1-(5-Methyl-2-thiazolyl)ethyl Chloride (18).—This chloride was prepared from alcohol **16** using phosphorus pentachloride to give a 67% yield of crude **18**. This was further purified by chromatography on silica gel to give 54% colorless chloride **18**: nmr ($CDCl_3$) δ 1.91 (d, 3, J_{CH,CH_3} = 7.0 Hz, $CHCH_3$), 2.41 (d, 3, $J_{4\text{-}H,5\ CH_3}$ = 1.1 Hz, 5-CH_3), 5.27 (q, 1, J_{CH,CH_3} = 7.0 Hz, $CHCH_3$), 7.33 (q, 1, $J_{4\text{-}H,5\text{-}CH_3}$ = 1.1 Hz, 4-H).

Anal. Calcd for C_6H_8ClNS: C, 44.58; H, 4.99; Cl, 21.93; N, 8.66; S, 19.84. Found: C, 44.43; H, 5.01; Cl, 21.94; N, 8.73; S, 19.74.

5-Methylthiothiazole (19).—Methyl mercaptan (27.7 ml, 0.5 mol) was added to 1 equiv of sodium methoxide in 175 ml of methanol at 0°. 5-Bromothiazole (32.8 g, 0.2 mol)[24] and 0.01 g of potassium iodide were added, and the solution was heated under reflux for 5 hr. The resulting clear solution and white precipitate wee taken up in 100 ml of water. The aqueous solution was then extracted with 3 × 200 ml of ether. The combined ether layers were dried ($MgSO_4$) and concentrated to give an oil which was distilled under reduced pressure to give 6.85 g (26%) of pure 5-methylthiothiazole (**19**): bp 132–134° (50 mm); nmr ($CDCl_3$) δ 2.47 (s, 3, SCH_3), 7.75 (s, 1, 4-H), 8.82 (s, 1, 2-H).

Anal. Calcd for $C_4H_5NS_2$: C, 36.61; H, 3.85; S, 48.93. Found: C, 36.76; H, 4.07; S, 49.10.

(24) H. C. Beyerman, P. H. Berben, and J. S. Bontekoe, *Recl. Trav. Chim., Pays-Bas*, **73**, 325 (1954).

1-(5-Methylthio-2-thiazolyl)ethanol (20).—Metalation of **18** with butyllithium at −80° and addition of a threefold excess of acetaldehyde afforded crude **20**. Distillation afforded pure **20** in 79% yield: bp 106.0–106.5° (0.2 mm); nmr ($CDCl_3$) δ 1.58 (d, 3, J = 6.2 Hz, $CHCH_3$), 2.45 (s, 3, SCH_3), 5.02 (s, 1, OH), 5.02 (q, 1, J = 6.2 Hz, $CHCH_3$), 7.42 (s, 1, 4-H).

Anal. Calcd for $C_6H_9NOS_2$: C, 41.12; H, 5.18; S, 36.59. Found: C, 41.03; H, 5.09; S, 36.32.

1-(5-Methylthio-2-thiazolyl)ethyl Chloride (21).—Treatment of **20** with phosphorus pentachloride in methylene chloride and isolation gave **21** in 96% yield as a light yellow oil. Further purification to obtain a sample for kinetic studies was accomplished by chromatography on silica gel: nmr ($CDCl_3$) δ 1.92 (d, 3, J = 6.7 Hz, $CHCH_3$), 2.48 (s, 3, SCH_3), 5.25 (q, 1, J = 6.7 Hz, $CHCH_3$), 7.53 (s, 1, 4-H).

Kinetic Procedures.—Kinetic procedures have been reported previously.[3]

Registry No.—**1**, 40982-18-1; **2**, 40982-19-2; **5**, 20155-81-1; **5** lithium salt, 40982-21-6; **6**, 40982-22-7; **7**, 40982-23-8; **8**, 5053-24-7; **9**, 40982-25-0; **9** lithium salt, 40982-26-1; **10**, 40982-27-2; **11**, 14542-13-3; **12**, 40982-28-3; **13**, 40982-29-4; **14**, 40982-30-7; **15**, 40982-31-8; **16**, 3581-89-3; **17**, 40982-32-9; **18**, 40982-33-0; **19**, 40982-34-1; **20**, 40982-35-2; **21**, 40982-36-3; 2-methylthiazole, 3581-87-1; acetaldehyde, 75-07-0; *p*-nitrobenzoyl chloride, 122-04-3; methyl mercaptan, 74-93-1; 2-chlorothiazole, 3034-52-4; 5-bromothiazole, 3034-55-7.

Transmission of Substituent Effects in Heterocyclic Systems. Rates of Solvolysis of Substituted 1-(4-Thiazolyl)ethyl Chlorides[1,2]

DONALD S. NOYCE* AND STEVEN A. FIKE

Department of Chemistry, University of California, Berkeley, California 94720

Received April 3, 1973

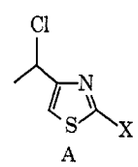
Electrophilic substituent constants, σ_m^+, have been found unacceptable for correlating the relative rates of solvolysis of 1-(2-substituted 4-thiazolyl)ethyl chlorides in 80% ethanol. Likewise, σ_m is also unsatisfactory. These data are discussed in light of several other heterocyclic systems, where similarly poor correlations have been found. It is suggested that judicious comparison of appropriately substituted pyridines and thiazoles provides an excellent working model for treatment of these substituent effects. Limited results on the rates of solvolysis of 1-(4-substituted 2-thiazolyl)ethyl chlorides support these conclusions.

This paper reports an examination of the effectiveness of substituents in promoting the solvolysis reaction of 1-(4-thiazolyl)ethyl chloride. This system is of particular interest as it relates to other five-membered heterocyclic systems and the failure of electrophilic substituent constants to reproduce adequately relative reactivities when the substituent and the reacting side chain are in a nonconjugating, or "pseudo-meta," relationship.

Earlier papers from these laboratories pointed out that Brown's electrophilic substituent constants,[3] *i.e.*, σ_m^+, do not provide a suitable basis for correlation in analogous furans,[4] benzofurans[5] and benzothiophenes.[6] It is only coincidental that σ_m^+ is satisfactory in the case of thiophene derivatives.[7] Further, σ_m^+ likewise fails to correlate substituent effects on the rate of solvolysis of 6-substituted 2-(2-pyridyl)-2-chloropropanes.[8] It was suggested that an independent set of substituent constants is needed for this structural situation.

Imoto and Otsuji, *et al.*,[9,10] have reported the application of the Hammett equation to the rates of saponification of ethyl 2-substituted 4-thiazolylcarboxylates and, with the dissociation constants of the corresponding acids, they obtained generally good correlations with σ_m except for the 2-amino substituent. It is interesting to note that this was the only substituent they studied with a very strong resonance capability.

We have previously examined a series of 1-(5-thiazolyl)ethanol derivatives,[2,11] and observed that σ_p^+ usefully correlates the relative reactivity of this series. The present results of rate measurements on a series of substituted 1-(4-thiazolyl)ethyl chlorides (A) are



A

2, X = H
4, X = CH_3
7, X = C_6H_5
11, X = Br
14, X = SCH_3

(1) Supported in part by a grant from the National Science Foundation, GP-6133X.

(2) Previous paper: D. S. Noyce and S. A. Fike, *J. Org. Chem.*, **38**, 3318 (1973).

(3) H. C. Brown and Y. Okamoto, *J. Amer. Chem. Soc.*, **80**, 4979 (1958).

(4) D. S. Noyce and H. J. Pavez, *J. Org. Chem.*, **37**, 2620, 2623 (1972).

(5) D. S. Noyce and R. W. Nichols, *J. Org. Chem.*, **37**, 4306, 4311 (1972).

(6) D. A. Forsyth and D. S. Noyce, *Tetrahedron Lett.*, 3893 (1972); D. A. Forsyth, Ph.D. dissertation, University of California, Berkeley, 1973.

(7) D. S. Noyce, C. A. Lipinski, and R. W. Nichols, *J. Org. Chem.*, **37**, 2615 (1972).

(8) D. S. Noyce and J. A. Virgilio, *J. Org. Chem.*, **38**, 2660 (1973).

(9) E. Imoto and Y. Otsuji, *Bull. Univ. Osaka Prefect. Ser. A.*, **6**, 115 (1958); *Chem. Abstr.*, **53**, 3027*h* (1959).

(10) Y. Otsuji, T. Kimura, Y. Sugimoto, E. Imoto, Y. Omori, and T. Okawara, *Nippon Kagaku Zasshi*, **80**, 1024, 1297 (1959).

(11) D. S. Noyce and S. A. Fike, *J. Org. Chem.*, **38**, 3316 (1973).

given in Table I. Except for 1-(2-bromo-4-thiazolyl)-ethyl chloride (**11**), every substituent is activating.

TABLE I

RATE CONSTANTS FOR SOLVOLYSIS OF SUBSTITUTED 1-(4-THIAZOLYL)ETHYL CHLORIDES IN 80% ETHANOL

Compd solvolyzed	T, °C	10^5k, sec^{-1}	Rel rate	σ_m^+
2 (H)	45.00	11.1 ± 0.3[a]	1.00	
11 (2-Br)	45.00	1.28 ± 0.03	0.11	0.405
	75.00	24.6 ± 0.4		
4 (2-CH_3)	25.00	9.01 ± 0.08		
	45.00	72.3 ± 1	6.29	−0.066
7 (2-C_6H_5)	45.00	28.0 ± 0.5	2.43	+0.109
	60.00	124 ± 3		
	75.00	425		
14 (2-*S*-CH_3)	25	6.70 ± 0.06		
	45	67.2 ± 1	5.85	+0.158
	60	295 ± 4		

[a] Reported previously.[11]

This clearly reveals that application of σ_m^+ would be unsatisfactory, for, as column 5 of Table I shows, both positive and negative substituent constants are involved. Notable, also, is the strongly activating influence of methyl (**4**). The sixfold rate increase is unusual, and is to be contrasted with the effect of a methyl group introduced in the meta position in benzene derivatives. For benzyl systems $k_{m\text{-Me}}/k_H$ ratios are typically near 2.[12] This activation is also reminiscent of what is seen in the furan series for 1-(5-methyl-3-furyl)ethanol and 1-(4-methyl-2-furyl)ethanol derivatives.[4] In those instances a greater preponderance of a resonance component from the substituent was implicated as being responsible for the observed rate acceleration, both from application of CNDO/2 calculations and from consideration of the treatment of Swain and Lupton[13] in terms of $\mathcal{F}$ and $\mathcal{R}$.

With the recognition that σ_m^+ is an unsatisfactory basis for correlation of the observed sequence of reactivities, we have examined several other alternatives for correlating the relative reactivities. Both σ_m^+ and σ_m are clearly unsatisfactory. Interesting from a pragmatic point of view, σ_p is better. The change in regional charge Δq[14] as evaluated from CNDO/2 calculations represents a distinct improvement. However this approach still appears to underestimate the importance of the resonance component of the total substituent effect. However, highly satisfactory results are obtained, resulting in a very good correlation of the present series with reactivities observed for 6-substituted 2-pyridyl systems by Noyce and Virgilio.[8] The common feature of these two families, with the substituent and reacting side chain flanking the –N= nitrogen, merits comment.

It is constructive to further consider this observed relationship in terms of the balance of field ($\mathcal{F}$) and resonance ($\mathcal{R}$) effects. The Swain and Lupton equation (1) encompasses the earlier treatment of Charton[15]

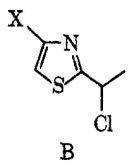
$$\sigma_x = f\mathcal{F} + r\mathcal{R} \quad (1)$$

of substituent influences on dissociation constants of 2-substituted pyridines, which Charton[15] expressed as eq 2.

$$\sigma_T = \lambda\sigma_I + \delta\sigma_R \quad (2)$$

Analysis of the present data in terms of either equation emphasizes the large fractional dependence upon the resonance capabilities of the substituent. In fact the blend of field (inductive) and resonance effects is dominated by resonance effects.

4-Substituted 1-(2-Thiazolyl)ethanol Derivatives (B).—The remaining isomeric family of substituted thiazoles is that represented by structure B. For three



B

15, X = CH_3
17, X = C_6H_5
20, X = H

substituted compounds, **15**, **17**, and **20**, the rates of reaction are given in Table II. Again, the striking

TABLE II

RATE CONSTANTS FOR THE SOLVOLYSIS OF 4-SUBSTITUTED 1-(2-THIAZOLYL)ETHYL CHLORIDES IN 80% ETHANOL

Compd solvolyzed	T, °C	10^5k, sec^{-1}	Rel rate
1-(2-Thiazolyl)ethyl Chloride (**20**)	45.00	0.464[a]	1.00
1-(4-Methyl-2-thiazolyl-ethyl Chloride (**15**)	45.00	5.15 ± 0.2	11.1
	60.00	24.4 ± 1	
	75.00	99.3 ± 3	
1-(4-Phenyl-2-thiazolyl)-ethyl Chloride (**17**)	45.00	1.54 ± 0.05	3.3
	75.00	37.9 ± 0.6	
1-(4,5-Dimethyl-2-thiazolyl)ethyl Chloride (**19**)	25.00	68 ± 3	
	45.00	593	1275

[a] From ref 11.

activation by methyl (k_{15}/k_{20} = 11) is to be noted; it indicates a larger dependence upon a resonance component of the total substituent effect than is incorporated in σ_m^+. Further, phenyl (**17**) as a substituent also accelerates the rate of solvolysis. Thus, the results for this very limited set of compounds suggest that the conclusions reached above are also applicable to series B.

Experimental Section[16]

1-(4-Thiazolyl)ethanol (**1**) and **1-(4-Thiazolyl)ethyl chloride** (**2**) have been reported.[11]

1-(2-Methyl-4-thiazolyl)ethanol (**3**).—2-Methyl-4-formylthiazole was prepared by the method of Baganz and Ruger,[17] mp 56–57° (lit.[17] mp 57°), and treated with methylmagnesium bromide to afford alcohol **3** in 78% yield: bp 73–74° (2.0 mm); nmr ($CDCl_3$) δ 1.53 (d, 3, *J* = 6.3 Hz, $CHCH_3$), 2.65 (s, 3, 2-CH_3), 4.40 (s, 1, OH), 4.95 (q, 1, *J* = 6.3 Hz, $CHCH_3$), 6.95 (s, 1, 5-H).

Anal. Calcd for C_6H_9NOS: C, 50.32; H, 6.34; N, 9.78; S, 22.39. Found: C, 50.57; H, 6.49; N, 9.59; S, 22.18.

(12) Exemplary are the following: cumyl chlorides, 2.0, 2.28 [Y. Okamoto, T. Inukai, and H. C. Brown, *J. Amer. Chem. Soc.*, **80**, 4972 (1968)]; benzhydryl chlorides, 2.1 [J. F. Norris and J. T. Blake, *ibid.*, **50**, 1808 (1928)]; benzyl tosylates 2.65 [A. Streitwieser, *et al.*, *ibid.*, **92**, 5141 (1970)].

(13) C. G. Swain and E. C. Lupton, Jr., *J. Amer. Chem. Soc.*, **90**, 4328 (1968).

(14) D. S. Noyce and R. W. Nichols, *Tetrahedron Lett.*, 3889 (1972).

(15) M. Charton, *J. Amer. Soc.*, **86**, 2033 (1964).

(16) Melting points and boiling points are uncorrected. Routine infrared spectra were recorded using a Perkin-Elmer Infracord Model 137. Nmr spectra were obtained using a Varian Associates Model T-60 spectrometer. Elemental analyses were determined by the Chemical Analytical Services Laboratory, College of Chemistry, Berkeley, Calif.

(17) H. Baganz and J. Rüger, *Chem. Ber.*, **101**, 3872 (1968).

1-(2-Methyl-4-thiazolyl)ethyl chloride (4) was prepared from alcohol 3 using phosphorus pentachloride. The chloride was not distilled but characterized by nmr and elemental analysis: nmr ($CDCl_3$) δ 1.92 (d, 3, J = 6.6 Hz, $CHCH_3$), 2.73 (s, 3, 2-CH_3), 5.18 (q, 1, J = 6.6 Hz, $CHCH_3$), 7.17 (s, 1, 5-H).

Anal. Calcd for C_6H_8ClNS: C, 44.58; H, 4.99; Cl, 21.93; N, 8.66. Found: C, 44.70; H, 4.90; Cl, 21.92; N, 8.54.

1-(2-Phenyl-4-thiazolyl)ethanol (6).—2-Phenyl-4-formylthiazole (5) was prepared by the procedure of Baganz and Ruger,[17] mp 48.5–49.0° (lit.[17] mp 52°). Treatment of 5 with methylmagnesium bromide afforded alcohol 6 in 92% yield, separated from small amounts of 5 by chromatography on silica gel: nmr ($CDCl_3$) δ 1.57 (d, 3, J = 6.4 Hz, $CHCH_3$), 4.38 (s, 1, OH), 5.03 (q, 1, J = 6.4 Hz, $CHCH_3$), 7.28 (m, 3, *m*- and *p*-phenyl H), 7.80 (m, 3, 5-H and *o*-phenyl H).

Anal. Calcd for $C_{11}H_{11}NOS$: C, 64.36; H, 5.40; N, 6.82; S, 15.62. Found: C, 64.11; H, 5.28; N, 6.64; S, 15.76.

1-(2-Phenyl-4-thiazolyl)ethyl chloride (7) was prepared from alcohol 6 using phosphorus pentachloride: nmr ($CDCl_3$) δ 1.92 (d, 3, J_{CH,CH_3} = 6.8 Hz, $CHCH_3$), 5.25 (q, 1, J_{CH,CH_3} = 6.8 Hz, $CHCH_3$), 7.17 (s, 1, 5-H), 7.33 (m, 3, *m*- and *p*-phenyl H), 7.87 (m, 2, *o*-phenyl H).

Anal. Calcd for $C_{11}H_{10}ClNS$: C, 59.06; H, 4.50; N, 6.26; S, 14.33. Found: C, 58.97; H, 4.52; N, 6.32; S, 14.34.

4-Formylthiazole Ethylene Acetal (8).—A solution of 4-formylthiazole (4.1 g, 0.0363 mol), ethylene glycol (2.21 ml, 0.04 mol), and *p*-toluenesulfonic acid (0.1 g) in 150 ml of benzene was heated with refluxing. Water was removed with the aid of a Dean-Stark trap. After refluxing for 2.5 hr, the solution was washed with 3 × 30 ml of 2 *N* sodium bicarbonate. The benzene solution was dried ($MgSO_4$) and concentrated to give 3.80 g (67%) of a light yellow oil which was distilled to yield the pure acetal 8: bp 115–116° (10 mm); ir (neat) 2920, 1470, 1430, 1385, 1325 cm^{-1}; nmr ($CDCl_3$) δ 4.07 (m, 4, OCH_2CH_2O), 6.03 (s, 1, acetal H), 7.45 (d, 1, $J_{2,5}$ = 2.1 Hz, 5-H), 8.88 (d, 1, $J_{2,5}$ = 2.1 Hz, 2-H).

Anal. Calcd for $C_6H_7NO_2S$: C, 45.85; H, 4.49; S, 20.39. Found: C, 45.88; H, 4.67; S, 20.52.

2-Bromo-4-formylthiazole (9).—To a stirred solution of dry ether (500 ml) at −80° under nitrogen atmosphere was added the acetal 8 (16.3 g, 0.104 mol) in 100 ml of ether. Simultaneously from another dropping funnel, *n*-butyllithium (0.115 mol, 71.3 ml in hexane) was added. After the 0.5-hr addition period, the cream-colored suspension was stirred for 45 min before bromine (0.115 mol, 6.32 ml) was added dropwise over a 2-min period. The Dry Ice–acetone bath was removed, and the light yellow solution was stirred for 1 hr before being quenched with 100 ml of water. The layers were separated, and the aqueous phase was extracted with 3 × 50 ml of ether. The combined ether extracts were dried ($MgSO_4$) and concentrated to yield a yellow oil which had spectral properties representative of the desired aldehyde 9 and its ethylene acetal. This oil and 0.1 g of *p*-toluenesulfonic acid were dissolved in 150 ml of dioxane and 100 ml of water and the solution was stirred at 85° for 16 hr. The resulting light brown solution was evaporated to dryness, and the residue was digested in 400 ml of methylene chloride and washed with 3 × 50 ml of water. The organic layer was dried ($MgSO_4$) and concentrated to give 14.0 g (57%) of light brown crystals which were recrystallized from hexane to yield pure 9: mp 121–123°; nmr ($CDCl_3$) δ 7.10 (s, 1, 5-H), 9.88 (s, 1, CHO).

1-(2-Bromo-4-thiazolyl)ethanol (10).—To a partially dissolved solution of 2-bromo-4-formylthiazole (14.0 g, 0.0729 mol) in 400 ml of dry ether in an ice bath under nitrogen atmosphere was slowly added methylmagnesium bromide (0.071 mol, 24.2 ml of a 2.95 *M* solution in ether). Following the 50-min addition period, the solution was stirred for 30 min before removing the ice bath. After the light tan solution was stirred for an additional 30 min, the solution was quenched with 100 ml of water. The layers were separated and the aqueous phase was extracted with 4 × 50 ml of ether. The aqueous phase was then saturated with ammonium chloride and again extracted with ether (3 × 50 ml). The combined ether were dried ($MgSO_4$) and concentrated to give 12.5 g (83%) of the alcohol 10 and starting material 9 (10% by nmr). The alcohol was purified by elution from a 40-cm column of silica gel with 250 ml of 90% hexane–10% ether: nmr ($CDCl_3$) δ 1.57 (d, 3, J_{CH,CH_3} = 6.6 Hz, $CHCH_3$), 2.90 (s, 1, OH), 4.97 (q, 1, J_{CH,CH_3} = 6.6 Hz, $CHCH_3$), 7.12 (s, 1, 5-H).

1-(2-Bromo-4-thiazolyl)ethyl chloride (11) was prepared from alcohol 10 by treatment with phosphorus pentachloride. Work-up in the usual fashion afforded 79% crude 11 which was further purified by chromatography over silica gel: nmr ($CDCl_3$) δ 1.85 (d, 3, J_{CH,CH_3} = 6.6 Hz, $CHCH_3$), 5.10 (q, 1, J_{CH,CH_3} = 6.6 Hz, $CHCH_3$), 7.22 (s, 1, 5-H).

2-Methylthio-4-formylthiazole (12).—4-Formylthiazole ethylene acetal (8, 10.0 g) was metalated with *n*-butyllithium at −80°. After the 20-min addition period, the light tan solution was stirred for an additional 20 min before the rapid addition of methyl disulfide (twofold excess). During the 10-min period, before the Dry Ice–acetone bath was removed, there was no noticable color change in the reaction. The solution was stirred for an additional 45 min before being quenched with 75 ml of water. The resulting clear layers were separated, and the aqueous phase was extracted with 3 × 30 ml of ether. The combined ether extracts were dried ($MgSO_4$) and evaporated to give a yellow oil.[18]

This crude material and *p*-toluenesulfonic acid (0.1 g) were dissolved in 100 ml of dioxane and 100 ml of water and stirred at 75° for 15 hr. The resulting solution was evaporated to dryness, and the tan solid was digested in 300 ml of methylene chloride and washed with 50 ml of water. The organic phase was dried ($MgSO_4$) and concentrated to give 9.5 g (93%) of yellow crystals having excellent spectral properties. The product was purified by recrystallization from hexane to give white flakes of pure aldehyde 12: mp 74.5–76.0°; nmr ($CDCl_3$) δ 2.75 (s, 3, SCH_3), 8.02 (s, 1, 5-H), 10.0 (s, 1, CHO).

Anal. Calcd for $C_5H_5NOS_2$: C, 37.72; H, 3.16; S, 40.27. Found: C, 37.60; H, 3.25; S, 40.38.

1-(2-Methylthio-4-thiazolyl)ethanol (13).—Treatment of aldehyde 12 with methylmagnesium bromide in ether afforded alcohol 13 in 91% yield, further purified by chromatography on silica gel: nmr ($CDCl_3$) δ 1.53 (d, 3, J_{CH,CH_3} = 6.2 Hz, $CHCH_3$), 2.60 (s, 3, SCH_3), 4.90 (q, 1, J_{CH,CH_3} = 6.2 Hz, $CHCH_3$), 6.97 (s, 1, 5-H).

Anal. Calcd for $C_6H_9NOS_2$: C, 41.12; H, 5.18; S, 36.59. Found: C, 40.90; H, 5.14; S, 36.78.

1-(2-Methylthio-4-thiazolyl)ethyl Chloride (14).—Treatment of alcohol 13 with phosphorus pentachloride in methylene chloride gave chloride 14 in 87% yield: mp 104–105°; nmr ($CDCl_3$) δ 1.85 (d, 3, J = 6.6 Hz, $CHCH_3$), 2.67 (s, 3, 2-SCH_3), 5.13 (q, 1, J = 6.6 Hz, $CHCH_3$), 7.08 (s, 1, 5-H).

Anal. Calcd for $C_6H_8ClNS_2$: C, 37.20; H, 4.16; N, 7.23; S, 33.10. Found: C, 37.22; H, 4.32; N, 7.14; S, 33.22.

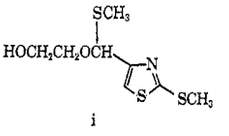
1-(4-Methyl-2-thiazolyl)ethyl Chloride (15).—To a stirred solution of 1-(4-methyl-2-thiazolyl)ethanol[19] (5.45 g, 0.038 mol) in 60 ml of carbon tetrachloride at room temperature under nitrogen, phosphorus pentachloride (7.94 g, 0.038 mol) was slowly added. After the initial reaction subsided, the light yellow solution was stirred for 2 hr. Ether (100 ml) was added, and the mixture was stirred with a slurry of aqueous sodium bicarbonate (5 ml). The organic layer was separated, dried ($MgSO_4$), and distilled to give 3.29 g (54%) of pure chloride 15: bp 71° (4 mm); nmr ($CDCl_3$) δ 1.80 (d, 3, J = 7.0 Hz, $CHCH_3$), 2.28 (d, 3, $J_{5,4-CH_3}$ = 1.0 Hz, 4-CH_3), 5.18 (q, 1, J = 7.0 Hz, $CHCH_3$), 6.75 (q, 1, $J_{5,4-CH_3}$ = 1.0 Hz, 5-H).

Anal. Calcd for C_6H_8ClNS: C, 44.58; H, 4.99; Cl, 21.93; N, 8.66; S, 19.84. Found: C, 44.61; H, 5.14; Cl, 22.12; N, 8.59; S, 19.90.

1-4-Phenyl-2-thiazolyl)ethyl Chloride (17).—1-(4-Phenyl-2-thiazolyl)ethanol (16)[20] was converted to chloride 17, by treatment of 16 with phosphorus pentachloride in methylene chloride: yield 84%; mp 36.5–37.5°; nmr ($CDCl_3$) δ 1.95 (d, 3, J = 6.5 Hz, $CHCH_3$), 5.37 (q, 1, J = 6.5 Hz, $CHCH_3$), 7.35 (m, 3, *m*- and *p*-phenyl H), 7.37 (s, 1, 5-H), 7.85 (m, 2, *o*-phenyl H).

---

(18) This oil had spectral properties indicative of the mixed thioacetal i: nmr ($CDCl_3$) δ 2.38 (s, 3, SCH_3), 2.63 (s, 3, 2-SCH_3), 4.03 (s, 5, OCH_2CH_2OH), 5.90 (s, 1, acetal H), 7.23 (s, 1, 5-H).



i

(19) R. Breslow and E. McNelis, *J. Amer. Chem. Soc.*, **81**, 3080 (1959); improved yields (76%) were obtained using an excess of acetaldehyde.

(20) 1-(4-Phenyl-2-thiazolyl)ethanol is conveniently prepared by metalation of 4-phenylthiazole with butyllithium followed by treatment with acetaldehyde: yield 71%; mp 73–74° (lit. mp 76°) [J. Folin and T. B. Johnson, *J. Amer. Chem. Soc.*, **53**, 1473 (1931)].

Anal. Calcd for $C_{11}H_{19}ClNS$: C, 59.05; H, 4.51; Cl, 15.85; N, 6.26. Found: C, 58.97; H, 4.34; Cl, 16.05; N, 6.37.

1-(4,5-Dimethyl-2-thiazolyl)ethanol (18).—Metalation of 4,5-dimethylthiazole with *n*-butyllithium at −80° was followed by addition of a threefold excess of acetaldehyde. Isolation in the usual fashion afforded **18** in 71% yield: bp 186–188° (150 mm) [lit.[21] bp 120–123° (10 mm)]; mp 53–55°; nmr ($CDCl_3$) δ 1.52 (d, 3, J = 6.5 Hz, $CHCH_3$), 2.22 (s, 3, 4-CH_3), 2.27 (s, 3, 5-CH_3), 5.00 (q, 1, J = 6.5 Hz, $CHCH_3$), 5.70 (s, 1, OH).

Anal. Calcd for $C_7H_{11}NOS$: C, 53.47; H, 7.05; N, 8.91. Found: C, 53.29; H, 7.02; N, 8.85.

1-(4,5-Dimethyl-2-thiazolyl)ethyl chloride (19) was prepared from **18** using phosphorus pentachloride: bp 151–157° (44 mm); nmr ($CDCl_3$) δ 1.88 (d, 3, J = 6.5 Hz, $CHCH_3$), 2.30 (6, 4-CH_3 and 5-CH_3), 5.23 (q, 1, J = 6.5 Hz, $CHCH_3$).

Anal. Calcd for $C_7H_{10}ClNS$: C, 47.86; H, 5.74; Cl, 20.18; N, 7.94; S, 18.25. Found: C, 47.98; H, 5.97; Cl, 20.32; N, 8.08; S, 18.10.

Kinetic procedures have been described previously.[5]

Registry No.—**3**, 41029-77-0; **4**, 41029-78-1; **5**, 20949-81-9; **6**, 41029-80-5; **7**, 41029-81-6; **8**, 41029-82-7; **9**, 5198-80-1; **10**, 41029-84-9; **11**, 41029-85-0; **12**, 41029-86-1; **13**, 41029-87-2; **14**, 41029-88-3; **15**, 41029-89-4; **16**, 41029-90-7; **17**, 41029-91-8; **18**, 7531-72-8; **19**, 41029-93-0; 2-methyl-4-formylthiazole, 20949-84-2; 4-formylthiazole, 3364-80-5; ethylene glycol, 107-21-1; *p*-toluenesulfonic acid, 104-15-4; 1-(4-methyl-2-thiazolyl)ethanol, 7586-99-4; 4,5-dimethylthiazole, 3581-91-7; *n*-butyllithium, 109-72-8; thioacetal i,[18] 41029-97-4.

(21) J. Okimaya, *Nippon Kagaku Zasshi*, **87**, 594 (1966); *Chem. Abstr.*, **65**, 15362*C* (1966).

Syntheses with N-Protected 2-Lithioindoles

RICHARD J. SUNDBERG* AND HENRY F. RUSSELL

Department of Chemistry, University of Virginia, Charlottesville, Virginia 22901

Received April 18, 1973

A series of potential N-protecting groups which would permit syntheses *via* N-protected 2-lithioindoles has been investigated. These include the methoxymethyl, benzyloxymethyl, benzyl, benzenesulfonyl, trimethylsilyl, and *tert*-butyldimethylsilyl groups. The methoxymethyl and benzenesulfonyl derivatives of indole have been shown to be satisfactorily lithiated and to give addition reactions with typical carbonyl and cyano compounds. The benzenesulfonyl group has a major advantage over the methoxymethyl group for subsequent removal. A number of new 2-acylindoles and 2-indolylcarbinols prepared by these reactions are described. Certain competing reactions leading to by-products have also been detected and are described.

It was demonstrated some years ago[1] that 1-methylindole could be efficiently converted to the 2-lithio derivative by lithiation with *n*-butyllithium. Although there has subsequently been some use of this reaction in synthetic work,[2-4] the utility of this particular lithium derivative is restricted to *N*-alkylindoles, since there is no suitable means for subsequently dealkylating the reaction products. Since 2-lithioindoles could provide a quite general synthetic route to 2-substituted indoles, we have undertaken efforts to develop a procedure for lithiation of indoles substituted by a group which could subsequently be removed under relatively mild conditions. We report here our examination of the methoxymethyl, benzyloxymethyl, benzyl, benzenesulfonyl, trimethylsilyl, and *tert*-butyldimethylsilyl groups for this purpose.[5]

Synthesis of N-Protected Indoles.—The data of Cardillo, *et al.*, indicate that syntheses of 1-alkylated indole could be expected to proceed very efficiently in dipolar aprotic solvents.[6] We found it convenient to effect the alkylations in dimethyl sulfoxide. The sodium salt of dimethyl sulfoxide was generated in the usual way,[7] and indole was then added, forming the sodium salt. The alkylating agent was then added. The yields of **1a**, **1b**, **1c**, and **1d** by this procedure were excellent.[8] Others[9] have recommended hexamethylphosphoramide as a solvent or cosolvent for indole alkylations. The *N*-silyl compounds **1e** and **1f** were prepared in tetrahydrofuran solution because of the reactivity of the silyl chlorides toward dimethyl sulfoxide.

Lithiation.—The extent of lithiation was determined by treating a solution of the N-substituted indole in ether, THF, or tetramethylethylenediamine (TMEDA) with *tert*-butyllithium, quenching with D_2O, and determination of the extent and location of deuterium incorporation by analysis of the mass spectrum. Details of the mass spectral analysis are given in the Experimental Section. The results are summarized in Table I. Of the systems studied only **1a** and **1d** gave relatively clean-cut 2 deuteration. Only these two systems were, therefore, subjected to study with respect to use as a protecting group in subsequent synthetic transformations.

Our studies have given some insight into the course of the reaction of the other four systems with *tert*-butyllithium, which we will summarize here briefly. Not surprisingly, the benzyl compound **1c** is lithiated competitively at the benzyl methylene group. The mass spectrum of recovered **1c** indicates 55% incorporation of D at that position with only 15% lithiation at

(1) D. A. Shirley and P. A. Roussel, *J. Amer. Chem. Soc.*, **75**, 375 (1953).

(2) F. E. Ziegler and E. B. Spitzner, *J. Amer. Chem. Soc.*, **92**, 3492 (1970).

(3) J. Kebrle and K. Hoffmann, *Gazz. Chim. Ital.*, **93**, 238 (1963).

(4) J. Kebrle, A. Rossi, and K. Hoffmann, *Helv. Chim. Acta*, **42**, 907 (1959).

(5) Some previous work using these or similar groups on indole or related heterocycles follows. (a) Methoxymethyl: M. H. Karger and Y. Mazur, *J. Amer. Chem. Soc.*, **91**, 5663 (1969). (b) Benzyloxymethyl: H. J. Anderson and J. K. Groves, *Tetrahedron Lett.*, 3165 (1971). (c) Arenesulfonyl: R. E. Bowman, D. D. Evans, and P. J. Islip, *Chem. Ind. (London)*, 33 (1971); R. E. Bowman, D. D. Evans, J. Guyett, H. Nagy, J. Weale, D. J. Weyell, and A. C. White, *J. Chem. Soc., Perkin Trans. 1*, 1926 (1972); W. A. Remers, R. H. Roth, G. J. Gibs, and M. J. Weiss, *J. Org. Chem.*, **36**, 1232 (1971); R. E. Bowman, D. D. Evans, J. Guyett, H. Nagy, J. Weale, and D. J. Weyell, *J. Chem. Soc., Perkin Trans. 1*, 438 (1973). (d) Trialkylsilyl (previous preparation of N-silated indole has been recorded but we are not aware of examples where the group has been employed specifically as a protecting group): R. Fessenden and D. F. Crowe, *J. Org. Chem.*, **26**, 4638 (1961).

(6) B. Cardillo, G. Casnati, A. Pochini, and A. Ricca, *Tetrahedron*, **23**, 3771 (1967).

(7) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **84**, 866 (1962); **87**, 1353 (1965).

(8) Excellent results in dimethyl sulfoxide using potassium hydroxide as the base have been reported recently: H. Heaney and S. V. Ley, *J. Chem. Soc., Perkin Trans. 1*, 498 (1973).

(9) (a) G. M. Rubottom and J. C. Chabala, *Synthesis*, 566 (1972); (b) M. G. Reinecke, J. F. Sebastian, H. W. Johnson, and C. Pyun, *J. Org. Chem.*, **37**, 3066 (1972).