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Iodide Dealkylation of Benzyl, PMB, PNB, and *t*-Butyl *N*-Acyl Amino Acid Esters via Lithium Ion Coordination

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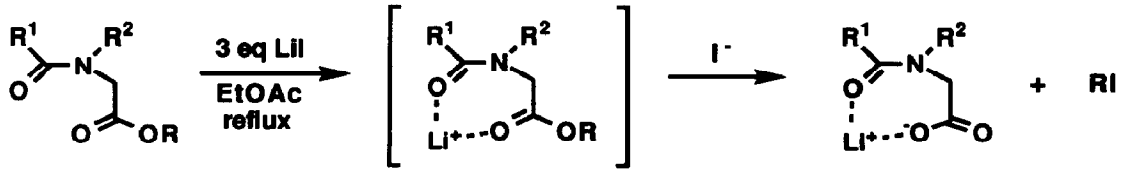
Key Words: ester dealkylation; deesterification; lithium iodide; N-acyl amino acid esters; beta-lactams

Abstract: Lithium iodide promotes ester dealkylation in compounds containing an amide carbonyl in the γ-position to the ester carbonyl, as is found in *N*-acyl amino acid esters. Activation of the ester carbonyl via lithium ion coordination is facilitated by aprotic non-polar solvents such as THF and EtOAc. This process is not limited to methyl esters but readily dealkylates benzyl, PMB, PNB, and *t*-butyl esters and is especially suitable for use with ß-lactam esters because of the mild conditions.

Traditionally, ester cleavages with lithium iodide have been performed with a tertiary amine as the solvent and are run at that amine's boiling point.[1,2] However, these reactions are limited to methyl esters. Dialkyl amides like DMF may also be used as solvents.[3,4] DMF facilitates nucleophilic substitution by halide ions, but reactions in this solvent, as in the tertiary amines, are slow and require high temperatures. These harsh conditions are not suitable for sensitive compounds, including many ß-lactams.[5] Magnesium iodide has been reported to remove esters from aliphatic and aromatic carboxylic acids in aprotic non-polar solvents,[6] but one to five days are required to complete the reaction. We report here a faster, milder method for cleaving a variety of normal esters using lithium iodide in aprotic non-polar solvents which is specific for compounds containing an amide carbonyl in the γ-position to the ester carbonyl (as in *N*-acyl amino acid esters and ß-lactams). This arrangement brings into play coordination with the lithium ion. In these systems there is a "pulling factor" via coordination with lithium ion and a "pushing factor" from the nucleophilic iodide ion both of which contribute to the carbon-oxygen bond cleavage.[7] In contrast the lithium iodide in refluxing pyridine system looses the "pulling factor" because coordination of the oxygen with lithium ion is minimal in pyridine.

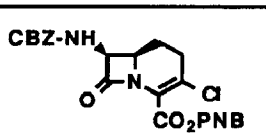
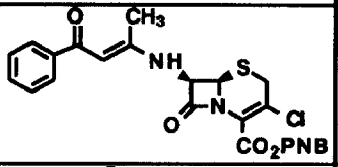
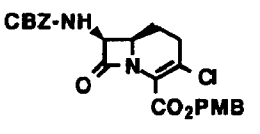
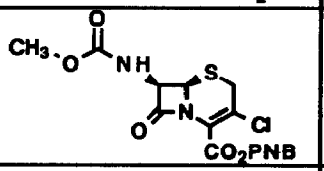
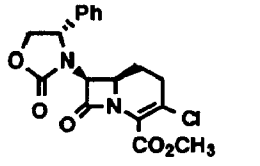
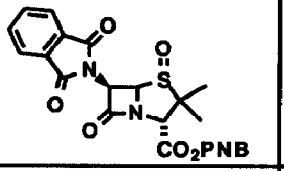
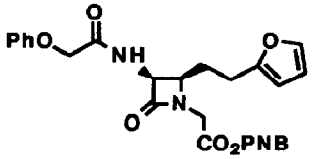
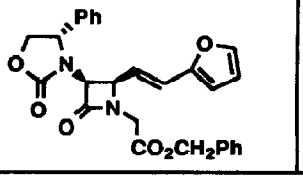


R = Benzyl, *p*-Methoxybenzyl (PMB), *p*-Nitrobenzyl (PNB), *t*-Butyl, Me

Deesterification is effected by using 3 equivalents of lithium iodide in an aprotic non-polar solvent with a dielectric constant less than ten. Preferred solvents are ethyl acetate ($\varepsilon = 6.0$) and tetrahydrofuran ($\varepsilon = 7.6$); however, other solvents can be employed. For example, dichloromethane ($\varepsilon = 8.9$) gives a clean reaction, but the rate is significantly slower because of the lower reflux temperature. Activation by the lithium ion seems to be lost if the solvent dielectric constant is above ten.[8] The reaction is run at temperatures from room temperature to the reflux temperature of the solvent, and reaction times vary from a few minutes up to 24 hours depending upon the substrate and solvent used. Because of the activation provided by coordination to lithium the method is not restricted to methyl esters but readily dealkylates benzyl, *p*-nitrobenzyl (PNB), *p*-methoxybenzyl (PMB) and even *t*-butyl esters.

This method is especially useful for removing ester protecting groups from ß-lactam compounds because of the mild conditions. Table 1 shows examples of ß-lactam compounds which were readily deesterified.[9] However, there is a limitation for the more reactive bicyclic ß-lactams in that normal amide side chains cannot be employed. In these cases intramolecular attack of the amide oxygen opened the ß-lactam.[10] The ß-lactam carbonyl is involved in coordination of the lithium ion and made more reactive in much the same way as if it were protonated, causing the ß-lactam ring to open in one instance before the reflux temperature was reached.

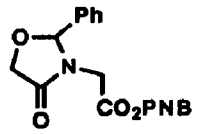
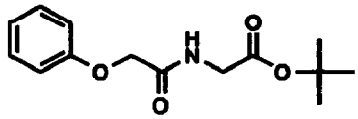
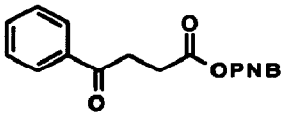
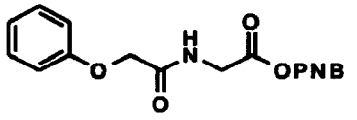
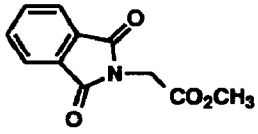
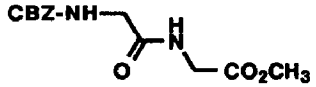
Table 1. Ester Cleavage With LiI: ß-Lactam Examples

COMPOUND	Yield[a] of Acid as Li^+ Salt	COMPOUND	Yield[a] of Acid as Li^+ Salt
	76% EtOAc 3 hr.		70% THF 12 hr.
	56% EtOAc 3 hr.		95% EtOAc 1.5 hr.
	55% (93% in situ) EtOAc 4.5 hr.		60%[b] EtOAc 2.25 hr.
	98% EtOAc 5 hr.		26%[b] (70% in situ) EtOAc 16 hr.

a) The yields reported are of isolated, crystalline solids; *in situ* yields are taken from HPLC area percents.
b) Isolated as the acid.

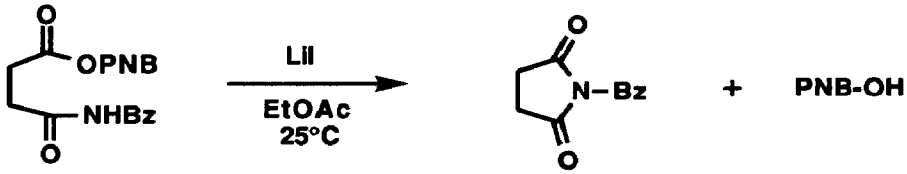
The lithium iodide dealkylation was also run on many non-ß-lactam compounds with a variety of ester groups. Results indicate that a carbonyl in the γ-position to the ester carbonyl is essential for ester activation by coordination with lithium ion. While *N*-acyl amino acid esters are obvious candidates for this reaction, we found one γ-keto ester which underwent ester dealkylation, although very slowly. Examples of these compounds are shown in Table 2.

Table 2. Ester Cleavage With LiI: γ-Carbonyl Examples

COMPOUND	Yield[a] of Acid as Li^+ Salt	COMPOUND	Yield[a] of Acid as Li^+ Salt
	87% EtOAc 7.5 hr.		53%[b] EtOAc 23 hr.
	72% EtOAc 96 hr.		85% EtOAc 24 hr.
	92% EtOAc 20 hr.		35%[b] EtOAc 36 hr.

a) The yields reported are of isolated, crystalline solids. b) Isolated as the acid.

There are a few γ-amido carbonyl compounds which do not give the desired ester cleavage reaction; for example, a succinic acid derivative cyclized rapidly at room temperature to give the succinimide. In this case the amide nitrogen was on the opposite side of the γ-carbonyl and available to form a five-membered ring.



However for *N*-acyl amino acid esters, including most ß-lactams, lithium iodide dealkylation in aprotic nonpolar solvents is an attractive alternative for removing a variety of esters. The lower temperatures and the choice of solvents make it a mild method for use with sensitive substrates.

References and Notes:

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5. While the method is not general, some carbacephems and monocyclic ß-lactams are stable enough to survive lithium iodide in refluxing pyridine; see: a) Mochida, K.; Hirata, T. *Chem. Pharm. Bull.*, **1988**, *36*, 3642-3645 and b) Bose, A. K.; Tsai, M.; Sharma, S. D.; Manhas, M. S. *Tett. Lett.*, **1973**, *39*, 3851-3852.
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