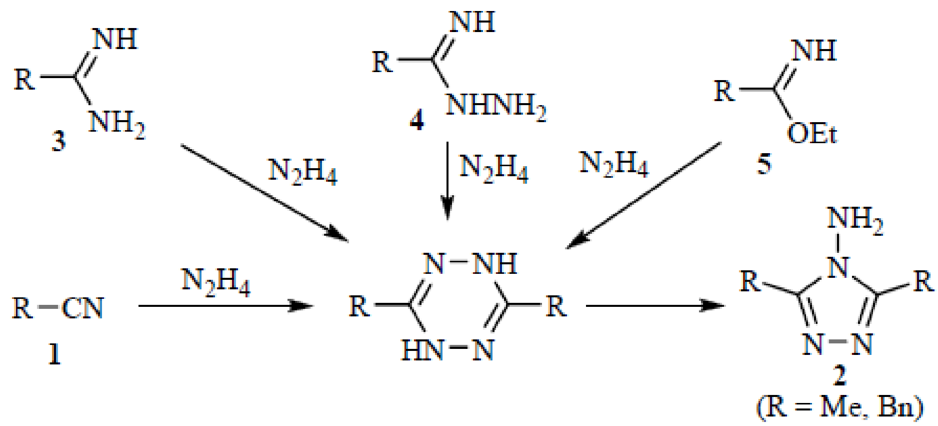
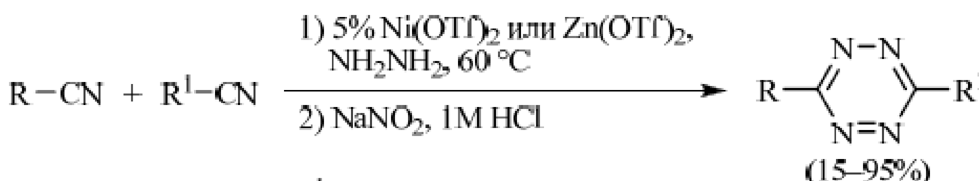
Review of Tetrazine Synthesis

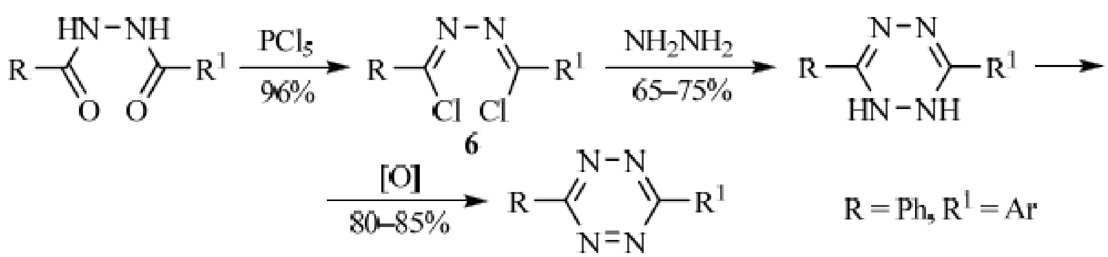
What follows are reactions that result in tetrazines from the references I was able to obtain. They are just brief examples of what you can find in these references. I hope this will save you some time.

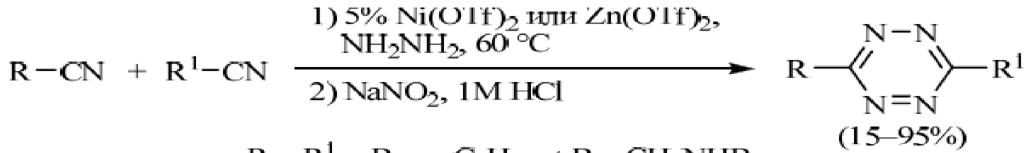


R = $R^1C_6H_4$, 2-пиридил, 2-тиенил, 2-пирролил, 1,2,3,4-тетразол-1-ил, ферроценил

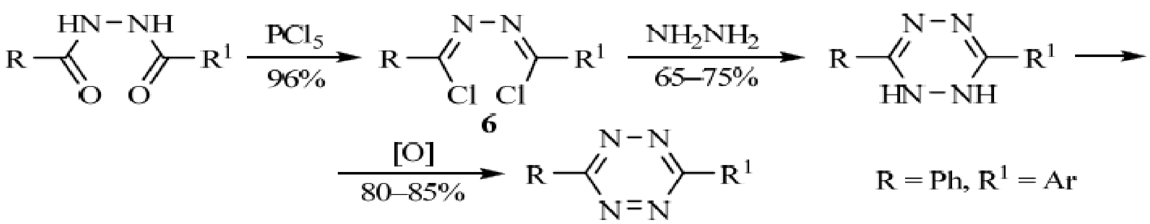


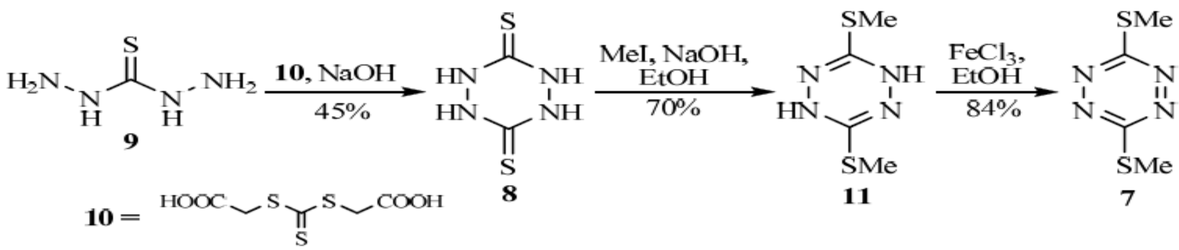
R = R[1] = Bn, n-C_5H_{11}, t-Bu, CH_2NHBoc;
R = Me, R[1] = 2-пирролил, 4-$BocNHCH_2C_6H_4$, 4-$HOCH_2C_6H_4$, 4-IC_6H_4, 4-HOC_6H_4, 4-$HOOCCH_2C_6H_4$, Bn, $HOCH_2CH_2$, $BocNHCH_2$, n-C_5H_{11};
R = Bn, R[1] = n-C_5H_{11}; R = H, R[1] = 4-$HOCH_2C_6H_4$

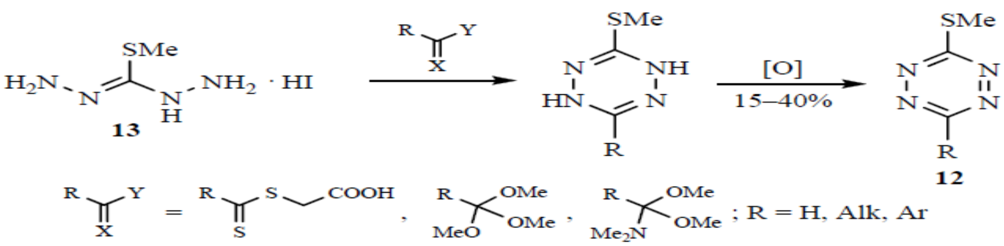


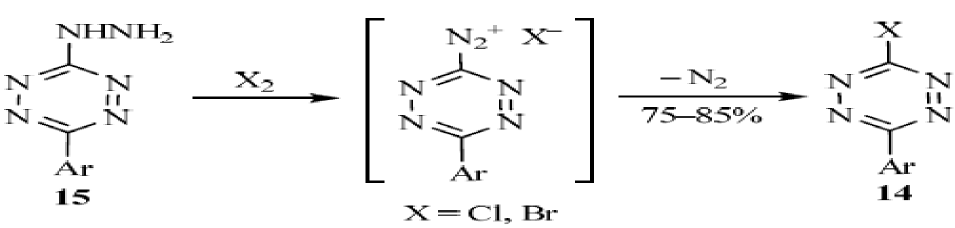


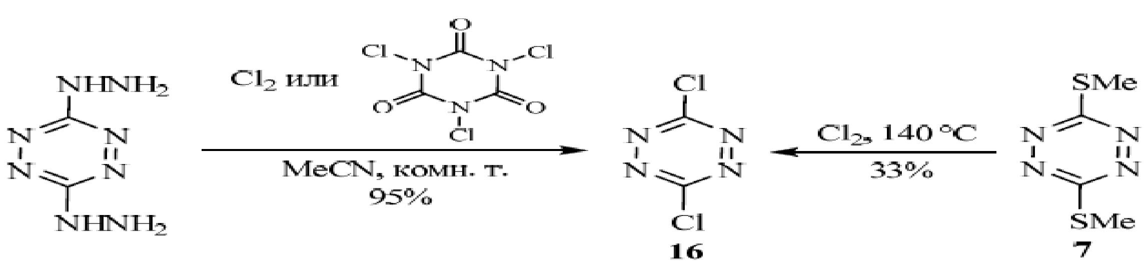
R = R[1] = Bn, *n*-C_5H_{11}, *t*-Bu, CH_2NHBoc;
R = Me, R[1] = 2-пирролил, 4-$BocNHCH_2C_6H_4$, 4-$HOCH_2C_6H_4$, 4-IC_6H_4, 4-HOC_6H_4,
4-$HOOCCH_2C_6H_4$, Bn, $HOCH_2CH_2$, $BocNHCH_2$, *n*-C_5H_{11};
R = Bn, R[1] = *n*-C_5H_{11}; R = H, R[1] = 4-$HOCH_2C_6H_4$





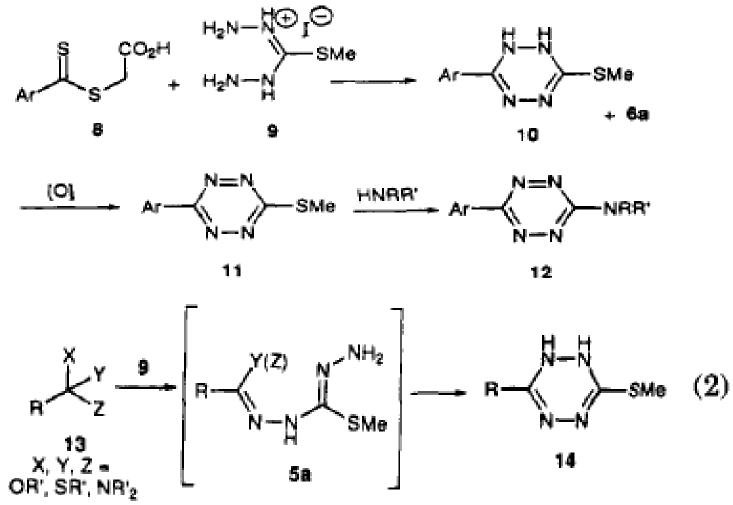






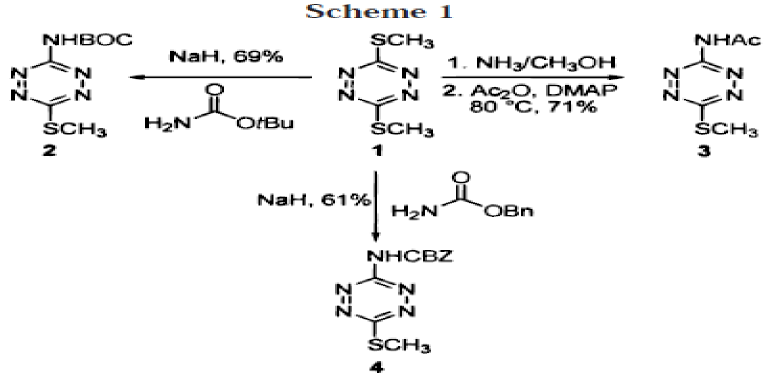
Tolshchina, SG, Rusinov, GL, & Charushin, VN (2013). 1, 2, 4, 5-Tetrazines and Azolo [1, 2, 4, 5] tetrazines: Synthesis and Reactions with Nucleophiles. *Chemistry of Heterocyclic Compounds*, *49*(1), 66-91.

The above is a selection of the reactions reviewed(1994-2013) in this very detailed Russian reference.

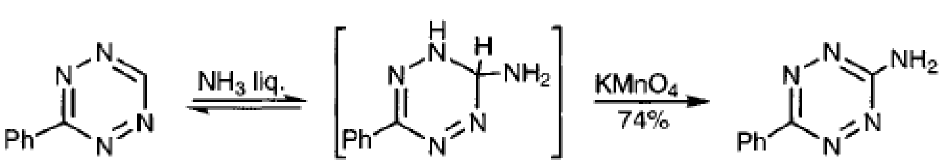


Fields, S. C., Parker, M. H., & Erickson, W. R. (1994). A simple route to unsymmetrically substituted 1, 2, 4, 5-tetrazines. *The Journal of Organic Chemistry*, *59*(26), 8284-8287.

Scheme 1

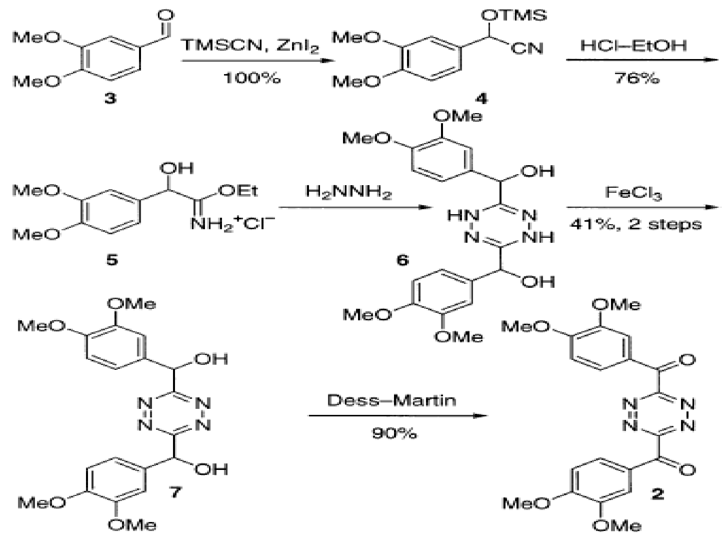


Boger, D. L., Schaum, R. P., & Garbaccio, R. M. (1998). Regioselective inverse electron demand Diels− Alder reactions of N-acyl 6-amino-3-(methylthio)-1, 2, 4, 5-tetrazines. *The Journal of organic chemistry*, *63*(18), 6329-6337.



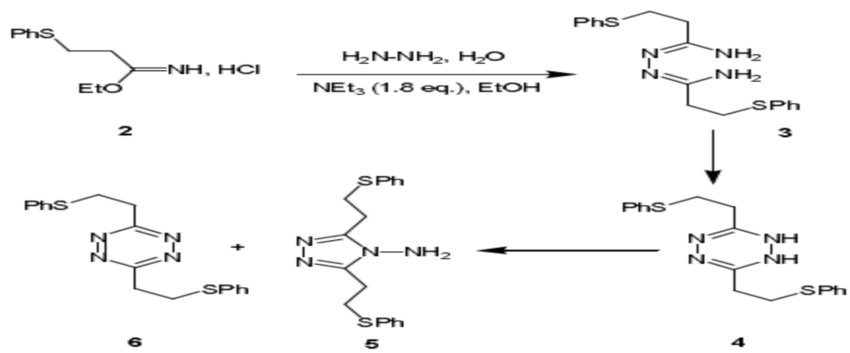
Counotte-Potman, A., & Van Der Plas, H. C. (1981). A new synthesis of 6-(alkyl) amino-3-aryl (alkyl)-1, 2, 4, 5-tetrazines. *Journal of heterocyclic chemistry*, *18*(1), 123-127.

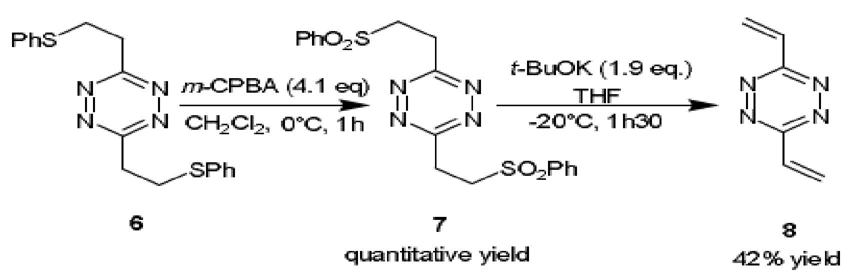
SCHEME 1



3594 *J. Org. Chem., Vol. 68, No. 9, 2003*

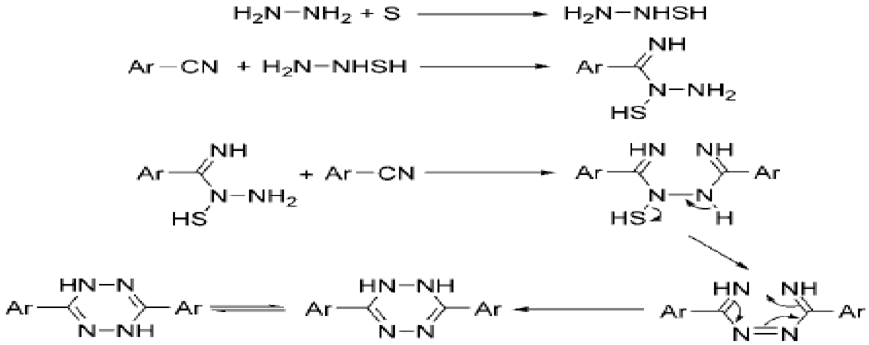
Soenen, D. R., Zimpleman, J. M., & Boger, D. L. (2003). Synthesis and Inverse Electron Demand Diels− Alder Reactions of 3, 6-Bis (3, 4-dimethoxybenzoyl)-1, 2, 4, 5-tetrazine. *The Journal of organic chemistry*, *68*(9), 3593-3598.



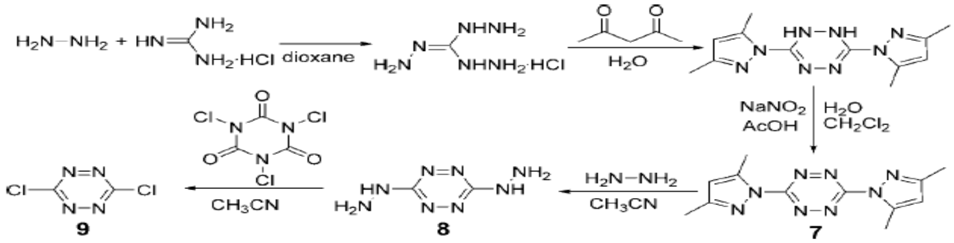


Pican, S., Lapinte, V., Pilard, J. F., Pasquinet, E., Beller, L., Fontaine, L., & Poullain, D. (2009). Synthesis of 3, 6-Divinyl-1, 2, 4, 5-Tetrazine, the First Member of the Elusive Vinyltetrazine Family. *Synlett*, (5), 731-734.

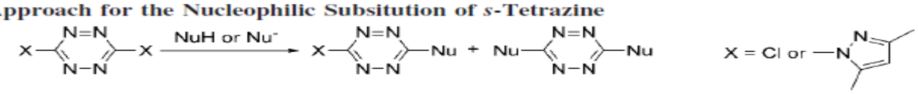
Scheme 2. Proposed Mechanism for the Sulfur-Assisted Pinner Synthesis of Dihydro-*s*-tetrazines



Scheme 3. Synthesis of the 3,6-Dichloro-*s*-tetrazine

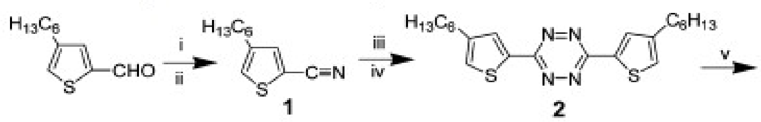


Scheme 4. General Approach for the Nucleophilic Subsitution of *s*-Tetrazine



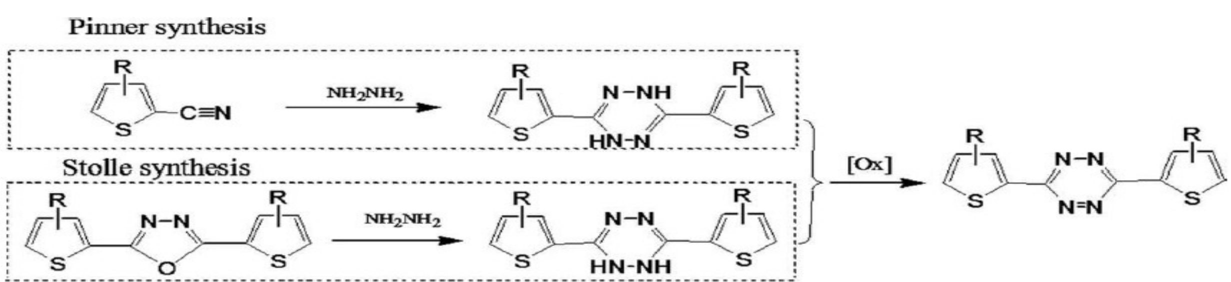
Clavier, G., & Audebert, P. (2010). s-Tetrazines as building blocks for new functional molecules and molecular materials. *Chemical reviews*, *110*(6), 3299-3314. Excellent review

Scheme 2. Synthesis of the Polymer PCPDTTTz[a]



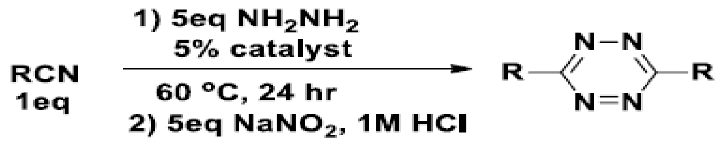
[a] (i) $NH_2OH\cdot HCl$, pyridine, ethanol, 80 °C, 16 h; (ii) Ac_2O, KOAc, 140 °C, 3 h; (iii) $NH_2NH_2\cdot H_2O$, sulfur, ethanol, reflux, 2 h; (iv) isoamyl nitrite,

Li, Z., Ding, J., Song, N., Lu, J., & Tao, Y. (2010). Development of a new s-tetrazine-based copolymer for efficient solar cells. *Journal of the American Chemical Society*, *132*(38), 13160-13161.

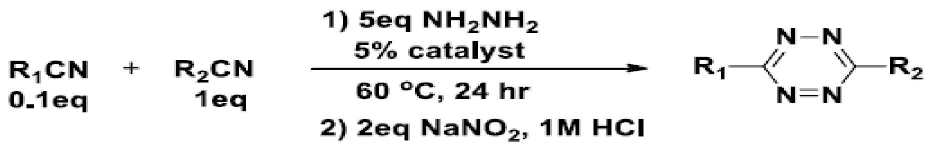


SCHEME 2 Pinner and Stollé synthesis for the preparation of tetrazines.

General procedure for synthesis of 3,6-dialkyl 1,2,4,5-tetrazine:



General procedure for synthesis of 3-alkyl-6-aryl or alkyl-1,2,4,5-tetrazine:

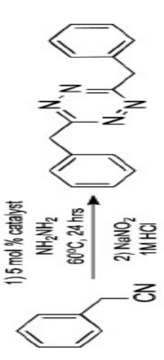


when R_1 is N-Boc-pyrrole, the Boc will be deprotected to give pyrrole

Note that both R1CN and R2CN should be equal.

Yang, J., Karver, M. R., Li, W., Sahu, S., & Devaraj, N. K. (2012). Metal-catalyzed one-pot synthesis of tetrazines directly from aliphatic nitriles and hydrazine. *Angewandte Chemie International Edition*, *51*(21), 5222-5225.

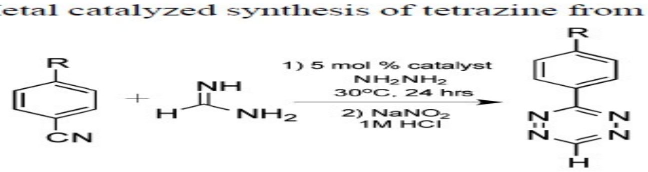
Survey of metal catalysts

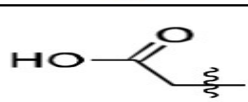
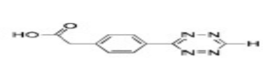
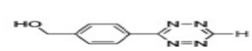
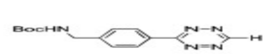


catalyst	yield[a]	catalyst	yield[a]	catalyst	yield[a]
none	0%	$Cu(OAc)_2$	59%	$NiCl_2$	73%
$Zn(OAc)_2$	38%	$MnBr_2$	55%	NiI_2	93%
$ZnCl_2$	11%	$CuBr_2$	23%	$Ni(OTf)_2$	95%
$ZnBr_2$	40%	$CoCl_2 \cdot 6H_2O$	13%	CuOAc	53%
ZnI_2	68%	$MgCl_2$	63%	CuCl	12%
$Zn(OTf)_2$	70%	$Yb(OTf)_3$	31%	CuBr	42%
$Cu(OTf)_2$	11%	$Sc(OTf)_3$	26%	CuI	50%
$MgBr_2$	15%	$Ni(acac)_2$	10%	Cu(OTf)	57%

[a] yields reported after isolation by silica flash chromatography

Metal catalyzed synthesis of tetrazine from aromatic nitriles and formamidine.

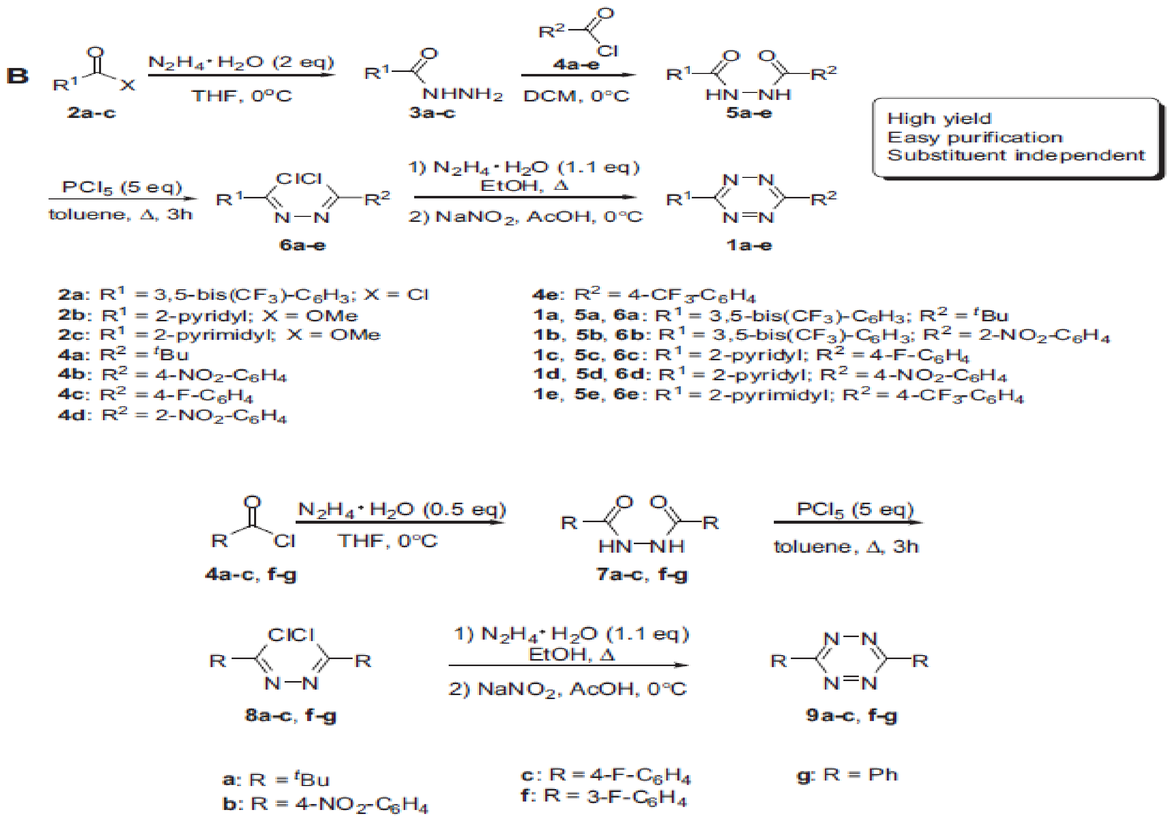


entry	R	catalyst	product	yield
17		Ni		74%
18		Ni		64%
19[b]		Zn		70%

[a] yields reported after isolation by silica flash chromatography

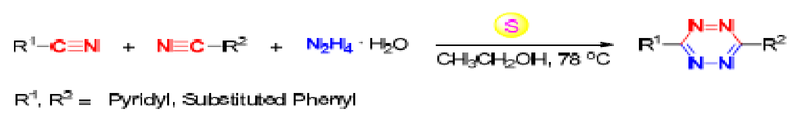
[b] required use of DMF as cosolvent and 36 hours of reaction

Yang, J., Karver, M. R., Li, W., Sahu, S., & Devaraj, N. K. (2012). Metal-catalyzed one-pot synthesis of tetrazines directly from aliphatic nitriles and hydrazine. *Angewandte Chemie International Edition*, *51*(21), 5222-5225.

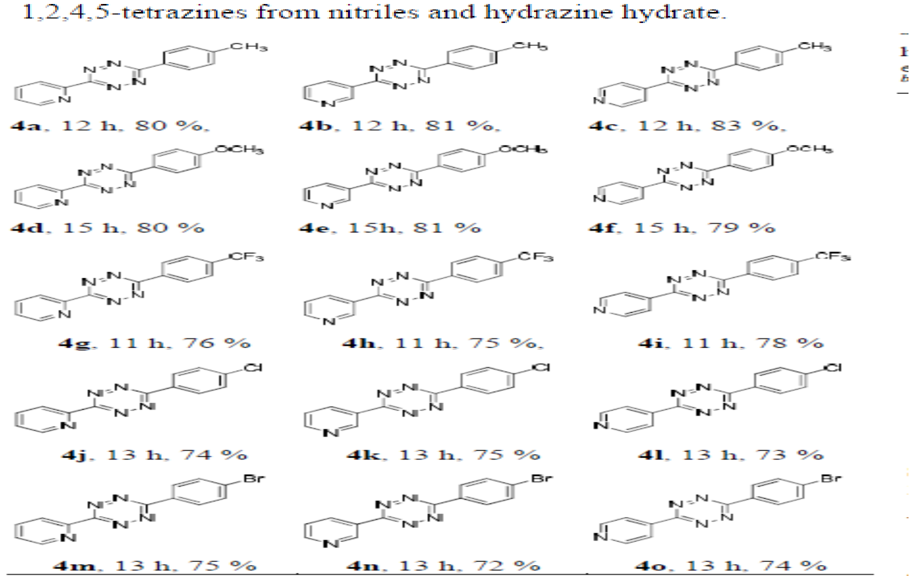


Scheme 2 Synthesis of symmetrically 3,6-substituted 1,2,4,5-tetrazine via 1,2-dichloromethylenehydrazines.

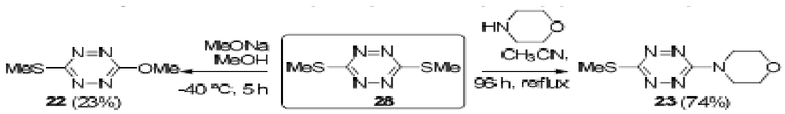
Wang, D., Chen, W., Zheng, Y., Dai, C., Wang, L., & Wang, B. (2013). A general and efficient entry to asymmetric tetrazines for click chemistry applications. *Heterocyclic Communications*, *19*(3), 171-177.



Scheme 1 Preparation of 3,6-unsymmetrically disubstituted-1,2,4,5-tetrazines from nitriles and hydrazine hydrate.

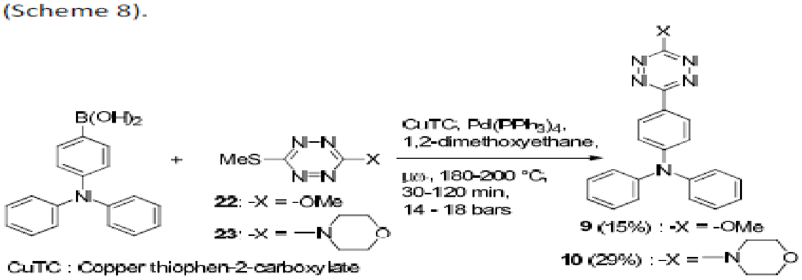


Li, C., Ge, H., Yin, B., She, M., Liu, P., Li, X., & Li, J. (2015). Novel 3, 6-unsymmetrically disubstituted-1, 2, 4, 5-tetrazines: S-induced one-pot synthesis, properties and theoretical study. *RSC advances*, *5*(16), 12277-12286.



Scheme 7. Synthesis of the tetrazine precursors **22** and **23**

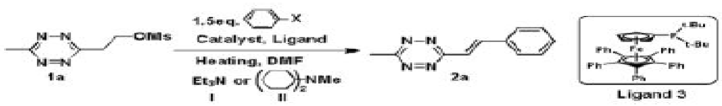
A Suzuki-Miyaura cross-coupling between triphenylamine boronic acid and each precursor **22** and **23** gave the expected products **9** and **10** with respectively 15% and 29% yields (Scheme 8).



Scheme 8. Synthesis of compounds **9** and **10**

Quinton, C., Alain-Rizzo, V., Dumas-Verdes, C., Clavier, G., Vignau, L., & Audebert, P. (2015). Triphenylamine/tetrazine based π-conjugated systems as molecular donors for organic solar cells. *New Journal of Chemistry*, *39*(12), 9700-9713.

Optimization of the reaction conditions.[a]



Entry	Cat., Ligand	Heat, Time	Base	Yield (%)[d]
1[b]	10% $Pd(PPh_3)_4$	80°C, 90 min	I	0
2[b]	10% $Pd(PPh_3)_4$	50°C, MW 30 min	II	55
3[b]	10%$Pd_2(dba)_3$40% $P(o\text{-}Tol)_3$	50°C, MW 30 min	II	80
4[c]	3%$Pd_2(dba)_3$,12%$(t\text{-}Bu)_3P^+BF^-_4$	60°C, MW 40 min	II	58
5[b], [c]	3%$Pd_2(dba)_3$12% ligand 3	50°C, MW 30 min	II	99

[a] All reactions were carried out on a 0.02 mmol scale in 1.5 mL DMF. Ms – Mesyl group. MW – microwave.

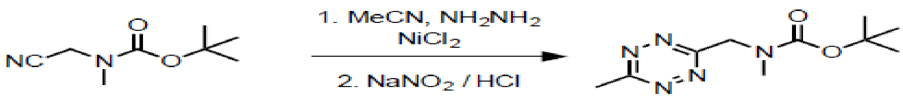
[b] Iodobenzene as starting material.

[c] Bromobenzene as starting material.

[d] Isolated yield based on 1a, no (Z)-3-methyl-6-styryl-s-tetrazine was observed.

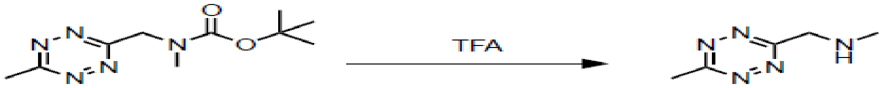
Wu, H., Yang, J., Šečkutė, J., & Devaraj, N. K. (2014). In Situ Synthesis of Alkenyl Tetrazines for Highly Fluorogenic Bioorthogonal Live-Cell Imaging Probes. *Angewandte Chemie*, *126*(23), 5915-5919.

tert-butyl N-methyl-N-((6-methyl-1,2,4,5-tetrazin-3-yl)methyl)carbamate (9)



8 9

N-methyl-1-(6-methyl-1,2,4,5-tetrazin-3-yl)methanamine (1)



9 1

Denk, C., Svatunek, D., Mairinger, S., Stanek, J., Filip, T., Matscheko, D., ... & Mikula, H. (2016). Design, synthesis, and evaluation of a low-molecular-weight 11C-labeled tetrazine for pretargeted PET imaging applying bioorthogonal in vivo click chemistry. *Bioconjugate Chemistry*, *27*(7), 1707-1712.

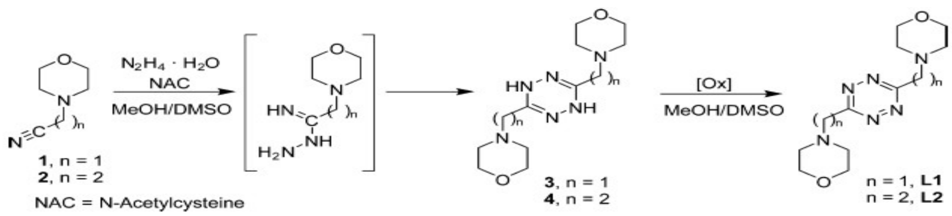
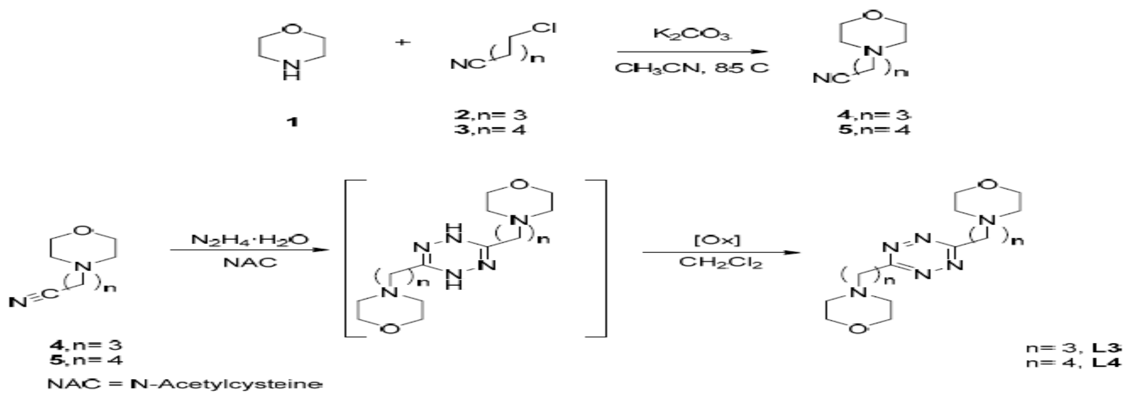


Figure 1. Synthetic scheme for the preparation of tetrazine ligands **L1** and **L2**.

Savastano, M., Bazzicalupi, C., Giorgi, C., García-Gallarín, C., Lopez de la Torre, M. D., Pichierri, F., ... & Melguizo, M. (2016). Anion complexes with tetrazine-based ligands: formation of strong anion− π interactions in solution and in the solid state. *Inorganic chemistry*, *55*(16), 8013-8024.



Scheme 1. Synthesis of **L3** and **L4** ligands.

Savastano, M., García-Gallarín, C., Giorgi, C., Gratteri, P., López de la Torre, M. D., Bazzicalupi, C., ... & Melguizo, M. (2019). Solid State and Solution Study on the Formation of Inorganic Anion Complexes with a Series of Tetrazine-Based Ligands. *Molecules*, *24*(12), 2247.

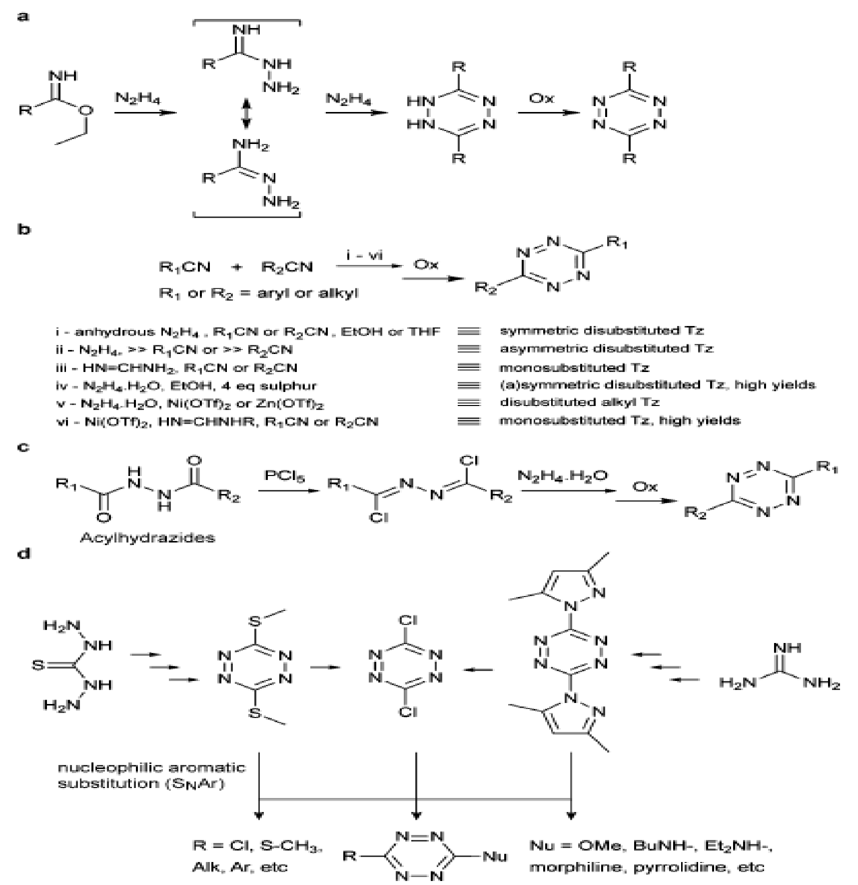
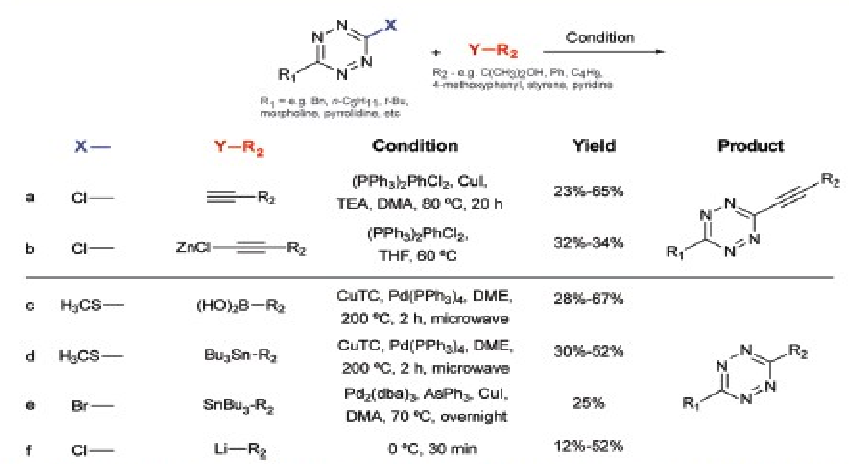


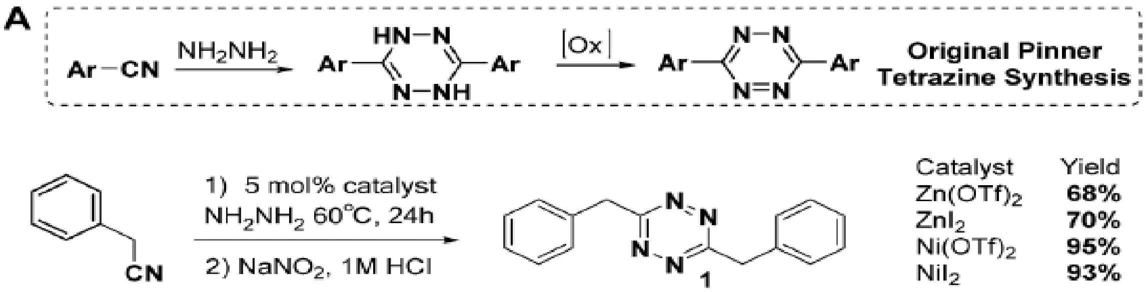
Fig. 9 Classic synthesis routes for tetrazines using (a) imidoesters, (b) nitriles, (c) acylhydrazides and (d) nucleophilic aromatic substitution.



	X—	Y—R₂	Condition	Yield
a	Cl—	≡—R_2	(PPh$_3$)$_2$PhCl$_2$, CuI, TEA, DMA, 80 °C, 20 h	23%-65%
b	Cl—	ZnCl—≡—R_2	(PPh$_3$)$_2$PhCl$_2$, THF, 60 °C	32%-34%
c	H$_3$CS—	(HO)$_2$B—R_2	CuTC, Pd(PPh$_3$)$_4$, DME, 200 °C, 2 h, microwave	28%-67%
d	H$_3$CS—	Bu$_3$Sn-R_2	CuTC, Pd(PPh$_3$)$_4$, DME, 200 °C, 2 h, microwave	30%-52%
e	Br—	SnBu$_3$-R_2	Pd$_2$(dba)$_3$, AsPh$_3$, CuI, DMA, 70 °C, overnight	25%
f	Cl—	Li—R_2	0 °C, 30 min	12%-52%

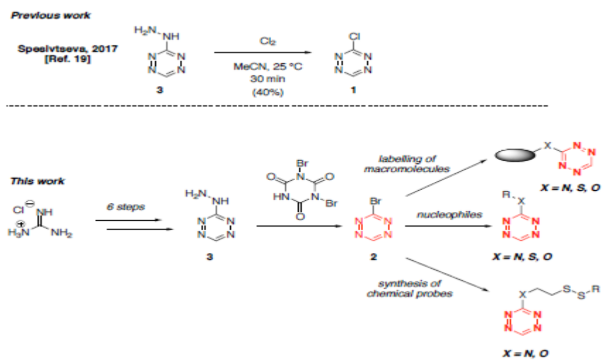
Fig. 10 Tetrazine crosslinking reactions based on C–C bond formation.

Oliveira, B. L., Guo, Z., & Bernardes, G. J. L. (2017). Inverse electron demand Diels–Alder reactions in chemical biology. *Chemical Society Reviews*, *46*(16), 4895-4950.



Wu, H., & Devaraj, N. K. (2018). Advances in tetrazine bioorthogonal chemistry driven by the synthesis of novel tetrazines and dienophiles. *Accounts of chemical research*, *51*(5), 1249-1259.

Scheme 1. 3-Bromotetrazine (2) as a promising precursor for the synthesis of *s*-tetrazines.



Schnell, S., Hoff, L., Panchagnula, A., Sieber, S., Linden, A., & Gademann, K. (2019). 3-Bromotetrazine: A Versatile Precursor for the Synthesis of 3-Monosubstituted s-Tetrazines and the Labelling of Macromolecules.

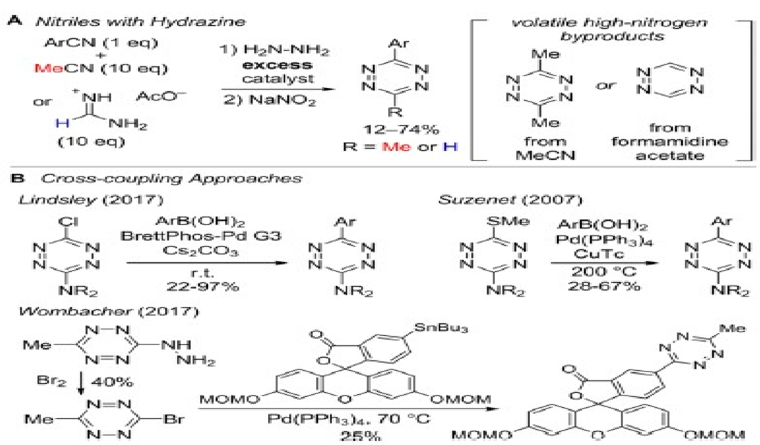


Figure 2. (A) Tetrazine synthesis based on condensation of nitriles or Pinner reagents with hydrazine. (B) Cross-couplings of tetrazine electrophiles with arylboronic acids have been limited to *N*-substituted tetrazines, which are deactivated for bioorthogonal chemistry applications. Stille coupling has been used to couple 3-bromo-6-methyltetrazine to fluorophores.

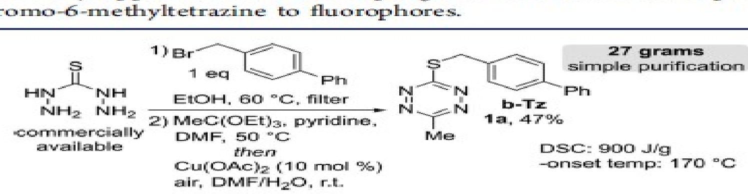


Figure 3. Decagram synthesis and thermal stability of b-Tz (**1a**).

Lambert, W. D., Fang, Y., Mahapatra, S., Huang, Z., Am Ende, C. W., & Fox, J. M. (2019). Installation of Minimal Tetrazines through Silver-Mediated Liebeskind–Srogl Coupling with Arylboronic Acids. *Journal of the American Chemical Society*, *141*(43), 17068-17074.

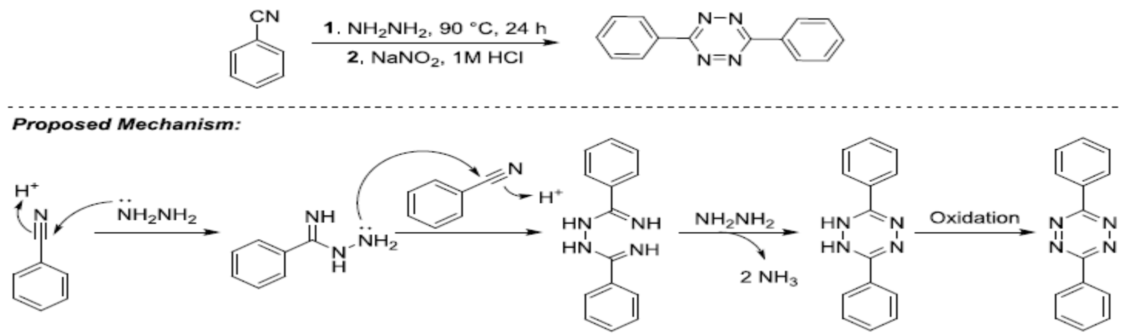


Figure 1.7. Condensation of two aromatic nitriles in the presence of hydrazine.

This is but one example from this excellent synthesis review.

Gambardella, A. (2019). Synthesis of s-Tetrazines for biomedical applications.

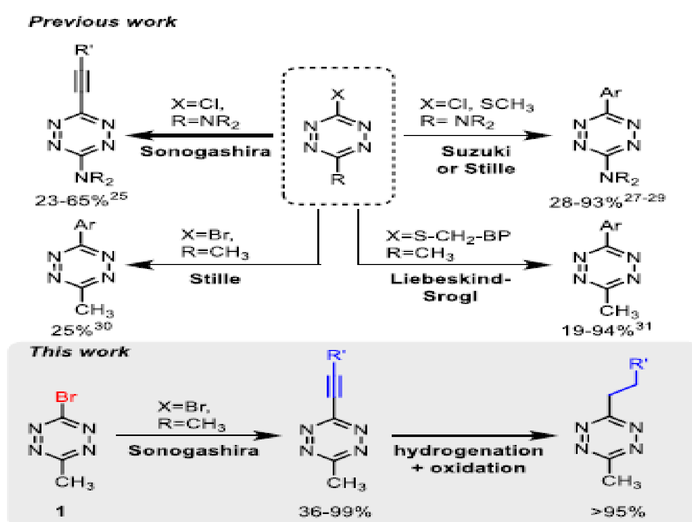
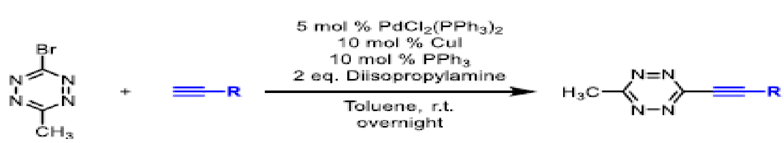


Figure 1: Overview of the reported metal-catalysed cross-couplings with 1,2,4,5-tetrazines.



Ros, E., Prades, A., Forson, D., Smyth, J., Verdaguer, X., de Pouplana, L. R., & Riera, A. (2020). Synthesis of 3-alkyl-6-methyl-1, 2, 4, 5-tetrazines via a Sonogashira-type cross-coupling reaction. *Chemical Communications*.

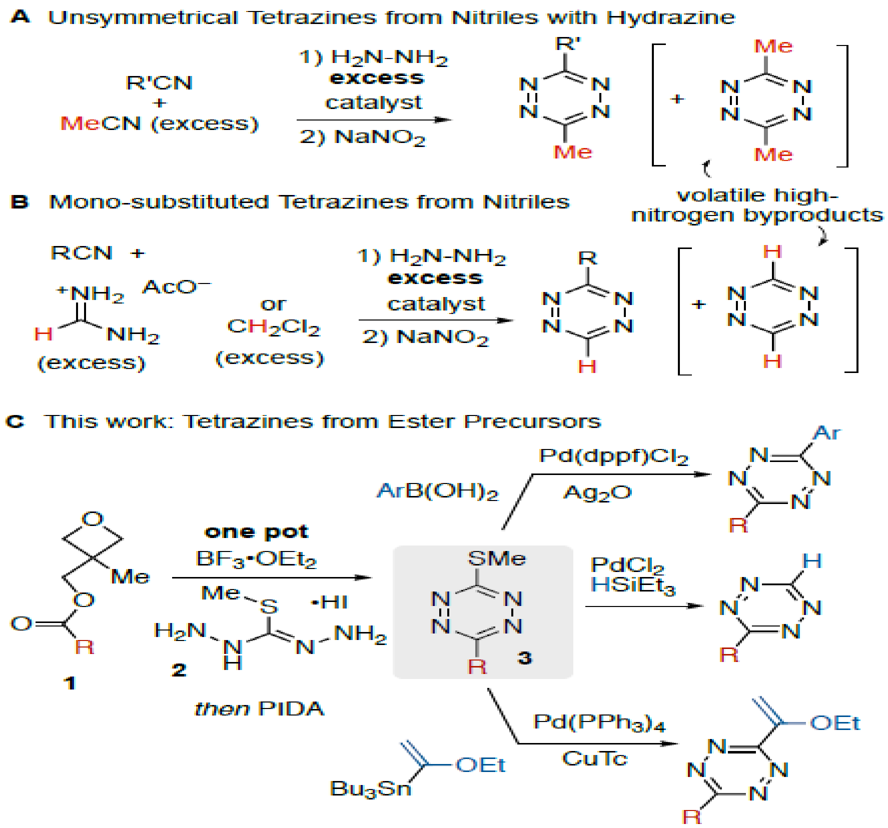


Figure 2. Selected methods of tetrazine synthesis

Xie, Y., Fang, Y., Huang, Z., Tallon, A. M., am Ende, C. W., & Fox, J. M. (2020). Divergent Synthesis of Monosubstituted and Unsymmetrical 3, 6-Disubstituted Tetrazines from Carboxylic Ester Precursors. Angew Chem Int Ed Engl

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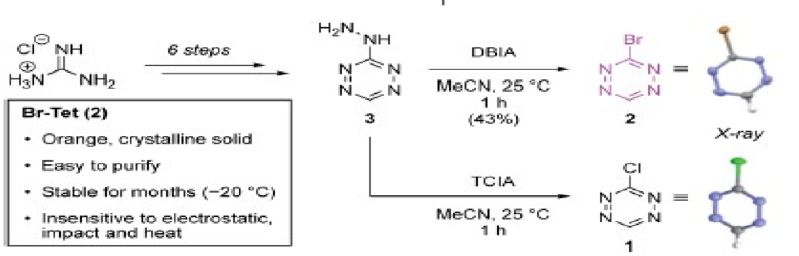
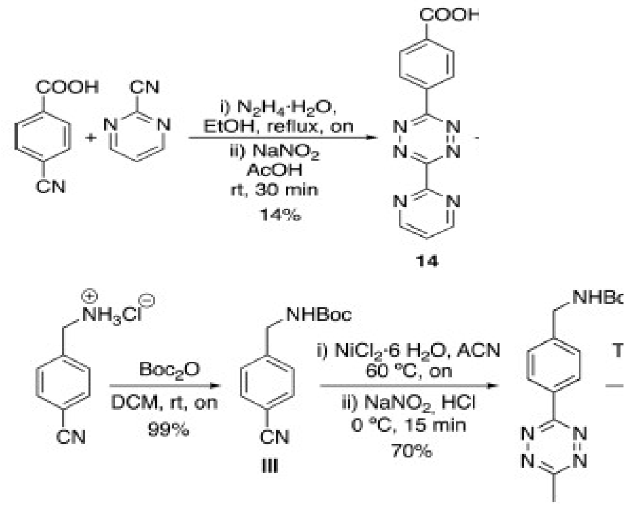


Scheme 2 Synthesis of Br-Tet (2). Synthesis of 3-chlorotetrazine (1) and novel 3-bromotetrazine (2) from guanidine hydrochloride. DBIA = dibromoisocyanuric acid; TCIA = trichloroisocyanuric acid

Schnell, S. D., Hoff, L. V., Panchagnula, A., Wurzenberger, M. H., Klapötke, T. M., Sieber, S., ... & Gademann, K. (2020). 3-Bromotetrazine: labelling of macromolecules via monosubstituted bifunctional s-tetrazines. *Chemical Science*, *11*(11), 3042-3047.



Agramunt, J., Ginesi, R., Pedroso, E., & Grandas, A. (2020). Inverse Electron-Demand Diels–Alder Bioconjugation Reactions Using 7-Oxanorbornenes as Dienophiles *The Journal of Organic Chemistry*, *85*(10), 6593-6604.

Dr. Robert B. Login rloginconsulting.com