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A SIMPLE METHOD FOR COUPLING ALDEHYDES TO SOLID SUPPORT†

William A. Metz,* Winton D. Jones, Fred L. Ciske, and Norton P. Peet

Hoechst Marion Roussel Inc., 2110 E. Galbraith Road, Cincinnati, Ohio 45215, U.S.A.

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Abstract: A new method for attaching aldehydes to solid supports has been developed employing a 2,2-bis(hydroxymethyl)propionic acid (DMPA®) functionalized resin. High loading levels are obtained for both aryl and alkyl aldehydes protected as their respective acetals. Treatment of the derivatized resin with 95% TFA then cleanly affords the recovered aldehyde in high yield.

Several methods exists for the synthesis and/or protection of aldehydes on solid support.[1–5] One approach involves the synthesis of peptide C-terminal aldehydes via attachment of the aldehyde to a solid support as a semicarbazone.[1] An alternative strategy applicable for the solid phase synthesis of peptidic C-terminal aldehydes[2] and small molecule aldehydes[3] uses $LiAlH_4$ reduction of resin supported Weinreb amides.[6] Additional methods have engaged either an intermediary oxazolidine[4] or a photoremovable acetal.[5]

Our interest in developing a facile method for attaching an aldehyde to solid support,[7] allowing subsequent chemical modification of the attached molecule and release as an aldehyde, has evolved from a desire to rapidly generate a series of chromone-3-carboxaldehyde analogs. While attempts to use the semicarbazone approach to form the semicarbazone of 6-bromochromone-3-carboxaldehyde were successful, attempts to attach this to solid support under usual amide coupling conditions only resulted in ring-opening of the pyranone. Chromone-3-carboxaldehydes are known to undergo nucleophilic attack at the 2-position to give a ring-opened product[8] and formation of the semicarbazone did not stabilize the ring sufficiently. We have found that the methyl acetal of chromone-3-carboxaldehydes stabilizes the pyranone ring, making it less susceptible to nucleophilic attack.[9] Chemical modification of the chromone acetal followed by deprotection with mild aqueous acid then affords the modified aldehyde in excellent yields. It was reasoned that if an acetal could be prepared with an additional functional group to allow attachment to solid support it may be possible to perform the chemical modifications and cleave the modified chromone-3-carboxaldehyde from the resin with aqueous acid. Here in we describe such a method for the attachment of small molecule aldehydes to solid support and their cleavage under mild conditions to give the modified aldehyde in high yield and purity.

The commercially available and inexpensive 2,2-bis(hydroxymethyl)propionic acid (DMPA®) was chosen as the linker for the strategy. The carboxylic acid serves as the attachment point to the resin and the tertiary methyl group both prevents possible hydride migration and stabilizes the acetal. Acetal formation was achieved by treating 6-bromochromone-3-carboxaldehyde **1** with one equivalent of DMPA® in toluene at 80 °C

†Dedicated with appreciation to Professor Stan S. Hall on occasion of his 60th birthday.

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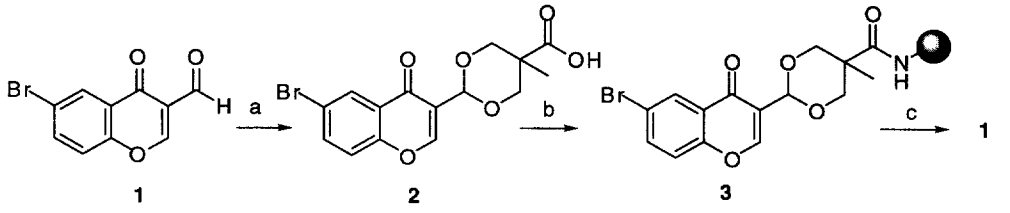
with 1.0 mol% of *p*-TsOH (Scheme 1). Upon heating, the suspension became a clear colorless mixture and within 0.5 h a white precipitate had formed. The precipitate was collected, washed several times with Et_2O and dried under vacuum to give the chromone acetal **2** as a white powder (mp 275–276 °C) in 89.4% yield.



Scheme 1. (a) DMPA®, toluene, Δ; (b) $TGNH_2$, HOBt, DIC, DMF; (c) 95% TFA/H_2O.

The chromone acetal **2** then was coupled to amino-functionalized Tenta Gel® resin (0.26 meq/g) using standard amide coupling conditions until a negative Kaiser test was observed.[10] The chromone-3-carboxaldehyde **1** then is released from the resin by treatment with 95% aqueous TFA (15 min) in 96% yield.[11]

To explore the versatility of this method, several commercially available aldehydes were submitted to these conditions. The acetals were easily formed in good yield (60–97%) without the need for purification (Table 1). A number of these acetals were then coupled to Tenta Gel S NH_2® resin (0.26 meq/g) using HOBt, DIC and catalytic *N*-methylimidazole in DMF. Upon release from the resin as described (*vide supra*), the aldehydes were recovered in excellent yield.

Table 1

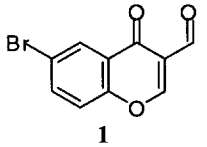
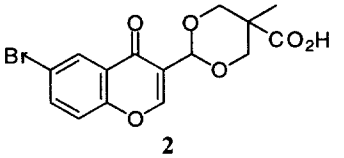
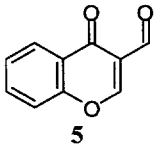
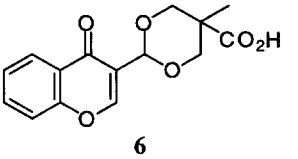
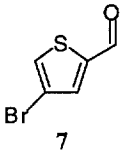
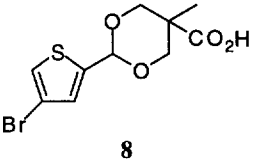
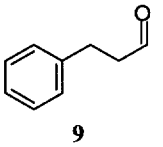
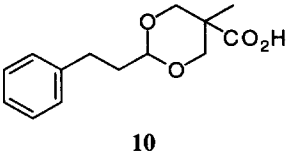
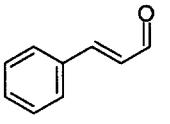
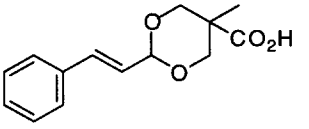
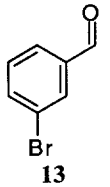
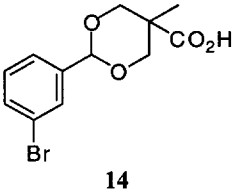
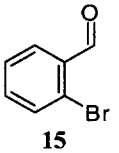
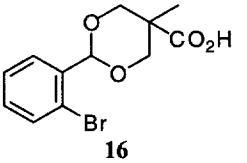
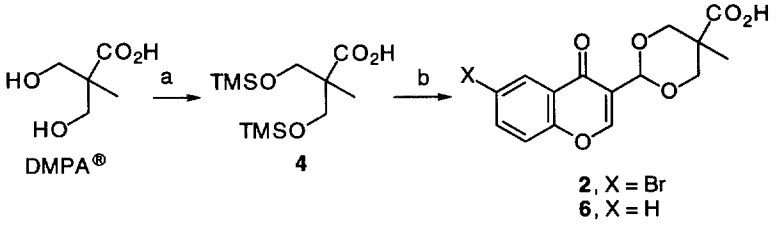
Aldehyde	Product	%Yield[a]	mp °C
 **1**	 **2**	89 (94)	275–276
 **5**	 **6**	77 (86)	214–215
 **7**	 **8**	71	168–169
 **9**	 **10**	85	167–168.5

Table 1 continued.

Aldehyde	Product	%Yield[a]	mp °C
 **11**	 **12**	60	163–164
 **13**	 **14**	67	176–178
 **15**	 **16**	97	168–169

[a]Yields in parenthesis are reaction yields using the TMS ether of DMPA®.

As a modification to this method, there is precedence for acetalization using alkyloxysilanes under mild, aprotic conditions.[12] Therefore, DMPA® was suspended in CH_2Cl_2 at rt under N_2 and 2.1 equiv of TMSCl was added followed by 2.1 equiv of Et_3N (Scheme 2). After 2 h most of the suspended solid had dissolved. The reaction mixture was diluted with additional CH_2Cl_2 and washed successively with H_2O, brine and dried ($MgSO_4$). Concentration under vacuum gave the TMS ether **4** as a viscous colorless oil (61%). This intermediate was treated with the chromone-3-carboxaldehydes **1** and **5**, shown in Table 1, to give the acetals **2** and **6** in improved yield.[13]



Scheme 2. (a) TMSCl, Et_3N, CH_2Cl_2, rt; (b) chromone-3-carboxaldehyde, TMSOTf, CH_2Cl_2, 0 °C.

The method described herein is a facile and efficient means for the attachment of small molecule aldehydes protected as their acetals to a solid support. Subsequent cleavage from the resin with 95% TFA/H_2O provides the recovered aldehyde in good yield. Furthermore by preforming the silyl ether of DMPA® it is possible to prepare these acetals at 0 °C to ambient temperatures.

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References and Notes

1. Murphy, A. M.; Dagnino, Jr., R.; Vallar, P. L.; Trippe, A. J.; Sherman, S. L.; Lumpkin, R. H.; Tamura, S. Y.; Webb, T. R. *J. Am. Chem. Soc.* **1992**, *114*, 3156.
2. (a) Fehrentz, J. A.; Paris, M.; Heitz, A.; Velek, J.; Liu, C.-F.; Winternitz, F.; Martinez, J. *Tetrahedron Lett.* **1995**, *36*, 7871. (b) Fehrentz, J. A.; Paris, M.; Heitz, A.; Velek, J.; Winternitz, F.; Martinez, J. *J. Org Chem.* **1997**, *62*, 6792.
3. Dinh, T. Q. and Armstrong, R. W. *Tetrahedron Lett.* **1996**, *37*, 1161.
4. Ede, N. J. and Brag, A. M. *Tetrahedron Lett.* **1997**, *38*, 7119.
5. Aurell, M. J.; Boix, C.; Ceita, M. L.; Llopis, C.; Tortajada, A.; Mestres, R. *J. Chem. Res. (M)* **1995**, 2569.
6. Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.
7. For recent review on polymer supported reactions see: (a) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1997**, *53*, 5643. (b) Chaiken, I. M.; Janda, K. D. *Molecular Diversity and Combinatorial Chemistry, Libraries and Drug Design*; ACS: Washington, D. C., 1996; Conference Proceedings Series III.
8. Ghosh, C. K.; Khan, S. *Synthesis* **1981**, 719.
9. Jones, W. D.; Ciske, F. L. Unpublished results.
10. The reaction is performed in a syringe (10 mL) equipped with a sintered frit, the Tenta Gel® resin is preswollen in DMF, and an excess of **2** (3 equiv) is added. After reaction overnight on an orbital shaker, the resin is washed thoroughly with DMF, CH_2Cl_2 and finally MeOH.
11. A TLC (Et_2O-Hx, 1/1) study showed that the acetal **2** is stable to 1 N HCl and HOAc for 16 h at rt. Only after 16 h is some aldehyde **1** formed upon standing in 1 N HCl. Upon treatment of **2** with Amberlyst®15 in MeOH/H_2O, or aqueous TFA (5% or 50%) for 1 h at rt, varying amounts of **1** were formed.
12. (a) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357. (b) Murata, S.; Noyori, R. *Tetrahedron Lett.* **1981**, *22*, 2107. (c) Noyori, R.; Murata, S.; Suzuki, M. *Tetrahedron* **1981**, *37*, 3899. (d) Hwu, J. R.; Leu, L.-C.; Robl, J. A.; Anderson, D. A.; Wetzel, J. M. *J. Org. Chem.* **1987**, *52*, 188. (e) Enders, D.; Reinhold, U. *Synlett* **1994**, 792.
13. The preparation of **2** is illustrative. **5-methyl-2-(6-bromo-4-oxo-4*H*-1-benzopyran-3-yl)-1,3-dioxane-5-carboxylic acid**. To 2,2-bis(hydroxymethyl)propionic acid (DMPA, 1.34 g, 10 mmol) suspended in CH_2Cl_2 (20 mL) at rt, under N_2, was added chlorotrimethylsilane (2.1 equiv, 2.7 mL), followed by Et_3N (2.1 equiv, 2.9 mL). The reaction was stirred (2 h) then quenched with H_2O, extracted with CH_2Cl_2, dried ($MgSO_4$), and concentrated to provide the TMS ether of DMPA **4** as a colorless oil in 60–70% yield. To bromochromone aldehyde **1** (253 mg, 1.0 mmol) in a separate 50 mL round bottom flask, dissolved in CH_2Cl_2 (5 mL) at icebath temperature, was added **4** (1.0 equiv, 280 mg) followed by 1 mol% trimethylsilyl trifluoromethanesulfonate (TMSOTf, 0.01 mmol, 1.9 μL). Immediately the colorless reaction became yellow. After 5 min a white ppt started to form. The reaction was stirred at icebath temperature for 1 h then diluted with Et_2O and the solid was collected, washed with additional Et_2O and dried under vacuum to afford **2** (344 mg, 93.2%) as a white solid; mp 275–276 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.6 (bs, 1H), 8.26 (s, 1H), 8.12 (d, J = 2.4 Hz), 8.00 (dd, J = 8.9, 2.5 Hz, 1H), 7.67 (d, J = 8.9 Hz, 1H), 5.68 (s, 1H), 4.40 (d, J = 11 Hz, 2H), 3.70 (d, J = 11 Hz, 2H), 0.95 (s, 3H). Anal. calcd for $C_{15}H_{13}BrO_6$: C, 48.80; H, 3.55. Found: C, 48.27; H, 3.96.