Pergamon

Tetrahedron Letters, Vol. 36, No. 8, pp. 1267-1270, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)00003-8

Selective Deprotection of Allyl Amines using Palladium

Sandrine Lemaire-Audoire, Monique Savignac, and Jean Pierre Genêt*

Ecole Nationale Supérieure de Chimie de Paris Laboratoire de Synthèse Organique associé au CNRS.
11, rue Pierre et Marie Curie - 75231 Paris - France

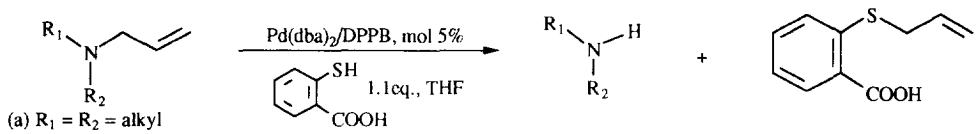
Jean-Marie Bernard

Rhône Poulenc - Centre de Recherche des Carrières - 85 rue des Frères Perret - 69192 Lyon - France

Key Words : Allylamines, desallylation, sequential deprotection, π-allyl palladium methodology.

Abstract : Mono and diallylamines can be cleaved using Pd(0) catalyst and 2-mercaptobenzoic acid as nucleophile.This methodology has been successfully used for the sequential deprotection of diallylamines. The yields of desallylation are good to quantitative.

We have previously reported that allyl carbamates and carbonates are cleaved under aqueous[1] and anhydrous[2] conditions using Pd(0) catalysts and nitrogen or sulfur nucleophiles as allyl scavengers. These new and efficient systems are of easy practical use and totally avoid side reactions.
Next, we investigated the deprotection of allylamines. In the litterature, the methods for desallylation of allylamines involve, in a first step, isomerization[3] of the double bond in the presence of transition metals, followed by cleavage of the enamine. Recently, Guibé[4] proposed a new deprotective procedure for the desallylation of mono and diallylamines in the presence of Pd(0) catalyst and N,N-dimethyl barbituric acid as carbon nucleophile. We also found that 2-mercaptobenzoic acid is as an efficient allyl trapping agent for the deprotection of allylamines[5] derived from primary and secondary amines, under anhydrous conditions.

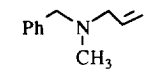
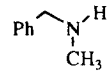
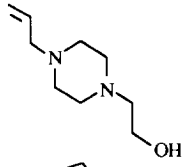
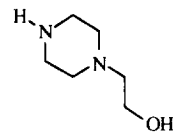
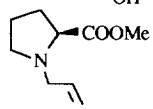
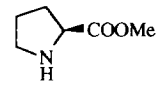
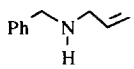
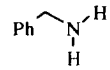
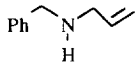
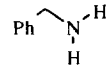
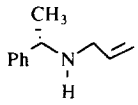
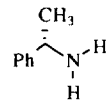


(a) $R_1 = R_2 =$ alkyl
(b) R_1 = alkyl, $R_2 = H$

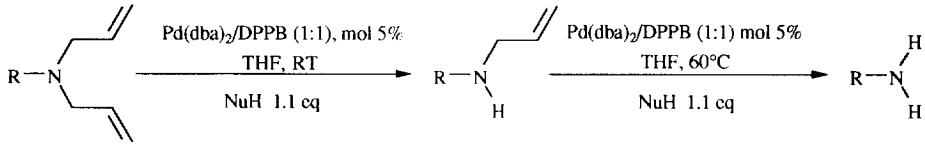
As shown in Table 1, tertiary allylamines are cleaved in the presence of the preformed catalyst Pd(dba)2/DPPB (1:1) and 1.1 equivalent of 2-mercaptobenzoic acid, at room temperature (entries 1 to 3). The deprotected secondary amines are recovered in quantitative yield, after 15 to 30 minutes[6]. However, when N-allyl benzylamine was treated under the same procedure (entry 4), no deprotection took place, even after 3 days, suggesting that secondary allylamines would require stronger conditions to be cleaved. The reaction was thus performed at 60°C, allowing the removal of the allyl group in 100% yield, within 30 minutes (entry 5).These conditions were also applied to N-allyl-α-methyl benzylamine which was quantitatively desallylated at 60°C, without affecting the chirality of the substrate (entry 6).

Furthermore, the 2-thio allyl benzoic acid by product formed in this desallylation procedure can be easily eliminated by simple acido-basic treatment.

Table 1 : Desallylation of tertiary and secondary allylamines using $Pd(dba)_2$/DPPB (1:1) catalyst

Entry	Substrates	Temp. (°C)	Time	Products	Yield (%)
1		20	25 min		100
2		20	30 min		100
3			15 min		100
4		20	3 d		0
5		60	30 min		100
6		60	15 min		100

Taking advantage of the different reactivity of secondary and tertiary allylamines towards our desallylation system, we anticipated that it would be possible to remove selectively one allyl group from diallylamines, at room temperature to give the corresponding monoallylamines. In a second step, the other allyl moiety would be cleaved at higher temperature.

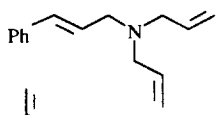
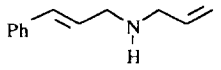
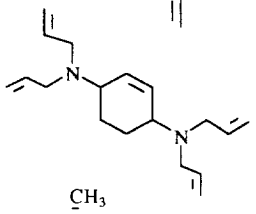
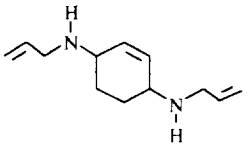
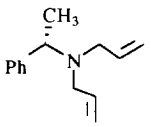
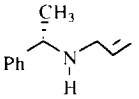
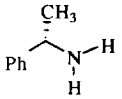
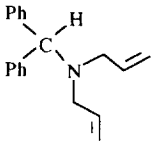
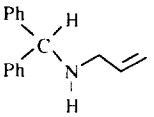
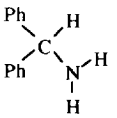
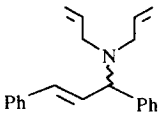
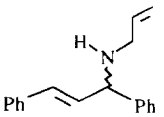
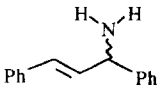


Indeed, we were pleased to find that, as shown in table 2, 3-N,N-diallylamino-1-phenyl propene was selectively monodesallylated in the presence of 1.1 equivalent of sulfur nucleophile, at 20°C, in 79% yield (entry 1). The same selective monodeprotection was achieved on a disubstituted cyclohexene derivative (entry 2), giving bis-1,4-N-allylamino cyclohex-2-ene in quantitative yield within 90 minutes.

Then, the second allyl group can be cleaved using a higher temperature. In this way, the monoallylamine coming from selective monodeprotection of N,N-diallyl-α-methylbenzylamine (entry 3) was further desallylated using 5% of catalyst and 1.1 equivalent of 2-mercaptobenzoic acid at 60°C, to recover the parent amine in quantitative yield.

The same two-step desallylation was performed on N,N-diallylaminodiphenyl methane (entry 4) and 1,3-diphenyl-3-N,N-diallylaminopropene (entry 5) allowing us to isolate the monodeprotected products in good yields (82 and 70% respectively); the latter were fully and quantitatively deprotected in a second step using a higher temperature. These examples illustrate the versatility of our desallylation conditions which permit the sequential removal of allyl groups from diallylamines.

Table 2 : Selective deprotection of diallylamines using Pd(0) catalyst and 2-mercaptobenzoïc acid as nucleophile

Entry	Substrate	Product	Time (min)	Yield[a] (%)	Product	Time (min)	Yield (%)
1			60	79			
2			90	98[b]			
3			30	89		15	100
4			120	82		20	100
5			30	70		120	61

a) isolated yield; b) 2-mercaptobenzoïc acid 2.1 eq.

Lastly, as we expected, it was possible to recover primary amines from direct didesallylation of diallylamines, using 2.1 equivalent of 2-mercaptobenzoïc acid at 60°C (Table 3). In this way, diallylamines derived from L-phenylalanine ethyl ester (entry 1) and 4-methyl cyclohexylamine (entry 2) were fully deprotected in excellent yields, within 15 to 30 minutes.

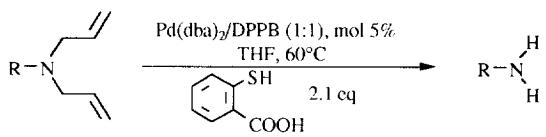
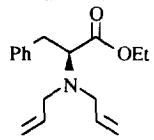
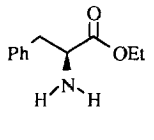
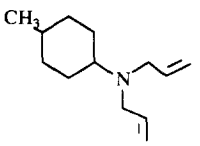
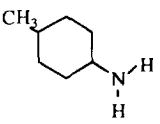


Table 3 : Complete desallylation of diallylamines

Entry	Substrate	Product	Time (min)	Yield[a] (%)
1			15	100
2			30	97

a) crude product

In summary, this desallylation procedure using $Pd(dba)_2$/DPPB catalyst and 2-mercaptobenzoic acid, a crystalline and inexpensive allyl trapping agent, is easy to perform. The by-product and the catalyst can be eliminated by acido-basic treatment, giving clean crude products that can be used without further purification. This system proved to be very efficient for the desallylation of secondary and tertiary allylamines. Moreover, the sequential deprotection of diallylamines can be applied to the differentiation of the two N-H groups of primary amines which may be independently functionalized. To our best knowledge, this is the first example of selective monodeprotection of diallylamines using π-allyl palladium methodology. We are currently investigating synthetic applications of this method.

Acknowledgements. S.Lemaire-Audoire thanks the Ministry of Research and Higher Education for a grant (1994-1996).

References and notes :

1 a) Genêt, J.P.; Blart, E.; Savignac, M. and Paris, J.M. *Tetrahedron Lett.* **1993**, *34*, 4189-4192; b) Genêt, J.P.; Blart, E.; Savignac, M.; Lemeune, S.; Lemaire-Audoire, S.; Paris, J.M. and Bernard, J.M. *Tetrahedron* **1994**, *50*, 497-503..

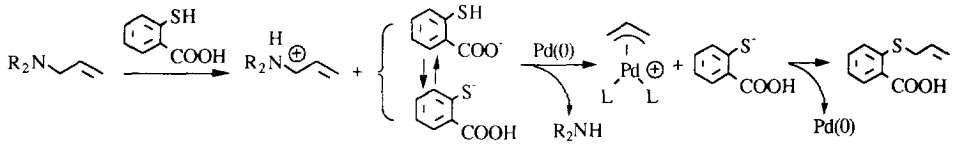
2 Genêt, J.P.; Blart, E.; Savignac, M.; Lemeune, S.; Lemaire-Audoire, S. and Bernard, J.M. *Synlett*, 1993, 680-682.

3 a) Moreau, B.; Lavielle, S.and Marquet, A. *Tetrahedron Lett.* **1977**, *30*, 2591-2594; b) Laguzza, C.B. and Ganem, B. *Tetrahedron Lett.* **1981**, *22*, 1483-1486; c) Sundberg, R.J.; Hamilton, C.S. and Laurino, J.P. *J. Org. Chem.* **1988**, *53*, 976-983;d) Ziegler, F.E.; Brown, E.G. and Sobalov, S.B. *J. Org. Chem.* **1990**, *55*, 3961; e) Ito, H.; Taguchi, T. and Hanzawa, Y. *J. Org. Chem.* **1993**, *58*, 774-778.

4 Garro-Helion, F.; Mermouk, A. and Guibé, F. *J. Org. Chem.* **1993**, *58*, 6109-6113.

5 Genêt, J.P.; Blart, E.; Savignac, M.; Lemaire-Audoire, S. and Bernard, J.M. French patent RP 93039 (june 1993).

6 The proposed mechanism for such efficient desallylation procedure involves a first step of protonation of the allylamine with 2-mercaptobenzoïc acid, followed by rapid equilibrium giving the thiolate which traps the π-allyl palladium intermediate generated in the catalytic cycle.



7 Typical procedure : A mixture of $Pd(dba)_2$ (mol 5%) and DPPB (mol 5%) in THF (0.5 ml) was stirred at room temperature, under argon atmosphere, for 15 minutes. The preformed catalyst and 2-mercaptobenzoic acid (1.1 to 2.1 eq.) were added to a solution of mono or diallylamine in THF and the reaction mixture was stirred under argon atmosphere at 20 to 60°C. After completion (the reaction was monitored by TLC and GC), the mixture was treated by a solution of 10% HCl and extracted by AcOEt to eliminate the by-product and the catalyst in organic layer. The aqueous layer containing the protonated amine was basified with 1M NaOH and extracted by AcOEt. The organic layer was dried over $MgSO_4$ and concentrated in vacuo, affording clean crude products. If necessary, further purification was performed by flash chromatography.

(*Received in France* 17 *November* 1994; *accepted* 20 *December* 1994)