Synthesis of a Novel Series of 3-Substituted [1]Benzothieno[3,2-*d*]pyrimidine Derivatives

Farag El-Telbany

Organic Chemistry Department, Faculty of Pharmacy,
Cairo University, Cairo, Egypt

Robert O. Hutchins*

Department of Chemistry, Drexel University,
Philadelphia, PA 19104 USA

Received August 13, 1984

A series of 3-substituted [1]benzothieno[3,2-*d*]pyrimidine derivatives has been synthesized as possible anti-leukemic agents by condensation of methyl 3-(ethoxymethylene)amino-2-benzothiophene carboxylate (II) with a variety of amines to afford the corresponding 3-aryl and 3-alkyl [1]benzothieno[3,2-*d*]pyrimidin-4(3*H*)-ones, III and IV, respectively. In addition, Mannich reactions of [1]benzothieno[3,2-*d*]pyrimidin-4(3*H*)-one (VIII) with formaldehyde and secondary amines gave the expected derivatives, IX. 3-Amino[1]benzothieno[3,2-*d*]-pyrimidin-4(3*H*)-one (VI) reacted with substituted aromatic aldehydes in the presence of boron trifluoride to yield the corresponding imines VII.

J. Heterocyclic Chem., **22**, 401 (1985).

Substituted pyrimidines have attracted considerable synthetic interest since members of this class possess effectiveness as sedatives, anti-inflammatory agents, CNS depressants, diuretics, hypocholesteroiemics, anti-allergics and anti-tussive compounds [1-8]. Our interests in thienopyrimidines [9] coupled with their potential activity as anti-leukemic agents stimulated this investigation of the synthesis of a variety of 3-substituted [1]benzothieno-[3,2-*d*]pyrimidin-4(3*H*)-ones.

Condensation of methyl 3-amino-2-benzothiophenecarboxylate (I) with equimolar quantities of ethyl orthoformate and *p*-bromoaniline in refluxing decalin gave a crystalline product identified as 3-(*p*-bromophenyl)[1]benzothieno-[3,2-*d*]pyrimidin-4(3*H*)-one, (IIIc, ir: 1710, C=O, no NH band, see Experimental). Alternatively, VIc was prepared in a two step process involving initial condensation of I with ethyl orthoformate [10] to generate the imidate II followed by reaction with *p*-bromoaniline. Imidate II proved to be a key intermediate for subsequent conversion to a number of related 3-substituted pyrimidines. Thus, reaction of II with aniline or the *m*-chloro-, *p*-iodo-, *p*-hydroxy- or *p*-methoxyaniline analogs afforded the respective 3-aryl[1]benzothieno[3,2-*d*]pyrimidin-4(3*H*)-ones IIIa-d in 64-83% yields (Table I). Likewise, the corresponding 3-alkyl derivatives IVa-c were conveniently available *via* condensation of II with appropriate primary amines at 100° (Table I).

Treatment of II with hydrazine hydrate afforded 3-amino[1]benzothieno[3,2-*d*]pyrimidin-4(3*H*)-one (VI) which

Scheme I

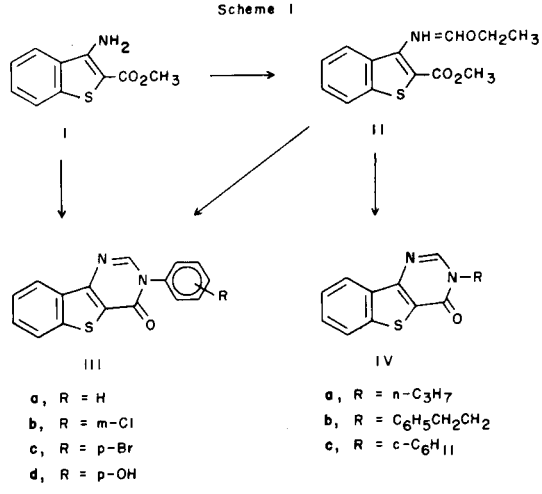


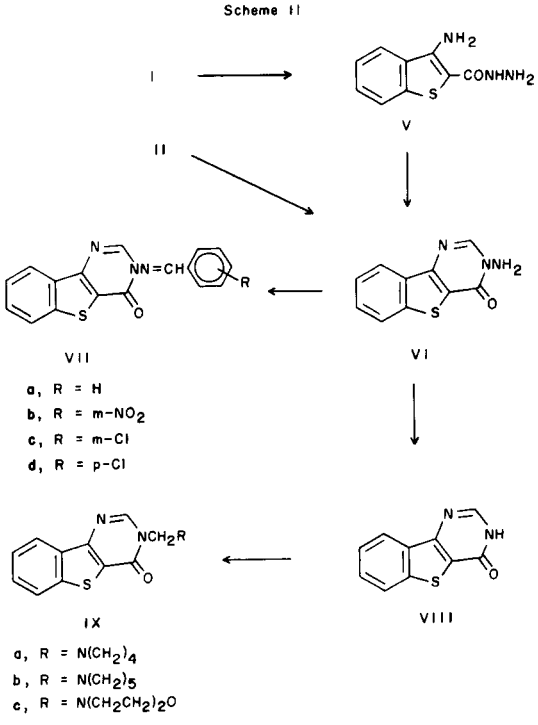
Table I

Data for 3-Substituted [1]Benzothieno[3,2-*d*]pyrimidine-4(3*H*)-ones

Compound [a]	% Yield	Mp °C (crystallization solvent)	IR	Analysis Calcd. C	Calcd. H	Found C	Found H
IVa	96	154-155 (aq EtOH)	1660	63.91	4.95	64.05	4.88
IVb	77	166-168 (aq EtOH)	1655	70.56	4.60	70.81	4.60
IIIa	64	220-222 (aq DMF)	1660	69.04	3.62	68.77	3.59
IIIb	65	250-251 (aq EtOH)	1690	61.44	2.90	61.55	2.23
IIId	85	235-237 (DMF)	1640	65.29	3.40	65.27	3.55
VIIa	92	212-214 (DMF)	1675	66.88	3.61	66.76	3.91
VIIb	92	245-246 (DMF)	1600	58.28	2.86	58.39	2.76
VIId	93	280-282 (DMF)	1650	60.08	2.97	59.81	3.48
IXb	77	115-117 (Ben-pet Et)	1660	64.21	5.68	63.94	5.88
IXc	95	115-116 (Ben-pet Et)	1665	59.80	4.98	59.81	5.11

[a] All compounds gave nmr spectra consistent with the structures.

Scheme II



was alternatively obtained from I by initial conversion into the corresponding carbohydrazide V followed by treatment with ethyl orthoformate. Formation of pyrimidones instead of the previously reported seven-membered ring triazepenones [11,12] was demonstrated by nitrous acid deamination to the known pyrimidone [13,14] [1]benzothieno[3,2-*d*]pyrimidin-4(3*H*)-one (VIII). Condensation of III with various aromatic aldehydes (boron trifluoride, chloroform) afforded the corresponding imines VII in 91-95% yields. Reaction of V with formaldehyde and secondary amines (ambient temperature) yielded the corresponding Mannich-type bases [15] IX in 77-95% yields.

Several of the above described compounds (IVa, VIIb, c, d and IXc were tested for anti-leukemic activity according to a standard protocol [16]. In this assay only IXc showed presumptive activity; confirmatory testing is presently being conducted.

EXPERIMENTAL

Melting points were determined on a Mel-Temp apparatus and are uncorrected. The pmr spectra were recorded on a Varian A-60 spectrometer using TMS as an internal standard. Signals are reported in ppm. The ir spectra were determined as potassium bromide disks on a Perkin-Elmer 457 spectrometer. Absorptions were reported in cm^{-1}. Mass spectra were measured on a Finnegan 4023 instrument. Microanalyses were performed by Microanalysis Inc., Wilmington, DE 19808. Methyl 3-aminobenzo-[*b*]thiophene-2-carboxylate (I) and [1]benzothieno[3,2-*d*]pyrimidin-4(3*H*)-one (VIII) were prepared according to reported procedures [13,14].

3-(*p*-Bromophenyl)[1]benzothieno[3,2-*d*]pyrimidin-4(3*H*)-one (IIIc).

Method A.

A mixture of I (2.0 g, 10 mmoles), *p*-bromoaniline (1.7 g, 10 mmoles) and ethyl orthoformate (22.5 g, 150 mmoles) in decalin (25 ml) was refluxed for 10 hours, cooled, diluted with petroleum ether and the colorless solid which separated collected and recrystallized from aqueous DMF to yield 2.3 g (65%) of VIc, mp 280-281°; ir: ν 3000 (CH), 1710 (C=O), 1620 (N=C), 760 (CS) cm^{-1}; nmr (DMSO-d_6): 7.1 (d, 4H), 7.5-8.5 (m, 5H).

Anal. Calcd. for $C_{16}H_9BrNOS$: C, 53.78; H, 2.52. Found: C, 53.74; H, 2.82.

Method B.

Methyl 3-(Ethoxymethylene)amino-2-benzo[*b*]thiophenecarboxylate, (II).

A mixture of I (2.0 g, 10 mmoles) and ethyl orthoformate (10 g, 70 mmoles) was refluxed for 1 hour. Excess ethyl orthoformate was distilled under vacuum and the residue extracted with petroleum ether which was evaporated to furnish II as a pale yellow solid. Recrystallization from petroleum ether gave thin needles, mp 75-76°; ir: 1230 (CO), 1650, 1510 (C=C and C=N), 1710 cm^{-1} (C=O, ester); nmr (deuteriochloroform): δ 1.5 (t, 3H), 3.9 (s, 3H), 4.6 (d, 2H), 7.3-7.75 (m, 5H).

Anal. Calcd. for $C_{12}H_{13}NO_3$: C, 59.31; H, 4.94. Found: C, 59.37; H, 4.90.

3-Alkyl[1]benzothieno[3,2-*d*]pyrimidin-4(3*H*)-ones (IVa-c, Table I).

The general procedure is illustrated for the preparation of 3-cyclohexyl[1]benzothieno[3,2-*d*]pyrimidin-4(3*H*)-one (IVc). A mixture of II (0.50 g, 2 mmoles) and cyclohexylamine (5 ml, 50% aqueous solution, 2.5 mmoles) was heated at 100° for 30 minutes. The mixture was cooled, diluted with water, treated with dilute hydrochloric acid to remove excess amine and the resulting solid collected and recrystallized from aqueous ethanol to yield 0.47 g (83%) of IVc, mp 183-184°; ir: 1650 (C=O), 1600 (C=N), 750 cm^{-1} (CS); nmr (deuteriochloroform): δ 1.2-2.2 (m, 11H), 7.25-8.5 (m, 5H).

Anal. Calcd. for $C_{16}H_{16}N_2OS$: C, 67.60; H, 5.63. Found: C, 67.33; H, 5.87.

3-Amino-2-benzothiophenecarboxyhydrazide (V).

A mixture of I (2.0 g, 10 mmoles) and hydrazine hydrate (4 ml, 80% solution, 40 mmoles) was refluxed in ethanol (4 ml) for 2 hours, cooled, and the colorless solid which separated recrystallized from benzene to yield 1.7 g (80%) of V, mp 165-167°; ir: 3310 (NH), 1660 cm^{-1} (C=O); nmr (deuteriochloroform): δ 1.35-1.45 (m, 10H), 2.1 (s, 2H), 2.7 (s, 2H), 7.4-7.6 (m, 4H); ms: Calcd. for MW 207. Found: 207.

Anal. Calcd. for $C_9H_9N_3OS$: C, 52.17; H, 4.34. Found: C, 52.47; H, 4.47.

3-Amino[1]benzothieno[3,2-*d*]pyrimidin-4(3*H*)-one (VI). Method A.

A mixture of II (0.50 g, 2 mmoles) and hydrazine hydrate (5 ml, 80% solution, 40 mmoles) was refluxed for 10 minutes, diluted with water and the resulting solid collected and recrystallized from aqueous DMF to yield 0.30 g (80%) of VI, mp 225-227°; ir: 3400 (NH), 1670 (C=O), 1620 (C=N), 750 cm^{-1} (C-S); nmr (DMSO-d_6): 3.35 (s, 2H), 6.15 (s, 1H), 7.55-7.85 (m, 4H).

Anal. Calcd. for $C_{10}H_7N_3OS$: C, 55.28; H, 3.24. Found: C, 55.09; H, 3.27.

Method B.

A mixture of V (0.50 g, 2 mmoles) and ethyl orthoformate (0.50 g, 3 mmoles) was heated at 180° for 20 minutes. The initial melt solidified. Trituration and recrystallization of the solid from aqueous DMF yielded 0.30 g (80%) of VI, mp 225-227°.

[1]Benzothieno[3,2-*d*]pyrimidin-4(3*H*)-one (VIII).

A suspension of VI (0.50 g, 2 mmoles) in 50% aqueous acetic acid (30 ml) was warmed to 45-50° and then treated with sodium nitrite (0.50 g, 7.2 mmoles) in portions. The mixture was heated (45-50°) until the evolution of nitrogen dioxide ceased, the resulting solution was cooled and diluted with water. The solid product was purified by dissolving in sodium hydroxide solution (10%) and reprecipitating with dilute hydrochloric acid followed by recrystallization from aqueous DMF to yield 0.20 g

(50%) of VIII, mp 308-309°, (lit [13], 308-309°).

3-Substituted-aminomethyl[1]benzothieno[3,2-*d*]pyrimidin-4(3*H*)-ones IXa-c.

The general procedure is illustrated for the preparation of 3-pyrrolidinomethylamino[1]benzothieno[3,2-*d*]pyrimidin-4(3*H*)-one (IXa). To a mixture of V (2.0 g, 10 mmoles) and pyrrolidine (2.8 g, 40 mmoles) was added formaldehyde (5.5 ml of a 40% aqueous solution, 20 mmoles). The reaction mixture was cooled (10-15°) and the resulting precipitate filtered, washed with petroleum ether and recrystallized from the same solvent to afford IXa (2.7 g, 95%), mp 150-152°; ir: 1165 (C=O), 1620 cm^{-1} (C=N); nmr (deuteriochloroform): δ 1.65-1.95 (m, 4H), 2.7-2.9 (t, 4H), 5.15 (s, 2H), 7.45-8.4 (m, 5H).

Anal. Calcd. for $C_{15}H_{15}N_3OS$: C, 63.15; H, 5.26. Found: C, 62.67; H, 5.50.

3-(Substituted-benzylideneamino)[1]benzothieno[3,2-*d*]pyrimidin-4(3*H*)-ones VIIa-e, (Table I).

The general procedure is presented for the preparation of 3-(*m*-chlorobenzylideneamino)[1]benzothieno[3,2-*d*]-4(3*H*)-one, VIIc. A mixture of III (0.20 g, 1 mmole), *m*-chlorobenzaldehyde (0.56 g, 4 mmoles), boron trifluoride etherate (0.5 ml), dry ethanol (2 ml) and chloroform (25 ml) was refluxed for 2 hours. The solid which separated upon cooling was recrystallized from DMF to yield 0.30 g (95%) of VIId, mp 233-235°; ir: 1630 (C=O), 1610 (C=N), 750 cm^{-1} (C-S).

Anal. Calcd. for $C_{17}H_{10}ClN_3OS$: C, 60.10; H, 2.94. Found: C, 59.63; H, 3.27.

REFERENCES AND NOTES

[1] M. S. Manhas, S. D. Sharma and S. G. Amin, *J. Med. Chem.*, **15**, 106 (1972).

[2] M. B. Devani, C. J. Shishoo, M. S. Pathak, S. H. Parikh, G. F. and A. C. Padhya, *J. Pharm. Sci.*, **65**, 660 (1976).

[3] German Patent 2,264,222 (1973); *Chem. Abstr.*, **79**, 78837 (1973).

[4] Belgian Patent 769,844 (1972); *Chem. Abstr.*, **77**, 5512 (1972).

[5] K. Thomas, British Patent 1,057,612 (1967); *Chem. Abstr.*, **67**, 100149 (1967).

[6] E. Worrum and G. Ohnacker, Belgian Patent 699,347 (1966); *Chem. Abstr.*, **64**, 8203 (1966).

[7] F. Sauter, German Patent 2,210,503 (1972); *Chem. Abstr.*, **77**, 164752 (1972).

[8] D. T. Conner, R. J. Sorenson, F. J. Tinney, W. A. Cetenko and J. J. Kerbleski, *J. Heterocyclic Chem.*, **19**, 1185 (1982).

[9] F. A. El-Telbany, *Pharmazie*, **35**, 326 (1980).

[10] C. Runti, C. Nisi and L. Sindellari, *Ann. Chim. (Rome)*, **15**, 719 (1961).

[11] N. P. Peet, S. Sunder and D. L. Trepanier, *Indian J. Chem.*, **14B**, 701 (1976).

[12] G. T. Panse and S. K. Kamat, *ibid.*, **13B**, 834 (1975).

[13] M. Robba, P. Touzot and H. El-Kashef, *J. Heterocyclic Chem.*, **17**, 923 (1980).

[14] J. R. Beck and J. A. Yahner, *J. Org. Chem.*, **38**, 2450 (1973).

[15] These condensations represent a modified version of the Mannich reaction in which an acidic imide hydrogen is replaced by a substituted aminomethyl group.

[16] R. I. Geran, N. H. Greenberg, M. M. MacDonald, A. M. Schum and B. J. Abbott, *Cancer Chemother. Rep.*, **3**, 1 (1972). Screening data summary, interpretation and outline of current screen, institution Booklet 14, National Cancer Institute, Bethesda, MD. The compounds were evaluated by the Drug Evaluation Branch, Drug Research and Development, Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Department of Education and Welfare, Bethesda, MD.