Facile Removal Strategy for Allyl and Allyloxycarbonyl Protecting Groups Using Solid-Supported Barbituric Acid under Palladium Catalysis

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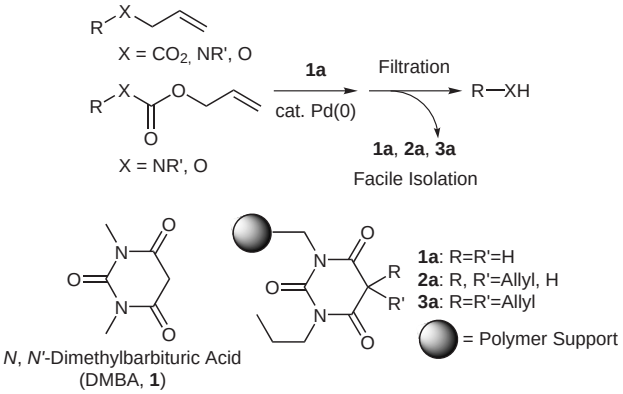
Abstract: Solid-supported barbituric acid can be used for the palladium(0)-catalyzed deprotection of allyl amines, carbamates, carbonates, esters and ethers. This solid-supported reagent facilitates isolation and purification of the deprotected compounds, especially acids and amines.

Key words: allyl and allyloxycarbonyl groups, palladium(0)-catalyzed deprotection, solid-supported barbituric acid, facile isolation, highly polar compounds

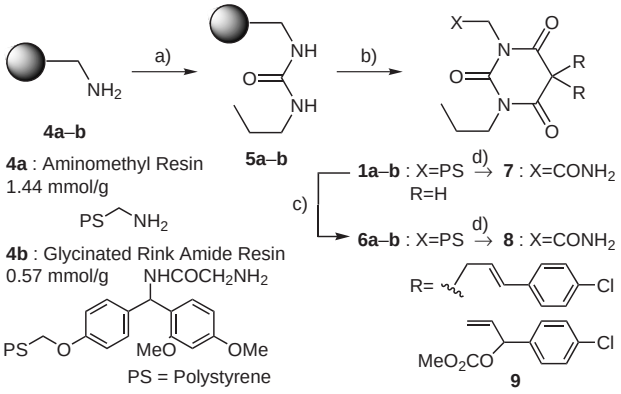
Protection and deprotection strategies are unavoidable and ubiquitous in modern organic synthesis.[1] The latter process frequently produces highly polar deprotected compounds such as acids and amines difficult to isolate. It is desirable for their isolation and purification to avoid aqueous work up and column chromatography. On the other hand, solid-supported reagents have been often employed for solution-phase organic synthesis to save labor in isolation and purification of the products and facilitate parallel synthesis in solution-phase.[2] These reagents are the most suitable for the deprotection strategy because the deprotected products can be isolated by filtration and subsequent evaporation without aqueous work up. We recently reported the palladium(0)-catalyzed mild and selective deprotection of allyl ethers employing *N*,*N*′-dimethylbarbituric acid (DMBA, **1**),[3] which can also deprotect other allyl derivatives such as allyl amines,[4a] carbamates[4b] and esters.[4c] Herein we describe the facile deprotection strategy for allyl derivatives using solid-supported barbituric acid **1a** (Scheme 1).

Initially, we carried out the synthesis of the solid-supported barbituric acid **1a**,**b** based on condensation of malonic acid with polymer-supported urea **5a**,**b** (Scheme 2).[5] The urea **5a**,**b** was prepared by treatment of aminomethyl resin **4a** or glycinated Rink amide resin **4b** with *n*-propyl isocyanate. Conventional methods for the synthesis of barbituric acids in solution-phase using malonic acid and acetic anhydride[6] or diethyl malonate and sodium ethoxide[7] were found to be unsuitable for the polymer-supported urea **5a**,**b**.[8] Fushiya reported an unconventional method,[9] in which *N*,*N*′-dicyclohexylcarbodiimide (DCC) condenses an urea composed of only acyclic primary amines with malonic acid selectively though DCC itself can react with



Scheme 1 Facile deprotection strategy for allyl derivatives using solid-supported barbituric acid **1a**.

malonic acid to give *N*,*N*′-dicyclohexylbarbituric acid.[10] To our surprise, this method was applicable to the less reactive polymer-supported urea **5a**,**b** and provided the barbituric acid **1a**,**b** in good conversion even when a little excess of reagents were used.[11] Loading of **1a** was determined by elemental analysis of chlorine after derivatization to **6a** with 1-(4′-chlorophenyl)-prop-2-enyl methyl carbonate **9**[12] under palladium catalysis. The formation of the barbituric acid **1a** and its derivative **6a** was confirmed by spectra data[13] of the cleaved residue **7** and **8** from the corresponding Rink amide resin **1b** and **6b** respectively.



Scheme 2 Synthesis of solid-supported barbituric acid **1a**,**b**
Reactions and conditions: a) *n*-PrNCO (4 equiv), CH_2Cl_2, 30 °C, 24 h; b) 0.45 M Malonic Acid (3 equiv for **5a**, 6 equiv for **5b**), 0.90 M DCC (6 equiv for **5a**, 12 equiv for **5b**) in THF, 0 °C to r.t., 4 h, loading: 1.15 mmol/g for **1a**; c) **9** (10 equiv), 25 mol% $Pd(PPh_3)_4$, THF, r.t., 12 h, loading: 0.85 mmol/g for **4a**; d) 95% aq TFA, r.t., 2 h, 84% yield of **7** for **1b**, 70% yield of **8** for **6b**.

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Next, the obtained solid-supported barbituric acid **1a** was employed for the deprotection of alkyl allyl ether **10a**–**e** to compare its reactivity with the one of soluble DMBA (**1**) (Table 1, entry 1–5). The reaction was carried out in THF containing **10a**–**e** (1 equiv), $Pd(PPh_3)_4$ (0.05 equiv per allyl group) and **1a** (1.2 equiv per allyl group) at 90 °C for 24 hours to give the parent alcohol **12a**–**e** in excellent yield as well as **1**. Allyl aryl ether **10f**–**k** containing both electron-withdrawing and electron-donating groups and allyl carbonate **11a**–**e** could also be deprotected (Table 1, entry 6–16). Various functional groups were stable to the reaction conditions and thioether moiety in **10e** and **11e** did not poison the catalyst.

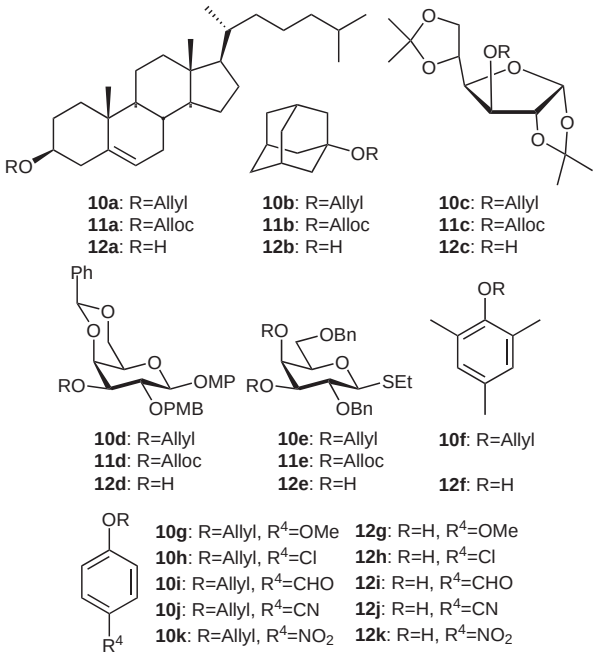
The key feature of this method is its simple work up for the isolation of the deallylated products. Removal of an excess of **1a** and allylated side products **2a**,**3a** on solid-support formed in the deallylation could be achieved only by filtration (Scheme 1). The products obtained after evaporation were pure enough to be used for the next reaction such as acylation without further purification. In this connection, the yields in Table 1, Table 2 and Table 3 refer to the further purified products by column chromatography on silica gel to remove a catalytic amount of any palladium compounds.

Finally, this protocol was applied to the deprotection of allyl esters, carbamates and amines, which produces the corresponding acids and amines including highly polar compounds difficult to isolate and purify (Table 2, Table 3).

Deprotection of allyl ester **13a**–**c** was complete within 1 hour at room temperature to give the corresponding aromatic and aliphatic acid **18a**–**c** in high yields (Table 2, entry 1–3). Allyl ester in **13c**[14] could be selectively removed without affecting allyl amine moiety (Table 2, entry 3). Removal of monomethyl-substituted allyl ester, i.e. methallyl ester in **14a** and crotyl ester in **15a**, took longer reaction time to complete (Table 2, entry 4, 5). More hindered cinnamyl ester **16a** and prenyl ester **17a** could also be deprotected on heating at 60 °C (Table 2, Entry 6, 7).

Although allyl carbamate **19a**–**f** disappeared within 1 hour at room temperature under the deprotection conditions to give the desired amine **22a**–**f**, the deprotection of allyl carbamate **19d**–**f** was accompanied by production of allyl amine **20d**–**f** (Table 3, entry 1–3 vs 4–6). The side products would probably result from nucleophilic attack of secondary amine **22d**–**f** formed in situ to the (π-allyl)palladium complex to compete with **1a** and could be converted into the deallylated amine **22d**–**f** on heating at 40 °C (Table 3, entry 4–6) as well as the deprotection of allyl amine **20a**–**f** and **21a**,**b** (Table 3, entry 7–14). It was necessary for complete recovery of secondary aliphatic amine **22e** to wash the resin with 2 M solution of ammonia in methanol because the solid-supported barbituric acid **1a** was acidic enough to form its salt with **22e** (Table 3, entry 5, 11). It is noteworthy that water-soluble amino acid **22f** was easily purified by washing the resin with ethyl acetate to remove any impurities followed by elution with methanol (Table 3, entry 6, 12).

Table 1 Palladium(0)-Catalyzed Deprotection of Allyl Ether **10a**–**k** and Allyl Carbonate **11a**–**e** and Using **1a**



10a: R=Allyl **10b**: R=Allyl **10c**: R=Allyl
11a: R=Alloc **11b**: R=Alloc **11c**: R=Alloc
12a: R=H **12b**: R=H **12c**: R=H

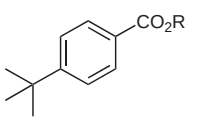
10d: R=Allyl **10e**: R=Allyl **10f**: R=Allyl
11d: R=Alloc **11e**: R=Alloc
12d: R=H **12e**: R=H **12f**: R=H

10g: R=Allyl, R^4=OMe **12g**: R=H, R^4=OMe
10h: R=Allyl, R^4=Cl **12h**: R=H, R^4=Cl
10i: R=Allyl, R^4=CHO **12i**: R=H, R^4=CHO
10j: R=Allyl, R^4=CN **12j**: R=H, R^4=CN
10k: R=Allyl, R^4=NO_2 **12k**: R=H, R^4=NO_2

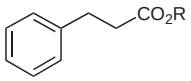
Entry	Substrate	Temp (°C)	Product	Yield (%)
1	**10a**	90	**12a**	86
2	**10b**	90	**12b**	86
3	**10c**	90	**12c**	95
4	**10d**	90	**12d**	100
5	**10e**	90	**12e**	80
6	**10f**	40	**12f**	80
7	**10g**	70	**12g**	100
8	**10h**	60	**12h**	86
9	**10i**	r.t.	**12i**	88
10	**10j**	r.t.	**12j**	92
11	**10k**	r.t.	**12k**	100
12	**11a**	r.t.	**12a**	98
13	**11b**	r.t.	**12b**	87
14	**11c**	r.t.	**12c**	100
15	**11d**	r.t.	**12d**	87
16	**11e**	r.t.	**12e**	81

Thus, we have achieved the simple synthesis of solid-supported barbituric acid from commercially available aminomethyl polystyrene resin and its utilization for the deprotection of allyl derivatives. We proved that it is as reactive to the deallylation as *N*,*N*′-dimethylbarbituric acid and saves labor in isolation and purification of

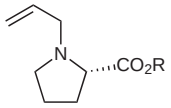
Table 2 Palladium(0)-Catalyzed Deprotection of Allyl Ester **13a–c** and Substituted Allyl Ester **14a–17a** Using **1a**



13a: R= $CH_2CH=CH_2$ (Allyl)
14a: R= $CH_2CMe=CH_2$ (Methallyl)
15a: R= $CH_2CH=CHMe$ (Crotyl)
16a: R= $CH_2CH=CHPh$ (Cinnamyl)
17a: R= $CH_2CH=CMe_2$ (Prenyl)
18a: R= H



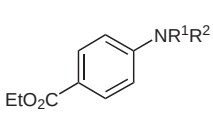
13b: R=Allyl
18b: R=H

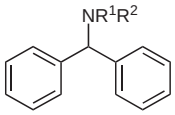


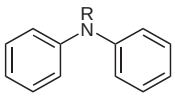
13c: R=Allyl
18c: R=H

Entry	Substrate	Temp (°C)	Product	Yield (%)
1	**13a**	r.t.	**18a**	90
2	**13b**	r.t.	**18b**	100
3	**13c**	r.t.	**18c**	80
4	**14a**	r.t.	**18a**	100
5	**15a**	r.t.	**18a**	100
6	**16a**	60	**18a**	100
7	**17a**	60	**18a**	92

Table 3 Palladium(0)-Catalyzed Deprotection of Allyl Carbamate **19a–f** and Allyl Amine **20a–f** and **21a–b** Using **1**a



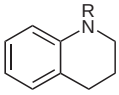




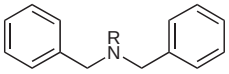
19a: R^1, R^2=Alloc, H
20a: R^1, R^2=Allyl, H
21a: R^1=R^2=Allyl
22a: R^1=R^2=H

19b: R^1, R^2=Alloc, H
20b: R^1, R^2=Allyl, H
21b: R^1=R^2=Allyl
22b: R^1=R^2=H

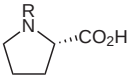
19c: R=Alloc
20c: R=Allyl
22c: R=H



19d: R=Alloc
20d: R=Allyl
22d: R=H



19e: R=Alloc
20e: R=Allyl
22e: R=H



19f : R=Alloc
20f : R=Allyl
22f : R=H

Entry	Substrate	Temp (°C)	Product	Yield (%)
1	**19a**	r.t.	**22a**	94
2	**19b**	r.t.	**22b**	88
3	**19c**	r.t.	**22c**	100
4	**19d**	r.t.–40	**22d**	92
5	**19e**	r.t.–40	**22e**	91
6	**19f**	r.t.–40	**22f**	93
7	**20a**	40	**22a**	81
8	**20b**	40	**22b**	85
9	**20c**	40	**22c**	91
10	**20d**	40	**22d**	86
11	**20e**	40	**22e**	93
12	**20f**	40	**22f**	86
13	**21a**	40	**22a**	91
14	**21b**	40	**22b**	73

the deallylated compounds. Further studies on organic synthesis using solid-supported barbituric acid derivatives are underway in our laboratory.

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(5) A mixture of **4a** (5.01 g, 7.21 mmol), dry CH_2Cl_2 (30 mL) and propyl isocyanate (2.7 mL, 28.8 mmol) was agitated at 30 °C for 24 h on an orbit shaker. The resin was filtered and washed with DMF (4 × 40 mL), $CHCl_3$ (4 × 40 mL), MeOH (4 × 40 mL) and Et_2O (1 × 40 mL) to give **5a**. A solution of DCC (8.91 g, 43.2 mmol) in dry THF (12 mL) was added dropwise to a stirred mixture of **5a**, malonic acid (2.25 g, 21.6 mmol) and dry THF (36 mL) at 0 °C under Ar. When addition was complete, the mixture was stirred for additional 3 h at r.t. Then, the mixture was diluted with MeOH (100 mL) and heated at 60 °C to dissolve by-products. The resin was collected by filtration and washed with hot DMF (4 × 40 mL), $CHCl_3$ (4 × 40 mL), MeOH (4 × 40 mL) and Et_2O (1 × 40 mL) to give **1a** (6.24 g, quant.).

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(13) Spectra data of **7**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.70 (br s, 2 H), 4.57 (s, 2 H), 3.84 (t, 2 H, *J* = 7.7 Hz), 3.75 (s, 2 H), 1.63 (tq, 2 H, *J* = 7.7, 7.4 Hz), 0.94 (t, 3 H, *J* = 7.4 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 168.2, 164.8, 164.5, 151.5, 43.7, 43.2, 39.4, 21.1, 11.0. IR(neat): ν_{max} = 3348, 3199, 2966, 2935, 1659, 1410, 1362, 1289, 1204, 1177, 1140, 1086, 936, 758 cm^{-1}. MS (EI): *m/z* (relative intensity) = 227 (5.6) $[M]^+$, 210 (6.5), 184 (96), 169 (37), 143 (77), 98 (81), 56 (100). HRMS (EI) calcd for $C_9H_{13}N_3O_4$ $[M]^+$ 227.0906. Found: 227.0910. Spectra data of **8**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.27–7.23 (m, 8 H), 6.41 (d, 2 H, *J* = 15.7 Hz), 6.11 (dt, 2 H, *J* = 15.7, 7.7 Hz), 5.93–5.61 (m, 2 H), 4.55 (s, 2 H), 3.75 (t, 2 H, *J* = 7.7 Hz), 3.00–2.87 (m, 4 H), 1.41 (tq, 2 H, *J* = 7.7, 7.4 Hz), 0.73 (t, 3 H, *J* = 7.4 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 171.0, 170.5, 168.3, 150.4, 135.1, 134.3, 133.5, 128.8, 127.7, 122.7, 57.2, 43.6, 43.4, 42.5, 21.1, 10.9. IR (neat): ν_{max} = 3466, 3363, 2966, 2935, 1675, 1490, 1424, 1405, 1283, 1092, 971, 756 cm^{-1}. MS (EI): *m/z* (relative intensity) = 527 (32) $[M]^+$, 510 (42), 385 (42), 376 (36), 359 (87), 331 (52), 287 (26), 246 (72), 240 (72), 223 (53), 151 (100), 116 (53), 115 (52). HRMS (EI) calcd for $C_{27}H_{27}Cl_2N_3O_4$ $[M]^+$ 527.1379. Found: 527.1401.

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