tetrahydroquinoxaline-2,3-dione (**1**): A General Procedure*

A solution of 4-chloro-N-(2'-cyanoethyl)-2-nitroaniline (2.0 g, 8.86 mmol) in ethanol (40 ml) was added 0.5 g Pd/C (5 %) and stirred at rt and under 1 atm H_2 for 5 h. Filtration and evaporation yield N-(2'-cyanoethyl)-2-amino-4-chloroaniline [^{1}H-NMR ($CDCl_3$): 6.76 (q, 1H, 5-CH, 7 Hz, 2 Hz), 6.74 (d, 1H, 3-CH, 2 Hz), 6.56 (d, 1H, 6-CH, 7 Hz), 3.45 (br. s, 3H, NH), 3.45 (m, 2H, CH_2), 2.65 (m, 2H, CH_2)] as a solid. 1,2-diaminobenzene is dissolved in diethyl oxalate (30 ml).

Scheme 2

The resulting solution is evaporated on a rotary vaporator with an 80 °C bath at ca. 20 mbar overnight to afford a dark solid, which was filtered, washed with ether and dried in vacuo to give 6-chloro-1-(2'-cyanoethyl)-1,2,3,4-tetrahydroquinoxaline-2,3-dione (**1**, 910 mg, 41 % based on the 2-nitroaniline derivative used). M.p. >250 °C. IR (KBr): 3245 (NH), 2258 (C≡N), 1705 and 1669 (C=O). ^{1}H-NMR ((D_6)DMSO): 12.08 (br. s, 1H, NH), 7.55 (d, 1H, H-C(8), 9 Hz), 7.22 (q, 1H, H-C(7), 9 Hz, 2 Hz) 7.19 (d, 1H, H-C(5), 2 Hz), 4.20 (m, 2H, CH_2), 2.45 (m, 2H, CH_2). (+)-FAB MS: 250 ($[M+H]^+$).

*N-(2'-Cyanoethyl)-6-trifluoromethyl-1,2,3,4-tetrahydroquinoxaline-2,3-dione (**2**)*

2-Amino-N-(2'-cyanoethyl)-4-trifluoromethylaniline (1.65 g, 7.2 mmol, prepared by hydrogenation of the corresponding 2-nitroaniline derivative as described above) in diethyl oxalate (25 ml) was evaporated as described above for 3 h to give white solid, which was filtered, washed with ether and dried in vacuo to give N-(2'-cyanoethyl)-6-trifluoro-1,2,3,4-tetrahydromethylquinoxaline-2,3-dione, a white powder (**2**, 580 mg, 29 %). M.p. 245-246 °C. IR (KBr): 3100 (NH), 2260 (C≡N), 1700 (C=O). ^{1}H-NMR ((D_6)DMSO): 12.11 (br. s, 1H, NH), 7.74 (d, 1H, H-C(8), 9 Hz), 7.51 (q, 1H, C-H(7), 9 Hz, 2 Hz) 7.47 (d, 1H, H-C(5), 2 Hz), 4.21 (m, 2H, CH_2), 2.46 (m, 2H, CH_2). (+)-FAB MS: 284 ($[M+H]^+$).

*1-Phenyl-1,2,3,4-tetrahydroquinoxaline-2,3-dione (**3**)*

A solution of 2-aminodiphenylamine (Fluka, purum) (8.54 g, 46 mmol) in diethyl oxalate (150 ml) was evaporated as described above except at 90 °C for 4 h to give white solid, which was filtered, washed with ether and dried in vacuo to give the known [15] compound 1-phenyl-1,2,3,4-tetrahydroquinoxaline-2,3-dione (**3**, 4.08 g, 37 %). M.p. >290 °C. IR (KBr): 3460, 3000, 1700 and 1657 (C=O), 1590 (Ar). ^{1}H-NMR ((D_6)DMSO): 12.07 (br. s, 1H, NH), 7.6 (m, 3H), 7.4 (m, 2H) 7.22 (q, 1H), 7.17 (m, 1H), 6.99 (m, 1H), 6.33 (q, 1H). (+)-FAB MS: 239 ($[M+H]^+$).

*1,2,3,4-Tetrahydro-6-methylquinoxaline-2,3-dione (**4**)*

Similarly, as described above, evaporation of a solution of 3,4-diaminotoluene (Fluka, pract.) (8.13 g, 66.5 mmol) in diethyl oxalate (85 ml) at 50 °C for 5h led to a brown-gray solid, which was filtered, washed with ether and dried in vacuo to give a pale-gray powder, 1,2,3,4-tetrahydro-6-methylquinoxaline-2,3-dione (**4**, 3.24 g, 27.1 %). M.p. >290 °C (lit. [8] m.p. >340 °C). IR (KBr): 3440, 3000, 1700 (C=O), 1625 (Ar). ^{1}H-NMR ((D_6)DMSO):11.84 (br. d, 2H, NH), 7.00 (d, 1H, H-C(8)), 6.91 (br. s, 1H, H-C(5)), 6.89 (d, 1H, H-C(7)), 2.23 (s, 3H, CH_3). (+)-FAB MS: 177 ($[M+H]^+$).

*6-Chloro-1,2,3,4-tetrahydroquinoxaline-2,3-dione (**5**)*

A solution of 4-chloro-1,2-phenylenediamine (Fluka, pract.) (6.16 g, 43.2 mmol) in diethyl oxalate (65 ml) was evaporated as described above except at 50 °C for 5.5 h to give a black solid, which was filtered and washed sequentially with CH_2Cl_2 and ether, and then dried in vacuo. The pale-gray powder is identified as 6-chloro-1,2,3,4-tetrahydroquinoxaline-2,3-dione (**5**, 5.0 g, 59 %). M.p. >290 °C (lit. [8] m.p.>320 °C (dec.)]. IR (KBr): 3432, 3000, 1700 (2 C=O), 1630 (Ar). ^{1}H-NMR ((D_6)DMSO):12.00 (br. s, 2H, NH), 7.13 (s, 3H, Ar-H). (+)-FAB MS: 197 ($[M+H]^+$). Analysis ($C_8H_5ClN_2O_2$), theoretical Cl 18.03 %, found Cl 17.99 %.

*1,2,3,4-tetrahydroquinoxaline-2,3-dione (**6**)*

A solution of 1,2-phenylenediamine (29.2 g, 0.27 mol) in diethyl oxalate (100 ml) was evaporated by stirring in vacuo in an oil bath at 80 °C and *ca*. 20 mbar overnight. The brown solid formed was filtered, washed several times with diethyl ether and vacuum-dried to give a pale-brown solid 1,2,3,4-tetrahydroquinoxaline-2,3-dione (**6**, 17.5 g, 40 %). M.p. >290 °C (lit. [8] m.p.>360 °C]. ^{1}H-NMR ((D_6)DMSO):11.55 (br. s, 2H, NH), 7.52 (m, 4H, Ar-H).

Acknowledgements. The author would like to thank Dr. Vittorio Rasetti for his support, Martin Kessler, Kaspar Zimmermann, Angelo Storni, Peter Schäublin, Paul Schultheiss, Robert Mah for numerous discussions and Dr. Claude Piguet and Dr. Rainer Hildebrand for making helpful suggestions.

References and Notes

1. (a) Ohmori, J.; Sakamoto, S.; Kubota, H.; Shimizu-Sasamata, M.; Okada, M.; Kawasaki, S.; Hidaka, K.; Togami, J.; Furuya, T.; Murase, K. *J. Med. Chem.* **1994**, *37*, 467-475, and literature citated therein.
(b) Epperson, J. R.; Hewawasam, P.; Meanwell, N. A.; Boissard, C. G.; Gribkoff, V. K.; Post-Munson, D. *Bioorg. Med. Chem. Lett*. **1993**, *3*, 2801-2804 and literature citated therein.
2. Nagata, R.; Tanno, N.; Kodo, T.; Ae, N.; Yamaguchi, H.; Nishimura, T.; Tatsuno, T.; Nakamura, M.; Ogita, K.; Yoneda,Y. *The 207th American Chemical Society National Meeting*, San Diego, California, March 13-17, 1994, Poster, MEDI 181, 16 March 1994.
3. Kulagowski, J. J.; Baker, R.; Curtis, N. R.; Leeson, P. D.; Mawer, I. M.; Moseley, A. M.; Ridgill, M. P.; Rowley, M.; Stansfield, I.; Foster, A. C.; Grimwood, S.; Hill, R. G.; Kemp, J. A.; Marshall, G. R.; Saywell, K. L.; Tricklebank, M. D. *J. Med. Chem.* **1994**, *37*, 1402-1405.

4. (a) Cheeseman, G. W. H.; Cookson, R. F. Condensed Pyrazines. In *The Chemistry of Heterocyclic Compounds*; vol. 35, Weissberger, A.; Taylor, E. C. series editors; John Wiley & Sons, Inc.: New York, 1979; pp.78-111.
(b) Kurasawa, Y.; Takada, A. *Heterocycles* **1985**, *23*, 2083-2119.
5. (a) Lin, S.-K. *Youji Huaxue*, 1987, 418-424; *Chem. Abstr.* 1988, **108**, 112273.
(b) Lin, S.-K. *J. Photochem.*, 1987, **37**, 363-377.
(c) Kawata, H.; Kikuchi, K.; Kokubun, H. *J. Photochem.*, 1983, **21**, 343.
(d) Jarrar, A. A.; Fataftah, Z. A. *Tetrahedron*, 1977, **33**, 2127.
(e) Cheeseman, G. W. H.; Törzs, E. S. G. *J. Chem. Soc. C*, **1966**, 157.
6. (a) Patai, S. *Chemistry of the Amino Group*; Interscience: New York, 1968; Patai, S. *The Chemistry of Amino, Nitroso and Nitro Compounds and Their Derivatives*; Wiley: New York, 1982.
(b) Rylander, P. N. *Hydrogenation Methods*; Academic Press: New York, 1985, Ch.8.
7. Phillips, M. A. *J. Chem. Soc*. **1928**, 2393-2399.
8. Obafemi, C. A.; Pfleiderer, W. *Helv. Chim. Acta*. **1994**, *77*, 1549-1556.
9. Piguet, C.; Bocquet, B.; Hopfgartner, G. *Helv. Chim. Acta*. **1994**, *77*, 931-942.
10. This rotavapor technique has been successfully used for the preparation of other more complicated quinoxaline-2,3-diones with good yields (>75 %) if the reactions run for a longer time (also, Zimmermann, K.; Kessler, M. private communications.). No reactions are observable if ambient pressure was used.
11. The release of gases at ambient pressures is utilised in many chemical reactions: Sabongi, G. J. *Chemical Triggering, Reactions of Potential Utility in Industrial Processes*; In *Topics in Applied Chemistry*; Katritzky, A. R.; Sabongi, G. J. Series Editors; Plenum Press: New York, 1987, Ch.1.
12. (a) Lin, S. -K. *J. Chem. Inf. Comp. Sci*. **1996**, *36*, 367-376.
(b) Lin, S. -K. *J. Theor. Chem.* **1996**, *1*, in press.
(c) Lin, S. -K. *Gibbs Paradox of Entropy of Mixing: Experimental facts, Its Rejection, and the Theoretical Consequences.* Paper presented at the Second International Congress on Theoretical Chemical Physics, New Orleans, Louisiana, April 9-13 1996.
(d) Lin, S. -K. *The Nature of the Chemical Process. 2. Mixing and Separation.* Paper tpresented at the Fourth World Congress of Theoretically Oriented Chemists, Jerusalem, Israel, July 7-12 1996.
13. Very recently, Mueller-Westerhoff and Zhou also reported the extraordinary reactivity of dialkyl oxalates towards the amide formations from secondary amines: Mueller-Westerhoff, U. T.; Zhou, M. *SYNLETT* **1994**, 975-984; Mueller-Westerhoff, U. T.; Zhou, M. *Tetrahedron Lett.* **1993**, *34*, 571-574.
14. Lin, S. -K.; Rasetti, V. *Helv. Chim. Acta*. **1995**, *78*, 857-865.
15. *Berlst*. vol.24, E II, p.200.

Supporting samples are available from MDPI: **6**, 17.5 g, MDPI 666.