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Chemoselective deprotection of *N*-allylic amines using DDQ

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ABSTRACT

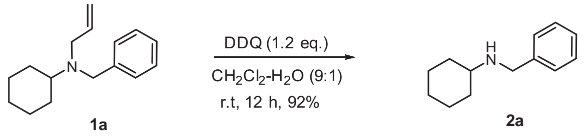
A highly chemoselective and simple method for the deprotection of *N*-allylic amines using DDQ has been developed. The use of DDQ in dichloromethane–water provides a mild and efficient one-step deallylation of a wide variety of orthogonally protected tertiary amine derivatives.

Protecting groups often play a crucial role in many complex synthetic strategies.[1] The choice of protecting groups is one of the decisive factors in the successful realization of a complex demanding synthetic project. The allyl moiety is a protecting group that permits orthogonal protection strategies with a wide range of protecting groups and thus finds increasing application in the synthesis of complex natural products.[2] The transition-metal-catalyzed methods[3] are the most widely and commonly used methods for allyl group deprotection. But selectivity can still be a problem, since *O*-allyl derivatives are cleaved faster than *N*-allyl derivatives in most cases. Reductive metals are not selective either.[4] An important drawback of the π-allyl–palladium methodology is the requirement of stoichiometric amounts of a nucleophilic compound, which acts as the allyl group scavenger. Selectivity is also a problem with chloroformate-mediated processes,[5] which are capable of cleaving different types of N–C bonds. New procedures involving Grubb's-type catalysts have also emerged in the last few years,[6] yet selectivity remains the problem with these methods. In view of this we became interested in the development of an alternative N-deallylation method that can smoothly provide free amines.

The high oxidation potential (E_0) of DDQ has resulted in the extensive use of this compound as a dehydrogenating agent in organic synthesis.[7] Even though *O*-allyl ethers are oxidatively cleaved in the presence of DDQ,[8] this reaction has not been developed further into a method of synthetic interest for the cleavage of *N*-allylic bond.[9] We now report that the *N*-allylic group can be cleaved oxidatively from a wide variety of orthogonally protected tertiary amine derivatives using DDQ as a dehydrogenating reagent.

Our studies began with the reaction of a series of allyl substrates on aliphatic, alicyclic, and benzylic amines. We carried out reaction initially by choosing compound **1a** as a model substrate (Scheme 1). DDQ was added to a solution of compound **1a** in dichloromethane–water (9:1) (Table 1, entry 1) and the resulting dark red solution stirred at room temperature overnight, during which time a pale yellow hydroquinone derivative was precipitated. The reaction proceeded smoothly, however it was found that correct work-up of the reaction was crucial. The optimized procedure involved extraction with several portions of CH_2Cl_2 and washing with saturated sodium bicarbonate solution, followed by loading the crude residue (after removal of the volatiles) directly onto a short basic alumina flash column, eluting with hexane–DCM to afford 92% yield of *N*-deallylated secondary amine **2a** (Table 1, entry 1).

The reaction was studied in a variety of solvents and the results are summarized in Table 1. It was observed that the presence of water and its amount along with an organic solvent plays an important role in the reaction. Decrease of the water ratio somewhat lowered the yield and increased the reaction time (Table 1, entry 2). In the absence of water, most of the amine **1a** was



Scheme 1.

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Table 1
Oxidative cleavage of compound **1a** with DDQ in various solvents at room temperature

Entry	Solvent system	DDQ (equiv)	Time (h)	Yield (%)
1	CH_2Cl_2–H_2O (9:1)	1.2	12	92
2	CH_2Cl_2–H_2O (9.7:0.3)	1.2	22	70
3	CH_2Cl_2	1.2	48	Trace
4	Hexane–H_2O (9:1)	1.2	24	0
5	Dioxane–H_2O (9:1)	1.2	10	Complex mixture
6	THF–H_2O (9:1)	1.2	12	Complex mixture
7	Toluene–H_2O (9:1)	1.2	36	45
8	$CHCl_3$–H_2O (9:1)	1.2	24	60
9	EtOAc–H_2O (9:1)	1.2	12	Complex mixture
10	MeOH–H_2O (9:1)	1.2	6	Complex mixture
11	CCl_4–H_2O (9:1)	1.2	24	20
12	MeCN–H_2O (9:1)	1.2	14	85

Table 2
Oxidative cleavage of compound **1a** with DDQ under various reaction conditions

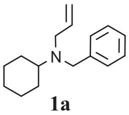
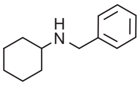
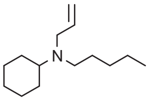
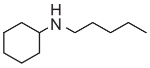
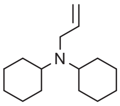
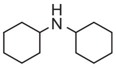
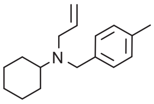
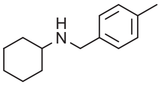
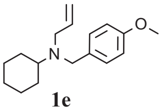
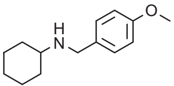
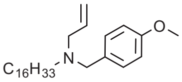
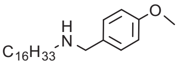
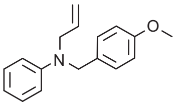
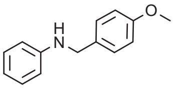
Entry	Reaction conditions	Time (h)	Yield (%)
1	0.8 equiv DDQ, CH_2Cl_2–H_2O (9:1) rt	20	45
2	1 equiv DDQ, CH_2Cl_2–H_2O (9:1) rt	18	80
3	1.2 equiv DDQ, CH_2Cl_2–H_2O (9:1) rt	12	92
4	1.2 equiv DDQ, CH_2Cl_2–H_2O (9:1) 0 °C	24	35
5	1.2 equiv DDQ, MeCN–H_2O (9:1) 70 °C	6	78

recovered (entry 3). No deallylation product was obtained when the reaction was carried out in hexane–water (entry 4). The reactions were performed in other solvents such as THF, toluene, $CHCl_3$, MeOH, CCl_4, MeCN, EtOAc, and dioxane (Table 1, entries 5–12). However, in most of the cases, a complex mixture was obtained (entries 5, 6, 9 and 10). The rate of the reaction became slower when $CHCl_3$, CCl_4, or toluene were used as the solvent (entries 7, 8, and 11). Interestingly, the yield of reaction in MeCN was comparable to that in CH_2Cl_2 (Table 1, entry 12). The use of 1.2 equiv of DDQ in a solvent mixture of CH_2Cl_2–H_2O (9:1) has an additional merit. The weakly acidic $DDQH_2$ (2,3-dichloro-5,6-dicyanohydroquinone) that precipitated during the reaction is almost insoluble in both CH_2Cl_2 and H_2O, so the reaction medium was constantly kept almost neutral as long as the reaction proceeded (Table 1, entry 1).[8–10]

This is sometimes very important in the case of substrates bearing acid-sensitive functional and protecting groups. Based on the above investigations; CH_2Cl_2 was preferred as the reaction media to perform the deallylation reaction.

In principle, a stoichiometric amount of DDQ should be sufficient for the oxidative cleavage of *N*-allylic amines, however the reaction progressed slowly, probably because of competitive aqueous decomposition of DDQ.[11] To circumvent this problem, the DDQ was added in small portions every 20 min (3–4 portions) and this slow addition of DDQ resulted in high yield of products. Variation in the number of equivalents of DDQ was then examined (Table 2). Low yield of the product was obtained and mostly starting material

Table 3
Chemoselective deprotection of *N*-allylic amines[12]

S. No.	Substrate	Product	Time (h)	Yield[a] (%)
1	 **1a**	 **2a**[14]	12	92
2	 **1b**	 **2b**	18	85
3	 **1c**	 **2c**	18	90
4	 **1d**	 **2d**	12	80
5	 **1e**	 **2e**[14]	6	55
6	 **1f**	 **2f**[14]	7	50
7	 **1g**	 **2g**	3	35

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