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THIOLACTAMS IN ALKALOID SYNTHESIS: A PARTICULARLY SHORT SYNTHESIS OF dl-Δ^7-MESEMBRENONE

Arthur S. Howard, Ruth B. Katz and Joseph P. Michael*

Department of Chemistry, University of the Witwatersrand, Jan Smuts Avenue, Johannesburg, South Africa 2001.

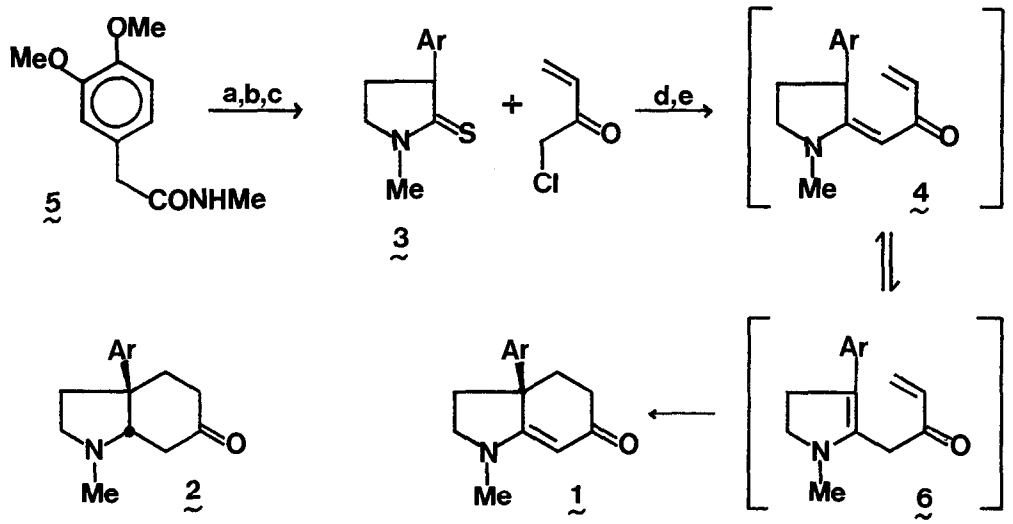
Summary. The title compound was prepared from chloromethyl vinyl ketone and 1-methyl-3-(3,4-dimethoxyphenyl)pyrrolidine-2-thione in a novel one-pot procedure involving S-alkylation, sulphur extrusion and intramolecular cyclisation of the resulting vinylogous enamide.

Δ^7-Mesembrenone (1), the (-)-isomer of which is a minor constituent of Sceletium namaquense,[1] has recently been synthesised in both chiral forms[2] and as the racemate.[3] The (-)-compound had previously been obtained by dehydrogenation of natural mesembrine (2);[4] it may itself be converted to mesembrine by reduction with lithium in liquid ammonia.[2,3] Although (1) itself has attracted little synthetic attention, there are several published syntheses of (2);[5] closest in spirit to the present work are those routes which construct the bicyclic system by Robinson annelation between Δ^2-pyrrolines and methyl vinyl ketone.[6]

Our own route to (1) makes use of the Eschenmoser sulphide contraction,[7] a reaction already exploited by us and others in alkaloid synthesis.[8] The novel feature of our route is the use of chloromethyl vinyl ketone[9] as an umpoled four-carbon Robinson annelating agent. We felt that if this reagent were capable of S-alkylating an appropriately arylated thiolactam (3), then the vinylogous enamide (4) resulting from the extrusion of sulphur from the salt thus formed might be induced to undergo intramolecular Michael reaction either thermally or after deprotonation, yielding by this process the desired product (1) (see Scheme).

The thiolactam (3)[10] was synthesised from the dianion of amide (5)[11] and 1-bromo-2-chloroethane followed by thiation with Lawesson's reagent[12] in 60% overall yield. When (3) was treated with chloromethyl vinyl ketone in nitromethane (reflux, 24 h) followed by addition of the hindered base diisopropylethylamine, (room temperature), the desired compound (1) was obtained as a solid, m.p. 139-141°C,[13] in 70% yield. The spontaneous ring closure of the putative vinylogous enamide intermediate (4) is remarkable, and presumably requires the participation of the endocyclic enamine tautomer (6) in order to accomplish so easy a ring closure. The structure of (1) was confirmed by comparing its spectra with those of of an authentic sample of racemic (1),[13] by preparation and characterisation of its methiodide,[4] and by comparison with a sample prepared by diethyl azodicarboxylate-induced dehydrogenation[4] of (-)-mesembrine (2).[14]

The tandem sulphide contraction-Robinson annelation procedure described above effects a conspicuously more efficient synthesis of the mesembrine skeleton than has previously been reported. The method should prove to be a useful addition to the methodology for nitrogen-containing fused bicyclic systems, and we are exploring its utility in other alkaloid syntheses.



Conditions: (a) 2.2 eq. BuLi, THF, 0°C, 10 min; (b) $BrCH_2CH_2Cl$, 0°C to room temp., 1.5h; (c) Lawesson's reagent, toluene, reflux, 8h; (d) nitromethane, reflux, 24h; (e) $i\text{-}Pr_2NEt$, room temp., 24h.

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