SYNTHESIS AND REACTIONS OF 2,4-DISUBSTITUTED BENZO[b]FURANO-, BENZO[b]THIENO- AND INDOLO[3,2-d]-1,3-OXAZINIUM SALTS

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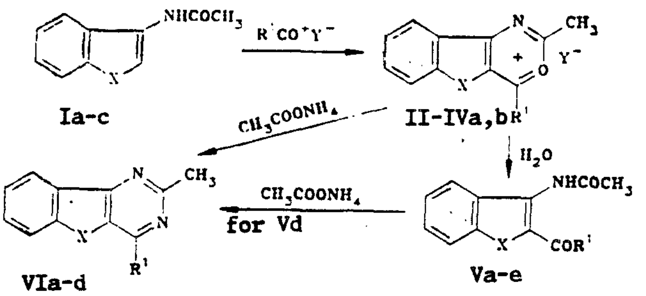
Under acid catalyzed acylation 3-acetamidobenzo[b]furan, -benzo[b]thiophene, and indole undergo heterocyclization to condensed 1,3-oxazinium salts. Treatment of the salts with ammonium acetate in acetic acid gives the corresponding benzo[b]furano- and benzo[b]thieno[3,2-d]pyrimidines and 2-acetyl-3-acetamidoindole gives pyrimido[5,4-d]indole.

The synthesis and reactions of monocyclic 1,3-oxazinium salts is well known [1-3]. Condensed 1,3-oxazinium salts have been little investigated because of the lack of a convenient synthetic method. We have previously shown that o-acetamidobenzophenones and 2-benzoyl-3-acetamidobenzo[b]furans in the presence of acetic anhydride and perchloric acid form the corresponding 1,3-oxazinium salts [4-6]. However, this method is limited by the poor availability of aminohetaryl ketones.

Within the framework of synthesizing condensed 1,3-oxazinium salts we have investigated the acid-catalyzed acylation of acetamido benzo[b]furans, benzo[b]thiophenes, and indoles. Acylation of the amides Ia-c occurs at the free α-position of the heterocycle. Under the reaction conditions the formed 2-acyl-3-acetamido derivatives cyclize to the corresponding 1,3-oxazinium salts II-IV.

The reaction occurs only in the presence of a twofold excess of catalyst ($HClO_4$, $SbCl_5$) since one equivalent of catalyst is bound by the starting I.



a X=O; b X=S; c X=NH

The structures of II-IV are confirmed by their IR spectra, which show absorption for the oxazinium cation bonds at 1640-1610 cm^{-1}.

Under normal conditions the perchlorates IIa-IVa and IVb undergo hydrolysis to the 2-acetyl-3-acetamido Va, c-e, as indicated by the appearance of IR absorption bands for $NHCOCH_3$ (3270, 1630 cm^{-1}) and COR (1670 cm^{-1}). Oxazinium salts containing $SbCl_6^-$ are unstable in air.

Compounds Va-e can be prepared in high yields by hydrolysis of salts IIa, b-IVa, b using aqueous alcohol.

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TABLE 1. Physical Data for II-VI

Compound	Empirical formula	R¹	X	Y	mp, °C*	Yield, %
IIa	$C_{12}H_{10}ClNO_6$	CH_3	O	ClO_4^-	140	57
IIb	$C_{17}H_{12}Cl_6NO_2Sb$	C_6H_5	O	$SbCl_6^-$	200	77
IIIa	$C_{12}H_{10}ClNO_5S$	CH_3	S	ClO_4^-	120	79
IIIb	$C_{12}H_{10}Cl_6NOSSb$	CH_3	S	$SbCl_6^-$	145	88
IVa	$C_{12}H_{14}ClN_2O_5$	CH_3	NH	ClO_4^-	135	37
IVb	$C_{13}H_{13}ClN_2O_5$	C_2H_5	NH	ClO_4^-	130	38
Va	$C_{12}H_{11}NO_3$	CH_3	O		138 ... 139	78
Vb	$C_{17}H_{13}NO_3$	C_6H_5	O		145	90
Vc	$C_{12}H_{11}NO_2S$	CH_3	S		155 ... 156	81
Vd	$C_{12}H_{12}N_2O_2$	CH_3	NH		231	75
Ve	$C_{13}H_{14}N_2O_2$	C_2H_5	NH		188	78
VIa	$C_{12}H_{10}N_2O$	CH_3	O		90 ... 91	88
VIb	$C_{17}H_{12}N_2O$	C_6H_5	O		132 ... 133	90
VIc	$C_{12}H_{10}N_2S$	CH_3	S		110 ... 111	84
VId	$C_{12}H_{11}N_3$	CH_3	NH		202 ... 203	74

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*IIa-IVa were crystallized from a mixture of acetic anhydride–ether (2:1); IIb, IIIb from acetic anhydride; Va-e, VIa-c from aqueous alcohol.

TABLE 2. PMR Spectra of II-VI

Compound	δ, ppm*
IIa	2,77 (3H, s, 4-CH_3); 2,87 (3H, s, 2-CH_3); 7,66 ... 8,00 (4H, m, H_{arom})
IIb	2,85 (3H, s, 2-CH_3); 7,8 ... 8,4 (9H, m, H_{arom})
IIIa, b	2,77 (3H, s, 4-CH_3); 2,87 (3H, s, 2-CH_3); 7,50 ... 7,95 (4H, m, H_{arom})
IVa	2,83 (6H, s, 2 and 4-CH_3); 7,46 ... 7,90 (4H, m, H_{arom})
IVb	1,73 (3H, t, 4-β-CH_3); 2,83 (3H, s, 2-CH_3); 3,16 (2H, q., 4-α-CH_2); 7,40 ... 8,00 (4H, m, H_{arom})
Vc	2,20 (3H, s, 2-$COCH_3$); 2,50 (3H, s, 3-$NHCOCH_3$); 7,43 ... 8,00 (4H, m, H_{arom})
VIa	2,43 (3H, s, 4-CH_3); 2,67 (3H, s, 2-CH_3); 7,07 ... 6,70 (4H, m, H_{arom})
VIb	2,67 (3H, s, 2-CH_3); 7,10 ... 7,80 (8H, m, H_{arom})
VIc	2,60 (3H, s, 4-CH_3); 2,73 (3H, s, 2-CH_3); 7,50 ... 8,00 (4H, m, H_{arom})
VId	2,66 (3H, s, 4-CH_3); 2,71 (3H, s, 2-CH_3); 7,20 ... 8,16 (4H, m, H_{arom})

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*For IIa, b-IVa, b the solvent was CF_3COOH; for Vc, VIa-d, CD_3CN.

Oxazinium salts IIa, b, IIIa were converted to the corresponding hetaryl[3,2-d]pyrimidines VIa-c by refluxing with excess ammonium acetate in glacial acetic acid.

Under these conditions the indolo[3,2-d]oxazinium salts IVa, b give oily products, which probably is due to the formation of an anhydro base (subsequently polymerizing). 2,4-Dimethylpyrimido[5,4-b]indole (VId) was obtained from 2-acetyl-3-acetamidoindole Vd.

Additional evidence for the structure of the 2,4-dimethylbenzo[b]thieno[3,2-d]pyrimidine VIc comes from its reductive desulfurization by Raney nickel to the known 2,6-dimethyl-4-phenylpyrimidine [7].

EXPERIMENTAL

The IR spectra were recorded in Vaseline oil on a UR-20 instrument and PMR spectra on a Tesla BS-467 (60 MHz) using TMS internal standard.

Physical parameters for II-VI are given in Tables 1 and 2. Elemental analytical data for II-VI agreed with that calculated.

Perchlorates IIa-IVa, IVb. HCl_4 (70%, 2 ml) was added to a solution of the amide Ia-c (0.01 mole) in acetic anhydride (15 ml) and dry ether (5 ml) (for IVa at 0°C a mixture of 2 ml of 70% $HClO_4$ and 4 ml of acetic anhydride was used and for IVb, propionic anhydride). The mixture was kept at 45°C for 1 h (15 min at 20°C for IVa, b), filtered, washed with a mixture of acetic anhydride–ether (1:1), and then ether and dried in vacuo.

Hexachloroantimonates IIb, IIIb. The acid chloride (0.02 mole) was added to a solution of amide Ia, b (0.01 mole) in dry CCl_4 (20 ml) and $SbCl_5$ (0.02 mole) was added with cooling and stirring. The precipitate was filtered after 15 min, washed with CCl_4. and then ether.

2-Benzoyl(acetyl)-3-acetamido Benzo[b]furan, Benzo[b]thiophene, and Indole (Va-e). The corresponding oxazinium salt (1 g) was dissolved in alcohol (10 ml), refluxed for 5 min, filtered, diluted with water (10 ml), cooled, and the precipitate filtered off.

Benzo[b]furano- and Benzo[b]thieno[3,2-d]pyrimidines (VIa-c). A mixture of the corresponding oxazinium salt (0.01 mole), ammonium acetate (10 g), and acetic acid (80 ml) was refluxed for 3 h and 50 ml acetic acid removed in vacuo. The residue was cooled, poured into water (100 ml), and neutralized with aqueous ammonia. The precipitated crystals were filtered off.

2,4-Dimethylpyrimido[5,4-b]indole (VId) was obtained similarly from 2-acetyl-3-acetamidoindole Vd.

Reductive Desulfurization of 2,4-Dimethylbenzo[b]thieno[3,2-d]pyrimidine. A mixture of VIc (1.07 g, 5 mmoles) and Raney nickel (10 g) in methanol (50 ml) was refluxed with stirring for 10 h, cooled, the nickel filtered off, and methanol distilled off. The residue was distilled in vacuo to give 48% of product with bp 100°C (1 mm Hg). The literature [7] gives bp 112°C (2 mm Hg).

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