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SELECTIVE NUCLEOPHILIC SUBSTITUTIONS ON TETRAZINES

Zoltán Novák, Beatrix Bostai, Márton Csékei, Krisztián Lőrincz, and András Kotschy*

Department of General and Inorganic Chemistry, Eötvös Loránd University, Pázmány Péter s. 1/A, H-1117 Budapest, Hungary; kotschy@para.chem.elte.hu

Abstract – A series of tetrazine derivatives bearing a leaving group were reacted with different nucleophiles to undergo either the expected substitution reaction or an unexpected exchange of the other substituent of the tetrazine ring selectively. The influence of the choice of nucleophile as well as the substituents on the tetrazine was examined in detail and the interpretation of the results was also supported by quantum chemical calculations.

INTRODUCTION

The chemistry of tetrazines has gained increased attention in the last decades,[1] due mostly to their applications in organic synthesis,[2-6] crop protection[7,8] and pyrotechnic applications.[9-11] A major limitation of their use is however the small number of non-symmetrically substituted tetrazines which is mostly due to the difficulty of their preparation. The problematic step of their synthesis is usually the formation of the tetrazine core from the appropriately substituted carboxylic acid derivatives, that is biased by low yield and a difficult separation procedure. An alternative approach is utilizing the fact that the presence of the four nitrogen atoms in the tetrazine core leads to an increased reactivity towards nucleophiles. These reactions however were mostly limited to nitrogen[12-16] and oxygen[17-20] nucleophiles so far, and there are only a few reports on the use of carbon nucleophiles.[21-23] Some of the intermediates formed through nucleophilic addition[12] also require a subsequent oxidation to the aromatic product, which limits the number of substituents that are tolerated. An optimal solution to this problem could be the use of tetrazines that bear two leaving groups and on treatment with nucleophiles undergo sequential displacement.

Such systems, if easily available, would allow the selective preparation of a series of non-symmetrically substituted tetrazines. Their use, on the other hand, also posts some questions that should be answered: i) is the displacement of the first leaving group selective regardless of the nucleophile used ? ii) does the

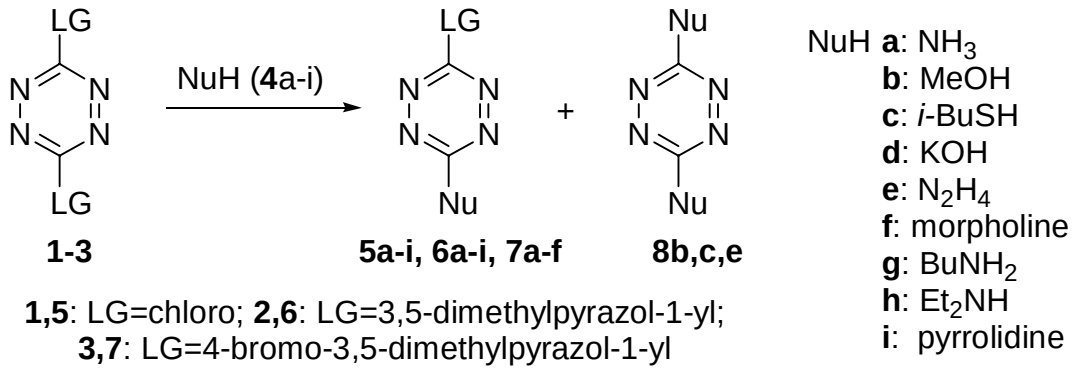
selectivity of the second nucleophilic displacement depend on the nature of the substituent introduced in the first step ?

To answer these questions we reacted three easily available tetrazine derivatives (**1-3**) with a series of different nucleophiles (**4a-i**) in the hope of achieving selective displacement of one of the leaving groups. Following these reactions we chose a representative sample of the formed products that still retain one of the leaving groups (**5a-c**, **6a-c**, **7a-c**) and reacted them with potassium hydroxide and hydrazine hydrate to determine the site of the attack of the incoming reagent.

RESULTS AND DISCUSSION

The three symmetrical tetrazine derivatives selected for the first set of reactions included 3,6-dichlorotetrazine (**1**)[7], 3,6-bis(3,5-dimethylpyrazol-1-yl)tetrazine (**2**)[24] and its brominated derivative 3,6-bis(4-bromo-3,5-dimethylpyrazol-1-yl)-tetrazine (**3**).[14] Their preparation utilizes the same, easily accessible starting material, 1,4-dihydro-3,6-bis(3,5-dimethylpyrazol-1-yl)-tetrazine,[24] which is either reacted with hydrazine and chlorine to give **1**, or oxidized by nitrous gases to **2** and further brominated by NBS to give **3**.

In the first set of experiments 3,6-dichlorotetrazine (**1**) was reacted with a series of nucleophiles (**4a-i**). In agreement with our expectations the chlorine atoms of **1** are both good leaving groups although the introduction of electron donating substituents led to a marked decrease of reactivity, which in turn allowed for the isolation of selectively substituted derivatives **(5a-b**,**f-i)** (Table 1.).



Scheme 1.

Table 1. The preparation of tetrazines by nucleophilic substitution. Isolated yields of the mono- and disubstituted tetrazines from the reaction of **1-3** with nucleophiles (**4a-i**).

tetrazine	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**2**	**2**	**2**	**2**
NuH	**4a**	**4b**	**4c**	**4f**	**4g**	**4h**	**4i**	**4a**	**4b**	**4c**	**4d**
monosubstitution	78 %	52 %	5 %[a]	83%	65%	89%	68%	96%	80%	66%	78%
disubstitution		39 %	76%						3%[a]	12%	

tetrazine	**2**	**2**	**2**	**2**	**2**	**3**	**3**	**3**	**3**	**3**	**3**
NuH	**4e**	**4f**	**4g**	**4h**	**4i**	**4a**	**4b**	**4c**	**4d**	**4e**	**4f**
monosubstitution	85%	77%	91%	46%	74%	72%	63%	23%	81%	67%	83%
disubstitution							8%[a]	43%			

[a]Based on the NMR spectra of the crude product.

The use of hydrazine or potassium hydroxide led only to decomposition (polymerization), while methanol (**4b**) and isobutyl mercaptan (**4c**) showed a marked tendency for disubstitution, giving higher amounts of **8b** or **8c** even when used in a 1:1 ratio. In case of the methoxy substitution (**8b**) the highest selectivity was obtained by the slow addition of a 1:1 mixture of the methanol and triethylamine (used to bind the liberated HCl) to the solution of **1** in methyl *tert*-butyl ether (MTBE) and the reaction mixture was worked up straight after the addition. In case of isobutyl mercaptan (**4c**) only a minor amount (*ca*. 5%) of **5c** was formed and the rest of **1** was converted to the disubstituted product (**8c**). In order to prepare **5c** for the follow up studies we replaced one of the substituents in **8c** with hydrazine (a near quantitative reaction at ambient temperature using 2 eq. hydrazine hydrate) and converted this compound to **5c** in good yield by bubbling chlorine through its solution.[21] The selective substitution of one chlorine in **1** by amines (**4a**,**f-i**) proceeded readily by the addition of 2 eq. amine to **1** in MTBE and the products **(5a**,**f-i)** were isolated in good yield.

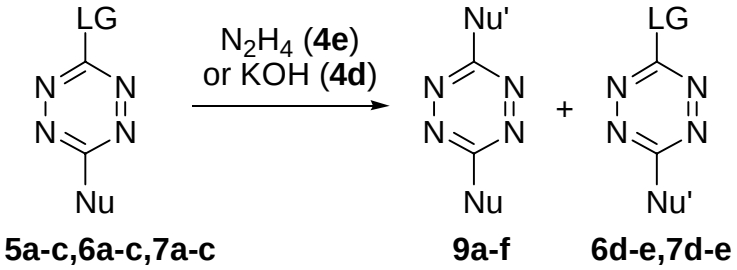
The nucleophilic displacement reactions on dipyrazolyltetrazine (**2**), in part already known from the literature,[15-24] showed an increased selectivity towards monosubstitution and resulted in the expected products (**6a-f**) in good yield. Of the nucleophiles used methanol, and isobutyl mercaptan were found to be the most reactive, where the reaction conditions had to be selected carefully. For example the highest selectivity in the reaction of **2** with methanol (**4b**) was achieved by the slow addition of the calculated amount of methanol to the solution of **2** in pyridine. The reagent in this series which showed a tendency to favour disubstitution even when being present in smaller than equivalent amounts was isobutyl mercaptan (**4c**). In this reaction the selectivity could only be improved by pushing the process to disubstitution (**8c**). Although undesired in our case but this convenient and high yielding process might open up a new route to 3,6-bis(alkylthio)- and arylthiotetrazines, the later class being only scarcely represented in the literature.[25,26] In a similar attempt **2** was treated with an excess of base in methanol as solvent but we were unable to convert it completely to **8b** as the prolonged reaction time or heating also initiated its decomposition.

The introduction of a bromine atom onto the leaving group on the tetrazine core (**3**) led only to a minor but marked increase in the reactivity of the tetrazine core. Amines (**4a,f**) and hydrazine (**4e**) that gave selective mono substitution with **2** behaved likewise when reacted with **3**. With other, more reactive nucleophiles (**4b,c**) the selectivity of the process deteriorated and larger amounts of the disubstituted products were

formed. Potassium hydroxide showed a clear preference for monosubstitution both with **2** and **3** which might be attributed to two factors: the increased electron density of the tetrazine ring in the primary substitution products (**6d, 7d**) and the fact that **6d** and **7d** are highly insoluble and precipitate from the reaction mixture as soon as they are formed.

After establishing that it is possible to achieve selective substitution on symmetrically substituted tetrazines, the reactivity of non-symmetrically substituted tetrazines towards nucleophiles was also examined (Scheme 2). Our selection included the tetrazines (**5a-c**, **6a-c**, **7a-c**) and the selected nucleophiles were the soft hydrazine (**4e**) and hard potassium hydroxide (**4d**).

The reactions were carried out in acetonitrile at room temperature treating the tetrazines with 1 equivalent of the appropriate nucleophile. The product distribution was determined from the reaction mixture after evaporating the volatiles under vacuum by NMR spectroscopic investigations in DMSO-d_6. The results are summarized in Table 2.



5: LG=chloro; **6**: LG=3,5-dimethylpyrazol-1-yl;
7: LG=4-bromo-3,5-dimethylpyrazol-1-yl

Scheme 2.

Table 2. Product distribution in the reaction of some selected tetrazines (**5a-c**, **6a-c**, **7a-c**) with different nucleophiles.[a]

tetrazine	**5a-c**	**6a**	**6b**	**6c**	**7a**	**7b**	**7c**
nucleophile	**4e**	**4e**	**4e**	**4e**	**4e**	**4e**	**4e**
"normal" substitution	dec.	100% **9a**[27]		100% **9c**	100% **9a**[27]		100% **9c**
"*ipso*" substitution	dec.		100% **6e**			100% **7e**	

tetrazine	**5a-c**	**6a**	**6b**	**6c**	**7a**	**7b**	**7c**
nucleophile	**4d**	**4d**	**4d**	**4d**	**4d**	**4d**	**4d**
"normal" substitution	dec.			34% **9f**			66% **6f**
"*ipso*" substitution	dec.	100% **6d**	100% **6d**	66% **6d**	100% **7d**	100% **7d**	34% **7d**

[a]Determined by the NMR spectral investigation of the crude product

Unfortunately – analogous to dichlorotetrazine – the chlorotetrazines (**5a-c**) gave only decomposition when reacted with hydrazine or potassium hydroxide. When tetrazines (**6a-c**) and (**7a-c**) were reacted with the

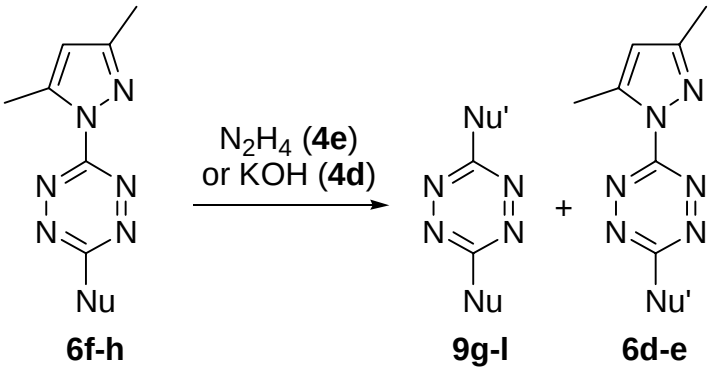
selected nucleophiles they all showed outstanding reactivity, but the course of the process depended both on the nature of the reagent and the leaving group. Towards the soft hydrazine the reactivity of the leaving groups decreased in the methoxy>pyrazolyl >amino, mercapto order. It was only **6b** and **7b** that gave "*ipso*"-substitution. In each other case the pyrazolyl moiety of the tetrazine was exchanged selectively. The reaction mixtures in most cases contained some unreacted starting material too.

When the hard nucleophile potassium hydroxide was reacted with the selected tetrazines the order of leaving groups changed to methoxy, amino>bromopyrazolyl> mercapto >pyrazolyl. In contrast with the previous case the only selective transformation we could initiate was the "*ipso*"-substitution. The fact that the methoxide group acted as a superior leaving group might be attributed to its lower basicity (compared to the pyrazolide ion), whereas in the isobutylmercaptotetrazines (**6c, 7c**) steric factors could also influence the regioselectivity. In case of the amino group it is less clear that what drives the nucleophile to attack at C3 or C6. Our assumption is that besides the steric factors (*vide infra*) the ability of the $-NH_2$ group to participate in a tautomeric equilibrium might also enhance the electrophilic nature of C6.

To obtain a more detailed picture of the factors influencing the regioselectivity of the nucleophilic substitution reactions on non-symmetrically substituted tetrazines we reacted a series of 6-amino substituted 3-dimethylpyrazolyltetrazines with hydrazine and potassium hydroxide (Scheme 4). Our selection included the butylamino (**6g**), diethylamino (**6h**) and morpholino (**6f**) derivatives. The results are summarized in Table 3.

The results show a clear trend, especially when the reactions of the 6-amino analogue (**6a**) are also included in the comparison. With the soft hydrazine all tetrazines react at C3 and give displacement of the pyrazole unit. The crude reaction mixture of **6g** and **6h** also show the presence of another product, a tetrazine where the pyrazole is exchanged to a hydrogen, with a characteristic singlet signal for its hydrogen in the ^{1}H NMR spectra at 9.69 and 9.46 ppm respectively with the corresponding ^{13}C NMR signals at 152.46 and 151.99 ppm. We attribute this unexpected but not unprecedented transformation to the redox character of hydrazine.[28]

In the reaction of the aminotetrazines and potassium hydroxide we established that the more substituents are present on the nitrogen atom attached to the tetrazine, the worse leaving group it is. At one end in **6a** only the amino group acted as a leaving group while at the other end in the morpholino analogue (**6f**) the pyrazole ring was replaced selectively. In order to establish the rationale behind this trend a series of quantum chemical calculations were carried out modelling the reaction of ammonia with these four different tetrazines (**6a**, **6f**, **6g**, **6h**).[29]



Scheme 3.

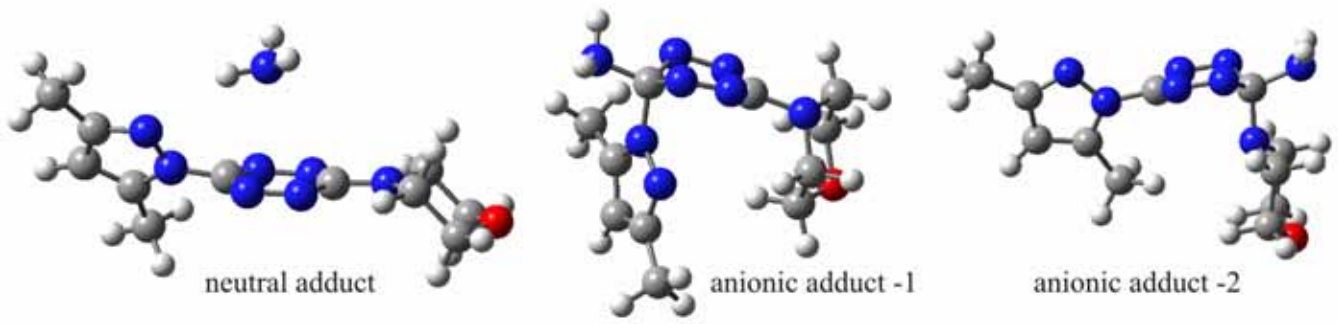
Table 3. Product distribution in the reaction of some 6-amino-3-(3',5'-dimethypyrazol-1'-yl)tetrazines (**6f-h**) with different nucleophiles.[a]

tetrazine	**6f**	**6g**	**6h**	**6f**	**6g**	**6h**
nucleophile	**4e**	**4e**	**4e**	**4d**	**4d**	**4d**
"normal" substitution	100% **9g**	100% **9h**[b]	100% **9i**[b]	100% **9j**	29% **9k**	57% **9l**
"*ipso*" substitution					71% **6d**	43% **6d**

[a]Determined by the NMR spectral investigation of the crude product

[b]Converts partially to the appropriate monosubstituted tetrazine.

Our first working hypothesis formulated that the substitutions follow an addition-elimination path and as the leaving groups might also act as nucleophiles, the product distribution would be determined by the relative energies of the intermediates (thermodynamic control). In the first step of calculations ammonia was added onto the C-3 and C-6 positions of the tetrazines but the optimized structures revealed the preference of all these tetrazines (**6a**,**f**,**g**,**h**) to form a neutral adduct in which the ammonia is coordinated to the tetrazine core through its lone pair from the top of the ring (Scheme 4.). This surprising behaviour might be attributed to the electron deficient nature of the tetrazine core.[30]



Scheme 4. The optimized structure of the neutral and the anionic adducts between ammonia and 6-morpholino-3-(3',5'-dimethylpyrazol-1'-yl)tetrazine (**6f**).

Since the formation of covalent adducts between ammonia and the tetrazines was ruled out by the calculations we assumed that at some stage the nucleophile (ammonia) might be deprotonated in the

process. This would lead to the formation of anionic adducts with an amide group attached either to the C3 or the C6 atom. In the next series of calculations an amide ion was attached to the C-3 or C-6 positions of the tetrazines, and after the geometry optimizations we obtained the expected structures (*e.g.* the adducts depicted in Scheme 4). Comparison of their calculated heats of formation (Table 4) showed that the intermediates with the amide attached next to the pyrazole (C3) are energetically favoured over the attachment of the amide ion to C6. In the light of this finding we presume that the hydrazine approaches the tetrazine from the top forming a donor-acceptor complex. This complexation increases the acidity of the HN bonds in hydrazine and facilitates its deprotonation. The formed anion attacks the tetrazine core and leads selectively the thermodynamically more favoured substitution products.

Table 4. The calculated differences of the heats of formations for the different anionic amide adducts[a] (kJ/mol, I-PCM solvent model-acetonitrile) and the atomic charges for the sites of attack of the different 6-substituted 3-(3',5'-dimethylpyrazol-1'yl)tetrazines (all calculated on the HF/6-311G level)

	6a	**6g**	**6h**	**6f**
ΔH_f(A2)-ΔH_f(A1)	14.319	13.164	18.886	7.8915
Charge at C3	0.675	0.668	0.709	0.679
Charge at C6	0.750	0.750	0.756	0.789

[a]A1: addition of amide ion onto C-3; A2: addition of amide ion onto C-6.

The reaction of the same tetrazines with potassium hydroxide shows a more complex picture. We expect that the thermodynamically favored route in this series is also the replacement of the pyrazole unit. The facts that in most cases the exchange of the amine is also observed and that the selectivity of the process shows a marked trend suggest the presence of competing driving forces. Contrary to hydrazine which presumably approaches the tetrazine ring as a neutral nucleophile the hydroxide ion has a negative charge. Theoretical examination of the starting tetrazines (**6a,f,g,h**) revealed (Table 4) that the carbon atom bearing the amine substituent (C6) has a more positive character than the carbon bearing the pyrazole (C3) in each of them. This suggest that the approach of the hydroxide ion should be directed through electrostatic interaction to C6 (kinetic control).[31]

The recognition that in the reaction of the selected tetrazines with potassium hydroxide normal substitution is favoured thermodynamically and "*ipso*"-substitution is favoured kinetically still leaves open the question of the observed trend in selectivity. We don't have a clear explanation for this but believe that the different steric demand of the amine groups might play a key role in determining the outcome of the process. The smaller is the amine substituent, the smaller steric hindrance it exhibits towards the incoming nucleophile It is important to note however, that according to the calculations both substituents attach to the tetrazine ring through a planar nitrogen atom,[32] which leaves only little room for differentiation.

In summary, we established that 3,6-dichlorotetrazine (**1**), 3,6-bis(3,5-dimethylpyrazol-1-yl)tetrazine (**2**) and 3,6-bis(4-bromo-3,5-dimethylpyrazol-1-yl)tetrazine (**3**) undergo nucleophilic substitution with a variety of nucleophiles to give mono- and/or disubstituted products depending on the nature of the leaving group and the nucleophile used. Some of the nucleophiles introduced (e.g. alkoxides, mercaptans) were found to act as leaving groups in subsequent nucleophilic substitution reactions. In case of aminotetrazines the selectivity of the second substitution was largely dependent on the nature of the amine substituent and the nucleophile used. The origin of the observed regioselectivity was rationalized using quantum chemical calculations.

EXPERIMENTAL

Melting points were determined on a hotplate and are uncorrected. ^{1}H NMR spectra were measured at 250 MHZ and ^{13}C spectra at 62.5 MHZ. NMR shifts are given in ppm. For ^{1}H NMR spectra the residual peak of $CHCl_3$ (7.26 ppm) and CH_3SOCH_3 (2.50 ppm) were used as the internal reference, while for ^{13}C NMR spectra the central peak of $CDCl_3$ (77.0 ppm) and the central peak CD_3SOCD_3 (39.43 ppm) were used as the reference. ^{15}N-NMR signals were indirectly obtained by detection of protons (2D-HMBC) and their chemical shifts are given upfield from liquid nitromethane as external reference Silica gel was used for flash column chromatography.

6-Amino-3-chlorotetrazine (5a):[9] 1.00 g (6.62 mmol) of 3,6-dichlorotetrazine (**1**) was dissolved in 30 mL of methyl *tert*-butyl ether (MTBE). Ammonia was bubbled through the solution at 25^{o}C for 10 min. The suspension was filtered through a Celite pad. After removal of the solvent the crude product was purified by silica gel column chromatography using hexane-ethyl acetate (10:1) eluent mixture to give 679 mg of an orange solid. Crude product was recrystallised from cyclohexane. Yield : 78%. mp: 94-97^{o}C; ^{1}H NMR ($CDCl_3$), δ: 8.25 (s, 2H); ^{13}C NMR ($CDCl_3$), δ: 163.1, 158.9.

3-Chloro-6-methoxytetrazine (5b): 0.5 g (3.30 mmol) of 3,6-dichlorotetrazine (**1**) was dissolved in 9 mL of acetonitrile. At 25^{o}C 0.190 g (3.51 mmol) of $NaOCH_3$ in 3 mL of methanol was added dropwise to the solution. The reaction mixture was stirred at 25^{o}C until completion by TLC. After removal of the solvent the crude product was purified by silica gel column chromatography using hexane-ethyl acetate (10:1) eluent mixture to give 250 mg of an orange solid. Yield: 52%. mp: 66-68^{o}C; ^{1}H NMR ($CDCl_3$), δ: 4.33 (s, 3H); ^{13}C NMR ($CDCl_3$), δ: 166.9, 164.4, 57.4. MS (70 eV); *m/z (%)*: 149 (10), [$M^{+\bullet}$]; 148 (30); 146 (60); 83 (30); 76 (50); 62 (40); 57 (100); 56 (45); 48 (40); 35 (30).

3-Chloro-6-isobutylmercaptotetrazine (5c): 0.45 g (2.25 mmol) of 3-hydrazino-6-isobutylmercapto-tetrazine (**9c**) was dissolved in 10 mL of acetonitrile. Dry chlorine was bubbled through the solution at 25^{o}C for 10 min. The suspension was filtered through a Celite pad. After removal of the solvent the crude product was purified by silica gel column chromatography using hexane-ethyl acetate (10:1) eluent mixture to give

230 mg of a red oil as product. Yield: 50%. ^{1}H NMR ($CDCl_3$), δ: 3.2 (d, 2H, *J*= 6.75 Hz), 2.13-1.98 (m, 1H), 1.10 (d, 6H, *J*= 6.75 Hz); ^{13}C NMR ($CDCl_3$), δ: 176.4, 165.4, 39.2, 28.0, 21.8; IR(KBr) ν_{max}: 2962, 2930, 2872, 1465, 1387, 1234, 1169, 1132, 1052, 885 cm^{-1}; Anal. Calcd for $C_6H_9N_4ClS$: C, 35.21; H, 4.43; N, 27.37; Found: C, 34.96; H, 4.40; N, 27.61.

General procedure for the synthesis of 3-chloro-6-amino substituted tetrazines (5f-i): To one equivalent of 3,6-dichlorotetrazine (**1**) dissolved in 25 mL of MTBE 2 equivalents of the appropriate amine were added dropwise at rt. After completion of the reaction the solvent was evaporated and the crude product was purified by the given method.

3-Chloro-6-morpholinotetrazine (5f)[7]: 0.732 g (4.85 mmol) of **1** afforded 810 mg of **5f** as red solid after recrystallization from cyclohexane. Yield : 83%. mp: 115-117^{o}C ^{1}H NMR ($CDCl_3$), δ: 3.98-3.95 (br, 4H), 3.85-3.81(br, 4H); ^{13}C NMR ($CDCl_3$), δ: 160.3, 159.5, 66.2, 43.8.

6-Butylamino-3-chlorotetrazine (5g): 1.00 g (6.62 mmol) of **1** gave 802 mg of **5g** as a red solid after silica gel column chromatography using hexane-ethyl acetate (10:1) eluent mixture. Yield : 65%. mp: 28-30^{o}C; ^{1}H NMR ($CDCl_3$), δ: 5.90 (br, 1H), 3.60 (q, 5H, *J*=6.0 Hz), 1.75-1.64 (m, 2H), 1.52-1.38 (m, 2H), 0.97 (t, 3H, *J*=7.5 Hz); ^{13}C NMR ($CDCl_3$), δ: 159.1, 158.1, 41.5, 31.0, 19.9, 13.7; IR(KBr) ν_{max}: 2965, 2930, 2863, 1468, 1389, 1141, 1077, 851 cm^{-1}; Anal. Calcd for $C_6H_{10}N_5Cl$: C, 38.41; H, 5.37; N, 37.33; Found C, 38.59; H, 5.31; N, 36.99.

3-Chloro-6-diethylaminotetrazine (5h): 1.00 g (6.62 mmol) of **1** afforded 1.09 g of **5h** as red oil after column chromatography Yield : 89%; ^{1}H NMR ($CDCl_3$), δ: 3.75 (q, 4H, *J* = 7.25 Hz), 1.24 (t, 6H, *J*=7.0 Hz); ^{13}C NMR ($CDCl_3$), δ: 159.5, 158.7, 42.6, 12.2; IR(KBr) ν_{max}: 2979, 2938, 2876, 2356, 2139, 1559, 1445, 1304, 1206, 953 cm^{-1}; Anal. Calcd for $C_6H_{10}N_5Cl$: C, 38.41; H, 5.37; N, 37.33; Found C, 38.52; H, 5.41; N, 37.07.

3-Chloro-6-pyrrolidinotetrazine (5i)[7]: 1.00 g (6.62 mmol) of **1** afforded 880 mg of **5i** as a red solid after recrystallization from cyclohexane. Yield : 68%. mp: 85-87^{o}C; ^{1}H NMR ($CDCl_3$), δ: 3.73-3.68 (br, 4H), 2.13-2.07(br, 4H); ^{13}C NMR ($CDCl_3$), δ: 158.9, 158.7, 46.9, 25.2.

6-Amino-3-(3,5-dimethylpyrazol-1-yl)tetrazine (6a)[24]: 5.00 g (18.5 mmol) of 3,6-bis(3,5-dimethyl-pyrazol-1-yl)tetrazine (**2**) was dissolved in toluene (115 mL) and ammonia gas was bubbled through the solution for 1 h. The precipitated product was filtered and washed with ether and recrystallization from ciklohexane give 3.38 g of **6a**. Yield: 96%. mp: 208-209^{o}C; ^{1}H NMR(DMSO-d_6), δ: 8.18 (s, 2H), 6.16 (s, 1H), 2.37 (s, 3H), 2.20 (s, 3H). ^{13}C NMR (DMSO-d_6), δ: 163.3, 157.3, 150.2, 141.5, 108.6, 13.6, 12.4. MS (EI, 70eV) m/z (ion, relative intensity %): 247(26), 122(100), 121(95), 106(31), 99(11), 80(27), 67(34), 55(56), 53(59). IR(KBr) ν_{max} : 3357, 3275, 3182, 1624, 1572, 1521, 1483, 1453, 1396, 1288, 1077, 1044, 1023, 976, 959, 858, 790, 770, 611 cm^{-1}; Anal. Calcd for $C_7H_9N_7$: C, 43.97; H, 4.74; N, 51.28. Found: C, 44.21; H, 4.78; N, 50.04.

3-(3,5-Dimethylpyrazol-1-yl)-6-methoxytetrazine (6b)[14]**:** 0.270 g (1 mmol) of 3,6-bis(3,5-dimethyl-pyrazol-1-yl)tetrazine (**2**) was dissolved in 4 mL of pyridine. The solution was heated up to 55°C and after the addition of the mixture of 2 mL of pyridine and 0.3 mL of methanol it was stirred until completion (4 h). The solvent was evaporated and the crude product was purified by silica gel column chromatography using hexane-ethyl acetate (10:1) eluent mixture affording 165 mg of pink solid as product. Yield: 80%. mp.:157-158°C ^{1}H NMR (DMSO-d_6), δ: 6.42 (s, 1H), 4.39 (s, 3H), 2.64 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (DMSO-d_6), δ: 166.1, 158.7, 152.5, 142.3, 109.9, 56.7, 13.6, 13.0. MS (70 eV; EI); *m/z (%)*: 207 (20 %, [$M^{+\bullet}$], 206 (90%), 121 (100%), 106 (85%), 80 (90 %), 53 (90%).

3-(3,5-Dimethylpyrazol-1-yl)-6-isobutylmercaptotetrazine (6c): 0.270 g (1 mmol) of 3,6-bis(3,5-dimethylpyrazol-1-yl)tetrazine (**2**) was dissolved in 7 mL of acetonitrile. A mixture of 120 μL (97.9 mg, 1.1 mmol) of isobutyl mercaptan and 280 μL (203 mg, 2 mmol) of triethylamine was added to the solution followed by stirring at rt for 15 h. After the removal of the solvent the crude product was purified by silicagel column chromatography using hexane-ethyl acetate (10:1) eluent mixture affording 175 mg of red solid as product. The crude product was recrystallized from cyclohexane. Yield: 66.3%. mp: 87-88°C; ^{1}H NMR ($CDCl_3$), δ: 6.14 (s, 1H), 3.26 (d, 2H, J = 6.7Hz), 2.65 (s, 3H), 2.35 (s, 3H), 2.09-1.98 (m, 1H), 1.10 (d, 6H, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$), δ: 174.6, 172.9, 154.3, 143.6, 124.5, 111.9, 39.5, 28.6, 22.2, 14.9, 14.2; IR(KBr) ν_{max}: 2959, 2925, 2868, 1683, 1585, 1489, 1461, 1399, 1367, 1197, 1046, 971, 911 cm^{-1}; Anal. Calcd for $C_{11}H_{16}N_6S$: C, 49.98; H, 6.10; N, 31.79; Found: C, 50.31; H, 6.14; N, 31.53.

Potassium 6-(3,5-Dimethylpyrazol-1-yl)tetrazin-3-olate (6d): 0.270 g (1 mmol) of 3,6-bis(3,5-dimethylpyrazol-1-yl)tetrazine (**2**) was dissolved in 5 mL of dichloromethane. 56 mg (1mmol) of KOH was added to the solution and it was stirred vigorously for 2 h. The suspension was filtered and the solid was purified by washing with ether to give 180 mg of purple solid as pure product. Yield: 78%. mp: 315-317°C; ^{1}H NMR ($CDCl_3$), δ: 6.03 (s, 1H), 2.22 (s, 3H), 2.16 (s, 3H); ^{13}C NMR ($CDCl_3$), δ: 164.7, 152.7, 147.9, 140.1, 106.2, 13.2, 11.3; IR(KBr) ν_{max}: 3452, 3310, 2924, 1694, 1592, 1489, 1269, 1087, 1046, 1024, 971, 766 cm^{-1}; Anal. Calcd for $C_7H_7N_6KO$: C, 36.51; H, 3.06; N, 36.50; Found C, 36.37; H, 3.35; N, 34.91.

6-(3,5-Dimethylpyrazol-1-yl)-3-hydrazinotetrazine (6e)[15]**:** 1.00 g (3.7 mmol) of 3,6-bis(3,5-dimethyl-pyrazol-1-yl)tetrazine (**2**) was dissolved in 10 mL of acetonitrile. 200 μL (200 mg, 6.25 mmol) of hydrazine hydrate was added to the solution and it was stirred for 15 min. The precipitated red solid was filtered to give 645 mg of product. Yield: 85%. mp.: 146-148°C. ^{1}H NMR($CDCl_3$), δ: 9,75 (br, 1H), 6.17 (s, 1H), 4.60 (br, 2H), 2.37 (s, 3H), 2.21 (s, 3H); ^{13}C NMR ($CDCl_3$), δ: 162.9, 156.9, 149.9, 141.2, 108.3, 13.2, 12.0.

General procedure for the preparation of 3-(3,5-dimethylpyrazol-1-yl)-6-amino substituted tetrazines (6f-i): A solution of 3,6-bis(3,5-dimethyl-pyrazol-1-yl)tetrazine (**2**) in toluene (20 mL/g) was treated with 1 equivalent of the appropriate amine and stirred at rt. After completion of the reaction the solvent was removed under reduced pressure and purification gave the desired products as solids.

3-(3,5-Dimethylpyrazol-1-yl)-6-morpholinotetrazine (6f)[14]**:** 2,16 g (8.0 mmol) of **2** gave 1.60 g of **6f** as red crystals after recrystallization from n-heptane. Yield: 77%. mp: 114-116°C; ^{1}H NMR($CDCl_3$), δ: 6.08 (s, 1H), 4.01 (t, 4H, *J* = 4.9 Hz), 3.85 (t, 4H, *J* = 4.9 Hz), 2.55 (s, 3H), 2.33 (s, 3H); ^{13}C NMR ($CDCl_3$), δ: 160.9, 157.4, 152.6, 142.3, 110.1, 66.8, 44.4, 14.1, 13.9; MS (EI, 70eV) m/z (relative intensity, %): 261(26), 121(52), 67(67), 55(100). IR(KBr) ν_{max} : 2990, 2918, 2858, 1572, 1534, 1484, 1450, 1396, 1360, 1305, 1261, 1121, 1084, 944 cm^{-1}; Anal. Calcd for $C_{11}H_{15}N_7O$: C, 50.57; H, 5.79; N, 37.52. Found: C, 50.75; H, 5.92, N, 37.71.

6-Butylamino-3-(3,5-dimethylpyrazol-1-yl)tetrazine (6g): 5.00 g (18.5 mmol) of **2** gave 4.160 g **6g** as red solid after recrystallization from n-heptane. Yield: 91.0%. mp: 93-95°C; ^{1}H NMR(DMSO-d_6), δ: 8.83 (br, 1H), 6.20 (s, 1H), 3.50 (q, 2H, *J* = 5.8 Hz), 2.42 (s, 3H), 2.25 (s, 3H), 1.69-1.61 (m, 2H), 1.48-1.39 (m, 2H), 0.96 (t, 3H, *J* = 7.3 Hz). ^{13}C NMR (DMSO-d_6), δ: 161.1, 156.5, 149.8, 141.1, 108.1, 74.6, 30.2, 19.4, 13.5, 13.1, 12.0. MS (EI, 70eV) m/z (relative intensity,%): 192(9), 191(63), 121(100), 106(54), 94(14), 80(26), 67(36), 54(47), 53(96). IR(KBr) ν_{max} :3255, 3066, 2965, 2932, 2862, 1588, 1485, 1435, 1366, 1304, 1145, 1097, 1068, 1045, 991, 956, 799, 704 cm^{-1}; Anal. Calcd for $C_{11}H_{17}N_7$: C, 53.42; H, 6.93; N, 39.65. Found: C, 53.44; H, 6.81; N, 38.22.

6-Diethylamino-3-(3,5-dimethylpyrazol-1-yl)tetrazine (6h)[14]**:** 1.00 g (3.70 mmol) of **2** gave 0.420 g (1.702 mmol) of **6h** as red crystals after silicagel column chromatography using hexane-ethyl acetate eluent mixture. Yield: 46%. mp: 66-68°C; ^{1}H NMR($CDCl_3$), δ: 5.99 (s, 1H), 3.16 (q, 4H, *J* = 7.3 Hz), 2.45 (s, 3H), 2.25 (s, 3H), 1.28 (t, 6H, *J* = 7.3 Hz). ^{13}C NMR ($CDCl_3$), δ: 168.4, 155.2, 151.0, 141.7, 108.8, 42.8, 14.0, 13.4, 11.7. MS (EI, 70eV) m/z (relative intensity, %): 247(22, $(M]^+$), 122(37), 99(30), 98(86), 83(100), 70(24), 67(25), 55(87). IR(KBr) ν_{max} : 3092, 2978, 2931, 1574, 1545, 1488, 1454, 1433, 1402, 1378, 1352, 1275, 1192, 1131, 1097, 1073, 1021, 971, 832, 748,576 cm^{-1}; Anal. Calcd for $C_{11}H_{17}N_7$: C, 53.42; H, 6.93; N, 39.65. Found: C, 53.12; H, 6.92, N, 39.01.

3-(3,5-Dimethylpyrazol-1-yl)-6-pyrrolidinotetrazine (6i)[14]**:** 1.00 g (3.70 mmol) of **1** gave 670 mg of **6i** as red crystals after recrystallization from n-heptane. Yield: 74%. mp: 120-122°C ^{1}H NMR ($CDCl_3$), δ: 6.03 (s, 1H), 3.95 (t, 4H, *J*=4.8 Hz), 3.79 (t, 4H, *J*=5.0 Hz), 2.50 (s, 3H), 2.28 (s, 3H); ^{13}C NMR ($CDCl_3$), δ: 160.2, 156.7, 151.9, 141.7, 109.5, 66.1, 43.7, 13.5, 13.3.

6-Amino-3-(2-bromo-3,5-dimethylpyrazol-1-yl)tetrazine (7a): 0.428 g (1 mmol) of 3,6-bis(4-bromo-3,5-dimethyl-pyrazol-1-yl)tetrazine (**3**) was dissolved in 10 mL of toluene and ammonia gas was bubbled through the solution for 30 min. The precipitated orange product was filtered and washed with ether to give 199 mg product. The crude product was recrystallized from acetonitrile. Yield: 72%. mp: 105-108°C; ^{1}H NMR (DMSO-d_6), δ: 3.30 (s, 2H); 2.39 (s,3H); 2.23 (s, 3H); ^{13}C NMR (DMSO-d_6), δ: 163.6; 150.4, 148.8, 139.7, 97.4, 12.4, 11.9. MS (70eV, EI): m/z (%): 272 (10%, $M^{+\bullet}$];271 (37); 269 (40); 199 (100); 201 (85); 120 (55); 93 (85); 79 (80); 42 (65); IR(KBr) ν_{max}: 3310, 3191, 3104, 2979, 2739, 1697, 1657, 1582, 1532,

1494, 1452, 1300, 1095, 1041 cm^{-1}; Anal. Calcd for $C_7H_8N_7Br$: C, 31.13; H, 2.99; N, 36.30; Found C, 31.69; H, 3.04; N, 36.25.

3-(2-Bromo-3,5-dimethylpyrazol-1-yl)-6-methoxytetrazine (7b): 0.428 g (1 mmol) of 3,6-bis(4-bromo-3,5-dimethyl-pyrazol-1-yl)tetrazine (**3**) was dissolved in 4 mL of pyridine. The solution was heated up to 55^oC and after the addition of a mixture of 2 mL of pyridine and 0.3 mL of methanol it was stirred until completion (4 h) The solvent was evaporated and the crude product was purified by silicagel column chromatography using hexane-ethyl acetate (10:1) eluent mixture affording 180 mg of pink solid as product. The crude product was recrystallized from acetonitrile. Yield: 63%. mp: 91-92 ^oC; ^1H NMR ($CDCl_3$), δ: 4.32 (s, 3H), 2.63 (s, 3H), 2.35 (s, 3H); ^{13}C NMR ($CDCl_3$), δ: 166.3, 151.9, 142.3, 140.2, 101.0, 56.9, 13.1, 12.5. IR(KBr) ν_{max}: 2960, 2922, 1566, 1503, 1446, 1410, 1381, 1063, 1007, 952 cm^{-1}; Anal. Calcd for $C_8H_9N_6OBr$: C, 33.70; H, 3.18; N, 29.48; Found: C, 33.48; H, 3.32; N, 29.04.

3-(2-Bromo-3,5-dimethylpyrazol-1-yl)-6-isobutylmercaptotetrazine (7c): 0.600 g (1.4 mmol) of 3,6-bis(4-bromo-3,5-dimethyl-pyrazol-1-yl)tetrazine (**3**) was dissolved in 12 mL of dichloromethane. A mixture of 160 μL (135 mg, 1.5 mmol) of isobutyl mercaptan and 284 mg (392 μL, 2.8 mmol) of triethylamine was added to the solution it was and stirred for 15 h at rt. After evaporation of the solvent the crude product was purified by silicagel column chromatography using hexane-ethyl acetate (10:1) eluent mixture affording 109 mg of red solid as product. The crude product was recrystallized from acetonitrile. Yield: 23%. mp: 56-58^oC; ^1H NMR ($CDCl_3$), δ: 3.24 (d, 2H, J = 6.5 Hz), 2.65 (s, 3H), 2.34 (s, 3H), 2.13-1.97 (m, 1H), 1.08 (d, 6H, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$), δ : 174.8, 173.1, 152.5, 140.5, 124.1, 39.0, 28.1, 21.8, 13.6, 12.7; IR(KBr) ν_{max}: 2957, 2925, 2871, 1570, 1494, 1455, 1396, 1366, 1200, 1052, 1012, 914 cm^{-1}; Anal. Calcd for $C_{11}H_{15}N_6BrS$: C, 38.49; H, 4.40; N, 24.48; Found C, 38.36; H, 4.28; N, 24.34.

Potassium 6-(2-bromo-3,5-dimethylpyrazol-1-yl)tetrazin-3-olate (7d): 1.00 g (2.34 mmol) of 3,6-bis(4-bromo-3,5-dimethyl-pyrazol-1-yl)tetrazine (**3**) was dissolved in 20 mL of dichloromethane. 131 mg (2.34 mmol) of KOH was added to the solution and the mixture was stirred vigorously for 2 h. The suspension was filtered and the solid was purified by washing with ether affording 585 mg of purple solid as pure product. Yield: 81%. mp: 335-337 ^oC; ^1H NMR (DMSO-d_6), δ : 2.29 (s, 3H); 2.17 (s, 3H). ^{13}C NMR (DMSO-d_6), δ: 152.4, 150.7, 146.5, 138.3, 95.1, 12.0, 10.7. IR(KBr) ν_{max}: 3455, 3307, 2966, 2926, 1694, 1592, 1494, 1448, 1417, 1391, 1367, 1270, 1067, 972 cm^{-1}; Anal. Calcd for $C_7H_6N_6OBrK$: C, 27.19; H, 1.96; N, 27.18; Found C, 27.02; H, 2.13; N, 26.81.

6-(2-Bromo-3,5-dimethylpyrazol-1-yl)-3-hydrazinotetrazine (7e): 230 μL (230 mg, 7.02 mmol) of hydrazine hydrate was added to the suspension of 1.00 g (2.3 mmol) of 3,6-bis(4-bromo-3,5-dimethyl-pyrazol-1-yl)tetrazine (**3**) in 20 mL of acetonitrile and it was stirred for 15 min at rt. The precipitated red solid was filtered affording 440 mg of product. The crude product was recrystallized from acetonitrile. Yield: 67%. mp: 165-166 ^oC; ^{1}HNMR (DMSO-d_6), δ : 8.15 (s, 1H); 4.50 (br s, 2H); 2.00 (s 3H); 2.15 (s

3H); ^{13}C NMR (DMSO-d_6), δ: 163.2, 162.9, 156.6, 148.4, 139.1, 12.0, 11.4; IR(KBr) ν_{max}: 3304, 3165, 3025, 2954, 1633, 1569, 1490, 1455, 1429, 1388, 1369, 1063, 1011, 955 cm^{-1}; Anal. Calcd for $C_7H_9N_8Br$: C, 29.49; H, 3.18; N, 39.30; Found C, 28.91; H, 3.39; N, 40.11.

3-(2-Bromo-3,5-dimethylpyrazol-1-yl)-6-morpholinotetrazine (7f)[14]**:** 0.428 g (1.0 mmol) of 3,6-bis(4-bromo-3,5-dimethyl-pyrazol-1-yl)-1,2,4,5-tetrazine was dissolved in 6 mL of toluene and 170 μL of morpholine (2.0 mmol, 0.174 mg) was added to this solution. The reaction mixture was stirred for 16 h at 25^{o}C. The toluene was removed under reduced pressure and the remaining red solid was recrystallized from n-heptane, resulting in 0.282 g pure product (red crystals). Yield: 83%. mp:146-148^{o}C. ^{1}HNMR (DMSO-d_6), δ: 3.93-3.89 (m, 4H); 3.79-3.76 (m, 4H), 2.41 (s, 3H); 2.24 (s, 3H); ^{13}C NMR (DMSO-d_6), δ: 160.3, 156.0, 148.7, 139.3, 97.3, 65.5, 43.6, 12.2, 11.6.

3,6-Dimethoxytetrazine (8b)[18]**:** 0.305 g (2 mmol) of 3,6-dichlorotetrazine (**1**) was dissolved in 4 mL of acetonitrile. To the solution was added dropwise the mixture of 0.227 g (4.1 mmol) of NaOMe and 4 mL of methanol. After 3 h stirring the solvent was evaporated and the crude product was purified by silicagel column chromatography using hexane-ethyl acetate (10:1) eluent mixture affording 110 mg of pink crystals. Yield: 39%. mp.: 62-63^{o}C. ^{1}H NMR ($CDCl_3$), δ: 4.25 (s, 6H); MS (70 eV); m/z (ion, intensity %): 143 (20, [$M^{+\bullet}$]); 142 (90); 114 (30); 58 (100); 42 (40); 30 (35).

3,6-Bis(isobutylmercapto)tetrazine (8c): 1.00 g (6.6 mmol) of 3,6-dichlorotetrazine (**3**) was dissolved in 25 mL of acetonitrile and a mixture of 1.44 mL (1.17 g, 13 mmol) of isobutyl mercaptan and 1.8 mL (1.31 g, 13 mmol) of triethylamine was added to the solution. After 30 min stirring the solvent was removed and the crude product was purified by silica gel column chromatography using hexane-ethyl acetate eluent mixture affording 1.30 g of red oil as product. Yield: 76%. ^{1}H NMR ($CDCl_3$), δ: 3.14 (d, 4H, *J*=6.6 Hz), 2.04-1.93 (m, 2H), 1.04 (d, 12H, *J*=6.6 Hz); ^{13}C NMR ($CDCl_3$), δ: 172.6, 38.6, 27.9, 21.7; IR(KBr) ν_{max}: 2960, 2871, 2271, 1548, 1464, 1407, 1367, 1233, 1169, 1047, 883 cm^{-1}; Anal. Calcd for $C_{10}H_{18}N_4S_2$: C, 46.48; H, 7.02; N, 21.68; Found C, 46.65; H, 6.78; N, 22.11. The same product could also be obtained in good yield by treating a slurry of **2** or **3** in acetonitrile with an excess of isobutylmercaptan.

6-Hydrazino-3-isobutylmercaptotetrazine (9c): 1.30 g (5 mmol) 3,6-bis(isobutylmercapto)tetrazine was dissolved in 20 mL of acetonitrile and 0.238 mL (5.0 mmol) of hydrazine hydrate was added to the solution. The reaction mixture was stirred for 2 h at rt, then the solvent was removed and the crude product was purified by silica gel column chromatography using hexane-ethyl acetate eluent mixture affording 0.86 g of red oil as product. Yield: 86%.^{1}H NMR (DMSO-d_6), δ : 9.38 (br, 1H), 4.52 (br, 2H), 3.11 (d, 2H, J=6.7 Hz), 1.95-1.81 (m, 1H), 1.00(d, 6H, J=6.7 Hz). ^{13}C NMR (DMSO-d_6), δ: 165.1, 162.8, 38.3, 27.9, 21.5. IR(KBr) ν_{max}: 3310, 3153, 3020, 2960, 2855, 2278, 1577, 1484, 1416, 1376, 1242, 960 cm^{-1}; Anal. Calcd for $C_6H_{12}N_6S$: C, 35.98; H, 6.04; N, 41.96; Found C, 35.78; H, 6.00; N, 42.11.

3-Hydrazino-6-morpholinotetrazine (9g): 0.20 mL (200 mg, 6.25 mmol) of hydrazine hydrate was added to the solution of 0.60 g (2.29mmol) of **4** in 10 mL of acetonitrile at rt. The reaction mixture was stirred for 1.5 h and then the precipitated red solid was filtered. The product was recrystallized from acetonitrile. Yield: 0.43 g, 82%. mp: 186-188°C; ^{1}H NMR ($CDCl_3$), δ: 6.39 (t, 1H, *J* = 1.9 Hz), 3.97 (d, 2H) , 3.84 (t, 4H, *J* = 4.9 Hz), 3.81 (t, 4H, *J* = 4.9 Hz); ^{13}C NMR ($CDCl_3$), δ: 162.5, 151.4, 66.8, 44.8. IR(KBr) ν_{max}: 2979, 1920, 2867, 1642, 1503, 1444, 1348, 1305, 1248, 1119, 1065, 1039, 969, 938 cm^{-1}; Anal. Calcd for $C_6H_{11}N_7O$: C, 36.54; H, 5.62; N 49,72; Found: C, 36.54; H, 5.88; N, 49.86.

General procedure for the nuclephilic substitution on tetrazines with KOH. 0.5 mmol of tetrazine (**5a-c, 6a-c, 7a-c**) was dissolved in 3 mL of dichloromethane and 0.5 mmol of KOH was added to the solution and it was stirred for 4 h at rt. Then the solvent was removed and the crude product distribution was determined by ^{1}H NMR and ^{13}C NMR spectroscopic investigations in DMSO-d_6:

Potassium 3-(isobutylmercapto)tetrazin-6-olate (9f): ^{1}H NMR (DMSO-d_6), δ : 2.62 (d, 2H, J=6.7 Hz); 1.90-1.82 (m, 1H), 0.96 (d, 6H, J=6.7 Hz). ^{13}C NMR (DMSO-d_6), δ: 47.1, 27.5, 21.3.

Potassium 6-morpholinotetrazin-3-olate (9j): ^{1}H NMR (D_2O), δ: 3.66-3.64 (br, 4H), 3.34-3.32 (br, 4H); ^{13}C NMR (D_2O), δ:166.8, 159.2, 66.3, 45.4.

Potassium 6-butylaminotetrazin-3-olate (9k): ^{1}H NMR (DMSO-d_6), δ : 3.17 (m, 2H), 1.49-1.27 (m, 4H), 0.88 (t, 3H, *J*=7.0 Hz). ^{13}C NMR (DMSO-d_6), δ: 163.3, 157.5, 41.4, 31.4, 19.7, 12.2.

Potassium 6-diethylaminotetrazin-3-olate (9l): ^{1}H NMR (DMSO-d_6), δ : 3.46 (q, 4H, *J*=6.7 Hz), 1.07 (t, 6H, *J*=6.7 Hz). ^{13}C NMR (DMSO-d_6), δ: 166.3, 156.4, 41.2, 13.0.

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REFERENCES AND NOTES

1. J. Sauer, "1,2,4,5-Tetrazines" in 'Comprehensive Heterocyclic Chemistry Vol. 2: 1,2,4,5-Tetrazines', Volume Editor A. J. Boulton, ed. by A. R. Katritzky, C. W. Rees and E. F. Scriven, Pergamon Press, 1996, pp. 901-955.
2. D. L. Boger and S. M. Weinreb, 'Hetero Diels-Alder Methodology in Organic Synthesis', Academic Press, Inc., New York, 1997.
3. D. L. Boger and J. Hong, *J. Am. Chem. Soc.*, 2001, **123**, 8515.
4. D. L. Boger and S. E. Wolkenberg, *J. Org. Chem.*, 2000, **65**, 9120.
5. D. L. Boger, C. W. Boyce, M. A. Labroli, C. A. Sehon and Q. Jin, *J. Am. Chem. Soc.*, 1999, **121**, 54.

6. J. S. Panek and B. Zhu, *Tetrahedron Lett.,* 1996, **37**, 8151.
7. U. Schirmer, B. Wuerzer, N. Meyer, F. A. Neugebauer and H. Fischer, DE Patent No. 3508214, 1986 (*Chem. Abstr.,* 1987, **106**, 45718).
8. W. Zambach, R. Naef, S. Trah, A. Jeanguenat, M. Eberle and A. Steiger, WO Patent Appl. 0078739, 2000 (*Chem. Abstr.,* 2001, **134**, 71613).
9. D. E. Chavez and M. A. Hiskey, *J. Energetic Materials,* 1999, **17**, 357.
10. H-H. Licht and H. Ritter, *J. Energetic Materials,* 1994, **12**, 223.
11. M. A. Hiskey, D. E. Chavez and D. Naud, U.S. Patent, 6458227, 2002 (*Chem. Abstr*., 2001, **137**, 265190).
12. A. Counotte-Potman, H. C. van der Plas and B. van Veldhuizen, *J. Org. Chem.,* 1981, **46**, 2138.
13. D. L. Boger, R. P. Schaum and R. M. Garbaccio, *J. Org. Chem.,* 1998, **63**, 6329.
14. N. I. Latosh, G. L. Rusinov, I. N. Ganebnykh and O. N. Chupakin, *Russian J. Org. Chem.,* 1999, **35**, 1363.
15. C. Glidewell, P. Lightfoot, B. J. L. Royles and D. M. Smith, *J. Chem. Soc., Perkin Trans. 2.,* 1997, 1167.
16. H. J. Marcus and A. Remanich, *J. Org. Chem.,* 1963, **28**, 2373.
17. S. M. Sakya, K. K. Groskopf and D. L. Boger, *Tetrahedron Lett.,* 1997, **38**, 3805.
18. F. A. Neugebauer and H. Fischer, *Liebigs. Ann. Chemie,* 1982, 387.
19. X. Yang and G. Seitz, *Arch. Pharm. (Weinheim),* 1992, **325**, 563.
20. G. Seitz and J. Richter, *Chemiker-Zeitung,* 1989, **113**, 254.
21. A. Mangia, F. Bartesi and U. Amendola, *J. Heterocycl. Chem.,* 1977, **14**, 587.
22. H. Yamanaka and S. Ohba, *Heterocycles,* 1990, **31**, 895.
23. S. C. Benson, L. Lee, L. Yang and J. K. Snyder, *Tetrahedron,* 2000, **56**, 1165.
24. M. D. Coburn, G. A. Buntain, B. W. Harris, M. A. Hiskey, K-Y. Lee and D. G. Ott, *J. Heterocyclic Chem.,* 1991, **28**, 2049.
25. G. Seitz and J. Richter, *Chem. Ber.,* 1989, **122**, 2177.
26. J. L. Johnson, B. Whitney and L. M. Werbel, *J. Heterocycl. Chem.,* 1980, **17**, 501.
27. H. J. Marcus, U.S. Patent, 3244702, 1966 (*Chem. Abstr*., 1966, **64**, 104313).
28. We found earlier that 6-morfolino-3-(3,5-dimethylpyrazol-1-yl)tetrazine (**6f**) gave 3-morpholinotetrazine as the main product when reacted with methylhydrazine in acetonitrile. ^{1}H NMR ($CDCl_3$, 500 MHz), δ: 9.59 (s, 1H), 4.00 (t, 4H, J=5.0 Hz), 3.89 (t, 4H, J=5.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 162.2, 152.8, 66.8, 43.9; ^{15}N NMR (50.68 MHz, $CDCl_3$), δ: 389.1, 341.7, 83.7.
29. The structures were optimized at the HF/3-21G level and the energies were calculated on a HF/6-311G basis using the I-PCM solvent model with acetonitrile as solvent. All calculations were carried out

using the Gaussian 98 program package: Gaussian 98 (Revision A.10), M. J. Frisch, G. W. Trucks, H. B.Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, Jr., R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, P. Salvador, J. J. Dannenberg, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, A. G. Baboul, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, J. L. Andres, C. Gonzalez, M. Head-Gordon, E. S. Replogle, and J. A. Pople, Gaussian, Inc., Pittsburgh PA, 2001.

30. For an example of tetrazine charge transfer complexes see: W. J. Wang and C. Y. Shaow, *Synthetic Metals,* 1991, **42**, 1723.
31. Another fact in favour of the presence of kinetic controll in the attack of hydroxide ions on tetrazines is the fact that the formed products, contrary to hydrazine substitution, are significantly more electron rich than the starting tetrazines and therefore reluctant to react with nucleophiles.
32. These results are in good agreement with the X-Ray structures reported by Smith and coworkers. For details see ref. 1