Dephosphorylation of Cyano Diethyl Phosphates by Reduction with Lithium–Liquid Ammonia: An Efficient Method for Conversion of Carbonyl Compounds into Nitriles

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Cyano diethyl phosphate derivatives of aromatic carbonyl compounds and α,β-unsaturated ketones were successively dephosphorylated by reduction with lithium in liquid ammonia followed by treatment with isoprene or alkyl halides to give β,γ-unsaturated nitriles or α-alkyl-β,γ-unsaturated nitriles in moderate to good yields.

Conversion of carbonyl groups into nitriles is an important procedure as a one-carbon homologation in organic synthesis and has been extensively investigated.[1] Conventional methods involve the conversion of carbonyl compounds to the methoxycarbonyl hydrazone,[2] *p*-tolylsulphonylhydrazone,[3] or 2,4,6-tri-isopropylphenylsulphonylhydrazone[4] followed by reaction with hydrogen cyanide, and the use of tosylmethyl isocyanide (TosMIC) in the presence of a strong base.[5] However, limitations on the starting carbonyl compounds and the use of hydrogen cyanide or strong bases are serious disadvantages of these reactions. We have focused on the utility of cyano diethyl phosphates (cyano phosphates), which are readily prepared from a variety of carbonyl compounds with diethyl phosphorocyanidate [$(EtO)_2P(=O)CN$; DEPC] and lithium cyanide, in organic synthesis.[6] Numerous methods have been developed for the radical deoxygenation of alcohols.[7] Recently, we identified an efficient method for conversion of aromatic and α,β-unsaturated carbonyl compounds into nitriles *via* cyano phosphates by reduction with lithium in liquid ammonia and now report experimental details.

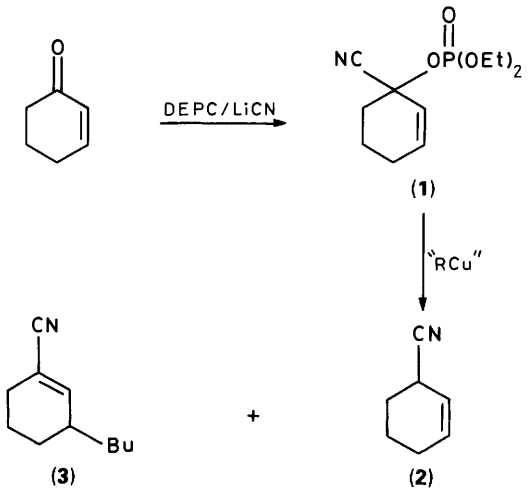
Results and Discussion

We have previously demonstrated the regioselective alkylation of cyano phosphates derived from α,β-unsaturated ketones with organocopper reagents to give α-alkylated β,γ-unsaturated nitriles and its application to the synthesis of natural products.[8] In the course of this investigation, we incidentally discovered that the cyano phosphate (**1**) reacted with lithium dibutylcuprate (Bu_2CuLi) to give 3-butylcyclohex-1-enecarbonitrile (**3**) (30%) and the dephosphorylated cyclohex-2-enecarbonitrile (**2**) (44%). In contrast, when $BuCu{\cdot}BF_3$ was employed, compound (**3**) was selectively obtained, whereas use of higher-order cuprates such as Bu_2CuLi_2CN or $Bu_3SnCuLiCN$ generated the reduced product (**2**) in good yield. Results are summarised in Table 1.

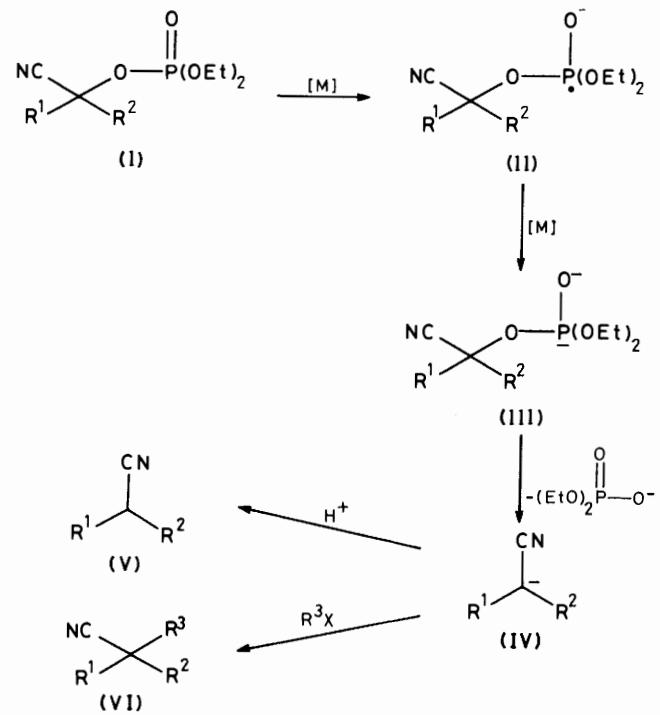
Reductive dephosphorylation of cyano phosphate can be formally explained in terms of two one-electron transfers to a P=O double bond to form a dianion (III) followed by dephosphorylation to yield the nitrile anion (IV).[7] Ireland *et al.* have developed an effective method for deoxygenation of alcohols by reduction of phosphates or phosphoramides with $Li/EtNH_2$.[9] These findings suggested to us that cyano phosphates would undergo dephosphorylation under dissolving metal reduction conditions (*e.g.* $Li/Liq.\ NH_3$), as shown in Scheme 1.

We first explored the reductive dephosphorylation of the cholest-4-ene derivative (**5**). Treatment of cholest-4-en-3-one (**4**) with DEPC (3 mol equiv.) and LiCN (3 mol equiv.) in tetrahydrofuran (THF) gave compound (**5**),[10] which was, without purification, reduced with Li (7 mol equiv.) in liq. NH_3 in the presence or absence of t-butyl alcohol (1.2 mol equiv.) at −78 °C to give a mixture of cholest-4-ene (**7**) (26 or 20%) and cholest-4-ene-3-carbonitrile (**6**) as an epimeric mixture (66 or 80%) (Table 2, entry 1 or 2) after quenching with NH_4Cl. When reduction was carried out under refluxing conditions (at −33 °C) in the presence of t-butyl alcohol,[11] compound (**7**) was obtained in quantitative yield (entry 3). Interestingly, reduction of (**5**) using sodium benzoate (entry 5) as a quenching agent gave the unsaturated nitrile (**6**), predominantly. The highest yields of (**6**) were attained by quenching the reaction mixture with isoprene as shown in entry 6. Thus, the scope and limitation for the conversion of a variety of α,β-enones to β,γ-unsaturated nitriles using the reaction conditions of entry 6 in Table 2 were investigated. The results are summarized in Table

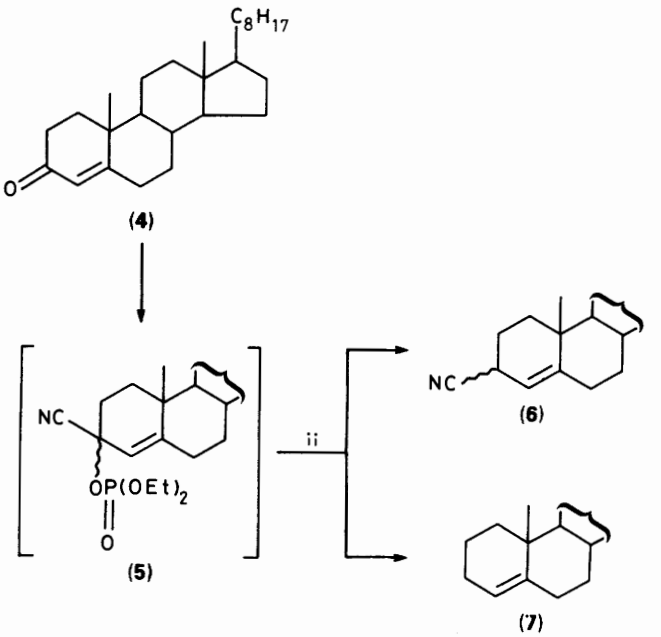
Table 1. Coupling reaction of the cyano phosphate (**1**) with organocopper reagents.



'RCu'(equiv.)	% Yield (2)	(3)
Bu_2CuLi (3)	44	30
Bu_2CuLi (1.2)	18	55
Bu_2CuLi_2CN (3)	84	—
$BuSnCuLiCN$ (3)	78	—
$BuCu{\cdot}BF_3$ (3)	—	73



Scheme 1.



Scheme 2. *Reagents:* i, DEPC/LiCN/THF; ii, see Table 2

3. Cyclic enones with a methoxymethoxy group (entry 1) and isolated double bond (entry 2) gave the corresponding unsaturated nitriles (**8**) and (**9**) *via* cyano phosphates in excellent yields. It is noteworthy that no isomerized or reduced alkenes were formed in the reduction step. In addition, the cyanation can be realized with aromatic ketones (entries 3–5) and an aldehyde (entry 6). Cyanation of 4-isobutylacetophenone followed by alkaline hydrolysis of the resulting 2-arylacetonitrile (**10**) generated the non-steroidal anti-inflammatory agent ibuprofen, in 89% overall yield.[1] Furthermore, the acyclic unsaturated aldehyde, citral, could be successively converted into the β,γ-unsaturated nitrile (**14**) (entry 7) in 86% yield, a result clearly superior to that using the TosMIC method reported by van Leusen.[12] Unfortunately, our reductive dephosphorylation was unpromising with cyano phosphates derived from saturated ketones.

Marshall previously reported that α,α-disubstituted allylic cyano compounds, prepared by alkylation of conjugated nitriles, serve as useful precursors to alkenes upon treatment with dissolving metals.[13] Thus, attention was turned to reductive dephosphorylation with alkylation of cyano phosphates derived from conjugated enones to give allylic cyano

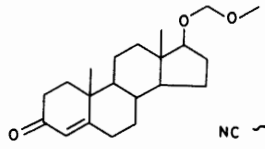
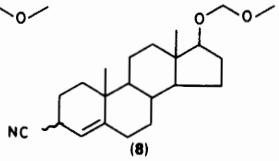
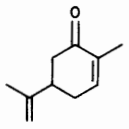
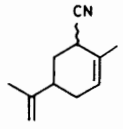
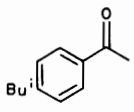
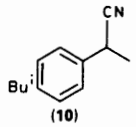
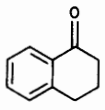
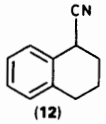
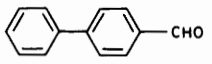
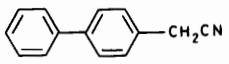
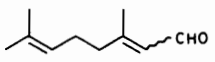
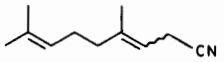
Table 2. Reduction of the cyano phosphate (**5**) with Li in liquid ammonia.

Entry	T/°C	Quenching agent	% Yield (6)	% Yield (7)
1	−78	NH_4Cl	66	26[a]
2	−78	NH_4Cl	80	20
3	−33	NH_4Cl	—	99[a]
4	−33	NH_4Cl	27	73
5	−78	$PhCO_2Na$	70	8
6	−78	Isoprene	98	—

[a] ButOH (1.2 equiv.) was added.

Table 3. Conversion of carbonyl compounds to nitriles *via* cyano phosphates.[a]

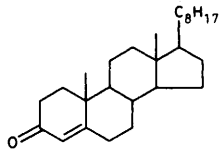
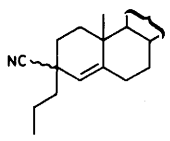
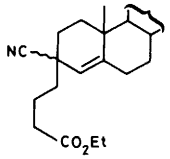
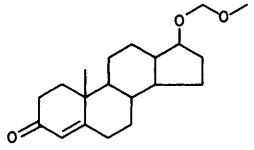
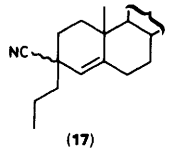
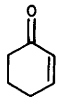
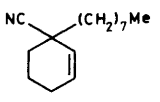
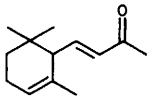
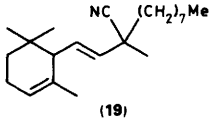
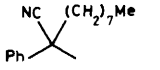
$R^1R^2C{=}O \longrightarrow R^1R^2CHCN$

Entry	Carbonyl compound	Product	% Yield
1		 (**8**)	91
2		 (**9**)	89
3		 (**10**)	89
4	$Ph_2C{=}O$	Ph_2CHCN (**11**)	84
5		 (**12**)	72
6		 (**13**)	75
7		 (**14**)	86

[a] *Reagents and conditions:* i, DEPC/LiCN; ii, Li/liq. NH_3; iii, isoprene.

Table 4. Conversion of carbonyl compounds to nitriles with alkylation *via* cyano phosphates.[a]

$R^1R^2C{=}O \longrightarrow R^1R^2R^3CCN$

Entry	Carbonyl compound	R^3X	Product	% Yield
1		C_3H_7I	 (15)	86
2		C_3H_7Br		81
3		C_3H_7Cl		*b*
4		$EtO_2C(CH_2)_3I$	 (16)	83
5		$EtO_2C(CH_2)_3Br$		47
6		C_3H_7Br	 (17)	81
7		$Me(CH_2)_7I$	 (18)	68
8		$Me(CH_2)_7I$	 (19)	83
9		$Me(CH_2)_7I$	 (20)	54

[a] *Reagents and conditions:* i, DEPC/LiCN; ii, Li/liq. NH_3; iii, R^3X. [b] Compounds (**6**) (96%) and (**7**) (3%) were obtained.

compounds, which have a quaternary carbon centre bearing a cyano group. In order to permit alkylation of the nitrile anion (IV) to give (VI) (Scheme 1), cyano phosphate (**5**) was reduced with Li/liq. NH_3 and the reaction mixture was then quenched with propyl iodide (or bromide) instead of isoprene to give the α-alkylated nitrile (**15**) as an epimeric mixture in 86% (81%) yield (Table 4, entries 1 and 2). When propyl chloride was used as alkylating agent, however, the alkylated product was not isolated, and only reduced products [(**6**) (96%) and (**7**) (3%)] were obtained.

In this way, cyclic or acyclic enones and aromatic ketone were readily converted to α-alkylated nitriles (**16**)–(**20**) *via* cyano phosphates in moderate to good yields (Table 4). Thus, the foregoing method is quite general for conversion of aromatic and α,β-unsaturated carbonyl compounds to β,γ-unsaturated and α-alkyl-β,γ-unsaturated nitriles, which are promising intermediates in organic synthesis.

Experimental

IR spectra were recorded on a Shimadzu IR 435 spectrophotometer. ^1H and ^{13}C NMR spectra were determined with a Varian Gemini-200 spectrometer (tetramethylsilane as internal standard), and mass spectra with a Hitachi M-80 instrument. Extracts from reaction mixtures were dried over anhydrous sodium sulphate. For column chromatography, SiO_2 (Merck Art 9385) was used. 1-Cyanocyclohex-2-enyl diethyl phosphate (**1**),[9] and 3-cyanocholest-4-enyl diethyl phosphate (**5**)[11] were prepared by the methods previously described.

Reaction of the Phosphate (**1**) *with Cuprates.*—The general procedure for reaction of cyano phosphates (I) with cuprates is reported previously.[9] $Bu_3SnCuLiCN$ was prepared by the method of Piers.[15]. After usual work-up, the products were purified by column chromatography with benzene–hexane (1:1) to give 3-butylcyclohex-1-enecarbonitrile (**3**) from the first fraction.

Cholest-4-ene-3-carbonitrile (**6**).—*General reduction procedure.* To a solution of cholest-4-en-3-one (193 mg, 0.5 mmol) and DEPC (245 mg, 1.5 mmol) in THF (10 ml) was added LiCN (50 mg, 1.5 mmol). The mixture was stirred at room temperature for 10 min, diluted with water (10 ml), then extracted with hexane–ethyl acetate (1:1) (50 ml). The extract was washed with water and brine, dried, and evaporated to give the cyano phosphate (**5**). To a stirred solution of Li (24 mg, 3.5 mmol) in freshly distilled ammonia (10 ml) at −78 °C was added a solution of (**5**) in THF (2 ml). The mixture was stirred for 10 min, then treated with isoprene (0.3 ml) to discharge the blue colour. The ammonia was allowed to evaporate off, saturated aqueous ammonium chloride was added, and the mixture was extracted with hexane (50 ml). The extract was washed with water, dried, and evaporated. The residue was purified by column chromatography with benzene–hexane (1:1) as eluant to give the *carbonitrile* (**6**) (195 mg, 98%) as a colourless solid, a 7:1 epimeric mixture from its ^1H NMR spectrum [$\delta_H(CDCl_3)$ 5.19 (major) and 5.24 (minor) (each s, 4-H)]; m.p. 114–116 °C (from acetone–methanol); $\delta_C(CDCl_3)$ of major isomer 113.05 (4-C), 122.56 (CN), 150.14 (5-C) and of minor isomer 112.54 (4-C), 122.14 (CN), 151.33 (5-C); $\nu_{max}(CHCl_3)$ 2 240 cm^{-1} (CN); *m/z* 395 (M^+) (Found: C, 84.9; H, 11.4; N, 3.5. $C_{28}H_{45}N$ requires C, 85.0; H, 11.5; N, 3.5%).

17β-*Methoxymethoxyandrost-4-ene-3-carbonitrile* (**8**). The crude product obtained by the general procedure from the enone (166 mg, 0.5 mmol) was purified to give the *carbonitrile* (**8**) (156 mg, 91%), as a 4:1 epimeric mixture from its ^1H NMR spectrum [$\delta_H(CDCl_3)$ 5.19 (major) and 5.24 (minor) (each s, 4-H)]; m.p. 106–108 °C (from ethanol); $\nu_{max}(CHCl_3)$ 2 240 cm^{-1} (CN); *m/z* 343 (M^+) (Found: C, 77.0; H, 9.7; N, 4.0. $C_{22}H_{33}NO_2$ requires C, 76.9; H, 9.7; N, 4.1%).

2-*Methyl-5-isopropenylcyclohex-2-enecarbonitrile* (**9**). The crude product obtained by the general procedure from carvone (150 mg, 1 mmol) was purified to give (**9**)[16] (143 mg, 89%) as an oil, which was a mixture of *cis*- and *trans*-isomers in a ratio of 1:1; ν_{max}(film) 2 240 cm^{-1} (CN); $\delta_H(CDCl_3)$ 3.08 and 3.25 (each m, CHCN), 4.96 (m, $=CH_2$), 5.61 (br s, =CH); *m/z* 161 (M^+) (Found: M^+, 161.1212. $C_{11}H_{15}N$ requires M, 161.1204).

2-(4-*Isobutylphenyl*)*propionitrile* (**10**). The crude product obtained by the general procedure from 4-(2-methylpropyl)-acetophenone (170 mg, 0.5 mmol) was purified to give (**10**) (83 mg, 89%) as an oil. This was identical with an authentic sample[1] by comparison of IR [ν_{max}(film) 2245 cm^{-1} (CN)] and ^1H NMR spectra [$\delta_H(CDCl_3)$ 0.9 (d, *J* 7.5 Hz, $CHMe_2$], 1.62 (d, *J* 7.5 Hz, C*H*Me), 1.85 (m, CH_2CH), 2.46 (d, *J* 7.5 Hz, CH_2), 3.86 (q, *J* 7.5 Hz, CHCN), and 7.2 (m, ArH).

Diphenylacetonitrile (**11**). The crude product obtained by the general procedure from benzophenone (182 mg, 1 mmol) was purified to give (**11**) (161 mg, 84%); m.p. 69–70 °C (from light petroleum) (lit.,[5] m.p. 67–71 °C); $\delta_H(CDCl_3)$ 5.13 (s, CHCN) and 7.34 (s, ArH).

Tetrahydronaphthalene-1-carbonitrile (**12**). The crude product obtained by the general procedure from α-tetralone (146 mg, 1 mmol) was purified to give (**12**)[1] (113 mg, 72%); $\nu_{max}(CHCl_3)$ 2 240 cm^{-1} (CN); $\delta_H(CDCl_3)$ 1.7–2.2 (m, CH_2CH_2), 2.5–3.0 (m, $ArCH_2$), 3.80 (t, *J* 6.2 Hz, CHCN), and 7.0–7.4 (m, ArH); *m/z* 157 (M^+).

Biphenyl-4-ylacetonitrile (**13**). The crude product obtained by the general procedure from the aldehyde (182 mg, 1 mmol) was purified to give (**13**) (145 mg, 75%); m.p. 88–89 °C (from tetrachloromethane (lit.,[17] 94–95 °C); $\delta_H(CDCl_3)$ 3.77 (s, CH_2CN) and 7.3–7.7 (m, ArH).

4,8-*Dimethylnona-3,7-dienenitrile* (**14**). The crude product obtained by the general procedure from citral (152 mg, 1 mmol) was purified to give (**14**)[18] (140 mg, 86%); ν_{max}(film) 2 245 cm^{-1} (CN); $\delta_H(CDCl_3)$ 1.57, 1.66, and 1.73 (each s, Me), 2.04 (br s, CH_2CH_2), 3.01 (d, *J* 7 Hz, CH_2CN), and 4.9–5.2 (m, 2 × =CH); *m/z* 163 (M^+).

3-*Propylcholest-4-ene-3-carbonitrile* (**15**).—*General alkylative reduction procedure*. To a stirred solution of Li (24 mg, 3.5 mmol) in freshly distilled ammonia (10 ml) at −78 °C was added a solution of the cyano phosphate (**5**), prepared from the enone (**4**) (193 mg, 0.5 mmol), in THF (2 ml). The solution was stirred for 10 min, then a solution of propyl iodide (255 mg, 1.5 mmol) in THF (1 ml) was added, whereupon the blue color discharged. The mixture was stirred for 20 min and then the ammonia was allowed to evaporate off, saturated aqueous ammonium chloride was added, and the mixture was extracted with hexane (50 ml). The extract was washed with water, dried, and evaporated. The residue was purified by column chromatography with benzene–hexane (1:1) as eluant to give the *carbonitrile* (**15**) (187 mg, 86%) as a colourless solid, a 4:1 epimeric mixture from its ^1H NMR spectrum [$\delta_H(CDCl_3)$ 5.20 (major) and 5.10 (minor) (each s, 4-H)]; m.p. 65–67 °C (from methanol); $\delta_C(CDCl_3)$ of major isomer 149.16 (4-C), 124.64 (CN), 118.86 (5-C) and of minor isomer 149.84 (4-C), 123.89 (CN), 119.17 (5-C); $\nu_{max}(CHCl_3)$ 2 230 cm^{-1} (CN); *m/z* 437 (M^+) (Found: C, 84.9; H, 11.9; N, 3.3. $C_{31}H_{51}N$ requires C, 85.05; H, 11.7; N, 3.2%).

Ethyl 3-(3-*Cyanocholest-4-en-3-yl*)*propionate* (**16**). The crude product obtained by the general procedure from the enone (**4**) (116 mg, 0.3 mmol) and ethyl 4-iodopropionate (218 mg, 0.9 mmol) was purified to give (**16**) (127 mg, 83%), as a 4:1 epimeric mixture from its ^1H NMR spectrum [$\delta_H(CDCl_3)$ 5.09 (minor) and 5.19 (major) (s, 4-H)]; ν_{max}(film) 2 235 (CN) and 1 735 cm^{-1} (CO); *m/z* 509 (M^+) (Found: M^+, 509.4234. $C_{34}H_{55}NO_2$ requires *M*, 509.4230).

17β-*Methoxymethoxy-3-propylandrost-4-ene-3-carbonitrile* (**17**). The crude product obtained by the general procedure from the enone (166 mg, 0.5 mmol) and propyl bromide (185 mg, 1.5 mmol) was purified to give the *carbonitrile* (**17**) (156 mg, 81%), as a 3:1 epimeric mixture from its ^1H NMR spectrum [$\delta_H(CDCl_3)$ 5.10 (minor) and 5.20 (major) (s, 4-H)]; m.p. 103–105 °C (from methanol); $\nu_{max}(CHCl_3)$ 2 235 cm^{-1} (CN); *m/z* 385 (M^+) (Found: C, 77.7; H, 10.4; N, 3.7. $C_{25}H_{39}NO_2$ requires C, 77.9; H, 10.2; N, 3.6%).

1-*Octylcyclohex-2-enecarbonitrile* (**18**). The crude product obtained by the general procedure from the enone (96 mg, 1 mmol) and octyl iodide (720 mg, 3 mmol) was purified to give (**18**) (149 mg, 68%); $\nu_{max}(CHCl_3)$ 2230 cm^{-1} (CN); $\delta_H(CDCl_3)$ 0.9 (t, *J* 7 Hz, Me), 1.2–2.2 (m, CH_2 × 10), 5.56 (br d, *J* 11 Hz, 2-H), and 5.89 (m, 3-H); *m/z* 219 (M^+) (Found: M^+, 219.1984. $C_{15}H_{25}N$ requires *M*, 219.1985).

3-*Methyl*-1-(2,6,6-*trimethylcyclohex-2-en-1-yl*)*undec-1-ene-3-carbonitrile* (**19**). The crude product obtained by the general procedure from α-ionone (192 mg. 1 mmol) and octyl iodide (720 mg, 3 mmol) was purified to give (**19**) (261 mg, 83%); ν_{max} (film) 2 240 cm^{-1} (CN); $\delta_H(CDCl_3)$ 0.85 (m, 3 × Me), 1.2–1.7 (m, MeCCN, =CMe, CH_2 × 8), 2.05 (m, =CCH, $=CCH_2$), 5.15 (d, *J* 15 Hz, =CHCCN), 5.41 (br s, =CH), and 5.65 (dd, *J* 9, 15 Hz, CH); *m/z* 315 (M^+) (Found: M^+, 315.2926. $C_{22}H_{37}N$ requires *M*, 315.2924).

2-*Methyl-2-phenyldecanenitrile* (**20**). The crude product obtained by the general procedure from acetophenone (120 mg, 1 mmol) and octyl iodide (720 mg, 3 mmol) was purified to give (**20**) (131 mg, 54%); ν_{max}(film) 2 240 cm^{-1} (CN); $\delta_H(CDCl_3)$ 0.84 (t, *J* 7 Hz, CH_2Me), 1.1–1.5 (m, CH_2 × 6), 1.71 (s, Me), 1.89 (t, *J* 6.5 Hz, CH_2), and 7.35 (m, ArH); *m/z* 243 (M^+) (Found: M^+, 243.1980. $C_{17}H_{25}N$ requires *M*, 243.1985).

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