J. Org. Chem. 1982, 47, 3785–3787

C_{10} toward C_{14}, and the intermediate tertiary carbocations are in equilibrium with the corresponding trisubstituted olefins. The interconversion between C_{10}^+, C_9^+, C_8^+, and C_{14}^+ proceeds by 1,2 hydrogen shifts or by a protonation–deprotonation mechanism. The reactions afford the thermodynamically favored products **2** and **4**, both with a 14β-H stereochemistry.[13]

Experimental Section

Isoconessine,[6] di-*N*-cyanoisoconessine,[6] and neoconessine[7] were prepared by the literature procedures. The corresponding polydeuterated species were obtained by using the same methods except that sulfuric acid and acetic acid were replaced by D_2SO_4 and by CH_3COOD, respectively. These reagents were obtained from Merck, Germany.

Tritiated sulfuric acid was prepared by the literature procedure[17] by using oleum 20%. Isoconessine-t_x was obtained from tritiated sulfuric acid and conessine in the same way as the nonlabeled compound.[6]

^1H and ^2H NMR spectra were recorded at 400 and 61.4 MHz, respectively, on a Bruker WM-400 spectrometer. The ^3H NMR spectrum was recorded at Saclay on a Bruker spectrometer operating at 106.7 MHz. The carbon-13 NMR spectra were obtained on a Bruker WM-250 spectrometer. For the spectrum of the deuterated materials simultaneous proton and deuterium decoupling was used without any lock system for field stabilization. During these experiments a delay time of 20 s was employed.

Mass spectra were recorded at Gif on a MS-50 spectrometer. Measurement of the radioactivity was carried out using standard procedures.

Acknowledgment. We thank Dr. L. Pichat, Service des Molécules Marquées, CEN Saclay, for his interest in this work.

Registry No. 1, 546-06-5; **2**, 7348-67-6; **3**, 17942-15-3; **4**, 10106-53-3.

---

[17] Lee, C. C.; Ko, E. C. F. *Can. J. Chem.* **1980**, *58*, 1.

Solvent Nucleophilicity of 2,2,2-Trifluoroethanol–Ethanol Mixtures[1]

Dennis N. Kevill* and Wan Ahmad Kamil

Department of Chemistry, Northern Illinois University, DeKalb, Illinois 60115

Received March 26, 1982

Recently a scale of solvent nucleophilicities (N_{KL}) was developed[2] on the basis of the specific rates of solvolysis of the triethyloxonium ion at 0.0 °C. It was proposed that this scale had an important advantage over a scale based upon an initially neutral substrate such as methyl *p*-toluenesulfonate[3] in that for a series of commonly used aqueous–organic solvents the contribution to the linear free-energy relationship (LFER) which is governed by solvent influence upon the leaving group is reduced by approximately one order of magnitude.[2] Accordingly, errors in either the value chosen to scale the influence of solvent properties upon the initial state to transition-state variation within the leaving group (*m* value) or the *Y* scale used as a measure of these solvent properties (solvent-ionizing power in the case of an initially neutral substrate), as introduced into the two-term (extended) Grunwald–Winstein equation[4] (eq 1), have minimal influence upon the calculated solvent nucleophilicity values (*N*).

Table I. Solvolysis Data for Triethyloxonium Hexafluorophosphate at 0.0 °C and *tert*-Butyldimethylsulfonium Trifluoromethanesulfonate at 50.0 °C in TFE-EtOH Mixtures

%EtOH (v/v)	log $(k/k_0)_{Et_3O^+}$ [a]	Y^+ [b]	N_{KL}
100	0.598	0.196	0.49
90	0.567		
80	0.405	0.061	0.37
70	0.191	−0.020	0.20
60	−0.051	−0.043	−0.03
50	−0.168	−0.126	−0.10
40	−0.421	−0.221	−0.30
30	−0.714	−0.334	−0.53
20	−0.915	−0.406	−0.69
10	−1.173	−0.513	−0.89
0	−2.173	−0.510	−1.89

[a] Decimal logarithm of the specific rate of solvolysis of Et_3O^+ at 0.0 °C relative to the specific rate of solvolysis in 80% aqueous ethanol ($74 \times 10^{-5}\ s^{-1}$). [b] Decimal logarithm of the specific rate of solvolysis of $t\text{-}BuS^+Me_2$ at 50.0 °C relative to the specific rate of solvolysis in 80% aqueous ethanol ($8.9 \times 10^{-6}\ s^{-1}$).

$$\log (k/k_0) = lN + mY \tag{1}$$

The *l* value governing the influence of solvent nucleophilicity on the specific rate of solvolysis (*k*) of a substrate in a given solvent relative to the specific rate of solvolysis in 80% (v/v) aqueous ethanol (k_0) was assigned a value of unity for the triethyloxonium ion, and a scale of Y^+ values based upon the specific rate of solvolysis (*k*) of the *tert*-butyldimethylsulfonium ion[5] relative to its specific rate of solvolysis in 80% (v/v) aqueous ethanol (k_0) was developed (eq 2) for use within eq 1.

$$\log (k/k_0)_{t\text{-}BuS^+Me_2} = Y^+ \tag{2}$$

Ethanol–2,2,2-trifluoroethanol (TFE) mixtures are virtually isodielectric, but the nucleophilicity of ethanol is considerably greater than that of TFE, and the solvent nucleophilicity of the mixtures will vary considerably with composition. Three solvent nucleophilicity values (*N*) for TFE–EtOH mixtures based on methyl *p*-toluenesulfonate and *tert*-butyl chloride solvolysis[6] have recently been supplemented[7] to cover the full range of composition, with *Y* values based on *p,p′*-dichlorobenzhydryl chloride solvolysis[8] being used.

In order to compare *N* values[6,7] with N_{KL} values for TFE–EtOH mixtures, we have measured the specific rates of solvolysis of the triethyloxonium ion and the *tert*-butyldimethylsulfonium ion for those TFE–EtOH compositions for which Kaspi and Rappoport[7] tabulate *N* values.

Swain, Kaiser, and Knee[5] used the chloride gegenion in their solvolysis studies of the *tert*-butyldimethylsulfonium ion. Since it has been shown[9] that, in aprotic solvents such as acetonitrile, chloride ion can promote a bimolecular

---

[1] Abstracted, in part, from the M.S. thesis of W.A.K., Northern Illinois University, May 1981.

[2] Kevill, D. N.; Lin, G. M. L. *J. Am. Chem. Soc.* **1979**, *101*, 3916.

[3] Schadt, F. L.; Bentley, T. W.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1976**, *98*, 7667.

[4] Winstein, S.; Grunwald, E.; Jones, H. W. *J. Am. Chem. Soc.* **1951**, *73*, 2700.

[5] Swain, C. G.; Kaiser, L. E.; Knee, T. E. C. *J. Am. Chem. Soc.* **1958**, *80*, 4092.

[6] da Roza, D. A.; Andrews, L. J.; Keefer, R. M. *J. Am. Chem. Soc.* **1973**, *95*, 7003.

[7] Kaspi, J.; Rappoport, Z. *J. Am. Chem. Soc.* **1980**, *102*, 3829.

[8] Rappoport, Z.; Ben-Yacov, H.; Kaspi, J. *J. Org. Chem.* **1978**, *43*, 3678.

[9] Kevill, D. N.; Dorsey, J. E. *J. Org. Chem.* **1969**, *34*, 1985.

0022-3263/82/1947-3785$01.25/0

Table II. Comparison of log $(k/k_0)_{\mathrm{MeOTs}}$[a,b] and N[a] Values for TFE–EtOH Mixtures at 50.0 °C

% EtOH (v/v)	100	80	70	60	50	40	30	20	10	0
log $(k/k_0)_{\mathrm{MeOTs}}$	−0.53	−0.55	−0.60	−0.68	−0.80	−0.95	−1.11	−1.43	−1.74	−2.54
N	0.09	−0.09	−0.23	−0.42	−0.63	−0.87	−1.13	−1.55	−1.97	−2.74

[a] The k and N values are from ref 7. [b] The k_0 value (22.2×10^{-6} s^{-1}) is from: Robertson, R. E. *Can. J. Chem.* **1953**, *31*, 589.

elimination reaction of *tert*-butyl chloride, we have incorporated instead the weakly basic trifluoromethanesulfonate. In two instances a comparison can be made, at 50.0 °C our specific rate of ethanolysis of 13.9 (±0.4) × 10^{-6} s^{-1} is some 16% lower than the 16.6 × 10^{-6} s^{-1} reported earlier,[5] and our k_0 value of 8.9 (±0.5) × 10^{-6} s^{-1} is some 23% lower than the value of 11.5 × 10^{-6} s^{-1} reported earlier.[5,10]

The experimental results are reported, as log $(k/k_0)_{\mathrm{Et_3O^+}}$ and Y^+ values, in Table I. The k_0 value for $\mathrm{Et_3O^+}$ (74 × 10^{-5} s^{-1}) was reported previously.[2] Table I also contains N_{KL} values calculated, as previously,[2] by using eq 3.

$$N_{\mathrm{KL}} = \log (k/k_0)_{\mathrm{Et_3O^+}} - 0.55Y^+ \qquad (3)$$

The log $(k/k_0)_{t\text{-}\mathrm{BuS^+Me_2}}$ values (Y^+ values) give a good linear correlation (correlation coefficient $r = 0.993$) against the Y values for the TFE–EtOH mixtures[7] but with a slope of −0.237 ± 0.010 (standard error), as opposed to the value of −0.09 found to hold[2,5] for aqueous–ethanol, aqueous–methanol, and aqueous–acetone mixtures.

The similarity in the values for log $(k/k_0)_{\mathrm{Et_3O^+}}$ and N_{KL} reported within Table I illustrates the relatively small corrections that have to be applied for the effect of varying solvent composition upon the development of the incipient diethyl ether molecule at the transition state. By contrast, the development of the incipient *p*-toluenesulfonate anion in methyl *p*-toluenesulfonate solvolyses has, at the higher ethanol content compositions, an appreciable contribution to the LFER, as can be seen by comparing the log $(k/k_0)_{\mathrm{MeOTs}}$ and N values of Table II.

For comparison of the N_{KL} values (based on an ethyl derivative) and the N values[7] (based on a methyl derivative), the N values have been scaled by applying a factor of 0.83 (the l value reported[3] for ethyl *p*-toluenesulfonate). A plot of 0.83 N vs. N_{KL} (Figure 1) gives a reasonably good linear relationship (correlation coefficient $r = 0.988$), with a slope of 1.05 ± 0.06 (standard error), very close to the ideal value of unity, but with an intercept of −0.44 ± 0.04 (standard error), indicating the N_{KL} values to be consistently some 0.4 of a unit more positive than the corresponding 0.83N values. This interrelationship lends further support to the belief that solvent nucleophilicity scales developed by using a positively charged substrate can also be applied to the solvolyses of neutral substrates.[2,11]

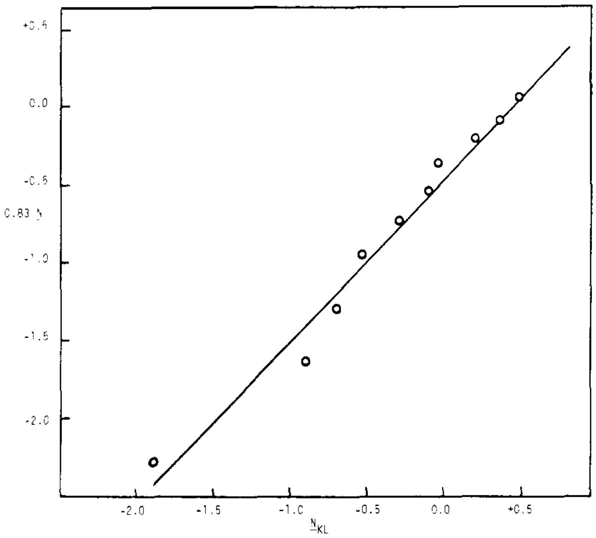


Figure 1. Comparison of N values (from ref 7) with N_{KL} values (this investigation) for 2,2,2-trifluoroethanol–ethanol mixtures.

Experimental Section

NMR spectra were recorded by using a Varian A60A instrument, and elemental analyses were obtained by using a Perkin-Elmer Model 240 elemental analyzer.

***tert*-Butyldimethylsulfonium iodide** was prepared as described previously:[5] NMR ($\mathrm{CD_3CN}$) δ 1.52 (s, 9 H), 2.81 (s, 6 H).

***tert*-Butyldimethylsulfonium trifluoromethanesulfonate** was prepared by dissolving 2.0 g of the iodide in 75 mL of acetonitrile. An equivalent amount of silver trifluoromethanesulfonate (Aldrich) was then added. After filtration from the precipitated silver iodide, the solution was concentrated to 10 mL, and excess cold benzene was added. The precipitated white crystals were removed by filtration, washed with a little benzene, and allowed to dry overnight in a desiccator: decomposition point 173–175 °C; NMR ($\mathrm{CD_3CN}$) δ 1.50 (s, 9 H), 2.71 (s, 6 H). Anal. Calcd for $\mathrm{C_7H_{15}S_2O_3F_3}$: C, 31.35; H, 5.59. Found: C, 31.17; H, 5.59.

Triethyloxonium hexafluorophosphate (Aldrich-Cationics) was used as received.

Solvents. Absolute ethanol was purified as described previously.[12] The 2,2,2-trifluoroethanol (Aldrich Gold Label) was purified by either of two literature methods,[13,14] both of which gave a satisfactory product. Preparation of mixtures was on a volume to volume basis at 25.0 °C.

Rate Measurements. All runs were performed at least in duplicate.

The solvolysis of 0.01 M *tert*-butyldimethylsulfonium trifluoromethanesulfonate was at 50.0 °C (±0.17 °C), and 5.00-mL portions were transferred from 50.0 mL of bulk solution at appropriate time intervals into 20 mL of acetone at 0.0 °C and titrated against a standardized solution of NaOMe in MeOH to a resorcinol blue (Lacmoid) end point. Experimental infinity titers obtained after 10 half-lives were in good agreement (±2%) with calculated values.

The specific rates of solvolysis of the triethyloxonium hexafluorophosphate were determined as previously described for aqueous–organic mixtures,[2] except that portions were removed into 20 mL of acetone at −78 °C rather than into acetone saturated with lithium chloride. Also, the (k/k_0) value for TFE (−2.17) is comparable to that of acetonitrile (−2.70), and, for solvolysis in pure TFE, the salt was added directly rather than as a stock solution in acetonitrile. Also, because of the slow reaction in pure TFE, experimental "infinity titers" were obtained by transferring, at the beginning of the run, a 5.00-mL portion into 10 mL of methanol and allowing the mixture to stand for 7 h before addition of 20 mL of acetone and titration in the usual manner.

---

(10) Consistent with these differences, it is reported in ref 5 that, in 90% (v/v) aqueous acetone, *tert*-butyldimethylsulfonium ion with the weakly basic perchlorate as the gegenion solvolyzed 15% slower than with chloride as the gegenion.

(11) Peterson, P. E.; Vidrine, D. W.; Waller, F. J.; Henrichs, P. M.; Magaha, S.; Stevens, B. *J. Am. Chem. Soc.* **1977**, *99*, 7968.

(12) Lund, H.; Bjerrum, J. *Chem. Ber.* **1931**, *64*, 210.

(13) Shiner, V. J., Jr.; Dowd, W.; Fisher, R. D.; Hartshorn, S. R.; Kessick, M. A.; Milakofsky, L.; Ripp, M. W. *J. Am. Chem. Soc.* **1969**, *91*, 4838.

(14) Rappoport, Z.; Kaspi, J. *J. Am. Chem. Soc.* **1974**, *96*, 4518.

J. Org. Chem. 1982, 47, 3787-3788

Registry No. Triethyloxonium hexafluoxophosphate, 17950-40-2; *tert*-butyldimethylsulfonium trifluoromethanesulfonate, 82510-92-7; *tert*-butyldimethylsulfonium iodide, 918-03-6; silver trifluoromethanesulfonate, 2923-28-6.

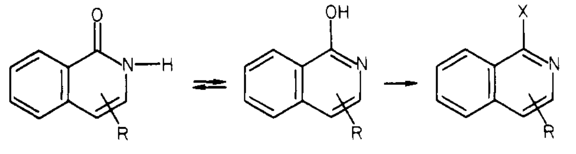
Convenient Preparation of 3-Substituted 1(2*H*)-Isoquinolinones

Graham S. Poindexter

Chemical Research Department, Pharmaceutical Division, Mead Johnson and Company, Evansville, Indiana 47721

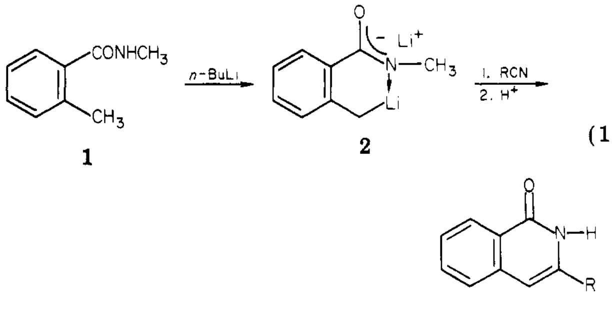
Received March 9, 1982

Isoquinolinones or the tautomeric hydroxyisoquinolines



X = H, halo, alkoxy, amino, etc.

are important synthetic precursors to many biologically active isoquinoline structures. Except for a recent report describing photochemical $S_{RN}1$ reactions between 2-halobenzamides and enolates,[1] efficient methods for their preparation are limited. These include acylation–hydration–cyclization sequences of *o*-toluonitriles,[2] butyl nitrite ring expansions of substituted 1-indanones,[3] and other less general methods.[4] We report an efficient and convenient one-pot procedure for the preparation of 3-substituted 1(2*H*)-isoquinolinones **3** by the reaction of organic nitriles with dilithio anion **2** derived from *N*,2-dimethylbenzamide (**1**, eq 1).

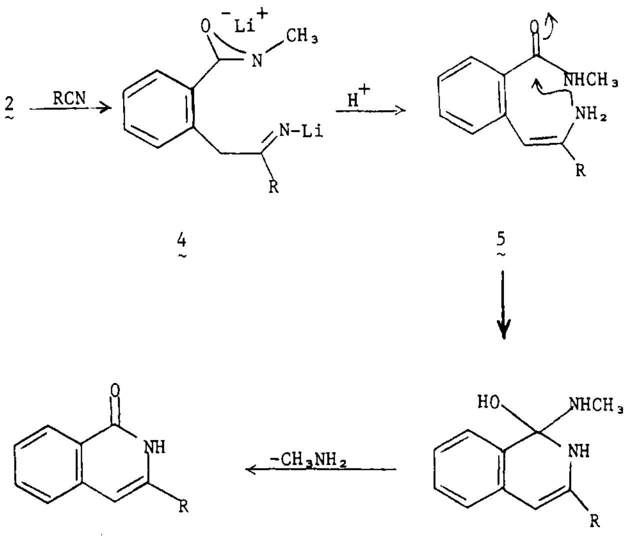


1 2 (1)

3

Hauser has shown that amide **1** can be readily dimetalated by employing 2 equiv of *n*-butyllithium and subsequently reacted with either aldehydes or ketones to furnish various δ-hydroxy amides.[5] Similarly, we have observed that reaction of dilithio anion **2** with organic nitriles yields isoquinolinones **3**. Thus treatment of a tetrahydrofuran solution of amide **1** with 2.1 equiv of *n*-butyllithium at 0 °C resulted in the formation of dianion **2** as evidenced by its orange-red color. Dimetalation was judged complete after 45 min as determined by ^{1}H NMR analysis of a D_2O-quenched aliquot. After the solution cooled to −50 °C and was treated with 1.25 equiv of benzonitrile, the dark solution was warmed to room temperature and quenched with a saturated ammonium chloride solution. Workup afforded an excellent yield of 3-phenyl-1(2*H*)-isoquinolinone (**3c**).[6] The results and yields of this and similar reactions using additional nitriles are summarized in Table I.

Scheme I



4 5

3 6

Addition of either acetonitrile or propionitrile to dianion **2** failed to give any of the desired isoquinolinones **3** (R = CH_3 and C_2H_5) even with the use of tetramethylethylenediamine as a complexing agent. Presumably the acidity of the α-protons of these nitriles renders them susceptible to trans metalation with **2** and subsequent self-condensation.[8] In contrast, use of less acidic, secondary or tertiary, aliphatic nitriles (entries 1 and 2, Table I) resulted in the formation of the desired isoquinolinones **3a** and **3b** in moderate yields of 42% and 48%, respectively. Higher efficiencies were realized by use of aryl and heteroaryl nitriles (entries 3–6) which furnished the respective isoquinolinones **3c–f** in yields ranging from 58% to 87%. However, reaction with either 2- or 3-pyridinenitrile afforded complex mixtures of products presumably via addition to the pyridine ring.

As suggested by the mechanism shown in Scheme I, addition of the nitrile to dianion **2** would yield adduct **4**, which on quenching with ammonium chloride and tautomerization would give enamino amide **5**.[9] Although this intermediate was never isolated, cyclization to **6** would be expected to occur readily followed by loss of methylamine to furnish the observed products **3**. Cyclization of such enamines is not limited to *o*-amides. After metalation of

---

[1] Beugelmans, R.; Bois-Choussy, M. *Synthesis* **1981**, 729.

[2] Boyce, W. T.; Levine, R. *J. Org. Chem.* **1966**, *31*, 3807.

[3] (a) Mariconi, E. J.; Creegan, F. J. *J. Org. Chem.* **1966**, *31*, 2090. (b) Schnur, R. C.; Howard, H. R. *Tetrahedron Lett.* **1981**, *22*, 2843.

[4] (a) Belgaonkar, V. H.; Usgaonkar, R. N. *Indian J. Chem.* **1975**, *13*, 336. (b) Van Der Goot, H.; Oostendorp, J. G.; Nauta, W. T. *Eur. J. Med. Chem.—Chim. Ther.* **1975**, *10*, 603. (c) Wilson, J. W.; Anderson, E. L.; Ullyot, G. E. *J. Org. Chem.* **1951**, *16*, 800. (d) Cologne, J.; Weinstein, G. *Bull. Soc. Chim. Fr.* **1952**, 462. (e) Modi, A. R.; Usgaonkar, R. N. *Cur. Sci.* **1976**, *45*, 832. (f) Kasahara, A. Japanese Kokai, 76143672, 1976; *Chem. Abstr.* **1977**, *87*, 39289. (g) Mikol, G. I.; Boyer, J. H. *J. Org. Chem.* **1972**, *37*, 724. (h) Eloy, F.; Deryckere, A. *Helv. Chem. Acta* **1969**, *52*, 1755.

[5] (a) Mao, C.-L.; Barnish, I. T.; Hauser, C. R. *J. Heterocycl. Chem.* **1969**, *6*, 83. (b) Vaulx, R. L.; Puterbaugh, W. H.; Hauser, C. R. *J. Org. Chem.* **1964**, *29*, 3514.

[6] Dimetalation of 2-methylbenzoic acid according to the method of Creger[7] followed by reaction with benzonitrile also furnished isoquinolinone **3c**, albeit in much lower yield.

[7] Creger, P. L. *J. Am. Chem. Soc.* **1970**, *92*, 1396.

[8] Wakefield, B. J. "The Chemistry of Organolithium Compounds"; Pergamon Press: Oxford, England, 1974; pp 116–121.

[9] A referee has suggested enamine **5** to probably exist as the tautomeric imine on the basis of earlier results of Ahlbrecht (Ahlbrecht, H.; Rauchschwalbe, G. *Tetrahedron Lett.* **1971**, 4897).