

A General One-Step Synthesis of Nitriles from Ketones Using Tosylmethyl Isocyanide. Introduction of a One-Carbon Unit¹

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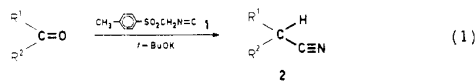
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Ketones are converted efficiently, in one step, to nitriles ($R_2CO \rightarrow R_2CHC\equiv N$) at temperatures between 0 and 45 °C by the use of TosMIC (tosylmethyl isocyanide) and base. This conversion is effectively a reductive cyanation, unlike the classical cyanohydrin reaction. The reaction is shown to be generally applicable.

Tosylmethyl isocyanide (TosMIC, 1) is a synthon with diverse and steadily expanding applications. Thus far emphasis in the chemistry of TosMIC has centered mainly on heterocyclic synthesis. The preceding paper in this series deals with the synthesis of imidazoles from TosMIC and aldimines,^{2a} and summarizes other azole (and azoline) syntheses.² The present paper will show, however, that the application of TosMIC by no means is restricted to the domain of heterocyclic synthesis only.

We here wish to concentrate on the use of TosMIC in an efficient, direct conversion of ketones to nitriles:³



TosMIC adds one carbon unit to a ketone, as in the classical cyanohydrin reaction,⁴ but without the simultaneous formation of an α -hydroxy group. In this sense the reaction of TosMIC is a "reductive cyanation". Reaction 1 is unique because it allows the ketone \rightarrow nitrile conversion to be carried out in a single operation.^{5,6}

Obviously, the nitriles can be exploited further, for instance, by conversion to carboxylic acids or derivatives thereof.^{6,7} A reaction of TosMIC with aldehydes and ketones leading in two steps via *N*-(1-tosyl-1-alkenyl)formamides to carboxylic acids has been reported independently by Schöllkopf et al.,^{8a} and this reaction has later been shown to proceed through nitriles (as in eq 1).^{8b}

Dehydration of aldoximes also leads to nitriles, however, with the same number of carbon atoms as in the starting aldehydes,⁹ and therefore is a process quite different from reaction 1.

Results and Discussion

The synthesis of nitriles according to eq 1 is applicable to a wide variety of different ketones (Table I). The substrates range from simple aliphatic and aromatic ketones to sterically hindered ones, including camphor and β,β -dimethyl- α -tetralone (to give **2c** and **2g**, respectively). Also, the cyanation can be realized with 3- and 17-steroidal ketones (**2h-k**). So far only the severely hindered carbonyl of di-*tert*-butyl ketone has resisted reaction, whereas *tert*-butyl methyl ketone (pinacolone) and diisopropyl ketone are convertible (**2q** and **2p**).

Reaction Conditions. The conditions of reaction 1 were adapted to differences in reactivity of the ketones concerned. Typically, for ketones of normal reactivity *t*-BuOK was added at 0 °C to a solution of a ketone and 1.0–1.5 equiv of TosMIC in 1,2-dimethoxyethane (containing a little *t*-BuOH or EtOH). The reaction went to completion in 1–2 h at room temperature (**2a,b,d,e,i-k,m-o**). Under these mild conditions, however, camphor and diisopropyl ketone gave only trace amounts of nitrile (**2c,p**), and *tert*-butyl methyl ketone gave no more than 36% of 2-cyano-3,3-dimethylbutane (**2q**).

The best way to convert camphor to 2-cyanocamphane (**2c**) was with 3 equiv of TosMIC in dimethyl sulfoxide (containing some MeOH) at a slightly elevated temperature (45 °C). Thus, 80% of **2c** was obtained after 70 h. In hexamethylphosphoric triamide (HMPT) the same reaction went faster (17 h), but the product was less pure. Comparable reaction conditions were used with success for other sterically hindered ketones (nitriles **2g,p,q**). Benzophenone and α -tetralone,¹⁰ which did not react in DME, were also converted to the corresponding nitriles (**2l,f**) in Me₂SO and HMPT, respectively.

Reaction Scheme. A rationale for reaction 1 is given in

Scheme I. Proposed Mechanism for Conversion of Ketones to Nitriles with TosMIC According to Equation 1

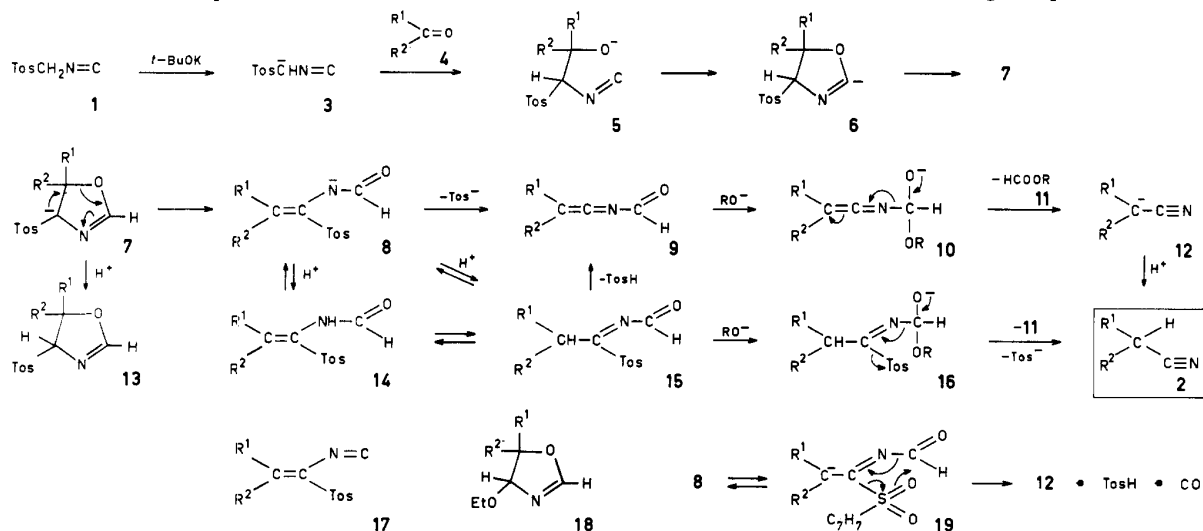


Table I. Nitriles Synthesized from Ketones and Tosylmethyl Isocyanide (TosMIC) According to Equation 1

Substrate ^a and product	Registry no.	TosMIC equiv	Base (equiv) and solvent ^b	Time, h	Temp, ^c °C	Isolated yield, %	Bp or mp, °C	Lit. data
Adamantanone*	700-58-3							
2-Cyanoadamantane (2a)		1.3	<i>t</i> -BuOK (2.4), DME	1.5	35	93	~180	166–175 ²⁴
2-Cyanoadamantane (2a)		1.3	<i>t</i> -BuOK (3.5), Me ₂ SO	17	20	84		
2-Norbornanone*	497-38-1							
2-Cyanonorbornane (2b) ^d		1.3	<i>t</i> -BuOK (3.5), Me ₂ SO	17	20	73	48–51 (endo)	51 ²⁵
2-Cyanonorbornane (2b) ^e		1.3	EtONa (1.3), DME	2.5	20	62		
(+)-Camphor*	464-49-3							
2-Cyanocamphane (2c) ^f		3	<i>t</i> -BuOK (7), Me ₂ SO	70	45	80	135–148	26
2-Cyanocamphane (2c)		3	<i>t</i> -BuOK (7), HMPT	17	45	73		
2-Cyanocamphane (2c)		1.1	<i>t</i> -BuOK (2), DME	1.5	20	<5		
Cycloheptanone	502-42-1							
Cyanocycloheptane (2d)		1.1	<i>t</i> -BuOK (2), DME	1.5	20	80	85–86 (10 mm)	85–86 (10 mm) ³³
Cyclohexanone	108-94-1							
Cyanocyclohexane (2e)		1.0	<i>t</i> -BuOK (2), DME	1.5	20	80	62–67 (12 mm)	67 (10 mm) ³³
α-Tetralone	529-34-0							
1-Cyano-1,2,3,4-tetrahydronaphthalene (2f)		3	<i>t</i> -BuOK (5), HMPT	21	20	47	Chromat ^g	109–111 (1.5 mm) ³⁴
β,β-Dimethyl-α-tetralone*	2977-45-9							
1-Cyano-2,2-dimethyl-1,2,3,4-tetrahydronaphthalene (2g)		3	<i>t</i> -BuOK (7), HMPT	40	45	76	<i>h</i>	
Estrone 3-methyl ether	1624-62-0							
17β-Cyano-1,3,5(10)-estratrien-3-ol methyl ether (2h)		1.3	<i>t</i> -BuOK (3.5), Me ₂ SO	17	20	69	205–207	207–210 ^{6b}
Androsta-1,4-diene-3,17-dione*	897-06-3							
17-Cyanoandrosta-1,4-dien-3-one (2i) ⁱ		1.3	EtONa (1.2), DME	2	20	47	159–164	
5α-Cholestan-3-one	566-88-1							
3-Cyano-5α-cholestane (2j) ^j		1.3	<i>t</i> -BuOK (2.5), DME	5	20	85	114–121	<i>k</i>
5β-Cholestan-3-one	601-53-6							
3-Cyano-5β-cholestane (2k) ^l		1.5	<i>t</i> -BuOK (3), DME	5	20	53	57–72	36
Benzophenone*	119-61-9							
Diphenylacetone nitrile (2l)		1.3	<i>t</i> -BuOK (3.5), Me ₂ SO	17	20	69	67–71	74 ³⁰
Acetophenone	98-86-2							
2-Phenylpropionitrile (2m)		1.0	<i>t</i> -BuOK (2), DME	1.5	20	68	74–78 (2 mm)	100 (8 mm) ³⁷
<i>p</i> -Bromoacetophenone*	99-90-1							
2- <i>p</i> -Bromophenylpropionitrile (2n)		1.0	<i>t</i> -BuOK (2), DME	1.5	20	79	112–116 (1 mm)	
Di- <i>n</i> -propyl ketone	123-19-3							
4-Cyanoheptane (2o)		1.2	<i>t</i> -BuOK (2.5), DME	1.5	20	74	<i>m</i>	183–184 ³³
Diisopropyl ketone	565-80-0							
3-Cyano-2,4-dimethylpentane (2p)		3	<i>t</i> -BuOK (7), HMPT	70	45	65	<i>n</i> ²¹ D	170–171 } ³⁸
3-Cyano-2,4-dimethylpentane (2p)		1.0	<i>t</i> -BuOK (2), DME	1.5	20	<5	1.4177 ⁿ	<i>n</i> ²³ D 1.4158 }
<i>tert</i> -Butyl methyl ketone ^p	75-97-8							
2-Cyano-3,3-dimethylbutane (2q)		1.3	<i>t</i> -BuOK (3.5), Me ₂ SO	17	20	70	40–42 (15 mm)	151–152 } ³⁹
2-Cyano-3,3-dimethylbutane (2q)		1.0	<i>t</i> -BuOK (2), DME	1.5	20	36	<i>n</i> ²⁵ D	<i>n</i> ²⁵ D 1.4092 }
Di- <i>tert</i> -butyl ketone	815-24-0							
3-Cyano-2,2,4,4-tetramethylpentane	62796-07-0	3	<i>t</i> -BuOK (7), HMPT	170	45	<i>o</i>		67–78 (10 mm) ⁴⁰

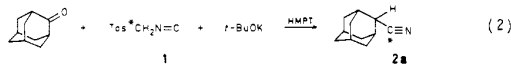
^a Substrates are marked with an asterisk when further details are given in the Experimental Section. ^b Alcohol (1–2 equiv) was added in all cases (see text and Experimental Section). ^c All reactions were started around 0 °C, and usually after 15 min continued at the temperature indicated. ^d Endo–exo = 4:3. ^e Endo–exo = 1:1. ^f Endo–exo = 4:1 or 1:4. ^g Hydrolyzed (NaOH, 30% H₂O₂) to amide, mp 163–165 °C (lit.³⁴ 165–167 °C). ^h See Experimental Section. ⁱ α:β = 1:1 (see Table II, Experimental Section). ^j α:β = 0.7 (Table II). ^k Lit.³⁵ 3α–C≡N, mp 166–168 °C; 3β–C≡N, mp 142–144 °C. ^l α:β = 0.9 (Table II). ^m Short-path distilled, bath temperature 64 °C (12 mm). ⁿ As *m*, 65 °C (13 mm). ^o 65% of ketone recovered. ^p Pinacolone.

Scheme I. An important aspect of the proposed mechanism is the ring opening of 7 to 8; beyond that stage the mechanism is more speculative. The following observations are consistent with Scheme I: (1) A ^{14}C label in the methylene group of 1 appears integrally in the nitrile 2a (cf. eq 2). (2) In addition to 2a, ethyl formate (11) has been detected qualitatively ($\text{RO}^- = \text{EtO}^-$), which accounts for the fate of the isocyano carbon of 1. (3) The reaction can be interrupted at the stage of 7 as well as 8 to give 13 or 14. (4) Under the conditions of reaction 1 both 13 and 14 can be converted to 2, and further also 13 to 14 ($\text{R}^1 - \text{R}^2 = \text{pentamethylene}$). (5) Rapid H-D exchange is observed in 13 ($\text{R}^1 = \text{R}^2 = \text{Me}$) at C(4) only (with K_2CO_3 in $\text{CD}_3\text{OD}-\text{DME}$). For further details concerning these arguments and the (as yet unsolved) question of a one-step or two-step cycloaddition of 3 to 6, we refer to previous discussions^{2a,3,8,11} and the Experimental Section of the present paper.

An alternative mechanism involving a base-catalyzed condensation of 1 and a ketone to give 17 (Scheme I), followed by addition of water to 14 and eventually formation of 2 (and 13), is highly unlikely. Compounds 17 have not been detected, even though they are expected not to be hydrated to 14 under the conditions of the reaction.¹²

In the second part of Scheme I attack of a nucleophile at the carbonyl of 9 or 15 is assumed.^{3a,3b} The postulated intermediates 9 and 15 both possess a second carbon center that might well be more electrophilic than the carbonyl. (This may be true in particular for the $\text{N}=\text{C}-\text{Tos}$ group¹³ of 15; also, nucleophilic reactions of ketenimines are well known¹⁴.) However, initial nucleophilic attack at these other centers does not necessarily preclude the formation of 2. In addition to the nucleophiles RO^- ($\text{R} = \text{Me}, \text{Et}, \text{or } t\text{-Bu}$) reacting with 9 or 15, TosMIC anion (3) may act as such in some cases.¹⁵

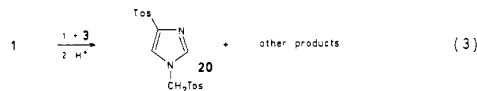
Occasionally, reaction 1, when carried out in Me_2SO or HMPT, was accompanied by evolution of gas. For the reaction of 1 with adamantanone in HMPT the gas was shown spectroscopically (MS and IR) to be carbon monoxide. This reaction gave 73% of 2-AdC \equiv N and 44% of CO (determined gravimetrically and volumetrically after CuO oxidation to CO_2). Carbon monoxide might be formed by decomposition of the hypothetical mixed anhydride $p\text{-CH}_3\text{C}_6\text{H}_4\text{S}(\text{O})\text{CHO}$ (or the isomeric TosCHO), which could result from nucleophilic action of Tos $^-$, possibly through 19. Alternatively, CO could arise from decomposition of *tert*-butyl formate (11, $\text{R} = t\text{-Bu}$) in the medium used here.¹⁶ These assumptions at least account for the fact that the CO was not radiolabeled when the reaction was performed with Tos $^{14}\text{C}_2\text{H}_2\text{N}=\text{C}$ (eq 2).



Competing Reactions. 4-Tosyl-2-oxazolines (13, and 7, Scheme I) play a crucial role in the reaction of TosMIC with ketones (and aldehydes).¹⁷ Compounds 13 can be converted not only to nitriles 2 but also to tosylalkenylformamides 14 as discussed above. With EtONa or EtOTf in EtOH (or $\text{EtOH}-\text{DME}$) 13 will give 4-ethoxy-2-oxazolines¹⁸ 18, which are convenient precursors for the synthesis of α -hydroxy aldehydes.¹⁹ By a proper choice of the conditions of the reaction of TosMIC with ketones either of the products 2, 13, 14, or 18 can be obtained exclusively; therefore special attention should be given to these conditions.

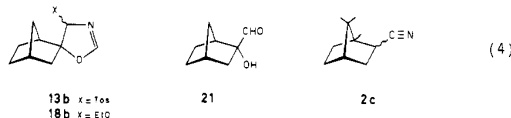
The tosyloxazolines 13 are obtained in protic solvents using weak bases (e.g., K_2CO_3 in MeOH ,^{2b,20} or NaCN in EtOH ^{8a}). In an aprotic medium ($t\text{-BuOK}$ in THF) at -10°C the reaction goes one step further to give 8 (14),⁸ but at temperatures of $20\text{--}45^\circ\text{C}$ the reaction slowly continues to go all the way to nitriles 2. This last process is speeded up considerably by addition of 1–2 equiv of an alcohol ($t\text{-BuOH}$ or better MeOH

or EtOH) to the aprotic solvent (DME).²¹ However, the addition of more alcohol should be avoided, otherwise 4-alkoxy-2-oxazolines (18) will be formed as well. The role of the added alcohols is explained (in part) by their contribution to the reaction step $9 \rightarrow 12$ (or $15 \rightarrow 2$).



TosMIC itself is known to undergo a base-catalyzed cyclodimerization to give inter alia imidazole 20 (eq 3).^{2a} This explains the low yields of nitriles 2 obtained previously with the less reactive (usually sterically hindered) ketones (Table I, e.g., 2c, p, q, reactions in DME). The cyclodimerization of TosMIC, visualized as a reaction of TosMIC anion (3) with TosMIC,^{2a} can be suppressed effectively by working in Me_2SO (or HMPT) with 2 equiv of $t\text{-BuOK}$ with respect to TosMIC. Thus, TosMIC will be transformed completely into its anion 3.²² These conditions then allow reaction 1 to be carried out at 45°C for prolonged periods to achieve a high yield conversion of the less reactive ketones without appreciable loss of TosMIC.

Stereochemistry. The endo–exo ratio of 2-cyanonorbornane (2b) is nearly 1:1 (by GLC and NMR). This ratio may well reflect thermodynamic control through 12 (Scheme I), but most certainly is not the result of indiscriminatory attack of TosMIC anion (3) on norbornanone from both the exo and endo side. In fact, we have established previously that the large TosMIC anion attacks norbornanone only from the exo side, as expected, to give 13b (4). This was concluded from the stereochemistry of the derivative 18b and its subsequent hydrolysis to 2-endo-hydroxynorbornane-2-exo-carboxaldehyde (21) exclusively.^{18,19}



Camphor with its hindered exo side required accordingly a rather long reaction time to provide 80% of 2-cyanocamphane (2c, a mixture of unassigned endo and exo isomers, ratio of 4:1). Likewise, mixtures of α - and β -cyanosteroids were obtained for 2i–k, although from estrone 3-methyl ether only the 17β -cyano compound (2h) was found (after crystallization^{6b}). The ratio of the epimers 2i–k was determined by ^1H NMR (Table II, in Experimental Section).

Experimental Section

General remarks are as in ref 2a. Carbon-14 radioactivity was measured with a Nuclear Chicago Unilux III Scintillation Counter.

Starting Materials. Commercially available ketones were used as such. Estrone 3-methyl ether and 5α -cholestan-3-one were purchased from Steraloids Inc., Pawling, N.Y. Samples of androsta-1,4-dien-3-one and 5β -cholestan-3-one were donated by Gist-Brocades N.V., Delft, Holland. TosMIC (1) was prepared as described in ref 2a or purchased from Ofichem, Gieten, Holland. ^{14}C -Labeled formaldehyde was obtained from NEN Chemicals, Frankfurt, Germany.

Synthesis of Nitriles from Ketones and TosMIC (1). The following selected procedures are illustrative. Table I summarizes the conditions used in the reactions not described in detail.

2-Cyanoadamantane (2a). Solid $t\text{-BuOK}$ (28.0 g, 0.24 mol, 95%, Merck) was added portionwise to a stirred and cooled solution of adamantanone (15.0 g, 0.10 mol) and TosMIC (25.0 g, 0.13 mol) in a mixture of 350 mL of DME and 10 mL of absolute EtOH while keeping the temperature between 5 and 10°C . Stirring was continued, first for 30 min without cooling, then for 30 min at $35\text{--}40^\circ\text{C}$. The suspension thus obtained was cooled to room temperature with stirring. The precipitate (TosK) was removed and extracted with DME. The combined DME solutions were concentrated to 25–35 mL and purified by flushing the concentrate over a 5-cm thick layer of alumina (ca. 200 g, on a Buchner funnel) with 250 mL of petroleum ether (bp $40\text{--}60^\circ\text{C}$). Removal of the solvent provided 14–15 g (87–93%) of

near-white **2a**, melting range 160–180 °C (sealed tube). Despite the wide melting range, this material is over 99.8% pure according to GLC (2-m SE-30 column, 190 °C). Charcoal treatment gave completely white material, melting in the same range. The melting point of **2a** is an unreliable criterion for purity; a value as high as 184–187 °C has been found occasionally.²³

The same reaction has been carried out successfully with EtONa,³ and also with *t*-BuOK in Me₂SO or HMPT. Hydrolysis of **2a** with HBr in AcOH provided adamantane-2-carboxylic acid (95%, mp 143–144 °C, lit.²⁴ 62%).

2-Cyanonorbornane (2b). To an ice-cooled solution of TosMIC (1.3 g, 6.5 mmol) in dry Me₂SO (7.5 mL) was added all at once 2.25 g (ca. 18 mmol) of solid *t*-BuOK. After stirring for 5 min under N₂ 0.25 mL of MeOH was added, then 0.55 g (5.0 mmol) of 2-norbornanone, and the mixture was stirred for 17 h at room temperature. (After 10 min some foaming was observed, indicating the evolution of CO, cf. **2a**, below.) The reaction mixture was diluted with water (150 mL), acidified with 2 N HCl to pH ~6, and extracted with petroleum ether (bp 40–60 °C). The combined extracts were washed once with saturated NaCl solution and dried (Na₂SO₄). Short path distillation (at 20 mm) gave 0.44 g (73%) of **2b**, consisting of a mixture of endo:exo = ca. 4:3 as determined by analytical GLC (Carbowax 20M, 120 °C). Partial separation by GLC (same column) provided a sample of pure endo-**2b**, mp 48–51 °C (sealed tube) (lit.²⁵ mp 51 °C).

2-Cyanocamphane (2c). A reaction mixture was prepared analogously to **2b** from TosMIC (3.0 g, 15 mmol), (+)-camphor (0.76 g, 5.0 mmol), *t*-BuOK (4.5 g, ca. 36 mmol), 15 mL of Me₂SO, and 0.25 mL of MeOH. The mixture was stirred under N₂ for 1 h at room temperature and then for 70 h at 45 °C. (The camphor carbonyl was still present in IR after 17 h.) Workup as for **2b** gave after removal of the petroleum ether a semisolid brown residue, which was sublimed (150 °C, 20 mm) to give 0.65 g (80%) of **2c**, mp 135–148 °C (sealed tube).²⁶ This mixture of endo and exo isomers (4:1 or 1:4 by GLC on Carbowax 20M; 140 °C) gave one sharp C≡N band in IR (Nujol) at 2270 cm⁻¹. Anal. (of endo–exo mixture). Calcd for C₁₁H₁₇N: C, 80.93; H, 10.50; N, 8.58. Found: C, 80.9; H, 10.5; N, 8.4.

In the separatory funnel some impure insoluble material was left behind, and was shown to contain ca. 1 g of unreacted TosMIC.

1-Cyano-2,2-dimethyl-1,2,3,4-tetrahydronaphthalene (2g) was prepared similarly to **2b** from β,β-dimethyl-α-tetralone²⁷ (1.74 g, 10 mmol), TosMIC (6.0 g, 30 mmol), *t*-BuOK (9.0 g, ca. 72 mmol), and 40 mL of HMPT (dried over sieves) and 0.5 mL of MeOH, initially at 0 °C, then 40 h at 45 °C. The residue was submitted to short path distillation (at ca. 120 °C, 14 mm) yielding 1.41 g (76%) of impure **2g** as a colorless liquid: IR (neat) 2260 cm⁻¹; ¹H NMR (CCl₄) δ 1.09 (s, 3, CH₃), 1.16 (s, 3, CH₃), 1.4–1.8 (m, 2, 3-CH₂), 2.73 (t, 2, 4-CH₂), 3.50 (s, 1, CHC≡N), 6.8–7.4 (m, 4, aromatic). For characterization **2g** (0.92 g) was hydrolyzed by 17 h of reflux in AcOH (2.5 mL) and 48% HBr (10 mL) to give 0.14 g (15%) of 2,2-dimethyl-1,2,3,4-tetrahydronaphthalene-1-carboxamide, mp 121–122 °C (from the Me₂CO–pentane), IR (Nujol) 1650 cm⁻¹. Anal. Calcd for C₁₃H₁₇NO: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.8; H, 8.5; N, 6.8.

Mixture of 17α- and 17β-Cyanoandrosta-1,4-dien-3-one (2i). To a stirred solution of androsta-1,4-diene-3,17-dione (1.14 g, 4.0 mmol) and TosMIC (0.98 g, 5.0 mmol) in 20 mL of dry DME, cooled in ice–salt to 0 °C, was added a freshly prepared solution of sodium (0.12 g, 5.0 mmol) in 2 mL of absolute EtOH and 4 mL of DME at such a rate that the temperature did not exceed 3 °C. After stirring for 1 h at 0 °C and then 1 h at room temperature, the reaction mixture was diluted with water, extracted with Et₂O, and dried (MgSO₄). After removal of the solvent, the sticky residue was chromatographed by preparative TLC (silica gel, benzene–MeOH 10:1) providing 0.55 g (47%) of **2i**. Crystallization from Et₂O–pentane (1:1) gave analytically pure **2i**: mp 159–164 °C; IR (Nujol) 2240 (C≡N), 1660 (C=O), 1620 and 1610 cm⁻¹ (C=C); ¹H NMR (CDCl₃) δ 0.92 and 1.02 (two singlets of equal intensity, total 3 H, 18β-CH₃), 1.27 (s, 3, 19β-CH₃), 1.3–2.7 (br m, 15), lines at 7.25, 7.10, and 6.40, 6.35, 6.20, 6.15 (AB q, partially split into a doublet, 3, vinyl H's). The peaks at 0.92 and 1.02 account for a ratio 17β-C≡N:17α-C≡N ~ 1:1. Anal. Calcd for C₂₀H₂₅NO (mixture of epimers): C, 81.25; H, 8.52; N, 4.74. Found: C, 80.4; H, 8.4; N, 4.7.

Diphenylacetonitrile (2l) was prepared analogously to **2b** from 1.82 g (10 mmol) of benzophenone. By extraction with Et₂O 2.6 g of solid material was obtained. The solid was extracted with a boiling mixture of 150 mL of petroleum ether (bp 40–60 °C) and 50 mL of Et₂O. The residue provided 0.48 g (21%) of 4-tosylloxazole,¹⁵ mp 157–162 °C (from EtOH), reported^{6b} mp 166 °C. The concentrated filtrate gave after crystallization from petroleum ether 1.33 g (69%) of **2l**, mp 67–71 °C (lit.³⁰ mp 74 °C).

2-p-Bromophenylpropionitrile (2n). A solution prepared by dissolving *t*-BuOK (2.25 g, 18 mmol) in 7 mL of warm *t*-BuOH was

Table II. ¹H NMR Data of Cyano Steroids 2i–k

Compd		Chemical shift (rep), δ ppm			
		18-Me	19-Me	3-H	α/β
2i	17α-C≡N	0.92	1.27		1
2i	17β-C≡N	1.02	1.27		
2j	3α-C≡N	0.65 (0.65)	0.78 (0.79)	2.90 (2.95) ^a	0.7
2j	3β-C≡N	0.65 (0.65)	0.85 (0.82)	2.34 (2.34) ^a	
2k	3α-C≡N	0.65	0.91 ^b	2.90	0.9
2k	3β-C≡N	0.65	0.94 ^b		

^a The values in parentheses are from the literature.²⁸ ^b Comparable δ values for the 18-Me and 19-Me in 3α-hydroxy-5β-androstane are 0.65 and 0.91; for 3β-hydroxy-5β-androstane they are 0.65 and 0.98.²⁹

added to a stirred solution of *p*-bromoacetophenone (2.0 g, 10 mmol) and TosMIC (2.0 g, 10 mmol) in 35 mL of dry DME cooled in ice–salt, at such a rate that the temperature did not exceed 0 °C. After 15 min the mixture was warmed to room temperature and stirring was continued for 1 h. The mixture was concentrated to 20% of the original volume, diluted with water, and extracted with pentane. After drying (MgSO₄), distillation gave 1.65 g (79%) of **2n** as a colorless liquid: bp 112–116 °C (1 mm); IR (neat) 2245 cm⁻¹ (C≡N); ¹H NMR (CDCl₃) δ 1.60 (d, 3, CH₃, *J* = 7 Hz), 3.85 (q, 1, CH, *J* = 7 Hz), 7.15, 7.30 and 7.45, 7.60 (AB q, 4, aromatic).

Analysis of CO Evolved in Reaction 2a. The evolution of gas observed in a number of the above reactions when carried out in Me₂SO or HMPT was identified qualitatively as carbon monoxide by mass spectral analysis and IR. For the quantitative determination (as CO₂) in essence a microanalytical elemental analysis unit was used. The reaction was carried out by adding all at once 150 mg (1.0 mmol) of adamantane to a stirred and ice-cooled mixture of TosMIC (260 mg, 1.3 mmol), HMPT (1.5 mL), MeOH (0.05 mL), and *t*-BuOK (450 mg, ca. 3.6 mmol) in a slow stream of He (15–20 mL/min). During 6 h the gas stream was passed through a trap cooled at –196 °C, then through a tube with CuO heated at 800 °C, and finally through a preweighed tube containing Colorcarb (Perkin-Elmer). An increase in weight of 18.3–20.3 mg was found, corresponding to 42–46% of CO (calculated on adamantane). The reaction mixture contained 73% of **2a** and 7% of starting ketone.

Synthesis of ¹⁴C-Labeled TosMIC. Tos¹⁴CH₂N=C was prepared in two steps following the procedure in ref 2a on a 1/10 scale. To the reaction mixture was added ca. 0.02 mL of a 1% solution of ¹⁴CH₂O with a specified activity of 0.05 mCi. The yield was 15.6 g (49%) of Tos¹⁴CH₂NHCHO, mp 107–110 °C, specific activity 0.08 μCi/mmol. Dehydration of 2.67 g of this material provided 1.20 g of Tos¹⁴CH₂N=C, mp 111–114 °C.

Reaction of Adamantanone with ¹⁴C-Labeled TosMIC. The reaction with Tos¹⁴CH₂N=C was carried out in HMPT as above (three times that scale). To absorb the ¹⁴CO₂, the He–CO₂ stream from the CuO tube was now passed through 2 mL of a 1 M solution of Hyamine hydroxide³¹ in methanol in a 10-mL volumetric flask. After shutting off the gas stream the flask was filled up to 10.00 mL with MeOH and the quantity of CO₂ was determined by titration. The specific activity of the CO₂ (20% yield) was <0.0001 μCi/mmol. 2-Cyanoadamantane (55%) had a specific activity of 0.08 μCi/mmol.

5,5-Pentamethylene-4-tosyl-2-oxazoline (13e).³² A mixture of TosMIC (0.65 g, 3.3 mmol), cyclohexanone (0.33 g, 3.4 mmol), and K₂CO₃ (0.24 g, 1.7 mmol) was stirred for 1.5 h in 8 mL of MeOH at room temperature, then diluted with ice–water, and the precipitate was crystallized from acetone–water, providing 0.81 g (83%) of **13e**: mp 131.5–132 °C; IR (KBr) 1622 (C=N), 1330–1300 and 1150 cm⁻¹ (SO₂); ¹H NMR (CDCl₃) δ 2.44 (s, 3, CH₃), 1.68 (br s, *c*-Hex), 4.68 (d, 1, 4-CH, *J* = 1.5 Hz), 7.05 (d, 1, 2-CH, *J* = 1.5 Hz), 7.35 and 7.84 (two d, 4, aromatic, *J* = 8.5 Hz). Anal. Calcd for C₁₅H₁₉NO₃S: C, 61.41; H, 6.53; N, 4.77; S, 10.93. Found: C, 61.3; H, 6.5; N, 4.8; S, 11.0.

Cyanocyclohexane (2e) from 13e and from 14e. A solution of **13e** (0.58 g, 2.0 mmol) in 15 mL of DME and 0.1 mL of absolute EtOH was stirred for 1 h at 40 °C with *t*-BuOK (0.45 g, 3.6 mmol) and worked up as described for **2n** to give 0.13 g (60%) of **2e**, bp 64–66 °C (12 mm).

Similarly, *N*-(1-tosylcyclohexylidene)methylformamide^{8a} (**14e**, 1.75 g, 5.9 mmol) was converted with *t*-BuOK (1.23 g, 10 mmol) in 20 mL of DME and 5 mL of *t*-BuOH to give 0.59 g (90%) of **2e**.

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Registry No.—2a, 35856-00-9; *endo*-2b, 3211-87-8; *exo*-2b, 3211-90-3; *endo*-2c, 62796-09-2; *exo*-2c, 62796-08-1; 2d, 32730-85-1; 2e, 766-05-2; 2f, 56536-96-0; 2g, 62796-10-5; 2h, 57764-88-2; 17 α -2i, 62796-11-6; 17 β -2i, 62796-12-7; 3 α -2j, 1251-67-8; 3 β -2j, 1251-66-7; 3 α -2k, 62796-13-8; 3 β -2k, 62796-14-9; 2l, 86-29-3; 2m, 1823-91-2; 2n, 42186-06-1; 2o, 13310-75-3; 2p, 62391-96-2; 2q, 21101-85-9; 13e, 52568-58-8; 14e, 39031-25-9; 2,2-dimethyl-1,2,3,4-tetrahydronaphthalene-1-carboxamide, 62796-15-0; 4-tosyloxazole, 57764-94-0; Tos¹⁴CH₂N=C, 62796-16-1; ¹⁴CH₂O, 3046-49-9; Tos¹⁴CH₂NHCHO, 62796-17-2; TosMIC, 36635-61-7.

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Aminations with Ammonia and Formamide. Synthesis of Terephthalamide and of *p*-Nitroaniline

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Ammonolysis of potassium methyl terephthalate (2k) to potassium terephthalamate (3k) is markedly accelerated by formamide solvent. No corresponding acceleration is seen with other amides, such as mono- or dimethylformamide or acetamide. Negligible hydrolysis to ammonium terephthalate (4a) occurs. An efficient procedure for the Hofmann conversion of potassium terephthalamate (3k) to *p*-aminobenzoic acid is reported. Ammonolysis of *p*-nitrochlorobenzene occurs rapidly in formamide solvent at 200–220 °C to furnish high yields of *p*-nitroaniline. *p*-Chlorobenzotrifluoride and 1,2,4-trichlorobenzene are not aminated under these conditions.

We sought to develop an economical synthesis of *p*-aminobenzoic acid from commercial dimethyl terephthalate (DMT, 1).¹ Attempts to half-ammonolyze DMT to methyl

terephthalamate (3e) were unsuccessful, since all conditions tried formed excessive amounts of terephthaldiamide. However, half-hydrolysis of DMT by potassium hydroxide in