Synthesis of New 2*H*,4*H*-Benzopyrano[3,4-*b*]pyridine-1,3,5-trione Derivatives *via* Carbon Suboxide

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Received August 11, 1997

The new 2*H*,4*H*-[1]benzopyrano[3,4-*b*]pyridine-1,3,5-trione derivatives **10a-f** were prepared in the following three steps: first the preparation of new *N*-(*tert*-butoxycarbonyl)-3-amino-2*H*-1-benzopyran-2-one derivatives **5a-f** by reaction of coumarin-3-carboxylic acids and diphenylphosphorylazide, then hydrolysis of **5a-f** with gaseous hydrogen chloride to give the corresponding amines **7a-f**, and finally the preparation of **10a-f** by reaction of **7a-f** and carbon suboxide in the presence of a Lewis acid.

J. Heterocyclic Chem., **35**, 117 (1998).

Coumarin derivatives are known to be a very interesting class of natural or synthetic compounds [1,2], whose biological activity varies according to the substituents on the benzopyran ring [3,4]. Though no detailed study of the structure-activity relationship of these compounds, their antibacterial [5-7], antifungal [8], antitumour [9,10], and anti-HIV [11,12] activity has been published recently.

Continuing our research on the synthesis and activity of coumarin compounds *via* carbon suboxide [13-17], in this study we prepared new *N*-(*tert*-butoxycarbonyl)-3-amino-2*H*-1-benzopyran-2-one derivatives **5a-f** and new 2*H*,4*H*-[1]benzopyrano[3,4-*b*]pyridine-1,3,5-trione derivatives **10a-f**, that can be structurally compared to analogous compounds of known pharmacological activity [18] (Scheme). By reacting equimolar amounts of coumarin-3-carboxylic acids **1a-f** with triethylamine (**2**) and diphenylphosphorylazide (**3**) [19] in *t*-butyl alcohol (**4**), derivatives **5a-f** were obtained in good yields. The structures of the compounds **5a-f** have been assigned from their analytical and ir, ^{1}H nmr and mass spectral data (Table 1). The ir spectra revealed presence of the characteristic absorption of the NH and CO lactonic and carbamic groups. The ^{1}H nmr spectra showed the signal of the methine proton at δ between 8.09 and 8.61, and all mass spectra show a base peak at [M^+ -$C_5H_9O_2$]. These derivatives have been hydrolyzed in the heterogeneous phase with gaseous hydrogen chloride for **6**, to give quantitative yields of the known coumarin-3-amino derivatives **7a-f** [20-22]. For this reason gaseous hydrogen chloride was used, since the hydrolysis of bases in the long run promotes the opening of the coumarin ring, and the hydrolysis of acids leads to very low yields.

Subsequently, by reacting equimolar amounts of **7a-f** with carbon suboxide (**8**) in anhydrous acetone solutions and in presence of catalytic amounts of anhydrous aluminum chloride (**9**), new pyridincoumarins **10a-f** were obtained (Table 2). A possible mechanism of this reaction is the nucleophilic attack of nitrogen by carbon suboxide with formation of an unstable ketene intermediate [23], that leads to pyridincoumarin derivatives *via* a Friedel Krafts reaction.

Scheme

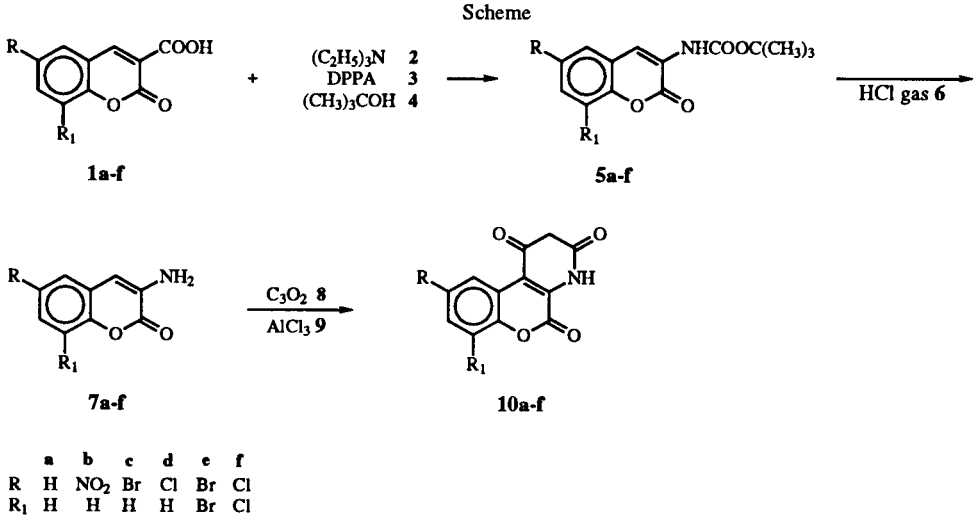

Table 1

Some Physicochemical Properties and Spechal Findings of **5a-f**

No.	R	R_1	Yield (%)	Mp (°C)	Formula	Analysis (%) Calcd./Found C	H	N	FTIR (cm^{-1})	^1H NMR δ ppm	MS m/z
5a	H	H	82	85-86	$C_{14}H_{15}NO_4$	64.36 64.50	5.79 5.75	5.36 5.40	3395 1715 1690	(deuteriochloroform): 12.00 (s, 1H, NH exchanged with deuterium oxide), 8.20 (s, 1H, CH), 7.39-7.19 (m, 4H, Ar), 1.46 [s, 9H, 3(CH_3)]	261 161
5b	NO_2	H	80	132-134	$C_{14}H_{14}N_2O_6$	54.90 54.85	4.61 4.62	9.15 9.18	3400 1720 1690	(deuteriochloroform): 12.00 (s, 1H, NH exchanged with deuterium oxide), 8.27 (s, 1H, CH), 7.37-7.19 (m, 3H, Ar), 1.47 [s, 9H, 3(CH_3)]	306 206
5c	Br	H	80	104-105	$C_{14}H_{14}BrNO_4$	49.56 49.45	4.16 4.20	4.13 4.11	3390 1715 1690	(dimethyl-d_6 sulfoxide): 12.00 (s, 1H, NH exchanged with deuterium oxide), 8.59 (s, 1H, CH), 7.95-7.22 (m, 3H, Ar), 1.47 [s, 9H, 3(CH_3)]	340 240
5d	Cl	H	80	158-160	$C_{14}H_{14}ClNO_4$	56.94 57.02	4.78 4.81	4.75 4.75	3390 1720 1710	(dimethyl-d_6 sulfoxide): 12.00 (s, 1H, NH exchanged with deuterium oxide), 8.61 (s, 1H, CH), 7.93-7.28 (m, 3H, Ar), 1.53 [s, 9H, 3(CH_3)]	295 195
5e	Br	Br	88	130-132	$C_{14}H_{13}Br_2NO_4$	40.30 40.21	3.14 3.20	3.36 3.39	3380 1720 1700	(dimethyl-d_6 sulfoxide): 11.90 (s, 1H, NH exchanged with deuterium oxide), 8.09 (s, 1H, CH), 7.69-7.45 (m, 2H, Ar), 1.46 [s, 9H, 3(CH_3)]	419 319
5f	Cl	Cl	82	148-150	$C_{14}H_{13}Cl_2NO_4$	51.06 51.15	3.98 4.00	4.26 4.21	3310 1730 1710	(dimethyl-d_6 sulfoxide): 11.90 (s, 1H, NH exchanged with deuterium oxide), 8.17 (s, 1H, CH), 7.99-7.70 (m, 2H, Ar), 1.45 [s, 9H, 3(CH_3)].	314 214

Table 2

Some Physicochemical Properties and Spectral Findings of **10a-f**

No.	R	R_1	Yield (%)	Mp (°C)	Formula	Analysis (%) Calcd./Found C	H	N	FTIR (cm^{-1})	^1H NMR δ ppm (Dimethyl-d_6 sulfoxide)	MS m/z
10a	H	H	38	>230	$C_{12}H_7NO_4$	62.89 62.81	3.08 3.10	6.11 6.15	3400 1720 1650 1595	10.90 (s, 1H, NH exchanged with deuterium oxide), 8.20-7.30 (m, 4H, Ar), 3.75 (s, 2H, CH_2)	229 M^+
10b	NO_2	H	32	>230	$C_{12}H_6N_2O_6$	52.57 52.65	2.21 2.23	10.22 10.15	3400 1730 1640 1595	10.95 (s, 1H, NH exchanged wtih deuterium oxide), 8.20-7.57 (m, 3H, Ar), 3.78 (s, 2H, CH_2)	274 M^+
10c	Br	H	35	>230	$C_{12}H_6BrNO_4$	46.78 46.69	1.96 1.96	4.55 4.57	3410 1735 1624 1594	9.50 (s, 1H, NH exchanged with deuterium oxide), 8.20-7.50 (m, 3H, Ar), 3.76 (s, 2H, CH_2)	308 M^+
10d	Cl	H	35	>230	$C_{12}H_6ClNO_4$	54.67 54.58	2.29 2.30	5.31 5.28	3410 1730 1620 1595	9.50 (s, 1H, NH exchanged with deuterium oxide), 8.22-7.58 (m, 3H, Ar), 3.75 (s, 2H, CH_2)	263 M^+
10e	Br	Br	40	>230	$C_{12}H_5Br_2NO_4$	37.24 37.33	1.30 1.29	3.62 3.65	3398 1720 1650 1590	9.45 (s, 1H, NH exchanged with deuterium oxide), 8.23-7.99 (m, 2H, Ar), 3.72 (s, 2H, CH_2)	387 M^+
10f	Cl	Cl	30	>230	$C_{12}H_5Cl_2NO_4$	48.35 48.42	1.69 1.70	4.70 4.65	3400 1735 1625 1600	9.46 (s, 1H, NH exchanged with deuterium oxide), 8.20-7.97 (m, 2H, Ar), 3.70 (s, 2H, CH_2).	298 M^+

EXPERIMENTAL

Melting points were determined using a Kofler apparatus and are uncorrected. The FT ir spectra were recorded on a Perkin Elmer System 2000 spectrophotometer using potassium bromide mulls. The ^{1}H nmr spectra were recorded on a Varian Unity 300 spectrometer; chemical shifts are reported in ppm from hexamethyldisiloxane as an internal standard and are given in δ units. Mass spectra were taken with a QMD 1000 instrument (Fisons instrument) at 70 eV using a direct inlet system. Elemental analyses (C, H, N) were carried out with a Carlo Erba model 1106 Elemental Analyzer.

Commercially available reagent-grade reagents and solvents were used. Carbon suboxide was prepared from the pyrolysis of di-*O*-acetyltartaric anhydride [24]. Acids **1b-f** were prepared from 2-hydroxybenzaldehyde derivatives [25] according to the literature [26]. Starting materials were purchased from Aldrich Chemical Co. All compounds and solvents were rigorously dried before use.

N-(*tert*-Butoxycarbonyl)-3-amino-2*H*-1-benzopyran-2-ones **5a-f** and 2*H*-1-Benzopyran-2-one-3-amino Derivatives **7a-f**. General Procedure.

Triethylamine (50 mmoles) and subsequently diphenylphosphorylazide (50 mmoles) were added dropwise to a refluxing solution of **1a-f** (50 mmoles) in *t*-butyl alcohol (150 ml) with stirring. The reaction was refluxed for another 24 hours. Upon completion, the solution was filtered and concentrated under reduced pressure, giving as residue as dense oil that was solidified with isopropyl ether. The crude solid was crystallized from hot methanol to give coumarins **5a-f**.

Gaseous hydrogen chloride was added slowly with stirring to a suspension of these coumarins in chloroform. Upon completion the chloroform solution containing the hydrolysate was concentrated under vacuum to give quantitative yields of the known **7a-f**.

2*H*,4*H*-[1]Benzopyrano[3,4-*b*]pyridine-1,3,5-trione Derivatives **10a-f**. General Procedure.

Carbon suboxide (8 mmoles) was added over 1 hour at -70° to a stirred solution of **7a-f** (8 mmoles) in anhydrous acetone (300 ml) in the presence of a catalytic amount of aluminum chloride. Upon completion, the mixture was allowed to stand at 0° for 5 hours, then at room temperature for 120 hours with continuous stirring. After filtration and solvent evaporation, the residual oil was converted into a powder with petroleum and isopropyl ether, and recrystallized by hot methanol and water (1:1) to yield **10a-f**.

Acknowledgements.

This work was supported by Ministero dell'Universita e della Ricerca Scientifica e Tecnologica (MURST research funds 60%).

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