on silica gel, eluting with cyclohexane–ethyl acetate (4:6).

2-(1-Methylpyrrol-2-yl)pyridine (α-Nicotyrine) (30):[12] 97% pure by GC analysis; IR 1585, 1560, 1540 cm^{-1}; ^1H NMR δ 8.48 (m, 1 H), 7.47 (m, 2 H), 6.95 (m, 1 H), 6.67 (m, 1 H), 6.53 (m, 1 H), 6.14 (m, 1 H), 3.95 ppm (s, 3 H, Me); MS *m/e* (relative intensity) 158 (M^+, 50), 157 (100), 130 (20), 78 (18), 51 (10).

3-(1-Methylpyrrol-2-yl)pyridine (β-Nicotyrine) (31):[13] 96% pure by GC analysis; IR 1590, 1565, 1535 cm^{-1}; ^1H NMR δ 8.65 (s, 1 H), 8.46 (m, 1 H), 7.60 (m, 1 H), 7.20 (m, 1 H), 6.67 (m, 1 H), 6.20 (m, 2 H), 3.57 ppm (s, 3 H, Me); MS *m/e* (relative intensity) 158 (M^+, 100), 157 (56), 130 (31), 42 (17), 63 (17), 51 (15), 116 (13), 117 (12), 89 (11), 90 (10).

Synthesis of (*Z*)-7-Nonadecen-11-one (27). Potassium *tert*-butoxide (0.42 g, 3.75 mmol) is added to a suspension of triphenylheptylphosphonium bromide (**26**, 1.75 g, 4 mmol) in anhydrous THF (10 mL), with stirring at 0 °C, under an argon atmosphere. After 30 min the mixture is cooled to −78 °C, and a solution of 4-oxodecanal (**15**, 0.75 g, 3.75 mmol) in THF (5 mL) is added dropwise. The reaction mixture is stirred at −78 °C for 3 h and then allowed to reach room temperature overnight with stirring. After quenching with saturated aqueous solution of sodium chloride (10 mL) the organic phase is extracted with ether (3 × 20 mL) and dried over sodium sulfate. The residue is purified by flash chromatography on silica gel, eluting with cyclohexane, to give 1.38 g (67%) of pure **27**: IR 1720 cm^{-1}; ^1H NMR δ 5.37 (m, 2 H), 2.40 (m, 6 H), 2.05 (m, 20 H), 0.89 ppm (t, 3 H); MS *m/e* 280 (M^+); the *Z*:*E* ratio of 98.6:1.4 was determined by GLC on glass capillary Supelcowax column (30 m, 0.33 mm, 0.25 μm) at 130 °C: retention times, 37.38 min (*Z* isomer) and 39.26 min (*E* isomer).

Acknowledgment. This work was supported by a grant from the Ministero della Pubblica Istruzione, Roma.

Registry No. **8a**, 39662-63-0; **8b**, 39662-64-1; **9b**, 131684-94-1; **10b**, 131684-95-2; **11a**, 131684-96-3; **12a**, 131684-97-4; **13a** (R = n-C_6H_{13}), 131685-01-3; **13a** (R = n-C_8H_{17}), 131685-02-4; **13a** (R = Ph), 131685-03-5; **14a**, 43160-78-7; **15a**, 56268-03-2; **16a**, 56139-59-4; **16b**, 75424-63-4; **17**, 25435-63-6; **18**, 131684-98-5; **19**, 76014-80-7; **20**, 131684-99-6; **21**, 10202-74-1; **22**, 131685-00-2; **26**, 13423-48-8; (*Z*)-**27**, 63408-45-7; **28**, 17285-54-0; **29**, 494-98-4; **30**, 525-75-7; **31**, 487-19-4; n-hexylmagnesium, 3761-92-0; phenylmagnesium chloride, 100-59-4; 2-bromopyridine, 109-04-6; 3-bromopyridine, 626-55-1; 1-ethoxydodec-2-en-4-one, 131685-04-6.

Cyano Phosphate: An Efficient Intermediate for the Chemoselective Conversion of Carbonyl Compounds to Nitriles[1]

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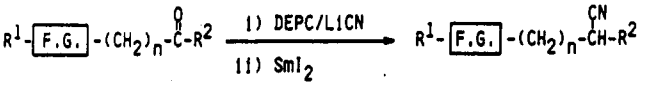
Received June 8, 1990

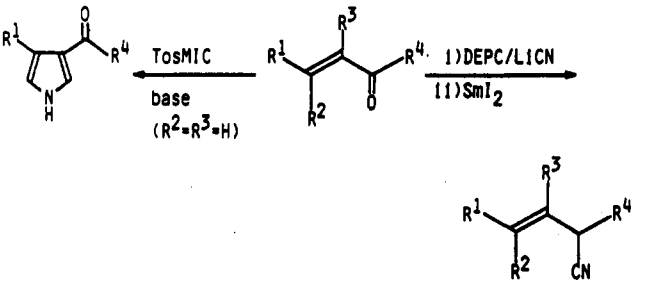
Cyanohydrin diethyl phosphates, readily obtained from various ketones and aldehydes by reaction with diethyl phosphorocyanidate and lithium cyanide, reacted chemoselectively with samarium(II) iodide in THF to give the corresponding nitriles in excellent yields. This method was also found applicable to α,β-unsaturated carbonyl compounds via cyano phosphates to give β,γ-unsaturated nitriles, not obtainable by standard methods, without isomerization of the double bonds.

The conversion of carbonyl groups into nitriles is important for one-carbon homologation in organic synthesis.[2] Cyanation with tosylmethyl isocyanide (TosMIC), developed by van Leusen,[3] is widely used for the one-pot conversion of ketones to nitriles and is frequently used for cyanation in organic synthesis. However, it involves the use of *t*-BuOK and generally gives low yields in the case of aliphatic and α,β-unsaturated aldehydes.[4] α,β-Unsaturated ketones[5] generally give only 3-acylpyrroles by this procedure without generation of nitriles. There is the alternative method for the cyanation of carbonyl groups using 2,4,6-triisopropylbenzenesulfonohydrazide (TPSH)[6] followed by refluxing of the hydrazones with excess potassium cyanide in methanol. In spite of these efforts to convert carbonyl compounds to nitriles, no general method for the chemoselective cyanation of carbonyl compounds bearing various functional groups is presently available. Reported here is a novel and efficient method for the

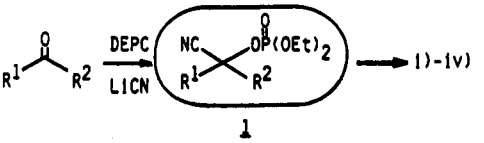
Scheme I



F.G. = alcohol, ether, epoxide, acetal, ester, amine, carbamate, amide, sulfonylamide, alkene, alkyne



Scheme II



1

chemoselective conversion of carbonyl compounds into nitriles via cyanohydrin *O,O'*-diethyl phosphates (cyano phosphates). By this method, the conversion of α,β-unsaturated carbonyl compounds into the corresponding

(1) For a preliminary account of this work, see: Yoneda, R.; Harusawa, S.; Kurihara, T. *Tetrahedron Lett.* **1989**, *30*, 3681.
(2) (a) Martin, S. F. *Synthesis* **1979**, 633. (b) Harusawa, S.; Nakamura, S.; Yagi, S.; Kurihara, T.; Hamada, Y.; Shioiri, T. *Synth. Commun.* **1984**, *14*, 1365 and references cited therein.
(3) Oldenziel, O. H.; van Leusen, D.; van Leusen, A. M. *J. Org. Chem.* **1977**, *42*, 3114.
(4) van Leusen, A. M.; Oomkes, P. G. *Synth. Commun.* **1980**, *10*, 399.
(5) (a) van Leusen, A. M.; Siderius, H.; Hoogenboon, B. E.; van Leusen, D. *Tetrahedron Lett.* **1972**, 5337. (b) Cheng, D. O.; LeGoff, E. *Tetrahedron Lett.* **1977**, 1469.
(6) Jiricny, J.; Orene, D. M.; Reese, C. B. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1487.

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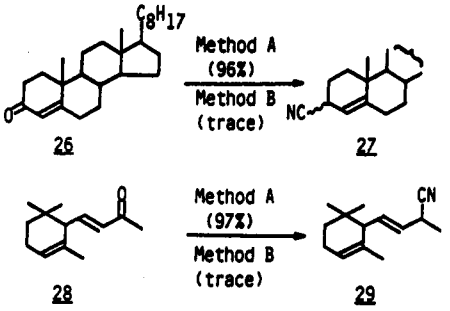
Scheme III[a]



[a] Method A: (i) DEPC/LiCN; (ii) SmI_2. Method B: TosMIC.

nitriles was successfully conducted (Scheme I).

It has already been shown that cyano phosphates 1 (Scheme II), readily obtained from carbonyl compounds with *O,O'*-diethyl phosphorocyanidate [$(EtO)_2P(O)CN$] (DEPC) and lithium cyanide in THF,[7] can serve as versatile intermediates in organic synthesis:[8] (i) α,β-unsaturated nitrile synthesis,[7] (ii) regiospecific Friedel–Crafts type arylation,[9] (iii) γ-hydroxy α,β-unsaturated nitrile synthesis via [3,3]sigmatropic rearrangement,[9b,10] (iv) regiospecific alkylation by reactions with organocopper reagents,[11] (v) use as an acyl anion equivalent,[12] and others.[13]

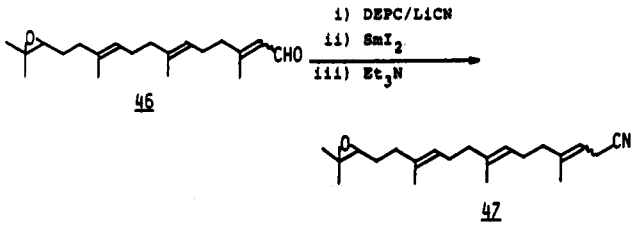
The cyano phosphates of aromatic and α,β-unsaturated carbonyl compounds were recently shown to be readily deoxygenated to give nitriles by reduction with lithium in liquid ammonia,[14] though with some restriction. This reductive deoxygenation can be explained in terms of two one-electron transfers to the P=O double bond.[15] Unfortunately, this procedure cannot be used for the cyano phosphates of saturated aliphatic carbonyl compounds, since only a complex mixture is obtained. Thus, attention was directed to reactions of cyano phosphate 1 with samarium(II) iodide (SmI_2),[16] widely noted not only for its moderate reducing power for organic compounds but also for its ease of handling in THF.

Results and Discussion

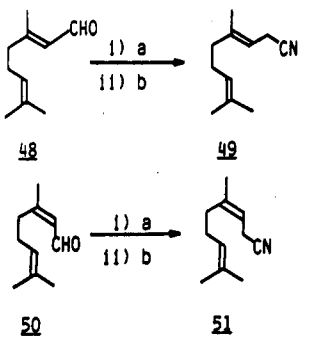
Treatment of crude cholestan-3-one (2) cyano phosphate with freshly prepared SmI_2 in THF[16] in the presence of *t*-BuOH (1 equiv) at room temperature gave a desirable cholestane-3-carbonitrile (3) in 83% yield. Thus, various aliphatic carbonyl compounds can be converted into nitriles. The results obtained by this method are summarized in Table I.

Interesting features of this method should be pointed out. Other steroidal ketones 4 and 6 having methoxy-

Scheme IV



Scheme V[a]



[a] (a) DEPC/LiCN; (b) SmI_2.

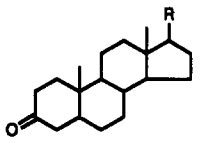
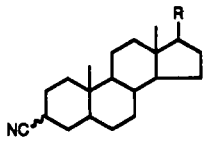
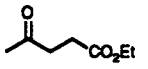
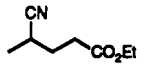
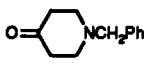
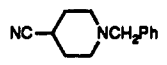
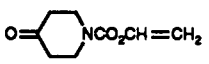
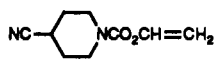
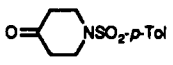
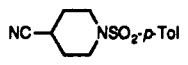
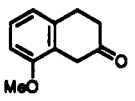
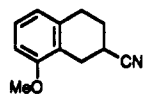
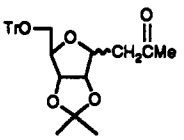
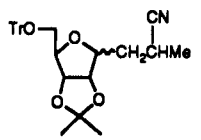
methoxy as well as free hydroxy groups also gave the corresponding nitriles 5 and 7 in excellent yields. Thus, the chemoselectivity for cyanation by our method was investigated, since no systematic studies have been done so far. Although the representative methods (TosMIC and TPSH) mentioned above are widely used for the conversion of simple ketones and aldehydes having no other functional groups to nitriles, the present method provided nitriles from aliphatic ketones bearing ester (entry 7), amine (entry 8), vinyl carbamate (entry 9), sulfamoyl (entry 10), and aromatic methoxy (entry 11) functions in good yields. Moreover, the cyanation of glycosyl ketone[17] (entry 12) having trityl and acetonide functions as protecting groups was conducted in 61% yield by a slightly modified procedure.

This reaction was successfully extended to α,β-unsaturated carbonyl compounds under neutral conditions to obtain nitriles not usually accessible by the TosMIC method.[5] Cholest-4-en-3-one (26) and α-ionone (28) gave the corresponding nitriles (27 in 96% and 29 in 97% yields) without any products with isomerization and reduction of the double bond, respectively (Scheme III). But, under general TosMIC conditions[18] in the presence of *t*-BuOK in DME, nitriles 27 and 29 were detected only on TLC, along with significant amounts of unidentified products. These results clearly demonstrate the superiority of the present method over the TosMIC method. Other intriguing examples of this method are reactions of enal 34 and 36,[19] ynone 38, 40, and 42 (entries 5–7), and quinone 44 (entry 8) cyano phosphates[9a] with SmI_2, to afford the corresponding nitriles 35, 37, 39, 41, and 43 and *p*-hydroxybenzonitrile (45) (Table II, entries 1–8).

It is significant that cyanation of the epoxy aldehyde 46[20]

(7) Harusawa, S.; Yoneda, R.; Kurihara, T.; Hamada, Y.; Shioiri, T. *Tetrahedron Lett.* **1984**, *25*, 427.
(8) For a review, see: Kurihara, T.; Harusawa, S.; Yoneda, R. *J. Synth. Org. Chem. Jpn.* **1988**, *46*, 1164.
(9) (a) Kurihara, T.; Harusawa, S.; Hirai, J.; Yoneda, R. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1771. (b) Kurihara, T.; Miki, M.; Santo, K.; Harusawa, S.; Yoneda, R. *Chem. Pharm. Bull.* **1986**, *34*, 4620.
(10) Kurihara, T.; Miki, M.; Yoneda, R.; Harusawa, S. *Chem. Pharm. Bull.* **1986**, *34*, 2747.
(11) Yoneda, R.; Harusawa, S.; Yoneda, R. *J. Chem. Soc., Perkin Trans. 1* **1988**, 3163.
(12) (a) Kurihara, T.; Santo, K.; Harusawa, S.; Yoneda, R. *Chem. Pharm. Bull.* **1987**, *35*, 4777. (b) Yoneda, R.; Santo, K.; Harusawa, S.; Kurihara, T. *Synth. Commun.* **1987**, *17*, 921.
(13) Kurihara, T.; Hanakawa, M.; Harusawa, S.; Yoneda, R. *Chem. Pharm. Bull.* **1986**, *34*, 4545.
(14) Yoneda, R.; Osaki, H.; Harusawa, S.; Kurihara, T. *J. Chem. Soc., Perkin Trans. 1* **1990**, 607.
(15) Hartwig, W. *Tetrahedron* **1983**, *39*, 2609.
(16) (a) Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693. (b) Kagan, H. B.; Namy, J. L. *Tetrahedron* **1986**, *42*, 6573.
(17) After the end of the reaction with SmI_2, the reaction mixture was quenched by the addition of SiO_2 instead of 10% HCl in order to avoid hydrolysis of the acetonide function.
(18) Oldenziel, O. H.; Wildman, J.; van Leusen, A. M. *Org. Synth.* **1977**, *57*, 8.
(19) Compound 36 was prepared according to a literature method: Babler, J. H.; Coghlam, M. J. *Synth. Commun.* **1976**, *6*, 469.
(20) Compound 46 was prepared from geranyllinalool via the acetate 64 according to a literature method: Hanzlik, R. P. *Org. Synth.* **1977**, *56*, 112.

Table I. Conversion of Carbonyl Compounds to Nitriles via Cyano Phosphates

entry	carbonyl compd	product	reactn[a] time, h	yield, %
1	 2, R = C_8H_{17}	 3	3	83
2	4, R = OCH_2OCH_3	5	3	84
3	6, R = OH	7	4	92
4	adamantanone (8)	adamantane-2-carbonitrile (9)	4	100
5	cyclohexadec-5-enone (10)	cyclohexadec-5-enecarbonitrile (11)	3	97
6	phenylpropanal (12)	4-phenylbutyronitrile (13)	3	82
8	 14	 15	2	80
8	 16	 17	2	79
9	 18	 19	1	92
10	 20	 21	0.25	92
11	 22	 23	4	88
12	 24	 25	3	61

[a] Referred to the time of the reaction of the cyano phosphates with SmI_2.

is possible by a combination of cyanophosphorylation and SmI_2 reduction followed by recyclization of the oxirane ring opening product[21] with triethylamine, to give the epoxy nitrile **47** in 54% yield (Scheme IV).

To assess the reaction's influence on the geometry of the double bond, the cyanations of geranial (**48**)[22] and neral (**50**)[22] were carried out under ordinary conditions to give the nitriles (**49** in 88% and **51** in 91% yields). No isomerized products were formed according to the ^1H and ^{13}C NMR spectra of the respective crude reaction products (Scheme V).

The present method was also applied to aromatic carbonyl compounds (Table II, entries 9–14). Interestingly, aromatic and heteroaromatic ketone cyano phosphates reacted much faster with SmI_2, giving excellent yields of the nitrile, than aliphatic ketone cyano phosphates. One major advantage of this method is that even Uhle's ketone[23] **56** and methoxynaphthyl ketone **62** cyano phosphates, subject to debenzoylation or reduction of aromatic ring by our preceding method,[14] can be converted into nitriles **57** and **63** in excellent yields. Hydrolyses of the nitriles **61** and **63** gave the corresponding carboxylic acids quantitatively. Thus, the simple and high-yield synthesis of antiinflammatory agents ibuprofen and naproxen is possible.

In conclusion, we have developed a new method for converting various carbonyl compounds possessing multiple functions and sensitive functions in their molecules, via cyano phosphate, into nitriles.

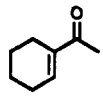
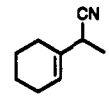
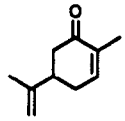
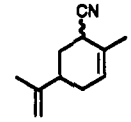
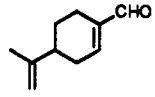
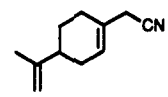
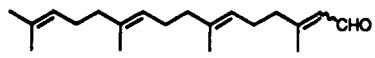
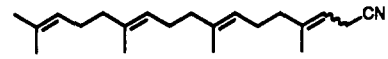
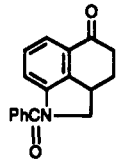
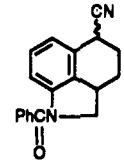
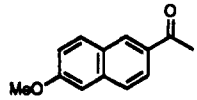
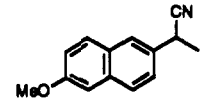
Experimental Section

Melting points were measured on a Yanagimoto apparatus. Melting points and boiling points stated are uncorrected. The Kugelrohr distillation temperatures are oven temperatures, not boiling points as stated. IR spectra were recorded on a Shimadzu IR-435 spectrophotometer. ^1H and ^{13}C NMR spectra were obtained in $CDCl_3$ with a Varian Gemini-200 spectrometer; signals are given in parts per million. Low-resolution (MS) and high-resolution mass spectra (HRMS) were obtained on a Hitachi M-80 instrument. All reactions were carried out under a nitrogen atomosphere. For column chromatography, SiO_2 (Merck 9385) was used. 5-Cyclohexadecen-1-one (**10**) and geranyllinalool were purchased from Tokyo Kasei Kogyo Co., Ltd.

General Procedure for the Preparation of Nitriles from Carbonyl Compounds. A carbonyl compound (0.5 mM) was stirred with DEPC (245 mg, 1.5 mM) and LiCN (24.5 mg, 1.5 mM) in THF (10 mL) for 10–30 min at room temperature. H_2O (10 mL) was added, and the mixture was extracted with EtOAc–hexane (1:1) (50 mL). The extract was washed with brine (2 × 20 mL), dried ($MgSO_4$), and evaporated under reduced pressure. A solution of the crude cyano phosphate **1** thus obtained and *t*-BuOH (37 mg, 0.5 mM) in THF (5 mL) was added to a solution of SmI_2, prepared from Sm (345 mg, 2.3 mM) and diiodoethane (413 mg, 1.5 mM), in THF (10 mL) at room temperature. The mixture was stirred for an appropriate time with monitoring by

(21) Matsukawa, M.; Tabuchi, T.; Inanaga, J.; Yamaguchi, M. *Chem. Lett.* **1987**, 2101.
(22) Yamazaki, S.; Yamazaki, Y. *Chem. Lett.* **1989**, 1361.
(23) Kornfeld, E. C.; Fornefeld, E. J.; Kline, G. B.; Mann, M. J.; Morrison, D. E.; Jones, R. G.; Woodward, R. B. *J. Am. Chem. Soc.* **1956**, *78*, 3087.

Table II. Conversion of Carbonyl Compounds to Nitriles via Cyano Phosphates

entry	carbonyl compd	product	reactn[a] time, h	yield, %
1	 **30**	 **31**	0.25	86
2	 **32**	 **33**	0.5	86
3	 **34**	 **35**	0.5	90
4	 **36**	 **37**	0.25	93
5	oct-3-yn-2-one (**38**)	oct-3-yne-2-carbonitrile (**39**)	0.5	98
6	4-phenylbut-3-yn-2-one (**40**)	4-phenylbut-3-yne-2-carbonitrile (**41**)	0.5	85
7	2-heptynal (**42**)	3-octynenitrile (**43**)	0.5	60
8	*p*-benzoquinone (**44**)	4-hydroxybenzonitrile (**45**)	0.2	82[b]
9	benzophenone (**52**)	diphenylacetonitrile (**53**)	0.2	90
10	2-acetylpyridine (**54**)	2-(pyridin-2-yl)propionitrile (**55**)	0.2	69
11	 **56**	 **57**	0.5	92
12	benzaldehyde (**58**)	phenylacetonitrile (**59**)	2	85
13	4-isobutylacetophenone (**60**)	2-(4-isobutylphenyl)propiononitrile (**61**)	0.2	94
14	 **62**	 **63**	0.2	96

[a] Referred to the time of the reaction of the cyano phosphates with SmI_2. [b] Yield from the cyano phosphate.

TLC. The reaction mixture was quenched by the addition of 10% HCl (10 mL) and extracted with ether (2 × 50 mL). The extracts were washed with 5% $Na_2S_2O_3$ (10 mL), H_2O (10 mL), and brine (10 mL) and dried ($MgSO_4$). After removal of the solvent under reduced pressure, the residue was purified by column chromatography to give nitrile.

Identification of Products. Adamantane-2-carbonitrile (**9**),[18] 4-phenylbutyronitrile (**13**),[24] *N*-benzylpiperidine-4-carbonitrile (**17**),[25] cholest-4-ene-3-carbonitrile (**27**),[14] 2-(cyclohexen-1-yl)-propiononitrile (**31**),[26] 2-methyl-5-(1-methylethenyl)cyclohex-2-enecarbonitrile (**33**),[14] (*E*)-4,8-dimethylnona-3,7-dienenitrile (**49**),[27] (*Z*)-4,8-dimethylnona-3,7-dienenitrile (**51**),[28] diphenylacetonitrile (**53**),[14] phenylacetonitrile (**59**),[24] 2-(4-isobutylphenyl)propiononitrile (**61**),[14] and 2-(6-methoxynaphthalen-2-yl)propiononitrile (**63**)[2b] were identified by comparison of their spectroscopic behaviors with those described in the references or with authentic samples. The other products were confirmed by spectroscopic and elemental analyses as shown below.

Cholestane-3-carbonitrile (3): purified by column chromatography (benzene–hexane, 1:1) to give a white solid, which was an epimeric mixture (α:β = 6:4) in its ^{1}H NMR spectrum. Recrystallization from a MeOH–acetone mixture gave the α-isomer: mp 163–166 °C (lit.[3] mp 166–168 °C).

17β-(Methoxymethoxy)androstane-3-carbonitrile (5): purified by column chromtography (benzene–hexane, 1:1) to give a white solid, which is an epimeric mixture (α:β = 7:3); ^{1}H NMR δ 2.40 (β-isomer) and 2.90 (α-isomer) (1 H, each br). Recrystallization from EtOH gave the α-isomer: mp 132–134 °C; IR (Nujol) 2240 cm^{-1}; MS, m/z 345 (M^+). Anal. Calcd for $C_{22}H_{35}NO_2$: C, 76.47; H, 10.21; N, 4.05. Found: C, 76.69; H, 10.21; N, 4.08.

17β-Hydroxyandrostane-3-carbonitrile (7): purified by column chromatography (EtOAc–hexane, 1:1) to give a white solid, which is an epimeric mixture (α:β = 6:4) in its ^{1}H NMR spectrum. Recrystallization from MeOH gave the α-isomer: mp 229–230 °C (lit.[6] mp 216–217 °C).

Cyclohexadec-5-enecarbonitrile (11): purified by column chromatography (benzene–hexane, 1:1) to give a colorless oil; bp 156 °C (2 Torr); IR (film) 2240 cm^{-1}; ^{1}H NMR δ 1.1–1.7 (22 H, m), 2.2 (4 H, br s), 2.5 (1 H, m), 5.3 (2 H, m); MS, m/z 247 (M^+); HRMS calcd for $C_{17}H_{29}N$ MW 247.2298, found 247.2299 (M^+). Anal. Calcd for $C_{17}H_{29}N$: C, 82.85; H, 11.82; N, 5.66. Found: C, 82.51; H, 11.97; N, 5.72.

Ethyl 4-cyanopentanoate (15): purified by column chromatography (benzene) to give an oil; bp 110 °C (5 Torr) (Kugelrohr); IR (film) 2240, 1730 cm^{-1}; ^{1}H NMR δ 1.23 (3 H, t, J = 7 Hz), 1.30 (3 H, d, J = 7 Hz), 1.85 (2 H, m), 2.47 (2 H, m), 2.73 (1 H, m); MS, 155 (M^+); HRMS calcd for $C_8H_{13}NO_2$ MW 155.0946, found 155.0946 (M^+). Anal. Calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 61.97; H, 8.45; N, 8.94.

***N*-[(Vinyloxy)carbonyl]piperidine-4-carbonitrile (19)**: purified by column chromatography (EtOAc–benzene, 1:1) to give

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(25) Knabe, J.; Reischig, D. *Arch. Pharm. (Weinheim, Ger.)* **1984**, *317*, 353.
(26) Honkanen, E.; Pippuri, A.; Kairisalo, P.; Nore, P.; Karppanen, H.; Paakkari, I. *J. Med. Chem.* **1983**, *26*, 1433.
(27) Hoye, T. R.; Karth, M. J. *J. Org. Chem.* **1978**, *43*, 3693.
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a colorless oil; bp 140 °C (0.4 Torr) (Kugelrohr); IR (film) 2245, 1710 cm^{-1}; ^1H NMR δ 1.85 (4 H, m), 2.83 (1 H, m), 3.5 and 3.66 (each 2 H, each m), 4.44 (1 H, br d, J = 6 Hz), 4.75 (1 H, br d, J = 14 Hz), 7.12 (1 H, dd, J = 14, 6 Hz); MS, m/z 180 (M^+); HRMS calcd for $C_9H_{12}N_2O_2$ MW 180.0898, found 180.0899 (M^+). Anal. Calcd for $C_9H_{12}N_2O_2$: C, 59.98; H, 6.71; N, 15.55. Found: C, 60.02; H, 6.88; N, 15.32.

***N*-Tosylpiperidine-4-carbonitrile (21)**: purified by column chromatography (EtOAc–benzene, 1:1) to give a solid, which was recrystallized from a mixture of EtOAc–hexane; mp 141–143 °C (colorless needles); IR (Nujol) 2245, 1320, 1150 cm^{-1}; ^1H NMR δ 1.95 (4 H, m), 2.42 (3 H, s), 2.7 (1 H, m), 3.08 (4 H, m), 7.31 and 7.62 (each 2 H, each d, J = 8 Hz). Anal. Calcd for $C_{13}H_{16}N_2O_2S$: C, 59.06; H, 6.10; N, 10.61. Found: C, 59.19; H, 6.08; N, 10.57.

8-Methoxy-1,2,3,4-tetrahydronaphthalene-2-carbonitrile (23): purified by column chromatography (EtOAc–benzene, 1:10) to give a solid, which was recrystallized from a mixture of benzene-hexane; mp 79-81 °C (colorless needles); IR (Nujol) 2230 cm^{-1}; ^1H NMR δ 2.1 (2 H, m), 2.9 (5 H, m), 3.8 (3 H, s), 6.65 (1 H, d, J = 7 Hz), 6.70 (1 H, d, J = 7 Hz), 7.1 (1 H, t, J = 7 Hz). Anal. Calcd for $C_{12}H_{13}NO$: C, 76.97; H, 7.00; N, 7.48. Found: C, 77.12; H, 7.03; N, 7.45.

4-(2,6,6-Trimethylcyclohex-2-en-1-yl)but-3-ene-2-carbonitrile (29): purified by column chromatography (benzene–hexane, 1:1) to give a colorless oil; bp 130 °C (0.6 Torr) (Kugelrohr); IR (film) 2245 cm^{-1}; ^1H NMR δ 0.80 (3 H, s), 0.87 (3 H, s), 1.38 (3 H, d, J = 7 Hz), 1.57 (3 H, s), 2.05 (3 H, m), 3.29 (1 H, q, J = 7 Hz), 5.2–5.7 (3 H, m); MS, m/z 203 (M^+); HRMS calcd for $C_{14}H_{21}N$ MW 203.1673, found 203.1684 (M^+). Anal. Calcd for $C_{14}H_{21}N$: C, 82.70; H, 10.41; N, 6.89. Found: C, 82.78; H, 10.46; N, 6.80.

4-(1-Methylethenyl)cyclohex-1-enecarbonitrile (35): purified by column chromatography (benzene–hexane, 1:1) to give a colorless oil; bp 110 °C (0.7 Torr) (Kugelrohr); IR (film) 2240 cm^{-1}; ^1H NMR δ 1.4–1.7 (2 H, m), 1.71 (3 H, s), 1.8–2.2 (5 H, m), 2.98 (2 H, s), 4.68 and 4.72 (each 1 H, each s), 5.78 (1 H, br s); MS, m/z 161 (M^+); HRMS calcd for $C_{11}H_{15}N$ MW 161.1204, found 161.1204 (M^+). Anal. Calcd for $C_{11}H_{15}N$: C, 81.93; H, 9.38; N, 8.69. Found: C, 81.87; H, 9.40; N, 8.65.

4,8,12,16-Tetramethylheptadeca-2,7,11,15-tetraenenitrile (37): purified by column chromatography (benzene–hexane, 1:1) to give a colorless oil; IR (film) 2235 cm^{-1}; ^1H NMR δ 1.58, 1.66 and 1.73 (15 H, each br s), 2.0 (12 H, br s), 3.0 (1 H, d, J = 7.2 Hz), 5.1 (4 H, m); MS, m/z 299 (M^+); HRMS calcd for $C_{21}H_{33}N$ MW 299.2611, found 299.2595 (M^+).

Oct-3-yne-2-carbonitrile (39): purified by column chromatography (benzene–hexane, 1:1) to give a colorless oil; IR (film) 2250 cm^{-1}; ^1H NMR δ 0.87 (3 H, t, J = 8 Hz), 1.35 (4 H, m), 1.51 (3 H, d, J = 7 Hz), 2.36 (2 H, m), 3.50 (1 H, m); MS, m/z 136 (M^+ + 1); HRMS calcd for $C_9H_{14}N$ MW 136.1126, found 136.1148 (M^+ + 1).

4-Phenylbut-3-yne-2-carbonitrile (41): purified by column chromatography (benzene–hexane, 1:1) to give a colorless oil; IR (film) 2240 cm^{-1}; ^1H NMR δ 1.69 (3 H, d, J = 7 Hz), 3.81 (1 H, q, J = 7 Hz), 7.4 (5 H, m); MS, m/z 155 (M^+); HRMS calcd for $C_{11}H_9N$ MW 155.0734, found 155.0739 (M^+).

3-Octynenitrile (43): purified by column chromatography (benzene–hexane, 1:1) to give a colorless oil; IR (film) 2300, 2250 cm^{-1}; ^1H NMR δ 0.87 (3 H, t, J = 7 Hz), 1.89 (4 H, m), 2.14 (2 H, m), 3.28 (2 H, br s); MS, m/z 122 (M^+ + 1); HRMS calcd for $C_8H_{12}N$ MW 122.0968, found 122.0961 (M^+ + 1).

2-(Pyridin-2-yl)propiononitrile (55): purified by column chromatography (benzene) to give a colorless oil; IR (film) 2250 cm^{-1}; ^1H NMR δ 1.67 (3 H, d, J = 6.5 Hz), 4.03 (1 H, q, J = 6.5 Hz), 7.2-7.8 (3 H, m), 8.58 (1 H, br s). Anal. Calcd for C_7H_7NO: C, 72.70; H, 6.10; N, 21.20. Found: C, 72.86; H, 6.25; N, 21.47.

1-Benzoyl-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole-5-carbonitrile (57): purified by column chromatography (EtOAc–benzene, 1:10) to give a solid, which was recrystallized from EtOAc; mp 150–151 °C; IR (Nujol) 2240, 1620 cm^{-1}; ^1H NMR δ 3.22 (1 H, m), 3.61 (1 H, m), 3.39 (1 H, m), 4.30 (1 H, br m), 7.0–7.6 (8 H, m); MS, m/z 288 (M^+); HRMS calcd for $C_{19}H_{16}N_2O$ MW 288.1261, found 288.1258 (M^+). Anal. Calcd for $C_{19}H_{16}N_2O$: C, 79.14; H, 5.59; N, 9.72. Found: C, 79.05; H, 5.61; N, 9.63.

1-(2′,3′-*O*-Isopropylidene-5′-trityl-D-ribofuranosyl)-propan-2-one (24). Dimethyl (2-oxopropyl)phosphonate (3.2 g, 20 mM) was added to a suspension of 50% NaH (0.96 g, 20 mM) in dimethoxyethane (DME) (60 mL) at room temperature. After the reaction mixture was stirred for 25 min, a solution of 2,3-isopropylidene-5-*O*-trityl-D-ribofuranose[29] (8.6 g, 20 mM) in DME (40 mL) was added and the mixture was stirred for 2 h. The reaction mixture was quenched by the addition of H_2O (20 mL) and extracted with ether (100 mL × 2). The extract was dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography (benzene–hexane, 1:1) to give **24** (8.25 g, 87%) as a colorless syrup: IR (film) 1710 cm^{-1}; ^1H NMR δ 1.29, 1.46, and 1.51 (6 H, s), 2.18 and 2.20 (3 H, s), 2.74 and 2.87 (2 H, d, J = 5.5 Hz), 3.18 (2 H, m), 4.1–4.8 (4 H, m), 7.2–7.6 (15 H, m); MS, m/z 472 (M^+); HRMS calcd for $C_{30}H_{32}O_5$ MW 472.2248, found 472.2257 (M^+).

1-(2′,3′-*O*-Isopropylidene-5′-*O*-trityl-D-ribofuranosyl)-propane-2-carbonitrile (25). The reaction mixture obtained by the general procedure from **24** (236 mg, 0.5 mM) was quenched by the addition of SiO_2 (5 g), and the solvent was removed under reduced pressure. The residual SiO_2 was submitted to column chromatography (EtOAc–benzene, 1:10) to give **25** (147 mg, 61%) as a colorless syrup: IR (film) 2240 cm^{-1}; ^1H NMR δ 1.5 (9 H, m), 2.1 (2 H, m), 3.0 (1 H, m), 3.3 (2 H, m), 4.2–4.9 (4 H, m), 7.4–7.6 (15 H, m); MS, m/z 483 (M^+); HRMS calcd for $C_{31}H_{33}NO_4$ MW 483.2407, found 483.2418 (M^+).

3,7,11,15-Tetramethylhexadeca-2,6,10,14-tetraenal (36). Geranyllinalool (2.9 g, 10 mM) was added to a suspension of pyridinium chlorochromate (PCC)[19] (8.6 g, 40 mM) in CH_2Cl_2 (10 mL) with stirring. After the mixture was stirred for 22 h, H_2O (300 mL) was added and the mixture was extracted with ether (100 mL × 5). The extracts were washed successively with 5% NaOH (100 mL), H_2O (100 mL), and 10% HCl (100 mL), followed by a saturated $NaHCO_3$ solution, and dried ($MgSO_4$). After removal of the solvent, the residue was purified by column chromatography (EtOAc–benzene, 1:1) to give **36**[30] (2.18 g, 75%) as a colorless oil, which was a mixture of *E* and *Z* forms, *E*:*Z* = 2:1, from the ^1H NMR spectrum.

4-Hydroxybenzonitrile (45). The crude product obtained by the general procedure from diethyl 1-cyano-4-oxocyclohexa-2,5-dienyl phosphate[9a] (119 mg, 0.44 mM) was purified by column chromatography (EtOAc–benzene, 1:3) to give **45** (43 mg, 82%) as colorless crystals, whose IR spectrum was identical with that of an authentic sample.[9a]

3,7,11,15-Tetramethyl-14,15-epoxyhexadeca-2,6,10-trienal (46). According to the method for the preparation of 10,11-epoxyfarnesol,[20] 3,7,11,15-tetramethylhexadeca-2,6,10,14-tetraenyl acetate (6.27 g, 18.9 mM), prepared according to the method of Nazarov,[31] was derived to 3,7,11,15-tetramethyl-14,15-epoxyhexadeca-2,6,10-trienol (2.58 g, 45%). This was dissolved in petroleum ether (100 mL), MnO_2 (11.6 g, 130 mM) was added, and the suspended mixture was vigorously stirred for 24 h. MnO_2 was filtered off through Celite, and the filtrate was condensed to give a residue. This was purified by column chromatography (EtOAc–benzene, 1:10) to give **46** (1.79 g, 31%) as a colorless oil, which was a mixture of *E* and *Z* forms, *E*:*Z* = 7:3; IR (film) 1660 cm^{-1}; ^1H NMR δ 1.24 (3 H, br s), 1.28 (3 H, s), 2.68 (1 H, m), 5.1 (2 H, m), 5.86 (1 H, d, J = 7 Hz), 9.88 and 9.97 (1 H, each d, J = 7 Hz); MS, m/z 304 (M^+); HRMS calcd for $C_{20}H_{32}O_2$ MW 304.2436, found 304.2400 (M^+).

4,8,12,16-Tetramethyl-15,16-epoxyheptadeca-3,7,11-trienenitrile (47). To a solution of crude product obtained by the general procedure from **46** (144 mg, 0.5 mM) in $CHCl_3$ (5 mL) was added Et_3N (0.1 mL, 1.5 mM), and the mixture was stirred at room temperature for 10 min. The $CHCl_3$ solution was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (benzene–hexane, 1:1) to give **47** (75 mg, 54%) as a colorless oil: IR (film) 2250 cm^{-1}; ^1H NMR δ 1.23 (3 H, br s), 1.27 (3 H, s), 2.68 (1 H, m), 3.0 (2 H, d, J =

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7 Hz), 5.1 (3 H, m); MS, m/z 315 (M^+); HRMS calcd for $C_{21}H_{33}NO$ MW 315.2559, found 315.2558 (M^+).

Acknowledgment. We are grateful to Professor Lewis N. Mander, Australian National University, for supplying us with a sample of 5-methoxy-2-tetralone. This work was supported in part by a Grant-in Aid for the Encouragement of Young Scientists, Japan (to R.Y.).

Supplementary Material Available: Spectral data for compounds **3**, **9**, **17**, **31**, **36**, **49**, and **51** and copies of ^1H NMR and IR spectra of compounds **25**, **37**, **39**, **41**, **43**, and **47** and ^1H NMR spectra of compounds **24** and **46** (15 pages). Ordering information is given on any current masthead page.

Alkyl Substituent Effects on the Neutral Hydrolysis of 1-Acyl-(3-substituted)-1,2,4-triazoles in Highly Aqueous Reaction Media. The Importance of Solvation

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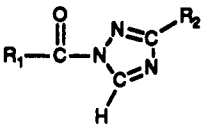
Received June 1, 1990

The importance of solvation in determining substituent effects of alkyl groups has been assessed in a quantitative study of the medium effects of ethanol and 1-propanol on the neutral hydrolysis of 18 1-acyl-(3-substituted)-1,2,4-triazoles in highly aqueous solutions. The dependence of the pseudo-first-order rate constants for hydrolysis on the molality of added cosolvent is analyzed in terms of pairwise Gibbs function interaction parameters and individual group contributions to the overall medium effect. It is found that the alkyl substituent effects depend on the presence of the cosolvent and that this medium dependence is different for different alkyl groups. In addition, the effect is sensitive to the position of the substituent and the overall hydrophobicity of the substrate. Alkyl substituent effects have also been examined for the acid-catalyzed hydrolysis of a series of 1-acyl-(3-substituted)-1,2,4-triazoles. The solvation dependence of alkyl substituent effects is discussed in terms of changes in hydration of the substrate during the activation process.

Noncovalent intermolecular interactions in highly aqueous solutions between chemically inert cosolvents and reacting substrates can seriously affect rate constants of many types of reactions.[2,3] These medium effects are largely governed by the overlap of hydration shells of both substrate and activated complex with the hydration shell of the cosolvent. In the case of cosolvents containing hydrophobic groups, the magnitude of the solvent effect is often dominated by the change in hydrophobicity of the reacting molecule(s) during the activation process.[4]

Recently we proposed a quantitative treatment for the analysis of medium effects on (in)organic reactions in highly aqueous solvent systems.[5-7] The medium effects were analyzed in terms of pairwise Gibbs energy interaction parameters, which reflect pairwise interactions of both substrate and activated complex with the cosolvent molecule. The theory has been critically tested on a hydrolysis reaction in water in the presence of N-substituted ureas[6] and mono- and polyhydric alcohols.[7] Careful application of additivity schemes[7] allowed a subdivision of medium effects of cosolvents into group contributions to the overall medium effect.

Here, we present a combined quantitative study of substituent effects of alkyl groups[8] and medium effects of ethanol and 1-propanol on the pseudo-first-order rate constants for the pH-independent hydrolysis of 18 1-acyl-(3-substituted)-1,2,4-triazoles (**1a-j**, **2a,b**, **3a-c**, **4a,b**, **5**) in highly aqueous solutions. A large set of substrates was examined in an attempt to subject our quantitative theory to a rigorous test. Furthermore, kinetic medium effects and substituent effects for the water-catalyzed hydrolysis are compared with a relevant set of data for the acid-catalyzed hydrolysis.



1a, R_1 = Me, R_2 = H
b, R_1 = Et, R_2 = H
c, R_1 = *n*-Pr, R_2 = H
d, R_1 = *i*-Pr, R_2 = H
e, R_1 = *i*-Bu, R_2 = H
f, R_1 = *s*-Bu, R_2 = H
g, R_1 = *t*-Bu, R_2 = H
h, R_1 = *n*-Pent, R_2 = H
i, R_1 = 3-Pent, R_2 = H
j, R_1 = Ph, R_2 = H

2a, R_1 = Me, R_2 = *t*-Bu
b, R_1 = Me, R_2 = Cl
3a, R_1 = Et, R_2 = Me
b, R_1 = Et, R_2 = *t*-Bu
c, R_1 = Et, R_2 = Ph
4a, R_1 = *t*-Bu, R_2 = Me
b, R_1 = R_2 = *t*-Bu
5, R_1 = R_2 = Ph

Substituent effects of alkyl groups on rate constants and equilibrium constants in solution have been studied extensively.[9-15] Although it is now generally agreed that

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0022-3263/91/1956-1832$02.50/0