AMINOMETHYLATION OF DERIVATIVES OF 2-AMINO-3-ETHOXYCARBONYL-4-ARYLTHIOPHENE

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2-Amino-3-ethoxycarbonyl-4-arylthiophene derivatives are aminomethylated with bisdimethylaminomethane and bisdiethylaminomethane to give a number of Mannich bases.

Aminomethylation of thiophene usually involves the α hydrogen atom, and gives a mixture of primary, secondary, and tertiary amines [1, 2].

We have [3] offered a method of preparing dialkylaminomethyl derivatives of 2-amino-3-ethoxycarbonyl-4-arylthiophene. Reaction is effected by heating, in solvents inert to bisdialkylaminomethanes, aminothiophenes and bisdimethylaminomethane (I) or bisdiethylaminomethane (II). The resultant Mannich bases are isolated, in the usual way, as hydrochlorides (table).

The dialkylaminomethyl group enters the thiophene ring at the 5 position free from a substituent. There is no substitution of the hydrogen of the amino group of the 2-aminothiophene derivatives. This is confirmed by the IR spectra of the products exhibiting an intense absorption band at 3400–3300 cm^{-1}, characteristic of the free NH_2 group. Furthermore our observation that 2-amino-3-ethoxycarbonylthiophene derivatives substituted at positions 4 and 5 do not undergo the reaction is indirect proof that aminomethylation takes place at a substituent-free α position in aminothiophenes.

EXPERIMENTAL

Aminomethylation of 2-amino-3-ethoxycarbonylthiophene derivatives. A mixture of 0.01 mole 2-amino-3-ethoxycarbonylthiophene, 0.0175 mole bisdialkylaminomethane, and 5 ml dioxane (as solvent) was refluxed for 2 hr 30 min. Then excess bisdialkylaminomethane and solvent were vacuum-distilled off. The residue was dissolved in a minimum quantity of dry ether and neutralized with an ether solution of HCl (Congo Red). The solid hydrochloride was filtered off, and left overnight in a vacuum-desiccator over alkali, then recrystallized. The table gives data for the hydrochlorides of the Mannich bases.

REFERENCES

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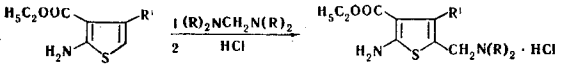
Hydrochlorides of Dimethylaminomethyl and Diethylaminomethyl Derivatives of 2-Amino-3-ethoxycarbonyl-4-arylthiophene



Aminothiophene, mole	Bisdialkylaminomethane		Compounds obtained			Decomp. temperature, °C	Formula	Found, %					Calculated, %					Yield, %
	No.	Quantity, mole	No.	R	R¹			C	H	Cl	N	S	C	H	Cl	N	S	
0.01	I	0.0175	III	CH_3	C_6H_5	220—222, MeOH-Me_2CO (1 : 1)	$C_{16}H_{20}N_2O_2S \cdot HCl$	56.74 56.48	6.01 6.03	—	8.48 8.43	—	56.37	6.21	—	8.21	—	72
0.02	I	0.03	IV	CH_3	4′-$CH_3C_6H_4$	200—202, MeOH-Et_2O (1 : 2)	$C_{17}H_{22}N_2O_2S \cdot HCl$	57.65 57.20	6.50 6.45	10.12 9.92	7.65 7.41	8.85 9.00	57.53	6.53	9.99	7.89	9.03	66
0.0058	I	0.006	V	CH_3	4′-$C_2H_5C_6H_4$	212—214, MeOH	$C_{18}H_{24}N_2O_2S \cdot HCl$	57.97 58.18	6.72 6.60	9.46 9.51	7.63 7.70	8.58 8.79	58.59	6.83	9.61	7.59	8.69	42
0.02	I	0.03	VI	CH_3	2′,4′-$(CH_3)_2C_6H_3$	214—216, MeOH-Et_2O (1 : 2)	$C_{18}H_{24}N_2O_2S \cdot HCl$	58.48 58.67	6.82 7.05	9.61 9.42	7.70 7.77	8.98 8.93	58.59	6.83	9.61	7.59	8.69	66
0.005	I	0.007	VII	CH_3	2′,5′-$(CH_3)_2C_6H_3$	Above 220, MeOH-Et_2O (1 : 4)	$C_{18}H_{24}N_2O_2S \cdot HCl$	58.42 58.85	6.65 6.98	9.64 9.57	7.55 7.48	8.83 9.12	58.59	6.83	9.61	7.59	8.69	55
0.005	I	0.007	VIII	CH_3	2′,4′-$(CH_3O)_2C_6H_3$	Above 200, MeOH-Et_2O (1 : 2)	$C_{18}H_{24}N_2O_4S \cdot HCl$	—	—	8.49 8.44	6.59 6.65	7.92 7.76	—	—	8.84	6.99	7.99	71
0.02	I	0.03	IX	CH_3	2′,5′-$(CH_3O)_2C_6H_3$	194—195, MeOH-Et_2O (1 : 1)	$C_{18}H_{24}N_2O_4S \cdot HCl$	54.17 54.30	6.19 6.20	8.79 8.86	6.88 7.10	7.76 7.68	53.92	6.29	8.84	6.99	7.99	80
0.02	II	0.03	X	C_2H_5	4′-$CH_3C_6H_4$	Above MeOH-Et_2O (1 : 1)	$C_{19}H_{26}N_2O_2S \cdot HCl$	59.97	7.10	9.01 8.78	7.13 7.34	8.43 8.25	59.59	7.11	9.26	7.32	8.37	63
0.0046	II	0.005	XI	C_2H_5	2′,4′-$(CH_3O)_2C_6H_3$	202—204, MeOH-Et_2O (1 : 2)	$C_{20}H_{28}N_2O_4S \cdot HCl$	55.91	6.85	8.06 7.94	6.24 6.12	7.41 7.60	55.74	7.25	8.23	6.50	7.44	46
0.02	II	0.03	XII	C_2H_5	2′,5′-$(CH_3O)_2C_6H_3$	206—208, MeOH-Et_2O (1 : 1)	$C_{20}H_{28}N_2O_4S \cdot HCl$	55.93	7.00	8.15 8.14	6.52 6.27	7.48 7.73	55.74	7.25	8.23	6.50	7.44	75