JOC*Note*

A Novel Two-Carbon Homologation with *N*-Vinylacetamides and Ethyl Vinyl Ether as Acetaldehyde Anion Equivalents in the Synthesis of 9*H*-Xanthene, 9*H*-Thioxanthene, and 9,10-Dihydro-9-acridine Carboxaldehydes

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Abstract: An efficient synthesis of 9*H*-xanthene-9-carboxaldehyde (**3a**), 9*H*-thioxanthene-9-carboxaldehyde (**3b**), and 9,10-dihydro-10-methyl-9-acridinecarboxaldehyde (**3c**) by a novel two-carbon homologation of xanthydrol (**1a**), thioxanthydrol (**1b**), and 9,10-dihydro-10-methyl-9-acridinol (**1c**), respectively, using *N*-vinylacetamides (**2a**,**b**) or ethyl vinyl ether (**2c**) as acetaldehyde anion equivalents, is described.

Xanthene-, thioxanthene-, and acridine-containing molecules are of biological importance.[1−3] Unnatural amino acids containing these tricyclic ring systems may also be useful in drug discovery.[1] Synthesis of alanine analogues with these moieties would require 9*H*-xanthene-9-carboxaldehyde (**3a**), 9*H*-thioxanthene-9-carboxaldehyde (**3b**), and 9,10-dihydro-10-methyl-9-acridinecarboxaldehyde (**3c**) as important synthons. Our goal was to develop an efficient and economical synthesis of these aldehydes. In this paper we describe our results on a new synthesis of aldehydes **3a**−**c** by a novel two-carbon homologation of xanthydrol (**1a**), thioxanthydrol (**1b**), and 9,10-dihydro-10-methyl-9-acridinol (**1c**), respectively, using *N*-vinylacetamides (**2a**,**b**) or ethyl vinyl ether (**2c**) as acetaldehyde anion equivalents (Scheme 1). While the reactions of carbocations with enamides, silyl enol ethers, and enol ethers are known,[4−12] to the best of our knowledge such a two-carbon homologation of **1a**−**c** with **2a**−**c** is not reported in the literature.

SCHEME 1

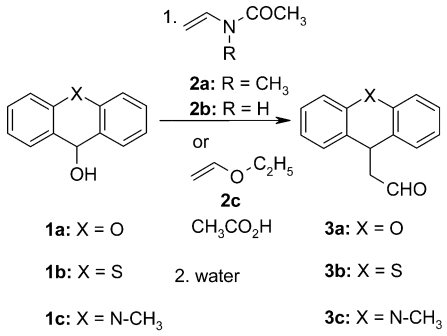
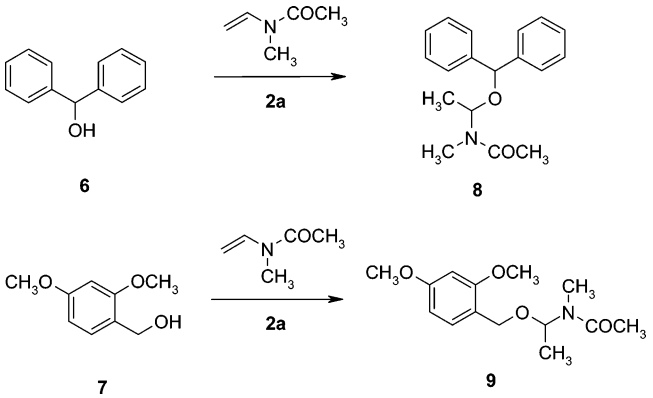


TABLE 1. Two-Carbon Homologation with 2a−c

entry	alcohol	reagent	product	isolated yield (%)
1	**1a**	**2a**	**3a**	90
2	**1a**	**2b**	**3a**	85
3	**1a**	**2c**	**3a**	92
4	**1b**	**2a**	**3b**	95
5	**1b**	**2b**	**3b**	90
6	**1b**	**2c**	**3b**	90
7	**1c**	**2a**	**3c**	68
8	**1c**	**2c**	**3c**	65

SCHEME 2



Reaction of xanthydrol (**1a**) with *N*-methyl-*N*-vinylacetamide (**2a**) was selected as the representative example to develop suitable conditions. Thus, reaction of **1a** with **2a** in the presence of $BF_3{\cdot}Et_2O$ in dichloromethane yielded a complicated mixture. Interestingly, the same reaction in trifluoroacetic acid afforded 9*H*-xanthene-9-ylidene-acetaldehyde (**4**)[13] in 17% yield along with xanthene and 9-xanthenone. The desired aldehyde **3a** was formed only in trace amounts. However, this reaction in glacial acetic acid at room temperature afforded the

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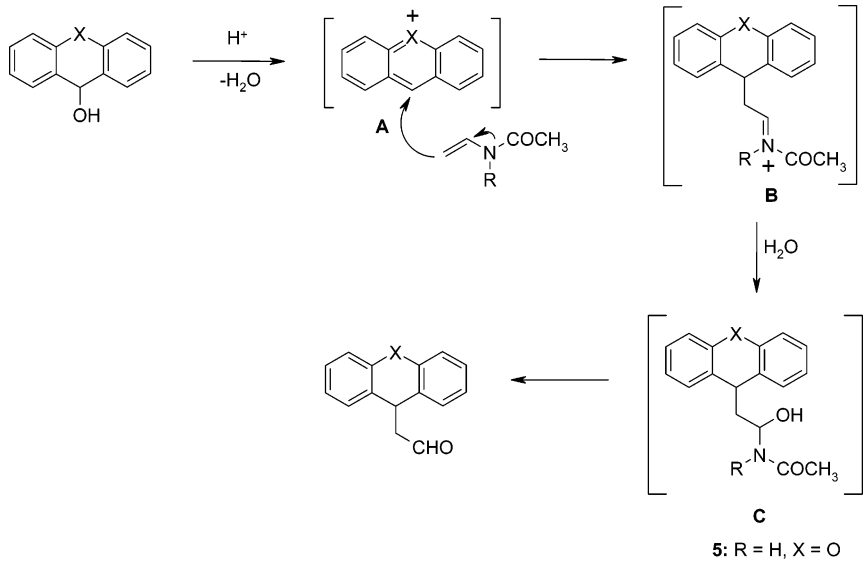
SCHEME 3



desired aldehyde **3a** in 90% yield (entry 1, Table 1). No α,*β*-unsaturated aldehyde (**4**) could be detected. The structure of **3a** was further confirmed by its oxidation to 9*H*-xanthene-9-acetic acid, and by comparison of the spectroscopic data of this acid with those of an authentic sample.[14] Similarly, use of *N*-vinylacetamide (**2b**) instead of **2a** furnished aldehyde **3a** in 85% yield (entry 2). The reaction of **1a** with ethyl vinyl ether (**1c**) in acetic acid also afforded **3a** in 92% yield (entry 3). The two-carbon homologation of thioxanthydrol (**1b**) and 9,10-dihydro-10-methyl-9-acridinol (**1c**) with **2a**−**c** was studied under these newly developed conditions. The results are listed in Table 1. In all cases the yields of **3b** and **3c** were good to excellent.

The reaction of diphenylmethanol (**6**) and 2,4,-dimethoxybenzyl alcohol (**7**) with **2a** did not give any of the expected homologated products. In both cases, *O*-protected derivatives **8** and **9** were isolated in 74% and 61% yield, respectively (Scheme 2). These results suggested that this method has a limited scope.

The proposed mechanism for the two-carbon homologation of **1a**−**c** with **2a**,**b** is illustrated in Scheme 3. An initial reaction of alcohol (**1a**−**c**) with an acid leads to the cationic intermediate **A**, which undergoes a nucleophilic attack by **2a**,**b** to *N*-acyliminium ion **B**.[4] Intermediate **B** is quenched by water to afford **C**, which hydrolyzes to the desired aldehyde. Evidence for this sequence was obtained by isolation of **5** as a precipitate formed during reaction of **1a** with **2b**. Hydrolysis of isolated **5** afforded **3a**. The mechanism of the reaction of ethyl vinyl ether (**2c**) with **1a**−**c** would be similar.

In summary, an efficient synthesis of 9*H*-xanthene-9-carboxaldehyde (**3a**), 9*H*-thioxanthene-9-carboxaldehyde (**3b**), and 9,10-dihydro-10-methyl-9-acridinecarboxaldehyde (**3c**) by a novel two-carbon homologation of xanthydrol (**1a**), thioxanthydrol (**1b**), and 9,10-dihydro-10-methyl-9-acridinol (**1c**), respectively, using *N*-vinylacetamides (**2a**,**b**) or ethyl vinyl ether (**2c**) as acetaldehyde anion equivalents, is described.

Experimental Section

General Procedure. The alcohol (**1a**−**c**, 5.0 mmol) and *N*-vinylacetamide, *N*-methyl-*N*-vinylacetamide, or ethyl vinyl ether (**2a**−**c**, 6.0 mmol) were mixed, and the flask was immersed in an ice bath. To the mixture was added glacial acetic acid (8.0 mL). The ice bath was removed, and the reaction mixture was stirred at room temperature for 1 h. The completion of the reaction was monitored by TLC.

Water (1.0 mL; or 1.0 mL of concentrated HCl in the case of **2b**) was added to the mixture, and stirring was continued for an additonal 1 h. The reaction mixture was poured onto ice (20.0 g) and extracted with ethyl acetate (30.0 mL). The organic layer was washed with saturated $NaHCO_3$ (3 × 20.0 mL) and brine (20.0 mL), dried over anhydrous Na_2SO_4, and concentrated. The crude product was purified by silica gel chromatography.

9*H*-Xanthene-9-carboxaldehyde (3a): oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.85 (dd, J = 1.7 and 6.4 Hz, 2H), 4.62 (t, J = 6.4 Hz, 1H), 7.0−7.15 (m, 4H), 7.15−7.30 (m, 4H), 9.69 (t, J = 1.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 33.4, 54.2, 116.7, 123.6, 124.3, 128.2, 128.5, 152.1, 200.4. Anal. Calcd for C_{15} $H_{12}O_2$: C, 80.34; H, 5.39. Found C, 79.92; H, 5.32.

9*H*-Thioxanthene-9-carboxaldehyde (3b): oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.92 (dd, J = 1.5 and 7.1 Hz, 2H), 4.70 (t, J = 7.1 Hz, 1H), 7.15−7.28 (m, 4H), 7.32−7.46 (m, 4H), 9.64 (t, J = 1.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 43.0, 45.7, 126.8, 126.9, 127.2, 128.8, 132.7, 137.0, 200.7. Anal. Calcd for C_{15} H_{12}-OS: C, 74.97; H, 5.03; S, 13.34. Found: C, 74.70; H, 4.99; S, 13.20.

9,10-Dihydro-10-methyl-9-acridinecarboxaldehyde (3c): mp 85−86 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.67 (dd, J = 2.1 and 6.8 Hz, 2H), 3.41 (s, 3H), 4.55 (t, J = 6.8 Hz, 1H), 6.80−7.10 (m, 4H), 7.15−7.30 (m, 4H), 9.65 (t, J = 2.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 33.0, 38.7, 50.7, 112.4, 121.0, 126.1, 127.4, 127.9, 142.6, 201.5. Anal. Calcd for C_{16} H_{15}NO: C, 80.99; H, 6.37; N, 5.90. Found: C, 81.04; H, 6.43; N, 5.78.

Isolation of *N*-[1-(Hydroxy)-2-(9*H*-xanthen-9-yl)ethyl]-acetamide (5). Xanthydrol (**1a**, 5.0 mmol) and *N*-vinylacetamide (**2b**, 6.0 mmol) were mixed, and the flask was immersed in an ice bath. To the mixture was added glacial acetic acid (8.0 mL). The ice bath was removed, and the reaction mixture was

(13) 9*H*-Xanthene-9-ylidene-acetaldehyde (**4**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.47 (d, J = 7.7 Hz, 1H), 7.19−7.36 (m, 4H), 7.42−7.59 (m, 2H), 7.67 (dd, J = 1.5 and 7.7 Hz, 1H), 7.73 (dd, J = 1.5 and 7.9 Hz, 1H), 10.05 (d, J = 7.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 117.2, 117.3, 119.0, 120.5, 121.7, 123.7, 124.0, 124.5, 130.1, 131.6, 132.1, 144.4, 151.2, 152.5, 191.9; MS (CI/NH_3) 223.0 (MH^+). Structure **4** was further confirmed by its hydrogenation and by comparison of the spectroscopic data of the resulting hydrogenated product with those of an authentic sample of **3a**.

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stirred at room temperature for 1 h. The reaction mixture was filtered and the solid was washed with hexane and dried (it contained acetic acid). The solid was stirred with aqueous $NaHCO_3$ and ethyl acetate. The organic layer was separated, dried over anhydrous Na_2SO_4, and concentrated to afford **5** (yield 50%): mp 128−129 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.55−1.70 (m, 1H), 1.72−1.92 (m, 1H), 1.8 (s, 3H), 4.05 (t, J = 7.3 Hz, 1H), 5.02−5.19 (m, 1H), 5.78 (d, J = 5.1 Hz, 1H, OH), 7.05−7.20 (m, 4H), 7.22−7.34 (m, 3H), 7.36−7.45 (m, 1H), 8.28 (d, J = 9 Hz, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 23.2, 35.5, 47.2, 69.8, 116.52, 116.56, 123.7, 123.8, 125.7, 126.2, 128.09, 128.16, 129.0, 129.3, 151.98, 152.04, 169.1; MS (ESI) 328 [M + HCOO]$^-$.

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Supporting Information Available: ^{1}H NMR and ^{13}C NMR data for compounds **8** and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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