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# A Novel Dilithiation Approach to 3,4-Dihydro-2*H*-1,3-benzothiazines, 3,4-Dihydro-2*H*-1,3-benzoxazines, and 2,3,4,5-Tetrahydro-1,3-benzothiazepines

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**Abstract:** 3,4-Dihydro-2*H*-1,3-benzothiazines **4**, 3,4-dihydro-2*H*-1,3-benzoxazines **9**, and 2,3,4,5-tetrahydro-1,3-benzothiazepines **6** were synthesized by directed ortho-lithiation of thiophenols and phenols and by side-chain lithiation of substituted thiophenols, respectively, in one-pot by reacting with *N*,*N*-bis[(benzotriazol-1-yl)methyl]amines **3** as 1,3-biselectrophile synthons.

1,3-Benzothiazines and 1,3-benzoxazines are of significant pharmacological interest.[1−7] Benzothiazepines are also potent bradykinin agonists[8] and have shown activity as endogenous natriuretic factors,[9] enzyme inhibitors,[10] muscle relaxants, anticonvulsants,[11] sedatives, and hypnotics.[12] Campiani and co-workers have developed novel pyrrolo[2,1-*b*][1,3]benzothiazepines as antipsychotic agents with serotonin and dopamine antagonist properties.[13]

Synthetic approaches for 3,4-dihydro-2*H*-1,3-benzothiazines include (Scheme 1, Supporting Information): (i) condensation of 4,5-dimethoxy-2-mercaptobenzylammonium chloride with an aromatic aldehyde in the presence of potassium carbonate[14] and (ii) cycloaddition of benzothiete with corresponding substituted imines.[15] We have found no literature for the synthesis of 2,3,4,5-tetrahydro-1,3-benzothiazepines.

Many reports on the synthesis of 3,4-dihydro-2*H*-1,3-benzoxazines (Scheme 2, Supporting Information) describe (i) Mannich condensation of phenol and a primary amine with formaldehyde,[5b,16] (ii) condensation of *o*-hydroxybenzylamine with an aldehyde,[17] (iii) rearrangement reactions of 2-(allyloxy)benzylamine with $H_2$/CO in the presence of rhodium catalysts,[18] (iv) condensation of a 4-substituted phenol with 1,3,5-trimethyl-hexahydro-*s*-triazine in the presence of oxalyl chloride,[19] (v) reaction of 1-(bromomethyl)-2-(chloromethoxy)benzene with primary amines,[20] and (vi) dehydration of *N*-(2-hydroxybenzyl)-3-aminopropanoic acid in the presence of sulfuric acid.[21]

Directed ortho-metalation methodology offers a predictable and widely applicable synthetic strategy for the regiospecific construction of heterocyclic compounds.[22] Directed ortho-lithiations of thiophenol and phenol have been developed.[23] We now show that such directed ortho-lithiations of thiophenols and phenol provide a novel benzotriazole-mediated approach to 3,4-dihydro-2*H*-1,3-benzothiazines, 1,3-benzoxazines, and 2,3,4,5-tetrahydro-

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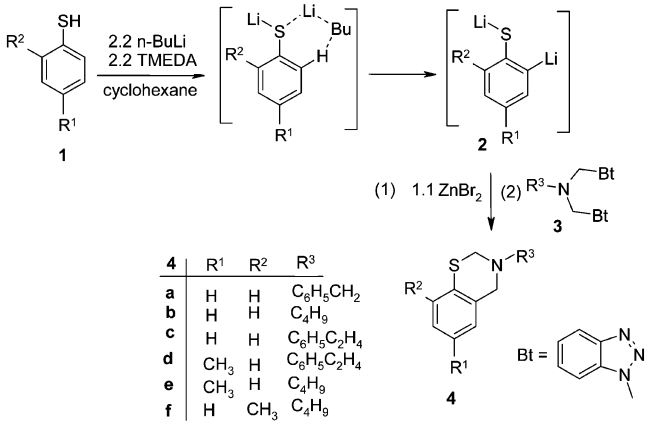
**SCHEME 1**




| 4 | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| a | H | H | $C_6H_5CH_2$ |
| b | H | H | $C_4H_9$ |
| c | H | H | $C_6H_5C_2H_4$ |
| d | $CH_3$ | H | $C_6H_5C_2H_4$ |
| e | $CH_3$ | H | $C_4H_9$ |
| f | H | $CH_3$ | $C_4H_9$ |

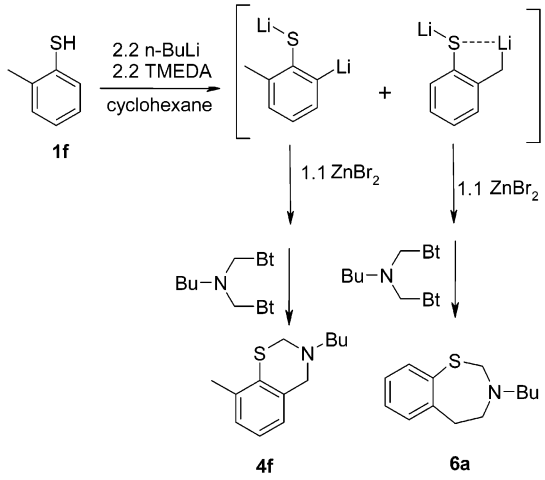
1,3-benzothiazepines (via side-chain lithiation of substituted thiophenols) in synthetically useful yields.

*N*,*N*-Bis[(benzotriazol-1-yl)methyl]amines (**3**), readily prepared from 1-(hydroxymethyl)benzotriazole and amines or from benzotriazole, formaldehyde, and amines, are useful as nitrogen atom centered 1,3-biselectrophile synthons.[24] In the present paper, [3 + 3] cyclizations provided 3,4-dihydro-2*H*-1,3-benzothiazines and -1,3-benzoxazines, and [3 + 4] cyclizations gave 2,3,4,5-tetrahydro-1,3-benzothiazepines using the reaction of 1,3-biselectrophile synthons **3** with 1,3- or 1,4-dianions generated by dilithiations of phenol and substituted thiophenols.

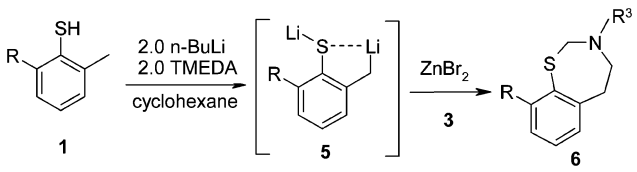
**Synthesis of 3,4-Dihydro-2*H*-1,3-benzothiazines 5 by Directed Ortho-Lithiation of Thiophenols.** Thiophenols **1** are known to react with 2.2 equiv of *n*-butyllithium (*n*-BuLi) and 2.2 equiv of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) to form lithium dianions **2** in cyclohexane at room temperature.[23a] However, the strong basicity of the lithium-paired dianions **2** probably destroys the 1,3-biselectrophile synthons **3**, because direct addition of compounds **3** to the solution of **2** did not yield any promising results. Fortunately, initial treatment of dianions **2** with 1.1 equiv of $ZnBr_2$, then reacted readily with **3** to give 3,4-dihydro-2*H*-1,3-benzothiazines **4** in good yields (Scheme 1). Structures of **4** were characterized by $^1H$ and $^{13}C$ NMR and microanalysis. In the $^1H$ NMR, two distinct singlets, usually at 4.50−4.63 and 3.90−4.04 ppm, were ascribed to the $N\underline{CH_2}S$ and $N\underline{CH_2}Ar$ groups, respectively.

Although reactions were successful using aliphatic amines **3** ($R^3$ = aliphatic group) as 1,3-biselectrophile synthons, the expected 1,3-benzothiazine **4** was not obtained using reagents **3** derived from aromatic amines in these reactions; reactions attempted with phenyl and with 4-methoxyphenyl derivatives (**3**, $R^3 = C_6H_5$, 4-$CH_3OC_6H_4$) did not give desired products either for 1,3-benzothiazines or for 1,3-benzoxazines. A possible reason could be that the activated benzene ring in such derivatives **3** reacted with other components in the reaction system.

**SCHEME 2**




**SCHEME 3**




| 6 | R | $R^3$ |
|---|---|---|
| a | H | $C_4H_9$ |
| b | $CH_3$ | $C_4H_9$ |
| c | $CH_3$ | $C_6H_5C_2H_4$ |
| d | H | $C_6H_5C_2H_4$ |

When 2-methylthiophenol was used as the starting material, another product, 3-butyl-2,3,4,5-tetrahydro-1,3-benzothiazepine (**6a**) (25%), was obtained along with the desired **4f**. This indicates that side-chain lithiation also proceeds under these reaction conditions (Scheme 2). Attempts to increase the yield of **4f** failed.

**Synthesis of 2,3,4,5-Tetrahydro-1,3-benzothiazepines 6 Using Side-Chain Lithiation.** Side-chain lithiation frequently occurs prior to ring ortho-lithiation to give dilithiated species.[23a] When a mixture of exactly 2.0 equiv of *n*-BuLi and 2.0 equiv of TMEDA was used as a base to dilithiate 2-methylthiophenol (**1f**, $R^1$ = H, $R^2 = CH_3$), only the side-chain dianion **5** was formed and addition of **3** led to the formation of compound **6a** as the sole product (Scheme 3). This fact demonstrates that side-chain lithiation is prior to ring ortho-lithiation. Other 1,3-benzothiazepines **6** were obtained using similar reaction conditions starting from various substituted thiophenols and **3**. All products were confirmed by their $^1H$ and $^{13}C$ NMR and microanalysis data. In $^1H$ NMR spectra, a singlet around 4.4 ppm was ascribed to $S\underline{CH_2}N$ group in the seven-membered ring. At room temperature, two protons of $N\underline{CH_2}CH_2Ar$ in the ring were absent because it showed a very broad peak from 2.8 to 3.3 ppm. When the spectrum was run at 60 °C, a broad singlet for four protons appeared around 3.07−3.10 ppm. Apparently, this peak is due to the overlap of $N\underline{CH_2}CH_2Ar$ in the ring and $N\underline{CH_2}R$ substitution at the 3-position. An additional

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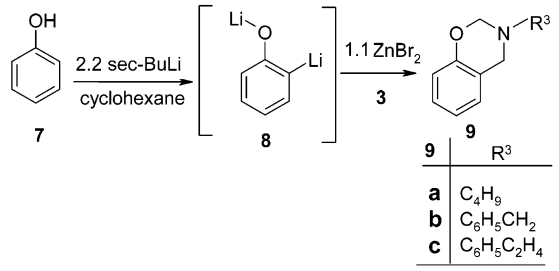
**SCHEME 4**




| 9 | $R^3$ |
|---|---|
| a | $C_4H_9$ |
| b | $C_6H_5CH_2$ |
| c | $C_6H_5C_2H_4$ |

quaternary carbon in the APT spectra of compounds **6** as compared to **1** confirmed the cyclization.

**Synthesis of 3,4-Dihydro-2*H*-1,3-benzoxazines 9 in One-Pot Reactions.** We also extended the methodology of directed ortho-lithiation used to synthesize 1,3-benzothiazines **5** for the synthesis of 3,4-dihydro-2*H*-1,3-benzoxazines **9** with slight modification. However, we do not find extra advantage of our methodology as compared to previously reported methods. Treatment of phenol (**7**) with 2.2 equiv of *s*-BuLi in cyclohexane gave the dianion **8** at room temperature.[23b] Subsequent addition of zinc bromide and aliphatic amines **3** gave products **9** in 66−70% (Scheme 4). Structures **9** were clearly supported by their $^1$H and $^{13}$C NMR and microanalysis data. In their $^1$H NMR spectra, two sharp singlets at around 4.87 and 3.99 ppm were attributed to the $NCH_2O$ and $NCH_2Ar$ groups of the ring. One more tertiary carbon, which was observed in aromatic field in APT experiments, further confirmed the cyclization. All examples of **9** were successfully obtained when $R^3$ in compounds **3** was an aliphatic group. No desired products were isolated if aromatic amines **3** were used.

In summary, a novel approach to 3,4-dihydro-2*H*-1,3-benzothiazines, 1,3-benzoxazines, and 2,3,4,5-tetrahydro-1,3-benzothiazepines was successfully achieved by the directed ring ortho-lithiation or side-chain lithiation of substituted thiophenols and phenol and reaction of them with compounds **3**. However, while this methodology is successful for a range of aliphatic amines, we failed to isolate expected products for aromatic amines.

## Experimental Section

Cyclohexane was dried by successive addition of freshly cut sodium pieces until no further hydrogen evolution was observed. THF was distilled from sodium-benzophenone prior to use. All of the reactions were carried out under $N_2$.

**Synthesis of 3,4-Dihydro-2*H*-1,3-benzothiazines 4.** To a solution of *n*-BuLi (6.9 mL, 11.0 mmol, 1.60 M in hexane) and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA, 1.28 g, 11.0 mmol) in dry cyclohexane (5 mL) was added the corresponding thiophenol (5 mmol) dropwise at room temperature under nitrogen. The formed mixture was stirred for 19 h at room temperature and then cooled to 0 °C. $ZnBr_2$ (1.35 g, 6.0 mmol) in THF (5 mL) was added to the yellow solution. After 30 min, the corresponding amine **3** (5 mmol) in THF (10 mL) was added. The mixture was allowed to stir at room temperature overnight. Then, it was filtered, and the filter cake was washed with $Et_2O$ three times. The combined organic solution was washed with saturated $NH_4Cl$, 1 M NaOH, and brine and dried over $MgSO_4$. The solvent was evaporated in vacuo, and the residue was purified by column chromatography (eluent EtOAc/hexanes = 1/100 → 1/50).

**3-Benzyl-3,4-dihydro-2*H*-1,3-benzothiazine (4a):** pink needles (from hexanes/EtOAc); yield, 54%; mp 57−58 °C; $^1$H NMR $\delta$ 7.45−7.36 (m, 5H), 7.19−7.06 (m, 3H), 6.98 (d, $J$ = 7.5 Hz, 1H), 4.59 (s, 2H), 4.08 (s, 2H), 3.90 (s, 2H); $^{13}$C NMR $\delta$ 137.9, 133.0, 129.2, 128.6, 128.4, 127.6, 127.4, 127.4, 126.9, 124.3, 55.4, 54.9, 53.9. Anal. Calcd for $C_{15}H_{15}NS$: C, 74.65; H, 6.26; N, 5.80. Found: C, 74.40; H, 6.62; N, 5.85.

**Synthesis of 2,3,4,5-Tetrahydro-1,3-benzothiazepines 6.** To a solution of *n*-BuLi (6.25 mL, 10.0 mmol, 1.60 M in hexane) and TMEDA (1.15 g, 10.0 mmol) in dry cyclohexane (5 mL) was added substituted thiophenol (5 mmol) dropwise at room temperature under nitrogen. The formed mixture was stirred for 24 h and then cooled to 0 °C. $ZnBr_2$ (1.35 g, 6.0 mmol) in THF (5 mL) was added to the yellow solution. After 30 min, the corresponding amine **3** (5 mmol) in THF (10 mL) was added. The mixture was allowed to stir for 24 h at room temperature. Then, it was filtered, and the filter cake was washed with $Et_2O$ three times. The combined organic solution was washed with saturated $NH_4Cl$, 1 M NaOH, and brine and dried over $MgSO_4$. The solvent was evaporated in vacuo and the residue was purified by column chromatography (eluent EtOAc/hexanes = 1/100 → 1/50).

**3-Butyl-2,3,4,5-tetrahydro-1,3-benzothiazepine (6a):** colorless oil; yield, 45%; $^1$H NMR ($CDCl_3$, 60 °C) $\delta$ 7.44 (d, $J$ = 7.0 Hz, 1H), 7.08−7.00 (m, 3H), 4.39 (s, 2H), 3.07 (br s, 4H), 2.93 (t, $J$ = 7.0 Hz, 2H), 1.51−1.44 (m, 2H), 1.41−1.34 (m, 2H), 0.95 (t, $J$ = 7.0 Hz, 3H); $^{13}$C NMR $\delta$ 146.3, 138.3, 132.5, 130.1, 127.0, 126.0, 62.4, 52.3, 50.0, 33.0, 29.2, 20.6, 14.0. Anal. Calcd for $C_{13}H_{19}NS$: C, 70.53; H, 8.65; N, 6.33. Found: C, 70.88; H, 8.70; N, 6.22.

**Synthesis of 3,4-Dihydro-2*H*-1,3-benzoxazines 9.** To a solution of phenol (5 mmol) in dry cyclohexane (5 mL) was added *s*-BuLi (7.2 mL, 11.0 mmol, 1.50 M in hexane) dropwise at 0 °C. The reaction mixture was stirred for 8 h at room temperature under nitrogen and then cooled to 0 °C. $ZnBr_2$ (1.35 g, 6.0 mmol) in THF (10 mL) was added to the yellow solution. After 30 min, the corresponding amine **3** (5 mmol) was added. The mixture was allowed to stir at room temperature overnight. Then, the resulting mixture was filtered, and the filter cake was washed with EtOAc three times. The combined organic solution was washed with saturated $NH_4Cl$, 1 M NaOH, and brine and dried over $MgSO_4$. The solvent was evaporated in vacuo and the residue was purified by column chromatography (eluent EtOAc/hexanes = 1/10).

**3-Butyl-3,4-dihydro-2*H*-1,3-benzoxazine (9a):** colorless oil; yield, 70%; $^1$H NMR $\delta$ 7.11 (t, $J$ = 7.3 Hz, 1H), 6.95 (d, $J$ = 7.0 Hz, 1H), 6.86 (t, $J$ = 7.0 Hz, 1H), 6.77 (d, $J$ = 8.2 Hz, 1H), 4.87 (s, 2H), 3.99 (s, 2H), 2.74 (t, $J$ = 7.3 Hz, 2H), 1.60−1.50 (m, 2H), 1.41−1.29 (m, 2H), 0.92 (t, $J$ = 7.0 Hz, 3H); $^{13}$C NMR $\delta$ 154.2, 127.6, 127.5, 120.4, 120.3, 116.3, 82.4, 51.1, 50.2, 30.3, 20.4, 14.0. Anal. Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.59; H, 9.25; N, 7.71.

**Supporting Information Available:** Characterization data for compounds **4b**−**f**, **6b**−**d**, and **9b,c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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