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<td>Author(s)</td>
<td>Hagimori, Masayori; Matsui, Sayaka; Mizuyama, Naoko; Yokota, Kenichirou; Nagaoka, Junko; Tominaga, Yoshinori</td>
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Novel Synthesis of 4H-Quinolizine Derivatives Using Sulfonyl Ketene Dithioacetals


Keywords: 4H-quinolizine derivatives / sulfonyl ketene dithioacetal / desulfurization / fluorescence / organic light-emitting diode

In the synthesis of fluorescent 4H-quinolizine derivatives involving the use of a sulfonyl ketene dithioacetal, we found a novel reaction in which the remaining methylsulfanyl group was replaced with a proton after the ring closure reaction in the quinolizine skeleton. The reaction of 3,3-bis(methylsulfanyl)-2-phenylsulfonyl-acrylonitriles (1a, b) with 2-pyridylacetanilide (2a) in the presence of potassium carbonate as a base in DMSO afforded 4-imino-2-methylsulfanyl-3-phenylsulfonyl-4H-quinolizine-1-carbonitriles (3a, b). The methylsulfanyl group at the 2-position of 3a, b was readily removed under methanol reflux conditions to afford 4-imino-3-phenylsulfonyl-4H-quinolizine-1-carbonitriles (4a, b) in good yields. Alkyl 3-phenylsulfonyl-4H-quinolizine-1-carboxylates (4c–f) were directly synthesized from sulfonyl ketene dithioacetal (1a, b) with alkyl 2-pyridylacetates (2b, c) without desulfurization using metallic reagents. In addition, fluorescent properties of these compounds were investigated.

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Results and Discussion

The reaction of 3,3-bis(methylsulfanyl)-2-(phenylsulfanyl)-acrylonitrile (1a)2 with 2-pyridylacetanilide (2a) in the presence of potassium carbonate (base) in dimethyl sulfide (DMSO) at room temperature for 4 h afforded the expected product, 4-imino-2-methylsulfanyl-3-phenylsulfonyl-4H-quinolizine-1-carbonitrile (3a), in 82% yield (Scheme 1). Compound 3a was presumed to be formed by the addition of a nucleophile to a ketene dithioacetal, elimination of a methylsulfanyl group, and subsequent cyclization; further, 3a was readily converted to 4-imino-3-phenylsulfonyl-4H-quinolizine-1-carbonitrile (4a) by the elimination of a methylsulfanyl group in quantitative yield under reflux for 5 h in methanol (Scheme 2). When ammonia or aqueous NaOH solution was substituted for methanol, desired product was not obtained. Compounds 3b and 4b were also prepared from 1b and 2a, respectively, in a manner similar to that described for the preparation of 3a and 4a. In the methylsulfanyl group in compounds 3a, b, there is a strong interaction between the sulfur of the methylsulfanyl group and an oxygen in the sulfonyl group.3 The methylsulfanyl groups in compounds 3a, b are readily attacked by nucleophilic molecules such as water or methanol, and protonation at the 2-position of compound 3 occurred to produce 4a, b in good yields.

Introduction

 Appropriately functionalized ketene dithioacetals (cyano, methoxycarbonyl, sulfonyl, nitro, acyl) are versatile reagents that have been extensively utilized as building blocks in heterocyclic synthesis.1 The sulfonyl ketene dithioacetals, 3,3-bis(methylsulfanyl)-2-phenylsulfonyl-acrylonitriles (1a, b), are used as two- or three-carbon fragments for the synthesis of heterocyclic compounds having sulfonyl or cyano groups. These ketene dithioacetals are readily prepared by the condensation of phenylsulfonyl acetonitriles with carbon disulfide in the presence of sodium hydroxide, followed by methylation with dimethyl sulfate.2 It has been reported that 4-imino-2-methylsulfanyl-4H-quinolizine derivatives are synthesized from the corresponding 2-pyridylacetanilide and ketene dithioacetals under basic conditions; some of these 4H-quinolizine derivatives exhibit fluorescence.3 In general, one methylsulfanyl group in ketene dithioacetals having two methylsulfanyl groups is eliminated in the reaction, and consequently, the corresponding heterocycles in which one more methylsulfanyl group remains are obtained. In the synthesis of 4H-quinolizine derivatives, we found a novel reaction in which the remaining methylsulfanyl group of the quinolizine skeleton was replaced with a proton after the ring closure reaction in mild conditions. In this paper, we report the synthesis of 4-imino-4H-quinolizine derivatives by a novel synthesis method involving the use of a ketene dithioacetal and the fluorescent properties of these derivatives.
The vital part of this reaction is the displacement of the methylsulfanyl group at the 2-position by a proton after the ring closure reaction in the quinolizine skeleton. A part of the pyridine ring in the quinolizine skeleton becomes electron-deficient due to electron-withdrawing groups (e.g., cyano, sulfonyl, and imino groups), and a sulfur atom of the methylsulfanyl group becomes electron-deficient due to strong interaction between the sulfur atom of the methylsulfanyl group and an oxygen atom of the sulfonyl group. The calculation of atomic partial charges by AM1 method of MOPAC supported the hypothesis that the intramolecular interaction between the sulfur atom of the methylsulfanyl group and an oxygen atom of the neighboring sulfonyl group causes the electron-deficiency of the sulfur atom. S–O interaction and the electron-deficient effect in the pyridine ring enables nucleophilic attack of water or methanol anions on the sulfur atom in the methylsulfanyl group. The “de-methylsulfanyl reaction” is easily initiated if the cyano group at the 1-position on the quinolizine ring is changed to a methyl or an ethyl ester group. In this case, when the reaction mixture was poured into water, the de-methylsulfanyl products were directly obtained from the alkali solution. An interaction effect between the oxygen atom of the carboxyl group of an ester and a sulfur atom of the methylsulfanyl group was produced in these reactions, but the reaction yield did not exceed 50%.

After removing pure product 4c, the filtrate was acidified with 10% hydrogen chloride solution to afford red crystals in 48% yield. The $^1$H-NMR spectrum of this product exhibited signals corresponding to the hydrogen bonding between the NH group and an ester carbonyl group at 14.20 ppm and methyl protons of the methylsulfanyl group at 2.14 ppm and methyl protons of the tolyl group at 3.39 and 3.51 ppm (ratio 1:1). The $^1$H-NMR measurement revealed that the products were a mixture of the non-closed compounds 5a and 6a. After the purification of crude products, this product was identified as 2Z, 3E methyl 4-cyano-3-methylsulfanyl-4-phenylsulfonyl-2-(1H-pyrid-2-ylidene)butenolate on the basis of spectral (IR, UV, NMR, mass) and elemental analysis. Compounds 5b–d or 6b–d were also synthesized from 1a, b and 2b, c in a similar manner to 5a, 6a (Table 2). The x-ray analysis of 5b conclusively established that the structure of this compound is as shown in Figure 1. These products were not converted to quinolizine derivatives under basic or acidic reaction conditions in DMSO.
Schwarz et al. carried out detailed research on the UV-visible spectra of quinolizine derivatives. Other authors have carried out research on the synthesis of 4H-quinolizines in studies of [3.3.3]cyclazine derivatives, but fluorescence was not investigated. An organic light-emitting diode (OLED) that emits light in the solid state was recently investigated. The fused 2-pyrone derivative, namely, the pyrano[3,4-d]state was recently investigated. The fused 2-pyrone derivative, namely, the pyrano[3,4-d]quinolizine derivative, exhibits red fluorescence in the solid state; however, previously synthesized fluorescent materials were not able to show sufficient fluorescence when used in devices et al.9 There remains an interest in the fluorescence of compounds with a quinolizine skeleton. The fluorescence of synthesized 4-imino-3-phenylsulfonyl-4H-quinolizine derivatives in the solid state is of great interest to our research group.

The UV–vis absorption and fluorescence emission data of 3a, b and 4a–f were analyzed in solution (dichloromethane) and solid states, respectively, at room temperature (Table 3). The spectroscopic properties—absorption maxima (λmax), molar absorptivities (ε), fluorescence maxima (Em max), and relative fluorescent intensities (RI)—are listed in Table 3. The Em max of 3a, b and 4a–f were in the range 507–522 nm in dichloromethane and 528–564 nm in the solid states. With regard to Em max, the obvious substitution effects at the 1- or 2-position of the 4H-quinolizine ring were not observed. On the other hand, the RIs of 4a, b were slightly stronger than those of 3a, b in dichloromethane and solid states, indicating that desulfurization at the 2-position of the 4H-quinolizine influenced the RI. Compounds 4c–f exhibited strong fluorescence in the solid states; in particular, 4c–e emitted stronger fluorescence than Alq3. This suggests that the ester groups at the 1-position have a significant effect on the fluorescent intensity. In dichloromethane solutions of 4c–f, the obvious substitution effects on the RI were not observed. Compounds 3a, b and 4a–f exhibited significantly larger Stokes’ shifts (SS) in dichloromethane, indicating that the S1 states of these compounds were stabilized by a solvent polarization field. The F value, which is the difference between the Em values in the solid and solution states, varied from 17 nm to 44 nm in all compounds. The crystal structure of compounds 4a, 4c were determined by X-ray crystallographic analysis. Single crystals of 4a, 4c were obtained by the recrystallized from MeOH and acetonitrile. The crystal analysis of 4a, 4c as shown in Figure 2 and 3 suggests that the π–π stacking interactions of aromatic rings is not existence. In these 4H-quinolizine derivatives, the packing structure does not affect the solid state fluorescence.

Table 3. UV and fluorescence data for 4H-quinolizine derivatives in dichloromethane and in solid states.

<table>
<thead>
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<th>No.</th>
<th>λmax (nm)</th>
<th>ε (10^4)</th>
<th>Em max (nm)</th>
<th>RI</th>
<th>m.p (°C)</th>
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<td>3a</td>
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<td>336</td>
<td>344</td>
<td>6a</td>
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<tr>
<td>3b</td>
<td>314</td>
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<td>344</td>
<td>5a</td>
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<td>336</td>
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<td>336</td>
<td>344</td>
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<td>206</td>
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Figure 2. X-ray crystallography of 4a

Figure 3. X-ray crystallography of 4c

Conclusions

The reaction of 3,3-bis(methylsulfanyl)-2-phenylsulfonyl-acrylonitriles (1a, b) with 2-pyridylacetonitrile (2a) in the presence of potassium carbonate as a base in DMSO afforded 4-imino-2-methylsulfanyl-3-phenylsulfonyl-4H-quinolizine-1-carbonitriles (3a, b). A methylsulfanyl group at the 2-position on 4H-quinolizine-1-carbonitriles was readily removed under...
methanol reflux conditions to afford 4-imino-3-phenylsulfonyl-4H-quinolizine-1-carbonitriles (4a, b) in good yields. Alkyl 3-phenylsulfanyl-4H-quinolizine-1-carboxylates (4c–f) were directly synthesized from sulfonyl ketene dithioacetal (1a, b) with alkyl 2-pyridylacetates (2b, c), without carrying out desulfurization involving the use of any metallic reagents. The synthesized 4-imino-3-phenylsulfonyl-4H-quinolizine derivatives exhibited strong fluorescence in solid states, suggesting that it is possible to obtain a design for enhancing fluorescence intensity without changing their fluorescence wavelength.

Experimental Section

General Procedures. Identifications of compounds and measurements of properties were carried out by various techniques using the following equipment. Melting points were determined in a capillary tube and were uncorrected. IR spectra were recorded in potassium bromide pellets on a JASCO 810 or Shimazu IR-460 spectrometer. UV absorption spectra were determined in 95% ethanol on a Hitachi 323 spectrophotometer. Fluorescence spectra were determined on Shimazu RF-5300pc. NMR spectra were determined on Shimazu RF-6000pc. MS spectra were determined on Shimazu QP-2010 (70 eV). The reaction mixture was poured into 200 mL of ice-water and acidified with 10% hydrochloric acid. The precipitate that appeared was collected by filtration, washed with mixture was stirred and heated for 30 min at 50-60°C. The reaction mixture was poured into 200 mL of ice-water and acidified with 10% hydrochloric acid. The precipitate that appeared was collected by filtration, washed with water. The precipitate that appeared was collected by filtration, washed with water. The precipitate that appeared was collected by filtration, washed with water. The precipitate that appeared was collected by filtration, washed with water.

Method of Measurement of Fluorescence.

(a) In the solid state: A powder sample of subject compound is heaped in a tray. After covering the sample with a quartz plate, this part was fixed in fluorescence spectrometer. After fixing the fluorescent wavelength, the excitation spectrum was determined by the scanning with the fluorescent wavelength. Similarly, fluorescent spectrum was obtained after scanning with the excitation wavelength. After obtaining these results, the excitation wavelength was decided and the fluorescence spectrum measured. The fluorescent relative intensity was determined using Alq3 as the standard.

(b) Fluorescence of Alq3 and test compounds was measured at an excitation wavelength of 345 nm. b) In solution: The fluorescence spectra in solution were determined by using DCM: [4-(dicyanomethylene)-2-methyl-6-(4-dimethylaminostyryl)-4-methylpyran] as a standard compound.

4-Imino-3-phenylsulfonyl-4H-quinolizine-1-carbonitrile (3a).

This compound (1.31 g, 4.1 mmoles) was prepared in 81% yield from 4-Imino-3-phenylsulfonyl-4H-quinolizine-1-carboxylate (4c). 1H NMR (300 MHz, CDCl3): δ 1.98 (6H, s, OMe 2), 3.51 (3H, s, OMe 2), 6.42-6.61 (2H, m, pyridyl-H), 7.15-7.25 (1H, m, 9-H), 10.11 (1H, s, N-H). 13C NMR (100 MHz, CDCl3): δ 19.63, 85.74, 115.74, 116.58, 117.36, 118.56, 118.66, 121.93, 123.13, 123.18, 132.44, 132.47, 136.78, 140.48, 149.70, 151.61. Ms: m/z 336 (M++1, 6), 335 (M+, 12), 304 (28), 303 (100), 214 (26), 167 (51), 127 (33).

4-Imino-4-phenylsulfonyl-4H-quinolizine-1-carbonitrile (4a). A solution of 0.36 g (1.0 mmol) of 3a in 100 mL of MeOH was refluxed for 5 h. After removal of the solvent, the residue was washed with 10 mL of MeOH to give 0.31 g of orange crystals in 100% yield. An analytical sample was rechromatographed on a mixture of MeOH and toluene (3:2). Fluorescence orange leaflets, mp 208-209°C. IR (KBr, cm-1): 3337 (C-NH), 2210 (CN), 1608, 1500, 1298, 1095, 583 cm-1. UV (EtOH) λ max (log ε): 385.5 (3.35), 315.9 (3.05), 282.0 (3.41). Fluorescence (solid): Ex: 339 mm, Em: 546 mm; RI=0.89. 1H NMR (300 MHz, CDCl3): δ: 7.54-7.62 (2H, m, phenyl-H), 7.85 (1H, m, 8-H), 7.87-7.95 (2H, m, phenyl-H), 7.93 (1H, d, J=7.0 Hz, 6-8), 8.27 (1H, s, 2-H), 8.11 (1H, br, N-H), 9.73 (1H, d, J=7.7 Hz, 9-H). 13C NMR (100 MHz, CDCl3): δ: 117.36, 122.50, 127.06, 128.66, 131.99, 133.09, 138.94, 143.13, 147.53, 150.53, 151.46. Ms: m/z 370 (M++1, 4), 369 (M+, 69), 368 (15), 305 (28), 304 (100), 214 (26), 167 (51), 127 (33).

4-Imino-3-phenylsulfonyl-4H-quinolizine-1-carbonitrile (4b). This compound (0.32 g, 1.0 mmole) was prepared in 100% yield from 0.37 g (5.0 mmole) of 3b in a manner similar to that described for the synthesis of 4a. An analytical sample was recrystallized from DMF to give orange needles, mp 180-184°C. IR (KBr, cm-1): 3347 (C-NH), 2208 (CN), 1614, 1490, 1292, 1095, 570 cm-1. UV (EtOH) λ max (log ε): 451.3 (3.67), 383.0 (3.65), 328.5 (3.41), 278.5 (3.85). Fluorescence (solid): Ex: 344 mm, Em: 556 mm; RI=0.42. 1H NMR (300 MHz, CDCl3): δ: 2.41 (3H, s, Me), 7.21 (1H, m, 7-H), 7.32 (2H, m, phenyl-H), 7.81 (1H, m, 8-H), 7.83 (2H, m, phenyl-H), 7.86 (1H, J=6.6 Hz, 6-8), 8.26 (1H, s, 2-H), 8.78 (1H, br, N-H), 9.61 (1H, d, J=7.8 Hz, 9-H). 13C NMR (100 MHz, CDCl3): δ: 21.57, 80.04, 115.18, 116.62, 117.28, 122.43, 127.06, 127.10, 127.22, 132.27, 138.82, 144.07, 147.41, 150.41, 151.45. Ms: m/z 324 (M++1, 5), 323 (M+, 23), 259 (21), 258 (100), 168 (25), 167 (33), 114 (13).

4-Imino-3-phenylsulfonyl-4H-quinolizine-1-carboxylate (4d).

To a solution of standard sample and all subject compounds were measured in CHCl3 solution (1.0×10-3M) on 480 nm excitation.
Reaction of 1b with 2b

Compound 4d (0.3 g, 2.0 mmoles) was synthesized in 46% yield from 2b (1.5 g, 10.0 mmoles) and 1b (1.98 g, 5.0 mmoles) in a manner similar to that described for the preparation of 4c. An analytical sample was recrystallized from EtOH to give yellow needles. 5d, 6d (0.92 g, 2.2 mmoles) was synthesized in 44% yield in manner similar to that described for the preparation of 5a, 6a. An analytical sample was recrystallized from MeOH to give red crystals.

Ethyl 4-imino-3-tolylsulfonyl-4′-quinolizine-1-carboxylate (4f): mp 177-178°. IR (KBr, cm⁻¹): 3203 (NH), 1747 (CO), 1747, 1515, 1513. UV (EtOH) λ (log ε): 435.5(3.12), 364.5(3.17), 271(3.34). Fluorescence (solid): Ex, 332 nm; Em, 336 nm, RI=0.62. Fluorescence (CHCl₃): Ex, 284 nm, Em, 519 nm; RI=0.25. 1H NMR (300 MHz, CDCl₃) δ: 1.42 (CH₃, s), 3.90 (CH₃, Me), 1.24 (3H, s, SMe), 3.04 (2H, m, 9-H), 7.69 (1H, m, OCH₂-CH₃), 7.31 (1H, m, 8-H), 7.85 (2H, d, J=7.9 Hz, phenyl-H), 7.77 (1H, m, 7-H), 8.48 (2H, d, J=7.9 Hz, phenyl-H), 8.56 (1H, s, CH=, NH), 8.77 (1H, s, 2-H), 11.70 (1H, d, J=9.0 Hz, -OH), 9.67 (1H, d, J=8.1 Hz, -OH). 13C NMR (100 MHz, CDCl₃) δ: 15.14, 21.67, 21.54, 21.73, 50.72, 51.10, 81.40, 110.57, 110.85, 111.94, 114.12, 114.73, 117.80, 117.77, 127.77, 128.10, 128.35, 129.58, 133.36, 133.35, 136.95, 138.72, 138.97, 139.06, 144.22, 145.41, 150.85, 150.82, 150.69, 166.65, 174.03, 174.17. MS: m/z 636 (M ++1, 9), 392 (M +, 92), 236 (100), 164 (25), 99 (21). Anal. Calcd. for C₁₉H₁₈N₂O₄S₂: C, 55.65; H, 4.15; N, 7.21. Found: C, 55.70; H, 4.04; N, 6.96.

Reaction of 1b with 2b

Compound 4d (0.3 g, 2.0 mmoles) was synthesized in 46% yield from 2b (1.5 g, 10.0 mmoles) and 1b (1.98 g, 5.0 mmoles) in a manner similar to that described for the preparation of 4c. An analytical sample was recrystallized from EtOH to give yellow needles. 5d, 6d (0.92 g, 2.2 mmoles) was synthesized in 44% yield in manner similar to that described for the preparation of 5a, 6a. An analytical sample was recrystallized from MeOH to give red crystals.

Methyl 4-imino-3-tolylsulfonyl-4′-quinolizine-1-carboxylate (4f): μ=152-157°. IR (KBr, cm⁻¹): 3356 (NH), 1690 (CO), 1618, 1489, 578. UV (EtOH) λ (log ε): 437.0 (4.03), 364.5 (4.06), 272.0 (4.19). Fluorescence (solid): Ex, 339 nm; Em, 528 nm; RI=1.44. Fluorescence (CHCl₃): Ex, 284 nm; Em, 511 nm; RI=0.47. 1H NMR (300 MHz, CDCl₃) δ: 2.39 (3H, s, Me), 3.56 (3H, s, OMe), 7.18 (1H, m, 7-H), 7.20 (2H, J=8.4 Hz, phenyl-H), 7.80 (1H, m, 8-H), 7.84 (1H, d, J=8.4 Hz, phenyl-H), 8.60 (1H, brs, NH), 8.85 (1H, n-H), 9.31 (1H, d, J=9.0 Hz, -OH), 9.76 (1H, d, J=8.1 Hz, -OH). 13C NMR (100 MHz, CDCl₃) δ: 21.56, 51.59, 97.15, 113.19, 119.68, 124.94, 127.17, 129.85, 130.94, 131.71, 142.49, 174.31. Ms: m/z 371 (M ++1, 9), 370 (M +, 40), 306 (23), 305 (100), 277 (28), 225 (25). Anal. Calcd. for C₁₉H₁₈N₂O₄S₂: C, 55.65; H, 4.15; N, 7.21. Found: C, 55.70; H, 4.04; N, 6.96.


In the synthesis of 4H-quinolizine derivatives involving the use of a sulfonyl ketene dithioacetal, we found a novel reaction in which the remaining methylsulfanyl group is replaced with a proton after the ring closure reaction in the quinolizine skeleton. A methylsulfanyl group at the 2-position on 4H-quinolizin-4-one was readily removed under methanol reflux conditions to afford 3-phenylsulfonyl 4H-quinolizin-4-ones (5a, b) in good yields. Alkyl 3-phenylsulfonyl-4H-quinolizine-1-carboxylates (5c–f) were directly synthesized from sulfonyl ketene dithioacetal (1a, b) with alkyl 2-pyridylacetates (2b, c), without carrying out desulfurization involving the use of any metallic reagents. We presumed that S-O interaction and the electron-deficient effect in the pyridine ring enables nucleophilic attack of water or methanol anions on the sulfur atom in the methylsulfanyl group.

The synthesized 4-imino-3-phenylsulfonyl-4H-quinolizine derivatives exhibited strong fluorescence in solid states. An organic light-emitting diode (OLED) that emits light in the solid state have recently received considerable attention due to their potential application in next-generation display devices. Our findings will contribute to the development of OLED materials.