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RECYCLIZATION OF 2-OXOTETRAHYDRO-1,3-OXAZINES ACCOMPANIED BY
DECARBOXYLATION: A CONVENIENT SYNTHESIS OF
TETRAHYDROPYRIDINE, QUINOLIZIDINE, AND INDOLIZIDINE SKELETONS

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Ethyl 6-vinyl-2-oxotetrahydro-1,3-oxazine-5-carboxylate derivatives were converted with decarboxylation into ethyl 2-substituted 1,2,5,6-tetrahydropyridine-5-carboxylates by heating with 1,8-diazabicyclo[5.4.0.]undec-7-ene in dimethylsulfoxide at 120°C. This convenient method was used to synthesize quinolizidine, indolizidine skeletons and the alkaloid, (±)-lupinine.

KEYWORDS — 2-oxotetrahydro-1,3-oxazine; tetrahydropyridine; quinolizidine; indolizidine; (±)-lupinine; (±)-lysergic acid; decarboxylation; DBU

Cyclic carbamates, such as 2-oxotetrahydro-1,3-oxazines and oxazolidin-2-ones, have been used for the stereochemically controlled synthesis¹⁾ and stereochemical assignment²⁾ of 1,3-amino alcohols and 1,2-amino alcohols.

Recently we have reported a novel transformation of ethyl 2-(N-Boc-N-methyl)-aminomethyl-3-hydroxy-3-arylpropionates into 6-aryl-2-oxotetrahydro-1,3-oxazines (1)³⁾ by treatment with methanesulfonyl chloride (MsCl)/triethylamine (TEA), and also a mechanistic consideration for the formation of 1.⁴⁾ We report here an efficient recyclization of 6-vinyl-substituted 2-oxotetrahydro-1,3-oxazines accompanied by decarboxylation to give tetrahydropyridine derivatives by heating with 1,8-diazabicyclo[5.4.0.]undec-7-ene (DBU) in dimethylsulfoxide (DMSO) as shown in Chart 1.

Chart 1

In general, β -elimination can take place via a carbanion mechanism in compounds with $-\text{CN}$, $-\text{NO}_2$, and $-\text{C}=\text{O}$ groups in the β -position of the leaving group in the presence of bases.⁵⁾ With this in mind, since 5-ethoxycarbonyl-2-oxo-1,3-oxazine (**1**) is regarded as a β -amidoxy ester, **1** was treated with lithium diisopropylamide (LDA) at -78°C in THF, and the E- and Z-mixture of ethyl β -methylamino-methylcinnamate (**3**) was isolated. Heating **1** with DBU in DMSO at 120°C also afforded **3** in good yield. At this point we realized that if vinyl groups were present at the 6-position of 2-oxotetrahydro-1,3-oxazine, cyclization could be effected and this result might be useful for the preparation of tetrahydropyridine skeletons. Accordingly, by heating the 6-styryl derivative (**2**) with DBU in DMSO, cyclization proceeded readily to yield 2-phenyltetrahydropyridine (**4**) in quantitative yield, presumably via diene⁶⁾ as shown in Chart 2.

Chart 2

This method was applicable to the conversion of the oxazinone (**6**), which is an unavoidable side-product (ca. 30% yield) in our procedure⁷⁾ starting from the aldehyde (**5**) for the total synthesis of (+)-lysergic acid, to the key intermediate (**7**) in quantitative yield.⁸⁾

Chart 3

Additionally, the quinolizidine and indolizidine skeletons were synthesized. Aldol condensation of the anion of N-Boc-2-piperidineacetate (**8a**)⁹⁾ with acrolein (LDA/THF/ -78°C) afforded the alcohol (**9a**) in 95% yield as a diastereoisomeric mixture, which was then treated with MsCl/TEA in dichloromethane. The products were separated by column chromatography (silica gel/benzene : EtOAc, 2 : 1) to

give the cyclic carbamate (**10a**)¹⁰ and the mesylate (**11a**)¹⁰ (ca. 1:1) in 85% combined yield. Deprotection of **11a** followed by heating with DBU in DMSO according to our previous manner⁷) gave quinolizidine (**12a**)¹¹ in 67% yield. [IR (neat)

Chart 4

ν 2800, 2755 (Bohlmann band), 1705 (CO), 1640 (C=C) cm^{-1} ; ^1H NMR (CDCl_3) δ 6.82 (1H, m)]. Heating **10a** with DBU (2 eq) in DMSO at 120°C for 4 h gave **12a** in 82% yield. Further, without isolation of the intermediates, **9a** was subjected to the following sequence in turn: i) MsCl/TEA/r.t. , ii) HCl/EtOAc/r.t. , iii) DBU/DMSO/ 120°C . The final reaction product was purified by column chromatography (silica gel/ $\text{CHCl}_3\text{:MeOH}$, 20:1) to afford **12a** in 85% overall yield from **10a**. Catalytic hydrogenation (PtO_2/H_2 in MeOH) of **12a** and lithium aluminum hydride reduction of the resulting saturated ester gave (+)-lupinine (**13**), mp $50\text{--}51^\circ\text{C}$, in 65% yield. Their IR and ^1H NMR spectral data were identical with those reported.¹²) Application of the same sequences to the N-Boc-pyrrolidineacetate (**8b**)⁹) provided a route to indolizidine (**12b**) [^1H NMR (CDCl_3) δ 3.40 (1H, m), 6.90 (1H, m)] after purification by column chromatography at the end of the process, without isolation of the intermediates, in 81% overall yield. Similarly, the intermediates, cyclic carbamate (**10b**) (66%) and mesylate (**11b**) (22%), were isolated and converted to indolizidine (**12b**) in 64% yield from the former and 87% yield from the latter under the same conditions as above. Attempted synthesis of (+)-elaeokamine A from **12b** was unsuccessful, because of the instability of **12b** for further reactions, as demonstrated by Watanabe.¹³)

In conclusion, we provided a simple method for the conversion of 2-oxotetrahydro-1,3-oxazines having vinyl substituents at the 6-position into tetrahydropyridines. Further work is now in progress to extend our scheme to the synthesis of simple indolizidine and quinolizidine alkaloids.

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