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Arylmethyl esters as protecting groups for carboxylic, carbonic and carbamic acids: deprotection via homogeneous palladium-catalyzed hydrogenolysis

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Abstract

4-Quinolylmethyl (4-QUI) esters of carboxylic acids and 1-naphthylmethyl (1-NAP) esters of carbonic and carbamic acids are reduced by palladium-catalyzed hydrogenolysis by formate anion. The reaction conditions are compatible with the presence of a benzyl ester and of an alkene double bond.

Keywords: catalysis; palladium; palladium compounds; protecting groups; quinolines.

The benzyl group is one of the most popular protecting groups of carboxylic acids used in organic synthesis.[1,2] Its cleavage is realized by a simple heterogeneous (Pd/C)-catalyzed hydrogenolysis, but this method could be a serious drawback in synthesis if competitive hydrogenolysis (of other reductive functional groups) and of course hydrogenation (of unsaturated carbon–carbon bonds) are possible. Recently, Spencer et al. developed a new benzyl-type protecting group for carboxylic acids, i.e. the 2-naphthylmethyl (2-NAP) group.[3] 2-NAP esters are selectively cleaved in the presence of benzyl esters because of the higher binding affinity of the former to the metal surface. However, control of the reaction conditions is probably necessary to avoid a complete deprotection of a 2-NAP benzyl dissymmetric diester.

We have developed in the last few years the palladium-catalyzed nucleophilic substitution of 1-NAP acetate **1** (R=CH_3) and analogous substrates (R^1=H, CH_3; position 1 or 2; R=CH_3 or OCH_3, etc.) by sodium dimethylmalonate to give compounds of type **3** (Eq. 1, Nu=$CH(CO_2CH_3)_2$).[4–6]

We report in this communication our preliminary results on the palladium-catalyzed homogeneous cleavage by ammonium formate (Eq. 1, Nu=H) of 4-quinolylmethyl (4-QUI) esters **2** of carboxylic acids and of 1-NAP esters **1** of carbonic (R=OR′) and carbamic (R=N(R′)R″) acids.

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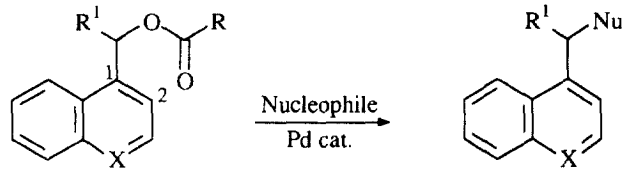
Table 1
Deprotection of 4-QUI esters **2**

Entry	Substrate	R	Product	Isolated Yield (%)
1	**2a**	$(CH_2)_{10}CH_3$	**5a**	85
2	**2b**	$(CH_2)_8CH{=}CH_2$	**5b**	95
3	**2c**	C_6H_5	**5c**	80
4	**2d**	$(CH_2)_5COCH_3$	**5d**	92
5	**2e**	$(CH_2)_2CO_2CH_2CH_3$	**5e**	88
6	**2f**	$(CH_2)_8CO_2CH_2C_6H_5$	**5f**	95

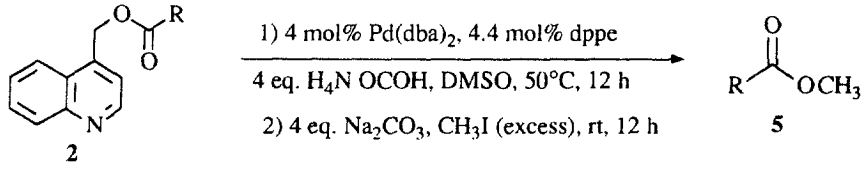


(1)

1: X = CH, R^1 = H
2: X = N, R^1 = H

3: X = CH, R^1 = H
4: X = N, R^1 = H

Preliminary experiments on 1-NAP **1** and 4-QUI **2** acetates (R=CH_3) showed a higher reactivity of the latter in the substitution by sodium dimethylmalonate. Similar results were obtained in the reduction by ammonium formate. This reaction was faster in DMSO solution, probably owing to a higher solubility of ammonium formate in this solvent. We thus adopted the reaction conditions depicted in Eq. 2 for the study of the deprotection reaction. Esters **2** were prepared in good yields by standard esterification (RCOCl, Et_3N, catalytic DMAP in Et_2O) of 4-quinolylmethanol. The produced carboxylates were transformed into their methyl esters **5** to facilitate isolation, purification and analysis of the product. Results are collected in Table 1.



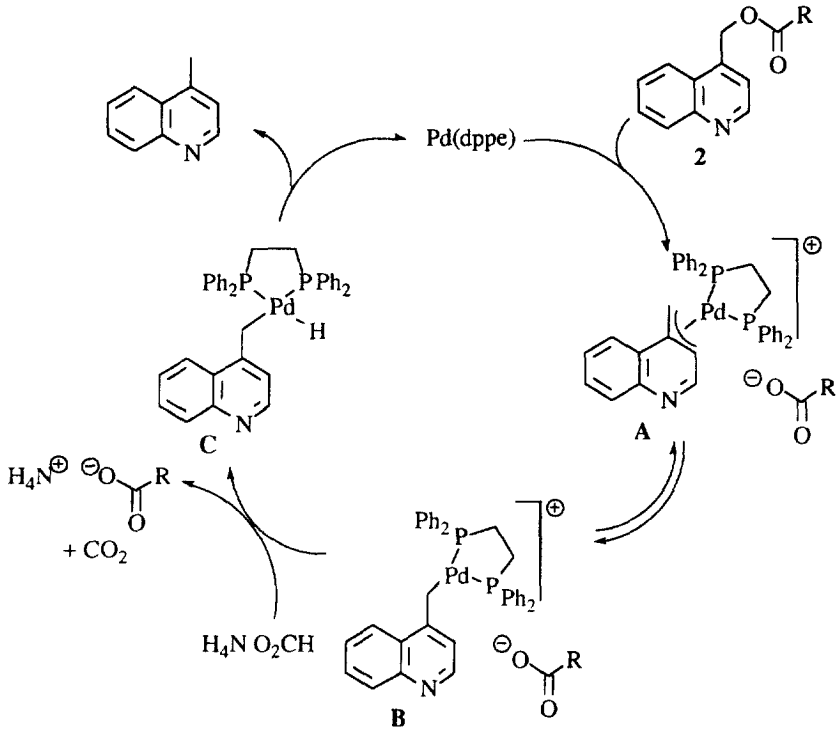
(2)

$Pd(dba)_2$ = bis(dibenzylideneacetone)palladium(0); dppe = 1,2-bis(diphenylphosphino)ethane

The deprotection reaction was accomplished in good yields (80–95%). The cleavage of the 4-QUI group did not affect several reductive substituents or functional groups such as carbon–carbon double bond (entry 2), ketone (entry 4), and ethyl and benzyl esters (entry 5 and 6). In the case of the substrate **2f**, we observed a total selectivity of the reaction and only the 4-QUI group was removed and the benzyl one left intact. So we obtained here a similar result to Spencer,[3] but for a different reason. Moreover, since the oxidative addition (see below) is not observed on a benzyl substrate,[4] control of the reaction conditions is not required to prevent the cleavage of the benzyl group.

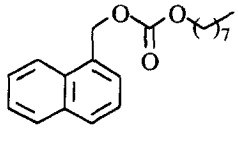
The mechanism of the reaction is probably as depicted in Scheme 1 by analogy with the 'allyl capture' by a nucleophile.[7] First, oxidative addition of the substrate **2** to the dppe-palladium(0) complex gave the cationic palladium(II) intermediate **A**. We had already observed that this step requires a diphosphine

ligand,[5] but in the case of formate as nucleophile reacting on π-allyl complexes, two monophosphine ligands are needed because one is lost to allow the coordination of the hydride.[8] Here, a dynamic equilibrium between the η^3-complex **A** and the η^1-complex **B** may be responsible for the creation of a vacant site on palladium. Reaction of ammonium formate would give complex **C** with liberation of carbon dioxide and ammonium carboxylate. Finally, reductive elimination led to 4-methylquinoline and closed the catalytic cycle.



Scheme 1.

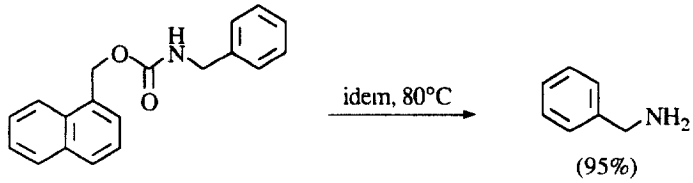
Next, we tried to extend this methodology to the protection of alcohols and amines with an analogue of the Alloc (allyloxycarbonyl) group,[7] but all attempts to prepare carbonates (R=OR′) and carbamates (R=N(R′)R″) of type **2** failed in our hands, probably because of the presence of the pyridyl nitrogen. So we decided to study the deprotection reaction starting from compounds of type **1**. Although the synthesis of such substrates is presently unsatisfactory (in situ formation of the chloroformate of 4-quinolylmethanol by the phosgene route), we were pleased to observe a clean reaction in the two following examples producing 1-octanol and benzylamine (Eqs. 3 and 4, respectively). Carbamate **1b** was less reactive and heating to 80°C was necessary.



1a

2 mol% $Pd(dba)_2$, 2.5 mol% dppe
4 eq. H_4N OCOH, DMSO, 50°C, 12 h

$n\text{-}C_8H_{17}OH$ (93%) (3)



1b (4)

In summary, we have developed a new type of protecting groups for carboxylic acids, alcohols and amines. The deprotection reaction is based on the palladium(0)-catalyzed nucleophilic substitution of arylmethylesters we had previously described. This methodology is compatible with reducible functional groups (ketone and ester), with carbon–carbon double bonds, and with the benzyl protecting group.

Work is actually in progress in this laboratory to study the scope of this reaction, in particular the tolerance for other functional groups and the application to the case of α-amino acids for peptide synthesis.

The deprotection of ester **2a** is representative: to a DMSO (1 mL) solution of $Pd(dba)_2$ (11.5 mg, 0.02 mmol) and dppe (8.8 mg, 0.022 mmol) in a Schlenk tube was added a solution of **2a** (170.7 mg, 0.5 mmol) in DMSO (1 mL) under an argon atmosphere. After stirring for 0.25 h at room temperature, this solution was added to a suspension of ammonium formate (126 mg, 2 mmol) in 2 mL of DMSO. The reaction mixture was stirred at 50°C for 12 h, cooled to room temperature, then 1 mL of 2 M Na_2CO_3 and 1 mL of iodomethane were added. After stirring for 12 h, the reaction mixture was diluted with diethyl ether (10 mL) and washed with 2×20 mL water and with 2×20 mL 0.5% aqueous HCl. The aqueous phases were extracted with 20 mL of diethyl ether and the combined ethereal phases were dried ($MgSO_4$), and concentrated. The crude product was purified by flash chromatography (silica, heptane/ethyl acetate 8/2) to give product **5a** (91 mg, 0.43 mmol, 85% yield).

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