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SYNTHESIS OF PYRIDO[3′,2′:4,5]THIENO[2,3-*c*]CINNOLINES — A NEW HETEROCYCLIC SYSTEM

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Pyrido[3′,2′:4,5]thieno[2,3-c]cinnolines, new heterocyclic compounds, were obtained in three steps: 1) alkylation of 3-cyanopyridine-2(1H)-thiones by o*-nitrobenzyl bromide to give 2-(*o*-nitrobenzyl)thio-3-cyanopyridines, 2) closure of the thiophene ring in these intermediates to give 3-amino-2-(*o*-nitrophenyl)thieno[2,3-*b*]pyridines, and 3) closure of the pyridazine ring by condensation of the amino and nitro groups in triethyl phosphite, leading to the final heterocyclic system.*

Condensed cinnolines hold great interest in light of the broad spectrum of their useful properties [1]. The major method for constructing such heterocyclic systems involves intramolecular cyclization of aryldiazonium salts [1]. This approach has been used for the synthesis of such condensed heterocyclic systems as benzo[*c*]cinnolines [1, 2] and thieno-[2,3-*c*(3,2-*c*)]cinnolines [3]. However, *o*-aryl- or *o*-hetarylanilines, the starting compounds for these syntheses, are usually difficult to obtain. This lack of availability has limited the compounds of this class, as described [1].

In the present work, we propose a new approach for construction of the cinnoline system involving formation of a $-N=N-$ double bond by the reaction of NH_2 and NO_2 groups in $P(OEt)_3$. Intermolecular reactions of this type leading to arylazo compounds have not yet been reported. A similar method has been proposed for ring closure in 2-amino-2′-nitrodiphenyl, which, upon treatment with trimethylbenzylammonium hydroxide, gives a cyclic azoxy compound, namely, benzo[*c*]cinnoline oxide [4, 5].

Previously unreported 3-amino-2-(2-nitrophenyl)thieno[2,3-*b*]pyridines (Ia-Ig, see Scheme) were selected as the starting compounds for the synthesis of fused cinnolines. Several published studies have been devoted to the synthesis of analogous compounds (R^1, R^2, R^3 = H, Me, R^4 = H, R^5 = NO_2) containing a 4-nitrophenyl substituent by cyclization of the corresponding 2-(4-nitrobenzyl)thio-3-cyanopyridines in the presence of sodium ethylate in ethanol [6-8].

According to the proposed scheme, alkylation of deprotonated 3-cyano-1(2H)-pyridinethiones (IIa-IIg) by 2- or 4-nitrobenzyl bromide leads to benzylthiopyridines (IIIa-IIIg). The next step involves deprotonation of the acidic methylene group in III by the action of KOH as a base and subsequent closure of the thiophene ring by a Thorpe–Ziegler reaction to give thienopyridines (Ia-Ig). We have shown that the nitrophenyl group in this case is also a sufficiently strong electron-withdrawing substituent for carrying out such a cyclization. The feasibility of obtaining I directly from starting pyridinethiones II without isolation of intermediate pyridines III is not excluded though isolation of the intermediate is desirable for obtaining the desired thienopyridine in pure form and good yield.

The PMR and IR spectral data were sufficiently informative to establish the structures of I and III. Thus, the IR spectra of pyridines III have a band for the 3-CN group in the vicinity of 2220 cm^{-1}. This band disappears after closure of the thiophene ring and formation of I and several bands appear at ~3360 cm^{-1} characteristic for the NH_2 group. The PMR signal for the methylene group in pyridines III at ~4.80 ppm is also diagnostic. This signal is lacking in the spectra of I, and a broad singlet at 4.50-6.00 ppm appears for the amino group.

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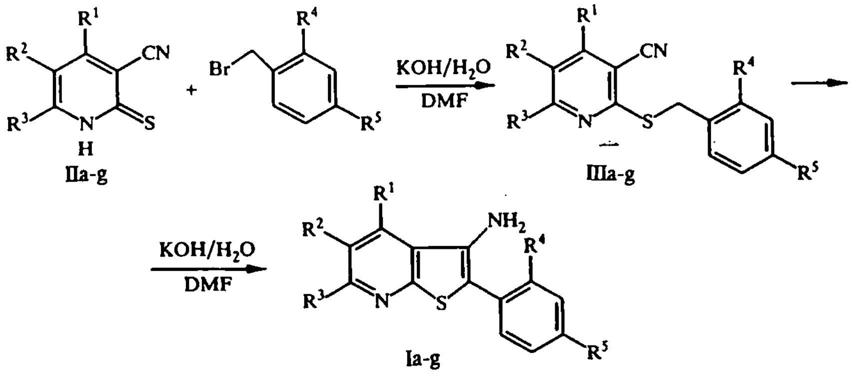
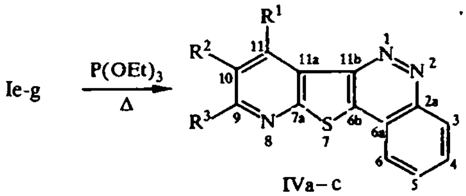


I—III a $R^1 = R^2 = R^4 = H$, R^3 = 2-thienyl (Het), $R^5 = NO_2$; b $R^1 = CF_3$, $R^2 = R^4 = H$, R^3 = Het, $R^5 = NO_2$; c $R^1 = R^4 = H$, $R^2 = CN$, $R^3 = NH_2$, $R^5 = NO_2$; d $R^1 = R^4 = H$, $R^2 + R^3 = (CH_2)_3$, $R^5 = NO_2$; e $R^1 = R^2 = CH_3$, $R^2 = R^5 = H$, $R^4 = NO_2$; f $R^1 = R^2 = R^5 = H$, R^3 = Het, $R^4 = NO_2$; g $R^1 = CF_3$, $R^2 = R^5 = H$, R^3 = Het, $R^4 = NO_2$

3-Amino-2-(2-nitrophenyl)thieno[2,3-*b*]pyridines Ie-Ig undergo pyridazine ring closure upon heating at reflux in triethyl phosphite to give pyrido[3′,2′:4,5]thieno[3,2-*c*]cinnolines (IVa-IVc):



IV a $R^1 = R^3$ = Me, R^2 = H; b $R^1 = R^2$ = H, R^3 = Het; c $R^1 = CF_3$, R^2 = H, R^3 = Het

The mechanism for the intramolecular cyclization of the amino and nitro groups in this case probably involves consecutive steps featuring deoxygenation of the nitro group, formation of the corresponding nitroso compound, and condensation of the amino and nitroso groups, leading to the final condensed cinnoline. The structure of IVa-IVc was supported by PMR and IR spectroscopy and mass spectrometry. The spectral data for these compounds are given in Table 3. Closure of the cinnoline ring is indicated by the lack of the PMR signal for the NH_2 group, lack of IR bands for the NH_2 and NO_2 groups, the mass spectral data, and downfield shift of the PMR signal for the R^1 substituent, which is characteristic for such systems [9].

Thus, we have developed a new method for the synthesis of condensed cinnolines based on the closure of a pyridazine ring in 3-amino-2-(2-nitrophenyl)thieno[2,3-*b*]pyridines.

EXPERIMENTAL

The melting points were determined on a Koeffler block. The IR spectra were taken on a Specord M-80 spectrometer for KBr pellets and the PMR spectra were taken on a Bruker WM-200 spectrometer at 200 MHz for solutions in DMSO-d_6. The mass spectra were taken on a Varian MAT mass spectrometer at 70 eV. The elemental analysis for C, H, and N was carried out on a Perkin–Elmer C,H,N-analyzer. The characteristics of products I, III, and IV are given in Tables 1-3.

The starting 3-cyanopyridine-1(2H)-thiones were obtained according to our previous procedure [10].

2-(Nitrobenzyl)thio-3-cyanopyridines (IIIa-IIIg). A sample of 3 mmoles KOH as a 10% aqueous solution was added to a solution of 3 mmoles IIa-IIg in 10 ml DMF followed by 3 mmoles corresponding benzyl bromide. The reaction mixture was maintained for 3-5 min at room temperature. The product was then precipitated by adding water, filtered off, washed with ethanol and hexane, and dried in the air. The mass spectrum for IIIe (*m/z*, intensity): 299 (M^+, 1%), 281 (4%), 251 (5%), 164 (100%).

TABLE 1. Physical Indices for 2-(Nitrobenzyl)thio-3-cyanopyridines III

Compound	Chemical formula	Found, % / Calculated, %			mp, °C	IR spectrum, ν, cm^{-1}	PMR spectrum, δ, ppm, coupling constant (*J*), Hz	Yield, %
		C	H	N				
IIIa	$C_{17}H_{11}N_3O_2S_2$	57,61 57,78	3,25 3,14	11,93 11,89	191...193	2220 (CN), 1560 (C=N), 1510 (NO_2)	4,75 (2H, s, CH_2); 7,23 (1H, d.d, *J* = 4,5, 4-H_{Het}); 7,77 (4H, m, 5-H, 3-H_{Het}, 2-and 6-H_{Ar}); 7,95 (1H, d, *J* = 5, 5-H_{Het}); 8,15 (3H, m, 4-H, 3- and 5-H_{Ar})	85
IIIb	$C_{18}H_{10}N_3F_3O_2S_2$	51,22 51,30	2,27 2,39	10,05 9,97	234...236	2220 (CN), 1590 (C=N), 1524 (NO_2)	4,79 (2H, s, CH_2); 7,26 (1H, d.d, *J* = 4,5, 4-H_{Het}); 7,77 and 8,14 (2 × 2H, AA'XX', 4H_{Ar}); 7,91 (1H, d, *J* = 4, 3-H_{Het}); 8,12 (1H, s, 5-H); 8,23 (1H, d, *J* = 5, 5-H_{Het})	94
IIIc	$C_{14}H_9N_5O_2S$	54,15 54,01	2,84 2,91	22,63 22,50	245...247	3450, 3350, 3250 (NH_2), 2230 (CN), 1650, 1600 (C=N), 1535 (NO_2)	4,57 (2H, s, CH_2); 7,77 and 8,14 (2 × 2H, AA'XX', 4H_{Ar}); 7,98 (2H br. s, NH_2); 8,24 (1H, s, 4-H)	70
IIId	$C_{16}H_{13}N_3O_2S$	61,66 61,72	4,11 4,21	13,48 13,50	182...184	2224 (CN), 1600 (C=N), 1523 (NO_2)	2,09 (2H, q, *J* = 7, 6-CH_2); 2,88 (2H, t, *J* = 7, 5-CH_2); 3,00 (2H, t, *J* = 7, 7-CH_2); 4,62 (2H, s, SCH_2); 7,70 and 8,15 (2 × 2H, AA'XX', 4H_{Ar}); 7,95 (1H, s, 4-H)	53
IIIe	$C_{15}H_{13}N_3O_2S$	60,25 60,19	4,29 4,38	14,08 14,04	150...152	2222 (CN), 1585 (C=N), 1540 (NO_2)	2,38 (3H, s, 4-CH_3); 2,50 (3H, s, 6-CH_3); 4,82 (2H, s, CH_2); 7,09 (1H, s, 5-H); 7,53 (1H, t, *J* = 8, 4-H_{Ar}); 7,69 (1H, t, *J* = 8, 5-H_{Ar}); 7,80 (1H, d, *J* = 8, 6-H_{Ar}); 8,01 (1H, d, *J* = 8, 3-H_{Ar})	85
IIIf	$C_{17}H_{11}N_3O_2S_2$	57,67 57,78	3,07 3,14	11,80 11,89	135...137	2227 (CN), 1574 (C=N), 1524 (NO_2)	4,94 (2H, s, CH_2); 7,24 (1H, d.d, *J* = 4,5, 4-H_{Het}); 7,57 (1H, t, *J* = 8, 4-H_{Ar}); 7,68 (1H, t, *J* = 8, 5-H_{Ar}); 7,82 (3H, m, 6-H_{Ar}, 3-H_{Het} and 5-H); 7,98 (1H, d, *J* = 5, 5-H_{Het}); 8,08 (1H, d, *J* = 8, 3-H_{Ar}); 8,18 (1H, d, *J* = 9, 4-H)	81
IIIg	$C_{18}H_{10}N_3F_3O_2S_2$	51,26 51,30	2,46 2,39	10,00 9,97	190...193	2224 (CN), 1588 (C=N), 1530 (NO_2)	4,97 (2H, s, CH_2); 7,30 (1H, d.d, *J* = 4,5, 4-H_{Het}); 7,57 (1H, t, *J* = 8, 4-H_{Ar}); 7,68 (1H, t, *J* = 8, 5-H_{Ar}); 7,85 (1H, d, *J* = 8, 6-H_{Ar}); 7,95 (1H, d, *J* = 4, 3-H_{Het}); 8,11 (1H, d, *J* = 8, 3-H_{Ar}); 8,19 (1H, s, 5-H); 8,27 (1H, d, *J* = 5, 5-H_{Het})	91

TABLE 2. Physical Indices for 3-Amino-2-nitrophenylthieno[2,3-*b*]pyridines I

Compound	Chemical formula	Found, % / Calculated, %			mp, °C	IR spectrum, ν, cm^{-1}	PMR spectrum, δ, ppm, coupling constant (*J*), Hz	Yield, %
		C	H	N				
Ia	$C_{17}H_{11}N_3O_2S_2$	57,65 57,78	3,20 3,14	11,98 11,89	>270	3360 (NH_2), 1580 (C=N), 1515 (NO_2)	6,00 (2H, br. s, NH_2); 7,20 (1H, d.d, *J* = 4,5, 4-H_{Het}); 7,68 (1H, d, *J* = 4, 3-H_{Het}); 7,85 and 8,25 (2 × 2H, AA'XX', 4H_{Ar}); 7,88 (1H, d, *J* = 5, 5-H_{Het}); 7,96 (1H, d, *J* = 9, 5-H); 8,46 (1H, d, *J* = 9, 4-H)	78
Ib	$C_{18}H_{10}N_3F_3O_2S_2$	51,20 51,30	2,31 2,39	10,88 9,97	185...187	3535 (NH_2), 1595 (C=N), 1520 (NO_2)	5,05 (2H, s, NH_2); 7,24 (1H, d.d, *J* = 4,5, 4-H_{Het}); 7,78 (1H, d, *J* = 4, 3-H_{Het}); 7,94 and 8,33 (2 × 2H, AA'XX', 4H_{Ar}); 8,11 (1H, d, *J* = 5, 5-H_{Het}); 8,24 (1H, s, 5-H)	85
Ic	$C_{14}H_9N_5O_2S$	54,08 54,01	2,81 2,91	22,45 22,50	>270	3450, 3385 (NH_2), 2225 (CN), 1650, 1590 (C=N), 1525 (NO_2)	6,13 (2H, s, 3-NH_2); 7,06 (2H, s, 6-NH_2); 7,73 and 8,19 (2 × 2H, AA'XX', 4H_{Ar}); 8,58 (1H, s, 4-H)	64
Id	$C_{16}H_{13}N_3O_2S$	61,65 61,72	4,17 4,21	13,57 13,50	>270	3455, 3345, 3230 (NH_2), 1595 (C=N), 1510 (NO_2)	2,14 (2H, q, *J* = 7, 6-CH_2); 3,00 (4H, t, *J* = 7, 5-and 7-CH_2); 6,00 (2H, s, NH_2); 7,83 and 8,22 (2 × 2H, AA'XX', 4H_{Ar}); 8,22 (1H, s, 4-H)	95
Ie	$C_{15}H_{13}N_3O_2S$	60,11 60,19	4,34 4,38	13,95 14,04	158...160	3500 (NH_2), 1605 (C=N), 1527 (NO_2)	2,50 (3H, s, 6-CH_3); 2,74 (3H, s, 4-CH_3); 4,60 (2H, s, NH_2); 7,00 (1H, s, 5-H); 7,66 (2H, m, 4-H and 5-H_{Ar}); 7,79 (1H, d, *J* = 8, 6-H_{Ar}); 8,05 (1H, d, *J* = 8, 3-H_{Ar})	80
If	$C_{17}H_{11}N_3O_2S$	57,71 57,78	3,09 3,14	11,81 11,89	168...172	3285 (NH_2), 1580 (C=N), 1535 (NO_2)	5,30 (2H, br.s, NH_2); 7,19 (1H, d.d, *J* = 4,5, 4-H_{Het}); 7,67 (3H, m, 3-H_{Het}, 4-and 5-H_{Ar}); 7,78 (1H, d, *J* = 8, 6-H_{Ar}); 7,86 (1H, d, *J* = 5, 5-H_{Het}); 7,92 (1H, d, *J* = 9, 5-H); 8,08 (1H, d, *J* = 8, 3-H_{Ar}); 8,34 (1H, d, *J* = 9, 4-H)	55
Ig	$C_{18}H_{10}N_3F_3O_2S_2$	51,21 51,30	2,43 2,39	10,06 9,97	179...182	3580 (NH_2), 1595 (C=N), 1540 (NO_2)	4,50 (2H, s, NH_2); 7,24 (1H, d.d, *J* = 4,5, 4-H_{Het}); 7,27 (3H, m, 4-and 5-H_{Ar}, 3-H_{Het}); 7,87 (1H, d, *J* = 8, 6-H_{Ar}); 8,12 (1H, d, *J* = 5, 5-H_{Het}); 8,17 (1H, d, *J* = 8, 3-H_{Ar}); 8,26 (1H, s, 5-H)	70

TABLE 3. Physical Indices for Pyrido[3′,2′:4,5]thieno[2,3-c]cinnolines IV

Compound	Chemical formula	$\frac{\text{Found, \%}}{\text{Calculated, \%}}$			mp, °C	IR spectrum, ν, cm^{-1}	PMR spectrum, δ, ppm, coupling constant (J), Hz	Yield, %
		C	H	N				
IVa	$C_{15}H_{11}N_3S$	$\frac{67,97}{67,90}$	$\frac{4,06}{4,18}$	$\frac{15,76}{15,84}$	266...267	2930, 2860 (CH), 1590, 1570, 1445	2,66 (3H, s, 9-CH_3); 3,17 (3H, s, 11-CH_3); 7,44 (1H, s, 10-H); 8,02 (2H, m, 4-and5-H); 8,26 (1H, d. $J = 8$, 3-H); 8,65 (1H, d, $J = 8$, 6-H)	30
IVb	$C_{17}H_9N_3S$	$\frac{64,07}{63,93}$	$\frac{2,74}{2,84}$	$\frac{13,22}{13,16}$	>270	2960 (CH), 1585, 1455	7,26 (1H, d.d, $J = 4{,}5$, 4-H_{Het}); 7,78 (1H, d, $J = 4$, 3-H_{Het}); 8,08 (3H, m, 4-and5-H, 5-H_{Het}); 8,28 (1H, d, $J = 9$, 10-H); 8,33 (1H, m, 3-H); 8,70 (1H, m, 6-H); 9,08 (1H, d, $J = 9$, 11-H)	32
IVc*	$C_{18}H_8F_3N_3S_2$	$\frac{55,73}{55,81}$	$\frac{1,96}{2,08}$	$\frac{10,78}{10,85}$	>270	2940 (CH), 1565, 1450	7,29 (1H, d.d, $J = 4{,}5$, 4-H_{Het}); 7,85 (1H, d, $J = 4$, 3-H_{Het}); 8,10 (2H, m, 4-and5-H); 8,24 (1H, d, $J = 5$, 5-H_{Het}); 8,47 (1H, d, $J = 8$, 3-H); 8,52 (1H, s, 10-H); 8,71 (1H, d, $J = 8$, 6-H)	40

3-Amino-2-nitrophenylthieno[2,3-*b*]pyridines (Ia-Ig). Two or three drops of 10% aq. KOH were added to a solution of 1 mmole IIIa-IIIg in DMF and the mixture was maintained at room temperature for 2 h. The product was precipitated by adding water, filtered off, washed with ethanol and hexane, and dried in the air. The mass spectrum for Ie (*m/z*): 299 (M^+, 100%), 282 (71%), 254 (63%), 165 (93%).

Pyrido[3′,2′:4,5]thieno[3,2-*c*]cinnolines (IVa-IVc). A solution of 1 mmole Ia-Ig in 5 ml triethyl phosphite was heated at reflux for 6 h. Triethyl phosphite was distilled off in vacuum and the residue was covered with ethanol. The crystalline precipitate formed after 30 min was filtered off, washed with ethanol and hexane, and dried in the air. An analytically pure sample was obtained by reprecipitation of the product obtained from DMSO. The mass spectrum for IVa (*m/z*): 265 (M^+, 100%), 252 (5%), 236 (14%), 222 (6%).

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