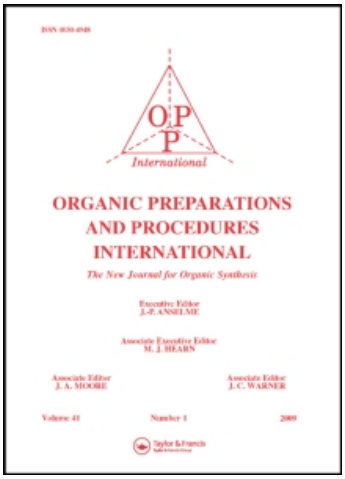


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

CHEMISTRY OF COUMARINS. ANNELATION OP COUMARIN SING *via* REACTIONS OF 3-AMINO-4-HYDROXYCOUMARIN

I. Tabakovic[a]; K. Tabakovic[a]; M. Trkovnik[a]; Z. Stunic[a]
[a] Laboratory of Organic Chemistry and Biochemistry Technological Faculty, "Djuro Pucar Stari" University, Banja Luka, Yugoslavia

To cite this Article Tabakovic, I. , Tabakovic, K. , Trkovnik, M. and Stunic, Z.(1985) 'CHEMISTRY OF COUMARINS. ANNELATION OP COUMARIN SING *via* REACTIONS OF 3-AMINO-4-HYDROXYCOUMARIN', Organic Preparations and Procedures International, 17: 2, 133 — 137
To link to this Article: DOI: 10.1080/00304948509355485
URL: http://dx.doi.org/10.1080/00304948509355485

ORGANIC PREPARATIONS AND PROCEDURES INT. 17(2), 133-154 (1985)

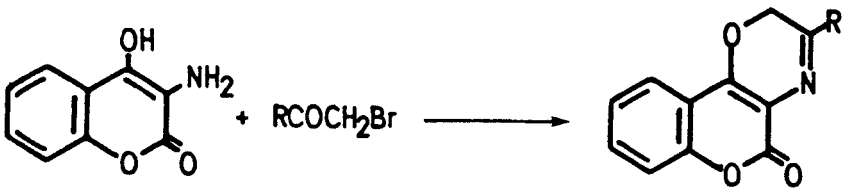
OPPI BRIEFS

CHEMISTRY OF COUMARINS. ANNELATION OF COUMARIN RING via REACTIONS OF 3-AMINO-4-HYDROXYCOUMARIN

Submitted by I. Tabakovic*, K. Tabakovic, M. Trkovnik and Z. Stunic
(04/04/84)

Laboratory of Organic Chemistry and Biochemistry
Technological Faculty, "Djuro Pucar Stari" University
78000 Banja Luka, YUGOSLAVIA

3-Amino-4-hydroxycoumarin (1) comprises the structural nucleus of the antibiotic novobiocin[1] which possesses antibacterial and fungicidal properties of its own.[2,3] Several 4-hydroxy and 4-aminocoumarin derivatives, especially those with nitrogen function in 3-position, are endowed with potential therapeutic properties.[4] The preparation of a wide range of coumarins annelated in the 3,4-position has been reviewed.[5] As continuation of our work on the chemistry of coumarin derivatives,[6] we studied the reactions of 3-amino-4-hydroxycoumarin (1) with α-bromocarbonyl compounds (2), 1,2-dibromoethane and N,N-dimethylformamide dimethylacetal, leading to the synthesis of new classes of compounds.

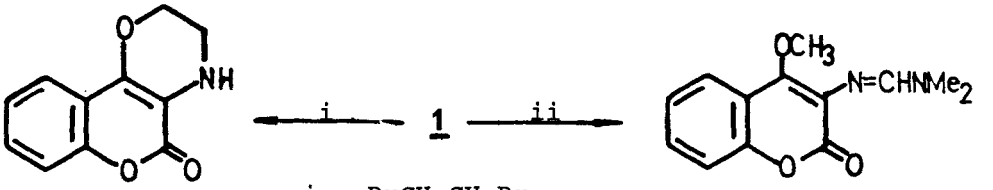


1 2 3

Reactions of 3-amino-4-hydroxycoumarin (1) with α-bromocarbonyl compounds (2) were carried out by refluxing 1 with the appropriate reactant in ethanol with sodium acetate as a base. The formation of the product can be rationalized in terms of an intermolecular condensation between the

amino and carbonyl groups, followed by intramolecular displacement of bromide. In all cases, good to excellent yields (56-84%) were obtained in relatively short times (1-6 hrs).

Treatment of 1 with 1,2-dibromoethane was performed at reflux in dilute acetone in order to circumvent intermolecular side-reactions. TLC of the crude mixture indicated the presence of three additional products; after recrystallization, the novel 5H:benzopyrano[3,4-d]morpholin-5-one (4) was



4 5

obtained in 25% yield as a pure compound. The reaction of 1 with N,N-dimethylformamide dimethylacetal did not afford the expected oxazole derivative;[7] instead, after separation of unreacted 1, compound 5 was obtained as a single product (Scheme 2).

EXPERIMENTAL SECTION

All mps are uncorrected. Infrared spectra were recorded on a Perkin-Elmer M-377 spectrophotometer (KBr pellets), ^{1}H NMR spectra on a Perkin-Elmer R 12A (60 MHz) spectrometer and mass spectra on a Hitachi Perkin-Elmer RMV-GL spectrometer (at 75 eV). 3-Amino-4-hydroxycoumarin was prepared according to the known procedure.[8]

3-Phenyl-3,4-dehydro-5H-benzopyrano[3,4-e]morpholin-5-one (3a).- A solution of 1 (0.18 g, 1 mmol), phenacyl bromide 0.19 g (1 mmol) and sodium acetate (0.08 g, 1 mmol) in 96% EtOH (25 ml) was refluxed for 3 hrs, concentrated to half its volume under reduced pressure and poured into water. The precipitated 3a (0.27 g, 84%) was collected and recrystallized from ethanol-water (8:2), mp. 195-197°.

3-(p-Bromophenyl)-3,4-dehydro-5H-benzopyrano[3,4-e]morpholin-5-one (3b) obtained as described above from 1 and p-bromophenacyl bromide (reflux time

3 hrs) in 69% yield (product precipitated on standing overnight) of yellow crystals, mp. 207-208° (96% EtOH); compound 3c was obtained as described above in 66% yield as yellow crystals, mp. 227-228 (96% EtOH).

3-Carboxy-3,4-dehydro-5H-benzopyrano[3,4-e]morpholin-5-one (3d).- A solution of 1 (0.18 g, 1 mmol), bromopyruvic acid (0.17 g, 1 mmol) in 96% EtOH (25 ml) was refluxed 2 hrs and then a solution of sodium acetate (0.08 g, 1 mmol) in water (5 ml) was added. The solution was heated under reflux for 1 hr. and the resulting solution was cooled to room temperature. An aqueous solution (15 ml) of CH_3COOH (5 ml) was added and the mixture was allowed to stand overnight in the refrigerator. The precipitate (0.16 g, 56%) was collected and recrystallized from EtOH-H_2O (7:3), mp. 198-200°.

TABLE. IR, NMR and Analytical Data on 3a-d

Cmpd	IR[a] (cm^{-1})	NMR (δ)		Elemental Analyses Calculated (Found)		
	C=O	ArH	CH_2	C	H	N
3a	1720	7.6-8.4	5.93	73.64(73.52)	3.97(3.90)	5.05(5.17)
3b	1720	7.3-8.0	5.50	57.30(57.60)	2.80(3.03)	3.93(3.90)
3c	1715	7.3-8.2	5.50	78.18(78.12)	4.24(4.51)	3.96(3.91)
3d	1710[b]	--	--	58.77(58.68)	2.85(2.84)	5.71(5.59)

a) In DMSO-d_6 b) 1745 cm^{-1} for CO_2H

5H-Benzopyrano[3,4-d]morpholin-5-one (4).- A mixture of 1 (1.5 g, 7.2 mmol), anhydrous K_2CO_3 (1.16 g, 8.4 mmol) and 1,2-dibromoethane (1.35 g, 7.2 mmol) in acetone (250 ml) was refluxed 15 hrs. The solvent was evaporated under reduced pressure and the crude residue was extracted with ethyl acetate, giving 0.43 g (25%) of 4 which was recrystallized from 96%

EtOH, mp. 146-148°. IR (cm^{-1}): 3345 (NH), 1682 (C=O, pyrone), 1605 (C=C, aromatic), 1352 (C-O-C). ^1H NMR (DMSO-d_6): δ 7.35-7.80 (m, 4H, ArH), 5.57 (broad, s, 1H, NH), 4.42 (t, 2H, CH_2), 2.53 (m, 2H, CH_2). MS, m/e (relative intensity): 203 (M^+, 100), 162 (23), 121 (42) 121 (42), 120 (59), 92 (28).

Anal. Calcd. for $C_{11}H_9NO_3$: C, 65.01; H, 4.47; N, 6.89

Found: C, 65.26; H, 4.68; N, 6.58

3-(N,N-Dimethylaminomethylene)amino-4-methoxybenzopyren-2-one (5).- A solution of 1 (0.18 g, 1 mmol) and N,N-dimethylformamide dimethylacetal (1.2 ml, 10 mmol) in toluene (30 ml) was refluxed 3 hrs. The solution was cooled to room temperature, filtered from a small amount of unreacted 1, and evaporated under reduced pressure to give 0.12 g (43%) of 7 which was recrystallized from 96% EtOH, mp. 93-94°.

IR (cm^{-1}): 2960 (C-H), 1710 (C=O, pyrone), 1630 (C=N), 1605 (C=C, aromatic). ^1H NMR (DMSO-d_6): δ 8.32 (s, 1H, CH), 7.25-7.95 (m, 4H, ArH) 4.3 (s, 3H, OCH_3), 3.15 (s, 6H, CH_3). MS, m/e (relative intensity): 246 (55), 233 (10), 232 (38), 131 (21), 93 (17), 85 (71), 71 (21), 44 (100), 42 (90).

Anal. Calcd. for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.69; N, 11.38

Found: C, 63.20; H, 5.41; N, 11.41.

REFERENCES

1. C. F. Spencer, J. O. Rodin, E. Walton, F. W. Holly and K. Folkers, J. Am. Chem. Soc., 80, 140 (1958).
2. K. Okumura, K. Ashino and T. Okuda, Yukugaku Zasshi, 81, 1482 (1961); CA, 56, 7938d (1962).
3. A. Del. Campo and P. L. Fazzi, Riv. Sieroterap Ital., 33, 389 (1958); CA, 56, 10447b (1958).
4. D. R. Buckle, B. C. Cantello, H. Smith and B. A. Spicer, J. Med. Chem.,

18, 391 (1975).

5. M. Darbarwar and V. Sundaramurthy, Synthesis, 337 (1982).

6. a) M. Trkovnik, M. Kekic, M. Kules and A. Gorenc, Z. Naturforsch. 206, 237 (1979); b) M. Trkovnik, M. Kules and M. Krunic, Org. Prep. Proced. Int., 7, 25 (1975); c) I. Tabakovic, M. Trkovnik, M. Badusic and K. Tabakovic, Synthesis 8, 590 (1979); d) K. Tabakovic, I. Tabakovic, M. Trkovnik, A. Juric and N. Trinajstic, J. Heterocyclic Chem., 17, 801 (1980); e) K. Tabakovic and I. Tabakovic, Croatica Chem. Acta, 54, 451 (1981); f) Z. Stunic, M. Trkovnik, M. Lacan and R. Jankovic, J. Heterocyclic Chem., 18, 511 (1981); g) I. Tabakovic, Z. Grujic and Z. Bejtovic, ibid., 20, 635 (1983); h) K. Tabakovic, I. Tabakovic, M. Trkovnik and N. Trinajstic, Ann., 1901 (1983).

7. M. Nishi, S. Tanimoto, M. Okano and R. Oda, Yuki Gosei Kagaku Kyokai Shi, 27, 754 (1969); CA, 71, 101438y (1969).

8. M. Trkovnik, M. Lacan, Z. Stunic and D. Nahmijaz, Org. Prep. Proced. Int., 7, 47 (1975).