SYNTHESIS OF CHIRAL 3-SUBSTITUTED 2,4(1*H*,3*H*)-QUINAZOLINEDIONES

Perséphone Canonne*

Département de chimie, Université Laval, G1K 7P4, Québec, Canada

Mohamed Akssira*, Abdelaziz Dahdouh, Hicham Kasmi, and Mohamed Boumzebra

Département de chimie, Faculté des sciences, Université Abdelmalek Essaadi, B.P. 2121, Tétouan, Maroc

Abstract - 2-Carbomethoxyphenyl isocyanate and 6-nitro-2-carbomethoxyphenyl isocyanate were generated in situ from half-esters, and then converted into the corresponding quinazolinediones using α-amino acids. This useful annelation process was found to be a general method for the formation of various chiral 3-substituted quinazolinediones.

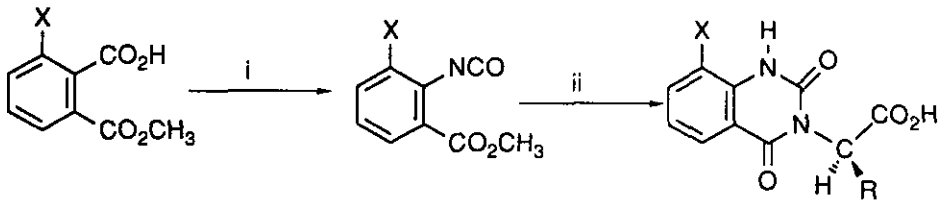
Derivatives of the quinazolinedione system are of great interest for their pharmacological properties,[1-4] and therefore there are numerous methods for the preparation of these heterocyclic compounds in the literature.[5-8] Most of the described syntheses of these heterocyclic compounds start from derivatives of anthranilic acid and are built up by sequential formation of the amide bonds.

Papadopoulos[9] prepared the 3-carbomethoxymethyl-2,4(1*H*,3*H*)-quinazolinedione by a reaction of anthranilic acid with ethyl isocyanoacetate. Furthermore, it has been reported that the 2-carbomethoxyphenyl isocyanate[10] reacts

with benzoic hydrazide to afford 2-amino-1,4-quinazolinedione derivatives.[11]

Recently, we described the synthesis of 1,4-benzodiazepinediones,[12] compounds containing anthranilic acid derivatives and α-amino acids. In continuation of our research in the field of heterocyclic amino acids, we now report a simple method for the preparation of 3-substituted-2,4(1*H*,3*H*)-quinazolinedione derivatives in which the nitrogen of the amino acid is incorporated into the fused pyrimidine ring at position 3.

The reaction of isocyanate intermediates **3** and **4** (generated in situ from half-esters **1** and **2**) with various α-amino acids afforded 3-carbomethoxymethyl-2,4(1*H*,3*H*)-quinazolinediones **6**-**10** and their 8-nitro derivatives **11**-**14** (Scheme 1).



1 : X = H **3** **6** - **10**

2 : X = NO_2 **4** **11** - **14**

i : 1) $ClCO_2C_2H_5/(C_2H_5)_3N$; 2) NaN_3/C_6H_6

ii : **5** (a-f) /H_2O-Dioxan ;50 °C

5 = Amino acid : a) Gly ; b) (L)-Ala ; c) (DL)-Ala ; d) (L)-Leu ; e) (L)-Phe ; f) (L)-Asp

Scheme 1

Following the method reported by Weinstock and co-workers,[13] we took advantage of the Curtius rearrangement to convert the starting phthalic half-esters[14] **1** and **2** to carbomethoxyphenyl isocyanate intermediates **3** and **4**. In order to prepare the desired 3-substituted-2,4(1*H*,3*H*)-quinazolinediones, the acid moiety of the phthalic half-esters was activated with ethyl chloroformate in triethylamine and dry tetrahydrofuran, followed by the addition of aqueous

sodium azide to give the acyl azide. After aqueous work-up and extraction with toluene, the tetrahydrofuran was evaporated and the resulting toluene solution was brought to reflux for 2 h. The toluene was removed at reduced pressure to leave the carbomethoxyphenyl isocyanate intermediates **3** and **4** in 90% yield.

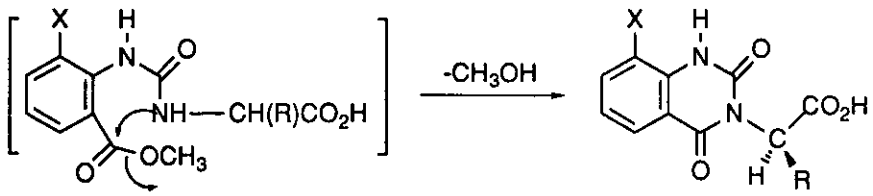
Subsequently, reaction of an equimolar amino acid **5** with 2-carbomethoxyphenyl isocyanate intermediates **3** and **4** was carried out in a mixture of dioxane and water in slightly alkaline media (pH 8-9). Under these mild conditions either at room temperature or by gentle heating (around 70°C) the desired 2,4(1*H*,3*H*)-quinazolinediones **6-10** and **11-14** were produced in good yields (Table 1). For aspartic acid, it was usually necessary to protect the two acid groups with an excess of sodium hydroxide. The formation of **6-10** and **11-14** proceeded through nucleophilic attack of the amino nitrogen of α-amino acid on the isocyanate group of **3** and **4** to give *o*-carbomethoxyureide intermediate (I) (Scheme 2). Subsequent ring closure with the elimination of methanol completed the quinazolinedione structure.

Table 1: Synthesis of 2,4(1*H*,3*H*)-quinazolinediones

Isocyanate	Amino acid	Product	Yield (%)	mp[a] (°C)	$[\alpha]_D^{20}$ (c;CH_3OH)[b]
3	Gly	**6**	86	299-301	–
3	(L)-Ala	**7a**	90	268-270	−58.10°(1.222)
3	(DL)-Ala	**7b**	90	268-270	–
3	(L)-Leu	**8**	87	202-204	−46.29°(1.188)
3	(L)-Phe	**9**	90	233-235	−18.00°(1.214)
3	(L)-Asp	**10**	85	248-250	−17.41°(1.378)
4	Gly	**11**	85	292-294	–
4	(L)-Ala	**12**	80	282-284	−17.07°(1.30)
4	(L)-Leu	**13**	85	160-162	−13.51°(0.59)
4	(L)-Phe	**14**	87	150-154	−10.16°(1.20)

a) Quinazolinediones were recristallized in methanol

b) c: concentration g/100 ml



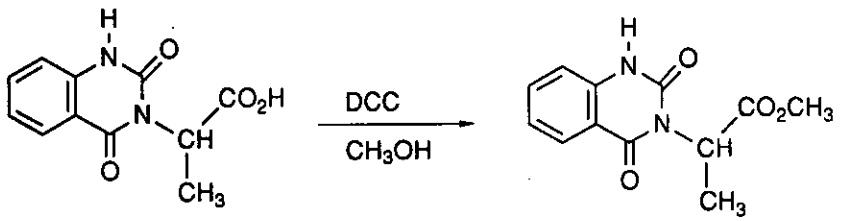
I

6 - 14

Scheme 2

It is noteworthy that the yields of all the 3-substituted 2,4(1*H*,3*H*)-quinazolinediones are very high. Moreover, the structures of all the compounds thus obtained were characterized spectroscopically and gave satisfactory results in elemental analysis.

During these transformations no racemization of chiral centers occurred. Indeed, by addition of tris[3-(heptafluoropropylhydroxymethylene)-D-camphorato]europium(III) as a chiral shift reagent to the chloroform solution of the two isomers **15a** and **15b** (obtained by esterification of the quinazolinediones **7a** and **7b**) (Scheme 3), the racemic compound **15b** showed two peaks in the OCH_3 region, whereas the (L) isomer **15a** showed only one peak under the same conditions.



7 a

7 b

15 a

15 b

Scheme 3

As is shown in Table 1, we developed a simple and short enantioselective and high yield synthesis of various 3-substituted quinazolinediones using easily available starting materials.

EXPERIMENTAL

Melting points were taken for samples in capillary tubes with an Electrothermal apparatus and are not corrected. The ir spectra were determined on a Shimadzu IR-435 instrument and the nmr spectra were recorded with Varian EM-360 and Varian-200 spectrometers using tetramethysilane as internal standard. Mass spectra were obtained using JEOL JMS DX 100 and DX 300 spectrometers. Optical rotations were determined with a Perkin Elmer Model 141 polarimeter. Elemental analyses were carried out by C. N. R. S. Center, Montpellier, France. Reagents and solvents were purified in the usual way.

2-Carbomethoxyphenyl isocyanate (3)

To a cold solution (−10°C) of half-ester **1** (1 g, 5.55 mmol) and triethylamine (1.55 ml, 11.11 mmol) in tetrahydrofuran (15 ml) was added dropwise ethyl chloroformate (0.8 ml, 8.33 mmol), and the resulting solution was stirred with ice cooling for 1 h. Tlc analysis showed complete conversion to a very non-polar material. A solution of NaN_3 (0.9 g, 13.87 mmol) in H_2O (5.4 ml) was then added dropwise with continued stirring for 1 h. The reaction mixture was diluted with H_2O (50 ml) and extracted with toluene (3 × 10 ml). The combined organic phase was washed with brine, dried ($NaSO_4$), filtered and concentrated to *ca.* half volume in vacuo (to remove the tetrahydrofuran). The toluene solution was then slowly brought to reflux. After 1.5 h, the yellow solution was cooled to room temperature and concentrated to 0.9 g (92%) of crude isocyanate **3**, which was used without purification. Ir (neat) 2260, 1725 cm^{-1}; ^1H nmr ($CDCl_3$) δ 3.80 (s, 3H), 7.35 (m, 2H), 7.70 (m, 1H), 7.76 (m, 1H); ms (m/z) 177 (M^+).

6-Nitro-2-carbomethoxyphenyl isocyanate (4)

As in the formation of 2-carbomethoxyphenyl isocyanate **3**, 6-nitro half-ester **2** (1 g, 4.44 mmol) gave 0.88 g (90%)

of crude isocyanate **4**, which was used without purification; ir (neat) 2260, 1730 cm^{-1}; ^1H nmr ($CDCl_3$) δ 3.90 (s, 3H), 7.60 (m, 1H), 7.90 (m, 1H), 8.10 (m, 1H); ms (m/z) 222 (M^+).

General Procedure: Preparation of 3-Substituted 2,4(1*H*,3*H*)-quinazolinediones (6-10) and (11-14)

The isocyanate intermediate was added to a solution of 1.5 equivalents of α-amino acid **5** in a mixture of water (10 ml), dioxane (10 ml) and sodium hydroxyde (1 M, 10 ml). The mixture was stirred at 50°C for 4 h. The volatile components were evaporated in vacuo, water was added to the solid residue and acidified with hydrochloric acid (10%) to pH 3. The precipitate was collected by filtration to give the corresponding 1,4-quinazolinedione.

The following substances were prepared via this general procedure.

3-Carboxymethyl-2,4(1*H*,3*H*)-quinazolinedione (6)

mp 299-301°C (methanol) (lit.,[15] mp 296-298°C); 86% yield; ir (KBr) 3270, 1710, 1660, 1630 cm^{-1}; ^1H nmr (DMSO-d_6) δ 4.65 (s, 2H, CH_2), 7.24 (m, 2H, ArH), 7.69 (dd, J = 6, 6.5 Hz, 1H, ArH), 7.96 (d, J = 6.5 Hz, 1H, ArH), 11.64 (s, 1H, NH); ms (m/z) 221 (M + 1); Anal. Calcd for $C_{10}H_8N_2O_4$: C, 54.54, H, 3.66; N, 12.72. Found: C, 54.63; H, 3.72; N, 12.80.

3-[(*S*)-1-Carboxyethyl]-2,4(1*H*,3*H*)-quinazolinedione (7a)

mp 268-270°C (methanol); 90% yield; $[\alpha]_D$ = −58.1° (c 1.22, CH_3OH); ir (KBr) 3260, 1725, 1650, 1620 cm^{-1}; ^1H nmr (DMSO-d_6) δ 1.75 (d, J = 7 Hz, 3H, CH_3), 5.53 (q, J = 7 Hz, 1H, CH-N), 7.24 (m, 2H, ArH), 7.69 (dd, J = 6, 6.5 Hz, 1H, ArH), 7.96 (d, J = 6.5 Hz, 1H, ArH), 10.82 (s, 1H, NH); ms (m/z) 235 (M + 1); Anal. Calcd for $C_{11}H_{10}N_2O_4$: C, 56.43; H, 4.30; N, 11.96. Found: C, 56.30; H, 4.47; N, 11.85.

3-(1-Carboxyethyl)-2,4(1*H*,3*H*)-quinazolinedione (7b)

mp 268-270°C (methanol); 90% yield; ir (KBr) 3280, 1725, 1650, 1620 cm^{-1}; ^1H nmr (DMSO-d_6) δ 1.74 (d, J =

7Hz, 3H, CH_3), 5.52 (q, J = 7 Hz, 1H, CH-N), 7.24 (m, 2H, ArH), 7.68 (dd, J = 6, 6.5 Hz, 1H, ArH), 7.96 (d, J = 6.5 Hz, 1H, ArH), 10.82 (s, 1H, NH); ms (m/z) 235 (M + 1).

3-[(*S*)-1-Carboxyisobutyl]-2,4(1*H*,3*H*)-quinazolinedione (8)

mp 202-204°C (methanol); 90% yield; $[\alpha]_D$ = −46.29° (c 1.18, CH_3OH); ir (KBr) 3260, 1725, 1650, 1620 cm^{-1}; ^1H nmr (DMSO-d_6) δ 0.86 (d, J = 7.5 Hz, 3H, CH_3), 0.88 (d, J = 7.5 Hz, 3H, CH_3), 1.51 (m, 1H, $CH(CH_3)_2$), 1.95 (m, 2H, $CH_2CH(CH_3)_2$), 5.32 (dd, J = 6.5, 10 Hz, 1H, CH-N), 7.24 (m, 2H, ArH), 7.69 (dd, J = 6, 6.5 Hz, 1H, ArH), 7.96 (d, J = 6.5 Hz, 1H, ArH), 11.15 (s, 1H, NH); ms (m/z) 277 (M + 1); Anal. Calcd for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.79; N, 10.14. Found: C, 60.99; H, 6.03; N, 10.08.

3-[(*S*)-1-Benzyl-1-carboxymethyl]-2,4(1*H*,3*H*)-quinazolinedione (9)

mp 233-235°C (methanol); 90% yield; $[\alpha]_D$ = −18° (c 1.21, CH_3OH); ir (KBr) 3270, 1720, 1650, 1620 cm^{-1}; ^1H nmr (DMSO-d_6) δ 3.45 (d, J = 10 Hz, 1H, CH_2Ph), 3.50 (d, J = 6.5 Hz, 1H, CH_2Ph), 5.62 (dd, J = 6.5, 10 Hz, 1H, CH-N), 7.10 (m, 7H, ArH), 7.52 (m, 1H, ArH), 7.93 (m, 1H, ArH), 8.50 (br, 1H, NH); ms (m/z) 311 (M + 1); Anal. Calcd for $C_{17}H_{14}N_2O_4$: C, 65.79; N, 4.54; N, 9.02. Found: C, 65.83;, H, 4.91; N, 8.98.

3-[(*S*)-1,2-Dicarboxyethyl]-2,4(1*H*,3*H*)-quinazolinedione (10)

mp 248-250°C (methanol); 85% yield; $[\alpha]_D$ = −17.41° (c 1.37, CH_3OH); ir (KBr) 3260, 1720, 1660, 1620 cm^{-1}; ^1H nmr (DMSO-d_6) δ 2.85 (d, J = 6 Hz, 1H, CH_2CO_2H), 3.25 (d, J = 8 Hz, 1H, CH_2CO_2H), 5.97 (dd, J = 6, 8 Hz, 1H, CH-N), 7.24 (m, 2H, ArH), 7.69 (m, 1H, ArH), 7.96 (m, 1H, ArH), 9.10 (br, 1H, NH); ms (m/z) 279 (M + 1); Anal. Calcd for $C_{12}H_{10}N_2O_6$: C, 51.80; H, 3.62; N, 10.06. Found: C, 51.99; H, 3.68; N, 9.98.

3-Carboxymethyl-8-nitro-2,4(1*H*,3*H*)-quinazolinedione (11)

mp 292-294°C (methanol); 85% yield; ir (KBr) 3245, 1720, 1650, 1620 cm^{-1}; ^1H nmr (DMSO-d_6) δ 4.66, (s, 2H,

CH_2), 7.40 (d, J = 6.5 Hz, 1H, ArH), 7.53 (d, J = 6.5 Hz, 1H, ArH), 7.85 (t, J = 6.5 Hz,-1H, ArH); ms (m/z) 266 (M + 1); Anal. Calcd for $C_{10}H_7N_3O_6$: C, 45.29; H, 2.66; N, 15.84. Found: C, 45.35; H, 2.98; N, 15.93.

3-[(*S*)-1-Carboxyethyl]-8-nitro-2,4(1*H*,3*H*)-quinazolinedione (12)

mp 282-284°C (methanol); 80% yield; $[\alpha]_D = -18°$ (c 1.3, CH_3OH); ir (KBr) 3240, 1720, 1660, 1610 cm^{-1}; ^1H nmr (DMSO-d_6) δ 1.55 (d, J = 7.5 Hz, 3H, CH_3), 4.50 (q, J ≈ 7.5 Hz, 1H, CH-N), 7.40 (d, J = 6.5 Hz, 1H, ArH), 7.54 (d, J = 6.5 Hz, 1H, ArH), 7.85 (t, J = 6.5 Hz, 1H, ArH), ms (m/z) 280 (M + 1); Anal. Calcd for $C_{11}H_9N_2O_4$: C, 47.31; H, 3.24; N, 15.05. Found: C, 47.43; H, 3.40; N, 15.01.

3-[(*S*)-1-Carboxyisobutyl]-8-nitro-2,4(1*H*,3*H*)-quinazolinedione (13)

mp 160-162°C (methanol); 85% yield; $[\alpha]_D = -13.5°$ (c 0.6, CH_3OH); ir (KBr) 3240, 1715, 1660, 1620 cm^{-1}; ^1H nmr (DMSO-d_6) δ 0.87 (d, J = 7.5 Hz, 3H, CH_3), 0.90 (d, J = 7.5 Hz, 3H, CH_3), 1.51 (m, 1H, $CH(CH_3)_2$), 1.95 (m, 2H, CH_2), 5.31 (dd, J = 6.5, 10 Hz, 1H, CH-N), 7.40 (d, J = 6.5 Hz, 1H, ArH), 7.50 (d, J = 6.5 Hz, 1H, ArH), 7.87 (t, J = 6.5 Hz, 1H, ArH); ms (m/z) 322 (M + 1); Anal. Calcd for $C_{14}H_{15}N_3O_6$: C, 52.33; H, 4.70; N, 13.07. Found: C, 52.05; H, 4.75; N, 13.06.

3-[(*S*)-1-Benzyl-1-carboxymethyl]-2,4(1*H*,3*H*)-quinazolinedione (14)

mp 154-155°C (methanol); 87% yield: $[\alpha]_D = -10.1°$ (c 1.2, CH_3OH); ir (KBr) 3240, 1715, 1650, 1610 cm^{-1}; ^1H nmr (DMSO-d_6) δ 3.46 (d, J = 10 Hz, 1H, CH_2Ph), 3.50 (d, J = 6.5 Hz, 1H, CH_2Ph), 5.60 (dd, J = 6.5, 10 Hz, 1H, CH-N), 7.42 (d, J = 6.5 Hz, 1H, ArH), 7.53 (d, J = 6.5 Hz, 1H, ArH), 7.87 (t, J = 6.5 Hz, 1H, ArH); ms (m/z) 356 (M + 1); Anal. Calcd for $C_{17}H_{13}N_3O_6$: C, 57.46; H, 3.68; N, 11.82. Found: C, 57.21; H, 3.39; N, 11.67.

3-(1-Carbomethoxyethyl)-2,4(1*H*,3*H*)-quinazolinedione (15)

The isomers ***15a*** and ***15b*** were synthesized by the method of Ziegler and Berger.[15] The quinazolinediones **7a** and

7b (0.5 g, 2.3 mmol), DCC (0.51 g, 2.5 mmol) and DMAP (28 mg, 0.23 mmol) are stirred in 10 ml of methanol. After workup, 3-(1-carbomethoxyethyl)-2,4(1*H*,3*H*)-quinazolinediones **15a** and **15b** were obtained in 96% yield. mp 135°C (hexane); ^{1}H nmr ($CDCl_3$) δ 1.73 (d, J = 7.5 Hz, 3H, CH_3), 3.80 (s, 3H, OCH_3), 5.73 (q, J = 7.5 Hz, 1H, CH-N), 7.24 (m, 2H, ArH), 7.69 (m, 1H, ArH), 7.96 (m, 1H, ArH), 10.50 (br, 1H, NH); Exact mass for $C_{12}H_{12}N_2O_4$: calcd, 248.0798; found, 248.0795.

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