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IMIDOYLATION REACTION: (±)-LUPININE SYNTHESIS

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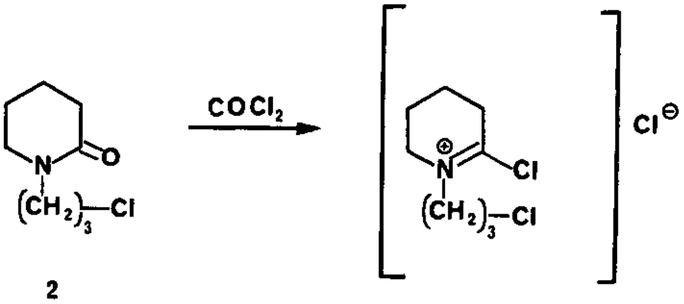
Abstract - A short and simple synthesis of (±)-lupinine is described. The key intermédiate in this sequence is an exocyclic vinylogous urethane, prepared by an imidoylation reaction which involves an intramolecular cyclization.

Numerous alkaloids have a nitrogen atom bridging two rings, including substituted pyrrolizidines, indolizidines and quinolizidines. Here we report a sequence which can be used for the synthesis of these types of alkaloids. The key step in this approach is the imidoylation reaction which permits the preparation of vinylogous urethanes (4), the exocyclic enamines being stabilized by the ester function. These cyclic β-enaminoesters react with the halogen atom by an intramolecular alkylation to give bicyclic structures. The literature[1-6] reports various synthesis of lupinine (7), but only a few examples permit access to 1,10-dehydrolupinate (5)[5,6] ; our own work was performed to study the preparation of functionalized quinolizidines of this type.

A toluenic suspension of the sodium salt of 2-piperidone (1), formed by reaction with one equivalent of sodium hydride, reacts regiospecifically with the 1-chloro-3-bromopropane in the presence of a catalytic amount of tetrabutylammonium bromide leading to the N-chloropropyl derivative (2), bp 91°C/0.01 torr ; ir (neat) ν 1640 cm^{-1} ; ^1H-nmr ($CDCl_3$) δ 1.71-2.56 (m, 8H), 3.26-3.71 (m, 6H), yield 76 %. A toluenic solution of phosgene (20 %) transforms the lactam to the corresponding imidoyl chloride ;



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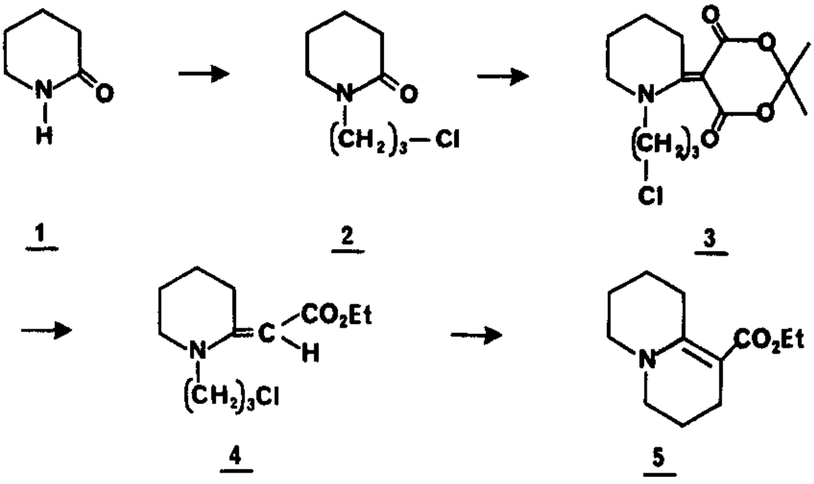
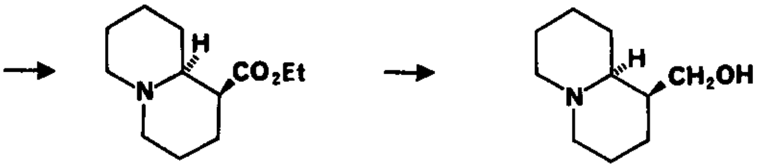
this salt reacts regiospecifically with the isopropylidene malonate (Meldrum's acid), in the presence of triethylamine, to produce β-enaminodiester 3, m p 176°C (EtOH) ; i r ($CH\,Br_3$) ν 1690, 1635, 1560 cm^{-1} ; ^1H - n m r ($CDCl_3$) δ 1.72 (s, 6H) , 1.70-2.50 (m, 6H), 3.25-4.00 (m, 8H) ; yield 50 %.

We call this reaction an imidoylation reaction in contrast to the acylation of active methylene compounds by acyl chlorides.

Compounds 3 undergoes a monodecarboxylating transesterification by refluxing an ethanolic solution containing boron trifluoride etherate to give the β-enaminoester 4, having structure E, bp 95-97°C/ 0.05 torr ; i r (neat) ν 1680, 1570 cm^{-1} ; ^1H - n m r ($CDCl_3$) δ 1.25 (t, 3H, J = 7 Hz), 1.40-2.30 (m, 6H), 2.90-3.65 (m, 8H), 4.04 (q, 2H, J = 7 Hz), 4.57 (s, 1H) ; yield 90 %. Attempts intramolecular alkylation via heating in a solvent (EtOH, CH_3CN ...) failed, however a reflux in acetonitrile in the presence of sodium iodide, after neutralisation, gave the ethyl 1.10-dehydrolupinate (5), bp 89°C/0.05 torr ; i r (neat) ν 1670, 1550 cm^{-1} ; ^1H - n m r ($CDCl_3$) δ 1.23 (t, 3H, J = 7 Hz), 1.40-2.00 (m, 6H), 2.20-2.50 (m,2H), 2.90-3.30 (m, 6H), 4.07 (q, 2H, J = 7 Hz) ; yield 70 %. The reduction of the β-enaminoester 5 into lupinate (6) has been realized by Golberg's method[7], using sodium borohydride, bp 65°C/ 0.01 torr ; i r (neat) ν 1720 cm^{-1} ; yield 94 %. Afterwards, the ester function of 6 is reduced by lithium aluminium hydride yielding (±)-lupinine (7), m p 58 °C (hexane) ; i r (neat) ν 3200 cm^{-1} ; ^1H - n m r ($CDCl_3$) δ 5.12 (1H exchanged with D_2O) ; yield 60 %.





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This synthesis of the (+)-lupinine from 2-piperidone is the most direct method described to date. The extension of this work to the synthesis of bicyclic compounds having various sizes is in progress.

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