A General One-Step Synthesis of Nitriles from Ketones Using Tosylmethyl Isocyanide. Introduction of a One-Carbon Unit[1]

Otto H. Oldenziel, Daan van Leusen, and Albert M. van Leusen*

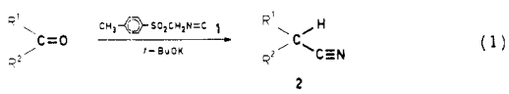
Department of Organic Chemistry, The University, Zernikelaan, Groningen, The Netherlands

Received February 7, 1977

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]



(1)

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 → 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 Me_2SO 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

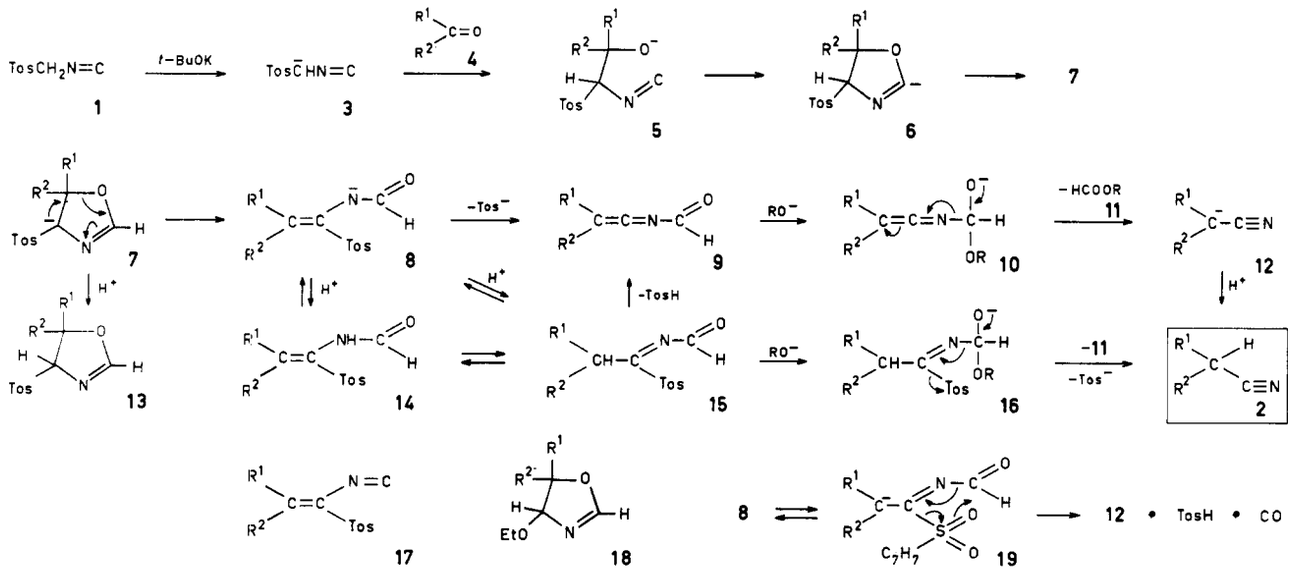


Table I. Nitriles Synthesized from Ketones and Tosylmethyl Isocyanide (TosMIC) According to Equation 1

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	*t*-BuOK (2.4), DME	1.5	35	93	~180	166–175[24]
2-Cyanoadamantane (**2a**)		1.3	*t*-BuOK (3.5), Me_2SO	17	20	84		
2-Norbornanone*	497-38-1							
2-Cyanonorbornane (**2b**)[d]		1.3	*t*-BuOK (3.5), Me_2SO	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	*t*-BuOK (7), Me_2SO	70	45	80	135–148	[26]
2-Cyanocamphane (**2c**)		3	*t*-BuOK (7), HMPT	17	45	73		
2-Cyanocamphane (**2c**)		1.1	*t*-BuOK (2), DME	1.5	20	<5		
Cycloheptanone	502-42-1							
Cyanocycloheptane (**2d**)		1.1	*t*-BuOK (2), DME	1.5	20	80	85–86 (10 mm)	85–86 (10 mm)[33]
Cyclohexanone	108-94-1							
Cyanocyclohexane (**2e**)		1.0	*t*-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	*t*-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	*t*-BuOK (7), HMPT	40	45	76	*h*	
Estrone 3-methyl ether	1624-62-0							
17β-Cyano-1,3,5(10)-estratrien-3-ol methyl ether (**2h**)		1.3	*t*-BuOK (3.5), Me_2SO	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	*t*-BuOK (2.5), DME	5	20	85	114–121	*k*
5β-Cholestan-3-one	601-53-6							
3-Cyano-5β-cholestane (**2k**)[l]		1.5	*t*-BuOK (3), DME	5	20	53	57–72	[36]
Benzophenone*	119-61-9							
Diphenylacetonitrile (**2l**)		1.3	*t*-BuOK (3.5), Me_2SO	17	20	69	67–71	74[30]
Acetophenone	98-86-2							
2-Phenylpropionitrile (**2m**)		1.0	*t*-BuOK (2), DME	1.5	20	68	74–78 (2 mm)	100 (8 mm)[37]
p-Bromoacetophenone*	99-90-1							
2-*p*-Bromophenylpropionitrile (**2n**)		1.0	*t*-BuOK (2), DME	1.5	20	79	112–116 (1 mm)	
Di-*n*-propyl ketone	123-19-3							
4-Cyanoheptane (**2o**)		1.2	*t*-BuOK (2.5), DME	1.5	20	74	*m*	183–184[33]
Diisopropyl ketone	565-80-0							
3-Cyano-2,4-dimethylpentane (**2p**)		3	*t*-BuOK (7), HMPT	70	45	65	$n^{21}D$ 1.4177[n]	170–171 } [38]
3-Cyano-2,4-dimethylpentane (**2p**)		1.0	*t*-BuOK (2), DME	1.5	20	<5		$n^{23}D$ 1.4158 }
tert-Butyl methyl ketone[p]	75-97-8							
2-Cyano-3,3-dimethylbutane (**2q**)		1.3	*t*-BuOK (3.5), Me_2SO	17	20	70	40–42 (15 mm) }	151–152 } [39]
2-Cyano-3,3-dimethylbutane (**2q**)		1.0	*t*-BuOK (2), DME	1.5	20	36	$n^{25}D$ 1.4099 }	$n^{25}D$ 1.4092 }
Di-*tert*-butyl ketone	815-24-0							
3-Cyano-2,2,4,4-tetramethylpentane	62796-07-0	3	*t*-BuOK (7), HMPT	170	45	*o*		67–78 (10 mm)[40]

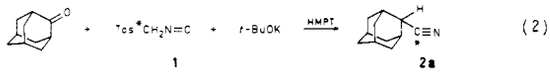
[a] Substrates are marked with an asterisk when further details are given in the Experimental Section. [b] Alcohol (1–2 equiv) was added in all cases (see text and Experimental Section). [c] All reactions were started around 0 °C, and usually after 15 min continued at the temperature indicated. [d] Endo–exo = 4:3. [e] Endo–exo = 1:1. [f] Endo–exo = 4:1 or 1:4. [g] Hydrolyzed (NaOH, 30% H_2O_2) 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 (RO^- = 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** ($R^1 - R^2$ = pentamethylene). (5) Rapid H–D exchange is observed in **13** ($R^1 = R^2$ = Me) at C(4) only (with K_2CO_3 in CD_3OD–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,8b] 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 N=C-Tos group[13] of **15**; also, nucleophilic reactions of ketenimines are well known[14].) However, initial nucleophilic attack at these other centers does not necessarily preclude the formation of **2**. In addition to the nucleophiles RO^- (R = Me, Et, or *t*-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≡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*-$CH_3C_6H_4S(O)OCHO$ (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**, R = *t*-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 $Tos^{14}CH_2N{=}C$ (eq 2).

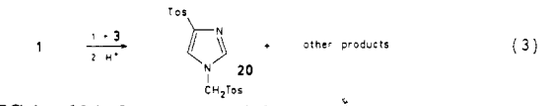


(2)

1 2a

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 EtOTl in EtOH (or EtOH–DME) **13** will give 4-ethoxy-2-oxazolines[18] **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.

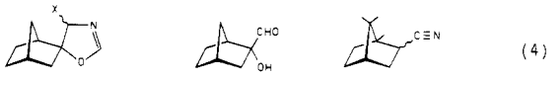
The tosyloxazolines **13** are obtained in protic solvents using weak bases (e.g., K_2CO_3 in MeOH,[2b,20] or NaCN in EtOH[8a]). In an aprotic medium (*t*-BuOK in THF) at −10 °C the reaction goes one step further to give **8** (**14**),[8] but at temperatures of 20–45 °C the reaction slowly continues 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*-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** → **12** (or **15** → **2**).



(3)

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*-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]



(4)

13b X = Tos
18b X = EtO

21 2c

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*-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 35–40 °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 40–60 °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 Me_2SO 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 Me_2SO (7.5 mL) was added all at once 2.25 g (ca. 18 mmol) of solid *t*-BuOK. After stirring for 5 min under N_2 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 (Na_2SO_4). 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 Me_2SO, and 0.25 mL of MeOH. The mixture was stirred under N_2 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 $C_{11}H_{17}N$: 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-tetralone[27] (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 (CCl_4) δ 1.09 (s, 3, CH_3), 1.16 (s, 3, CH_3), 1.4–1.8 (m, 2, 3-CH_2), 2.73 (t, 2, 4-CH_2), 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 Me_2CO–pentane), IR (Nujol) 1650 cm^{-1}. Anal. Calcd for $C_{13}H_{17}NO$: 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 Et_2O, and dried ($MgSO_4$). 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 Et_2O–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 ($CDCl_3$) δ 0.92 and 1.02 (two singlets of equal intensity, total 3 H, 18β-CH_3), 1.27 (s, 3, 19β-CH_3), 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 $C_{20}H_{25}NO$ (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 Et_2O 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 Et_2O. The residue provided 0.48 g (21%) of 4-tosyloxazole,[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 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 ($MgSO_4$), 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 ($CDCl_3$) δ 1.60 (d, 3, CH_3, J = 7 Hz), 3.85 (q, 1, CH, J = 7 Hz), 7.15, 7.30 and 7.45, 7.60 (AB q, 4, aromatic).

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]

Analysis of CO Evolved in Reaction 2a. The evolution of gas observed in a number of the above reactions when carried out in Me_2SO or HMPT was identified qualitatively as carbon monoxide by mass spectral analysis and IR. For the quantitative determination (as CO_2) 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 adamantanone 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 adamantanone). The reaction mixture contained 73% of **2a** and 7% of starting ketone.

Synthesis of ^{14}C-Labeled TosMIC. Tos$^{14}CH_2N$=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 $^{14}CH_2O$ with a specified activity of 0.05 mCi. The yield was 15.6 g (49%) of Tos$^{14}CH_2NHCHO$, mp 107–110 °C, specific activity 0.08 μCi/mmol. Dehydration of 2.67 g of this material provided 1.20 g of Tos-$^{14}CH_2N$=C, mp 111–114 °C.

Reaction of Adamantanone with ^{14}C-Labeled TosMIC. The reaction with Tos$^{14}CH_2N$=C was carried out in HMPT as above (three times that scale). To absorb the $^{14}CO_2$, the He–CO_2 stream from the CuO tube was now passed through 2 mL of a 1 M solution of Hyamine hydroxide[31] 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 CO_2 was determined by titration. The specific activity of the CO_2 (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 K_2CO_3 (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} (SO_2); ^1H NMR ($CDCl_3$) δ 2.44 (s, 3, CH_3), 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 $C_{15}H_{19}NO_3S$: 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-tosylcyclohexylidenemethyl)formamide[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**.

Acknowledgment. This work was supported by the Netherlands Foundation for Chemical Research (SON) with a fellowship to O.H.O. The authors are indebted to Dr.

Vaalburg and Mrs. H. D. Beerling-Van der Molen for technical assistance in the radioactivity measurements, to Mr. A. F. Hamminga for support in the CO determination, and to Gist-Brocades N.V., Delft, for a generous gift of two steroids.

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; 17α-**2i**, 62796-11-6; 17β-**2i**, 62796-12-7; 3α-**2j**, 1251-67-8; 3β-**2j**, 1251-66-7; 3α-**2k**, 62796-13-8; 3β-**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; $Tos^{14}CH_2N{=}C$, 62796-16-1; $^{14}CH_2O$, 3046-49-9; $Tos^{14}CH_2NHCHO$, 62796-17-2; TosMIC, 36635-61-7.

References and Notes

(1) Chemistry of Sulfonylmethyl Isocyanides. 13. For parts 12 and 14, see ref 2a and 2b, respectively.
(2) (a) A. M. van Leusen, J. Wildeman, and O. H. Oldenziel, *J. Org. Chem.*, **42**, 1153 (1977); (b) A. M. van Leusen and J. Wildeman, *Synthesis*, 501 (1977).
(3) Part of this work was presented in preliminary form: (a) O. H. Oldenziel and A. M. van Leusen, *Tetrahedron Lett.*, 1357 (1973); (b) *Synth. Commun.*, 281 (1972).
(4) D. T. Mowry, *Chem. Rev.*, **42**, 231 (1948).
(5) For recent multistep processes via addition of HCN to hydrazone derivatives, see F. E. Ziegler and P. A. Wender, *J. Am. Chem. Soc.*, **93**, 4318 (1971); S. Cacchi, L. Caglioti, and G. Paolucci, *Chem. Ind. (London)*, 213 (1972).
(6) After publication of our preliminary communications[3] other research groups too have applied this synthetic principle with success. Of their contributions the following published results have come to our attention: (a) E. J. Rauckman, G. M. Rosen, and M. B. Abou-Donia, *J. Org. Chem.*, **41**, 564 (1976); (b) J. R. Bull and A. Tuinman, *Tetrahedron*, **31**, 2151 (1975); (c) S. Kishimoto and S. Noguchi, Japan Kokai 75 59,359 [*Chem. Abstr.*, **83**, 131366k (1975)]; (d) B. S. E. Carnmalm, T. DePaulis, S. B. Ross, S. I. Ramsby, N. E. Stjernstrom, and S. O. Ogren, German Offen 2 360 027 [*Chem. Abstr.*, **81**, 169367h (1974)]; (e) R. W. Freerksen and D. S. Watt, *Synth. Commun.*, **6**, 447 (1976); (f) T. Sasaki, S. Eguchi, and M. Mizutani, *Tetrahedron Lett.*, 2685 (1975); (g) M. L. Raggio and D. S. Watt, *J. Org. Chem.*, **41**, 1873 (1976); (h) G. Büchi, D. Berthet, R. Decorzant, A. Grieder, and A. Hauser, *ibid.*, **41**, 3208 (1976).
(7) For a recent modification of the reaction of nitriles to amides, see J. H. Hall and M. Gisler, *J. Org. Chem.*, **41**, 3769 (1976); The conversion $>CHC{\equiv}N \rightarrow >C(OH)C{\equiv}N$ was described recently: E. Vedejs and J. E. Telschow, *ibid.*, **41**, 740 (1976), and ref 6e. For the reversal of reaction 1 (i.e., $>CHC{\equiv}N \rightarrow >C{=}O$) see S. J. Selikson and D. S. Watt, *ibid.*, **40**, 267 (1975).
(8) (a) U. Schöllkopf, R. Schröder, and E. Blume, *Justus Liebigs Ann. Chem.*, **766**, 130 (1972); (b) U. Schöllkopf and R. Schröder, *Angew. Chem., Int. Ed. Engl.*, **12**, 407 (1973).
(9) Recent leading references: E. Vowinkel and J. Bartel, *Chem. Ber.*, **107**, 1221 (1974); J. B. Hendrickson, K. W. Bair, and P. M. Keehn, *Tetrahedron Lett.*, 603 (1976); A. Antonowa and S. Hauptmann, *Z. Chem.*, **16**, 17 (1976); T.-L. Ho and C. M. Wong, *Synth. Commun.*, **5**, 299 (1975); see further ref 3a.
(10) The low reactivity of α-tetralone may be due to enolization.
(11) D. Hoppe, *Angew. Chem., Int. Ed. Engl.*, **13**, 789 (1974) (review).
(12) T. Saegusa and Y. Ito in "Isonitrile Chemistry", I. Ugi, Ed., Academic Press, New York, N.Y., 1971, Chapter 4.
(13) Cf. J. C. Jagt and A. M. van Leusen, *J. Org. Chem.*, **39**, 564 (1974).
(14) G. R. Krow, *Angew. Chem., Int. Ed. Engl.*, **10**, 435 (1971).
(15) For example, in the reaction of benzophenone and TosMIC (see Experimental Section), 21% of 4-tosyloxazole was isolated in addition to **2l** (69%). The former compound is the expected product of formylation of TosMIC[6b] (cf. ref 20). Here, formylation may occur by **9**, **11**, or **15**.
(16) This view may derive some support from E. Gordon, S. J. W. Price, and A. F. Trotman-Dickenson, *J. Chem. Soc.*, 2813 (1957); H. N. Barham and L. W. Clark, *J. Am. Chem. Soc.*, **73**, 4638 (1951).
(17) A number of reactions discussed here for ketones are observed for aldehydes as well.[8,18,20] However, in the case of aldehydes, the tosyloxazolines **13** (R^1 = H) can undergo another type of reaction, i.e., the elimination of TosH to oxazoles.[20,8] For that reason we have left aldehydes out of the discussion in the present paper.
(18) O. H. Oldenziel and A. M. van Leusen, *Tetrahedron Lett.*, 163 (1974). The reaction **13** → **18** is not a direct substitution of Tos, but a double addition–elimination involving two molecules of EtOH via 2-ethoxy-3-oxazolines: O. H. Oldenziel, Thesis, Groningen 1975, Chapter 5.
(19) O. H. Oldenziel and A. M. van Leusen, *Tetrahedron Lett.*, 167 (1974).
(20) A. M. van Leusen, B. E. Hoogenboom, and H. Siderius, *Tetrahedron Lett.*, 2369 (1972).
(21) We prefer the use of DME over THF (mostly used by Schöllkopf's group[8]), but this does not affect the argument.
(22) Tuinman[6b] has previously recommended for the same reason the use of 10 equiv of *t*-BuOK for reactions in DME–*t*-BuOH.
(23) This procedure has been submitted in a more elaborate form for publication in *Organic Syntheses*.
(24) H. Stetter and V. Tilmanns, *Chem. Ber.*, **105**, 735 (1972).
(25) K. Alder, K. Heimbach, and R. Reubke, *Chem. Ber.*, **91**, 1516 (1958).
(26) A mp of 163 °C is reported for a 2-cyanocamphane of unspecified stereochemistry: J. Houben and H. Doescher, *Chem. Ber.*, **43**, 3435 (1910).
(27) M. Mousseron, R. Jacquier, and H. Christol, *Bull. Soc. Chim. Fr.*, 346 (1957).
(28) K. Tori and T. Komeno, *Tetrahedron*, **21**, 309 (1965).
(29) R. F. Zürcher, *Helv. Chim. Acta*, **44**, 1380 (1961); **46**, 2058 (1963).
(30) R. Stollé and F. Schmidt, *Chem. Ber.*, **45**, 3113 (1912).
(31) See H. P. Sherr, Y. Sasaki, A. Newman, J. G. Banwell, H. N. Wagner, and T. R. Hendrix, *N. Engl. J. Med.*, **285**, 656 (1971).
(32) B. E. Hoogenboom, not published previously, Internal Report, Groningen 1970–1971; cf. U. Schöllkopf and R. Schröder, *Angew. Chem., Int. Ed. Engl.*, **11**, 311 (1972).
(33) E. Müller and H. Huber, *Chem. Ber.*, **96**, 670 (1963).
(34) J. F. Bunnett and J. A. Skorcz, *J. Org. Chem.*, **27**, 3836 (1962).
(35) R. W. Horobin, N. R. Kahn, and J. McKenna, *Tetrahedron Lett.*, 5087 (1966).
(36) D. N. Jones, R. Grayshan, and K. J. Wyse, *J. Chem. Soc. C*, 2027 (1970).
(37) Beilstein, **9**, E III, 2421.
(38) R. F. Brown and N. M. van Gulick, *J. Am. Chem. Soc.*, **77**, 1083 (1955); F. C. B. Marshall, *J. Chem. Soc.*, 2754 (1930).
(39) C. G. Overberger and M. B. Berenbaum, *J. Am. Chem. Soc.*, **74**, 3293 (1952).
(40) M. S. Newman, A. Arkell, and T. Tukunaga, *J. Am. Chem. Soc.*, **82**, 2498 (1960).

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

Christian S. Rondestvedt, Jr.

Research and Development Division Publication No. 548, Jackson Laboratory, Organic Chemicals Department, E. I. du Pont de Nemours and Company, Wilmington, Delaware, 19898

Received March 23, 1977

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