New Method of Synthesis of 1,5-Benzodiazepin-2-ones from 4-Hydroxycoumarin

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A new method of synthesis of 1,5-benzodiazepine-2-ones, from 4-hydroxycoumarin and substituted 1,2-phenylenediamines by heating in xylene or acetic acid-ethanol, is reported.

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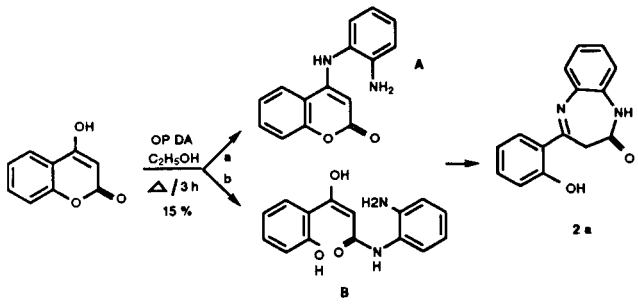
A number of studies have dealt with the action of amino derivatives on 4-hydroxycoumarin. Of note is the synthesis of 4-aminocoumarins by condensation of primary and secondary amines under reflux in xylene [1], and pyrazole derivatives by opening of the coumarin ring by the action of hydrazines [2,3].

In the course of our research on the synthesis of new heterocyclic compounds of potential biological interest from 4-hydroxycoumarin, we studied the condensation of various diamines. We first investigated the 1,2-phenylenediamines which are employed from 1,3-bifunctional compounds [4-8] in the synthesis of benzodiazepines of pharmacological importance [9-15] because there are no reports to our knowledge in the literature.

In the first instance we heated 1,2-phenylenediamine (OPDA) with the 4-hydroxycoumarin in solution in ethanol. The reaction was followed by tlc (eluent: dichloromethane-methanol, 10/1 v/v), which demonstrated the formation of a single product in low yield. Inspection of the ^1H nmr spectrum (80 Mhz, DMSO-d_6) showed the presence of two singlets in identical proportions at δ = 14.07 and δ = 10.71 ppm, corresponding to exchangeable protons (disappearance on addition of deuterium oxide), the presence of multiplets between δ = 6.92 and δ = 7.97 ppm from aromatic protons, the presence of the singlet at δ = 3.61 ppm from CH_2 protons, and the disappearance of the singlet at δ = 5.59 ppm from the ethylenic proton of 4-hydroxycoumarin.



Nucleophilic attack of the diamine can take place on either the 2 or 4 positions of the coumarin ring, giving rise to compounds **A** or **B**, which by internal cyclisation produce the same heterocyclic derivative.

The structure 4-(2'-hydroxyphenyl)-1,5-benzodiazepin-2-one (**2a**) was indicated by the nmr spectrum, which ruled out structures **A** and **B** as well as the product of condensation of a second molecule of coumarin on the free NH_2 group. This structure was confirmed by elemental analysis and mass spectrometry, where apart from the molecular ion peak at 252, a peak at 210 was observed due to the characteristic loss for this type of compound of the -CH_2CO fragment [16-18]. In view of the low yield (15%), we attempted to optimize the reaction conditions, and carried out a study in different solvents.

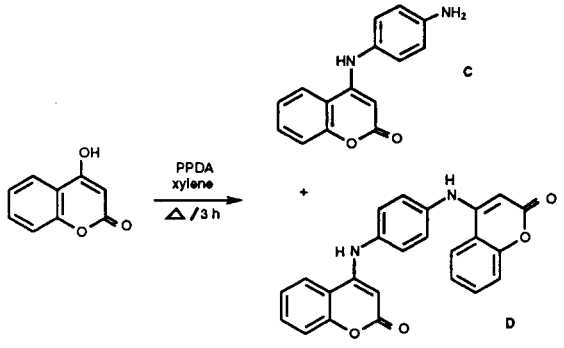
Solvents	Yield %
Ethanol	15
Dioxan	25
DMF	70
Acetic acid-ethanol v/v	70
Toluene	75
Xylene	85

The highest yield was obtained in xylene. We also found that there was little further reaction after 3 hours reflux.

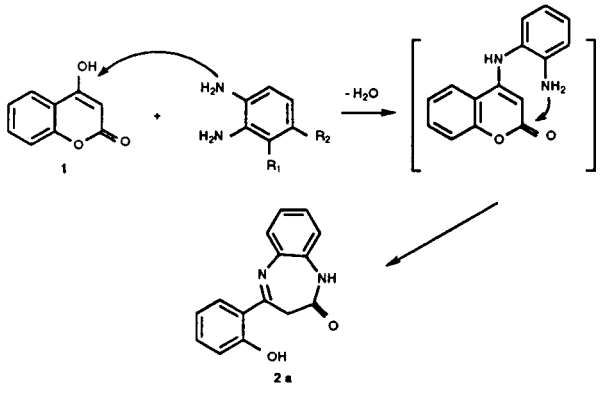
Since the 1,5-benzodiazepin-2-one can be formed *via* two routes (a or b), we studied the reaction mechanism to find out which site (2 or 4) of the coumarin ring underwent the first nucleophilic attack by 1,2-phenylenediamine. In these experiments, we employed 1,4-phenylenediamine (PPDA) as it cannot give rise to 1,5-benzodiazepin-2-one *via* an intramolecular cyclisation, and compound **A** or **B** can only be formed by an intermolecular condensation of the free NH_2 group onto a second molecule of 4-hydroxycoumarin. This reaction was followed by tlc, which showed the formation of two compounds in different proportions. The two products were

separated on the basis of their different solubilities in methanol. The ^1H nmr spectrum (200 MHz, DMSO-d_6) of the major species showed a singlet at δ = 5.02 ppm attributed to an ethylenic proton, peaks from aromatic protons between δ = 6.65 and δ = 8.23 ppm, two singlets due to exchangeable protons at δ = 5.14 and δ = 9.0 ppm (2/1 ratio), and the disappearance of the singlet at δ = 12.39 ppm from the OH group of 4-hydroxycoumarin.

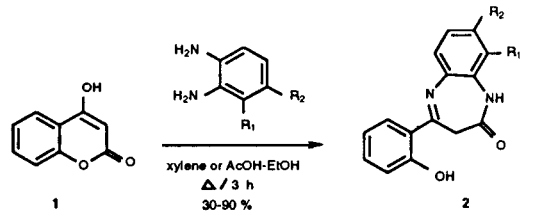
The structure of this compound was assigned as *N*-coumarinyl-1,4-phenylenediamine **C**, indicating that the diamine condenses on the 4 position of the coumarin ring. The minor species **D** was derived from condensation of a second molecule of 4-hydroxycoumarin onto the free NH_2 group of the major species.



These observations indicated a two stage reaction for the formation of 1,5-benzodiazepin-2-one: a) condensation of 1,2-phenylenediamine onto the 4 position of 4-hydroxycoumarin with elimination of a molecule of water; b) intramolecular cyclization of the compound formed by nucleophilic attack of the free NH_2 group on position 2 with opening of the coumarin ring.



This new method of synthesis was applied to 1,2-phenylenediamines bearing various substituents such as Cl, F, CH_3, NO_2, and COOH in different positions, under the optimized reaction conditions described above.



2a	R_1 = H	R_2 = H	**2e**	R_1 = H	R_2 = Cl
2b	R_1 = H	R_2 = CH_3	**2f**	R_1 = H	R_2 = NO_2
2c	R_1 = CH_3	R_2 = H	**2g**	R_1 = H	R_2 = COOH
2d	R_1 = H	R_2 = F			

The reaction was followed by tlc, which showed in all cases that a condensation reaction gave rise to a single product. The structures could be determined by reference to the substituent on the ring [19-21]. For example, if the substituent is a donor group (Cl, F, CH_3), the NH_2 group at position 1 reacts first, while for electron attracting substituents (NO_2, COOH), the NH_2 group at position 2 reacts first. Yields were high except for the 1,2-phenylenediamines bearing NO_2 or COOH groups, which did not react in xylene. This was accounted for by the attractive effect of the substituents, which attenuated the nucleophilicity of the NH_2 groups. The presence of a methyl group in the α position to the NH_2 group did not reduce its reactivity as the corresponding 1,5-benzodiazepin-2-one was obtained in 60% yield.

In view of the lack of reaction of compounds **2f** and **2g**, we attempted to devise a method of favoring nucleophilic attack of diamines bearing an electron attracting group. This was achieved in acidic medium (acetic acid-ethanol v/v), and the corresponding 1,5-benzodiazepin-2-ones were obtained in moderate yields (30% for R_2 = NO_2 and 60% for R_2 = COOH).

On the basis of these results, we developed a new route to the 1,5-benzodiazepin-2-ones from 4-hydroxycoumarin and substituted 1,2-phenylenediamines by refluxing in either xylene or acetic acid-ethanol. We also determined the reaction mechanism. This synthetic method has the advantage of simplicity as it can be readily carried out with commercially available reagents. It is also selective as only a single product is formed in good yield. The synthethized compounds possess several reactive sites, and may be employed as synthons in routes to other heterocyclic compounds.

EXPERIMENTAL

Melting points were determinated in an Electrothermal apparatus. ^1H nmr spectra were recorded on a Bruker AC 80 instrument (solvent DMSO-d_6), and mass spectra on a Nermag R 1010 spectrometer (70 ev, electron impact). Elemental analysis was carried out at the Interuniversity microanalysis center in Toulouse.

4-(2'-Hydroxyphenyl)-1,5-benzodiazepin-2-ones.

General Procedure.

A solution of 4-hydroxycoumarin (1.62 g, 0.01 mole), 1,2- or 1,4-phenylenediamine (0.01 mole) in xylene (50 ml) or acetic acid-ethanol v/v (20/20) was refluxed for 3 hours. The precipitate which formed while hot or on cooling to room temperature was washed with hexane or ether and then recrystallized.

4-(2'-Hydroxyphenyl)-1,5-benzodiazepin-2-one (**2a**).

This compound was crystallized from acetonitrile (yield = 85%), mp 267-268°; ^{1}H nmr: δ 3.61 (s, 2H, CH_2), 6.92-7.97 (m, 8H, Ar), 10.71 (s, 1H, NH), 14.07 (s, 1H, OH); ms: (m/z, %): 252 (M^+, 68), 210 (100), 182 (20), 91 (29), 77 (28), 65 (36).

Anal. Calcd. for $C_{15}H_{12}N_2O_2$: C, 71.43; H, 4.76; N, 11.11. Found: C, 71.17; H, 4.76; N, 11.16.

4-(2'-Hydroxyphenyl)-8-methyl-1,5-benzodiazepin-2-one (**2b**).

This compound was crystallized from dioxan (yield = 75%), mp 305-306°; ^{1}H nmr: δ 2.34 (s, 3H, CH_3), 3.59 (s, 2H, CH_2), 6.89-7.96 (m, 7H, Ar), 10.63 (s, 1H, NH),14.12 (s, 1H, OH); ms: (m/z, %): 266 (M^+, 68), 224 (100), 196 (2), 91 (4), 77 (6), 65 (4).

Anal. Calcd. for $C_{16}H_{14}N_2O_2$: C, 72.18; H, 5.26; N, 10.52. Found: C, 71.86; H, 5.18; N, 10.35.

4-(2'-Hydroxyphenyl)-9-methyl-1,5-benzodiazepin-2-one (**2c**).

This compound was crystallized from acetonitrile (yield = 60%), mp 268-269°; ^{1}H nmr: δ 2.40 (s, 3H, CH_3), 3.58 (s, 2H, CH_2), 6.91-7.98 (m, 7H, Ar), 10.63 (s, 1H, NH), 14.35 (s, 1H, OH); ms: (m/z, %): 266 (M^+, 58), 224 (100), 196 (15), 91 (15), 77 (17), 65 (12).

Anal. Calcd. for $C_{16}H_{14}N_2O_2$: C, 72.18; H, 5.26; N, 10.52. Found: C,72.02; H, 5.20; N, 10.37.

8-Fluoro-4-(2'-hydroxyphenyl)-1,5-benzodiazepin-2-one (**2d**).

This compound was crystallized from dioxan (yield = 75%), mp 280-281°; ^{1}H nmr: δ 3.64 (s, 2H, CH_2), 6.93-7.99 (m, 7H, Ar), 10.70 (s, 1H, NH), 13.63 (s, 1H, OH); ms: (m/z, %): 270 (M^+, 100), 228 (2), 200 (1), 91 (1), 77 (1), 65 (1).

*Anal.*Cald. for $C_{15}H_{11}FN_2O_2$: C, 66.66; H, 4.07; N, 10.37. Found: C, 66.64; H, 4.07; N, 10.35.

8-Chloro-4-(2'-hydroxyphenyl)-1,5-benzodiazepin-2-one (**2e**).

This compound was crystallized from dioxan (yield = 90%), mp 262-263°; ^{1}H nmr: δ 3.66 (s, 2H, CH_2), 6.91-7.97 (m, 7H, Ar), 10.77 (s, 1H, NH), 13.74 (s, 1H, OH); ms: (m/z, %): 286 (M^+, 46), 244 (100), 216 (16), 91 (17), 77 (14), 65 (12).

Anal. Calcd. for $C_{15}H_{11}ClN_2O_2$: C, 62.82; H, 3.83; N, 9.77. Found: C, 62.53; H, 3.76; N,9.74.

4-(2'-Hydroxyphenyl)-8-nitro-1,5-benzodiazepin-2-one (**2f**).

This compound was crystallized from dioxan (yield = 30%, acetic acid-ethanol),mp 199-200°; ^{1}H nmr: δ 3.81 (s, 2H, CH_2), 6.81-8.25 (m, 7H, Ar), 11.00 (s, 1H, NH), 13.37 (s, 1H, OH); ms: (m/z, %) 297 (M^+, 100), 255 (67), 91 (45), 77 (31), 65 (22).

Anal. Calcd. for $C_{15}H_{11}N_3O_4$: C, 60.60; H, 3.70; N, 14.14. Found: C, 60.37; H, 3.63; N, 14.10.

8-Carboxy-4-(2'-hydroxyphenyl)-1,5-benzodiazepin-2-one (**2g**).

This compound was crystallized from dioxan (yield = 60%, acetic acid-ethanol), mp 277-278°; ^{1}H nmr: δ 3.67 (s, 2H, CH_2), 6.92-7.99 (m, 7H, Ar), 10.84 (s, 1H, NH), 13.18 (s, 1H, OH), 13.72 (s, 1H, OH); ms: (m/z, %): 296 (M^+, 76), 254 (100), 226 (13), 91 (8), 77 (8), 65 (7).

*Anal.*Calcd. for $C_{16}H_{12}N_2O_4$: C, 64.86; H, 4.05; N, 9.45. Found: C, 64.47; H, 4.00; N, 9.37.

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