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An Alternative Route for Carboni–Lindsey Reaction: N,N Cycloaddition of an Alkene to *s*-Tetrazine

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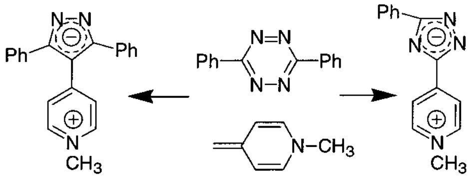
ABSTRACT



Quantum mechanical calculations show that N,N cycloaddition of alkenes and alkynes to *s*-tetrazines is possible as an alternative to the well-known C,C cycloaddition (Carboni–Lindsey reaction). Formation of 1,2,4-triazole derivatives (formal product of N,N cycloaddition) along with the pyrazole (formal product of C,C cycloaddition) corroborates this theoretical prediction.

Since Carboni and Lindsey[1] reported that aromatic fluoroalkyl 1,2,4,5-tetrazines react with simple alkenes and alkynes to form 1:1 cycloadducts with subsequent loss of nitrogen under mild conditions, more than 800 articles, including several reviews,[2] have been published on the topic. However, all of the literature covering this abundance of research carried out on the inverse [4 + 2] cycloaddition on 1,2,4,5-tetrazines deals only with the C,C (3,6) cycloaddition with loss of nitrogen. Products stemming from N,N (1,4) cycloaddition have not been reported, and even the possibility of this alternative route has never been discussed.

We found that, according to quantum mechanical calculations,[3] both routes, C,C and N,N cycloaddition and subsequent loss of nitrogen or hydrogen cyanide, are possible. Thus, in the case of acetylene (Scheme 1), both cycloaddition and elimination steps are always exothermic and the total energy gain amounts to 96−113 kcal/mol and 53−68 kcal/mol (R = MeO, H, CN), for **1** → **2** → **4** and **1** → **3** → **5** conversions, correspondingly. In the case of ethylene cycloaddition (Scheme 2), the total energy gain is smaller and amounts to 56−69 kcal/mol (**1** → **6** → **8**) and 2−16 kcal/mol (**1** → **7** → **9**), but **1** → **7** conversion is slightly endothermic when R = H (4.4 kcal/mol) and R = MeO (1.4 kcal/mol). Interestingly, this general trend does not depend on the level of theory, and similar results were obtained on both DFT (B3LYP/6−31(d)) and semiempirical (PM3) levels. The cycloaddition reaction should be more sensitive to steric hindrance. Indeed, according to PM3 calculations on the cycloaddition of acetylenes to diphenyl *s*-tetrazine, the C,C cycloadduct is more stable than the N,N cycloadduct by 18.3 kcal/mol for acetylene, by 15.6 kcal/mol for dimethyl acetylene, and by 11.0 kcal/mol for di-isopropyl acetylene

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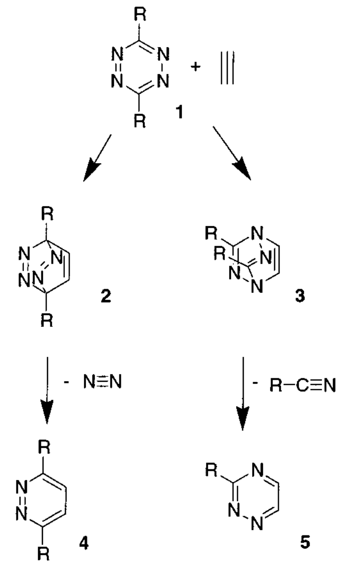
(1) Carboni, R. A.; Lindsey, R. V. *J. Am. Chem. Soc.* **1959**, *81*, 4342.

(2) Sauer, J. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: Oxford, 1996; Vol. 6, p 901. (b) Sauer, J.; Heldmann, D. K.; Hetzenegger, J.; Krauthan, J.; Sichert, H.; Schuster, J. *Eur. J. Org. Chem.* **1998**, 2885. (c) Boger, D. L. *Chem. Rev.* **1986**, *86*, 781.

(3) Calculations were performed on the B3LYP/6-31(d) level using Jaguar 3.5 software, Schroedinger, Inc., Portland, Oregon, 1998.

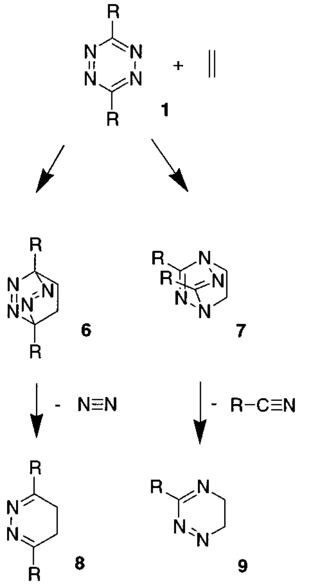
10.1021/ol015918p CCC: $20.00

Scheme 1. Cycloaddition of Acetylene to *s*-Tetrazines



but is by 6.8 kcal/mol *less* stable for di-*tert*-butyl acetylene. Therefore, the use of appropriately substituted components might afford N,N cycloadducts or products of their further conversions, as major products.

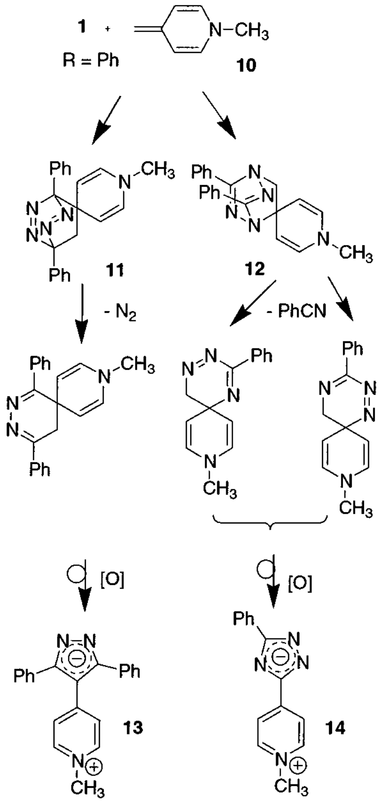
Scheme 2. Cycloaddition of Ethylene to *s*-Tetrazines



We found the first experimental proof for the above possibility, using 3,6-diphenyl-1,2,4,5-tetrazine[4] (**1**, R = Ph) and 1-methyl-4-methylene-1,4-dihydropyridine (**10**), easily available from 1,4-dimethyl pyridinium iodide[5] and triethylamine.[6] Derivative **10** combines high chemical reactivity and exhibits noticeable steric hindrance in the reaction of C,C cycloaddition with **1** according to the molecular model.

When a mixture of **1**, 1,4-dimethyl pyridinium iodide and triethylamine was reacted in DMF for 24 h, the major isolated product was the pyrazole derivative **13**,[7] which formally corresponds to C,C cycloaddition, nitrogen elimination, rearrangement, and oxidation steps (Scheme 3). However,

Scheme 3. Cycloaddition of 1-Methyl-4-methylene-1,4-dihydropyridine **10** to 3,6-Diphenyl-1,2,4,5-tetrazine.



refluxing a mixture of **1**, 1,4-dimethyl pyridinium iodide and triethylamine in ethanol for 24 h afforded only **14**[8] as a major product. Formation of **14** can be rationalized by N,N cycloaddition, benzonitrile elimination, rearrangement, and oxidation steps (Scheme 3). Indeed, formation of benzonitrile was proven by GC−MS of the final reaction mixture.

Tetrazine derivative **1** (R = Ph) did not react with triethylamine under the above conditions and could be

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[4] Abdel-Rahman, M. O.; Kira, M. A.; Tolba, M. N. *Tetrahedron Lett.* **1968**, *35*, 3871.

[5] Gibson, H. W.; Bailey, F. C. *Tetrahedron* **1974**, *30*, 2050.

[6] (a) Kovalev, E. G.; Rusinov, G. L.; Anufriev, V. A.; Egorova, L. G. *Khim. Geterosikl. Soedin*. **1990**, 1038. (b) Kovalev, E. G.; Rusinov, G. L.; Aleksandrov, G. G.; Anufriev, V. A.; Sidorov, E. O.; Chernyshev, A. I. *Khim. Geterosikl. Soedin*. **1991**, 1545.

[7] **Data for 13:** yellow crystals from water, mp 222−224 °C, 45% yield. HRMS calcd for $C_{21}H_{17}N_3$: M, 311.1422. Found: *m/z* 311.1410. ^1H NMR (200 Hz, DMSO-d_6, TMS) δ 4.10 (s, 3H), 7.35 (m, 12H), 8.49 (d, 2H, J = 6.7 Hz). ^{13}C NMR (500 Hz, DMSO-d_6 TMS) δ 46.42, 111.14, 125.71, 127.59, 128.46, 128.62, 133.42, 143.90, 149.52, 151.54.

[8] **Data for 14:** yellow crystals from water, mp 236−238 °C. 52% yield. HRMS calcd for $C_{14}H_{12}N_4$: M, 236.1062. Found: *m/z* 236.1055. ^1H NMR (500 Hz, DMSO-d_6, TMS) δ 4.19 (s, 3H), 7.27 (t, 1H, J = 7.7 Hz), 7.39 (t, 2H, J = 7.5 Hz, J = 7.8 Hz), 8.10 (d, 2H, J = 7.5 Hz), 8.38 (d, 2H, J = 6.7 Hz), 8.67 (d, 2H, J = 6.7 Hz). ^{13}C NMR (500 Hz, DMSO-d_6, TMS) δ 46.71, 120.86, 125.84, 127.39, 128.64, 134.49, 144.97, 148.27, 158.15, 164.82. X-ray structure experiment will be published elsewhere.

quantitatively recovered from the reaction mixture. A product corresponding to N,N cycloaddition was also obtained, albeit in a lower yield, when 1-methyl-2-methylene-1,2-dihydropyridine was used.

The betaine **14** exhibits strong negative solvatochromism; an intensive absorption band was observed in acetonitrile at 375 nm, in acetone at 400 nm, in methylene chloride at 416 nm, and in chloroform at 426 nm. A perchlorate salt of **14** was isolated upon addition of perchloric acid. Its structure was also confirmed by X-ray experiment[9] (Figure 1).

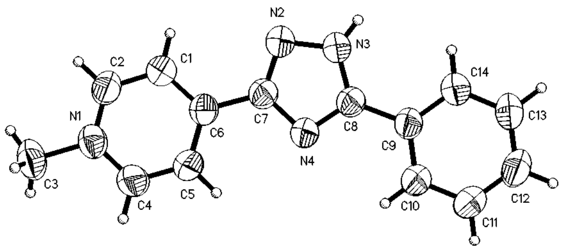

Figure 1. ORTEP drawing of **14**$\cdot HClO_4\cdot H_2O$ at the 50% probability level (the perchlorate anion and water molecule not shown). Selected bond lengths: 1.324(4) Å (N1−C2), 1.367(5) Å (C1−C2), 1.381(4) Å (C1−C6), 1.464(5) Å (C6−C7), 1.309(4) Å (C7−N2), 1.358(4) Å (C7−N4), 1.351(4) Å (N2−N3), 1.338(4) Å (N3−C8), 1.326(4) Å N4−C8.

In summary, the possibility of N,N cycloaddition as an alternative route for Carboni−Lindsey reaction has been predicted by DFT quantum mechanical calculations. Products, formally corresponding to N,N cycloaddition of a reactive alkene to *s*-tetrazine, have been isolated for the first time. We cannot fully exclude the possibility that the real mechanism involves a stepwise addition, and a detailed study of the reaction is currently under way. However, the alternative route expands the synthetic potential of *s*-tetrazines and, in particular, might serve as an additional approach toward 3,5-disubstituted-1,2,4-triazoles, which are of considerable biological interest.[10]

Acknowledgment. The authors thank Dr. A. Ellern for X-ray structure determination.

Supporting Information Available: A table with quantum mechanical calculation results. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) A colorless prism of **14**$\cdot HClO_4\cdot H_2O$ (0.2 × 0.3 × 0.6) is triclinic: $C_{14}H_{15}ClN_4O_5$, space group *P*-1, $Z = 4$, at 298(2) K; $a = 8.2608(12)$, $b = 14.0335(18)$, $c = 14.249(2)$, $\alpha = 87.694(4)°$, $\beta = 79.789(4)°$, $\gamma = 83.691(4)°$ Å, $V = 1615.5(4)$ Å^3, $\rho_{calcd} = 1.434$ Mg/m^3, $F(000) = 724$. Intensity data were collected with BRUKER diffractometer (6K CCD detector, λ(Mo Kα) = 0.711069 Å, graphite monochromator, 1080 frames with a scan width of 0.3° in ω for hemisphere coverage of reciprocal space and 50 frames for decay correction, exposure time of 10 s/frame, integration with Bruker SAINT software package using a wide-frame integration algorithm. Data were corrected for absorption using SADABS program. The structure was solved by direct methods and refined by least squares in full-matrix anisotropic approximation for all non-hydrogen atoms. A total of 12103 reflections were collected ($2\theta < 46.6°$), of which 4627 reflections were independent ($R_{int} = 0.0342$). Structure was refined to R1 = 0.0566, wR2 = 0.1648, GOF = 1.058, 496 parameters. The hydrogen atoms were included with geometrically calculated positions and refined using riding model. Bruker SHELX software package was used for all calculations and drawings. Atomic coordinates, bond lengths and angles, and anisotropic parameters have been deposited at the Cambridge Crystallographic Data Center. The authors are thankful to Dr. A. Ellern for the X-ray experiment.

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