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SYNTHESIS AND CHARACTERIZATION OF NOVEL 7-HYDROXYCOUMARIN DERIVATIVES

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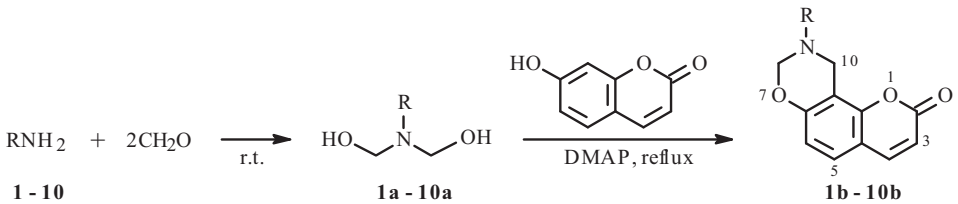
The synthesis of several coumarin Mannich bases is described. The reaction of natural 7-hydroxycoumarin with primary amines and two equivalents of formaldehyde in the presence of a base catalyst was studied. Several novel N*-substituted angular 9,10-dihydro-2*H*,8*H*-chromeno[8,7-e][1,3]oxazin-2-ones were synthesized. Different aliphatic and aromatic amines have been used in the reaction, and the corresponding products were obtained with moderate to relatively good yields.*

Keywords: 7-hydroxycoumarin, amines, oxazine, aminomethylation, Mannich reaction.

Coumarins are a very large group of 1,2-benzopyrone derivative that are widely distributed in a variety of natural plant sources. Coumarins and their derivatives have attracted considerable attention due to their wide range of biological activities such as antibacterial, antifungal, antiviral, antitubercular, antimalarial, anticoagulant, anti-inflammatory, anticancer, antioxidant, and so on. Much effort, including the separation and purification of naturally occurring coumarins from a variety of plants, as well as artificial synthesis of coumarin compounds with novel structures and properties, has been focused on the research and development of coumarins as potential drugs. So far, some coumarins, for example, warfarin, acenocoumarol, armillarisin A, hymecromone, and carbochromene have been approved for therapeutic purpose in clinic. More importantly, an increasing number of coumarin compounds have displayed great potency in the treatment of various types of diseases [1–5].

Hence, the preparation of novel coumarin derivatives or modification of the natural 7-hydroxycoumarin seems an interesting issue from both the chemical and biological points of view. The interest of investigators in the chemistry of Mannich bases is constantly increasing, and this is due to not only their valuable pharmacological characteristics but also to the possibility of formation of water-soluble salts suitable for studying of their biological activity. The aim of our work was to develop procedures for synthesizing new aminomethyl derivatives of 7-hydroxycoumarin.

Mannich reaction conditions with appropriate ratio of substrate, amine, and formaldehyde in the presence of a base [KOH, *N*,*N*-dimethylaminopyridine (DMAP)] is known to produce 3,4-dihydro-1,3-benzoxazine derivatives through electrophilic substitution of [6–10].



R = 4-CH_3O-C_6H_4- (**1a,b**); 4-CH_3-C_6H_4- (**2a,b**); 4-Cl-C_6H_4- (**3a,b**); 4-O_2N-C_6H_4- (**4a,b**)
C_6H_5- (**5a,b**); C_6H_5-CH_2- (**6a,b**); *n*-C_3H_7- (**7a,b**); *n*-C_4H_9- (**8a,b**); s-C_4H_9- (**9a,b**)
n-C_6H_{13}- (**10a,b**)

Scheme 1

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TABLE 1. Melting Points and Yields of Compounds **1b–10b**

Compound	Mp, °C	Yield, %	Compound	Mp, °C	Yield, %
1b	146–147	78	**6b**	122–123	93
2b	131–132	75	**7b**	67–68	44
3b	159–160	83	**8b**	61–63	52
4b	173–174	40	**9b**	58–59	47
5b	156–157	88	**10b**	88–89	48

TABLE 2. ^{1}H NMR Spectra of **1b–10b** (9,10-Dihydro-2*H*,8*H*-chromeno[8,7-e][1,3]oxazin-2-ones) ($CDCl_3$, δ, ppm, J/Hz)

Compound	H-3*	H-4*	H-5*	H-6*	H-8	H-10	N(9) Substituent
1b	6.23	7.60	7.24	6.76	5.37	4.74	3.74 (3H, s); 6.81 (2H, d); 7.10 (2H, d)
2b	6.23	7.60	7.23	6.75	5.41	4.79	2.26 (3H, s); 7.06 (2H, d); 7.08 (2H, d)
3b	6.25	7.61	7.25	7.76	5.39	4.78	7.07 (2H, d); 7.22 (2H, d)
4b	6.29	7.64	7.30	6.82	5.49	4.93	7.15 (2H, d); 8.19 (2H, d)
5b	6.23	7.63	7.23	6.75	5.43	4.82	6.96 (2H, t); 7.14 (2H, d); 7.27 (1H, t)
6b	6.22	7.63	7.27	6.79	4.93	4.18	3.90 (2H, s); 7.31 (2H, t); 7.32 (2H, t); 7.35 (1H, d)
7b	6.23	7.62	7.24	6.73	4.94	4.17	0.93 (3H, t); 1.60 (2H, sex); 2.69 (2H, t)
8b	6.20	7.62	7.24	6.73	4.93	4.17	0.93 (3H, t); 1.36 (2H, sex); 1.58 (2H, quin); 2.72 (2H, t)
9b	6.24	7.63	7.23	6.72	5.86 (d) 4.99 (d)	4.20	0.90 (3H, t); 1.09 (3H, d); 1.42 (1H, m); 1.63 (1H, m); 2.88 (1H, sex)
10b	6.24	7.62	7.24	6.73	4.94	4.17	0.89 (3H, t); 1.25–1.30 (8H, m); 1.56 (2H, m); 2.71 (2H, t)

*H-3 (1H, d, ^{2}J = 9.5); H-4 (1H, d, ^{2}J = 9.5); H-5 (1H, d, ^{2}J = 8.6); H-6 (1H, d, ^{2}J = 8.6).

It is well known that several products may be formed during the Mannich reaction, depending on the substrate structures and equivalents of formaldehyde [6]. The pyranodihydrobenzoxazines have been prepared by reaction of equimolar amounts of primary amine and 7-hydroxycoumarin and two equivalents of formaldehyde or paraformaldehyde in the presence of catalytic amounts of KOH [7–12]. This condensation was also carried out in acetic acid [13].

Pyranodihydrobenzoxazines are also formed by the action of formalin on Mannich base prepared from primary amines [7]. Obviously, the synthesis of pyranodihydrobenzoxazines is a two-step process. 7-Hydroxycoumarin was added to the *N*,*N*-di(hydroxymethyl)amine formed *in situ* by the reaction of formaldehyde (as formalin) with an adequate primary amine (Scheme 1). A simultaneously occurring base-catalyzed *C*-and *O*-alkylation between the *N*,*N*-di(hydroxymethyl)amine and 7-hydroxycoumarin then resulted in the formation of the final cyclic product [14–16].

Therefore, we annellated a 1,3-oxazine ring to the coumarin system via the reaction of 7-hydroxycoumarin and the already formed *N*,*N*-di(hydroxymethyl)amine in the presence of DMAP, and the 1,3-oxazine ring was added exclusively to the 7,8-positions of the coumarin system.

Substituted anilines [4-methoxyaniline (**1**), 4-methylaniline (**2**), 4-chloroaniline (**3**), 4-nitroaniline (**4**), aniline (**5**)], benzylamine (**6**), and aliphatic amines [*n*-propylamine (**7**), *n*-butylamine (**8**), *sec*-butylamine (**9**), and *n*-hexylamine (**10**)] were used as the amine in this condensation.

If aniline were used as the amine, the experimental result showed that addition of the 1,3-dihydroxazine ring to the coumarin system depended strongly on the structures of the starting anilines. The 9,10-dihydro-2*H*,8*H*-chromeno-[8,7-e][1,3]oxazin-2-ones were not formed if anilines containing strong electron withdrawing or bulky substituents in the *ortho*-position to the amine were used. The presence of strong electron withdrawing groups in positions *meta* or *para* to the amine had little effect on the reaction. Pyranodihydrobenzoxazines were formed in satisfactory yields [14, 15].

As expected, the reaction of benzylamines and aniline with 7-hydroxycoumarin resulted in the formation of the corresponding products with a satisfactory yield. The 1,3-dihydroxazine ring was smoothly annellated to 7-hydroxycoumarin using aliphatic amines regardless of the structure or the presence of substituents. The reaction of 7-hydroxycoumarin with 4-nitroaniline did not give the desired product, which can be attributed to the reduced nucleophilicity of the amine group in that compound. Also, we could not synthesize pyranodihydrobenzoxazines using 2-aminopyrimidine as the amine.

The structure of the synthesized derivatives **1b–10b** was confirmed by NMR spectroscopy. Thus, in the ^{1}H NMR spectra of **1b–10b**, the signal for the H-8 proton of the coumarin ring disappears, and two 2H singlets appear for methylenes that were characteristic of an annellated 1,3-dihydroxazine ring. For *N*-aryl derivatives **1b–5b** and benzylamine **6b**, the 10-CH_2 and 8-CH_2 methylenes resonated at 4.18–4.93 and 4.93–5.49 ppm, respectively. However, the ^{1}H NMR spectra of *N*-alkylamine derivatives **7b–10b** showed singlet peaks for 10-CH_2 and 8-CH_2 at 4.17–4.20 and 4.93–5.86 ppm, respectively.

EXPERIMENTAL

The course of reactions and purity of the products were monitored by TLC on Merck 60 F_{254} plates with elution by $CHCl_3$–CH_3OH (9:1 or 19:1). Melting points were determined by an Electrothermal 9100 melting point equipment. NMR spectra were recorded on a Bruker Avance 400 (400 MHz) spectrometer in $CDCl_3$ using tetramethylsilane as an internal standard.

General procedure for the preparation of the 9,10-dihydro-2*H*,8*H*-chromeno[8,7-e][1,3]oxazin-2-ones **1b–10b**. A solution of the appropriate primary amine (4.4 mmol) in dioxane (10 mL) was treated with formalin solution (35%, 0.9 mL, 10 mmol). The resulting mixture was held at room temperature and stirred vigorously for the required times: 3–5 h for substituted anilines and benzylamines and 2 h for aliphatic amines. Then, hydroxycoumarin (0.85 g, 4 mmol) and a catalytic amount of DMAP (20 mg) were added, and the reaction mixture was heated to 100°C. The reaction was continued for 10–15 h in the case of substituted anilines and benzylamines and 7 h for aliphatic amines. The course of all the reactions was monitored by TLC. After completion of the reaction, the solvent was removed in a rotary evaporator. The oily residue was recrystallized from 2-propanol. Final purification of the products was carried out by preparative thin-layer chromatography (PTLC) using laboratory-prepared plates with a thickness of 1 mm and $CHCl_3$–CH_3OH as eluent. The melting points and yields of the synthesized products are given in Table 1. The spectral data of the products are summarized in Table 2.

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