Tetrahedron Letters 55 (2014) 1141–1144

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Pd(II)-catalyzed deprotection of acetals and ketals containing acid sensitive functional groups ☆

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ARTICLE INFO

Article history:
Received 7 October 2013
Revised 9 December 2013
Accepted 17 December 2013
Available online 25 December 2013

Keywords:
Acetals
Catalysis
Hydrolysis
Palladium
Acetal deprotection

ABSTRACT

The pincer complex [Pd(C^1,O^1,N^1-L)(NCMe)]ClO_4 (L = monoanionic ligand resulting from deprotonation of the acetyl group of the dimethyl monoketal of 2,6-diacetylpyridine) is used for the high-yield and selective catalytic hydrolysis of aliphatic, aromatic, cyclic, and acyclic dimethyl-acetals, -ketals, and dioxolanes, even in the presence of large substituents. Other protecting groups, such as THP or TBDMS, or very acid-sensitive alcohols were not affected. The catalyst is easily prepared in high yield from $Pd(AcO)_2$ and 2,6-diacetylpyridinium perchlorate stable to air and moisture, easily and fully recoverable and reusable.

Introduction

Protection and deprotection of functional groups are key in many multi-step organic syntheses. Therefore, the development of new mild, efficient, and selective reagents to remove established protecting groups is a valuable endeavor. In particular, the deprotection of acetals and ketals[1] to give the corresponding carbonyl compounds has a very important role in total synthesis.[2–4]

Many reagents have been developed for this purpose, for example, organic acids, metal chlorides, coordination complexes,[2] inorganic salts,[2,3,5–9] and organic compounds.[2,10,11] While these reagents are useful toward functionally poor organic molecules they (1) are not efficient to all kinds of acetals and ketals,[2,7,8,12] (2) use acidic medium unsuitable for compounds containing acid sensitive functional groups[2,5] or (3) give unwanted side-reactions with other protecting groups (tetrahydropyranyl (THP), methoxymethyl ether (MOM), or silyl ethers).[2,9,10] In the last decade, some methodologies have been highlighted over the rest, such as the use of triethylsilyl trifluoromethanesulfonate (TESOTf) + base,[11,13] that selectively unmasks acetals in the presence of ketals in good yields, Bi(III)[14] and In(III)[3,15] salts that deprotect acetals and ketals in the presence of THP and silyl ether protecting groups. Only one example of Pd-catalyzed deprotection of acetals and ketals has been reported by Lipshutz et al.[16] Low catalyst loading of [$PdCl_2(NCMe)_2$] is able to afford the corresponding carbonyl groups in good yields but competitive reactions are given with the THP alcohol protecting group.

Results and discussion

We have recently isolated a family of Pd(II) pincer complexes [Pd(C^1,O^1,N^1-L)(L^1)]ClO_4[17] (L = monoanionic ligand resulting from the cyclopalladation of 2,6-diacetylpyridine (Scheme 1), L^1 = MeCN (**1**), PPh_3 (**2**) and other N-, P-donor ligands) and some containing C-donor ligands obtained from the hydrolysis of the corresponding monoketal derivatives [Pd(C^1,O^1,N^1-L′)(L^1)]ClO_4 (L′, see Scheme 1; L^1 = MeCN (**A1**), PPh_3 (**A2**). Complex **1** can also be prepared from $Pd(OAc)_2$ and 2,6-diacetylpyridinium perchlorate.[17] The pincer ligands L and L′ provide palladium complexes with interesting properties. Thus, L′ is able to stabilize complexes of Pd(IV), which are, in general, highly unstable; in addition, some Pd(II) and Pd(IV) derivatives of L or L′ are catalysts.[17–19]

The above-mentioned hydrolytic process did not occur in neutral homologous complexes of **A**, for example in [Pd(O^1,C^1,N^1-L′)Cl], suggesting that it could be caused by increasing the acidic character of the Pd(II) center in the cationic complexes **A**. To test if this hydrolysis could also occur with an 'external' acetal we attempted to use **A1** (L^1 = MeCN) or **A2** (L^1 = PPh_3) as the catalyst for the hydrolysis of decanal dimethylacetal (DDMA). However, although it occurred, the process was very slow (Table 1) and curiously, the intramolecular hydrolysis did not take place while there was

☆ The patent of this method has been applied for (P201031021).

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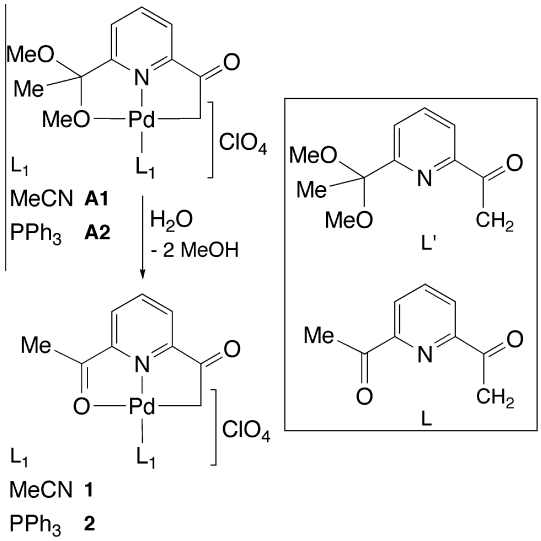
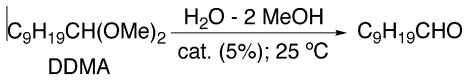
http://dx.doi.org/10.1016/j.tetlet.2013.12.067



Scheme 1. Synthesis of complexes **1** and **2**.

Table 1
Deprotection of DDMA with various catalysts



Cat.	Time (h)	Yield[a] (%)
1	8	95
A1	16	36
A2	16	6
$[PdCl_2(NCMe)_2]$[16]	16	30
$[Pd(AcO)_2]$	16	0
10% AcOH	16	0

[a] Determined by ^{1}H NMR.

DDMA in solution. This suggested us that the intermolecular hydrolysis occurred by replacement of the ketal group of the ligand by DDMA, preventing the intramolecular hydrolysis, and not by replacement of the ligand L[1], which, in addition, would be very unlikely in the case of PPh_3 (**A2**). The greater reaction rate when **A1** was used as the catalyst instead of **A2** could be attributable to a higher steric hindrance produced by the bigger phosphine ligand. Consequently, we thought that complex **1** could be better as catalyst than complexes **A** because the acetyl group is smaller than the ketal group, it is electron-withdrawing instead of electron-donating, making the metal center more acidic, and the Pd–O bond in **1** is weaker than in the **A**-type complex with L[1] = 2,6-$Me_2C_6H_3$-NC.[17] We selected DDMA for the test because the catalytic deprotection of some long chain aliphatic substrates has failed[8] and, particularly, the only reported catalytic hydrolysis of DDMA reached only 17% yield.[20]

The deprotection of DDMA using **1** as the catalyst was also compared to that of $[PdCl_2(NCMe)_2]$, which is the only palladium compound reported for this type of catalytic reactions,[16] as well as to $Pd(AcO)_2$ or 10% of AcOH. The reactions were performed at room temperature in wet acetonitrile with 5% mol amount of the catalyst.[21] Complex **1** was by far the best catalyst for the reaction (Table 1). We have recently reported that **1** showed also to be a good precatalyst for some room temperature Pd(II)/Pd(IV) Heck-type reactions.[19]

In order to optimize the reaction conditions, we carried out some experiments at room temperature varying the amount of **1** added to the mixture (Table 2). Decanal was obtained in quantitative yields after 5.5–36 h depending on the concentration of the catalyst (1–10%, respectively). When the temperature of the reaction was increased to 50 °C, 98% yield was obtained after 5 min using 1% mol of **1**. Therefore, the latter reaction conditions can be used for hydrolyzing non-temperature sensitive substrates.

Table 2
Deprotection of DDMA at different concentrations of **1**, temperatures, and reaction times to reach >90% yield of decanal

Mol % of **1**	Temp (°C)	Time	Yield[a] (%)
1	25	36 h	92
3	25	12 h	96
5	25	8 h	95
10	25	5.5 h	97
1	50	5 min	98

[a] Determined by ^{1}H NMR.

In order to know the potential of our methodology, a number of aliphatic, aromatic, cyclic, and acyclic dimethylacetals, dimethylketals, and dioxolanes were selected as substrates (Table 3). The reactions were performed in wet acetonitrile using 1% mol of **1** as the catalyst.[22]

All deprotection reactions led to the corresponding carbonyl compounds in more than 95% yield in the range of 1–120 min at room temperature or by heating at 50 °C. As expected, ketals (entry 4, Table 3) were more easily hydrolyzed than the corresponding acetals (entry 5). Moreover, dioxolane derivatives were somewhat more resistant than the corresponding dimethoxy compounds (entry 6). This methodology is compatible with the presence of other protecting groups such as *tert*-butyldimethylsilylether (TBDMS, entry 8) or acid-labile tetrahydropyranyl (THP, entry 7). However, in $[PdCl_2(NCMe)_2]$-catalyzed reactions of protected acetal compounds bearing THP groups, both hydrolytic processes are in competition.[16] We have also successfully deprotected two ketals containing really acid-sensitive hydroxy groups (entries 9 and 10)[23] that could easily dehydrate, giving the corresponding α,β-unsaturated carbonyl compounds, if acid deprotecting reagents were used. Thus, it has been observed dehydration in attempts to deprotect **18**[24] and **20**.[25] These are very remarkable results because deprotection of compound **18** has only been accomplished with $(NH_4)_2[Ce(NO_3)_6]$ (CAN)[9,26] but the hydrolysis of substrates similar to **20** has failed using $TiCl_4$ as the catalyst or HCl in THF.[25,27] We have found that $[PdCl_2(NCMe)_2]$ (1%, 50 °C, 1 h) does not deprotect **20**. However, neither $(MeO)_2CH(CH_2)_3NH_2$, or its BOC-protected derivative, nor $(MeO)_2CHCH_2CN$ were hydrolyzed in the presence of **1**, probably because they N-coordinate to Pd preventing the coordination of the ketal group.

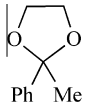
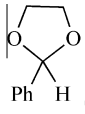
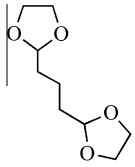
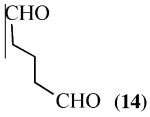
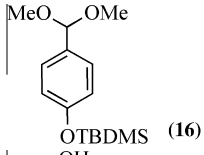
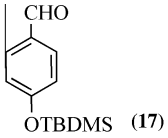
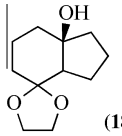
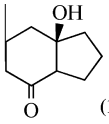
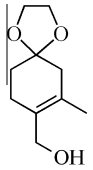
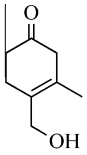
A large-scale deprotection of DDMA (40 mmol-scale) has been carried out obtaining 96% isolated yield of the desired aldehyde.

Complex **1** is stable during the hydrolysis reaction and can be easily recovered (95%) and reused. As complex **1** can also be obtained (and isolated in 94% yield) by reaction of $Pd(OAc)_2$ and 2,6-diacetylpyridinium perchlorate,[17] we have also used complex **1** as the catalyst for the deprotection of DDMA preparing it in situ by successive addition of equimolecular amounts of 2,6-diacetylpyridinium perchlorate and $Pd(OAc)_2$ to MeCN. We have proved that palladium acetate or the acetic acid by-product did not affect the catalytic hydrolysis of DDMA (Table 1). The ^{1}H NMR of CD_3CN solutions of reaction mixtures shows that the formation of the catalyst is quantitative and instantaneous.

Conclusions

In conclusion, we have developed a new efficient and mild methodology for the deprotection of cyclic and acyclic acetals

Table 3
Deprotection of selected acetals and ketals[a]

Entry	Substrate	Product	Time (min)	Temp (°C)	Yield[b] (%)
1	$Me_2C(OMe)_2$ (**3**)	$Me_2C(O)$ (**4**)	10	25	99
2	$MeCH(OMe)_2$ (**5**)	MeCHO (**6**)	1	50	99
3	$C_9H_{19}CH(OMe)_2$ (**7**)	$C_9H_{19}CHO$ (**8**)	5	50	98
4	 (**9**)	PhC(O)Me (**10**)	7	50	98
5	 (**11**)	PhCHO (**12**)	12	50	98
6	 (**13**)	 (**14**)	120	50	95
7	$THPO(CH_2)_2OH$ (**15**)	No reaction	960	25	–
8	 (**16**)	 (**17**)	10	25	99
9	 (**18**)	 (**19**)	10	50	96
10	 (**20**)	 (**21**)	5	50	98

[a] Using 1% mol of **1** as the catalyst.
[b] Yields determined by ^1H NMR.

and ketals using $[Pd(O^1,C^1,N^1\text{-L})(NCMe)]ClO_4$ as the catalyst. We achieve quickly, in very good yields, and under mild conditions the corresponding carbonyl compounds without side-reactions, even in the presence of other protecting groups such as THP or TBDMS and very acid sensitive alcohols. The hydrolysis without dehydration of alcohol **20** and the high yield of the dehydration of DDMA are unprecedented. Viewed as a whole, and having in mind its hydrolytic properties, the catalyst offers unique properties: it is easily prepared in high yield from commercial products, $Pd(OAc)_2$, 2,6-diacetylpyridine and $HClO_4$, fully recoverable, reusable, and stable in the solid state and in solution even in the presence of air and moisture.

Acknowledgments

We thank Ministerio de Educación y Ciencia (Spain), FEDER (Grant CTQ2011-24016) and Fundación Séneca (Grants 04539/GERM/06 and 03059/PI/05) for financial support and a Grant to F.J.-H.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.12.067.

References and notes

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21. *Large-scale hydrolysis of decanal dimethyl acetal catalyzed by complex* ***1***: To a solution of decanal dimethyl acetal (10 mL, 41.02 mmols) and water (2 mL) in acetonitrile (50 mL), compound **1** was added (168.1 mg, 0.41 mmols). The resulting orange solution was heated at 50 °C. After 20 min, the solution was concentrated (6 mL) and diethyl ether was added (15 mL) to precipitate an orange solid that was filtered off, washed with diethyl ether, and dried in vacuo. Yield: 161.3 mg, 0.39 mmols (95%). The filtrate was washed with saturated aqueous solution of $MgSO_4$ and the solvent was removed in vacuo to obtain decanal of 98% of purity. Yield: 6.20 g, 39.42 mmols, 96%.
22. *Typical procedure for the catalytic deprotection reaction*: An NMR tube was charged with decanal dimethyl acetal (48.3 L, 0.198 mmols), water (100 L), catalyst **1** (8.07 mg, 0.002 mmols), and acetonitrile-d_3 (500 L). The tube was shaken until complete dissolution. The sample was heated at 50 °C and NMR spectra were recorded every 5 min. Conversion was calculated integrating the aldehyde proton and referenced with the solvent residual peaks. More experimental details in the Supplementary material.
23. *Experimental procedure for the synthesis of compound* ***21***: An NMR tube was charged with compound **20** (24.80 mg, 0.135 mmols), water (100 L), catalyst **1** (0.53 mg, 0.0013 mmols) and acetonitrile-d_3 (500 L). The tube was shaken until complete dissolution. The sample was heated at 50 °C and NMR spectra was recorded after 5 min. Compound **21** was detected in 98% conversion. ^{1}H NMR (300 MHz, acetonitrile-d_3): 4.07 (s, 2H, –CH_2OH), 2.78 (br, 2H, H2), 2.48–2.37 (m, 4H, H6+H5), 1.69 (s, 3H, Me). ^{13}C{1H} NMR (75.45 MHz, acetonitrile-d_3) 212.9 (C1), 131.5 (C4), 128.3 (C3) 61.5 (CH_2OH), 46.0 (C2), 39.5 (C6), 28.0 (C5), 18.4 (Me). See Supplementary material for atom numbering of **21**. HRMS calc for $C_8H_{13}O_2$ $[M+H]^+$ m/z 141.0910, found m/z 141.0915.
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