Indian Journal of Chemistry
Vol. 41B, September 2002, pp. 1946-1949

Note

Bisazaheterocycles : Part VII — Synthesis of novel bisquinazolinonyl β-lactams

P S N Reddy*, P Pratap Reddy & T Vasantha

Department of Chemistry, Osmania University, Hyderabad 500 007, India

Received 15 March 2001; accepted (revised) 14 February 2002

The synthesis of bisquinazolinonyl β-lactams as probes for multi-receptor sites is reported.

Earlier, we reported[1] a facile synthesis of 4-heteryl β-lactams from 2-chloromethyl-3-methyl-4-oxo-3*H*-quinazoline. Its extension to bis-β-lactams as probes for multi-receptor sites of the lactam ring is reported herein.

Sharma and his co-workers[2] reported the conversion of monocyclic β-lactams to di-β-lactams by annelation of a Schiff's base to an appropriate β-lactam acid in dichloromethane containing $POCl_3$/TEA. In our procedure, 2-chloromethyl-3-methyl-4-oxo-3*H*-quinazoline **1** was reacted with 1,4-phenylenediamine **2a** in refluxing DMF to isolate 1,4-[N,N″-bis((3-methyl-4-oxo-3*H*-quinazolin-2-yl)methyl)]phenylene-diamine **3a**. The UV spectrum of **3a** showed absorptions at 348, 318, 266, 223 and 206 nm. The IR spectrum (KBr) showed a sharp peak at 3370 cm^{-1} due to aniline NH. The ^1H NMR spectrum recorded in TFA showed two singlets at δ 4.0 (6H, 2×N-CH_3) and at δ 5.2 (4H, 2×N-CH_2) and a multiplet at δ 7.95 - 8.3 accounting for ten aromatic protons. A low field doublet peak at δ 8.6 (J = 8 Hz) integrating for two protons is due to the *peri*-protons of the two quinazolinone moieties.

The amine **3a** was converted to its dichloroacetyl derivative, 1,4-[N,N′-dichloroacetyl-N,N′-bis((3-methyl-4-oxo-3*H*-quinazolin-2-yl)methyl)]phenylene-diamine **4a** [UV : λ_{max} at 316, 305, 266, 224 and 205 nm; IR (KBr, cm^{-1}) : 1679 (C=O);^1H NMR (DMSO-d_6, δ ppm) : 3.55 (s, 6H, 2×N-CH_3), 4.15 (s, 4H, 2×N-CH_2), 5.1 (s, 4H, 2×$COCH_2Cl$), 7.4 - 7.8 (m, 10H, Ar-H) and 8.15 (d, J = 7 Hz, 2H, *peri*-proton)], by treating with chloroacetyl chloride in acetone containing potassium carbonate medium. Cyclisation of **4a** in DMF containing potassium carbonate yielded a high melting, chlorine free (*vide* Lassaigne's test) compound characterised as 1,4-[bis-(4-(3-methyl-4-oxo-3*H*-quinazolin-2-yl)-2-oxo-azetidin-1-yl)]benzene **5a**. The UV spectrum of **5a** showed λ_{max} at 316 and 269 nm. The IR spectrum (KBr) exhibited carbonyl absorption of β-lactam (1734 cm^{-1}) and quinazolinone (1670 cm^{-1}).

The above method is extended to four other diamines, *viz* benzidine, *o*-tolidine, 4,4′-methylenedianiline and 3,3′-dimethoxy-4,4′-methylenedianiline. In all these cases, the corresponding bisquinazolinonyl β-lactams **5** (**Table I, Scheme I**) were obtained as final products, thus providing a facile and general method for the synthesis of the title compounds.

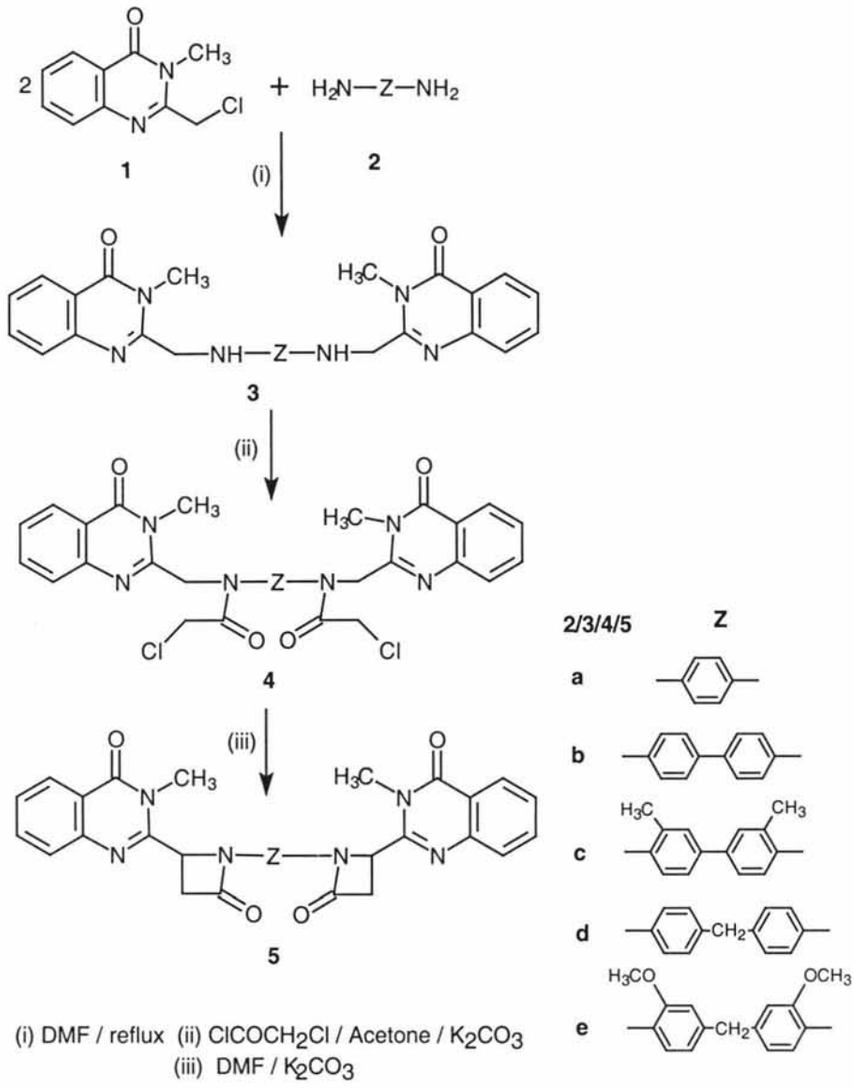
Experimental Section

Melting points were determined in capillaries using Polman digital melting point apparatus (Model No. Mp96) and are uncorrected. UV spectra (in nm) were recorded in methanol on a Shimadzu 1520 ultraviolet-visible spectrophotometer; IR (in cm^{-1}) spectra in KBr pellets on a Shimadzu 435 instrument; and ^1H NMR spectra on a Varian Gemini (200 MHz) spectrophotometer with TMS as internal standard (chemical shifts in δ ppm). The solvent in which the NMR spectra were recorded is indicated at the appropriate places. LSIMS / FAB mass spectra were recorded on a VG AUTOSPEC mass spectrometer.

[N,N′-Bis((3-methyl-4-oxo-3*H*-quinazolin-2-yl)methyl)]aryldiamine 3 : General procedure. Method A. A mixture of **1** (2 mmoles) and the appropriate aryldiamine **2** (1.0 mmole) was refluxed in ethanol (60 mL). The refluxing period varied from 1 to 2 hr depending on the nature of the diamine. The resultant **3** that separated out from the hot reaction mixture was filtered, dried, dissolved in hot chloroform, cooled and passed through a column of alumina (~150 mesh) using benzene-ethyl acetate as eluent. The characterisation data of **3a-e** are given in **Table I.**

Method B. A mixture of **1** (2 mmole) and the appropriate aryldiamine **2** (1.0 mmole) was refluxed in DMF (20 mL) for 1hr. The resultant **3** that separated out from the hot reaction mixture was filtered and repeatedly washed with hot ethanol.

[N, N′-Dichloroacetyl-N, N′-bis((3-methyl-4-oxo-3*H*-quinazolin-2-yl)methyl)]aryldiamine 4. General



Scheme I

Table I—Characterisation data of compounds **3, 4** and **5**

Compd	Z	Yield (%)	m.p. °C	UV (nm)	^{1}H NMR (δ, ppm)
3a	1,4-C_6H_4	30	220	348 318 266 223	4.0 (s, 6H, 2×N-CH_3), 5.2 (s, 4H, CH_2), 7.95 - 8.3 (m, 10H, Ar-H), 8.6 (d, J = 8 Hz, 2H, *peri*-proton)
3b	4,4′-C_6H_4-C_6H_4	40	255	303 207	3.7 (s, 6H, 2×N-CH_3), 4.5 (s, 4H, CH_2), 6.8-7.9 (m, 14H, Ar-H), 8.25 (d, J = 8 Hz, 2H, *peri*-proton)
3c	4,4′-C_6H_3(3-CH_3)–C_6H_3(3′-CH_3)	35	302	313 304 277 223	1.25 (s, 6H, 2×Ar-CH_3), 3.5 (s, 6H, 2× N-CH_3), 4.4 (s, 2H, NH), 4.6 (s, 4H, 2× CH_2), 7.42 – 7.7 (m, 12H, Ar-H), 8.25 (d, J = 10 Hz, 2H, *peri*-proton)

—Contd

Table I—Characterisation data of compounds **3, 4** and **5** (— *Contd*)

Compd	Z	Yield (%)	mp °C	UV (nm)	^{1}H NMR (δ, ppm)
3d	4,4′-C_6H_4-CH_2-C_6H_4	38	205	385 304 253 225 206	3.65 (s, 6H, 2×N-CH_3), 3.85 (s, 2H, 2×Ar-CH_2-Ar), 4.35 (s, 4H, 2×CH_2), 6.7 – 7.7 (m, 14H, Ar-H), 8.3 (d, J = 9 Hz, 2H, *peri*-proton)
3e	4,4′-C_6H_3(3-OCH_3)-CH_2-C_6H_3(3′-OCH_3)	40	220	348 268 207	3.6 (s, 6H, 2×N-CH_3), 3.75 (s, 2H, 2× Ar-CH_2-Ar), 3.85 (s, 6H, 2×OCH_3), 4.35 (d, 4H, 2×CH_2), 5.5 (s, 2H, NH), 6.55 – 7.75 (m, 12H, Ar-H), 8.2 (d, J = 8.75 Hz, 2H, *peri*-proton)
4a	1,4-C_6H_4	70	230	316 305 266 224 205	3.55 (s, 6H, 2×N-CH_3), 4.15 (s, 4H, 2×NCH_2), 5.1 (s, 4H, 2×$COCH_2$) , 7.4 – 7.8 (m, 10H, Ar-H), 8.15 (d, J = 7 Hz, 2H, *peri*-proton)
4b	4,4′-C_6H_4-C_6H_4	85	150	267	3.65 (s, 6H, 2×N-CH_3), 4.05 (s, 4H, 2×NCH_2), 5.05 (s, 4H, 2×$COCH_2$) 7.4-7.8 (m, 14H, Ar-H), 8.25 (d, J = 8 Hz, 2H, *peri*-proton)
4c	4,4′-C_6H_3(3-CH_3)-C_6H_3(3′-CH_3)	80	180	267	2.4 (s, 6H, 2×Ar-CH_3), 3.65 (s, 6H, 2×N-CH_3), 3.9 (s, 4H, 2×NCH_2), 4.25 (d, J_{gem} = 15Hz, 2H, 2×COCH), 5.6 (d, J_{gem} = 15Hz, 2H, 2×COCH), 7.3 – 7.8 (m, 12H, Ar-H), 8.25 (d, J = 7.5 Hz, 2H, *peri*-proton)
4d	4,4′-C_6H_4-CH_2-C_6H_4	78	130	316 305 266	3.65 (s, 6H, 2×N-CH_3), 3.7 (s, 2H, 2× Ar-CH_2-Ar), 3.85 (s, 4H, 2×NCH_2), 5.5 (s, 4H, 2×$COCH_2$), 7.1 – 7.8 (m, 14H, Ar-H), 8.2 (d, J = 8 Hz, 2H, *peri*-proton)
4e	4,4′-C_6H_3(3-OCH_3)-CH_2--C_6H_3(3′-OCH_3)	85	180	316 305 266	3.65 (s, 6H, 2×N-CH_3), 3.7 (s, 6H, 2 × OCH_3), 3.9 (s, 4H, 2×NCH_2), 3.92 (s, 2H, 2×Ar-CH_2-Ar), 4.65 (d, J_{gem} =16Hz, 2H, 2×COCH), 5.35 (d, J_{gem} = 16Hz, 2H, 2×COCH), 6.6 – 7.7 (m, 12H, Ar-H), 8.25 (d, J = 10 Hz, 2H, *peri*-proton)
5a	1,4-C_6H_4	80	>300	316 269	4.5 (d, J_{gem} = 12 Hz, 2H), 4.8 (s, 6H, 2 × N-CH_3), 5 (dd, $J_{3,4cis}$ =12 Hz., 2H), 8.2 – 9 (m, 10H, Ar-H), 9.2 (d (br), 2H, *peri*-proton)
5b	4,4′-C_6H_4-C_6H_4	70	206	—	—
5c	4,4′-C_6H_3(3-CH_3) C_6H_3(3′-CH_3)	85	240	278	2.4 (s, 6H, 2×Ar-CH_3), 3.6 (s, 6H, 2 × N-CH_3), 3.95 (dd, 2H, 2×NCH), 4.4 (d, J = 15Hz, 2H, 2×CHCO,), 5.5 (d, J = 15Hz, 2H, 2×COCH), 7.3 – 7.9 (m, 12H, Ar-H), 8.15 (d, J = 8.5 Hz, 2H, *peri*-proton)
5d	4,4′-C_6H_4-CH_2-C_6H_4	83	>300	—	—
5e	4,4′-C_6H_3(3-OCH_3)-CH_2- C_6H_3(3′-OCH_3)	72	230	316 301 277	3.65 (s, 6H, 2× N-CH_3), 3.7 (s, 6H, 2 × OCH_3) , 3.9 (s, 2H, 2×Ar-CH_2-Ar), 3.9 (dd, 2H, 2×NCH), 4.6 (d, J = 15Hz, 2H, 2×COCH), 5.35 (d, J = 15Hz, 2H, 2×COCH), 6.6 – 7.7 (m, 12H, Ar-H), 8.25 (d, J = 8.75 Hz, 2H, *peri*-proton)

^{1}H NMR : **3a** was recorded in TFA; **3b, 4a,4d,4e** and **5c** were recorded in DMSO-d_6 ; **3c,3d, 3e, 4b, 4c** and **5e** were recorded in $CDCl_3$; **5a** was recorded in TFA and H_2O

FAB mass : **4c** ; 709 (M^+ + H, 94%) and **5c** ; 637 (M^+ + H, 35%)

procedure. To a mixture of **3** (1 mmole) and potassium carbonate (3 g) was added chloroacetyl chloride dropwise in acetone (70 mL) at room temperature for 2 hr and filtered. Acetone was removed under vacuum from the filtrate, and water (10 mL) was added to the residue. The product **4** that separated out was filtered, dried and purified either by repeatedly washing with hot solvent (**4b**, ethanol), or by column chromatography over neutral alumina column (~150 mesh) using benzene (**4c, 4d** and **4e**) or 1:1

benzene-ethyl acetate (**4a**) as eluents. The characterisation data of **4a-e** are given in **Table I.**

[Bis-(4-(3-methyl-4-oxo-3*H*-quinazolin-2-yl)-2-oxo-azetidin-1-yl)]benzene/biphenyl/diphenylmethane 5 : General procedure. Compound **4** (1 mmole) was dissolved in DMF (5 mL) and potassium carbonate (2 g) was added to the solution. The reaction mixture was stirred at room temperature for 2-4 hr and filtered. The filtrate was poured into water (60 mL). The product **5** that separated out was filtered, dried and purified by recrystallisation from DMF (**5a**) or by column chromatography over neutral alumina (~150 mesh) by using benzene (**5e**) or 1:1 benzene – ethyl acetate (**5c**) or repeatedly washing with hot solvents (**5b**; ethanol, **5d**; DMF). The characterisation data of **5a-e** are given in **Table I**.

Acknowledgement

One of the authors (T V) is thankful to UGC, New Delhi for the award of Research Fellowship.

References

1 Reddy P S N, Vasantha T & Naga Raju Ch, *Indian J Chem*, 38B, **1999**, 40.

2 (a) Sarma S D & Mehra Usha, *Indian J Chem*, 22B, **1983**, 545.
(b) Sarma S D, Gupta P K, Bindra J & Sunita, *Tetrahedron Lett*, **1980,** 3295.