Tetrahedron Letters, Vol.31, No.16, pp 2277-2280, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

THERMAL REARRANGEMENT OF α-HYDROXY IMINES WITH AN α-ALLYL OR AN α-PROPARGYL SUBSTITUENT

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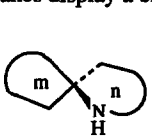
Summary. In refluxing diglyme, the title α-hydroxy imines 7 and 8 rearrange cleanly to amino ketones 9 and 10 substituted on the carbon α to nitrogen by an allyl or a propargyl group. In the case of α-hydroxy imine 9, the migration of the allyl group occurs with an allylic transposition.

The 1-azaspiro [m,n] alkane skeleton 1 is an important structural feature of a variety of natural alkaloids. This spiro ring system is found in histrionicotoxin 2 [1] and its congeners,Cephalotaxus alkaloids such as 3 [2] and in a novel alkaloid 4 which has a degraded homoerythrina-type structure [3]. In addition, simple synthetic 1-azaspiranes display a broad spectrum of pharmacological activities [4].



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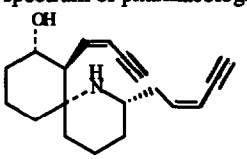

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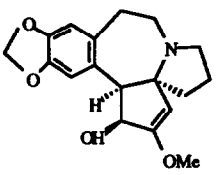

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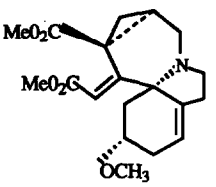

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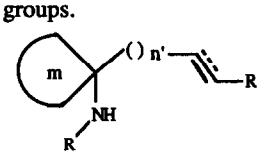
In spite of the great amount of synthetic effort directed towards 2 [1] and 3 [2] during the last decade, there is still a need for a simple and general method which allows the preparation of functionalized 1-azaspiranes 1.

Such methods could take advantage of the electrophile-assisted heterocyclization of unsaturated amines of type 5 [5] or of the intramolecular Michael addition of substrates such as 6, where E_1 and E_2 are electron-withdrawing groups.



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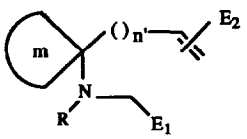

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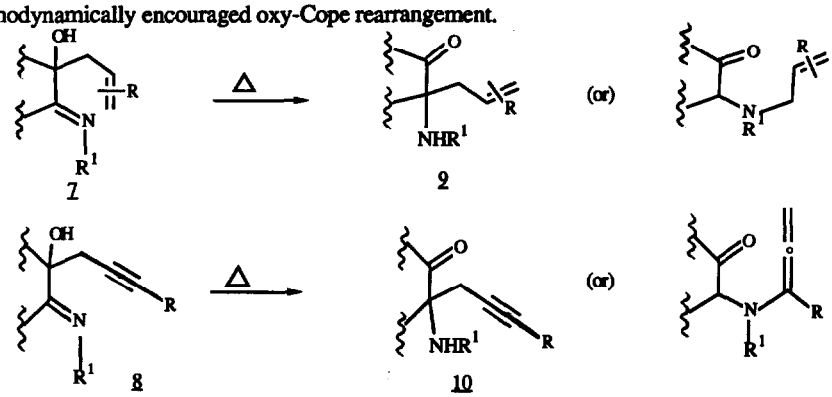
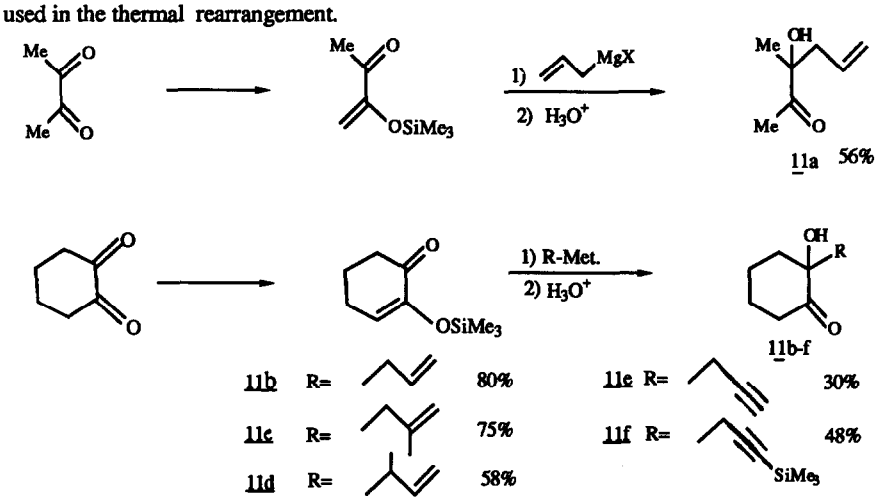
Consequently, an efficient way to synthesize diversely substituted amines bearing an unsaturated moiety at the α-carbon atom was needed. In the search of such compounds, we became interested in the thermal behaviour of 2- hydroxy-2-allyl-1-imines 7 and 2-hydroxy-2-propargyl-1-imines 8, a benzilic-type rearrangement of which could lead respectively to unsaturated amines 9 and 10. This transposition was described and studied principally from a mechanistic view point but with a limited number of migrating groups (methyl, phenyl) [6] and a poor application in organic synthesis [7]. Moreover, in the case of hydroxy-imines 7 and 8, the result was not obvious since these compounds can also rearrange by a [3, 3] sigmatropic process.

The unfavorable character of the 1-aza-Cope process [8] can be, in these cases, overriden by the thermodynamically encouraged oxy-Cope rearrangement.



The synthesis of the required α-hydroxy imines 7 and 8 was achieved in three steps in a straightforward fashion starting from 1,2-cyclohexanedione or 2,3-butanedione : addition of allylic or propargylic Grignard reagents and of lithio derivative of 1-trimethylsilyl propyne to the monoenol silyl ethers of the diones, easily prepared as previously described [9], gave, after hydrolysis, the ketols 11 in acceptable yields (30-80 %) [10] (Scheme 1). Reaction of these ketols with one molar equivalent of a primary amine in refluxing toluene under typical Dean-Stark conditions afforded quantitatively compounds 7 and 8 which, without further purification, were used in the thermal rearrangement.

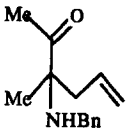
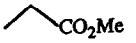
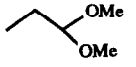
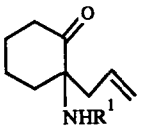
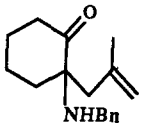
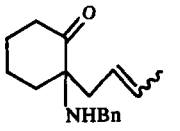
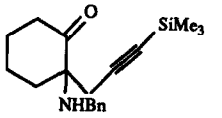


Scheme 1

Generally, the ketols 11 were treated with benzylamine (R^1 = Bn) . In the case of 11b, several primary amines were used to study the eventual influence of the nitrogen substituent on the course of the rearrangement, and also to generate substrates of type 6 having an activating group β to the nitrogen.

All the obtained hydroxy imines 7 and 8 were then heated in refluxing diglyme for three hours. The results of these experiments are summarized in Table .

- Thermal rearrangement leads exclusively to amino ketones 9 or 10 resulting from a benzylic-type transposition. Compounds resulting from an eventual 1-aza oxy-Cope rearrangement were never observed. The

Starting ketol	α-hydroxy imine	Rearranged Product (yield [a])
11a	7a R^1 = Bn	 9a (65 %)
11b	7b R^1 = Bn 7c R^1 =  7d R^1 =  7e R^1 = 	 9b (62 %) 9c (25 %) 9d (65 %) 9e (69 %)
11c	7f R^1 = Bn	 9f (53 %)
11d	7g R^1 = Bn (2 diastereoisomers)	 9g (31 %) E / Z 50 / 50
11e	8a R^1 = Bn	— [b]
11f	8b R^1 = Bn	 10a (58 %)

a yields are given for products isolated by column chromatography [10]

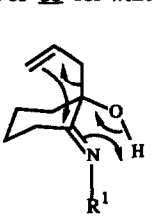
b only degradation products were detected

Table

yield of the transposition is generally acceptable and the entire sequence constitutes an easy access to precursors of functionalized 1-aza spiro systems.

- In every case, the thermal rearrangement is equilibrated as previously mentioned for related compounds [6]. After three hours at 160°, about 10 % of α-hydroxy imine 7 or 8 remains. The extension of the reaction time does not modify the ratios 7/9 or 8/10 but does decreases the yield (polymerization).

- α-Hydroxy imine 7g rearranges with complete allylic transposition. This supports, in the case of allylic compounds, rearrangement of type a . Conversely, the allenic isomer of 10a was not observed in the transformation of 8b for which a mechanism of type b is probably more representative.



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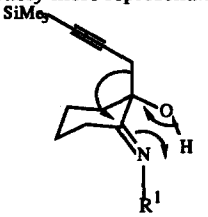

b

- The corresponding imine of each pure diastereoisomeric α-ketol 11d, gave in the rearrangement conditions, the same E/Z mixture of 9g accompanied by both diastereoisomers of the starting material. This observation is in good agreement with the equilibrated character of the transposition 7 → 9.

In conclusion, the thermal rearrangement of α-hydroxy imines bearing an α-allyl or an α-propargyl substituent to α-amino ketones 9 or 10 seems quite general. We are currently studying the potential of these last compounds in the synthesis of functionalized 1-azaspirane systems.

References and notes

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(Received in France 2 December 1989)