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A facile preparation of modified hydrophilic azulene derivatives

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ABSTRACT

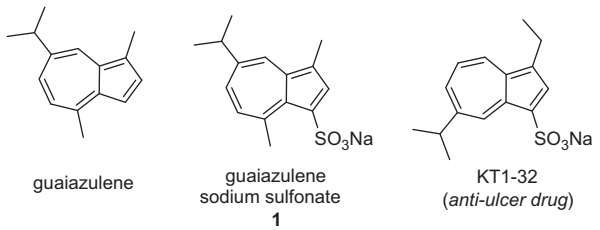
A simple procedure was developed for the preparation of hydrophilic azulene derivatives from an abundant and commercially available source of guaiazulene sodium sulfonate **1**. This protocol may open up an efficient route for the preparation of a series of hydrophilic azulene derivatives.

Guaiazulene is a known active component of the essential oil of *Guaiacum officinalis* L., and it has been used as an anti-allergenic- and anti-inflammatory agent for many years.[1] Guaiazulene is an FDA-approved cosmetic color additive and has potential applications as a pharmaceutical. Of these, guaiazulene sodium sulfonate **1** (Fig. 1), a hydrophilic guaiazulene derivative, has found widespread use in clinical applications as an anti-inflammatory and anti-ulcer agent.[2] Guaiazulene and its derivatives have been obtained by the dehydrogenation of hydroazulene sesquiterepenes of plant origin, which are more readily available than other synthesized azulene compounds. Structurally similar hydrophilic azulenes, such as KT1-32 (Fig. 1) are also used as anti-ulcer drugs.[3] Their preparation is fairly different from that of guaiazulenes. Hydrophilic azulenes are generally synthesized by introducing hydrophilic moieties after multistep construction of azulene nucleus from troponoids or phenols.[4] Thus the preparation of derivatives with greater structural diversity involves an inconvenient conversion sequence.[4c]

Sulfonation is a critical reaction utilized to impart water-solubility to hydrophobic molecules.[5] Sulfonate salts of active pharmaceutical ingredients are particularly useful in the pharmaceutical industry. The poor solubility of sulfonated molecules in most organic solvents complicates their synthesis and purification, thus relegating this modification to the final synthetic step in most cases. Thus, appropriate protection of sulfonate is important.

Over the past few decades, we have investigated the development of convenient and safe methods for synthesizing azulene derivatives from guaiazulene.[6] In continuation of our study, we set out to explore the utility of readily available, mass-produced **1** as a starting material. To the best of our knowledge, synthetic conversion of **1** into compounds with versatile applicability has been rarely reported thus far.[7,8] **1** consists of an azulene ring with a 1,4,7-alkyl side-chain and a 3-substituted sodium sulfonate group. We envisaged the conversion of the alkyl group of **1** into a functional group such as the formyl group, thus providing a direct pathway to hydrophilic azulenes.

Aryl aldehydes are important industrial materials and serve as principal synthetic intermediates in the production of dyes, agricultural chemicals and pharmaceuticals.[9] General oxidation of aromatic alkyl groups into aryl aldehydes is well known in the literature. In the field of azulene chemistry, the oxidation of alkyl side-chain in azulenes is not easy since the azulene nucleus is sensitive to oxidation reagents, such as chromic acid, nitric acid, and permanganate.[10,11] Kurokawa and co-workers reported that oxidation of the 1-methyl group of guaiazulene into a formyl group using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), proceeded only if an appropriate substituent was introduced at the 3-position.[11b] As a pilot experiment, we attempted direct oxidation of sulfonate **1** by DDQ, but it is not successful.



guaiazulene

guaiazulene sodium sulfonate **1**

KT1-32 (*anti-ulcer drug*)

Figure 1. Pharmaceutically active azulenes.

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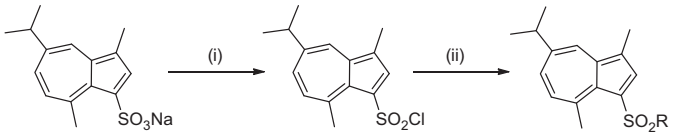
Table 1
Protection of sulfonate **1**



Entry	RH	Product	Method[a]	Time (h)	Yield (%)
1	*n*-PrNH$_2$	**3a**	A	1.5	72 (31)[b]
2	*i*-PrNH$_2$	**3b**	A	2.5	62 (34)[b]
3	NH$_2$OH.HCl	**3c**	A	1.5	62
4	*p*-MeOC$_6$H$_5$NH$_2$	**3d**	A	1.5	89
5	MeOH	**4a**	B	1	67
6	EtOH	**4b**	B	2	80
7	*i*-PrOH	**4c**	B	2.5	69
8	C$_6$H$_5$CH$_2$OH	**4d**	B	2.5	45

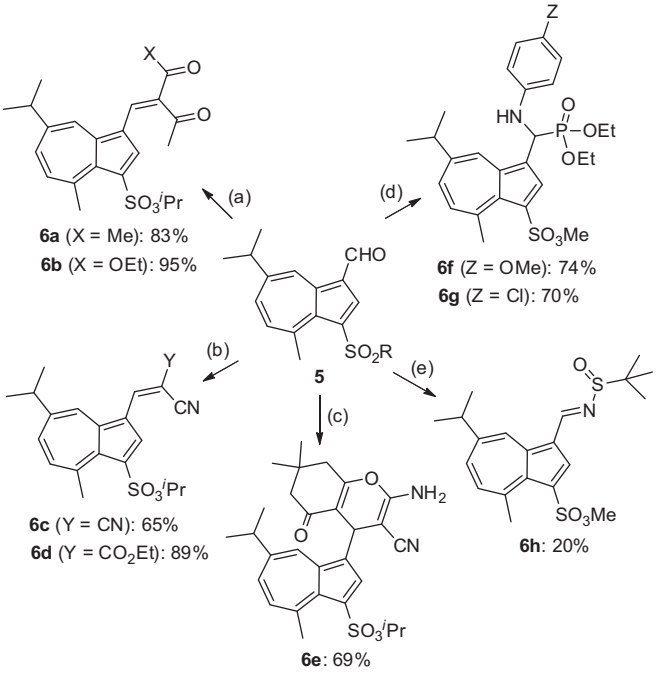
[a] Method A; (i) (COCl)$_2$, DMF, Et$_2$O, 0 °C, 10 min. (ii) Amine (RH), Na$_2$CO$_3$.10H$_2$O, 5 °C. Method B; (i) (COCl)$_2$, DMF, DCM, 0 °C, 10 min. (ii) Alcohol (RH), pyridine, rt.
[b] Yields in parentheses are literature yields reported in Ref. 7 and have been provided for comparison. Reaction conditions described in Ref. 7 are as follows; (i) (COCl)$_2$, cat. DMF, DCM, pyridine, 0 °C, 10 min. (ii) Amine, Et$_3$N, pyridine.

Evidently, suitable protection of the sulfonate moiety of **1**, which enables **1** to be stable under various reaction conditions and to be deprotected easily after reactions, is needed. Herein we demonstrate a simple transformation of **1** into aldehyde **5** (vide infra), enabling the preparation of various hydrophilic azulenes bearing a functionalized side-chain.

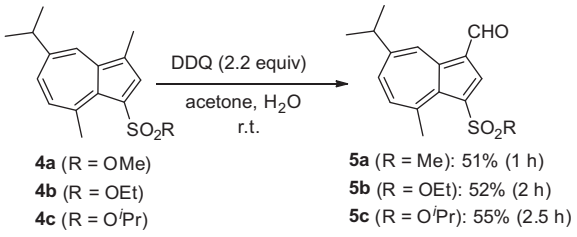
Initially we attempted a one-pot protection of sulfonate **1** through in situ generation of sulfonyl chloride **2**. Recently, an analogous approach was described by Yin and co-workers, but the reaction condition was not examined in detail despite low yields (20–48%).[7] Thus, we evaluated to establish whether in situ generation of sulfonyl chloride **2** (Table 1) was possible.[12] A solution of oxalyl chloride in ether was dropped slowly into a stirred solution of **1** and DMF in ether, which was maintained at 0 °C. After 10 min, *n*-propylamine and Na$_2$CO$_3$.10H$_2$O were added to afford the desired sulfonamide **3a** in 72% yield (entry 1). The yields in parentheses in Table 1 demonstrated some improvement on yields in the literature.[7] Other amines were suited to the reaction and gave **3b–3d** in moderate to good yields (entries 2–4). Once a clear in situ generation of sulfonyl chloride **2** was established, we proceeded to prepare the sulfonate ester instead of sulfonamide by considering facile deprotection after functionalization. In situ treatment of sulfonyl chloride **2** with methanol afforded the corresponding sulfonate ester **4a** in 67% yield (entry 5). Alcohols that are commonly used in industries, such as ethanol and isopropanol also produced sulfonate esters **4b** and **4c** in 80% and 69% yields, respectively, (entries 6–7), and the use of benzylic alcohol yielded the poorest conversion (entry 8). We confirmed that the procedure reported by Yin[7] was not suitable for the preparation of these sulfonate esters. Thus, we have established a useful procedure for conversion of hydrophilic **1** into sulfonate ester **4a–4d**, which reduces the complicacies of treatment and purification in further transformations.

With protected sulfonates in hand, we turned our attention toward oxidation of 1-methyl groups of **4a–4c**. DDQ-oxidation of alkyl group of azulene is a common reaction,[11] but its application to azulene bearing sulfonate moiety was not examined so far. To a solution of **4** in acetone–water was added 2.2 equiv of DDQ at room temperature. To our delight, the desired aldehydes **5a–5c** were obtained in 51–55% yields (Scheme 1).[13]

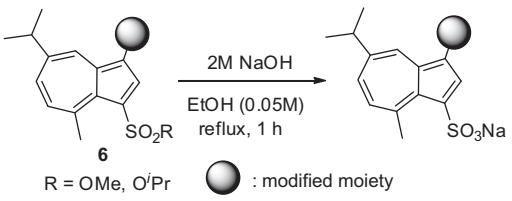
We have ascertained that prepared aldehydes **5**[14] could be applied to various transformations as presented in Scheme 2.[15] Knoevenagel condensation and Michael addition proceeded smoothly to afford the corresponding azulenes **6a–6e**.[16,17] Azulenes bearing an α-amino phosphonate[18,19] or a sulfonylimino moiety[20,21] were also obtained. In the course of these transformations, hydrolysis of the sulfonic ester moieties was not observed, demonstrating that appropriately protected **5** is a suitable precursor for various hydrophilic azulene derivatives. Notably the deprotection of these modified sulfonate esters proceeded smoothly under mild condition (Scheme 3).[22]



Scheme 2. Various transformations from **5**. Reagents and conditions: (a) **5c** (1.0 equiv), pentane-2,4-dione (1.0 equiv) or ethyl-3-oxobutanoate (1.6 equiv), Yb(OTf)$_3$ (0.1 equiv), Ac$_2$O (2.0 equiv), CH$_3$NO$_2$, 18 h, rt. (b) **5c** (1.0 equiv), malononitirile (2.0 equiv) or 2-ethoxyacetonitrile (2.0 equiv), cat. piperidine, EtOH, 1 h, rt. (c) **5c** (1.0 equiv), malononitirile (1.0 equiv), dimedone (1.0 equiv), piperidine (0.1 equiv), DCM, 24 h, reflux. (d) **5a** (1.0 equiv), 4-methoxyaniline (1.0 equiv) or 4-chloroaniline (1.0 equiv), diethyl phosphite (1.0 equiv), Sc(OTf)$_3$ (0.1 equiv), THF, 24 h, rt. (e) **5a** (1.0 equiv), (*R*)-(+)-2-methylpropane-2-sulfinamide (1.0 equiv), CuSO$_4$ (1.5 equiv), DCM, 18 h, rt.



Scheme 1. Oxidation of 1-methyl group of **4** by DDQ.



Scheme 3. Deprotection of sulfonate ester **6**.

In summary, the facile synthesis of hydrophilic azulene derivatives bearing a range of functional groups is demonstrated.[23] The selection of sulfonate esters as protecting groups was prompted by the evaluation of their properties, namely, their stability toward various reaction conditions and the ease with which they may be cleaved to create hydrophilic forms under mild conditions, thereby providing access to preparative routes for a diverse range of hydrophilic azulenes. Related products described herein may be useful intermediates for the development of pharmacologically active agents containing the azulene skeleton. The facile and efficient synthesis of other azulene derivatives is now in progress in our laboratory.

References and notes

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12. We found that the addition of extra pyridine adversely affected this reaction. A typical procedure for the preparation of sulfonate esters: (Table 1, entry 7): To a stirred solution of **1** (10 mmol) and DMF (1.2 mL) in dichloromethane (50 mL), maintained at 0 °C, a solution of oxalyl chloride (25 mmol) in dichloromethane (10 mL) was added slowly, and the resultant solution was stirred at the same temperature. After 10 min, isopropanol (10 mL) and pyridine (2 mL) were added and the mixture stirred for 2.5 h. After the reaction was completed, the resultant mixture was extracted with dichloromethane, washed with aqueous sodium hydroxide, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (6:1 hexane–ether as eluent) to give **4c** as purple prisms (69%) mp: 99 °C. ^{1}H NMR($CDCl_3$) δ: 1.27 (6H, d, J = 6.0 Hz), 1.39 (6H, d, J = 6.8 Hz), 2.59 (3H, s), 3.15 (1H, sep, J = 6.8 Hz), 3.33 (3H, s), 4.74 (1H, sep, J = 6.0 Hz), 7.42 (1H, d, J = 11.1 Hz), 7.62 (1H, d, J = 11.1 Hz), 8.19 (1H, s), 8.31 (1H, s). MS: calcd for $C_{18}H_{24}O_3S$: 320.1446, found: 320.1565.
13. A typical procedure for the oxidation by employing DDQ (Scheme 1): to a stirred solution of **4c** (1.0 mmol) in acetone/water (9:1, 50 mL), DDQ (2.2 mmol) was added at room temperature. The resultant mixture was extracted with chloroform, washed with water, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (3:1 hexane–acetone as eluent) to give **5c** as red prisms (55%). mp: 133 °C. ^{1}H NMR($CDCl_3$) δ:1.32 (6H, d, J = 6.0 Hz), 1.44 (6H, d, J = 6.8 Hz), 3.28 (1H, sep, J = 6.8 Hz), 3.42 (3H, s), 4.86 (1H, sep, J = 6.0 Hz), 7.82 (1H, d, J = 10.8 Hz), 7.91 (1H, dd, J = 2.0, 10.8 Hz), 8.74 (1H, s), 10.10 (1H, d, J = 2.0 Hz), 10.24 (1H, s). MS: calcd for $C_{18}H_{22}O_4S$: 334.1239, found: 334.3614.
14. The reactivity of sulfonylazulene carbaldehydes is quite different due to the electron-withdrawing sulfonyl group and their poorer solubility. The protection of the sulfonyl group is plausible for the effective transformations.
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17. A typical procedure for Knoevenagel condensation and Michael cyclization (Scheme 2): to a stirred solution of **5c** (0.20 mmol) in DCM (5 mL), malononitrile (0.20 mmol), dimedone (0.20 mmol), and piperidine (0.02 mmol) were added and refluxed for 24 h. The resultant mixture was extracted with chloroform, washed with water, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (2:1 hexane–ether as eluent) to give **6e** as purple needles (69%). mp: 131 °C. ^{1}H NMR($CDCl_3$) δ:1.03 (3H, s), 1.12 (3H, s), 1.24 (6H, t, J = 6.4 Hz), 1.45 (6H, dd, J = 2.0, 6.8 Hz), 2.13–2.24 (2H, m), 2.44–2.57 (2H, m), 3.21 (1H, sep, J = 6.8 Hz), 3.31 (3H, s), 4.53 (2H, s), 4.66 (1H, sep, J = 6.4 Hz), 5.07 (1H, s), 7.46 (1H, d, J = 11.2 Hz), 7.67 (1H, dd, J = 2.0, 11.2 Hz), 8.07 (1H, s), 8.86 (1H, s). MS: calcd for $C_{29}H_{34}N_2O_5S$: 522.2188, found: 522.2940.
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19. A typical procedure for the preparation of azulenes bearing an α-amino phosphonate group (Scheme 2): to a stirred solution of **5a** (0.75 mmol) in THF (5 mL), 4-methoxyaniline (0.75 mmol), diethyl phosphite (0.75 mmol), and $Sc(OTf)_3$ (0.075 mmol) were added at room temperature and stirred for 24 h. The resultant mixture was extracted with chloroform, washed with water, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (1:1 hexane–acetone as eluent) to give **6f** as purple prisms (74%). mp: 156 °C. ^{1}H NMR($CDCl_3$) δ:1.08 (3H, t, J = 7.0 Hz), 1.28 (3H, t, J = 7.0 Hz), 1.37 (6H, t, J = 7.0 Hz), 3.14 (1H, sep, J = 6.9 Hz), 3.30 (3H, s), 3.67 (6H, s), 3.75–3.82 (1H, m), 3.97–4.03 (1H, m), 4.07–4.16 (2H, m), 4.41 (1H, t, J = 7.8 Hz), 5.28 (1H, dd, J = 7.2, 22.4 Hz), 6.55 (2H, d, J = 8.8 Hz), 6.65 (2H, d, J = 9.2 Hz), 7.52 (1H, d, J = 11.2 Hz), 7.69 (1H, dd, J = 2.0, 11.2 Hz), 8.43 (1H, d, J = 2.4 Hz), 8.65 (1H, d, J = 2.0 Hz). MS: calcd for $C_{27}H_{36}NO_7PS$: 549.1950, found: 549.2579.
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21. A typical procedure for the synthesis of azulenes bearing a sulfonylimino group (Scheme 2): to a stirred solution of **5a** (0.50 mmol) in DCM (3 mL), (*R*)-(+)-2-methylpropane-2-sulfinamide (0.50 mmol), CuSO4 (0.75 mmol) were added at room temperature and stirred for 18 h. The resultant mixture was extracted with dichloromethane, washed with water, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (4:1 hexane–acetone as eluent) to give **6h** as red prisms (20%). mp: 150 °C. ^{1}H NMR($CDCl_3$) δ:1.31 (9H, s), 1.42 (6H, dd, J = 2.8, 7.2 Hz), 3.22 (1H, sep, J = 6.9 Hz), 3.37 (3H, s), 3.85 (3H, s), 7.73 (1H, d, J = 11.2 Hz), 7.85 (1H, dd, J = 2.4, 11.2 Hz), 8.71 (1H, s), 9.00 (1H, s), 9.82 (1H, d, J = 2.0 Hz). MS: calcd for $C_{20}H_{27}NO_4S_2$: 409.1381, found: 409.4801.
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23. Typically, sulfonylation of azulenes bearing electron-donating groups can smoothly proceed (see Refs. 4,7). However, in the case of the electron-deficient carbonylazulenes in this study, introduction of sulfonate moiety into azulene ring in the last step did not smoothly proceed and requires very harsh conditions. In this point, our procedure starting from the sulfonylated azulene has some advantages.