Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 821–823
Tetrahedron Letters

# Synthesis of methyleneaminodipeptides via ring opening of a 2-(*t*-butoxycarbonylmethyl)aziridine derivative

Josiane Thierry* and Vincent Servajean

*Institut de Chimie des Substances Naturelles, CNRS, 91198 Gif-sur-Yvette Cedex, France*

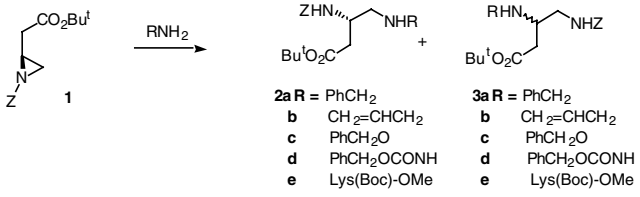
Received 22 August 2003; revised 30 October 2003; accepted 7 November 2003

**Abstract**—The reactivity of 2-(*t*-butoxycarbonylmethyl)aziridine-1-carboxylic acid benzyl ester has been studied with various *N*-nucleophiles. The ring-opening reaction was always regioselective, the nucleophile attacking preferentially the less hindered carbon of the aziridine. The reaction was used to prepare a methyleneamino pseudodipeptide using the α-amine of a lysine ester.

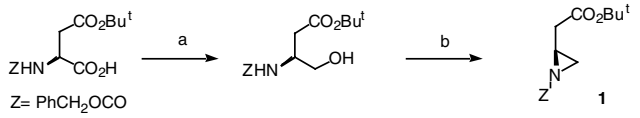

During the course of our program on the synthesis of analogues of the tetrapeptide AcSDKP,[1] an inhibitor of the hematopoietic stem cells, we had to prepare pseudopeptides of the methyleneoxy and methyleneamino types. To reach this goal, we envisioned using a single intermediate, which could yield both types of pseudopeptides, and that the aziridine derived from the β-amino alcohol Asp-ol could be such an intermediate.

Aziridines have recently attracted considerable attention in synthesis,[2] as they are reactive intermediates, which can be opened with a variety of nucleophiles such as amines, alcohols, thiols or carbanionic species. Although most reports deal with activated aziridines, mainly sulfonamides, we considered using a carbamate-protected aziridine as the required synthon. The reactivity of the aziridine **1** has been explored with simple amines and with the L-lysine derivative H-L-Lys(Boc)-OMe (Scheme 1).

The aziridine **1** was obtained from the amino alcohol Z-L-Asp(OBu$^t$)-ol, itself derived from the amino acid Z-L-Asp(OBu$^t$)-OH,[3] in 90% yield by way of a Mitsunobu reaction[4] (Scheme 2).




**Scheme 1.** Ring-opening reactions of aziridine **1** with *N*-nucleophiles.




**Scheme 2.** Synthesis of aziridine **1** (a) (i): isobutyl chloroformate, *N*-methylmorpholine, −15 °C, (ii): $NaBH_4$, $H_2O$, −10 °C; (b) $PPh_3$, DEAD, THF, 30 min, 0 °C, 18 h, rt, 60–90% for two steps.

The results of the reaction of **1** with various amines according to the conditions reported in the literature[5] are recorded in Table 1.

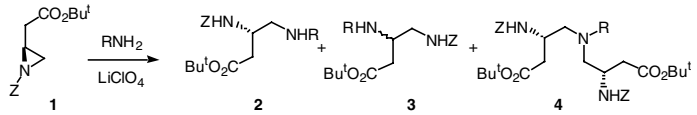
All the reactions were run in acetonitrile with 1.2 equiv of nucleophile and 1 equiv of $LiClO_4$,† (except for entry d, where 2.4 equiv of benzylcarbazate were used), at 80 °C (except for entry b where the reaction was run at

*Keywords*: Pseudopeptides methyleneamino; Aziridine opening; Microwaves; Lithium perchlorate; Solvent-free reaction.
* Corresponding author. Tel.: +1-69-823126; fax: +1-69-07-7247; e-mail: josiane.thierry@icsn.cnrs-gif.fr

† Note: Lithium perchlorate in organic solvents is a potential explosive hazard. It must be handled in small amounts and with appropriate care.

0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2003.11.047

**Table 1.** Reactivity of **1** towards *N*-nucleophiles




| Entry | R | Reaction time (h) | Yield[a] **2** + **3** (%) | Ratio **3**:**2** | Yield[a] **4** (%) |
|---|---|---|---|---|---|
| **a** | $PhCH_2$ | 22 | 60 | 1:11 | 3 |
| **b** | $CH_2{=}CH{-}CH_2$ | 29 | 60[b] | 1:11 | 6 |
| **c** | $PhCH_2O$ | 22 | 61 | 1:4 | — |
| **d** | $PhCH_2OCONH$ | 8 days | 63 | 1:14 | — |
| **e** | L-Lys(Boc)-OMe | 18 | 83 | —[c] | 5 |

[a] Isolated yield of purified products. Yields have not been optimized.
[b] Aziridine **1** (6%) was recovered.
[c] **3e** was not isolated.

45 °C). The compounds obtained through purification by silica gel flash chromatography were characterized by IR, $^1H$ NMR, $^{13}C$ NMR, and mass spectroscopy.

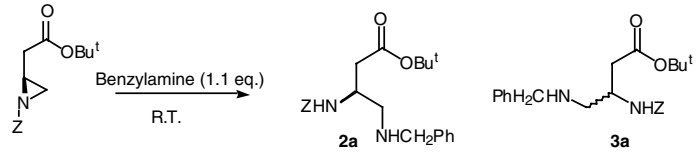
All the reactions were slow and gave satisfactory yields. The regioselectivity was in most cases high yielding a large excess of **2**, the regioisomer resulting from the attack of the nucleophile on the least substituted carbon. The best yield was obtained with the lysine derivative (entry e). This reaction yielded compound **2e** (Z-L-Asp(OBu$^t$)Ψ($CH_2NH$)-L-Lys(Boc)-OMe), methyleneamino pseudodipeptide, which can be further elongated as the protecting groups are orthogonal. The 1,2-diamines **2a**–**d** are interesting synthetic intermediates as they are β-amino acids substituted at C-4.

Small amounts of compounds **4a**, **4b**, and **4e** were isolated. They are formed by the attack of the respective secondary amine **2** on **1** and their formation could be avoided by using an excess of the original amine nucleophile.[6]

The aziridine **1** was also treated with benzylamine (1.2 equiv) in THF in the presence of $Yb(OTf)_3$ (0.1 equiv) at 45 °C according to the conditions reported by Meguro et al.[7] The reaction was rather slow (65 h) and yielded a mixture of regioisomers (72%) in a ratio (**3a**:**2a**) of 1:8 along with a 12% yield of **4a**.

In order to achieve improved regioselectivity, the use of a solid support was considered. In another set of experiments, aziridine **1** was treated with 1.1 equiv of benzylamine on different solid supports: alumina (activated or unactivated), silica gel, or Bentonite under solvent-free conditions (Table 2). The reaction was run in most cases at room temperature.

**Table 2.** Ring-opening of **1** under solvent-free conditions with benzylamine




| Entry | Support[a] | Conditions | Yield[b] **2a** + **3a** (%) | Ratio **3a**:**2a** |
|---|---|---|---|---|
| 1 | Activated alumina[c] | 9 d | 53 | 1:9 |
| 2 | Activated alumina[c] | 2.7 d, rt, MW,[e] 3 h | 34 | —[d] |
| 3 | Alumina | 6.6 d | 60 | 1:11 |
| 4 | Silica gel | 8.6 d | 46 | 1:5 |
| 5 | Silica gel | 4.8 d, rt, MW,[e] 3 h | 46 | 1:2.4 |
| 6 | Bentonite | 8.6 d | 55 | —[d] |
| 7 | Bentonite | MW,[e] 1 h | 60[f] | 1:11 |

[a] Support (600 mg/mmol): Alumina for chromatography (70–230 mesh) from Merck; Silica gel for chromatography (230–400 mesh) from Merck; Bentonite from Aldrich. Aziridine **1** was dispersed on the solid support along with benzylamine (1.1 equiv). The products were extracted from the solid support by triturating the solid with $CH_2Cl_2$/MeOH 80/20.
[b] Isolated yield of purified products. Yields have not been optimized.
[c] Neutral alumina was activated by heating in an oven at 550 °C for 18 h.
[d] Product **3a** was not isolated.
[e] Microwave experiments were conducted in sealed tubes with a monomodal apparatus: Discover from CEM μ Waves (Orsay, France). Experiment parameters were: power: 40 W, temperature: 80 °C.
[f] **4a** (4%) was also isolated.

All the reactions proceeded very slowly, taking several days to reach completion. The use of activated alumina yielded a mixture of regioisomers **2a** and **3a** (53%). Unactivated alumina gave a comparable yield and a similar ratio of **2a** and **3a** (entries 1 and 3). Activation of the reaction with microwaves for 3 h resulted in a lower yield but only **2a** was obtained (entry 2). The same phenomenon was not observed when the reaction mixture was exposed on silica gel to microwaves since the same overall yield of **2a** and **3a** was obtained. However, it is noteworthy that the ratio of **3a**:**2a** was significantly different (entries 4 and 5). Bentonite seems to be the most appropriate support; the reaction was considerably faster when exposed to microwaves while the same yield of regioisomers and a good regioselectivity in favor of **2a** was obtained in both cases (entries 6 and 7).

The ring-opening reaction of aziridine **1** with different *N*-nucleophiles demonstrates good regioselectivity, the major regioisomer resulting from the attack on the secondary carbon. The compounds obtained through this reaction are valuable polyfunctionalized intermediates.[8] Some of them (**2a**–**b**, **2e**, **3a**–**b**) may be further transformed as they are orthogonally protected. We have presented here a new route to methyleneamino pseudopeptides, which represents a valid alternative to the existing methology.[9] The conditions are mild enough to be applied to most α-amino esters or highly functionalized amines as nucleophiles.

The solvent-free reaction of **1** with benzylamine on Bentonite under microwave activation gave the same results as the classical reaction but in a much shorter time and represents a significant improvement in the procedure.

## References and notes


1. Gaudron, S.; Adeline, M.-T.; Potier, P.; Thierry, J. *J. Med. Chem.* **1997**, *40*, 3963–3968.
2. (a) McCoull, W.; Davis, F. A. *Synthesis* **2000**, 1347–1365; (b) Zwanenburg, B.; ten Holte, P. In *Topics in Current Chemistry*; Springer Verlag: Berlin, Heidelberg, 2001; Vol. 216, pp 93–124; (c) Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247–258.
3. Rodriguez, M.; Llinares, S.; Doulut, S.; Heitz, J.; Martinez, J. *Tetrahedron Lett.* **1991**, *32*, 923–926.
4. Mitsunobu, O. *Synthesis* **1981**, 1–28.
5. Anaya de Parrodi, C.; Vasquez, V.; Quintero, L.; Juaristi, E. *Synth. Commun.* **2001**, *31*, 3295–3302.
6. Lake, F.; Moberg, C. *Eur. J. Org. Chem.* **2002**, 3179–3188.
7. Meguro, M.; Asao, N.; Yamamoto, Y. *Tetrahedron Lett.* **1994**, *35*, 7395–7398.
8. Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580–2627.
9. (a) Szelke, M.; Leckie, B.; Hallett, A.; Jones, D. M.; Sueiras, J.; Atras, B.; Lever, A. F. *Nature (London)* **1982**, *299*, 555–557; (b) Martinez, J.; Bali, J.-P.; Rodriguez, M.; Castro, B.; Magous, R.; Laur, J.; Lignon, M.-F. *J. Med. Chem.* **1985**, *28*, 1874–1879.