A Convenient Synthesis of a Novel Fused Tetracyclic Heterocoumarin

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Received August 24, 2004

New tetracyclic 6*H*-[1]benzopyrano[3,4-*e*]pyrazolo[1,5-*a*]pyrimidin-6-ones (**4a-e**) have been synthesized through the condensation under acidic conditions of [1]benzopyrano[4,3-*c*][1,5]-benzodiazepin-7(8*H*)-one (**1**) and a series of 3,4-disubsituted 5-amino-1*H*-pyrazoles **3a-e**.

J. Heterocyclic Chem., **42**, 169 (2005).

Introduction.

Coumarins constitute a very relevant family of compounds that have been developed as anticoagulant drugs such as warfarin [1], antibiotic agents such as novobiocin [2] or antitumour agents [3]. Particularly varied biological activity of coumarins fused with other heterocycles in the 3,4-position has been reported [4,5].

For this purpose, the recent literature is enriched with progressive findings about the synthesis of such scaffolds [6-8]. In the light of our interest in the synthesis of novel molecules featuring heterocyclic moieties fused onto the coumarin ring [9], we report here an efficient access to novel tetracyclic coumarino-pyrazolopyrimidines.

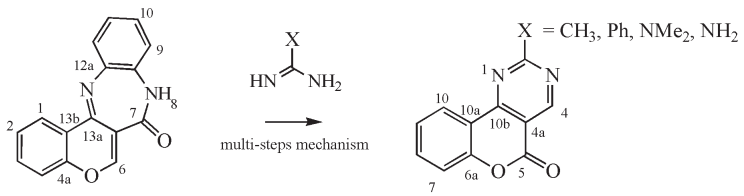
Results and Discussion.

Among the already known routes to coumarins [3,4]-fused to five, six and seven-membered rings the most commonly used strategy involves the condensation between 3-formyl-4-hydroxycoumarin, 4-chloro- or 4-azido-3-formylcoumarin and binucleophiles such as hydrazines, hydroxylamine, guanidines, *o*-phenylenediamines and α-amino methylenic compounds, leading to coumarin-annelated pyrazoles, isoxazoles, pyrimidines [10], benzodiazepines [11] and pyrroles [12] respectively. In this context we have recently developed an easy route to different tricyclic fused heterocoumarins through the interaction between the benzopyrano-benzodiazepinone **1** and several two- functional *N*-nucleophiles. In particular when amidines and guanidines were reacted with **1** under mild basic conditions the reaction offered the coumarino-pyrimidine **2** as a result of a multiple-steps sequence involving successive ring-opening and recyclization processes [9].

The versatility of this reaction stimulated us to propose our newly reported approach to heterocyclic ambident nitrogen-nucleophiles. Consequently, 5-amino-1*H*-pyrazole (**3**), which incorporates a free amino function at the α-position relative to the pyrazole ring NH group, represents the building block of choice for fusing a pyrazolo-pyrimidine moiety to the *c* face of the coumarin ring. In fact as pyrazolopyrimidines themselves form a part of many heterocycles of biological interest [13,14], having both nuclei fused within a same molecular framework may result in new compounds with interesting potential pharmacological profiles. Moreover a search of the literature yielded only one reference to the synthesis of the coumarino-pyrazolopyrimidine skeleton which was a report of Govori *et al.* [15] who recently prepared some 6*H*-[1]benzopyrano[3,4-*e*]pyrazolo[1,5-*b*]pyrimidin-6-one derivatives from 4-chlorocoumarin-3-carbonitrile and pyrazole **3**. Our target system being a regioisomer of these compounds remains thus hitherto unknown.

The reaction between **1** and aminopyrazoles **3** appears to strongly depend on experimental conditions, thus after several variations we have found that heating a solution of the reactants in glacial acetic acid for a relatively short time (around ten minutes) afforded exclusively the anticipated

Scheme 1



1 **2**

molecule **4**. The products that precipitated on cooling the stirred reaction mixture were isolated in an almost pure form and showed as a blue color on tlc under uv-light (365 nm). Moreover, TLC analysis of the mother liquors revealed the presence of *o*-phenylenediamine, identification of which arose from comparison with an authentic sample. This is consistent with what we observed earlier when reacting **1** with some 1,2- and 1,3-*N*-binucleophiles [9].

The reaction mechanism, as depicted in Scheme 2, is assumed to start by nucleophilic attack of the NH_2 group in pyrazole **3** to the 6-position of **1** with concomitant opening of the chromone ring followed by condensation of the pyrazolic sp_3-hybridized nitrogen with the imine function at the benzodiazepinone ring. Subsequent cleavage of the so-reduced C-N bond in *i'* then occurs as a result of heteroaromatization of the newly formed pyrimidine nucleus enabling intermediate *i''* to form then recyclizing into **4** *via* an *in situ* lactonization reaction with loss of an *o*-phenylenediamine molecule.

The structures of compounds **4a-e** have been fully characterized by elemental analysis, IE mass spectrometry, ^1H, ^{13}C NMR, and two-dimensional COSY and HMBC COSY and HMBC experiments for derivative **4b**. From the COSY spectrum we detected correlations of H-11 with the multiplet at 7.67 ppm (2H) and with the triplet at 7.96 ppm (1H), which was undoubtedly attributed to H-9. The resonance corresponding to H-9 is found to correlate with both H-8 and H-10, which overlap as a multiplet around 7.67, showing that H-10 is, in turn, found to correlate with H-11. In addition a whole set of linkages confirming the molecular skeleton was deduced from the HMBC spectrum. Thus we detected long-range correlations between the methyl protons and both C-2 (159.4 ppm) and C-3 (83.7 ppm) also, H-5 correlates simultaneously with C-5 (152.5 ppm), C-5a (106.0 ppm), C-6 (158.1 ppm) and C-11b (142.2 ppm) which in turn correlates with H-11. Thereby [C_{Me}-C_2-C_3], [C_5-C_{5a}-C_6] and [C_5-C_{5a}-C_{11b}- C_{11a}-C_{11}] chains were confirmed, which support the proposed skeleton.

A complete ^{13}C assignment for compounds **4** was established and is listed in Table 1. Nevertheless whereas the 2D-nmr investigations do not permit to unequivocally distinguish between the two possible coumarino-pyrazolo-

Scheme 2

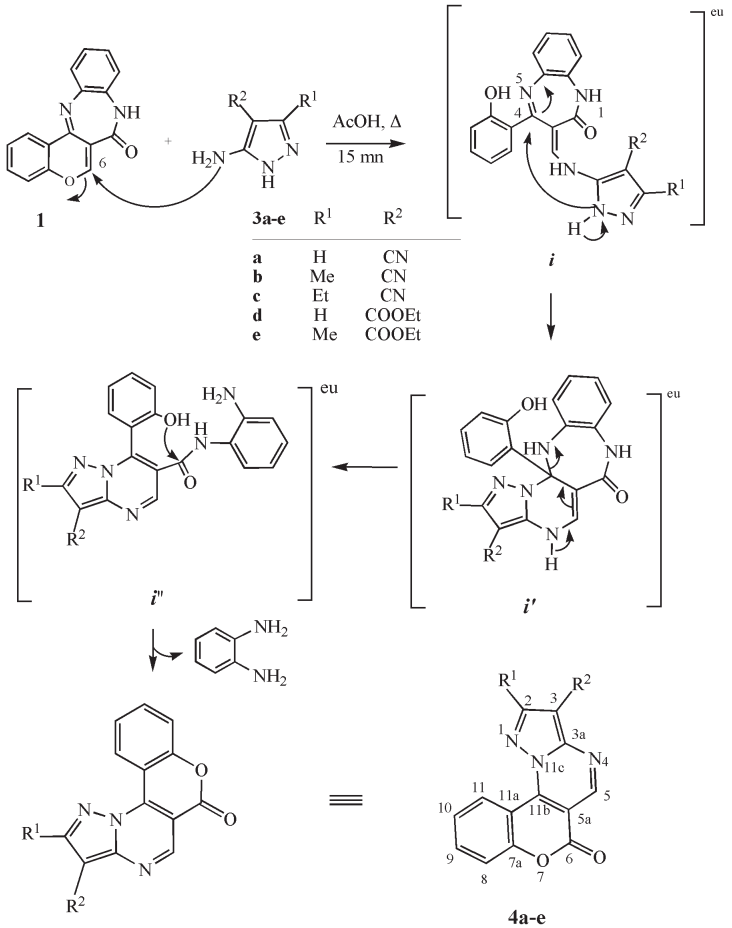


Table 1

^{13}C- NMR Data for compounds 4a-e at 125.77 MHz in DMSO-d_6

Compound Carbon		**4a** [a]	**4b** [b]	**4c**	**4d**	**4e**
C-2		149.9	159.4	164.0	149.6	160.5
C-3		84.4	83.7	82.6	104.2	103.1
C-3a		152.8	152.8	153.0	149.6	150.9
C-5		153.3	152.5	152.6	152.6	151.9
C-5a		106.8	106.0	106.1	105.8	104.2
C-6		158.5	158.1	158.1	158.6	158.6
C-7a		154.6	154.1	154.1	154.5	154.5
C-8		118.3	117.8	117.8	118.2	117.9
C-9		136.6	136.0	136.0	136.1	135.5
C-10		126.1	125.5	125.5	125.8	125.5
C-11		130.1	129.8	129.8	130.2	131.0
C-11a		111.7	111.4	111.4	111.9	111.6
C-11b		143.3	142.2	142.3	142.6	141.7
R^2:	CN	113.0	112.6	112.6	-	-
	CO	-	-	-	161.6	162.8
	CH_3	-	-	-	14.9	14.6
	CH_2	-	-	-	60.7	60.9
R^1:	CH_3	-	13.7	12.2	-	15.8
	CH_2	-	-	21.5	-	-

[a] Compound **4a** was dissolved in $CDCl_3$; [b] The NMR ^{13}C spectrum for **4b** was recorded at 150 MHz.

pyrimidine systems, an X-ray analysis enabled us to assign the correct regioisomer thereby confirming our above-proposed mechanism pathway (see Figure 1).

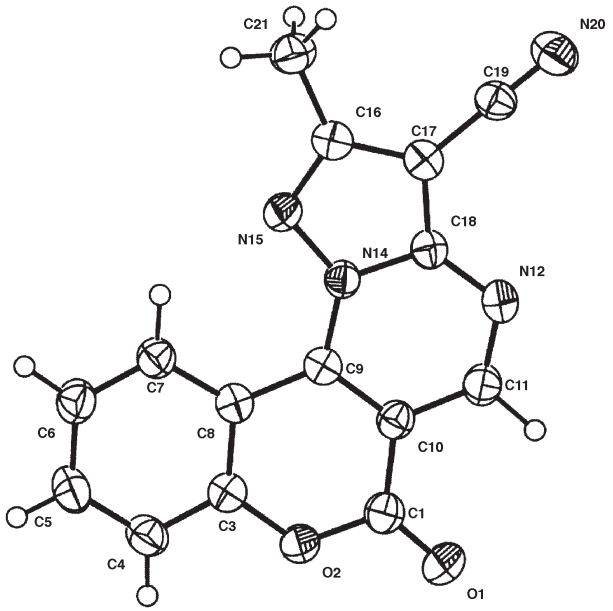


Figure 1. ORTEP view of 4b. Displacement ellipsoids are scaled to 50 % level.

To resume, the key benzopyrano-benzodiazepinone 1 demonstrates certain utility for the construction of the coumarino[3,4-*e*]pyrazolo[1,5-*a*]pyrimidines system with regard to both novelty of structure and versatility of the procedure, which utilizes readily available inexpensive starting materials and simple experimental protocoles.

EXPERIMENTAL

General.

Benzopyrano-benzodiazepinone **1** was prepared following our previously described procedure [16] following the two steps formylation-cyclization reaction between 4-(2-hydroxyphenyl)-1,5-benzodiazepin-2-one [17] and excess DMFDMA. Aminopyrazoles **3a-e** were synthesized according to known methods [18].

Melting points were taken on a Buchi-510 capillary apparatus. ^{1}H and ^{13}C NMR spectra were recorded at 500 MHz on an Avance-500 Bruker spectrometer whereas 2D experiments were performed at 600 MHz on a Bruker DRX-600 instrument. Dimethylsulfoxyde-d_6 was the solvent unless otherwise mentioned. Mass spectra were obtained with an Automass Multi Thermo Finnigan (electron impact mode, 70 *eV*). Analytical thin layer chromatography was performed using aluminium sheets of Merck silica gel 60 F_{254}, 0.2 mm, which were developed with ethyl acetate. Elemental analysis for derivatives **4b** and **4c** were performed at the *Institut de Chimie des Substances Naturelles. CNRS de Gif-sur-Yvette, France.*

General Procedure for the Preparation of Coumarino-pyrazolopyrimidines (**4a-e**).

To a solution of 786 mg (3 mmol) of compound **1** in glacial acetic acid (10 mL) was added an equimolar amount of 5-aminopyrazole (**3a-e**), the mixture was heated for 10 to 15 minutes and then left to cool at room temperature while stirring allowing products **4a-e** to precipitate. The solid was collected by filtration, washed with diethylether, dried and recrystallized from tetrahydrofurane, (recrystallization of derivatives **4a** and **4d** (R^1= H) should preferably be preceded by a flash chromatography of the crude).

3-Cyano-6*H*-[1]benzopyrano[3,4-*e*]-pyrazolo[1,5-*a*]pyrimidin-6-one (**4a**).

Compound **4a** formed light brownish crystals; m.p. 217 °C; yield 50 %. ^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 7.59-7.65 (m, 2H, H-8, H-10), 7.93 (t, 1H, H-9, $J_{9\text{-}(8,10)}$= 7.5 Hz), 9.20 (s, 1H, H-2) 9.66 (d, 1H, H-11, $J_{11\text{-}10}$= 8.1 Hz), 9.38 (s, 1H, H-5). MS (IE): m/z, (%): 262 (100) [$M^{+\cdot}$], 237 (58), 88 (30), 75 (37), 53 (43).

Anal. Calcd. for $C_{14}H_6N_4O_2$: C, 64.13; H, 2.31; N, 21.37; O, 12.20. Found C, 64.39; H, 2.68; N, 20.95; O, 12.17.

3-Cyano-2-methyl-6*H*-[1]benzopyrano[3,4-*e*]pyrazolo[1,5-*a*]-pyrimidin-6-one (**4b**).

Compound **4b** was obtained as pale yellow crystals in 75 % yield; m.p. 208 °C. ^{1}H-NMR (600 MHz, DMSO-d_6): δ (ppm) 2.73 (s, 3H, Me), 7.67-7.68 (m, 2H, H-8, H-10), 7.96 (t, 1H, H-9, J= $J_{9\text{-}(8,10)}$= 7.5 Hz), 9.36 (s, 1H, H-5), 9.78 (d, 1H, H-11, $J_{11\text{-}10}$= 8.1 Hz). MS (IE): m/z, (%): 276 (100) [$M^{+\cdot}$], 100 (35), 88 (56), 75 (43).

Anal. Calcd. for $C_{15}H_8N_4O_2$: C, 65.22; H, 2.92; N, 20.28; O, 11.58. Found: C, 64.98; H, 3.04; N, 20.37; O, 11.61.

3-Cyano-2-ethyl-6*H*-[1]benzopyrano[3,4-*e*]-pyrazolo[1,5-*a*]-pyrimidin-6-one (**4c**).

Compound **4c** was obtained as pale yellow crystals in 85 % yield; m.p. 217 °C. ^{1}H-NMR (500 MHz, DMSO-d_6): δ (ppm) 1.44 (t, 3H, CH_3), 3.12 (q, 2H, CH_2, $J_{CH3\text{-}CH2}$= 7.2 Hz), 7.64-7.74 (m, 2H, H-8, H-10), 7.96 (t, 1H, H-9, $J_{9\text{-}(8,10)}$= 7.5 Hz), 9.30 (s, 1H, H-5), 9.77 (d, 1H, H-11, $J_{11\text{-}10}$= 8.1 Hz). MS (IE): m/z, (%): 290 (100) [$M^{+\cdot}$], 88 (23), 75 (25), 53 (30).

Anal. Calcd. for $C_{16}H_{10}N_4O_2$: C, 66.20; H, 3.47; N, 19.30; O, 11.02. Found C, 66.41; H, 3.39; N,19.14; O,11.06.

3-Ethylcarboxylate-6*H*-[1]benzopyrano[3,4-*e*]-pyrazolo[1,5-*a*]-pyrimidin-6-one (**4d**).

Compound **4d** was obtained as light brownish crystals in 45 % yield; m.p. 317 °C. ^{1}H-NMR (500 MHz, DMSO-d_6): δ (ppm) 1.35 (t, 3H, CH_3), 4.37 (q, 2H, CH_2, $J_{CH3\text{-}CH2}$= 7.1 Hz), 7.65-7.67 (m, 2H, H-8, H-10), 7.94 (t, 1H, H-9, $J_{9\text{-}(8,10)}$= 7.5 Hz), 9.03 (s, 1H, H-2), 9.40 (s, 1H, H-5), 9.83 (d, 1H, H-11, $J_{11\text{-}10}$= 8.1 Hz). MS (IE): m/z, (%): 309 (59) [$M^{+\cdot}$], 264 (100), 237 (100), 88 (32), 75 (60), 53 (47).

Anal. Calcd. for $C_{16}H_{11}N_3O_4$: C, 62.14; H, 3.58; N, 13.59; O, 20.69. Found C, 62.02; H, 3.91; N, 13.17; O, 20.28.

3-Ethylcarboxylate-2-methyl-6*H*-[1]benzopyrano[3,4-*e*]pyrazolo-[1,5-*a*]pyrimidin-6-one (**4e**).

Compound **4e** was obtained as pale yellow crystals in 65 % yield; m.p. 317 °C. ^{1}H-NMR (500 MHz, DMSO-d_6): δ (ppm) 1.44 (t, 3H, CH_3), 2.82 (s, 3H, CH_3), 3.46 (q, 2H, CH_2, $J_{CH3\text{-}CH2}$= 6.9 Hz), 7.47 (d, 1H, H-8), 7.52 (t, 1H, H-10, $J_{8\text{-}10}$= 8.3 Hz), 7.79 (t, 1H, H-9, $J_{9\text{-}(8,10)}$= 7.4 Hz), 9.42 (s, 1H, H-5), 9.93 (d, 1H, H-11, $J_{11\text{-}10}$= 8.3 Hz). MS (IE): m/z, (%): 323 (75) [$M^{+\cdot}$], 278(100), 251 (100), 238 (75), 88 (40), 75 (71), 53 (35).

Anal. Calcd. for $C_{17}H_{13}N_3O_4$: C, 63.16; H, 4.05; N, 13.00; O; 19.79%. Found C, 63.27; H, 3.95; N, 12.71; O, 20.27.

Acknowledgment.

The authors thank Dr. Pascal Retailleau at the X-ray Crystallographic Service, *ICSN. CNRS de Gif-sur-Yvette*, for the X-ray resolution of compound **4b**.

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