iodide (0.90 g, 6.3 mmol) was added dropwise. This was stirred for a further 1 hr, poured into ice–water (100 ml), and extracted with ether (2 × 150 ml). The combined ether extracts were dried ($MgSO_4$) and evaporated under vacuum to give a light yellow oil. Molecular distillation gave 0.98 g (90%) of 2-*tert*-butyl-5-phenylthiadiazole (**23**): ir (NaCl) 1470, 1460, 1430 cm^{-1}; nmr ($CDCl_3$) δ 8.1–7.8 (m, 2), 7.6–7.3 (m, 3), 1.44 (s, 9).

Anal. Calcd for $C_{12}H_{14}N_2S$: C, 66.04; H, 6.47. Found: C, 66.07; H, 6.61.

Attempted Dimerization of 2,4-Dimethylthiazole with Excess Base. *n*-Butyllithium (11.1 ml, 25.0 mmol) in hexane was added dropwise to a stirred solution (N_2) of 2,4-dimethylthiazole (1.12 g, 10.0 mmol) in dry tetrahydrofuran (25 ml) at −78°. The resulting wine-colored reaction mixture was allowed to warm to room temperature and stirred for 8 hr. Quenching with deuterium oxide and extraction with ether followed by molecular distillation gave 0.96 g (84%) of 2-deuteriomethyl-5-deuterio-4-methylthiazole: nmr ($CDCl_3$) δ 6.66 (s, 0.1 H), 2.63 (t, 1:1:1, CH_2D), 2.40 (s, 3).

Formation of Mixed Dimer 24. *n*-Butyllithium (3.2 ml, 7.3 mmol) in hexane was added dropwise to a stirred solution (N_2) of 2,4-dimethylthiazole (0.92 g, 8.1 mmol) in dry tetrahydrofuran (30 ml) at −78°. The resulting wine-colored reaction mixture was stirred for 1 hr at −78° and then a solution of 2-methyl-4-phenylthiazole (1.42 g, 8.1 mmol) in dry tetrahydrofuran (10 ml) was added. This was allowed to warm to room temperature, quenched with ice–water (100 ml) 8 hr later, and extracted with ether (2 × 150 ml). The combined ether extracts were dried ($MgSO_4$) and evaporated under vacuum to give a yellow oil. Molecular distillation at an oil bath temperature of 105° (0.08 Torr) gave dimer **4** (R = CH_3) (36%) and 2-methyl-4-phenylthiazole (79%). Further distillation at an oil-bath temperature of 145–150° (0.08 Torr) gave mixed dimer **24** (19%) as a viscous oil: ir (NaCl) 1635, 1530, 1495, 1450 cm^{-1}; nmr ($CDCl_3$) δ 8.05–7.75 (m, 2), 7.60–7.35 (m, 3), 6.77 (s, 1), 4.33 (AB q, 2), 3.77 (s, 2), 2.43 (s, 3), 1.80 (s, 3).

A repeat experiment using 1.90 equiv of *n*-butyllithium to form the dilithiothiazole, followed by the addition of 2-methyl-4-phenylthiazole and work-up as above, gave the symmetrical dimer **4** (32%) and the mixed dimer **24** (11%) along with starting material (82%).

Acknowledgment. The authors wish to express their gratitude to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Science Foundation for financial support of this work.

Registry No.—**1** (R = CH_3), 541-58-2; **1** (R = C_6H_5), 1826-16-0; **1** (R = *p*-$CH_3OC_6H_4$), 50834-78-1; **4** (R = CH_3), 41898-76-4; **4** (R = C_6H_5), 50834-81-6; **4** (R = *p*-$CH_3OC_6H_4$), 50834-82-7; **5** (X = S), 1456-72-0; **5** (X = O), 4046-03-1; **8**, 50883-40-4; **18** (R = CH_3), 41898-82-2; **18** (R = $CH_2C_6H_5$), 50834-83-8; **19**, 41898-84-4; **20**, 50834-84-9; **23**, 50834-85-0; **24**, 50834-86-1.

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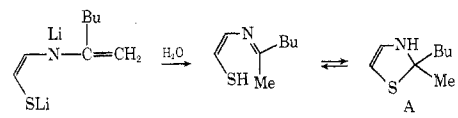
(4) We wish to thank Professor S. Hunig, Wurzburg, for his comments and suggestions pertaining to this scheme.
(5) The possibility of the excess *n*-butyllithium reacting with the proposed ketenimine intermediates **9** or **22** was ruled out on two counts: (a) the high recovery (85%) of starting 2,4-dimethylthiazole and (b) products derived from such a reaction would lead to butylated thiazolines A which were sought but not found.



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The Chemistry of Metalated Heterocycles. The Site of Metalation of 2-Methyl-4-Substituted 1,3-Thiazoles. Electronic, Steric, and Isotope Effects

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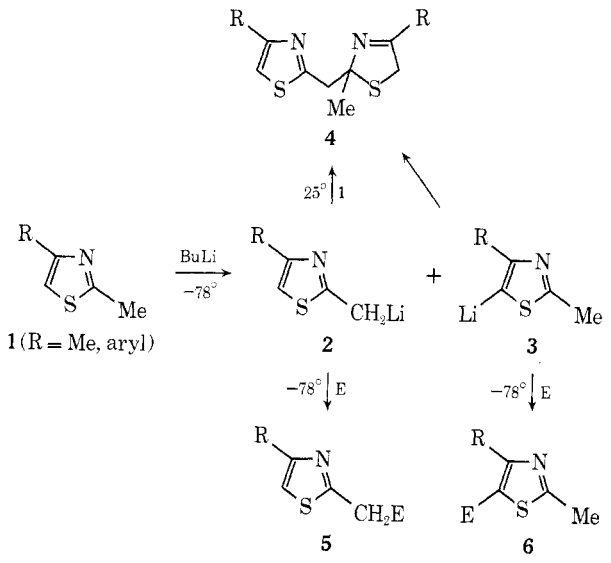
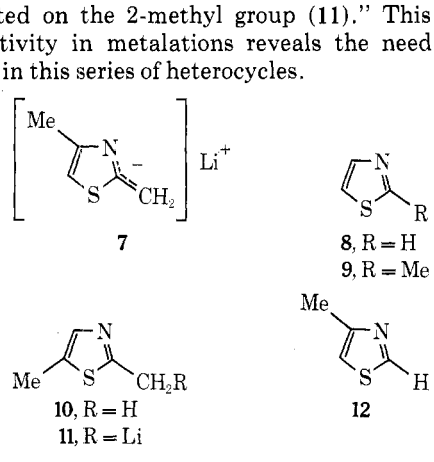
Metalation of 2-methyl-4-aryl-1,3-thiazoles proceeds predominantly at the C-5 position, whereas metalation of the 4-alkyl derivative occurs at the 2-methyl group. It is shown that the anions generated at −78° are the result of the respective kinetic acidities of these positions. Furthermore, at elevated temperatures, the thermodynamic acidities prevail, producing the lithio methyl anions regardless of the nature of the 4 substituent. An apparent primary kinetic isotope effect for the C-5 ring proton has been determined and agrees well with the isotope effect for other heterocyclic protons.

In the previous article[1] dealing with metalation of thiazoles **1** and related compounds, the lithio salt **2** was shown to alkylate trace quantities of the nonmetalated derivative **1** producing dimeric products **4** in high yield. This process appears only to take place if the solution of the lithiated thiazole **2** is allowed to warm from its temperature of formation (−78°) to ambient. However, if the lithiated thiazole is treated with an electrophile, E, at −78°, two alkylated products **5** and **6** are obtained. The ratio of these products is heavily dependent upon the nature of the 4 substituent, R, in the starting thiazole (Table I). Although Metzger[2] has reported, in an extensive temperature study on the metalation of 2-methylthiazole (**1**, R = H), that the two lithio salts **2** and **3** are formed independently and not through proton–metal exchange, it was felt that further evidence of this claim was necessary. In addition, examination of Table I reveals that metalation and subsequent alkylation of thiazoles containing the 4-aryl substituent leads to predominantly the 5-alkylthiazole **6**. On the other hand, when the 4 substituent is methyl, me-



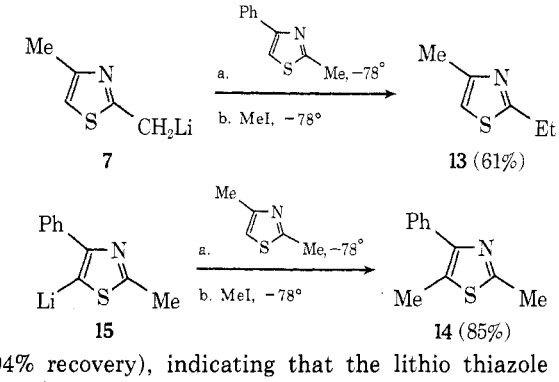
talation and alkylation take place mainly on the 2-methyl group, affording **5**. The trend depicted in Table I seems to be consistent with an inductive effect on the 5 position by the 4 substituent. Thus, aryl substituents with their −I effect tend to weaken the C–H bond of the 5 position, making proton removal a favorable process relative to that in the 2-methyl group.

When a methyl group is situated at the 4 position, its +I effect decreases the acidity at C-5, thus allowing the methyl protons at C-2 to be abstracted. The lithio salt derived from proton abstraction at C-2 should, however, be rather stable owing to its delocalized nature (**7**) and it is surprising that the side chain competes poorly for the *n*-butyllithium even in the 4-aryl substituted case. Ring-proton abstraction from heterocyclic systems is a well-known phenomenon, particularly in the thiophene series,[3] and Metzger[4] reported that the 2-H in thiazole **8** is readily removed by organolithium bases as is the methyl proton in 2-methylthiazole (**9**). Nevertheless, a recent review[5] stated that "even 4-methylthiazole (**12**) is metalated (and alkylated) at the 2 position. In fact, the preference for this position is so dominant that 2,5-dimethylthiazole (**10**) is metalated on the 2-methyl group (**11**)." This description of reactivity in metalations reveals the need for further studies in this series of heterocycles.



In order to confirm the fact that two distinct lithiated thiazoles (**2** and **3**) were indeed formed independently and, therefore, allowing the safe assumption that the product ratios in Table I are the result of the respective kinetic acidities of protons at C-5 and the 2-methyl group, several studies were undertaken to shed light on these points.

The first study was designed to assess the degree of proton transfer among the various possible lithio salts. This involved crossover experiments at −78 and 25° using thiazoles bearing different substituents. Reaction of 2,4-dimethylthiazole with 0.9 equiv of *n*-butyllithium at −78° generated **7**, which was treated with 2-methyl-4-phenylthiazole (**1**, R = Ph) after 2.5 hr and then quenched with methyl iodide after an additional 2.5 hr. The products isolated were **13** and the starting 2-methyl-4-phenylthiazole



(94% recovery), indicating that the lithio thiazole **7** did not abstract a proton from the former at −78°. The absence of **14** from the product mixture confirmed this result. Similarly, a reverse crossover experiment was performed by forming the lithio derivative of 2-methyl-4-phenylthiazole **15** followed by sequential addition of 2,4-dimethylthiazole (**1**, R = Me) and methyl iodide, both at −78°. The products isolated were **14** and starting 2,4-dimethylthiazole. Again, the absence of **13** from this experiment precluded lithium–hydrogen exchange under these conditions. It may, therefore, be concluded that the product ratios given in Table I are the result of independent metalation of the 2-methyl and the C-5 positions in a kinetically controlled process.

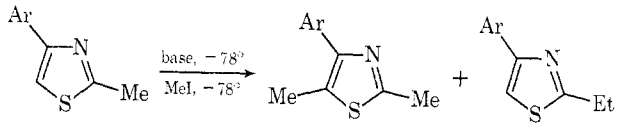
Since 2-methyl-4-arylthiazoles form the 5-lithio salt **3** (R = aryl) predominantly, as seen by alkylation data in Table I, the question immediately is raised, "How does **3** proceed on to the dimer **4**?" The above study already has shown that at −78° there is no lithium–hydrogen exchange. However, since the dimers are formed by allowing a solution of the lithio thiazoles to warm to ambient temperatures, lithium–hydrogen exchange (intra- or intermolecular) must take place and allow **3** to form **2**. The latter is a necessary precursor to dimerization. In order to test this hypothesis, another crossover experiment was performed involving **15**, generated at −78°, adding 2,4-di-

Table I
Reaction of 2-Methyl-4-Substituted 1,3-Thiazoles with *n*-Butyllithium and Electrophiles (E) at −78°

1, R	E	% 5[a]	% 6[a]
Me	MeI	88	12
Me	$PhCH_2Cl$	90	10[d]
Ph	MeI	4[b]	91
Ph	EtI	7[b]	86
p-MeOPh	MeI	6[b]	86
p-ClPh	MeI	3[b]	93
Ph	Me_3SiCl	4[c]	96
Ph	PhCHO		97
Ph		No reaction	
H	MeI	3–23	27–70[e]

[a] Relative yields determined by vpc. In all cases 3–8% starting thiazole was detected. Material balance was greater than 99%. [b] Contained, in addition to **5** and **6**, 5–8% of disubstituted thiazoles presumably by further alkylation of **5** with small amounts of *n*-butyllithium. [c] Decomposed upon exiting from vpc. [d] L. J. Altman and S. L. Richheimer, *Tetrahedron Lett.*, 4709 (1971), reported only crude alkylation product as being mainly **5**. [e] Data of J. Crousier and J. Metzger, *Bull. Soc. Chim. Fr.*, 4134 (1967). Reaction gave 26–50% starting thiazole, when anion formation and methylation were performed at −25 to −90°.

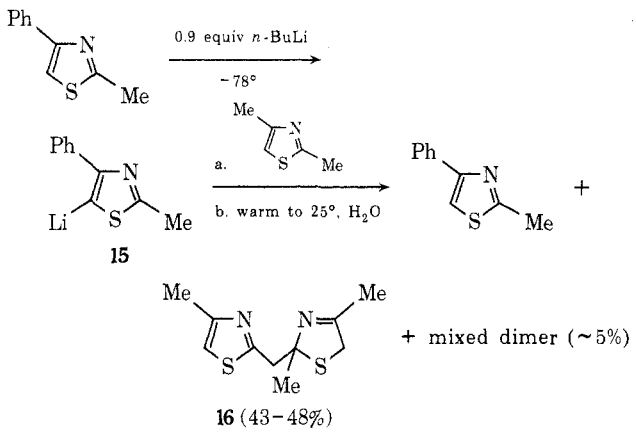
Table II
Metalation and Methylation of 2-Methyl-4-arylthiazoles with Various Bases



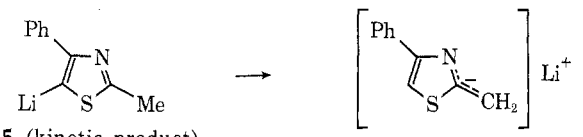
Ar	Base[a]	%[b]	%[b,c]
Ph	*n*-BuLi	94.8	5.2
Ph	$(i\text{-Pr})_2$NLi	90.0	10.0
Ph	*t*-BuLi	34.0	66.0
p-MeOPh	*n*-BuLi	92.0	8.0
p-MeOPh	$(i\text{-Pr})_2$NLi	80.0	20.0
p-MeOPh	*t*-BuLi	22.0	78.0

[a] 0.6–0.8 equiv of base used to avoid polyalkylation. [b] Average value for triplicate runs. [c] Starting material was recovered (25–40%) in all cases owing to the deficiency of base employed.

methylthiazole at this temperature, and allowing the solution to warm to room temperature. The products recovered were 2-methyl-5-phenylthiazole (75–80%), the symmetrical dimer **16** (43–48%), and a small amount (5%) of



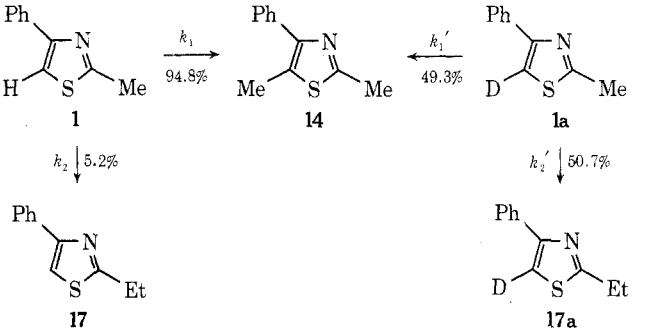
mixed dimers. This result indicates strongly that, *although no lithium–hydrogen exchange occurs at −78°, it does indeed become an important process at higher temperatures.* Thus, the question of how the lithio salt **3** leads to the dimer **4** (R = Ph) appears to have been answered. In the previous paper on this subject,[1] the reverse of the crossover experiment just described (**15** → **16**) was discussed in order to confirm that 2-lithiomethylthiazoles **2** do add to the C=N link of another thiazole molecule to ultimately form dimeric products. It would appear that the lithio salt **15** is kinetically formed at low temperatures owing to the −I effect of the adjacent aryl group, but as the energy of the system is increased (warming to room temperature) the acidity of the 2-methyl group by virtue of its incipient delocalized anion **15a** will prevail. It was therefore desirable to ascertain the relative acidities of the C-5 and 2-methyl protons in a competitive study and toward various bases.



15 (kinetic product) **15a** (thermodynamic product)

Treatment of an equimolar mixture of 2-methyl-4-phenylthiazole and 2,4-dimethylthiazole with *ca.* 0.5 equiv of *n*-butyllithium at −78° gave, after quenching with methyl iodide, 2,5-dimethyl-4-phenylthiazole (**14**, 43–45%) and 2-ethyl-4-methylthiazole (**13**, 3–4%). These data indicate that proton removal from the 5 position is preferred over that from the 2-methyl group when both are allowed to compete for a deficiency of base. This is, therefore, consistent with the previous claim that the −I effect of the phenyl substituent increases the kinetic acidity of the C-5 proton over the acidity of the 2-methyl group. When bases of varying steric bulk were added to 2-methyl-4-arylthiazoles at −78°, followed by methylation to establish the site of metalation, it was found that the C-5 proton is removed preferentially by small bases, whereas the 2-methyl protons are removed by larger bases (Table II). Of further interest is the fact that, even though the C-5 proton was shown to be kinetically more acidic at −78°, the strongest base employed (*i.e., tert*-butyllithium) leads to mainly methyl proton abstraction. This may be due to a combination of steric factors (since the C-5 proton is less accessible owing to the adjacent aryl group) and the decrease in selectivity of proton abstraction by the stronger base. In any event, the acidity of the C-5 and 2-methyl protons are probably very close in order to produce this significant change in product ratios. It is also noteworthy to mention that the presence of the methoxyl substituent in Table II had little effect upon the product ratios when compared to the phenyl substituent regardless of the base employed. This further substantiates the −I effect operating in the proton abstraction process.

To further support the apparently small acidity differences in the C-5 and 2-methyl protons, an isotope study was undertaken. Owing to the high percentage of metalation in the 5 position of 2-methyl-5-phenylthiazole (**1**, R = Ph) it was a simple matter to prepare, by deuteration with D_2O, the 5-deuterio derivative **1a** (>95% D). Treatment of **1a** with *n*-butyllithium and methyl iodide at −78° gave 49.3% of the 2,5-dimethylthiazole **14** and 50.7% of the 2-ethyl-5-deuteriothiazole **17a**. This result is in sharp



contrast to the 94.8% of **14** and 5.2% of **17** obtained with the protiothiazole **1**. By assigning relative rates k_1 and k_1' to represent the rate of proton abstraction for the C-5 position of **1** and **1a**, respectively, an apparent kinetic isotope effect may be calculated. The relative rates k_2 and k_2' would be expected to be equal, since there should be little difference in the ease of proton removal from the 2-methyl group in **1** and **1a**. Since $k_1'/k_2' = 49.3/50.7 = 0.97$ and $k_1/k_2 = 94.8/5.2 = 18.2$, then we may write, assuming $k_2 = k_2'$, that $k_1/k_1' = k_H/k_D = 18.8$ at −78°. Translating this isotope effect to its value at 35°, using the relationship described by Hine,[6] gives $k_H/k_D = 6.4$. This is in excellent agreement with the primary kinetic isotope effect of 6.6 reported for the metalation of thiophene.[7]

The experimental isotope effect was shown to be valid by testing it in a competition experiment. Metalation of an equimolar mixture of the 5-protio- (**1**) and 5-deuterio- (**1a**) thiazoles with 0.4 equiv of *n*-butyllithium (−78°) followed by introduction of methyl iodide gave, in addition to 63% recovered starting material, 37% of **14** and (**17** + **17a**) in the ratio of 90.5:9.5. By using the total relative rates

given above, $(k_2 + k_2')$ and $(k_1 + k_1')$, the calculated isomer distribution for **14** and (**17** + **17a**) is 90.6:9.4. These results are qualitatively consistent with those obtained in the separate experiments and provide further evidence that two distinct lithio thiazoles are formed under kinetically controlled conditions and maintain their integrity prior to methylation.

In summary, the kinetic acidity of the C-5 and 2-methyl protons at −78° are quite close. When the 4 substituent is methyl (or alkyl) the +I effect increases the electron density at the 5 position, thus rendering the proton less acidic, and allows the 2-methyl protons to be preferentially removed. When the 4 substituent is aryl (regardless of its mesomeric nature) the −I effect is the only important one and this reduces the electron density at the 5 position, causing proton removal to be favored. This type of inductive effect in heterocyclic systems undergoing metalation has previously been pointed out.[8] On the other hand, when thermodynamic conditions are brought into play, namely, allowing the solutions of lithio salts to warm, the 2-methyl protons are indeed more acidic and lithium–hydrogen exchange ensues to produce predominantly the more stable anions.

Experimental Section[9]

General Procedure for Metalation and Alkylation of 2-Methyl-4-Substituted Thiazoles (1). A. *n*-Butyllithium. *n*-Butyllithium (10.0 mmol) in hexane was added dropwise to a stirred solution (N_2) of **1** (10.0 mmol) in dry tetrahydrofuran (30 ml). After stirring for 0.5–1.0 hr, the electrophile (1.2–1.3 equiv) was added dropwise. The reaction mixture was stirred for a further 1–3 hr, allowed to warm to room temperature, poured into water (saturated with sodium chloride), and extracted with ether (2 × 125 ml). The combined ether extracts were dried ($MgSO_4$) and evaporated under vacuum to give an oil. This material was analyzed directly by glpc on column A.[9] Each peak was collected and identified by its nmr spectrum.[10] The quantitative results are summarized in Table I. Table II summarizes the results when a deficiency of base (0.6–0.8 equiv) was employed.

B. Lithio Diisopropylamide. Metalation of **1** (R = Ph, *p*-$CH_3OC_6H_4$) with lithio diisopropylamide (0.6–0.8 equiv) prepared as previously described,[11] methylation with methyl iodide, work-up, and analyses of products were identical with the above-described procedure. The results are summarized in Table II.

C. *tert*-Butyllithium. Metalation of **1** (R = Ph, *p*-$CH_3OC_6H_4$) with *tert*-butyllithium (0.6–0.8 equiv), methylation with methyl iodide, work-up, and analyses of products were identical with the above-described procedure. The results are summarized in Table II.

Attempted Intermolecular Hydrogen–Lithium Exchange at −78°. A. 2-Methyllithio-4-methylthiazole (2, R = CH_3) and 2-Methyl-4-phenylthiazole (1, R = Ph). *n*-Butyllithium (4.4 ml, 9.8 mmol) in hexane was added dropwise to a stirred solution (N_2) of **1** (R = CH_3) (1.17 g, 10.3 mmol) in dry tetrahydrofuran (30 ml) at −78°. The resulting wine-colored reaction mixture was stirred for 1 hr at −78° and then a solution of **1** (R = Ph) (1.68 g, 9.6 mmol) in dry tetrahydrofuran (10 ml) was added. This was stirred for 2.5 hr (−78°) and methyl iodide (1.81 g, 12.7 mmol) was added dropwise. The resulting light yellow colored reaction mixture was stirred for a further 1 hr at −78°, poured into ice-water (150 g, saturated with sodium chloride), and extracted with ether (2 × 150 ml). The combined ether extracts were dried ($MgSO_4$) and evaporated carefully under vacuum to give a light yellow oil. Molecular distillation at room temperature (0.03 Torr) gave 0.79 g (61%) of a colorless liquid whose nmr spectrum was almost identical with that of 2-ethyl-4-methylthiazole. Further distillation at an oil bath temperature of 80–95° (0.03 Torr) gave 1.58 g (94% recovery) of 2-methyl-4-phenylthiazole (**1**, R = Ph). Glpc on column A exhibited the presence of only **1** (R = Ph).

B. 2-Methyl-4-phenyl-5-lithiothiazole (3, R = Ph) and 2,4-Dimethylthiazole (1, R = CH_3). Metalation of **1** (R = Ph) with *n*-butyllithium (0.90 equiv), addition of **1** (R = CH_3) (1.1 equiv), quenching with methyl iodide (−78°), and work-up as described above gave a light yellow oil. Molecular distillation at room temperature (0.03 Torr) gave a 68% recovery of **1** (R = CH_3). Glpc on column A exhibited the presence of only **1** (R = CH_3). Further molecular distillation gave an almost colorless oil. Glpc on column A exhibited the presence of **1** (R = Ph) (9.0%), **14** (86.5%), and **17** (4.5%).

Intermolecular Hydrogen–Lithium Exchange at 25°. 2-Methyl-4-phenyl-5-lithiothiazole (3, R = Ph) and 2,4-Dimethylthiazole (1, R = CH_3). *n*-Butyllithium (3.2 ml, 7.2 mmol) in hexane was added dropwise to a stirred solution of 2-methyl-4-phenylthiazole (**1**, R = Ph) (1.40 g, 8.00 mmol) in dry tetrahydrofuran (30 ml) at −78°. The resulting yellow-colored solution was stirred for 1 hr at −78° and then **1** (R = CH_3) (1.36 g, 12.0 mmol) was added in one portion. This was then allowed to warm to room temperature, at which time the reaction mixture was wine in color. After stirring for 4.5 hr (room temperature), the reaction mixture was quenched with ice-water (40 ml) and extracted with ether (2 × 125 ml). The combined ether extracts were dried ($MgSO_4$) and evaporated under vacuum to give a yellow oil. Molecular distillation at an oil bath temperature of 110° (0.07 Torr) gave 0.38 g (47%) of dimer **16** and 1.06 g (76% recovery) of **1** (R = Ph).

Metalation and Methylation of 2-Methyl-4-phenyl-5-deuteriothiazole (1a). *n*-Butyllithium (2.7 ml, 6.1 mmol) in hexane was added to a stirred solution (N_2) of **1a**[12] (1.40 g, 8.00 mmol) in dry tetrahydrofuran (30 ml) at −78°. Quenching with methyl iodide (−78°) and work-up was the same as that described above. Glpc analyses (average of three runs) on column A exhibited the presence of **14** (36.4%), **17a** (37.4%), and starting material **1a** (26.2%).

Competitive Metalation–Methylation of 2-Methyl-4-phenylthiazole (1, R = Ph) and 2-Methyl-4-phenyl-5-deuteriothiazole (1a). *n*-Butyllithium (1.3 ml, 3.0 mmol) in hexane was added dropwise to a stirred solution (N_2) of **1** (R = Ph) (1.40 g, 8.0 mmol) and **1a** (1.41 g, 8.0 mmol) in dry tetrahydrofuran (30 ml) at −78°. Quenching with methyl iodide at −78° and work-up was the same as that previously described. Glpc analyses (average of three runs) on column A exhibited the presence of starting material(s) (62.8%), **14** (33.7%), and **17a** (3.5%).

Competitive Metalation–Methylation of 2,4-Dimethylthiazole (1, R = Me) and 2-Methyl-4-phenylthiazole (1, R = Ph). *n*-Butyllithium (1.55 ml, 3.5 mmol) in hexane was added dropwise to a stirred solution (N_2) of **1** (R = Me) (0.81 g, 7.1 mmol) and **1** (R = Ph) (1.25 g, 7.1 mmol) in dry tetrahydrofuran (45 ml) at −78°. Quenching with methyl iodide at −78° and work-up as described previously gave **13** (3–4%), **14** (43–45%), **1** (R = Me, 96–97%), and **1** (R = Ph, 55–57%).

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Registry No.—**1** (R = Me), 541-58-2; **1** (R = Ph), 1826-16-0; **1** (R = *p*-MeOPh), 50834-78-1; **1** (R = *p*-ClPh), 24840-75-3; **1a**, 50834-79-2; **2** (R = Me), 20155-91-3; **3** (R = Ph), 50834-80-5; **16**, 41898-76-4.

References and Notes

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(12) Prepared in quantitative yield by metalation with 1.1 equiv of *n*-butyllithium and quenching with D_2O at −78°. The deuterium incorporation at C-5, under these conditions, was shown to be >95% by nmr spectroscopy.