

SYNTHESIS OF NEW FUSED BENZOPYRANO-BENZODIAZEPINONES

Rafik Gharbi, Belsem Trimeche and Zine Mighri *

Laboratoire de Chimie des Substances Naturelles et de Synthèse Organique
Faculté des Sciences de Monastir - 5000, Monastir, Tunisia.

Marie-Thérèse Martin

Institut de Chimie des Substances Naturelles - CNRS, 91198 Gif-sur-Yvette, France.

Abstract : The synthesis of a new series of compounds, the [1]benzopyrano[4,3-c]1,5-benzodiazepin-2(3*H*)-ones **7a-d** by condensation of 4-(2-hydroxyphenyl)-1,5-benzodiazepin-2-ones **4a-d** with *N,N*-dimethylformamide dimethylacetal (DMFDMA) **5** in good yields is reported.

Introduction

A number of studies have been carried out on the reaction of 4-hydroxycoumarin with nitrogen nucleophiles such as amines (1), diamines (2,3) and hydrazines (4,5). Thus, it was reported that the reaction between 4-hydroxycoumarin **1** and methylhydrazine or arylhydrazines gives the 3-(2-hydroxyphenyl)-1-methyl-2-pyrazolin-5-one **2a** and the 1-aryl-3-(2-hydroxyphenyl)-2-pyrazolin-5-ones **2b** respectively. Compounds **2a,b** treated with triethyl orthoacetate and diethoxymethyl acetate were then converted to the corresponding [1]benzopyrano[4,3-c]pyrazolin-5(2*H*)-ones **3a-c** (4,5). We also noticed that the reaction between chromone-3-carboxylic acid and phenylhydrazine has been shown to be an efficient way to 2-phenyl-[1]benzopyrano[4,3-c]pyrazol-3(2*H*)-one **3d** (6). Another but, lengthier, route to **3c** and **3d** was published by Colotta *et al* (7) and involved reaction of 3-ethyl-(1-benzyloxyphenyl)-3-oxopropanoate and arylhydrazines.

On another hand, the reaction of 4-hydroxycoumarin with 1,2-phenylenediamines has been found to give rise to 4-(2-hydroxyphenyl)-1,5-benzodiazepin-2-ones **4** after the opening of the coumarin ring (2) (figure 1).

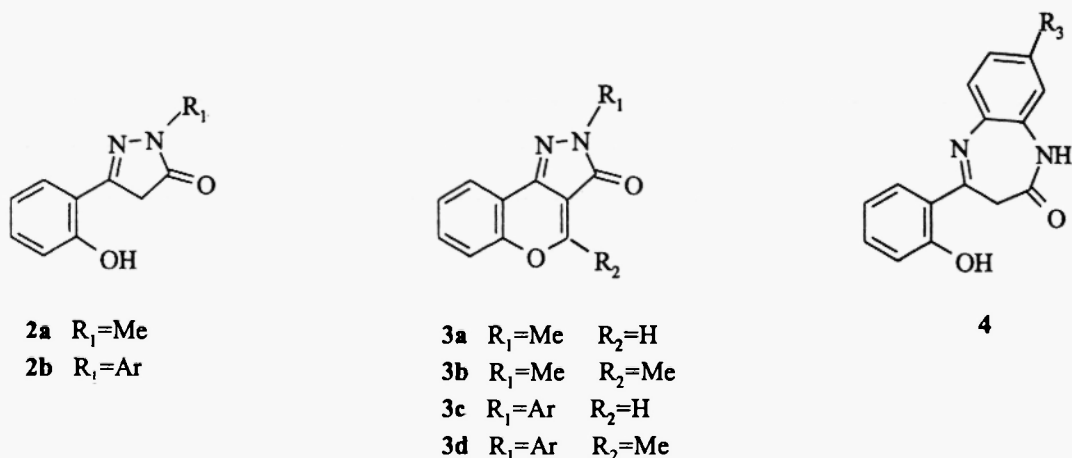


Figure 1 : structures of compounds **2**, **3** and **4**

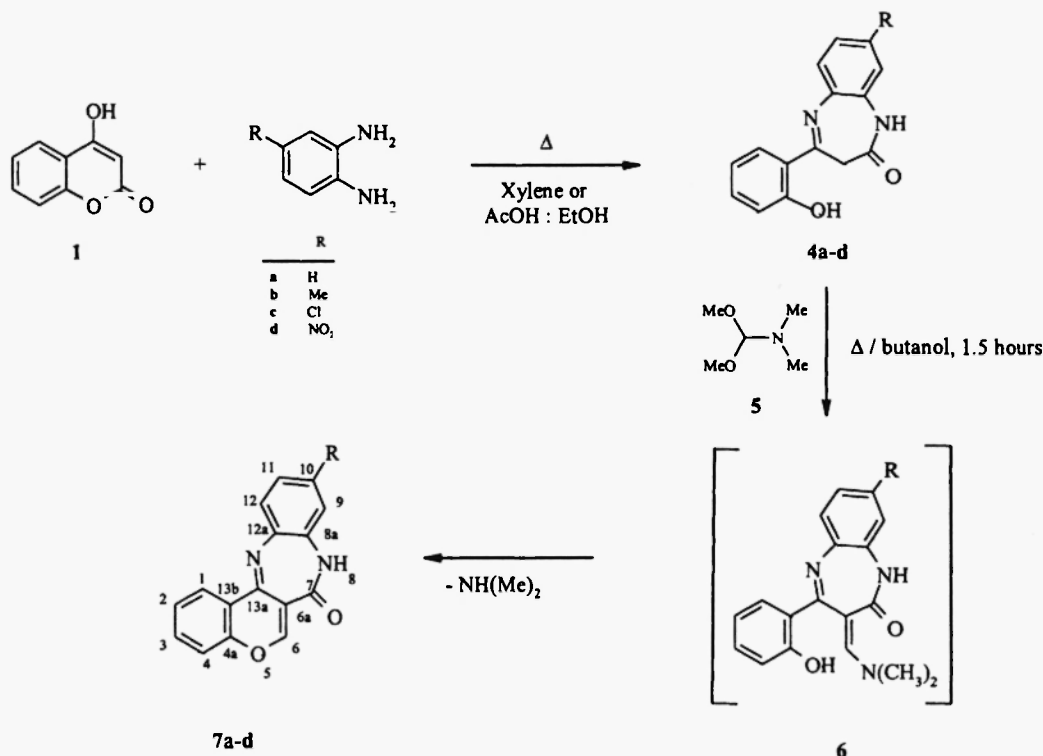
Results and Discussion

In the search of routes to new polycyclic heterocycles of biological interest from 4-hydroxycoumarin (8-10), we report here a simple preparation of 13-substituted [1]benzopyrano[4,3-*c*]1,5-benzodiazepin-2(3*H*)-ones **7a-d** from the reaction of *N,N*-dimethylformamide dimethylacetal (DMFDMA) **5** and 4-(2-hydroxyphenyl)-1,5-benzodiazepin-2-ones **4a-d**. Thus we have found that refluxing a solution of the benzodiazepinone **4** and 3 equivalents of DMFDMA in butanol for 1.5 hours, led to a series of the hitherto unreported compounds **7a-d**. A control by thin layer chromatography, (eluent: chloroform-ethyl acetate, 8:2) showed in all cases that the reaction gave rise to a single product that precipitate in the reactional mixture while hot. It is believed that under reaction conditions, the 3-dimethylaminomethylen-2-(2-hydroxyphenyl)-1,5-benzodiazepin-7-one **6** (non isolable) undergoes further cyclisation *via* loss of dimethylamine to yield final isolable product (scheme 1).

Trials for the preparation of compounds **7** using other routes failed, thus refluxing an equimolar ratio of 1,5-benzodiazepin-2-one **4** and aniline in the presence of excess ethyl orthoformate does not give any product (**7**). On another hand, we have projected to reach heterocycles **7** from the reaction of *o*-phenylenediamines with chromones bearing a functional group in 3-position. Nevertheless, we found that the direct reaction between the diamine and chromone-3-carboxylic acid and related esters has been recently investigated (11) and gave a variety of products other than the aforementioned compounds **7**.

All the products were obtained as solids, and their structures were elucidated by ir measurements, mass spectrometry, and nmr experiments: mono-dimensional: ^1H , ^{13}C ; two-dimensional homonuclear ^1H - ^1H (COSY) and two-dimensional heteronuclear ^1H - ^{13}C (HMQC, HMBC).

Inspection of compound **7a** ^1H nmr spectrum at (400 MHz, DMSO-*d*) showed the presence of a singlet at $\delta=10.15$ ppm corresponding to the lactamic proton H_8 . The spectrum, also, displayed a multiplet around 8.30 ppm due to overlapped signals relatives to protons H_6 and H_1 . The chemical shifts $\delta=8.29$ ppm and $\delta=8.30$ ppm were, then, attributed to H_6 and H_1 respectively, on the basis of the direct correlation cross peaks (H_6 - C_6 , $\delta\text{C}_6=157.2$ ppm) and (H_1 - C_1 , $\delta\text{C}_1=125.8$ ppm) deduced from the HMQC spectrum. The set of peaks between $\delta=7.01$ ppm and $\delta=7.60$ ppm was attributed to the aromatic protons of both the benzopyrane and the benzodiazepinone moieties. Inspection of the HMBC spectrum showed that protons H_6 and H_8 both correlate with the quaternary carbon C_{6a} at $\delta=114.0$ ppm and the one of the carbonyl at $\delta=163.8$, consequently, this indicates a C_6 - C_{6a} - C_7 -N linkage. We also underscored correlation cross peaks of H_6 and H_1 with a same quaternary carbon C_{13b} at $\delta=145.2$ ppm suggesting a C_1 - C_{13b} - C_{13a} - C_{6a} - C_6 connection. Thus, the use of 2D nmr experiments permits unambiguous and complete ^1H and ^{13}C nmr assignments for compounds **7a-d** and an establishing of a whole set of linkages that confirms the molecular skeleton.



Scheme 1 : synthesis of compounds 7a-d

Conclusion

On the basis of the above-described results, we developed a route to new fused Benzopyrano-Benzodiazepinones from 4-(2-hydroxyphenyl)-1,5-benzodiazepin-2-ones and *N,N*-dimethylformamide dimethylacetal. Unambiguous elucidation of the molecular skeleton was performed using 2D nmr spectroscopic methods. The synthesis has the advantage of simplicity, it is also selective as only a single product is formed in good yield. Moreover, tetracyclic heterocycles 7 contain both benzopyrane and 1,5-benzodiazepin-2-one frameworks and may exhibit biological activity.

Experimental

Melting points were taken on a Buchi-510 capillary melting point apparatus. Infrared spectra (potassium bromide) were run on a Perkin-Elmer IR-197 infrared spectrometer. The mass spectra were measured using an AEI MS-50 mass spectrometer operating in electron impact mode at 70 eV. ¹H and ¹³C nmr spectra were recorded on a Bruker spectrometer AC-300 using TFA-*d* (all the samples have been found to be very soluble in this solvent) whereas 2D experiments were performed on an AM-400 Bruker spectrometer in DMSO-*d* thus to observe peaks relative to exchangeable protons.

The starting materials 4a-d were prepared according to the literature (2) by refluxing, for 3 hours, a solution of 4-hydroxycoumarin 1 and a series of selected various commercially available substituted 1,2-phenylenediamines in xylene or acetic acid-ethanol (v:v). The precipitate, that formed while hot or on cooling at room temperature, was washed with ether before recrystallization in the appropriate solvent.

General Procedure for the preparation of compounds 7a-c.

A stirred solution of 4-(2'-hydroxyphenyl)-1,5-benzodiazepin-2-ones 4 (1 mmol) and *N,N*-dimethylformamide dimethylacetal 5 (0.42 ml, 3 mmol), in butanol (15 ml) was refluxed for 1.5 hours. The precipitate generally formed while hot, was filtered, washed with ether then recrystallized in the suitable solvent.

Benzopyrano-Benzodiazepinone 7a (R=H).

Compound **7a** was crystallized from toluene as yellow crystals (yield = 75 %), m.p. 272 °C, MS (IE), m/z 262.9 [M^+], IR (cm^{-1}) $\nu_{\text{C-N}}=1620$, $\nu_{\text{C-O}}=1678$, $\nu_{\text{N-H}}=3207$, ^1H nmr (TFA- d), δ (ppm) : 8.68 (d, 1H, H_1 , $J=8.0$ Hz), 8.05 (m, 1H, H_2), 8.30 (m, 1H, H_3), 8.05 (m, 1H, H_4), 9.50 (s, 1H, H_6), 7.34 (d, 1H, H_9 , $J=7.4$ Hz), 7.62 (m, 1H, H_{10}), 7.46 (m, 1H, H_{11}), 7.66 (m, 1H, H_{12}), ^{13}C nmr, δ (ppm) : $C_1=125.3$, $C_2=132.4$, $C_3=141.5$, $C_4=122.3$, $C_{4a}=157.3$, $C_6=169.5$, $C_{6a}=111.2$, $C_7=165.9$, $C_{8a}=128.9$, $C_9=124.5$, $C_{10}=134.1$, $C_{11}=129.4$, $C_{12}=127.0$, $C_{12a}=128.1$, $C_{13a}=156.9$, $C_{13b}=116.8$.

Benzopyrano-Benzodiazepinone 7b (R=Me).

Compound **7b** was crystallized from DMF as yellow crystals (yield = 78%), m.p. 349 °C, MS (IE), m/z 276.1 [M^+], IR (cm^{-1}) $\nu_{\text{C-N}}=1620$, $\nu_{\text{C-O}}=1677$, $\nu_{\text{N-H}}=3204$, ^1H nmr (TFA- d), δ (ppm): 8.57 (d, 1H, H_1 , $J=8.1$ Hz), 7.95 (m, 1H, H_2), 8.22 (dd, 1H, H_3 , $J=7.6, 7.7$ Hz), 7.95 (m, 1H, H_4), 9.38 (s, 1H, H_6), 2.43 (s, 3H, Me), 7.35 (brs, 1H, H_9), 7.35 (brs, 1H, H_{11}), 7.12 (d, 1H, H_{12} , $J=8.4$ Hz), ^{13}C nmr, δ (ppm) : $C_1=125.1$, $C_2=132.4$, $C_3=141.3$, $C_4=122.2$, $C_{4a}=157.1$, $C_6=169.4$, $C_{6a}=111.0$, $C_7=165.6$, $C_{8a}=127.7$, $C_9=126.9$, $C_{10}=141.1$, C-Me=20.9, $C_{11}=134.8$, $C_{12}=124.4$, $C_{12a}=126.2$, $C_{13a}=156.7$, $C_{13b}=116.7$.

Benzopyrano-Benzodiazepinone 7c (R=Cl).

Compound **7c** was crystallized from DMF as yellow crystals (yield = 87%), m.p. 329 °C, MS (IE), m/z 296.1 [M^+], IR (cm^{-1}) $\nu_{\text{C-N}}=1620$, $\nu_{\text{C-O}}=1681$, $\nu_{\text{N-H}}=3201$, ^1H nmr (TFA- d), δ (ppm) : 8.65 (d, 1H, H_1 , $J=8.7$ Hz), 8.03 (dd, 1H, H_2 , $J=8.7, 7.1$ Hz), 8.30 (d, 1H, H_3 , $J=8.0, 7.1$ Hz), 8.04 (d, 1H, H_4 , $J=8.0$ Hz), 9.50 (s, 1H, H_6), 7.66 (brs, 1H, H_9), 7.52 (brd, 1H, H_{11} , $J=8.5$ Hz), 7.25 (d, 1H, H_{12} , $J=8.5$ Hz), ^{13}C nmr, δ (ppm) : $C_1=125.5$, $C_2=132.6$, $C_3=141.8$, $C_4=122.4$, $C_{4a}=157.4$, $C_6=170.1$, $C_{6a}=111.3$, $C_7=165.7$, $C_{8a}=129.1$, $C_9=126.7$, $C_{10}=135.6$, $C_{11}=133.8$, $C_{12}=125.7$, $C_{12a}=127.6$, $C_{13a}=157.9$, $C_{13b}=116.7$.

Benzopyrano-Benzodiazepinone 7d (R=NO₂).

Compound **7d** was crystallized from dioxane as yellow crystals (yield = 45 %), m.p. 252 °C, MS (IE), m/z 307.1 [M^+], IR (cm^{-1}) $\nu_{\text{C-N}}=1620$, $\nu_{\text{C-O}}=1679$, $\nu_{\text{N-H}}=3203$, ^1H nmr (TFA- d), δ (ppm) : 9.04 (d, 1H, H_1 , $J=8.1$ Hz), 8.37 (m, 1H, H_2), 8.62 (t, 1H, H_3 , $J=7.8$ Hz), 8.38 (m, 1H, H_4), 9.90 (s, 1H, H_6), 8.53 (brs, 1H, H_9), 8.53 (brs, 1H, H_{11}), 8.21 (d, 1H, H_{12} , $J=9.1$ Hz), ^{13}C nmr, δ (ppm) : $C_1=125.8$, $C_2=133.1$, $C_3=142.5$, $C_4=122.6$, $C_{4a}=157.9$, $C_6=170.5$, $C_{6a}=111.7$, $C_7=165.5$, $C_{8a}=130.5$, $C_9=120.0$, $C_{10}=150.6$, $C_{11}=123.6$, $C_{12}=128.6$, $C_{12a}=133.7$, $C_{13a}=158.8$, $C_{13b}=116.9$.

Aknowledgements

A part of this work has been performed in the I.C.S.N.-C.N.R.S. (Gif-sur-Yvette), thus we are grateful to Professor Pierre Potier and Dr Christian Marazano for the facilities provided.

References

- 1 P. Ollinger, O. S. Wolfbeis and H. Junek, *Moastch. Chem.*, **106**, 963-971, (1975).
- 2 M. Hamdi, O. Grech, R. Sakellariou, V. Speziale, *J. Heterocyclic Chem.*, **31**, 509-511, (1994).
- 3 M. Hamdi, S. Cottet, C. Tedeschi and V. Speziale, *J. Heterocyclic Chem.*, **34**, 1821-1823, (1997).
- 4 B. Chantegrel, S. Gelin, *Synthesis*, 548-549, (1985).
- 5 J. A. Froggett, M. H. Hockley and R. B. Titman, *J. Chem. Res. (S)*, 30-31, (1997).
- 6 C. K. Ghosh and K. K. Mukhopadhyay, *Synthesis*, 779-781, (1978).
- 7 V. Colotta, L. Ceochi, F. Melani, G. Palazzino and G. Filacchioni, *Tet. Lett.*, **28**, n° 43, 5165-5168, (1992).
- 8 M. Hamdi, R. Sakellariou, V. Speziale, *J. Heterocyclic Chem.*, **29**, 1817-1819, (1992).
- 9 J. H. Boyer, in *Heterocyclic Compounds* (R. C. Elderfield, ed), Vol. 2, John Wiley, New York, p. 193, 213 (1961).
- 10 A. El Kihel, M. Benchidmi, M. Essassi, P. Bauchat and R. Dannion-Bougot, *Synth. Comm.*, **29**, n° 14, 2435-2445, (1999).
- 11 F. Risitano, G. Grassi and F. Foti, *J. Heterocyclic Chem.*, **38**, 1083-1086, (2001).

Received on June 10, 2002