

# New unsymmetrical alkyl-*s*-tetrazines: original syntheses, fluorescence and electrochemical behaviour†

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Despite previous report of failure of this reaction, a series of new monoalkyltetrazines and a dialkyltetrazine have been prepared by nucleophilic aromatic substitution, albeit sometimes in moderate yields. In addition to the original synthetic procedure, the fluorescence and electrochemical behaviour of these new compounds have been reported.

## Introduction

*s*-Tetrazines chemistry has been known for more than a century,<sup>1</sup> and their photophysical<sup>2</sup> and electrochemical<sup>3</sup> properties have been briefly reported in the past. However regarding the recent interest in conjugated molecules and materials,<sup>4</sup> the *s*-tetrazine building block is more and more recognised as a very promising and fascinating one. *s*-Tetrazines are electroactive heterocycles, having a very high electron affinity, and in addition, they have a low lying  $\pi^*$  orbital, inducing a low energy  $n-\pi^*$  transition in the visible range, which makes them highly coloured, and sometimes fluorescent. The chemistry of *s*-tetrazines has been recently reviewed by us and others.<sup>5</sup>

From our previous work,<sup>6</sup> and other reports,<sup>3,7</sup> it is known that direct substitution on the carbon atom of the tetrazine ring is possible essentially with nucleophiles where the nucleophilic pair is centered on an heteroatom. With carbon-centered nucleophiles, the situation is more complicated. Some work reported that soft carbanions could lead to nucleophilic substitution.<sup>8</sup> On the other hand Kotschy *et al.* have shown that an azaphilic attack occurred with harder carbon-centered nucleophiles (like Grignard reagents or alkyllithium) leading often to non-aromatic and unstable adducts,<sup>9</sup> which was apparently a lock to the access of useful alkyl tetrazines. While

Kotschy *et al.* tried to rationalise this within the framework of the Hard Soft Acid Base (HSAB) theory<sup>10</sup> in the case of carbon nucleophiles, the situation is likely more complicated, since both hard (alkoxides or amines) and soft (thiols) heteroatomic nucleophiles readily react with chlorotetrazines. On the other hand, one may notice that the application field of the HSAB theory has been recently seriously questioned, especially in the case of bidentate nucleophiles.<sup>11</sup>

In this article, we demonstrate that indeed, the conditions for nucleophilic attack on tetrazines are probably not determined by the hard/soft character of the nucleophiles, but rather depend on different considerations like the relative kinetics of competing reactions, among which the often neglected electron transfer. We have found that the  $S_NAr$  reaction on the tetrazine ring is strongly dependant on temperature, and, under carefully controlled conditions, the selectivity of the substitution reaction could be reversed, taking place on the carbon atom instead of the nitrogen. We report here several example of  $S_NAr$  substitution on chlorotetrazines with alkyl lithium reagents, leading to various new alkyl tetrazines. In addition, we also studied their photophysical and electrochemical properties. It is worth noticing that, while we were performing this work, an interesting extension of the classical Pinner method using Lewis acids appeared and provided a concurrent useful way of elaboration of dialkyltetrazines.<sup>12</sup>

## Results and discussion

We have tested the reaction of butyllithium with various chlorotetrazines, both at low temperature ( $-78\text{ }^\circ\text{C}$ ), and at  $0\text{ }^\circ\text{C}$ . The results were striking in the fact that at low  $T$ , the main observation was degradation of the tetrazines, along with a small amount of C-substitution products. On the other hand, when the reaction was performed at  $0\text{ }^\circ\text{C}$ , moderate yields of C-substitution were obtained exclusively on the C-Cl position, without any aza-addition products or  $S_NAr$  on the other carbon (Table 1).

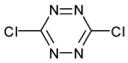
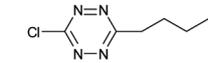
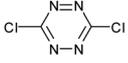
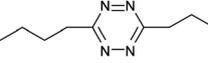
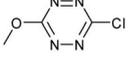
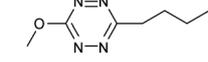
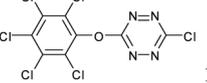
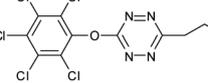
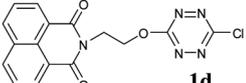
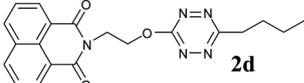
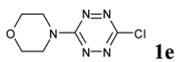
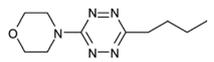
The reactivity of tetrazines towards organometallic reagents, is not trivial at all. These very reactive nucleophiles, which can

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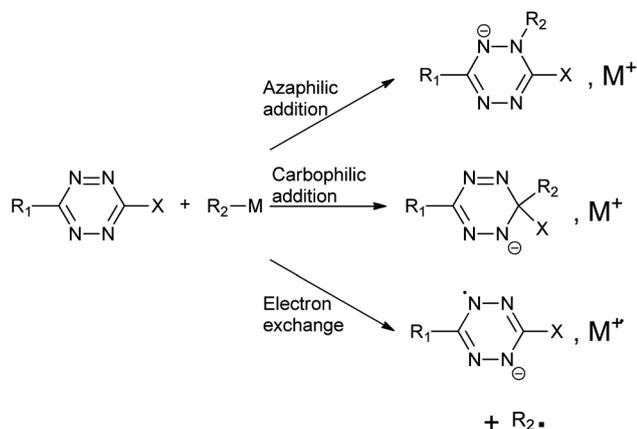
Table 1 Reaction yields of *n*-butyl-*s*-tetrazine<sup>a</sup>

Reactant	Product	Yield/%
		35
		16 <sup>b</sup>
		52
		30
		18
		45

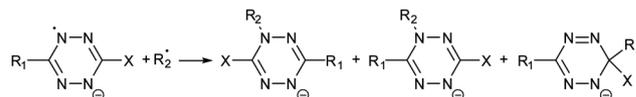
<sup>a</sup> Reaction conditions: *n*-BuLi (1.2 eq.) in THF at 0 °C. <sup>b</sup> 2.4 equivalents of *n*-BuLi were used.

attack on both reactive places on the tetrazine ring, are also good electron donors. This opens the possibility of electron transfer which is likely to be a pathway of consideration with tetrazines since they are strongly electron-deficient rings. Hence, a competition between three possible reactional pathways (Scheme 1) could occur depending on the temperature.

This was an obvious reasoning regarding competition between nucleophilic attack and electron transfer, since it has long been remarked that in analogous cases in heterocyclic chemistry electron transfer was strongly favoured at low temperatures, while nucleophilic attack became dominant upon rising *T*. This has been thoroughly discussed, especially in the case of S<sub>N</sub>Ar reactions on activated benzenoid aromatics within several articles from the Lund's group past work.<sup>13</sup> In addition, while an initial electron transfer usually leads to



Scheme 1 Possible reaction pathways between *s*-tetrazine and a nucleophile.



Scheme 2 Possible addition sites of a radical on a stable *s*-tetrazine anion-radical.

substitution products when the initially produced anion-radical can quickly expell a leaving anionic group, on the other hand the production of a relatively stable anion-radical always leads to aza-addition products (Scheme 2) as demonstrated in the case of fluorenone.<sup>14</sup> We have shown in the past<sup>15</sup> that tetrazines anion-radicals are always stable, even in the case of dichloro-tetrazine, a very unusual situation triggered by the very high electron affinity of this peculiar heterocycle.

Altogether, the aza-addition can proceed, as shown on Scheme 1, both by direct attack on the nitrogen atom of the tetrazine, or on the other hand through a first electron transfer step, followed by coupling between the anion-radical and the radical created after the electron transfer step. Since, according to Kotschy,<sup>9</sup> aza-addition products are obtained at low *T*, it is likely that they are obtained through an electron transfer-radicals coupling reaction instead of a direct attack on a nitrogen atom. As can be seen from Table 1, at 0 °C, the C-substitution tolerates several other different groups on the remaining carbon of the tetrazine ring with reasonable yields. Only the disubstitution by butyl carbanions occurs with a low yield, while the reason for this is not obvious.

We have investigated the physicochemical characteristics of the new tetrazines obtained, namely their absorption, fluorescence and reduction potential. Since alkyl groups do not exhibit a mesomeric donor character, which could raise the π-orbital of the tetrazine ring close to the LUMO, all tetrazines substituted by an alkyl group and an alkoxide or two alkyl groups are fluorescent. Typical fluorescence spectra are given in Fig. 1 and show that the inductive effect of the *n*-butyl induces a slight bathochromic effect.

All spectroscopic and electrochemical data of the new tetrazines are reported in the Table 2. In order to get rid of any perturbation due to the “antenna” effect in compounds **1d** and **2d**, the excitation was made in the visible absorption band. It can be observed that in some occasions very high fluorescence

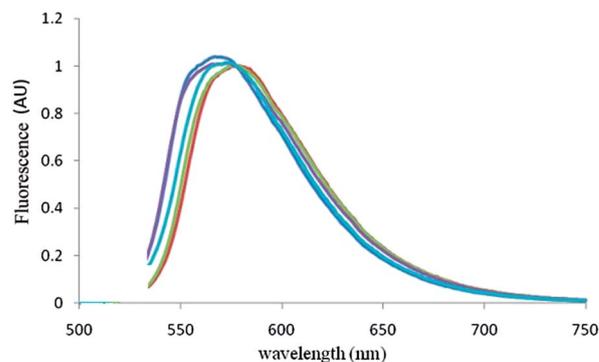


Fig. 1 Fluorescence spectra for compounds **2a** (purple), **3a** (red), **2b** (green), **2c** (blue) and **2d** (light blue) in dichloromethane;  $\lambda_{\text{ex}} = 520 \text{ nm}$ .

Table 2 Spectroscopic characteristics of butyl-s-tetrazines and their chloro counterparts recorded in dichloromethane ( $C \approx 10^{-6}$  M)

Compound	$\lambda_{\text{abs}}/\text{nm}$	$\epsilon/\text{L mol}^{-1} \text{cm}^{-1}$	$\lambda_{\text{em}}/\text{nm}$	$\phi_{\text{F}}$	$\tau_{\text{F}}/\text{ns}^a$	$E^{\circ}/\text{V}^b$
1a <sup>c</sup>	515	460	551; 567	0.14	58	-0.68
1b <sup>c</sup>	520	1900	567	0.38	160	-0.99
2a	520	730	563 <sup>d</sup>	0.52	159	-0.87
3a	528	660	576 <sup>e</sup>	0.14	39	-1.19
2b	526	520	576 <sup>f</sup>	0.21	45	-1.19
1c <sup>g</sup>	518	822	566	0.09	—	-0.63
2c	525	540	572 <sup>h</sup>	0.37	112	-0.92
1d <sup>i</sup>	517	400	562	0.32	158	-0.86
2d	526	180	572 <sup>f</sup>	0.18	59	-1.63
2e	425; 529	720; 320	—	—	—	-1.21

<sup>a</sup>  $\lambda_{\text{ex}} = 520$  nm. <sup>b</sup> vs.  $\text{Ag}/10^{-1}$  M  $\text{Ag}^+$ . <sup>c</sup> Data taken from ref. 15. <sup>d</sup>  $\lambda_{\text{ex}} = 520$  nm. <sup>e</sup>  $\lambda_{\text{ex}} = 528$  nm. <sup>f</sup>  $\lambda_{\text{ex}} = 526$  nm. <sup>g</sup> Data taken from ref. 6b. <sup>h</sup>  $\lambda_{\text{ex}} = 525$  nm. <sup>i</sup> Data taken from ref. 16.

yields are obtained from dissymmetrical alkyl tetrazines; for example tetrazine 2a has the highest fluorescence yield known to date. Similarly to previously observed, the symmetrical tetrazines display lower yields in the 15% range, which tends to demonstrate an influence of the dipole moment on the fluorescence yield.

As previously observed,<sup>15,16</sup> all the new tetrazines can be reversibly reduced to their stable anion radical, which does not show any tendency to expel a chloride anion, when this is possible, even in the case where a donor alkyl group is present on the other side of the molecule. The redox potentials are shifted to more negative values when an alkyl chain replaces an electron withdrawing group, as it could be expected.

## Conclusions

We have described a new way of preparing dissymmetrical alkyl tetrazines starting from chlorotetrazines, through a general nucleophilic substitution method with organolithium reagents. We have shown that control of the reaction temperature around 0 °C was essential to the success of the reaction, which tends in addition to show that the previously observed azaphilic addition is likely to proceed through a two-step mechanism involving a first electron transfer followed by a coupling step between the radical and the anion-radical initially formed. Some of the new tetrazines formed display in addition among the highest fluorescence yields observed in this family of compounds.

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