Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters 49 (2008) 2748–2751
Tetrahedron Letters

Nucleophilic substitution with amines: dihydro-1,2,4,5-tetrazines are more useful precursors than 1,2,4,5-tetrazines

Arnaud Cutivet, Emmanuel Leroy, Eric Pasquinet *, Didier Poullain

Commissariat à l'Energie Atomique, BP 16, 37260 Monts, France

Received 13 July 2007; revised 22 February 2008; accepted 27 February 2008
Available online 4 March 2008

Abstract

A one step synthesis of (di)alkylamino-substituted 1,2,4,5-tetrazines direct from 3,6-disubstituted-1,2-dihydro-1,2,4,5-tetrazine precursors is described. A comparative study revealed that the described method not only avoids the up-to-now required oxidation step but also lower reaction times and/or temperatures compared to usual protocols. The efficiency of the reaction was highlighted by a practical synthesis of 3,6-bis(methylamino)-1,2,4,5-tetrazine using aqueous methylamine. Other primary and secondary amines were also found to give disubstitution products when reacted with 3,6-bis(methylsulfanyl)-1,2,4,5-dihydrotetrazine.

Keywords: Dihydrotetrazines; Tetrazines; Nucleophilic substitution; Methylamine; Oxidation

Due to their large scope of applications, tetrazine-based compounds have been the subject of numerous studies.[1] Tetrazines are widely known to react in inverse demand Diels–Alder reactions[2–6] and exhibit energetic,[7–11] dye,[12] insecticide,[13] optical,[14,15] electrochemical[16] and biomedical[17,18] properties. The electron deficient tetrazine ring leads to an increased reactivity towards nucleophiles. Therefore, nucleophilic aromatic substitution of 3,6-disubstituted-1,2,4,5-tetrazines was widely employed to synthesize new unsymmetrical or symmetrical tetrazines, unavailable by other synthetic methods. A wide range of nitrogen, oxygen and sulfur nucleophiles was used in such processes.[19–27] Commonly, the first leaving group was rapidly displaced, with the second displacement requiring more drastic conditions.

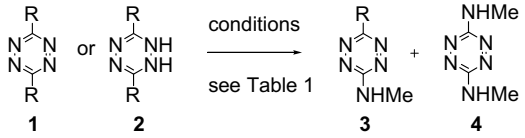
The electrophilic partners were mostly 3,6-bis(methylsulfanyl)-1,2,4,5-tetrazine **1a**,[28] 3,6-bis(3,5-dimethylpyrazol-1-yl)-1,2,4,5-tetrazine **1b**,[20,29] 3,6-bis(4-bromo-3,5-dimethylpyrazol-1-yl)-1,2,4,5-tetrazine[24,25] and 3,6-dichloro-1,2,4,5-tetrazine.[27,30] All of these are easily available aromatic 1,2,4,5-tetrazines obtained by the oxidation of the corresponding dihydro-1,2,4,5-tetrazines.

Herein, we report the synthesis of (di)alkylamino-substituted 1,2,4,5-tetrazines which were obtained, contrary to the usual pattern, directly from a dihydrotetrazine compound rather than from an aromatic tetrazine. This is of practical significance, since the oxidation step may be somewhat cumbersome. For example, 3,6-bis(3,5-dimethylpyrazol-1-yl)-dihydro-1,2,4,5-tetrazine **2b** is converted to 3,6-bis(3,5-dimethylpyrazol-1-yl)-1,2,4,5-tetrazine **1b** using N_2O_4,[20] a highly toxic and corrosive gas. To the best of our knowledge, there is only one example of substitution on a dihydro-1,2,4,5-tetrazine (**2b**, hydrazine as the nucleophile).[30] Yield, detailed experimental conditions and comparison with the usual reaction on the corresponding 1,2,4,5-tetrazine[31] were not specified.

In particular, we addressed the synthesis of 3,6-bis(methylamino)-1,2,4,5-tetrazine **4** (Scheme 1). This compound was claimed to exhibit herbicide properties[32] and stimulated the curiosity of different groups of physical chemists.[21,22,33] In the only reported synthesis of **4**,[21] 3,6-bis(methylsulfanyl)-1,2,4,5-tetrazine **1a** underwent nucleophilic substitution by gaseous methylamine.

* Corresponding author. Tel.: +33 0 247345694; fax: +33 0 247345142.
E-mail address: eric.pasquinet@cea.fr (E. Pasquinet).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.02.145



Scheme 1. Synthesis of methylamino-substituted 1,2,4,5-tetrazines from (dihydro)-1,2,4,5-tetrazines bearing leaving groups.

We investigated the methylamination reaction in detail, using different methylamine reactants and two electrophilic dihydro-1,2,4,5-tetrazine precursors. The corresponding tetrazines in their aromatic form were also included for comparison purpose (Table 1). Ethanolic methylamine solutions or methylamine hydrochloride in the presence of a base both lead to extensive degradation. Methylamine in water or in THF was found more suitable and was used throughout the study. As expected, mono- and disubstitution products were observed depending on the conditions.

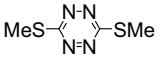
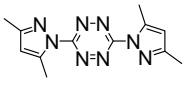
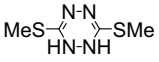
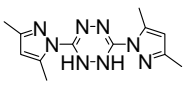
Aqueous methylamine in acetonitrile always resulted in a higher or faster conversion in **4** than $MeNH_2$ in THF. This is certainly because the medium was more polar using the former conditions (entries 6, 7 and 2, 3). Concerning the aromatic starting materials, we also noticed that **1b** was more prone to disubstitution than **1a** using the THF conditions, suggesting that the dimethylpyrazolyl moiety was more easily displaced than the methylsulfanyl group (entries 1 and 2).

But the more striking result of this study is that disubstitution was a much more efficient process when dihydrotetrazine precursors were used instead of the usual tetrazine counterparts. For example, in the bis(dimethylpyrazolyl) series, the disubstituted product **4** was almost the only product detected when dihydrotetrazine precursor **2b** was used as the starting material, whereas the intermediate monoaminated compound **3** was the major product in the case of tetrazine **1b** under the same conditions (entries 2, 6 and 3, 7).

This result is important from a mechanistic point of view. As a matter of fact, one could have thought that the first step of the process was oxidation of the dihydrotetrazine precursor to the corresponding tetrazine followed by substitution on the aromatic product. However, this hypothesis was ruled out since in this case the whole oxidation/substitution process could not have been faster than the substitution reaction on tetrazine as the starting material. Thus, this clearly shows that methylamination is faster on dihydrotetrazine precursors than on tetrazine counterparts. The reason for this could be that nucleophilic substitution is expected to be easier on a non-aromatic compound. A completely different pathway such as a S_N(ANRORC) process is also possible, since substituted tetrazines are known to undergo such reactions.[34] Methylamine also has been involved in S_N(ANRORC) pathways in other aza-aromatic series.[35,36]

The final, spontaneous oxidation step is still not fully understood. As a matter of fact, the reaction was carried out in relatively concentrated solutions in a sealed vessel. Under the same conditions, dissolved or atmospheric oxygen would only partially account for oxidation. The deep red colour which developed quickly when the reaction mixture was exposed to ambient air suggested that oxidation occurred spontaneously during treatment.

Table 1
Methylamination conditions and results

Entry	Starting material	Conditions	Methylamine[a]	Ratio **3**:**4**[b] (%)	Yield of **4**[c] (%)
1	 **1a**	THF, 40 °C, 24 h	2 M THF solution	100:0	—
2	 **1b**	THF, 40 °C, 24 h	2 M THF solution	76:24	6
3	**1b**	MeCN, rt,[d] 12 h	40 wt % aqueous solution	53:47	35
4	 **2a**	MeCN, rt, 4 d	40 wt % aqueous solution	2:98	70
5	**2a**	MeCN, rt, 24 h	Anhydrous	58:42	22
6	 **2b**	THF, 40 °C, 24 h	2 M THF solution	4:96	45
7	**2b**	MeCN, rt, 12 h	40 wt % aqueous solution	0:100	24

[a] In all cases, a large excess of methylamine was added (20 equiv).
[b] Determined by integration of appropriate ^{1}H NMR signals in the crude product.
[c] Isolated yield of pure product.
[d] rt: Room temperature.

As in the tetrazine series, the dihydro-1,2,4,5-tetrazine bearing dimethylpyrazole as the leaving group was more rapidly substituted by methylamine than the corresponding bis(methylsulfanyl) derivative. However, chromatographic removal of the dimethylpyrazole formed in the substitution process was difficult, thus decreasing the yields of pure 3,6-bis(methylamino)-1,2,4,5-tetrazine **4** (entries 6 and 7). Therefore, even if disubstitution required longer times, 3,6-bis(methylsulfanyl)-1,2-dihydro-1,2,4,5-tetrazine **2a** was our best choice of precursor since the by-product methanethiol was pumped off with the solvent during work-up. The isolated yield was 70%, a satisfying result considering that the up-to-now required oxidation step was avoided (entry 4).[37]

Interestingly, using liquefied gaseous methylamine with our optimal conditions only resulted in a 22% yield due to low conversion (mono- and disubstituted products were formed in nearly equal amounts, entry 5).

The substitution reaction on dihydro-1,2,4,5-tetrazine **2a** was extended to other common amines (Scheme 2, Table 2).[38] Ethylamine was as effective as methylamine and the monosubstitution product was not detected when the reaction was conducted at 50 °C. The expected disubstitution product **6a** was obtained in 89% yield. Surprisingly, the other primary amine benzylamine reacted poorly. Even at 70 °C, only 17% of 3,6-bis(benzylamino)-1,2,4,5-tetrazine **6b** was isolated along with 77% of the monosubstituted product **5b**. However, a secondary amine, pyrrolidine, was also shown to give the corresponding disubstituted product **6c** in satisfactory yield (52%). The monosubstituted compound **5c** was also observed (15% yield).

In conclusion, we have disclosed a convenient one step methylamination of dihydro-1,2,4,5-tetrazines leading to methylamino-substituted 1,2,4,5-tetrazines. This process avoids both the oxidation step to obtain the usual tetrazine precursor and the use of gaseous methylamine, thus providing a practical synthesis of 3,6-bis(methylamino)-1,2,4,5-tetrazine **4**. A comparative study revealed that dihydrotetrazine precursors are more prone to substitution than their tetrazine counterparts. The method was also extended to other amines, thus highlighting the versatility of this reaction.

2a **5a-c** **6a-c**

Scheme 2. Synthesis of (di)alkylamino-substituted 1,2,4,5-tetrazines.

Table 2
Substitution of **2a** with various amines: conditions and results

R′	R″	Temperature (°C)	Monosubstitution product (isolated yield)	Disubstitution product (isolated yield)
H	Et	50	—	**6a** (89%)
H	Bn	70	**5b** (77%)	**6b** (17%)
–$(CH_2)_4$–		50	**5c** (15%)	**6c** (52%)

References and notes

1. (a) Saracoglu, N. *Tetrahedron* **2007**, *63*, 4199–4236; (b) Neunhoeffer, H. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 3; (c) Sauer, J. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. 6.
2. Hamasaki, A.; Ducray, R.; Boger, D. L. *J. Org. Chem.* **2006**, *71*, 185–193.
3. Soenen, D. R.; Zimpleman, J. M.; Boger, D. L. *J. Org. Chem.* **2003**, *68*, 3593–3598.
4. Wan, Z. K.; Woo, G. H. C.; Snyder, J. K. *Tetrahedron* **2001**, *57*, 5497–5507.
5. Kotschy, A.; Novák, Z.; Vincze, Z.; Smith, D. M.; Hajós, G. *Tetrahedron Lett.* **1999**, *40*, 6313–6316.
6. Seitz, G.; Overheu, W. *Arch. Pharm.* **1977**, *310*, 936–938.
7. Chavez, D. E.; Hiskey, M. A.; Gilardi, R. *Org. Lett.* **2004**, *6*, 2889–2891.
8. Talawar, M. B.; Sivabalan, R.; Senthilkumar, N.; Prabhu, G.; Asthana, S. N. *J. Hazard. Mater.* **2004**, *113*, 11–25.
9. Pagoria, P. F.; Lee, G. S.; Mitchell, A. R.; Schmidt, R. D. *Thermochim. Acta* **2002**, *384*, 187–204.
10. Oxley, J. C.; Smith, J. L.; Chen, H. *Thermochim. Acta* **2002**, *384*, 91–99.
11. Chavez, D. E.; Hiskey, M. A.; Gilardi, R. D. *Angew. Chem., Int. Ed.* **2000**, *39*, 1791–1793.
12. Kotone, A.; Hoda, M. (Sakai Chem. Int. Co. Ltd) Jpn. Pat. 24002, 1971.
13. Tsuda, S.; Manabe, Y.; Tsuji, K. (Sumitomo Chem. Co. Ltd) Jpn. Pat. 107254, 1988.
14. Audebert, P.; Miomandre, F.; Clavier, G.; Vernières, M.-C.; Badré, S.; Méallet-Renault, R. *Chem. Eur. J.* **2005**, *11*, 5667–5673.
15. Gückel, F.; Maki, A. H.; Neugebauer, F. A.; Schweitzer, D.; Vogler, H. *Chem. Phys.* **1992**, *164*, 217–227.
16. Audebert, P.; Sadki, S.; Miomandre, F.; Clavier, G.; Vernières, M.-C.; Saoud, M.; Hapiot, P. *New. J. Chem.* **2004**, *28*, 387–392.
17. Hu, W.-X.; Rao, G.-W.; Sun, Y.-Q. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1177–1181.
18. Rao, G.-W.; Hu, W.-X. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3174–3176.
19. Boger, D. L.; Zhang, M. J. *J. Am. Chem. Soc.* **1991**, *113*, 4230–4234.
20. Coburn, M. D.; Buntain, G. A.; Harris, B. W.; Hiskey, M. A.; Lee, K.-Y.; Ott, O. G. *J. Heterocycl. Chem.* **1991**, *28*, 2049–2050.
21. Fisher, H.; Müller, T.; Umminger, I.; Neugebauer, F. A. *J. Chem. Soc., Perkin. Trans. 2* **1988**, 413–421.
22. Gleiter, R.; Schehlmann, V.; Spanget-Larsen, J. *J. Org. Chem.* **1988**, *53*, 5756–5762.
23. Gong, Y.-H.; Audebert, P.; Tang, J.; Miomandre, F.; Clavier, G.; Badre, S.; Méallet-Renault, R.; Marrot, J. *J. Electroanal. Chem.* **2006**, *592*, 147–152.
24. Latosh, N. I.; Rusinov, G. L.; Ganebnykh, I. I.; Chupakhin, O. N. *Russ. J. Org. Chem.* **1999**, *35*, 1363–1371.
25. Novak, Z.; Bostai, B.; Csekei, M.; Lorincz, K.; Kotschy, A. *Heterocycles* **2003**, *60*, 2653–2668.
26. Rusinov, G. L.; Latosh, N. I.; Ganebnykh, I. I.; Ishmetova, R. I.; Ignatenko, N. K.; Chupakhin, O. N. *Russ. J. Org. Chem.* **2006**, *42*, 757–765.
27. Schirmer, U.; Wuerzer, B.; Meyer, N.; Neugebauer, F. A.; Fisher, H. DE Patent 3,508,214, 1986; *Chem. Abstr.* **1987**, *106*, 45718.
28. Sandström, J. *J. Acta Chem. Scand.* **1961**, *15*, 1575–1578.
29. Butler, R. N.; Scott, F. L.; Scott, R. D. *J. Chem. Soc.* **1970**, 2510–2512.

30. Chavez, D. E.; Hiskey, M. A. *J. Energy Mater.* **1999**, *17*, 357–377.
31. Chavez, D. E.; Hiskey, M. A. *J. Pyrotechnics* **1998**, *7*, 11–14.
32. Lutz, A. W.; Child, R. G.; Walworth, B. L. U.S. Patent 3,155,488, 1964; *Chem. Abstr.* **1965**, *62*, 1976.
33. Waluk, J.; Larsen-Spanget, J.; Thulstrup, E. W. *Chem. Phys.* **1995**, *200*, 201–213.
34. Counotte-Potman, A. D.; Van der Plas, H. C. *J. Heterocycl. Chem.* **1978**, *15*, 445–448.
35. Oostven, E. A.; Van der Plas, H. C. *Recl. Trav. Chim. Pays-Bas* **1976**, *95*, 209–211.
36. Al-Azmi, A.; Booth, B. L.; Carpenter, R. A.; Carvalho, M. A.; Marrelec, E.; Pritchard, R. G.; Proença, M. F. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2532–2537.
37. *3,6-Bis(methylamino)-1,2,4,5-tetrazine* **4**:[21] To a solution of 3,6-bis(methylsulfanyl)-1,2-dihydro-1,2,4,5-tetrazine **2b** (2.0 g, 11.3 mmol) in MeCN (3 mL) was added a 40 wt % aqueous methylamine solution (19.4 mL, 226 mmol). The mixture was stirred in a sealed vessel at room temperature for 4 days. After completion, excess methylamine was removed under vacuum. The aqueous phase was further extracted with CH_2Cl_2 (3 × 60 mL). The organic extracts were combined, dried on $MgSO_4$ and then concentrated to give, after flash chromatography (heptane–ethyl acetate, 7:3), 3,6-bis(methylamino)-1,2,4,5-tetrazine **4** as a red solid (1.105 g, 70%). IR (ATR): 3323, 2924, 1694, 1413 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.10 (d, 6H, $^3J = 5.0$ Hz), 5.10 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.6, 161.1); ^{15}N NMR (40 MHz, $CDCl_3$): δ −39.2, −322.2; MS (CI^-, NH_3): m/z (%) = 139 (100, $[M^{\cdot -}]$); Anal. Calcd for $C_4H_8N_6$ (140.08): C, 34.28; H, 5.75; N, 59.97. Found: C, 34.71; H, 5.89; N, 58.07.
38. *3,6-Bis(ethylamino)-1,2,4,5-tetrazine* **6a**: The compound was synthesized as for **4**, using a 70 wt % aqueous ethylamine solution. Conditions and yield: see Scheme 2 and Table 2. IR (ATR): 3245, 2975, 2873, 1550, 1444, 1387, 1352 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.30 (t, 6H, $^3J = 7.2$ Hz), 3.52 (dq, 4H, $^3J = 7.2$ Hz, $^3J = 1.3$ Hz), 5.01 (br s, 2H); ^{13}C NMR (1050 MHz, $CDCl_3$): δ 14.8, 36.6, 160.6; HRMS (CI^+) m/z: $[M+H]^+$ calcd for $C_6H_{13}N_6$, 169.1202; found, 169.1200. *3,6-Bis(benzylamino)-1,2,4,5-tetrazine* **6b**: The compound was synthesized as for **4**. Conditions and yield: see Scheme 2 and Table 2. IR (ATR): 3247, 3028, 1558, 1455, 1426, 1352 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 4.69 (s, 4H), 5.51 (br s, 2H), 7.37 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 45.7, 127.6, 127.8, 128.7, 138.2, 160.6; HRMS (CI^+) m/z: $[M+H]^+$ calcd for $C_{16}H_{17}N_6$, 293.1515; found, 293.1523. The monosubstitution product was also isolated: *3-benzylamino-6-methylsulfanyl-1,2,4,5-tetrazine* **5b**: IR (ATR): 3063, 2925, 1590, 1565, 1505, 1496, 1451, 1429 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.67 (s, 3H), 4.75 (d, 2H, $^3J = 5.3$ Hz), 5.94 (s, 1H), 7.38 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.6, 45.2, 127.8, 127.8, 128.8, 137.2, 160.8, 167.5; HRMS (CI^-) m/z: $[M]^-$ calcd for $C_{10}H_{11}N_5S$, 233.0735; found, 233.0746. *3,6-Bis(pyrrolidino)-1,2,4,5-tetrazine* **6c**:[21] The compound was synthesized as for **4**. Conditions and yield: see Scheme 2 and Table 2. IR (ATR): 2974, 2875, 1505, 1457 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.97 (m, 4H), 3.51 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 24.9, 46.2, 158.2. The monosubstituted product was also isolated: *3-methylsulfanyl-6-pyrrolidino-1,2,4,5-tetrazine* **5c**:[22] IR(ATR): 2979, 2927, 2878, 1538, 1455, 1428 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.01 (m, 4H), 2.61 (s, 3H), 3.59 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.2, 24.8, 46.3, 158.4, 164.1.