Intramolecular Free Radical Cyclisation of α-Anilino Alkenenitriles

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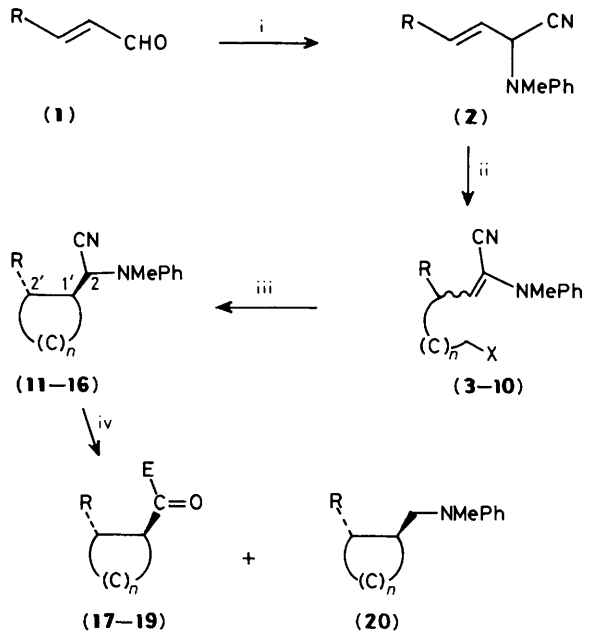
Upon treatment with tributylstannane, 2-anilino 2-alkenenitriles having halo substituents at appropriate positions undergo radical cyclisations to give cycloalkyl α-aminonitriles in a stereoselective manner.

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-anilinonitrile 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-anilinonitriles 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, %)
E-(**3**)	Ph	$(CH_2)_4Br$	1.5	(**11a**) (87), (**11b**) (5)[d]
Z-(**3**)	Ph	$(CH_2)_4Br$	1.5	(**11a**) (83), (**11b**) (4)
Z-(**4**)	Ph	$(CH_2)_3Cl$	3	(**12a**) (10), (**12b**) (25)[e]
Z-(**5**)	Ph	$(CH_2)_2CHBrMe$	2	(**13a**) (30), (**13b**) (34), (**13c**) (21)
(**6**)	Ph	$CH_2C(Br)CH_2$	2	—[f]
(**7**)	Ph	$CH_2C_6H_4$-*o*-Br	8	(**14a**) (60), (**14b**) (20)
E-(**8**)	Me	$(CH_2)_4Br$	4	(**15a**) (70), (**15b**) (15)
Z-(**9**)	Me	$(CH_2)_3Cl$	24	(**16a**) (3), (**16b**) (7)[g]
Z-(**10**)	Me	$(CH_2)_3Br$	1	(**16a**) (24), (**16b**) (59)

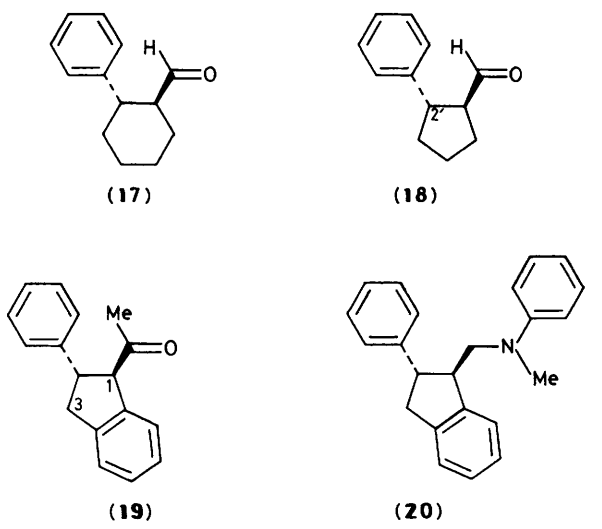
[a] The reactant (0.02 M) in mild refluxing benzene (anhydrous and deoxygenated) was treated with a benzene solution (0.2 M) of Bu^n_3SnH (1.1 equiv.) and azoisobutyronitrile (AIBN) (0.1 equiv.) by dropwise addition over a period of 30 min. [b] Time after complete addition of Bu^n_3SnH. [c] The products 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 = $CH_2CH{=}CH_2$) and recovered 45% of reactant. [g] 86% of reactant (*E*-form) was recovered.



Scheme 1. *Reagents and conditions*: i, $PhMeNH_2^+Cl^-$, Et_2O, KCN, H_2O, 0 °C, 2 h; ii, LDA (Bu^tOK), dihalide, −78 °C (0 °C), 1—2 h; iii, Bu^n_3SnH, AIBN cat., PhH, 80 °C; iv, for alkylation: LDA, THF, halide (excess), −78 °C to room temperature; for hydrolysis: $CuSO_4$, H_2O, MeOH, 0 °C, 3 h; for reductive decyanation: $NaBH_4$, 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 Bu^n_3SnH 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 $CuSO_4$ 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 $NaBH_4$,[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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