Brief Communications

Synthesis of 4-aryl-2,6,6-trimethyl-5-oxo-5,6-dihydro-4*H*-thieno[3,2-*b*]pyrroles

*V. Z. Shirinian, D. M. Nikalin, and M. M. Krayushkin**

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences,
47 Leninsky prosp., 119991 Moscow, Russian Federation.
Fax: +7 (095) 137 6939. E-mail: mkray@mail.ioc.ac.ru

The method for the synthesis of 4-aryl-2,6,6-trimethyl-5-oxo-5,6-dihydro-4*H*-thieno[3,2-*b*]pyrroles from accessible 4-aminothiophene derivatives was developed.

Key words: indolin-2-one, thieno[3,2-*b*]pyrrolin-5-one, 2-bromo-2-methylpropanoyl bromide, Friedel—Crafts alkylation.

Indolin-2-ones are widely used in medicine, agriculture, and as starting material for the synthesis of various natural compounds.[1—5] However, its analogs are poorly studied; relevant information is very scarce.[6—8] For instance, some derivatives of thieno[2,3-*b*]pyrrolin-5-one were patented as analgesics and antipyretics.[7]

The goal of this study was to develop methods for the synthesis of thieno[3,2-*b*]pyrrolin-5-ones from easily accessible 4-aminothiophenes[9] **1** (Scheme 1).

Acylation of aminothiophenes with 2-bromo-2-methylpropanoyl bromide was carried out in methylene chloride in the presence of pyridine. Corresponding amides **2a**—**d** were isolated in 67—90% yields. The target thieno[3,2-*b*]pyrrolin-5-ones were obtained by intramolecular Friedel—Crafts cyclization of amides **2a**—**d** in the presence of $TiCl_4$, $AlCl_3$, and $AlBr_3$. By analogy with the Stolle synthesis[10] of indolinones from α-chloroacetanilides and $AlCl_3$ without a solvent, we heated melts of amides **2b**—**d** with aluminum chloride for a long period of time. However, the reaction mixture resinified in all cases. Prolonged refluxing (10 h) of amides **2a**—**c** in dichloroethane in the presence of $TiCl_4$ or $AlCl_3$ also resulted in resinification. With nitrobenzene as a solvent and $AlBr_3$ as a catalyst, amides **2a**—**c** were converted into the starting amines **1a**—**c**.

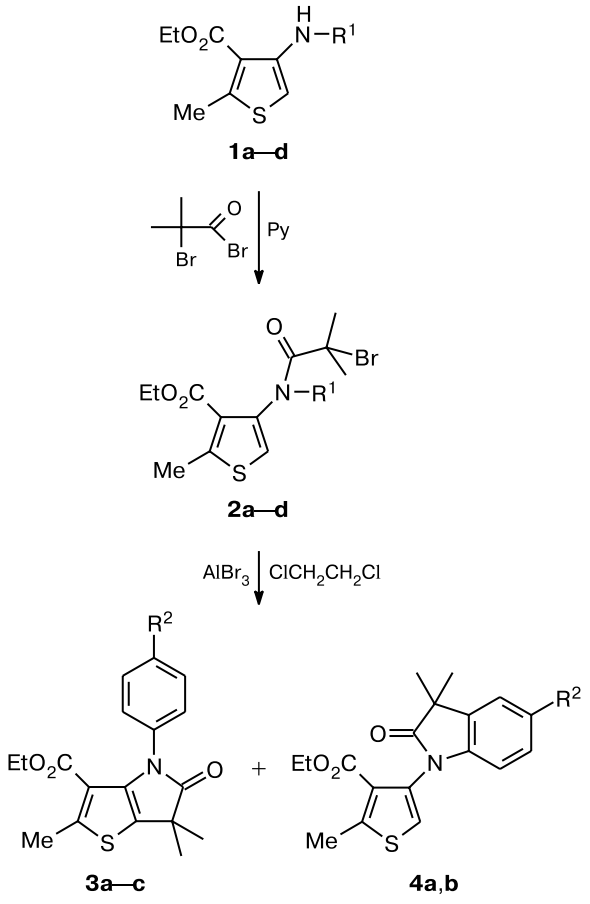
The target thieno[3,2-*b*]pyrrolin-5-ones **3a**—**c** were obtained in moderate yields with aluminum bromide as a catalyst (double molar excess of $AlBr_3$ provides the best results). Intramolecular cyclization of amides **2a** and **2b** containing aromatic substituents at the nitrogen atom affords indolin-2-ones **4a**,**b** as by-products. Note that hydroxy compounds **3b** and **4b** obtained from amide **2b** form as a result of the C—O bond cleavage either in the methoxy group of amide **2b** or in the initially formed products of its cyclization.

An attempt to obtain *N*-methylthienopyrrolin-5-one by cyclization of amide **2d** under these conditions failed. Probably, the nitrogen atom in compound **2d**, which is

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 8, pp. 1776—1779, August, 2003.

1066-5285/03/5208-1873 $25.00

Scheme 1



1, **2:** R^1 = 4-MeC_6H_4 (**a**), 4-$MeOC_6H_4$ (**b**), Ph (**c**), Me (**d**)
3: R^2 = Me (**a**), OH (**b**), H (**c**)}
4: R^2 = Me (**a**), OH (**b**)

more basic than the N atom in acylated arylaminothiophenes **2a—c**, is coordinated by $AlBr_3$; this reduces the electron density in the thiophene ring and hence impedes intramolecular alkylation.

Thus, 4-aryl-2,6,6-trimethyl-5-oxo-5,6-dihydro-4*H*-thieno[3,2-*b*]pyrroles can be obtained from accessible 4-aminothiophene derivatives.

Experimental

^1H and ^{13}C NMR spectra were recorded on a Bruker AM-300 radiospectrometer in $CDCl_3$. Mass spectra were recorded on a Kratos instrument (EI, 70 eV, direct inlet probe). Melting points were determined on a Boetius microscope stage and are given noncorrected. The completion of the reactions was inferred from TLC data (Silufol UV-254, light petroleum—ethyl acetate (6 : 1) as an eluent). Silica gel (Acros Co., C.A.S.-7631-86-9, 0.060—0.200 mm) was used for column chromatography. Amines **1a—d** were prepared according to a known procedure.[9]

Acylation of arylamino- and alkylaminothiophenes (general procedure). 2-Bromo-2-methylpropanoyl bromide (0.15 mL, 1.2 mmol) was added dropwise to a stirred solution of compound **1** (1 mmol) and pyridine (80 mg, 1.2 mmol) in 3 mL of methylene chloride. The reaction was exothermic. The reaction mixture was refluxed for 1.5 (**1d**) or 7 h (**1a—c**). After the reaction was completed, the reaction mixture was poured into water, the products were extracted with methylene chloride, and the solvent was removed. The residue was washed with light petroleum, and the precipitate was filtered off. The properties of amides **2a—d** are given in Tables 1 and 2.

Cyclization of amides 2a—c (general procedure). Aluminum bromide (540 mg, 2 mmol) was added to a solution of compound **2** (1 mmol) in 6 mL of dichloroethane. The reaction mixture was refluxed with stirring for 2.5 h. After the reaction was completed (TLC), the reaction mixture was poured into 100 mL of water with ice and acidified with HCl (10 mL). The

Table 1. Spectral characteristics of the compounds obtained

Compound	^1H NMR ($CDCl_3$, δ, *J*/Hz)	^{13}C NMR ($CDCl_3$, δ)	MS, *m/z*, $[M]^+$
2a	1.37 (t, 3 H, $OCH_2C\underline{H}_3$, J = 7); 1.81 (s, 6 H, 2 Me); 2.33 (s, 3 H, $C_6H_4\underline{C}H_3$);); 2.63 (s, 3 H, 2 Me); 4.32 (q, 2 H, $OC\underline{H}_2Me$, J = 7); 6.97 (s, 1 H, CH); 7.13 (d, 2 H, C_6H_4, J_1 = 8.6, J_2 = 2.9); 7.36 (d, 2 H, C_6H_4)	—	424
2b	1.38 (t, 3 H, $OCH_2C\underline{H}_3$, J = 7); 1.82 (s, 6 H, 2 Me); 2.67 (s, 3 H, 2 Me); 3.80 (s, 3 H, OMe); 4.35 (q, 2 H, $OC\underline{H}_2Me$, J = 7); 6.95 (s, 1 H, CH); 6.85 (dd, 2 H, C_6H_4, J_1 = 8.8, J_2 = 2.9); 7.95 (dd, 2 H, C_6H_4, J_1 = 8.8, J_2 = 2.9)	170.0 (COO); 162.8 (C=O); 158.5 ($\underline{C}OMe$); 147.3 ($\underline{C}_{thioph}Me$); 142.0 ($\underline{C}_{thioph}N$); 136.1 ($C_{benz}N$); 129.3 (2 C_{benz}); 125.1 ($\underline{C}_{thioph}CO$); 118.9 ($C_{thioph}H$); 113.8 (2 C_{benz}); 60.4 ($O\underline{C}H_2Me$); 58.2 (CBr); 55.2 (OMe); 32.6, 29.5 (2 C, $C(\underline{C}H_3)_2$); 16.7 (Me); 14.2 ($OCH_2\underline{C}H_3$)	440
2c	1.35 (t, 3 H, $OCH_2C\underline{H}_3$, J = 7); 1.82 (s, 6 H, 2 Me); 2.66 (s, 3 H, 2 Me); 4.31 (q, 2 H, $OC\underline{H}_2Me$, J = 7); 7.02 (s, 1 H, CH); 7.22—7.48 (m, 5 H, C_6H_5)	170.0 (COO); 163.0 (C=O); 146.4 ($\underline{C}_{thioph}Me$); 143.1 ($\underline{C}_{thioph}N$); 141.5 ($C_{benz}N$); 128.8 (2 C_{benz}); 127.9 (2 C_{benz}); 127.2 (C_{benz}); 125.6 ($\underline{C}_{thioph}CO$); 119.8 ($C_{thioph}H$); 60.6 ($O\underline{C}H_2Me$); 58.5 (CBr); 32.7, 30.7 (2 C, $C(\underline{C}H_3)_2$); 16.7 (Me); 14.3 ($OCH_2\underline{C}H_3$)	410

(*to be continued*)

Table 1 (*continued*)

Compound	^{1}H NMR ($CDCl_3$, δ, *J*/Hz)	^{13}C NMR ($CDCl_3$, δ)	MS, *m/z*, $[M]^+$
2d	1.33 (t, 3 H, $OCH_2C\underline{H}_3$, J = 7); 1.85 (s, 3 H, Me); 1.92 (s, 3 H, Me); 2.70 (s, 3 H, 2 Me); 3.24 (br.s, 3 H, NMe); 4.29 (q, 2 H, $OC\underline{H}_2Me$, J = 7); 7.12 (s, 1 H, CH)	—	348
3a	0.84 (t, 3 H, $OCH_2C\underline{H}_3$, J = 7); 1.49 (s, 6 H, 2 Me); 2.38 (s, 3 H, $C_6H_4\underline{C}H_3$); 2.64 (s, 3 H, 2 Me); 3.65 (q, 2 H, $OC\underline{H}_2Me$, J = 7); 7.16 (d, 2 H, C_6H_4, J_1 = 8.0, J_2 = 2.3); 7.22 (d, 2 H, C_6H_4)	183.1 (CON); 163.0 (COO); 146.4 ($C_{benz}N$); 140.0 ($\underline{C}_{thioph}Me$); 136.7 ($C_{thioph}N$); 134.8 ($\underline{C}_{benz}Me$); 129.4 (2 C_{benz}); 124.7 ($\underline{C}_{thioph}CO$); 124.6 (2 C_{benz}); 118.0 ($\underline{C}_{thioph}CMe_2$); 60.7 ($O\underline{C}H_2Me$); 46.2 ($\underline{C}Me_2$); 25.5 (2 C, $C(\underline{C}H_3)_2$); 21.0 ($C_6H_4\underline{C}H_3$); 15.6 (Me); 13.5 ($OCH_2\underline{C}H_3$)	343
3b	0.91 (t, 3 H, $OCH_2C\underline{H}_3$, J = 7); 1.48 (s, 6 H, 2 Me); 2.62 (s, 3 H, 2 Me); 3.66 (q, 2 H, $OC\underline{H}_2Me$, J = 7); 6.01 (br.s, 1 H, OH); 6.73 (d, 2 H, C_6H_4, J_1 = 8.9, J_2 = 3.0); 7.06 (d, 2 H, C_6H_4)	184.5 (CON); 163.3 (COO); 155.8 (COH); 146.6 ($\underline{C}_{thioph}Me$);140.3 ($C_{benz}N$); 129.2 ($C_{thioph}N$); 126.6 (2 C_{benz}); 124.8 ($\underline{C}_{thioph}CO$); 117.9 ($\underline{C}_{thioph}CMe_2$); 116.2 (2 C_{benz}); 61.1 ($O\underline{C}H_2Me$); 46.4 ($\underline{C}Me_2$); 25.5 (2 C, $C(\underline{C}H_3)_2$); 15.7 (Me); 13.8 ($OCH_2\underline{C}H_3$)	345
3c	0.80 (t, 3 H, $OCH_2C\underline{H}_3$, J = 7); 1.45 (s, 6 H, 2 Me); 2.61 (s, 3 H, 2 Me); 3.58 (q, 2 H, $OC\underline{H}_2Me$, J = 7); 7.21—7.48 (m, 5 H, C_6H_5)	182.9 (CON); 162.8 (COO); 146.5 ($C_{benz}N$); 139.8 ($\underline{C}_{thioph}Me$); 137.6 ($C_{thioph}N$); 128.8 (2 C_{benz}); 126.8 (C_{benz}); 124.8 ($\underline{C}_{thioph}CO$); 124.7 (2 C_{benz}); 118.0 ($\underline{C}_{thioph}CMe_2$); 60.6 ($O\underline{C}H_2Me$); 46.2 ($\underline{C}Me_2$); 25.6 (2 C, $C(\underline{C}H_3)_2$); 15.6 (Me); 13.5 ($OCH_2\underline{C}H_3$)	329
4a	1.05 (t, 3 H, $OCH_2C\underline{H}_3$, J = 7); 1.49 (s, 6 H, 2 Me); 2.35 (s, 3 H, 5 Me); 2.76 (s, 3 H, 2 Me); 4.11 (q, 2 H, $OC\underline{H}_2Me$, J = 7); 6.50—7.28 (m, 3 H, C(4), C(6), C(7)); 7.11 (s, 1 H, CH)	—	343
4b	1.05 (t, 3 H, $OCH_2C\underline{H}_3$, J = 7); 1.49 (s, 6 H, 2 Me); 2.73 (s, 3 H, 2 Me); 4.11 (q, 2 H, $OC\underline{H}_2Me$, J = 7); 4.91 (br.s, 1 H, OH); 6.48—6.79 (m, 3 H, C(4), C(6), C(7)); 7.11 (s, 1 H, CH)	—	345

Table 2. Melting points, yields, and elemental analysis data of the compounds obtained

Compound	M.p. /°C	Molecular formula	Found / Calculated (%)				Yield (%)
			C	H	S	Br	
2a	102	$C_{19}H_{22}BrNO_3S$	54.04 / 53.78	5.42 / 5.23	7.62 / 7.56	18.52 / 18.83	90
2b	95	$C_{19}H_{22}BrNO_4S$	52.04 / 51.82	5.20 / 5.04	7.09 / 7.28	17.91 / 18.15	85
2c	100	$C_{18}H_{20}BrNO_3S$	52.41 / 52.69	5.28 / 4.91	7.62 / 7.81	19.14 / 19.47	67
2d	Oil	$C_{13}H_{18}BrNO_3S$	44.99 / 44.84	5.48 / 5.21	8.92 / 9.21	22.58 / 22.94	71
3a	92	$C_{19}H_{21}NO_3S$	65.90 / 66.45	6.09 / 6.16	9.30 / 9.34	—	24
3b	165	$C_{18}H_{19}NO_4S$	62.81 / 62.59	5.80 / 5.54	8.91 / 9.28	—	18
3c	78	$C_{18}H_{19}NO_3S$	65.13 / 65.63	6.01 / 5.81	9.32 / 9.73	—	22
4a	127	$C_{19}H_{21}NO_3S$	65.99 / 66.45	6.28 / 6.16	9.04 / 9.34	—	18
4b	189	$C_{18}H_{19}NO_4S$	63.03 / 62.59	6.02 / 5.54	9.22 / 9.28	—	14

products were extracted with chloroform (3×20 mL). The combined organic layers were successively washed with dilute HCl and water and dried over $CaCl_2$. The solvent was removed, and the residue was chromatographed in a column with light petroleum—ethyl acetate (6 : 1) as an eluent. The first fraction corresponded to 4-aryl-2,6,6-trimethyl-5-oxo-5,6-dihydro-4*H*-thieno[3,2-b]pyrroles **3a**—**c**, while the second was 3-ethoxycarbonyl-2-methyl-4-(5-R-3,3-dimethyl-2-oxo-2,3-dihydro-1*H*-indol-1-yl)thiophenes **4a**,**b** (in the case of **2c**, no second fraction was present). The characteristics of the compounds obtained are given in Tables 1 and 2.

References

1. R. P. Robinson and K. M. Donahue, *J. Org. Chem.*, 1991, **56**, 4805.
2. J. Guillanmel, P. Demerseman, J.-M. Clavel, and R. Royer, *J. Heterocycl. Chem.*, 1980, **17**, 1531.
3. R. Sarges, H. R. Howard, B. K. Koe, and A. Weissman, *J. Med. Chem.*, 1989, **32**, 437.
4. A. Canas-Rodrigues and P. R. Leeming, *J. Med. Chem.*, 1972, **15**, 762.
5. M. E. Migaud, R. C. Wilmouth, G. I. Mills, G. J. Wayne, C. Risley, C. Chambers, J. F. Macdonald, and C. J. Schofield, *Chem. Commun.*, 2002, 1274.
6. D. Geffken, *Arch. Pharm.*, 1987, **8**, 743.
7. Ger. Offen 2,920,861 (1979); *Chem. Abstr.,* 1980, 92, 110838m.
8. D. Geffken and G. Groll, *Pharmazie*, 1993, **48**, 801.
9. V. I. Shvedov, V. K. Vasil´eva, and A. N. Grinev, *Khim. Geterotsikl. Soedin.*, 1970, 1602 [*J. Heterocycl. Compd.*, 1970 (Engl. Transl.)].
10. R. Stolle, *Chem. Ber.*, 1914, **47**, 2120.

Received February 26, 2003;
in revised form May 13, 2003