Synthesis of 1-Azaspiroundecane Ring System via Thorpe–Ziegler Annulation of 2-Cyano-2-(4-Cyano-Tethered) Arylpiperidines

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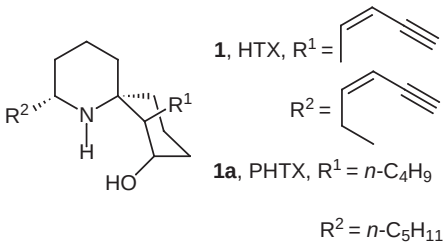
Received 21 February 2002

Abstract: An efficient stereocontrolled route to the 1-azaspiro[5.5]undecan framework of the histrionicotoxin alkaloids, employing anodic cyanation and Thorpe–Ziegler cyclization as key steps, is described. In the process of gaining information concerning the hydrolysis of the cyanoenamine function in **8**, an unexpected intramolecular Friedel–Crafts type reaction provided the aza-fluorene **10**.

Key-words: spiro compounds, stereoselective synthesis, lithiation, annulation, nitriles

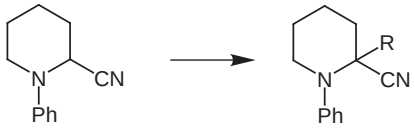
The 2-spiropiperidine framework has been found in large number of alkaloids isolated from skin extracts of the Columbian 'poison-arrow' frog *Dendrobates Histrionicus*.[1] The unique biological activities[2] of the naturally occurring histrionicotoxin **1** or its saturated congener, perhydrohistrionicotoxin **1a** (Figure) has stimulated the development of numerous approaches for the rapid and stereoselective construction of their heterocyclic core.[3,4]



Figure

However, the creation of a new spiro carbon center in the position α to the nitrogen atom remains one of the major difficulties found in all these studies. In this context, α-aminonitriles[5] occupied an important position in that they are considered as a valuable source of carbanions ideally suited for the creation of hindered quaternary centers.[6] As a part of our ongoing program aimed at the electrochemical synthesis of various α-aminonitriles, we became attracted to the preparation of piperidine ring systems substituted at the 2,2 position of the nitrogen atom.[7] Several studies have shown that such systems appears to be valuable precursors for the creation of a new spiro carbon center after several chemical transformations.[8] The purposes of this study were two-fold. Firstly, to widen the scope of our electrochemical methodology aimed at the synthesis of new α-aminonitrile systems and their subsequent utilization for further chemical purposes; secondly, to evaluate if, in a final step, the unprecedented application of the Thorpe–Ziegler[9] annulation procedure to the above mentioned systems could provide an efficient entry into the 1-azaspiro[5.5]undecan ring system.

It is now well reported that α-aminonitriles can serve both as an α-aminocarbanion and an imine or an iminium ion precursor.[10] In the first mode of reactivity, the acidic proton can be removed in the presence of bases to generate a nitrile-stabilized carbanion which, in turn, can be alkylated with a great variety of electrophiles.[11] The high yields and diastereoselectivities generally observed in this sequence prompted us to undertake a rapid investigation concerning the propensity of our metallated α-cyanoamines to form a new C-C bond α to the nitrogen atom. Several bifunctional α-aminonitriles were thus prepared (Equation and Table). The lithiation procedures were carried out after the dissolution of the requisite aminonitrile **2**[12] in THF, employing a 2 M solution of LDA in THF–*n*-heptane, at temperatures ranging from –30 °C to –20 °C. After one hour of stirring, the electrophiles were added to the cold solutions before warming to ambient temperature.



rac-**2** *rac*-**3a-g**

Equation

An additional two hours of stirring at that temperature and work-up, afforded the expected adducts **3a–f** from good to excellent yields (Table, entries 1-6). Conversely, using undecyl bromide as a bulky electrophile (entry 7), the reaction was half completed, and led to the recovery of the starting material **2** together with the undecyl derivative **3g**. This drawback was overcome by a prolonged reaction time (up to 18 h) at ambient temperature to yield **3g** as a sole product. Reaction with benzaldehyde (entry 4) provides substitution products as a mixture of *syn* and *anti*

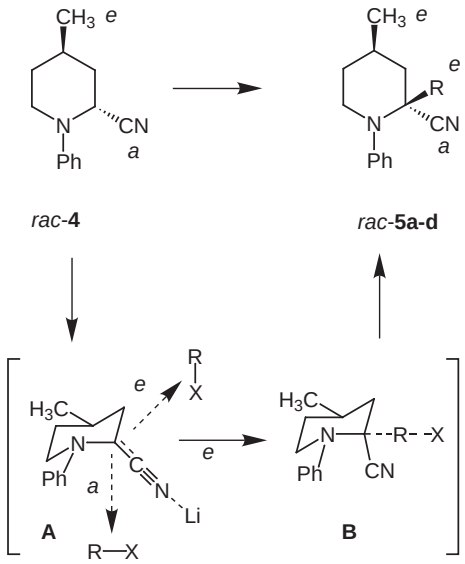
Synlett 2002, No. 6, 04 06 2002. Article Identifier:
1437-2096,E;2002,0,06,0895,0898,ftx,en;G04902ST.pdf.

ISSN 0936-5214

Table Alkylation of α-Aminonitrile **2** and **4**

Entry	Electrophile	Product	Time (h)	Yield[a,b] (%)
1	CH_3I	**3a**, R= CH_3	1	90
2	*n*-C_3H_7Br	**3b**, R = *n*-C_3H_7	2	97
3	*n*-$C_5H_{11}Br$	**3c**, R = *n*-C_5H_{11}	2	95
4	C_6H_5CHO	**3d**, R = C_6H_5CHOH *syn*/*anti*: 43/57	2	100
5	$Cl(CH_2)_4Br$	**3e**, R = $(CH_2)_4Cl$	2	95
6	allylBr	**3f**, R = Allyl	1	95
7	*n*-$C_{11}H_{23}Br$	**3g**, R = *n*-$C_{11}H_{23}$	18	90
8	CH_3I	**5a**, R = CH_3	2	90
9	*n*-C_3H_7Br	**5b**, R = *n*-C_3H_7	2	88
10	*n*-$C_5H_{11}Br$	**5c**, R = *n*-C_5H_{11}	2	92
11	$Cl(CH_2)_4Br$	**5d**, R = $(CH_2)_4Cl$	2	95

[a] Yields are of isolated products
[b] All new compounds had satisfactory elemental analysis, and the ^1H, ^{13}C NMR and mass spectra were consistent with the proposed structures.



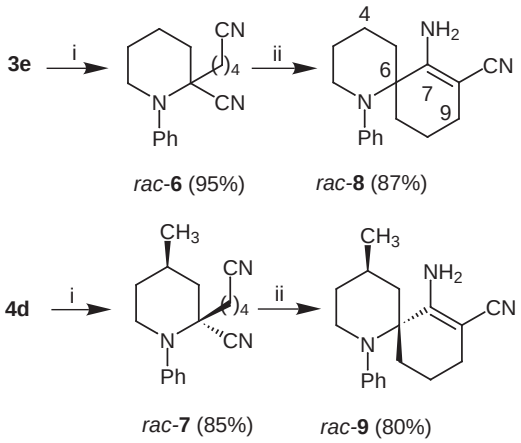
Scheme 1

isomers in nearly equal amounts. Upon chromatographic purification, one of the diastereomers crystallized, and a further X-ray diffraction performed on a single crystal revealed that both the alcohol and the cyano functions were in a *syn* configuration.[13]

The stereochemical outcome of the lithiation-alkylation procedure has been investigated using the *trans* α-aminonitrile **4**[12] as substrate. The procedure was similar to that reported for the synthesis of **3a**–**g** and afforded the expected adducts **5a**–**d** in good yields (Table, entries 8–11). We were pleased to find that in all cases both the ^1H and ^{13}C NMR spectra revealed the presence of a single diastereomer (*de* ~99%). Cyano-stabilized carbanions constitute an important class of intermediates as underscored by a series of reviews.[14] Despite their broad utilization in chemistry, the exact nature of such species has remained an open question.[15] Therefore, during the last decade, the structural aspect of various stabilized carbanions has become a subject of growing interest.[16] In this context, lithiated α-aminonitriles occupied an important position in chemistry due to their broad range of applications including the synthesis of natural or biologically active compounds. The structure of metallated α-aminonitriles has been recently determined by Enders and coworkers.[17] It has been clearly demonstrated by X-ray and by spectroscopic methods that nitrile anions should be considered as complex aggregates with charge delocalization over the ketene imine moiety. Under our reaction conditions, it seems likely that deprotonation of **4** yielded the intermediate species **A** (Scheme 1) which, in a second step is attacked from the equatorial direction (*e*)[18] by the entering electrophile to produce the energetically favored reactant like transition state **B**. Hence, the alkylation procedure proceeded with retention of configuration at C-2.

The dinitriles **6** and **7** were readily prepared by heating **3e** and **4d** (DMSO, 70 °C) with a two-fold excess of sodium cyanide in the presence of a catalytic amount (5 mol%) of tetrabutylammonium iodide.[19] Evidence for the incorporation of the cyano group to the molecules was provided by the analysis of the ^1H NMR spectrum of **6**[20] and **7** in which triplet signals (2 H) attributed to the terminal CH_2 groups were found at δ = 2.20. Similarly, the ^{13}C NMR spectrum displayed two quaternary CN signals in the region δ = 119–121.

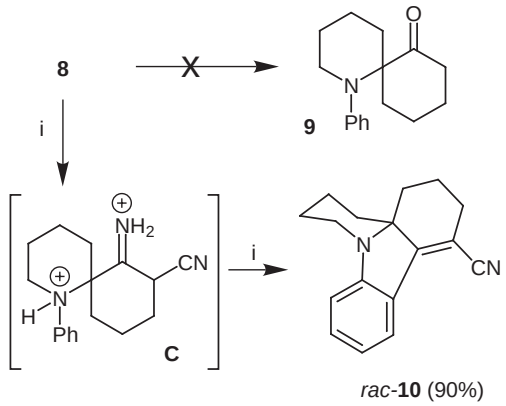
As a useful method of assembling medium to large sized-rings,[21] we decided to make use of the Thorpe–Ziegler annulation procedure to construct the aza-spiroundecan ring system. In our case, dinitriles **6** and **7** were ideally suited for such a cyclization since only the less hindered primary cyanide reacts with the base to produce the terminal nitrile-stabilized carbanion. Furthermore, it was felt that the angular cyano group was considered as an integral part of the final compound (future C-7). Traditionally, dinitriles derivatives were cyclized with alkoxide bases,[22] but catalytic[23] or radical[24] cyclization methods using iridium hydride complexes or the couple Bu_3SnH–AIBN, respectively, have been recently reported. After few attempts,[25] we rapidly observed that Thorpe–Ziegler products **8** and **9** (Scheme 2) could be readily obtained, employing LDA (1 equiv) as a base and THF as the solvent. The IR spectrum of **8** showed a characteristic absorption at 2185 cm^{-1} suggesting that the nitriles groups were transformed into the requisite enaminonitrile function. Further evidence for the formation of the cyanoenamine moiety was provided by the analysis of the ^{13}C NMR spectrum of **8** in which the quaternary sp^2 hybridized carbons C-7 and C-8 were found at δ = 161.75 and δ = 74.90, respectively.



Scheme 2 (i) NaCN (2 equiv), DMSO, *n*-Bu_4NI (5 mol%), 70 °C, 12 h; (ii) LDA, THF, –78 °C to r.t., 2 h.

Both the spiro derivatives **8** and **9** were crystallized from a mixture of diethyl ether and petroleum ether. An X-ray diffraction performed on single crystals obtained in this way definitively ascertained the spirocyclic structure of **8** and **9**.[13] This study also indicates that the 4-Me group and the cyanoenamine function were in a *trans* disposition.

Acid hydrolysis (Scheme 3) of the cyanoenamine function in **6** did not give the expected cyclohexanone **9** but rather the aza-benzo[*k*]fluorene **10**. The reaction was performed in refluxed *t*-BuOH in presence of aqueous HCl. After work-up and filtration over a silica column, **10** was obtained as the sole product. The polycyclic structure of **10** was determined by ^1H and ^{13}C NMR experiments, which were further confirmed by an X-ray diffraction study.[13] Some points of note arise from this result.



Scheme 3 (i) *t*-BuOH, HCl (15%), 83 °C, 50 min.

Firstly, this intramolecular condensation should be considered as a Friedel–Crafts type reaction with the protonated cyanoimine **C** – or a synthetic equivalent – acting as key intermediate. Secondly, although protonated amines are considered as deactivating – *I* groups, and direct *meta* substitution, the proximity of both the reactive centers constitute the driving force of that condensation.

In summary, we have developed a new and concise approach for the construction of 1-azaspirocycles featuring anodic cyanation and Thorpe-Ziegler cyclization as keysteps. A C-4 methyl-substituted piperidine derivative was a convenient substrate to study the stereochemical outcome of the lithiation-alkylation procedure. Our first attempts aimed at the hydrolysis of the β-cyanoenamine function afforded the unreported aza-fluorene **10**, which displays interesting fluorescent properties which are currently under investigations. Although a limited number of examples have been studied, the overall sequence described in this paper should represent a straightforward route from piperidine derivatives to the corresponding spiro systems.

Acknowledgement

R. M. thanks the MENRT for a grant.

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(25) A solution (20 mL, THF) of **6** (0.5 g, 1.87 mmol) was cooled to –30 °C and treated dropwise (by syringe) with a 2 M solution of LDA (0.94 mL, 1.87 mmol). The solution was allowed to warm to –20 °C and maintained at that temperature for 1 h, before being stirred at r.t. for 3 h. The reaction mixture was quenched with water and extracted with CH_2Cl_2. The organic phases were combined, dried over $MgSO_4$, and concentrated in vacuo. The crude material was purified over a silica column (diethyl ether–petroleum ether, 1:1) to afford **8** (0.433 g, 87%).