1,2,4,5-Tetrazines as Oxidant and Reactant with DBU: An Unexpected Formation of a Novel Fused Tetraheterocyclic Azepine

Robert E. Sammelson,[†] Marilyn M. Olmstead,[†] Makhluf J. Haddadin,*[,‡] and Mark J. Kurth*[,†]

[†]*Department of Chemistry, University of California, One Shields Avenue, Davis, California 95616-5295,*[‡] *and Department of Chemistry, American University of Beirut, Beirut, Lebanon*

mjkurth@ucdavis.edu, haddadin@aub.edu.lb

Received September 14, 2000

Introduction

The first 1,2,4,5-tetrazine derivative was prepared by Pinner over 100 years ago.[1] Tetrazines,[2] which are highly π-deficient systems, have been utilized as dienophiles in inverse electron demand cycloadditions,[3] including condensation reactions with enamines and enolates.[4] In particular, the condensation of 1,2,4,5-tetrazines (**I**, Figure 1) with the enolates of aldehydes and ketones have been reported in the synthesis of pyridazines **II**,[5] 1,2-diazocines,[6] and heterocyclic molecular clefts.[7] In all these enolate reactions, the ketone or aldehyde contains at least two protons on the same α-carbon, which allows for the concomitant dehydration after condensation and extrusion of nitrogen.

Results and Discussion

The reaction of amidines with 1,2,4,5-tetrazines has previously been reported to give 1,2,4-triazines **III**.[8] In this reaction, benzamidine was employed, which allows for elimination of ammonia after initial cycloaddition. In this study, we were curious if an N-substituted amidine, such as DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), would deliver **IV** which could not achieve aromatization by elimination. In our search for unaromatized dihydrotriazine **IV**, attempts conducted at lower temperatures (rt to refluxing MeOH) showed no reaction between 3,6-diphenyl-1,2,4,5-tetrazine **1a** (Scheme 1) and DBU. When the reaction was carried out in triglyme at reflux (216 °C), the reaction did proceed, and the intense purple hue of the tetrazine gradually disappeared. Isolation of the reaction product, however, did not yield **IV** but rather **2a** (Figure 2), which contains an unexpected 5,6,6,7-fused heterocyclic ring system.

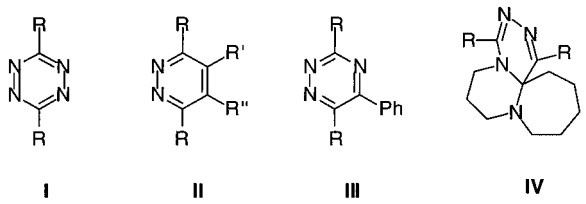
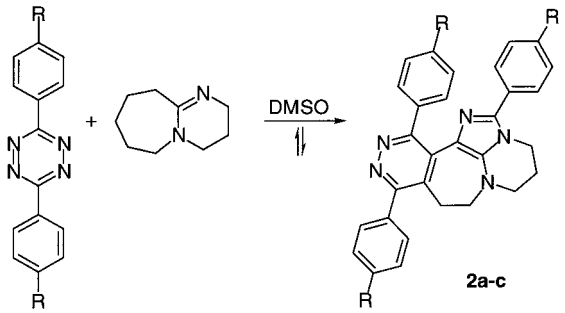


Figure 1. Adducts **II**−**IV** from reaction of π-deficient tetrazine **I**.

Scheme 1. Imidazopyridazinopyrimidinoazepines from Reaction of Tetrazines with DBU



1a-c R a = H, b = Me, c = OMe

We have examined this interesting finding in an attempt to determine its scope and limitations. Mechanisic considerations[9] and experimental observations (i.e., minimized side-products as judged by TLC) indicated that a 5:1 stoichiometric ratio of tetrazine to DBU was most effective. Next, the removal of the triglyme from the reaction mixture was problematic and a more efficient method of purification was sought. When the reaction was conducted in refluxing *m*-xylene (bp 138−9 °C), it was incomplete (presence of tetrazine by TLC) even after 2 days. The best solvent found for the reaction and subsequent purification of product **2a** was DMSO (bp 189 °C). The reaction of other s-tetrazines [bis(4-methylphenyl)tetrazine **1b** and bis(4-methoxyphenyl)tetrazine **1c**] with DBU were also examined and found to yield the corresponding azepine heterocycles **2b** and **2c**. Isolated yields of **2a**−**c** ranged from 38 to 45%. The reactivity of 3,6-di-(2-pyridyl)-1,2,4,5-tetrazine was much greater; employing toluene at reflux resulted in the starting tetrazine being consumed within 1 h. Unfortunately, any material that was formed decomposed quickly and could not be isolated.

Products **2a**−**c**, with their 4-aminoimidazole moiety, appeared red to orange on silica gel,[10] and their struc-

[†] University of California.
[‡] American University of Beirut.

(1) Pinner, A. *Ann. Chem.* **1897**, *297*, 221−71.
(2) (a) Neunhoeffer, H. Tetrazines and Pentazines. In *Comprehensive Heterocyclic Chemistry*; Boulton, A. J., McKillop, A., Eds.; Pergamon Press: New York, 1984; Vol. 3, pp 531−72. (b) Katritzky, A. R.; Soloducho, J.; Belyakov, S. *ARKIVOC* **2000**, *1*, 46−51. (c) Lim, C. L.; Pyo, S. H.; Kim, T. Y.; Yim, E. S.; Han, B. H. *Bull. Korean Chem. Soc.* **1995**, *16*, 374−7. (d) Sauer, J. In *Comprehensive Heterocyclic Chemistry II*; Boulton, A. J., Ed.; Pergamon: New York, 1996; Vol. 6, pp 901−95.
(3) (a) Carboni, R. A.; Lindsey, R. V. *J. Am. Chem. Soc.* **1959**, *81*, 4342−6. (b) Sauer, J.; Heinrichs, G. *Tetrahedron Lett.* **1966**, 4979−84. (c) Boger, D. L. *Tetrahedron* **1983**, *39*, 2869−939. (d) Boger, D. L.; Schaum, R. P.; Garbaccio, R. M. *J. Org. Chem.* **1998**, *63*, 6329−37. (e) Warrener, R. N.; Margetic, D.; Amarasekara, A. S.; Butler, D. N.; Mahadevan, I. B.; Russell, R. A. *Org. Lett.* **1999**, *1*, 199−202. (f) Benson, S. C.; Lee, L.; Yang, L.; Snyder, J. K. *Tetrahedron* **2000**, *56*, 1165−80.
(4) Boger, D. L. *Chem. Rev.* **1986**, *86*, 781−793.
(5) Haddadin, M. J.; Firsan, S. J.; Nader, B. S. *J. Org. Chem.* **1979**, *44*, 629−30.
(6) Haddadin, M. J.; Agha, B. J.; Salka, M. S. *Tetrahedron Lett.* **1984**, *25*, 2577−80.
(7) Haddadin, M. J.; Wang, Y.; Frenkel, S.; Bott, S. G.; Yang, L.; Braterman, P. S.; Carvallo, C.; Marchand, A. P.; Watson, W. H.; Kashyap, R. P.; Krawiec, M.; Bourne, S. A. *Heterocycles* **1994**, *37*, 869−82.
(8) Figeys, H. P.; Mathy, A. *Tetrahedron Lett.* **1981**, *22*, 1393−6.

(9) This is determined by analyzing the products which show 2 equiv of tetrazine are used as reactant in condensing with the DBU core and 3 equiv are consumed in oxidizing the DBU-containing intermediates.

10.1021/jo001363k CCC: $19.00
Published on Web 11/28/2000

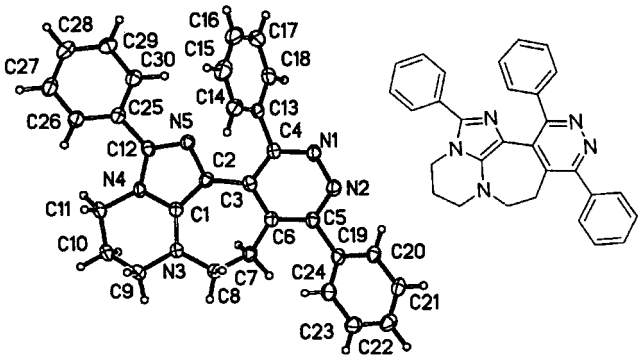


Figure 2. X-ray crystal structure of **2a**.

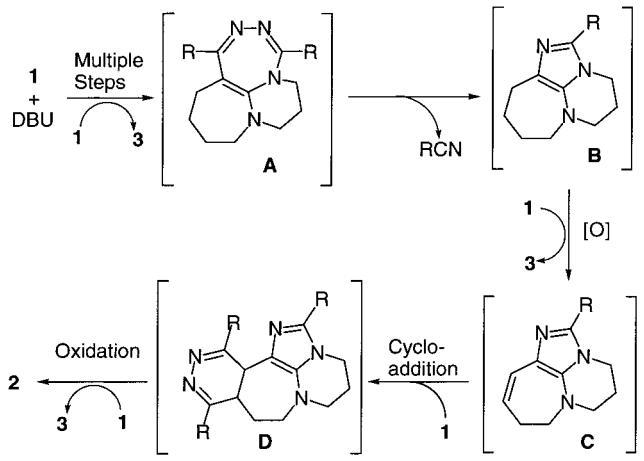
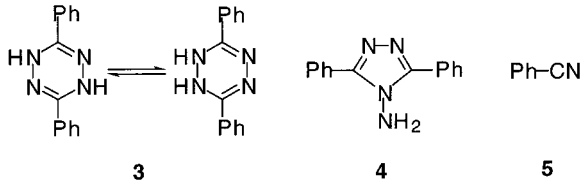


Figure 3. Mechanistic rationale for **1** + DBU → **2**.

tures were established by spectroscopic data. In addition, the structure of **2a** was verified by X-ray crystallography (Figure 2).

Formation of **2** can be rationalized by a mechanism[11] which involves intermediates shown in Figure 3. In this process, DBU acts as both reactant and reducing agent while the tetrazine acts as both reactant and oxidizing agent. Nazer and Haddadin[12] observed the reductive effect of DBU on *o*- and *p*-nitrobenzaldehydes, which were reduced to the corresponding aminobenzoic acids. Furthermore, Sauer et al. recently described the use of 1,2,4,5-tetrazine as both reactant and oxidizing agent.[13]

While it is possible that triazepine ring contraction with extrusion of benzonitrile could succeed tetrahydroazepine oxidation and cycloaddition, this is not likely given the relative instability of triazepines at these elevated reaction temperatures (189 °C).[14] Intermediate



3 4 5

Figure 4. Side-products from the reaction of **1** + DBU.

D undergoes subsequent oxidation to **2** with another molecule of tetrazine acting as the oxidizing agent. Attempts to isolate any of these or other intermediates were unsuccessful. However, the reduced form of tetrazine, dihydrotetrazine **3**, is formed in each of the adduct oxidation steps and was isolated from the reaction mixture (Figure 4). Furthermore, rearrangement of **3** to the aminotriazole **4** was also observed.[15] When the reaction (utilizing **1a**) was carried out with triglyme as solvent, the aroma of benzonitrile (**5**) was detected, and a swab of the condensate in the reflux condenser showed this substance to be identical to authentic benzonitrile by reverse-phase HPLC. The possibility that the imidazole ring resulted from the participation of benzonitrile (formed by the decomposition of **1a**) was ruled out by finding no reaction upon heating DBU with benzonitrile in triglyme at reflux. In addition, diphenyltetrazine (**1a**) was found to be stable in triglyme under these reaction times (up to 3 h). These findings support the postulate of a seven-membered triazepine ring (**A**) being formed, which contracts with extrusion of the aryl nitrile to deliver amino imidazole **B** (Figure 3).

Conclusion

It is noteworthy that this novel reaction involves the sequential addition of amidines, enamines, and dienamines (originally present or generated from DBU) to the tetrazine moiety. It also demonstrates the oxidative nature of 1,2,4,5-tetrazines. In addition, our finding establishes the reductive effect of DBU in that the oxidized DBU core is present in these tetraheterocyclic azepine products. These 2,8,11-triaryl-3*H*,4*H*,5*H*,6*H*,7*H*-imidazo[4,5,1-*ef*][1,3]-diazaperhydroino[1,2-*f*]pyridazino-[4,5-*d*]azepines are a new class of the $C_3N_2C_4N_2C_4N_2C_6N$ fused heterocyclic ring system.

Experimental Section

General Procedures. Melting points were determined using an Electrothermal 9100 apparatus and are uncorrected. Infrared spectra were taken on the solids with the use of a refractive spectrophotometer. ^{1}H and ^{13}C NMR were measured in $CDCl_3$ (unless otherwise noted) at 300 and 75 MHz, respcecitvely. Elemental analysis was preformed by Midwest Microlabs, Indianapolis, IN. Dimethyl sulfoxide purchased from Fischer Scientific was distilled, with the first 20% being discarded, onto molecular sieves. The dihydrotetrazines were prepared from their corresponding nitriles and hydrazine monohydrate with sulfur in EtOH.[16] Oxidation to the tetrazines was accomplished by adding sodium nitrate portionwise to a mixture of the dihydrotetrazine in acetic acid.[17]

2,8,11-Triphenyl-3*H*,4*H*,5*H*,6*H*,7*H*-imidazo[4,5,1-*ef*][1,3]-diazaperhydroino[1,2-*f*]pyridazino[4,5-*d*]azepine (2a). To

(10) Solutions of these adducts turned from yellow to red on addition of acetic acid or picric acid.

(11) The proposed reaction mechanism is included in the Supporting Information as Figure S1.

(12) Unpublished results on the reaction of DBU with *o*-nitrobenzaldehyde (Professors Nazer, M. Z. and Haddadin, M. J.): *o*-Nitrobenzaldehyde (0.5 g) was dissolved in dry THF (5 mL), and DBU (0.6 mL) was added. After one week at room temperature, the solvent was removed, water (10 mL) was added, and the solution was made slightly acidic with dilute HCl. This was extracted with ether, dried, and concentrated to a volume of about 5 mL. An equal volume of pentane was added, and slow evaporation deposited crystals that proved to be anthranilic acid (unoptimized yield 50 mg) as determined by mixed mp, IR, and NMR.

(13) Sauer, J.; Heldmann, D. K.; Hetzenegger, J.; Krauthan, J.; Sichert, H.; Schuster, J. *Eur. J. Org. Chem.* **1998**, 2885−96.

(14) Sharp, J. T. Triazepines. In *Comprehensive Heterocyclic Chemistry*; Lwowski, W., Ed.; Pergamon Press: New York, 1984; Vol. 7, pp 636−41.

(15) Bentiss, F.; Lagrenee, M.; Barbry, D. *Tetrahedron Lett.* **2000**, *41*, 1539−41.

(16) Abdel-Rahman, M. O.; Kira, M. A.; Tolba, M. N. *Tetrahedron Lett.* **1968**, *35*, 3871−2.

(17) Guither, W. D.; Coburn, M. D.; Castle, R. N. *Heterocycles* **1979**, *12*, 745−9.

1.68 g (7.18 mmol) of diphenyltetrazine in 15 mL of dimethyl sulfoxide was added 0.219 g (1.44 mmol) of DBU. This mixture was then heated at reflux under nitrogen for 2 h. The solution was cooled to room temperature, dichloromethane (20 mL) was added followed by H_2O (15 mL). The aqueous layer was removed, and the organic layer was washed twice more with H_2O. The white precipitate, if any, was filtered and washed with several small amounts of dichloromethane. The concentrated organic layer was submitted to flash chromatography on silica gel with EtOAc followed by 9:1 EtOAc:MeOH and provided **2a** as a yellow solid (0.295 g, 45%). Mp 245−8 °C dec; IR 3056, 2935, 1570, 1531, 1465 cm^{-1}; ^1H NMR δ 2.13 (quint, J = 6 Hz, 2H), 3.07 (m, 2H), 3.39 (t, J = 6 Hz, 2H), 3.72 (m, 2H), 4.08 (t, J = 6 Hz, 2H), 7.16−7.65 (m, 15H); ^{13}C NMR δ 22.4, 30.8, 42.9, 47.6, 56.2, 112.6, 127.2, 127.47, 127.52, 128.0, 128.26, 128.34, 129.5, 129.7, 130.0, 132.7, 133.3, 137.9, 140.3, 140.8, 141.1, 149.1, 157.3, 158.3. Anal. Calcd for $C_{30}H_{25}N_5$: C, 79.10; H, 5.53; N, 15.37. Found: C, 79.32; H, 5.61; N, 14.99.

2,8,11-Tris(4-methylphenyl)-3*H*,4*H*,5*H*,6*H*,7*H*-imidazo-[4,5,1-*ef*][1,3]-diazaperhydroino[1,2-*f*]pyridazino[4,5-*d*]-azepine (2b). The procedure described for **2a** was employed to scale with the following differences: 1.02 g (3.89 mmol) of diphenyltetrazine, 0.116 g (0.76 mmol) of DBU, and eluent for flash chromatography was EtOAc and gave 0.143 g, 38%. Mp 295−8 °C dec; IR 3028, 2917, 1584, 1510, 1479, 1382 cm^{-1}; ^1H NMR δ 2.11 (quint, J = 6 Hz, 2H), 2.33 (s, 3H), 2.43 (s, 3H), 2.47 (s, 3H), 3.03 (m, 2H), 3.32 (t, J = 6 Hz, 2H), 3.67 (m, 2H), 4.02 (t, J = 6 Hz, 2H), 7.08 (s, 4H), 7.22 (d, J = 8 Hz, 2H), 7.28 (d, J = 8 Hz, 2H), 7.43 (d, J = 8 Hz, 2H), 7.52 (d, J = 8 Hz, 2H); ^{13}C NMR δ 21.2, 21.3, 21.4, 22.5, 30.7, 42.9, 47.7, 56.6, 112.6, 127.3, 127.5, 128.1, 128.9, 129.0, 129.5, 129.7, 132.6, 133.2, 135.1, 136.7, 137.9, 138.1, 140.3, 140.8, 157.2, 158.1.[18]

(18) See Supporting Information.

2,8,11-Tris(4-methoxyphenyl)-3*H*,4*H*,5*H*,6*H*,7*H*-imidazo-[4,5,1-*ef*][1,3]-diazaperhydroino[1,2-*f*]pyridazino[4,5-*d*]-azepine (2c). The procedure described for **2a** was employed to scale with the following differences: 1.08 g (3.66 mmol) of diphenyltetrazine, 0.111 g (0.73 mmol) of DBU gave 0.155 g, 39%. Mp 266−9 °C dec; IR 2956, 2832, 1586, 1505, 1240, 1175, 1029 cm^{-1}; ^1H NMR δ 2.12 (quint, J = 6 Hz, 2H), 3.07 (m, 2H), 3.35 (t, J = 6 Hz, 2H), 3.69 (m, 2H), 3.80 (s, 3H), 2.87 (s, 3H), 3.90 (s, 3H), 4.04 (t, J = 6 Hz, 2H), 6.83 (d, J = 9 Hz, 2H), 6.96 (d, J = 9 Hz, 2H), 7.02 (d, J = 9 Hz, 2H), 7.19 (d, J = 9 Hz, 2H), 7.50 (d, J = 9 Hz, 2H), 7.62 (d, J = 9 Hz, 2H); ^{13}C NMR ($CDCl_3$/DMSO-d_6) δ 22.2, 30.6, 42.6, 47.5, 55.09, 55.15, 55.23, 56.4, 112.1, 112.7, 113.5, 113.6, 114.3, 122.5, 128.9, 130.0, 130.7, 130.8, 132.6, 133.0, 140.1, 140.7, 156.2, 157.3, 158.9, 159.3, 159.5.[18]

Acknowledgment. We acknowledge Mr. Joshua Halsey for the initial experiments that led to this work. M.J.H. is grateful to the American University of Beirut for a sabbatical leave at the University of California, Davis. The authors are thankful to Professor Costas H. Issidorides for many helpful discussions. We are grateful to the National Science Foundation for financial support of this research. The 300 and 400 MHz NMR spectrometers used in this study were funded in part by a grant from NSF (CHE-9808183).

Supporting Information Available: ^1H and ^{13}C spectra of **2b** and **2c**, a complete reaction mechanism, and the crystal structure data for **2a** are included. This material is available free of charge via the Internet at http://pubs.acs.org.

JO001363K