A Mild PPTS-Catalyzed Acetalization of α,β-Unsaturated Aldehydes: The First Single-Step Protocol towards Benzylic Acetals

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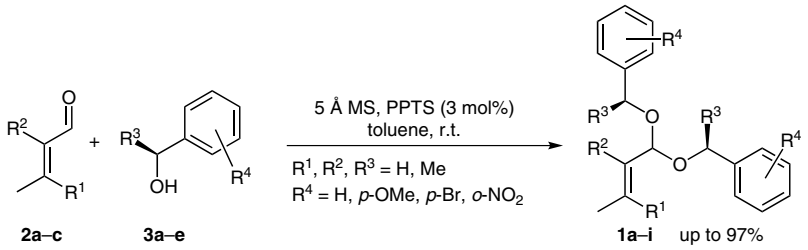
Abstract: A mild and convenient procedure for the synthesis of highly sensitive benzylic acetals from α,β-unsaturated aldehydes and the corresponding benzylic alcohols is reported. The new method provides a single-step access to these compounds for the first time. The applications of pyridinium *p*-toluenesulfonate (PPTS) as a very mild Brønsted acid catalyst and 5 Å molecular sieves (MS) as the dehydrating agent were found to be essential. Furthermore, an application of the acetals in the synthesis of 1-functionalized dienes is exemplified.

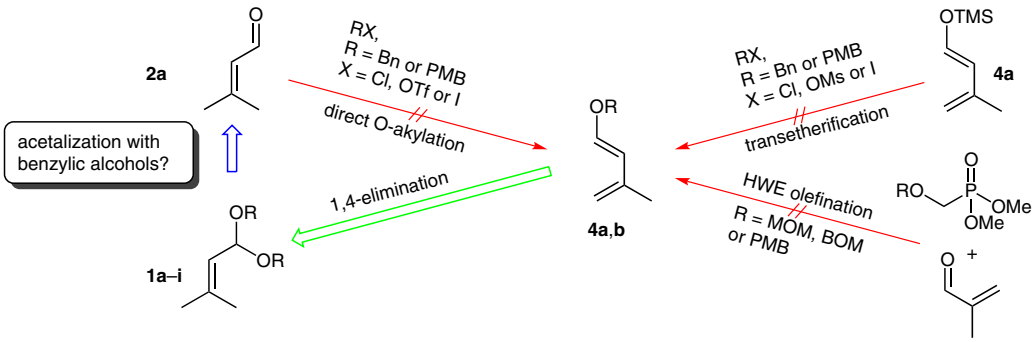
Key words: acetals, zeolites, molecular sieves, dienes, aldehydes



Scheme 1 PPTS-catalyzed and 5 Å MS mediated synthesis of benzylic acetals from α,β-unsaturated aldehydes

As part of our ongoing research on natural product synthesis we aimed to synthesize 1-benzyloxydienes **4** as shown in Scheme 2. A number of 1-oxygenated dienes have been studied as versatile building blocks in various syntheses as, for example, in Diels–Alder reactions.[1] However, the synthesis of *O*-alkyl-substituted dienes is not well documented in the literature, while the synthesis of O-methylated, O-silylated and O-acetylated dienes is well established.[1d,2] Therefore, a general route to this important class of dienes was devised. However, all of our early attempts to synthesize alkyl-(3-methyl)butadienyl ethers **4** by conventional methods failed (Scheme 2). In our hands the direct O-alkylation of the correspondent aldehyde **2a** remained unsuccessful, despite the use of different bases as KH or NaHMDS and several benzylic electrophiles as halides or triflates (Scheme 2).[3]

The same results were found when an indirect approach was chosen. While the TMS protected diene **4a** was readily accessible, the transetherification using *t*-BuOK as a base and different electrophiles failed to generate the desired 1-alkoxydiene **4** (Scheme 2).[2] Another approach examined was based on a Horner–Wadsworth–Emmons



Scheme 2 Attempts towards the synthesis of 1-oxygenated alkyl-substituted dienes **4**

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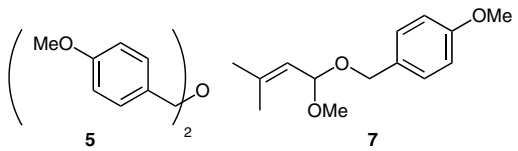
(HWE) olefination. However, despite the fact that a number of different bases (NaHMDS, KHMDS, LDA, and *s*-BuLi) as well as different solvent systems (DME, THF, n-Bu_2O) were tested, the method could not be successfully applied (Scheme 2).[4]

Results thus obtained led us to a different retrosynthetic approach. Based on the findings from Duhamel's group, we decided to synthesize the dienes using an 1,4-elimination from the corresponding α,β-unsaturated acetals **1a–i** (Scheme 2).[5] Hence the first goal was to access to the corresponding acetals. To the best of our knowledge there has been only one published method to synthesize benzylic acetals; a two-step method, which was developed by Noyori et al., based on the application of TMS-protected benzylic alcohols at –78 °C in CH_2Cl_2 with 10 mol% TMSOTf as a catalyst.[6] The described method was found to not be applicable to solve our specific problem. Instead of the desired acetals often only dibenzyl ether **5** formation and/or decomposition took place (Figure 1).

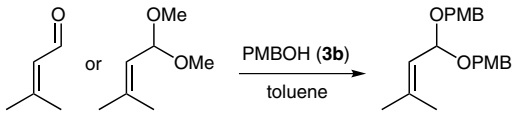


5 7

Figure 1 Regularly observed by-products **5** and **7**

The same results were found when using different known acetalization conditions including a variety of Brønsted or Lewis acid catalysts [CSA, PTS, $(NH_4)_2SO_4$, TPPMS, I_2, or $In(OTf)_3$] (Table 1, entry 5).[7] In all cases no improvement could be achieved when different solvents and drying agents such as $MgSO_4$ or MS 3Å/4Å were applied (Table 1, entry 6). In fact, in most cases bis-PMB ether **5** was formed as the major product, indicating that the applied acids were too strong. A transacetalization approach published by Nakabayashi et al. was also investigated.[8] Thus, the aldehyde **2b** was converted to its dimethoxyacetal **6**[9] with trimethyl orthoformate in MeOH using 1 mol% $In(OTf)_3$ as a catalyst in very high yields (99%).[7d] Dimethoxyacetal **6** was used in a consecutive step for the transacetalization with $(NH_4)_2SO_4$ as a catalyst (Table 1, entry 1). This time we were pleased to find that under these conditions the desired product **1c** was formed along with the bis-PMB ether **5**. Another by-product that could be identified was a mixed methoxy-OPMB acetal **7**, an intermediate of the reaction (Figure 1). Different experiments were carried out to optimize the obtained result and it was noticed that with increasing catalyst loading and reaction time the amount of by-product **7** could be decreased. The yield of acetal **1c** did not increase since the formation of bis-PMB ether **5** was rising at the same time. Another difficulty was the somehow complicated separation of acetal **1c** and ether **5**, which made several chromatographic steps necessary to obtain the clean product **1c** in 36% yield. It could be shown that the use of stronger acids such as CSA, PTSA, and Amberlyst 15 led to the formation of bis-PMB ether **5**, while the use of $In(OTf)_3$ led to complete decomposition. In contrast, no decomposition or bis-PMB ether **5** formation was observed when the weak Brønsted acid pyridinium *p*-toluenesulfonate (PPTS) was used. Hence the direct acetalization of aldehyde **2b** was reinvestigated (Table 1, entries 7, 8). The very mild acid PPTS was chosen as the catalyst. After several attempts applying $MgSO_4$, 3Å, or 4Å MS as drying agents, the acetalization took place in the presence of 5 Å MS (entry 8). The reaction proceeds in toluene at room temperature as a slow, but very clean reaction with no formation of ether by-product **5** or decomposition. After optimizing the equivalents of the benzylic alcohol **3b** (10 equiv were found to be optimal), the 3-methylbut-2-enal bis(*p*-methoxybenzyl) acetal (**1c**) was isolated in good yield (87%). It is noteworthy that the obtained acetals are very prone to decomposition upon acidic treatment and that therefore an important aspect of the optimization was to find the right chromatographic conditions. A vacuum distillation must be excluded because polymerization was observed upon heating the acetal **1c**. Addition of Et_3N to the mobile phase did not give satisfying results, but the use of a double-walled, water-cooled column (ca. 5 °C) led to fast and clean isolation of the product without considerable decomposition of acetals **1a–i**. It was also found that while the NMR spectra of acetals **1a–i** could be recorded in $CDCl_3$, for extended periods they must be stored in a freezer to avoid decomposition.

Table 1 Acetalization/Transacetalization Conditions



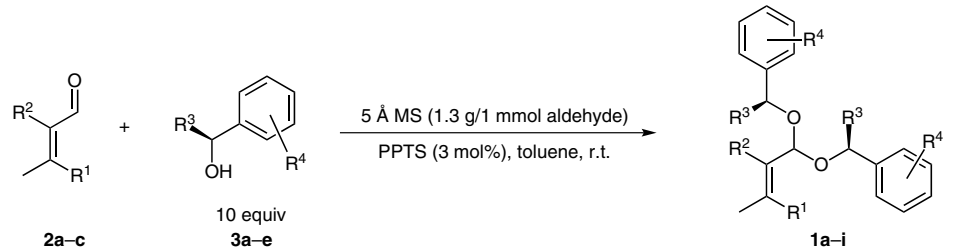
2b 6 1c

Entry	SM[a]	Catalyst	Additive	Result	Yield (%)
1[b]	**6**	$(NH_4)_2SO_4$	–	mixture of **5**, **7**, and **1c**	36
2	**6**	H^{+c}	–	$(PMB)_2O$	–
3	**6**	$In(OTf)_3$	–	dec.	–
4	**6**	PPTS	–	no reaction	–
5	**2b**	H^{+c}	–	$(PMB)_2O$	–
6	**2b**	H^{+c}	var.[d]	$(PMB)_2O$	–
7	**2b**	PPTS	var.[d]	–	–
8	**2b**	PPTS	5 Å MS	clean reaction	87

[a] Starting material.
[b] Reaction was conducted at 120 °C.
[c] CSA, TSA, and Amberlyst 15 were independently tested.
[d] $MgSO_4$, 3 Å MS, and 4 Å MS were tested as drying agents.

With the new and convenient protocol in our hand the scope of the protocol was explored. A number of acetals **1a–i** starting from the α,β-unsaturated aldehydes **2a–c** and

Table 2 Results of the Direct Acetalization of α,β-Unsaturated Aldehydes Using Benzylic Alcohols



2a–c **3a–e** **1a–i**

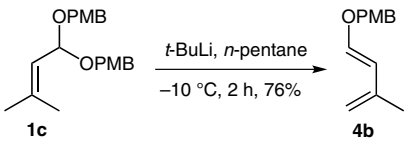
Entry	**2**	R^1	R^2	**3**	R^3	R^4	Time (d)	Product	Yield (%)[a]
1	**2a**	H	H	**3a**	H	H	1	**1a**	45
2	**2a**	H	H	**3b**	H	*p*-OMe	1	**1b**	33
3[b]	**2b**	Me	H	**3b**	H	*p*-OMe	1	**1c**	87
4	**2b**	Me	H	**3a**	H	H	2	**1d**	97
5	**2b**	Me	H	**3c**	Me	H	14	**1e**	71
6[c]	**2b**	Me	H	**3d**	H	*o*-NO_2	27	**1f**	28
7[c]	**2b**	Me	H	**3e**	H	*p*-Br	27	**1g**	82
8	**2c**	H	Me	**3a**	H	H	9	**1h**	79
9	**2c**	H	Me	**3b**	H	*p*-OMe	8	**1i**	76

[a] Isolated yield after column chromatography.
[b] Conducted on a 30 mmol scale.
[c] Only 5 equiv of the corresponding alcohol were used.

different benzylic alcohols **3a**–**e** were synthesized (Scheme 1, Table 2).

We found that high to very high yields (71–97%) could be obtained using 3-methylbut-2-enal (**2b**) and different benzylic alcohols **3a**, **3b**, and **3e** (Table 2, entries 3–5 and 7). Using aldehyde **2b** and *p*-methoxybenzyl alcohol (**3b**) the reaction was scaled up to 30 mmol without any loss of the yield (entry 3). In the case of the sterically more hindered aldehyde **2c** (R^2 = Me) the reaction time needed to be increased from 1 or 2 days to 8 or 9 days to gain good results (76–79%) (entries 8 and 9). On the other hand, acetals derived from sterically less hindered aldehyde **2a** (entries 1 and 2) were formed very quickly (full conversion was determined), but also were very sensitive to decomposition so that even after several attempts the products could be isolated only in moderate yields (33–45%). Utilization of chiral alcohol **3c** led also to a decreased reaction rate and the product could be isolated after 14 days in 71% yield (entry 5). When only 5 equivalents of the corresponding alcohol were used, the formation of the acetal became very slow (entries 6 and 7). In the case of *o*-nitro- and *p*-bromobenzyl alcohols (**3d** and **3e**) a high conversion could only be detected after a prolonged time period (entries 6 and 7). The moderate yield of acetal **1f** (entry 6) can therefore not be explained by a low conversion and is most probably due to its sensitivity to light. In all cases the excess of benzylic alcohol **3a**–**e** could be easily recovered after column chromatography with yields between 74% and 91% based on the unconverted alcohol. As expected, ketones, for example, cyclohexenone, were found to be not reactive enough and therefore no conversion was achieved using the described method. However, surprisingly, cinnamaldehyde was also not converted into its bis(*p*-methoxybenzyl) acetal.

With such results in hand our attention was turned towards the synthesis of the *p*-methoxy-substituted 1-oxydiene **4b**. Applying the protocol published by Duhamel et al.,[5a] the desired diene **4b** could be isolated in 76% yield (Scheme 3). The 1,4-elimination reaction was found to be highly reproducible even on a large (29 mmol) scale. Even though diene **4b** is highly volatile and very sensitive towards acidic conditions, purification could be achieved by using a water-cooled column and an *n*-pentane–Et_2O (95:5) mixture for chromatography.



1c **4b**

Scheme 3 Synthesis of diene **4b**

In conclusion, we have developed a mild and convenient protocol for the synthesis of otherwise difficult to synthesize benzylic acetals **1a**–**i**. The uses of the mild Brønsted acid PPTS as the catalyst and 5 Å MS as a dehydrating agent are the key features of the new method. It allows a

simple access to these acetals even on a large scale. Furthermore, the method, combined with the shown 1,4-elimination, opens a new route to the class of alkyl-substituted 1-oxydienes **4**, which are important intermediates in a number of reactions such as Diels–Alder reactions.

Unless otherwise specified the reactions were carried out by using standard Schlenk techniques under an atmosphere of dry N_2 with magnetic stirring. Glassware was oven-dried at 120 °C overnight. Solvents were dried and purified by conventional methods prior to use. All the reagents were used as purchased from commercial suppliers without further purification. Common solvents for chromatography [petroleum ether (PE; 40–60 °C), EtOAc, *n*-pentane, Et_2O] were distilled prior to use. Flash column chromatography was performed on silica gel 60, 0.040–0.063 mm (230–400 mesh) using a water-cooled column. TLC was performed on pre-coated plastic sheets with detection by UV (254 nm) and/or by staining with cerium molybdenum solution. ^{1}H and ^{13}C NMR spectra were recorded at r.t.; chemical shifts are given in ppm relative to internal standard TMS (^{1}H: δ [Si(CH_3)$_4$] = 0.00 ppm) or relative to the resonance of the solvent (^{13}C: δ (*C*DCl$_3$) = 77.0 ppm). Coupling constants *J* are given in Hz. Higher-order δ and *J* values are not corrected. ^{13}C signals were assigned by means of C, H, COSY and HSQC or HMBC spectroscopy. Melting points are uncorrected.

Acetals 1a–i; General Procedure

To a solution of aldehyde **2a–c** (3.0 mmol) in toluene (10 mL) were added molecular sieves (5 Å, 4 g), benzylic alcohol **3a–e** (38.6 mmol, 12.7 equiv), and PPTS (20 mg, 0.08 mmol, 0.03 equiv). The suspension was stirred at r.t. until no further conversion could be observed as judged by ^{1}H NMR analysis. After diluting with EtOAc (100 mL) and filtering through a pad of Celite, the mixture was washed with sat. aq $NaHCO_3$ (30 mL) and brine (30 mL), and dried ($MgSO_4$). The solvents were removed under reduced pressure and the crude product was subjected to column chromatography using a double-walled, water-cooled column (PE–EtOAc) providing the acetals **1a–i** as colorless oils.

But-2-enal Bis(*p*-methoxybenzyl) Acetal (1b)

According to the General Procedure, but-2-enal (**3a**; 0.3 mL, 3.6 mmol) was treated with *p*-methoxybenzyl alcohol (**2b**; 6.0 mL, 45.3 mmol, 12.7 equiv). The reaction was worked up after 1 d and the acetal **1b** was isolated after column chromatography (PE–EtOAc, 95:5) as a colorless oil (380 mg, 33%); R_f = 0.3 (PE–EtOAc, 90:10).

FT-IR (film): 3000, 2936, 2836, 1612, 1586, 1512, 1464, 1301, 1244, 1173, 1108, 1028, 1007, 964, 817, 756 cm^{-1}.

^{1}H NMR (600 MHz, CDCl$_3$): δ = 1.75 (dd, ^3J = 6.6 Hz, ^4J = 1.7 Hz, 3 H, 4-H), 3.80 (s, 6 H, 6′-H), 4.48 (d, ^2J = 11.4 Hz, 2 H, 1′-H$_a$), 4.57 (d, ^2J = 11.4 Hz, 2 H, 1′-H$_b$), 5.03 (d, ^3J = 5.4 Hz, 1 H, 1-H), 5.61 (ddq, ^3J = 15.5 Hz, ^3J = 5.4 Hz, ^4J = 1.7 Hz, 1 H, 2-H), 5.88 (dq, ^3J = 15.5 Hz, ^3J = 6.6 Hz, 1 H, 3-H), 6.88 (d, ^3J = 8.6 Hz, 4 H, 4′-H), 7.27 (d, ^3J = 8.6 Hz, 4 H, 3′-H).

^{13}C NMR (151 MHz, CDCl$_3$): δ = 17.7 (C-4), 55.3 (C-6′), 66.8 (C-1′), 100.3 (C-1), 113.8 (C-4′), 128.4 (C-2), 129.4 (C-3′), 130.3 (C-2′), 130.4 (C-3), 159.1 (C-5′).

MS (EI, 70 eV): *m*/*z* (%) = 121 (100%, $C_8H_9O^+$).

HRMS (FT-ICR-MS): *m*/*z* calcd for $C_{20}H_{25}O_4$ + Na: 351.1752; found: 351.1567.

***p*-Methoxybenzyl 3-Methylbuta-1,3-dienyl Ether (4b)**

To a solution of acetal **1c** (10 g, 29.2 mmol) in *n*-pentane (360 mL) at –10 °C was added a solution of *t*-BuLi in *n*-pentane (1.7 M, 40 mL, 68 mmol) within 1 h. After the addition, the ice bath was removed and the reaction mixture was stirred at r.t. until the TLC analysis showed full conversion (ca. 1 h). The mixture was diluted with Et_2O (400 mL), and washed with H_2O (100 mL) and brine (100 mL). The organic phase was dried ($MgSO_4$) and the solvents were carefully evaporated at 40 °C/300 mbar (product is volatile). The crude product was purified using a water-cooled (ca. 5 °C) chromatographic column (*n*-pentane–Et_2O, 95:5) yielding diene **4b** as colorless crystals (4.55 g, 76%); mp 45–50 °C; R_f = 0.4 (*n*-pentane–Et_2O, 95:5).

FT-IR (film): 2920, 1635, 1515, 1331, 1250, 1175, 1033, 936, 877, 813 cm^{-1}.

^{1}H NMR (600 MHz, CDCl$_3$): δ = 1.81 (s, 3 H, 3-CH$_3$), 3.81 (s, 3 H, 6′-H), 4.70 (s, 1 H, 4-H$_a$), 4.74 (s, 2 H, 1′-H), 4.78 (s, 1 H, 4-H$_b$), 5.77 (d, ^3J = 12.8 Hz, 1 H, 2-H), 6.60 (d, ^3J = 12.8 Hz, 1 H, 1-H), 6.90 (d, ^3J = 8.7 Hz, 2 H, 4′-H), 7.28 (d, ^3J = 8.7 Hz, 2 H, 3′-H).

^{13}C NMR (151 MHz, CDCl$_3$): δ = 19.0 (C-3-CH$_3$), 55.3 (C-6′), 71.5 (C-1′), 110.0 (C-2), 111.8 (C-4), 114.0 (C-4′), 128.9 (C-2′), 129.3 (C-3′), 139.7 (C-3), 147.9 (C-1), 159.5 (C-5′).

MS (EI, 70 eV): *m*/*z* (%) = 204.0 (10, [(M)$^+$]), 121 (100, $C_8H_9O^+$).

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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