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FACILE SYNTHESIS OF COUMARINYL ISOTHIOCYANATE FROM AMINO COUMARIN

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One-pot conversion of amino coumarin to corresponding coumarinyl isothiocyanate using carbon disulfide, iodine, and pyridine is described. In this reaction, pyridine acts as a solvent as well as a catalyst to give coumarinyl isothiocyanate. Excellent yield, short reaction time, and mild reaction conditions make this method a useful synthetic procedure for one-pot preparation of coumarinyl isothiocyanate.

Keywords: Amino coumarin; coumarinyl isothiocyanate; iodine; pyridine; pyridinium hydroiodide

Coumarins constitute an important class of benzopyrones, exhibiting a broad range of biological activities such as anticoagulant,[1] antimicrobial,[2] antibacterial,[3] anticancer,[4] and anti-HIV activity[5]. The interesting biological activities of the coumarins make them attractive targets in organic synthesis. Similarly, isothiocyanates constitute an important class of compounds in organic chemistry.[6] The attraction of isothiocyanate as synthons is obviously due to its diverse reactions and easy availability. It undergoes nucleophilic addition reactions, cycloaddition to unsaturated systems, Diels–Alder reaction, and reaction with bifunctional compounds to yield heterocyclic derivatives.[7] Isothiocyanates have found application in the agrochemical and pharmaceutical industries.[8] They have attracted attention as potent and selective inhibitors of carcinogenesis in various animal models.[9]

In view of these observations and in continuation of our work on coumarin-based heterocycles,[10,11] it was of interest to synthesize new chemical entities incorporating the two active pharmacophores (namely, coumarin and isothiocyanate) in a single molecular framework using aminocoumarin as a basic building block.

Isothiocyanate can be prepared by various procedures.[12–14] The choice of method for the preparation of the isothiocyanate depends on the starting compound, which is suitable for the required type of isothiocyanate. From primary amines, isothiocyanates can be obtained either directly by the action of some sulfur compounds (e.g., thiophosgene, dithiocarbamoyl chloride, trichloromethyl

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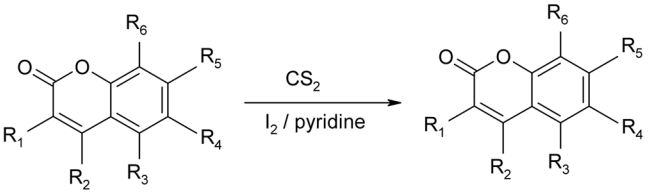
sulfide, etc.) or by converting them into suitable intermediate (dithiocarbamates, dithiocarbazates, thioureas, etc.), which are then decomposed to isothiocyanates by reaction with various agents. However, these methods are not useful for amino coumarin, because these methods require highly basic condition and give poor yields. Also, some of these reagents are hazardous and toxic. Moreover, many of these recently developed methods require harsh reaction conditions and have limitations for their applications. Dey and Seshadri[15] synthesized coumarinyl isothiocyanate using dicoumarinylthiocarbamide, which decomposed to isothiocyanates by reaction with acetic anhydride. When used to synthesize isothiocyanates, this method gave poor yields and hence is little used. Development of a facile synthetic procedure for the preparation of coumarinyl isothiocyanate is therefore important.

We have developed and report here a facile method for generating a single isothiocyanate group on a coumarin using iodine as a catalyst under mild conditions (Scheme 1). The use of molecular iodine in organic synthesis has been known for a long time. In recent years, molecular iodine has received considerable attention as an inexpensive, non-toxic, and readily available catalyst for various organic transformations[16] under mild and convenient conditions to afford the corresponding products in excellent yields with high selectivity.

In the exploratory studies, the reaction of amino coumarin with carbon disulfide in the presence of iodine and pyridine at 0°C was carried out in different solvents (Table 1). It should be noted that in this proposed reaction, 1 mol of amino coumarin requires 1 mol of iodine and 2 mol of pyridine and yields 1 mol of coumarinyl isothiocyanate and 2 mol of pyridinium hydroiodide. In this reaction, coumarinyl thiourea is formed as a by-product in a minor amount. The catalyst exhibited high activity in all the solvents explored, and in every case, good to excellent yields were observed. Based on this study, pyridine was selected as the solvent for further examination of this process. Iodine was used as a catalyst to eliminate the hydrogen sulfide to form hydrogen iodide, and the simultaneous use of pyridine combined immediately with



(1a-h) **(2a-h)**

1a: R_1,R_2,R_3,R_6=H, R_4=NH_2, R_5=CH_3.
1b: R_1,R_3,R_6=H, R_2, R_5=CH_3, R_4= NH_2.
1c: R_1,R_3,R_6=H, R_2=CH_3, R_5=OCH_3, R_4= NH_2.
1d: R_1,R_2,R_3,R_5,R_6=H, R_4= NH_2.
1e: R_1= NH_2, R_2,R_3,R_4,R_5,R_6=H.
1f: R_1= NH_2,R_2=CH_3, R_5=OCH_3,R_3,R_4,R_6=H.
1g: R_1,R_3,=H, R_2, R_5,R_6=CH_3, R_4= NH_2.
1h: R_1,R_3,R_4,R_6=H, R_5= NH_2, R_2=CH_3.

2a: R_1,R_2,R_3,R_6=H, R_4=NCS, R_5=CH_3.
2b: R_1,R_3,R_6=H, R_2, R_5=CH_3, R_4=NCS.
2c: R_1,R_3,R_6=H, R_2=CH_3, R_5=OCH_3, R_4=NCS.
2d: R_1,R_2,R_3,R_5,R_6=H, R_4=NCS.
2e: R_1=NCS, R_2,R_3,R_4,R_5,R_6=H.
2f: R_1=NCS,R_2=CH_3, R_5=OCH_3,R_3,R_4,R_6=H.
2g: R_1,R_3,=H, R_2, R_5,R_6=CH_3, R_4=NCS.
2h: R_1,R_3,R_4,R_6=H, R_5=NCS, R_2=CH_3.

Scheme 1. Coumarinyl isothiocyanate **(2a–h)** from amino coumarin **(1a–h)**.

Table 1. Effect of solvent on the synthesis of coumarinyl isothiocyanate

Entry	Solvent	Reaction time (h)	Yield (%)
1	Pyridine	3.0	89
2	THF	3.0	62
3	Toluene	3.0	45
4	1,4-Dioxane	3.0	56
5	CH_3CN	3.0	51

the liberated hydrogen iodide to form pyridinium hydroiodide and sulphur.[17] A solution of iodine in carbon disulfide was added dropwise to a suspension of amino coumarin in pyridine at 0°C.[18] The contents were stirred for 3.0 h giving coumarinyl isothiocyanate **(2a–h)** in moderate to good yield (Table 2).

EXPERIMENTAL

Melting points were taken in open capillaries and are uncorrected. Purity of the compounds was checked by thin-layer chromatography (TLC). Infrared (IR) spectra (ν_{max} in cm^{-1}) were recorded on a Perkin Elmer Fourier transform (FT)–IR instrument. NMR (^1H and ^{13}C) were measured with a on 300-MHz Jeol NMR AL300 instrument using tetramethylsilane (TMS) as standard and $CDCl_3$ as a solvent, and mass spectra were determined on a Shimadzu GC-MS QP-2010 instrument.

Typical Procedure

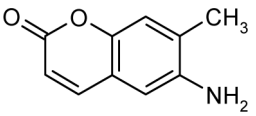
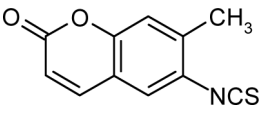
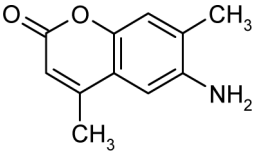
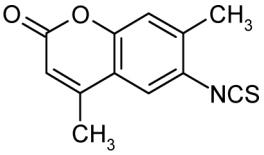
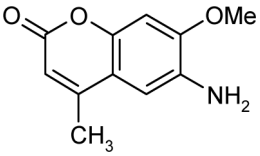
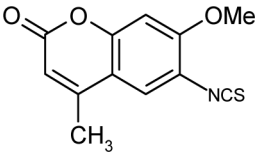
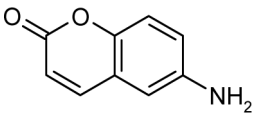
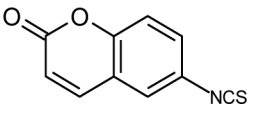
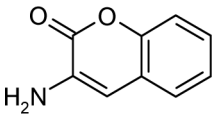
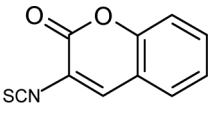
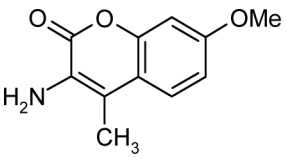
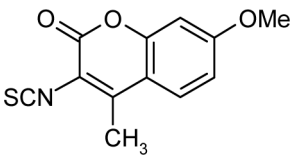
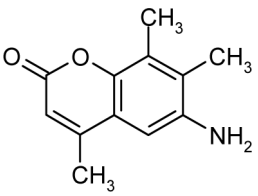
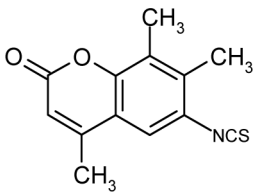
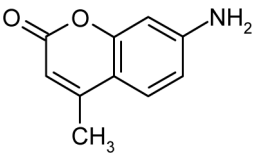
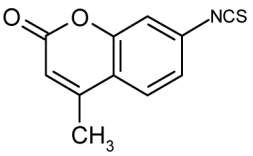
A solution of iodine (10 mmol) in 20 ml of carbon disulfide was added dropwise to a suspension of amino coumarin (10 mmol) in 15 ml of pyridine at 0°C. The contents were stirred for 3.0 h. A white solid separated out. The reaction mixture was distilled until all traces of carbon disulfide and pyridine had been driven out. Treatment of the residue with diluted HCl renderd soluble any unaffected amine and pyridine, and it was purified using column chromatography with hexane and ethyl acetate (90:10) as eluent.

Representative Spectral Data

6-Isothiocyanato-7-methyl-benzopyran-2-one (2a). IR (KBr): 3076, 3030, 2957, 2079, 1726, 1624, 1131, 1103, 887 cm^{-1}. ^1H NMR: δ 7.60 (d, 1H, $J = 9$ Hz, C_4-H), 7.33 (s, 1H, C_5-H), 7.19 (s, 1H, C_8-H), 6.41 (d, 1H, $J = 9$ Hz, C_3-H), 2.48 (s, 3H, C_7-CH_3). ^{13}C NMR: δ 160.0, 152.3, 142.0, 139.6, 136.8, 127.2, 124.4, 118.7, 117.5, 117.1, 18.9. Mass (m/z %): M^+ 217 (100), 189 (37), 160 (40), 131 (22), 117 (15), 102 (42), 89 (27), 77 (75), 63 (48).

6-Isothiocyanato-4,7-dimethyl-benzopyran-2-one (2b). IR (KBr) 3082, 3046, 2962, 2114, 1734, 1620, 1261, 1095, 1024, 872, 801 cm^{-1}. ^1H NMR: δ 7.33 (s, 1H, C_5-H), 7.11 (s, 1H, C_8-H), 6.22 (s, 1H, C_3-H), 2.40 (s, 3H, C_7-CH_3), 2.33

Table 2. Synthesis of coumarinyl isothiocyanate **(2a–h)** from amino coumarin **(1a–h)**

Entry	Substrate (**1**)	Product (**2**)	Yield (%)	Mp (°C)
a			89	192–94
b			84	230–32
c			77	165–68
d			88	184–86
e			69	115–17
f			71	165–68
g			85	174–76
h			80	177–79

(s, 3H, C_4-CH_3). ^{13}C NMR: δ 160.1, 151.8, 151.2, 139.5, 136.5, 127.1, 121.6, 118.9, 118.8, 115.5, 18.8, 18.6. Mass (m/z %): M^+ 231 (100), 202 (44), 188 (10), 170 (18), 145 (15), 115 (21), 102 (8).

6-Isothiocyanato-7-methoxy-4-methyl-benzopyran-2-one (2c). IR (KBr) 3071, 2965, 2089, 1718, 1632, 1549, 1344, 1313, 1244, 1177, 1107, 850 cm^{-1}. ^1H NMR: δ 7.65 (s, 1H, C_8-H), 7.58 (s, 1H, C_5-H), 6.35 (s, 1H, C_3-H), 3.91 (s, 3H, C_7-OCH_3), 2.49 (s, 3H, C_4-CH_3).

6-Isothiocyanato-benzopyran-2-one (2d). IR (KBr) 3085, 3063, 2084, 1721, 1618, 1562, 1179, 1106, 888, 821 cm^{-1}. ^1H NMR: δ 7.64 (d, 1H, $J = 9$ Hz, C_4-H), 7.24–7.40 (m, 3H, C_5, C_7 & C_8-H), 6.48 (d, 1H, $J = 9$ Hz, C_3-H). Mass (m/z %): M^+ 203 (100), 175 (48), 146 (12), 117 (8), 103 (6), 89 (13).

3-Isothiocyanato-benzopyran-2-one (2e). IR (KBr) 3057, 2952, 2010, 1725, 1624, 1450, 1129, 1112, 771, 758 cm^{-1}. ^1H NMR: δ 7.25–7.56 (m, 5H). Mass (m/z %): M^+ 203 (100), 175 (44), 146 (19), 120 (38), 103 (11), 87 (10), 63 (14).

3-Isothiocyanato-7-methoxy-4-methyl-benzopyran-2-one (2f). IR (KBr) 3082, 2916, 2008, 1720, 1614, 1554, 1380, 1303, 1253, 1150, 1067, 859 cm^{-1}. ^1H NMR: δ 7.48 (d, 1H, $J = 9$ Hz, C_6-H), 6.90 (d, 1H, $J = 9$ Hz, C_5-H), 6.85 (s, 1H, C_8-H), 3.89 (s, 3H, C_7-OCH_3), 2.48 (s, 3H, C_4-CH_3). Mass (m/z %): M^+ 247 (100), 232 (7), 219 (11), 204 (62), 148 (7), 116 (17), 89 (20), 63 (9).

6-Isothiocyanato-4,7,8-trimethyl-benzopyran-2-one (2g). IR (KBr) 3051, 2963, 2137, 1738, 1560, 1386, 1260, 1096, 1020, 883, 803 cm^{-1}. ^1H NMR: δ 7.33 (s, 1H, C_5-H), 6.30 (s, 1H, C_3-H), 2.40 (m, 9H, C_4,C_7, C_8-CH_3). ^{13}C NMR: δ 160.0, 151.6, 150.0, 137.4, 135.5, 126.6, 119.3, 119.2, 118.2, 115.2, 18.6, 15.8, 12.3. Mass (m/z %): M^+ 245 (100), 216 (30), 202 (18), 184 (21), 174 (9), 159 (16), 128 (14), 115 (22), 108 (11), 91 (16), 77 (20).

7-Isothiocyanato-4-methyl-benzopyran-2-one (2h). IR (KBr): 3076, 3030, 2957, 2079, 1726, 1624, 1131, 1103, 887 cm^{-1}. ^1H NMR: δ 7.04–7.14 (m, 2H, C_8-H & C_6-H), 7.53 (d, 1H, $J = 9$ Hz, C_5-H), 6.16 (s, 1H, C_3-H), 2.32 (s, 3H, C_4-CH_3).

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