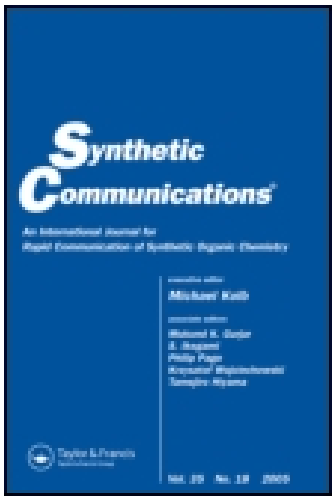
This article was downloaded by: [UQ Library]
On: 15 June 2015, At: 02:51
Publisher: Taylor & Francis
Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

SYNTHESIS OF 2,4-DIAMINO-5- (FUR-2-OYL), (THIEN-2-OYL), AND (PYRID-2-OYL)THIAZOLES

S. K. Chithralekha Devi [a] & K. N. Rajasekharan [b]

[a] Department of Chemistry , University of Kerala , Trivandrum, Kerala, 695 581, India

[b] Department of Chemistry , University of Kerala , Trivandrum, Kerala, 695 581, India

Published online: 12 Dec 2006.

To cite this article: S. K. Chithralekha Devi & K. N. Rajasekharan (2002) SYNTHESIS OF 2,4-DIAMINO-5- (FUR-2-OYL), (THIEN-2-OYL), AND (PYRID-2-OYL)THIAZOLES, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 32:10, 1523-1528, DOI: 10.1081/SCC-120004141

To link to this article: http://dx.doi.org/10.1081/SCC-120004141

PLEASE SCROLL DOWN FOR ARTICLE

Taylor & Francis makes every effort to ensure the accuracy of all the information (the "Content") contained in the publications on our platform. However, Taylor & Francis, our agents, and our licensors make no representations or warranties whatsoever as to the accuracy, completeness, or suitability for any purpose of the Content. Any opinions and views expressed in this publication are the opinions and views of the authors, and are not the views of or endorsed by Taylor & Francis. The accuracy of the Content should not be relied upon and should be independently verified with primary sources of information. Taylor and Francis shall not be liable for any losses, actions, claims, proceedings, demands, costs, expenses, damages, and other liabilities whatsoever or howsoever caused arising directly or indirectly in connection with, in relation to or arising out of the use of the Content.

This article may be used for research, teaching, and private study purposes. Any substantial or systematic reproduction, redistribution, reselling, loan, sub-licensing, systematic supply, or distribution in any form to anyone is expressly forbidden. Terms & Conditions of access and use can be found at http://www.tandfonline.com/page/terms-and-conditions

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

©2002 Marcel Dekker, Inc. All rights reserved. This material may not be used or reproduced in any form without the express written permission of Marcel Dekker, Inc.

SYNTHETIC COMMUNICATIONS, 32(10), 1523–1528 (2002)

SYNTHESIS OF 2,4-DIAMINO-5-(FUR-2-OYL), (THIEN-2-OYL), AND (PYRID-2-OYL)THIAZOLES

S. K. Chithralekha Devi and K. N. Rajasekharan*

Department of Chemistry, University of Kerala,
Trivandrum, Kerala 695 581, India

Downloaded by [UQ Library] at 02:51 15 June 2015

ABSTRACT

The synthesis of 5-furoyl-, thienoyl- or pyridoyl-2,4-diaminothiazoles, as the thiazole analogs of the cytotoxic marine alkaloid dendrodoine, is reported. A preliminary study on a tandem bromination-heterocyclization approach, amenable for a combinatorial synthesis of 2,4-diaminothiazoles, is also described.

Key Words: Analogs; Dendrodoine; Diaminothiazoles; Acylthiazoles

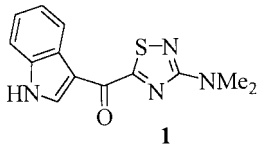
Among terrestrial or marine alkaloids, dendrodoine or 3-(*N*,*N*-dimethylamino)-5-indol-3-oyl-1,2,4-thiadiazole **1** isolated[1] from the marine tunicate *Dendrodoa grossularia* is unique in that it incorporates a thiadiazole ring, a rare structural feature. Dendrodoine has been reported to be cytotoxic to lymphoma cells L1210 in vitro.[1,2] Despite these reports, further studies on dendrodoine or on its analogs seem not to have appeared.

*Corresponding author. E-mail: rajkn@vsnl.com

Copyright © 2002 by Marcel Dekker, Inc.

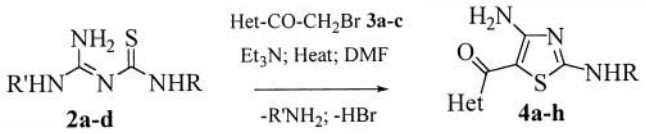
MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

©2002 Marcel Dekker, Inc. All rights reserved. This material may not be used or reproduced in any form without the express written permission of Marcel Dekker, Inc.



1

With our interest[3] in the synthesis of 2,4- diamino-5-ketothiazoles, we noted that the replacement of the thiadiazole ring of dendrodoine by a thiazole ring would allow three substituents to be placed on the five-membered ring as against the original two in **1**, and thereby providing further structural diversity. This idea has prompted us to explore the synthesis of 5-heteroyldiaminothiazoles as analogs of dendrodoine.



2a-d **4a-h**

2a: R = 4-ClC_6H_4, R′ = H; **2b:** R = C_6H_5, R′ = H; **2c:** R = 4-$MeOC_6H_4$, R′ = H; **2d:** R = Et, R′ = NO_2; **4a**: R = 4-ClC_6H_4, Het = 2-Furyl; **4b:** R = C_6H_5, Het = 2-Furyl; **4c:** R = 4-$MeOC_6H_4$, Het = 2-Furyl, H; **4d:** R = 4-ClC_6H_4, Het = 2-Thienyl; **4e:** R = C_6H_5, Het = 2-Thienyl; **4f:** R = 4-$MeOC_6H_4$, Het = 2-Thienyl, H; **4g:** R = Et, Het = 2-Thienyl; **4h:** R = 4-ClC_6H_4, Het = 2-Pyridyl.

We have shown earlier that amidinothioureas,[3] nitroamidinothioureas[4] and thiocarbamoylamidinopyrazoles[5] are useful precursors for 2,4-diaminothiazoles. These thiourea derivatives provide four ring atoms for the thiazole ring construction and thus act as [C-N-C-S] synthons. The remaining carbon of the thiazole is sourced from a halomethyl group of α-haloketones or similar reactive halomethyl compounds. This [4 + 1] heterocyclization reaction[3] is now adopted for the synthesis of novel 5-fur-2-oyl, 5-thien-2-oyl and 5-pyrid-2-oyl derivatives of 4-amino-2-arylaminothiazoles as dendrodoine analogs. Thus, the reaction of 1-amidino-3-(4-chlorophenyl)thiourea **2a** with 2-bromoacetylfuran **3a** in *N*,*N*-dimethylformamide (DMF) in the presence of triethylamine afforded a compound which showed in its ^{1}H NMR spectrum the characteristic multiplet-doublet-doublet signal pattern assignable to H-4, H-3 and H-5 of a 2-substituted furan, as well as a pair of doublets due to a 4-chlorophenylamino group. Two broad signals, which disappeared in the presence of D_2O, could be ascribed to NH and NH_2 groups. Based on this and other physical data given in the experimental

Downloaded by [UQ Library] at 02:51 15 June 2015

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

©2002 Marcel Dekker, Inc. All rights reserved. This material may not be used or reproduced in any form without the express written permission of Marcel Dekker, Inc.

section, the above compound was formulated as 4-amino-2-(4-chlorophenyl)-amino-5-fur-2-oylthiazole **4a**. Similar reactions using the amidinothioureas **2b–c** or 1-ethyl-3-(*N*-nitroamidino)thiourea **2d** with 2-bromoacetylfuran **3a** and 2-bromoacetylthiophene **3b** afforded the diaminothiazoles **4b–g** in 50–70% yield. The required bromoacetyl derivatives were obtained by the bromination of 2-acetylfuran and thiophene using copper bromide.[6] Due to their highly lachrymatory nature, these were used as such. A one-pot tandem bromination-heterocyclization protocol was developed for the synthesis of 4-amino-2-(4-chlorophenylamino)-5-(pyrid-2-oyl)thiazole (**4h**). The bromination of 2-acetylpyridine was done in DMF at 80–85°C in the presence of azoisobutyronitrile (AIBN), and the 2-bromoacetylpyridine so formed was in situ reacted with the required amidinothiourea. This modification, though found unsuitable for 2-acetylfuran, is expected to be an operationally simpler route to 2,4-diamino-5-ketothiazoles. A separate preparation of the α-haloketones could be avoided, which would be suitable for a solution-phase combinatorial approach to these compounds. This idea is currently under evaluation using a variety of methyl ketones.

EXPERIMENTAL

Reagents and solvents were from Merck India and Fluka. ^{1}H NMR and mass spectra were run on Bruker AC300F and JEOL D-300 spectrometers. Melting points are uncorrected. Elemental analysis was done at Central Drug Research Institute, India.

General Procedure for the Synthesis of 2,4-Diamino-5-(fur-2-oyl) or 5-(Thien-2-oyl)thiazoles 4a–g

To copper(II) bromide (1.7 mmol) in dry ethyl acetate (10 ml), 2-acetylfuran or thiophene (1 mmol) dissolved in ethyl acetate (2 ml) was added and the above mixture was stirred and refluxed for 2 h. The completion of the reaction was indicated by a color change of the reaction mixture from green to amber. To the reaction mixture, a small amount of Norit was added, stirred and filtered. This filtrate, on evaporation under reduced pressure at room temperature and purification using a short column of silica gel, afforded a yellow pasty mass of 2-bromoacetylfuran (65%) or 2-bromoacetylthiophene (76%). These were used as such [**CAUTION:** These bromoacetyl compounds are highly lachrymatory, cause severe irritation and therefore must be handled with due precautions!]. The 2-bromoacetylfuran or thiophene (**3a**, **b**) thus obtained (1 mmol) was added to 1-ami-

Downloaded by [UQ Library] at 02:51 15 June 2015

©2002 Marcel Dekker, Inc. All rights reserved. This material may not be used or reproduced in any form without the express written permission of Marcel Dekker, Inc.

dino-3-arylthiourea or 1-alkyl-3-(*N*-nitroamidino)thiourea (1 mmol) in DMF (5 ml) and the reaction mixture was briefly warmed. To the warm solution, triethylamine (1.1 mmol) was added and the solution was kept at 80–85°C for 15 min. It was then cooled and added to cold water with constant stirring. The yellow precipitate formed was filtered, washed with water and dried. The crude material was purified by crystallization. The details of the thiazoles thus prepared are: *4-Amino-2-*(*4-chlorophenylamino*)*-5-*(*fur-2-oyl*)*-thiazole* **4a:** crystallized from benzene-petroleum ether, yield 62%, m.p. 227–230°C. Analysis: Found: C, 52.8; H, 3.0; N, 13.0%: Calc. for $C_{14}H_{10}ClN_3O_2S$ (319.8): C, 52.6; H, 3.2; N, 13.1%. IR (KBr) cm^{-1}: 3181, 1599, 1547, 1484, 1439, 1228, 1095, 1022, 828, 744. ^{1}H NMR: (300 MHz, DMSO-d_6) δ: 6.71 (m, H-4), 7.13 (d, *J* 2 Hz, H-3), 7.45 (d, 2H, *J* 8.3 Hz, 2 ArH), 7.73 (d, 2H, *J* 8.3 Hz, 2ArH), 7.95 (d, *J* 1.6 Hz, H-5), 8.43 (broad, NH_2), 10.98 (s, NH). EIMS: *m*/*z* (%): 321 (M + 2, 39), 319 (M^+, 100), 318 (34), 224 (8), 153 (23), 140 (30), 126 (12), 111 (13), 95 (54), 67 (13). *4-Amino-5-*(*fur-2-oyl*)*-2-phenylaminothiazole* **4b:** crystallized from benzene–petroleum ether, yield 54%, m.p. 170–172°C. Analysis: Found: C, 58.9; H, 3.7; N, 14.9%: Calc. for $C_{14}H_{11}N_3O_2S$ (285.3): C, 58.9; H, 3.9; N, 14.7%. IR (KBr) cm^{-1}: 3444, 3272, 3018, 1627, 1594, 1574, 1528, 1497, 1481, 1438, 1254, 1223, 1187, 1106, 1018, 885, 752, 690, 649. EIMS: *m*/*z* (%): 285 (M^+, 100), 284 (21), 218 (6), 190 (3), 140 (19), 119 (35), 95 (33), 92 (10), 77 (16), 67 (5). *4-Amino-5-*(*fur-2-oyl*)*-2-*(*4-methoxyphenylamino*)*thiazole* **4c:** crystallized from benzene–petroleum ether, yield 50%, m.p. 212–215°C. Analysis: Found: C, 57.3; H, 4.3; N, 13.2%: Calc. for $C_{15}H_{13}N_3O_3S$ (315.4): C, 57.1; H, 4.2; N, 13.3%. IR (KBr) cm^{-1}: 3143, 1597, 1568, 1545, 1514, 1483, 1441, 1246, 1175, 1090, 1017, 886, 830, 751. ^{1}H NMR: (300 MHz, DMSO-d_6) δ: 3.84 (s, OCH_3), 6.50–6.53 (m, H-4), 6.95 (d, *J* 5.8 Hz, 2 ArH), 7.15 (d, *J* 2 Hz, H-3), 7.36 (d, *J* 5.8 Hz, 2 ArH), 7.52 (d, *J* 1.6 Hz, H-5), 8.33 (broad, NH_2), 10.85 (s, NH). EIMS: *m*/*z* (%): 315 (M^+, 100), 314 (16), 285 (71), 284 (18), 219 (21), 207 (16), 165 (8), 150 (10), 149 (30), 140 (36), 122 (35), 107 (16), 95 (67), 67 (19). *4-Amino-2-*(*4-chlorophenylamino*)*-5-*(*thien-2-oyl*)*thiazole* **4d:** crystallized from benzene, 65%, m.p. 230–232°C. Analysis: Found: C, 50.0; H, 3.1; N, 12.6%: Calc. for $C_{14}H_{10}ClN_3OS_2$ (335.8): C, 50.1; H, 3.0; N, 12.5%. IR (KBr) cm^{-1}: 3400, 3273, 2284, 1605, 1552, 1492, 1235, 1090, 1058, 1011, 820, 751, 686, 653. ^{1}H NMR: (300 MHz, DMSO-d_6) δ: 7.1 (m, H-4), 7.42 (d, *J* 8.8 Hz, 2 ArH), 7.59 (d, *J* 3.6 Hz, H-3), 7.69 (d, *J* 8.8 Hz, 2 ArH), 7.81 (d, *J* 4.8 Hz, H-5), 8.29 (broad, NH_2), 11.0 (s, NH). EIMS: *m*/*z* (%): 337 (M + 2, 21), 335 (M^+, 74), 334 (58), 252 (4), 224 (4), 223 (8), 169 (4), 156 (25), 155 (11), 153 (23), 152 (6), 126 (12), 111 (100), 83 (18). *4-Amino-2-phenylamino-5-*(*thien-2-oyl*)*thiazole* **4e:** crystallized from benzene, yield 62%, m.p. 149–150°C. Analysis: Found: C, 55.9; H, 3.8; N, 14.1%: Calc. for $C_{14}H_{11}N_3OS_2$ (301.4): C, 55.

Downloaded by [UQ Library] at 02:51 15 June 2015

©2002 Marcel Dekker, Inc. All rights reserved. This material may not be used or reproduced in any form without the express written permission of Marcel Dekker, Inc.

8; H, 3.7; N, 13.9%. IR (KBr) cm^{-1}: 3268, 1594, 1536, 1429, 1233, 1082, 1042, 823, 750, 712, 693. ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 7.08 (t, *J* 4.4 Hz, 2 ArH), 7.16–7.3 (m, H-4 and 1 ArH), 7.36–7.46 (m, 2 ArH), 7.51 (d, *J* 4.8 Hz, H-3), 7.62 (d, *J* 3.6 Hz, H-5), 8.4 (broad, NH_2), 10.82 (s, NH). EIMS: *m*/*z* (%): 301 (M^+, 100), 300 (75), 218 (4), 190 (3), 156 (14), 150 (5), 119 (40), 111 (50), 92 (9), 83 (9), 77 (17). *4-Amino-2-(4-methoxyphenylamino)-5-(thien-2-oyl)thiazole* **4f:** crystallized from benzene, yield 60%, m.p. 215–217°C. Analysis: Found: C, 54.3; H, 4.1; N, 12.6%: Calc. for $C_{15}H_{13}N_3O_2S_2$ (331.4): C, 54.4; H, 4.0; N, 12.7%. IR (KBr) cm^{-1}: 3382, 3271, 2835, 2285, 1602, 1557, 1515, 1455, 1311, 1233, 1096, 1052, 868, 825, 782, 755, 713, 674, 641. ^{1}H NMR: (300 MHz, DMSO-d_6) δ: 3.77 (s, OCH_3), 6.98 (d, *J* 9.1 Hz, 2 ArH), 7.20 (m, H-4), 7.50–7.60 (m, H-3 and 2 ArH), 7.81 (d, *J* 4.9 Hz, H-5), 8.3 (broad, NH_2), 10.73 (s, NH). EIMS: *m*/*z* (%): 331 (M^+, 100), 330 (56), 165 (6), 156 (12), 149 (25), 148 (21), 122 (32), 111 (60), 83 (17). *4-Amino-2-ethylamino-5-(thien-2-oyl)thiazole* **4g:** crystallized from benzene, yield 70%, m.p. 212–215°C. Analysis: Found: C, 47.4; H, 4.3; N,16.6%: Calc. for $C_{10}H_{11}N_3OS_2$ (253.4): C, 47.4; H, 4.4; N, 16.6%. IR (KBr) cm^{-1}: 3093, 3030, 2284, 1563, 1509, 1445, 1346, 1249, 1228, 1157, 1101, 1075, 1038, 937, 829, 796, 704. EIMS: *m*/*z* (%): 253 (M^+, 100), 252 (81), 183 (2), 170 (5), 156 (15), 142 (4), 141 (5), 111 (58), 83 (17), 71 (38).

Synthesis of 2,4-Diamino-5-(pyrid-2-oyl)thiazole 4 h by One-Pot Bromination-Cyclization Procedure

To a solution of 2-acetylpyridine (1 mmol) in DMF (2 ml), AIBN (100 mg) was added and warmed to 70–75°C. To this, bromine in DMF (1 mmol, 0.53 ml of a solution of 1 ml bromine in 9 ml DMF) was added and heated for 2 min. The 1-amidino-3-(4-chlorophenyl)thiourea (1 mmol), dissolved in DMF (3 ml) was added to the above solution. Triethylamine (2 mmol, 0.30 ml) was then added and the mixture was heated for 15 min at 80–85°C. The reaction mixture was cooled and poured in to ice-cold water. The deep yellow precipitate obtained was collected and purified using column chromatography (silica gel, 60–120 mesh, petroleum ether–ethyl acetate, 1 : 3) to afford *4-amino-2-(4-chlorophenylamino)-5-(pyrid-2-oyl)thiazole* **4h:** yield 75%, m.p. 277–279°C. Anal. Found: C, 54.4; H, 3.5; N, 16.8%. Calc. for $C_{15}H_{11}ClN_4OS$ (330.8): C, 54.5; H, 3.4; N, 16.9%. IR (KBr) cm^{-1}: 3460, 3240, 3160, 1600, 1580, 1560, 830. ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 7.18 (d, *J* 4.4 Hz, 2 ArH), 7.36 (m, 2 ArH), 7.83–7.9 (m, H-4, H-5 and NH_2), 8.25 (d, *J* 5.4 Hz, pyridine H-3), 8.64–8.7 (m, pyridine H-6), 10.92 (s, NH).

Downloaded by [UQ Library] at 02:51 15 June 2015

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

©2002 Marcel Dekker, Inc. All rights reserved. This material may not be used or reproduced in any form without the express written permission of Marcel Dekker, Inc.

REFERENCES

1. Heitz, S.; Durgeat, M.; Guyot, M.; Brassy, C.; Bachet, B. Tetrahedron Lett. **1980**, *21*, 1457–1458.
2. Helbecque, N.; Moquin, C.; Bernier, J.L.; Morel, E.; Guyot, M.; Henichart, J.P. Cancer Biochem. Biophys. **1987**, *9*, 271–279.
3. Rajasekharan, K.N.; Nair, K.P.; Jenardanan, G.C. Synthesis **1986**, 353–355.
4. Binu, R.; Thomas, K.K.; Jenardanan, G.C.; Rajasekharan, K.N. Org. Prep. Procedures Intl. **1998**, *30*, 93–96.
5. Binu, R.; Deepa, S.; Rajasekharan, K.N. Synth. Commun. **1998**, *28*, 3625–3632.
6. King, L.C.; Ostrum, G.K. J. Org. Chem. **1964**, *29*, 3459–3461.

Received in the UK February 14, 2001

Downloaded by [UQ Library] at 02:51 15 June 2015