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ASYMMETRIC SYNTHESIS IV[1]. PREPARATION OF CHIRAL α-AMINONITRILES FROM A NEW N-CYANOMETHYL-1,3-OXAZOLIDINE SYNTHON

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Abstract :

The synthesis of (-)-N-cyanomethyl-4-phenyl-1,3-oxazolidine 1 is reported. Good yields and moderate diastereomeric excesses (d.e.s.) of mono- and di-substituted α-aminonitriles were obtained from this simple chiral template.

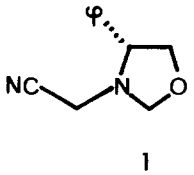
The preparation of optically active amines, aminoalcohols and aminoacids, because of their potential biological properties, is an important problem in synthetic chemistry. α-Aminonitriles[2a] are attractive starting materials for these syntheses if one considers that they include three reactive centers. Although the anions of N-dialkylaminoacetonitriles have been used, they have mainly been considered as masked acyl fonctions and not for preparing α-substituted aminonitriles[2b]. Thus chiral α-mono substituted aminonitriles, which are key intermediates in the preparation of aminoacids have been synthesized from aldehydes or related derivatives[3].

We now report the synthesis of an unsubstituted α-aminonitrile 1 bearing a 1,3-oxazolidine chiral moiety[4] and our first results concerning the diastereoselective mono- and di-substitution at the α-position of the cyano group. Among the desirable structural features of this new synthon is the facile deprotection of the primary amine fonction.

The condensation of (-) phenylglycinol with formaldehyde in the presence of KCN led, in a "one-pot reaction", to the formation of 1[5] (fig. 1) as an oil, ($[\alpha]^{20}$-173° ($CHCl_3$, c 1.4)) in 94% yield.

The substitution of the anion derived from 1 can in principle lead to a large variety of optically active α-aminonitriles that would be otherwise difficult or impossible to prepare using alternative methods. It turned out that such a reaction is possible and alkylation of the anion of 1 with a series of alkyl halides (methyl iodide, ethyl, propyl, benzyl and allyl bromides) afforded compounds 2 and 3[6,7,8] (Table 1). The diastereomers 2 a-e (major) and 3 a-e (minor) have been easily separated in their pure form by flash chromatography.

Diastereomeric excesses (d.e.s.) were determined in the crude mixtures of the aminonitriles by integration of the methylene protons N-CH_2-O in the ^{1}H NMR spectra (200 MHz) : 2 δ 4.45 and 4.85ppm (J_{AB} = 2.5 Hz) ; 3 δ 4.55 and 4.70ppm (J_{AB} = 4.5 Hz). Tentative assignement of the absolute configuration at the new chiral center was made by observation of a downfield position for the methine H-6 of the major isomer 2 (Table 1)



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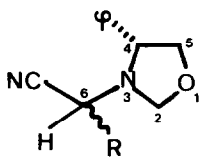
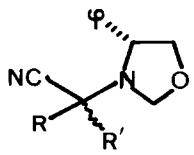


2 (major)
3 (minor)



4 (major)
5 (minor)

Fig. 1

	R	yield* (%)	d.e. (%)	$[\alpha]_D^{20}$ (c,$CHCl_3$) 2	3	δ H-6 (ppm) 2(S)	3(R)
a	CH_3	55	38	-282° (2.4)	-141° (0.35)	3.71	3.91
b	CH_2CH_3	60	50	-221° (3.1)	-142° (0.48)	3.49	3.67
c	$CH_2CH_2CH_3$	65	62	-370° (1.7)	-246° (0.28)	3.60	3.75
d	$CH_2CH{=}CH_2$	51	44	-244° (1.8)	-167° (0.54)	3.61	3.81
e	CH_2Ph	65	68	-155° (1.5)	-154° (1.9)	3.87	3.98

Table I : alkylation of 1 with alkyl halides R-X

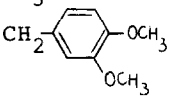
	R	R'	yield* (%)	d.e. (%)	absolute conf. of major 4	δ CH_3 (ppm) 4	5
a	CH_3	CH_2CH_3	70	64	S	1.23	1.46
b	CH_2CH_3	CH_3	68	36	R	1.46	1.23
c	CH_3	CH_2Ph	73	52	S	1.08	1.34
d	CH_2Ph	CH_3	68	40	S	1.08	1.34
e	CH_3		72	50	S	1.11	1.34

Table II : alkylation of 2 and 3 with alkyl halides R'-X

* pure isolated products ; overall yield.

as previously observed for the S isomer in the series of α-aminonitriles derived from (S)-α-methylbenzylamine[3a]. Additionnal support for the S absolute configuration of 2 was obtained by transformation of the mixture of diastereomers 2b and 3b (d.e. 50%) into (-)-(S)-α-aminobutyric acid ($[\alpha]_D^{20}$ - 7.5° (c 2, HCl 5N), lit $[\alpha]_D^{20}$ - 20.4° (c 2, HCl 5N)[9]) by acid hydrolysis and hydrogenolysis[10].

Di-alkylated products 4 a-e and 5 a-e were easily prepared by metalation of the diastereomeric mixtures 2 and 3 a,b or e and reaction with alkyl halides (Table 2). The d.e.s. were measured by integration of the cleanly separated CH_3 signals in the ^1H NMR spectra of the crude mixtures. In these cases no separation of the diastereomers could be achieved. The absolute configurations for the major isomers 4c and 4e were assigned as S by comparison of the δ CH_3 signals of the major and minor isomers with the reported values for analogous α-aminonitriles derived from (S)-α-methylbenzylamine[11]. For compound 4a we propose using the above argument the S absolute configuration. This assignement was confirmed by transformation of a mixture of derivatives 4a and 5a (d.e. 64%) into (+)-S-isovaline $\left[[\alpha]_D^{20} + 4.4° \text{ (c 0.49, } H_2O\text{), lit. } [\alpha]_D^{20} + 11.9° \text{ (c 0.78, } H_2O\text{)}^{12} \right]$.

As expected a reverse introduction of the substituents changed the absolute configuration of the major isomer (4b vs 4a). Surprisingly for 4c and 4d the major stereomer S was always formed.

A working model, in agreement with the observed results, is that the more stable conformation - owing to minimal non-bonded repulsions - of the deprotonated α-aminonitriles 2[8] (fig. 2) reacts with the alkylating agents from the less hindered face. When R = H, CH_3 or C_2H_5, the C1 conformer is more stable and the preferential attack of

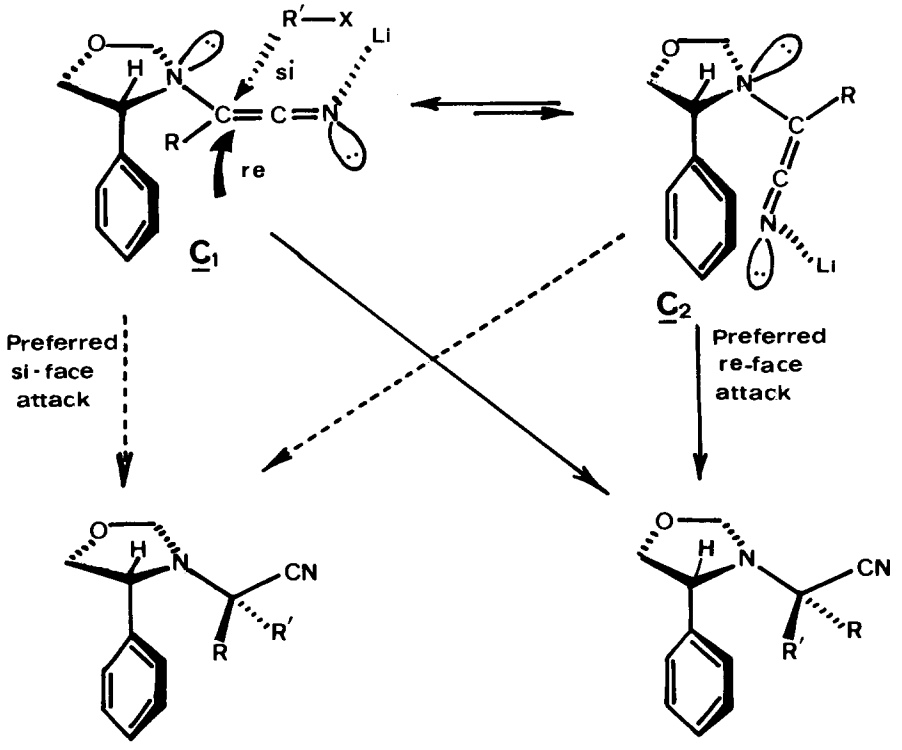


Fig. 2

the electrophilic species from the less hindered si-face leads to the major products 2 (having the S configuration) and 4, whereas the C2 conformer is preferred when R = CH_2Ph due to steric interaction between the phenyl group and the large R benzyl substituent. So the major S diastereomer 4d is obtained from both 2a and 2e.

Efforts are presently being made to complete the development of the chiral cyanomethyloxazolidine 1 as a general synthon for the preparation of various chiral aminoacids, aminoalcohols, amines, etc.

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5 Preparation of 1 : to a stirred solution of (-) phenylglycinol (23.62g, 0.16 mol), KCN (10.4g, 0.16 mol) in water (650mL) at pH ~ 3 (citric acid) was added over 30 min at r.t. a solution of formaldehyde (40%, 260mL). The reaction mixture was stirred for an additionnal 30 min, then basified (Na_2CO_3) and extracted (CH_2Cl_2). The combined organic fractions were washed with water, dried (Na_2SO_4) and concentrated to give a yellow oil which was purified by flash chromatography (SiO_2, hexane-AcOEt, 80-20). 1 was obtained as a colorless oil (31.15 g ; 94% yield).

6 All new compounds showed satisfactory analytical and spectroscopic data.

7 In a typical experiment, to a stirred solution of LDA/HMPA (1/1 ; 1.1 eq. 0.48M in THF) at -78°, was added 1 (1 eq., 0.66M in THF) via seringe over 5 min ; after 15 min 1.1 eq. of R-X was added. The reaction mixture was stirred for 1 h, quenched by NH_4Cl then extracted with ether, dried and concentrated to dryness. Flash chromatography of the residual oil (SiO_2, hexane-ACOEt, 85-15) yielded the separated isomers 2 and 3.

8 The alkylation reaction likely occured under kinetic control since using only 0.9 eq. of LDA instead of 1.1 eq. quite similar d.e. were obtained (32 vs 38% ; table I, a).

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