Chemistry of Heterocyclic Compounds, Vol. 33, No. 6, 1997

N-ACETYLCHLOROACETAMIDE IN THE SYNTHESIS OF FUNCTIONALLY-SUBSTITUTED PYRIDO[3′,2′:4,5]-THIENO[3,2-*d*]PYRIMIDIN-4(3H)-ONES

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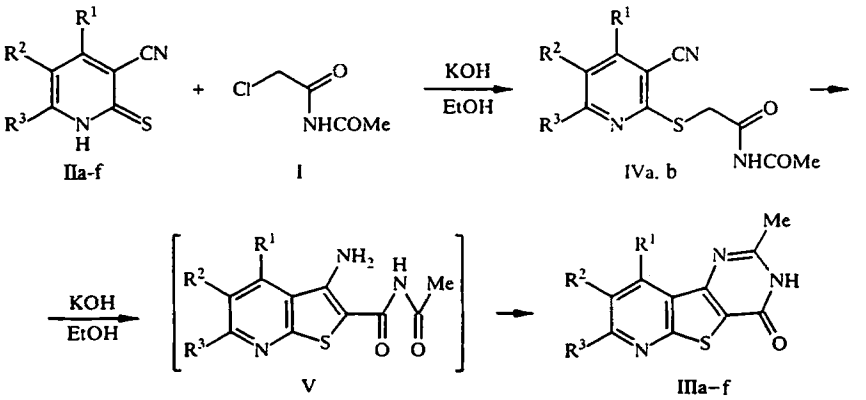
3-Cyano-2(1H)-pyridinethiones react with N-acetylchloroacetamide in ethanol in the presence of KOH to give pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-4(3H)-ones.

Functionally-substituted pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidinones hold interest as compounds, which may possess a broad range of biological activity. The known methods for the preparation of such compounds involve the reaction of 3-amino-2-carbamoylthienopyridines with acetonitrile in the presence of HCl in dioxane [1], acylation of 3-amino-2-ethoxycarbonylthienopyridines by acetic anhydride followed by treatment with ammonia [2], reaction of 3-amino-2-carbamoylthienopyridines with acetic anhydride [3-5] or triethyl orthoformate [6], and also acylation of 3-aminothieno-2-pyridinecarboxylic acid with subsequent reaction of the pyridothienooxazinone formed with ammonia [6]. These multistep procedures require vigorous conditions and do not always provide high yields. Furthermore, compounds with fused carbocyclic fragments containing an odd number of carbon atoms cannot be obtained using these methods.

We propose a new convenient method for the regioselective synthesis of functionally-substituted pyrido-[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4(3H)-ones starting from N-acetylchloroacetamide (I) and 3-cyano-2(1H)-pyridinethiones (IIa-IIf), which avoids the indicated drawbacks.

N-Acetylchloroacetamide I may be obtained by the acylation of chloroacetamide by acetic anhydride in the presence of acetyl chloride [7], reaction of chloroacetonitrile with glacial acetic acid [8], reaction of acetamide with chloroacetamide in the presence of HCl [8], and also the reaction of acetamide with chloroacetyl chloride [9].



II, III, IV a $R^1 = CF_3$, $R^2 = H$, $R^3 = Ph$; b $R^1 = R^3 = Ph$, $R^2 = H$; c $R^1 = R^2 = H$, $R^3 = Me$; d $R^1 = R^3 = Me$, $R^2 = H$; e $R^1 = H$, $R^2R^3 = (CH_2)_6$; f $R^1 = H$, $R^2R^3 = (CH_2)_5$

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 0009-3122/97/3306-0732$18.00

TABLE 1. Yields and Indices for III and IV

Compound	Chemical formula	Found, % / Calculated, %			mp, °C	IR spectrum ν, cm^{-1}	^1H NMR spectrum, δ, ppm (J, Hz)	Yield, % (method)
		C	H	N				
IIIa	$C_{17}H_{10}F_3N_3SO$	56,20 56,51	2,64 2,79	11,72 11,63	>280	2840, 1669 (C=O), 1607, 1583, 1555	2,49 (3H, s, CH_3); 7,57 (3H, m, *m*-H_{Ph} and *p*-H_{Ph}); 8,27 (2H, m, *o*-H_{Ph}); 8,38 (1H, s, 8-H)	69 (A), 81 (B)
IIIb	$C_{22}H_{15}N_3SO$	71,34 71,52	4,11 4,09	11,30 11,37	>280	2978, 1632 (C=O), 1588, 1575, 1543, 1522	2,22 (3H, s, CH_3); 7,52 (6H, m, *m*-H_{Ph} and *p*-H_{Ph}); 8,27 (4H, m, *o*-H_{Ph}); 7,98 (1H, s, 8-H)	72 (A), 79 (B)
IIIc	$C_{11}H_9N_3SO$	57,38 57,13	3,91 3,92	18,31 18,17	>280	2834, 1660 (C=O), 1560, 1561, 1506	2,45 (3H, s, 2-CH_3); 2,65 (3H, s, 7-CH_3); 7,49 and 8,42 (2H, AB, J = 7, 8-H and 9-H)	69
IIId	$C_{12}H_{11}N_3SO$	58,71 58,76	4,36 4,52	17,29 17,13	>280	2852, 1666 (C=O), 1603, 1541, 1439	2,47 (3H, s, 2-CH_3); 2,60 (3H, s, 7-CH_3); 2,92 (3H, s, 9-CH_3); 7,22 (1H, s, 8-H)	71
IIIe	$C_{16}H_{17}N_3SO$	64,34 64,19	5,51 5,72	13,95 14,04	>280	2921, 1665 (C=O), 1590, 1550, 1508	1,31 (4H, m, 9-CH_2 and 10-CH_2); 1,72 (4H, m, 8-CH_2 and 11-CH_2); 2,44 (3H, s, CH_3); 2,92 (2H, m, 12-CH_2); 3,06 (4H, m, 7-CH_2); 8,28 (1H, s, 13-H)	57
IIIf	$C_{13}H_{11}N_3SO$	60,92 60,68	4,52 4,31	16,45 16,33	>280	2855, 1668 (C=O), 1593	2,17 (2H, m, 8-CH_2); 2,42 (3H, s, CH_3); 3,06 (4H, m, 7-CH_2 and 9-CH_2); 8,29 (1H, s, 12-H)	63
IVa	$C_{17}H_{12}F_3N_3SO_2$	53,49 53,82	3,20 3,19	11,25 11,08	207...208	2999, 2212 (CN), 1621 (C=O), 1601, 1560, 1536	2,15 (3H, s, CH_3); 4,52 (2H, s, CH_2); 7,57 (3H, m, *m*-H_{Ph} and *p*-H_{Ph}); 8,22 (3H, m, *o*-H_{Ph} and 8-H); 11,20 (1H, s, NH)	94
IVb	$C_{22}H_{17}N_3SO_2$	67,94 68,20	4,55 4,42	10,92 10,85	193...195	3042, 2210 (CN), 1650 (C=O), 1590, 1570	2,19 (3H, s, CH_3); 4,50 (2H, s, CH_2); 7,55 (6H, m, *m*-H_{Ph} and *p*-H_{Ph}); 7,74 (2H, m, *o*-$H_{7\text{-}Ph}$); 7,90 (1H, s, 8-H); 8,20 (2H, m, *o*-$H_{9\text{-}Ph}$); 11,05 (1H, s, NH)	90

We have already reported the use of cascade reactions in the synthesis of pyridothienopyridines, pyridothienopyrimidines, thienopyridines, and thiazolopyridines [10-13]. In the present work, this method is extended to the synthesis of pyridothienopyrimidinones.

3-Cyano-2(1H)-pyridinethiones IIa-IIf react with N-acetylchloroacetamide in ethanol in the presence of KOH to give pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4(3H)-ones (IIIa-IIIf). The mechanism for the formation of III may be seen as a sequence of alkylation steps at the sulfur atom, Thorpe–Ziegler reaction leading to closure of the thiophene ring, and intramolecular condensation of the amino and carbonyl groups to give a pyrimidine ring. Intermediates could be isolated when 4-trifluoromethyl-6-phenylpyridinethione IIa and 4,6-diphenylpyridinethione IIb were used, namely, 2-(N-acetylcarbamoylthio)-3-cyanopyridines (IVa and IVb). 3-Amino-2-(N-acetylcarbamoyl)thieno[2,3-*b*]pyridines (V), which are formed as intermediates during the reaction, could not be isolated, probably due to rapid cyclization leading to the final tricyclic products.

The products were identified by IR and PMR spectroscopy and elemental analysis. The yields and indices of IIIa-IIIf, IVa, and IVb are given in Table 1.

The PMR spectra of IV show signals for the methyl protons of the acetyl fragment at 2.15-2.19 ppm and of the methylene unit at 4.50-4.52 ppm. The methylene unit signals are lacking in tricyclic products III, while the signals for the methyl group are shifted downfield (2.42-2.49 ppm). An exception is found for diphenylpyridine IIIa, whose methyl protons appear at 2.22 ppm.

The IR spectra of monocyclic products IV show cyano group signals at 2210-2212 cm^{-1} and carbonyl group signals at 1620-1650 cm^{-1}. Cyano group signals are lacking in tricyclic products III. The carbonyl fragment signal appears at 1632-1670 cm^{-1} in III.

Thus, we have developed a new, regioselective synthesis for functionally-substituted pyridothieno- 4(3H)-pyrimidinones starting from a functional reagent, namely, N-acetylchloroacetamide, and 3-cyano-2(1H)- pyridinethiones. This method yields previously unavailable compounds containing an odd number of methylene groups in the carbocyclic fragment such as IIIf.

EXPERIMENTAL

The melting points were determined on a Koefler block. The IR spectra were taken on a Specord M80 spectrometer, while the PMR spectra were taken on a Bruker spectrometer at 200 MHz in DMSO-d_6. Elemental analysis for C, H, and N was carried out on a Perkin–Elmer C,H,N-analyzer. The yields and physical indices of III and IV are given in Table 1.

N-Acetylchloroacetamide I was obtained according to Polya and Spotswood [7].

2-(N-Acetylcarbamoylthio)-3-cyanopyridines (IVa and IVb). A sample of 2 mmoles 10% aq. KOH was added to a solution of 2 mmoles pyridinethione IIa or IIb in 20 ml ethanol. The mixture obtained was heated to 50°C and, after 2 min, 2 mmoles N-acetylchloroacetamide I was added. The reaction mixture was maintained at 50°C for 30 min and cooled. The product was precipitated by adding a small amount of water. The product was washed with 60:40 ethanol–water and hexane and dried in the air.

Pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4(3H)-ones (IIIa-IIIf). A. A sample of 2 mmoles 10% aq. KOH was added to a solution of 2 mmoles pyridinethione IIa-IIf in 20 ml ethanol. The mixture was heated to 50°C and, after 2 min, 2 mmoles N-acetylchloroacetamide I was added. The mixture obtained was maintained at 50°C for 30 min and then an additional 2 mmoles 10% aq. KOH was added. The reaction mixture was then heated at reflux for 1.5 h and cooled. A dilute solution of hydrochloric acid was added to bring the reaction mixture to pH 7. The precipitated product was filtered off, washed with ethanol and hexane, and dried in the air.

B. A sample of 1.5 mmoles 2-(N-acetylcarbamoyl)-3-cyanopyridine IVa or IVb was heated in ethanol with 1.5 mmoles 10% aq. KOH at reflux for 1.5 h. The reaction mixture was cooled and dilute hydrochloric acid was added until the mixture was brought to pH 7. The precipitated product was filtered off, washed with ethanol and hexane, and dried in the air.

This work was supported by the Russian Basic Research Fund (Grant No. 96-03-32012a).

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