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ELECTROPHILIC SUBSTITUTION IN BENZO[B]THIENO[2,3-C]PYRIDINE. ACYLATION

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A study has been made of the acetylation and benzoylation of substituted benzo[b]thieno[2,3-c]pyridines. It has been shown that acetylation proceeds exclusively at position 8, whereas benzoylation leads to a mixture of products of substitution at positions 6 and 8. The molecules in question have been calculated in the PPP and MNDO approximations.

We recently reported on features of nitration in a series of benzo[b]thieno[2,3-c]pyridines. It was shown that, in contrast to the nitration of β-carbolines, where two isomeric mononitro compounds are formed at positions 6 and 8, the nitration of benzo[b]thieno[2,3-c]pyridines that are not substituted in the benzene ring proceeds exclusively at position 6, regardless of the reaction conditions (nitric acid concentration and temperature).

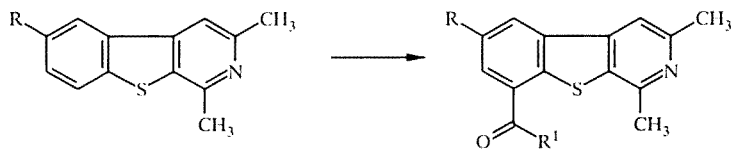
Continuing our study of electrophilic substitution in benzo[b]thieno[2,3-c]pyridines, we carried out the acylation (acetylation and benzoylation) of a number of these pyridines. The reaction was performed by heating a mixture of the corresponding pyridine base (or its hydrochloride) with a twofold excess of $AlCl_3$ and an acylating agent at 100-110°C. The isomers were separated and purified by column chromatography on Al_2O_3 or silica gel (Table 1), and were identified on the basis of their PMR spectra (Table 2).

We found that acylation of 1,3-dimethylbenzo[b]thieno[2,3-c]pyridine Ia by acetyl chloride leads exclusively to the formation of the 8-acetyl derivative IIa with a yield of 68%. A similar picture is observed for 1-ethyl-3-methyl-benzo[b]thieno[2,3-c]pyridine Ib.

Ia, b IIa, b

Ia, IIa) R = CH_3; IIb), IIb) R = C_2H_5

Acylation of 1,3,6-trimethyl- (Ic) and 1,3-dimethyl-6-chloro- (Id) benzo[b]thieno[2,3-c]pyridines also leads to their 8-acetyl or 8-benzoyl derivatives.



Ic, d IIc, IIIc, IId

Ic, IIc) R = R^1 = CH_3; IIIc) R = CH_3, R^1 = Ph; Id, IId) R = Cl, R^1 = CH_3

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TABLE 1. Characteristics of Compounds II-VI

Compound	Empirical formula	mp. °C	R_f	Eluent for Chromatography	Yield, %
IIa	$C_{15}H_{13}NOS$	221...222	0,71	Benzene- acetonitrile, 5 : 1	68,5
IIIa	$C_{20}H_{15}NOS$	127,5...128,5	0,32	Benzene- ethyl acetate, 5 : 1*	81**
IVa	$C_{20}H_{14}ClNOS$	193...195	0,38	Benzene- ethyl acetate, 5 : 1*	63**
Va	$C_{20}H_{15}NOS$	201...203	0,18	Benzene- ethyl acetate, 5 : 1*	19**
VIa	$C_{20}H_{14}ClNOS$	203,5...205,5	0,19	Benzene- ethyl acetate, 5 : 1*	37**
IIb	$C_{16}H_{15}NOS$	236...237	0,67	Benzene- acetonitrile, 5 : 1	70
IIc	$C_{16}H_{15}NOS$	265...267	0,39	Benzene- chloroform, 6 : 1	74
IIIc	$C_{21}H_{17}NOS$	170...172	0,61	Benzene- chloroform, 6 : 1	76
IId	$C_{15}H_{12}ClNOS$	252...254	0,63	Benzene- chloroform, 6 : 1	33
IIe	$C_{21}H_{17}NOS$	179...181	0,52	Benzene- chloroform, 15 : 1	52
IIf	$C_{17}H_{17}NOS$	146...146,5	0,64	Benzene- chloroform, 15 : 1	81

*Silufol UV-254.

**Content of isomer (%) in mixture.

TABLE 2. Spectral Characteristics of Compounds II-VI

Compound	PMR spectrum, δ, ppm (and SSCC, J, Hz)
Ia	7.55 (4-H), 8.02 (5-H), 7.40 (6-H, 7-H), 7.80 (8-H)
Ia*	7.63 (4-H), 7.92 (5-H), 7.18 (6-H), 7.21 (7-H), 7.50 (8-H)
IIa	2.77 (6H, s, 1,3-$(CH_3)_2$), 2.88 (3H, s, 8-CH_3(CO)), 7.65 (1H, t, 6-H), 7.88 (1H, s, 4-H), 8,23 (1H, t, J = 8,7, 5-H), 8,53 (1H, t, J = 8,7, 7-H)
IIb	1.64 (3H, t, CH_2CH_3), 2.99 (3H, s, 3-CH_3), 3.18 (3H, s, 8-CH_3(CO)), 3.32 (2H, d, CH_2CH_3), 7.67 (1H, t, 6-H), 7.85 (1H, s, 4-H), 8.25 (1H, d, J = 8.5, 5-H), 8.56 (1H, d, J = 8.5, 7-H)
IIc	2.75 (3H, s, 6-CH_3), 2,76 (6H, s, 1,3-$(CH_3)_2$), 2,80 (3H, s, 8-CH_3(CO)), 7,86 (1H, s, 4-H), 8.35 (1H, s, 5-H), 8,63 (1H, s, 7-H)
IId	2.76 (3H, s, 3-CH_3), 2,77 (3H, s, 1-CH_3), 2,81 (3H, s, 8-CH_3(CO)), 7,87 (1H, s, 4-H), 8.35 (1H, s, 5-H), 8.63 (1H, s, 7-H)
IIe	2.58 (3H, s, 8-CH_3), 2.75 (3H, s, 3-CH_3), 2.84 (3H, s, 1-CH_3), 7.51...7.66 (3H, m, Ph(CO)), 7.78 (1H, s, 5-H), 7.94 (1H, s, 4-H), 8.06...8,14 (2H, m, Ph(CO)), 8.68 (1H, s, 7-H)
IIf	2.46 (3H, s, 8-CH_3), 2.69 (3H, s, 5-CH_3), 2.72 (3H, s, 3-CH_3), 2.78 (3H, s, 1-CH_3), 2.91 (3H, s, 6-CH_3(CO)), 7.56 (1H, s, 7-H), 7,86 (1H, s, 4-H)
IIIa	2.71 (3H, s, 3-CH_3), 2,76 (3H, s, 1-CH_3), 7.48...7.66 (3H, m, Ph(CO)), 7.80 (1H, s, 4-H), 8,00...8.07 (2H, m, Ph(CO)), 8.10 (2H, s, 7.8-H), 8,83 (1H, s, 5-H)
IIIc	2.45 (3H, s, 6-CH_3), 2.75 (3H, s, 3-CH_3), 2.81 (3H, s, 1-CH_3), 7,48...7.63 (3H, m, Ph(CO)), 7.81 (1H, s, 5-H), 7,87 (1H, s, 4-H), 7,93...8,00 (2H, m, Ph(CO)), 8.26 (1H, s, 7-H)
IVa	2,73 (3H, s, 3-CH_3), 2.79 (3H, s, 1-CH_3), 7,58 (2H, d, J = 10, 4-ClC_6H_4(CO)), 7,97 (1H, s, 4-H), 7.99 (2H, d, J = 10, 4-ClC_6H_4(CO)), 8.11 (1H, d, J = 8, 8-H), 8.19 (1H, d, J = 8, 7-H), 8.87 (1H, s, 5-H)
Va	2,78 (3H, s, 3-H_3), 2,85 (3H, s, 1-CH_3), 7,48...7,68 (5H, m, 4-H, 6-H, Ph(CO)), 7,87...7.95 (2H, m, Ph(CO)), 8,04 (1H, d, J = 7.6, 5-H), 8,54 (1H, d, J = 7.6, 7-H)
VIa	2,77 (3H, s, 3-CH_3), 2,85 (3H, s, 1-CH_3), 7,58 (2H, d, J = 7,3, 4-ClC_6H_4(CO)), 7.68 (1H, t, 6-H), 7.84 (1H, s, 4-H), 7.91 (2H, d, J = 7,3, 4-ClC_6H_4(CO)), 8.04 (1H, d, J = 7.3, 5-H), 8,62 (1H, d, J = 7,3, 7-H)

*Calculated data.

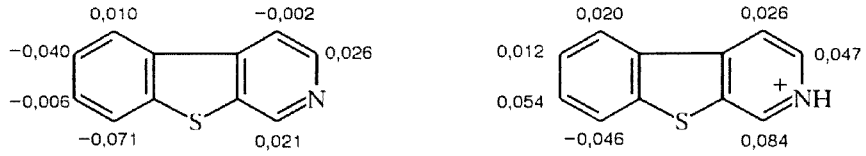
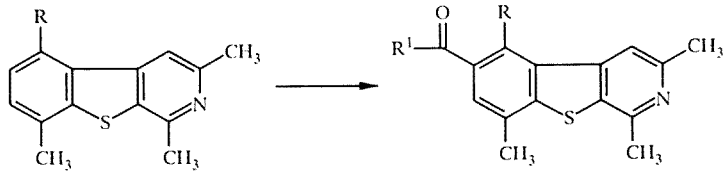


Fig. 1. Distribution of residual charges in molecule of benzo[b]thieno[2,3-c]pyridine.

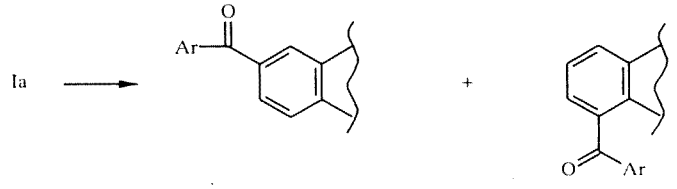
If position 8 is blocked by a methyl group, as in 1,3,8-trimethylbenzo[b]thieno[2,3-c]pyridine (If), products of acylation at position 6 are formed.



Ie, f IIe, f

Ie, IIe) R = H, R^1 = Ph; If, IIf) R = R^1 = CH_3

A different distribution of isomers is observed in the benzoylation of Ia by benzoyl chloride and 4-chlorobenzoyl chloride. In this case we isolated two products of substitution at positions 6 and 8, with preferential formation of the 6-derivative (Table 1).



IIIa, IVa Va, VIa

IIIa,Va) Ar = Ph; IVa,VIa) Ar = 4-ClC_6H_4

For identification of the acylation products, it is convenient to use PMR spectrometric data (Table 2). The most informative signal is that of the proton in position 5. This signal is a singlet with substitution in position 6, and a doublet with substitution in position 8.

In the IR spectra of the acyl derivatives of benzo[b]thieno[2,3-c]pyridines, we observe absorption bands characteristics for the acyl groups – 1690 cm^{-1} for acetyl, 1670 cm^{-1} for aroyl.

Attention is directed to the substantial difference between the directions of substitution in nitration and acylation of benzo[b]thieno[2,3-c]pyridines (Table 3). With the aim of determining the reasons for such differences, we carried out a calculation of the molecules in question, in the π-electron approximation (PPP version), since positional reactivity in heterocyclic compounds is usually related to the distribution of residual charges; and, where this concept is valid, it is the most convenient. As characteristics of the sulfur and nitrogen atoms we used parameters that had been used within this scheme in application to complex dye molecules [2], when for simplicity the S: parameters do not differ from the C: parameters. The initial geometry was based on equilateral hexagons and an equal-angle pentagon (see Fig. 1). In order to judge whether this approximation is realistic, we used the same calculation scheme [3] to calculate chemical shifts of the protons of the benzene fragment for the original molecule of benzo[b]thieno[2,3-c]pyridine (Table 2). An evaluation of the positional reactivity in the PPP approximation shows that, for both the protonated and nonprotonated forms of these molecules, attack by the electrophile

TABLE 3. Comparison of Nitration and Acylation of Various Benzo[b]thieno[2,3-c]pyridines

Compound	Distribution of isomers (%)*	
	nitration [1]	acylation
Ia	6-NO_2 (55), 6,8-NO_2 (45)	8-CH_3CO (68,5), 6-PhCO (81), 8-PhCO (19), 6-(4-ClC_6H_4CO) (63), 8-(4-ClC_6H_4CO) (37)
Ic	5-NO_2 (88), 8-NO_2 (8), 5,7-$(NO_2)_2$ (4)	8-CH_3CO (74,3), 8-PhCO (76,5)
Ie	6-NO_2 (71)	6-PhCO (52,5)
Id	5-NO_2 (20), 7-NO_2 (32), 8-NO_2 (48)	8-CH_3CO (33)

*In the case of a single isomer, the number shown in parentheses denotes the percentage yield.

TABLE 4. Results from Quantum-Chemical Calculations of Benzo[b]thieno[2,3-c]pyridines in MNDO Approximation

Compound	Effective charges on atoms (au) and square of LCAO coefficients for HOMO (in parentheses)			
	$C_{(5)}$	$C_{(6)}$	$C_{(7)}$	$C_{(8)}$
Benzo[b]thieno[2,3-c]pyridine	-0,012 (0,068)	-0,066 (0,104)	-0,040 (0,000)	-0,035 (0,105)
Ia	-0,012 (0,045)	-0,066 (0,089)	-0,040 (0,001)	-0,035 (0,079)
6-Chlorobenzo[b]thieno[2,3-c]-pyridine	0,004 (0,046)	-0,011 (0,108)	-0,024 (0,004)	-0,032 (0,076)
Id	0,003 (0,035)	-0,010 (0,086)	-0,025 (0,003)	-0,032 (0,063)
6-Methylbenzo[b]thieno[2,3-c]-pyridine	0,006 (0,059)	-0,107 (0,127)	-0,023 (0,005)	-0,038 (0,088)
8-Methylbenzo[b]thieno[2,3-c]-pyridine	-0,008 (0,075)	-0,069 (0,104)	-0,022 (0,000)	-0,075 (0,118)
Benzo[b]thieno[2,3-c]-pyridinium cation	0,037 (0,200)	-0,062 (0,153)	0,027 (0,004)	-0,034 (0,221)
6-Chlorobenzo[b]thieno[2,3-c]-pyridinium cation	0,049 (0,158)	-0,016 (0,205)	0,038 (0,010)	-0,029 (0,124)
6-Methylbenzo[b]thieno[2,3-c]-pyridinium cation	0,049 (0,179)	-0,095 (0,211)	0,037 (0,005)	-0,036 (0,147)
8-Methylbenzo[b]thieno[2,3-c]-pyridinium cation	0,038 (0,212)	-0,065 (0,104)	0,039 (0,024)	-0,067 (0,252)

should take place at position 8, which is actually observed only for acylation. With the aim of obtaining additional information, we carried out a calculation of these compounds in the semiempirical MNDO approximation [4].

Because of the difficulties that exist in establishing a scale of reactivity indexes for heterocyclic compounds in various processes, in particular electrophilic substitution, we have used an isolated-molecule approximation [5] to analyze the influence of the effective charge of the atoms and also the magnitude of the LCAO coefficients on the direction of electrophiles of the NO_2^+ type add at position 6: In this case, the direction of electrophilic substitution is determined by the magnitude of the effective negative charge on the atoms of the benzene ring, which is the greatest on the $C_{(6)}$ atom. For "soft" electrophiles such as CH_3CO^+, the decisive factor in determining the orientation is apparently the electron density of the HOMO on the atoms, which is proportional to the squares of the LCAO coefficients. In this case, substitution at $C_{(8)}$ has the advantage. As shown above, a similar picture is observed when using the PPP approximation. For electrophiles that are "intermediate" in hardness, such as $ArCO^+$, the two positions – $C_{(6)}$ and $C_{(8)}$ – are approximately equivalent in terms of susceptibility to electrophilic attack. If a reaction position in a benzo[b]thienol[2,3-c]pyridine is occupied by a substituent, alternative variants of electrophilic substitution are realized.

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EXPERIMENTAL

The PMR spectra were taken in a Gemini-200 instrument (200 MHz), solvent pyridine-d_5, internal standard TMS. The characteristics of compounds II-VI and the corresponding PMR spectra are presented in Tables 1 and 2. The purity and isomer contents of these compounds were monitored by means of TLC on Alufol and Silufol UV-254 plates. The isomers were separated by column chromatography on Al_2O_3 (neutral) or silica gel (Table 1), followed by recrystallization from acetonitrile.

Elemental analyses of compounds II-VI for C, N, H, S, and Cl matched the calculated values.

General Method for Acylation of Compounds Ia-f. A 2.6-mmole quantity of compound Ia-f is mixed with 5.2 mmoles of the acylating agent and 5.2 mmoles of $AlCl_3$. The mixture is heated at 100-110°C for 3 h. The procedures used for recovery and isolation of the compounds depend on which acylating agent is used. With acetyl chloride, the reaction mixture is transferred to acidified ice water and then filtered; the residue is washed with water on the filter and then air-dried. In the case of an aroyl chloride, the reaction mixture is transferred to strongly alkaline ice water and filtered; the residue is washed on the filter with water and then air-dried.

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