Heteroatom Chemistry
Volume 5, Number 2, 1994

Synthesis and Rearrangement of Triazinoquinazolines

Yehia A. Ibrahim* and Ahmed H. M. Elwahy

Department of Chemistry, Faculty of Science, Cairo University, Giza, A. R. Egypt

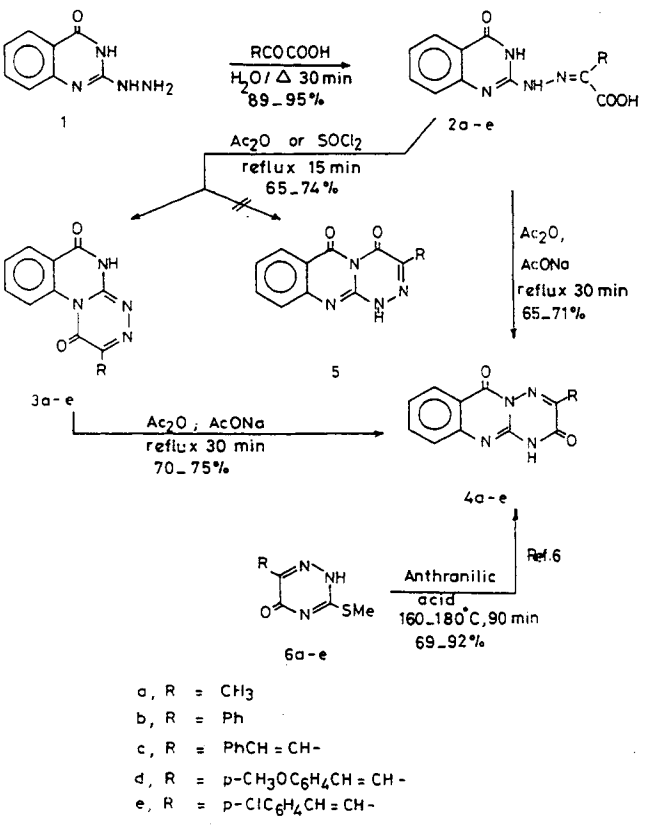
Received 9 September 1993; revised 28 October 1993

ABSTRACT

Selective syntheses of triazino[4,3-a]quinazolines **3a–e** *and their isomeric triazino[3,2-b]quinazolines* **4a–e** *by cyclization of the appropriate* α*-keto acid hydrazones* **2a–e** *under different reaction conditions are described. The angular triazinoquinazolines* **3a–e** *were readily rearranged to the corresponding linear isomers* **4a–e** *when heated in acetic anhydride in the presence of sodium acetate. This rearrangement was proposed to proceed via the intermediate isomeric triazino[3,4-b]quinazolines* **5a–e**. *The N-methyl derivative* **10** *(of the intermediate* **5b***) was prepared and rearranged to* **11**, *which is the N-methyl derivative of* **4b**.

Cyclocondensatiom of hydrazino nitrogen heterocycles such as **1** can lead to different possible isomeric condensed systems through involvement of N-1 or N-3 in the condensation reaction [1–5]. Additional isomeric products may also result through rearrangement reactions.

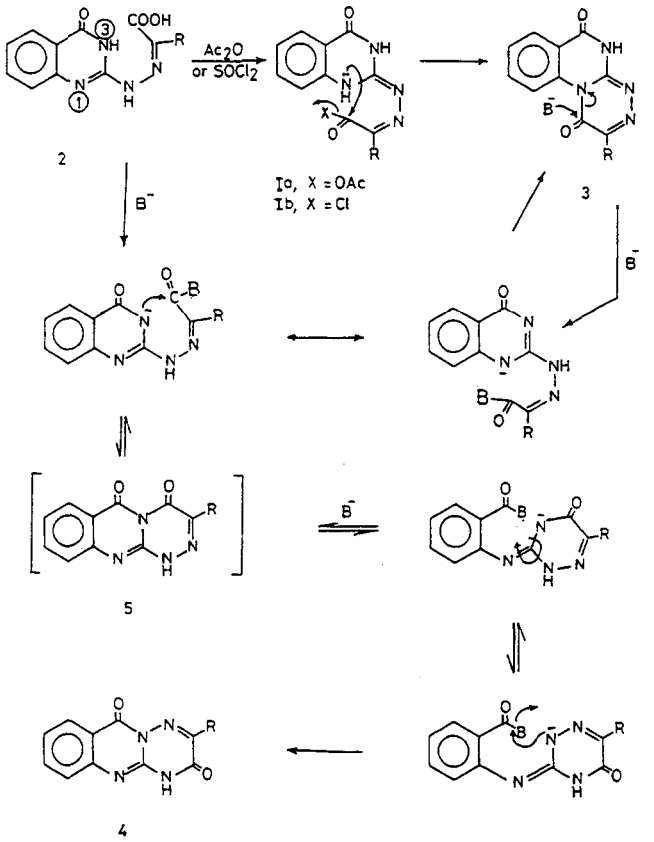
In the present investigation, the cyclocondensation of **1** with α-keto acids was carefully studied under different reaction conditions in order to obtain the different possible isomeric products. Thus, condensation of 2-hydrazinoquinazolin-4(3H)-one (**1**) with α-keto acids, namely, pyruvic acid, phenylglyoxylic acid, benzylidenepyruvic acid, *p*-methoxybenzylidenepyruvic acid, and *p*-chlorobenzylidenepyruvic acid, in hot water gave the corresponding α-keto acid hydrazones **2a–e**, respectively. Cyclizations of the latter compounds were achieved, depending on the reaction conditions, to give in each case two isomeric as-triazinoquinazolines **3a–e**, **4a–e**, but in no case was any of the third isomeric possible ring system **5a–e** (Scheme 1) detected. Thus, when compounds **2a–e** were heated under reflux for 15 minutes in thionyl chloride or acetic anhydride, the corresponding 1,6-dioxo-5,6-dihydro-1H-as-triazino[4,3-a]quinazolines **3a–e** were obtained in good yields. On the



SCHEME 1

*To whom correspondence should be addressed.

1042-7163/94/$5.00 + .25



SCHEME 2

other hand, heating compounds **2a–e** in acetic anhydride in the presence of sodium acetate led to the formation of the corresponding 3,10-dioxo-3,4-dihydro-10H-as-triazino[3,2-b]quinazolines **4a–e**, respectively. Attempts to cyclize compounds **2a–e** in refluxing acetic acid were unsuccessful, and the starting materials were recovered completely unchanged even after 10 hours of heating.

The structures of the two isomeric products **3a–e** and **4a–e** were inferred from the following facts.

1. All isomers **3a–e** showed one of the aromatic protons (H-10) unexpectedly downfield at around δ = 9.2 due to the anisotropic effect of C^1=0. The isomeric systems **4a–e** showed their aromatic protons no further downfield than δ = 8.25.
2. Compounds **4a–e** were found to be identical with authentic samples prepared by cyclocondensation of anthranilic acid with the appropriate 3-methylthio-1,2,4-triazin-5(2H)-ones **6a–e** [6,7].
3. Compounds **3a–e** underwent rearrangement to give the linear isomers **4a–e** when heated in acetic anhydride containing sodium acetate.

The possible reaction pathways leading to the cyclization of compounds **2** into the two isomeric triazinoquinazolines **3** and **4** and the rearrangement of **3** into **4** are outlined in Scheme 2. Thus, in the presence of acetic anhydride or thionyl chloride, the mixed anhydride **Ia** or the acid chloride **Ib** is formed, which is then attacked by the more basic nitrogen (N-1) to give the angular isomers **3**. On the other hand, in a basic medium, N-1 or N-3 attacks reversibly the carboxyl group leading to the isomeric triazinoquinazolines **3** or **5**, respectively. Compounds **5** also undergo reversible quinazoline ring opening, in the same basic medium, with subsequent reclosure to give irreversibly the more stable isomeric tricyclic system **4** (Scheme 2).

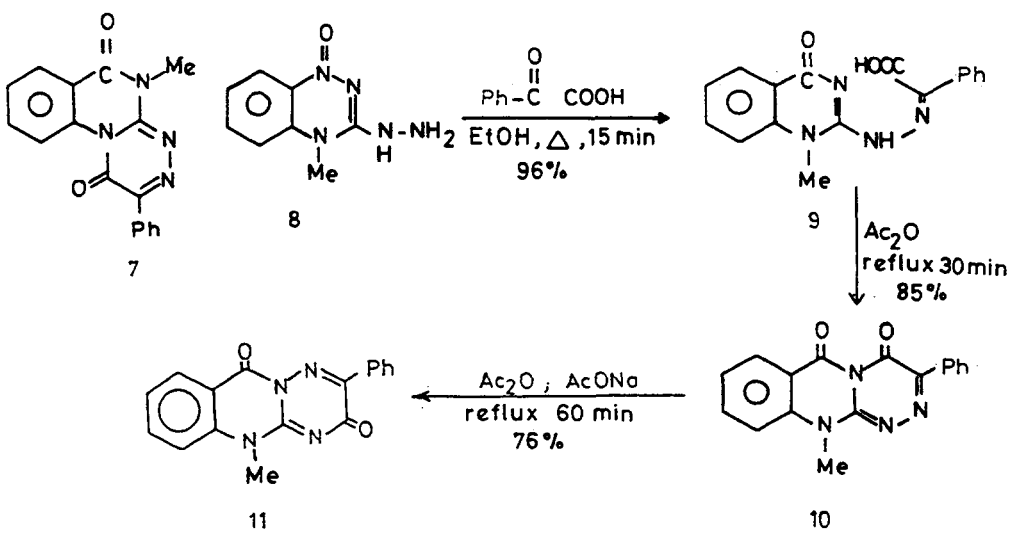


TABLE 1

Compound	Mp, °C	Yield, %	Formula (MW)	Anal. % Calcd. Found C	H	N
2a	240 (dec)	95	$C_{11}H_{10}N_4O_3$ (246.23)	53.66	4.09	22.75
				53.50	3.90	22.60
2b	257 (dec)	92	$C_{16}H_{12}N_4O_3$ (308.30)	62.34	3.92	18.17
				62.40	4.10	17.90
2c	232 (dec)	89	$C_{18}H_{14}N_4O_3$ (334.34)	64.67	4.22	16.76
				64.40	4.30	16.50
2d	230 (dec)	95	$C_{19}H_{16}N_4O_4$ (364.36)	62.63	4.43	15.38
				62.40	4.10	15.60
2e	240 (dec)	93	$C_{18}H_{13}N_4O_3Cl$ (368.78)	58.63	3.55	15.19
				58.40	3.70	15.30
3a	285–287	65	$C_{11}H_8N_4O_2$ (228.21)	57.89	3.53	24.55
				58.10	3.30	24.60
3b	284–286	72	$C_{16}H_{10}N_4O_2$ (290.38)	66.20	3.47	19.30
				66.10	3.20	19.20
3c	282–284	71	$C_{18}H_{12}N_4O_2$ (316.32)	68.35	3.82	17.71
				68.10	3.60	17.80
3d	280–282	74	$C_{19}H_{14}N_4O_3$ (346.35)	65.89	4.07	16.18
				66.00	4.10	16.30
3e	294–296	69	$C_{18}H_{11}N_4O_2Cl$ (350.73)	61.64	3.16	15.97
				61.50	3.20	16.10
4a	>300	65	$C_{11}H_8N_4O_2$ (228.21)	57.89	3.53	24.55
				57.70	3.70	24.80
4b	>300	69	$C_{16}H_{10}N_4O_2$ (390.38)	66.20	3.47	19.30
				66.40	3.70	19.40
4c	>300	72	$C_{18}H_{12}N_4O_2$ (316.32)	68.35	3.82	17.71
				68.40	4.20	18.00
4d	>300	74	$C_{19}H_{14}N_4O_3$ (346.35)	65.89	4.07	16.18
				65.70	4.20	16.30
4e	>300	71	$C_{18}H_{11}N_4O_2Cl$ (350.77)	61.64	3.16	15.97
				61.80	3.20	16.10

The proposed mechanism was substantiated by the following facts.

1. Heating of compound **3b** in the presence of acetic acid and fused sodium acetate led to ring opening; and the corresponding hydrazone **2b** was formed.
2. Compound **7** [8] was unaffected when heated under reflux for a long time in acetic anhydride and sodium acetate. This fact indicates that the blocking of the quinazoline N-3 retarded rearrangement.
3. Treatment of compound **9** (prepared by condensation of the hydrazinoquinazoline **8** [9] with phenylglyoxylic acid) with acetic anhydride led to the formation of compound **10**. The latter underwent rearrangement to give the stable isomer **11** upon treatment with acetic anhydride and sodium acetate. The isomers **10** and **11** showed their aromatic protons no further downfield than δ = 8.5. The instability of compounds **5** and **10** is due to the imide nature of the bridgehead nitrogen atoms which facilitate the nucleophilic attack of weak bases on the respective carbonyl groups leading to opening and recyclization to give either the starting materials **5** and **10**, (reversible reaction) or the final more stable products **4** and **11**, respectively.

EXPERIMENTAL

All melting points are uncorrected. The IR spectra (KBr) were recorded with a Unicam SP 1200 infrared spectrophotometer. The ^{1}H NMR spectra were determined on a Varian GEMINI 200 200-MHz spectrometer. Microelemental analyses were carried out at the Microanalytical Centre, Cairo University. Compounds prepared by different procedures were confirmed by mixture melting point tests and by identity of IR spectra and ^{1}H NMR spectra.

Preparation of α-Keto Acid Hydrazones **2a–d**

A mixture of **1** [10] (10 mmol) and the appropriate α-keto acid (10 mmol) in water (20 mL) was heated

TABLE 2 Spectral Data of Compounds ***3a–e*** and ***4a–e***

		^1H NMR (DMSO-d_6), δ			IR (cm^{-1})		
Compound	*CH = CH,*	*ArH's*	*NH*	*Other H's*	*C=0*		*NH*
3a	7.7–7.88 (m, 3H)	9.2 (d, 1H)	13.0 (s, 1H)	2.3 (s, 3H)	1710,	1720	3240
3b	7.52–8.3 (m, 8H)	9.2 (d, 1H)	12.9 (s, 1H)		1680,	1730	3270
3c	7.52–8.25 (m, 10H)	9.22 (s, 1H)	13.3 (s, 1H)				
3d	6.95–8.20 (m, 9H)	9.22 (s, 1H)	13.3 (s, 1H)	3.8 (s, 3H)	1680,	1715	3250
3e	7.32–8.25 (m, 9H)	9.23 (d, 1H)	13.3 (s, 1H)		1680,	1720	3300
4a	7.32–8.18 (m, 4H)		12.9 (s, 1H)	2.28 (s, 3H)	1655,	1710	3170
4b	7.42–8.2 (m, 9H)		12.92 (s, 1H)		1666,	1720	3040
4c	7.3–8.25 (m, 11H)		12.9 (s, 1H)		1665,	1730	3050
4d	7.0–8.2 (m, 10H)		12.9 (s, 1H)	3.92 (s, 3H)			
4e	7.3–8.22 (m, 10H)		12.9 (s, 1H)				

The signal at δ = 9.22–9.23 in compounds ***3a–e*** appears as a doublet with J = 8 Hz.

under reflux for 15 minutes, during which time a crystalline precipitate began to separate. After the mixture had cooled, each product was collected, dried, and purified by dissolving it in aqueous 5% sodium hydroxide solution, filtering the solution, and reprecipitating the product with concentrated hydrochloric acid. Each was obtained as a yellow precipitate of **2a–d** in almost quantitative yield (Table 1).

1,6-Dioxo-5,6-dihydro-1H-as-triazino[4,3-a]-quinazolines **3a–e**

A mixture of each of **2a–e** (10 mmol) and acetic anhydride or thionyl chloride (20 mL) was heated under reflux for 1/2 hour. The solvent was then evaporated in vacuo, and the remaining solid was triturated with ethanol and crystallized from DMF to give yellow crystals of **3a–e** (Table 1).

3,10-Dioxo-3,4-dihydro-10H-as-triazino[3,2-b]-quinazolines **4a–e**

(a) A mixture of each of **2a–e** (10 mmol) and fused sodium acetate (0.5 g) in acetic anhydride (20 mL) was heated under reflux for 1/2 hour. The solvent was then removed in vacuo, and each remaining solid was crystallized from DMF to give crystals of **4a–e**; yield 65–71%; identical with authentic samples [6] (mixed mp, IR, NMR) (Table 2). (b) A mixture of each of **3a–e** (10 mmol) and fused sodium acetate (0.5 g) in acetic anhydride (20 mL) was heated under reflux for 1/2 hour. The solvent was then removed in vacuo, and the remaining material was crystallized from DMF to give crystals of **4a–e**; yields 70–75%; identical with the previous compounds.

Action of Acetic Acid and Sodium Acetate on **3b**

A mixture of **3b** (10 mmol), fused sodium acetate (0.5 g), and acetic acid (20 mL) was heated under reflux for 1 hour. The solvent was removed in vacuo, and the remaining solid was triturated with ethanol and purified by dissolving it in cold aqueous sodium carbonate (5%, 20 mL), filtering the solution and reprecipitating the product with conc HCl to give the yellow precipitate of **2b** (mixed mp).

1-Methylquinazolin-4(1H)-on-2-ylhydrazone **9**

A mixture of **8**[9] (10 mmol) and phenylglyoxylic acid (10 mmol) in ethanol (20 mL) was heated under reflux for 15 minutes. After the mixture had been cooled, the precipitate was collected and recrystallized from acetic acid to give yellow crystals of **9**; yield 96%; mp 220–222°C. $C_{17}H_{14}N_4O_3$ calcd: C, 63.35; H, 4.38; N, 17.38; found: C, 63.40; H, 4.60; N, 17.30.

4,6-Dioxo-6H,11H-11-methyl-3-phenyl-as-triazino[3,4-b]quinazoline (**10**)

A mixture of **9** (10 mmol) and acetic anhydride (20 mL) was heated under reflux for 15 minutes. The

solvent was then removed in vacuo, and the remaining solid was triturated with ethanol and crystallized from DMF to give yellow crystals of **10**; yield 85%; mp 229–231°C. IR: ν = 1660, 1710 cm^{-1} (C=0).

^1H NMR (DMSO-d_6): δ = 3.92 (s, 3H, NCH_3), 7.39–8.32 (m, 9H, ArH's). $C_{17}H_{12}N_4O_2$ calcd: C, 67.10; H, 3.97; N, 18.40; found: C, 67.40; H, 4.10; N, 18.20.

2,6-Dioxo-2H,11H-11-methyl-3-phenyl-astriazino[3,2-b]quinazoline (**11**)

A mixture of **10** (10 mmol) and sodium acetate (0.5 g) in acetic anhydride (20 mL) was heated under reflux for 1/2 hour. The solvent was removed in vacuo, and the remaining solid was crystallized from DMF to give yellow crystals of **11**; yield 76%; mp 269–271°C. IR: ν = 1670, 1720 cm^{-1} (C=0).

^1H NMR (DMSO-d_6) δ = 3.84 (s, 3H, NCH_3), 7.52–8.31 (m, 9H, ArH's). $C_{17}H_{12}N_4O_2$ calcd: C, 67.10; H, 3.97; N, 18.40; found: C, 67.30; H, 3.80; N, 18.10.

REFERENCES

[1] J. Daunis, R. Jacquier, P. Viallefont, *Bull. Soc. Chim. Fr.* 1969, 2492.

[2] J. Hadacek, *Spisy Prirodovedecke Fac. Univ. Brno*, 1960, 22; *Chem. Abstr., 55*, 1964, 25977.

[3] A. Dornow, H. Pietsch, P. Marx, *Chem. Ber., 97*, 1964, 2647.

[4] F. D'Alo, A. Masserini, *Ann. Chim. (Ital.), 57*, 1967, 366.

[5] K. Hirota, H. Sajiki, P. Z. Ni, Y. Kitade, Y. Maki, *Tetrahedron 46*, 1990, 3431 and references cited therein; Y. Kitade, K. Hirota, Y. Maki, *J. Chem. Research (S)*, 1993, 2.

[6] S. A. L. Abdel-Hady, M. A. Badawy, Y. A. Ibrahim, W. Pfleiderer, *Chem. Ber., 117*, 1984, 1077.

[7] M. A. Badawy, S. A. L. Abdel-Hady, M. M. Eid, Y. A. Ibrahim, *Chem. Ber., 117*, 1984, 1083.

[8] M. A. Badawy, S. A. L. Abdel-Hady, A. H. Mahmoud, Y. A. Ibrahim, *J. Org. Chem., 55*, 1990, 344.

[9] A. H. M. Elwahy: M. Sc. Thesis, Cairo University, Giza, Egypt, 1988.

[10] W. D. Dean, E. P. Papadopoulos, *J. Heterocyclic Chem., 19*, 1982, 11.