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ARYNIC CONDENSATION OF KETONE ENOLATES 19.[1] SYNTHESIS OF POLYCYCLIC PHENYLETHANOLAMINES

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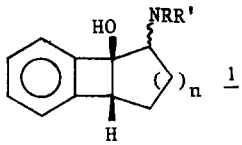
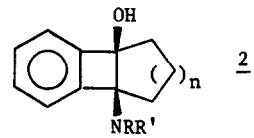
Summary : *A series of new polycyclic phenylethanolamines is efficiently synthesized by arynic condensation of α-aminoketone enolates in the presence of the complex base* $NaNH_2$-Bu^tONa.

Phenylethanolamines possess a wide spectrum of biological activities of use in medicinal chemistry.[2] These biological properties depend on the structure in which the phenylethanolamine pharmacophore is included, as well as on the spatial arrangement of the hydroxy- and amino-groups.[3] Taking these observations into account, we have undertaken the design of new synthetic pathways leading to phenylethanolamines and to new structures possessing a phenylethanolamine arrangement.

A first multistep synthesis of some new trans phenylethanolamines 1 (R=H, R'=Pr^i, Bu^t ; n=2,3,4) with antispasmodic properties was published.[4]

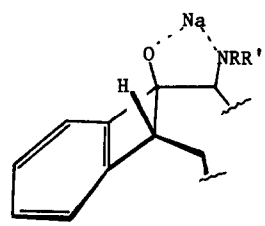


1



2

From our results concerning arynic condensations of ketone enolates, we wondered whether structures 1 or 2 could not be obtained by direct condensation of benzyne on α-aminoketone enolates. Recently, we showed[5] that arynic condensations of 1,2-diketone monoketal enolates lead essentially to the formation of benzocyclobutenol derivatives. We attributed this interesting result to a complexation of the cation of the intermediate alkoxide by the oxygens of the ketal group. It was also of interest to know whether such an effect could be obtained from the nitrogen of α-aminoketones, as in A.

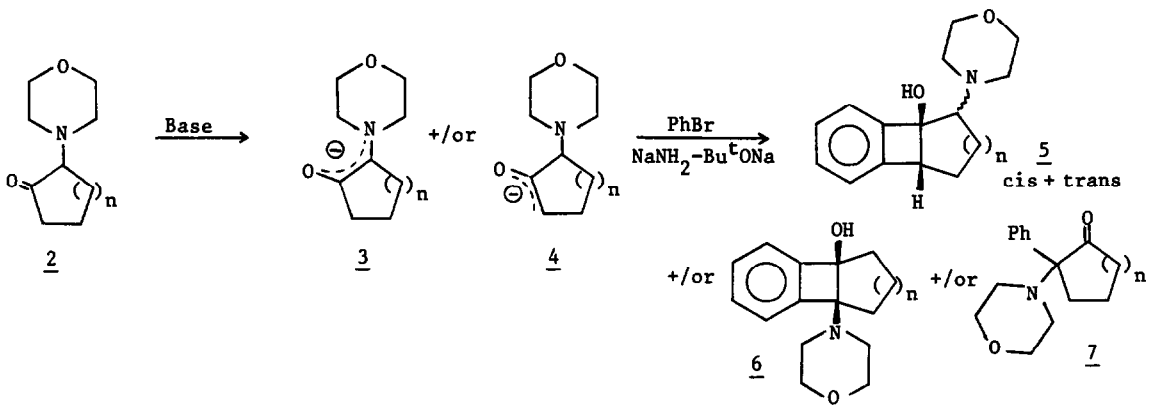


A

In the present note, we wish to report the first results obtained in this approach with α-morpholinoketones.

Ketone enolates were prepared from the corresponding aminoketones[6] either by reaction with lithium diisopropylamide (LDA) in THF or by reaction with the complex base $NaNH_2$-$BuONa$.[7] The ketone enolates are not good activating agents of $NaNH_2$ and the arynic condensations had therefore to be performed in the presence of the complex base.

The reactions observed during this study are summarized as follows :



2 3 4 5 6 7

We have reported in the Table the most significant results obtained from a systematic study of the condensation of α-morpholinocycloheptanone enolate as well as some results concerning α-morpholinocyclohexanone and -cyclopentanone.

Whatever the structure of the ketone may be, LDA leads only to the less substituted kinetic enolates and then to amino-alcohols 5. However a long time (run 2) allows a reequilibration of the enolates during the arynic condensation, and then the formation of the new amino-alcohols 6.

With α-morpholinocyclohexanone, the arynic condensation had to be performed with a 1/1 aminoketone/bromobenzene ratio in order to avoid the formation of phenylketone 7.

For the present time we have no rational explanation concerning the variations of the cis/trans ratios of amino-alcohols 5.

Enolate formation with the complex base always led to a mixture of enolates 3 and 4. In these conditions, amino-alcohol 6 was formed only from α-morpholinocycloheptanone (runs 3-6). High temperature preparation of ketone enolates (compare runs 3 and 4), as well as long reaction times (compare runs 5 and 6), favor the formation of 6. Unfortunately, with α-morpholinocyclohexanone, alcohol 6 was replaced by the formation of the phenylketone 7. Up to now all our attempts to change these results have been unsuccessful.

From a comparison of these first results with those obtained with the corresponding unsubstituted cyclanones[8] it appears that the α-amino group has only a small influence on the pathway followed by the arynic condensations. Particularly, the formation of benzocyclobutenols 5 is far from being strongly favored by the presence of nitrogen.

However these new easy reactions allow the synthesis of a number of new phenylethanolamines of types 1 and 2.

The biological properties of these derivatives are presently studied : they present interesting in vitro relaxant activities.

TABLE

Run		Enolates formation conditions	Condensation Solvent/T°C/t(h)	5 Isolated yield (cis/trans) %[a] [c]	6 Isolated yield %[a] [d]	7 Isolated yield %[a] [e]	Recovered aminoketone 2
1	n=3	LDA, THF 0.5 h/25°C	DME/25/0.5	54 (69)[b] (63/37)	-	-	22
2		LDA, THF 0.5 h/0°C	DME/-25/18	29 (39)[b] (86/14)	15 (20)[b]	-	25
3		CB, DME 3 h/0°C	DME/0/1	45 (56)[b] (78/22)	14 (17)[b]	-	20
4		CB, DME 3 h/25°C	DME/0/1	30 (39)[b] (73/27)	31 (41)[b]	-	24
5		CB, THF 3 h/25°C	THF/25/0.5	45 (55)[b] (49/51)	16 (19)[b]	-	18
6		CB, THF 3 h/25°C	THF/-25/18	29 (35)[b] (97/3)	34 (41)[b]	-	18
7		LDA, THF 0.5 h/0°C	DME/0/2.5	53 (74)[b] (0/100)	-	-	28
8	n=2	LDA, THF 0.5 h/0°C	THF/0/5	40 (80)[b] (42/58)	-	-	50
9		CB, DME 3 h/25°C	DME/0/1	7 (9)[b] (0/100)	-	45 (56)[b]	19
10	n=1	LDA, THF 0.5 h/0°C	DME/0/3	33 (40)[b] (not determined)	-	-	17
11		LDA, THF 0.5 h/0°C	DME/-30/20	37 (45)[b] (not determined)	-	7 (9)[b]	18

CB = complex base

[a] Yield based on the starting α-aminoketone

[b] Yield based on the α-aminoketone disappeared

[c] mp : for 5 cis (n = 3) 120°C ; (n = 2) 102°C ; for 5 trans (n = 3) 151°C

[d] mp : for 6 (n = 3) 98°C

[e] mp : for 7 (n = 2) 108°C ; (n = 1) 86°C.

General procedures and identifications - The reactions were carried out with magnetic stirring under a nitrogen atmosphere and monitored by GLC analysis.

Method A :

The enolate preparation with the complex base - A solution of tBuOH (30 mM for the ratio PhBr/2 = 2/1 and 15 mM for the ratio PhBr/2 = 1/1) in THF (or DME) (10 ml) was added dropwise to a suspension of $NaNH_2$ (105 mM for the ratio PhBr/2 = 2/1 and 60 mM for the ratio PhBr/2 = 1/1) in THF (or DME)

(20 ml) and the mixture was heated at 45°C for 2 h ; the α-aminoketone 2 (15 mM) diluted in THF (or DME) (10 ml) was added at room temperature and the reaction mixture was stirred for 3 h at the temperature indicated in the Table. A solution of bromobenzene (30 mM for the ratio PhBr/2 = 2/1 and 15 mM for the ratio PhBr/2 = 1/1) in THF (or DME) (10 ml) was slowly added at the temperature and for the time indicated in the Table. Upon completion, the mass was poured on ice, extracted with diethyl ether, washed twice with water, and dried over $MgSO_4$. After evaporation of the solvents under reduced pressure, the different components of the mixture were separated by chromatography on a silica gel column of by HPLC.

Method B :

The enolate preparation with LDA - Di-isopropylamine (16 mM) in THF (20 ml) under dry nitrogen at 0°C was treated with n-BuLi (1.6 M ; 10 ml). After 15 min, the α aminoketone 2 (15 mM) in THF (10 ml) was added. To a CB prepared as above ($NaNH_2/Bu^tONa$ = 60 mM/30 mM for the ratio PhBr/2 = 2/1 and 30 mM/15 mM for the ratio PhBr/2 = 1/1) was added the lithio enolate then the bromobenzene (30 mM for the ratio PhBr/2 = 2/1 and 15 mM for the ratio PhBr/2 = 1/1) at the temperature and for the time indicated in the Table. The work-up was then carried out as described under method A.

Amino-alcohols 5 and 6 were identified by their combustion analysis and IR, UV, ^1H and ^{13}C NMR spectra. The stereochemistry of amino-alcohols 5 cis and trans for n = 3, 2 was confirmed by comparison of the trans amino-alcohol with an authentic sample prepared as described in ref.[4] Finally, aminoketones 7 were identified by physical and spectroscopic data (combustion analysis and IR, ^1H and ^{13}C NMR spectra).

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