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Installation of Photolabile Carbonyl-Protecting Groups under Neutral Conditions without Using Any Other Chemical Reagents

Pengfei Wang,*[a] Yun Wang,[a] Huayou Hu,[a] and Xing Liang[a]

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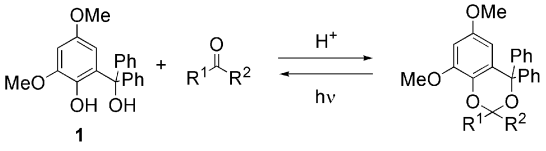
Methods of installing photolabile protecting groups for carbonyl compounds under neutral conditions without using any other chemical reagents are described.

Introduction

Acid-catalyzed formation of 1,3-dioxane ring systems are commonly applied to protect carbonyl groups in organic synthesis.[1] Recently, we have demonstrated that derivatized salicyl alcohols (such as **1** in Scheme 1) are useful in protecting carbonyl groups as robust photolabile protecting groups (PPGs).[2] Similar to other 1,3-dioxane formation reactions, installation of these PPGs requires an acid catalyst.[3]



Scheme 1. Photolabile carbonyl-protecting group.

One of the appealing features of PPGs is that they are typically removed upon irradiation under neutral conditions without using any chemical reagents. It will be of interest if installation of PPGs could also be carried out under green-chemistry conditions. Not only would such a method provide an alternative access to the synthesis of photosensitive acetals/ketals but it could also be valuable for the protection of acid-sensitive carbonyl compounds.

Results and Discussion

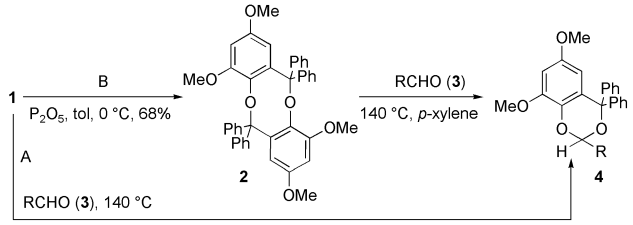
Herein we report neutral protocols for synthesizing 1,3-dioxanes from salicyl alcohol **1** or the quinone methide dimer **2** (derived from **1**) with various aldehydes without using any other chemical reagents.

[a] Department of Chemistry, the University of Alabama at Birmingham,
901 14th Street South, Birmingham, Alabama 35294, USA
Fax: +1-205-934-2543
E-mail: wangp@uab.edu

Thus, the reaction of 3-[(TBS)oxy]propanal (**3a**) with salicyl alcohol **1** at 140 °C afforded the desired acetal **4a** in 94% yield (Table 1, Entry 1), whereas the conventional procedures requiring an acid catalyst[2] led to considerable decomposition of the aldehyde **3a**, and the yield of **4a** was lower than 40%. The new protocol appeared to be a general method for the protection of aldehydes. Some representative aldehydes reacted with **1** smoothly at 140 °C and provided the desired acetals **4** in excellent yields (Table 1). It is noteworthy that solvent was typically not required. When a solvent such as *p*-xylene was used, as anticipated, the reactions became considerably slower. It took 2 h for the reaction of **3b** and **1** to reach completion with 97% yield without *p*-xylene, but 6.5 h to reach completion with 96% yield in a 0.05 M solution of **3b** in *p*-xylene. Prolonged heating at 140 °C increased the byproducts. Decomposition of acetal **4** at the reaction temperature seemed not to be a major source of these byproducts because, for example, only less than 5% of pure **4c** decomposed after heating at 140 °C for 15 h. It was assumed that the byproducts were mainly from decomposition of salicyl alcohol **1**. Indeed, when only **1** was subject to the reaction conditions, the same byproducts were generated. Elevating of the reaction temperature above 140 °C accelerated the reaction rate, taking only 20 min for the reaction of **3b** and 2 equiv. of **1** to reach completion with 97% yield at 180 °C (Table 1, Entry 2). However, the rates of the side reactions also accelerated, leading to more of the byproducts from the excess of **1**, which could complicate purification.

To our delight, the unusual quinomethide dimer **2**,[4] serendipitously synthesized by treating **1** with phosphorus pentoxide (P_2O_5) in toluene at 0 °C, also underwent thermal reaction with aldehydes to provide acetals in excellent yields (Table 1). Typically, the reactions of aldehydes with dimer **2** required a solvent (e.g. *p*-xylene) for a more homogeneous phase at 140 °C. Without *p*-xylene, a homogeneous phase could not be achieved even at 180 °C. The heterogeneous-

Table 1. Formation of acetal **4** under neutral conditions.



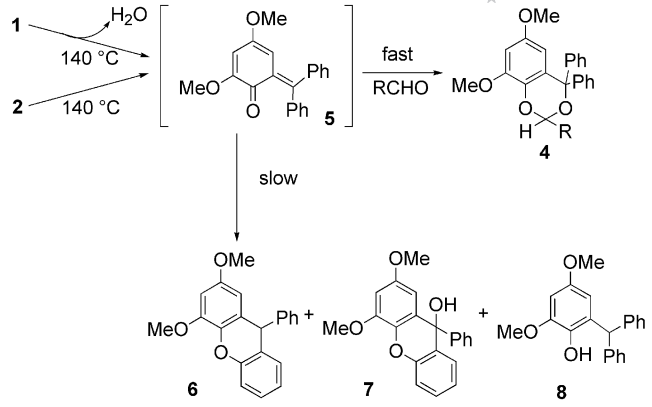
Entry	Aldehyde	Yield of **4** (%) Method A[a]	Method B[b]
1	3-[(TBS)oxy]propanal (**3a**)	94 (3 h)[c]	94 (4 h)
2	3-phenylpropanal (**3b**)[2]	97 (2 h) 96 (6.5 h)[d] 97 (20 min)[e]	99 (2 h)
3	4-phenoxybenzaldehyde (**3c**)[2]	98 (9.5 h)	96 (9.5 h)
4	*m*-anisaldehyde (**3d**)	97 (6 h)	99 (6 h)
5	2-ethylhexanal (**3e**)	99 (8.5 h)	99 (8.5 h)
6	(*E*)-2-heptenal (**3f**)	83 (8.5 h)	93 (8 h)

[a] Aldehyde **3** (0.05 mmol) and salicyl alcohol **1** (0.1 mmol) heated at 140 °C under argon without solvent. [b] Aldehyde **3** (0. 05 mmol) and dimer **2** (0.05 mmol) in 1.0 mL of *p*-xylene heated at 140 °C. [c] Aldehyde **3** (0.05 mmol) and salicyl alcohol **1** (0.1 mmol) heated at 140 °C under argon with two drops of *p*-xylene. [d] In 1.0 mL of *p*-xylene. [e] At 180 °C, no solvent.

phase reactions typically led to poor yields. For example, the reaction between **2** and **3b** at 180 °C without solvent resulted in a maximal 45% yield of **4b** in 1 h based on ^{1}H NMR analysis, and then the yield began to decrease due to decomposition of **4b**. In *p*-xylene, reaction of aldehydes with dimer **2** at 140 °C seemed to be more efficient than with **1** (e.g. for **3b**, 99% in 2 h with **2** vs. 96% in 6.5 h with **1** under the same conditions) (Table 1, Entry 2). Interestingly, dimer **2** seemed to be more reactive in *p*-xylene than without it. When dimer **2** was heated neat at 180 °C for 1 h, only less than 5% of **2** reacted based on ^{1}H NMR analysis. However, more than 90% of **2** (0.02 mmol, in 25 μL of *p*-xylene) reacted at 180 °C within 1 h, and more than 60% of **2** (0.1 mmol, in 0.1 mL of *p*-xylene) reacted at 140 °C within 5 h.

We postulated that acetal **4** was formed from a cyclization reaction of the aldehyde with the reactive quinone methide intermediate **5** generated in situ from the dehydration reaction of **1** or from the thermal decomposition of the dimer **2** (Scheme 2). The reaction between aldehyde **3** and **5** was much faster than the side reactions of **5**. These side reactions resulted in byproducts **6**–**8**.

The same byproducts were also obtained from heating **1** neat at 140 °C, **2** in *p*-xylene or DMF at 180 °C, or the thermal decomposition of **4**. At 140 °C, heating of PPG **1** neat for 5 h resulted in a reaction mixture of **6**, **7**, **8**, and unreacted **1** in a ratio of 1:0.16:0.16:0.1 (Figure 1). Typically, xanthene **6** was the major byproduct, suggesting that PPG **1** type compounds can be useful precursors for preparing substituted xanthenes. It should be pointed out that the amounts of the byproducts and their relative ratio changed with reaction conditions such as reaction time, temperature, and other factors including solvent, and presence of air and water. For example, addition of water to the thermal reaction of **1** decreased the amount of **6**, whereas the amounts of **7** and **8** increased and kept at a 1:1 ratio. When the reaction was carried out in the presence of air, more **7** formed.



Scheme 2. Mechanism of acetal formation reaction.

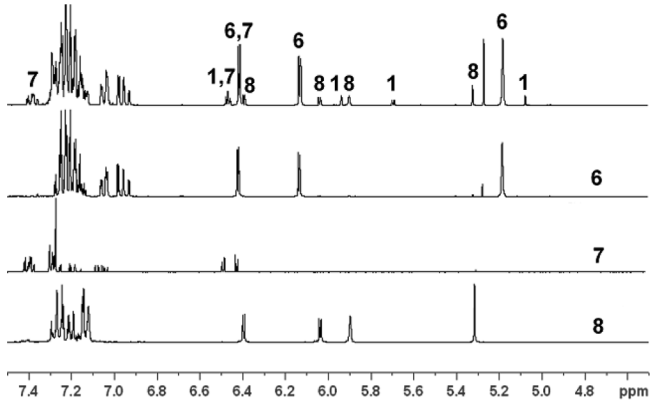


Figure 1. Thermal reaction of **1** at 140 °C.

The current neutral protocols are not efficient in converting ketones to ketals, and the yields were lower than those of the aldehyde cases under the same conditions. For example, the maximal yield of the desired ketal from the reaction of 4-phenylcyclohexanone with **1** was only 64%, obtained after 5 h of heating at 140 °C.[5] The relative low yields were rationalized as the result of slow cyclization between a ketone and the intermediate **5**, leading predominantly to competitive side reactions. In addition, the instability of ketals formed by **1** with different ketones could also contribute to the low yields. For example, 10% of the ketal from 4-phenylcyclohexanone decomposed at 140 °C under argon in 15 h, and as high as 87% of the ketal from 4-(4-methoxyphenyl)-2-butanone decomposed under the same conditions in 17 h. The latter observation probably explains the difficulty in preparing that particular ketal by the neutral thermal protocols.

The new protocol can also be utilized for acetal formation reactions of aldehydes with other α,α-diphenylsalicyl alcohols. For example, 5-methoxy-α,α-diphenylsalicyl alcohol reacted with 3-phenylpropanal (**3b**) in *p*-xylene and

afforded the corresponding acetal in 99% yield in just 1 h, faster than the reaction of **3b** with **1** under the same conditions (i.e. 96% in 6.5 h) (Table 1, Entry 2).

Conclusions

Novel neutral methods of installing PPGs onto carbonyl groups have been developed. They can be a useful complement to the conventional acid-catalyzed approaches, especially valuable for the protection of acid-sensitive carbonyl compounds. The side reaction of the postulated quinomethide intermediate to **6** can possibly lead to a simple entry into the synthesis of various substituted xanthene skeletons.

Experimental Section

Quinone Methide Dimer 2: To a solution of PPG **1** (235 mg, 0.7 mmol) in 10 mL of toluene in an ice bath was added P_2O_5 (298 mg, 2.1 mmol). The reaction mixture was stirred at 0 °C for 22 h. The dark red mixture was then poured into saturated $NaHCO_3$ solution and extracted with ethyl acetate (30 mL × 3). The combined organic layers were washed with brine, dried with Na_2SO_4, filtered and concentrated. Flash column chromatography on silica gel (eluted with CH_2Cl_2/petroleum ether, 2:1) afforded **2** (150 mg, 68%) as a white solid. R_f = 0.3 (CH_2Cl_2/petroleum ether, 2:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.54–7.02 (br. s, 20 H), 6.33 (d, J = 2.9 Hz, 2 H), 6.07 (d, J = 2.9 Hz, 2 H), 3.62 (s, 3 H), 2.85 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 155.9, 155.4, 139.3, 137.2, 127.4 (br.), 107.9, 98.0, 93.6, 55.7, 55.4 ppm. IR (neat): $\tilde{\nu}$ = 3089, 3048, 3003, 2962, 2933, 2840, 1593, 1458, 1332, 1221, 1201 cm^{-1}. HRMS (ESI): calcd. for $C_{42}H_{37}O_6$ [M + H$^+$] 637.2590; found 637.2585.

General Procedure of Protecting Aldehydes under Neutral Conditions: PPG agent **1** (0.1 mmol) and aldehyde (0.05 mmol) were stirred at 140 °C under argon. Upon completion, the reaction mixture was purified by flash column chromatography to afford the desired acetal.

4a: 24 mg (94%). R_f = 0.27 (petroleum ether/ethyl acetate, 9:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.37–7.21 (m, 10 H), 6.40 (d, J = 2.8 Hz, 1 H), 5.93 (d, J = 2.8 Hz, 1 H), 5.13 (dd, J = 6.1, 4.5 Hz, 1 H), 3.87 (s, 3 H), 3.80–3.67 (m, 2 H), 3.59 (s, 3 H), 2.19–2.09 (m, 3 H), 0.73 (s, 9 H), –0.08 (s, 3 H), –0.09 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 152.5, 148.9, 146.0, 144.0, 136.7, 129.3, 128.1, 127.99, 127.97, 127.8, 127.4, 125.9, 104.6, 98.6, 93.3, 84.2, 58.1, 56.0, 55.5, 37.9, 25.8, 18.1, –5.48, –5.54 ppm. IR (neat): $\tilde{\nu}$ = 2955, 2929, 2856, 1602, 1492, 1471, 1447, 1406, 1360, 1338, 1281, 1233, 1201, 1156, 1094, 1058 cm^{-1}. HRMS (ESI): calcd. for $C_{30}H_{38}O_5Si$ [M] 506.2489; found 506.2487.

4d: 22 mg (97%). R_f = 0.4 (petroleum ether/ethyl acetate, 5:1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.48–7.13 (m, 13 H), 6.91–6.87 (m, 1 H), 6.44 (d, J = 2.8 Hz, 1 H), 6.00 (d, J = 2.8 Hz, 1 H), 5.88 (s, 1 H), 3.86 (s, 3 H), 3.81 (s, 3 H), 3.61 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 159.6, 152.8, 149.2, 145.6, 144.0, 138.8, 136.9, 129.4, 129.3, 128.22, 128.17, 128.13, 127.8, 127.5, 125.9, 119.0, 114.7, 112.2, 104.6, 98.9, 94.6, 85.1, 56.0, 55.5, 55.3 ppm. IR (neat): $\tilde{\nu}$ = 2935, 1603, 1464, 1280, 1226, 1199, 1156, 1055, 1027 cm^{-1}. HRMS (ESI): calcd. for $C_{29}H_{26}NaO_5$ [M + Na$^+$] 477.1678; found 477.1676.

4e: 22 mg (99%). R_f = 0.5 (petroleum ether/ethyl acetate, 5:1). ^{1}H NMR ($CDCl_3$, 400 MHz, characteristic peaks): δ = 7.35–7.24 (m, 10 H), 6.39 (d, J = 2.8 Hz, 1 H), 5.95 (d, J = 2.8 Hz, 1 H), 4.92 (d, J = 3.5 Hz, 1 H), 4.89 (d, J = 3.5 Hz, 1 H), 3.85 (s, 3 H), 3.58 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 152.4, 149.10, 149.09, 146.3, 144.38, 144.37, 137.24, 137.22, 129.59, 129.57, 128.1, 127.9, 127.8, 127.3, 125.71, 125.70, 104.6, 104.5, 98.94, 98.88, 96.44, 96.38, 83.99, 83.97, 56.17, 56.16, 55.5, 43.6, 43.5, 29.1, 29.0, 28.2, 27.2, 23.2, 23.0, 21.6, 20.6, 14.2, 13.9, 11.6, 11.4 ppm. IR (neat): $\tilde{\nu}$ = 2956, 2932, 1600, 1492, 1467, 1447, 1279, 1233, 1200, 1156, 1088, 1057, 1027, 991 cm^{-1}. HRMS (ESI): calcd. for $C_{29}H_{35}O_4$ [M + H$^+$] 447.2535; found 447.2532.

4f: 18 mg (83%). R_f = 0.37 (petroleum ether/ethyl acetate, 9:1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.44–7.18 (m, 10 H), 6.40 (d, J = 2.8 Hz, 1 H), 5.92 (d, J = 2.8 Hz, 1 H), 5.90–5.74 (m, 2 H), 5.35 (d, J = 5.2 Hz, 1 H), 3.87 (s, 3 H), 3.59 (s, 3 H), 2.07 (q, J = 6.3 Hz, 2 H), 1.43–1.23 (m, 4 H), 0.87 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 152.6, 149.0, 145.7, 143.9, 137.2, 136.6, 129.2, 128.2, 128.1, 128.0, 127.8, 127.5, 125.9, 125.5, 104.5, 98.6, 94.9, 84.5, 56.0, 55.5, 31.8, 30.6, 22.3, 13.9 ppm. IR (neat): $\tilde{\nu}$ = 2927, 1600, 1492, 1468, 1444, 1227, 1200, 1155 cm^{-1}. HRMS (ESI): calcd. for $C_{28}H_{30}NaO_4$ [M + Na$^+$] 453.2042; found 453.2037.

Thermal Reaction of 1: Salicyl alcohol **1** (34 mg, 0.1 mmol) in a flame-dried Schlenk vessel was heated at 140 °C under argon for 5 h. A dark red oil was obtained. A partial ^{1}H NMR spectrum of the reaction mixture is shown in Figure 1. Yields of **6**, **7**, and **8** were 70%, 11%, and 11%, respectively (based on ^{1}H NMR integration). Several small-scale reactions under slightly different reaction conditions were combined for flash column chromatography to afford **6**, **7** and **8** for characterization.

6: R_f = 0.73 (petroleum ether/ethyl acetate, 5:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.27–7.14 (m, 7 H), 7.05 (d, 7.8 H), 6.98–6.94 (m, 1 H), 6.42 (d, J = 2.7 Hz, 1 H), 6.13 (d, J = 2.7 Hz, 1 H), 5.18 (s, 1 H), 3.93 (s, 3 H), 3.67 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 155.2, 150.9, 148.8, 146.3, 135.2, 129.5, 128.7, 128.1, 127.8, 126.7, 125.1, 123.9, 123.2, 116.8, 103.6, 98.8, 56.2, 55.5, 45.0 ppm. IR (neat): $\tilde{\nu}$ = 2360, 2342, 1624, 1483, 1456, 1244, 1206, 1153, 1117, 1052 cm^{-1}. HRMS (ESI): calcd. for $C_{21}H_{19}O_3$ [M + H$^+$] 319.1334; found 319.1328.

7: R_f = 0.67 (petroleum ether/ethyl acetate, 3:1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.41–7.36 (m, 3 H), 7.30–7.23 (m, 5 H), 7.17 (tt, J = 7.2, 1.6 Hz, 1 H), 7.09–7.02 (m, 1 H), 6.47 (d, J = 3.0 Hz, 1 H), 6.41 (d, J = 3.0 Hz, 1 H), 3.94 (s, 3 H), 3.67 (s, 3 H), 2.72 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 155.7, 149.9, 148.8, 148.2, 134.8, 129.3, 129.1, 128.4, 128.1, 127.1, 127.0, 126.4, 123.9, 117.1, 101.8, 100.5, 71.1, 56.6, 56.0 ppm. IR (neat): $\tilde{\nu}$ = 1581, 1482, 1453, 1292, 1233, 1206, 1153 cm^{-1}. HRMS (ESI): calcd. for $C_{21}H_{18}NaO_4$ [M + Na$^+$] 357.1103; found 357.1096.

8: R_f = 0.4 (CH_2Cl_2/petroleum ether/ethyl acetate, 1:8:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.30–7.12 (m, 10 H), 6.40 (d, J = 2.8 Hz, 1 H), 6.05 (d, J = 2.7 Hz, 1 H), 5.91 (s, 1 H), 5.33 (s, 1 H), 3.85 (s, 3 H), 3.63 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 152.6, 146.8, 143.3, 137.5, 129.8, 129.3, 128.2, 126.2, 106.5, 97.0, 56.0, 55.6, 49.8 ppm. IR (neat): $\tilde{\nu}$ = 3520, 3025, 2938, 2838, 1600, 1494, 1466, 1453, 1430, 1374, 1242, 1198, 1148, 1078, 1054 cm^{-1}. HRMS (ESI): calcd. for $C_{21}H_{21}O_3$ [M + H$^+$] 321.1491; found 321.1483.

Acknowledgments

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[1] T. W. Greene, P. G. M. Wuts, *Protective groups in organic synthesis*, Wiley, New York, **1999**.

[2] a) P. Wang, H. Hu, Y. Wang, *Org. Lett.* **2007**, *9*, 1533–5; b) P. Wang, H. Hu, Y. Wang, *Org. Lett.* **2007**, *9*, 2831–3; c) P. Wang, Y. Wang, H. Hu, C. Spencer, X. Liang, L. Pan, *J. Org. Chem.* **2008**, *73*, 6152–7.

[3] a) However, in view of the structure of **1**, we realized that the mechanism of 1,3-dioxane formation from **1** and carbonyl compounds under acidic conditions could be different from that of carbonyl compounds with other 1,3-diols.[1,3b] It is likely that a trityl carbocation intermediate is first generated from **1** upon acid treatment. Subsequent nucleophilic attack by the carbonyl oxygen atom led to the corresponding oxonium cation, which cyclized to the desired acetal/ketal. We observed that the dimethyl ketal of 4-(4-methoxyphenyl)butan-2-one failed to react with **1** to produce the desired ketal, whereas the corresponding ketone underwent clean reactions under the same conditions, and the dimethyl ketal readily reacted with other simple 1,3-diols to produce the corresponding 1,3-dioxanes. b) E. V. Gromachevskaya, A. G. Sakhabutdinov, V. G. Kul'nevich, I. S. Arustamova, R. B. Valeev, B. A. Bazhenov, *Chem. Heterocycl. Compd.* **1991**, *27*, 502–503.

[4] a) It is well documented that quinone methides could easily dimerize and trimerize to form spiro compounds.[4b] But the unambiguous structure of **2** is supported by spectroscopic data. b) L. Jurd, J. N. Roitman, *Tetrahedron* **1979**, *35*, 1567–1574.

[5] a) The product is a mixture of two diastereomers. Similar diastereomeric products were also observed in the reaction of the ketone with 5-methoxy-α,α-diphenylsalicyl alcohol.

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