Heterocyclic Compounds III. Synthesis of Some Substituted Thienopyrimidines (1)

M. S. Manhas and S. D. Sharma

Department of Chemistry and Chemical Engineering, Stevens Institute of Technology, Hoboken, New Jersey 07030

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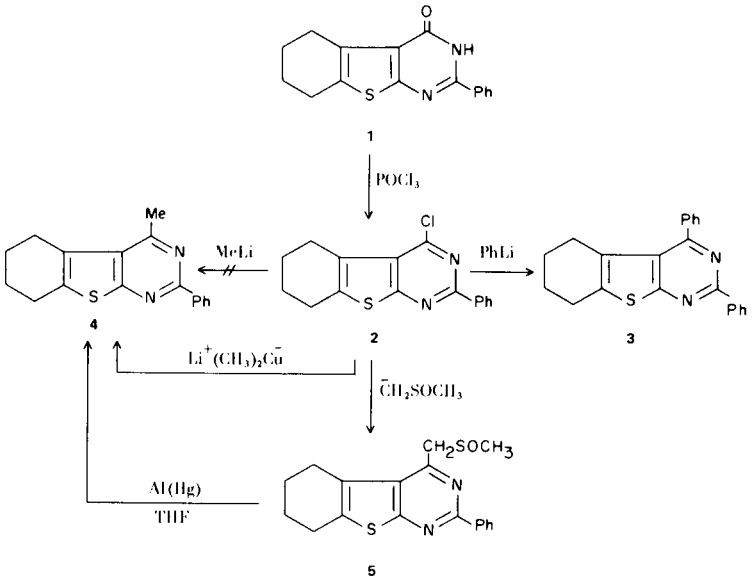
Several substituted quinazolones have been found to be therapeutically active (2). Since thienopyrimidones are isosteric with quinazolones, it appeared to be of interest to undertake the synthesis of this class of compounds. In an earlier publication (1b) we described the synthesis of 4-oxo-2-phenyl-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidine (**1**). In the present communication we wish to report some reactions of **1**.

4-Pyrimidones (3) and 4-quinazolones (4) undergo facile reaction with phosphorus oxychloride to give the corresponding 4-chloro derivatives. Analogously **1** can be converted to **2** in high yield by refluxing with phosphorus oxychloride. When a dimethylformamide solution of **1** is treated with phosphorus oxychloride (5) spontaneous reaction takes place and the chloro compound **2** separates as a crystalline solid in 10-15 minutes.

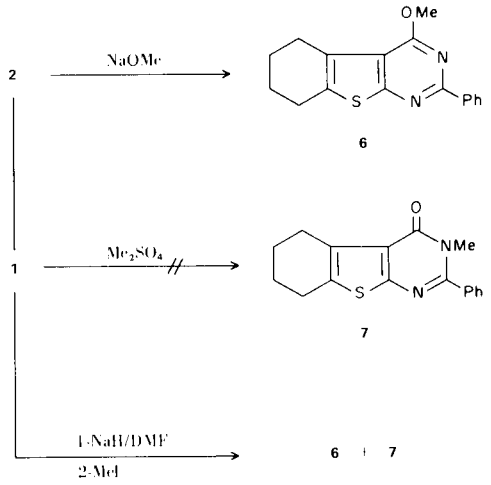
Treatment of **2** with phenyllithium in tetrahydrofuran gave the 4-phenyl derivative **3** in good yield. Under similar conditions methyllithium failed to produce the 4-methyl derivative **4**. The only product isolated from the reaction mixture was **1** which arise from **2** by hydrolysis during work up.

Methylsulfinyl carbanion has been used as a powerful nucleophile to generate C-C bonds (6). Reaction of **2** with this anion in dimethyl sulfoxide afforded **5** in high yield. The nmr spectrum of this compound showed the methylene protons adjacent to the sulfoxide function as an AB pattern with a coupling constant of 13 cps. The sulfoxide **5** was reduced to **4** with aluminum amalgam (7,8) in aqueous tetrahydrofuran solution. It was found that **4** could also be obtained in almost quantitative yield by the treatment of **2** with lithium dimethylcopper complex (9). It is worth noting that satisfactory yields of the alkylated product have been reported in the past only when bromo- or iodo- substituted aliphatic or aromatic compounds were used as substrates in this type of reaction. Recently Bose and co-workers (10) have studied the reaction of this complex with 9-halophenanthridines and observed that C-9 methylation could not be accomplished when the 9-chloro compound was employed. Therefore, it appears that the chlorine in **2** is particularly reactive.

Attempts to prepare the *N*-methyl derivative **7** by treating **1** with an aqueous or alcoholic solution of potassium hydroxide and dimethyl sulfate (11) under various



reaction conditions were not successful. In all cases the starting amide **1** was recovered unchanged. However, when **1** was treated with sodium hydride in dimethylformamide at 40° followed by reaction with methyl iodide, a mixture of products was isolated. The nmr spectrum of the crude product showed singlets at τ 6.58 and 5.93 indicating the presence of *N*-methyl- (**7**) and *O*-methyl- (**6**) derivatives in equal amounts (12). Repeated crystallization of the crude mixture was used for the separation of **6** and **7** - the *N*-methyl derivative **7** being the less soluble constituent. The structure of the *O*-methyl derivative **6** was confirmed by comparison with an authentic sample prepared by reacting **2** with sodium methoxide in methanol.



EXPERIMENTAL

Melting points are uncorrected. Infrared spectra were recorded with a Perkin-Elmer Infracord. Nmr spectra were taken in deuteriochloroform on a Varian A60A spectrometer using tetramethylsilane as an internal standard. Mass spectra were obtained using a RMU-7 mass spectrometer. Microanalyses were performed by A. Bernhardt, Mikroanalytisches Laboratorium in Max-Planck Institute, Mulheim (Ruhr), West Germany.

4-Chloro-2-phenyl-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidine (**2**).

4-Oxo-2-phenyl-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidine (1.5 g.) was treated with 40 ml. of phosphorus oxychloride at room temperature first and then under reflux for ½ hour. The reaction mixture was poured into an excess of cold water and stirred vigorously when a white solid separated. This material was collected under suction and recrystallized from methylene chloride, m.p. 171-172°, yield 5.3 g. (85%); nmr: τ 1.53 (m, 2H); 2.55 (m, 3H); 6.97 and 7.17 (b, 4H) and 8.10 (b, 4H).

Anal. Calcd. for $C_{16}H_{13}ClN_2S$: C, 64.01; H, 4.33; N, 9.33; S, 10.66; Cl, 11.67. Found: C, 63.84; H, 4.44; N, 9.20; S, 10.56; Cl, 11.68.

2,4-Diphenyl-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidine (**3**).

To a solution of 2 g. of the chloro compound (**2**) in anhydrous THF (25 ml.) cooled to 0° was added dropwise with constant stirring a THF solution of phenyllithium (2 g.) under nitrogen atmosphere. The contents were stirred for about 6 hours at 0° and then an additional 2 hours at room temperature. The excess reagent was destroyed with water and the solvent was evaporated under reduced pressure at room temperature. The residue was extracted with dichloromethane, the organic phase washed with brine, water and dried (magnesium sulfate). Removal of the solvent afforded the product as a yellow solid which was recrystallized from benzene, m.p. 195-196°, yield 1.45 g. (65%); nmr: τ 2.22 (m, 2H); 2.62 (m, 3H); 2.65 (S, 5H); 7.30 (b, 4H), and 8.20 (b, 4H).

Mass spectra showed molecular ion peak at m/e 342.

Anal. Calcd. for $C_{22}H_{18}N_2S$: C, 77.17; H, 5.30; N, 8.18. Found: C, 76.97; H, 5.40; N, 8.16.

2-Phenyl-4-methyl-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidine (**4**).

Lithium dimethylcopper reagent was prepared in anhydrous ether under nitrogen atmosphere according to the procedure of Corey and coworkers (10). The chloro compound (**2**, 1 g.) in THF solution was added to a five molar proportion of the above complex at 0°. The contents were stirred at this temperature for 6 hours and then left overnight at room temperature. The excess reagents were destroyed with a solution of ammonium chloride. The organic layer was separated and the aqueous phase extracted thoroughly with ether. The ethereal extracts were combined with the THF layer, washed with water, and dried (magnesium sulfate). Evaporation of the solvent gave the title compound which was crystallized from dichloromethane-hexane mixture, m.p. 128-129°, yield 0.7 g. (82%); nmr: τ 1.55 (m, 2H); 2.65 (m, 3H); 7.12 (b, 4H); 7.17 (S, 3H) and 8.12 (b, 4H).

Anal. Calcd. for $C_{17}H_{16}N_2S$: C, 72.85; H, 5.71; N, 10.05; S, 11.43. Found: C, 73.01; H, 5.63; N, 10.17; S, 11.38.

2-Phenyl-4-(methylsulfinylmethyl)-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidine (**5**).

A suspension of sodium hydride (1.25 g.) in dry dimethyl sulfoxide (40 ml.) was stirred at 70° under nitrogen. After the solution became clear and the evolution of hydrogen had ceased, it was cooled to 0°. A solution of 3 g. of the chloropyrimidine (**2**) in dry THF (40 ml.) was added dropwise with constant stirring to the above solution. After the addition was complete the reaction mixture was warmed to 50° and stirred for 2 hours and left overnight at room temperature. The contents were then diluted with ice cold water and extracted with dichloromethane. The organic layer was washed with brine followed by water and dried (magnesium sulfate). Evaporation of the solvent provided 2.8 g. of the title compound (80%), m.p. 153-154° (methylene chloride + hexane); nmr: τ 1.62 (m, 2H); 2.57 (m, 3H); 5.29 (d, 1H, J = 13 cps); 5.59 (d, 1H, J = 13 cps); 7.10 (b, 4H); 7.23 (S, 3H) and 8.08 (b, 4H); M^+, m/e 342.

Anal. Calcd. for $C_{18}H_{18}N_2OS_2$: C, 63.15; H, 5.34; N, 8.18. Found: C, 62.98; H, 5.34; N, 8.40.

Conversion of **5** into **4**.

The above sulfoxide (**5**, 1.3 g.) was dissolved in a mixture of 90 ml. of THF and 10 ml. of water. Freshly prepared amalgamated aluminum foil (1 g.) was added to the solution in small pieces and

allowed to react by stirring for 10 minutes at room temperature and then at reflux for additional 30 minutes. The reaction mixture was filtered and the inorganic products were washed with THF. The THF was removed from the combined filtrate and the washings under reduced pressure. The residue was extracted with ether. The removal of the solvent from the ethereal extract after drying, (magnesium sulfate) furnished 650 mg. (65%) of solid compound which was found to be identical with the previously prepared sample on the basis of undepressed mixture melting point and identity of spectral data.

2-Phenyl-4-methoxy-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]-pyrimidine (**6**).

A mixture of 3 g. of the chloro compound (**2**) and sodium methoxide (650 mg.) was refluxed for 6 hours in anhydrous methanol (50 ml.). The solvent was then removed on a rotary evaporator. The residue was extracted with dichloromethane washed with water and dried (magnesium sulfate). Removal of the solvent provided the methoxy compound as a white solid in quantitative yield, m.p. 164-165° (methylene chloride); nmr: τ 1.53 (m, 2H); 2.60 (m, 3H); 7.20 (b, 4H) and 8.19 (b, 4H); M^+ at m/e 296.

Anal. Calcd. for $C_{17}H_{16}N_2OS$: C, 68.90; H, 5.44; N, 9.45. Found: C, 68.85; H, 5.41; N, 9.38.

2-Phenyl-3-methyl-4-oxo-5,6,7,8-tetrahydro[1]benzothieno-[2,3-*d*]pyrimidine (**7**).

To a stirred solution of the amide (**1**, 3 g.) in anhydrous DMF (100 ml.) was added sodium hydride (500 mg. 50% dispersion in oil). The contents were maintained at 40° until hydrogen evolution had ceased. Methyl iodide (1.08 g.) was then added to this solution at room temperature with constant stirring under nitrogen atmosphere. The stirring was continued for 24 hours at room temperature. The solvent was then removed under reduced pressure and the residue (2 g., 70%) on recrystallization from methanol provided two solids in equal amounts. The more soluble component was recrystallized from dichloromethane and was found to be identical with **6** through its spectral data and melting and mixture melting points. The second solid (less soluble component) after recrystallization from methanol melted at 147° and showed a strong amide carbonyl absorption at 6 μ in its ir spectrum. This was characterized as the title compound; nmr: τ 2.55 (S, 5H); 6.58 (S, 3H); 6.95 (b, 2H); 7.20 (b, 2H) and 8.13 (b, 4H); mass spectra M^+ at m/e 296.

REFERENCES

(1a) M. S. Manhas and J. R. McCoy, *J. Chem. Soc. (C)*, 1419 (1969); (b) M. S. Manhas, V. V. Rao, P. A. Seetharaman, D. Succardi, and J. D. Pazdera, *ibid.*, 1937 (1969) may be considered as part I and part II respectively in this series.

(2) For a detailed account see ref. 3, p. 490.

(3) D. J. Brown, "The Pyrimidines", Interscience Publishers, New York, N. Y. (1962), p. 162. Also see "The Pyrimidines" Supplement I, p. 110.

(4) W. L. F. Armarego in "Fused Pyrimidines" Part I, D. J. Brown, Ed., Interscience Publishers, New York, N. Y. (1967), p. 222.

(5) Also see H. Eilingsfeld, M. Seefelder, and H. Weidingen, *Angew. Chem.*, 72, 836 (1960).

(6) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, 84, 866 (1962); *ibid.*, 87, 1345 (1965).

(7) E. J. Corey and M. Chaykovsky, *ibid.*, 86, 1639 (1964).

(8) H. D. Becker, G. J. Mikol, and G. A. Russell, *ibid.*, 85, 3410 (1963).

(9) E. J. Corey and G. H. Posner, *ibid.*, 89, 3911 (1967).

(10) A. K. Bose, M. S. Manhas, S. D. Sharma, S. G. Amin, and H. P. S. Chawla, *Syn. Comm.*, 1, 33 (1971).

(11) K. Ganpathi, C. V. Deliwala, and M. V. Shirsat, *Proc. Ind. Acad. Sci.* (A), 16, 115 (1942); through *Chem. Abstr.*, 37, 1403 (1943).

(12) P. Aeberli and W. Houlihan, *J. Org. Chem.*, 33, 2402 (1968).