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Microwave-assisted *N*-Boc deprotection under mild basic conditions using $K_3PO_4·H_2O$ in MeOH

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ABSTRACT

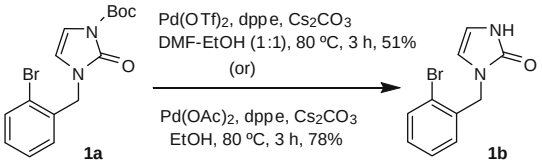
A simple and efficient method for the deprotection of secondary Boc-protected amino compounds under mild basic conditions using $K_3PO_4·H_2O$ in MeOH assisted by microwave irradiation has been presented.

The protection of amines with *tert*-butyloxycarbonyl (Boc) group is a widely used reaction in organic synthesis because of its inertness toward catalytic hydrogenolysis and resistance toward hydrolysis under most basic conditions and nucleophilic reagents.[1] *N*-Boc deprotection is generally achieved under mild acidic conditions[1] such as trifluoroacetic acid (TFA), either neat or in combination with CH_2Cl_2, HCl in EtOAc, H_2SO_4 in *t*BuOAc, *p*TSA, methanesulfonic acid in *t*BuOAc–CH_2Cl_2, aqueous phosphoric acid (H_3PO_4) in THF,[2] or with Lewis acids such as $BF_3·OEt_2$, TMSI, TMSOTf, $TiCl_4$, $SnCl_4$, $AlCl_3$, $Sn(OTf)_2$, and $ZnBr_2$.[1,3] The deprotection can also be carried out with montmorillonite K-10 clay,[4] silica gel at low pressure,[5] ceric ammonium nitrate (CAN),[6] $CeCl_3·7H_2O$–NaI system,[7] tetrabutylammonium fluoride (TBAF),[8] and by thermolytic conditions.[9] There are a few methods available for the cleavage of *N*-Boc group under basic conditions. The Boc group present on an activated amine such as a pyrrole or indole can be cleaved under strong basic conditions using NaOMe.[10] Tom and co-workers developed a method for the deprotection of primary Boc-protected amines under strong basic conditions using NaO*t*Bu in slightly wet 2-methyltetrahydrofuran or tetrahydrofuran.[11] Recently, methods for the cleavage of the Boc group under basic conditions such as Cs_2CO_3–imidazole in acetonitrile,[12] Na_2CO_3 in DME–H_2O mixture[13] have been reported.

Microwave (MW)-assisted organic synthesis was first reported by Gedye and co-workers in 1986.[14] Since then, the use of microwave irradiation has become the method of choice for many chemists and biochemists for a multitude of reactions. It has been successfully applied in numerous organic reactions.[15] Recently, microwave-assisted Boc deprotections with silica gel[16] and trifluoroacetic acid[17] have been reported. Herein, we report a simple and very efficient method for the rapid deprotection of *N*-Boc group under microwave conditions using the mild base $K_3PO_4·H_2O$ in MeOH.

In the course of our ongoing research program to synthesize imidazoisoindol-3-one derivatives[18] from 2-bromobenzyl imidazolinone derivative **1a** by a palladium-catalyzed C–H insertion reaction using $Pd(OTf)_2$, 1,2-bis(diphenylphosphino)ethane (dppe), and Cs_2CO_3 in DMF–EtOH, we serendipitously noticed the complete deprotection of *N*-Boc group without any expected cyclized product (Scheme 1). Attempted C–H insertion in the presence of $Pd(OAc)_2$, dppe, and Cs_2CO_3 in EtOH also removed *N*-Boc group giving 2-bromobenzyl imidazolinone **1b** in an improved yield, but with minor impurities. Replacement of the solvent EtOH with MeOH resulted in a clean removal of *N*-Boc moiety yielding **1b** without any impurities. Encouraged by this observation, we were interested in a detailed study of *N*-Boc deprotection under different basic conditions.

In our quest of a 'greener' approach toward *N*-Boc deprotection, we have carried out a series of experiments using *tert*-butyl 3-benzyl-2,4-dioxoimidazolidine-1-carboxylate (**2a**) under different reaction conditions (Scheme 2). The compound **2a** was prepared from hydantoin in two steps by first treating with BnBr and NaH,[19] and then with $(Boc)_2O$ and Et_3N. Firstly, the treatment of **2a** with Cs_2CO_3 in boiling MeOH for 15 min cleanly deprotected the Boc moiety to furnish 3-benzylimidazolidine-2,4-dione (**2b**).[19] Conducting the same experiment using a catalytic amount of Cs_2CO_3, under microwave conditions,[20] drastically reduced the reaction time to 2 min. To investigate the role of the solvent, we subjected **2a** to microwave irradiation in MeOH without adding any base. We were surprised to observe 90% conversion after



Scheme 1.

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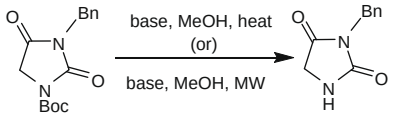


2a **2b**

Scheme 2.

Table 1
Optimization of the reaction conditions

Entry	Base (equiv)	Condition	Time	Yield[a] (%)
1	Cs_2CO_3 (1.2)	MeOH, reflux	15 min	96
2	Cs_2CO_3 (0.1)	MeOH, MW	2 min	95
3	—	MeOH, MW	15 min	90[b]
4	—	DMF, MW	20 min	5[b]
5	—	DMSO, MW	20 min	5[b]
6	—	CH_3CN, MW	20 min	Trace
7	—	THF, MW	20 min	NR
8	K_2CO_3 (1.2)	MeOH, reflux	15 min	95
9	K_2CO_3 (0.1)	MeOH, MW	3 min	92
10	Na_2CO_3 (1.2)	MeOH, reflux	30 min	95
11	Na_2CO_3 (0.1)	MeOH, MW	4 min	92
12	Li_2CO_3 (1.2)	MeOH, reflux	4 h	92
13	$KHCO_3$ (1.2)	MeOH, reflux	3 h	100[b]
14	$KHCO_3$ (1)	MeOH, MW	5 min	95
15	$NaHCO_3$ (1.2)	MeOH, reflux	3 h	100[b]
16	$NaHCO_3$ (1)	MeOH, MW	5 min	95
17	$K_3PO_4{\cdot}H_2O$ (0.2)	MeOH, reflux	30 min	95
18	$K_3PO_4{\cdot}H_2O$ (0.2)	MeOH, MW	2 min	95
19	Na_2CO_3 (1.2)	DME–H_2O, reflux	2 h	53
20	Na_2CO_3 (1.2)	DME–H_2O, MW	2 h	53
21	Cs_2CO_3 (1)	CH_3CN, reflux	24 h	Trace
22	Cs_2CO_3 (1)	CH_3CN, MW	10 min	NR

[a] Isolated yield.
[b] Conversion based on TLC and LCMS.

15 min. We then examined other solvents such as DMF, DMSO, CH_3CN, and THF (Table 1, entries 3–7). These results clearly demonstrate the importance of a suitable protic solvent and a catalytic amount of base to accelerate the deprotection phenomenon.

We next examined various bases such as K_2CO_3, Na_2CO_3, Li_2CO_3, $KHCO_3$, $NaHCO_3$, and $K_3PO_4{\cdot}H_2O$ in MeOH with both conventional heating and microwave irradiation (Table 1). Although different bases were able to induce the cleavage of *N*-Boc moiety of **2a** to afford **2b**,[21] we were interested in developing mild basic conditions with an easy work-up sequence which would serve as a green protocol. Due to the dramatic reduction in reaction times and the nearly identical yields under microwave conditions and conventional heating, we chose to use the catalytic amount of $K_3PO_4{\cdot}H_2O$ for further Boc deprotection studies.

The use of the mild base, $K_3PO_4{\cdot}H_2O$, offers many advantages such as exclusion of anhydrous reaction conditions, simple filtration of the base, and the removal of MeOH to provide the free amine intermediates which can be taken forward for the next step without any purification.[18] Based on the above factors, we believe that the present study is a greener approach compared to the previously reported methods.

To explore the scope and limitations of this reaction, we investigated the Boc deprotection of various *N*-Boc-protected compounds (Table 2). All *N*-Boc-protected compounds were prepared from the corresponding starting free amines by reacting with $(Boc)_2O$, Et_3N and a catalytic amount of DMAP either in THF or in CH_2Cl_2 at ambient temperature. It was quite interesting to observe the Boc cleavage of many of the substrates to some extent in the absence of the base under microwave conditions. Primary Boc-protected amines are inert to the cleavage of the Boc group as the deprotection of doubly Boc-protected 2-phenylethanamine **8a,** and tryptophan derivative **9a** gave the corresponding mono Boc-protected derivatives **8b** and **9b**, respectively. The Boc-protected

Table 2
Rapid deprotection of *N*-Boc compounds

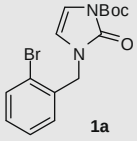
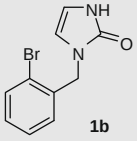
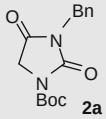
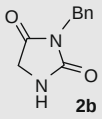
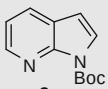
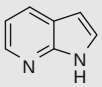
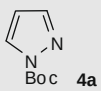
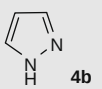
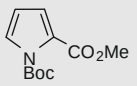
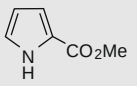
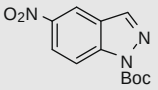
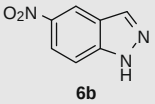
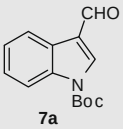
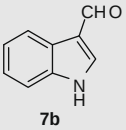
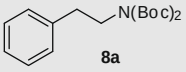
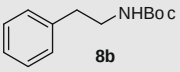
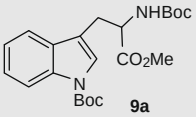
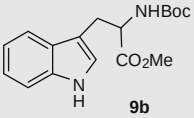
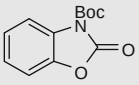
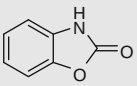
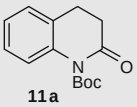
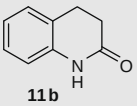
Entry	Substrate	$K_3PO_4{\cdot}H_2O$	Conditions	Time	Product	Yield[a] (%)
1	 **1a**	—	MeOH, MW	10 min	 **1b**	25[b]
		20 mol %	MeOH, MW	3 min		96
		20 mol %	MeOH, reflux	30 min		97
2	 **2a**	—	MeOH, MW	15 min	 **2b**	90[b]
		20 mol %	MeOH, MW	2 min		95
		20 mol %	MeOH, reflux	30 min		95
3	 **3a**	—	MeOH, MW	20 min	 **3b**	10[b]
		20 mol %	MeOH, MW	2 min		98
		20 mol %	MeOH, reflux	15 min		98
4	 **4a**	—	MeOH, MW	20 min	 **4b**	99
		20 mol %	MeOH, MW	2 min		93
		20 mol %	MeOH, reflux	15 min		93
5	 **5a**	—	MeOH, MW	20 min	 **5b**	60[b]
		20 mol %	MeOH, MW	2 min		92
		20 mol %	MeOH, reflux	15 min		92

Table 2 (*continued*)

Entry	Substrate	$K_3PO_4 \cdot H_2O$	Conditions	Time	Product	Yield[a] (%)
6	 **6a**	—	MeOH, MW	20 min	 **6b**	99
		20 mol %	MeOH, MW	2 min		97
		20 mol %	MeOH, reflux	15 min		93
7	 **7a**	—	MeOH, MW	20 min	 **7b**	60[b]
		20 mol %	MeOH, MW	2 min		100
		20 mol %	MeOH, reflux	15 min		100
8	 **8a**	—	MeOH, MW	20 min	 **8b**	0
		100 mol %	MeOH, MW	8 min		93
		100 mol %	MeOH, reflux	10 h		97
9	 **9a**	—	MeOH, MW	20 min	 **9b**	5[b]
		100 mol %	MeOH, MW	5 min		72
		100 mol %	MeOH, reflux	8 h		62
10	 **10a**	—	MeOH, MW	10 min	 **10b**	96
11	 **11a**	—	MeOH, MW	20 min	 **11b**	87

[a] Isolated yield, all compounds were either identified with authentic commercially available samples, or new, fully characterized by ^1H NMR, ^{13}C NMR, and MS.
[b] Conversion based on TLC and LCMS.

aliphatic secondary amines are also unreactive under the present conditions.[22] Most *N*-Boc-protected heterocyclic compounds cleanly underwent the deprotection except **10a** and **11a** (Table 2, entries 10 and 11). Use of 20 mol % of $K_3PO_4 \cdot H_2O$ in both microwave and conventional heating conditions resulted in the cleavage of oxazolone moiety **10a** to give *tert*-butyl 2-hydroxyphenylcarbamate (**10c**).[23] Fortunately, microwave irradiation of **10a** in MeOH without any base afforded the desired deprotection in excellent yield. Similarly, *tert*-butyl 2-oxo-3,4-dihydroquinol-ine-1(2*H*)-carboxylate (**11a**)[24] in MeOH under microwave irradiation conditions gave 3,4-dihydroquinolin-2(1*H*)-one (**11b**) in good yield. Our methodology greatly compliments previously reported strong basic *N*-Boc deprotection methods due to its ability to deprotect heteroaromatic secondary amines, amides, and heterocyclic compounds.[10]

In summary, we have developed a mild, simple, and efficient method for the deprotection of secondary Boc-protected amino compounds under basic conditions assisted by microwave irradiation. The scope for the chemoselective deprotection of different *N*-Boc groups has been demonstrated.

Acknowledgments

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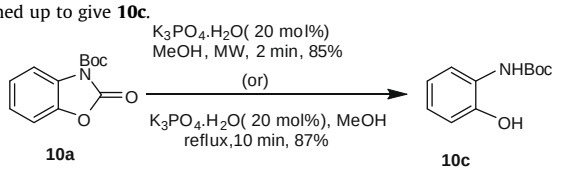
References and notes

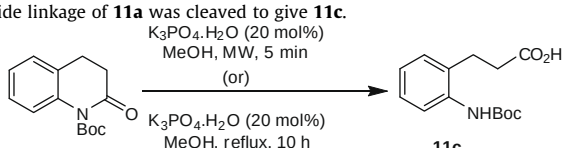
1. (a) Greene, T. W.; Wuts, P. G. M. *Protective groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons, 1999. and references cited therein; (b) Philip, J. K. *Protecting Groups*, 3rd ed.; Georg Thieme: Stuttgart, New York, 2005. and references cited therein.
2. Li, B.; Bemish, R.; Buzon, R. A.; Chiu, C. K.-F.; Colgan, S. T.; Kissel, W.; Le, T.; Leeman, K. R.; Newell, L.; Roth, J. *Tetrahedron Lett.* **2003**, *44*, 8113.
3. Bose, D. S.; Kumar, K. K.; Narsimha Reddy, A. V. *Synth. Commun.* **2003**, *33*, 445. and references cited therein.
4. Shaikh, N. S.; Gajare, A. S.; Deshpande, V. H.; Bedekar, A. V. *Tetrahedron Lett.* **2000**, *41*, 385.
5. Appelquist, T.; Wenbo, D. *Tetrahedron Lett.* **1996**, *37*, 1471.
6. (a) Hwu, J. R.; Jain, M. L.; Tsay, S.-C.; Hakimelahi, G. H. *Tetrahedron Lett.* **1996**, *37*, 2035; (b) Kuttan, A.; Nowshudin, S.; Rao, M. N. A. *Tetrahedron Lett.* **2004**, *45*, 2663.
7. Marcantoni, G.; Massccesi, M.; Torregiani, E.; Bartoli, G.; Bosco, M.; Sambri, L. *J. Org. Chem.* **2001**, *66*, 4430.
8. (a) Routier, S.; Saugé, L.; Ayerbe, N.; Coudert, G.; Mérour, J.-Y. *Tetrahedron Lett.* **2002**, *43*, 589; (b) Jacquemard, U.; Bénéteau, V.; Lefoix, M.; Routier, S.; Mérour, J.-Y.; Coudert, G. *Tetrahedron* **2004**, *60*, 10039.
9. (a) Rawal, V. H.; Jones, R. J.; Cava, M. P. *J. Org. Chem.* **1987**, *52*, 19; (b) Wasserman, H. H.; Berger, G. D.; Cho, K. R. *Tetrahedron Lett.* **1982**, *23*, 465.
10. (a) Hasan, I.; Marinelli, E. R.; Lin, L.-C. C.; Fowler, F. W.; Levy, A. B. *J. Org. Chem.* **1981**, *46*, 157; (b) Ravinder, K.; Reddy, V.; Mahesh, K. C.; Narasimhulu, M.; Venkateswarlu, Y. *Synth. Commun.* **2007**, *37*, 281.
11. Tom, J. N.; Simon, W. M.; Frost, H. N.; Ewing, M. *Tetrahedron Lett.* **2004**, *45*, 905.
12. Mohapatra, D. K.; Durugkar, K. A. *Arkivoc* **2005**, 20.
13. Kazzouli, S. A.; Koubachi, J.; Berteina-Raboin, S.; Mouaddib, A.; Guillaumet, G. *Tetrahedron Lett.* **2006**, *47*, 8575.
14. Gedye, R.; Smith, F.; Westaway, K.; Ali, H.; Baldisera, L. *Tetrahedron Lett.* **1986**, *27*, 279.
15. (a) Hayes, B. L. *Microwave Synthesis Chemistry at the Speed of Light*; CEM Publishing: Matthews, NC, 2002; (b) Loupy, A. *Microwaves in Organic Synthesis*, 1st ed.; Wiley-VCH GmbH & KGaA: Weinheim, 2002; (c) Kappe, C. O.; Stadler, A. In *Microwaves in Organic and Medicinal Chemistry*; Manhold, R., Kubinyi, H., Folkers, G., Eds., 1st ed.; Wiley-VCH GmbH & KGaA: Weinheim, 2005.

16. Siro, J. G.; Martín, J.; García-Navío, J. L.; Remuiñan, M. J.; Vaquero, J. J. *Synlett* **1998**, 147.
17. Srinivasan, N.; Yurek-George, A.; Ganesan, A. *Mol. Divers.* **2005**, *9*, 291.
18. Dandepally, S. R.; Williams, A. L. submitted for publication.
19. Martinez, A.; Alonso, M.; Castro, A.; Dorronsoro, I.; Gelpi, J. L.; Luque, F. J.; Perez, C.; Moreno, F. J. *J. Med. Chem.* **2005**, *48*, 7103.
20. CEM Explorer™ a single-mode automated microwave reactor was used for all the microwave irradiation assisted reactions.
Conditions for MeOH solvent: Set temperature 120 °C; Ramp time 2.5 min (temperature usually reached by 1.5 min); observed pressure 100 psi (maximum pressure 250 psi); initial observed power 100 W, after ramp 50 W (maximum power 300 W); stirring on; cooling on.
21. *Typical experimental procedure: (a) Microwave irradiation in CEM Explorer reactor*: A mixture of *tert*-butyl 3-benzyl-2,4-dioxoimidazolidine-1-carboxylate (**2a**) (100 mg, 0.344 mmol) and $K_3PO_4{\cdot}H_2O$ (16 mg, 0.069 mmol) in MeOH (2 mL) was taken in a 10 mL microwave tube, and the tube was sealed with a pressure cap. The tube was submitted to microwave irradiation for 2 min at 120 °C. The solvent was evaporated under vacuo, the residue suspended in EtOAc, and the insoluble mixture was filtered off through a short silica gel bed. The filtrate was concentrated to obtain 3-benzylimidazolidine-2,4-dione (**2b**) (62 mg, 95%) as a white solid. Mp: 122–124 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 3.97 (s, 2H), 4.67 (s, 2H), 5.69 (br s, 1H), 7.28–7.36 (m, 3H), 7.36–7.44 (m, 2H).(b) *Conventional heating*: To a solution of **2a** (100 mg, 0.344 mmol) in MeOH (2 mL) was added $K_3PO_4{\cdot}H_2O$ (16 mg, 0.069 mmol) and heated at reflux for 30 min. Reaction was worked up as described above to give the product **2b** (62 mg, 95%) as a white solid.
22. The attempted Boc cleavage of *tert*-butyl 4-(3-hydroxyphenyl)piperazine-1-carboxylate using $K_3PO_4{\cdot}H_2O$ (2 equiv) in MeOH with both microwave irradiation (30 min) and conventional heating (24 h) failed to give 3-(piperazin-1-yl)phenol.
23. When substrate **10a** was treated with base in boiling MeOH, the oxazolone ring opened up to give **10c**.



10a **10c**

24. Amide linkage of **11a** was cleaved to give **11c**.



11a **11c**