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Self-assembling of aminopyrazine fluorescent dyes and their solid state spectra, Part 2

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Abstract

2,5-Diamino-3,6-dicarboxy pyrazine derivatives have a strong intramolecular charge-transfer chromophoric system and are new fluorescent candidates for many applications. The thioester and carbamoyl derivatives were newly synthesized and their solid state spectra were evaluated with respect to their molecular stacking. Hydrophobic interactions of the n-butyl groups were observed but intermolecular $\pi - \pi$ interactions were not observed from the X-ray crystal analysis of 2,5-diamino-3,6-bis(butoxycarbonyl)pyrazine. These space-filling intermolecular interactions of dicyanopyrazines make it possible to construct strong three dimensional molecular stacking in single crystals, which affect their solid state absorption spectra. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Dicyanopyrazine fluorescent dyes; Self-assembling; Solid state spectra; Space-filling intermolecular interaction; X-ray crystal analysis

1. Introduction

2,5-Diamino-3,6-dicyanopyrazine derivatives have a small chromophoric system but have strong fluorescence even in the solid state [1,2]. The development of new fluorescent chromophores has many potential interests, e.g. in applications such as electroluminescence devices, solar energy collecting systems and nonlinear optical devices. We have previously reported the syntheses and solid state spectra of 2,5-diamino-3,6-dicyanopyrazine derivatives [2], and their self-assembling properties and fluorescence properties in the solid state were discussed with respect to their chemical structure.

The dicyanopyrazine moiety has a strong electron withdrawing ability, and derivatives thereof can be are expected to have strong intra- and inter-molecular charge-transfer interactions in their self-assembled aggregates. Three dimensional molecular stacking was performed by the intermolecular interactions, which controlled special functionalities such as color changes in crystal morphology, organic nonlinear optical properties etc [3,4].

We now report the synthesis of some new aminopyrazine fluorescent dyes, and a study of the self-assembling of their chromophores, which affects

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their solid state fluorescence properties. The reaction of diethyl phosphorocyanidate (DEPC) with carboxylic acids in the presence of nucleophiles has been known to give carboxyl derivatives such as amides, thioesters and carboxylic esters [5–8]. Many aminopyrazine amides and thioesters were synthesized, and their absorption and fluorescence spectra in solution and the vapor deposited thin film were evaluated to correlate their structure with their molecular stacking behaviors. The X-ray crystal analysis of 2,5-diamino-3,6-bis(butoxy-carbonyl)pyrazine was conducted to evaluate intermolecular interactions.

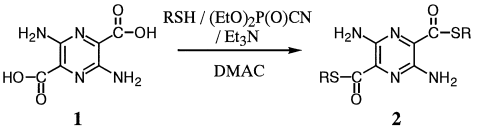
2. Results and discussion

2.1. 2,5-Diaminopyrazine-3,6-dialkylthioesters 2

2,5-Diamino-3,6-dicarboxypyrazine **1** was previously synthesized by hydrolysis of the cyano groups in 2,5-diamino-3,6-dicyanopyrazine [2]. Compound **1** is very important in the synthetic strategy to develop new fluorescent dye materials. The synthesis of the 2,5-diaminopyrazine-3,6-dialkyl-thioesters **2** was carried out by reaction of **1** with alkylthiols in dimethylacetamide in the presence of diethyl phosphorocyanidate (Scheme 1). Dyes **2a–2f** were obtained in yields of 5–49%, which are influenced by the steric parameters of the substituent *R*. The absorption and fluorescence spectra of **2a–2f** are summarized in Table 1.

The differences in λ_{max} and F_{max} from the solid state to solution are indicated by $\Delta\lambda$ and ΔF respectively. Small substituent effects of *R* on the λ_{max} value in chloroform were observed, which is reasonable considering the electron donating properties of the alkylthio (*SR*) group. On the other hand, the λ_{max} values in the vapor deposited thin film of **2a–2e** shifted to shorter wavelength of 3–20 nm compared to those in solution, but that of **2f** showed a bathochromic shift of 29 nm. Hypsochromic shift of λ_{max} in the solid state was unexpected, and could be caused by the interlayer interatomic interactions decreasing the charge-transfer character of the chromophoric system, i.e. the electron donating sulfur atom may be oriented upper or down on the pyrazine ring, which decreases the electron withdrawing character of the pyrazine ring.

Regular and strong molecular stacking in dyes **2b**, **2d** and **2e** were observed from their solid state absorption spectra, which showed a small half-band width in comparison with that in solution (Fig. 1). It is generally known that dye aggregates such as J-aggregate show very sharp absorption spectra accompanied by a large bathochromic shift of λ_{max} compared to the corresponding monomeric form. These spectral changes are due to intermolecular transition moment interactions in the aggregate [9]. In the case of these dyes, **2b** has an n-butyl group, and both **2d** and **2e** have a benzyl group, which may give rise to effective



1 **2**

No.	R	yield (%)	No.	R	yield (%)
2a	Et	49	**2d**	CH_2–Ph	24
2b	n-Bu	29	**2e**	CH_2–Ph–OCH_3	21
2c	Ph	5	**2f**	CH_2–Ph–Cl	17

Scheme 1.

Table 1
Visible and fluorescence spectra of compound **2** in chloroform and solid state

No.	λ_{max} (nm)		$\Delta\lambda$[b] (nm)	F_{max} (nm)		ΔF[e] (nm)	SS[f] (nm)
	In $CHCl_3$	In film[a]		In $CHCl_3$[c]	In film[d]		
2a	494	491	−3	597	603	6	103
2b	496	481	−15	591	626	35	95
2c	505	485	−20	598	–[g]	–[g]	93
2d	497	485	−12	596	650	54	99
2e	498	483	−15	594	628	34	96
2f	501	530	29	596	657	61	95

[a]Vapor deposited thin film.
[b]$\Delta\lambda = \lambda_{max}$(film)$-\lambda_{max}$(soln).
[c]F_{max}(soln.) excited at λ_{max}(soln) value.
[d]Solid state F_{max} excited at λ_{max}(film) value.
[e]$\Delta F = F_{max}$(solid)$-F_{max}$(soln).
[f]Stokes' shift.
[g]No fluorescence detected.

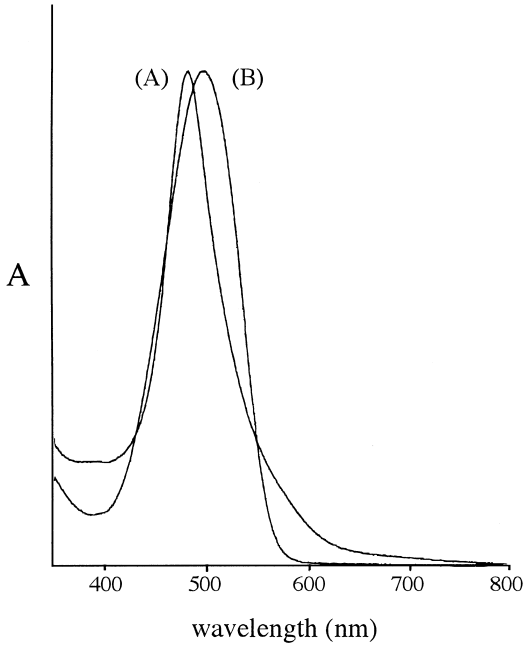


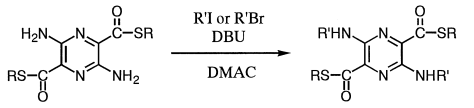
Fig. 1. Differences in absorption spectra of **2e** in (A) the solid state and (B) in chloroform.

molecular stacking in the solid state. For example, the X-ray crystal data of 2,5-diamino-3,6-bis(n-butoxy-carbonyl)pyrazine **5b**, the oxygen analogue of **2b**, showed strong molecular stacking affected by hydrophobic interactions of the butyl group, as shown in the following.

2.2. 2,5-Bis(alkylamino)pyrazine-3,6-dialkylthioester **3**

2,5-Bis(alkylamino)pyrazine-3,6-dialkylthioester **3** were synthesized by the reaction of **2** with the appropriate alkyl halide in the presence of diazabicycloundecene (DBU) in dimethylacetamide (Scheme 2). Their visible and fluorescence spectra in solution and the solid state are shown in Table 2.

Dye **2a** absorbed at 494 nm in chloroform but the bis(ethylamino) analogue **3a**, having strong donors absorbed at 567 nm, and the intramolecular charge-transfer chromophoric system of **3** was thus confirmed. The λ_{max} values of **2a–2c** shifted to longer wavelength by 34–43 nm in comparison with those of the corresponding esters **5a–5c**



No.	R = R'	No.	R	R'
3a	Et	**3d**	Et	CH_2-Ph
3b	n-Bu	**3e**	n-Bu	CH_2-Ph
3c	CH_2-Ph	**3f**	CH_2-Ph-OCH_3	CH_2-Ph
		3g	CH_2-Ph-Cl	CH_2-Ph

Scheme 2.

Table 2
Visible and fluorescence spectra of compound **3** in chloroform and the solid state

No.	λ_{max} (nm)		$\Delta\lambda$[b] (nm)	F_{max} (nm)		ΔF[e] (nm)	SS[f] (nm)
	In $CHCl_3$	In film[a]		In $CHCl_3$[c]	In film[d]		
3a	567	550	−17	667	655	−12	100
3b	576	620	44	687	672	−15	111
3c	562	591	29	667	669	2	105
3d	561	608	47	656	669	13	95
3e	556	580	24	659	643	−16	103
3f	560	589	29	652	666	14	92
3g	566	611	45	653	686	33	87

[a]Vapor deposited thin film.
[b]$\Delta\lambda = \lambda_{max}$(film)$-\lambda_{max}$(soln).
[c]F_{max}(soln.) excited at λ_{max}(soln) value.
[d]Solid state F_{max} excited at λ_{max}(film) value.
[e]$\Delta F = F_{max}$(solid)$-F_{max}$(soln.)
[f]Stokes' shift.

which indicated that the alkylthioester group was a much stronger acceptor than the alkoxy carbonyl group. A similar bathochromic shift of 55 nm was observed between **3a** and the corresponding alkoxy ester [2].

Substituent effects of R and R' in **3** were very small in solution, and the λ_{max} values varied from 556 to 576 nm. The Stokes' shift of **3** were quite large, around 100 nm, and similar shifts were also observed in the case of the analogous alkoxy carbonyl derivatives [2]. On the other hand, λ_{max} values in the solid state underwent large changes, depending on the substituents present, from 550 nm (**3a**) to 620 nm (**3b**). The $\Delta\lambda$ value, the difference of λ_{max} from the solid state to solution,

changed from −17 to 47 nm. It is proposed that a bulky substituent such as the benzyl group, inhibits intermolecular $\pi-\pi$ interactions of the chromophores, thus showing small $\Delta\lambda$ and ΔF values [2]. In the case of **3a**, a negative $\Delta\lambda$ of 17 nm was obtained, which has been observed previously in the case of the corresponding alkoxy carbonyl derivatives [2]. These results indicate that molecular stacking in the solid state, occurs, and in which the donor-acceptor chromophoric character will be partially cancelled by the intermolecular interactions with increasing steric requirements of the substituents, lower intermolecular interactions of the chromophores will occur, and small $\Delta\lambda$ and small or negative ΔF, were observed. Negative ΔF values for **3a**, **3b** and **3e** are due to the loss of coplanarity of the π-system in the solid state because of steric repulsion between the substituents.

2.3. 2,5-Diamino-3,6-bis(N,N-dialkylcarbamoyl) pyrazine **4**

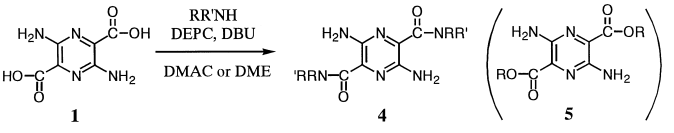
The syntheses of **4** containing N,N-dialkylcarbamoyl groups was carried out by reaction of **1** with secondary amines in the presence of DEPC and DBU in dimethyl acetamide (Scheme 3). Absorption and fluorescence characteristics of **4** compared with those of **5**, the alkoxycarbonyl derivatives, are summarized in Table 3.

Dye **4a** absorbed at 394 nm and dye **5a** absorbed at 460 nm. The large hypsochromic shift from **5a** to **4a** is explained by decrease of the electron withdrawing ability of the carbonyl moiety. The λ_{max} values of **4d–4g**, having monoalkyl carbamoyl groups absorbed at much longer wavelength than those of the dialkylcarbamoyl derivatives **4a–4c**. In comparison with the solid state absorption spectra of **4b** and **5b** the value is different considerably, from 3 nm for **4b** to 65 nm for **5b**. These results indicate that **4b** and **5b** have a different molecular stacking in the solid state, which was caused by the differences in the steric requirements of the alkoxy (**5b**) and dialkylamino (**4b**) moieties. Dyes **4** have small $\Delta\lambda$ and ΔF, values as in the case of dyes **3**, and are caused by steric hindrance of

Table 3
Visible and fluorescence spectra of compound **4** in chloroform and solid state

No.	λ_{max} (nm)		$\Delta\lambda$[b]	F_{max} (nm)		ΔF[e] (nm)	SS[f] (nm)
	In $CHCl_3$	In film[a]		In $CHCL_3$[c]	In film[d]		
4a	394	398	4	529	512	−17	135
4b	395	398	3	527	535	8	132
4c	405	410	5	540	546	6	135
4d	446	472	26	531	554	23	85
4e	450	472	22	537	557	10	87
4f	451	457	6	533	530	−3	82
4g	450	458	8	533	451	8	83
5a[g]	460	522	62	546	610	64	86
5b[g]	457	503,522[h]	46, 65	546	571	25	89
5c[g]	462	507, 550[h]	45, 88	548	609	61	86

[a]Vapor deposited thin film.
[b]$\Delta\lambda = \lambda_{max}$(film)$-\lambda_{max}$(soln.).
[c]F_{max}(soln) excited at λ_{max}(soln.) value.
[d]Solid state F_{max} excited at λ_{max}(film) value.
[e]$\Delta F = F_{max}$(solid)$-F_{max}$(soln.).
[f]Stokes' shift.
[g]Previous report [2].
[h]Shoulder.



1 4 5

No.	R = R'
4a	Et
4b	n-Bu
4c	CH_2-Ph

No.	R	R'
4d	Cyclohexyl	H
4e	CH_2-Ph	H
4f	CH_2-Ph-CH_3	H
4g	CH_2-Ph-OCH_3	H

No.	R
5a	Et
5b	n-Bu
5c	CH_2-Ph

Scheme 3.

the dialkylcarbamoyl groups preventing the effective intermolecular $\pi - \pi$ interactions. The, less hindered dye **5** showed relatively large $\Delta\lambda$ values, and the hindered dye **4** showed a small value.

The Stokes' shifts of **4a–4c** were larger than those of **4d–4g** indicating much more stabilization in the emission state of **4a–4c**, i.e. the sterically hindered **4a–4c** in the ground state are much more stabilized in the excited state in comparison with those of less hindered **4d–4g**. The $\Delta\lambda$ values of dyes **4** were generally smaller than those of dyes **5**, which showed that less intermolecular interactions were observed in dyes **4**.

The crystal structure of **5b** was determined by X-ray analysis, and the molecular stacking behavior was evaluated from the points of intermolecular $\pi - \pi$ interactions and the hydrophobic interactions of the butyl groups in the crystal.

2.4. *X-ray crystal analysis of* **5b**

Single crystals of **5b** were obtained from their chloroform solution by slow evaporation of the solvent. The X-ray crystal analysis of **5b** was carried out to evaluate the relationship between the crystal structure and electronic spectral properties. The crystal system of **5b** is triclinic, and the space group is $P\bar{1}$. Details of the crystal data are summarized in the experimental section, the molecular structure of **5b** is shown in Fig. 2.

The butoxy carbonyl groups were oriented in the *trans*-configuration. The π-chromophroric system was completely planar, but the butyl groups are oriented out of plane from the C(5) (Fig. 3).

The *cis*-conformation was observed from O(2) to C(6), which is considered to control the molecular stacking by the intermolecular hydrophobic interaction of the butyl groups in single crystals (Fig. 3). Intermolecular charge-transfer interactions between the π-systems was not observed from the molecular overlap structures (Figs. 3 and 4).

Consequently, **5b** did not have strong intermolecular $\pi - \pi$ interactions and therefore showed a relatively small $\Delta\lambda$ of 65 nm in comparison with the methoxycarbonyl analogue, in which a $\Delta\lambda$ value of 94 nm was observed [2]. The methoxy group is spatially smaller than the butoxy group and stronger intermolecular $\pi - \pi$ interactions are concluded

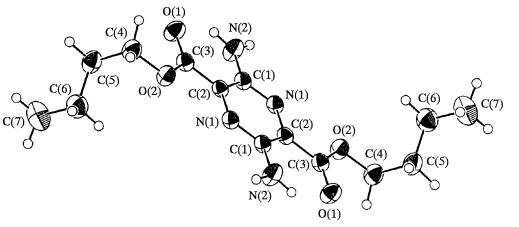


Fig. 2. Molecular structure of **5b** in the crystal.

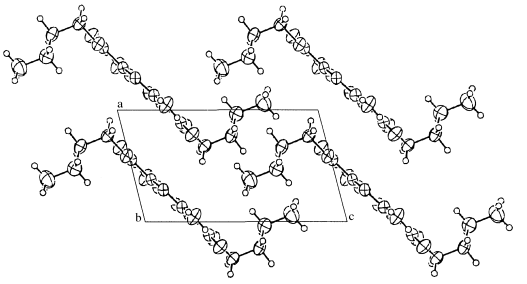


Fig. 3. Molecular stacking of **5b** and the intermolecular interactions of π-systems in the distances of 2.7–2.9 Å.

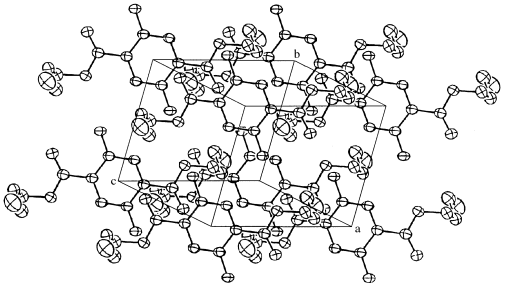


Fig. 4. Less intermolecular overlap of the π-systems in **5b**.

to reset in the larger $\Delta\lambda$ value. The relationship between larger $\Delta\lambda$ value and stronger intermolecular $\pi - \pi$ interactions of aminonaphthoquinones has been previously reported [3,4].

3. Experimental

3.1. *Materials and equipments*

Melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. Column chromatography was performed on Wako gel C-300. IR spectra were

recorded on a Nicolet FT/IR Impact 400D spectrophotometer. ^{1}H NMR spectra were obtained with a FT-NMR QE 300MHz Shimadzu spectromer, UV–Vis spectra on a Hitachi U-3410 spectrophotomer and fluorescence spectra a Hamamatsu photonic multi-channel analyzer PMA-11 and a Jasco SM-3 type monochrometer as a light source. Preparation of vapor deposited thin film of compounds was performed using a Nippon Shinku Kikou VSP-060. Microanalyses were performed on a Yanaco CHN MT-3 and MS spectra were obtained with a M-80 B Hitachi mass spectrometer. N,N-Dimethylacetamide (DMAC) and 1,2-dimethoxyethane (DME) were stored over 4 Å molecular sieves. All reagents were used without further purification. 2,5-Diaminopyrazine-3,6-dicarboxylic acid was synthesized as previously reported [2].

3.2. *Preparation of single crystal of* **5b** *and crystal data*

Red crystals of **5b** were obtained from their chloroform solution by slow evaporation of the solvent over 1 week; X-ray crystal analysis was carried out and the data obtained are as follows: formula: $C_{14}H_{22}N_4O_4$; formula weight: 310.00; crystal system: triclinic; lattice parameters: $a = 5.993$ (1) Å, $b = 6.469$ (2) Å, $c = 10.852$ (2) Å, $\alpha = 104.65$ (2)°, $\beta = 100.58$ (2)°, $\gamma = 101.07$ (2)°, Å, $V = 387.3$ (2) Å^3, Z values: 1; space group: $P\bar{1}$, no. of reflections measured: 1667; residuals R and Rw: 0.034 and 0.035; goodness of fit: 1.326.

3.3. *General procedure for the 2,5-diaminopyrazine-3,6-dialkylthioesters* **2**

To a solution of the aminopyrazine carboxylic acid **1** (0.51 mmol) in 7 ml of DMAC, a solution of the appropriate thiol (2.5 mmol) and DEPC (1.8 mmol) in 5 ml of DMAC was added and then triethylamine (2.2 mmol) was dropped in at room temp. The reaction mixture was stirred for 3 h. at room temp. and worked-up as follows.

3.3.1. *Method A* (**2a-d**)

The reaction mixture was poured into water 60 ml and extracted with ethyl acetate. The ethyl acetate layer was evaporated to give the crude product, which was then purified by column chromatography by using dichloromethane as eluent.

3.3.2. *Method B* (**2e**)

The reaction mixture was poured into water 60 ml and extracted with chloroform. The chloroform layer was evaporated and an obtained crude product was recrystallized with chloroform to give **2e**.

3.3.3. *Method C* (**2f**)

The reaction mixture was poured into water 60 ml. The precipitate was filtered, washed with methanol and recrystallized from chloroform to give **2f**.

Characterisation data for these compounds is given below.

3.4. *2,5-Diaminopyrazine-3,6-diethylthioester* **2a**

Red solid; 49%; mp: 166–167°C; d_H ($CDCl_3$) 5.93 (4 H, s, br), 2.97 (4 H, q, J 7.4), 1.32 (6 H, t, J 7.5); ν cm^{-1} (KBr) 3478, 3358, 2978, 1645, 1586, 1205, 906; EA, Calcd.: $C_{10}H_{14}N_4O_2S_2$ (C, 41.96; H, 4.90; N, 19.58) Found: (C, 41.97; H, 4.86; N, 19.40); m/z (M^+): 286.

3.5. *2,5-Diaminopyrazine-3,6-di*-n-*butylthioester* **2b**

Red solid; 29%; mp: 139–140°C; δ_H ($CDCl_3$) 5.94 (4 H, s, br), 2.96 (4 H, t, J 7.4), 1.63 (4 H, quint, J 7.6), 1.45 (4 H, sixt, J 7.4), 0.94 (6 H, t, J 7.2); ν cm^{-1} (KBr) 3494, 3364, 2956, 1662, 1586, 1199, 906; EA, Calcd.: $C_{14}H_{22}N_4O_2S_2$ (C, 49.12; H, 6.43; N, 16.37) Found: (C, 49.09; H, 6.42; N, 16.16); m/z (M^+): 342.

3.6. *2,5-Diaminopyrazine-3,6-diphenylthioester* **2c**

Violet solid; 5%; mp: 308–309°C; δ_H ($CDCl_3$) 7.51–7.47 (10 H, m), 5.94 (4 H, s, br); ν cm^{-1} (KBr) 3473, 3358, 2923, 1656, 1580, 1189, 884; EA, Calcd.: $C_{18}H_{14}N_4O_2S_2$ (C, 56.54; H, 3.66; N, 14.66) Found: (C, 56.45; H, 3.84; N, 14.32); m/z (M^+): 382.

3.7. *2,5-Diaminopyrazine-3,6-dibenzylthioester* **2d**

Violet solid; 24%; mp: 221–222°C; d_H ($CDCl_3$) 7.37–7.24 (10 H, m), 5.91 (4H, s, br), 4.19 (4 H, s);

ν cm^{-1} (KBr) 3473, 3358, 2929, 1645, 1590, 1194, 906; EA, Calcd.: $C_{20}H_{18}N_4O_2S_2$ (C, 58.54; H, 4.39; N, 13.66) Found: (C, 58.67; H, 4.49; N, 13.41); m/z (M^+): 410.

3.8. 2,5-Diaminopyrazine-3,6-di-p-methoxybenzylthioester **2e**

Red solid; 21%; mp: 218–219°C; δ_H (DMSO-d_6) 7.24 (4 H, d, J 8.7), 6.83 (4 H, d, *J* 8.7), 6.75 (4 H, s, br), 4.08 (4 H, s), 3.68 (6 H, s); ν cm^{-1} (KBr) 3483, 3364, 2940, 1651, 1586, 1199, 906; EA, Calcd.: $C_{22}H_{22}N_4O_4S_2$ (C, 56.17; H, 4.68; N, 11.91) Found: (C, 55.89; H,4.67; N, 11.61); m/z (M^+): 470.

3.9. 2,5-Diaminopyrazine-3,6-di-p-chlorobenzylthioester **2f**

Violet solid; 17%; mp: 268–271°C; δ_H (DMSO-d_6) 7.35 (8 H, s), 6.76 (4 H, s, br), 4.14 (4H, s); ν cm^{-1} (KBr) 3494, 3380, 2940, 1640, 1586, 1194, 911; EA, Calcd.: $C_{20}H_{16}N_4O_2S_2Cl_2$ (C, 50.21; H, 3.35; N, 11.72) Found: (C, 49.72; H, 3.38; N, 11.40); m/z (M^+): 478.

3.10. General procedure for the 2,5-bis(alkylamino) pyrazine-3,6-dialkylthioester **3**

DBU (0.67 mmol) was added to a solution of 0.15 mmol of the appropriate 2,5-diaminopyrazine-3,6-dialkylthioester **2** (**2a** for **3a** and **3d**; **2b** for **3b** and **3e**; **2d** for **3c**; **2e** for **3f**; **2f** for **3f**) and a alkyl halide (**3a**: 2.6 mmol of ethyl iodide, **3b**: 2.6 mmol of n-butyl iodide, **3c–3g**: 1.7 mmol of benzyl bromide) in 5 ml of DMAC. Thereafter the reaction was carried out as follows. (**3a**: 120°C, 4 h; **3b**: 120°C, 7 h; **3c**: 110°C, 1.5 h; **3d**: 110°C, 1 h; **3e**: 110°C, 1.5 h; **3f**: 105°C, 2 h; **3g**: 110°C, 1 h). The reaction mixture was poured into water 60 ml and extracted with ethyl acetate. The ethyl acetate extract was evaporated, and the residue purified by column chromatography using the following eluents: **3a**: chloroform:n-hexane (v/v: 5/2); **3b–3e**: dichloromethane: n-hexane (v/v: 3/2); **3f**: dichloromethane; **3g**: dichloromethane:n-hexane (v/v: 1/1).

Characterisation data for these compounds is given below

3.11. 2,5-Bis(ethylamino)pyrazine-3,6-diethylthioester **3a**

Violet solid; 36%; mp: 123–124°C; δ_H ($CDCl_3$) 7.21 (2 H, t, br, *J* 5.0), 3.50 (4 H, dq, *J* 5.6, 7.2), 2.93 (4 H, q, *J* 7.4), 1.32 (6 H, t, *J* 7.4), 1.29 (6 H, t, *J* 7.2); ν cm^{-1} (KBr) 3380, 2961, 1634, 1520, 1280, 1178, 911; EA, Calcd.: $C_{14}H_{22}N_4O_2S_2$ (C, 49.12; H, 6.43; N, 16.37) Found: (C, 50.00; H, 6.60; N, 15.68); m/z (M^+): 342.

3.12. 2,5-Bis(n-butylamino)pyrazine-3,6-di-n-butylthioester **3b**

Violet solid; 15%; mp: 39–40°C; δ_H ($CDCl_3$) 7.25 (2 H, t, br), 3.47 (4 H, q, *J* 6.9), 2.92 (4 H, t, *J* 7.4), 1.69–1.58 (8 H, m), 1.49–1.39 (8 H, m), 0.96 (6 H, t, *J* 7.2), 0.95 (6 H, t, *J* 7.2); ν cm^{-1} (KBr) 3386, 2961, 1640, 1537, 1172, 1085, 906; EA, Calcd.: $C_{22}H_{38}N_4O_2S_2$ (C, 58.15; H, 8.37; N, 12.33) Found: (C, 58.64; H, 8.41; N, 11.60); m/z (M^+): 454.

3.13. 2,5-Bis(benzylamino)pyrazine-3,6-dibenzylthioester **3c**

Violet solid; 14%; mp: 169–171°C; δ_H ($CDCl_3$) 7.66 (2 H, t, *J* 5.7), 7.41–7.22 (20 H, m), 4.65 (4 H, d, *J* 5.7), 4.15 (4 H, s); ν cm^{-1} (KBr) 3391, 2923, 1634, 1515, 1161, 1069, 868; EA, Calcd.: $C_{34}H_{30}N_4O_2S_2$ (C, 69.15; H, 5.08; N, 9.49) Found: (C,69.54; H,5.28; N, 8.86); m/z (M^+): 462.

3.14. 2,5-Bis(benzylamino)pyrazine-3,6-diethylthioester **3d**

Violet solid; 18%; mp: 157–158°C; δ_H ($CDCl_3$) 7.71 (2 H, t, br, *J* 5.9), 7.44–7.25 (10 H, m), 4.69 (4 H, d, *J* 5.7), 2.92 (4 H, q, *J* 7.4), 1.31 (6 H, t, *J* 7.4); ν cm^{-1} (KBr) 3380, 2929, 1634, 1520, 1161, 1074, 868; EA, Calcd.: $C_{24}H_{26}N_4O_2S_2$ (C, 61.80; H, 5.58; N, 12.02) Found: (C, 62.63; H, 5.91; N, 11.17); m/z (M^+): 466.

3.15. 2,5-Bis(benzylamino)pyrazine-3,6-di-n-butylthioester **3e**

Red solid; 13%; mp: 98–99°C; δ_H ($CDCl_3$) 7.71 (2 H, t, br, *J* 5.7), 7.43–7.24 (10 H, m), 4.68 (4 H, d,

J 5.7), 2.91 (4 H, t, *J* 7.4), 1.62 (4 H, quint, *J* 7.3), 1.44 (4 H, sixt, *J* 7.3), 0.94 (6 H, t, *J* 7.2); $\nu\,cm^{-1}$ (KBr) 3402, 2961, 1629, 1526, 1156, 1063, 889; EA, Calcd.: $C_{28}H_{34}N_4O_2S_2$ (C, 64.37; H, 6.51; N, 10.73) Found: (C, 64.52; H, 6.61; N, 10.46); *m/z* (M+): 522.

3.16. 2,5-Bis(benzylamino)pyrazine-3,6-di-p-methoxybenzylthioester **3f**

Violet solid; 36%; mp: 176–177°C; δ_H ($CDCl_3$) 7.66 (2 H, t, br), 7.41–7.21 (14 H, m), 6.84 (4 H, d, *J* 8.7), 4.65 (4 H, d, *J* 5.7), 4.11 (4 H, s), 3.78 (3 H, s); $\nu\,cm^{-1}$ (KBr) 3391, 2929, 1634, 1520, 1254, 1161, 868; EA, Calcd.: $C_{36}H_{34}N_4O_4S_2$ (C, 66.46; H, 5.23; N, 8.62) Found: (C, 66.74; H,5.32; N, 8.46); *m/z* (M+): 650.

3.17. 2,5-Bis(benzylamino)pyrazine-3,6-di-p-chlorobenzylthioester **3g**

Violet solid; 18%; mp: 156–157°C; δ_H ($CDCl_3$) 7.63 (2 H, t, br), 7.40–7.22 (18 H, m), 4.65 (4 H, d, *J* 5.7), 4.10 (4H, s); $\nu\,cm^{-1}$ (KBr) 3402, 2923, 1634, 1520, 1275, 1156, 868; EA, Calcd.: $C_{34}H_{28}N_4O_2S_2Cl_2$ (C, 61.91; H, 4.25; N, 8.50) Found: (C, 62.96; H, 4.79; N, 7.58); *m/z* (M^+): 659

3.18. General procedure for 2,5-diamino-3,6-bis(N,N-dialkylcarbamoyl)pyrazines **4**

To a solution of the aminopyrazine carboxylic acid **1** (0.51 mmol) in 7 ml of DME (**4a–4b**) or DMAC (**4c–4g**), a solution of amine (**4a**, **4d**: 4.5 mmol; **4b**: 1.8 mmol; **4c**, **4e–4g**: 2.5 mmol) and diethylphosphorocyanidate (DEPC, 1.8 mmol) in 5 ml of DME (**4a–4b**) or DMAC (**4c–4g**) was added. A solution of 1,8-diazabicyclo[5,4,0]-7-undecene (DBU, 1.3 mmol) in DME (**4a–4b**) or DMAC (**4c–4g**) 4 ml was then dropped in at 5°C and then the reaction mixtures were then stirred for 1 h and then worked up as follows.

3.19. Method A (**4a**, **4b** and **4e–4g**)

The reaction mixture was stirred at room temp. for 1 h and then poured into 50 ml of 5% NaOH, and left to stand overnight. The resulting precipitates were filtered and washed with water several times to give the crude product **4**. **4a**, **4b** and **4e–4g**, which were then purified by column chromatography using ethyl acetate:hexane (v/v:1/1) as eluent.

3.20. Method B (**4c**, **4d**)

The reaction mixture was stirred at room temp. for 0.5 h (**4c**) and 3 h (**4d**), and poured into 60 ml of water and extracted with ethyl acetate. The ethyl acetate extract was evaporated, and the residual product purified by column chromatography using ethyl acetate:hexane (v/v:1/1) as eluent, to give **4c** and **4d**.

Relevant characterisation data are shown below.

3.21. 2,5-Diamino-3,6-bis(N,N-diethylcarbamoyl)pyrazine **4a**

Pale yellow solid; 19%; mp: 154–155°C; δ_H ($CDCl_3$) 4.90 (4 H, s, br), 3.51 (4 H, q, *J* 7.2), 3.42 (4 H, q, *J* 6.8), 1.24 (12 H, t, *J* 7.1); $\nu\,cm^{-1}$ (KBr) 3467, 3320, 2978, 1613, 1444, 1194, 1129; EA, Calcd.: $C_{14}H_{24}N_6O_2$ (C, 54.55; H, 7.79; N, 27.27) Found: (C, 54.56; H, 7.74; N, 27.71); *m/z* (M^+): 308.

3.22. 2,5-Diamino-3,6-bis(N,N-di-n-butylcarbamoyl)pyrazine **4b**

Yellow solid; 33%; mp: 108–109°C; δ_H ($CDCl_3$) 4.86 (4 H, s, br), 3.45 (4 H, t, *J* 7.7), 3.38 (4 H, t, *J* 7.7), 1.66–1.55 (8 H, m), 1.38 (4 H, sixt, *J* 7.3), 1.21 (4 H, sixt, *J* 7.3) 0.96 (6 H, t, *J* 7.4), 0.85 (6 H, t, J 7.2); $\nu\,cm^{-1}$ (KBr) 3456, 3347, 2956, 2874, 1629, 1596, 1123; EA, Calcd.: $C_{22}H_{40}N_6O_2$ (C, 62.86; H, 9.52; N, 20.00) Found: (C, 63.22; H,9.50; N, 19.68); *m/z* (M+): 420.

3.23. 2,5-Diamino-3,6-bis(N,N-dibenzylcarbamoyl)pyrazine **4c**

Pale yellow solid; 11%; mp: 197–198°C; δ_H ($CDCl_3$) 7.31–7.27 (20 H, m), 4.94 (4 H, s, br), 4.63 (4 H, s), 4.61 (4 H, s); $\nu\,cm^{-1}$ (KBr) 3396, 3320, 2929, 1640, 1444, 1161, 704; EA, Calcd.: $C_{34}H_{32}N_6O_2$ (C, 73.38; H, 5.76; N, 15.11) Found: (C, 72.54; H, 5.71 N, 14.97); *m/z* (M^+): 556.

*3.24. 2,5-Diamino-3,6-bis(*N-*cyclohexylcarbamoyl)-pyrazine* **4d**

Yellow solid; 6%; mp: 212–214°C; δ_H ($CDCl_3$) 7.68 (2 H, d, br), 6.03 (4 H, s, br), 3.86 (2 H, m), 1.98 (4 H, m), 1.77 (4 H, m), 1.44–1.23 (8 H, m), 0.88 (4 H, m); $\nu\,cm^{-1}$ (KBr) 3424, 3326, 2929, 1629, 1580, 1243, 650; $C_{18}H_{28}N_6O_2$ (C, 60.00; H, 7.78; N, 23.33) Found: (C, 60.59; H, 7.86 N, 22.24); m/z (M^+): 360.

*3.25. 2,5-Diamino-3,6-bis(*N-*benzylcarbamoyl)pyrazine* **4e**

Yellow solid; 5%; mp: 220–221°C; δ_H ($CDCl_3$) 8.09 (2 H, t, br), 7.39–7.29 (10 H, m), 6.01 (4 H, s, br), 4.59 (4 H, d, J 6.0); $\nu\,cm^{-1}$ (KBr) 3467, 3347, 3282, 2923, 1565, 1520, 1172; $C_{20}H_{20}N_6O_2$ (C, 63.83; H, 5.32; N, 22.34) Found: (C, 64.09; H, 5.58 N, 21.23); m/z (M^+): 376.

*3.26. 2,5-Diamino-3,6-bis(*N-*(*p-*methyl)benzylcarbamoyl)pyrazine* **4f**

Yellow solid; 5%; mp: 184–186°C; δ_H ($CDCl_3$) 8.04 (2 H, t, br), 7.23 (4 H, d, J 8.1), 7.16 (4 H, d, J 8.1), 5.99 (4 H, s, br), 4.54 (4 H, d, J 6.0), 2.34 (6 H, s); $\nu\,cm^{-1}$ (KBr) 3418, 3337, 2923, 1656, 1520, 1172, 808; $C_{22}H_{24}N_6O_2$ (C, 65.35; H, 5.94; N, 20.79) Found: (C, 64.46; H, 6.00 N, 20.08); m/z (M^+): 404.

*3.27. 2,5-Diamino-3,6-bis(*N-*(*p-*methoxy)benzylcarbamoyl)pyrazine* **4g**.

Yellow solid; 5%; mp: 154–156°C; δ_H ($CDCl_3$) 8.01 (2 H, t, br, J 5.9), 7.27 (4 H, d, J 8.7), 6.88 (4 H, d, J 8.7), 5.99 (4 H, s, br), 4.52 (4 H, d, J 6.0), 3.80 (6 H, s); $\nu\,cm^{-1}\,cm^{-1}$ (KBr) 3478, 3347, 2929, 1651, 1515, 1248, 1031; $C_{22}H_{24}N_6O_2$ (C, 60.55; H, 5.50; N, 19.27) Found: (C, 61.23; H, 5.64 N,18.03); m/z (M^+): 436.

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