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(2-Benzothiazolyl)methyllithium reacts quickly at low temperature (−78°) with a variety of organic electrophiles like aldehydes, ketones, carboxylic esters, nitriles and acyl chlorides. Such reactions lead to an easy introduction of alcohol, keto-enol or amine-enamine functional groups in extracyclic position with a stereoselective preference. These polyfunctional compounds whose synthesis is difficult by other pathways, are interesting, in particular, because of their ability to form intramolecular hydrogen bonds.

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Usually the condensation of α-alkylated heterocyclic bases with some electrophiles has often been performed in the presence of a basic catalyst at a sufficiently high temperature. In the case of compounds with a reactive methylene group (*e.g.* malonic derivatives) the formation of a transient carbanion usually has been suggested. Most of the time it concerns condensations with carbonyl derivatives resulting in the formation of a double bond. Under these conditions it is difficult to isolate the transient carbinol which is prone to elimination. These limitations explain the search for methods allowing the quantitative isolation of the carbanion under mild conditions with good reactivity with most of the organic functional groups. In this field the most studied heterocycles are the pyridine [1-10] and pyrazine [11,12] rings and lead to original syntheses.

A very few examples are known with the 2-methylbenzothiazole [13-17] and the only described general method is a metalation procedure by alkaline amides [13] in liquid ammonia followed by a condensation reaction limited to aldehydes and ketones.

Another procedure makes use of amides [14] or sodium hydroxide [17] in *N,N*-dimethylformamide or dimethyl sulfoxide and gives good yields in the case of the reaction of the 2-methylbenzothiazole with aromatic aldehydes. Under these conditions, it is more reasonable to compare these reactions with those involving carbanions using basic catalysis (aldolization reaction types) than with those making use of organometallics.

A systematic study [18] directed towards the action of various bases with 2-methylbenzothiazole requires mild conditions for the metalation of this compound. For example at low temperature, the condensation of phenyllithium with 2-methylbenzothiazole using linear or cyclic ethers as solvents, yields quantitatively highly reactive anionic species between −78° and −35°.

We wish to report our results dealing with the reactivity of this kind of organometallic derivatives with different functional groups bearing aliphatic or aromatic substituants.

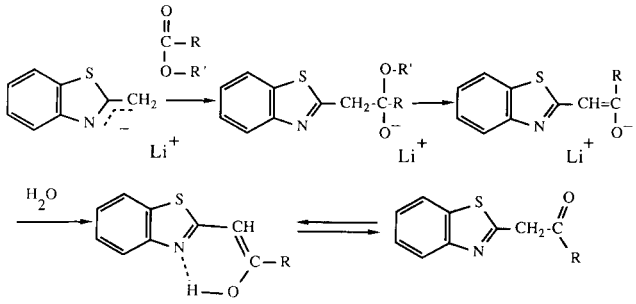
Results and Discussion.

We have only optimized the reaction with benzaldehyde (quantitative yield) and the determined standard conditions (experimental) have been applied to other electrophiles such as ketones, esters, nitriles and acid chlorides.

Reaction with Aldehydes and Ketones.

The reaction with carbonyl functions is nothing other than a simple addition and after hydrolysis, a secondary or a tertiary alcohol is obtained in good yields (compounds **1**, **2**, **3**, **4**). By increasing the temperature and under acid catalysis conditions, water elimination takes place with formation of a double bond conjugated with the heterocycle. In the case of esters, the experimental results lead to the following mechanism.

Scheme 1



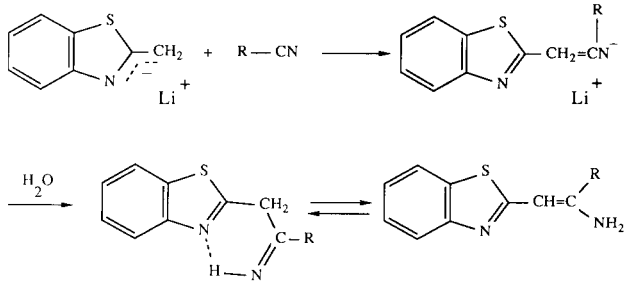
The final compound, the ketone, as reported (Scheme 1), is in fact in equilibrium with its enolic form which is stabilized by resonance and by the formation of an intramolecular hydrogen bond. The enolic form which is quite important in the solid state (compound **5** [ir spectrum: broad band between 3600 and 3300 cm^{-1}, strong band at 1610 cm^{-1}] is also the main populated tautomer in carbon tetrachloride [ir spectrum: strong band at 1610 cm^{-1} in comparison with the carbonyl band at 1680 cm^{-1}]). The keto/enol ratio can be evaluated by ^1H nmr: for compound **5** we have measured ketone = 35%, enol 65% (deuteriochloroform, 20°); enol = 100% (DMSO-d_6, 20°); for com-

pound **6** ketone = 92%, enol = 8% (deuteriochloroform, 20°). The largely higher enol content for compound **5** can be explained by its stabilization through conjugation with the benzene ring. These results are in agreement with those obtained in the pyridine series [4,5,19]. Nevertheless we do not observe any partial formation of a tertiary alcohol which would result from the carbanion attack onto the keto-group when the substituant R is aliphatic. *A priori* the absence of this reaction is surprising because the enol form in the case of pyridine derivatives is the most populated: this result might be explained by a very rapid attack of the ester by the carbanion. Compound **6** has been prepared already by a peculiar process [20] and a classical method [21] identical to the one for compound **5** but the yields are lower.

Reaction with Nitriles. For R = phenyl (compound **7**).

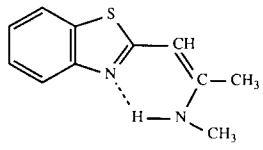
The product obtained leads to the following mechanism.

Scheme 2



This compound exists under the two imine and enamine forms. Indeed, its ir spectrum in the solid state exhibits a broad peak ranging from 2850 to 2960 cm^{-1} due to the methylene of the imine form and a strong band at 1620 cm^{-1} attributed both to the amino form (ν NH_2) and to the C=C double bond. In chloroform or carbon tetrachloride solution we observed the disappearance of the broad band in the 2850-2960 cm^{-1} domain and also of the band at 1585 cm^{-1} corresponding, in the solid state, to the imine C=N double bond. The ^1H nmr spectrum in deuteriochloroform solution presents in addition to the aromatic peaks, a single peak at 5.7 ppm integrating for one proton. In solution there is a predominance for the primary enamine form, a class of compounds which has not been easy to isolate. The imine form seems to be stabilized by an intramolecular hydrogen bond as observed in the case of the pyridinic derivatives [23].

Scheme 3

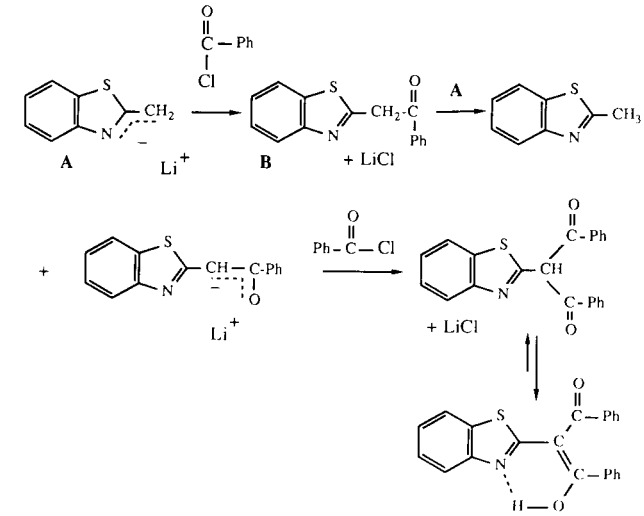


The peculiar stability of the enamine **7** might be attributed to the conjugation between the heterocycle and the benzene ring. For compound **8** (R = Me), after hydrolysis, we obtained a mixture containing 2-methylbenzothiazole and two other products which were difficult to separate. Based on thin layer chromatographic analysis and ir spectra, we can conclude to the occurrence of an enamine and a ketone. Prolonged contact with an aqueous acid solution led to the single compound **6**. The initially formed enamine, which is less stable than the previous on (R = phenyl) was subjected to spontaneous classical hydrolysis, which is well known for this type of function and equally observed in the case of identical reactions with 2-picoline [10].

Acid Chloride.

The action of benzoyl chloride affords a double acylation. The yield (calculated from the concentration of 2-methylbenzothiazole) was not surprisingly low because we used a stoichiometric amount of the two reactants. We can propose the following mechanism.

Scheme 4

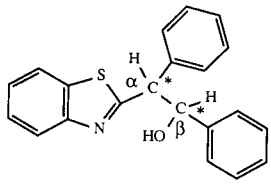


The initially formed ketone **B** is more acid than the 2-methylbenzothiazole. The remaining derivative **A** acts as a base and forms the enolate ion which is acylated by the acid chloride. This peculiar reaction was not observed in the case of 2-picoline. The ir and ^1H nmr spectra of compound **9** revealed its presence only in its enol form.

In order to expand the results of these reactions to other alkylated benzothiazole derivatives, attempts were made with the couple 2-benzylbenzothiazole/benzaldehyde. To obtain good yield (75%) required an increase in the reaction time of the aldehyde after metalation, because of the steric constraints and the stabilization through the benzene ring, the reactivity of the carbanion formed is

decreased. Compound **10** was obtained as a mixture of both two diastereoisomers.

Scheme 5



Its structure was confirmed by ^1H and ^{13}C nmr spectrometry and the stereoselective character of the reaction led to a 30/70 ratio of the diastereoisomers that is different in comparison with the basic catalysis conditions [17]. However, contrary to reference [17], we have attributed the highest vicinal coupling constant (antiperiplanar protons) in the *threo* form (30%) and the lowest constant (synclinal protons) to the *erythro* one (70%), both conformers being likely stabilized by the intramolecular hydrogen bond OH----N^3 benzothiazole.

Conclusion.

The anionic complex obtained by metalation of 2-methylbenzothiazole reacts easily with polar organic functional groups to form benzothiazoles bearing secondary functions which have been difficult to obtain by other pathways. The main advantages of these reactions are milder conditions, better yields and the ability of stereoselective syntheses.

EXPERIMENTAL

The ir spectra were recorded on Unicam SP-1200 and Perkin-Elmer 580 spectrophotometers. The ^1H and ^{13}C nmr spectra were measured for deuteriochloroform solutions (tetramethylsilane as the internal standard) with a JEOL JNM-FX 100 spectrometer operating respectively at 100 and 25 MHz. For compound **10** the ^1H nmr spectra were recorded on a Brücker AM 400 instrument. Mass spectra were measured with a LKB 2091 spectrometer at 12 and 70 eV (T = 280 K). All melting points were determined on Köfler apparatus. Elemental analyses were obtained from the service central d'Analyse du C.N.R.S..

General Procedure.

A solution of phenyllithium (25 mmoles, 1.4*M*) in a mixture of benzene-ether (70:30 v/v) was added dropwise with stirring and in an argon atmosphere over 10 minutes to a solution of 25 mmoles of 2-alkylbenzothiazole previously dissolved in 90 ml of anhydrous ether then refrigerated at −78°. After the solution had been stirred for a further few minutes a pale yellow precipitate appeared. A solution of 25 mmoles of the reactive polar organic compound in anhydrous ether was added dropwise immediately. Then the mixture reaction was kept for an additional hour at −78° under the same conditions. The mixture was then allowed to warm up to 0° before being hydrolysed by a 14*N* aqueous ammonia solution saturated with ammonium chloride at *p*H 8. For solid compounds the crude material was washed with hot light petroleum-ether to remove the remaining 2-methylbenzothiazole.

I (2-Benzothiazolyl)methyllithium.

Reaction with Benzaldehyde. (2-Hydroxy-2-phenyl)-2-ethylbenzothiazole (**1**).

The yield was 6.4 g (100%) when recrystallized from carbon tetrachloride, mp 152° (lit [13,15] 155°); ir (potassium bromide): ν OH 3250, C=N 1510, thiazole ring 1440 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.4 (d, 2H, CH_2), 5.25 (t, 1H, CH_2-C*H*), 4.35 (s, 1H, OH).

Anal. Calcd. for $C_{15}H_{13}NOS$: C, 70.60; H, 5.10; N, 5.48; S, 12.55. Found: C, 70.52; H, 5.14; N, 5.51; S, 12.41.

Reaction with Acetophenone. (2-Hydroxy-2-phenyl)-2-propylbenzothiazole (**2**).

An ochre solid was obtained from carbon tetrachloride, mp 107° (lit [13] 108°), yield 4.9 g (69%); ir (potassium bromide): ν OH 3270, CH_3 2960, C=N 1510, thiazole ring 1410 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.65 (s, 3H, CH_3), 3.5 (s, 2H, CH_2), 4.95 (s, 1H, OH).

Anal. Calcd. for $C_{16}H_{15}NOS$: C, 71.27; H, 5.57; N, 5.19; S, 11.90. Found: C, 71.56; H, 5.65; N, 5.19; S, 11.65.

Reaction with Benzophenone. (2,2-Diphenyl-2-hydroxy)-2-ethylbenzothiazole (**3**).

A white solid was obtained from carbon tetrachloride mp 214° (lit [13] 216°), yield 7.5 g (90%); ir (potassium bromide): ν OH 3270, C=N 1520, thiazole ring 1460 cm^{-1}; ^1H nmr (deuteriochloroform): δ 4.10 (s, 2H, CH_2), 6.03 (s, 1H, OH).

Anal. Calcd. for $C_{21}H_{17}NOS$: C, 76.11; H, 5.13; N, 4.22; S, 9.67. Found: C, 75.62; H, 5.19; N, 4.22; S, 9.48.

Reaction with Propanone. (2-Hydroxy-2-methyl)-2-propylbenzothiazole (**4**).

The crude material was purified by column chromatography silica gel [eluent toluene chloroform (70/30 v/v)] to give a colorless oil (3.54 g, 62%); ir: ν OH 3400, CH_3 2960, CH_2 2920, C=N 1520, thiazole ring 1440 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.34 (s, 3H, CH_3), 3.24 (s, 2H, CH_2), 4.10 (s, 1H, OH).

Anal. Calcd. for $C_{11}H_{13}NOS$: C, 63.43; H, 6.32; N, 6.76; S, 15.44. Found: C, 63.47; H, 6.16; N, 6.84; S, 15.46.

Reaction with Methyl Benzoate. 2-Phenacylbenzothiazole or (2-Hydroxy)-2-styrylbenzothiazole (**5**).

A yellow solid was obtained from methylcyclohexane, mp 110° (lit [20] 114°), yield 3.2 g (51%); ir (potassium bromide): ν OH 3600-3300, C=O 1680, (C=C enol) 1610, C=N 1570, thiazole ring 1430 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.74 (s, 2H, CH_2), 4.84 (s, 1H, OH), 6.38 (1H, S, C=CH); ms: m/e 253 (M^+), 176 (benzothiazole-CH_2=O), 142 (benzothiazole-CH_2), 105 (Ph-C=O).

Anal. Calcd. for $C_{15}H_{11}NOS$: C, 71.14; H, 4.35; N, 5.53; S, 12.65. Found: C, 70.80; H, 4.27; N, 5.67; S, 12.80.

Reaction with Ethyl Acetate. 2-Acetonylbenzothiazole or (2-Hydroxy)-2-propenylbenzothiazole (**6**).

A pale-orange solid was obtained from methylcyclohexane mp 112° (lit [21] 113°) yield 2.4 g (50%); ir (potassium bromide): ν 3600-3300, C=O 1720, C=C enol 1610, C=N 1540, thiazole ring 1430 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.10 (s, 3H, CH_3 enol), 2.33 (s, 3H, CH_3-C=O), 4.24 (s, 2H, CH_2), 5.63 (s, 1H, CH=).

Anal. Calcd. for $C_{10}H_9NOS$: C, 62.82; H, 4.71; N, 7.33; S, 16.75. Found: C, 62.1; H, 4.80; N, 7.55; S, 16.49.

Reaction with Benzonitrile. (2-Amino)-2-styrylbenzothiazole or (2-Imino)-2-phenethylbenzothiazole (**7**).

An ochre solid was obtained from carbon tetrachloride mp 120°, yield 4.6 g (75%); ir (potassium bromide): ν CH_2 2920, C=C nd NH_2 1620, C=N imine 1585, C=N heterocycle 1570, thiazole ring 1500; ^1H nmr (deuteriochloroform): δ 5.71 (s, 1H, CH=) no imine form; ms: m/e 252 (M^+), 236 (elimination of NH_2), 149 (2-methylbenzothiazole), 103 (benzonitrile) the two last peaks corresponding to a dissociation.

Anal. Calcd. for $C_{15}H_{12}N_2S$: C, 71.42; H, 4.76; N, 11.11; S, 12.70. Found: C, 71.34; H, 4.67; N, 11.06; S, 12.70.

Reaction with Acetonitrile. (2-Amino)-2-propenylbenzothiazole (**8**).

The liquid material was chromatographied on alumina with a mixture toluene-chloroform as the eluent (the gradient of chloroform varying from 20 to 100% by volume). 2-Methylbenzothiazole and a mixture of **6** and the enamine were isolated. The latter was completely transformed into **6** after a slight heating in a 20% ethanol aqueous solution added with a drop of sulfuric acid. On exposure to ambient air the compound released ammonia; ir (potassium bromide): ν NH_2 3580-3430, NH_2 1620, C=N heterocycle 1580, thiazole ring 1430 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.81 (s, 1H, CH), 5.50 (s, 1H, CH= enamine form).

Reaction with Benzoyl Chloride. (1-Benzoyl-2-hydroxy)-2-styrylbenzothiazole (**9**).

After washing with petroleum-ether, this compound was recrystallized from ethanol to yield 2.3 g (25% in comparison with 2-methylbenzothiazole) of a light yellow solid, mp 212°; ir (potassium bromide): ν OH 3480 (weak), C=O 1660, C=C 1595, C=N 1580, thiazole ring 1470 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7-8 (single broad band); ms: m/e 357 (M^+) single significant peak at 12 eV, appearance at 70 eV of many peaks of decomposition and rearrangement especially 252 (benzothiazole-CH-(C=O)-Ph), 105 (Ph-C=O), 77 (Ph) Ph = phenyl radical.

Anal. Calcd. for $C_{22}H_{15}NO_2S$: S, 8.96. Found: S, 8.98.

II (2-Benzothiazolyl)benzyllithium.

Reaction with Benzaldehyde. (1,2-Diphenyl-2-hydroxy)-2-ethylbenzothiazole (**10**).

The conditions of metalation of 2-phenylbenzothiazole were identical to those required for 2-methylbenzothiazole. After complete addition of benzaldehyde the mixture was carried on for 5 hours at −78°. The following steps were identical to those mentioned earlier in the general method.

The compound was only washed with petroleum-ether and obtained as a mixture of two diastereoisomers, yield 6 g (75%), mp 148°; ir (potassium bromide): ν OH 3360, C=N 1510, thiazole ring 1460 cm^{-1}; ir (for carbon tetrachloride solutions): ν OH (broad band) at 3450 cm^{-1}; ^1H nmr (deuteriochloroform): first diastereoisomer (30%) δ 4.589 (d, $JH_\alpha H_\beta$ = 8.25 Hz, 1H, H_α), 5.48 (d, 1H, H_β), 5.59 (br s, 1H, OH); second diastereoisomer (70%) 4.578 (d, $JH_\alpha H_\beta$ = 4 Hz, 1H, H_α), 5.59 (br d, 1H, OH), 5.78 (d, 1H, H_β); ^{13}C nmr: first diastereoisomer δ 57.53 (C_α), 75.59 (C_β); second diastereoisomer 58.58 (C_α), 78.1 (C_β). The other peaks are in good agreement with the proposed structure.

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