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# Fast ester cleavage of sterically hindered α- and β-aminoesters under non-aqueous conditions. Application to the kinetic resolution of aziridine esters

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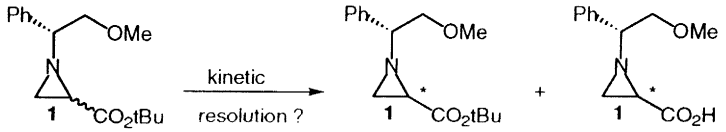
**Abstract**

Various protected α- and β-aminoesters undergo fast ester cleavage by treatment with *t*-BuOK in THF. The accelerating effect of a neighboring chelating group was used for the efficient kinetic resolution of non-racemic aziridine esters. 

In the preceeding paper we reported that aziridines **1** could be deprotonated and functionalized in a stereoselective way.[1] However, the obtention of each diastereomer required a chromatographic separation which proved to be tedious on a multigram scale. We therefore decided to investigate the ester cleavage of such species under kinetic resolution, which could lead to a diastereomerically pure water-soluble aziridino acid on the one hand, and its epimeric ester on the other hand (Scheme 1).




Scheme 1.

Esters are extensively used as a protective group for carboxylic acids, and numerous methods have been reported for their preparation and cleavage.[2] Among them, the cleavage of sterically hindered esters using non-aqueous conditions ($H_2O$, 2 equiv., *t*-BuOK, 8 equiv.) has been described by Gassman and Schenk.[3] The authors established that, under these conditions, deprotection of esters occurred via an acyl–oxygen cleavage ($B_{AC}2$), resulting from a tetrahedric intermediate (Scheme 2).

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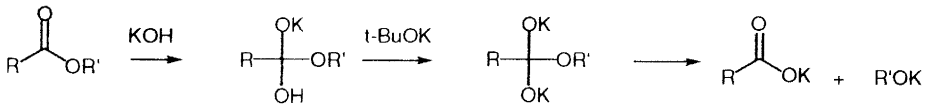
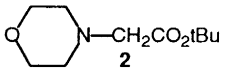
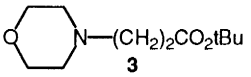
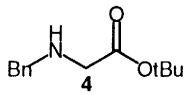
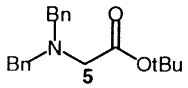
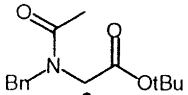
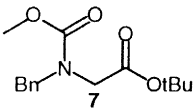
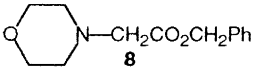
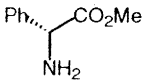



Scheme 2.

We assumed that the stabilization of such an intermediate by an intramolecular chelation could speed up the rate of hydrolysis. This hypothesis was first investigated on various α- and β-aminoesters (Table 1).

Table 1

RCOOR' —(t-BuOK, THF, 0 °C)→ RCOOH

| entry | compound | t-BuOK (eq.) | time (h.) | yield (%) |
|---|---|---|---|---|
| 1 |  **2** | 1.1 | 12 | 0 |
| | | 2 | 0.7 | quant. |
| | | 5 | 0.5 | quant. |
| 2 |  **3** | 5 | 2 | quant. |
| 3 |  **4** | 2 | 1 | 82 |
| | | 5 | 0.5 | 53 |
| 4 |  **5** | 2 | 6.5 | 0 |
| | | 5 | 1 | 71 |
| 5 |  **6** | 2 | 3.5 | quant. |
| | | 5 | 0.5 | 0 |
| 6 |  **7** | 5 | 2 | quant. |
| 7 |  **8** | 2 | 5 | 97 |
| 8 |  **9** | 5 | 0.25 | 35 |

Deprotections were performed under the following conditions: The aminoester (200 mg) was dissolved in 10 mL of freshly distilled THF at 0°C and potassium *t*-butoxide[4] was subsequently added. The reaction was monitored by thin layer chromatography.[5]

Two equivalents at least of *t*-BuOK are required to perform a complete deprotection (Table 1, entry 1) and rate acceleration is observed if three additional equivalents are added.[6] The β-aminoester **3** (entry 2) is deprotected as well, but the reaction proved to be slower than with the α-aminoesters. Cleavage also occurs with *N*-substituted glycine *t*-butyl ester (entry 3) whereas the rate of hydrolysis seems to be

slowed down if the nitrogen of glycine is sterically more crowded (entry 4). Indeed it has already been noticed that a dibenzylated nitrogen is a poor chelating group.[7]

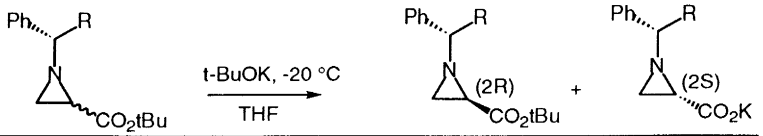
Interestingly, the deprotection of a *t*-butyl ester can be achieved in the presence of an amide or a carbamate function (entries 5 and 6). However in the former case, an excess of *t*-BuOK probably led to the hydrolysis of the amide, as previously described by Gassman and co-workers.[8] Benzylic aminoesters are also hydrolyzed, as shown in entry 7.

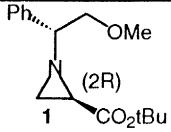
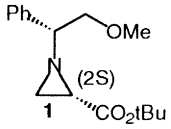
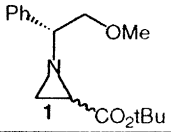
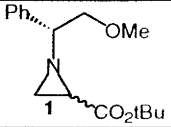
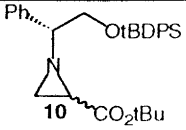
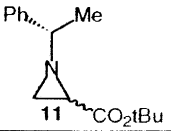
The major drawback of this method of deprotection is the highly basic medium. We observed complete racemization with chiral enolisable compounds such as *R*-(−)-phenylglycine methyl ester (entry 8).

Furthermore, the rate of deprotection proved to be faster in the presence of a chelating group (0.5 to 2 h) than in the case of simple esters (4–24 h).[3]

These results prompted us to study the influence of a chiral group involved in the transient chelated intermediate, which could lead to the kinetic resolution of non-enolisable aminoesters. This hypothesis was studied using several chiral aziridine esters[9] (Table 2).

Table 2




| Entry | Compound | t-BuOK (eq.) | time (h.) | ester yield ; (d.e.)* | acid yield ; (d.e.)* |
|---|---|---|---|---|---|
| 1 |  | 5 | 1.5 | 0 ; (-) | quant. ; (>95 %) |
| 2 |  | 5 | 1 | 0 ; (- ) | quant. ; (>95%) |
| 3 |  | 3 | 2 | 42% ; (>95%) | 58% ; (73%) |
| 4 |  | 5 | 1 | 50% ; (>95%) 2R | 48% ; (>95%) 2S |
| 5 |  | 5 | 2.5 | 80% ; (60%) | 20% ; (60%) |
| 6 |  | 5 | 1 | 50% ; (40%) | 50% ; (40%) |

* Determined by $^{1}H$ and $^{13}C$ NMR analysis of the crude reaction mixture.

Entries 1 and 2 show that both diastereomers are deprotected at −20°C, but at a different rate, and

without any detectable racemization. An efficient resolution is obtained with five equivalents of *t*-BuOK (entry 4). If only three equivalents of base are used, the reaction is slower and a small part of ester **1** (2*R*) is hydrolyzed (entry 3). If the oxygen of the side chain is sterically crowded (entry 7) or absent (entry 8), the resolution is incomplete.

These results suggest that the tetrahedric intermediate as proposed by Gassman and co-workers is probably better stabilized in the case of diastereomer **1** (2*S*) as compared to the diastereomer **1** (2*R*) and leads to differences in the ester cleavage and thereby kinetic resolution.

In summary, we presented here a cleavage of sterically crowded α- and β-aminoesters, using non-aqueous conditions. We established a stereoselective accelerating effect of a neighboring heteroatom in the deprotection procedure. This effect was used for the preparation of optically pure aziridine ester **1** (2*R*) and acid **1** (2*S*) through an efficient kinetic resolution. This method is of particular interest for the preparation of the above mentioned aziridines whose use in asymmetric synthesis is under investigation in our laboratory.

## Acknowledgements

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## References

1. Alezra, V.; Bonin, M.; Micouin, L.; Husson, H.-P. *Tetrahedron Lett*., **2000**, *41*, 651.
2. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd Ed; Wiley: New York, 1981.
3. Gassman, P. G.; Schenk, W. N. *J. Org. Chem.* **1977**, *42*, 918.
4. Unlike the Gassman standard procedure, no additional amount of water was needed to perform the reaction. We assume that moisture present in the solvent and in unsublimed potassium *t*-butoxide is enough to provide the KOH equivalent needed for the first step of the deprotection.
5. Typical procedures: (a) Deprotection of compound **4**: To a solution of aminoester **4** (200 mg, 0.9 mmol) in THF (10 mL) was added *t*-BuOK (203 mg, 1.8 mmol) at 0°C. Saturated $NH_4Cl$ aqueous solution (1 mL) was added after 1 h and the solvent was subsequently evaporated. The crude mixture was dissolved in a small amount of water, neutralized by an HCl 1N solution and concentrated. The crude mixture was triturated in MeOH and the solvent was evaporated to give 122 mg of amino acid (82%). (b) Kinetic resolution of esters **1**: To an equimolar solution of aziridines **1** (2*R*) and **1** (2*S*) (150 mg, 0.54 mmol) in THF (10 mL) was added *t*-BuOK (304 mg, 2.70 mmol) at −20°C. After 1 h was added a small amount of a saturated $NH_4Cl$ aqueous solution, the mixture was dried on magnesium sulfate and filtrated. THF was evaporated, the crude product was dissolved in a mixture of $H_2O/CH_2Cl_2$ and extracted three times with $CH_2Cl_2$. The organic phases were combined, dried and evaporated to give ester **1** (2*R*) as an oil (75 mg, 50%). The aqueous phase was treated as described for compound **3** (see Ref. 5a) to give acid **1** (2*S*) as its potassium salt (67 mg, 48%). **1** (2*R*).
6. 'Classical' saponification (KOH, $H_2O$, THF) of this compound required 24 h for completion.
7. (a) Chung, S.-K.; Kang, D.-H. *Tetrahedron: Asymmetry* **1997**, *8*, 3027. (b) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1531.
8. Gassman, P. G.; Hodgson, P. K. G.; Balchunis, R. J. *J. Am. Chem. Soc.* **1976**, *98*, 1275.
9. These compounds were prepared according to a reported procedure. (a) Harada, K.; Nakamura, I. *J. Chem. Soc., Chem. Commun.* **1978**, 522. (b) Häner, R.; Maetzke, T.; Seebach, D. *Helv. Chim. Acta* **1987**, *70*, 1676.