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TOTAL STEREOSPECIFICITY IN FREE RADICAL INTRAMOLECULAR ADDITION : CYCLISATION OF CIS AND TRANS 1-METHYL 4-HEXENYL N-CHLOROAMINES BY MEANS OF METALLIC SALTS

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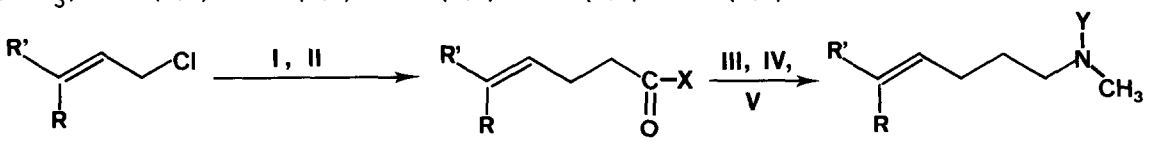
Summary : Extremely high stereospecificity (up to 100% diastereoisomeric purity) can be obtained for the metallic salts induced radical cyclisation of the cis and trans 1-methyl 4-hexenyl N-chloroamines. A possible mechanism for the highly effective trans-addition using metal-complexed aminyl radical is proposed.

Although a large number of radical additions to multiple bonds are known[1], there have been only a few reports on the application of these methods to stereospecific synthesis[2]. At very low temperature (-80°) it was found that hydrogen bromide[3], or deuterium bromide[4] add stereospecifically to olefins but around room temperature the preferred trans-addition apparently no longer holds and either of the olefin (cis or trans) is found to give the same mixture of products (threo and erythro).

Minisci[5] showed that the radical reaction of N-chloropiperidine with cyclohexene in presence of ferrous chloride mainly results in cis-addition. This unusual stereoselectivity was attributed to a coordination of the amino group with the metallic salt which is mainly responsible for the chlorine atom transfer[6]. Taking a look at the redox mechanism of the ω-ethylenic N-chloroamines cyclisation[7], we anticipated that, if metallic moiety could enable relatively rigid transition state, in a polydentate complex, an efficient stereospecific reaction should be obtained. Thus, we employed cis 5c and trans 5t 1-methyl 4-hexenyl N-chloroamines as substrates which could form erythro 6e and threo 6t 1-methyl 2-(1'-chloroethyl)pyrrolidines on reaction with reducing metallic salts. We describe here highly stereospecific radical synthesis of these β-fonctionnalized pyrrolidinic systems by means of redox reactions.

The ethylenic N-chloroamines 5c and 5t were efficiently prepared *via* the route shown in scheme 1. Cis[8] 1c or trans 1t crotyl chloride were reacted with sodium diethylmalonate in ethanol to afford respectively the cis (62%) or trans (83%) ethylenic diesters. Clean monodecarboxylation into 2c (90%) or 2t (69%) was achieved on refluxing the diesters in aqueous DMSO containing sodium chloride[12]. The latters were converted into amides 3c (98%) or 3t (97%) on standing for 3

days in a methanolic solution of methylamine and sodium methoxide[13]. Lithium aluminium hydride reduction of amides yielded amines 4c (80%, bp 43°/19 Torr) and 4t (90%, bp 47°/20 Torr). N-chlorination[14] gives 5c {99% ; IR δCsp^2-H cis 700cm^{-1} ; NMR, 60MHz, $\delta(CDCl_3)$ 5.40 (m,2), 2.85 (s,3), 2.75 (m,2), 2.00 (m,3), 1.60 (m,4)} and 5t {99% ; IR δCsp^2-H trans 965 cm^{-1} ; NMR, 60MHz, $\delta(CDCl_3)$ 5.45 (m,2), 2.90 (s,3), 2.80 (m,2), 2.00 (m,3), 1.60 (m,4)}.



1c R=Me, R'=H
t R=H, R'=Me

2c R=Me, R'=H, X=OEt
t R=H, R'=Me, X=OEt
3c R=Me, R'=H, X=NHMe
t R=H, R'=Me, X=NHMe

4c R=Me, R'=H, Y=H
t R=H, R'=Me, Y=H
5c R=Me, R'=H, Y=Cl
t R=H, R'=Me, Y=Cl

Reagents : I, EtONa, EtOH, $CH_2(CO_2Et)_2$; II, NaCl, DMSO, H_2O, 180°C ; III, $MeNH_2$, MeONa, MeOH ; IV, $LiAlH_4$, Et_2O ; V, ClONa, CH_2Cl_2, H_2O.

Scheme 1

Then, in a typical run of the redox cyclisation step, the reducing metallic salt (0.88 mmol. in 20 ml of 1:1 acetic acid-water) was slowly added (-10°, nitrogen stream) to a 1:1 acetic acid-water solution (40 ml) of 5 (8.8 mmol.).Diethylether was then added and the reaction mixture was made alkaline (10N NaOH, -15°), filtered, extracted with cold Et_2O, washed with water and dried. Solvent was removed without heating to leave the desired products which were, in some cases, contaminated with regenerated amine 4 or unreacted N-chloramine 5. The extent of stereospecificity was determined on the bases of NMR spectra {100MHz, $\delta(CDCl_3)$, 6e : 4.22 (d of q,1, J=6.6Hz, J'=4.2Hz at 30° and 2.9Hz at -20°), 3.0 (m,1) 2.37 (s,3), 2.25 (m,2), 1.7 (m,4), 1.47 (d,3, J=6.6Hz) ; 6t : 4.08 (d of q,1, J=6.6Hz, J'=4.8Hz at 30° and 4.4Hz at -20°), 3.1 (m,1), 2.37 (s,3), 2.25 (m,2), 1.7 (m,4), 1.44 (d,3, J=6.6Hz)}. The lowest coupling constant between the two protons beared by the two asymetric carbon atoms was assigned to the erythro isomer 6e. This is consistent with a dipolar and steric analysis of the privilegied rotamers of each diastereoisomer and with related attributions of configurations found in the litterature[15]. Moreover, this assignment is corroborated by the kinetic of the rearrangement into the piperidinic systems which is faster for 6e than for 6t.

Results on using a variety of reducing metallic salts are summarized in the table. Titanium trichloride or cuprous chloride lead to a poor stereospecificity and to a relatively high percentage of amine 4. When 1 equiv. of cupric chloride is used together with 0.1 equiv. of cuprous chloride (entries 5,6), the stereospecificity increases considerably while the percentage of amine 4 decreases. Ferrous sulfate or chloride have the advantages of a total stereospecificity and good yields but they have the disadvantage of a low conversion (46 to 67%) of the N-chloroamine when the 1:0.1 molar ratio of 5:MX_n is used. Cobalt acetylacetonate leads to a total stereospecificity but also to a large regeneration of 4.

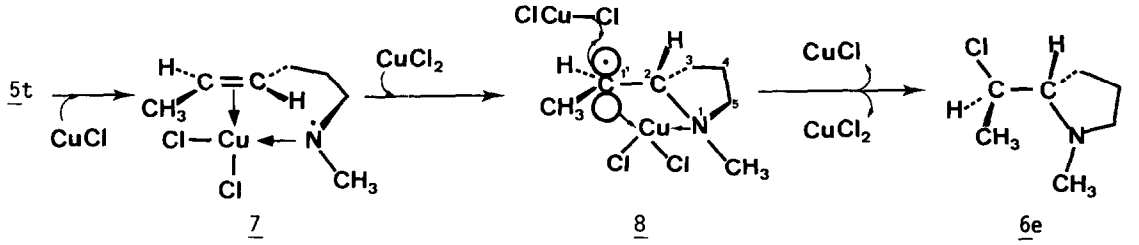
Homolytic fission of the nitrogen-chlorine bond (scheme 2) effected by the reducing metallic salt produced the metal-complexed aminyl radical 7 which underwent cyclisation by

Table. Radical cyclisation of N-chloroamines 5c and 5t by means of metallic salts ML_n

entry	substrate 5	ML_n	% Yield[a] 4 + 5 + 6	Molar ratio[b] 4[d]	5	6	Diastereoisomeric purity[c] 6e	6t
1	t	$TiCl_3$	74	5	0	95	58	42
2	c	$TiCl_3$	79	18	0	82	42	58
3	t	CuCl	79	16	0	84	55	45
4	c	CuCl	72	35	0	65	44	56
5	t	CuCl[e]	81	4	0	96	100	0
6	c	CuCl[e]	79	7	0	93	9	91
7	t	$FeSO_{4_f}$[f]	74	0	54	46	100	0
8	c	$FeSO_{4_f}$	93	2	45	54	0	100
9	t	$FeCl_{2_f}$	78	0	33	67	100	0
10	c	$FeCl_2$[f]	76	0	38	62	0	100
11	t	$Co(C_{10}H_{14}O_4)$	57[g]	45	0	55	100	0
12	c	$Co(C_{10}H_{14}O_4)$	67[g]	43	0	57	0	100

[a]Isolated yields based on 5. [b]Determinated by NMR analysis. [c]Determinated by NMR integration of the methyl protons of the two diastereoisomers. [d]The regenerated 4 maintains the original double bond stereochemistry. [e]A molar ratio of 1:0.1:1 of 5:CuCl:$CuCl_2$ is used . [f]Added in pure form. [g]Yield's fall due to hard filtration.

intramolecular addition to the double bond. The resulting carbon radical 8 abstracted a chlorine atom from 5, in a typical radical chain reaction, when titanium salts are used[16], or transferred a chlorine ligand from the other metallic salts, in a redox chain reaction[7]. We believe the cis N-chloroamine 5c forms preferentially the threo isomer 6t and the trans N-chloroamine 5t the erythro isomer 6e which means the intramolecular addition is trans (anti). This highly stereospecific trans-addition strongly suggest the existence of an hindered rotation about the C-2-C-1' bond in the radical 8. This can be due to the radical coordination with the metallic salt. The result may also imply that the rate of the chlorine transfer reaction, which is higher for redox chain reactions than for typical radical chain reactions[17], controls the extent of stereospecificity. This mecanism, illustrated for the cyclisation of 5t by means of the CuCl-$CuCl_2$ couple (scheme 2), appears to be the simplest and the best explanation of the observed facts.



Scheme 2

Since ionic chlorination of the corresponding β-amino-alcohols[15a] cannot be done stereo-

specifically by the classical ways[18], this radical ring closure appears to be useful for diastereospecific synthesis of variour β-chloro azacyclic compounds. Beyond its usefulness in organic synthesis, the result reported here lends new support to the notion that stereospecific biosynthesis can be controlled free-radical reactions[19].

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