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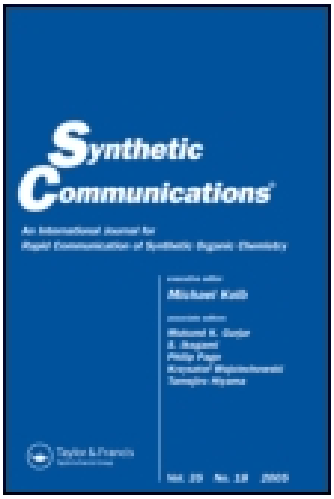

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N-Alkylation of Unsymmetrical 1,6-Dihydro-1,2,4,5-tetrazine Under Alkali Condition

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N-ALKYLATION OF UNSYMMETRICAL 1,6-DIHYDRO-1,2,4,5-TETRAZINE UNDER ALKALI CONDITION

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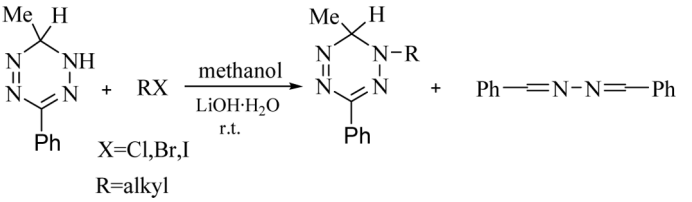
GRAPHICAL ABSTRACT



Abstract *6-Methyl-3-phenyl-1,6-dihydro-1,2,4,5-tetrazine was stable in alkali solution at room temperature and decomposed gradually to form 1,2-dibenzylidenehydrazine. The plausible mechanism of the reaction is discussed. Because it was stable for a period of time, a convenient and effective method for synthesis of 1-alkyl-1,6-dihydro-1,2,4,5-tetrazines has been developed. The starting 1,6-dihydro-1,2,4,5-tetrazine can be alkylated with alkyl halides in methanol and lithium hydroxide monohydrate as a base at room temperature.*

Keywords Alkyl halides; N-alkylation; 1,6-dihydro-1,2,4,5-tetrazine; lithium hydroxide; unsymmetrical

INTRODUCTION

1,6-Dihydro-1,2,4,5-tetrazine is an important compound for the synthesis of some 1,2,4,5-tetrazine derivatives, which have been found to show strong antitumor activity.[1] So far, a few reports have been published for 1,6-dihydro-1,2,4,5-tetrazines and their derivatives.[2,3] The only method described in the literature[3a] to synthesize 1-alkyl-3,6-dimethyl-1,6-dihydro-1,2,4,5-tetrazines **2** consists of the N-alkylation reaction between 3,6-dimethyl-1,6-dihydro-1,2,4,5-tetrazine **1** and alkyl halides in acetone in the presence of potassium carbonate (Scheme 1). This reaction needs longer reaction time (12 h) and gives lower yields because the products were always a mixture of the desired tertiary amine **2** and starting material **1**.

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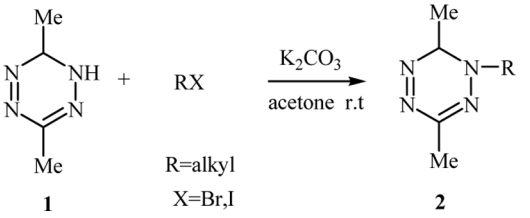

Scheme 1. Synthesis of 1-alkyl-3,6-dimethyl-1,2,4,5-tetrazine.

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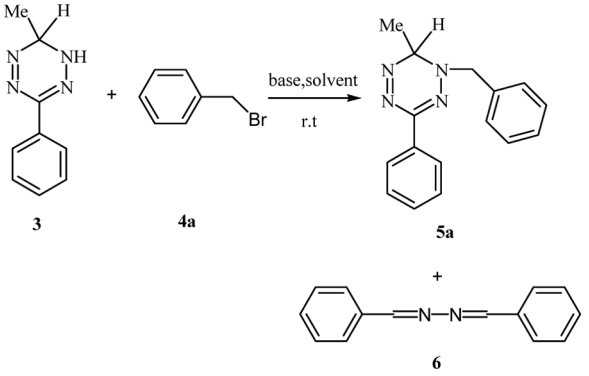
When we attempt to perform the N-alkylation reaction between 6-methyl-3-phenyl-1,6-dihydro-1,2,4,5-tetrazine **3**[2g] and benzyl bromide **4a** under the conditions employed by Jennison et al., no product **5a** formed after 42 h. In contrast, we got an unexpected product, which was identified as 1,2-dibenzylidene hydrazine **6** with 32% yield (entry 1, Table 1). This phenomena may result from the instability of 1,6-dihydro-1,2,4,5-tetrazine under alkali conditions. To explain the phenomena, a blank experiment was executed between **3** and NaOH as the base in methanol at room temperature. The relationship between reaction time and residual contents of **3** and **6** analyzed by high-performance liquid chromatography (HPLC) is shown in Fig. 1. From the figure, it is obvious that 1,6-dihydro-1,2,4,5-tetrazine **3** was almost stable for a period of time (0–8 hours) under alkali conditions. After that time, **3** decomposed quickly to form 1,2-dibenzylidenehydrazine **6**. We also changed the base to $LiOH \cdot H_2O$ and Et_3N and found similar results. The plausible mechanism for the formation of **6** is outlined in Scheme 2. Initially, on the effect of base, **3** deprotonates to form the anion **7**, which could be considered a homoaromatic anion,[2e–2f] **7** attacks the C3 position of **3** to form **8** via intramolecular decyclization,[4] which gives intermediate **9** after a 1,3-hydrogen shift and extrusion of molecular nitrogen.[5] Then, **9** gives **10** via elimination of 3-methyl-3H-diazirin; charge delocalization induces ring opening and leads to the generation of **11**. Finally, elimination of 3-methyl-3H-diazirin from **11** leads to the formation of **12**, which gets a proton from water to form the product **6**.

Once we have known where **6** came from, optimization was carried out to find favorable conditions for the N-alkylation of **3** with alkyl halides. The study was executed taking benzyl bromide **4a** as the standard alkyl halide to react with1,6-dihydro-1,2,4,5-tetrazine **3**. The influence of the base and solvent was investigated (Table 1).

As shown in Table 1, it is obvious that strong inorganic bases, such as NaOH or $LiOH \cdot H_2O$, were the most appropriate bases to carry out the N-alkylation reaction, affording the desired product **5a** in good yields. When increasing the equivalence of $LiOH \cdot H_2O$ from 1.0 to 2.0, the yields of **5a** decreased from 82% to 30% (entries 6 and 7), which may be caused by the side reaction between excessive alkali and **4a**.[6] The solvent also plays a crucial role, with methanol being the best for good conversions (entries 6, and 8–10, Table 1). Nonpolar solvents were not suitable.

Once the optimal conditions for the N-alkylation reaction between 3-phenyl-6-methyl-1,6-dihydro-1,2,4,5-tetrazine **3** and benzyl bromide **4a** had been found (entry 5, Table 1), the scope of this reaction was explored with a set of alkyl halides.

Table 1. N-Alkylation of **3** with **4a** under various conditions[a]



Entry	Base (equiv)	Solvent	Time (h)	Yield (%)[b]	
				5a	6
1[c]	K_2CO_3 (7.0)	Acetone	42	—	32
2[c]	Et_3N (1.0)	Acetone	42	10	45
3[c]	DMAP (1.0)	Acetone	42	12	35
4	DMAP (1.0)	MeOH	42	55	30
5	NaOH (1.0)	MeOH	5	76	—
6	$LiOH \cdot H_2O$ (1.0)	MeOH	5	82	—
7[c]	$LiOH \cdot H_2O$ (2.0)	MeOH	5	30	—
8	$LiOH \cdot H_2O$ (1.0)	MeCN	5	75	—
9	$LiOH \cdot H_2O$ (1.0)	THF	5	65	—
10[c]	$LiOH \cdot H_2O$ (1.0)	Toluene	5	—	6

[a]Reactions conditions: 3-phenyl-6-methyl-1,6-dihydro-1,2,4,5-tetrazine **3** (1.0 mmol, 1.0 equiv), benzyl bromide **4a** (1.0 equiv), base in corresponding solvent (20 ml) at room temperature.

[b]Isolated yields.

[c]These reactions retrieved **3** with yields of 50% (entry 1), 32% (entry 2), 35% (entry 3), 42% (entry 7), and 85% (entry 10), respectively.

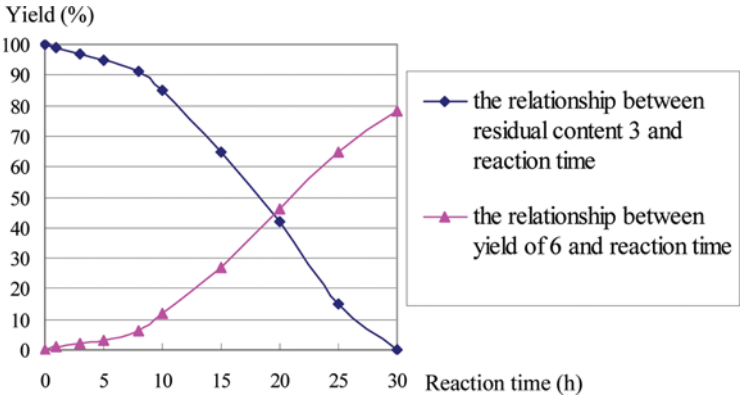


Figure 1. Decomposition **3** to form **6** under alkali condition.

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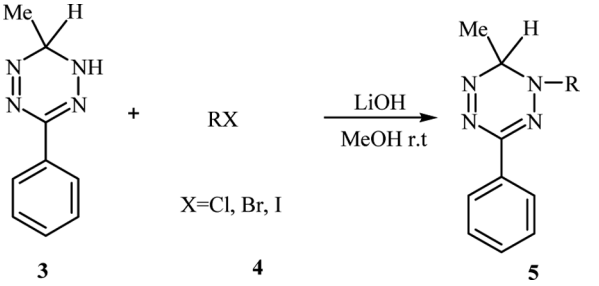
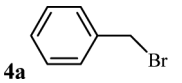
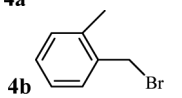
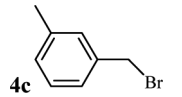
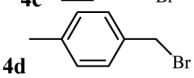
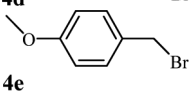
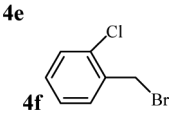
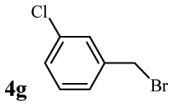
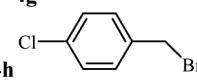
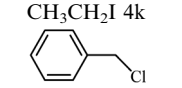
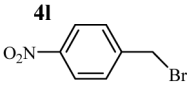
Table 2. Preparation of **5a–k**[a]

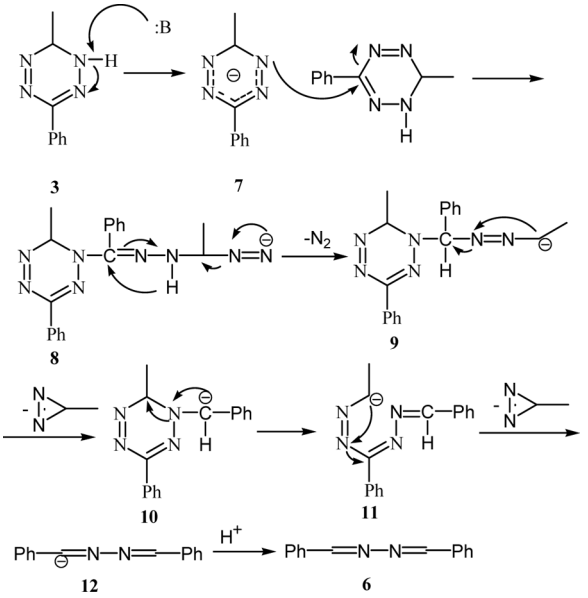


Entry	RX (R = Benzyl or alkyl, X = Cl or Br)	Time (min)	Yield (%)[b]
1	 **4a**	5	5a (82)
2	 **4b**	4	5b (85)
3	 **4c**	4	5c (76)
4	 **4d**	4	5d (68)
5	 **4e**	4	5e (90)
6	 **4f**	5	5f (74)
7	 **4g**	5	5g (65)
8	 **4h**	5	5h (62)
9	$CH_2=CHCH_2Br$ 4i	7	5i (65)
10	CH_3I 4j	8	5j (55)
11	CH_3CH_2I 4k	10	5k (48)
12[c]	 **4l**	10	5a (15)
13[c]	 **4m**	10	5m (0)

[a]Reactions conditions: 3-phenyl-6-methyl-1,6-dihydro-1,2,4,5-tetrazine **3** (1.0 mmol, 1.0 equiv), alkyl halides (1.0 equiv), and base (1.0 equiv) in methanol (20 ml) at room temperature.

[b]Isolated yields.

[c]These reactions retrieved **3** with yields of 65% (entry 12) and 85% (entry 13), respectively.



Scheme 2. Plausible mechanism to form **6**.

As can be see in Table 2, 1,6-dihydro-1,2,4,5-tetrazine **3** can be effectively alkylated with different alkyl halides **4** in moderate to good yields. As shown in **4a–h**, a variety of substituents were tolerated in *ortho*, *meta*, and *para* positions, and substrates with electron-donating groups showed a little more reactivity than those with electron-withdrawing groups (entries 2–5 and 6–8, respectively); no desired product **5m** was detected when 4-nitrobenzyl bromide **4m** reacted with **3** (entry 13). On the other hand, **4i–k** showed much less reactivity than **4a–h**; it afforded **5a–h** within 5 h, but it required a much longer reaction time (7–10 h) to afford **5i–k**. Benzyl chloride **4l** showed very low reactivity in this reaction.

CONCLUSION

In summary, it was found that 1,6-dihydro-1,2,4,5-tetrazine **3** was relatively stable for 8 h under alkali conditions, and because of this a convenient and efficient method for N-alkylation of 1,6-dihydro-1,2,4,5-tetrazines was developed via reaction of 3-phenyl-6-methyl-1,6-dihydro-1,2,4,5-tetrazine **3** with alkyl halides **4** under $LiOH \cdot H_2O$ and methanol in moderate to good yields.

EXPERIMENTAL

Compounds **4b–h** and **4m** were synthesized according to literature.[7] Other solvents and reagents were commercially available and used without further purification or purified by standard methods prior to use.

Melting points were carried on a XRC-1 apparatus and uncorrected. Infrared (IR) spectra were recorded from KBr discs on a Nicolex Fourier transform

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(FT)–IR-170 instrument. ^{1}H NMR spectra were run on a Bruker AC400 (400-MHz) spectrometer using tetramethylsilane (TMS) as internal standard and $CDCl_3$ as the solvent. High-resolution mass spectra (HRMS) were obtained on an Agilent 6210 turnover frequency (TOF) liquid chromatograph/mass spectrography (LC/MS). Thin-layer chromatography (TLC) was carried out on silica-gel UV-254 plates in the dichloromethane system.

General Procedure for the Preparation of 5

3-Phenyl-6-methyl-1,6-dihydro-1,2,4,5-tetrazine **3** (174 mg,1.0 mmol), LiOH · H_2O (42 mg, 1.0 mmol), and methanol (10 ml) were mixed. Alkyl halides (1.0 mmol) in methanol (10 ml) were added dropwise with stirring at room temperature. After the start 1,6-dihydro-1,2,4,5-tetrazine **3** was completely consumed (the reaction courses was monitored by TLC in the dichloromethane system), methanol was evaporated, and crude 1-alkyl-3-phenyl-6-methyl-1,6-dihydro-1,2,4,5-tetrazine **5** was obtained and purified by preparative TLC over silica gel PF_{254} (2 mm) (dichloromethane–petroleum ether 9:1). These products **5** easily decomposed gradually at room temperature and should be stored at −20 °C.

1-Benzyl-3-phenyl-6-methyl-1,6-dihydro-1,2,4,5-tetrazine (5a)

Mp: 101–103 °C. IR (KBr, cm^{-1}): 3064, 2986, 1636, 1455, 1406, 1356, 1161, 1071, 764, 736, 695. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.98 (d, 2H, $J = 7.6$ Hz), 7.44 (t, 2H, $J = 7.8$ Hz), 7.30–7.37 (m, 4H, ArH), 7.17 (d, 2H, $J = 6.8$ Hz), 4.84 (s, 2H), 2.95 (q, 1H, $J = 6.1$ Hz), 1.84 (d, 3H, $J = 6.4$ Hz). MS (m/z, %): 236 [M-28(N_2), 3], 133 (8), 118 (7), 103 (15), 91 (100), 77 (10). Anal. calcd. for $C_{16}H_{16}N_4$ (264.14): C, 72.70; H, 6.10; N, 21.20. Found: C, 72.40; H, 6.05; N, 21.45.

1-(2-Methylbenzyl)-3-phenyl-6-methyl-1,6-dihydro-1,2,4,5-tetrazine (5b)

Yellow liquid. IR (KBr, cm^{-1}): 3063, 2981, 2820, 1697, 1602, 1460, 1406, 1350, 1160, 752, 744, 694. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.95 (d, 2H, $J = 7.2$ Hz), 7.42 (t, 2H, $J = 7.4$ Hz), 7.33 (t, 1H, $J = 7.4$ Hz), 7.16–7.22 (m, 3H, ArH), 7.01 (d, 1H, $J = 6.8$ Hz), 4.89 (d, 1H, $J = 16.0$ Hz), 4.77 (d, 1H, $J = 16.0$ Hz), 3.27 (q, 1H, $J = 6.3$ Hz), 2.34 (s, 3H), 1.68 (d, 3H, $J = 6.0$ Hz). MS (m/z, %): 250 [M-28(N_2), 2], 146 (15), 132 (90), 105 (100), 91(5), 77 (32). HRMS (APCI): calcd. $C_{17}H_{19}N_4$ ($M + H^+$) 279.1610; found 279.1603.

1-(3-Methylbenzyl)-3-phenyl-6-methyl-1,6-dihydro-1,2,4,5-tetrazine (5c)

Yellow liquid. IR (KBr, cm^{-1}): 3027, 2922, 1607, 1447, 1404, 1384,1356, 1150, 761, 693. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.98 (d, 2H, $J = 7.6$ Hz), 7.43 (t, 2H, $J = 7.4$ Hz), 7.34 (t, 1H, $J = 7.4$ Hz), 7.21 (t, 1H, $J = 7.6$ Hz), 7.09 (d, 1H, $J = 7.6$ Hz), 6.96–6.98 (m, 2H, ArH), 4.80 (s, 2H), 2.96 (q, 1H, $J = 6.2$ Hz), 2.33 (s, 3H), 1.83 (d, 3H, $J = 6.4$ Hz). MS (m/z, %): 250 [M-28(N_2), 10], 224 (8), 147 (15), 132 (16), 106 (100), 91 (30), 77 (76). HRMS (APCI): calcd. $C_{17}H_{19}N_4$ ($M + H^+$) 279.1610; found 279.1628.

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1-(4-Methylbenzyl)-3-phenyl-6-methyl-1,6-dihydro-1,2,4,5-tetrazine (5d)

Mp: 81–83 °C. IR (KBr, cm^{-1}): 3024, 2936, 2817, 1633, 1445, 1402, 1384, 1151, 780, 761, 692. ^{1}H NMR ($CDCl_3$) δ ppm: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.97 (d, 2H, $J = 7.2$ Hz), 7.43 (t, 2H, $J = 7.8$ Hz), 7.34 (t, 1H, $J = 7.0$ Hz), 7.12 (d, 2H, $J = 8.0$ Hz), 7.06 (d, 2H, $J = 8.0$ Hz), 4.78 (t, 2H, $J = 16.4$ Hz), 2.96 (q, 1H, $J = 6.1$ Hz), 2.32 (s, 3H), 1.83 (d, 3H, $J = 6.0$ Hz). MS (m/z, %): 250 [M-28(N_2), 5], 147 (13), 132 (3), 105 (100), 91 (8), 77 (32). Anal. calcd. for $C_{17}H_{18}N_4$ (278.15): C, 73.35; H, 6.52; N, 20.13. Found: C, 73.42; H, 6.31; N, 20.25.

1-(4-Methoxybenzyl)-3-phenyl-6-methyl-1,6-dihydro-1,2,4,5-tetrazine (5e)

Yellow liquid. IR (KBr, cm^{-1}): 3062, 2921, 2926, 2835, 1610, 1405, 1352, 1249, 1176, 762, 695. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.97 (d, 2H, $J = 8.0$ Hz), 7.43 (t, 2H, $J = 7.8$ Hz), 7.34 (t, 1H, $J = 7.2$ Hz), 7.11 (d, 2H, $J = 8.0$ Hz), 6.85 (d, 2H, $J = 8.0$ Hz), 4.79 (d, 1H, $J = 16.0$ Hz), 4.74 (d, 1H, $J = 14.4$ Hz), 3.79 (s, 3H), 3.00 (q, 1H, $J = 6.3$ Hz), 1.83 (d, 3H, $J = 6.0$ Hz). MS (m/z, %): 266 [M-28(N_2), 5], 163 (15), 136 (8), 121 (100), 103 (32), 91 (17), 77 (42). HRMS (APCI): calcd. $C_{17}H_{19}N_4O$ ($M + H^+$) 295.1559; found 295.1562.

1-(2-Chlorobenzyl)-3-phenyl-6-methyl-1,6-dihydro-1,2,4,5-tetrazine (5f)

Yellow liquid. IR (KBr, cm^{-1}): 3060, 2984, 2937, 1591, 1471, 1444, 1384, 1307, 1157, 1036, 752, 693, 652. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.97 (d, 2H, $J = 8.0$ Hz), 7.42 (t, 2H, $J = 7.6$ Hz), 7.36 (t, 2H, $J = 7.2$ Hz), 6.98–7.25 (m, 2H, ArH), 6.96–6.98 (m, 1H, ArH), 5.04 (d, 1H, $J = 16.8$ Hz), 4.89 (d, 1H, $J = 16.4$ Hz), 3.02 (q, 1H, $J = 6.3$ Hz), 1.83 (d, 3H, $J = 6.4$ Hz). MS (m/z, %): 298 (M, 1), 270 [M-28(N_2), 10], 167 (45), 152 (14), 127 (100), 103 (52), 89 (55), 77 (32). HRMS (APCI): calcd $C_{16}H_{16}ClN_4$ ($M + H^+$) 299.1063; found 299.1062.

1-(3-Chlorobenzyl)-3-phenyl-6-methyl-1,6-dihydro-1,2,4,5-tetrazine (5g)

Yellow liquid. IR (KBr, cm^{-1}): 3061, 2985, 2938, 1597, 1474, 1405, 1389, 1150, 1071, 762, 694. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.97 (d, 2H, $J = 7.2$ Hz), 7.43 (t, 2H, $J = 7.2$ Hz), 7.35 (t, 1H, $J = 7.4$ Hz), 7.24 (m, 2H, ArH), 7.18 (s, 1H), 7.00–7.14 (m, 1H, ArH), 4.81 (d, 1H, $J = 15.6$ Hz), 4.76 (d, 1H, $J = 16.0$ Hz), 2.91 (q, 1H, $J = 6.1$ Hz), 1.87 (d, 3H, $J = 6.4$ Hz). MS (m/z, %): 270 [M-28(N_2), 8], 166 (10), 125 (100), 103 (40), 91 (28), 76 (18). HRMS (APCI): calcd. $C_{16}H_{16}ClN_4$ ($M + H^+$) 299.1063; found 299.1067.

1-(4-Chlorobenzyl)-3-phenyl-6-methyl-1,6-dihydro-1,2,4,5-tetrazine (5h)

Mp: 88–90 °C. IR (KBr, cm^{-1}): 3062, 2981, 2823, 1598, 1490, 1403, 1344, 1154, 1091, 1013, 780, 763, 694. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.95 (d, 2H, $J = 8.0$ Hz), 7.43 (t, 2H, $J = 7.6$ Hz), 7.35 (t, 1H, $J = 7.4$ Hz), 7.26 (d, 2H, $J = 8.0$ Hz), 7.07 (d, 2H, $J = 8.0$ Hz), 4.82 (d, 1H, $J_1 = 15.6$ Hz), 4.75 (d, 1H, $J = 16.0$ Hz), 2.91

(q, 1H, $J = 6.3$ Hz), 1.85 (d, 3H, $J = 6.4$ Hz). MS (m/z, %): 298 (M, 2), 270 [M-28(N_2), 15], 167 (40), 145 (15), 127 (100), 103 (65), 89 (60), 76 (33). Anal. calcd. for $C_{16}H_{15}ClN_4$ (298.10): C, 64.32; H, 5.06; N, 18.75. Found: C, 64.58; H, 4.92; N, 18.65.

1-Allyl-3-phenyl-6-methyl-1,6-dihydro-1,2,4,5-tetrazine (5i)

Yellow liquid. IR (KBr, cm^{-1}) 3062, 2927, 1732, 1626, 1578, 1448, 1405, 1356, 1170, 1073, 761, 693. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.94 (d, 2H, $J = 8.0$ Hz), 7.42 (t, 2H, $J = 7.4$ Hz), 7.34 (t, 1H, $J = 7.4$ Hz), 5.68–5.72 (m, 1H, CH=CH_2), 5.13 (q, 2H, CH=$\underline{CH_2}$), 4.25 (dd, 2H, $J_1 = 24.4$ Hz, $J_2 = 6.0$ Hz), 2.86 (q,1H, $J = 6.4$ Hz), 1.94 (d, 3H, $J = 6.4$ Hz). MS (m/z, %): 185 [M^+-28(N_2), 10], 178 (100), 161 (50), 134 (15), 118 (10), 89 (7). HRMS (APCI): calcd. $C_{12}H_{15}N_4$ ($M + H^+$) 215.1297; found 215.1294.

1-Methyl-3-phenyl-6-methyl-1,6-dihydro-1,2,4,5-tetrazine (5j)

Yellow liquid. IR (KBr, cm^{-1}): 3062, 2938, 1633, 1509, 1456, 1404, 1352, 1262, 1206, 1070, 799, 761, 695. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.93 (d, 2H, $J = 7.6$ Hz), 7.43 (t, 2H, $J = 7.6$ Hz), 7.34 (t, 1H, $J = 7.4$ Hz), 3.40 (s, 3H), 2.51 (q, 1H, $J = 6.1$ Hz), 2.07 (d, 3H, $J = 6.0$ Hz). MS (m/z, %): 188 (M, 1), 160 [M-28(N_2), 3], 103 (18), 76 (18), 63 (3), 57 (100). HRMS (APCI): calcd. $C_{10}H_{13}N_4$ ($M + H^+$) 189.1140; found 189.1147.

1-Ethyl-3-phenyl-6-methyl-1,6-dihydro-1,2,4,5-tetrazine (5k)

Yellow liquid. IR (KBr, cm^{-1}): 3060, 2979, 2935, 1639, 1626, 1447, 1405, 1306, 1072, 755, 692. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.85 (d, 2H, $J = 7.6$ Hz), 7.43 (t, 2H, $J = 7.2$ Hz), 7.34 (t, 1H, $J = 7.4$ Hz), 3.73 (m, 1H), 3.58 (m, 1H), 2.75 (q, 1H, $J = 6.3$ Hz), 1.97 (d, 3H, $J = 6.8$ Hz), 1.18 (t, 3H, $J = 7.4$ Hz). MS (m/z, %): 201 (M^+, 2), 173 (3), 131 (100), 104 (45), 89 (23), 77 (85). HRMS (APCI): calcd. $C_{11}H_{15}N_4$ ($M + H^+$) 203.1297; found 203.1307.

1,2-Dibenzylidene Hydrazine (6)

Mp: 92–94 °C (lit.[8] 92 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.68 (s, 2H), 7.85–7.87 (m, 4H, ArH), 7.46–7.48 (m, 6H, ArH). MS (m/z, %): 207 (M^+, 60), 180 (35), 131 (100), 104 (36), 89 (20), 77 (75).

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