

Intramolecular Free Radical Cyclisation of α -Anilino Alkenenitriles

Jim-Min Fang,* Han-Ting Chang, and Chun-Cheng Lin

Department of Chemistry, National Taiwan University, Taipei, 10764, Taiwan, Republic of China

Upon treatment with tributylstannane, 2-anilino 2-alkenenitriles having halo substituents at appropriate positions undergo radical cyclisations to give cycloalkyl α -aminonitriles in a stereoselective manner.

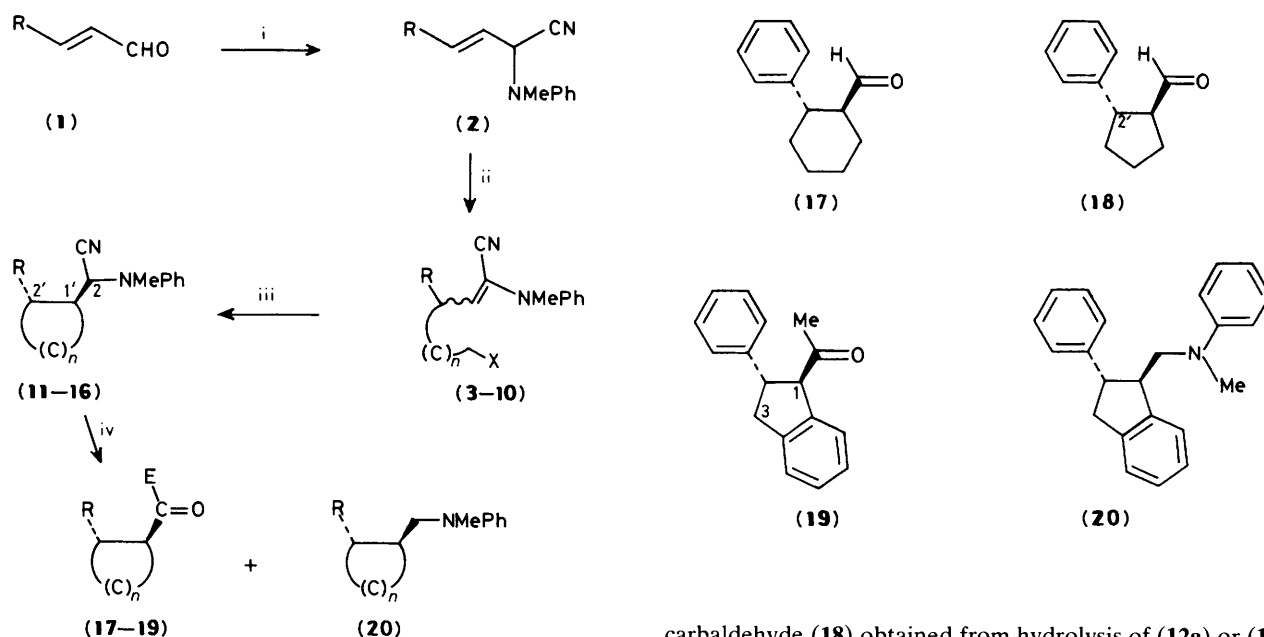
We report here an expedient method (Scheme 1) for the conversion of open-chained α,β -unsaturated aldehydes (**1**) to their corresponding cycloalkyl carbonyl compounds (**17**–**19**) and the amine (**20**). The main features in this sequence consisted of (i) using α -anilino nitrile as an Umpolung of the

carbonyl group, (ii) regioselective alkylation of the unsymmetric allylic anion with dihalides, (iii) intramolecular stereoselective free radical type addition to α -amino alkenenitriles, and (iv) elaboration of α -anilino nitriles to amines and carbonyl compounds.

Table 1. Intramolecular radical cyclisation of 2-anilino 2-alkenenitriles $RCH(Y)CH=C(NMePh)CN$.^a

Reactant	R	Y	Reaction ^b time (h)	Cyclisation products ^c (yield, %)
<i>E</i> -(3)	Ph	(CH ₂) ₄ Br	1.5	(11a) (87), (11b) (5) ^d
<i>Z</i> -(3)	Ph	(CH ₂) ₄ Br	1.5	(11a) (83), (11b) (4)
<i>Z</i> -(4)	Ph	(CH ₂) ₃ Cl	3	(12a) (10), (12b) (25) ^e
<i>Z</i> -(5)	Ph	(CH ₂) ₂ CHBrMe	2	(13a) (30), (13b) (34), (13c) (21)
(6)	Ph	CH ₂ C(Br)CH ₂	2	— ^f
(7)	Ph	CH ₂ C ₆ H ₄ - <i>o</i> -Br	8	(14a) (60), (14b) (20)
<i>E</i> -(8)	Me	(CH ₂) ₄ Br	4	(15a) (70), (15b) (15)
<i>Z</i> -(9)	Me	(CH ₂) ₃ Cl	24	(16a) (3), (16b) (7) ^g
<i>Z</i> -(10)	Me	(CH ₂) ₃ Br	1	(16a) (24), (16b) (59)

^a The reactant (0.02 M) in mild refluxing benzene (anhydrous and deoxygenated) was treated with a benzene solution (0.2 M) of Bu₃SnH (1.1 equiv.) and azoisobutyronitrile (AIBN) (0.1 equiv.) by dropwise addition over a period of 30 min. ^b Time after complete addition of Bu₃SnH. ^c The products have compatible elemental analysis and spectroscopic properties. ^d Isomers **a**, **b** and **c** are designated according to the eluting order on a μ -Porasil column. ^e A 63% of reactant (*E/Z* = 7:1) was recovered. ^f This reaction gave a 50% yield of reduction products (Y = CH₂CH=CH₂) and recovered 45% of reactant. ^g 86% of reactant (*E*-form) was recovered.



Scheme 1. Reagents and conditions: i, PhMeNH₂⁺Cl⁻, Et₂O, KCN, H₂O, 0 °C, 2 h; ii, LDA (Bu^tOK), dihalide, -78 °C (0 °C), 1–2 h; iii, Buⁿ₃SnH, AIBN cat., PhH, 80 °C; iv, for alkylation: LDA, THF, halide (excess), -78 °C to room temperature; for hydrolysis: CuSO₄, H₂O, MeOH, 0 °C, 3 h; for reductive decyanation: NaBH₄, EtOH, 30 °C, 20 h.

According to the Strecker method, cinnamaldehyde (or crotonaldehyde) was treated with potassium cyanide and *N*-methylaniline to give high yields (*ca.* 90%) of 2-anilino 3-alkenenitriles (**2**). Deprotonation of (**2**) [Bu^tOK or lithium di-isopropylamide (LDA), tetrahydrofuran (THF), 0 °C] and subsequent trapping of the resulting unsymmetric allylic anion with an appropriate dihalide electrophile gave, exclusively, γ -substitution products (**3–10**), usually as two geometric isomers.¹ The steric effect of the *N*-methylanilino group was apparent in the regiochemical outcome. The *E*- and *Z*-isomers of (**3**) were separated by chromatography and their structures were unambiguously determined.² However, it was found that subsequent reductive free radical reaction of either isomer gave the same cyclisation products (Table 1). Thus, the separation of the geometric isomers was unnecessary.

Compounds (**3–10**) with 1,1-captodative substitution are considered good radicophiles.³ Their facile radical cyclisations are predicted to occur at the β -carbons, *via* *exo*-transition states, to give mainly *trans*-products, by analogy to cyclisations of 4-substituted-5-hexenyl- and 5-substituted-6-heptenyl radicals.⁴ In agreement with this prediction, treatment of a refluxing benzene solution of 8-bromo-2-*N*-methylanilino-4-phenyl-oct-2-enenitrile [*E*-(**3**) or *Z*-(**3**)] with Buⁿ₃SnH in the presence of azoisobutyronitrile (AIBN) gave two *trans* cyclohexanes (**11a**) and (**11b**) having different C-2 chiralities. The *trans* diaxial orientation of 1'- and 2'-H was characterised by their large coupling constant of 11 Hz. Subsequent hydrolysis of aminonitrile (**11a**) (or **11b**) with CuSO₄ in aqueous MeOH gave rise to the sole product aldehyde (**17**) in the *trans* configuration ($J_{1',2'}$ 12 Hz).⁵ Similarly, cyclopentane

carbaldehyde (**18**) obtained from hydrolysis of (**12a**) or (**12b**) exhibited the 2'-H resonance at a low field of δ 3.32, indicating the deshielding effect of the adjacent carbonyl group.

The ring closure reactions for the R = Me series [compounds (**8–10**)] were carried out in a similar manner. *o*-Bromoaralkyl alkenenitrile (**7**) also readily underwent radical cyclisation to afford indanes (**14a**) and (**14b**).⁶ When a mixture of (**14a**) and (**14b**) (62 : 38) was subjected to reductive decyanation with NaBH₄,⁷ a 73% yield of amine (**20**) was isolated. The *trans*-configuration was inferred from the low field signal of 1'-H δ 3.74.⁸ Consecutive treatment of (**14**) with LDA and MeI, followed by hydrolysis, resulted in an 80% yield of ketone (**19**).⁹ The chloro compounds appeared to be less reactive than the corresponding bromo compounds. Besides small amounts of cyclisation products, 63% of (**4**) and 86% of (**9**) were recovered, respectively.

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