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Mild and efficient deprotection of allyl ethers of phenols and hydroxycoumarins using a palladium on charcoal catalyst and ammonium formate

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Abstract—An efficient procedure for the cleavage of allyl phenyl ethers and allyl coumarinyl ethers using a catalytic amount of 10% Pd/C in combination with ammonium formate is described. Allyl ethers of phenols are deprotected in preference to those of alcohols and this method is compatible with several reducible functional groups such as CHO, $COCH_3$, CO_2Et and $NHCOCH_3$.

Ammonium formate has been extensively used[1] as a hydrogen source in the presence of the hydrogen transfer catalyst, palladium on charcoal, for the reduction of a host of functionalities, including deprotection of *O*-benzyl ethers, 1,3-dibenzyluracils and deoxygenation of pyridine N-oxides. The use of this reagent system for the deallylation of allyl ethers of phenols and hydroxycoumarins is herein disclosed. Phenolic hydroxyl groups are ubiquitous in naturally occurring secondary metabolites of plant and animal origin.[2] Unlike alcohols, phenols, particularly polyphenols, are acidic in nature, oxidation-prone, sensitive to radicals and possess enhanced nucleophilicity. Therefore, protection of phenolic hydroxyl groups is of importance in multistep syntheses of biologically important natural products. The allyl group is a very useful phenol protecting group because of the stability of allyl ethers under acidic as well as under basic conditions. Allyl ethers are safety-catch, or two-stage protecting groups,[3] and their deprotection involves the two-step process of isomerization of the stable allyl (prop-2-enyl) ether to a labile prop-1-enyl ether as a prelude to hydrolytic cleavage.[4a–c] A second plausible mechanistic scenario[4d–f] for deprotection of aryl allyl ethers with Pd/C or Pd(0) complexes involves initial oxidative addition of palladium to the allyl ether to form a π-allyl palladium species. The aryloxy group in the resulting species is a competent leaving group and interception by even a weak nucleophile releases the aryloxy group to furnish the phenol. The known lability of allyl ethers[4g] under Suzuki reaction conditions ($Pd(PPh_3)_4$, K_3PO_4, DME, reflux) and the fact that Pd/C catalyzes Suzuki reactions also supports this view. Allylic carboxylates that are normally unreactive towards mild hydride transfer reagents such as $NaBH_4$ and $NaBH_4CN$ are analogously activated towards displacement by initial complex formation with Pd(0) derivatives and are removed in the presence of weak nucleophiles, e.g. BH_4^-, BH_3CN^-.[4h]

Previously, attempts towards the activation of allyl ethers under strongly basic conditions using potassium *tert*-butoxide[5] proved to be too harsh and sluggish. A more convenient strategy of deallylation is based on transition metal (Pd, Rd, Ir, Ru) catalyzed isomerization of the double bond to an enol ether followed by its hydrolysis to release the phenol. Deallylation protocols based on the use of a palladium metal catalyst are well-documented including 10% Pd/C in combination with *p*-toluenesulfonic acid,[6] 10% Pd/C with 10% methanolic KOH,[7] electrochemical cleavage employing $PdCl_2$,[8] and $Pd(PPh_3)_4$ with reducing agents such as $NaBH_4$,[4d] $LiBH_4$,[4f] Bu_3SnH[9] and $PdCl_2/CuCl/O_2$.[10] Recently, several one-step cleavage protocols based on $SmCl_3$,[11] NaI/Me_3SiCl,[12] $NiCl_2(dppp)/DIBALH$,[13] electrochemically generated nickel,[14] $SmI_2/H_2O/Et_3N$[15] and $CpRu^{III}PF_6$/quinaldic acid[16] catalysts have been described. Surprisingly, the deallylation of allyl ethers

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Keywords: Deallylation; Allyl phenyl ether; Allyl coumarinyl ether; Pd/C and ammonium formate.

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Table 1. Cleavage of allyl ethers of phenols and hydroxycoumarins with 10% Pd/C and HCO_2NH_4 in methanol

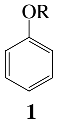
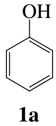
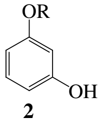
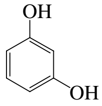
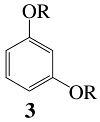
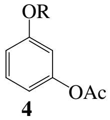
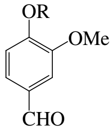
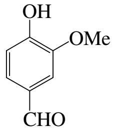
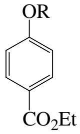
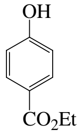
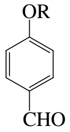
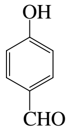
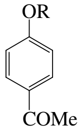
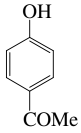
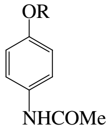
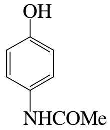
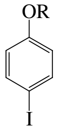
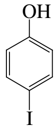
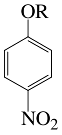
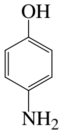
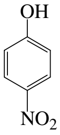
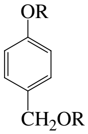
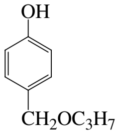
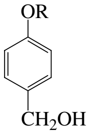
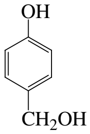
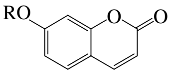
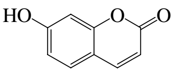
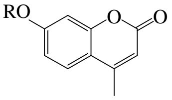
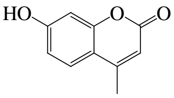
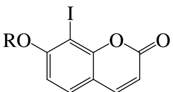
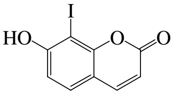
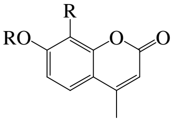
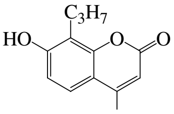
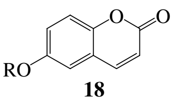
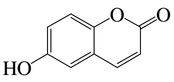
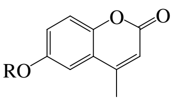
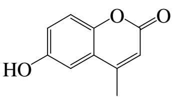
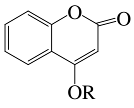
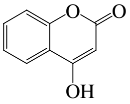
Entry	Substrate R = allyl	Product	Time[a] (h) [Yield[c] in (%)]
1	 **1**	 **1a**	(i) 8 [80] (ii) 0.5[b] [95]
2	 **2**	 **2a**	0.5[b] [98]
3	 **3**	**2** **2a**	9.5 [80] 1[d] [92]
4	 **4**	**2** **2a**	(i) 0.5[b] [98] (ii) 0.5[e] [96] 1.5[d] [86]
5	 **5**	 **5a**	6 [85]
6	 **6**	 **6a**	(i) 2 [92] (ii) 0.5[b] [98]
7	 **7**	 **7a**	(i) 5 [85] (ii) 0.5[b] [98]
8	 **8**	 **8a**	(i) 5 [90] (ii) 0.5[b] [92]
9	 **9**	 **9a**	(i) 7 [88] (ii) 1[b] [90]
10	 **10**	 **10a**	8[b] [85]
11(a)	 **11**	 **11a**	0.5[b] [72]
11(b)	**11**	**11a** +  **11b**	0.5[f] **11a** [5]; **11b** [70]
12	 **12**	 **12a**	0.5[b] [98]
13	 **13**	 **13a**	(i) 8 [90] (ii) 0.5[b] [96]
14	 **14**	 **14a**	(i) 15 [80] (ii) 1[b] [98]
15	 **15**	 **15a**	1[b] [95]
16	 **16**	 **16a**	1.5[b] [95]
17	 **17**	 **17a**	1[b] [92]
18	 **18**	 **18a**	1[b] [98]
19	 **19**	 **19a**	1.5[b] [95]

Table 1 (*continued*)

Entry	Substrate R = allyl	Product	Time[a] (h) [Yield[c] in (%)]
20	 **20**	 **20a**	1.5[b] [95]

[a] Refers to cleavage reactions conducted at room temperature (25 °C) using 10% Pd/C (30 mg) and HCO_2NH_4 (6 mmol) per mmol of substrate.

[b] Refers to cleavage time in refluxing methanol using identical amounts of reagents.

[c] Refers to yields of chromatographically isolated product characterized by comparison with authentic samples (mixed mp, co-TLC, superimposable IR) and spectral studies (IR, ^1H NMR, ^{13}C NMR and EMS).

[d] 10% Pd/C (40 mg), HCO_2NH_4 (10 mmol), in methanol (10 mL) under reflux.

[e] HCO_2NH_4 (6 mmol) was employed only; no Pd/C was used.

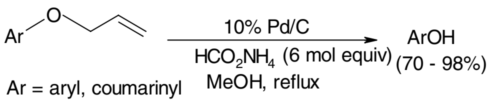
[f] 10% Pd/C (30 mg) and HCO_2NH_4 (4 mmol) were used per mmol of **11** in methanol under reflux.

of alcohols has engaged organic chemists more than their phenolic counterparts. We were interested in the deprotection of allyl coumarinyl ethers in connection with our studies on regioselective electrophilic substitution reactions[17] of these ethers. Further synthetic manipulations with hydroxycoumarins necessitated the release of hydroxycoumarins from *O*-allyl ethers. To achieve this aim, 10% Pd/C and ammonium formate seemed to be appropriate reagents. Ammonium formate is inexpensive, readily available, stable and nontoxic. Table 1 summarizes the results of cleavage of allyl ethers of phenols and hydroxycoumarins using a catalytic amount of 10% Pd/C with ammonium formate (Scheme 1).

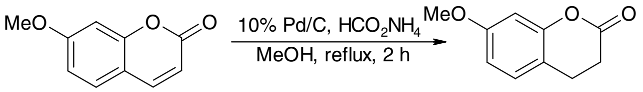
We chose *O*-allyl phenol **1** (entry 1) as the model substrate to optimize the conditions. It was observed that 1 mmol of **1** was cleaved after protracted treatment with 30 mg of Pd/C and 6 mmol of ammonium formate in methanol at room temperature (8 h) in acceptable yield (80%). The cleavage was markedly accelerated under reflux conditions furnishing phenol in an excellent yield (95%) within 30 min.[18] Notably, rigorous exclusion of water from the ammonium formate and methanol, as is common in transfer hydrogenations,[19,20] is not obviously essential in this case. Encouraged by the dual advantages of an improvement in yield and substantial reduction of reaction time we proceeded to conduct deprotections of several allyl aryl ethers including resorcinols[21] which are fairly well-represented in naturally occurring phenolics. This procedure worked well for most of the cases studied. The substantial difference in rates of cleavage at room temperature and under reflux conditions was found to be quite general. However, the cleavage at room temperature was more compatible with ethers bearing reducible or acid-labile functionalities. Whereas the *O*-allyl ether of 4-nitrophenol (**11**) (Table 1, entry 11(a)) underwent concomitant reduction of the nitro group, selective deallylation without affecting the nitro group could be accomplished using less (4 mol equiv) ammonium formate (Table 1, entry 11(b)). Sequential removal of the allyl groups of 1,3-di-*O*-allyloxybenzene (Table 1, entry 3) was possible at room temperature. An attempted cleavage of 3-acetoxyallyloxybenzene (**4**) only resulted in facile hydrolysis of the acetoxy group without affecting the allyl ether moiety. The use of an identical amount of ammonium formate, without Pd/C catalyst, gave the same product **2** in almost identical yield. Simultaneous deallylation and hydrolysis of the acetoxy group took place upon prolonged exposure to an excess of the reagents. However, the more acid-stable anilido function (Table 1, entry 9) was found to be intact under the deprotection conditions.

The di-*O*-allyl ether of 4-hydroxybenzyl alcohol (**12**) was deallylated to give 4-hydroxy-*n*-propylbenzyl ether (**12a**) demonstrating preferential cleavage of allyl phenyl ether. Cleavage of the C–O bond of the allyl ether of an alcoholic hydroxyl group was less straightforward and the allylic C=C bond was reduced prior to its isomerization to the prop-1-enyl ether. However, an ester group, in contrast to its reduction with $SmI_2/H_2O/Et_3N$,[15] remained unchanged. The method was also compatible with other reducible groups such as CHO and $COCH_3$. The iodo group (Table 1, entries 10 and 16) also withstood the reaction conditions. Deallylation of 4-allyloxyiodobenzene with electrochemically generated nickel[14] gave the corresponding phenol in low yield (11%) because of the high reactivity of nickel towards oxidative addition to the iodo group. It is also significant that the α,β-unsaturated lactone moiety of allyl coumarinyl ethers remained intact during cleavage (Table 1, entries 14–20) in view of the propensity for reduction of double bonds conjugated to the carbonyl group[20] of α,β-unsaturated aldehydes, ketones and esters[22] with Pd/C and ammonium formate. Attempted cleavage of 8-allyl-7-allyloxy-4-methylcoumarin (**17**) led to the preferential reduction of the isolated C=C bond of the 8-allyl group in the presence of the 3,4-double bond of the coumarin with concomitant deallylation. However, exposure of 7-methoxycoumarin (**21**) to the reagent in refluxing methanol for 2 h in a separate experiment resulted in the isolation of 7-methoxy-3,4-dihydrocoumarin (**21a**) in a yield of 96% (Scheme 2) demonstrating the reducibility of the 3,4-double bond of a coumarin moiety in the absence of a competing faster deally-lation.[24]

In conclusion, a clean, efficient, cleavage of allyl ethers of phenols and hydroxycoumarins employing a catalytic



Scheme 1.



21 **21a** (96%)

Scheme 2.

amount of 10% Pd/C in combination with ammonium formate is reported.

Acknowledgements

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18. *Representative procedure for the cleavage of allyl aryl ethers with 10% Pd/C and ammonium formate in methanol*: Ammonium formate (380 mg, 6 mmol) was added to a solution of the allyl phenyl ether (136 mg, ~1 mmol) in methanol (8 mL) containing 10% palladium on charcoal (30 mg) (Aldrich, USA). The reaction mixture was refluxed for 0.5 h and then allowed to cool. The solution was filtered through a pad of celite and the residue was washed with methanol (2×2 mL). The filtrate combined with washings was carefully evaporated under vacuum, triturated with water (5 mL) and extracted with dichloromethane (2×5 mL). Removal of the solvent and chromatography over silica gel (60–120 mesh) gave pure crystals of phenol (90 mg), mp 41–42 °C (lit.[23] 42 °C).
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24. The current deallylation may be an isomerization–hydrolysis sequence with ammonium formate acting as a mild hydrolytic cleaving agent for acid labile enol ethers generated by isomerization of allyl ethers with Pd/C. However, insertion of palladium between the C–O bond by oxidative addition and removal of ArO from the resulting π-allyl palladium complex by nucleophilic attack of formate is an equally possible mechanistic route.