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The synthesis of *N*-acyl-2-hydroxymethyl aziridines of biological interest

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Abstract—A practical synthesis of the title compounds from protected amino acylazides is described. All the compounds might be considered as a novel class of dipeptide isostere precursors; they all induce lymphocyte proliferation and protein production as observed from preliminary biological tests.

1. Introduction

In recent years, several papers and reviews have been published regarding a number of aspects of aziridines chemistry.[1–13] It is well known that natural or synthetic compounds that contain the aziridine moiety generally exhibit interesting biological activity such as antitumour[14] or protease inhibitor properties.[15] Of special interest for us was the assumption that *N*-alkoxy aziridines stimulate the production of leukocytes.[16] On the synthetic background, it is well known that vicinal azido alcohols and triphenylphosphine (Ph_3P) give five-membered intermediates that may afford aziridines spontaneously.[17]

We therefore assumed that under the same conditions an iminophosphorane derived from an amino acyl azide would react with an epoxide to yield an aziridine. Glycidol was considered to be the best epoxide since its alkoxide would react with an iminophosphorane to give a nitrogen nucleophile that would open the epoxide, thus leading to hydroxylated compounds that might be considered as analogues or precursors of hydroxy dipeptides isosteres.[18–20]

2. Results and discussion

In an initial attempt to check our hypothesis, racemates of phthalimido amino acids and glycidol were used as starting materials. Phthalimido amino acids were prepared according to modified literature procedures[21] and were recrystallized. They were further converted into azides according to Palomo and co-workers.[22] The azides were used without further purification in the next step to yield the target iminophosphoranes according to mechanism displayed in Scheme 1.

The iminophosphoranes were submitted to a dropwise addition of the glycidol oxyanion generated by treatment of the epoxy alcohol with NaH in dry ether.[23] The oxyanion might initiate attack on the phosphorus atom of **1** generating a nitrogen nucleophile that opens the epoxide ring, thus leading either to a five-membered (a) or a six-membered ring intermediate (b). However, we believe that the five-membered oxazaphospholidine would be more favoured.

After quenching the reaction mixture with an aqueous solution of NH_4Cl and removal of triphenylphosphine oxide, all compounds were purified on a silica gel column using petroleum ether–dichloromethane as the eluent. Satisfactory IR, ^1H NMR, ^{13}C NMR and microanalyses were obtained for all compounds and an example is detailed in the experimental (Table 1).

During NMR analysis, it was observed that signals were not pure multiplets, thus indicating the presence of a mixture of diastereoisomers. Of special interest were the doublet at 1.75 and the quartet at 4.92 ppm. Actually they were superimposed doublets and quartets of almost the same magnitude and could not be separated by NMR analysis.

Keywords: Aziridines; Peptide isosteres; Amino acids.
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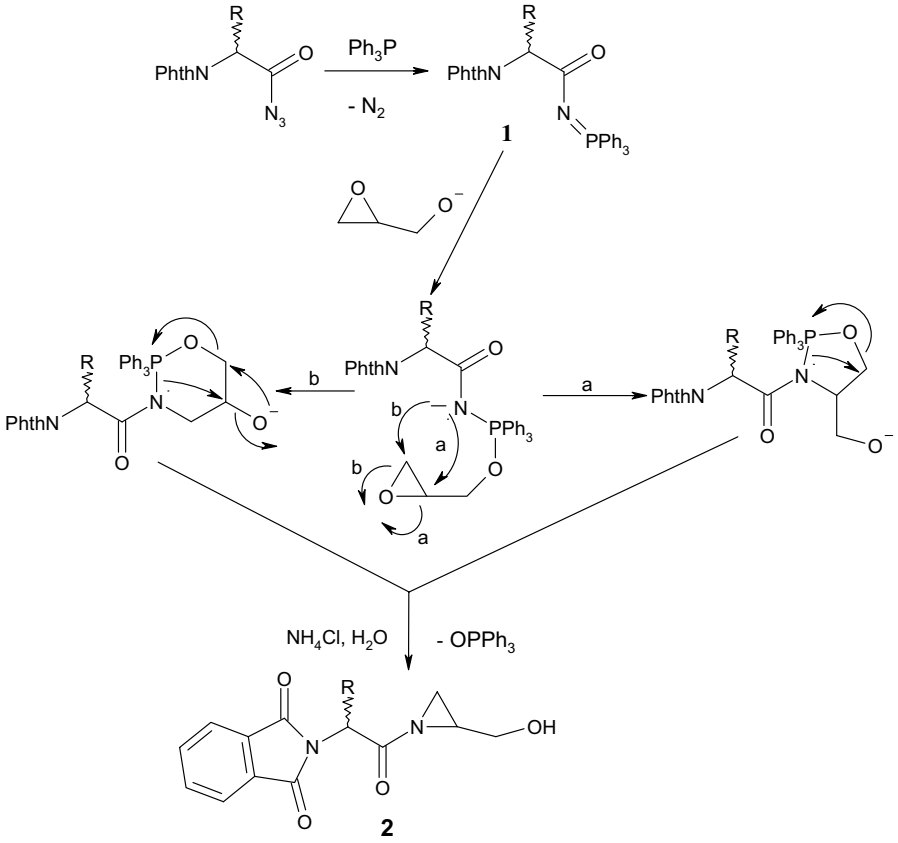
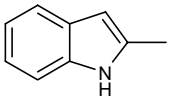


Scheme 1. Plausible mechanism for the conversion of the starting azides into aziridines.

Table 1. N-protected hydroxymethylaziridines

2	R	Yield (%)
a	H	51
b	Me	60
c	$PhCH_2$	98
d		96
e	$(H)PhthN(CH_2)_4$	60
f	Me_2CH	52
g	$(H)PhthNC_6H_4CONH$	45
h	Me_2CHCH_2	50

In vitro biological tests were performed on isolated human lymphocytes and each aziridine was used at successive concentrations of 100, 50 and 25 μM. Glycylaziridine (**2a**) was the most potent in inducing cell proliferation when used at any of the above-mentioned concentrations. Aminohippuryl aziridine (**2g**) was the only one to inhibit cell proliferation when a concentration of 100 μM was used. However, the same compound induced cell proliferation in the presence of concavalin-A at a concentration of 25 μM, whereas other aziridines induced lymphocyte proliferation along with protein synthesis to a lower extent than glycyl aziridine.

3. Conclusion

We have developed a straightforward synthesis leading to disubstituted aziridines of biological interest. The synthesis requires simple reagents and the overall procedure provides good to excellent yields of product **2**. In vitro preliminary biological studies performed with racemates have shown promising activity on the proliferation of lymphocytes. However, work with natural amino acids and both (*R*)- and (*S*)-glycidol is under investigation in order to obtain more accurate data on the biological activity dependence on stereochemistry as well as chemical and spectroscopic analytical data of pure stereoisomers.

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22. Arrieta, A.; Aizpurua, J. M.; Palomo, C. *Tetrahedron Lett.* **1984**, *25*, 3365–3368, Example of an acyl azide: Phthalimido alanylazide: yield: 78%; mp 79 °C (dec); IR (KBr): 2145, 1730, 1718 cm^{-1}. ^1H NMR ($CDCl_3$): 1.68 (d, $J = 8$ Hz, 3H, C**H**$_3$), 3.02 (q, $J = 8$ Hz, 1H, C**H**), 7.83 (s, 4H, **PhthN**).
23. Synthesis of aziridines. Typical procedure: 2-hydroxymethyl-1-(*N*-phtaloylalanyl) aziridine **2b**.
Solution A: *N*-acylazide (25 mmol) was introduced under nitrogen to a dry flask containing dry dichloromethane (100 mL). The solution was cooled to 0 °C and triphenylphosphine (25 mmol) was added in small portions and the solution was stirred for 2 h.
Solution B: In a separate flask, sodium hydride (27 mmol) previously washed with ether was introduced in ether (50 mL) and the suspension stirred under nitrogen. To the cooled suspension was added a solution of (±)-glycidol (25 mmol) dropwise in dry ether (50 mL) over 20 min. After the addition was complete, the mixture was stirred for an additional 30 min.
Solution B was then siphoned off under nitrogen into a constant-pressure dropping funnel mounted on the flask containing solution A; this solution was added dropwise to solution A cooled in an ice bath. Following addition, the mixture was warmed to 50 °C for 1.5 h and cooled to room temperature. A solution of 10% ammonium chloride was added and the mixture was extracted with dichloromethane (3 × 25 mL). The organic extracts were combined and dried over anhydrous $CaSO_4$.
After removal of the solvent, the residue was dissolved in cold anhydrous ether (100 mL) and triphenylphosphine oxide was filtered off under suction. This operation was repeated until no solid separated from the ethereal solution. After removal of the solvent, the residue was purified on a silica gel column using petroleum ether (bp 40–60 °C) and dichloromethane (4:1).
The resulting compound was stored in the cold under dry nitrogen. Yield: 70%; mp 60 °C; IR (KBr): 3457, 1711, 741. ^1H NMR ($CDCl_3$, 200 MHz): 1.15 (d, $J = 7.2$, 2H, C**H**$_2$), 1.5 (dd, $J = 6.6$, 2 Hz, 1H, C**H**), 1.75 (d, $J = 7.4$, 3H, C**H**$_3$), 3.0 (m, 2H, C**H**$_2$–OH), 4.92 (q, $J = 7.4$, 1H, C**H**), 7.35 (s, 4H, **Phth**). ^{13}C NMR ($CDCl_3$, 50 Hz): 15.98 (**C**H$_3$), 27 (**C**H$_2$), 29.56 (**C**H), 52.09 (**C**H$_2$–OH), 52.5 (Phth–**C**H–CO), 131, 132 (**C**Har), 137 (**C**ar), 168 (CH–**C**O–N), 179 (**C**O–N–**C**O). Calcd for $C_{14}H_{14}N_2O_4$: C, 61.34; H, 5.11; N, 10.22. Found: C, 61.40; H, 5.18; N, 10.10.