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ADDITON OF METALLO ENOLATES TO 1-ACYLPYRIDINIUM SALTS. A SHORT SYNTHESIS OF (±)-EPI-LUPININE

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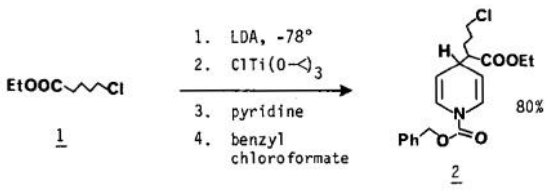
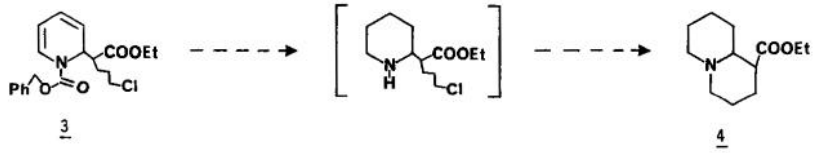
Summary: A synthesis of (±)-epi-lupinine was accomplished via the addition of the zinc enolate of ethyl 5-chlorovalerate to 1-(methoxycarbonyl)-4-trimethylstannylpyridinium chloride.

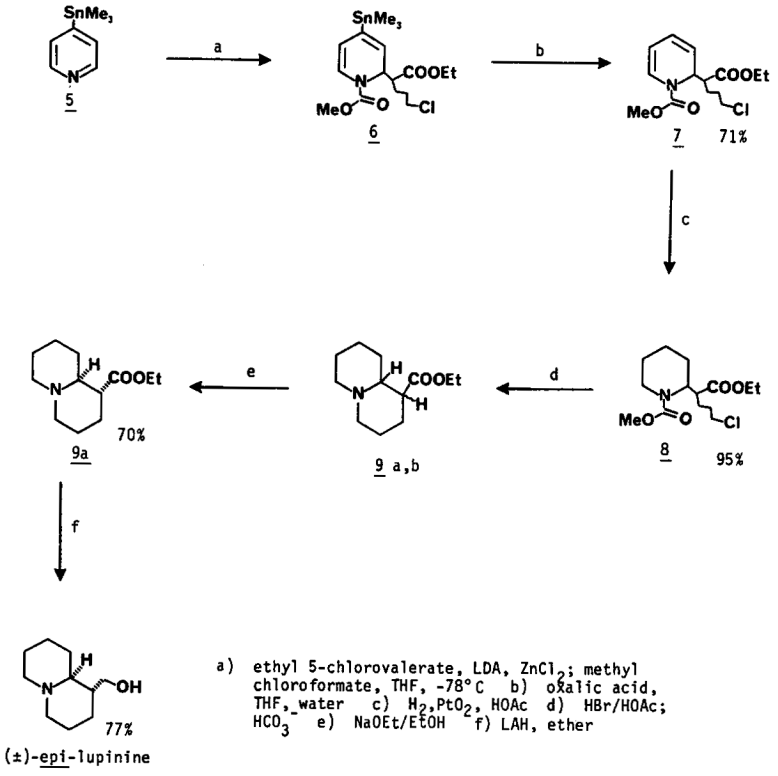
The addition of nucleophiles to 1-acylpyridinium salts has proven to be a valuable approach to the synthesis of substituted dihydropyridines and pyridines.[1,2] We recently developed a convenient and practical method for the synthesis of 4-(2-oxoalkyl)pyridines via the regioselective addition of titanium enolates to 1-acylpyridinium salts.[2k] In conjunction with that study, we explored the addition of the titanium enolate[3] of ethyl 5-chlorovalerate (1) to 1-(benzyloxycarbonyl)pyridinium chloride. The reaction was



regiospecific giving 1,4-dihydropyridine 2 in high yield. Although the stability of the metallo enolate of 1 and its regiospecific addition to a 1-acylpyridinium salt are interesting, a similar reaction which provides the 1,2-dihydropyridine 3 would be much more synthetically useful, for it would allow entry into the quinolizidine ring system (4) as shown below.



It was clear that in order to synthesize 3, or an equivalent, the 4-position of the 1-acylpyridinium salt must be blocked to force nucleophilic addition of the metallo enolate to occur at the 2-position of the pyridine ring. Since we have reported that a trimethylstannyl group at the 4-position of a 1-acylpyridinium salt acts as a blocking group toward Grignard addition,[21] we attempted to prepare 1,2-dihydropyridine 3 from 4-trimethylstannylpyridine.[4] Unfortunately, reaction of the titanium enolate of ester 1 and the 1-benzyloxycarbonyl salt of 4-trimethylstannylpyridine did not provide any of the desired 1,2-dihydropyridine 3. After several attempts, we were successful in preparing a derivative of 3 by using the zinc enolate of ester 1 and methyl chloroformate as the acyl halide. This success allowed us to plan and carry out a synthesis of (±)-epi-lupinine as shown in Scheme I.



Scheme I

Reaction of 4-trimethylstannylpyridine (5), the zinc enolate of ester 1, and methyl chloroformate gave the 4-trimethylstannyl-1,2-dihydropyridine 6. Crude 6 was treated with oxalic acid to effect removal[21] of the trimethylstannyl group, which provided 1-acyl-1,-2-dihydropyridine 7 in 71% overall yield from 5. Catalytic hydrogenation with PtO_2 catalyst gave piperidine derivative 8. The next step in the synthesis required the removal of the N-methoxycarbonyl group in the presence of the ethyl ester. HBr/HOAc has been reported to effect this selective transformation.[5] The piperidine 8 was treated with 30% HBr/HOAc for 12 hours at room temperature, concentrated, and neutralized with aqueous sodium bicarbonate. After stirring overnight, a 70% yield of ester 9 was obtained. The ratio of diastereomers was determined by GC to be 60:40 with ethyl epi-lupinate being the predominate diastereomer. The mixture of diastereomers was treated with sodium ethoxide in ethanol to effect epimerization.[6] Ethyl epi-lupinate (9a) was the only diastereomer detected in the crude product. Reduction of 9a with lithium aluminum hydride gave (±)-epi-lupinine[6,7,8] in 77% yield.

The addition of nucleophiles to 1-acylpyridinium salts appears to have considerable potential for the synthesis of quinolizidine and indolizidine alkaloids. Work is in progress to explore the scope of this approach.

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8. Mp 77-78°C[lit.[6] 78-79°C]; IR and ^{1}H, ^{13}C NMR spectra were in agreement with the reported[7] spectral data for (±)-epi-lupinine.

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