Versatile starting materials for novel 1,ω-bis(pyridin-4-ylphenoxy)alkanes, and their corresponding bis(thieno[2,3-*b*]pyridin-4-ylphenoxy) derivatives

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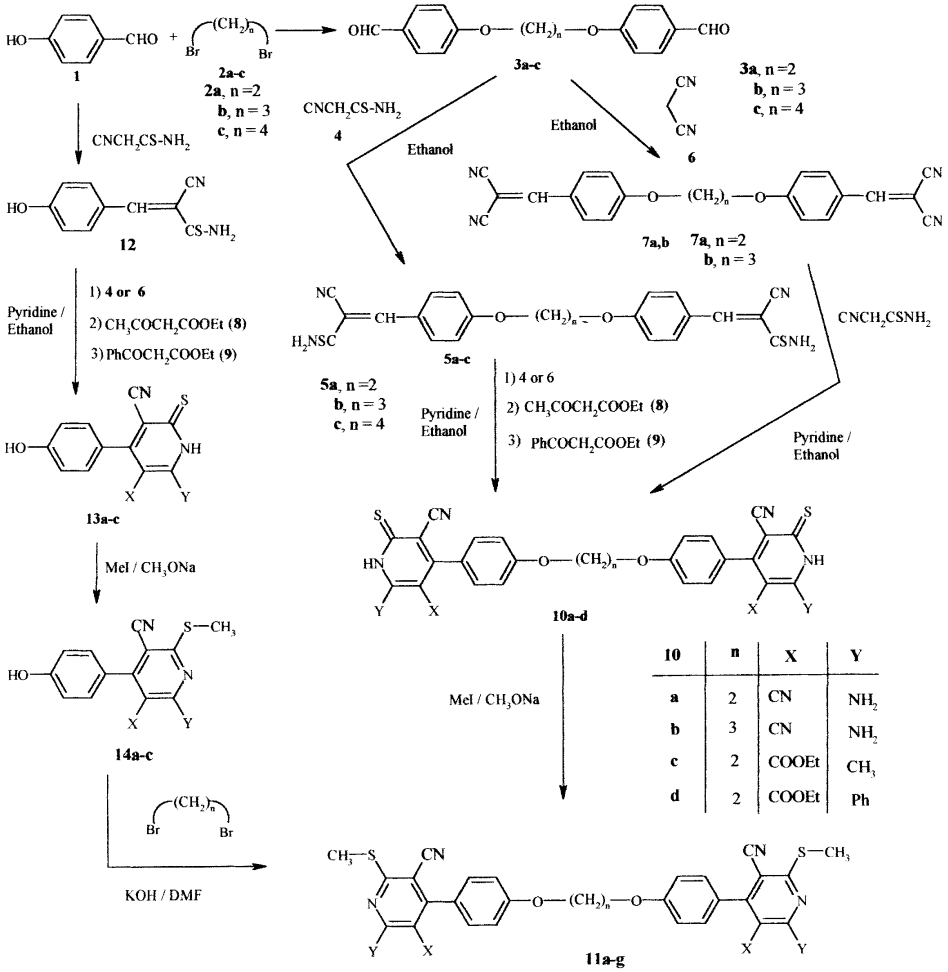
A synthesis is described, starting from *p*-hydroxybenzaldehyde, of some new bis(activated styrene) derivatives, and their conversion into novel bis(pyridin-4-yl) ethers and bis(thieno[2,3-*b*]pyridine) derivatives.

Keywords: 1,ω-bis(pyridin-4-ylphenoxy)alkanes, bis(thieno[2,3-b] pyridin-4-ylphenoxy) derivatives

In recent decades considerable attention has been devoted to the construction of new derivatives of pyridine-2-thiones and thieno[2,3-*b*]pyridine on account of their reported biological activities. Various series of substituted pyridine-2-thiones have been found to be useful as antibiotic[1-2], antiarteriosclerotic[3], antibacterial[4], antihyperglycemic[5] and antifungal[6] agents and as inhibitors of the blood coagulation factor.[7] Also, thieno[2,3-*b*]pyridine derivatives have been reported to be useful as antibiotics[8-11], drug intermediates[12], against endoparasiticides[13] and as antianaphylactic compounds.[14-15] Recently bis(compounds) have received great attention, not only for being model compounds for main chain poly-



13, 14	X	Y
a	CN	NH_2
b	COOEt	CH_3
c	COOEt	Ph

10	n	X	Y
a	2	CN	NH_2
b	3	CN	NH_2
c	2	COOEt	CH_3
d	2	COOEt	Ph

11	n	X	Y
a	2	CN	NH_2
b	3	CN	NH_2
c	4	CN	NH_2
d	2	COOEt	CH_3
e	3	COOEt	CH_3
f	2	COOEt	Ph
g	3	COOEt	Ph
h	4	COOEt	Ph

Scheme 1

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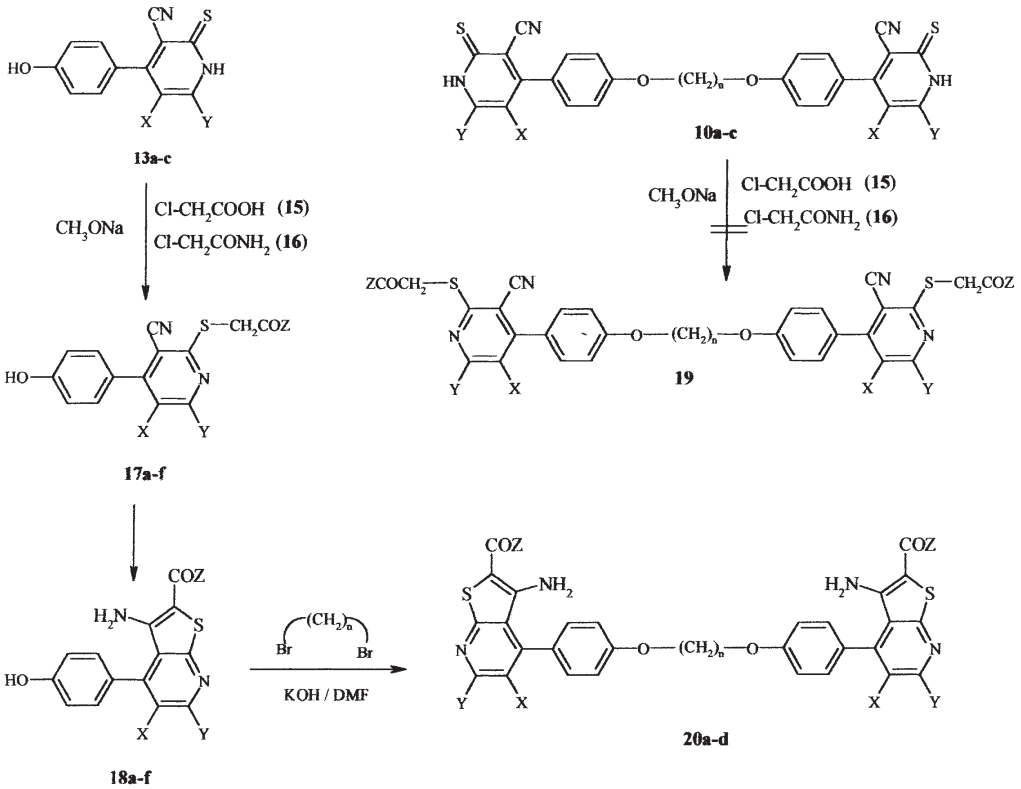
mers,[20–25] but also because many biologically active natural and synthetic products have molecular symmetry.[26] We have recently described the synthesis of some new bis(β-difunctional) building units and studied their use as intermediates in the synthesis of novel bis(5-membered heterocycles).[27] In continuation of our interest in this field, this paper describes the synthesis of some new bis(activated styrene) derivatives to explore their synthetic potential as starting materials for novel bis(pyridin-4-yl) ethers and bis(thieno[2,3-*b*]pyridine) derivatives and their utility as pharmacological agents.

Results and discussion

Two synthetic routes are described for the synthesis of the bis(2-methylthiopyridin-4-yl) ethers **11a–h** as outlined in Scheme 1. The starting compounds **5a–c** and **7a, b** needed in the present investigation were prepared by condensing the appropriate bis(aldehydes) **3a–c**[28] with 2-cyanothioacetamide (**4**) and malononitrile (**6**) in absolute ethanol containing triethylamine (TEA) as catalyst. Compounds **5a-c** have been reacted with a series of active methylene compounds, namely 2-cyanothioacetamide (**4**), malononitrile (**6**), ethyl acetoacetate (**8**) and ethyl benzoylacetate (**9**) in refluxing ethanol-pyridine mixture to give 35–40% of the corresponding bis(pyridin-4-yl) ethers **10a-d**. The latter were methylated to yield 50–60% of the corresponding bis(2-methylthio) derivatives **11a, b, d, f**. Compounds **10a, b** were alternatively obtained in 45% yield by reacting **7a, b** with **2** in refluxing ethanol-pyridine mixture.

In view of the low yields of the bis(pyridin-4-yl) ethers **10a–d** and their corresponding bis(methylthio) derivatives **11a, b, d, f,** we developed a second route (Scheme 1) for the preparation of **11a–h**. The pyridines **14a-c** were the key intermediates; their potassium salts (obtained from **14a-c** with KOH/MeOH) reacted with the appropriate dibromoalkanes **2b, c** in boiling DMF to give 60–68% yield of **11b, c, e, g, h**. Compounds **14a–c** were obtained in 70–75% yield by methylation of **13a–c** with methyl iodide in refluxing methanol containing sodium methoxide. Compounds **14a–c** were confirmed as the *S*-methyl derivatives by the IR and ^{1}H NMR spectra. Thus, the IR spectra of these compounds showed the absorption bands of phenolic OH at *ca*. 3330 cm^{-1}. Also their ^{1}H NMR spectra revealed singlet signals at δ ≅ 2.60 and δ ≅ 10.2 ppm, characteristic for SCH_3 and phenolic OH protons respectively.

Compounds **13a–c** were obtained by first condensation of 4-hydroxybenzaldehyde (**1**) with 2-cyanothioacetamide (**4**) in absolute ethanol containing TEA to give 2-cyano-3-(4-hydroxyphenyl)thioacrylamide (**12**).[29] Subsequent reaction of **12** with each of **4, 6, 8, 9** in refluxing ethanol containing TEA afforded the corresponding pyridine-2-thiones **13a–c**. The lat-



17,18	Z	X	Y
a	OH	CN	NH_2
b	NH_2	CN	NH_2
c	OH	COOEt	CH_3
d	NH_2	COOEt	CH_3
e	OH	COOEt	Ph
f	NH_2	COOEt	Ph

20	n	X	Y	Z
a	3	COOEt	CH_3	NH_2
b	4	COOEt	CH_3	NH_2
c	3	COOEt	Ph	NH_2
d	4	COOEt	Ph	NH_2

Scheme 2

ter were shown to exist mainly in the thione form by the strong absorption bands at $\nu \cong 3300$ and 1540 cm^{-1} characteristic for NH and C=S groups respectively.

With the pyridine-2-thiones **13a–c** and the bis(pyridin-4-yl) ethers **10a-c** now available, we attempted two routes to the synthesis of the bis(thieno[2,3-*b*]pyridin-4-yl) ethers **20a–d**, as outlined in Scheme 2. In the first route we tried alkylation of **10a–c** with chloracetic acid (**15**) or chloroacetamide (**16**) in methanolic sodium methoxide to give the corresponding bis-*S*-alkyl derivatives **19**. The latter would be expected to undergo cyclization in ethanolic potassium hydroxide to afford the target molecules **20**. Unfortunately we could not isolate pure samples of the alkyl products **19** under the conditions described.

In the second route the pyridine-2-thiones **13a–c** were easily converted into the corresponding *S*-(2-pyridyl)thioglycolic acids **17a, c, e** and 2-pyridylthioacetamides **17b, d, f** upon treatment with chloracetic acid (**15**) and chloroacetamide (**16**), respectively, in refluxing methanol containing sodium methoxide. Compounds **17a–f** could be cyclized to give the thieno[2,3-*b*]pyridine derivatives **18a–f** in 60-70% yields upon heating in ethanol with potassium hydroxide. The potassium salts of **18c-f** reacted with 1,3-dibromopropane (**2b**) and 1,4-dibromobutane (**2c**), respectively, in boiling DMF to furnish the corresponding bis(thieno[2,3-*b*]pyridine) derivatives **20a–d** in 60-65 % yield.

The substituted thieno[2,3-*b*]pyridine derivatives **18a, b** could not be converted into the corresponding bis(thieno[2,3-*b*]pyridin-4-yl) ethers under similar conditions. This may be attributed to the insolubility of these derivatives under the reaction conditions.

Techniques used: Elemental analysis, IR, ^1H NMR and MS.

References: 29

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References cited in this synopsis

1 K. Hirai, Y. Iwano, T. Nishi, A. Yoshida, K. Oda, H. Koyama, US Pat. 5,541,317; *Chem. Abstr*. **125**, 167690 (1996).
2 Y. Momose, H. Odaka, PCT Int. Appl. WO 97 36,882; *Chem. Abstr*. **117**, 331478 (1997).
3 A. Yoshida, H. Kogen, I. Hayakawa, K. Oda, T. Kasai, K. Shimada, Y. Yoshida, S. Ishihara, F. Saito, Y. Ohata, T. Koga, E. Kitazawa, T. Tokui, *JP* 09,202,775; *Chem. Abstr*. **127**, 234181 (1997).
4 J.D. Hinks, A.K. Takel, E. Hunt, PCT Int. Appl. WO 97 25,309; *Chem. Abstr*. **127**, 161997 (1997).
5 J. Wrobel, Z. Li, A. Dietrich, M. McCaleb, B. Mihan, J. Sredy, D. Sullivan, *J. Med. Chem.* **41**, 1084 (1998).
6 L. Muthusubramanian, R. B. Mitra, S. Rajkumar, V. S. S. Rao, *J. Chem. Technol. Biotechnol.* **72**, 164 (1998).
8 J. Aszodi, A. Bonnet, J.F. Chantot, *EP* 315,518; *Chem. Abstr*. **112**, 118535 (1990).
9 J. Aszodi, A. Bonnet, D.S. Gouin, *EP* 462,009; *Chem. Abstr*. **116**, 128504 (1992).
10 J.F. Chantot, D.S. Gouin, D, Humbert, J.G. Teutsch, *EP* 520,880; *Chem. Abstr*. **119**, 138972 (1993).
12 H. Schaefer, K. Gewald, H. Mueller, T. Jeschke, Ger. Pat. 285,356; *Chem. Abstr*. **114**, 228888 (1991).
13 N. Muller, W. Hallenbach, A. Harder, W. Lindner, EP 403,885; *Chem. Abstr*. **114**, 157181 (1991).
14 G. Wagner, S. Leistner, H. Vieweg, U. Krasselt, J. Prantz, *Pharmazie* **48**, 342 (1993).
15 N. Biowiss, U. Krasselt, S. Leistner, G. Wagner, *Pharmazie* **47**, 897 (1992).
20 A.G. Griffin, T.R. Britt, *J. Am. Chem. Soc.***103**, 4957 (1981).
21 G. Galli, M. Laus, A.S. Angeloni, *Makromol. Chem.* **187,** 289 (1986).
22 H. Ringsdorf, B. Schlarb, J. Venzmer, *Angew. Chem., Int. Ed. Engl.* **27,** 115 (1988).
26 E.J. Ariens, *Drug Design* **Vol 1**, Edited by Ariens E.J. (Academic Press, New York), 1 (1971).
27 A.H.M. Elwahy, A.A. Abbas, *Synth. Comm*., **30**, 2903 (2000).
28 W.J.P. Neish, *Rec. Trav. Chem*. **66**, 433 (1947); *Chem. Abstr*. **42**, 894 (1948).
29 J.S.A. Brunskill, A. De, D.F. Ewing, *J. Chem. Soc., Perkin Trans I*, 629 (1978).