METALLOPORPHYRIN-PROMOTED REARRANGEMENT OF 2-ALKYLOXAZIRIDINES

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Transformation of 2-alkyloxaziridines to the corresponding amides is efficiently catalyzed by high-valent metalloporphyrins. This novel rearrangement was used to create a peptide bond and the precursor of a dipeptide "aspartame" was obtained in good yield.

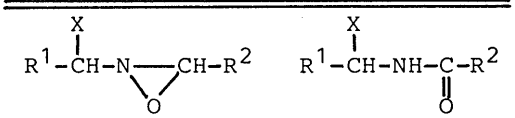
KEYWORDS 2-alkyloxaziridine; metalloporphyrin; rearrangement; Lewis acid; high-valent metal; dipeptide

Oxaziridines are rearranged into amides by heating or by irradiation with light.[1] Certain low-valent transition metals like $FeCl_2$[1b] also catalyze the rearrangements. These rearrangements have been explained as radical processes and are of considerable interest from the synthesis point of view.[2] The metal-catalyzed rearrangements apparently involve first one electron transfer from low-valent metals to oxaziridines and then metal-complexing between the resulting high-valent metals and the radical anion intermediate.[3] However, little is known about the reactivity of oxaziridines toward high-valent transition metals. If these rearrangement can be promoted by Lewis acids, higher-valent transition metals should be more effective than the corresponding lower-valent transition metals.

We report here a novel transformation of 2-alkyloxaziridines into amides in which high-valent transition metals catalyze the rearrangement, probably by an ionic mechanism. We studied first the effect on the simple metal salts of 2-alkyloxaziridines (**1**) (Table I) with a hydrogen atom at the C-3 position.

Attempts to rearrange oxaziridines (**1e-g**) with Lewis acids such as $AlCl_3$, $ZnCl_2$, $MnCl_2$, and $FeCl_3$ in CH_3CN were unsuccessful under various conditions, and p-nitrobenzaldehyde was the major product of the thermolyses. But the same reactions of **1a** with $AlCl_3$ and $FeCl_3$ under refluxing gave amides **2a** in low yields, 4% and 36% respectively. Metal chelates such as cobalt(III)acetylacetonate and vanadium oxyacetylacetonate also catalyze the rearrangement but the yields of amide **2a** were unsatisfactory (12% and 38%, respectively). From these preliminary surveys we expected that metal complexes of high-valent metals having planar structure would be efficient catalysts for the rearrangement. So we rearranged **1** in the presence of metalloporphyrins such as chloro-

Table I. Structure of Oxaziridines(1) and Amides(2)



(1) (2)

	R^1	R^2	X
a	Ph	Ph-NO_2-p	COOEt
b	Ph	Ph-OCH_3-p	COOEt
c	iso-Pr	Ph-NO_2-p	COOEt
d	Bz	iso-Pr	COOEt
e	H	Ph-NO_2-p	H
f	Me	Ph-NO_2-p	H
g	Ph	Ph-NO_2-p	H

tetraphenylporphyrin iron(III) (**TPPFeCl**) or chloro-tetraphenylporphyrin manganese(III) (**TPPMnCl**).

In a typical experiment, **TPPMnCl** (0.015 mmol) was added to a solution of **1a** (0.076 mmol) in benzene (10 ml), and the solution was refluxed for 14 h. Oxaziridines **1a-d** were rearranged smoothly to the corresponding amides **2a-d** in good yields. Similar results were obtained with the reactions under nitrogen. The control experiment without metalloporphyrins showed no thermal formation of amides **2**. As shown in Table II, **TPPMnCl** was a much better catalyst than **TPPFeCl** and the reactions with **1a-d** gave **2** in satisfactory yields. Although such conditions were less effective than the more common oxaziridines **1e-g** owing to their thermo-instability, the change of the reaction solvent from benzene to CH_3CN (i.e., the use of **TPPMnCl/CH_3CN** system) could shorten the reaction time and improve the yields of these amides (Table III). The rearrangements are also catalyzed efficiently

Table II. Metalloporphyrin-Promoted Rearrangement of 1 in Benzene[a)]

Compd	Yield of 2(%)[b)]	
	TPPFeCl	TPPMnCl
1a	95(89)	99
1b	90	90
1c	85	99
1d	82	88

a) Reactions were performed under reflux. Molar ratio of [1]:[metalloporphyrin] = 5:1. b) Determined by HPLC. c) Isolated yield.

Table III. TPPMnCl-Promoted Rearrangement of 1 in Acetonitrile

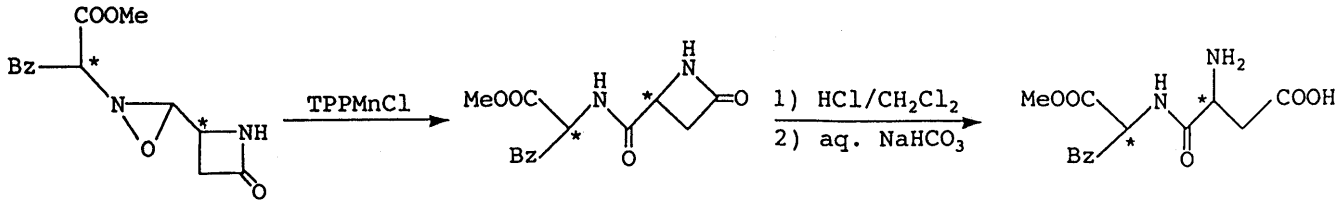
Compd	Molar ratio [1]:[TPPMnCl]	Condition		Yield of 2(%)[a)]
		Temp(°C)	Time	
1a	10 : 1	Reflux	4	99
1b	10 : 1	Reflux	4	90
1c	10 : 1	Reflux	4	95
1d	10 : 1	Reflux	4	92
1e	5 : 1	50	18	85[b)]
1f	5 : 1	50	18	90
1g	5 : 1	40	10	76[b)]

a) Isolated yields. b) p-Nitrobenzaldehyde was also obtained as by-product.

by other porphyrins with high-valent metal ions but seems to be influenced by the basicity of the axial ligand of the catalyst. For example, the reaction of **1a** with pyridine-tetraphenylporphyrin iron(III) in CH_3CN gave amide **2a** (90%) with a trace of p-nitrobenzaldehyde. However, in the same reaction with pyridine-tetraphenylporphyrin iron(II),[4)] the yield of **2a** decreased (24%) and the main product was p-nitrobenzaldehyde (61%). The formation of p-nitrobenzaldehyde can be explained by the pyridine-catalyzed eliminative ring cleavage of the oxaziridine.[5)] Consequently, **TPPMnCl/CH_3CN** is the most useful catalytic system for the oxaziridine-amide rearrangement of 2-alkyloxaziridines. In the reaction of **1d** (Table III), the proton on the C-3 position shifted in preference to the migration of the isopropyl group on the same carbon to the adjacent nitrogen. This, combined with the aforementioned results, indicates that the rearrangement proceeds by an ionic mechanism involving heterolytic cleavage of the N-O bond after the coordination of the high-valent metal ions to the oxygen atom of oxaziridines and eliminates the possibility of a radical mechanism.[1b)]

We next applied the present oxaziridine-amide rearrangement to a peptide bond formation. Oxaziridine **3**[2a)] (1.8 mmol) was treated with **TPPMnCl** (0.15 mmol) in CH_3CN (50 ml) at 50 °C for 12 h. After chromatography an aspartame precursor, **4**, was isolated in 82% yield without any decrease in the optical purity.[6)] The present method is superior to

the same photo-promoted rearrangement of 3 (60%) reported by Duhamel et al.[2a] The compound **4** could be converted to the dipeptide "aspartame"[7] by the known method.[8] Since the preparation of α-aminoaldehydes as the source of oxaziridines has been developed,[9] the **TPPMnCl**-promoted rearrangement will be a useful method for the peptide bond creation in a particular range of peptides.



3 **4** **aspartame**

Further works on the details of the reaction mechanism and the synthetic application of this novel rearrangement are in progress.

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6) Compound **4** mp 143.5-145°C (lit.[8] 144-145°C, lit.[2a] 143-144°C). $[\alpha]_D^{25}$ -43.6°(MeOH) (lit.[8] -45.3°, lit.[2a] -43.6°).

7) Aspartame: Methyl α-L-aspartyl-L-phenylalanine $[\alpha]_D^{25}$ +32° (AcOH), [lit. +32° : Y. Ariyoshi, T. Yamatani, N. Uchiyama, Y. Adachi, and N. Sato, Bull. Chem. Soc. Jpn., **46**, 1893, (1973)].

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(Received February 1, 1990)