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A Facile Deprotection of Secondary Acetamides

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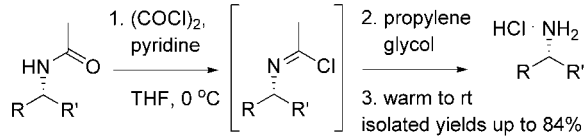
ABSTRACT



Imidoyl chlorides, generated from secondary acetamides and oxalyl chloride, can be harnessed for a selective and practical deprotection sequence. Treatment of these intermediates with 2 equiv of propylene glycol and warming enables the rapid release of amine hydrochloride salts in good yields. Notably, the reaction conditions are mild enough to allow for a swift deprotection with no observed epimerization of the amino center.

Recent years have seen an explosion in the design of novel asymmetric ligands for the catalytic hydrogenation of enamides to give protected chiral amines.[1] The acetyl group, widely utilized for its contribution to high stereoselectivities, is typically introduced at the enamide stage. We recently reported a metal-free, phosphine-based conversion of ketoximes to enacetamides, enabling in particular the formation of the difficult-to-access tetralone series of substrates.[2] However, as with the formation of these catalytic hydrogenation precursors, limited work has been reported to address the necessary deprotection of the chiral products.

Traditional methods of deacylation require harsh conditions and long reaction times.[3] Newer reports often utilize complex conditions or costly reagents or provide access only to the corresponding carboxylic acids or esters.[4] As none of the literature-based methods served our purpose, we chose to investigate alternatives to deliver target molecule **1** (Scheme 1). Herein we disclose the rapid and selective

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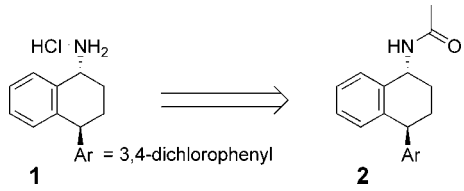
Scheme 1. Acetamide Deprotection



cleavage of secondary acetamides with no epimerization of the highly valuable chiral amino centers. The products may be obtained directly as stable hydrochloride salts or further derivatized.

Inspired by the utility of the Vilsmeier−Haack reagent,[5] we applied oxalyl chloride to the deprotection of our amide **2**.[6] While this reagent has been used for further functionalization, it has not been exploited for a straightforward deacetylation method.[7] Nonetheless, in the presence of base at 0 °C, secondary acetamides are activated to imidoyl chlorides for a subsequent reaction leading to amide bond cleavage.

In our initial attempts, we employed an excess of simple alcohols to quench the imidoyl chloride intermediates.[4g,i] However, we eventually settled on propylene glycol, a nontoxic reagent. Two equivalents of this additive caused complete collapse of the reactive intermediates to give amine hydrochlorides. In addition, it appears that this one-pot, two-step method shows selectivity for secondary acetamides over tertiary substrates or analogous secondary benzamides.

For selection of the ideal medium, we examined a series of solvents. Despite the fact that these reactions occur in biphasic slurries, tetrahydrofuran, ethyl acetate, dichloromethane, and acetonitrile all accomplished the desired transformation. We chose to proceed with THF for its overall preferable attributes.

Base is required to prevent decomposition of the imidoyl chloride intermediate. However, screening showed that only a select group could be utilized (Table 1). Though initially used in excess, we discovered that stoichiometric base was sufficient (vide infra). Pyridine and 2,6-lutidine worked best (entries 1, 9, and 10). The others, including aliphatic amines (entries 2−4) and heterogeneous reagents (entries 5−8), were detrimental to the reaction. Presumably, the pyridine-type reagents provided the appropriate basicity.

Table 1. Screening of Acid Scavenging Reagents

entry[a]	base	equiv	% amine[b]
1	2,6-lutidine	3.0	72
2	$EtN(iPr)_2$	3.0	18
3	4-Me-morpholine	3.0	23
4	1-Me-piperidine	3.0	9
5	4Å MS	excess	12
6	NaOAc	3.0	<5
7	$NaHCO_3$	3.0	<5
8	K_2CO_3	3.0	6
9	2,6-lutidine	2.0	94
10	pyridine	2.0	93

[a] All reactions were run with acetamide **2**, $(COCl)_2$ (1.3 equiv) and propylene glycol (3.0 equiv) at 0 °C. They were all conducted in CH_2Cl_2 with the exception of entries 9 and 10, which were run in THF. [b] HPLC area % of amine product relative to other components.

Beyond amide activation, the quenching reagent played a significant role in determining the best overall method (Table 2). Initially, we relied on driving the reaction with an excess of conventional alcohols (entry 1). Because our substrate showed difficulty in releasing the desired amine product from the intermediate, we explored alternative conditions. Treating the reactions with acid (entry 2) or base (entry 3) only accelerated decomposition pathways. However, a previous report employed *iso*-butyl alcohol (entry 4) or ethylene glycol (entry 5) for difficult substrates.[4i] In our case, the latter worked better, revealing accelerated collapse of the intermediate on prolonged agitation.

Table 2. Screening of Quenching Agents

entry[a]	quench	equiv	% amine[b]
1	EtOH	excess	24
2	1.25 M HCl in MeOH	excess	23
3	25 wt % NaOMe in MeOH	excess	38
4	*i*BuOH	3.0	35
5	ethylene glycol	6.0	67
6	propylene glycol	6.0	72
7	propylene glycol	2.0	91
8	1,3-propanediol	3.0	75

[a] All reactions run with acetamide **2**, $(COCl)_2$ (1.3 equiv), and 2,6-lutidine (3.0 equiv) at 0 °C except for entry 2 ($(COCl)_2$ (1.1 equiv)) and entries 7 and 8 (pyridine (2.0 equiv)). The reactions were all conducted in CH_2Cl_2 with the exception of entries 7 and 8, which were run in THF. [b] HPLC area % of amine product relative to other components.

Because of the toxicity concerns of ethylene glycol, we also investigated propylene glycol, a commonly used food additive. Interestingly, this diol provided a more dramatic accelerating effect, requiring only warming of the reaction to room temperature (Table 2, entries 6 and 7). Instead of a large excess of diol, 2 equiv was sufficient to drive the reaction to completion and allow direct isolation of the amine salt product. This final modification enabled the quick yet mild acetamide deprotection we desired.

(5) Tasneem, *Synlett* **2003**, 138–139.

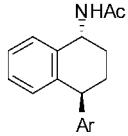
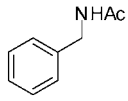
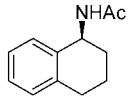
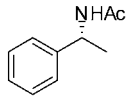
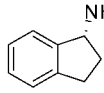
(6) We chose oxalyl chloride for ease of handling but also screened alternative agents to effect a similar reaction. Of these, triphosgene and phosphorus pentachloride provided positive data points, while thionyl chloride and phosphoryl chloride did not. For a related reference, see: Chauvette, R. R.; Pennington, P. A.; Ryan, C. W.; Cooper, R. D. G.; José, F. L.; Wright, I. G.; Van Heyningen, E. M.; Huffman, G. W. *J. Org. Chem.* **1971**, *36*, 1259.

(7) $(COCl)_2$ has been used to form other adducts with amides. For related references, see: (a) Sheehan, J. C.; Corey, E. J. *J. Am. Chem. Soc.* **1952**, *74*, 360. (b) Speziale, A. J.; Smith, L. R. *J. Org. Chem.* **1963**, *28*, 1805. (c) Shiozaki, M.; Ishida, N.; Iino, K.; Hiraoka, K. *Tetrahedron* **1980**, *36*, 2735. (d) Manley, P. J.; Bilodeau, M. T. *Org. Lett.* **2002**, *4*, 3127. (e) Lindström, J.; Johansson, M. H. *Synth. Commun.* **2006**, *36*, 2217.

The alcohol quenching process is also operative in the triflic anhydride-mediated amide cleavage methodology developed by Charette et al.[4g] With the imidoyl triflates, however, cryogenic conditions are necessary and an excess of base is recommended. With $(COCl)_2$, cooling to 0 °C with stoichiometric base is adequate. In addition, whereas the Tf_2O methodology has been demonstrated to deprotect a multitude of amides, it is surprisingly not applicable to all substrates, and in our case, this sequence led to an undesired product.[8]

Table 3 demonstrates that a variety of chiral benzylic substrates could be deprotected using this methodology, without epimerization. Our desired product (**1**, from acetamide **2**, entry 1) could be readily isolated from the reaction mixture as the HCl salt due to low solubility in the reaction medium.[9] However, since the solubilities of amine hydrochloride salts vary considerably, most amine products were further converted to phthalimide derivatives for ease of isolation.

Table 3. Deprotection of Benzylic Acetamides[a]

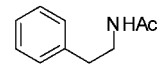
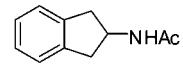
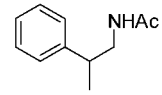
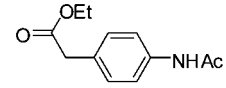
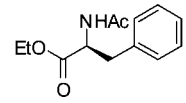
entry	substrate	% yield [b]
1[c]		A: 84 B: 84
2		A: 49 B: 84
3		B: 86
4		B: 86
5		B: 70

[a] Unoptimized yields. Conditions: (a) $(COCl)_2$ (1.1 equiv), pyridine (1.2 equiv), THF, 0 °C; (b) propylene glycol (2.0 equiv), warm to rt. [b] Yields refer to isolated products; A = amine hydrochloride salt, and B = phthalimide derivative. [c] Ar = 3,4-dichlorophenyl.

Table 4 exhibits that other substrates could also be successfully converted to the desired products. An aniline-type acetamide reacted favorably under these conditions (entry 5). Likewise, a protected amino acid was transformed successfully without detectable epimerization (entry 6). The product was derivatized as the benzyl carbamate for ease of isolation. This particular example illustrates that syntheses of unnatural amino acids could benefit tremendously from this methodology.[10]

(8) This material was not further characterized.
(9) Acetamide **2** was run successfully at 40 kg scale.

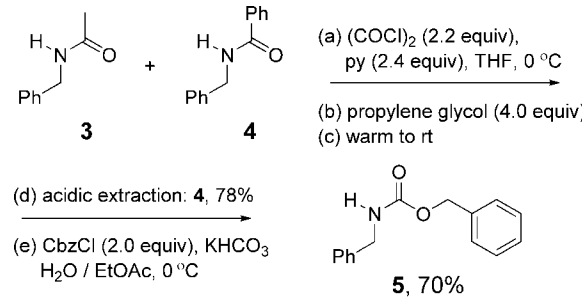
Table 4. Deprotection of Nonbenzylic Acetamides[a]

entry	substrate	% yield [b]
1		A: 52 B: 85
2		A: 70 B: 0
3		B: 86
4		B: 75
5		B: 63
6		B: 62 C: 57

[a] Unoptimized yields. Conditions: (a) $(COCl)_2$ (1.1 equiv), pyridine (1.2 equiv), THF, 0 °C; (b) propylene glycol (2.0 equiv), warm to rt. [b] Yields refer to isolated products. A: amine hydrochloride salt; B: phthalimide derivative; and C: Cbz-derivative.

Secondary benzamides and tertiary acetamides, including *N*-benzylbenzamide, *N*-phenethylbenzamide, (*S*)-*N*-(1-phenylethyl)benzamide, and *N*,*N*-dibenzyl-acetamide were surprisingly not susceptible to the described conditions and were recovered from the reaction mixture. In order to confirm this selectivity, competition experiments were run with 1 equiv each of reactive secondary acetamide **3** and the unreactive substrate present in the same reaction (Schemes 2 and 3).

Scheme 2. Secondary Benzamide versus Secondary Acetamide



In both cases, the unreacted amide substrate (**4** and **6**, respectively) could be extracted from the crude residue, while the deprotected component, benzyl amine, could be carried forward. This subtle specificity for secondary acetamides

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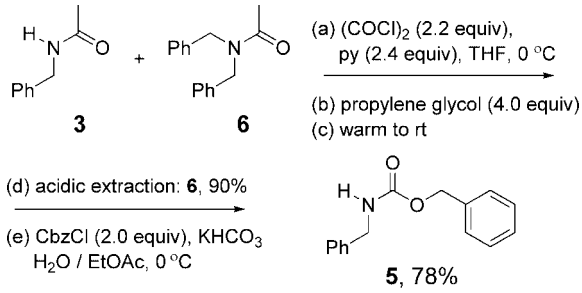
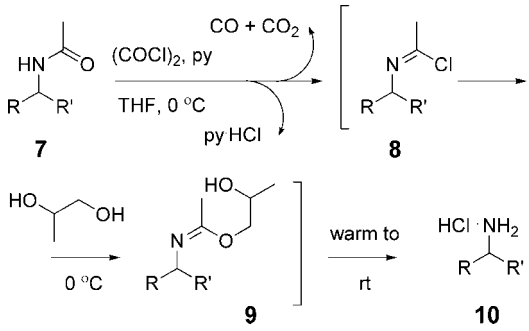
Scheme 3. Tertiary Acetamide versus Secondary Acetamide



should prove useful in the deprotection of differentially protected amines. In addition, it further demonstrates the mild nature of the conditions described in this communication.

With regard to reaction progression, it is well-known that in the presence of base, $(COCl)_2$ reacts with amide **7** to form imidoyl chloride **8** by loss of carbon monoxide and carbon dioxide (Scheme 4).[7d] Previously, similar species have been

Scheme 4. Proposed Reaction Progression



quenched with simple alcohols to effect conversion to imidoyl esters, followed by the eventual release of carboxylic ester and amine salt.[4g,i] With propylene glycol, we believe that a similar process occurs to yield **9**, requiring only warming to room temperature to release the desired amine hydrochloride salt **10**.[11]

On the basis of the observed difference in cleavage rates between ethylene and propylene glycol, we surmise that their dissimilar solubility profiles have a pronounced effect in the quenching phase of this slurry-based system.[12] After the quench, the additional methyl substituent of propylene glycol may contribute to an accelerated collapse of the intermediate imidoyl ester **9** by encouraging intramolecular attack of the second hydroxyl group. While simpler substrates can take advantage of this accelerated cleavage, they would also be likely to react with methanol or ethanol.

Most significant for this methodology from a safety standpoint is the rapid gas evolution upon initial reaction of $(COCl)_2$.[13] The exothermic process is readily handled on laboratory scale and is well-tolerated on scale-up with appropriate precautions. In addition, the evolution of CO is accompanied by 1 equiv of CO_2, diluting the gaseous byproduct stream. The base traps the HCl in solution until the primary amine is liberated at the end of the reaction cycle. Lastly, the imidoyl chloride intermediate calls for anhydrous conditions in order to prevent reversion to starting material.

In conclusion, we have developed a facile deprotection of secondary acetamides. The mild conditions enable a selective transformation with no epimerization of the prized amino center and isolation of the amine in hydrochloride salt form. This practical methodology should further encourage the use of catalytic asymmetric hydrogenation approaches to access chiral amines.

Acknowledgment. We thank Sepracor colleagues Drs. Tom Wagler and John Dankwardt for support, as well as Dr. Hal Butler and Ms. Denise Thompson for providing analytical assistance.

Supporting Information Available: Experimental details, ^1H and ^{13}C NMR spectra, and chiral assays for pertinent compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Bretherick, L. *Chem. Health Saf.* **2003**, *10* (4), 47.