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ETHYL 4-BROMOCROTONATE IN THE SYNTHESIS OF PYRIDO[3′,2′:4,5]THIENO[3,2-*d*]PYRIDIN-2(1H)-ONES

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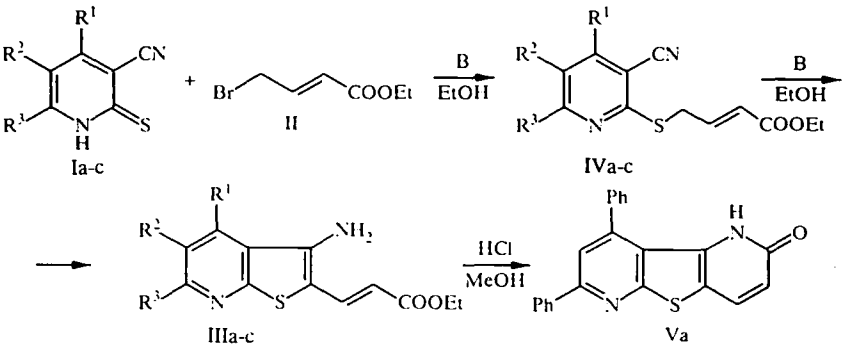
Pyrido[3′,2′:4,5]thieno[3,2-d]pyridin-2(1H)-ones were synthesized from 3-cyano-2(1H)-pyridinethiones and ethyl 4-bromocrotonate.

Substituted pyrido[3′,2′:4,5]thieno[3,2-*d*]pyridin-(1H)-ones hold interest since they possess a broad range of biological activity. A few methods have been described for construction of the pyrido[3′,2′:4,5]thieno[3,2-*d*]pyridine system. The first method involves closure of the pyridine ring as the result of the reaction of 3-aminothieno[2,3-*b*]pyridine with the acetal of malonodialdehyde [1]. The second method utilizes the reaction of 2-acyl-3-amino[2,3-*d*]pyridine with ethyl orthoformate or the diethyl acetal of dimethylformamide [2]. The third method involves cascade heterocyclization with 3-cyanopyridinethiones and 2-bromo-1-arylethylidenemalononitrile and leads to functionally substituted pyrido[3′,2′:4,5]-thieno[3,2-*d*]pyridines [3]. Pathways for the preparation of derivatives containing the 2(1H)-pyridinone fragment have not yet been reported.

In the present work, feasibility was demonstrated for the synthesis of such compounds starting from readily available 3-cyano-2(1H)-pyridinethiones and ethyl 4-bromocrotonate. This method is based on the strategy for the construction of heterocyclic systems through cascade reactions, previously employed in the synthesis of pyridothienopyridines, pyridothienopyrimidines, thienopyridines, and thiazolopyridines [3-6].

Substituted 3-cyano-2(1H)-pyridinethiones (Ia-Ic) react under basic conditions with ethyl 4-bromocrotonate (II) to give 3-amino-2-(2-carboethoxyvinyl)thieno[2,3-*b*]pyridines (IIIa-IIIc).

The mechanism for the formation of III may be seen as alkylation at the sulfur atom followed consecutively by a Thorpe–Ziegler reaction leading to a thiophene ring.



I, III, IV, V a $R^1 = R^3 = Ph$, $R^2 = H$; b $R^1 = R^3 = Me$, $R^2 = H$; c $R^2R^3 = (CH_2)_3$, $R^1 = H$

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TABLE 1. Physical Indices of III, IV, and Va

Compound	Chemical formula	Found, % / Calculated, %			mp, °C	IR spectrum, ν, cm^{-1}	PMR spectrum, DMSO-d_6, δ, ppm, coupling constant, Hz	Yield, %
		C	H	N				
IIIa	$C_{24}H_{20}N_2O_2S$	71,85 / 71,98	5,14 / 5,03	6,72 / 6,99	240	3375 (NH); 1690 (C=O); 1600, 1536	1,22 (3H, t, J = 7, $CH_2\underline{CH_3}$); 4,14 (2H, q, J = 7, $\underline{CH_2}CH_3$); 5,40 (2H, br. s, NH_2); 5,80 (1H, d, J = 15, $\underline{CH}CO_2Et$); 7,40...7,62 (8H, m, o- m-, p-$H_{4\text{-}Ph}$ and m-,p-$H_{6\text{-}Ph}$); 7,74 (1H, s, 5-H); 8,15 (1H, d, J = 15, $\underline{CH}CHCO_2Et$); 8,20...8,25 (2H, m, o-$H_{6\text{-}Ph}$)	56, 81*
IIIb	$C_{14}H_{16}N_2O_2S$	60,90 / 60,85	5,71 / 5,84	10,30 / 10,14	238...241 subl.	3245(NH); 1671(C=O); 1643, 1596, 1548	1,26 (3H, t, J = 7, $CH_2\underline{CH_3}$); 2,48 (3H, s, 6-CH_3); 2,71 (3H, s, 4-CH_3); 4,18 (2H, q, J = 7, $\underline{CH_2}CH_3$); 5,70 (1H, d, J = 15, $\underline{CH}CO_2Et$); 6,09 (2H, br. s, NH_2); 6,96 (1H, s, 5-H); 8,23 (1H, d, J = 15, $\underline{CH}CHCO_2Et$)	52, 79*
IIIc	$C_{15}H_{16}N_2O_2S$	62,38 / 62,48	5,41 / 5,59	9,84 / 9,71	229...231	3010 (NH); 1702 (C=O); 1609, 1479	1,22 (3H, t, J = 7, $CH_2\underline{CH_3}$); 2,12 (2H, q, J = 8,6-$\underline{CH_2}$); 2,47...2,53 (4H, m, 5-and 7-CH_2); 4,16 (2H, q, J = 7, $\underline{CH_2}CH_3$); 5,62 (1H, d, J = 15, $\underline{CH}CO_2Et$); 6,61 (2H, br. s NH_2); 8,00 (1H, s, 5-H); 8,16 (1H, d, J = 15, $\underline{CH}CHCO_2Et$)	58, 77*
IVa	$C_{24}H_{20}N_2O_2S$	71,71 / 71,98	5,06 / 5,03	7,14 / 6,99	119...120	2221 (CN); 1728 (C=O); 1655, 1578, 1532	1,20 (3H, t, J = 7, $CH_2\underline{CH_3}$); 4,11 (2H, q, J = 7, $\underline{CH_2}CH_3$); 4,29 (2H, d, J = 8, SCH_2); 6,18 (1H, d, J = 15, $\underline{CH}CO_2Et$); 7,03 (1H, d. t, J' = 15, J'' = 8, $\underline{CH}CHCO_2Et$); 7,50...7,63 (6H, m, m-, p-$H_{4\text{-}}$ and $_{6\text{-}Ph}$); 7,75 (2H, m, o-$H_{4\text{-}Ph}$); 7,91 (1H, s, 5-H); 8,27 (2H, m, o-$H_{6\text{-}Ph}$)	91
IVb	$C_{14}H_{16}N_2O_2S$	60,74 / 60,85	5,61 / 5,84	10,35 / 10,14	81...83	2221 (CN); 1725 (C=O); 1620, 1587	1,20 (3H, t, J = 7, $CH_2\underline{CH_3}$); 2,37 (3H, s, 4-CH_3); 2,43 (3H, s, 6-CH_3); 4,03...4,18 (4H, m, $\underline{CH_2}CH_3$ and SCH_2), 6,10 (1H, d, J = 15, $\underline{CH}CO_2Et$); 6,87 (1H, d. t, J' = 15, J'' = 8, $\underline{CH}CHCO_2Et$); 7,13 (1H, s, 5-H)	87
Vc	$C_{15}H_{16}N_2O_2S$	62,72 / 62,48	5,52 / 5,59	9,65 / 9,71	95...96	2222 (CN); 1710 (C=O); 1678, 1450	1,20 (3H, t, J = 7, $CH_2\underline{CH_3}$); 2,08 (2H, qn, †J = 8, 6-CH_2); 2,88 (2H, d, 5-CH_2); 2,97 (2H, d, 7-CH_2); 4,01...4,15 (4H, m, $\underline{CH_2}CH_3$ and SCH_2); 6,07 (1H, d, J = 15, $\underline{CH}CO_2Et$); 6,87 (1H, d. t, J' = 15, J'' = 8, $\underline{CH}CHCO_2Et$); 8,02 (1H, s, 8-H)	93
Va	$C_{22}H_{14}N_2OS$	74,49 / 74,55	4,10 / 3,99	7,76 / 7,90	>270	1670(C=O); 1554	6,79 (1H, d, J = 9, 3-H); 7,47...7,62 (6H, m, m-, p-H and p-$H_{4\text{-}}$ and $_{6\text{-}Ph}$); 7,20...7,30 (2H, m, o-$H_{9\text{-}Ph}$); 7,90 (1H, s, 8-H); 8,19...8,31 (3H, m, o-$H_{7\text{-}Ph}$ and 4-H)	33

*Yield according to method B.

†qn) Quintet.

These reactions occur under similar conditions, which permits us to obtain thienopyridines IIIa-IIIc in a single step. However, the yield of thienopyridines III is higher with the intermediate isolation of alkylation products IVa-IVc. The crotonic acid fragment in IIIa-IIIc contains a *trans*-double bond. Thus, spontaneous cyclization under basic conditions leading to a pyridine ring is impossible. Formation of a tricyclic product proved possible under acidic conditions when 3-amino-4,6-diphenyl-6-(2-carboethoxyvinyl)thieno[2,3-*b*]pyridine IIIa was used. The pyridine ring formation probably proceeds as the consecutive addition of hydrogen chloride at the double bond, closure of the piperidine ring, and subsequent aromatization leading to pyrido[3',2':4,5]thieno[3,2-*d*]pyridin-2(1H)-one (Va).

The products were identified by PMR and IR spectroscopy and elemental analysis. The physical indices of IIIa-IIIc, IVa-IVc, and Va are given in Table 1.

The IR spectra of monocyclic products IVa-IVc have CN group signals at 2221-2222 cm^{-1} and for carbonyl group signals at 1710-1729 cm^{-1}. There are no CN group signals in the spectra of IIIa-IIIc, while the carbonyl fragment appears at longer wavelengths (1671-1702 cm^{-1}). The signal for the C=O group in the spectrum of pyrido[3',2':4,5]thieno-[3,2-*d*]pyridin-2(1H)-one Va is found at 1670 cm^{-1}.

The coupling constant of the crotonic fragment protons in the PMR spectra of IIIa-IIIc and IVa-IVc is 15 Hz, indicating *trans* arrangement. The signals for the enone fragment in the spectrum of pyrido[3',2':4,5]thieno-[3,2-*d*]pyridin-2(1H)-one Va appear as a downfield AB system with coupling constant equal to 8 Hz. This indicates *cis* arrangement of these protons. The lack of signals for the carboethoxy group and elemental analysis data permit us to assign a structure with a 2(1H)-pyridinone ring.

Thus, we have demonstrated the feasibility of the preparation of pyrido[3',2':4,5]thieno[3,2-*d*]pyridin-2(1H)-ones, which are promising reagents in the synthesis of biologically active compounds.

EXPERIMENTAL

The melting points were determined on a Koeffler block. The IR spectra were taken on a Specord-M80 spectrometer for KBr pellets. The PMR spectra were taken for DMSO-d_6 solutions on a Bruker AC-200 spectrometer at 200 MHz. The elemental analysis for C, H, and N was carried out on a Perkin-Elmer C,H,N-analyzer. Products Ia-Ic were obtained according to standard methods [7]. The yields and physical indices of III, IV, and V are given in Table 1.

2-(3-Carboethoxy-2-propenylthio)-3-cyanopyridines (IVa-IVc). A sample of 2 mmoles KOH as a 10% aqueous solution was added to a suspension of 2 mmoles 3-cyano-2(1H)-pyridinethione in 15 ml ethanol. The mixture was heated until it became completely homogeneous. After 5 min, 2.1 mmoles ethyl 4-bromocrotonate was added and the reaction mixture was maintained for 5 h at room temperature. The precipitate of IV was filtered off, washed with a small amount of ethanol and hexane, and dried in the air.

3-Amino-6-(2-carboethoxyvinyl)thieno[2,3-*b*]pyridines (IIIa-IIIc). A sample of 2 mmoles KOH as a 10% aqueous solution was added to a suspension of 2 mmoles 3-cyano-2(1H)-pyridinone in 15 ml ethanol. The mixture was heated until it was entirely homogeneous and, after 5 min, 2.1 mmoles ethyl 4-bromocrotonate was added. After 30 min, 2 mmoles ethanolic sodium ethylate was added. The precipitate of III was filtered off, washed with a small amount of ethanol and hexane, and dried in the air.

B. A sample of 1 mmole ethanolic sodium ethylate was added to a solution of 1 mmole 2-thio(3-carboethoxy-2-propenyl)-3-cyanopyridine IV in 15 ml hot ethanol. The precipitate of III was filtered off, washed with a small amount of ethanol and hexane, and dried in the air.

7,9-Diphenylpyrido[3',2':4,5]thieno[3,2-*d*]pyridin-2(1H)-one (Va). A suspension of thienopyridine IIIa in methanol was heated at reflux in the presence of a catalytic amount of hydrochloric acid for 8 h. The reaction mixture was then neutralized by adding 10% aq. sodium carbonate (pH 7). The precipitate of Va was filtered off, washed with ethanol and hexane, and dried in the air.

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