Tetrahedron Letters No. 6, pp 369 - 372, 1975. Pergamon Press. Printed in Great Britain.

SYNTHESIS OF PYRROLIDINES BY INTRAMOLECULAR CARBANIONIC EPOXIDE OPENING[1]

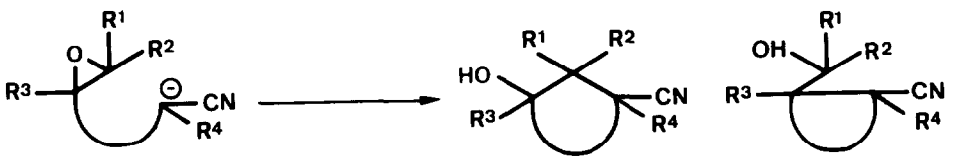
Roland Achini* and Wolfgang Oppolzer*

SANDOZ Ltd., Pharmaceutical Division, Chemical Research, Basle, Switzerland

(Received in UK 3 December 1974; accepted for publication 23 December 1974)

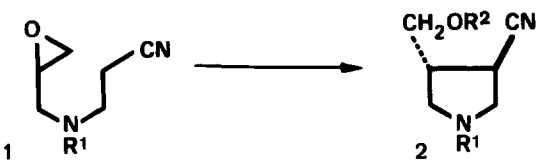
Intramolecular nucleophilic opening of epoxides by carbanions has been used to a limited extent for the construction of alicyclic compounds[2]. Recently G. Stork et al. developed and expanded this reaction into a more general synthetic method by using carbanions derived from nitriles and amide bases[3] (scheme 1).

SCHEME 1

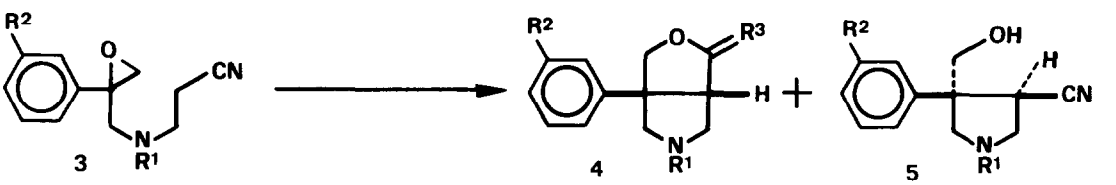


Our general interest in pyrrolidines and piperidines led us to examine the application of this principle to the synthesis of such heterocycles (schemes 2, 3).

SCHEME 2



SCHEME 3



a: $R^1=CH_3$, $R^2=H$
b: $R^1=CH_3$, $R^2=OCH_3$
c: $R^1=CH_2C_6H_5$, $R^2=H$
d: $R^1=CH_2C_6H_5$, $R^2=OCH_3$

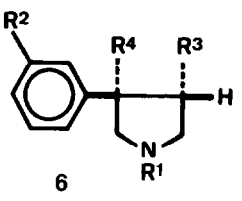
R^3=NH, O, H_2

Treatment of the epoxyaminonitrile **1** (R^1=CH_3)[4] with 1.2 equiv. of sodium hexamethyldisilazane in benzene at 25°C for 10 min. followed by addition of aqueous ammoniumchloride solution, work-up, and filtration with dichloromethane through 15 parts of aluminum oxide gave in 63-67% yield the oily pyrrolidine **2** (R^1=CH_3, R^2=H)[5], b.p. (bulb distillation) 140° (0.005 mm); $n_D^{24.2}$ 1.4747; mass spectrum (70eV)m/e 140(M^+), 109(M^+-CH_2OH); oxalate salt m.p. 148-50°C; which with acetic anhydride in pyridine gave the oily acetate **2** (R^1=CH_3, R^2=Ac), ir.(CH_2Cl_2) 2250, 1745, 1240 cm^{-1}; nmr.(d_6-DMSO) δ 2.05(3H, s), 2.25(3H, s), 2.4-3.2(6H), 4.0(2H, d, J=6 Hz, CH_2OAc). Similarly, stirring the epoxyaminonitrile **1** (R^1=$CH_2C_6H_5$)[6] with potassium amide in liquid NH_3-ether for one hour gave, in 72% yield after work-up and purification via its naphthaline-1,5-disulfonate salt (m.p. 216-8°C), the pyrrolidine **2** (R^1=$CH_2C_6H_5$, R^2=H); mass spectrum (70eV)m/e 216(M^+), 185(M^+-CH_2OH). The acetate of this product (R^2=Ac) showed spectral properties analogous to **2** (R^1=CH_3, R^2=Ac). The assignment of the trans stereochemistry at centres 3 and 4 of the compounds **2** is based on the observation that, contrary to the following examples, no iminolactones are formed, and that compounds **2** are stable to potassium ethylate in ethanol.

Phenyl-substituted pyrrolidines **4** were obtained by cyclization of crude epoxyaminonitriles **3**[7] with potassium amide in liquid NH_3-ether (1 hr. at -60°). Subsequent addition of a slight excess of aqueous ammonium chloride solution, evaporation of NH_3, acidification with conc. HCl (pH 2), and addition of aqueous $NaHCO_3$ solution after 30 min. (pH 8) gave, after extraction with dichloromethane, crude iminolactones **4** (R^3=NH), ir.(film) 3300-3200, 1680-1670 cm^{-1}, accompanied by minor amounts of nitriles **5**[9], ir.(film) 3500-3400, 2250 cm^{-1}. The byproducts **5** were converted to **4** (R^3=NH) by treating the mixtures with an excess of potassium ethylate in ethanol at 25°. Hydrolysis to the lactones **4** (R^3=O) was accomplished by treatment of the iminolactones with an excess of 1 N methanolic HCl for five hours at 50°C, evaporation, and addition of aqueous $NaHCO_3$ solution (pH 8). The pyrrolidine-lactones **4** (R^3=O) [ir.(CH_2Cl_2 or film)1770-1775 cm^{-1}] were characterized as follows: **a**: hydrogen maleinate, m.p. 170-1°C (free base m.p. 68-9°C); **b**: naphthaline-1,5-disulfonate, m.p. 273-6°C; **c**: (base) m.p. 79-81°C; **d**: hydrogen oxalate, m.p. 173-5°C; their structures follow from the nmr. spectra [($CDCl_3$)singlet or centre of AB system between δ 4.4 and 4.6 (2H, CH_2OCO), 2.5-3.5 (shifted to 3.3-4.3 in the salts, d_6-DMSO)(5H of pyrrolidine ring, AB+ABX), no protons at higher field than 2.4]. Moreover the lactones were transformed to derivatives **6**[10] and **4 c,d** (R^3=H_2)[11] whose ir. and nmr. spectra agree perfectly with the assigned structures.

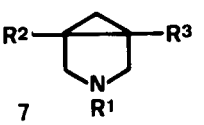
It is interesting to note that the carbanions of epoxides **1** and **3** attack the more substituted carbon atoms of the epoxide rings, rather than the primary car-

bon atoms. This is in contrast to the observation that similarly substituted aliphatic epoxynitriles give preferentially or exclusively cyclohexane rings[3], and parallels the case of ethyl 2-carboxyethyl-6,7-epoxy-heptanoate which was cyclized to a cyclopentane-lactone[2a]. Our results exemplify a short and generally efficient synthesis of novel, stereochemically pure, 3,4-substituted pyrrolidines via carbon-carbon bond formation, such compounds not being readily accessible by other routes[12]. These can be refunctionalized in a variety of ways; in particular, they are precursors for a rapid route to novel 3-azabicyclo[3.1.0]-hexanes 7[14].



6

	a	b	c
R^1	CH_3	CH_3	$CH_2C_6H_5$
R^2	H	OCH_3	H
R^3	CH_2OAc	CH_2OTs	COOEt
R^4	CH_2OAc	CH_2OTs	CH_2Br



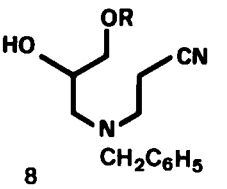
7

	a	b	c
R^1	CH_3	$CH_2C_6H_5$	$CH_2C_6H_5$
R^2	H	H	C_6H_5
R^3	CN	CN	COOEt

References and Footnotes

1. Presented at the autumn meeting of the Swiss Chemical Society in Neuchâtel, Switzerland, Oct. 11, 1974.
2. a) P.A. Cruickshank and M. Fishman, J. Org. Chem., 34, 4060 (1969);
   b) V.N. Yandovskii and B.A. Ershov, Russian Chemical Reviews, 41, 403 (1972);
   c) cf. reference 4 in 3a.
3. a) G. Stork, L.D. Cama, D.R. Coulson, J. Amer. Chem. Soc., 96, 5268 (1974);
   b) G. Stork, J.F. Cohen, ibid. 96, 5270 (1974);
   c) G. Stork, 23rd National Organic Chemistry Symposium, Amer. Chem. Soc., Tallahassee, Florida, June 17-21, 1973, Abstracts of Papers p. 139.
4. From epichlorohydrin and 3-methylaminopropionitrile (64%), cf. S.I. Sadykh-Zade and R.A. Sultanov, Zh. Organ. Khim., 2, 1166 (1966); Chem. Abstr., 66, 37703 v (1967).
5. All compounds were fully characterized by spectral methods (nmr. spectra: internal reference TMS, δ =0). All crystalline or distilled compounds gave satisfactory elemental analyses.
6. From epibromohydrin and 3-benzylaminopropionitrile, analogous to 4 (27% after chromato-

graphic separation from byproducts). A better overall yield of cyclization product **2** (R^1=$CH_2C_6H_5$, R^2=H) is obtained by reaction of 3-benzylaminopropionitrile with glycidol at 100° (exothermic) to diol **8** (R=H)-naphthaline-1,5-disulfonate, m.p. 215-8°C (88%), monotosylation (subsequent addition of 1.2 equiv. of N-methyl= morpholine and 1.05 equiv. of tosylchloride in dichloromethane at 25-35°C) to **8** (R=Ts) (not purified), and treatment with KOH in ether analogous to 4. The crude epoxide is cyclized in 44% yield from diol **8**(R=H).



8

7. From reaction of phenacylbromides or -chlorides with the appropriate 3-aminopropionitrile in acetone or chloroform in the presence of 1 equiv. of $EtN(i\text{-}Pr)_2$ or NEt_3 at 25-61°C and treatment of the aminoketonitriles so obtained (85-100%)[**a**: hydrogen maleinate, m.p. 113-5°C; **b**: hydrogen oxalate, m.p. 145-9°C; **c**: hydrogen maleinate, m.p. 119-120°C: **d**: naphthaline-1,5-disulfonate, m.p. 213-4°C] with dimethyloxosulfoniummethylid[8] (91-100%). For best yields the labile epoxides are cyclized without purification.
8. E.J. Corey and M. Chaykovsky, J. Amer. Chem. Soc. 87, 1353 (1965).
9. Isolated and fully characterized in the cases of **5a** (12%, hydrogen maleinate, m.p. 169-70°C) and **5c** (24%, amorphous).
10. **6a** (oil): 1. AlH_3/THF, 25°C (100%); 2. Ac_2O/pyridine.
6b, m.p. 92-4°C: 1. AlH_3/THF, 25°C (76% of diol-naphthaline-1,5-disulfonate, m.p. 161-3°C; 2. excess of TsCl/pyridine, -20°C (65%).
6c: treatment in a closed bottle for 2 days at 25°C with ethanolic HBr (prepared by saturation of ethanol with gaseous HBr at 0°C) (50%); m.p. of hydrogen oxalate 108-10°C.
11. **4c** (R^3=H_2)-hydrogen maleinate, m.p. 177-9°C, and **4d** (R^3=H_2)-hydrogen fumarate, m.p. 159-60°C: 1. AlH_3/THF, 25°C (70-72%, m.p. of diol with R^2=H 104-5°C); 2. 1 equiv. of TsCl/1 equiv. of N-methylmorpholine/CH_2Cl_2, 25°C (80-84%).
12. This method supplements the synthesis of 3,4-cis-substituted pyrrolidines by intramolecular ene-reactions[13] in that it gives trans-substituted products.
13. W. Oppolzer, E. Pfenninger, and K. Keller, Helv. Chimica Acta 56, 1807 (1973).
14. **7a,b** from **2** (R^1=CH_3, $CH_2C_6H_5$; R^2=H): 1. $NaNH_2$, benzene, 25°C, subsequent addition of TsCl → **2** (R^1=CH_3, R^2=Ts), m.p. 117-9°C, and **2**(R^1=$CH_2C_6H_5$, R^2=Ts), m.p. 84-6°C; 2. $(Me_3Si)_2NNa$, benzene, 25°C (80-100% overall). **7c** from **6c** with NaH/HMPA (100%). M.p. **7a**-hydrochloride 177-9°C; **7b**-hydrogen oxalate 184-6°C; **7c**-hydrogen oxalate 175-7°C.

---

* To whom inquiries should be sent.
≠ Present address: Département de Chimie Organique, Université de Genève, 1211 Genève 4, Switzerland.