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Simple and efficient cleavage of the *N*-(1-phenylethyl) unit of carboxamides with methanesulfonic acid

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Abstract—Cleavage of the *N*-(1-phenylethyl) unit of carboxamides using less than 1 equiv of MsOH in refluxing toluene was found to be simple and very efficient leading to the desired amides in good to excellent yields, and also proved to be more effective compared with reductive methods using hydrogen sources, or acid hydrolysis reagents such as TFA and TsOH. The method selectively cleaved only the *N*-(1-phenylethyl) group of *N*-benzyl-*N*-(1-phenylethyl)amides.

For the synthesis of biologically active heterocyclic or open-chain compounds bearing nitrogen atoms, benzylamine or its chiral versions have been increasingly used as protective reagents of functional groups, chiral templates and chiral auxiliaries. Over these benzylamine analogs, a chiral phenylethylamine proved to be especially useful for asymmetric Michael additions of secondary enamines derived from 1-phenylethylamine,[1] stereoselective 1,3-dipolar cycloadditions,[2] and enantioselective cyclization.[3] In this context, the effective cleavage of the *N*-(1-phenylethyl) group of chiral molecules derived from 1-phenylethylamine might be very useful for asymmetric synthesis of nitrogen containing compounds. The reported stereoselective syntheses using an enantiopure phenylethylamine have been mostly completed with cleavage of the *N*-(1-phenylethyl) group, which was generally accomplished by catalytic hydrogenation,[4] catalytic transfer hydrogenation[5] and other reducing reactions.[6] Although the methods using hydrogen for removal of the *N*-(1-phenylethyl) moiety have been generally applied to the majority of reactions, we were interested in a methodology avoiding the use of hydrogen in the course of our studies on the synthesis[7] of enantiopure 4-hydroxy-2-pyrrolidinone using one single enantiomeric 1-phenylethylamine. We herein report a simple and efficient method for cleavage of the *N*-(1-phenylethyl) unit on carboxamides using methanesulfonic acid in refluxing toluene.

Since hydrogenolysis to remove a benzyl group on an amide often was known to be difficult,[8] TFA in dichloromethane has been typically used for cleavage of a benzyl moiety of carboxamide linkers in solid phase synthesis.[9] Recently a method of acid hydrolysis using *p*-TsOH was also reported by Kan et al.[10] As substrates for a model reaction compared with these reagents, we have chosen two simple carboxamides **1** and **2** to examine the cleavage of the *N*-(1-phenylethyl) unit under various reaction conditions. The results obtained are reported in Table 1.

The reaction of **2** with 30% TFA in dichloromethane (rt or reflux, 6 h) remained unchanged; the treatment of **2** with 30% TFA in refluxing toluene for 6 h showed only a trace amount of the decomposed materials (ca. 10%) with mostly unchanged starting compound. The methods using 10% Pd/C with H_2 (25–50 °C, 24 h) or 10% Pd/C with HCO_2NH_4 in MeOH (25–64 °C, 24 h) with **2** also resulted in the recovery of the unchanged starting material proving that a benzyl group on an amide by hydrogenolysis is often impossible.[8] However, the use of MsOH (0.5–2 equiv, 6 h) in refluxing toluene ended up with the complete deprotection of **2**, while the other substrate **1** remained unchanged under the same condition. In order to compare the efficacy of acid hydrolysis reagents, protonic acids such as TFA, HCl,

Keywords: *N*-(1-Phenylethyl)carboxamides; Methanesulfonic acid; Deprotection.
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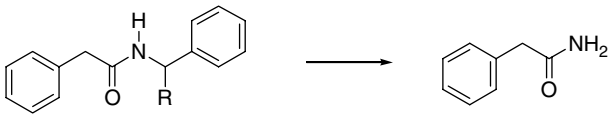
Table 1. Deprotection of carboxamides **1** and **2** under various conditions

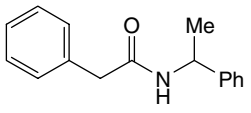
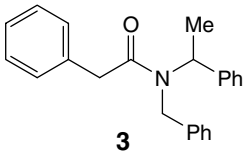
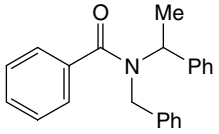
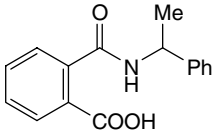
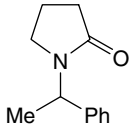
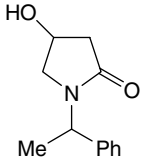
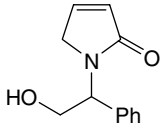
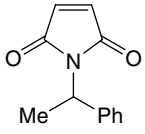
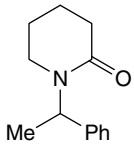
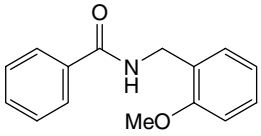


1 R = H
2 R = Me

Substrate	Reagents and conditions	Results
1	MsOH (4 equiv), toluene, 6 h, reflux	N.R.[a]
1	TsOH (4 equiv), toluene, 6 h, reflux	N.R.
2	MsOH (1 equiv), toluene, 6 h, reflux	Completed[b]
2	TsOH (4 equiv), toluene, 6 h, reflux	23%
2	30% TFA/DCM, 6 h, rt	N.R.
2	30% TFA/toluene, 6 h, reflux	Nearly unchanged[c]
2	HCl-saturated MeOH, 6 h, reflux	N.R.
2	10% Pd/C, H_2, MeOH, 24 h, 25–50 °C	N.R.

[a] N.R.: no reaction.
[b] The use of 0.5–2 equiv MsOH showed almost no difference leading to completion of the reaction in 3–6 h.
[c] Ca. 90% of the starting material unchanged based on ^{1}H NMR analysis.

Table 2. Deprotection of *N*-(1-phenylethyl)- or *N*-benzylcarboxamides with MsOH[a]

Substrate	Yield (%)	Substrate	Yield[b] (%)
 **2**	95	 **3**	85[c]
 **4**	90[c]	 **5**	75[d]
 **6**	92	 **7**	92
 **8**	Decomposed[e]	 **9**	Decomposed[e]
 **10**	95	 **11**	75

[a] All reactions were carried out using MsOH (1 equiv) in refluxing toluene for 6 h.
[b] Isolated yield.
[c] *N*-Benzyl group remained intact after reaction.
[d] The cyclized phtalimide was obtained in 75% yield.
[e] Cleavage was completed, but 10–20% of the deprotected products were detected with mostly decomposed products.

TsOH and MsOH were employed under several conditions. The use of 1 equiv of TsOH with **2** in refluxing toluene showed no reaction, while 4 equiv of TsOH (refluxing toluene) resulted in only 23% of the cleavage product with mostly unchanged starting material, indicating that MsOH was much more efficient than TsOH for cleavage of the *N*-(1-phenylethyl) moiety on an amide. The reaction of HCl-saturated MeOH (reflux, 6 h) with **2** was also noted unchanged. In cases where 1–4 equiv of MsOH or TsOH with **1** in refluxing toluene or TFA (refluxing dichloromethane) with **1** in the presence of anisole as a nucleophilic scavenger were used, no significant changes were also observed.

We have further attempted to explore the efficacy of the cleavage reaction with MsOH using various substrates prepared with enantiopure 1-phenylethylamine, of which the stereochemical integrity of **7** proved to be retained during the synthetic process.[7] Deprotections of *N*-(1-phenylethyl)carboxamides **2**–**5** using 1 equiv MsOH in refluxing toluene were completed in 3–6 h with good to excellent yields (75–95%) as shown in Table 2. It is interesting that the *N*-(1-phenylethyl) group of *N*-benzyl-*N*-(1-phenylethyl)amides **3** and **4** was selectively cleaved without any loss of the *N*-benzyl group. In case of 1-carboxyamide **5**, the cyclized phthalimide was only obtained in 75% yield, and with the cyclic amides **6**–**7** and **10**, excellent yields were also obtained in above 90%. Cleavages of pyrrolone **8** and maleimide **9** were completed in 6 h, but the deprotected products were detected in 10–20% with mostly decomposed products based on ^{1}H NMR analysis. Finally, the cleavage method was examined to find any applicability with *N*-benzylcarboxamides. *N*-(1-Methoxybenzyl)amide **11** which was more labile than phenylacetamide **1** was successfully debenzylated under the same condition; however, **1** remained unchanged despite of using 4 equiv MsOH.

In conclusion, a simple and efficient method using 0.5–1 equiv MsOH in refluxing toluene was found to be effectively applicable for cleavage of the *N*-(1-phenylethyl) unit on carboxamides. The method selectively cleaved only the *N*-(1-phenylethyl) group of *N*-benzyl-*N*-(1-phenylethyl)amides, and also was successful for removal of a methoxybenzyl group on a carboxamide.

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