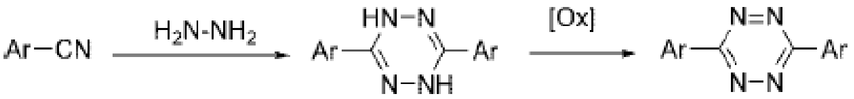
s-Tetrazine polymers

by: Robert B. Login rloginconsulting.com

s-Tetrazine has a long history in organic chemistry dating back more than a century to the Pinner reaction.

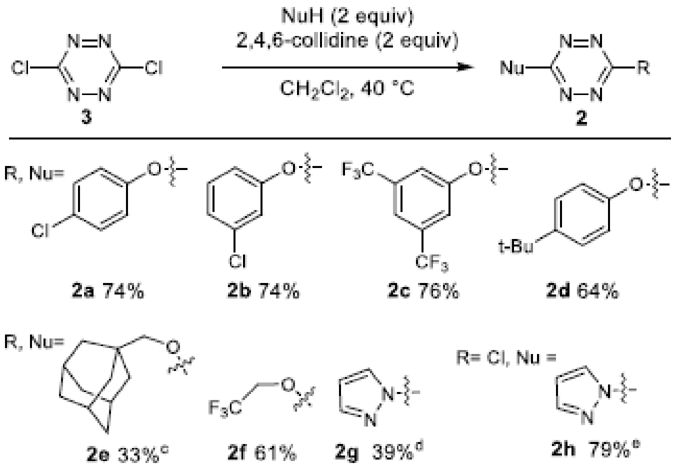
Scheme 1. Original Pinner Synthesis of Dihydro-*s*-tetrazines



Clavier, G., & Audebert, P. (2010). s-Tetrazines as building blocks for new functional molecules and molecular materials. *Chemical reviews*, *110*(6), 3299-3314.

I was looking for a useful reactive intermediate and found the following:

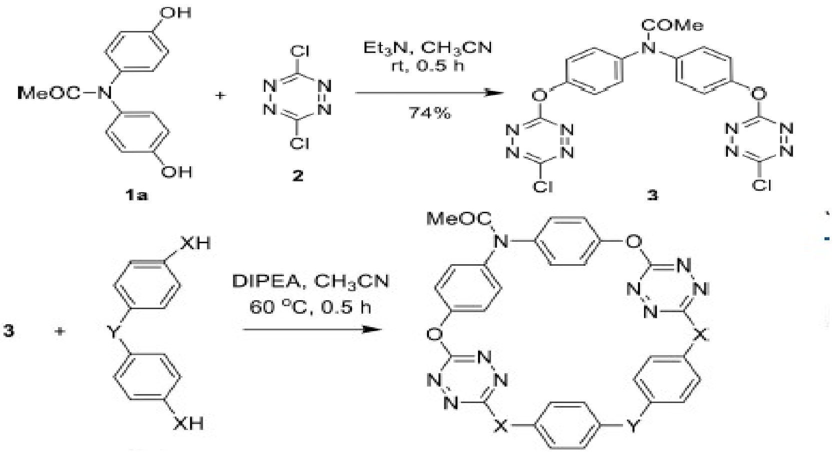
Scheme 2. Synthesis of 3,6-Dialkoxy-tetrazines from 3,6-Dichloro 1,2,4,5-Tetrazine 3[a,b]



[a]Reaction conditions: 3 (1.6 mmol), NuH (3.2 mmol), 2,4,6-collidine (3.2 mmol) in CH_2Cl_2 (20 mL) at reflux. [b]Isolated yields. [c]3 (1.6 mmol), NuH (3.2 mmol), 2,4,6-collidine (1.6 mmol, 1 equiv) in CH_2Cl_2 (20 mL) at reflux followed by addition of DMAP (1.6 mmol). [d]With CH_3CN as solvent. [e](1.6 mmol), NuH (1.6 mmol), 2,4,6-collidine (1.6 mmol) in CH_2Cl_2 (20 mL) at reflux.

Le, T., Courant, T., Merad, J., Allain, C., Audebert, P., & Masson, G. (2019). s-Tetrazine Dyes: A Facile Generation of Photoredox Organocatalysts for Routine Oxidations. *The Journal of Organic Chemistry*, *84*(24), 16139-16146.

Scheme 1. Preparation of Linear Tetramer 3 from the Reaction of 1a and 2

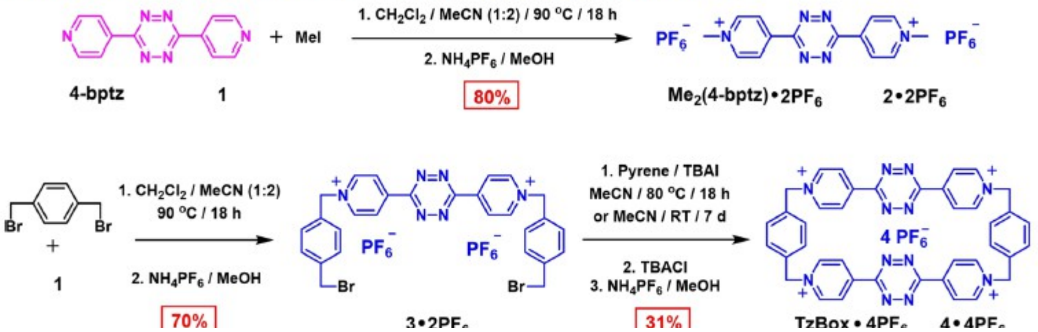


X=O Y=SO2 yield 73%

Zhao, M. Y., Wang, D. X., & Wang, M. X. (2018). Synthesis, structure, and properties of corona [6] arenes and their assembly with anions in the crystalline state. *The Journal of organic chemistry*, *83*(3), 1502-1509.

Dichlorotetrazine is readily available. The above corona[6]arene synthesis I find remarkable as I would have predicted a polymeric product and possibly it formed but was intractable? A very recent article indicates that only with pyrene(as a template) was their cyclic product produced.

Scheme 1. Synthesis of the Reference Compound Me$_2$(4-bptz)·2PF$_6$ and TzBox·4PF$_6$



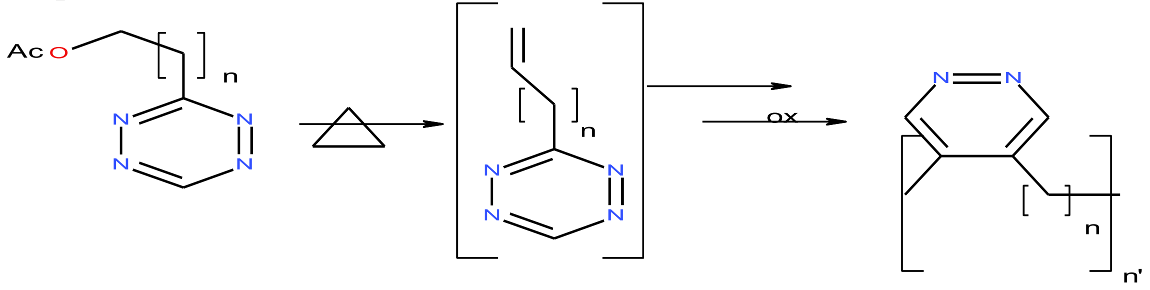
yield. Without the use of pyrene as a template in this reaction, the cyclophanes cannot be prepared.

Guo, Q. H., Zhou, J., Mao, H., Qiu, Y., Nguyen, M. T., Feng, Y., ... & Wasielewski, M. R. (2020). TetrazineBox: A Structurally Transformative Toolbox. *Journal of the American Chemical Society*, *142*(11), 5419-5428.

The pyrene holds the two reactants together because of the electron deficiency of the tetrazines enhanced by the cationic charges. Without the pyrene did a polymer form?

Here again I find the lack also of polymers somewhat disconcerting since my idea is to actively synthesize tetrazine polymers!

For example:



Scheme 1: Simple synthesis of a polymer where n is large enough to make its unsaturation electron rich enough to undergo iEDDA.

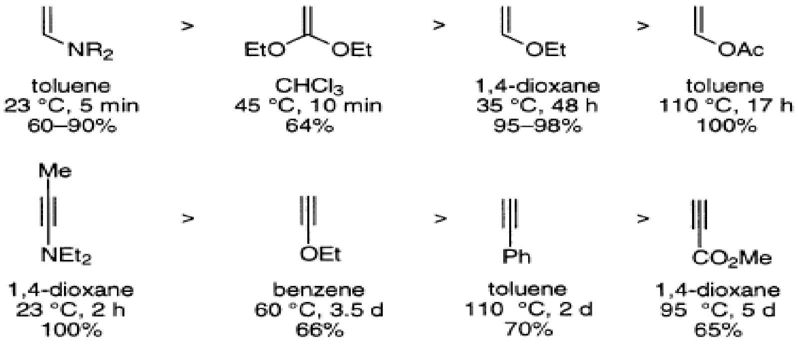
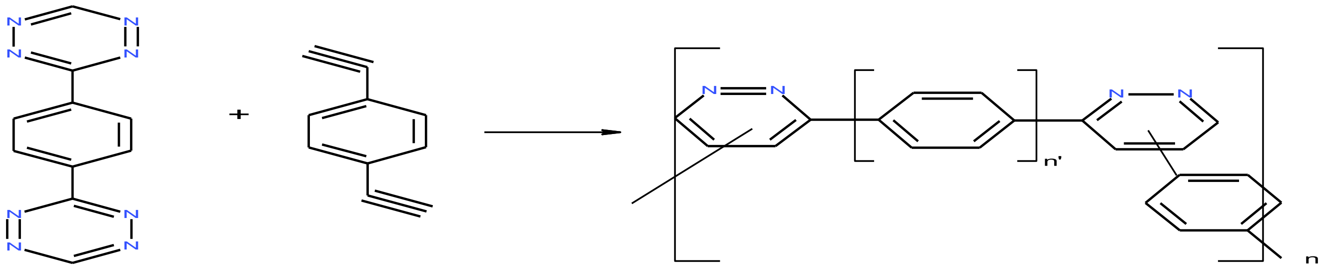


FIGURE 2. Relative dienophile reactivity toward 2.

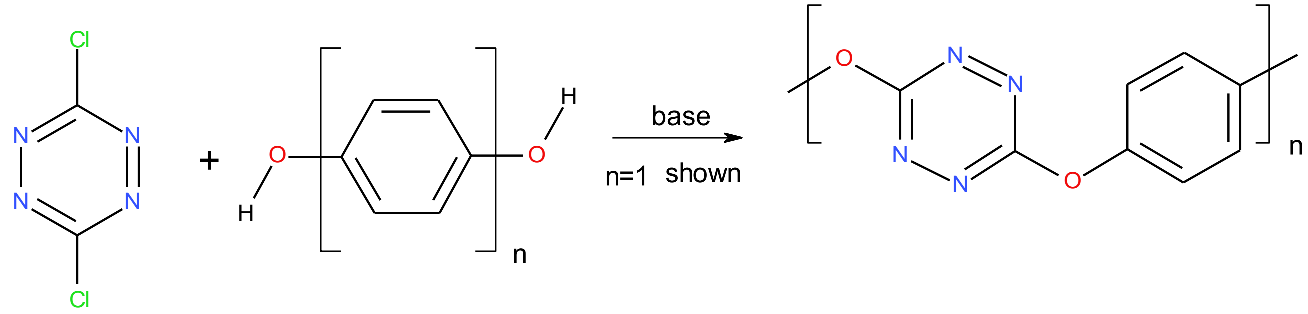
2 is a tetrazine derivative.

Soenen, D. R., Zimpleman, J. M., & Boger, D. L. (2003). Synthesis and Inverse Electron Demand Diels− Alder Reactions of 3, 6-Bis (3, 4-dimethoxybenzoyl)-1, 2, 4, 5-tetrazine. *The Journal of organic chemistry*,*68*(9), 3593-3598. Fig. 2 above shows the reactivity of unsaturation with iEDDA.

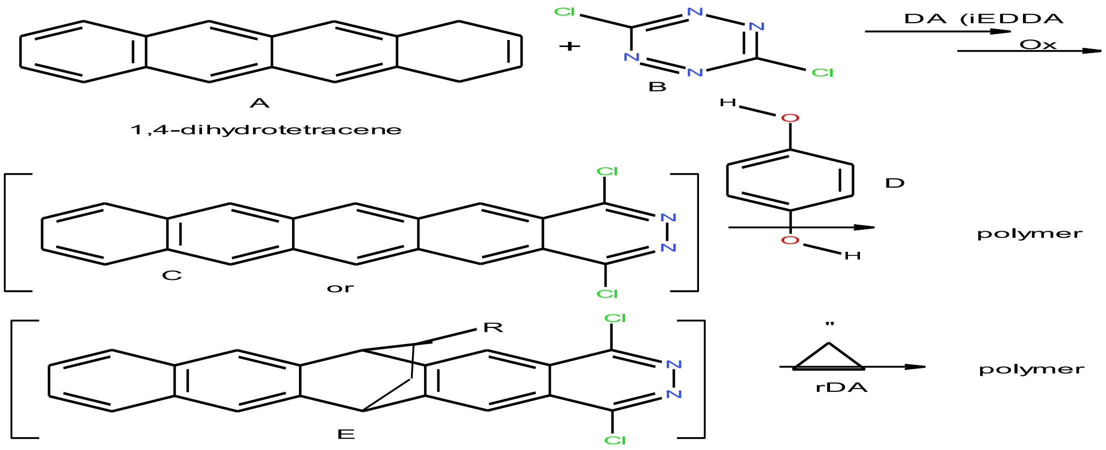


3-[4-(1,2,4,5-tetrazin-3-yl)phenyl]-1,2,4,5-tetrazine

Scheme 2: polyaromatic s-tetrazine polymer. The acetylenic groups can be located further away from its aromatic ring(s) or the associated aromatics could also have methoxy derivatives to increase the electron density of the dieneophile. Both starting compounds can also be polyaromatics or acenes like anthracene containing tetrazine substituents.



Scheme 3: The para-hydroxy derivative can be oligomeric and could be a dihydroxy phenolic derivative of other aromatics like napthalene or anthracene or other acenes. This idea has the possibility of then employing the polytetrazines in sudsequent Diels-Alder reactions post polymerization.



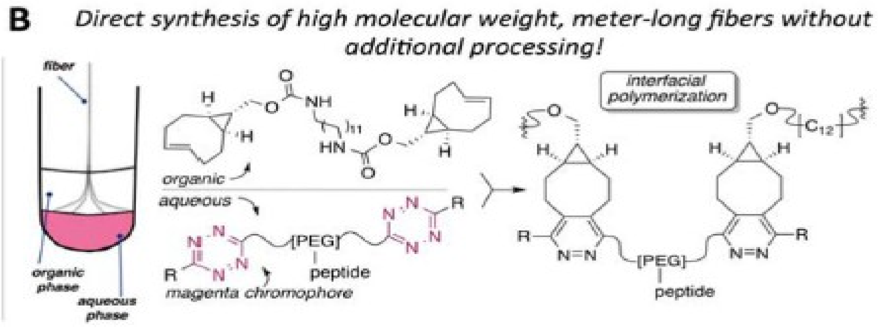
Scheme 4: Instead of dihydrotetracene other analogs like 1,4-dihydronapthalene are known compounds that could also work.

Polymer references:

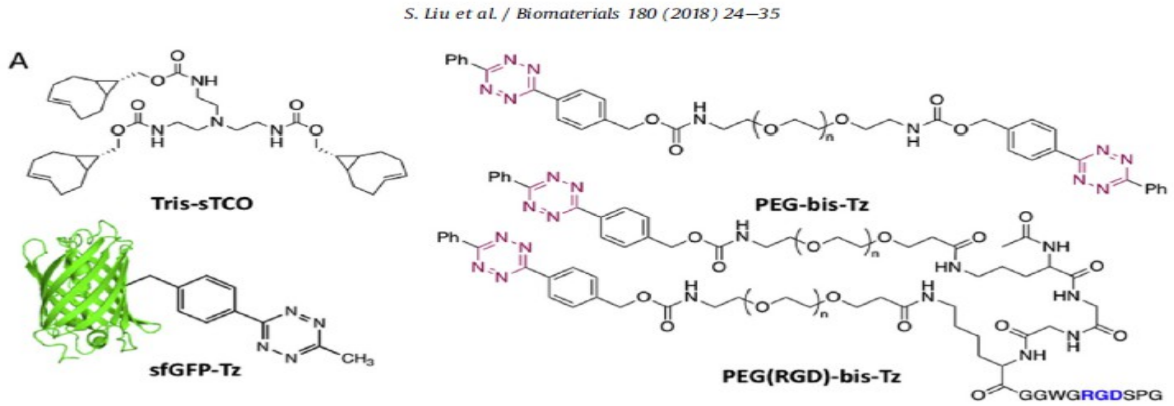
The following is I think the best reference I found in its introduction to polymerization.

Bagge, R. E. (2017). *Tetrazine Usage in the Synthesis and Post-Functionalization of Polymers Towards Generating Foams, Antioxidant-Rich Materials, and Optical Waveguides* (Doctoral dissertation, The University of Arizona).

(Found on line)



Liu, S., Zhang, H., Remy, R. A., Deng, F., Mackay, M. E., Fox, J. M., & Jia, X. (2015). Meter-long multiblock copolymer microfibers via interfacial bioorthogonal polymerization. *Advanced Materials*, *27*(17), 2783-2790.



Liu, S., Moore, A. C., Zerdoum, A. B., Zhang, H., Scinto, S. L., Zhang, H., ... & Jia, X. (2018). Cellular interactions with hydrogel microfibers synthesized via interfacial tetrazine ligation. *Biomaterials*,*180*, 24-35.

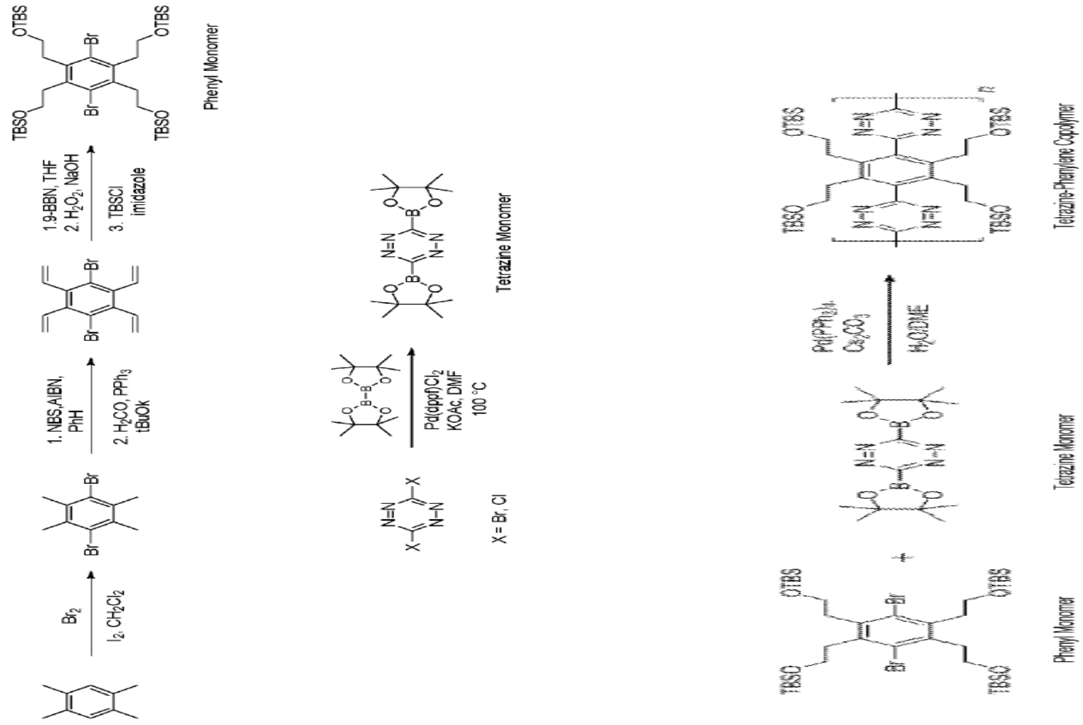
The above references illustrate that this DA reaction(IEDDA Inverse Electron Demand DA) can be employed to prepare polymers. But to get the most out of this polymerization I suggest more concentrated reactive groups as shown in schemes 1&2 above.
Because this reaction IEDDA can be employed in bioorthoganal reactions even in living cells has created a massive deluge of literature. Several reviews are available but I don't have access to all of them. I recommend:

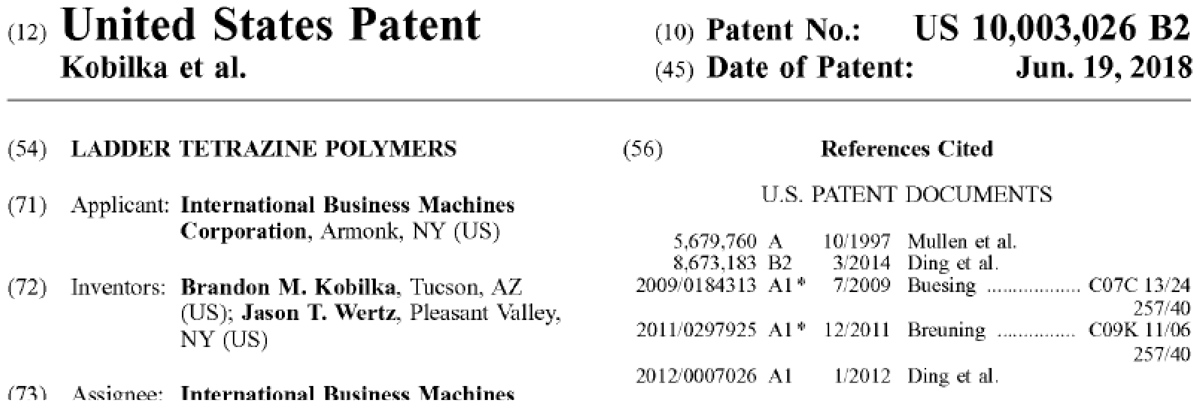
Zhang, J., Shukla, V., & Boger, D. L. (2019). Inverse Electron Demand Diels–Alder Reactions of Heterocyclic Azadienes, 1-Aza-1, 3-Butadienes, Cyclopropenone Ketals, and Related Systems. A Retrospective. *The Journal of organic chemistry*, *84*(15), 9397-9445. A monumental 45pp review of Prof Boger's work.

Gambardella, A. (2019). Synthesis of s-Tetrazines for biomedical applications. (Ph.D thesis nice review)

Qu, Y., Pander, P., Vybornyi, O., Vasylieva, M., Guillot, R., Miomandre, F., ... & Audebert, P. (2020). Donor–Acceptor 1, 2, 4, 5-Tetrazines Prepared by the Buchwald–Hartwig Cross-Coupling Reaction and Their Photoluminescence Turn-On Property by Inverse Electron Demand Diels–Alder Reaction. *The Journal of Organic Chemistry*, *85*(5), 3407-3416. Introduction has many references.

After reading numerous references looking for ideas similar to my proposals, I found the following patents.




(12) **United States Patent**
Kobilka et al.

(10) **Patent No.:** **US 10,003,026 B2**
(45) **Date of Patent:** **Jun. 19, 2018**

(54) **LADDER TETRAZINE POLYMERS**

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(73) Assignee: **International Business Machines**

(56) **References Cited**

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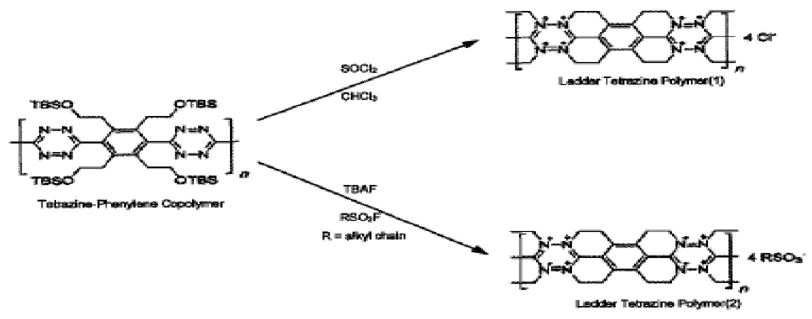
5,679,760 A 10/1997 Mullen et al.
8,673,183 B2 3/2014 Ding et al.
2009/0184313 A1* 7/2009 Buesing C07C 13/24 257/40
2011/0297925 A1* 12/2011 Breuning C09K 11/06 257/40
2012/0007026 A1 1/2012 Ding et al.

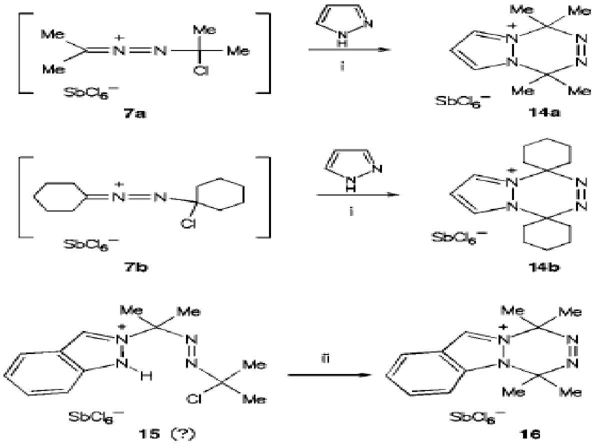
There are several patents in this series with different claims but with the same or very



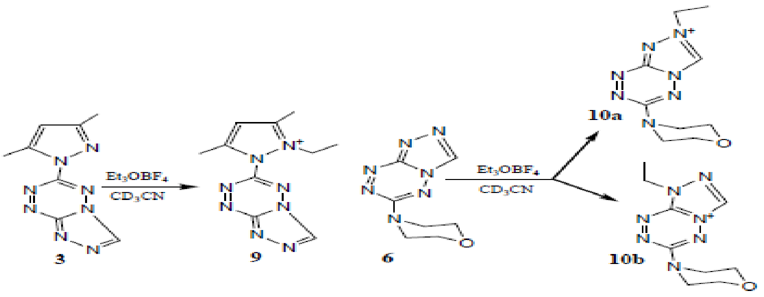
similar specifications.

Obviously I like the proposed chemistry up to a point where the s-tetrazines have positive charges(4quats) on the tetrazine nitrogens. I dont believe that is possible? Also the specifications show no actual synthesis but proposed synthesis, a paper reduction to practice. IBM is no light weight and I assume some real reason for these patents exists?

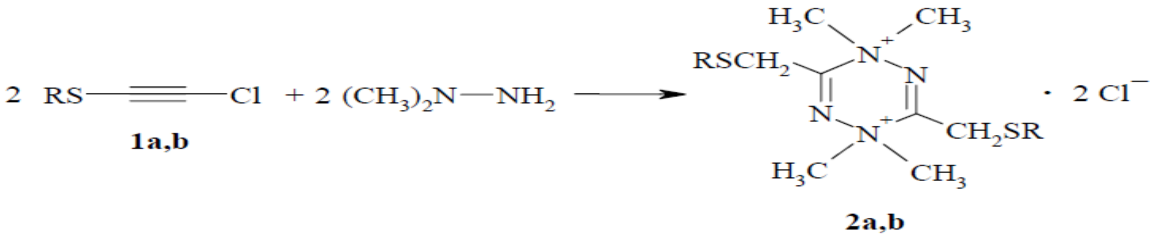
I searched for s-tetrazine quats or **tetrazinium** salts or cations. I found the following;



Al-Soud, Y. A., Shrestha-Dawadi, P. B., Winkler, M., Wirschun, W., & Jochims, J. C. (1998). 1-Aza-2-azoniaallene salts: reactions with azomethines and other N-nucleophiles. *Journal of the Chemical Society, Perkin Transactions 1*, (22), 3759-3766.



Novák, Z., Csámpai, A., & Kotschy, A. (2000). Synthesis and alkylation of some [1, 2, 4] triazolo [4, 3-b] tetrazines. *Arkivoc*, *3*, 259-265.

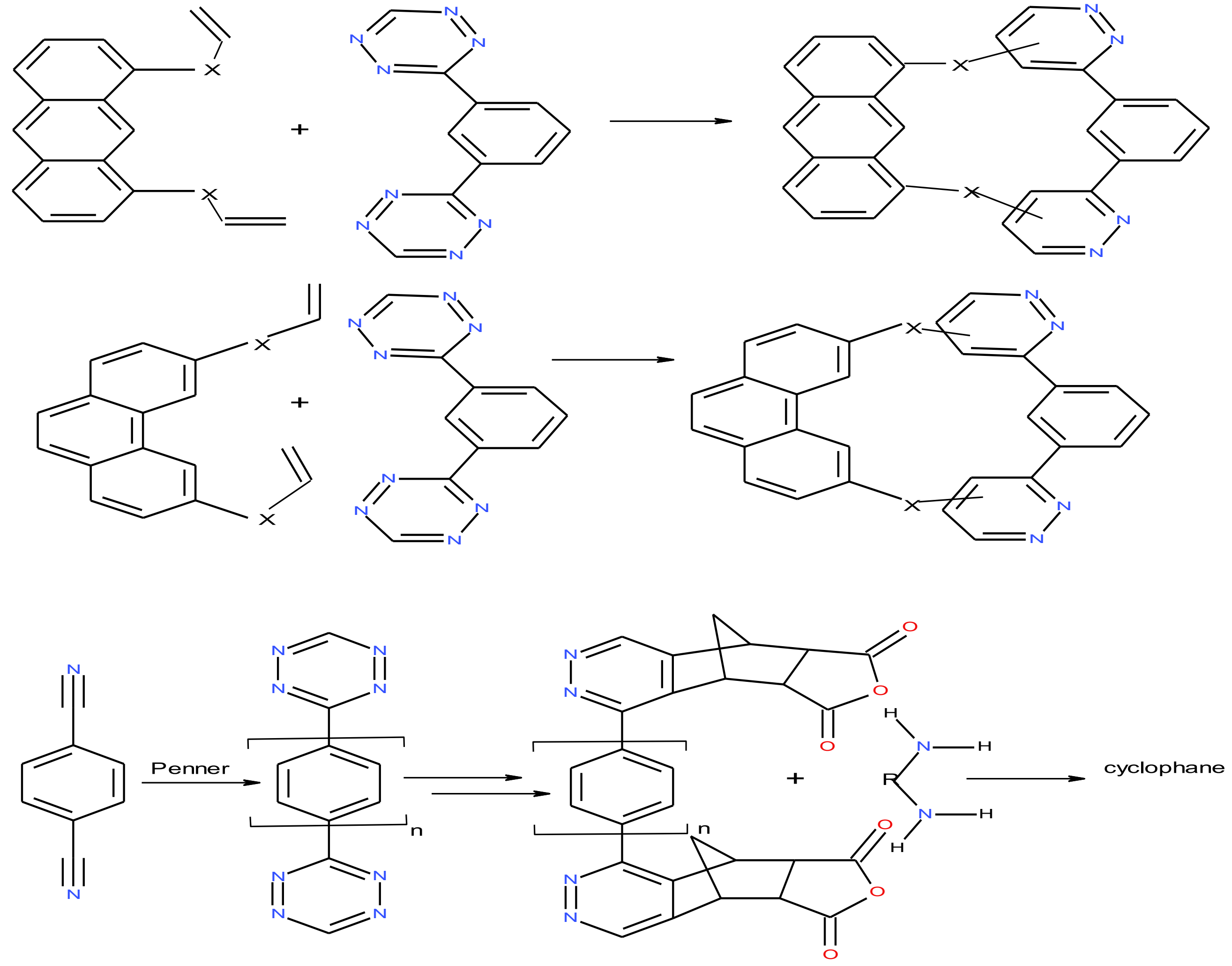


R = Et (a), *i*-Pr (b).

Voronkov, M. G., Lebedeva, I. P., Rakhlina, V. I., & D'yachkovab, S. G. (2005). A new route to functionally-substituted tetrazines. *Arkivoc*, *7*, 56-59.

Possibly there are more but this is what I found.

Cyclophanes:



Scheme 4: Pinner--Possible cyclophane synthesis. Dilution would favor the cyclophanes.
This is just an example and other structures could be conceived of but I think these make the point.

Thanks for reading these proposals!

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