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Mild non-transition metal catalyzed deprotection of *N*-allyloxycarbonyl amines

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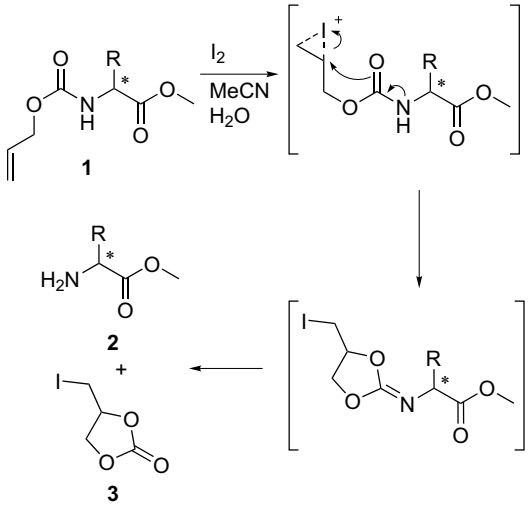
Abstract—A synthesis of methyl (2*S*)-2-amino-4-oxo-2,4-diphenylbutanoate has been achieved via a novel one-pot non-transition metal mediated deprotection of the *N*-allyloxycarbonyl amine using iodine in wet acetonitrile. The applicability of this transformation has been demonstrated by deprotecting a variety of *N*-allyloxycarbonyl amines, α-aminomethyl esters and simple *N*-allyloxycarbonyl alkyl amines. Deprotection occurs in high yield (82–93%) without erosion of the optical purity of the chiral substrates.

Protection of the highly reactive amino functionality as a carbamate (Alloc, BOC, Cbz, FMOC, etc.) is common practice in organic chemistry, especially in the total syntheses of biologically active compounds, combinatorial chemistry, and solid phase peptide methodology. In particular, the *N*-allyloxycarbonyl, or Alloc, moiety has seen increasingly widespread use in the recent past due to its ready availability, ease of installation, high stability under the range of pH's, temperatures and nucleophilic, oxidative, and reducing reaction conditions. Removal has typically been achieved chemoselectively under mild conditions using transition metal catalysts.[1,2] There are, however, drawbacks associated with these heavy metal-based deprotections, namely, the high cost of reagents, competitive allylamine formation, and difficulty of removing trace quantities of the metal, especially if it is in the last step of a manufacturing synthesis. Therefore, alternative methods of Alloc deprotection that do not use heavy metals were sought, but to the best of our knowledge they do not exist. In this letter, we would like to report a novel one-pot, high yielding, oxidative *N*-Alloc deprotection protocol of simple amines and α-aminomethyl esters via iodocyclization in acetonitrile/water (Scheme 1).

During the course of our research, enantiopure methyl (2*S*)-2-amino-4-oxo-2,4-diphenylbutanoate (**9**) was required (Scheme 2) and we opted to pursue **9** by the alkylation of an oxazolidinone precursor that should occur with high diastereoselectivity.[3] Carbamate, rather than carboxamide, protection of the nitrogen was necessary since carbamates give better yields and diastereomeric ratios of cis:trans oxazolidinone isomers than do amides.[4] Although we could prepare the ethyl carbamate derivative and alkylate it in high yield and selectivity, we were unsuccessful at the removal of the



Scheme 1. Proposed mechanism of iodine deprotection.

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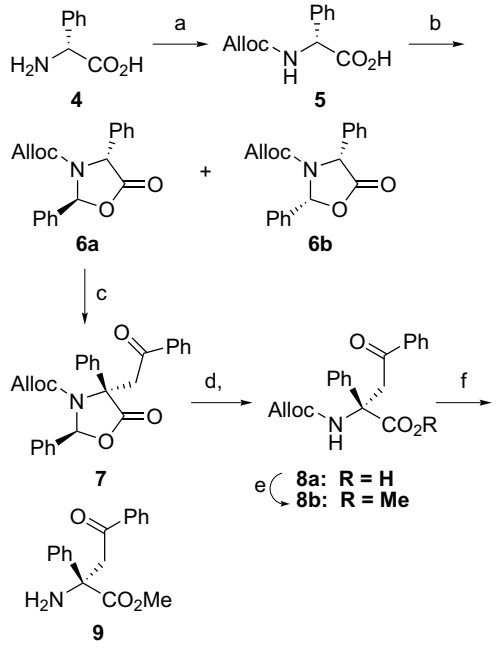


Scheme 2. Synthesis of methyl (2*S*)-2-amino-4-oxo-2,4-diphenylbutanoate **9**. Reagents and conditions: (a) Alloc-Cl, 5 N NaOH, THF, 0 °C, 15 min, 99%; (b) $PhCH(OMe)_2$, $PhSO_3H$, toluene, 85 °C, 200 Torr, 2–4 h; (c) LiHMDS, TMEDA, THF, −70 °C, 15 min, then 2-bromoacetophenone, −70 °C to rt, 30 min, 90%; (d) 4 N aq LiOH/MeOH, 16 h; (e) MeI, $NaHCO_3$, DMF, 1 h, 90% for two steps; (f) I_2, H_2O, MeCN, rt, 48 h, 87%.

carbamate even under forcing acidic or basic conditions. Therefore, we prepared the Alloc derivative with the expectation of milder removal after the alkylation using heavy metal-based conditions. Due to the problems associated with heavy metals, such as the expense and toxicity, we also desired to find an alternative procedure to remove the Alloc group. We expected that reaction of positive halogens would induce cyclization of the Alloc group followed by a hydrolysis to give the free amine and a neutral iodocarbonate **3**. The neutral carbonate **3** would be easily separated from the basic amine extractively (Scheme 1). Analogous halocyclization deprotection methodology has been used by Fraser-Reid[5] to remove pentenamide protecting groups, but has not been extended to carbamates to the best of our knowledge. Also, a 1,2 iodoetherification of the 3-methylbut-2-en-1-yl-carbamate (Preoc) group followed by zinc reduction has been recently reported by Vatèle, although in that paper, only simple addition of iodine and methanol across the double bond was observed.[6] C–N bond cleavage did not occur until treatment of the *β*-methoxyiodide with excess zinc.

(2*R*)-{[(allyloxy)carbonyl]amino}(phenyl)acetic acid (**5**) was prepared in near quantitative yield from *R*-(-)-2-phenylglycine (**4**) by the slow addition (1 h) of allyl chloroformate (1 equiv) to **4** in THF/5 N NaOH at 0 °C.[7] Upon acidification with 37% HCl and toluene extraction, **5** was obtained in 99% yield and >99% purity as assayed by HPLC and used directly in the oxazolidinone synthesis. Slight modification of the Karady protocol[3a] afforded a 15:1 mixture of trans:cis oxazolidinone isomers[8] in 74% yield when **5** was reacted with benzaldehyde dimethyl acetal.[9] Fortuitously, the trans-isomer proved highly crystalline and was isolated from a 1:1 mixture of toluene/heptane to provide **6a** in 60% yield and >99% purity as assayed by HPLC. Alkylation of **6a** with 2-bromoacetophenone at −70 °C gave **7** in 90% yield with >97% diastereoexcess.[10] Hydrolysis of **7** (4 N LiOH/MeOH) followed by esterification at ambient temperature (MeI/$NaHCO_3$) in dry DMF furnished Alloc-protected quaternary amino methyl-ester **8b** in 90% overall yield for the two steps after silica gel chromatography. A one pot methanolysis/deprotection of **7** was attempted in methanol with iodine, but only resulted in iodoetherification and diiodination of the allyl double bond.[11]

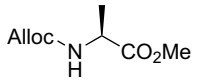
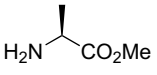
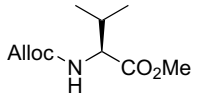
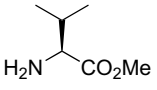
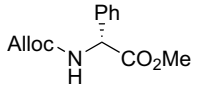
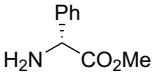
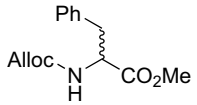
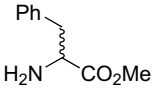
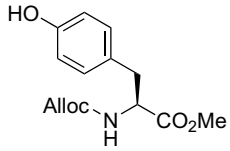
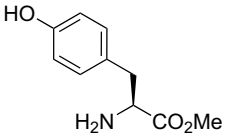
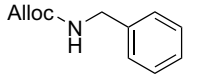
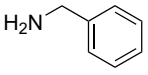
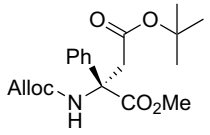
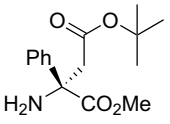
Following the original deprotection conditions of Fraser-Reid,[12] <15% yield of product was observed after 24 h when **8b** was reacted with iodine (3 equiv) in a 1:1 mixture of THF/water. When the reaction was run in 4:1 methanol/water, a mixture of the desired product **9** (22%), iodoetherification product (LCMS analysis), carboxylic acid **8a** (42%), as well as unreacted starting material **8b** were all observed. While a simple change in solvent to 4:1 acetonitrile/water minimized hydrolysis and improved the yield of the reaction to 48%, a mixture of iodohydrin side products was also observed. We sought to minimize iodohydrin formation by lowering the pH of the reaction mixture, however, the addition of acid had no effect on either the rate or yield of the reaction.[13] Upon optimization of the water content (3 equiv), an 87% yield of **9** was realized after 48 h at ambient temperature. Heating this reaction (40–60 °C) increased the reaction rate, but had deleterious effects on the yield of amine formation.

The scope and limitations of this transformation was determined by the deprotection of several *N*-allyloxycarbonyl-amino-methyl-esters and simple *N*-Alloc-amines.[14] As seen in Table 1, a variety of functional groups is well tolerated under our reaction conditions. Alkyl substituted amino-esters (examples 1 and 2), as well as phenyl and benzyl substituted compounds (examples 3–5), were deprotected in relatively high yields (82–92%). Iodination of phenyl rings, including electron rich aryl substituents, was not observed in our hands. A simple alkyl amine was also examined (example 6) and found to undergo the desired reaction in high yield (93%). Erosion of optical purity was monitored in each case by chiral SFC and found not to occur to any measurable extent.

The by-product of the deprotection, 4-iodomethyl-1,3-dioxolan-2-one (**3**), is a synthetically useful intermediate for various B-adrenergic blockers and antibacterial cephalosporin compounds.[15] We monitored the production of **3** by HPLC and chiral SFC to determine if any transfer of chirality from the substrate to the allyloxy moiety took place. Although **3** was examined from all deprotections, enantiomerically enriched iodo-carbonate has not been observed.

In conclusion, a high-yielding non-transition metal catalyzed Alloc liberation protocol has been developed and demonstrated on a variety of substrates. Minimiza-

Table 1. Iodocyclization deprotection of Alloc-carbamates in wet acetonitrile[a,b]

Entry	Substrate	Product	Yield (%)
1			86[c]
2			87[c]
3			89
4			92
5			82
6			93
7[d]			85[e]

[a] Product yields have not been optimized.
[b] Yields were determined by HPLC analysis versus a standard prepared from commercially available authentic material unless otherwise noted.
[c] Yields were determined by HPLC analysis of the rederivatized Alloc-protected amine versus a standard prepared from synthetically available material.
[d] The deprotection was performed at ambient temperature.
[e] Yields were determined by HPLC analysis versus a standard prepared from synthetically available material.

tion of iodohydrin formation by optimization of the water content proved key to maximizing the reaction yield. While optical purity of the substrates was not affected by the deprotection, no transfer of chirality to the iodocarbonate leaving group occurred.

Acknowledgements

The authors thank Mr. Robert Reamer for NOE experiments on compounds **6a** and **6b**, Ms. Mirlinda Biba for chiral SFC analysis, and Dr. Thomas J. Novak for HRMS analysis.

Supplementary data

Detailed experimental procedures for the preparation of **9**, as well as characterization data, is available free of charge via the Internet at http://pubs.acs.org. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.04.064.

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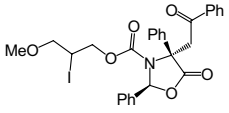
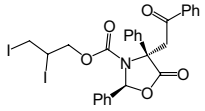
6. Vatèle, J. *Tetrahedron Lett.* **2003**, *44*, 9127–9129.
7. The use of other solvents (DCM, toluene) required elevated temperatures (23–50 °C) for the reaction to go to completion, and resulted in lower yields (88–95%).
8. The major isomer was determined to have trans configuration by NOE experiments.
9. To an 85 °C slurry of **5** and $PhSO_3H$ (2 mol%) in toluene (7.5 mL/g vs **5**) was added benzaldehyde dimethyl acetal (1.5 equiv) as a solution in toluene, slowly over 2 h. A mixture of methanol and toluene was distilled off over the course of the reaction under slight vacuum (200 Torr) to minimize esterification of the carbamate starting material. Toluene was continually added through the distillation to maintain the approximate starting volume.
10. The de was determined at methyl ester **8b** via SFC (Chiralcel OF column).
11.  and  were identified by LCMS of the crude reaction mixture of **7** with iodine in MeOH.
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13. In a simplified system, water acidified to pH 1, 2, 3, and 5 by aqueous HCl was used in the iodocyclization deprotection of Alloc-phenylglycine methyl ester. The reaction was monitored by HPLC over 24 h. No noticeable differences were observed between the reactions.
14. *Typical procedure*: To a solution of *N*-Alloc-amine or *N*-Alloc-amino-methyl ester (1.0 g) in dry acetonitrile (12 mL) at room temperature was added water (3 equiv) followed by iodine (3 equiv). The reaction mixture was heated to 60 °C and aged for 8–16 h. After such time, the reaction was cooled to 10 °C, quenched with a 20% solution of sodium sulfite, and extracted with CH_2Cl_2 (3×15 mL). The organic and aqueous layers were quantitatively assayed by HPLC for product.
15. (a) Olivero, A. G.; Cassel, J. M.; Poulsen, *J. R. PCT Int. Appl.* WO 93/22451, 1993; (b) Nagano, N.; Hara, R.; Murakami, Y.; Nakano, K.; Kouda, A.; Maeda, T.; Shibanuma, T.; Yamazaki, A.; Matsui, H. *Eur. Pat. Appl.* 84308969.9, 1985.