Addition of Metal Cyanides to Tosylhydrazones of Aldehydes in Aprotic Solvents: A New Method for One-Carbon Homologation of Aldehydes and for the Synthesis of α-(N^2-Tosylhydrazino)nitriles

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Received 17 February 2003

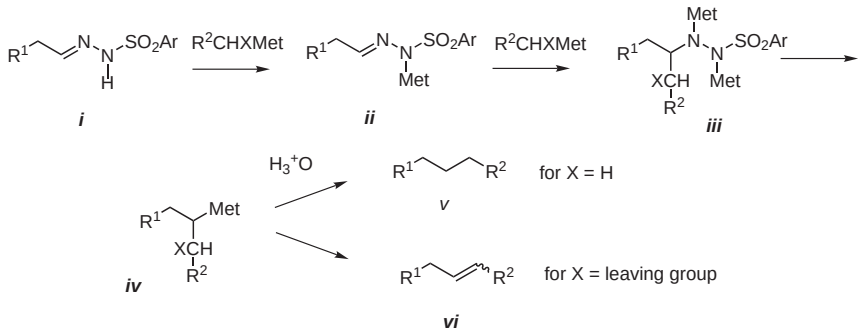
Abstract: One-carbon homologation of aldehydes to nitriles via reaction of the respective tosylhydrazones with trimethylsilyl cyanide, tributyltin cyanide and diethylaluminum cyanide with or without Lewis acid-type catalysts was examined. Representative tosylhydrazones on treatment with trimethylsilyl cyanide in the presence of trimethylsilyl triflate or scandium triflate afforded α-(N^2-tosylhydraziono)nitriles in excellent yields. The same adducts were also obtained using tributyltin cyanide/scandium triflate system or diethylaluminum cyanide at room temperature. Treatment of tosylhydrazones with trimethylsilyl cyanide/scandium triflate or with diethylaluminum cyanide in appropriate solvent at higher temperatures afforded the respective one-carbon extended nitriles in good yields. Some examples of the application of these reactions to polyfunctional compounds are given.

Key words: aldehyde arylsulfonylhydrazones, trimethylsilyl cyanide, trimethyltin cyanide, diethylaluminum cyanide, trimethylsilyl triflate, scandium triflate

Arylsulfonylhydrazones, readily accessible derivatives of aldehydes or ketones, display a remarkably broad range of chemical reactivity. Their main reactions involve a molecular fragmentation and expulsion of nitrogen as in the Bamford–Stevens rearrangement,[1] Eschenmoser fragmentation,[2] and the Shapiro reaction.[3,4] Fragmentation of tosylhydrazones of aldehydes across the N–N bond generating nitriles has also been recorded.[5,6] In certain cases, the arylsulfonylhydrazone function may serve for the formation of a new carbon–carbon bond in the α-position to the carbon–nitrogen bond. Thus, alkylation of tosylhydrazones either directly[7] or via the respective tosyl azoene has been reported.[8,9]

Reactions of arylsulfonylhydrazones with organometallic reagents ultimately resulting in replacement of the carbon–nitrogen bond by the carbon–carbon bond, i.e. 'reductive alkylation'[5,10] and olefination[6,11–13] present considerable synthetic potential. In the first step of these reactions, exchange of the tosylhydrazone proton with the metal cation occurs to give the metal derivative ***ii*** (Scheme 1). The next step consists in the addition of the organometallics to the carbon–nitrogen bond of ***ii*** to form bimetallic tosylhydrazine derivative ***iii***. Fragmentation of ***iii*** to a carbanionic species ***iv***, $ArSO_2Met$, and N_2 occurs next. Finally, protonation or elimination of the leaving group from ***iv*** would give ***v*** or ***vi***, respectively. Alternative mechanistic routes from metallated tosylhydrazone ***iii*** to products ***v*** or ***vi*** would lead through a carbenoid intermediate or involve concerted addition-tosylsulfinyl group elimination reactions. Notably, in transforming the aldehyde tosylhydrazone ***ii*** into products ***v*** or ***vi***, no reducing reagents are employed.

In order to develop a method for one-carbon homologation of aldehydes that does not involve reducing reagents and to assess stability of bimetallic tosylhydrazine derivatives of type ***iii*** in aprotic solvents, we have examined the reaction of selected tosylhydrazones with trimethylsilyl cyanide (TMSCN), tributyltin cyanide and diethylaluminum cyanide (Scheme 2).



Scheme 1

Synthesis 2003, No. 7, Print: 20 05 2003.
Art Id.1437-210X,E;2003,0,07,1049,1054,ftx,en;P01603SS.pdf.
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ISSN 0039-7881

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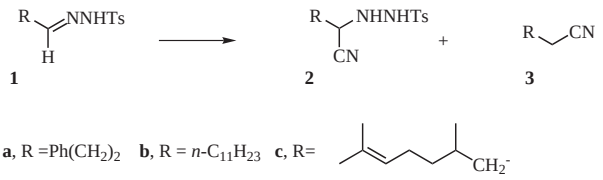
TMSCN did not react with tosylhydrazone **1a** in THF at room temperature. The same reagents in the presence of 15 mol% of TMSOTf afforded the adduct **2a** (Table 1, entry 1). The yield of the adduct **2a** was slightly improved by increasing the molar ratio of the catalyst (Table 1, entry 2). However, the product isolation was difficult due to partial polymerization of the solvent (gel formation). The use of dichloromethane and carrying the reaction at reflux temperature allowed to obtain the adduct **2a** in excellent yield (Table 1, entry 3). No cyanide **3a** could be detected even after prolonged heating of the reaction mixture indicating that the intermediate silylated adduct is stable. Preparation of adducts of type **2** in the reaction of tosylhydrazones with potassium cyanide in ethanol or in ethanol–acetic acid mixtures and their decomposition to nitriles **3** has been reported. However, under these conditions the addition reaction was reversible, which apparently impeded preparation of pure products.[14–16] Other tosylhydrazine derivatives have been prepared by reduction of the respective tosylhydrazones with triethylsilane in trifluoroacetic acid.[17]



Scheme 2

Adduct **2a** was obtained also in the reaction of **1a** with TMSCN in the presence of scandium triflate[18] in acetonitrile or in THF at room temperature (Table 1, entries 4 and 5). Treatment of **1a** with TMSCN in the presence of $Sc(OTf)_3$ in dichloromethane at room temperature afforded a mixture of adduct **2a** and cyanide **3a**. At reflux temperature cyanide **3a** was obtained in a high yield (Table 1, entries 6 and 7).

Similarly, adduct **3b** was prepared by the $Sc(OTf)_3$-promoted reaction of tosylhydrazone **1b**, which was prepared separately or generated in situ from the respective aldehyde and equimolar amount of tosylhydrazine, with TMSCN (Table 1, entries 8 and 9). In the latter case an excess

Table 1 The Reaction of Tosylhydrazone **1** with Metal Cyanides (Scheme 2)

Entry	1	Cyanide, mol equiv	Catalyst, mol%	Solvent, Temp, Time	Product 2	Yield (%)	Product 3	Yield (%)
1	**1a**	TMSCN, 2	TMSOTf, 15	THF, r.t., 15 h	**2a**	70	–	–
2	**1a**	TMSCN, 2	TMSOTf, 100	THF, r.t., 15 h	**2a**	75	–	–
3	**1a**	TMSCN, 2	TMSOTf, 15	CH_2Cl_2, reflux, 1 h	**2a**	93	–	–
4	**1a**	TMSCN, 2	$Sc(OTf)_3$, 30	MeCN, r.t., 15 h	**2a**	92	–	–
5	**1a**	TMSCN, 2	$Sc(OTf)_3$, 30	THF, r.t., 15 h	**2a**	75	-	–
6	**1a**	TMSCN, 2	$Sc(OTf)_3$, 30	CH_2Cl_2, r.t., 15 h	**2a**	43	**3a**	55
7	**1a**	TMSCN, 2	$Sc(OTf)_3$, 30	CH_2Cl_2, reflux, 3 h	–	–	**3a**	85
8	**1b**	TMSCN, 2.0	$Sc(OTf)_3$, 30	CH_2Cl_2, reflux, 3 h	–	–	**3b**	70
9	**1b**	TMSCN, 3.0	$Sc(OTf)_3$, 30	CH_2Cl_2, reflux, 3 h	–	–	**3b**	63[a]
10	**1a**	Bu_3SnCN, 1.5	$Sc(OTf)_3$, 30	CH_2Cl_2, r.t., 15 h	**2a**	75	–	–
11	**1a**	Bu_3SnCN, 1.5	$Sc(OTf)_3$, 30	MeCN, r.t., 15 h	**2a**	80	–	–
12	**1b**	Bu_3SnCN, 1.5	$Sc(OTf)_3$, 30	CH_2Cl_2, r.t., 15 h	**2b**	87	–	–
13	**1b**	Bu_3SnCN, 1.5	$Sc(OTf)_3$, 30	MeCN, r.t., 15 h	**2b**	90	–	–
14	**1a**	Et_2AlCN, 1.5	–	THF, r.t., 15 h	**2a**	85	–	–
15	**1a**	Et_2AlCN, 1.5	–	THF, reflux, 1 h	–	–	**3a**	73
16	**1a**	Et_2AlCN, 1.5	–	CH_2Cl_2, reflux, 1 h	–	–	**3a**	78
17	**1b**	Et_2AlCN, 2.0	–	CH_2Cl_2, reflux, 3 h	–	–	**3b**	55
18	**1b**	Et_2AlCN, 3.0	–	THF, reflux, 3 h	–	–	**3b**	50[a]
19	**1c**	Et_2AlCN, 2.5	–	THF, r.t., 15 h	**2c**	75[a]	–	–
20	**1c**	Et_2AlCN, 2.5	–	THF, reflux, 3 h	–	–	**3c**	68[a]

[a] Tosylhydrazone was prepared in situ from the corresponding aldehyde and tosylhydrzine.

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of the cyanide was used to accommodate for the presence of water. However, acid-labile citronellal tosylhydrazone **1c** (for preparation, see below) on treatment with TMSCN alone gave polymerization products.

Tributyltin cyanide, which is considered as an exceptionally mild and non-toxic cyanation reagent,[19,20] did not react with tosylhydrazone **1a** at room temperature neither alone nor in the presence of TMSOTf. However, treatment of **1a** with this reagent in the presence of $Sc(OTf)_3$ (30 mol%) in dichloromethane, cleanly afforded adduct **2a** (Table 1, entry 10). The best yield of **2a** was obtained with these reagents using acetonitrile as the solvent (Table 1, entry 11). Similarly, adducts **2b** were obtained when tosylhydrazone **1b** was treated with Bu_3SnCN in the presence of $Sc(OTf)_3$ (Table 1, entries 12 and 13). It should be noted that all products prepared using tributyltin cyanide contained some (5–10%) presumably tin-containing impurities, which could not be removed by chromatography on silica gel.

The reaction of tosylhydrazone **1a** with Et_2AlCN (1.5 equiv) in THF at room temperature afforded adduct **2a** in a 85% yield (Table 1, entry 14). Treatment of tosylhydrazone **1a** with diethylaluminum cyanide at reflux temperature in THF or in dichloromethane gave cyanide **3a** in high yields (Table 1, entry 15 and 16). It should be noted that the isolated hydrazine derivative **2a** could not be efficiently transformed into **3a** upon heating with or without added Et_2AlCN. In all cases complex mixtures of products were formed.

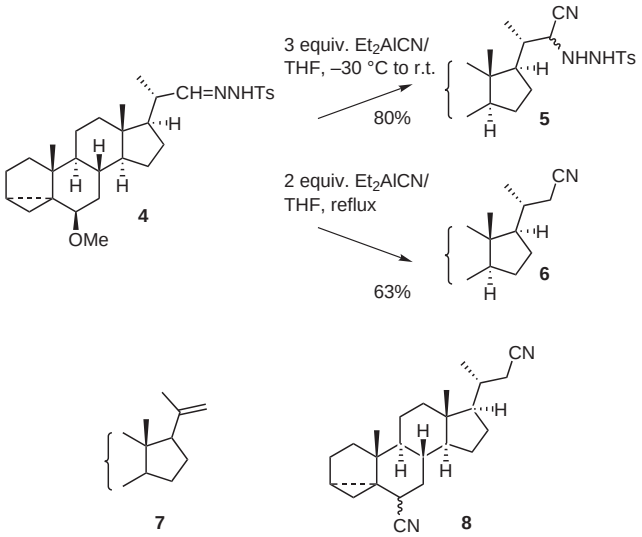
Tosylhydrazone **1b** on reaction with Et_2AlCN in THF at reflux temperature afforded cyanide **3b** in 55% yield. The analogous reaction with tosylhydrazone generated in situ afforded **3b** in 50% overall yield (Table 1, entries 17 and 18).

(*S*)-Citronellal tosylhydrazone **1c** turned out to be too unstable for isolation in a pure form. A solution of **1c** prepared in situ, in THF at room temperature, was treated with an excess of Et_2AlCN. Adduct **2c** (a mixture of diastereomers) was obtained in 75% yield. The same reagents at reflux temperature afforded cyanide **3c** in 68% yield (Table 1, entries 19 and 20).

Foregoing results show that reaction of aldehyde tosylhydrazones with metal cyanides with or without a promoter may be used for the synthesis one-carbon extended nitriles. It was of interest to examine compatibility of this reaction with some protective and functional groups.

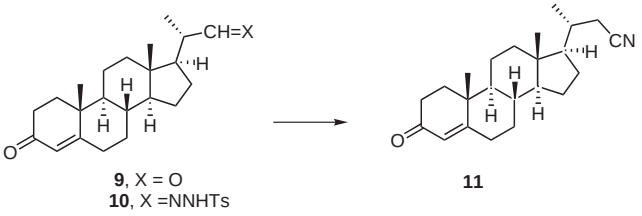
Tosylhydrazone **4** (Scheme 3), prepared[6] from the corresponding aldehyde, was treated with the examined cyanides under various conditions. Using 3 molar equivalents of Et_2AlCN in THF adducts **5** were obtained in a 80% yield, as a mixture of diastereomers in a ratio of 1:1. The diastereoisomers were separated by chromatography and fully identified. However, relative configuration at C-22 could not be assigned. The reaction of **4** with Et_2AlCN in THF at reflux temperature afforded nitrile **6**, which was isolated in a 63% yield along with some unconsumed starting material and the fragmentation product **7** (Scheme 3).

Reactions of **4** with $Bu_3SnCN/Sc(OTf)_3$ or TMSCN/TMSOTf systems affect the *i*-steroid system and occur sluggishly. For example, reaction with $Bu_3SnCN/Sc(OTf)_3$ in dichloromethane afforded a complex mixture of products out of which the dicyano derivative **8** was isolated.



Scheme 3

Next, we examined homologation of easily available aldehyde **9** that bears α,β-unsaturated ketone function. Aldehyde **9** in dichloromethane was allowed to react with tosylhydrazine (1 mol equiv) and then the tosylhydrazone **10**, in situ, was treated with TMSCN (3 mol equiv) and $Sc(OTf)_3$ (30 mol%). The product **11** was obtained in 63% yield (Scheme 4). The same nitrile was recently prepared from aldehyde **9** in a two-step procedure in which tributyltin hydride was used as a reducing agent.[21]



Scheme 4

On treatment of tosylhydrazone **10** (prepared in situ) with Et_2AlCN in THF at room temperature the corresponding tosylhydrazino-nitriles were formed, as judged from the TLC analysis. However, all attempts to isolate these products or to transform them into nitrile **11** failed.

In conclusion, it has been shown that tosylhydrazones of aldehydes afford the respective nitriles on reaction with metal cyanides in aprotic solvents. This reaction permits one-pot non-reductive homologation of aldehydes. It has

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been also shown that metal *p*-toluenesulfonylhydrazino derivatives corresponding to **2** are stable in aprotic solvents.

NMR spectra were recorded in $CDCl_3$ solutions, ^1H NMR at 200 MHz and ^{13}C NMR at 50 MHz on a Varian Gemini instrument or ^1H NMR at 500 MHz and ^{13}C NMR at 125 MHz on Bruker AMX spectrometers. Chemical shifts are given as δ values (ppm); DEPT sequence was used for assignment of multiplicities in ^{13}C NMR spectra. FT-IR spectra were taken using Perkin-Elmer Spectrum 2000 unit. MS (EI, 70 eV) were recorded on AMD 604 (AMD Intectra GmbH). Reactions were performed in flame-dried glassware under argon. Column chromatography was performed on Merck silica gel 60, 230–400 mesh, and TLC on Merck aluminum sheets, silica gel 60 S_{254}.

2-[2-(*p*-Toluenesulfonyl)hydrazino]-4-phenylbutyronitrile (2a)
To a stirred solution of tosylhydrazone **1a** (242 mg, 0.8 mmol) in THF (5 mL) at 0 °C was added dropwise Et_2AlCN (1 M in toluene, 1.2 mL, 1.2 mmol). The mixture was allowed to warm to r.t. and was set aside. After 15 h, aq HCl (1 M, 5 mL) was added and the mixture was extracted with EtOAc (2 × 15 mL). The combined organic extracts were washed with brine and dried ($MgSO_4$). The solvent was evaporated and the residue was chromatographed on silica gel (15 mL, hexanes–EtOAc, 9:1–6:1) to give adduct **2a** (225 mg, 85%).

IR (film): 3298 s, 3234 s, 3028 m, 2927 m, 2237 w, 1598 s, 1496 s, 1454 s, 1336 s, 1163 s, 1092 s, 814 s, 754 s, 702 s, 665 s, 553 s cm^{-1}.

^1H NMR (200 MHz): δ = 2.06 (m, 2 H), 2.47 (s, 3 H), 2.80 (t, *J* = 7.4 Hz, 2 H), 3.70 (t, *J* = 7.4 Hz, overlapping s, 2 H), 6.81 (br s, 1 H), 7.14–7.42 (m, 7 H), 7.84 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (50 MHz): δ = 21.57 (3), 31.30 (2), 32.24 (2), 52.00 (1), 119.07 (0), 126.42 (1), 128.21 (1), 128.39 (1) 128.59 (1), 129.65 (1), 134.30 (0), 139.54 (0), 144.42 (0).

HRMS (ESI/APCI): *m/z* calcd for $C_{17}H_{19}N_3NaO_2S$: 352.1090; found: 352.1100.

4-Phenylbutyronitrile (3a)
Using Et_2AlCN: To a stirred solution of tosylhydrazone **1a** (242 mg, 0.8 mmol) in THF (5 mL) at 0 °C was added dropwise Et_2AlCN (1 M in toluene, 1.2 mL, 1.2 mmol). The mixture was allowed to warm to r.t. in 1 h and then was refluxed for 1 h. After cooling, aq HCl (1 M, 5 mL) was added and the mixture was extracted with EtOAc (2 × 10 mL). The combined organic extracts were washed with brine (10 mL) and dried ($MgSO_4$). The solvent was evaporated and the residue was chromatographed on silica gel (15 mL, hexanes–EtOAc, 9:1–6:1) to furnish nitrile **3a** (85 mg, 73%).

Using Bu_3SnCN and TMSCN: Reactions of tosylhydrazone **1a** with Bu_3SnCN and TMSCN were carried out in an analogous way. The reagents were mixed in appropriate solvent at 0 °C, and the mixtures were allowed to warm to r.t. (ca. 1 h) and then were refluxed (Table 1).

2-[2-(*p*-Toluenesulfonyl)hydrazino]tridecanenitrile (2b)
To a stirred solution of tosylhydrazone **1b** (282 mg, 0.8 mmol) in MeCN (5 mL) at 0 °C were added Bu_3SnCN (380 mg, 1.2 mmol) and $Sc(OTf)_3$ (118 mg, 0.24 mmol 30% mmol) and the mixture was allowed to warm to r.t. and set aside. After 15 h, aq HCl (1 M, 5 mL) was added and the mixture was extracted with EtOAc (2 × 15 mL). The combined organic extracts were washed with brine and dried ($MgSO_4$): the solvent was evaporated and the residue was chromatographed on silica gel (15 mL, hexanes–EtOAc, 19:1–9:1) to afford adduct **2b** (273 mg, 90%).

IR (film): 3296 s, 3234 s, 2924 s, 2853 s, 2247 w, 1598 m, 1465 m, 1324 s, 1157s, 1092 m, 812 m, 668 m, 552 s cm^{-1}.

^1H NMR (200 MHz): δ = 0.88 (t, *J* = 6.8 Hz, 3 H), 1.15–1.4 (m, 18 H), 1.55–1.72 (m, 2 H), 2.43 (s, 3 H), 3.66 (dt, *J* = 7.5, 7.2 Hz, 1 H), 3.95 (dd, *J* = 7.6, 3.3 Hz, 1 H), 6.65 (d, *J* = 3.3 Hz, 1 H), 7.31 (d, *J* = 8.1 Hz, 2 H), 7.78 (d, *J* = 8.2 Hz, 2 H).

^{13}C NMR (50 MHz): δ = 14.10 (3), 21.59 (3), 22.67 (2), 25.42 (2), 28.84 (2), 29.30 (2), 29.31 (2), 29.46 (2), 29.58 (2), 30.77 (2), 31.89 (2), 53.14 (1), 119.26 (0), 128.24 (1), 129.62 (1), 134.44 (0), 144.37 (0).

HRMS (ESI/APCI): *m/z* calcd for $C_{20}H_{33}N_3NaO_2S$: 402.2186; found: 402.2187.

Tridecanenitrile (3b)
Using Et_2AlCN: To a stirred solution of tosylhydrazone **1b** (282 mg, 0.8 mmol) in THF (5 mL) at 0 °C was added Et_2AlCN (1 M in toluene, 1.6 mL, 1.6 mmol). The mixture was allowed to warm to r.t. (1 h) and then was refluxed for 3 h. After cooling, aq HCl (1 M, 5 mL) was added and the mixture was extracted with EtOAc (2 × 10 mL). The combined organic extracts were washed with brine (10 mL) and dried ($MgSO_4$). The solvent was evaporated and the residue was chromatographed on silica gel (15 mL, hexanes–EtOAc, 9:1) to give cyanide[22] **3b** (78 mg, 50%).

in situ Reaction Using Et_2AlCN: For the reaction of tosylhydrazone **1b** in situ, a solution the aldehyde (150 mg, 0.8 mmol) and $TsNHNH_2$ (150 mg, 0.8 mmol) in THF (5 mL) was stirred at room temperature for 30 min and then the foregoing procedure was followed.

Using Bu_3SnCN and TMSCN: In an analogous way, reactions with Bu_3SnCN and TMSCN were carried out (Table 1).

4,8-Dimethyl-2-[2-(*p*-toluenesulfonylhydrazino]non-7-enenitrile (2c)
To a solution of (*S*)-citronellal (154 mg, 1.0 mmol) in THF (5 mL) was added tosylhydrazine (187 mg, 1.0 mmol). The mixture was stirred at r.t. for 30 min, then it was cooled to 0 °C and Et_2AlCN (1 M in toluene, 2.5 mL, 2.5 mmol) was added. The mixture was set aside at r.t. After 15 h, aq HCl (1 M, 5 mL) was added and the product was extracted with EtOAc (2 × 10 mL). The combined organic extracts were washed with brine (10 mL) and dried ($MgSO_4$). The solvent was evaporated and the residue was chromatographed on silica gel (20 mL, hexanes–EtOAc, 9:1). Adduct **2c** was obtained as a mixture of diastereomers (262 mg, 75%).

IR (film): 3298 s, 3238 s, 2964 s, 2923 s, 2237 w, 1598 m, 1452 m, 1337 s, 1164s, 1093 m, 814 s, 666 s, 552 s cm^{-1}.

^1H NMR(200 MHz): δ = 0.84 (d, *J* = 6.3 Hz, 1.5 H), 0.85 (d, *J* = 6.0 Hz, 1.5 H) 1.59 (br s, 3 H), 1.68 (br s, 3 H), 1.0–2.0 (m, 7 H), 3.71 (m, 1 H), 2.42 (s, 3 H), 3.91 (m, 1 H), 5.04 (br t, *J* = 7.0 Hz, 1 H), 6.69 (d, *J* = 3.0 Hz, 1 H), 7.30 (d, *J* = 8.0 Hz, 2 H), 7.78 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (50 MHz): δ = 17.67 (3), 18.79 (3), 18.97 (3), 21.57 (3), 25.09 (2), 25.67 (1), 28.91 (1), 29.14 (1), 36.36 (2), 36.53 (2), 37.65 (2), 37.99 (2), 51.29 (1), 51.64 (1), 119.26 (0), 119.61 (0), 123.94 (1), 123.99 (1), 128.23 (1), 129.60 (1), 131.64 (0), 134.45 (0), 144.34 (0).

HRMS (ESI/APCI): *m/z* calcd for $C_{18}H_{27}N_3NaO_2S$: 372.1716; found: 372.1706.

4,8-Dimethylnon-7-enenitrile (3c)
A solution of (*S*)-citronellal (154 mg, 1.0 mmol) and tosylhydrazine (187 mg, 1.0 mmol) in THF (5 mL) was stirred 30 min at r.t., then it was cooled to 0 °C, and Et_2AlCN (1 M in toluene, 2.5 mL, 2.5 mmol) was added. The mixture was allowed to warm to r.t. and refluxed for 3 h. After cooling, aq HCl (1 M, 5 mL) was added and the

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product was extracted with EtOAc (2 × 10 mL). The combined organic extracts were washed with brine (10 mL) and dried ($MgSO_4$). The solvent was evaporated and the residue was chromatographed on silica gel (15 mL, hexanes–EtOAc, 9:1) to give cyanide **3c** (112 mg, 68%). ^1H and ^{13}C NMR spectra were in accord with those reported.[23]

6β-methoxy-22ξ-[2-(*p*-toluenesulfonyl)hydrazino]-23-nor-3α,5α-cyclo-5α-cholanenitrile (5)

To a stirred solution of tosylhydrazone **4**[6] (205 mg, 0.4 mmol) in THF (5 mL) at –30 °C was added dropwise Et_2AlCN (1 M in toluene, 1.2 mL, 1.2 mmol). The mixture was allowed to warm to r.t., and was set aside. After 15 h, aq HCl (1 M, 15 mL) was added and the product was extracted with EtOAc (2 × 10 mL). The combined organic extracts were washed with brine (10 mL) and dried ($MgSO_4$). The solvent was evaporated and the residue was chromatographed on silica gel (15 mL, hexanes–EtOAc, 9:1) to give adduct **5** (diastereomer A, 41 mg), a mixed fraction (50 mg), and adduct **5** (diastereomer B, 82 mg) in that order.

5; Diasteromer A

^1H NMR (500 MHz): δ = 0.46 (dd, *J* = 8.0, 5.1 Hz, 1 H), 0.67 (s, 3 H), 1.02 (s, 3 H), 1.07 (d, *J* = 7.1 Hz, 3 H), 0.64–2.0 (m, 21 H), 2.45 (s, 3 H), 2.79 (t, *J* = 2.6 Hz, 1 H), 3.33 (s, 3 H), 3.73 (dd, *J* = 10.2, 2.7 Hz, 1 H), 3.82 (dd, *J* = 10.2, 3.0 Hz, 1 H), 6.43 (d, *J* = 2.9 Hz 1 H), 7.34 (d, *J* = 8.0 Hz, 2 H), 7.82 (d, *J* = 8.3 Hz, 2 H).

^{13}C NMR (125 MHz): δ = 11.98 (3), 13.09 (2), 14.48 (3), 19.22 (3), 21.45 (1), 21.63 (3), 22.62 (1), 23.99 (2), 24.94 (2), 27.34 (2), 30.51 (1), 33.34 (2), 35.05 (2), 35.22 (0), 38.87 (1), 39.90 (2), 42.69 (0), 43.35 (0), 47.88 (1), 51.41 (1), 56.36 (1), 56.56 (3), 57.56 (1), 82.23 (1), 119.45 (0), 128.50 (1), 129.60 (1), 134.65 (0), 144.44 (0).

5; Diasteromer B

^1H NMR (500 MHz): δ = 0.44 (dd, *J* = 8.0, 5.1 Hz, 1 H), 0.65 (app. t, *J* = 4.5 Hz, 1 H), 0.69 (s, 3 H), 0.99 (d, *J* = 6.6 Hz, 3 H), 1.01 (s, 3 H), 0.75–2.0 (m, 20 H), 2.44 (s, 3 H). 2,77 (t, *J* = 2.6 Hz, 1 H), 3.32 (s, 3 H), 3.68 (dd *J* = 8.1, 3.2 Hz, 1 H), 4.02 (dd, *J* = 8.1, 2.7 Hz, 1 H), 6.52 (d, *J* = 2.6 Hz 1 H), 7.34 (d, *J* = 8.0 Hz, 2 H), 7.81 (d, *J* = 8.3 Hz, 2 H).

^{13}C NMR (125 MHz): δ = 12.33 (3), 13.06 (2), 14.22 (3), 19.17 (3), 21.35 (1), 21.55 (3), 22.62 (2), 23.97 (2), 24.86 (2), 24.92 (0), 27.42 (2), 30.47 (1), 33.29 (2), 35.07 (2), 37.74 (1), 39.91 (2), 42.95 (0), 43.28 (0), 47.77 (1), 52.63 (1), 56.04 (1), 56.53 (3), 57.76 (1), 82.21 (1), 117.70 (0), 128.23 (1), 129.73 (1), 134.71 (0), 144.53 (0).

In total 173 mg (80%) of adduct **5** was obtained. Analysis of the ^1H NMR spectra of the crude product indicated that diastereomers **A** and **B** are present in a ratio of ca. 1:1.

5; Diasteromers A/B

IR (film): 3303 m, 2938 s, 2212 w, 1598 m, 1457 m, 1385 m, 1164 s, 1092 s, 814 m, 702 s, 554 s cm^{-1}.

HRMS (ESI/APCI): *m/z* Calcd for $C_{31}H_{45}N_3O_2NaS$: 562.3074. Found: 562,3074.

6β-Methoxy-23-nor-3α,5α-cyclo-5α-cholanenitrile (6)

To a stirred solution of tosylhydrazone **4** (205 mg, 0.4 mmol) in THF (5 ml) at –30 °C was added dropwise Et_2AlCN (1 M in toluene, 0.8 mL, 0.8 mmol). The mixture was allowed to warm to r.t. in 1 h and then refluxed for 2 h. After cooling, aq HCl (1 M, 5 mL) was added and the product was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine and dried ($MgSO_4$). The solvent was evaporated and the residue was chromatographed on silica gel (15 mL, hexanes–EtOAc, 9:1, 6:1 and 4:1) to afford 6β-methoxy-3α,5α-cyclo-23,24-bisnor-5α-chol-20(22)-ene (26 mg, 20%), nitrile **6** (90 mg, 63%, ^1H and ^{13}C NMR spectra were in accord with those reported[24]), and unchanged starting material **4** (20 mg, 10%) in that order.

6ξ-Cyano-3α,5α-cyclo-24-nor-5α-cholanenitrile (8)

Reaction of **4** with $Bu_3SnCN/Sc(OTf)_3$ in CH_2Cl_2 afforded a complex mixture of products. The nitrile **8** was isolated from the product mixture by column chromatography on silica gel (eluent: hexane–EtOAc, 9:1 ♦ 6:1).

IR (film): 2941 m, 2233 m, 1461 m, 1383 m cm^{-1}.

^1H NMR (200 MHz): δ = 0.36 (dd, *J* = 8.5 Hz, 1 H), 0.76 (s, 3 H), 1.13 (s, 3 H), 1.16 (d, *J* = 6.6 Hz, 3 H), 0.60–2.04 (m, 21 H), 2.18–2.42 (m, 3 H).

^{13}C NMR (50 MHz): δ = 12.32, 12.67 (2), 18.59 (3), 19.34 (3), 22.57 (2), 24.03 (2), 24.66 (2), 24.85 (2), 26.23 (1), (3), 28.07 (2), 32.60 (1), 32.89 (2), 33.22 (2), 33.42 (1), 34.00 (0), 39.57 (2), 42.86 (0), 43.19 (0), 47.31 (1), 54.68 (1), 55.61 (3), 118.73 (0), 122.25 (0).

HRMS (ESI/APCI): *m/z* calcd for $C_{24}H_{34}N_2Na$: 373.2614; found: 373.2612.

3-Oxo-23-norchol-4-enenitrile (11)

A solution of aldehyde **9** (165 mg, 0.5 mmol) and tosylhydrazine (95 mg, 0.5 mmol) in CH_2Cl_2 (4 mL) was stirred at r.t. for 1 h. To the solution of tosylhydrazone **10** thus formed, were added TMSCN (150 mg, 1.5 mmol), and $Sc(OTf)_3$ (75 mg, 0.15 mmol, 30 mol%). The mixture was allowed to warm to r.t. (3 h) and then refluxed for 3 h. After cooling, aq HCl (1 M, 5 mL) was added and the product was extracted with EtOAc (2 × 10 mL). The combined organic extracts were washed with brine (10 mL) and dried ($MgSO_4$). The solvent was evaporated and the residue was chromatographed on silica gel (15 mL, hexane–EtOAc, 2:1→ 1:1) to give nitrile[21] **11** (107 mg, 63%).

^1H NMR (200 MHz): δ = 0.72 (s, 3 H), 1.15 (d, *J* = 6.8 Hz), 1.16 (s, 3 H), 0.80–2.54 (m, 23 H), 5.70 (s, 1 H).

^{13}C NMR (50 MHz): δ = 12.01,17.33, 19.23, 20.89, 24.01, 24.71, 27. 96, 31.83, 32.77, 33.49, 33.89, 35.50, 35.60, 38.49, 39.17, 42.45, 53.51, 54.66, 55.58, 118.79, 123.73, 171.15, 199.39.

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