Reaction of 3-(substituted phenyl)-6-methyl-1,6-dihydro-1,2,4,5-tetrazine with aryl isocyanates, chloroformates and acyl chlorides

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23 1,6-Dihydro-1,2,4,5-tetrazine derivatives **2a–n**, **3a–f**, **4a–c** have been synthesised by reaction of 3-(substituted phenyl)-6-methyl-1,6-dihydro-1,2,4,5-tetrazines (**1a–c**) with aryl isocyanates chloroformates and acyl chlorides, respectively. The yields were in the range 42–97%. It was found that a base promotes the reactions, and electron-withdrawing substituents in the benzene ring at C3 were beneficial to the yield. On substitution of the N(1) atom the conformation of the products at C(6) was inverted.

Keywords: 1,6-dihydro-1,2,4,5-tetrazine, isocyanate, chloroformate, acyl chloride, conformation, homoaromaticity

There are four possible series of dihydro-1,2,4,5-tetrazines, the 1,2-, 1,4-, 1,6- and 3,6-dihydro-1,2,4,5-tetrazines, respectively. There are many reports on the synthesis and biological activity of 1,4-dihydro- and 1,2-dihydro-1,2,4,5-tetrazine derivatives.[1-4] Our group has also synthesised many 1,4-dihydro-1,2,4,5-tetrazine and 1,2-dihydro-1,2,4,5-tetrazine derivatives, and some of them have been found to show strong antitumour activity.[5,6] However, there are only a few reports on the 1,6-dihydro-1,2,4,5-tetrazines and their derivatives.[7-12] Some 1-substituted 3,6-symmetrical dialkyl-1,6-dihydro-1,2,4,5-tetrazines have been synthesised and were considered as showing homoaromaticity.[10] Our group also has synthesised 1-substituted-3,6-dimethyl-1,6-dihydro-1,2,4,5-tetrazines and found some to show pesticide activity.[11] However, there are still no references reporting 1-substituted 3,6-unsymmetrically disubstituted 1,6-dihydro-1,2,4,5-tetrazines until now, on account of the difficult and troublesome work in the separation and purification of 3,6-unsymmetrical disubstituted 1,6-dihydro-1,2,4,5-tetrazines.

Recently, our group has reported the synthesis and X-ray crystallographic analysis of some 3-substituted phenyl-6-methyl-1,6-dihydro-1,2,4,5-tetrazines.[13] In continuation of this work, we set out to prepare some 1-substituted 3-(substituted phenyl)-6-methyl-1,6-dihydro-1,2,4,5-tetrazines by reaction of the 1-unsubstituted compounds with aryl isocyanates, chloroformates and acyl chlorides.

Results and discussion

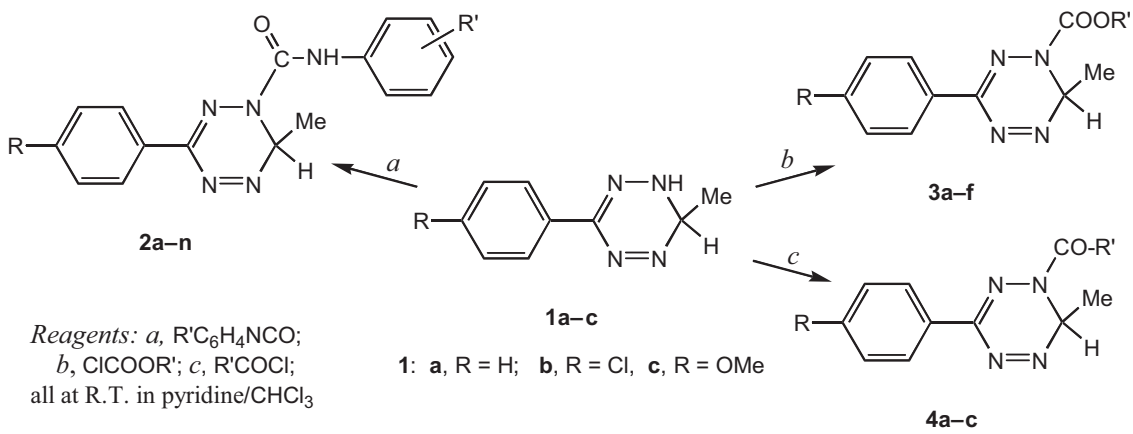
Initial studies were aimed at determining whether base may play a key role in the reaction. Using 3-phenyl-6-methyl-1,6-dihydro-1,2,4,5-tetrazine (**1a**) as the substrate, we examined the reaction of **1a** with equimolar proportions of phenyl isocyanate, methyl chloroformate and acetyl chloride, with and without the presence of base (1 equiv). The results are shown in Table 1. From the data it is clear that the reaction time when base is present is much shorter, and the yields of **2a** much higher. Additionally, when **1a** reacts with PhNCO in the presence of 4-(*N,N*-dimethylamino)pyridine (DMAP) or Et_3N instead of pyridine, the yield of **2a** decreased from 75% to 68% and 53%, respectively. When the solvent was changed from $CHCl_3$ to CH_2Cl_2, THF and MeCN in the presence of pyridine, the yields of **2a** decreased from 75% to 65%, 56% and 60%, respectively.

We used these results to prepare the three sets of 1,6-dihydro-1,2,4,5-tetrazine derivatives **2a–n**, **3a–f** and **4a–c**. The 3-(4-substituted phenyl)-6-methyl-1,6-dihydro-1,2,4,5-

Table 1 Reactions of dihydrotetrazine **1a–c** with PhNCO, MeOCOCl and MeCOCl

Reactant	Base	Solvent	Time/min	Product Yield[a]/%
PhNCO	Pyridine	$CHCl_3$	10	**2a** (75)
PhNCO	None	$CHCl_3$	600	**2a** (26)
MeOCOCl	Pyridine	$CHCl_3$	45	**3a** (95)
MeOCOCl	None	$CHCl_3$	900	**3a** (16)
MeCOCl	Pyridine	$CHCl_3$	30	**4a** (44)
MeCOCl	None	$CHCl_3$	720	**4a** (12.5)
PhNCO	Dmap	$CHCl_3$	10	**2a** (68)
PhNCO	Et_3N	$CHCl_3$	20	**2a** (54)
PhNCO	Pyridine	CH_2Cl_2	30	**2a** (65)
PhNCO	Pyridine	THF	15	**2a** (56)
PhNCO	Pyridine	MeCN	10	**2a** (60)

[a]Isolated yield.



Scheme 1 Preparation of 1,3,6-trisubstituted 1,6-dihydro-1,2,4,5-tetrazines.

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Table 2 Reactions of dihydrotetrazine **1a**: preparation of **2a–n**, **3a–f**, **4a–c**

Product	R	R′	Time/min	Yield/%[a]
2a	H	H	10	75
2b	H	*p*-CH_3	10	79
2c	H	*o*-Cl	10	79
2d	H	*p*-OCH_3	10	80
2e	H	*p*-NO_2	15	61
2f	Cl	*p*-OCH_3	10	81
2g	Cl	*p*-CH_3	10	88
2h	Cl	H	10	97
2i	Cl	*o*-Cl	10	80
2j	Cl	*p*-NO_2	15	75
2k	OCH_3	*p*-CH_3	10	41
2l	OCH_3	*o*-Cl	10	42
2m	OCH_3	*p*-OCH_3	10	42
2n	OCH_3	H	10	60
3a	H	CH_3	45	95
3b	H	CH_2Ph	60	64
3c	Cl	CH_2Ph	60	72
3d	Cl	CH_3	45	48
3e	OCH_3	CH_2Ph	60	44
3f	OCH_3	$CH_2CH_2CH_3$	60	55
4a	H	CH_3	30	44
4b	Cl	CH_3	30	67
4c	OCH_3	CH_2CH_3	40	69

[a]Isolated yields.

tetrazines **1a–c** (1 equiv.) were treated with substituted phenyl isocyanates (1 equiv.), chloroformates (1 equiv.) or acyl chlorides (1 equiv.), respectively, by stirring at room temperature in chloroform in the presence of pyridine (1 equiv.) for the indicated times as shown in Table 2.

As seen in Table 2, in **2a–n**, when the R′ group is fixed, the yields increased with increase of the electron-withdrawing ability of the R group (CH_3O < H < Cl). This could be explained by reference to Scheme 2. It can be seen that the key step of the reaction is the formation of the anion **5**, and the stability of **5** increases as the electron-withdrawing ability of the R group is enhanced. The chloroformates and acyl chlorides proved less reactive than the substituted phenyl isocyanates: to afford **2a–n** reaction times were within 10–15 min, but it required a little longer (30-60 min) to form **3a–f** and **4a–c**.

In our earlier work,[13] we have argued that **1a–c** show homoaromaticity. By analogy with 1-acetyl-3,6-dimethyl-1,6-dihydro-1,2,4,5-tetrazine,[10] **2a–n**, **3a–f** and **4a–c** can also be considered as homoaromatic. In **1a–c**, it was found that the C_6-methyl and methine protons resonated at about 2.0 and 2.4 ppm respectively, whereas in **2a–n**, **3a–f** and **4a–c** these protons resonate at about 1.0 and 6.9 ppm, respectively**.** In other words, in **1a–c**, the C_6-methyl was in the deshielded (equatorial) position and the methine proton was in the shielded position (axial position). In contrast, in **2a–n**, **3a–f** and **4a–c,** the C_6-methyl is in the shielded position (ax position) and the methine proton is in a strongly deshielded position (eq position). This is a result of the conformational inversion of the tetrazine ring as shown in Fig.1. The reason

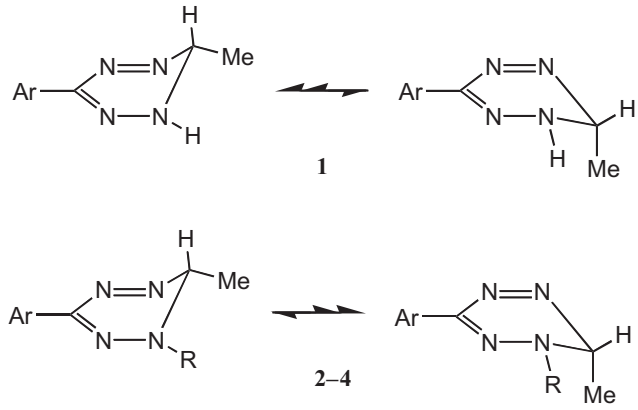


Fig. 1 Conformational preferences in **1** and **2–4.**

for this inversion may be the effect of steric hindrance of the group substituted at the N1 atom. This necessarily (for reasons of resonance) takes the equatorial position, and so forces the bulkier methyl group into the axial configuration.

Experimental

Melting points were carried out on a XRC-1 apparatus (Beijing Technical Instrument Co.). Infrared spectra were recorded, from KBr discs of solid materials, on a Nicolex FI-IR-170 instrument. ^{1}H NMR spectra were run on a Bruker AC400 (400 MHz).spectrometer using TMS as internal standard and $CDCl_3$ as the solvent. High resolution mass spectra (HRMS) were obtained on an Agilent 6210 TOF LC/MS. TCL was carried out on silica gel UV-254 plates, eluting with dichloromethane.

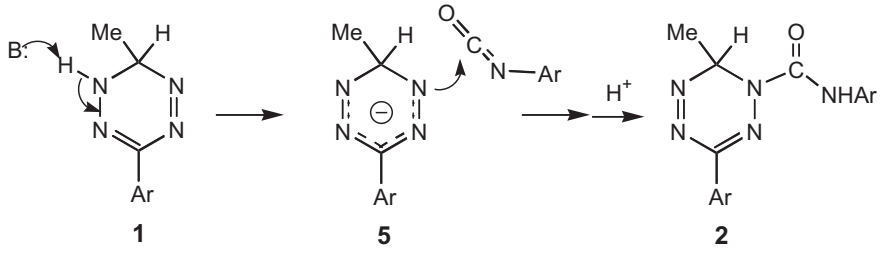
Compounds **1a–c** were synthesised by a literature method,[13] as were the substituted phenyl isocyanates.[14] Other solvents and reagents were commercially available and used without further purification or purified by standard methods prior to use.

Preparation of dihydrotetrazine arylaminocarboxamides **2a–n**, *general procedure*

3-(Substituted phenyl)-6-methyl-1,6-dihydro-1,2,4,5-tetrazine **1a–c** (3.0 mmol), chloroform (10 ml) and pyridine (0.25 ml, 3.1 mmol) were mixed. Substituted phenyl isocyanates (3.0 mmol) in chloroform (10 ml) were added dropwise with stirring at room temperature. After the starting 1,6-dihydro-1,2,4,5-tetrazine was completely consumed (the reaction courses was monitored by TLC), evaporation of the chloroform, the crude *N*-(substituted phenyl)-3-(substituted phenyl)-6-methyl-1,6-dihydro-1,2,4,5-tetrazine-1-carboxamide **2a–n** was obtained and purified by preparative thin-layer chromatography over silica gel PF_{254} (2 mm) dichloromethane: petroleum ether = 1 : 1).

N-Phenyl-6-methyl-3-phenyl-1,6-dihydro-1,2,4,5-tetrazine-1-carboxamide (**2a**): M.p. 96–98°C. IR (KBr, cm^{-1}) 3307 s (N–H), 2924 w (C–H), 1683 s (C=O), 1536 s (C=O–N) 1443 cm^{-1} s (ring). NMR: δ_H 8.63 (s, 1H), 8.15–8.17 (m, 2H, ArH), 7.51–7.55 (m, 3H, ArH), 7.28–7.40 (m, 5H, ArH), 6.91 (q, 1H, J = 6.4 Hz), 1.08 (d, 3H, J = 6.4 Hz). HRMS (APCI): calcd $C_{16}H_{16}N_5O$ (M + H^+) 294.1354; found 294.1305. Anal. Calcd for $C_{16}H_{15}N_5O$ (293.32): C, 65.52; H, 5.15; N, 23.88. Found: C, 65.43; H, 5.31; N, 24.02%.

N-(p-Methylphenyl)-6-methyl-3-phenyl-1,6-dihydro-1,2,4,5-tetrazine-1-carboxamide (**2b**): M.p. 115–117°C. IR: ν_{max} 3320 s (N–H), 2922 w (C–H), 1686 s (C=O), 1526 s (C=O–N) 1382 cm^{-1} s (ring). NMR: δ_H 8.57 (s, 1H), 8.16–8.18 (m, 2H, ArH), 7.54–7.57



Scheme 2 Proposed scheme for formation of amides **2.**

(m, 3H, ArH), 7.41 (d, 2H, *J* = 8.4 Hz), 7.17 (d, 2H, *J* = 8.4 Hz), 6.92 (q, 1H, *J* = 6.4 Hz), 2.34 (s, 3H), 1.09 (d, 3H, *J* = 6.4 Hz). HRMS (APCI): calcd $C_{17}H_{18}N_5O$ (M + H$^+$) 308.1511; found 308.1550. Anal. Calcd for $C_{17}H_{17}N_5O$ (307.35): C, 66.43; H, 5.58; N, 22.79. Found: C, 66.70; H, 5.56; N, 23.12%.

N-(o-Chlorophenyl)-6-methyl-3-phenyl-1,6-dihydro-1,2,4,5-tetrazine-1-carboxamide (**2c**): M.p. 108–110°C. IR: ν_{max} 3362 s (N–H), 2929 w (C–H), 1715 s (C=O), 1528 s (C=O–N), 1378 cm^{-1} s (ring). NMR: δ_H 9.44 (s, 1H), 8.30 (d, 1H, *J* = 8.0 Hz), 8.17–8.19 (m, 2H, ArH), 7.53–7.57 (m, 3H, ArH), 7.40 (d, 1H, *J* = 8.0 Hz), 7.31 (t, 1H, *J* = 8.0 Hz), 7.06 (t, 1H, *J* = 8.0 Hz), 6.88 (q, 1H, *J* = 6.4 Hz), 1.11 (d, 3H, *J* = 6.8 Hz). HRMS (APCI): Calcd for $C_{16}H_{15}ClN_5O$ (M + H$^+$): 328.0965; found 328.0983.

N-(p-Methoxyphenyl)-6-methyl-3-phenyl-1,6-dihydro-1,2,4,5-tetrazine-1-carboxamide (**2d**): M.p. 135–137°C. IR: ν_{max} 3305 s (N–H), 2921 w (C–H), 1683 s (C=O), 1538 s (C=O–N), 1378 cm^{-1} s (ring). NMR: δ_H 8.50 (s, 1H), 8.14–8.16 (m, 2H, ArH), 7.53–7.55 (m, 3H, ArH), 7.42 (d, 2H, *J* = 8.4 Hz), 6.84–6.91 (m, 3H), 3.81 (s, 3H), 1.07 (d, 3H, *J* = 6.4 Hz). HRMS (APCI): Calcd for $C_{17}H_{18}N_5O_2$ (M + H$^+$): 324.1460; found 324.1434.

N-(p-Nitrophenyl)-6-methyl-3-phenyl-1,6-dihydro-1,2,4,5-tetrazine-1-carboxamide (**2e**): M.p. 153–155°C. IR: ν_{max} 3397 s (N–H), 2981 w (C–H), 1692 s (C=O), 1540 s (C=O–N), 1387 cm^{-1} s (ring). NMR: δ_H 8.97 (s, 1H), 8.24 (d, 2H, *J* = 9.2 Hz), 8.15–8.18 (m, 2H, ArH), 7.72 (d, 2H, *J* = 9.2 Hz), 7.56–7.57 (m, 3H, ArH), 6.89 (q, 1H, *J* = 6.4 Hz), 1.11 (d, 3H, *J* = 6.8 Hz). HRMS (APCI): Calcd for $C_{16}H_{15}N_6O_3$ (M + H$^+$): 339.1206; found 339.1217.

3-(p-Chlorophenyl)-N-(p-methoxyphenyl)-6-methyl-1,6-dihydro-1,2,4,5-tetrazine-1-carboxamide (**2f**): M.p. 140–142°C. IR: ν_{max} 3318 s (N–H), 2982 w (C–H), 1699 s (C=O), 1538 s (C=O–N), 1415 s (ring), 736 cm^{-1} m (C–Cl). NMR: δ_H 8.46 (s, 1H), 8.08 (d, 2H, *J* = 8.8 Hz), 7.51 (d, 2H, *J* = 8.8 Hz), 7.41 (d, 2H, *J* = 9.2 Hz), 6.90 (d, 2H, *J* = 9.2 Hz), 6.90 (q, 1H, *J* = 6.4 Hz), 3.81 (s, 3H), 1.06 (d, 3H, *J* = 6.8 Hz). HRMS (APCI): Calcd for $C_{17}H_{17}ClN_5O_2$ (M + H$^+$): 358.1071; found 358.1083.

3-(p-Chlorophenyl)-6-methyl-N-(p-methylphenyl)-1,6-dihydro-1,2,4,5-tetrazine-1-carboxamide (**2g**): M.p. 149–151°C. IR: ν_{max} 3296 s (N–H), 2980 w (C–H), 1704 s (C=O), 1529 s (C=O–N), 1385 s (ring), 720 cm^{-1} m (C–Cl). NMR: δ_H 8.52 (s, 1H), 8.09 (d, 2H, *J* = 8.4 Hz), 7.51 (d, 2H, *J* = 8.4 Hz), 7.40 (d, 2H, *J* = 8.0 Hz), 7.16 (d, 2H, *J* = 8.0 Hz), 6.91 (q, 1H, *J* = 6.4 Hz), 2.34 (s, 3H), 1.07 (d, 3H, *J* = 6.4 Hz). HRMS (APCI): Calcd for $C_{17}H_{17}ClN_5O$ (M + H$^+$): 342.1122; found 342.1107.

3-(p-Chlorophenyl)-6-methyl-N-phenyl-1,6-dihydro-1,2,4,5-tetrazine-1-carboxamide (**2h**): M.p. 131–133°C. IR: ν_{max} 3295 s (N–H), 2983 w (C–H), 1692 s (C=O), 1540 s (C=O–N), 1384 s (ring), 689 cm^{-1} m (C-Cl). ^{1}H NMR ($CDCl_3$) δ ppm: 8.58 (s, 1H), 8.10 (d, 2H, *J* = 8.4 Hz), 7.52 (d, 4H, *J* = 8.0 Hz), 7.37 (t, 2H, *J* = 7.8 Hz), 7.15 (t, 1H, *J* = 7.2 Hz), 6.92 (q, 1H, *J* = 6.4 Hz), 1.08 (d, 3H, *J* = 6.8 Hz). HRMS (APCI): Calcd for $C_{16}H_{15}ClN_5O$ (M + H$^+$): 328.0965; found 328.0957.

N-(o-Chlorophenyl)-3-(p-chlorophenyl)-6-methyl-1,6-dihydro-1,2,4,5-tetrazine-1-carboxamide (**2i**): M.p. 136–138°C. IR: ν_{max} 3347 s (N–H), 2989 w (C–H), 1711 s (C=O), 1533 s (C=O–N), 1382 s (ring), 731 cm^{-1} m (C–Cl). NMR: δ_H 9.40 (s, 1H), 8.29 (d, 1H, *J* = 8.0 Hz), 8.12 (d, 2H, *J* = 8.4 Hz), 7.52 (d, 2H, *J* = 8.4 Hz), 7.41 (d, 1H, *J* = 8.0 Hz), 7.32 (t, 1H, *J* = 7.8 Hz), 7.07 (t, 1H, *J* = 7.8 Hz), 6.89 (q, 1H, *J* = 6.4 Hz), 1.11 (d, 3H, *J* = 6.4 Hz). HRMS (APCI): Calcd for $C_{16}H_{14}Cl_2N_5O$ (M + H$^+$): 362.0574; found 362.0562.

3-(p-Chlorophenyl)-6-methyl-N-(p-nitrophenyl)-1,6-dihydro-1,2,4,5-tetrazine-1-carboxamide (**2j**): M.p. 154–156°C. IR: ν_{max} 3397 s (N–H), 2981 w (C–H), 1742 m (C=O), 1539 s(C=O–N), 1384 s (ring), 1336 cm^{-1} s (Ar-NO_2). ^{1}H NMR ($CDCl_3$) δ ppm: 8.92 (s, 1H), 8.25 (d, 2H, *J* = 8.8 Hz), 8.20 (d, 2H, *J* = 8.4 Hz), 8.10 (d, 2H, *J* = 8.4 Hz), 7.73 (d, 2H, *J* = 8.8 Hz), 6.90 (q, 1H, *J* = 6.4 Hz), 1.11 (d, 3H, *J* = 6.8 Hz). HRMS (APCI): Calcd for $C_{16}H_{14}ClN_6O_3$ (M + H$^+$): 373.0816; found 373.0797.

3-(p-Methoxyphenyl)-6-methyl-N-(p-methylphenyl)-1,6-dihydro-1,2,4,5-tetrazine-1-carboxamide (**2k**): M.p. 117–119°C. IR: ν_{max} 3270 s (N–H), 2921 w (C–H), 1674 s (C=O), 1514 s (C=O–N), 1387 cm^{-1} m (ring). NMR: δ_H 8.54 (s, 1H), 8.10 (d, 2H, *J* = 8.8 Hz), 7.40 (d, 2H, *J* = 8.0 Hz), 7.16 (d, 2H, *J* = 8.0 Hz), 7.06 (d, 2H, *J* = 8.8 Hz), 6.88 (q, 1H, *J* = 6.4 Hz), 3.91 (s, 3H), 2.33 (s, 3H), 1.06 (d, 3H, *J* = 6.4 Hz). HRMS (APCI): Calcd for $C_{18}H_{20}N_5O_2$ (M + H$^+$): 338.1617; found 338.1647.

N-(o-Chlorophenyl)-3-(p-methoxyphenyl)-6-methyl-1,6-dihydro-1,2,4,5-tetrazine-1-carboxamide (**2l**): M.p. 145–148°C. IR: ν_{max} 3262 s (N–H), 2950 w (C–H), 1680 s (C=O), 1510 s (C=O–N), 1385 cm^{-1} m (ring). NMR: δ_H 9.42 (s, 1H), 8.31 (d, 1H, *J* = 8.4 Hz), 8.13 (d, 2H, *J* = 8.8 Hz), 7.41 (d, 1H, *J* = 8.0 Hz), 7.31 (t, 1H, *J* = 7.6 Hz), 7.07 (t, 3H), 6.86 (q, 1H, *J* = 6.4 Hz), 3.91 (s, 3H), 1.10 (d, 3H, *J* = 6.8 Hz). HRMS (APCI): Calcd for $C_{17}H_{17}ClN_5O_2$ (M + H$^+$): 358.1071; found358.1056.

N-(p-Methoxyphenyl) 3-(p-methoxyphenyl)-6-methyl-1,6-dihydro-1,2,4,5-tetrazine-1-carboxamide (**2m**): M.p. 124–126°C.IR: ν_{max} 3374 s (N–H), 2960 w (C–H), 1708 s (C=O), 1516 s (C=O–N), 1388 cm^{-1} m (ring). NMR: δ_H 8.48 (s, 1H), 8.10 (d, 2H, *J* = 8.8 Hz), 7.42 (d, 2H, *J* = 9.2 Hz), 7.06 (d, 2H, *J* = 8.8 Hz), 6.89 (d, 2H, *J* = 9.2 Hz), 6.88 (q, 1H, *J* = 5.6 Hz), 3.91 (s, 3H), 3.81 (s, 3H), 1.06 (d, 3H, *J* = 6.4 Hz). HRMS (APCI): Calcd for $C_{18}H_{20}N_5O_3$ (M + H$^+$): 354.1566; found 354.1571.

3-(p-Methoxyphenyl)-6-methyl-N-phenyl-1,6-dihydro-1,2,4,5-tetrazine-1-carboxamide (**2n**): M.p. 103–105°C. IR: ν_{max} 3356 s (N–H), 2923 w (C–H), 1706 s (C=O), 1509 s (C=O–N), 1385 cm^{-1} m (ring). ^{1}H NMR ($CDCl_3$) δ ppm: 8.61 (s, 1H), 8.11 (d, 2H, *J* = 8.8 Hz), 7.52 (d, 2H, *J* = 8.0 Hz), 7.36 (t, 2H, *J* = 7.8 Hz), 7.13 (t, 1H, *J* = 7.2 Hz), 7.06 (d, 2H, *J* = 8.8 Hz), 6.89 (q, 1H, *J* = 6.4 Hz), 3.91 (s, 3H), 1.07 (d, 3H, *J* = 6.4 Hz). HRMS (APCI): Calcd for $C_{17}H_{18}N_5O_2$ (M + H$^+$): 324.1460; found 324.1462.

Preparation of alkyl 1,6-dihydrotetrazine-1-carboxylates **3a-f**: *general procedure*

The dihydrotetrazine **1** (3.0 mmol) was taken up in chloroform (10 ml) containing pyridine (0.25 ml, 3.1 mmol) and stirred at room temperature while the chloroformate (3.0 mmol) in chloroform (10 ml) was added dropwise. After completion of the reaction (see Table 2) the separated solids were filtered off, chloroform was removed by evaporation and the residue purified by preparative thin-layer chromatography over silica gel PF_{254} (2 mm) (dichloromethane: petroleum ether = 6 : 4).

Methyl 6-methyl-3-phenyl-1,6-dihydro-1,2,4,5-tetrazine-1-carboxylate (**3a**): Oil. IR: ν_{max} 3090 w (ArH), 2956 w (C–H), 1730 s (C=O), 1390 cm^{-1} s (ring). NMR: δ_H 8.14-8.16 (m, 2H, ArH), 7.49–7.50 (m, 3H, ArH), 6.59 (q, 1H, *J* = 6.4 Hz), 3.95 (s, 3H), 1.07 (d, 3H, *J* = 6.4 Hz). HRMS (APCI): Calcd for $C_{11}H_{13}N_4O_2$ (M + H$^+$): 233.1039; found 233.1015.

Benzyl 3-phenyl-6-methyl-1,6-dihydro-1,2,4,5-tetrazine-1-carboxylate (**3b**): Oil. IR: ν_{max} 3046 w (ArH), 2973 w (C–H), 1748 s (C=O), 1392 cm^{-1} s (ring). NMR: δ_H 8.14-8.17 (m, 2H, ArH), 7.48–7.50 (m, 3H, ArH), 7.36–7.44 (m, 5H, ArH), 6.59 (q, 1H, *J* = 6.8 Hz), 5.36 (s, 2H), 1.07 (d, 3H, *J* = 6.8 Hz). HRMS (APCI): Calcd for $C_{17}H_{17}N_4O_2$ (M + H$^+$): 309.1352; found 309.1368.

Benzyl 3-(p-chlorophenyl)-6-methyl-1,6-dihydro-1,2,4,5-tetrazine-1-carboxylate (**3c**): M.p. 66–68°C.IR: ν_{max} 3050 w (ArH), 2979 w (C–H), 1727 s (C=O), 1393 cm^{-1} s (ring). NMR: δ_H 8.09 (d, 2H, *J* = 8.4 Hz), 7.39–7.48 (m, 5H, ArH), 7.36 (d, 2H, *J* = 8.4 Hz), 6.59 (q, 1H, *J* = 6.4 Hz), 5.36 (s, 2H), 1.07 (d, 3H, *J* = 6.4 Hz). HRMS (APCI): Calcd for $C_{17}H_{16}ClN_4O_2$ (M + H$^+$): 343.0962; found 343.0941.

Methyl 3-(p-chlorophenyl)-6-methyl-1,6-dihydro-1,2,4,5-tetrazine-1-carboxylate (**3d**): oil. IR: ν_{max} 3089 w (ArH), 2956 w (C–H), 1732 s (C=O), 1389 s (ring), 723 cm^{-1} m (C–Cl). ^{1}H NMR ($CDCl_3$) δ ppm: 8.09 (d, 2H, *J* = 8.8 Hz), 7.47 (d, 2H, *J* = 8.8 Hz), 6.60 (q, 1H, *J* = 6.5 Hz), 3.96 (s, 3H), 1.07 (d, 3H, *J* = 6.8 Hz). HRMS (APCI): Calcd for $C_{11}H_{12}ClN_4O_2$ (M + H$^+$): 267.0649; found 267.0641.

Benzyl 3-(p-methoxyphenyl)-6-methyl-1,6-dihydro-1,2,4,5-tetrazine-1-carboxylate (**3e**): Oil. IR: ν_{max} 3020 w (ArH), 2934 w (C–H), 1722 s (C=O), 1398 cm^{-1} s (ring). ^{1}H NMR ($CDCl_3$) δ ppm: 8.12 (d, 2H, *J* = 8.4 Hz), 7.35-7.46 (m, 5H, ArH), 7.02 (d, 2H, *J* = 8.4 Hz), 6.58 (q, 1H, *J* = 6.5 Hz), 5.36 (s, 2H), 3.89 (s, 3H), 1.07 (d, 3H, *J* = 6.4 Hz). HRMS (APCI): calcd $C_{18}H_{19}N_4O_3$ (M + H$^+$): 339.1457; found 339.1442.

Propyl 3-(p-methoxyphenyl)-6-methyl-1,6-dihydro-1,2,4,5-tetrazine-1-carboxylate (**3f**): M.p. 117–119°C.IR: ν_{max} 3049 w (ArH), 2939 w (C–H), 1701 s (C=O), 1391 cm^{-1} s (ring). ^{1}H NMR ($CDCl_3$) δ ppm: 8.12 (d, 2H, *J* = 8.8 Hz), 7.02 (d, 2H, *J* = 8.8 Hz), 6.57 (q, 1H, *J* = 6.4 Hz), 4.29 (t, 2H, *J* = 6.8 Hz), 3.90 (s, 3H), 1.79 (ddd, 2H, *J* = 7.2 Hz), 1.08 (d, 3H, *J* = 6.0 Hz), 1.01 (t, 3H, *J* = 7.4 Hz). HRMS (APCI): Calcd for $C_{14}H_{19}N_4O_3$ (M + H$^+$): 291.1457; found 291.1443.

Preparation of 1-acyl-1,6-dihydrotetrazines **4a–c**: *general procedure*

Following the method used for the synthesis of compounds **3**, but using acetyl or propionyl chloride (3.0 mmol) in lieu of the chloroformates. Purification by preparative thin-layer chromatography over silica gel PF_{254} (2 mm) (dichloromethane: petroleum ether 1 : 1).

1-Acetyl-6-methyl-3-phenyl-1,6-dihydro-1,2,4,5-tetrazine (**4a**): Oil. IR: ν_{max} 3090 w (ArH), 2918 w (C–H), 1706 s (C=O), 1382 cm^{-1} s (ring). NMR: δ_H 8.15–8.17 (m, 2H, ArH), 7.51–7.53 (m, 3H, ArH),

6.87 (q, 1H, J = 6.8 Hz), 2.49 (s, 3H), 1.06 (d, 3H, J = 6.4 Hz). HRMS (APCI): Calcd for $C_{11}H_{13}N_4O$ ($M + H^+$): 217.1089; found 217.1068.

1-Acetyl-3-(p-chlorophenyl)-6-methyl-1,6-dihydro-1,2,4,5-tetrazine (**4b**): M.p. 79–81°C. IR (KBr, cm^{-1}) 3050 w (ArH), 2974 w (C–H), 1696 s (C=O), 1385 s (ring), 717 m (C–Cl). ^{1}H NMR ($CDCl_3$) δ ppm: 8.10 (d, 2H, J = 8.0), 7.49 (d, 2H, J = 8.0), 6.87 (q, 1H, J = 6.7 Hz), 2.49 (s, 3H), 1.05 (d, 3H, J = 6.4 Hz). HRMS (APCI): Calcd for $C_{11}H_{12}ClN_4O$ ($M + H^+$): 251.0700; found 251.0705.

3-(p-Methoxyphenyl)-6-methyl-1-propionyl-1,6-dihydro-1,2,4,5-tetrazine (**4c**): M.p. 67–69°C. IR: ν_{max} 3010 w (ArH), 2934 w (C–H), 1722 s (C=O), 1398 cm^{-1} s (ring). NMR: δ_H 8.10 (d, 2H, J = 8.8 Hz), 7.03 (d, 2H, J = 8.8 Hz), 6.84 (q, 1H, J = 6.4 Hz), 3.89 (s, 3H), 2.95–3.05 (m, 1H, CH_2), 2.72–2.85 (m, 1H, CH_2), 1.20 (t, 3H, J = 7.6 Hz), 1.04 (d,3H, J = 6.4 Hz). HRMS (APCI): Calcd for $C_{13}H_{17}N_4O_2$ ($M + H^+$): 261.1352; found 261.1336.

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