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The (1-methyl)cyclopropyloxycarbonyl (MPoc) carbamate: a new protecting group for amines

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ABSTRACT

The (1-methyl)cyclopropyl carbamate (MPoc) group represents a new and useful protecting group for amines. It adds relatively little molecular weight and has a simple ^{1}H NMR spectrum. It is orthogonal to the commonly used BOC, Cbz, Alloc, and FMOC groups. MPoc protected amines are resistant to extremes of pH, amines, halogens, many oxidizing agents, and to hydrogenation at ambient temperature. The MPoc group is cleaved by exposure to hypobromous acid or upon hydrogenolysis over palladium at 80 °C.

The (1-methyl)cyclopropyl carbamate (MPoc) group has recently been introduced into medicinal chemistry as a versatile pharmacophore.[1] It is derived from 1-methylcyclopropanol (**1**), which is in turn prepared by the Kulinkovich cyclopropanation of an acetate ester.[2] We became interested in the chemistry of the MPoc group during the course of a recent medicinal chemistry program, with particular interest in its possible utility as a protecting group for amines. We report herein, that the MPoc group may be a useful protecting group for amines, one that is orthogonal to other common carbamate protecting groups such as *t*-butoxycarbonyl (BOC), benzyloxycarbonyl (Cbz), and (9-fluorenyl)methyl-oxycarbonyl (FMOC).

The MPoc group is introduced by way of the mixed carbonate **2**, as shown in Scheme 1. This substance is prepared from **1** and (4-nitro)phenyl chloroformate and pyridine.[3] The mixed carbonate is a crystalline solid, mp 46–48 °C, which may be stored for many months under ambient laboratory conditions without deterioration provided it is protected from moisture.

Treatment of a primary or secondary amine with **2** resulted in the rapid formation of the MPoc carbamate and 4-nitrophenol. Formation of the possible (4-nitro)-phenylcarbamate by-product was not detected. Extraction of the mixture with K_2CO_3 removed 4-nitrophenol, affording the MPoc carbamate in high yield. We prepared the model MPoc carbamates **4** and **5** to facilitate our study of the MPoc group. The secondary carbamate **4** was prepared as shown in Scheme 2;[4] the tertiary carbamate **5** was prepared similarly.[5]

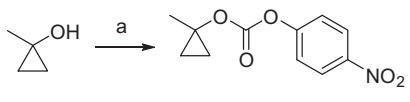
With **4** and **5** in hand, the MPoc group was subjected to a variety of typical reaction conditions, including acidic, basic, nucleophilic, oxidizing, and reducing conditions. In general, the MPoc group was notable for its resistance to nearly all of the reaction conditions evaluated (Table 1). No difference in reactivity was observed between the secondary carbamate **4** and the tertiary carbamate **5**.

Of note was the resistance of the MPoc group to harsh extremes of pH (entries 2, 3, 5, 10, 11). The MPoc group also resisted conditions typically used for the removal of other common protecting groups, such as the BOC group (entries 1 and 5), Cbz group (entries 3 and 9), Alloc group (entry 17) and FMOC group (entry 12).

Having established that the MPoc group was stable to a wide variety of experimental conditions, we sought to identify mild conditions by which the MPoc group might be removed. We centered our attention upon electrophilic reagents known to attack olefins, in the anticipation that similar electrophilic attack upon the cyclopropane ring[6] would facilitate decomposition of the MPoc group by the pathway shown in Scheme 3.

The MPoc group resisted attack by most of the reagents that are customarily used to transform alkenes into other functional groups, including the halogens (Cl_2, Br_2, and I_2; entries 1–3), permanganate ion, osmium tetroxide, lead tetraacetate,[7] thallic acetate,[8] and palladium chloride/cupric chloride (Table 2).

Again, no difference in reactivity was observed between the secondary carbamate **4** and the tertiary carbamate **5**. The MPoc group was cleaved by mercuric ion (entries 16–18); in these reactions elemental mercury could be observed at the completion of the reaction. Upon treatment of **5** with mercuric acetate in acetic acid as solvent, the amine product underwent reaction in situ with the



1 **2**

Scheme 1. Reagents and conditions: (a) 4-$O_2NC_6H_4OCOCl$ (1.1 equiv), pyridine (1.2 equiv) CH_2Cl_2, 0 °C, 90 min, 84%.

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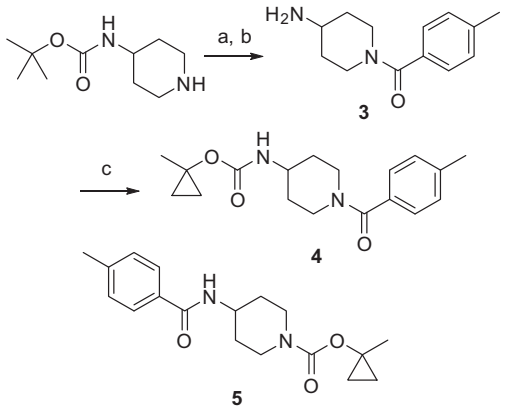


Scheme 2. Reagents and conditions: (a) 4-MeC_6H_4COCl 1 equiv), Et_3N (1.5 equiv), CH_2Cl_2, 0 °C, 3 h, 92%; (b) TFA (10 equiv), CH_2Cl_2, 20 °C, 30 min, 96%; (c) **2** (1 equiv), Et_3N (2 equiv), CH_2Cl_2, 20 °C, 89%.

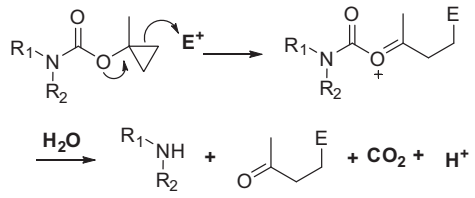
Table 1
Evaluation of MPoc stability of **4** and **5** towards various reagents[a]

Entry	Reagent (equiv)	Solvent	*T* (°C)	Time (h)	Conv'n[b] (%)
1	CF_3CO_2H (10)	CH_2Cl_2	25	48	NR
2	CF_3CO_2H	Neat	25	24	NR
3	33% HBr/AcOH	Neat	25	2	NR
4	33% HBr/AcOH	Neat	50	48	100
5	4M HCl/dioxane	Neat	50	48	NR
6	48% HBr $_{(aq)}$ (45)	AcOH	25	2	NR
7	48% HBr $_{(aq)}$ (45)	AcOH	50	48	100
8	1M HCl $_{(aq)}$ (5)	AcOH	50	48	NR
9	TMSBr (50)	MeCN	50	48	NR
10	1M NaOH $_{(aq)}$ (5)	THF/MeOH	50	48	NR
11	15M NH_4OH (10)	THF	25	48	NR
12	Et_2NH (5)	THF	50	48	NR
13	Et_3N (5)	THF	50	48	NR
14	$BnNH_2$ (2)	THF	50	48	NR
15	Et_3N (5)	MeOH	50	48	NR
16	$NaBH_4$ (5)	EtOH	50	48	NR
17	DMBA[c] (2), $Pd(PPh_3)_4$ (0.1)	THF	70	24	NR
18	NBS (1)	MeOH	50	48	NR
19	NCS (1)	MeOH	50	48	NR
20	HIO_4 (5)	THF/H_2O	50	48	NR
21	NaOCl (18)	THF	50	48	NR
22	H_2O_2 (35), $FeSO_4$ (1)	MeCN/H_2O	25	24	NR
23	$AgNO_3$ (2)	MeCN/H_2O	50	24	NR
24	CAN[d] (2)	MeCN/H_2O	25	24	NR
25	CAN (2), NaBr (1)	MeCN/H_2O	25	24	20
26	CAN (2), NaN_3 (1)	MeCN/H_2O	25	24	NR
27	CAN (2), NaSCN (1)	MeCN/H_2O	25	24	NR

[a] Experiments were performed using 0.1 mmol of **4** or **5** in 0.5 mL of solvent and monitored by LCMS and tlc.
[b] NR indicates that no amine product was observed by LCMS or tlc of the reaction mixture at the end of the experiment.
[c] DMBA: 1,3-dimethylbarbituric acid.
[d] CAN: ceric ammonium nitrate.

by-product methyl vinyl ketone to afford the amidoketone by-product **6** (Scheme 4) as the sole isolated product of the reaction. This side reaction was suppressed when TFA was used as solvent, and was not observed with the model substrate **4**.

Partial deprotection was observed by the action of ceric ammonium nitrate (CAN) and sodium bromide (entry 25, Table 1) and by

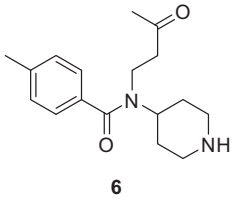


Scheme 3. Proposed mechanism for electrophilic removal of MPoc group.

Table 2
Evaluation of MPoc stability **4**/**5** towards electrophilic reagents known to react with alkenes[a]

Entry	Reagent (equiv)	Solvent	*T* (°C)	Time, (h)	Conv'n[b] (%)
1	I_2 (1)	MeOH/CH_2Cl_2	25	48	NR
2	Br_2 (1)	MeOH/CH_2Cl_2	25	48	NR
3	$NaClO_3$ (1)	6M HCl/AcOH	25	3	50[c]
4	$NaMnO_4$ (10)	Me_2CO	25	4	NR
5	HIO_4 (5), OsO_4 (0.1)	MeCN/H_2O	50	24	NR
6	HIO_4 (5), $RuCl_3$ (0.1)	MeCN/H_2O	50	24	Dec[d]
7	$Pd(OAc)_2$ (1)	AcOH/H_2O	50	48	5
8	$Pd(O_2CCF_3)_2$ (1)	TFA/H_2O	25	4	40
9	AgOAc (1)	AcOH/H_2O	50	48	NR
10	$Ag(O_2CCF_3)$ (1)	TFA/H_2O	25	2	NR
11	$Ag(O_2CF_3)$ (1)	TFA/H_2O	50	18	100
12	$Pb(OAc)_4$ (2)	AcOH	70	18	NR
13	$Tl(OAc)_3$ (2)	AcOH	70	18	5[e]
14	$PdCl_2$ (0.5), $CuCl_2$ (2)[f]	THF/H_2O	80	2	NR
15	$Hg(OAc)_2$ (1)	AcOH/H_2O	25	24	NR
16	$Hg(OAc)_2$ (1)	AcOH/H_2O	50	48	90
17	$Hg(O_2CCF_3)_2$ (1)	TFA/H_2O	25	2	100
18	$Hg(OAc)_2$ (1)	TFA/H_2O	25	2	100

[a] Experiments were performed using 0.1 mmol of **4** or **5** in 0.5 mL of solvent and monitored by LCMS and tlc.
[b] NR indicates that no amine product was observed by LCMS or tlc of the reaction mixture at the end of the experiment.
[c] Benzylic chlorination occurred; the MPoc group was unaffected.
[d] The MPoc starting material was decomposed to numerous unidentified products.
[e] Product was N-acetylated.
[f] Wacker oxidation.



Scheme 4. Product resulting from treatment of **5** with $Hg(OAc)_2$ in HOAc.

palladium trifluoroacetate (entry 8, Table 2). These observations suggested that perhaps the MPoc group could be removed under milder conditions without need for mercury compounds. A clue lay in the observation that partial deprotection occurred with CAN/NaBr but not with CAN alone or in combination with NaN_3 or NaSCN, which have also been reported to cleave 1-methylcyclopropanol.[9] The CAN/NaBr reaction could be driven further by the use of greater quantities of both reagents, but in all cases deprotection was incomplete and furthermore Ce(IV) was always fully reduced to Ce(III). This led us to speculate that perhaps the CAN/

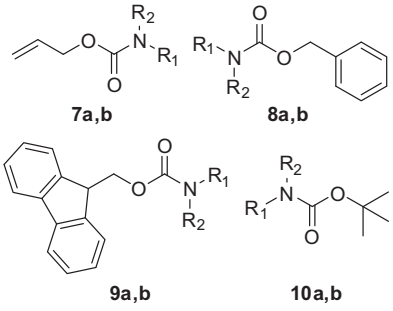
NaBr mixture served to generate small amounts of hypobromous acid (HOBr) in situ, and that the partial deprotection reaction that was observed was mediated by this reagent.

We were pleased to find that exposure of the MPoc group to hypobromous acid (generated in situ from *N*-bromosuccinimide and TFA) resulted in the rapid and complete deprotection of the MPoc group. Again, the by-product **6** was isolated when the reaction mixture was made alkaline. We therefore adjusted the workup conditions in the following manner: the deprotection mixture was treated with a small amount of sodium bisulfite to destroy electrophilic bromine species,[10] after which hydroxylamine hydrochloride (15 equiv) was added. The mixture was then made alkaline with sodium carbonate and extracted as usual.[11] Under these conditions, the by-product 4-bromo-2-butanone was consumed by reaction with hydroxylamine and remained in the aqueous phase; the deprotected amine was isolated in high yield.[12]

In order to establish that the MPoc group is orthogonal to other common protecting groups (BOC, CbZ, Alloc, FMOC), we prepared the model compounds **7a**–**10a** from the amine **3** (Scheme 5). The model compounds **7b**–**10b** were prepared similarly from 1-*N*-BOC-4-aminopiperidine.

These compounds were exposed to the hypobromous acid MPoc deprotection protocol described above. Results are summarized in Table 3.

We were surprised to observe that the BOC group was unaffected by these conditions (entries 6 and 10). No amine was detected when the BOC protected amines **10a** and **10b** were subjected to the hypobromous acid deprotection reaction; nor were any products of decomposition or other side reactions observed. In addition, the Cbz protected amines **8a** and **8b** were likewise unaffected by the conditions used to remove the MPoc group. The FMOC protected amines **9a** and **9b** underwent bromination under these conditions but were unaffected upon exposure to MPoc deprotection mediated by mercuric acetate (Table 2, entries 16 and 18) or catalytic hydrogenation (vide infra). Not surprisingly, the Alloc protected amines **7a** and **7b** underwent addition of HOBr to the allyl group.



Scheme 5. Model Alloc, Cbz, FMOC, and BOC substrates: (a) R_1 = (4-piperidin-1-yl)-*p*-toluamide; R_2 = H; (b) R_1 = R_2 = 4-(*p*-toluamido)-piperidine.

Table 3
Evaluation of stability of Alloc, Cbz, FMOC, and BOC protecting group models towards hypobromous acid conditions used to cleave the MPoc group[a]

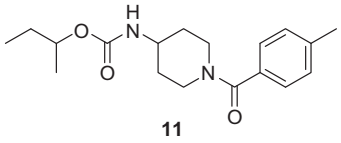
Entry	Substrate	Protecting group	Conv'n[b] (%)
1	**4**	MPoc	100
2	**5**	MPoc	100
3	**7a**	Alloc	*R*[c]
4	**8a**	CBZ	NR
5	**9a**	FMOC	*R*
6	**10a**	BOC	NR
7	**7b**	Alloc	*R*
8	**8b**	CBZ	NR
9	**9b**	FMOC	*R*
10	**10b**	BOC	NR

[a] Experiments were performed using 0.1 mmol of substrate, 0.2 mmol of NBS, and 0.3 mmol of TFA in 0.5 mL of 3/1 dioxane–water (v/v) at 50 °C for 2 h and monitored by LCMS and tlc.

[b] NR indicates that no amine product was observed by LCMS or tlc of the reaction mixture at the end of the experiment; starting material was subsequently recovered in >90% yield.

[c] Indicates that the protecting group underwent reaction with HOBr without production of the amine.

The MPoc protected amines **4** and **5** were also subjected to catalytic hydrogenation over the platinum group metals, since it is known that cyclopropanes can be cleaved under these conditions[13] and the Cbz group is most commonly cleaved by hydrogenation over palladium. Hydrogenolysis of the cyclopropane of **4** could be expected to afford **10** and/or the *sec*-butyl carbamate **11**, depending upon the regioselectivity of the hydrogenolysis.



Exposure of the MPoc protected amines **4** and **5** to hydrogenation over palladium on carbon at 25 °C resulted in no reaction. Under these conditions, the Cbz protected amines **8a** and **8b** were completely deprotected.

However, hydrogenation of **4** and **5** at 100 °C resulted in complete cleavage of the MPoc group to afford the amines. Neither the BOC nor the *sec*-butyl carbamate could be detected. Exposure of the BOC protected amines **10a** and **10b** to these conditions resulted in quantitative recovery of the BOC starting materials, eliminating a mechanism involving hydrogenolysis of the MPoc to a BOC group followed by thermolytic cleavage of the BOC group. Hydrogenolysis of the MPoc group was also effected by transfer hydrogenation using ammonium formate in ethanol at reflux.[14] Remarkably, exposure of the MPoc protected amines **4** and **5** to hydrogenation over Raney® nickel or platinum on carbon at 25 or 100 °C returned only unchanged starting material.

In conclusion, the (1-methyl)cyclopropyl carbamate (MPoc) group represents a new and potentially useful semi-permanent protecting group for amines. It adds relatively little molecular weight and has a simple ^{1}H NMR spectrum, with no resonances below 1.6 ppm. It is resistant to extremes of pH, amines, halogens and other oxidizing agents, and to hydrogenation at ambient temperature. It is cleaved upon exposure to hypobromous acid, followed by a hydroxylamine quench prior to workup. It is also cleaved by hydrogenolysis over palladium at 80 °C or higher. It is orthogonal to the commonly used BOC, Cbz, and FMOC groups, in that (a) the conditions for MPoc cleavage do not affect BOC, Cbz, and FMOC groups, and (b) the conditions for BOC, Cbz, FMOC (and Alloc) cleavage do not affect the MPoc group.

Acknowledgments

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References and notes

1. (a) See, for example, Epple, R; Lelais, G.; Nikulin, V.; Westscott-Baker, L. WO2010/6191 A1, 2010; *Chem. Abstr.* 152:144488.; (b) Neelamkavil, S. F.; Boyle, C. D.; Chackalamannil, S.; Greenlee, W. J. WO2010/9195 A1, 2010; *Chem. Abstr.* 152:192139.
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3. A solution of pyridine (1.7 mL) in 10 mL of CH_2Cl_2 was added dropwise over 10 min to a 0 °C solution of (1-methyl)cyclopropanol (1300 mg, 17 mmol) and 4-nitrophenyl chloroformate (3842 mg, 19 mmol) in 50 mL of CH_2Cl_2. The mixture was stirred for 90 min, then quenched with 50 mL of 0.1 M·H_2SO_4. The CH_2Cl_2 phase was washed with water, $NaHCO_3$, brine, and dried ($MgSO_4$). The $MgSO_4$ was filtered and the filtrate was diluted with twice its volume of hexane. A solid precipitate formed gradually. The mixture was filtered and the filtrate was concentrated to dryness to afford a colorless semisolid. This residue was digested with 50 mL of hexane, filtered while hot and the solid was washed with 2 × 10 mL of boiling hexane. The filtrate was concentrated to afford **2** as a white solid, mp 46–48 °C. ^{1}H NMR ($CDCl_3$) δ 0.72–0.82 (m, 2H), 1.02–1.15 (m, 2H), 1.66 (s, 3H), 7.38 (m, 2H), 8.27 (m, 2H). Calcd for $C_{11}H_{11}NO_5$: C 55.70%; H 4.67%; N 5.90%. Found: C 55.52%, H 4.52%, N 5.94%. It is important that Et_3N not be used in this reaction as it reacts with the chloroformate.
4. Mp 159–160 °C; ^{1}H NMR (DMSO-d_6, 90 °C) δ 0.49–0.67 (m, 2H) 0.69–0.85 (m, 2H) 1.27–1.43 (m, 2H) 1.48 (s, 3H) 1.78 (d, J = 13.08 Hz, 2H) 2.35 (s, 3H) 2.95–3.12 (m, 4H) 3.56 (br s, 1H) 6.71 (br s, 1H) 7.24 (s, 4H).
5. Mp 145–146 °C; ^{1}H NMR ($CDCl_3$) δ 0.62–0.66 (m, 2H) 0.84–0.90 (m, 2H) 1.37–1.45 (m, 2H) 1.56 (s, 3H) 2.00–2.07 (m, 2H) 2.40 (s, 3H) 2.93 (t, J = 12.20 Hz, 2H) 4.09–4.19 (m, 2H) 5.93 (d, J = 7.81 Hz, 1H) 7.24 (d, J = 8.29 Hz, 2H) 7.65 (d, J = 7.81 Hz, 2H).
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9. Jiao, J.; Nguyen, L. X.; Patterson, D. R.; Flowers, R. A., II *Org. Lett.* **2007**, *9*, 1323–1326.
10. The absence of electrophilic bromine species was confirmed by a negative test with KI—starch paper.
11. MPoc deprotection was accomplished by treatment of the MPoc substrate (0.2 M in 3/1 dioxane–water, v/v) with 2 equiv of NBS and 3 equiv of TFA at 50 °C for 2 h. Upon completion of the reaction, the mixture was diluted with twice its volume of water and HOBr was quenched with $NaHSO_3$. Hydroxylamine HCl (15 equiv) was dissolved in the mixture and the mixture was made alkaline with Na_2CO_3. The amine product was isolated by extraction with an appropriate solvent.
12. The MPoc group was also cleaved by a mixture of palladium trifluoroacetate (1 equiv), TFA (5 equiv) and benzoquinone (2 equiv) in aqueous THF; however, separation of desired product from the by-product quinhydrone was more difficult.
13. See, for example: Cheung, C. K.; Wedinger, R. S.; le Noble, W. J. *J. Org. Chem.* **1989**, *54*, 570–573.
14. The use of formic acid as hydrogen donor resulted in formation of the corresponding formamide.