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Efficient synthesis of trisubstituted [1]benzopyrano[4,3-*b*]pyrrol-4(1*H*)-one derivatives from 4-hydroxycoumarin

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Abstract—Various trisubstituted [1]benzopyrano[4,3-*b*]pyrrol-4(1*H*)-one derivatives have been synthesized from 4-hydroxycoumarin with a 30–40% yield over six steps. The key step of the synthesis is a base-promoted intramolecular cyclization of enamines **5**, followed by dehydration to generate the fused pyrrole ring.

The varied biological activity of coumarins fused with a pyrrole ring system[1–5] has continued to stimulate a great deal of interest in the development of new methodologies for the synthesis of multi-substituted [1]benzopyranopyrroles. In 1999, for instance, an interesting procedure was reported for synthesis of [1]benzopyrano[4,3-*b*]pyrrol-4(1*H*)-ones from *N*(α)-(2-oxo-2*H*-1-benzopyran-4-yl) Weinreb α-aminoamides.[6] However, this procedure employed the unstable *N*,*O*-dimethylhydroxylamine[7] as a protection group and 1,3-dicyclohexylcarbodiimide (DCC) as an activating group, which lowers the atom efficiency of the synthesis. Furthermore, it suffered from the need for expensive organometallic reagents (RLi or RMgBr, up to 3 equiv.) and low temperature (as low as −60°C). Recently, 4-chloro-3-formylcoumarin and α-amino derivatives have been used in the synthesis of 2-functionalized [1]benzopyrano[4,3-*b*]pyrrol-4(1*H*)-one derivatives via the Fischer–Fink reaction.[8] Although this new synthesis requires neither protection nor harsh conditions, there are still several drawbacks with this synthetic route. First, the competing Knorr-type transformation might be observed if the α-amino derivatives possess a low electrophilic group or very reactive alkyl ketone. Second, since the 3-formyl group on coumarin is highly susceptible to nucleophilic attack, a second attack of an α-amino derivative may occur, complicating the products. Third, only 1,2-disubstituted, but not 1,2,3-trisubstituted [1]benzopyrano[4,3-*b*]pyrrol-4(1*H*)-one derivatives can be prepared by this synthesis. Thus, an efficient and protection-free synthesis of multi-functionalized [1]benzopyrano[4,3-*b*]pyrrol-4(1*H*)-one derivatives from inexpensive materials under mild conditions remains to be discovered. Here, we report an efficient procedure for preparation of trisubstituted [1]benzopyrano[4,3-*b*]pyrrol-4(1*H*)-one derivatives by reacting 2-acyl-4-methoxycoumarin with α-amino derivatives (e.g. methyl glycinate and α-amino ketones) followed by intramolecular cyclization and dehydration.

The reactions, as shown in Scheme 1, were performed by *O*-acylation of commercially available 4-hydroxycoumarin **1** with various acyl chlorides in the presence of triethylamine in methylene chloride to give the corresponding enol esters **2**, which were further treated with potassium cyanide without purification at ambient temperature for two days to obtain a good yield of the isomerized 2-acyl-4-hydroxycoumarins **3**. Methylation of the 4-hydroxy group of **3** with diazomethane (generated by Diazald) in ether in an ice-bath afforded the corresponding methyl ethers **4** with a moderate yield. Following purification of methyl ethers **4** by chromatography, a 1,4-addition and elimination reaction of **4** with the appropriate α-amino derivatives using triethylamine as a base in methanol gave the precipitated enamines **5**, which were further treated with sodium methoxide without purification to yield the fused pyrroles **6**. In this multi-step reaction, sodium methoxide serves as a second stronger base to facilitate the cyclization and subsequent dehydration of **5**. The yields of products **6a**–**e** were, with one exception, uniformly excellent; only analogues with R_1 = ethyl afforded the

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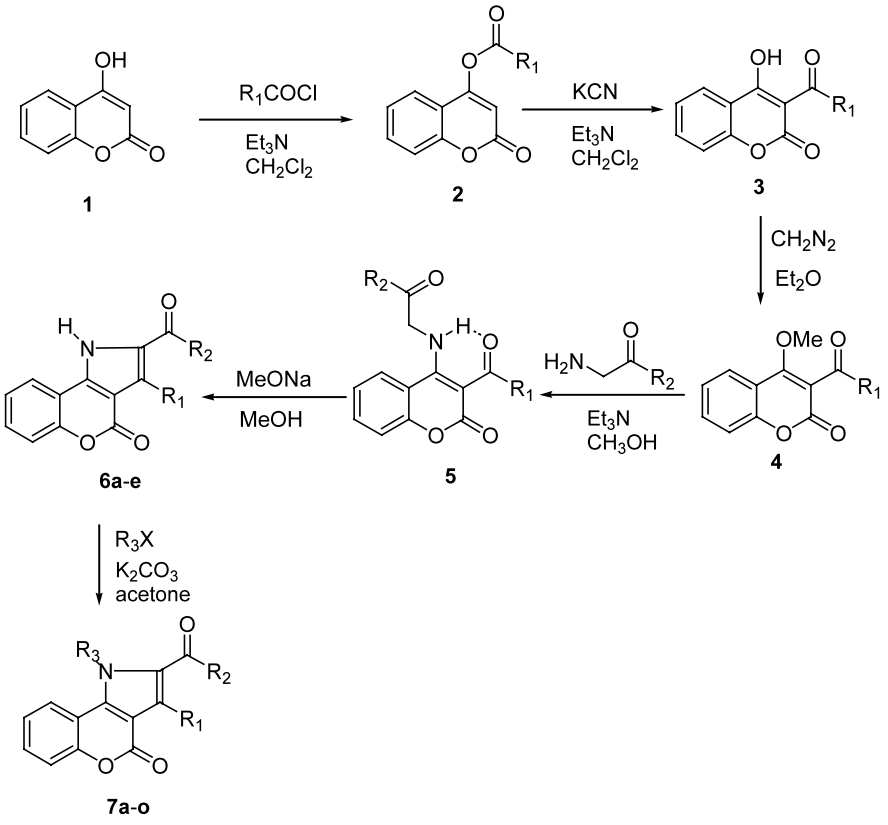
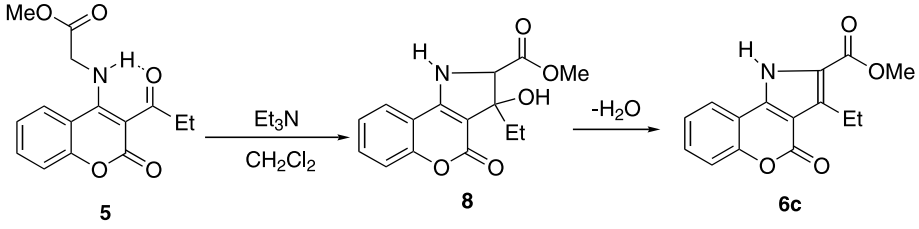


Scheme 1.

corresponding cyclized derivatives with less than 80% yield. Final *N*-alkylation of **6** with various alkyl halides using potassium carbonate as a base in dry acetone at room temperature led to the trisubstituted [1]benzopyranopyrroles **7** in a near quantitative yield.

The key feature of this synthesis was the methylation of planar 2-acylcoumarin **3** with diazomethane to increase their electrophilicity. The resulting dipolar repulsions between the C-2 carbonyl group and the other two oxygen atoms on the ring system of methyl ethers **4** cause deformation of the triketones from planarity[9] and result in their high susceptibility to nucleophilic attack on the C-4 position by a primary amine to regenerate the relatively stable intramolecular hydrogen bond, as indicated in enamines **5**. The mechanism for the intramolecular cyclizaiton reaction of enamines **5** to pyrroles **6** was confirmed by the isolation and identification of the intermediate alcohol **8**, as outlined in Scheme 2. Clearly, the process involves an expected based-promoted intramolecular cyclization reaction, followed by dehydration to generate the pyrrole ring as a stable end product. The pyrrole ring was identified from ^{1}H NMR spectra on the basis of a typical N–H shift at 8.8–8.4 ppm. The molecular structure of **7** was established by X-ray[10] crystallographic analysis of **7j** (Fig. 1), and the analogous structures of other products were determined by ^{1}H and ^{13}C NMR spectroscopy.

Twenty examples of the conversion of 4-hydroxycoumarin to various substituted fused pyrrole systems are listed in Table 1.[11] The results indicate that the present pyrrole synthesis has considerable versatility, since a variety of substituted fused pyrrole systems have been obtained from readily available starting materials, e.g. acyl chlorides, α-amino derivatives, and alkyl halides. Moreover, the overall yields of the substituted [1]benzopyranopyrroles in Table 1 ranged from 23 to 54%, which increases the attractiveness of the approach. Finally, no protections, deprotections or



Scheme 2.

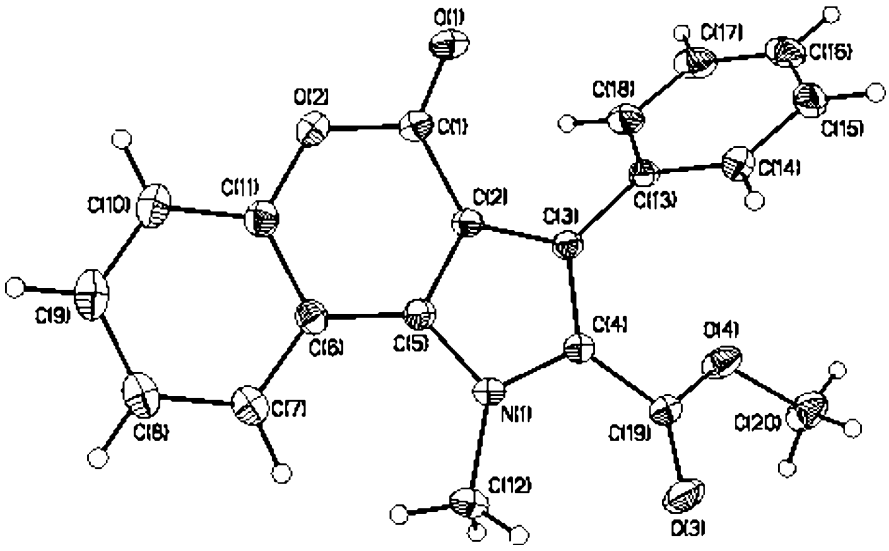


Figure 1. X-Ray crystal structure of **7j**.

Table 1. List of various prepared [1]benzopyrano[4,3-*b*]pyrrol-4(1*H*)-one derivatives

Entry	Compd	R_1	R_2	R_3	Formula	Mp (°C)	Yield[a] (%)
1	**6a**	Me	OMe	H	$C_{14}H_{11}NO_4$	295–296	28
2	**6b**	Me	*p*-C_6H_4Br	H	$C_{19}H_{12}BrNO_3$	363–364 (dec.)	28
3	**6c**	Et	OMe	H	$C_{15}H_{13}NO_4$	201–203	27
4	**6d**	Ph	OMe	H	$C_{19}H_{13}NO_4$	250–252	54
5	**6e**	Ph	*p*-C_6H_4Br	H	$C_{23}H_{14}BrNO_3$	351–353 (dec.)	49
6	**7a**	Me	OMe	Me	$C_{15}H_{13}NO_4$	192–193	25
7	**7b**	Me	OMe	Et	$C_{16}H_{15}NO_4$	186–187	24
8	**7c**	Me	OMe	Bn	$C_{21}H_{17}NO_4$	250–252	25
9	**7d**	Me	*p*-C_6H_4Br	Me	$C_{20}H_{14}BrNO_3$	249–250	25
10	**7e**	Me	*p*-C_6H_4Br	Et	$C_{21}H_{16}BrNO_3$	221–223	24
11	**7f**	Me	*p*-C_6H_4Br	Bn	$C_{26}H_{18}BrNO_3$	252–253	25
12	**7g**	Et	OMe	Me	$C_{16}H_{15}NO_4$	185–187	26
13	**7h**	Et	OMe	Et	$C_{17}H_{17}NO_4$	131–133	25
14	**7i**	Et	OMe	Bn	$C_{22}H_{19}NO_4$	118–120	23
15	**7j**	Ph	OMe	Me	$C_{20}H_{15}NO_4$	217–219	49
16	**7k**	Ph	OMe	Et	$C_{21}H_{17}NO_4$	201–202	47
17	**7l**	Ph	OMe	Bn	$C_{26}H_{19}NO_4$	163–164	49
18	**7m**	Ph	*p*-C_6H_4Br	Me	$C_{24}H_{16}BrNO_3$	262–263	45
19	**7n**	Ph	*p*-C_6H_4Br	Et	$C_{25}H_{18}BrNO_3$	214–215	44
20	**7o**	Ph	*p*-C_6H_4Br	Bn	$C_{30}H_{20}BrNO_3$	233–234	45

[a] Overall yield from 4-hydroxycoumarin to the final product.

harsh conditions are involved in the synthesis and the overall route offers the advantage of being relatively short. All reactions are carried out at room temperature and only one column chromatography is required in all six steps. These considerations suggest that the present synthetic method may offer certain advantages when substituted [1]benzopyranopyrroles are desired.

To summarize, we describe here an efficient route for the preparation of [1]benzopyrano[4,3-*b*]pyrrol-4(1*H*)-one derivatives from 4-hydroxycoumarin via readily accessible 2-acyl-4-methoxycoumarins. These compounds may facilitate the discovery of potential benzodiazepine receptor ligands.

Acknowledgements

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References

1. Colotta, V.; Cecchi, L.; Melani, F.; Filacchioni, G.; Martini, C.; Giannaccini, G.; Lucacchini, A. *J. Med. Chem.* **1990**, *33*, 2646–2651.
2. Colotta, V.; Cecchi, L.; Melani, F.; Filacchioni, G.; Martini, C.; Gelli, S.; Lucacchini, A. *Il Farmaco* **1991**, *46*, 1139–1154.

3. Colotta, V.; Cecchi, L.; Melani, F.; Filacchioni, G.; Martini, C.; Gelli, S.; Lucacchini, A. *J. Farm. Sci.* **1991**, *80*, 276–279.
4. Singh, P.; Ojha, T. N.; Sharma, R. C.; Tiwari, S. *Indian J. Chem., Sect. B* **1994**, *32B*, 555–561.
5. Branca, Q.; Jakob-Rotne, R.; Ketler, R.; Roever, S.; Scalone, M. *Chimia* **1995**, *49*, 381–385.
6. Alberola, A.; Alvaro, R.; Ortega, A. G.; Sadaba, M. L.; Sanudo, M. C. *Tetrahedron* **1999**, *55*, 13211–13224.
7. *N*,*O*-Dimethylhydroxylamine hydrochloride decomposes with the liberation of 1.5 kJ/g. The free base begins thermal decomposition at ~50°C. For a report of a fatal explosion due to detonation of the related, high-energy compound, hydroxylamine, see: *Chem. Eng. News* **1999**, Aug 16, 23.
8. Alberola, A.; Calvo, L.; Ortega, A. G.; Encabo, A. P.; Sanudo, M. C. *Synthesis* **2001**, 1941–1948.
9. For a similar example, see: Wu, C. S.; Huang, J. L.; Sun, Y. S.; Yang, D. Y. *J. Med. Chem.* **2002**, *45*, 2222–2228.
10. Crystallographic data (excluding structure factors) for **7j** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC-194324. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0) 1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
11. All new compounds exhibited satisfactory ^{1}H and ^{13}C NMR, IR, and low and high resolution mass spectroscopic data for the indicated structures. Representative procedure for preparation of **7j** from **4**: To a solution of 4-methoxy-3-benzoylcoumarin (50 mg, 0.18 mmol) in MeOH (2 mL) was added glycine methyl ester hydrochloride (120 mg, 0.22 mmol) and Et_3N (22.3 mg, 0.22 mmol) at room temperature. After completion of the reaction within 30 min (monitored by TLC), sodium methoxide (10.1 mg, 0.19 mmol) was added to the mixture and the solution was stirred overnight. The precipitate product **6d** was filtered and redissolved in acetone (2 mL). To this solution was added dry K_2CO_3 (30.0 mg, 1.5 mmol) and iodomethane (51.2 mg, 2.5 mmol). The resulting mixture was stirred for another 8 h at room temperature. After concentrated in vacuo, the residue was then extracted with ethyl acetate twice. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The crude final product **7j** was purified by column chromatography (EtOAc:hexanes = 2:8) to give a white solid in a 74% overall yield. Mp 217–219°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.12 (d, $J = 6.9$ Hz, 1H, Ar H), 7.50–7.34 (m, 8H, Ar H's), 4.39 (s, 3H, NCH_3), 3.60 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.9, 157.2, 152.9, 137.7, 132.8, 132.0, 129.9, 129.8, 127.6, 127.3, 125.7, 123.9, 122.2, 118.3, 113.9, 108.0, 51.6, 36.2. IR (KBr) ν 3006, 1732, 1695, 1506, 1458, 1431, 1213, 1127, 788, 756 cm^{-1}. HRMS (EI) calcd for $C_{20}H_{15}NO_4$ (M^+), 333.0997, found 333.0999.