Synthesis of 4*H*-3,1-Benzoxazin-4-ones and 4-(3*H*)Quinazolinones from Anthranilic Acids and their Derivatives by the Use of Triphenyl Phosphite and Pyridine

Guy Rabilloud and Bernard Sillion

Institut Français du Pétrole, Direction de Synthèse Organique, C.E.D.I., BP No. 3, 69390 Vernaison, France

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A series of 2-substituted 4*H*-3,1-benzoxazinones and 2,3-disubstituted 4-(3*H*)quinazolinones have been synthesized in mild conditions by the use of triphenyl phosphite and pyridine as cyclising medium. Benzoxazinones are produced either by ring closure of 2-(acylamino)benzoic acids or in the reaction of benzoic acid with anthranilic acids. In the presence of aniline, the reaction leads to quinazolinones.

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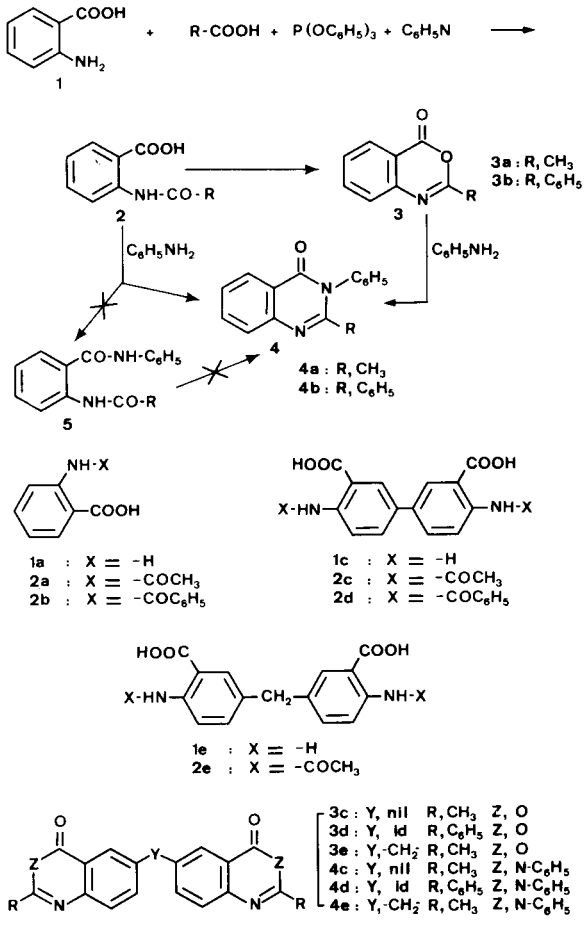
The substituted 4-(3*H*)quinazolinones and 4*H*-3,1-benzoxazin-4-ones have been extensively studied in recent years owing to their potential use as pharmaceutical agents (1-3) or as linking units as heat-stable polymers (4,5). Two methods are broadly used to prepare the 2,3-disubstituted 4-(3*H*)quinazolinones: the thermal or chemical dehydration of the *N*-substituted 2-(acylamino)-benzamides and the condensation reaction of primary amines with benzoxazinones (6,7). These latter compounds are generally prepared by the reaction of anthranilic acids with carboxylic acid anhydrides (8) or aromatic carboxylic acid chlorides (9).

Scheme I



In a previous communication (10), we have briefly described the reaction of benzoic acid with some 2-substituted anilines in a mixture of triphenyl phosphite and pyridine to prepare heterocyclic compounds. It has been shown that this medium is of limited usefulness with the exception of 2-aminobenzenethiol and 2-aminobenzoic acid, which readily produce 2-phenylbenzothiazole and 2-phenyl-4*H*-3,1-benzoxazine-4-one.

The mixture of phosphorus compounds and organic bases is known to undergo amide and ester linkages in very mild conditions (11) and its use has been extended to the synthesis of aliphatic and aromatic polyamides (12,13). We wish to describe in the present communication that a mixture of triphenyl phosphite and pyridine is a very convenient medium to promote the condensation and dehydration steps which lead to benzoxazinones and quinazolinones.

The condensation reaction of benzoic acid and anthranilic acid (**1a**) with an equimolecular amount of triphenyl phosphite in pyridine solution gave 2-phenyl-4*H*-3,1-benzoxazin-4-one (**3b**) in 96% yield. If aniline was added at this stage to the reaction mixture, 2,3-diphenyl-4-(3*H*)quinazolinone (**4b**) was produced in 92% yield.

We suggest that the reaction proceeds according to the indicated general scheme *via* the formation of an intermediate 2'-carboxybenzanilide (**2b**). Effectively, a series of 2-substituted 4*H*-3,1-benzoxazin-4-ones (**3**) were synthesized in nearly quantitative yields when 2-acylaminobenzoic acids (**2**) were heated with triphenyl phosphite in pyridine (Table I).

In the same way, 4-(3*H*)quinazolinones (**4**) were obtained in very good yields if the ring forming reaction of **2** was performed with the stoichiometric quantity of aniline (Table II). That the quinazolinone synthesis followed the indicated pathway instead of the possible formation of an intermediate diamide (**5**) was supported by two other experiments. In the first one, 2-(acetylamino)benzanilide (**5a**)

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Table I

2-Substituted 4*H*-1,3-Benzoxazine-4-ones (3) from 2-(Acylamino)benzoic Acids (2)

Starting Material	Reaction Time (hours)	Product No.	(R)	Yield (%)	M.p. (solvent) (°C)	Formula	Analyses Calcd. Found		
							C	H	N
2a	2	**3a**	(CH_3)	98	82 (hexane)	$C_9H_7NO_2$	67.07	4.38	8.69
							67.11	4.25	8.58
2b	5	**3b**	(C_6H_5)	96	123 (heptane)	$C_{14}H_9NO_2$	75.33	4.06	6.27
							75.19	4.12	6.22
1a + benzoic acid	4	**3b**	(C_6H_5)	86	id.	id.			
2c	3	**3c**	(CH_3)	95	335 (sublimation)	$C_{18}H_{12}N_2O_4$	67.50	3.78	8.75
							67.20	3.98	8.88
2d	5	**3d**	(C_6H_5)	90	380 (sublimation)	$C_{28}H_{16}N_2O_4$	75.67	3.63	6.30
							75.78	3.90	6.26
1c + benzoic acid	7	**3d**	(C_6H_5)	84	id.	id.			
2e	3	**3e**	(CH_3)	92	275 (sublimation)	$C_{19}H_{14}N_2O_4$	68.25	4.22	8.38
							68.03	4.43	8.41

Table II

Synthesis of2-Substituted 3-Phenyl 4-(3*H*)Quinazolinones (4)

Starting Material	Reaction Time (hours)	Product No.	(R)	Yield (%)	M.p. (solvent) (°C)	Formula	Analyses Calcd. Found		
							C	H	N
2a	3	**4a**	(CH_3)	84	147 (heptane)	$C_{15}H_{12}N_2O$	76.25	5.12	11.86
							76.32	5.31	11.76
2b	3	**4b**	(C_6H_5)	90	157 (ethanol)	$C_{20}H_{14}N_2O$	80.51	4.73	9.39
							80.44	4.85	9.43
1a + aniline + benzoic acid	7	id.		90	id.	id.			
2c	5	**4c**	(CH_3)	95	344 (chlorobenzene)	$C_{30}H_{22}N_4O_2$	76.58	4.71	11.91
							76.51	4.59	11.67
2d	8	**4d**	(C_6H_5)	82	445 (*N*-methyl-pyrrolidone)	$C_{40}H_{26}N_4O_2$	80.78	4.40	9.42
							80.76	4.62	9.29
1c + aniline + benzoic acid	11	id.		78	id.	id.			
2e	5	**4e**	(CH_3)	88	217 (chlorobenzene)	$C_{31}H_{24}N_4O_2$	76.84	4.99	11.56
							76.72	5.18	11.44

or 2-(benzoylamino)benzanilide (**5b**) were heated in the triphenyl phosphite-pyridine mixture. At the end of the reaction, more than 90% of the starting compounds were recovered with only 5 to 10% of the expected heterocycles **4a** and **4b**.

Conversely, the condensation reaction of 2-methyl-4*H*-3,1-benzoxazin-4-one (**3a**) with aniline yielded within minutes, 95% of 2-methyl-3-phenyl-4-(3*H*)quinazolinone (**4a**). This reaction is especially useful with poorly soluble starting compounds such as 4,4′-bis(acetylamino)-[1,1′-biphenyl]-3,3′-dicarboxylic acid (**2c**) and the other bis-anthranilic acid derivatives **2d** and **2e**.

The mild reaction conditions, the ease of work up and the high yields make that method particularly convenient to synthesize benzoxazinones and quinazolinones which are not readily accessible by other procedures.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage apparatus and with a Mel-Temp capillary melting point apparatus and are uncorrected. Infrared spectra were recorded with a Perkin-Elmer 257 grating spectrometer. Nmr spectra were obtained on a Hitachi-Perkin Elmer R24 spectrometer.

2-(Acetylamino)benzoic Acid (**2a**).

This compound was prepared according to the procedure of Zentmyer and Wagner (8), m.p. 182° (from ethyl acetate) (lit. (7,8) m.p. 182°); ir (potassium bromide): ν 3300 (N-H), 3100-2500 (O-H), 1695 (C=O, acid), 1675 cm^{-1} (C=O, amide); nmr (DMSO-d_6): δ 2.20 (s, 3H, CH_3), 7.1 (t, 1H, H-5), 7.57 (t, 1H, H-4), 8.02 (q, 1H, H-6), 8.55 ppm (q, 1H, H-3).

2-(Benzoylamino)benzoic Acid (**2b**).

This product was prepared as described by Yoda *et al.* (14), m.p. 181° (lit. (13) m.p. 179-183°); ir (potassium bromide): ν 3210 (N-H), 3100-2450 (O-H), 1672 (C=O, acid), 1655 cm^{-1} (C=O, amide).

4,4'-Bis(acetylamino)-[1,1'-biphenyl]-3,3'-dicarboxylic Acid (**2c**).

A suspension of benzidinedicarboxylic acid (**1c**) (100 g., 0.367 mole) in a mixture of acetic acid (350 ml.) and acetic anhydride (250 ml.) was stirred at room temperature for 20 hours and then heated to boiling for 1 hour. After cooling the precipitate was collected by filtration and washed with water, ethanol and diethyl ether. The crude product was twice recrystallized from dimethylacetamide to give 97 g. (74%) of **2c**, m.p. 346° dec (lit. (4) m.p. 350°); ir (potassium bromide): ν 3125 (N-H), 3000-2350 (O-H), 1695 (C=O, acid), 1675 cm^{-1} (C=O, amide); nmr (DMSO-d_6): δ 2.15 (s, 6H, CH_3), 7.35-7.95 (m, 4H aromatic), 8.30 ppm (d, 2H, H-5 and H-5').

Anal. Calcd. for $C_{18}H_{36}N_2O_6$: C, 60.67; H, 4.53; N, 7.86. Found: C, 60.65; H, 4.44; N, 7.83.

4,4'-Bis(benzoylamino)-[1,1'-biphenyl]-3,3'-dicarboxylic Acid (**2d**).

This compound was prepared according to a previously described procedure (5), m.p. 400-401° (from dimethylformamide) (lit. (5) m.p. 402°).

4,4'-Bis(acetylamino)diphenylmethane-3,3'-dicarboxylic Acid (**2e**).

A suspension of **1e** (100 g., 0.35 mole) in a mixture of acetic acid (100 ml.) and acetic anhydride (72 g.) was heated at reflux temperature for 4 hours. After cooling water (300 ml.) was added and the resulting precipitate was collected, washed with water and dried. The crude product was crystallized from acetic acid to give 103.7 g (80%) of **2e**, m.p. 238°; ir (potassium bromide): ν 3180 (N-H), 3000-2500 (O-H) 1695 (C=O, acid), 1670 cm^{-1} (C=O, amide); nmr (DMSO-d_6): δ 2.1 (s, 6H, CH_3), 3.75 (s, 2H, CH_2), 7.35 (d, 2H, H-6 and H-6'), 7.72 (s, 2H, H-2 and H-2'), 8.25 ppm (d, 2H, H-5 and H-5').

Anal. Calcd. for $C_{19}H_{18}N_2O_6$: C, 61.62; H, 4.90; N, 7.56. Found: C, 61.66; H, 4.78; N, 7.60.

2-Methyl-4*H*-3,1-benzoxazin-4-one (**3a**).

A mixture of **2a** (1.79 g., 10 mmoles), triphenyl phosphite (3.1 g., 10 mmoles) and pyridine (10 ml.) was heated under nitrogen at 100°. The reaction was followed by recording infrared spectra of the solution every 30 minutes and measuring the relative intensities of the carbonyl absorption bands at 1680 cm^{-1} for **2a** and at 1760 cm^{-1} for **3a**. The former disappeared in the course of 2 hours. At that time, gas chromatography analysis indicated that 98% of **2a** was dehydrated into **3a**. The same reaction was then performed with 0.1 mole of **2a**. Fractional distillation of the reaction mixture under reduced pressure afforded 14.5 g. (90%) of benzoxazinone (**3a**), m.p. 82° (from hexane) (lit. (7,8) m.p. 82°); ir (potassium bromide): ν 1760 (C=O) and 1646 cm^{-1} (C=N); nmr (deuteriochloroform): δ 2.45 (s, 3H, CH_3), 7.2-7.85 (m, 3H, aromatic), 8.03 ppm (q, 1H, H-5).

2-Phenyl-4*H*-3,1-benzoxazin-4-one (**3b**).

This compound was prepared as in the above example from **2b** (0.1 mole), triphenyl phosphite (0.1 mole) and pyridine (200 ml.) heated at 100° for 5 hours. The crude product was twice recrystallized from ethanol and heptane to give 96% of **3b**, m.p. 123° (lit (9,13) 123° and 120.5°); ir (potassium bromide): ν 1770 (C=O), 1615 cm^{-1} (C=N); nmr (deuteriochloroform): δ 7.2-7.7 (m, 6H, aromatic), 8.0-8.2 ppm (m, 3H, H-5, H-2' and H-6').

In another procedure, a mixture of benzoic acid (15 mmoles), 2-aminobenzoic acid (15 mmoles), triphenyl phosphite (15 mmoles) and pyridine (20 ml.) was heated under nitrogen at 100° for 4 hours. The major part of pyridine, phenol and other by-products was removed by distillation at reduced pressure and the residue was crystallized from heptane to give 86% of **3b**.

2,2'-Dimethyl-[6,6'-bi-4*H*-3,1-benzoxazine]-4,4'-dione (**3c**).

A mixture of **2c** (5.345 g., 15 mmole), triphenyl phosphite (9.31 g.) and pyridine (30 ml.) was heated at 100° under nitrogen. Precipitation of a pale yellow solid began after 0.5 hour and was complete after 3 hours. The precipitate was collected by filtration, washed with cold pyridine, benzene, diethyl ether and dried at 90° for 20 hours. The yield in crude **3c** was 4.2 g. (87.5%) but it could be increased to 97% by working on a 0.2 mole scale. The product was purified by sublimation at 310° *in vacuo*, m.p. 335° (lit. (4) m.p. 330-332°); ir (potassium bromide): ν 1757, 1740 (C=O), 1645 cm^{-1} (C=N); nmr (DMSO-d_6): δ 2.4 (s, 6H, CH_3), 7.3-7.8 (m, 4H, aromatic), 8.1 ppm (d, 2H, H-5 and H-5').

2,2'-Diphenyl-[6,6'-bi-4*H*-3,1-benzoxazine]-4,4'-dione (**3d**).

This product was prepared as in the above example from **2d** (15 mmoles), triphenyl phosphite (30 mmoles) and pyridine (30 ml.) at 100° for 5 hours. The crude product was sublimed at 330° to give 90% of pure **3d**, m.p. 376° (lit. (5) m.p. 380°); ir (potassium bromide): ν 1760 (C=O), 1625 cm^{-1} (C=N) nmr (DMSO-d_6): δ 7.28 (m, 10H, aromatic), 7.96 ppm (d, 2H, H-5 and H-5', J = 1.8 Hz).

6,6'-Methylenebis[2-methyl-4*H*-3,1-benzoxazin-4-one] (**3e**).

Using the same procedure, **2e** (370.4 g.) was treated with 2 moles of triphenyl phosphite in pyridine (3 l.) at 100° for 3 hours to give 308 g. (92%) of bisbenzoxazinone (**3e**). Two sublimations at 265-270° were necessary to obtain a pure product, m.p. 275°; ir (potassium bromide): ν 1760, 1740 (C=O), 1645 cm^{-1} (C=N); nmr (DMSO-d_6): δ 2.41 (s, 6H, CH_3), 4.05 (s, 2H, CH_2), 7.50 (d, 2H, H-8 and H-8', J = 7.2 Hz), 7.72 (q, 2H, H-7 and H-7', J = 2 Hz and 7.2 Hz), 8.01 ppm (d, 2H, H-5 and H-5', J = 2 Hz).

2-Methyl-3-phenyl-4-(3*H*)quinazolinone (**4a**).

A mixture of **2a** (1.79 g., 10 mmoles), aniline (0.93 g., 10 mmoles), triphenylphosphite (3.1 g., 10 mmoles) and pyridine (15 ml.) was heated under nitrogen at 100° for 3 hours. Pyridine was evaporated at reduced pressure and the residue was first treated with dilute hydrochloric acid and then with 10% sodium hydroxide. The crude product crystallized from heptane to give 1.98 g. (84%) of **4a**, m.p. 147° (lit. (7) m.p. 147-148°); ir (potassium bromide): ν 1675 (C=O), 1610 cm^{-1} (C=N); nmr (deuteriochloroform): δ 2.15 (s, 3H, CH_3), 7.0-7.7 (m, 8H, aromatic), 8.15 ppm (q, 1H, H-5).

2,3-Diphenyl-4(3*H*)quinazolinone (**4b**).

A mixture of benzoic acid (2.44 g., 0.02 mole) 2-aminobenzoic acid (2.74 g., 0.02 mole), triphenyl phosphite (6.2 g.) and pyridine (20 ml.) was heated under nitrogen at 100° for 4 hours. Then aniline (1.86 g., 0.02 mole) was added and the reaction was continued for a further 3 hours. The mixture was worked up as described in the above example and the crude product was crystallized from aqueous ethanol to yield 5.37 g. (90%) of **4b**, m.p. 157° (lit. (7,8) m.p. 121° and 157°); ir (potassium bromide): ν 1680 (C=O), 1615 cm^{-1} (C=N); nmr (deuteriochloroform): δ 7.25 (m, 11H, aromatic), 7.72 (q, 2H, H-2' and H-6'), 8,3 ppm (q, 1H, H-5).

Compound **4b** was also prepared in 90% yield by allowing to react equimolecular amounts of **2b**, aniline and triphenyl phosphite in pyridine at 100° for 3 hours.

2,2'-Dimethyl-3,3'-diphenyl-[6,6'-bi-3*H*-quinazoline]-4,4'-dione (**4c**).

A mixture of **2c** (5.345 g.), aniline (2.79 g.), triphenyl phosphite (5.31 g.) and pyridine was heated at 100° for 5 hours. The resulting precipitate was collected, washed with benzene and cold methanol and dried at 120° for 10 hours. The yield in crude product was 6.99 g. (99%), m.p. 325°. It was crystallized from chlorobenzene to give 6.25 g. (95%) of **4c**, m.p. 344°; ir (potassium bromide): ν 1692 (C=O), 1598 (C=N); nmr (pyridine-d_5): δ 2.25 (s, 6H, CH_3), 7.5 (broad s, 10H, aromatic), 7.88 (d, 2H, H-8 and H-8'), 8.1 (q, 2H, H-7 and H-7'), 8.7 ppm (d, 2H, H-5 and H-5').

2,2',3,3'-Tetraphenyl-[6,6'-bi-3*H*-quinazoline]-4,4'-dione (**4d**).

This compound was prepared as in the above example by the use of **2d** (15 mmoles) as starting compound. After a heating time of 8 hours, the yield in **4d** was 82%, m.p. 444° (from *N*-methylpyrrolidone) (lit. (5) m.p. 445°); ir (potassium bromide): ν 1680 (C=O), 1610 cm^{-1} (C=N).

The same compound was also prepared by first allowing to react **1c** (10

mmoles) and benzoic acid (20 mmoles) in triphenyl phosphite and pyridine at 100° for 5 hours, then adding aniline (20 mmoles), the reaction being continued for a further 6 hours. The yield in **4d** was 78%.

6,6'-Methylenebis[2-methyl-3-phenyl-4(3*H*)quinazolinone] (**4e**).

The reaction of **2e** with aniline in triphenyl phosphite and pyridine for 5 hours yielded 88% of **4e**, m.p. 219° (from chlorobenzene); ir (potassium bromide): ν 1690 (C=O), 1605 cm^{-1} (C=N); nmr (DMSO-d_6): δ 2.12 (s, 6H, CH_3), 4.01 (s, 2H, CH_2), 7.1-7.8 (m, 14H, aromatic), 8.1 ppm (d, 2H, H-5 and H-5').

2-(Acetylamino)-*N*-phenylbenzamide (**5a**).

This compound was prepared by two known procedures (15,16), m.p. 175° (lit. (15 m.p. 167-168°, (16) 178-179°); ir (potassium bromide): ν 3250 (N-H), 1670, 1650 cm^{-1} (C=O); nmr (deuteriochloroform): δ 2.2 (s, 3H, CH_3), 6.9-8.5 (m, 9H, aromatic), 9.05 and 10.4 ppm (2 broad s, 2H, NH).

Ring Closure of **5a**.

A mixture of **5a** (2.54 g.), triphenyl phosphite (3.1 g.) and pyridine (25 ml.) was heated at 100° for 2 hours. Pyridine was distilled at reduced pressure and the residue was washed with 10% hydrochloric acid, water, 5% sodium hydroxide and water. The crude product (2.42 g.) was crystallized from aqueous ethanol to yield 2.3 g. (90%) of unreacted **5a** and 0.11 g. of quinazolinone (**4a**).

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