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A MILD CONVERSION OF CARBOXYLIC ACIDS TO 2-OXAZOLINES AND THEIR UTILITY AS A CARBOXYL MASKING GROUP AGAINST LITHIUM ALUMINUM HYDRIDE

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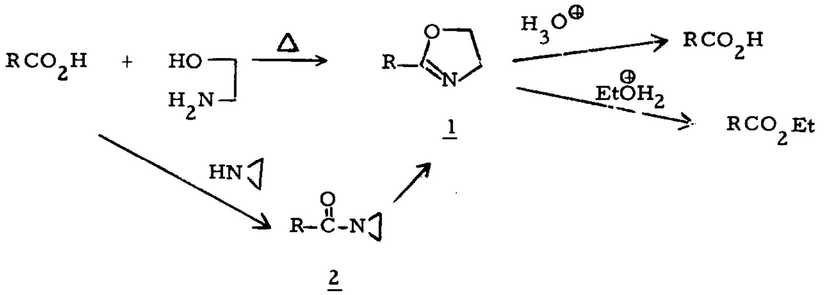
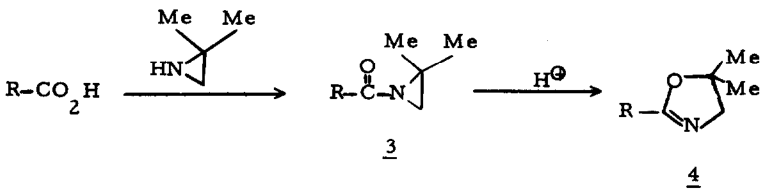
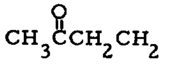
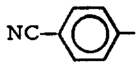
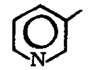
It was recently reported[1] that 2-oxazolines (1) may serve as useful protecting groups for carboxylic acids when Grignard reagents are employed. However, there are no general methods for transforming the carboxylic function into the 2-oxazoline which do not require high temperature (150-200°) or strongly acidic treatment[2], which preclude the presence of many functional groups. The well-known rearrangement of acyl aziridines (2) to oxazolines *via* thermal[3], acidic[4], or iodide-ion[5] assistance presented the possibility that this route may provide the mild conditions necessary to protect a carboxyl group. It was also important that an aziridine derivative be readily available, stable to storage, and safe to handle. These conditions were all fullfilled by 2,2-dimethylaziridine which was, contrary to reports[6], stable at room temperature for several months. There was no evidence of toxicological reactions to any of several experimentalists during this period.



The acylaziridines (3) were prepared in the usual fashion from carboxylic acids (dicyclohexylcarbodiimide (DCC) or their acid chlorides (Et_3N, benzene, 0°) affording good yields of product. When the rearrangements to 4 were attempted under the mildest conditions available, namely iodide-ion catalysis[5], no reaction occurred. Although, 1-(p-nitrobenzoyl)-2,2-dimethylaziridine has been reported to rearrange to the oxazoline[7], this method failed to give oxazolines bearing 2-alkyl groups. It appears that geminal-substituted aziridines as well as N-acyl substituents retard facile rearrangement with



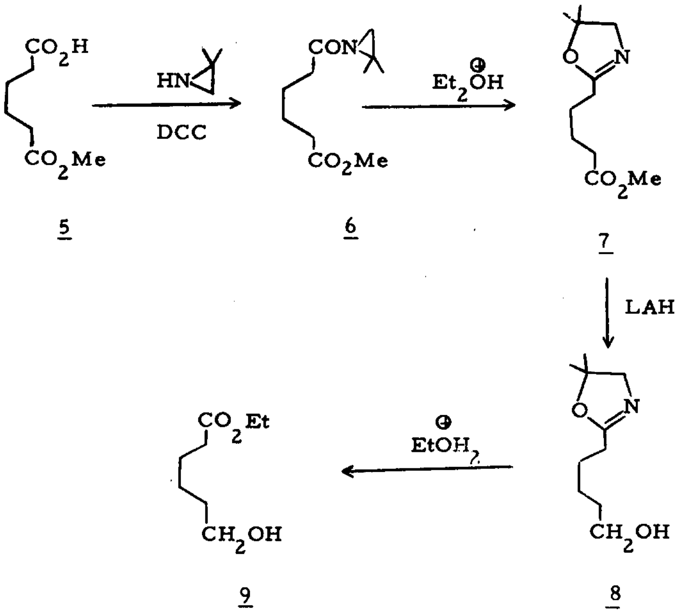
R	Method	(%)	(%)
 $CH_3\overset{O}{\overset{\|}{C}}CH_2CH_2$	DCC	95	80[a]
$MeO_2C\text{-}(CH_2)_4\text{-}$	DCC	85	80[a]
	$SOCl_2$	86	75[a]
	DCC	50	50[b]

a) 0.5 mole percent conc. sulfuric employed; b) 3 mole percent sulfuric employed.

iodide ion[5,7]. The other methods reported to effect this isomerization (conc. sulfuric acid solvent and thermolysis) are obviously unsuitable for the purposes sought. Furthermore, the use of Lewis acids ($AlCl_3$, $AlBr_3$, BF_3) in inert solvents (ether, heptane) failed to bring about the desired rearrangement although a report[8] described the successful implementation of this technique with unsubstituted acylaziridines. In summary, there seems to be no mild, general method to isomerize both acyl and aroylaziridines bearing the geminal methyl groups, 3. It is now reported that these rearrangements occur smoothly using a catalytic amount of sulfuric acid in ether or dichloromethane at room temperature for 6-16 hr. A preliminary survey indicates that the 2-oxazolines 4 are formed containing a variety of 2-substituents and these are indicated above. Of prime importance is the fact that carboxyl groups may now be masked with a convenient aziridine derivative to the 2-oxazoline. This is now the mildest conditions thus far reported since the reaction medium is acidic only during the very early stages of the rearrangement. The 5, 5-dimethyl-2-oxazolines (4) were found to behave in much the same manner as their 4, 4-dimethyl analogs reported earlier[1]. Of added interest was the observation that this simple masking group was totally inert to lithium aluminum hydride thus providing a useful new synthetic tool. The transformation of the half-ester of adipic acid 5 to ethyl

6-hydroxyhexanoate (9) will serve to demonstrate its usefulness.

The half-ester 5 (16.0 g) was treated at 5° with 1.0 equiv DCC in 100 ml of dichloromethane followed by addition of 1.1 equiv dimethylaziridine. After 16 hr at 25°, the urea was removed, the solution concentrated, and the residue (23 g) triturated with hexane (300 ml). Concentration of the hexane solution gave 18 g (84%) of 6 [bp 50° (0.3 mm), 1740, 1685 cm^{-1}][9]. Rearrangement was effected by stirring a solution of 6 (10.7 g) in 75 ml ether containing 1 drop conc. sulfuric acid overnight[9]. After washing with dilute bicarbonate, drying, and concentration of the etheral solution, an 80% yield of 7 [bp 50-60° (0.3 mm), 1740, 1665 cm^{-1}][9] was isolated. Reduction of 7 with lithium aluminum hydride was performed using 10.7g 7 and 2.1 g hydride in 100 ml ether. After stirring at 25° for 2 hr the mixture was quenched in ice-water and the ethereal extracts dried and concentrated. There was obtained, in 75% yield, the hydroxy-oxazoline 8 [bp 80° (0.3 mm), ~3300-3400, 1660 cm^{-1}][10] Hydrolysis of 8 was accomplished by heating to reflux a solution containing 7g in 200 ml 8% ethanolic sulfuric acid for 14 hr. Evaporation to 40-50 ml of solution followed by addition of 200 ml ether, washing with 10% bicarbonate, drying and concentration provided the hydroxyester 9 (82%, 3300-3400, 1735 cm^{-1}][11]



Continuing studies along these lines have recently shown that a) carboxylic esters may be converted to their corresponding acyl aziridines by use of the magnesium halide salts of 2, 2-dimethylaziridine and b) the potential also exists for direct conversion of carboxylic acids (and esters) to the 2-oxazolines by circumventing isolation of the intermediate acyl aziridine. These results will be reported in the full paper on this subject.

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6. Prepared by modification of the procedure given by K. N. Campbell, A. H. Sommers, and B. K. Campbell, Org. Syn. III, 148 (1955). It was not necessary to break the reaction flask to free the aziridinium sulfate, but to merely add the requisite amount of alkali solution and allow to stand until the mass disintegrates.
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8. H. W. Heine and Z. Proctor, ibid., 23, 1555 (1958).
9. The rearrangement of acylazridines has also been successful using catalytic amounts of 2, 5, 5-trimethyl-2-oxazoline as its sulfate or toluenesufonate salt, as well as catalytic amounts of potassium hydrogen sulfate in ether or dichloromethane. Under these conditions carboxylic acids containing acid sensitive groups (tetrahydropyranyl, 1, 3-dioxanyl, etc.) are stable to the rearrangement thus adding further versatility to this technique.
10. All compounds had totally consistent nmr spectra and satisfactory elemental analyses. Boiling points are those obtained from molecular distillation.
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