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Uncatalyzed Reaction of Silyl Ketene Acetals with Oxalyl Chloride: A Straightforward Preparation of Symmetrical Pulvinic Acids

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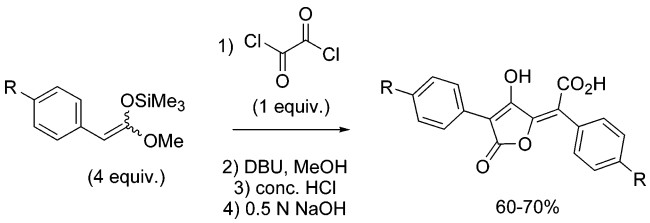
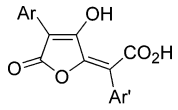


Several natural pulvinic acids were synthesized. Silyl ketene acetals derived from methyl arylacetates (4 equiv) reacted with oxalyl chloride at −78 °C, without the need of adding a catalyst. After treatment of the crude diketones with DBU and acidification with hydrochloric acid, symmetrical pulvinic acids methyl esters were obtained. Saponification of the methyl esters afforded the corresponding pulvinic acids in 60−70% overall yields from oxalyl chloride.

Pulvinic acids constitute a group of biologically active pigments found in mushrooms of the Boletales order and in lichens.[1] The common structural feature of these compounds is an unsaturated, hydroxylated γ-lactone substituted by a hydroxycarbonylalkylidene moiety. They differ by the nature of the aryl groups, which are often hydroxylated.



pulvinic acids

Structurally related compounds that bear two pulvinic chains have also been isolated.[2] Several syntheses of pulvinic acids have been reported.[3] Among these, the procedure originally described by Vollhardt was especially suitable for the preparation of symmetrical pulvinic acids (in which Ar = Ar′), because it makes use of the opening of the corresponding pulvinic dilactone. However, strong conditions are employed during the whole procedure, and we were interested in designing a smoother way to access to symmetrical pulvinic acids.

The reaction of silyl ketene acetals with acid chlorides has been shown to afford β-keto esters under a variety of conditions.[4] Thus, Lewis acids, amine, or elevated temperatures were employed to effect this transformation. More recently, Langer et al. have shown that 1,3-bis-silyl enol ethers react with oxalyl chloride to yield cyclocondensation adducts.[5] This method was applied to the synthesis of pulvinic derivatives.[6,7] To the best of our knowledge, the treatment of 2 equiv of silyl ketene acetals with oxalyl chloride has not previously been reported. Such reactions would in principle lead to 3,4-diketo-adipic diesters, which could serve as precursors to the corresponding pulvinic acids. Herein we thus will present the results of such a study and the ensuing preparation of pulvinic acids that was then made possible.

Three silylated ketene acetals **2a**−**c** derived from the corresponding methyl arylacetates **1a**−**c** were prepared in quantitative yields, according to the procedure described by Ainsworth et al.[8] (Scheme 1). They were then employed without further purification.

A preliminary study of the conditions of the reaction was carried out using silyl ketene acetal **2b** as the

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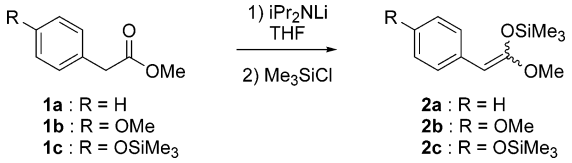
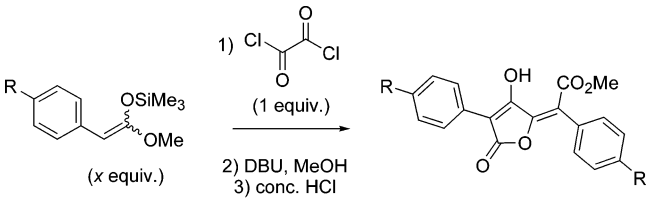
SCHEME 1



1a : R = H
1b : R = OMe
1c : R = $OSiMe_3$

2a : R = H
2b : R = OMe
2c : R = $OSiMe_3$

TABLE 1. Preparation of Methyl Pulvinates 4a−c



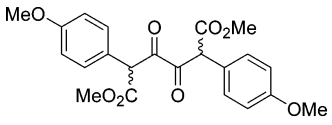
2a : R = H
2b : R = OMe
2c : R = $OSiMe_3$

4a : R = H
4b : R = OMe
4c : R = OH

entry	substrate	x	product	overall yield[c] (%)
1	**2b**	2	**4b**[a]	33
2	**2b**	2	**4b**[b]	48
3	**2b**	3	**4b**[b]	48
4	**2b**	4	**4b**[b]	74
5	**2a**	4	**4a**[b]	71
6	**2c**	4	**4c**[b]	60

[a] In this experiment, compound **4b** was purified by chromatography. [b] In these experiments, compounds **4a−c** were isolated by precipitation upon concentrated HCl addition. [c] Overall yield of isolated product, based on the quantity of oxalyl chloride employed.

reagent and titanium(IV) tetrachloride as the Lewis acid. Reactions were performed at −78 °C in methylene chloride, employing a 2:1 ratio of **2b** to oxalyl chloride and varying amounts of the Lewis acid. However, complex mixtures of compounds were invariably obtained, apparently resulting from a polymerization. An analogous result was obtained employing trimethylsilyl triflate as catalyst. We then performed the reaction at −78 °C in the absence of any catalyst.

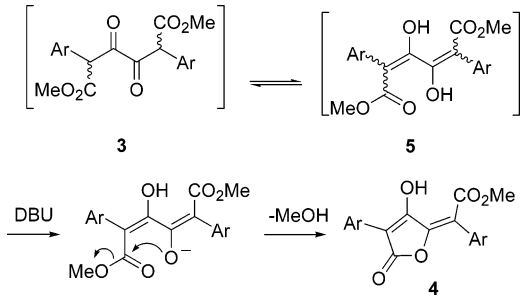


3b

This proved to be more satisfactory, since the ^{1}H NMR spectrum of the crude product was indicative of the presence of both diastereomers of compound **3b** (presence of two benzylic singlets at δ = 5.38 and 5.44 ppm); however, silica gel chromatography did not allow isolation of these compounds. Rather, products apparently arising from the cyclization of **3b** were obtained, although in modest yield. A sample of the diketone **3b**, obtained as a single diastereomer, was later isolated by recrystallization of the crude reaction product in methanol, albeit with a low yield (14%).

Finally, the crude product of the reaction of the silyl ketene acetal with oxalyl chloride was treated directly with a base (DBU), to favor the cyclization of the diketone to the corresponding pulvinic derivative. The results obtained in the preparation of methyl pulvinates **4a−c** are summarized in Table 1.

SCHEME 2



3 **5**

4

It was shown that the quantity of silylated compound **2b** employed had a clear effect on the yield of compound **4b** based on the quantity of oxalyl chloride employed. Although only 2 equiv of **2b** should be theorically necessary to obtain a quantitative formation of the expected adduct, the yield was much better using 4 equiv of substrate (entries 1−4). It could be reasoned that some of the substrate **2b** reacts with the formed β-keto ester, silylating it, and is converted to methyl arylacetate **1b**, which does not participate in the production of the pulvinate precursor. Ester **1b** was indeed observed in the ^{1}H NMR spectrum of a nonhydrolyzed reaction mixture conducted in CD_2Cl_2. Purification of **4b** was shown to be much more efficient using a simple precipitation in acidic medium rather than a silica gel chromatography (entry 2 versus entry 1). Using this convenient procedure, the overall yield for the transformation of oxalyl chloride to pulvinic derivative **4b** was 74%. Similar yields were obtained in the preparation of vulpinic acid (**4a**), a natural compound found in lichens, and methyl atromentate (**4c**). In the latter case, no specific step was needed for the cleavage of the trimethysilyl aryl ethers.

The relative configuration of the exocyclic double bond of the compounds synthesized was established by comparison of the physical and spectroscopic data reported for **4a**[3e,k,n,6,9] and **4b**.[3e,f,10] The cyclization of the crude diketone **3** is likely to proceed as described in Scheme 2. In the methanol solution, the diketone is in equilibrium with tautomers such as **5**, which under the influence of DBU cyclizes to the corresponding pulvinic derivative. After acidic treatment, compound **4** having the depicted configuration is obtained as a single isomer, which probably is thermodynamically favored.

Several pulvinic methyl esters are natural products. It was also of interest to prepare carboxylic acids **6a−c**, which are all natural pigments. They were cleanly obtained in good yields by saponification of the corresponding methyl esters (Scheme 3). Physical and spectroscopic data were in agreement with the reported data for pulvinic acid (**6a**)[3e,k,n] and atromentic acid (**6c**).[3f,o]

In conclusion, we have shown that silyl ketene acetals derived from methyl arylacetates react readily at low temperature with oxalyl chloride without the need of an activating agent, such as a Lewis acid. This allowed the straightforward preparation of symmetrical pulvinic

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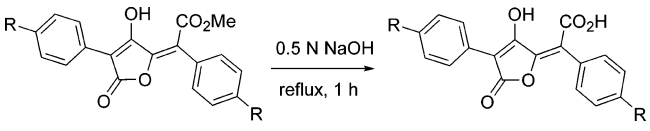
SCHEME 3



4a : R = H
4b : R = OMe
4c : R = OH

6a : R = H (95%)
6b : R = OMe (91%)
6c : R = OH (quant.)

acids. Further developments for the preparation of unsymmetrical pulvinic acids are in progress.

Experimental Section

General. THF was freshly distilled from sodium benzophenone ketyl. Methylene chloride was freshly distilled over P_2O_5. Moisture-sensitive reactions were performed in a flame-dried flask, under an argon atmosphere. TLC was performed with silica gel $60F_{254}$ plates, with detection by UV light and with an ethanol solution of phosphomolybdic acid. Column chromatography was on 40−63 μm silica gel. Melting points were uncorrected. NMR was at 300.13 MHz for ^{1}H, 75.47 or 100.624 MHz for ^{13}C. Chemical shifts (δ) are in ppm (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad); coupling constants (J) are in Hz.

Methyl 4-(Trimethylsilyloxy)phenylacetate (1c). Triethylamine (3.3 mL, 24 mmol) and chlorotrimethylsilane (3.3 mL, 26 mmol) were successively added to a stirred solution of methyl 4-hydroxyphenylacetate (1.65 g, 10 mmol) in THF (17 mL) at room temperature. The reaction mixture was stirred for 15 h, and then pentane (70 mL) was added. The suspension was filtered through a pad of Celite, under a nitrogen atmosphere. Concentration of the filtrate under vacuum afforded crude methyl 4-(trimethylsilyloxy)phenylacetate (2.38 g, quantitative) as a brown oil that was used in the next reaction without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.13 (d, J = 8.5 Hz, 2H), 6.79 (d, J = 8.5 Hz, 2H), 3.65 (s, 3H), 3.53 (s, 2H), 0.26 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.9, 154.0, 130.0 (2C), 126.6, 119.8 (2C), 51.5, 40.0, 13.8.

Preparation of Silyl Ketene Acetals. Typical Procedure. A solution of n-butyllithium (2 N in hexanes, 4.5 mL, 9 mmol) was added dropwise to a solution of diisopropylamine (1.5 mL, 10.8 mmol) in THF (10 mL) cooled at 0 °C. After 10 min at 0°C, the reaction mixture was cooled at −78 °C, and then methyl phenylacetate (1.3 mL, 9 mmol) was added dropwise. The reaction mixture was stirred at −78 °C for 1 h, and then chlorotrimethylsilane (1.5 mL, 11.25 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 15 h. Pentane (70 mL) was added, and the resulting suspension was filtered through a short pad of Celite. Concentration of the filtrate in vacuo afforded silyl ketene acetal **2a** (2.05 g, quantitative) as a colorless oil that was used in the next reaction without further purification.

1-Methoxy-2-(phenyl)-1-(trimethylsilyloxy)ethylene (2a).[8] Viscous, colorless oil. Mixture of E- and Z-isomers (ratio 70/30, according to ^{1}H NMR). IR (NaCl, thin film) ν_{max} = 2957, 1740, 1706, 1289, 1255, 1128 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (E-isomer) 7.45 (d, J = 7.9 Hz, 2H), 7.32−7.23 (m, 2H), 7.07 (t, J = 7.3 Hz, 1H), 4.77 (s, 1H), 3.76 (s, 3H), 0.37 (s, 9H). Characteristic ^{1}H NMR signal for Z-isomer: δ 4.64 (s, 1H).

1-Methoxy-2-(4-methoxyphenyl)-1-(trimethylsilyloxy)-ethylene (2b).[11] Viscous, colorless oil. Mixture of E- and Z-isomers (ratio 93/7, according to ^{1}H NMR). IR (NaCl, thin film) ν_{max} = 3057, 2956, 2838, 1740, 1657, 1610, 1510, 1249, 1069, 850 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (E-isomer) 7.38 (d, J = 6.7 Hz, 2H), 6.85 (d, J = 6.7 Hz, 2H), 4.68 (s, 1H), 3.79 (s, 3H), 3.69 (s, 3H), 0.33 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (E-isomer) 156.2, 153.6, 127.4 (3C), 113.4 (2C), 85.5, 55.0, 53.6, 0.0 (3C). Characteristic ^{1}H NMR signal for Z-isomer: δ 4.58 (s, 1H).

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1-Methoxy-1-(trimethylsilyloxy)-2-(4-trimethylsilyloxyphenyl)ethylene (2c). Brownish oil. Mixture of E- and Z-isomers (ratio 80/20, according to ^{1}H NMR). IR (NaCl, thin film) ν_{max} = 2960, 1745, 1657, 1606, 1508, 1451, 1346, 1256, 1167, 1070, 968, 916, 846, 757 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (E-isomer) 7.34 (d, J = 8.5 Hz, 2H), 6.77 (d, J = 8.5 Hz, 2H), 4.68 (s, 1H), 3.70 (s, 3H), 0.34 (s, 9H), 0.28 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (E-isomer) 156.8, 151.4, 129.8, 127.4 (2C), 119.6 (2C), 85.5, 53.5, 0.0 (3C). Characteristic ^{1}H NMR signals for Z-isomer: δ 4.58 (s, 1H), 3.66 (s, 3H), 0.31 (s, 9H), 0.29 (s, 9H).

Preparation of Pulvinic Esters. Typical Procedure. A solution of silylated compound **2b** (504 mg, 2 mmol) in methylene chloride (10 mL) was cooled under stirring at −78 °C. A solution of oxalyl chloride (44 μL, 0.5 mmol) in methylene chloride (5 mL) was added dropwise. The resulting yellow solution was stirred at −78 °C for 5 h. Saturated aqueous NH_4Cl (10 mL) was added via syringe, and the reaction mixture was allowed to warm to room temperature. The aqueous phase was extracted with methylene chloride (3 × 20 mL). The combined organic phases were dried over $MgSO_4$, and then concentrated under vacuum. A yellow solid was obtained (374 mg). The yellow solid was then dissolved in methylene chloride (5 mL) at room temperature under argon. DBU (151 μL, 1.01 mmol) was added, and the reaction mixture was stirred at room temperature for 5 h. Acetic acid (1 mL) was added, and then the reaction mixture was concentrated in vacuo. A 1:1 mixture of methanol and concentrated hydrochloric acid (3 mL) was added to the residue, leading to the precipitation of a red solid. The solid was filtrated and washed with acetic acid. Recrystallization (acetic acid) led to compound **4b** (171 mg, 74% yield) as red crystals.

Methyl 4,4′-Dimethoxypulvinate (4b). Red solid, mp 170 °C (lit.[3e] mp 177−178 °C; lit.[3f] mp 179−181°C). IR (KBr pellet) ν_{max} = 3439, 2631, 1771, 1677, 1600, 1248, 1063, 823 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 13.65 (s, 1H), 8.73 (s, 1H), 8.64 (s, 1H), 8.11 (d, J = 9.1 Hz, 2H), 7.18 (d, J = 8.6 Hz, 2H), 6.94 (d, J = 9.1 Hz, 2H), 6.92 (d, J = 8.6 Hz, 2H), 3.93 (s, 3H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 171.7, 165.9 (2C), 159.3 (2C), 158.5, 154.4, 131.2 (3C), 129.1 (3C), 114.8, 113.6 (4C), 105.8, 55.1 (2C), 54.1. Anal. Calcd for $C_{21}H_{18}O_7$: C, 65.96; H, 4.74. Found: C, 65.54; H, 4.71.

Vulpinic Acid (4a). Yellow solid, mp 151 °C (lit.[3e] mp 146−147 °C; lit.[3k] mp 146−148 °C; lit.[3n] mp 150−151 °C). IR (KBr pellet) ν_{max} = 2962, 2513, 1768, 1679, 1609, 1436, 1302, 1070, 952, 689 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 13.77 (s, 1H), 8.12 (d, J = 8.5 Hz, 2H), 7.50−7.25 (m, 8H), 3.88 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.4, 165.7, 160.1, 154.5, 131.8, 129.7 (2C), 128.8, 128.4 (2C), 128.2, 128.1, 127.9(2C), 127.6 (2C), 115.7, 104.8, 54.3. Anal. Calcd for $C_{19}H_{14}O_5$: C, 70.80; H, 4.38. Found: C, 70.79; H, 4.42.

Methyl Atromentate (4c). Red-brown powder, mp >300 °C (lit.[3f] mp 360−362 °C). IR (KBr pellet) ν_{max} = 3328, 3187, 2565, 1897, 1735, 1679, 1605, 1433, 1312, 1177, 1068, 834 cm^{-1}. ^{1}H NMR (acetone-d_6, 300 MHz): δ 13.79 (s, 1H), 8.73 (s, 1H), 8.64 (s, 1H), 8.04 (d, J = 6.7 Hz, 2H), 7.25 (d, J = 8.6 Hz, 2H), 6.94 (d, J = 6.7 Hz, 2H), 6.91 (d, J = 8.6 Hz, 2H), 3.93 (s, 3H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 173.3, 172.7, 164.4, 162.3, 161.5, 148.5, 135.0 (3C), 134.5 (3C), 119.5 (4C), 109.1, 107.6, 57.4 (2C). Anal. Calcd for $C_{19}H_{14}O_7$: C, 64.41; H, 3.98. Found: C, 64.08; H, 4.23.

Preparation of Pulvinic Acids. Typical Procedure. A 0.5 N sodium hydroxide solution (2 mL) was added to ester **4a** (57.7 mg, 0.179 mmol). The solution was refluxed for 1 h. After cooling to room temperature, 1 N hydrochloric acid was added until pH = 1. Filtration of the precipitate and washing with water afforded pulvinic acid **6a** as a yellow solid (52 mg, 95%).

Pulvinic Acid (6a). Yellow solid, mp 210−212 °C (lit.[3e] mp 216−217 °C; lit.[3k] mp 202−207 °C). IR (KBr pellet) ν_{max} = 3195, 2364, 1754, 1674, 1587, 1486, 1441, 1405, 1367, 1215, 1076, 1056, 961, 781, 701 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.14 (d, J = 8.5 Hz, 2H), 7.34−7.50 (m, 8H). ^{13}C NMR (CD_3OD, 75 MHz): δ 172.2, 165.9, 160.7, 153.0, 132.5, 129.0, 128.6, 127.6, 127.5, 127.2, 126.9, 126.7, 116.7, 102.6. HRMS (ESI-TOF) calcd for $C_{18}H_{13}O_5$ $(M + H)^+$ 309.0763, found 309.0727.

4,4′-Dimethoxypulvinic Acid (6b). Bright red solid, mp 180 °C. IR (KBr pellet) ν_{max} = 3478, 2963, 2512, 1766, 1679, 1592, 1512, 1473, 1417, 1366, 1305, 1242, 1103, 1058, 962, 830 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.11 (d, J = 9.1 Hz, 2H), 7.25 (d, J = 8.5 Hz, 2H), 6.95 (d, J = 9.1 Hz, 2H), 6.93 (d, J = 8.5 Hz, 2H). ^{13}C NMR (acetone-d_6, 100 MHz): δ 173.2, 165.9, 159.7, 159.5, 159.2, 154.5, 131.5 (2C), 128.9, 128.8, 125.2, 121.9, 115.7, 113.7(2C), 113.1 (2C), 103.6, 54.6 (2C). HRMS (ESI-TOF) calcd for $C_{20}H_{16}O_7Na$ $(M + Na)^+$ 391.0794, found 391.0778.

Atromentic Acid (6c). Red-brown solid, mp >300 °C (lit.[3f] mp 330−332 °C, lit.[3o] mp 287−289 °C). IR (KBr pellet) ν_{max} = 3306, 2931, 2500, 1757, 1705, 1675, 1599, 1513, 1450, 1428, 1367, 1233, 1055, 964, 837, 752, 702 cm^{-1}. ^1H NMR (acetone-d_6, 300 MHz): δ 8.04 (d, J = 9.1 Hz, 2H), 7.30 (d, J = 8.6 Hz, 2H), 6.93 (d, J = 9.1 Hz, 2H), 6.90 (d, J = 8.6 Hz, 2H). ^{13}C NMR (acetone-d_6, 75 MHz): δ 173.8, 166.8, 160.2, 158.0, 157.8, 154.9, 132.3, 131.9, 129.69, 125.1, 121.8, 116.7, 115.7, 115.1, 104.0. HRMS (ESI-TOF) calcd for $C_{18}H_{12}O_7Na$ $(M + Na)^+$ 363.0481, found 363.0488.

Dimethyl 3,4-Diketo-2,5-bis(4methoxyphenyl)adipate (3b). The procedure employed for the preparation of compound **4b** was carried out with the same quantities of reactants. After the first part of the procedure, the yellow solid obtained after removal of the solvents under vacuum (380 mg) was recrystallized with methanol (40 mL). Compound **3b** was obtained as a yellow solid (28 mg, 14%). ^1H NMR revealed that it is a single diastereomer; however, its configuration could not be determined. This compound was found to be unstable, leading to cyclization products, and no correct elemental analyses could be obtained. Yellow powder, mp 136 °C. IR (KBr pellet) ν_{max} = 2957, 2839, 1769, 1708, 1676, 1611, 1515, 1444, 1351, 1310, 1287, 1252, 1181, 1159, 1119, 1031, 1010, 954, 837, 798, 759 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.17 (d, J = 6.7 Hz, 4H), 6.86 (d, J = 6.7 Hz, 4H), 5.34 (s, 2H), 3.79 (s, 6H), 3.63 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 190.1 (2C), 168.2 (2C), 159.5 (2C), 130.8 (4C), 122.2 (2C), 114.0 (4C), 56.4 (2C), 55.0 (2C), 52.5 (2C).

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