Synthesis of 2-(*N*′-arylthioureido)styrenes as suitable intermediates for preparation of heterocyclic compounds

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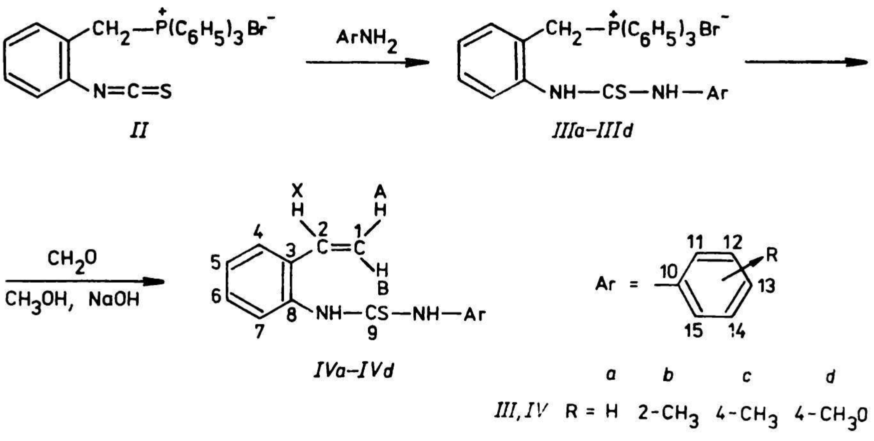
Dedicated to Professor P. Kristian, DrSc., in honour of his 60th birthday

By the reaction of 2-isothiocyanatobenzyltriphenylphosphonium bromide with aromatic amines, 2-(*N*′-arylthioureido)benzyltriphenylphosphonium bromides were prepared. These compounds undergo Wittig's reaction with formaldehyde in the presence of sodium hydroxide affording 2-(*N*′-arylthioureido)styrenes as final products. 2-[*N*′-(4-Tolyl)thioureido]styrene cyclizes by the action of bromine to 2-(4-tolylamino)-4-bromomethyl-4*H*-3,1-benzothiazinium bromide in 87 % yield. The structure of compounds was proved by spectral methods.

Путем реакции бромида 2-изотиоцианатобензилтрифенилфосфония с ароматическими аминами были получены бромиды 2-(*N*′-арилтиоуреидо)бензилтрифенилфосфония. Эти соединения вступают в реакцию Виттига с формальдегидом в присутствии гидроокиси натрия, ведущей к образованию 2-(*N*′-арилтиоуреидо)стиролов в качестве конечных продуктов. 2-[*N*′-(4-Толил)тиоуреидо]стирол циклизируется под действием брома в 2-(4-толиламино)-4-бромметил-4*H*-3,1-бензотиазиний бромид с 87 % выходом. Строение полученных соединений было доказано с помощью спектральных методов.

In the previous communication we have described synthesis of substituted 2-bromomethylphenyl isothiocyanates [1, 2]. We have found that reaction of the mentioned isothiocyanates with amines and phenols affords 4*H*-3,1-benzothiazines, *i.e.* addition to NCS group starts the reaction. Nucleophiles which are not able to give stable addition products with NCS group, as for example triphenylphosphine or pyridine, react with 2-bromomethylphenyl isothiocyanate (*I*) under formation of corresponding onium salts, as *e.g.* 2-isothiocyanatobenzyltriphenylphosphonium bromide (*II*) [3, 4] (Scheme 1). This isothiocyanate includes two electrophilic centres showing different reactivity. The carbon atom of N=C=S group is a typical centre of the attack of protic nucleophiles. The second reaction centre is CH_2 group which behaves itself as a C-acid owing to the electron-withdrawing effect of triphenylphosphonium group and by the reaction with bases is able to afford corresponding carbanion.



Scheme 1

In the preceeding works we have found that reaction of these compounds with strong bases, as *e.g.* aliphatic amines, sodium hydride in dimethyl sulfoxide, *etc.*, makes for 2,3-substituted indoles [4, 5].

In this paper we have studied some reactions of *II* with nitrogen nucleophiles having less basic character, as *e.g.* aromatic amines.

We have found that reactions of *II* proceed exclusively on the NCS group under formation of 2-(*N'*-arylthioureido)benzyltriphenylphosphonium bromides *IIIa*—*IIId* (Scheme 1, Table 1). The reaction can be realized by simple mixing of reaction components in methanol, ethanol or chloroform. Thioureas

Table 1

Characteristics of 2-(*N'*-arylthioureido)benzyltriphenylphosphonium bromides *IIIa*—*IIId*

Compound	Formula M_r	w_i(calc.)/% w_i(found)/%			Yield/% M.p./°C	IR, $\tilde{\nu}$/cm^{-1}
		C	H	N		ν(NH) ν(NHCS)
IIIa	$C_{32}H_{28}BrN_2PS$	65.86	4.83	4.80	86	3384
	538.53	65.79	4.81	4.85	212—214	1494
IIIb	$C_{33}H_{30}BrN_2PS$	66.32	5.06	4.68	91	3379
	579.56	66.35	5.11	4.71	172—173	1498
IIIc	$C_{33}H_{30}BrN_2PS$	66.32	5.06	4.68	96	3376
	579.56	66.31	5.11	4.70	221—222	1492
IIId	$C_{33}H_{30}BrON_2PS$	64.60	4.92	4.56	83	3380
	613.56	64.55	4.98	4.49	243—244	1498

IR spectra measured in KBr discs.

IIIa—*IIId* are crystalline compounds very little soluble in nonpolar organic solvents. They are sensitive to the effect of bases.

Reaction of *IIIa*—*IIId* with formaldehyde in the presence of sodium hydroxide in methanol affords 2-(N'-arylthioureido)styrenes *IVa*—*IVd* (Scheme 1, Table 2) in good yields. Their structure was proved by spectral methods. In the ^{1}H NMR spectra, there is characteristic presence of ABX spin system of alkene

Table 2

Characteristics of 2-(N'-arylthioureido)styrenes *IVa*—*IVd*

Compound	Formula M_r	w_i(calc.)/% w_i(found)/% C	 H	 N	Yield/%	M.p./°C
IVa	$C_{15}H_{14}N_2S$ 254.35	70.83 70.74	5.54 5.48	11.01 11.12	63	163—164
IVb	$C_{16}H_{16}N_2S$ 268.38	71.55 71.60	6.09 6.01	10.43 10.37	68	141—143
IVc	$C_{16}H_{16}N_2S$ 268.38	71.55 71.64	6.09 6.06	10.43 10.37	76	190—191
IVd	$C_{16}H_{16}ON_2S$ 284.38	67.57 67.51	5.67 5.63	9.85 9.83	58	198—199

Table 3

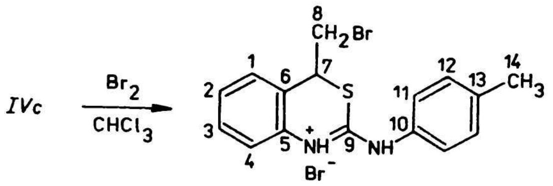
Spectral data for 2-(N'-arylthioureido)styrenes *IVa*—*IVd*

Compound	IR, $\tilde{\nu}$/cm^{-1} [a] ν(NH)	 ν(NHCS)	^{1}H NMR, δ/ppm [b] H(A)	 H(B)	 H(X)	 H_{arom}	Other protons
IVa [c]	3400	1503	5.51	7.22	8.08	6.86—7.30	
IVb [c,d]	3398	1500	5.62	7.24	8.11	6.83—7.21	2.2 (s, CH_3)
IVc [c,e,g]	3405	1498	5.60	7.21	8.12	7.00—7.50	2.28 (s, CH_3)
IVd [c,f]	3400	1496	5.73	7.31	8.23	6.75—7.57	3.78 (s, CH_3)

a) IR spectra measured in $CHCl_3$. *b*) ^{1}H NMR spectra measured in $CDCl_3$—$(CD_3)_2SO$ ($\varphi_r = 1:1$). *c*) $J_{AB} = 1.2$ Hz, $J_{AX} = 11$ Hz, $J_{BX} = 17.7$ Hz. *d*) ^{13}C NMR spectrum ($(CD_3)_2SO$), δ/ppm: 115.4 (C(1)), 132.3 (C(2)), 134.7 (C(3)), 125.3, 125.3, 125.9, 126.3, 126.6, 127.9, 128.0, 130.0 (C(4)—C(7), C(11)—C(14)), 137.6 (C(8)), 181.5 (C(9)), 136.4 (C(10)), 134.1 (C(15)), 17.6 (CH_3). *e*) ^{13}C NMR spectrum ($(CD_3)_2SO$), δ/ppm: 115.3 (C(1)), 132.3 (C(2)), 133.8 (C(3)), 125.1, 127.4, 127.7, 128.6 (C(4)—C(7)), 136.6, 136.4 (C(8), C(10)), 180.6 (C(9)), 123.7 (2 × C(11)), 128.6 (2 × C(12)), 133.5 (C(13)), 20.8 (CH_3). *f*) ^{13}C NMR spectrum ($(CD_3)_2SO$), δ/ppm: 115.1 (C(1)), 132.5 (C(2)), 132.3 (C(3)), 125.1, 126.1, 127.7, 128.5 (C(4)—C(7)), 133.7 (C(8)), 180 (C(9)), 137.2 (C(10)), 125.6 (2 × C(11)), 113.5 (2 × C(12)), 156.2 (C(13)), 55.1 (CH_3O). *g*) Mass spectrum, m/z (I_r/%): 268 ($M^{+\bullet}$, 31), 235 (44), 222 (27), 163 (81), 147 (29), 128 (51), 119 (51), 117 (43), 107 (95), 106 (100), 91 (49).

hydrogen atoms in styrene, where chemical shifts are little influenced by the thiourea residue ($\delta_{H(A)} = 5.6$ ppm, $\delta_{H(B)} = 7.2$ ppm, $\delta_{H(AX)} = 8.1$ ppm, $J_{AB} = 1.2$ Hz, $J_{AX} = 11$ Hz, $J_{BX} = 17.7$ Hz). In the ^{13}C NMR spectra, signals of carbon atoms of —CH═CH$_2$ bond occur in the region of $\delta_{CH} = 132.26$—132.49 ppm, $\delta_{CH_2} = 115$ ppm and signal of carbon atom in CS group at $\delta = 181$ ppm. The fragment ions observed in the mass spectrum of derivative *IVc* are also in accordance with the supposed structure (Table 3).

Mutually advantageous position of double bond and thiourea's arrangement of compounds *IV* can be utilized for synthesis of heterocyclic compounds. Thus, we have found that by the action of bromine, intramolecular cyclization of 2-[*N'*-(4-tolyl)thioureido]styrene (*IVc*) occurs under formation of 2-(4-tolylamino)-4-bromomethyl-4*H*-3,1-benzothiazinium bromide (*V*) (Scheme 2). Its structure was proved by the help of spectral method.



V

Scheme 2

Experimental

IR spectra of the prepared compounds were measured on an IR-75 (Zeiss, Jena) spectrophotometer in chloroform or KBr discs in the region of 800—4000 cm^{-1}. ^{1}H NMR spectra were obtained using Tesla BS 479 (80 MHz) and Tesla BS 567 (100 MHz) instruments and ^{13}C NMR spectra were taken on a Tesla BS 567 (25.12 MHz) instrument. Mass spectra ($U = 80$ eV) were recorded on a MAT 111 Varian spectrometer.

2-Isothiocyanatobenzyltriphenylphosphonium bromide (*II*) was prepared by the reaction of 2-bromomethylphenyl isothiocyanate with triphenylphosphine [4].

2-(N'-Arylthioureido)benzyltriphenylphosphonium bromides IIIa—IIId

Corresponding aromatic amine (0.01 mol) in ethanol (30 cm^3) was added to the solution of 2-isothiocyanatobenzyltriphenylphosphonium bromide (*II*) (0.01 mol) in ethanol (40 cm^3). Reaction mixture was left to stand overnight at room temperature. Separated crystals were sucked off, washed with ethanol (20 cm^3) and dried on air.

2-(N'-Arylthioureido)styrenes IVa—IVd

Formaldehyde (28 %, 30 cm^3) and sodium hydroxide (0.02 mol) in water (25 cm^3) were added to corresponding *IIIa—IIId* (0.01 mol) in ethanol (300 cm^3). Reaction mixture was stirred for 3 h at 30 °C. Then, additional portion of formaldehyde (28 %, 10 cm^3) was added and the mixture was left to stand overnight. Solvent was evaporated to 1/3 of initial volume. On standing, crystalline compounds *IVa—IVd* separated. Crystallization from ethanol was used for purification.

2-(4-Tolylamino)-4-bromomethyl-4H-3,1-benzothiazinium bromide (V)

To the suspension of *IVc* (2.68 g; 0.01 mol) in dry chloroform (20 cm^3), bromine (0.16 g; 0.01 mol) in chloroform (20 cm^3) was added under stirring at 10 °C. Reaction mixture was then stirred and heated under reflux for 1 h. After evaporation of chloroform *in vacuo*, the residue was recrystallized from a small amount of methanol yielding 87 % of product with m.p. = 141—142 °C. For $C_{16}H_{16}N_2SBr$ ($M_r = 428.3$) w_i(calc.): 44.82 % C, 3.73 % H, 6.53 % N; w_i(found): 44.80 % C, 3.76 % H, 6.51 % N. IR spectrum ($CHCl_3$), $\tilde{\nu}/cm^{-1}$: 3430 ν(NH). ^1H NMR spectrum ($CDCl_3$), δ/ppm: 2.47 (s, 3H, CH_3), 3.52 (d, 2H, CH_2), 4.51 (t, 1H, CH), 7.18—7.51 (m, 8H, H_{arom}), 11.81 (s, 1H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ/ppm: 126.8, 128.6, 130.5, 119.6 (C(1), C(2), C(3), C(4)), 139.8 (C(5)), 119.2 (C(6)), 34.0 (C(7)), 45.1 (C(8)), 165.7 (C(9)), 133.0, 131.5 (C(10), C(13)), 125.6, 130.5 (C(11), C(12)), 21.3 (C(14)). Mass spectrum, m/z (I_r/%): 348 ($M^{+\bullet}$ – HBr, 52), 266 (23), 253 (100), 233 (46), 136 (41), 118 (36), 106 (22).

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