Synthesis of substituted 7,8-di(propylsulfonyl)pyrrolo[1,2-*a*]pyrazines

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Heating of pyrazinium salts with *E*-1,2-dichloro-1,2-di(propylsulfonyl)ethene in chloroform in the presence of three-fold excess of Et_3N regiospecifically gives rise to substituted 7,8-di(propylsulfonyl)pyrrolo[1,2-*a*]pyrazines in high yields.

Key words: 7,8-di(propylsulfonyl)pyrrolo[1,2-*a*]pyrazines, pyrazinium salts, *E*-1,2-dichloro-1,2-di(propylsulfonyl)ethene, pyrazinium ylides.

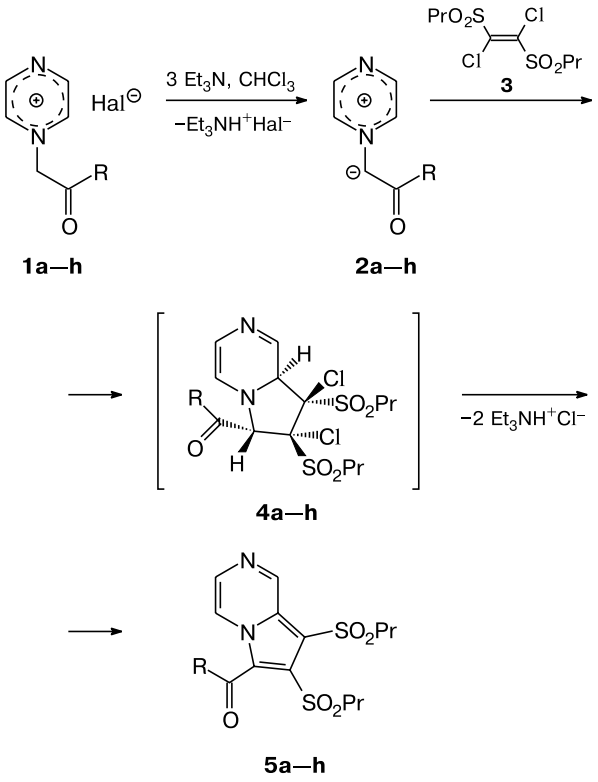
Substituted pyrrolopyrazines and their hydrogenated analogs attract a growing attention of chemists and biologists as potential class of biologically active substances.[1] For example, an intensive study of substituted pyrrolothienopyrazines revealed their high anti-tumor activity.[2,3] Alkaloids, such as brevianamide, barretin, cambines, *etc.*, contain fragments of substituted hydrogenated pyrrolopyrazines.[1] It is known[4—6] that many of these compounds have anti-microbial and anti-viral activity, including activity against the human immunodeficiency virus. Specific phytotoxins and selective herbicides[1] are also found among these substances.

However, so far this class of heterocycles remains poorly studied, apparently, because of a limited number of methods for their synthesis. The Chichibabin reaction, *viz.*, intramolecular condensation of 1-carbonylmethyl-2-methylpyrazinium salts under action of bases, is often used for the preparation of substituted pyrrolopyrazines.[7—9] In addition, a few examples for the construction of pyrrolopyrazine system by the reaction of 1,3-dipolar cycloaddition of pyrazinium ylides with unsaturated compounds are known.[10,11] It should be noted that the yield of target compounds is not high because of formation of by-products.

The reaction of 1,3-dipolar cycloaddition of sulfonyl-substituted unsaturated compounds with pyrazinium ylides has not been used for the synthesis of substituted pyrrolopyrazines. In continuation of our works on the synthesis of sulfonyl-substituted bicyclic azines with the bridgehead nitrogen atom,[12,13] we investigated the reaction of pyrazinium ylides with *E*-1,2-dichloro-1,2-di(propylsulfonyl)ethene for the first time (Scheme 1).

Pyrazinium salts **1** were treated with three-fold excess of Et_3N in $CHCl_3$ to generate pyrazinium ylides **2** followed by addition of *E*-1,2-dichloro-1,2-di(propylsulfonyl)-ethene (**3**). The reaction mixture was refluxed for 40 min and substituted 7,8-di(propylsulfonyl)pyrrolo[1,2-*a*]-pyrazines **5** were isolated in good yield (63—85%) (Table 1).

Scheme 1



2—5: R = 4-MeC_6H_4 (**a**), 4-EtC_6H_4 (**b**), 2,4-$Me_2C_6H_3$ (**c**), 4-$MeOC_6H_4$ (**d**), 3,4-$(MeO)_2C_6H_3$ (**e**), 4-FC_6H_4 (**f**), 4-ClC_6H_4 (**g**), 4-BrC_6H_4 (**h**)

Earlier,[13] we suggested a plausible mechanism for the 1,3-dipolar cycloaddition of *E*-1,2-di(alkylsulfonyl)-

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Table 1. Physico-chemical characteristics of substituted 7,8-di(propylsulfonyl)pyrrolo[1,2-*a*]-pyrazines **5**

Compound	M.p./°C (solvent)	Yield (%)	Found / Calculated (%)				Molecular formula
			C	H	N	S	
5a	166—167 ($CHCl_3$)	73	55.03 / 55.28	5.01 / 5.10	6.27 / 6.45	14.93 / 14.76	$C_{20}H_{22}N_2O_5S_2$
5b	154 (MeCOMe)	54	56.89 / 57.12	5.61 / 5.67	5.95 / 6.06	13.99 / 13.86	$C_{22}H_{26}N_2O_5S_2$
5c	174 ($CHCl_3$)	73	56.85 / 57.12	5.58 / 5.67	5.91 / 6.06	14.03 / 13.86	$C_{22}H_{26}N_2O_5S_2$
5d	124 ($CHCl_3$)	85	54.41 / 54.29	5.29 / 5.21	6.11 / 6.03	13.61 / 13.80	$C_{21}H_{24}N_2O_6S_2$
5e	176—177 ($CHCl_3$)	64	53.11 / 53.43	5.15 / 5.30	5.51 / 5.66	12.87 / 12.96	$C_{22}H_{26}N_2O_7S_2$
5f	166 (MeCOMe)	74	52.91 / 53.08	4.64 / 4.68	6.10 / 6.19	14.33 / 14.17	$C_{20}H_{21}FN_2O_5S_2$
5g	191 (MeOH)	65	51.39 / 51.22	4.57 / 4.51	5.89 / 5.97	13.45 / 13.67	$C_{20}H_{21}ClN_2O_5S_2$
5h	182 (MeOH)	63	46.55 / 46.79	4.09 / 4.12	5.37 / 5.46	12.71 / 12.49	$C_{20}H_{21}BrN_2O_5S_2$

Table 2. Spectroscopic characteristics of substituted 7,8-di(propylsulfonyl)pyrrolo[1,2-*a*]pyrazines **5**

Compound	IR, ν/cm^{-1}		^{1}H NMR, δ (*J*/Hz)	MS, *m/z* (I_{rel} (%))
	C=O	SO_2		
5a	1670	1324, 1148	0.88, 1.00 (both t, 3 H each, Me, J = 7.35); 1.61, 1.78 (both m, 2 H each, CH_2); 2.42 (s, 3 H, Me); 3.59 (m, 4 H, 2 CH_2SO_2); 7.39, 7.74 (both d, 2 H each, H(3), H(5), H(2), H(4) (C_6H_4), J = 8.09); 7.94 (d, 1 H, C(3)H, J = 4.41); 8.05 (d, 1 H, C(4)H, J = 5.15); 9.57 (s, 1 H, C(1)H)	434 $[M]^+$ (46)
5b	1668	1320, 1150	0.95, 1.07 (both t, 3 H each, Me, J_1 = 7.15, J_2 = 7.70); 1.27 (t, 3 H, Me (4-Et), J = 7.70); 1.66, 1.83 (both m, 2 H each, CH_2); 2.75 (q, 2 H, CH_2 (4-Et), J = 7.15); 3.58 (m, 4 H, 2 CH_2SO_2); 7.38, 7.72 (both d, 2 H each, H(3), H(5), H(2), H(6) (C_6H_4), J = 7.70); 7.92 (m, 2 H, C(3)H, C(4)H); 9.59 (s, 1 H, C(1)H)	462 $[M]^+$ (44)
5c	1668	1318, 1140	0.92, 1.07 (both t, 3 H each, Me, J = 7.32); 1.68, 1.86 (both m, 2 H each, CH_2); 2.39, 2.67 (both s, 3 H each, Me); 3.40, 3.62 (both m, 2 H each, CH_2SO_2); 7.01 (m, 2 H, H(3), H(5) (C_6H_3)); 7.22 (m, 1 H, H(6) (C_6H_3)); 7.80 (d, 1 H, C(3)H, J = 4.89); 7.93 (d, 1 H, C(4)H, J = 4.88); 9.80 (s, 1 H, C(1)H)	462 $[M]^+$ (42)
5d	1660	1328, 1140	0.98, 1.07 (both t, 3 H each, Me, J_1 = 7.15, J_2 = 7.70); 1.70, 1.85 (both m, 2 H each, CH_2); 3.55 (m, 4 H, 2 CH_2SO_2); 3.95 (s, 3 H, OMe); 7.05, 7.78 (both d, 2 H each, H(3), H(5) and H(2), H(4) (C_6H_4), J = 8.80); 7.95 (m, 2 H, C(3)H, C(4)H); 9.55 (m, 1 H, C(1)H)	469 $[M]^+$ (54)
5e	1660	1328, 1144	1.03 (m, 6 H, 2 Me); 1.83 (m, 4 H, 2 CH_2); 3.61 (m, 4 H, 2 CH_2SO_2); 3.94, 3.97 (both s, 3 H each, MeO); 6.83 (d, 1 H, H(5) (C_6H_3), J = 8.74); 7.02 (d, 1 H, H(6) (C_6H_3), J = 8.01); 7.62 (m, 2 H, H(2) (C_6H_3), C(3)H); 7.89 (d, 1 H, C(4)H, J = 5.25); 9.78 (s, 1 H, C(1)H)	494 $[M]^+$ (55)
5f	—	—	0.89, 1.00 (both t, 3 H each, Me, J = 7.35); 1.60, 1.78 (both m, 2 H each, CH_2); 3.59 (m, 4 H, 2 CH_2SO_2); 7.41 (t, 2 H, H(3), H(5) (C_6H_4), J = 8.83); 7.96 (m, 3 H, H(2), H(4) (C_6H_4) + C(3)H); 8.15 (d, 1 H, C(4)H, J = 4.42); 9.58 (s, 1 H, C(1)H)	452 $[M]^+$ (44)
5g	—	—	0.96, 1.06 (both t, 3 H each, Me, J_1 = 7.70, J_2 = 7.15); 1.65, 1.83 (both m, 2 H each, CH_2); 3.55 (m, 4 H, 2 CH_2SO_2); 7.58, 7.86 (both d, 2 H each, H(3), H(5) and H(2), H(6) (C_6H_4), J = 8.8); 7.94, 8.06 (both d, 1 H each, C(3)H, C(4)H, J = 4.95); 9.58 (s, 1 H, C(1)H)	468 $[M]^+$ (40)
5h	—	—	0.97, 1.08 (both t, 3 H each, Me, J = 7.35); 1.66, 1.83 (both m, 2 H each, CH_2); 3.55 (m, 4 H, 2 CH_2SO_2); 7.73, 7.78 (both d, 2 H each, H(3), H(5) and H(2), H(4) (C_6H_4), J = 8.09); 7.94, 8.06 (both d, 1 H each, C(3)H, C(4)H, J = 5.15); 9.59 (s, 1 H, C(1)H)	513 $[M]^+$ (42)

1,2-dichloroethenes with pyridinium ylides through the formation of hydrogenated intermediates **4**, the subsequent double dehydrochlorination of which, in case of the reaction of ethenes **1** with pyrazinium ylides, leads to substituted 7,8-di(propylsulfonyl)pyrrolo[1,2-*a*]pyrazines **5** (see Scheme 1).

The structures of compounds **5** were confirmed by elemental analysis data, ^{1}H NMR and IR spectroscopy, and mass spectrometry data (Tables 1 and 2). The IR spectra of compounds **5** contain absorption bands corresponding to the stretching vibrations of the carbonyl group (1712—1688 cm^{-1}) and the sulfonyl group[14] (1324—1308 and 1145—1140 cm^{-1}). A molecular ion peak $[M]^{\bullet+}$ is presented in the mass spectra of all the compounds synthesized. In the ^{1}H NMR spectra of compounds **5a—h**, the proton signals of the pyrazine fragment reveal themselves as two doublets (δ 7.62—7.94 (C(3)H) and 7.89—8.05 (C(4)H)) and a singlet (δ 9.56—9.80 (C(1)).

Experimental

IR spectra of compounds were recorded on a Perkin-Elmer-577 and Specord M82 spectrometers in $CHCl_3$ with d = 0.078 mm (a NaCl cuvette). ^{1}H NMR spectra were recorded on a Bruker DRX-500 (500 MHz) and Bruker WM-250 (250 MHz) spectrometers for 5—12% solutions in DMSO-d_6 with Me_4Si as the internal standard. Mass spectra were recorded on a FINNIGAN MAT INCOS 50 quadruple mass spectrometer with the energy of ionization 70 eV. Monitoring of the course of the reaction and the individuality of compounds synthesized were performed by TLC on Silufol UV-254 plates (eluent hexane—acetone, 2 : 1) with visualization in iodine vapors.

***E*-1,2-Dichloro-1,2-di(propylsulfonyl)ethene (3)** was synthesized by the method described earlier.[14]

Substituted 7,8-di(propylsulfonyl)pyrrolo[1,2-*a*]pyrazines 5a—h (general procedure). Triethylamine (0.003 mol) was added to a stirred solution of compound **1** (0.001 mol) in $CHCl_3$, then a solution of sulfone **3** was added dropwise. The reaction mixture was refluxed for 40 min (monitoring by chromatography). Then the reaction mixture was diluted with $CHCl_3$, washed with water, and dried with $MgSO_4$. After the solvent was evaporated, the solid residue was recrystallized. Characteristics of compounds **5a—h** are given in Tables 1 and 2.

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