A Novel Synthetic Route to Quinazoline-2,4-dione Dimer Derivatives

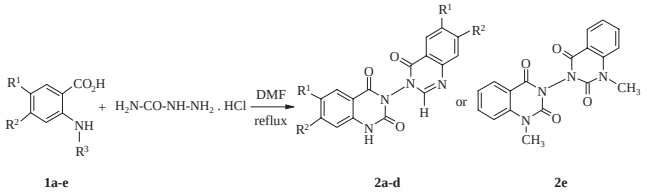
Farzad Nikpour* and Davood Sheikh
Department of Chemistry, Faculty of Sciences, University of Kurdistan, P.O. Box 66315-416, Sanandaj, Iran

(Received March 8, 2007; CL-070248; E-mail: fnikpour@uok.ac.ir)

A novel and simple one-pot synthesis of some quinazoline-2,4-dione dimer derivatives has been described via the condensation reaction of anthranilic acid derivatives with semicarbazide hydrochloride under reflux condition in DMF. The reactions proceed without use of any catalyst.

Quinazoline-2,4-diones are remarkable and interesting heterocyclic compounds due to their pharmacological and biological properties.[1–5] Owing to the potent activity of these compounds, considerable attention has been focused on their synthesis.[6]

In our previous work, simple synthesis of some 2,4(1*H*,3*H*)-quinazolinediones was investigated.[6a] Here, we report a novel synthesis of some dimeric quinazoline-2,4-diones. Synthesis of bis-quinazolinedione-like compounds has been reported already,[7] however, we have found a simple and interesting route to their synthesis. The ring closure reaction of anthranilic acid derivatives **1a**–**1e** with semicarbazide hydrochloride under reflux condition in DMF proceeds to the synthesis of compounds **2a**–**2d** and **2e** as major products[8] with moderate to good yields (Scheme 1).



1a-e **2a-d** **2e**

Scheme 1.

The whole reaction sequence runs in one-pot, without separation of the intermediates and without use of any acidic or basic catalyst. Results have been shown in Table 1.

It seems that the reaction begins with the nucleophilic attack of the anthranilic acid derivatives to semicarbazide hydrochloride and then proceeds via the intermolecular condensation reaction of the intermediates **3a**–**3e** with removal of water.

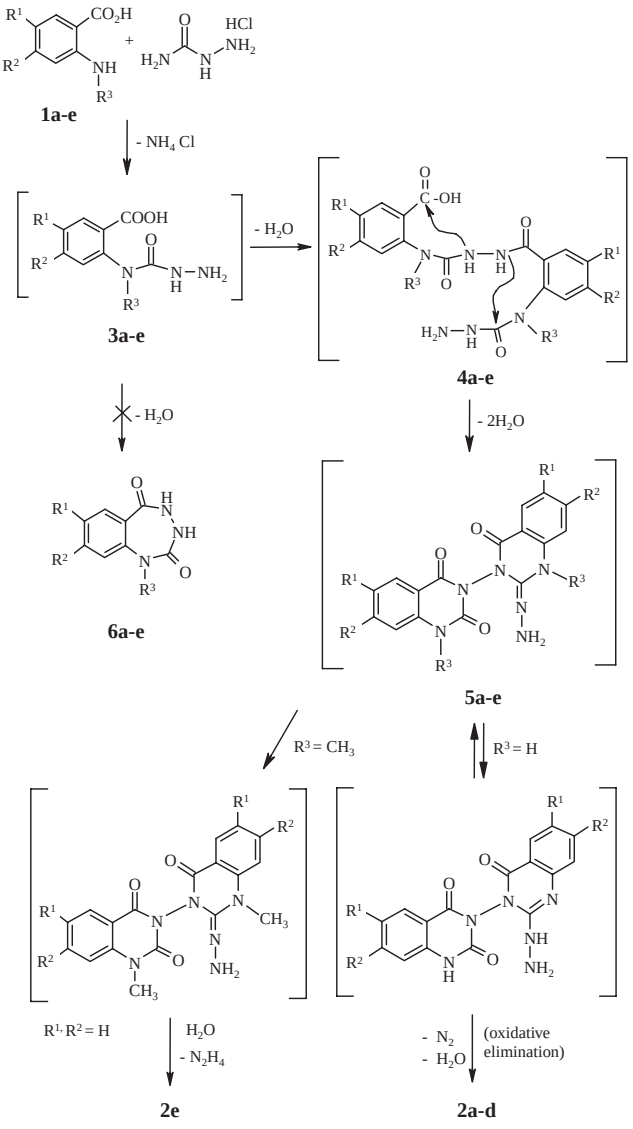
Table 1. Reaction of **1a**–**1e** with semicarbazide hydrochloride under reflux condition in DMF

	1			Product **2**[a]	
	R^1	R^2	R^3	Time /h	Yield /%[b]
a	H	H	H	5	53
b	Cl	H	H	6	60
c	Br	H	H	6	63
d	H	COOH	H	6	55
e	H	H	CH_3	5	64

[a]In all cases, the products were identified and characterized by their physical and spectral data. [b]Isolated yields.

Finally, cyclization of the intermediates **4a**–**4e** gives the mentioned compound **2a**–**2d** or **2e**. The proposed mechanism has been shown in Scheme 2. No yield of the benzotriazepine-2,5-diones **6a**–**6e** obtains from the intramolecular cyclization of **3a**–**3e**. We also observed no perceptible change in the products yields and the reaction times by using semicarbazide hydrochloride in the presence of bases such as pyridine, triethylamine and sodium bicarbonate solution in water.

In conclusion, a novel and simple synthesis of the quinazoline-2,4-diones **2a**–**2e** was investigated from the ring closure reaction of anthranilic acid derivatives with semicarbazide



1a-e **3a-e** **4a-e** **6a-e** **5a-e** **2e** **2a-d**

Scheme 2.

hydrochloride. The reactions run in one-pot without separation of intermediates. Moderate to good yields of the products obtained.

We are thankful to the University of Kurdistan Research Council for the partial support of this work.

References and Notes

1 a) G. M. Buckley, N. Davies, H. J. Dyke, P. J. Gilbert, D. R. Hannah, A. F. Haughan, C. A. Hunt, W. R. Pitt, R. H. Profit, N. C. Ray, M. D. Richard, A. Sharpe, A. J. Taylor, J. M. Whitworth, S. C. Williams, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 751. b) T. Noji, K. Nan-ya, M. Mizutani, C. Katagiri, J. Sano, C. Takada, S. Nishikawa, A. Karasawa, H. Kusaka, *Eur. J. Pharmacal.* **2002**, *454*, 85. c) I. A. Rivero, K. Espinoza, R. Somanathan, *Molecules* **2004**, *9*, 609.

2 M. M. Baraka, *Boll. Chim. Farm.* **2001**, *140*, 90.

3 H. Y. P. Choo, M. Kim, S. K. Lee, S. W. Kim, I. K. Chung, *Bioorg. Med. Chem.* **2002**, *10*, 517.

4 F. D. Therkelsen, A. L. Hansen, E. B. Pedersen, C. Nielsen, *Org. Biomol. Chem.* **2003**, *1*, 2908.

5 a) V. Colotta, D. Catarzi, F. Varano, F. R. Calabri, G. Filacchioni, C. Costaglib, A. Galli, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2345. b) T. P. Tran, E. L. Ellsworth, M. A. Stier, J. M. Domagala, H. D. H. Showalter, S. J. Gracheck, M. A. Shapiro, T. E. Joannides, R. Singh, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4405.

6 a) F. Nikpour, T. Paibast, *Chem. Lett.* **2005**, *34*, 1438. b) T. Mizuno, T. Iwai, Y. Ishino, *Tetrahedron Lett.* **2004**, *45*, 7073. c) D. Schwinn, H. Glatz, W. Bannwarth, *Helv. Chim. Acta* **2003**, *86*, 188. d) S. Makino, N. Suzuki, E. Nakanishi, T. Tsuji, *Synlett* **2001**, 0333. e) T. Okuzumi, E. Nakanishi, T. Tsuji, S. Makino, *Tetrahedron* **2003**, *59*, 5603. f) T. J. Connolly, P. McGarry, S. Sukhtankar, *Green Chem.* **2005**, *7*, 586. g) J. Vicente, J. A. Abad, J. L. Serrano, *Organometallics* **2005**, *24*, 5044. h) C.-S. Kim, C. Diez, K. C. Russell, *Chem. Eur. J.* **2000**, *6*, 1555. i) H. Shao, M. Colucci, S. Tong, H. Zhang, A. L. Castelhano, *Tetrahedron Lett.* **1998**, *39*, 7235.

7 a) G. M. Reddy, P. S. N. Reddy, *Indian J. Chem., Sect. B* **1998**, *37B*, 689. b) N. P. Peet, S. Sunder, *J. Org. Chem.* **1975**, *40*, 1909.

8 Substances were purchased commercially and used without further purification.
Some of the starting materials remain which may be removed by washing of the mixture with a solution of $NaHCO_3$ (except in the case **3d**). Also, a little of unknown by-products was obtained which must be separated by chromatography.
The reactions were carried out in DMF as an excellent polar-aprotic solvent with high boiling point. Also, DMF is soluble in water; therefore, in the work-up process, it is simple to remove the solvent and the residual semicarbazide hydrochloride by washing of the reaction mixture in water.
General reaction procedure: A mixture of 1 mmol of an anthranilic acid derivative **1a–1e**, 0.123 g (1.1 mmol) of semicarbazide hydrochloride and 1 mL of DMF in a 10 mL flask was refluxed for the times as indicated in Table 1. The mixture was washed with cold-water (three times). The solid residue was washed two times with a 10% solution of $NaHCO_3$ (except in the case **3d**) and then with water. The products were separated and purified by thin-layer chromatography on 20×20 plates of silicagel 60 GF_{254} with *n*-hexane/EtOAc eluent. The products dried first in air and then in oven (100 °C). For more purification, the products were recrystalized from EtOH or MeOH. Spectral data for:
Compound **2a**: mp 290 °C (dec.). IR (KBr): ν (cm^{-1}) 3240, 3170, 1725, 1710, 1698. ^{1}H NMR (DMSO-d_6): δ 12.12 (brs, 1H, NH), 8.51 (s, 1H, =CH), 8.01–7.97 (m, 1H, arom. H), 7.83–7.78 (m, 1H, arom. H), 7.36–7.30 (m, 2H, arom. H). ^{13}C NMR (DMSO-d_6): δ 160.2, 159.6, 157.7, 148.4, 148.2, 148.0, 147.5, 139.9, 137.0, 136.2, 128.3, 127.1, 124.0, 122.2, 116.5, 113.5. MS (EI): *m*/*z* (%) 322 ($M^{+\bullet}$, 20), 306 ($M^{+\bullet} - N_2 - H_2$, 86), 146 ($C_8H_4NO_2^+$, 100), 119 ($C_7H_5NO^{+\bullet}$, 43), 92 ($C_6H_6N^+$, 28).
Compound **2b**: mp 318 °C (dec.). IR (KBr): υ (cm^{-1}) 3275, 3160, 1749, 1705. ^{1}H NMR (DMSO-d_6): δ 11.80 (brs, 1H, NH), 8.27 (s, 1H, =CH), 8.24 (d, $^3J_{HH} = 2.3$ Hz, 1H, arom. H), 7.91 (dd, $^3J_{HH} = 8.5$ Hz, $^4J_{HH} = 2.3$ Hz, 1H, arom. H), 7.75 (dd, $^3J_{HH} = 8.2$ Hz, $^4J_{HH} = 2.1$ Hz, 1H, arom. H), 7.49 (m, 1H, arom. H), 7.27 (m, 2H, arom. H). ^{13}C NMR (DMSO-d_6): δ 159.6, 156.9, 148.5, 148.1, 147.1, 140.1, 140.0, 137.2, 133.3, 130.8, 130.1, 129.7, 128.8, 128.5, 123.2, 115.1. MS (EI): *m*/*z* (%) 378 [($M^{+\bullet} + 4$, 8)], 376 [($M^{+\bullet} + 2$, 51)], 374 ($M^{+\bullet}$, 74), 182 ($^{37}ClC_8H_3NO_2^+$, 34), 180 ($^{35}ClC_8H_3NO_2^+$, 100), 155 ($^{37}ClC_7H_4NO^{+\bullet}$, 21), 153 ($^{35}ClC_7H_4NO^{+\bullet}$, 61), 127 ($^{37}ClC_6H_4N^{+\bullet}$, 7), 125 ($^{35}ClC_6H_4N^{+\bullet}$, 16), 90 ($C_6H_4N^+$, 10), 75 ($C_6H_3^+$, 15).
Compound **2c**: mp 315 °C (dec.). IR (KBr): υ (cm^{-1}) = 3210, 1741, 1699. ^{1}H NMR (250.1 MHz in DMSO-d_6): δ 12.35 (brs, 1H, NH), 8.53 (s, 1H, =CH), 8.37 (d, $^3J_{HH} = 2.5$ Hz, 1H, arom. H), 8.38 (dd, $^3J_{HH} = 8.7$ Hz, $^4J_{HH} = 2.5$ Hz, 1H, arom. H), 8.09 (d, $^3J_{HH} = 2$ Hz, 1H, arom. H), 7.98 (dd, $^3J_{HH} = 8.5$ Hz, $^4J_{HH} = 2.2$ Hz, 1H, arom. H), 7.78 (d, $^3J_{HH} = 8.5$ Hz, 1H, arom. H), 7.28 (d, $^3J_{HH} = 8.7$ Hz, 1H, arom. H). ^{13}C NMR (62.9 MHz in DMSO-d_6): δ 159.0, 156.6, 148.4, 148.0, 146.5, 139.6, 139.2, 139.1, 130.7, 130.1, 129.2, 123.7, 121.4, 119.0, 115.7, 115.6. MS (EI): *m*/*z* (%) 466 [($M^{+\bullet} + 4$, 54)], 464 [($M^{+\bullet} + 2$, 96)], 462 ($M^{+\bullet}$, 50), 242 ($^{81}BrC_8H_5N_2O_2^{+\bullet}$, 14), 240 ($^{79}BrC_8H_5N_2O_2^{+\bullet}$, 12), 226 ($^{81}BrC_8H_5NO^+$, 92), 224 ($^{79}BrC_8H_5N_2O^{+\bullet}$, 100), 199 ($^{81}BrC_7H_4NO^{+\bullet}$, 55), 197 ($^{79}BrC_7H_4NO^{+\bullet}$, 53), 156 ($^{81}BrC_6H_3^{+\bullet}$, 21), 154 ($^{79}BrC_6H_3^{+\bullet}$, 23), 75 ($C_6H_3^+$, 44).
Compound **2d**: mp 270 °C (dec.). IR (KBr): υ (cm^{-1}) 3475, 3320–2540, 1735, 1710, 1701, 1692, 1675. ^{1}H NMR (DMSO-d_6): δ 12.38 (s, 1H, NH), 11.52 (s, 1H, CO_2H), 11.37 (s, 1H, CO_2H), 8.34–7.63 (m, 6H, arom. H), 8.42 (s, 1H, =CH). ^{13}C NMR (DMSO-d_6): δ 166.7, 162.8, 150.7, 141.3, 138.5, 136.8, 136.2, 127.9, 127.8, 127.1, 127.0, 126.9, 124.7, 122.9, 122.8, 116.8, 116.4, 115.1 MS (EI): *m*/*z* (%) 394 ($M^{+\bullet}$, 10), 206 ($C_9H_6N_2O_4^{+\bullet}$, 100), 190 ($C_9H_4NO_4^+$, 95), 163 ($C_9H_6N_2O_4^{+\bullet}$ − HNCO, 92), 145 ($C_8H_5N_2O^+$, 18), 136 ($C_7H_6NO_2^+$, 53).
Compound **2e**: mp 335 °C (dec.). IR (KBr): υ (cm^{-1}) 1723, 1692, 1608. ^{1}H NMR (250.1 MHz in DMSO-d_6): δ (ppm) 8.10 (m, 1H, arom. H), 7.91 (m, 1H, arom. H), 7.59 (m, 1H, arom. H), 7.42 (m, 1H, arom. H), 3.58 (s, 3H, NCH_3). ^{13}C NMR (62.9 MHz in DMSO-d_6): δ 159.6, 149.4, 140.7, 137.0, 128.7, 124.2, 115.8, 115.0, 31.8. MS (EI): *m*/*z* (%) 350 ($M^{+\bullet}$, 8), 176 ($C_9H_8N_2O_2^{+\bullet}$, 19), 160 ($C_8H_4N_2O_2^{+\bullet}$, 38), 133 ($C_8H_7NO^{+\bullet}$, 42), 105 ($C_7H_7N^{+\bullet}$ or $C_7H_5O^+$, 100), 104 ($C_7H_6N^+$ or $C_7H_4O^{+\bullet}$, 98), 77 ($C_6H_5^+$, 50).

Published on the web (Advance View) June 9, 2007; doi:10.1246/cl.2007.858