Facile Conversion of 1-Methyl Group of Guaiazulene into 1-Formyl Group

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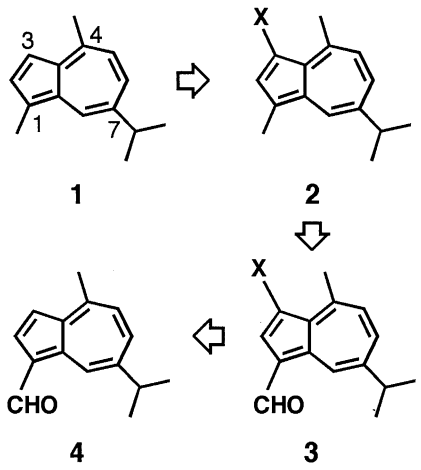
1-Formyl-7-isopropyl-4-methylazulene (**4**) has been synthesized by DDQ oxidation method of 1-methyl group of guaiazulene (**1**). The overall synthetic procedures from **1** to **4** were completed within 2 h, and almost quantitative yield was achieved. The compound (**4**) was inaccessible so far, because of a poor yield of **4** in its total synthesis (<5%, overall), as well as in its preparation by non-selective oxidation of **1** (<1%).

Guaiazulene (7-isopropyl-1,4-dimethyl-azulene, **1**), is well known as an anti-inflammatory agent[1] and many derivatives of **1** also show biological activities.[2] Since total syntheses of **1** hitherto-known are rather lengthy and the yields of **1** were very low,[3,4] **1** and its useful derivatives have been virtually obtained by the dehydrogenation of hydroazulene sesquiterpenes of plant origin.[5] Therefore, the development of the methodology for chemical conversion of **1** is especially important in the guaiazulene chemistry.

Abstraction of acidic 4-methyl proton from **1** by sodium N-methylanilinide provided an excellent method for introducing a variety of functional groups at 4-position on seven-membered ring.[6] On the other hand, there have been no effective way to functionalize 1-methyl group of **1**, because the reactivity of this proton is quite low towards most of reagents. This paper deals with the facile conversion of 1-methyl group into formyl group in **1**, with the intention to obtain the key function for introducing various substituents at 1-position.



Scheme 1.

DDQ oxidation is an unique technique to change the unreactive 1-methyl group into formyl group. Previously, it has been reported that the treatment of 1-methylazulene with DDQ gave 1-formylazulene in very high yield (90%).[7] However, a simple application of this method to **1** gave only a complex mixture, along with 1-formyl-7-isopropyl-4-methylazulene (**4**) in quite low yield (< 1%), the yield of which is similar to that in the oxidation of **1** by $KMnO_4$.[8] A further study showed that

Table 1. The oxidation of **2** with DDQ [1)]

run	X		time / min	yield of **3** / %
2 : DDQ = 1 : 2.1				
1	$COCH_3$	(**2a**)	10	91
2	CHO	(**2b**)	10	72
3	$COOCH_3$	(**2c**)	10	66
4	CN	(**2d**)	120	85
5	$COCCl_3$	(**2e**)	110	49
6	$COCF_3$	(**2f**)	15	26
7	NO_2	(**2g**)	120	43
2 : DDQ = 1 : 7				
8	$COCCl_3$	(**2e**)	5	>99

1) The reaction mixture was stirred in H_2O / acetone (1:9 v/v) at room temperature. The concentrations of the substrates were 0.025 mol dm^{-3}.

DDQ oxidation of 3-substituted guaiazulenes gave the corresponding 1-formyl derivatives in fairly good yield, while that of 2-substituted guaiazulene afforded only a complex mixture. This fact indicated that the protection of 3-position is inevitable in the oxidation of **1**.

In Table 1 are listed the reaction time and the yields of DDQ oxidation, obtained by treating 3-substituted compounds (**2**)[9] with double the molar quantity of DDQ in a H_2O / acetone solution (1:9 v/v) at room temperature. As clearly shown in this table, the compounds (**2a-2c**) afforded the corresponding 1-formyl derivatives in quite high yields, while other ones (**2e-2g**), having more electron-withdrawing substituents, led to less satisfactory results. These results indicate that the protection of 3-position using some electron-withdrawing groups do not obstruct the action of DDQ on 1-methyl group so much, though the reaction should be started with hydride abstraction from 1-methyl group to form a cation species.[10] The lower reactivity of **2d-2g** toward DDQ than **2a-2c** could be attributed to the more electron-withdrawing ability of 3-substituents. In an effort to improve the yield of the latter type of compounds, we fortunately found that DDQ oxidation of trichloroacetyl derivative (**2e**) proceeded quantitatively, when a large excess of DDQ was used. (run 8, Table 1)

These findings, together with the preceding observation that the trichloroacetyl (CCl_3CO) group can easily be hydrolyzed to carboxylic acid (and probably removed easily by decarboxylation),[11] suggested a simple route to convert guaiazulene (**1**) into 1-formyl derivative (**4**).

Figure 1 shows the overall synthetic scheme of 1-formyl derivative (**4**) from guaiazulene (**1**). The synthetic procedure is as follows.[12] The trichloroacetylguaiazulene (**2e**), which was easily obtained by treating **1** with trichloroacetic anhydride in CH_2Cl_2 in 98% yield, was stirred with 7 times the molar quantity of DDQ in H_2O / acetone (1:9 v/v) for 30 min at room temperature to give 1-formyl-7-isopropyl-4-methyl-3-(trichloro-

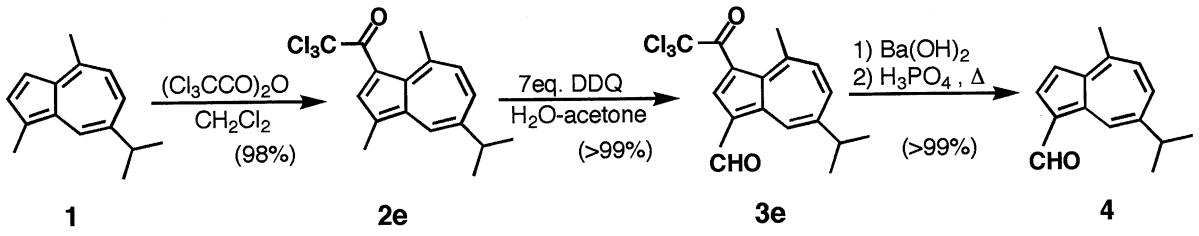


Figure 1. Synthetic scheme of **4** from guaiazulene (**1**).

acetyl)azulene (**3e**) in >99% yield, after passing through an alumina column. ^{1}H-NMR spectra of **3e** showed singlet peak at 10.27 ppm assignable to 1-formyl proton. Considerable down field shift by 1.7 ppm was observed for the H8 proton (10.00 ppm), which signal appeared at 8.30 ppm in **2e**. The m/z = 356 peak was found as M^+ and the pattern coefficients of M^+ on isotope ions also supported the structure of **3e**.[12] Attempted hydrolysis of trichloroacetyl group of **3e** into carboxyl group by NaOH or by KOH gave only an unidentified complex mixture, probably because the formyl group was decomposed in such a strong alkaline condition. On the contrary, hydrolysis of **3e** with milder alkaline $Ba(OH)_2$ was successfully attained. The reaction was performed by heating **3e** at 60 °C for 5 min in the presence of 10 times the molar quantity of $Ba(OH)_2$ in a H_2O / acetone solution (1:9 v/v). The end of the reaction was judged clearly by a color change of the mixture from deep-red to green. After the alkaline solution was acidified with 85% phosphoric acid, benzene was added in order to take up the decarboxylated product into upper benzene layer, because **4** can be considered to be insoluble in water. When the lower aqueous layer was heated by using water-bath (90 °C), the colorless upper benzene layer rapidly turned into reddish purple, indicating that the water-insoluble **4** was produced in aqueous layer and was taken up into organic layer. The colored benzene layer was repeatedly replaced with fresh one, till organic layer remained colorless by heating. The collected benzene solution was dried over $MgSO_4$, concentrated, and passed through alumina to afford **4** in quite high yield (>99%). This decarboxylation reaction completed within only 5 min.

Almost quantitative conversion of **1** into **4**, attained here, offered the first practical method to produce a large amount of **4** very easily, as a key compound for successive utilization. Hence, the reaction scheme established in this study would promise a useful procedure for introducing a variety of functional groups at 1-position of **1**. Such a trial is successfully in progress, seeking for new compounds carrying novel biological activities.

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11 See the literature of compound **2e** in Ref. 9.

12 The spectroscopic data of **2e**, **3e**, and **4** are as follows:
2e: red crystals (m.p. 92.0-93.5 °C), ^{1}H-NMR ($CDCl_3$, δ, TMS, 270 MHz) 1.39 (d, 6.84 Hz, 6H, -CH(C<u>H</u>$_3$)$_2$), 2.61 (s, 3H, 1-CH_3), 2.82 (s, 3H, 4-CH_3), 3.17 (quint., 6.84 Hz, -C<u>H</u>(CH$_3$)$_2$), 7.45 (d, 1H, 10.74 Hz, 5-H), 7.66 (dd, 10.74, 1.96 Hz, 6-H), 8.30 (d, 1H, 1.96 Hz, 8-H), 8.31 (s, 1H, 2-H), IR ($CHCl_3$, cm^{-1}) 1670 (C=O), 1180 (C-CO-C stretch), 690 (C-Cl stretch), MS (m/z): 356 (M^+;4%), 239 (M^+-CCl_3; 100%).
3e: red crystals (m.p. 118-120 °C), ^{1}H-NMR ($CDCl_3$, δ, TMS, 270 MHz) 1.44 (d, 6.59 Hz, 6H, -CH(C<u>H</u>$_3$)$_2$), 2.86 (s, 3H, 4-CH_3), 3.30 (quint., 6.59 Hz, -C<u>H</u>(CH$_3$)$_2$), 7.80 (d, 1H, 10.99 Hz, 5-H), 7.93 (dd, 10.99, 1.96 Hz, 6-H), 8.84 (s, 1H, 2-H), 10.00 (d, 1.96 Hz, 8-H), 10.27 (s, 1H, CHO), IR ($CHCl_3$, cm^{-1}) 2820, 2720 (CHO), 1690 (C=O), 1662 (C=O), MS (m/z): 356 (M^+; 4%), 239 (M^+-CCl_3; 100%). Relative intensity of M^+ peaks on isotope ratio Found: m/z 356, 100; 358, 94.6; 360, 36.0; 362, 2.3%. Calcd. for $C_{17}H_{15}O_2$<u>Cl</u>$_3$: m/z 356, 100; 358, 97.8; 360, 31.9; 362, 3.5%.
4: red-purple oil, ^{1}H-NMR ($CDCl_3$, δ, TMS, 270 MHz) 1.41 (d, 6.60 Hz, 6H, -CH(C<u>H</u>$_3$)$_2$), 2.94 (s, 3H, 4-CH_3), 3.24 (quint., 6.60 Hz, -C<u>H</u>(CH$_3$)$_2$), 7.27 (d, 1H, 4.40 Hz, 3-H), 7.51 (d, 10.99 Hz, 5-H), 7.73 (s, 1H, 10.99, 2.19 Hz, 6-H), 8.18 (d, 4.40 Hz, 2-H), 9.73 (d, 2.19 Hz, 8-H), 10.32 (s, 1H, CHO), IR ($CHCl_3$, cm^{-1}) 2820, 2720 (CHO), 1650 (C=O), MS (m/z): 212 (M^+; 100%), 197 (M^+-CH_3; 80%), 169 (M^+-CH(CH$_3$)$_2$; 20%).