The Reactivity of 3-Methyl-5-phenylisothiazole with Carbonyl Compounds

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The reactivity of 3-methyl-5-phenylisothiazole with carbonyl compounds in the presence of *n*-butyllithium and the system lithium isopropylcyclohexylamide-*N,N,N',N'*-tetramethylethylendiamine (LICA-TMEDA) is studied. *n*-Butyllithium is found to lead to higher yields of the hydroxy derivatives of the isothiazole compound than LICA-TMEDA. Ring opening products are not detected under the reaction conditions used.

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The isothiazole ring has a differential reactivity in the various positions of the heterocycle. The ^{1}H-nmr studies have shown that isothiazoles undergo deprotonation, H-5 exchanging readily under mildly basic conditions [1,2], H-3 more slowly and H-4 not exchanging readily.

5-Substituted isothiazoles have been obtained from 5-lithioisothiazole prepared from isothiazole in THF at -70° [3-7]. We have previously investigated the lithiation of 3,5-dimethylisothiazole at the C-4 position [8-10].

Proton exchange in the isothiazole ring methyl groups follows the same pattern, 5-methyl groups undergoing more rapid deprotonation than 3-methyl groups and the 4-methyl being reluctant to exchange its protons [11].

In this paper we report the lithiation of 3-methyl-5-phenylisothiazole in order to study the reactivity of the C-3 methyl group with carbonyl compounds.

Results and Discussion.

Recently we reported the use of lithium isopropylcyclohexylamide-*N,N,N',N'*-tetramethylethylendiamine (LICA-TMEDA), as a deprotonating system for 3-methyl-5-phenylisoxazole, with regioselective reaction at the C-3 methyl group [12]. In this work, we present the results of a comparative study of the reactivity of 3-methyl-5-phenylisothiazole with the aforementioned system and *n*-butyllithium.

3-Methyl-5-phenylisothiazole (**1**) reacts with oxo compounds, on the C-3 methyl group, in the presence of *n*-butyllithium and the system LICA-TMEDA, to lead to hydroxy derivatives of the isothiazole compound.

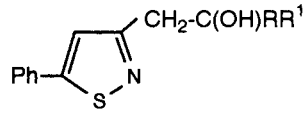
The reaction conditions and product yields are shown in Tables 1 and 2.

When the base used is *n*-butyllithium, the results are quite satisfactory, with the exception of acrolein and 3-buten-2-one, which gave yields of less than 30%. With these two compounds the low yield is due to the formation of polymerization products from the carbonyl compounds.

With the system LICA-TMEDA, the same two oxo compounds also gave lower yields than the other electrophiles used.

As shown in Tables 1 and 2, *n*-butyllithium which is a stronger base than the system LICA-TMEDA, allowed us to obtain better results in the formation of the carbanion on the C-3 methyl group of the isothiazole derivative. But, it is also important to point out that the differences are not very important, since the basicity of LICA is greatly increased by TMEDA which chelates the cation leaving a

Scheme I



2: R = H, R^1 = CH_2-CH_3
3: R = H, R^1 = CH=CH_2
4: R = H, R^1 = Ph
5: R = H, R^1 = CH=CH-Ph
6: R = CH_3, R^1 = CH_3
7: R, R^1 = $(CH_2)_4$
8: R, R^1 = $(CH_2)_5$
9: R = CH_3, R^1 = CH=CH_2
10: R = CH_3, R^1 = Ph
11: R = Ph, R^1 = Ph
12: R = CH_3, R^1 = CH=CH-Ph

Table 1

Reactions of 3-Methyl-5-phenylisothiazole with Oxo Compounds in the Presence of *n*-Butyllithium

Oxo Compound	Reaction Time (hours) (-78°C)	Conditions [a] Time (hours) (25°C)	Products (%)
Propionaldehyde	5	1	**2** (42)
Acrolein	5	1	**3** (25)
Benzaldehyde	5	1	**4** (86)
Cinnamaldehyde	5	1	**5** (51.5)
Acetone	5	1	**6** (67)
Cyclopentanone	5	1	**7** (39)
Cyclohexanone	5	1	**8** (56)
3-Buten-2-one	5	1	**9** (18)
Acetophenone	5	1	**10** (65)
Benzophenone	5	1	**11** (35)
Bencyclidenacetophenone	5	1	**12** (25)

[a] The molar ratio used in all these cases was *n*-butyllithium:isothiazole:oxo compound = 1,1,1.

Table 2

Reactions of 5-Phenyl 3-methylsothiazole with Oxo Compounds in the Presence of LICA-TMEDA

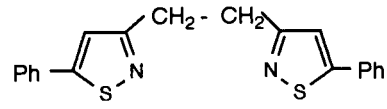
Oxo Compound	Reaction Time (hours) (-78°C)	Conditions [a] Time (hours) (25°C)	Products (%)
Propionaldehyde	5	1	**2** (35)
Acrolein	5	1	**3** (25)
Benzaldehyde	5	1	**4** (47)
Cinnamaldehyde	5	1	**5** (25)
Acetone	5	1	**6** (45)
Cyclopentanone	5	1	**7** (35)
Cyclohexanone	5	1	**8** (52)
3-Buten-2-one	5	1	**9** (16)
Acetophenone	5	1	**10** (40)
Benzophenone	5	1	**11** (20)
Bencyclidenacetophenone	5	1	**12** (60.5)

[a] The molar ratio used in all these cases was LICA:TMEDA: isothiazole:oxo compound = 1, 1.67, 1, 1.

greater negative charge on the carbanionic site.

Additionally, the presence of 1,2-bis(3-methyl-5-phenylisothiazolyl)ethane (**13**) (scheme II) is found in 6-14% yield when either *n*-butyllithium of LICA-TMEDA is used. Its formation is not easily explained, but it could be due to a free radical coupling mechanism. This compound is formed after the addition of the carbonyl compound since two experiments were carried out under the same conditions used for all these reactions but without addition of the oxo compoud. After hydrolysis the untransformed starting reagent could be recovered and no evidence of the dimer could be detected.

Scheme II



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Despite the data in the literature [4] showing ring opening of isothiazoles with *n*-butyllithium, in the reaction conditions we used, none of these ring opening products were found.

EXPERIMENTAL

Melting points are uncorrected. 3-Methyl-5-phenylisothiazole was prepared by established procedures [13]. Nuclear magnetic resonance spectra were obtained with a Bruker A.C.80 spectrometer using deuteriochloroform and carbon tetrachloride solutions and TMS as the standard reference; chemical shifts were measured on the δ scale. Electron ionization mass spectra were obtained using a Hewlett-Packard G.C./M.S. system 5988A. Elemental analyses were carried out with a Perkin-Elmer 240 B analyser. Merck silica gel 60 was used for column chromatography, solvents and reagents were purified by conventional methods.

General Procedure.

1. By the Use of *n*-Butyllithium.

A hexane solution (1.6 *M*) of *n*-butyllithium (0.011 mole) in dry THF (10 ml) was cooled at -78°. A solution of 3-methyl-5-phenylisothiazole (0.010 mole) in dry THF (10 ml) was added slowly under dry nitrogen. After cooling and stirring for 1 hour, a solution of the carbonyl compound (0.011 mole) in 10 ml of dry THF was added. The reaction mixture was kept at -78° for five hours and was then allowed to warm to room temperature. After one hour the mixture was hydrolysed with 50 ml of a saturated ammonium chloride solution and washed with dilute hydrochloric acid (1:10). The layers were then separated and the aqueous layer extracted with ether. After being dried over anhydrous magnesium sulfate, the organic layer was evaporated to give the crude products, which were purified by flash chromatography using methylene chloride-diethyl ether (30:1) as eluent.

2. By the Use of Lithium Isopropylcyclohexylamide and *N,N,N',N'*-Tetramethylethylendiamine.

A solution of isopropylcyclohexylamine (0.011 mole) in dry THF (10 ml) was cooled at -78°. A hexane solution (1.6 *M*) of *n*-butyllithium (0.011 mole) was added under dry nitrogen and after 10 minutes at -78°, the system was allowed to reach room temperature and then stirred for 30 minutes. The solution was then cooled at -78° and a solution of TMEDA (0.016 mole) in dry THF (10 ml) was added. A solution of 3-methyl-5-phenylisothiazole (0.010 mole) in 10 ml of dry THF was added dropwise over a period of 50 minutes. The resulting solution was stirred for 30 minutes and the oxo compound (0.011 mole) in dry THF (10 ml) was added. After five hours at -78°, the reaction mixture was allowed to warm to room temperature over a one hour period. A saturated ammonium chloride solution (50 ml) was added fol-

lowed by dilute hydrochloric acid. After the usual work-up, the residue was purified by flash column as before.

3-Methyl-5-phenylisothiazole (**1**).

This compound was obtained as a pale yellow solid, mp 69-70° (from ethanol); ^{1}H-nmr (deuteriochloroform): 7.62-7.25 (m, 5H), 7.17 (s, 1H), 2.52 (s, 3H); ^{13}C-nmr (deuteriochloroform): 167.46, 167.00, 130.80-126.24, 120.08, 18.81; ms: m/z (relative intensity) 176 (12), 175 ($M^{+\cdot}$, 100), 134 (31), 89 (10), 73 (10).

Anal. Calcd. for $C_{10}H_9NS$: C, 68.53; H, 5.18; N, 7.99. Found: C, 68.59; H, 5.19; N, 7.97.

3-(2-Hydroxybutyl)-5-phenylisothiazole (**2**).

This compound was obtained as a white solid, mp 48-49° (from ethanol); ^{1}H-nmr (deuteriochloroform): 7.63-7.29 (m, 5H), 7.22 (s, 1H), 4.25-3.82 (m, 1H), 3.46 (s, 1H), 2.99-2.87 (m, 2H), 1.68-1.41 (m, 2H), 1.09-0.89 (t, 3H); ^{13}C-nmr (deuteriochloroform): 169.80, 167.13, 130.55-126.30, 120.20, 71.55, 39.74, 29.56, 9.81; ms: m/z (relative intensity) 233 ($M^{+\cdot}$, 2), 215 (7), 204 (35), 176 (20), 175 (100), 174 (7), 134 (13), 115 (8), 102 (7), 77 (9), 59 (7).

Anal. Calcd. for $C_{13}H_{15}NOS$: C, 66.92; H, 6.48; N, 6.00. Found: C, 66.89; H, 6.45; N, 5.98.

3-(2-Hydroxy-3-butenyl)-5-phenylisothiazole (**3**).

This compound was obtained as a white solid, mp 60-61° (from ethanol); ^{1}H-nmr (deuteriochloroform): 7.62-7.32 (m, 5H), 7.23 (s, 1H), 6.18-5.77 (m, 1H), 5.43-5.04 (m, 2H), 4.72-4.48 (m, 1H), 3.71 (s, 1H), 3.07-2.97 (dd, 2H); ^{13}C-nmr (deuteriochloroform): 168.97, 167.31, 139.66, 130.56-126.39, 120.35, 114.87, 71.20, 40.12; ms: m/z (relative intensity) 231 ($M^{+\cdot}$, 11), 214 (23), 176 (11), 175 (100), 147 (7), 134 (14), 115 (8), 102 (7), 77 (11), 57 (20), 51 (9).

Anal. Calcd. for $C_{13}H_{13}NOS$: C, 67.50; H, 5.66; N, 6.06. Found: C, 67.43; H, 5.64; N, 6.08.

3-(2-Phenyl-2-hydroxyethyl)-5-phenylisothiazole (**4**).

This compound was obtained as a white solid, mp 92-93° (from ethanol); ^{1}H-nmr (deuteriochloroform): 7.59-7.21 (m, 10H), 7.11 (s, 1H), 5.24-5.08 (t, 1H), 4.03 (s, 1H), 3.28-3.13 (d, 2H); ^{13}C-nmr (deuteriochloroform): 169.26, 167.38, 143.47-125.66, 120.37, 72.65, 42.40; ms: m/z (relative intensity) 281 ($M^{+\cdot}$, 2), 176 (23), 175 (100), 134 (11), 107 (13), 79 (24), 77 (34).

Anal. Calcd. for $C_{17}H_{15}NOS$: C, 72.56; H, 5.37; N, 4.98. Found: C, 72.47; H, 5.39; N, 5.00.

3-(4-Phenyl-2-hydroxy-3-butenyl)-5-phenylisothiazole (**5**).

This compound was obtained as a yellow solid, mp 139-140° (from ethanol); ^{1}H-nmr (deuteriochloroform): 7.65-7.21 (m, 11H), 6.81-6.60 (dd, 1H), 6.42-6.15 (dd, 1H), 4.92-4.70 (q, 1H), 3.30-3.07 (dd, 2H); ^{13}C-nmr (deuteriochloroform): 169.10, 167.69, 136.72-126.60, 120.49, 71.24, 40.54; ms: m/z (relative intensity) 307 ($M^{+\cdot}$, 12), 176 (13), 175 (100), 134 (18), 133 (17), 115 (26), 103 (17), 77 (34), 55 (29), 51 (14).

Anal. Calcd. for $C_{19}H_{17}NOS$: C, 74.24; H, 5.57; N, 4.56. Found: C, 74.31; H, 5.59; N, 4.54.

3-(2-Methyl-2-hydroxypropyl)-5-phenylisothiazole (**6**).

This compound was obtained as a white solid, mp 43-44° (from ethanol); ^{1}H-nmr (deuteriochloroform): 7.65-7.26 (m, 5H), 7.23 (s, 1H), 3.66 (s, 1H), 2.99 (s, 2H), 1.28 (s, 6H); ^{13}C-nmr (deuteriochloroform): 169.49, 167.20, 130.67-126.51, 121.19, 70.50, 45.73, 29.33; ms: m/z (relative intensity) 233 ($M^{+\cdot}$, 2), 218 (29), 177 (17), 176 (48), 175 (100), 174 (19), 147 (15), 134 (32), 115 (18), 102 (14), 89 (10), 77 (18), 59 (71), 51 (11), 43 (30).

Anal. Calcd. for $C_{13}H_{15}NOS$: C, 66.92; H, 6.48; N, 6.00. Found: C, 66.95; H, 6.50; N, 6.02.

3-(1-Hydroxycyclopentyl)methyl-5-phenylisothiazole (**7**).

This compound was obtained as a white solid, mp 66-67° (from ethanol); ^{1}H-nmr (deuteriochloroform): 7.59-7.29 (m, 5H), 7.23 (s, 1H), 3.93 (s, 1H), 3.06 (s, 2H), 1.96-1.50 (m, 8H); ^{13}C-nmr (deuteriochloroform): 169.70, 166.64, 130.37-126.15, 120.64, 81.02, 43.45, 39.34, 23.49; ms: m/z (relative intensity) 259 ($M^{+\cdot}$, 5), 175 (100), 134 (17), 85 (18), 77 (21), 67 (16), 57 (21), 55 (41), 43 (36), 42 (24), 41 (64).

Anal. Calcd. for $C_{15}H_{17}NOS$: C, 69.46; H, 6.61; N, 5.40. Found: C, 69.49; H, 6.57; N, 5.38.

3-(1-Hydroxycyclohexyl)methyl-5-phenylisothiazole (**8**).

This compound was obtained as a white solid, mp 63-64° (from ethanol); ^{1}H-nmr (deuteriochloroform): 7.63-7.27 (m, 5H), 7.23 (s, 1H), 3.46 (s, 1H), 2.97 (s, 2H), 1.65-1.38 (m, 10H); ^{13}C-nmr (deuteriochloroform): 169.02, 166.78, 130.48-126.25, 121.17, 71.09, 44.29, 37.35, 25.50, 21.98; ms: m/z (relative intensity) 273 ($M^{+\cdot}$, 40), 230 (70), 177 (60), 176 (100), 175 (100), 147 (50), 134 (80), 115 (50), 81 (70), 55 (60), 41 (70).

Anal. Calcd. for $C_{16}H_{19}NOS$: C, 70.30; H, 7.00; N, 5.12. Found: C, 70.40; H, 6.97; N, 5.11.

3-(2-Methyl-2-hydroxy-3-butenyl)-5-phenylisothiazole (**9**).

This compound was obtained as a white solid, mp 48-49° (from ethanol); ^{1}H-nmr (deuteriochloroform): 7.62-7.32 (m, 5H), 7.20 (s, 1H), 6.14-5.80 (dd, 1H), 5.33-4.91 (m, 2H), 3.95 (s, 1H), 3.04 (s, 2H), 1.35 (s, 3H); ^{13}C-nmr (deuteriochloroform): 168.77, 167.04, 130.62-126.45, 144.20, 121.10, 112.26, 72.66, 44.58, 27.83; ms: m/z (relative intensity) 245 ($M^{+\cdot}$, 20), 228 (26), 177 (16), 176 (43), 175 (100), 174 (21), 147 (16), 134 (35), 115 (20), 102 (15), 77 (20), 71 (65), 43 (47).

Anal. Calcd. for $C_{14}H_{15}NOS$: C, 68.53; H, 6.16; N, 5.71. Found: C, 68.48; H, 6.19; N, 5.72.

5-Phenyl-3-(2-phenyl-2-hydroxypropyl)isothiazole (**10**).

This compound was obtained as a white solid, mp 73-74° (from ethanol); ^{1}H-nmr (deuteriochloroform): 7.53-7.10 (m, 10H), 6.91 (s, 1H), 4.68 (s, 1H), 3.26 (s, 2H), 1.57 (s, 3H); ^{13}C-nmr (deuteriochloroform): 168.65, 166.48, 147.30-124.45, 120.81, 73.84, 46.10, 29.66; ms: m/z (relative intensity) 295 ($M^{+\cdot}$, 1), 179 (12), 175 (100), 134 (10), 121 (15), 77 (23), 51 (10), 43 (67).

Anal. Calcd. for $C_{18}H_{17}NOS$: C, 73.19; H, 5.80; N, 4.74. Found: C, 73.14; H, 5.79; N, 4.76.

3-(2,2-Diphenyl-2-hydroxyethyl)-5-phenylisothiazole (**11**).

This compound was obtained as a white solid, mp 161-162° (from ethanol); ^{1}H-nmr (deuteriochloroform): 7.54-7.19 (m, 15H), 6.95 (s, 1H), 4.39 (s, 1H), 3.81 (s, 2H); ^{13}C-nmr (deuteriochloroform): 168.85, 167.18, 146.62, 126.10, 121.03, 78.02, 44.39; ms: m/z (relative intensity) 357 ($M^{+\cdot}$, 12), 324 (15), 252 (14), 183 (21), 176 (13), 175 (100), 134 (10), 105 (77), 77 (73), 51 (14).

Anal. Calcd. for $C_{23}H_{19}NOS$: C, 77.27; H, 5.36; N, 3.92. Found: C, 77.26; H, 5.38; N, 3.93.

3-(2-Hydroxy-2-methyl-4-phenyl-3-butenyl)-5-phenylisothiazole (**12**).

This compound was obtained as a white solid, mp 98-99° (from

ethanol); ^{1}H-nmr (deuteriochloroform): 7.58-7.25 (m, 10H), 7.21 (s, 1H), 6.75-6.55 (d, 1H), 6.39-6.19 (d, 1H), 4.11 (s, 1H), 3.15 (s, 2H), 1.45 (s, 3H); ^{13}C-nmr (deuteriochloroform): 168.80, 167.49, 136.98-126.39, 121.11, 72.77, 44.90, 28.30; ms: m/z (relative intensity) 321 ($M^{+\cdot}$, 5), 176 (12), 175 (100), 147 (45), 134 (15), 129 (16), 128 (13), 115 (10), 103 (13), 77 (19), 43 (24).

Anal. Calcd. for $C_{20}H_{19}NOS$: C, 74.73; H, 5.96; N, 4.36. Found: C, 74.71; H, 5.98; N, 4.34.

1,2-Bis(5-phenyl-3-isothiazolyl)ethane (**13**).

This compound was obtained as a white solid, mp 182-183° (from ethanol); ^{1}H-nmr (deuteriochloroform): 7.62-7.25 (m, 10H), 7.21 (s, 2H), 3.37 (s, 4H); ^{13}C-nmr (deuteriochloroform): 170.66, 167.65, 130.95-126.58, 119.73, 32.09; ms: m/z (relative intensity) 349 (22), 348 ($M^{+\cdot}$, 87), 227 (21), 188 (80), 147 (22), 134 (71), 121 (41), 115 (23), 102 (38), 91 (27), 89 (38), 77 (100), 76 (21), 51 (33).

Anal. Calcd. for $C_{20}H_{16}N_2S_2$: C, 68.93; H, 4.63; N, 8.04. Found: C, 68.96; H, 4.65; N, 8.06.

REFERENCES AND NOTES

[1] R. A. Olofson, J. M. Landsberg, R. O. Berry, D. Leaver, W. A. H. Robertson and D. M. Mckinnon, *Tetrahedron*, **22**, 2119 (1969).

[2] J. A. White and R. C. Anderson, *J. Heterocyclic Chem.*, **6**, 199 (1969).

[3] A. Adams and R. Slack, *J. Chem. Soc.*, 3061 (1959).

[4] M. P. L. Caton, D. H. Jones, R. Slack and K. R. H. Wooldridge, *J. Chem. Soc.*, 446 (1964).

[5] D. Buttimore, M. P. L. Caton, J. D. Renwick and R. Slack, *J. Chem. Soc.*, 7274 (1965).

[6] D. H. Jones, R. Slack and K. R. H. Wooldridge, *J. Chem. Soc.*, 3114 (1964).

[7] R. Kalish, E. Brogen, F. G. Field, T. Anton, T. V. Steppe and L. H. Sternbach, *J. Heterocyclic Chem.*, **12**, 49 (1975).

[8] A. Alberola, F. Alonso, P. Cuadrado and M. C. Sañudo, *Synth. Commun.*, **17**, 1207 (1987).

[9] A. Alberola, F. Alonso, P. Cuadrado and M. C. Sañudo, *Gazz. Chim. Ital.*, **177**, 461 (1987).

[10] A. Alberola, F. Alonso, P. Cuadrado and M. C. Sañudo, *J. Heterocyclic Chem.*, **25**, 235 (1988).

[11] K. R. H. Wooldridge, *Adv. Heterocyclic Chem.*, **14**, 1 (1972).

[12] A. Alberola, L. Calvo, T. R. Rodríguez and M. C. Sañudo, *J. Heterocyclic Chem.*, **29**, 445 (1992).

[13] M. S. Grant, D. L. Pain and R. Slack, *J. Chem. Soc.*, 3842 (1965).