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The azaphilic addition of organometallic reagents on tetrazines: scope and limitations☆

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Abstract—A series of tetrazines were reacted with organometallic reagents. Depending on the nature of the metal azaphilic addition, reduction of the tetrazine or simple complex formation was the predominant transformation and usually high selectivity was observed.

1. Introduction

The chemistry of tetrazines has gained increased attention in the last few decades,[1] due mostly to their applications in organic synthesis,[2] crop protection[3,4] and materials science.[5] Their basic structural feature, the electron-deficient heterocyclic core, is the key to their most extensively utilized transformation, the 'inverse electron-demand' Diels–Alder reaction, that provides an attractive route to pyridazines,[6–8] pyrroles,[9] and other condensed[10,11] and strained heterocyclic ring systems.[12] Another characteristic feature of the electron deficient aromatic ring is its reactivity towards nucleophiles that has been utilized in the preparation of non-symmetrically substituted tetrazines through their addition onto the ring[13] or substitution of leaving groups, such as chloro,[14,15] methylthio[16,17] or dimethylpyrazolyl[15,18,19] with nitrogen, oxygen or sulfur nucleophiles. The analogous reactions introducing carbon nucleophiles would also be of synthetic importance, but there are only a few know examples utilizing potassium cyanide[15] or malonates.[20,21] The cross-coupling reactions on tetrazines, also recently reported have only a limited scope.[22]

The use of reactive carbon nucleophiles, such as organolithium or Grignard reagents in an attempt to substitute 3,6-bis(methylthio)tetrazine led to the addition of the organic group onto a ring nitrogen atom.[23] The transformation, coined 'azaphilic addition' is quite unprecedented for other heterocycles, but had been reported previously for 3,6-diphenyltetrazine too.[24–27] A common feature of the published reactions is that they utilize either organolithium or Grignard reagents, and apparently no rationalization has been provided so far for this unusual transformation. To explore the generality of this reaction we decided to react a series of tetrazines with organometallic reagents. In the light of the fact that on the same tetrazine soft carbanions can initiate nucleophilic substitution,[20,21] while hard carbanions give azaphilic addition selectively,[23] we also wanted to explore the territory between this two 'extremes'. We planed to achieve this aim by reacting a series of organometallic reagents containing different metal residues with a tetrazine that is capable of undergoing nucleophilic substitution.

2. Results and discussion

The first tetrazine selected to test the generality of the azaphilic route was 3,6-bis(3′,5′-dimethylpyrazolyl)-tetrazine (**1**). The choice of **1** was based on two facts: the ease and economy of its preparation[28] and its well documented reactivity towards nitrogen and oxygen nucleophiles.[5,14,18,19] The first experiments, including the reaction of butyllithium, phenyllithium and phenylmagnesium chloride (Table 1, entries 1–3) with **1**, led to the formation of 1-butyl-1,4-dihydro-3,6-bis(dimethylpyrazolyl)tetrazine (**6a**) or 1-phenyl-1,4-dihydro-3,6-bis(dimethylpyrazolyl)-tetrazine (**6b**) in good yield, if the reaction mixtures were quenched at −78 °C, supporting the generality of the azaphilic pathway. On prolonged standing of the reaction mixture on air or letting it warm to room temperature, the yield of **6a** decreased considerably, especially when organolithium reagents were used. In entry 1, the formation

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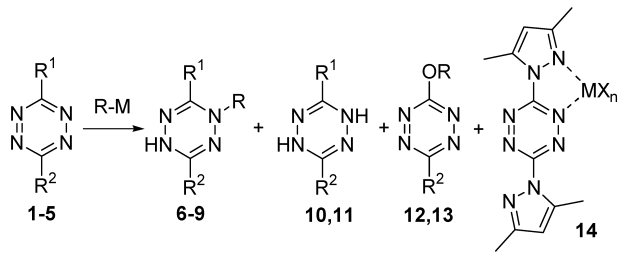
Table 1. Product distribution in the azaphilic addition of tetrazines **1-5** with organometallic reagents



1,6,10,12: R^1=R^2=3,5-dimethyl-pyrazol-1-yl; **2,7,11**: R^1=R^2=3-pyridyl
3,8,13: R^1=3,5-dimethyl-pyrazol-1-yl, R^2=morpholino; **4,9**: R^1=R^2=methyltio
5: R^1=morpholino, R^2=chloro

No.	SM	RM	**6-9**[a] (%)	**10**, **11** (%)	**12**, **13** (%)	**14**[b] (%)
1	**1**	BuLi	70[c]	5		
2	**1**	PhLi	62			
3	**1**	PhMgCl	85			
4	**1**	BuCuLiI[d]	60			40
5	**1**	BuZnBr[d]	85			15
6	**1**	PhZnBr	90			
7	**1**	PhZnBr[d]	45			35
8	**1**	$(C_3H_5)_3In_2Br_3$[e]	60			
9	**1**	$(C_3H_5)_3In_2Br_3$[f]	50[g]	50[g]		
10	**2**	BuLi	13	32		
11	**2**	BuMgI	96			
12	**2**	PhLi	35	25		
13	**2**	PhMgCl	58			
14	**3**	BuLi	13[h]		80	
15	**3**	BuMgI	43[h]		56	
16	**3**	PhLi	85[h]			
17	**3**	PhMgCl	90[h]			
18	**4**	BuLi	90			
19	**4**	PhLi	80			
20	**4**	PhMgCl	94			
21	**5**	PhMgCl	dec.			

[a] Numbers refer to isolated yields unless otherwise stated.
[b] Estimated value based on recovered starting material. Reverts to **1** on acidic workup.
[c] Converts partially to **12** on standing in air.
[d] Prepared by transmetallation form the appropriate lithiumorganic reagent and anhydrous metal halide.
[e] Prepared from In and allyl bromide.
[f] Barbier conditions (In, allyl bromide, THF/aq. NH_4Cl).
[g] Determined by NMR.
[h] Converts partially to **13** on standing in air.

of traces of the reduced starting material (**10**) was also observed.

Extension of the scope of the reaction by using Gilmann or organozinc reagents, prepared by the mixing of one equivalent of copper(I) iodide (entry 4) or zinc bromide (entry 5) with butyllithium prior to the addition to the tetrazine, led also to the formation of **6a**. The use of phenylzinc bromide, prepared through oxidative addition, gave **6b** in excellent yield (entry 6), while the same reagent prepared through transmetallation gave only a moderate yield of **6b** (entry 7). In each reaction, where the reagent was prepared by transmetallation (entries 4,5 and 7), we observed the formation of a salt-like byproduct, schematically represented as **14**, which reverted to **1** on acidic workup. The stability of **14** in the presence of organometallic reagents[29] is exacerbated by the addition of butyllithium to the preformed complex of **1** and CuI at −78 °C leading to marginal conversion to **6a**, which suggests that the coordinating ability of **1** to the organometallic reagent might also play an important role in the course of the azaphilic addition.

The reaction of allylindium reagents (entries 8 and 9) showed a marked dependence on the way the reagent was formed. Allylindium bromide, prepared from allyl bromide and indium in DMF (entry 8), gave good conversion and led only to azaphilic addition (**6c**). In the same reaction, using Barbier-type conditions[30] (entry 9), we also achieved full conversion but the crude product was a 1:1 mixture of the azaphilic adduct **6c** and reduced starting material (**10**) by NMR. We attributed the observed difference to the different mechanisms operating under the applied conditions.

In an attempt to broaden the scope of the azaphilic addition process other selected tetrazine derivatives (**2-5**) were also reacted with organometallic reagents (Table 1, entries 10–21). To our surprise, unlike in the case of **1**, organozinc and Gilmann reagents either failed to react with **2-5** or gave only poor conversion, which means that they are only of limited use from preparative point of view. Organolithium and Grignard reagents on the other hand reacted readily, and even the least reactive tetrazine (**2**) gave full conversion at ambient temperature. Our general observation in these experiments (entries 10–21) is the favored attack of the nucleophile at the ring nitrogen atom (azaphilic addition) although the different tetrazines showed characteristic side reactions too. 3,6-Di(3′-pyridyl)tetrazine (**2**) for example also underwent a competing reduction in the presence of organolithium reagents (entries 10 and 12, cf. with entry 1), while the analogous organomagnesium reagents gave only azaphilic addition. Another feature of **2** is the observation that this compound was the least reactive of the tetrazines examined. Complete conversion of **2** to **7a** or **7b** required warming of the reaction mixtures to ambient temperature.

The addition of the organometallic reagents onto 3-(3′,5′-dimethylpyrazol-1′-yl)-6-morpholino-tetrazine (**3**) had two interesting aspects (entries 14–17). The reaction proceeded regioselectively, as established by NOE experiments, and only the formation of adducts bearing the incoming nucleophile on a nitrogen atom next to the pyrazole moiety was observed. We attribute the selectivity of the addition to the coordinating ability of the pyrazole moiety which might anchor the organometallic reagent in the proximity of the site of observed attack. The intermediates and products formed in the reaction underwent a so far unprecedented transformation in the presence of oxygen. Their solution, when contacted with air, turned red and the formation of the appropriate butoxy- (**13a**) or phenoxy-morpholino-tetrazine (**13b**) was observed. The oxidative transformation proceeded the fastest when the reaction mixture containing **3** and an organolithium reagent was contacted with air and was the slowest in case of the oxidation of solutions of purified **8a** or **8b**. Although we have no sound mechanistic proposal for this oxidative transformation the above findings suggest that the opening step of the process is the electrophilic attack of oxygen on the tetrazine ring.

The reactions of 3,6-bis(methylthio)-tetrazine (**4**) with organolithium and Grignard reagents (entries 18–20) held

no surprise, and in analogy with an earlier report,[23] the azaphilic adducts **9a**,**b** were isolated in excellent yield in each case. Likewise, compounds **1** and **4** also reacted readily with the organometallic reagents even at −78 °C. On the other hand, we saw no sign of double addition or follow-up reactions when using organolithium reagents.[23]

In an attempt to extend the azaphilic addition to chloro-tetrazines, 3-chloro-6-morpholino-tetrazine (**6**)[14] was also reacted with organolithium and Grignard reagents. The former led to the decomposition of the starting material even at −78 °C, probably due to the presence of a lithium–chlorine exchange reaction, while in case of organomagnesium reagents, TLC analysis of the reaction mixtures revealed the formation of a new product, showing an azaphilic adduct-like behavior, that decomposed during workup.

Having demonstrated that organolithium and Grignard reagents initiate, in most cases, azaphilic addition on tetrazines we turned our attention to other organometallic reagents. In the next set of experiments the easily available and reactive dipyrazolyl-tetrazine (**1**) was reacted with a series of organometallic reagents prepared by transmetallation from butyllithium or phenyllithium and the appropriate metal halide.

Tuning the reactivity of butyllithium with cobalt or manganese salts (entries 22 and 23) led to a significant change in reactivity. Besides the formation of substantial amounts of the complex **14**, another product was isolated in both cases. The spectral data of this newly formed compound indicated substitution of one of the pyrazolyl units, but multidimensional NMR and MS experiments verified that it possesses a butoxy substituent (**12**) instead of the expected butyl group. Interestingly, when we carried out the same reaction using phenyllithium instead of butyl-lithium (entry 24) three products were formed: the azaphilic adduct (**6b**), the butoxy substituted tetrazine (**12**) and the complex (**14**), which suggests that the butoxy moiety in **12** is not coming from the organolithium reagent as in entry 14, which leaves tetrahydrofuran as the only potential source of butoxide ions. The capability of THF to undergo reductive ring opening is known[31,32] and the reducing ability of the butyl-metal-halides used might be further enhanced through β-hydride elimination under the applied conditions,[33] yielding the more reactive metal hydrides. By changing the solvent to diethyl ether in the same experiment we observed only complex formation, also supporting this hypothesis.[34]

Table 2. Product distribution in the reaction of **1** with other organo-metallic reagents

No.	SM	RM	**6**[a] (%)	**10** (%)	**12**[a] (%)	**14**[b] (%)
22	**1**	BuCoBr[c]			60	40
23	**1**	BuMnCl[c]			40	60
24	**1**	PhMnCl[c]	20		15	40
25	**1**	BuPbCl[c]	25		30	35
26	**1**	BuSnCl[c]		100[d]		
27	**1**	PhSnCl[c]		100[d]		
28	**1**	BuFeCl[c]		100[d]		
29	**1**	$BuCrCl_2$[c]		100[d]		

[a] Numbers refer to isolated yields unless otherwise stated.
[b] Estimated value based on recovered starting material. Reverts to **1** on acidic workup.
[c] Prepared by transmetallation form the appropriate lithiumorganic reagent and anhydrous metal halide.
[d] Determined by NMR. >99.9% means that no other identifiable compound was detected in the crude product.

A similar behavior was observed when butyllithium was mixed with lead(II) bromide (entry 25) prior to its addition to **1**. At the end of the reaction the azaphilic adduct (**6a**), the butoxy substituted tetrazine (**12**) and starting material (**1**), recovered after the decomposition of **14**, were isolated in similar yields.

The last group of organometallic reagents examined (entries 26–29) initiated the reduction of the tetrazine core selectively. Even careful investigation of the crude reaction mixtures revealed only the presence of **12** besides some highly polar decomposed material. It is worth mentioning that this transformation was selective, not only for butylmetal halides (entries 26,28, and 29) that are capable of producing metal hydrides through β-hydride elimination,[33] but also for phenyltin chloride (entry 27). The fact that these reagents reduced the tetrazine core and not the solvent, as in entries 22–25, is not well understood but might probably be attributed to the different complex forming aptitude of the added metal ions.

In summary, a series of organometallic reagents were reacted with different tetrazine derivatives and selective transformations, such as azaphilic addition, reduction or in certain cases nucleophilic displacement were observed. More polar organometallic reagents, especially lithium, magnesium and zinc derivatives, showed a marked affinity towards the nitrogen atom of the tetrazine core, a behaviour fairly unusual in heterocyclic chemistry. The oxidative rearrangement of the azaphilic adducts to alkoxy/aryloxy tetrazines was also observed in certain cases.

3. Experimental

3.1. General

Melting points were determined on a hotplate and are uncorrected. The ^1H and ^{13}C NMR spectra were recorded on a Brucker DRX-250 or DRX-500 spectrometer in $CDCl_3$ and CH_3SOCH_3. For ^1H 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. The IR spectra were obtained on a Bruker IFS-55 FTIR spectrometer. Combination gas chromatography and low resolution mass spectrometry was obtained on a Hewlett–Packard 5790A Gas Chromatograph (30 m×0.25 mm column with 0.25 μm RH-5 MS+coating, He carrier gas) and VG 12-250 Mass Spectrometer (Ion source: EI+, 70 eV, 250 °C; interface: 250 °C). Flash silica gel (0.040–0.063 mm) was used for flash column chromatography.

3.2. General procedure for the reaction of tetrazines 1-4 with organometallic reagents

All reactions were carried out under argon, using dry

glassware. THF was distilled from potassium/benzophenone. When the organometallic reagent was prepared by transmetallation a mixture of 1.1 mmol of the appropriate salt in abs. THF (3 mL) was treated with 1.1 mmol of the organolithium reagent and after stirring for 1 h at −40 °C the resulting mixture was added via a canula to the slurry of 1 mmol of the appropriate tetrazine in dry THF (3 mL) at −78 °C. The reaction was followed by TLC and upon completion (which in certain cases required warming to room temperature) it was quenched with aq. NH_4Cl, extracted with DCM, the combined organic phases were dried oveg $MgSO_4$ and the solvent was evaporated. The products were isolated by flash column chromatography using hexane–ethyl acetate mixtures as eluent.

3.2.1. 1-Butyl-3,6-bis(3′,5′-dimethylpyrazol-1′-yl)-1,4-dihydro-1,2,4,5-tetrazine (6a). Yellow oil, ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.92 (s, 1H), 5.88 (s, 1H), 5.82 (s, 1H), 3.03 (t, 2H, J=6.9 Hz), 2.40 (s, 3H), 2.22 (s, 3H), 2.15 (s, 3H), 2.11 (s, 3H), 1.48 (qi, 2H, J=6.9 Hz), 1.25 (sex, 2H, J=6.9 Hz), 0.77 (t, 3H, J=6.9 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 151.19, 150.43, 146.09, 145.91, 143.30, 142.81, 110.44, 107.41, 50.80, 30.30, 19.98, 14.47, 14.11, 14.02, 13.88, 11.70; MS (EI, 70 eV) m/z for $C_{16}H_{24}N_8$ (rel. intensity, ion): 328 (100, M^+), 271 (10), 189 (22), 164 (52), 151 (22), 122 (72), 97 (19), 81 (10); 54 (12); IR (KBr) ν_{max}: 3357, 2958, 2929, 2870, 2154, 1666, 1639, 1569, 1300, 1216, 1135, 1067, 1029, 970, 937, 900, 789 cm^{-1}. HRMS (EI) Calcd for $C_{16}H_{24}N_8$: m/z 328.2124. Found: m/z 328.2137.

3.2.2. 1-Phenyl-3,6-bis(3′,5′-dimethylpyrazolyl-1′-yl)-1,4-dihydro-1,2,4,5-tetrazine (6b). Yellow solid, mp: 45–46 °C (decomposition); ^{1}H NMR ($CDCl_3$, 250 MHz) 8.41 (br s, 1H), 7.18 (t, 2H, J=7.2 Hz), 6.97 (t, 1H, J=7.2 Hz), 6.92 (d, 2H, J=7.2 Hz), 6.05 (s, 1H), 5.79 (s, 1H), 2.64 (s, 3H), 2.25 (s, 3H), 2.18 (s, 3H), 2.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) 151.45, 150.93, 149.79, 142.79, 142.47, 141.38, 140.05, 128.57, 122.90, 117.04, 110.72, 107.73, 14.21, 13.58, 13.53, 11.05; MS (EI, 70 eV) m/z for $C_{18}H_{20}N_8$ (rel. intensity, ion): 348 (65, M^+), 272 (9, M-Ph), 198 (63), 122 (100), 77 (41); IR (KBr): 3350, 2926, 1663, 1639, 1599, 1582, 1570, 1496, 1457, 1414, 1399, 1366, 1077, 995, 969, 754, 693 cm^{-1}. HRMS (EI) Calcd for $C_{18}H_{20}N_8$: m/z 348.1811. Found: m/z 348.1819.

3.2.3. 1-Allyl-3,6-bis(3′,5′-dimethylpyrazol-1′-yl)-1,4-dihydro-1,2,4,5-tetrazine (6c). Yellow solid, mp: 84–85 °C (decomposition); ^{1}H NMR ($CDCl_3$, 500 MHz) 8.05 (s, 1H), 5.96 (s, 1H), 5.89 (s, 1H), 5.84 (ddt, 1H, J=16.9, 10.5, 6.4 Hz), 5.14 (dqa, 1H, J=16.9, 1.6 Hz), 5.08 (dqa, 1H, J=10.5, 1.6 Hz), 3.84 (dt, 2H, J=6.4, 1.6 Hz), 2.49 (s, 3H), 2.31 (s, 3H), 2.24 (s, 3H), 2.21 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): 150.94, 150.21, 145.90, 145.00, 143.16, 142.72, 133.96, 117.33, 110.11, 107.12, 53.99, 14.06, 13.68, 13.55, 11.49; MS (EI, 70 eV) m/z for $C_{15}H_{20}N_8$ (rel. intensity, ion) 312 (88, M^+), 271 (56, M-allyl), 215 (29), 164 (25), 122 (85), 97 (100); IR (KBr): 3209, 3138, 3075, 2961, 2927, 1690, 1571, 1490, 1415, 1362, 1261, 1172, 1078, 1025, 973, 798 cm^{-1}. HRMS (EI) Calcd for $C_{15}H_{20}N_8$: m/z 312.1811. Found: m/z 312.1809.

3.2.4. 1-Butyl-3,6-bis(3′-pyridyl)-1,4-dihydro-1,2,4,5-tetrazine (7a). ^{1}H NMR ($CDCl_3$, 250 MHz) 9.33 (dd, 1H, J=2.2, 0.8 Hz), 8.78 (dd, 1H, J=4.9, 1.7 Hz), 8.57 (br s, 1H), 8.50 (d, 1H, J=5.1 Hz), 8.42 (ddd, 1H, J=8.0, 2.2, 1.8 Hz), 7.49 (ddd, 1H, J=8.0, 4.9, 0.9 Hz), 7.23–7.14 (m, 3H), 2.78 (t, 2H, J=7.6 Hz), 1.62 (qi, 2H, J=7.7 Hz), 1.35 (sex, 2H, J=7.6 Hz), 0.91 (t, 3H, J=7.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): 151.56, 151.07, 150.06, 149.92, 148.17, 147.96, 136.79, 133.85, 127.90, 126.35, 123.68, 123.63, 52.63, 30.98, 19.99, 14.15; MS (EI, 70 eV) m/z for $C_{16}H_{18}N_6$ (rel. intensity, ion): 294 (5, M+), 224 (22), 161 (39), 145 (50), 132 (42), 118 (90), 104 (37), 78 (47), 51 (44), 43 (100).

3.2.5. 1-Phenyl-3,6-bis(3′-pyridyl)-1,4-dihydro-1,2,4,5-tetrazine (7b). Yellow solid, mp: 180–181 °C (decomposition); ^{1}H NMR ($CDCl_3$, 250 MHz) 9.03 (d, 1H, J=1.3 Hz), 8.65 (dd, 1H, J=4.3, 0.9 Hz), 8.55 (d, 1H, J=1.6 Hz), 8.46 (dd, 1H, J=4.9, 1.4 Hz), 8.07 (dt, 2H, J=7.8, 1.9 Hz), 7.39 (dt, 1H, J=8.2, 2.1 Hz), 7.31 (dd, 1H, J=8.0, 4.9 Hz), 7.17–7.04 (m, 5H, J=16.5 Hz), 6.93 (tt, 1H, J=7.1, 1.2 Hz); ^{13}C NMR ($CDCl_3$, 62.5 MHz) 151.67, 150.10, 150.01, 149.94, 147.45, 146.01, 141.14, 136.16, 134.01, 128.64, 128.30, 125.55, 123.64, 123.53, 122.81, 119.28; MS (EI, 70 eV) m/z for $C_{18}H_{14}N_6$ (rel. intensity, ion): 314 (55, M^+), 283 (12), 208 (14), 181 (30), 105 (100), 77 (70), 51 (65); IR (KBr): 3426, 3223, 3062, 3033., 2920.8, 1625, 1596, 1491, 1466, 1413, 1348, 1338, 1096, 1021, 988, 812, 764, 713, 697 cm^{-1}. HRMS (EI) Calcd for $C_{18}H_{14}N_6$: m/z 314.1280. Found: m/z 314.1270.

3.2.6. 4-Butyl-3-(3′,5′-dimethylpyrazol-1′-yl)-6-(*N*-morpholino)-1,4-dihydro-1,2,4,5-tetrazine (8a). Yellow oil, ^{1}H NMR ($CDCl_3$, 250 MHz) 7.60 (s, 1H), 5.95 (s, 1H), 3.72 (t, 4H, J=4.7 Hz), 3.37 (t, 2H, J=7.0 Hz), 3.04 (t, 4H, J=4.7 Hz), 2.46 (s, 3H), 2.19 (s, 3H), 1.68 (qi, 2H, J=14.7 Hz), 1.43 (sex, 2H, J=18.5 Hz), 0.94 (t, 3H, J=7.3 Hz); ^{13}C NMR ($CDCl_3$, 62.5 MHz): 154.22, 150.42, 149.82, 141.94, 109.74, 66.41, 49.70, 48.44, 30.65, 19.59, 13.73; MS (EI, 70 eV) m/z for $C_{15}H_{25}N_7O$ (rel. intensity, ion): 319 (45, M^+), 262 (65), 122 (83), 57 (50), 42 (100).

3.2.7. 4-Phenyl-3-(3′,5′-dimethylpyrazol-1′-yl)-6-(*N*-morpholino)-1,4-dihydro-1,2,4,5-tetrazine (8b). Yellow solid, mp: 170–171 °C (decomposition); ^{1}H NMR ($CDCl_3$, 500 MHz) 7.56 (s, 1H), 7.13 (dd, 2H, J=8.1, 7.2 Hz), 6.91 (t, 1H, J=7.2 Hz), 6.88 (d, 2H, J=8.1 Hz), 5.77 (s, 1H), 3.66 (t, 4H, J=4.8 Hz), 3.30 (t, 4H, J=4.8 Hz), 2.20 (s, 3H), 2.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) 156.08, 150.23, 142.41, 140.28, 139.43, 127.48, 121.44, 115.89, 106.66, 65.14, 45.34, 12.65, 10.02; MS (EI, 70 eV) m/z for $C_{17}H_{21}N_7O$ (rel. intensity, ion): 339 (7, M^+), 154 (95), 121 (38), 105 (35), 94 (86), 77 (24), 43 (100), 39 (53); IR (KBr): 3307, 2960, 2852, 1595, 1568, 1389, 1369, 1121, 761, 732, 698, 688 cm^{-1}. HRMS (EI) Calcd for $C_{17}H_{21}N_7O$: m/z 339.1808. Found: m/z 339.1802.

3.2.8. 1-Butyl-3,6-bis(methylthio)-1,4-dihydro-1,2,4,5-tetrazine (9a). Pink solid, mp: 39–40 °C (decomposition); ^{1}H NMR ($CDCl_3$, 250 MHz) 6.50 (s, 1H), 3.32 (t, 2H, J=7.3 Hz), 2.43 (s, 3H), 2.35 (s, 3H), 1.71 (qi, 2H, J=7.2 Hz), 1.38 (sex, 2H, J=7.2 Hz), 0.93 (t, 3H, J=7.3 Hz); ^{13}C NMR ($CDCl_3$, 62.5 MHz) 154.25, 150.43, 51.27, 29.98, 29.86, 19.87, 14.40, 13.38; MS (EI, 70 eV) m/z for $C_8H_{16}N_4S_2$ (rel. intensity, ion): 232 (100, M^+), 189 (50),

176 (17), 161 (7), 87 (6), 74 (48), 57 (7), 41 (15); IR (KBr): 3265, 2961, 2929, 2861, 1603, 1588, 1467, 1440, 1416, 1374, 1268, 1190, 1149, 1129, 776, 608 cm^{-1}. HRMS (EI) Calcd for $C_8H_{16}N_4S_2$: *m/z* 232.0816. Found: *m/z* 232.0814.

3.2.9. 1-Phenyl-3,6-bis(methylthio)-1,4-dihydro-1,2,4,5-tetrazin (9b). Pale orange solid, mp: 117–118 °C (decomposition); ^1H NMR ($CDCl_3$, 250 MHz) 7.36 (d, 2H, *J*=8.1 Hz), 7.27 (dd, 2H, *J*=8.1, 7.2 Hz), 7.13 (t, 1H, *J*=7.2 Hz), 7.10 (s, 1H), 2.40 (s, 3H), 2.25 (s, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) 152.25, 151.95, 142.14, 128.24, 125.97, 123.48, 14.74, 14.20; MS (EI, 70 eV) *m/z* for $C_{10}H_{12}N_4S_2$ (rel. intensity, ion): 252 (100, M^+), 150 (12), 135 (11), 91 (7), 74 (50), 65 (6), 51 (14); IR (KBr): 3282, 3258, 3054, 2926, 1613, 1590, 1490, 1416, 1283, 1170, 1151, 1070, 951, 764, 696 cm^{-1}. HRMS (EI) Calcd for $C_{10}H_{12}N_4S_2$: *m/z* 252.0503. Found: *m/z* 252.0502.

3.2.10. 3,6-Bis(3′-pyridyl)-1,4-dihydro-1,2,4,5-tetrazine (11).[35] ^1H NMR ($CDCl_3$, 250 MHz) 9.35 (s, 2H), 8.99 (d, 2H, *J*=1.8 Hz), 8.67 (dd, 2H, *J*=4.9, 1.6 Hz), 8.18 (dt, 2H, *J*=8.5, 1.8 Hz), 7.50 (dd, 2H, *J*=7.4, 4.7 Hz); ^{13}C NMR ($CDCl_3$, 62.5 MHz) 113.98, 110.14, 109.22, 96.43, 88.95, 86.58; MS (EI, 70 eV) *m/z* for $C_{12}H_{10}N_6$ (rel. intensity, ion): 238 (100, M^+), 105 (62), 78 (34), 51 (23); HRMS (EI) Calcd for $C_{12}H_{10}N_6$: *m/z* 238.0967. Found: *m/z* 238.0965.

3.2.11. 3-Butoxy-6-(3′,5′-dimethylpyrazol-1′-yl)-1,2,4,5-tetrazine (12). Red solid, mp: 28–29 °C; ^1H NMR ($CDCl_3$, 500 MHz) 6.08 (s, 1H), 4.60 (t, 2H, *J*=6.9 Hz), 2.57 (s, 3H), 2.29 (s, 3H), 1.86 (qi, 2H, *J*=6.9 Hz), 1.49 (sex, 2H, *J*=6.9 Hz), 0.94 (t, 3H, *J*=6.9 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): 166.66, 159.68, 153.81, 143.31, 11.37, 70.62, 30.98, 19.35, 14.54, 14.15, 14.05; MS (EI, 70 eV) *m/z* for $C_{11}H_{16}N_6O$ (rel. intensity, ion): 248 (24, M^+), 194 (5), 163 (6), 122 (100), 96 (7), 57 (18); IR (KBr): 2961, 2873, 1577, 1484, 1431, 1370, 1351, 1084, 953 cm^{-1}. HRMS (EI) Calcd for $C_{11}H_{16}N_6O$: *m/z* 248.1386. Found: *m/z* 248.1381

3.2.12. 3-Butoxy-6-(*N*-morpholino)-1,2,4,5-tetrazine (13a). Red solid, mp: 53–54 °C; ^1H NMR ($CDCl_3$, 250 MHz) 4.47 (t, 2H, *J*=6.6 Hz), 3.88–3.79 (m, 8H, *J*=11.1 Hz), 1.85 (qi, 2H, *J*=14.2 Hz), 1.50 (sex, 2H, *J*=18.7 Hz), 0.96 (t, 3H, *J*=7.4 Hz); ^{13}C NMR ($CDCl_3$, 62.5 MHz) 164.32, 161.33, 68.80, 66.34, 44.17, 30.69, 18.96, 13.67; MS (EI, 70 eV) *m/z* for $C_{10}H_{17}N_5O_2$ (rel. intensity, ion): 239 (93, M^+), 149 (71), 111 (67), 85 (100), 81 (49), 67 (67), 53 (88), 44 (66), 30 (57); IR (KBr): 2967, 2959, 2936, 2917, 2906, 2865, 1769, 1717, 1530, 1479, 1460, 1330, 1302, 1249, 1120, 1018, 967, 957, 936, 852, 569, 553 cm^{-1}. HRMS (EI) Calcd for $C_{10}H_{17}N_5O_2$: *m/z* 239.1382. Found: *m/z* 239.1371.

3.2.13. 3-Phenoxy-6-(*N*-morpholino)-1,2,4,5-tetrazine (13b). Red solid, mp: 95–97 °C; ^1H NMR ($CDCl_3$, 250 MHz) 7.91 (d, 2H, *J*=7.7 Hz), 7.50–7.35 (m, 3H), 3.87 (t, 4H, *J*=5.2 Hz), 3.76 (t, 4H, *J*=5.2 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz); 149.93, 146.95, 138.18, 128.00, 122.30, 120.42, 65.14, 43.99; MS (EI, 70 eV) *m/z* for $C_{12}H_{13}N_5O_2$ (rel. intensity, ion): 259 (5, M^+), 153 (52), 119 (100), 112 (3), 41 (38).

4. Supplementary Material

^1H and ^{13}C NMR spectra of the new compounds reported in Tables 1 and 2.

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