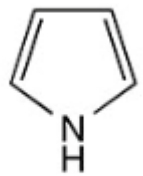
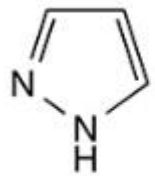
Ring Expansion Reactions of Aromatic Heterocycles

Balu Dherange

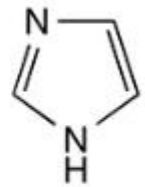
April 30, 2020



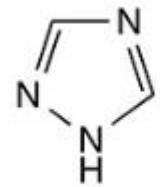
1*H*-pyrrole



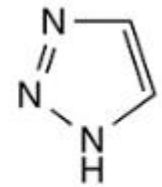
pyrazole



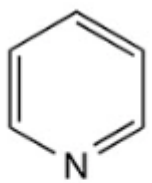
imidazole
pK_a: 6.9



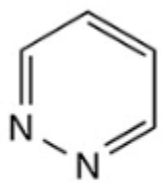
1,2,4-triazole



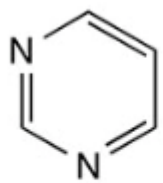
1,2,3-triazole
pK_a: 9.3



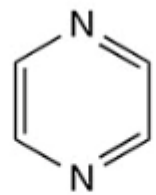
pyridine
pK_a: 5.2



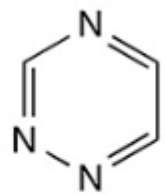
pyridazine



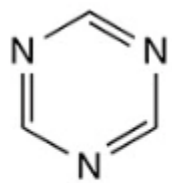
pyrimidine



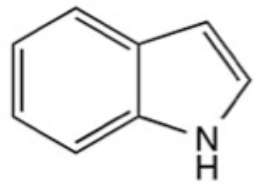
pyrazine



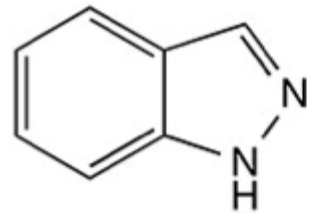
1,2,4-triazine



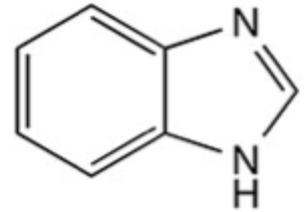
1,3,5-triazine



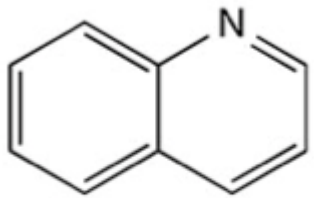
1*H*-indole



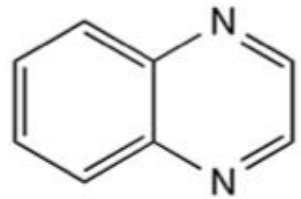
1*H*-indazole



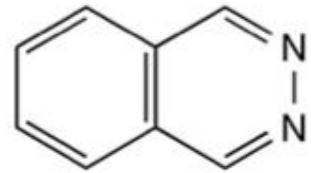
benzimidazole



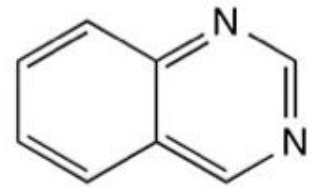
quinoline
pK_a: 4.92



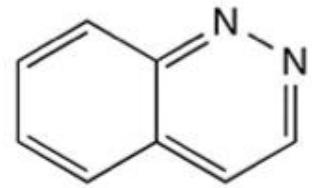
quinoxaline



phthalazine



quinazoline

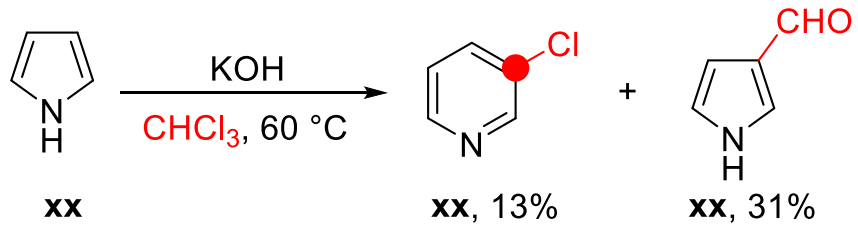


cinnoline

Synthesis of Pyridine/Quinoline

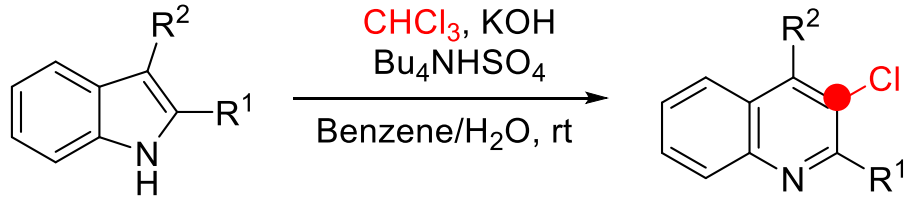
1. Carbene
    - 1A. Halocarbene
    - 1B. Allenylidene
    - 1C. Ylide
2. Cleavage/Reassembly

1A. Synthesis of Pyridine/Quinoline using Halocarbenes



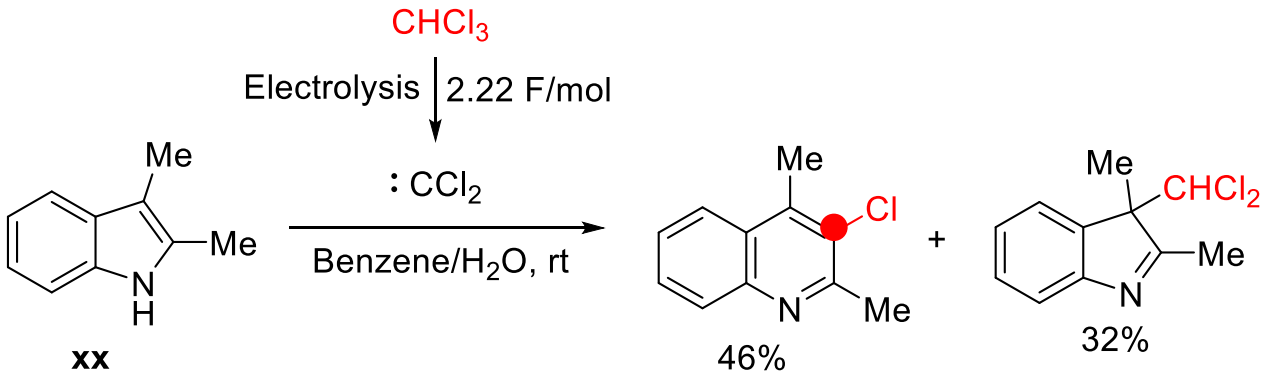
xx **xx**, 13% **xx**, 31%

Ciamician, G. L.; Dennstedt, M. *Ber.* **1881**, *14*, 1153
Ciamician, G. L.; Silber, P. *Ber.* **1885**, *18*, 721



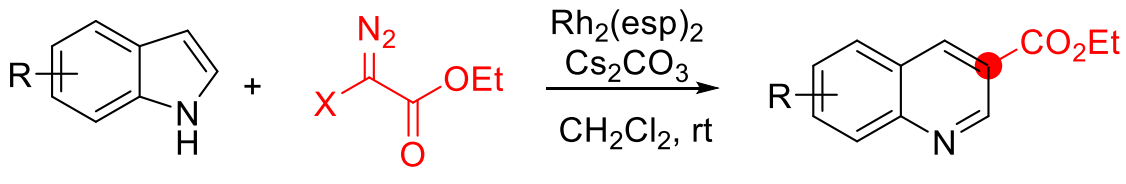
xx 70-80%

Joshi et al. *J. Ind. Chem. Soc.* **1993**, *6*, 567



xx 46% 32%

J. Org. Chem. **1995**, *60*, 2, 447

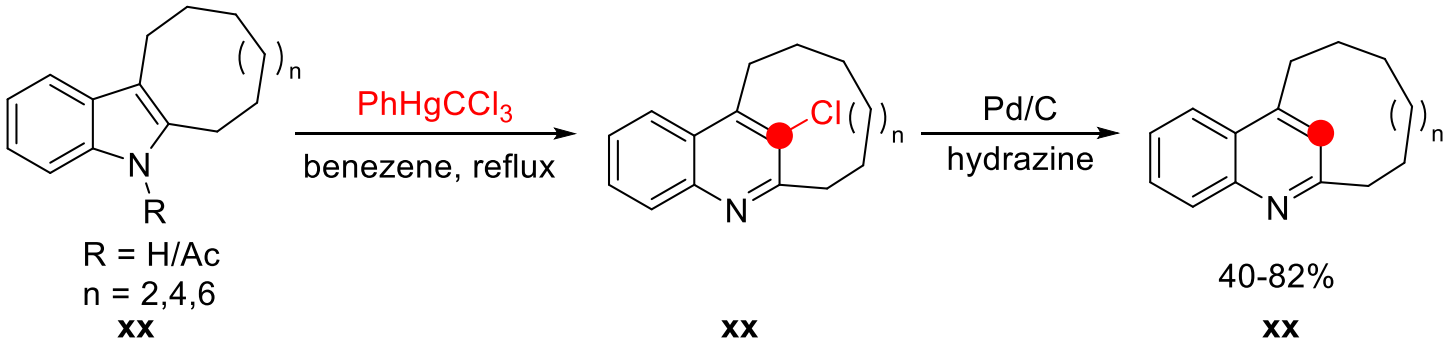


xx **xx** **xx**

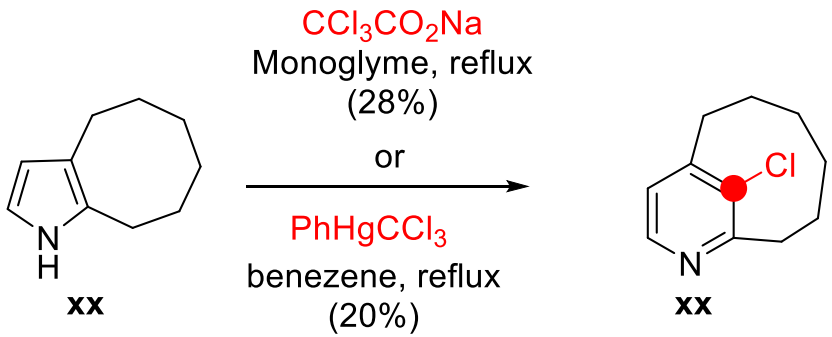
X = Cl, Br, I 40-94%

Beilstein J. Org. Chem. **2015**, *11*, 1944–1949.

1A. Synthesis of Pyridine/Quinoline using Halocarbenes

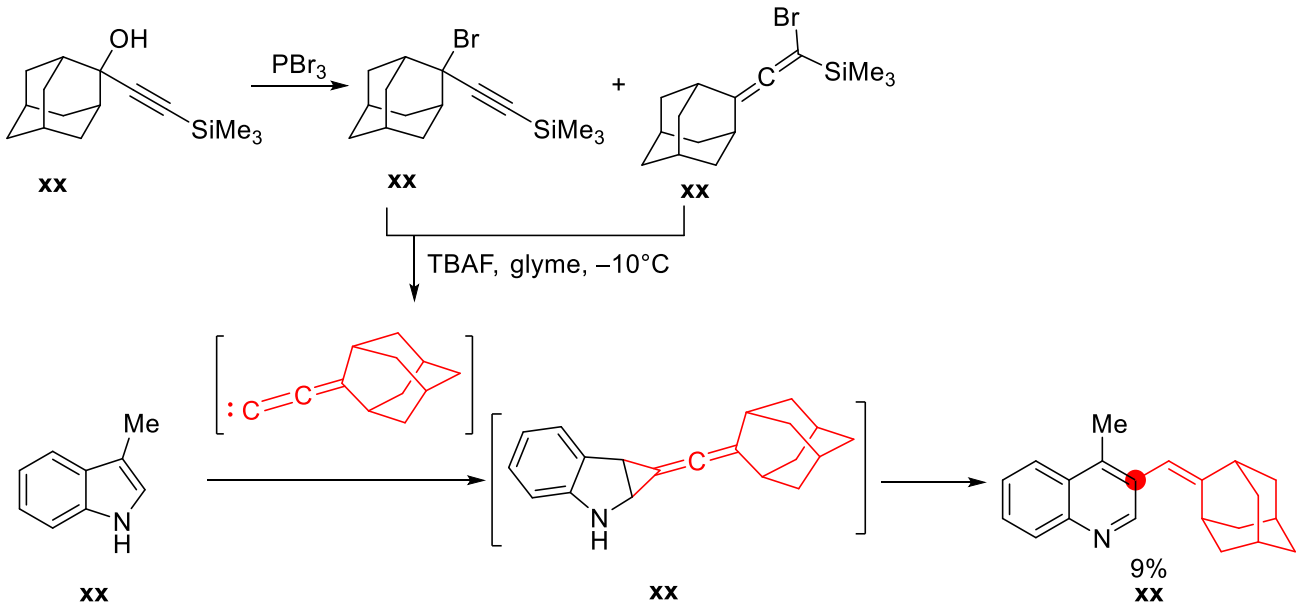


Parham, W. E.; Davenport, R. W.; Biasotti, J. B. *Tetrahedron Lett.* **1969**, *7*, 557-560



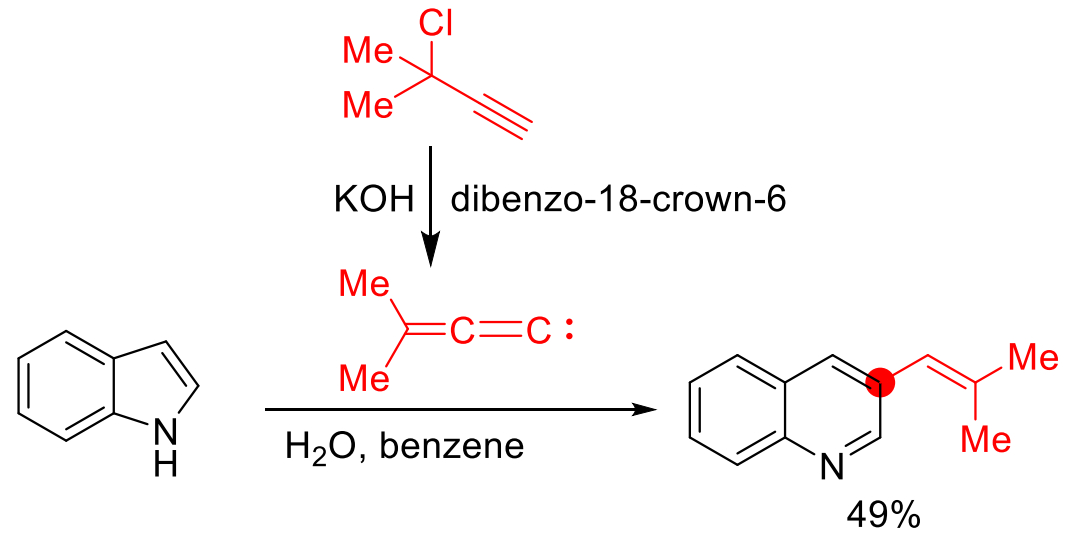
Dhanak, D.; Reese, C. B. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2829.

1B. Synthesis of Pyridine/Quinoline using Allenylidene



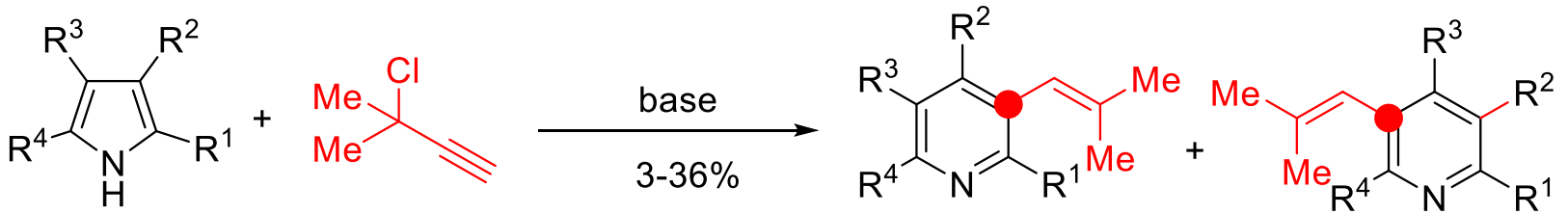
Shoji Eguchi, Tomoyuki Ikemoto, Yasuyuki Kobayakawa, Tadashi Sasaki *J. Chem. Soc., Chem. Commun.* **1985**, 958

1B. Synthesis of Pyridine/Quinoline using Allenylidene carbene



xx **xx**

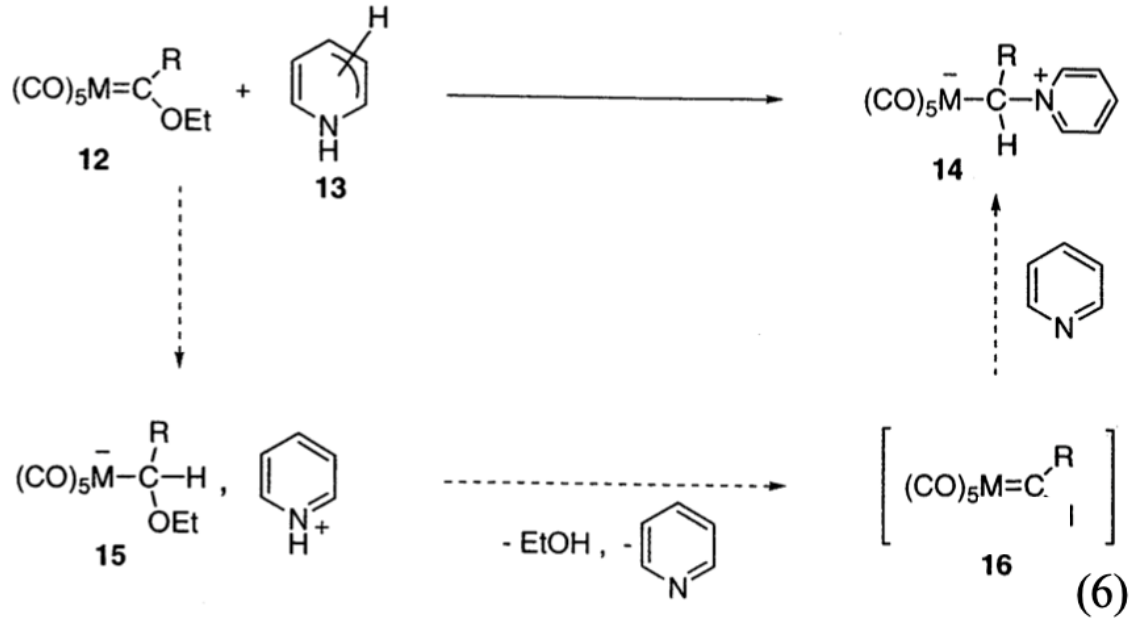
Ernest Wenkert, E. Charles Angelí, Vítor F. Ferreira, E. L. Michelotti, Serge R. Piettre, J.-H. Sheu, and Charles S. Swindell *J. Org. Chem.* **1986**, *61*, 2343-2351

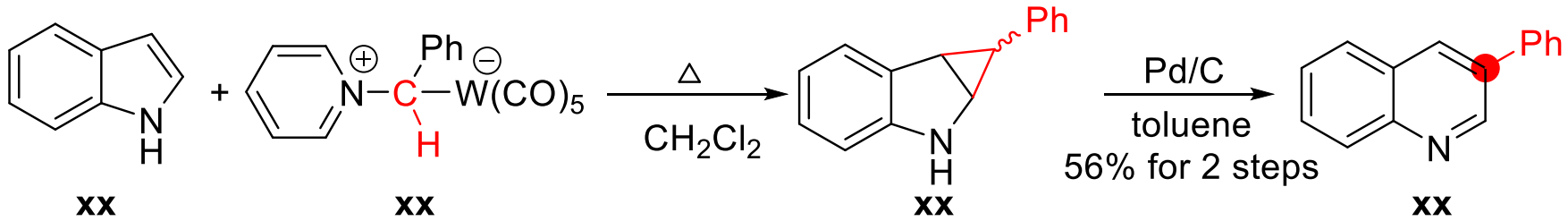


Pyrrole	% Attack on the 2,3-bond	% Attack on the 4,5-bond
2-Me	58	42
3-Me	78	22
2,3,4-Me_3	80	20
2,3,5-Me_3	89	11

Ian Birtwistle, *J. Chem. Soc. Per. Trans. I* **1987**, 1347

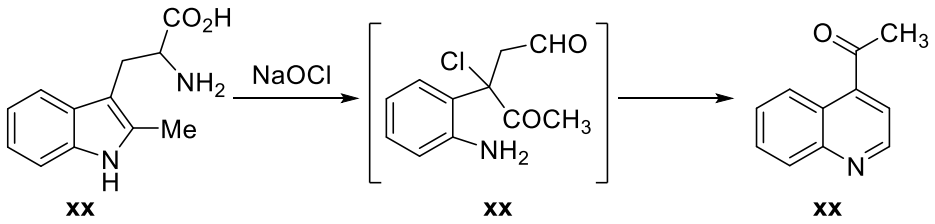
1C. Synthesis of Pyridine/Quinoline using Ylide





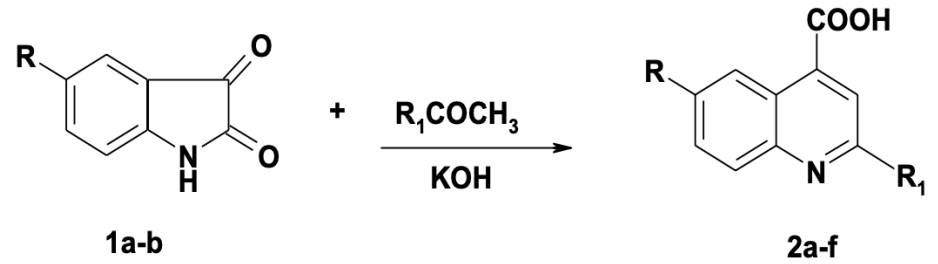
J. Organomet. Chem. **2001**, 617–618, 571

1D. Synthesis of Pyridine/Quinoline by Cleavage/Reassembly



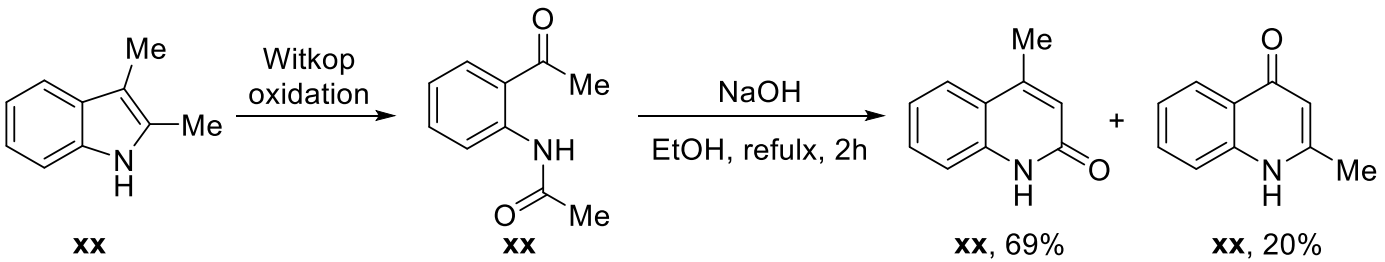
xx **xx** **xx**

Tetrahedron **1985**, *41*, 2109-2114



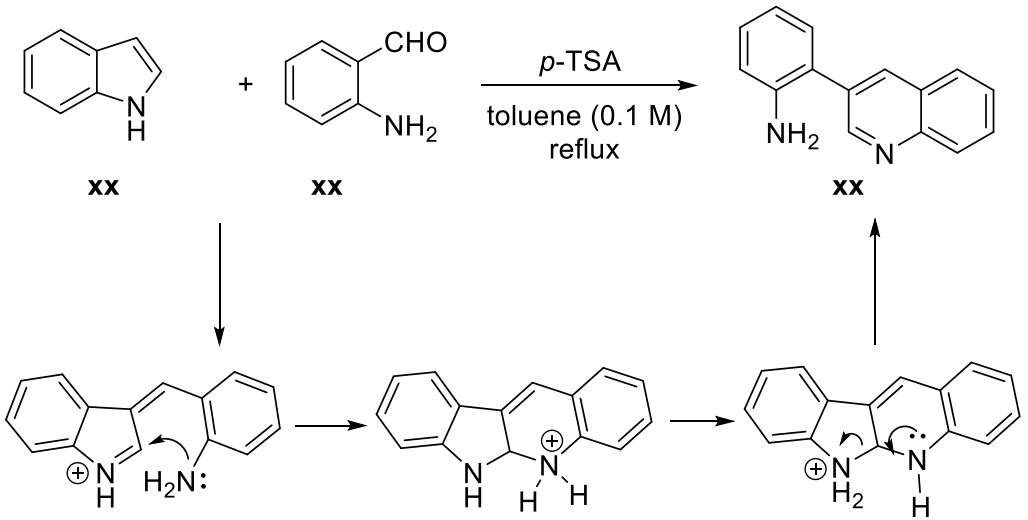
1a-b **2a-f**

Int. Lett. Chem., Phys. Astr. 2013-04-20 ISSN: 2299-3843, Vol. 12, pp 30-36



xx **xx** **xx**, 69% **xx**, 20%

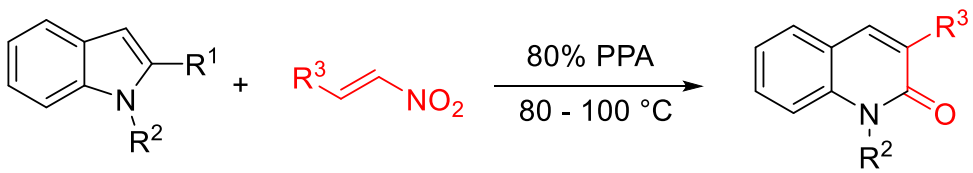
Synthesis **2017**, *49*, 1898–1904



xx **xx** **xx**

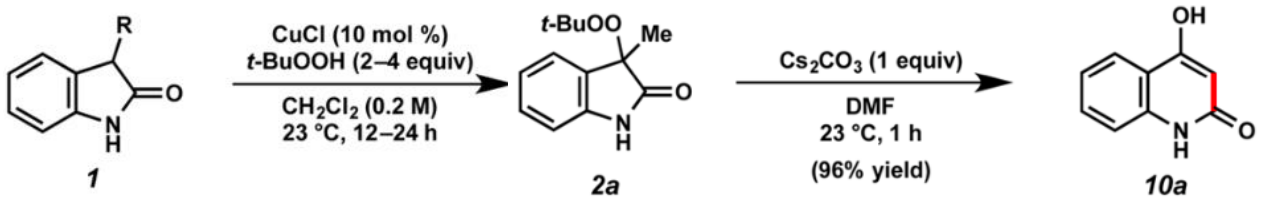
Chem. Sci., **2011**, *2*, 2178–2181

1D. Synthesis of Pyridine/Quinoline by Cleavage/Reassembly



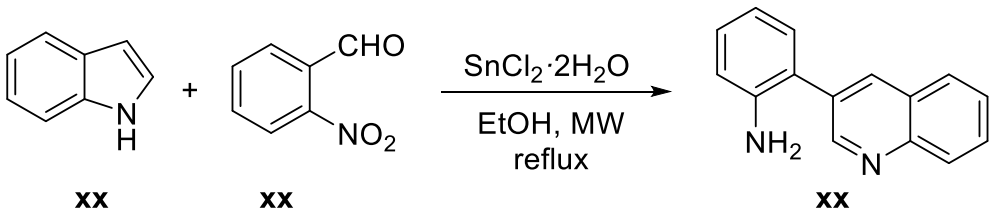
xx **xx**

RSC Adv. **2015**, *5*, 8647



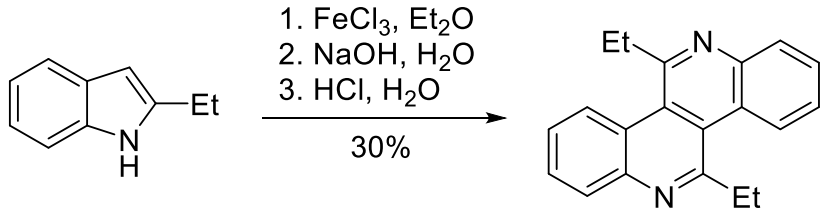
1 *2a* *10a*

Org. Lett. **2017**, *19*, 988–991



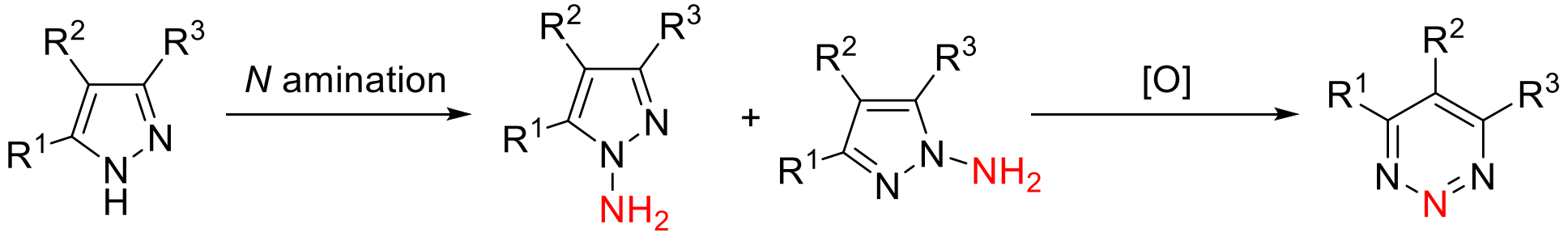
xx **xx** **xx**

Tetrahedron Lett. **2019**, *60*, 1221–1225



Tetrahedron Lett. **1998**, *39*, (23), 4119- 4122;

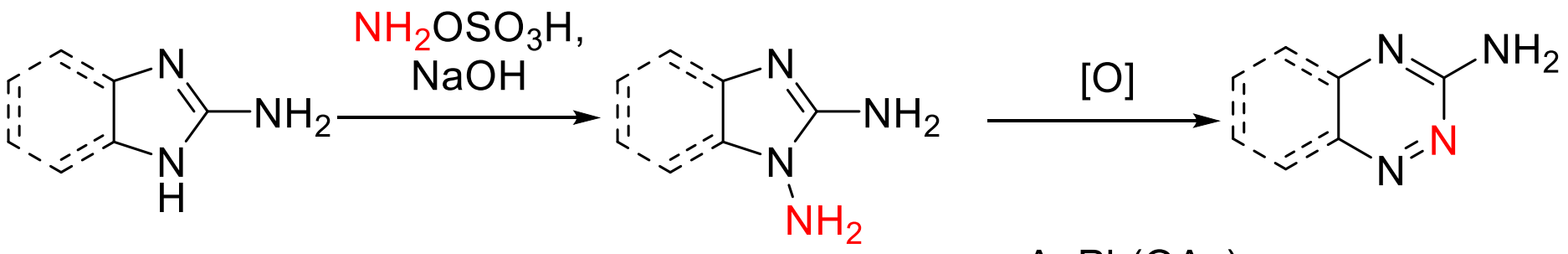
Methods for synthesis of 1,2,3-triazine



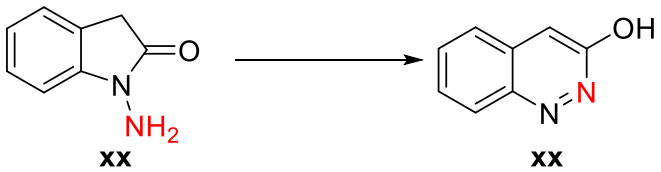
1. H_2NOSO_2Mes, NaH
2. H_2NOSO_3H, aq NaOH
3. a) HNO_3, AcOH then Ac_2O
   b) $LiAlH_4$

1. PbO_2
2. $NaIO_4$
3. I_2, $KHCO_3$
4. $Pb(OAc)_4$, CaO
5. Electrooxidation $LiClO_4$ (Pt)
6. NiO_2
7. KIO_4

Methods for synthesis of 1,2,4-triazole



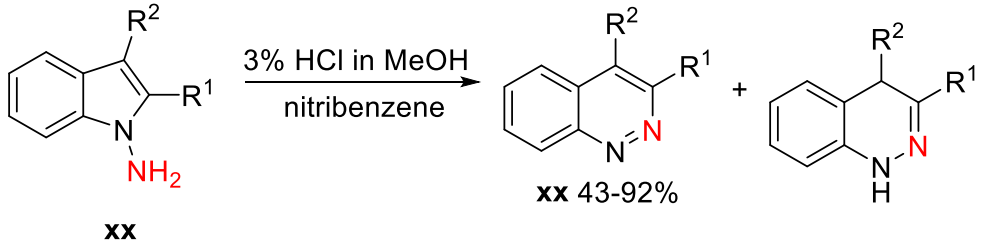
Methods for synthesis of benzo[c]pyridazine



A. $Pb(OAc)_4$, benzene
B. ^{t}-BuOCl

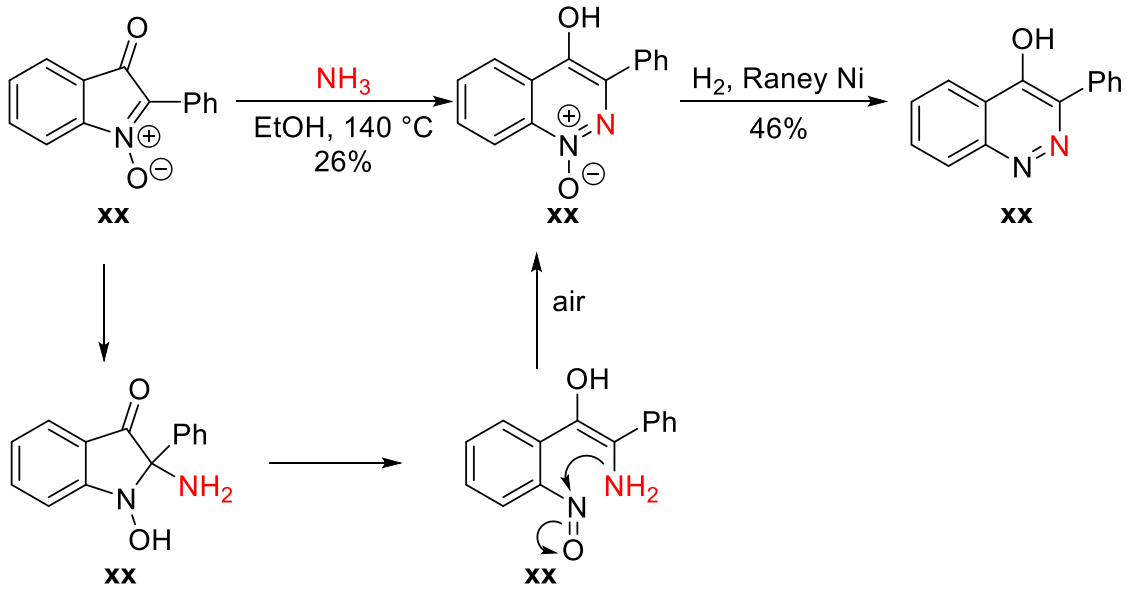
Baumgarten, H. E.; Creger, P. L.; Zey, R. L., *J. Am. Chem. Soc*. **1960**, *82*, 3977.

Baumgarten, H. E.; Wittman, W. F.; Lehmann, G. J., *J. Heterocycl. Chem*. **1969**, *6*, 333.



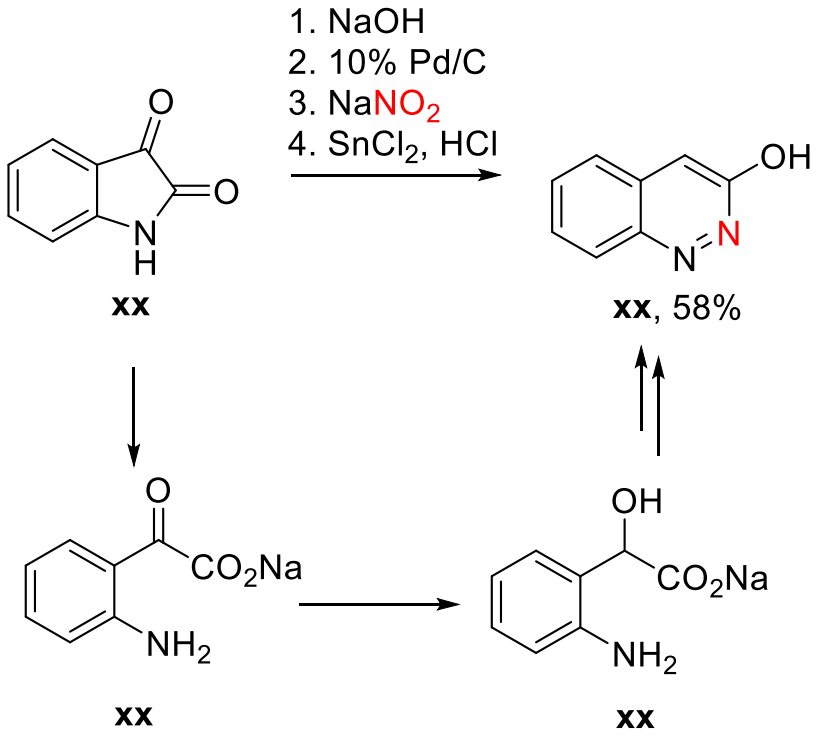
No nitrobenezene, 1,4-dihydrocinnolines were major product
M. Somei and K. Ura, *Chem. Lett.* **1978**, 707

Nitrobenzene -Benzopyridazine major Product
M. Somei, Y. Kurizuka *Chem. Lett*, **1979**, 127-128.

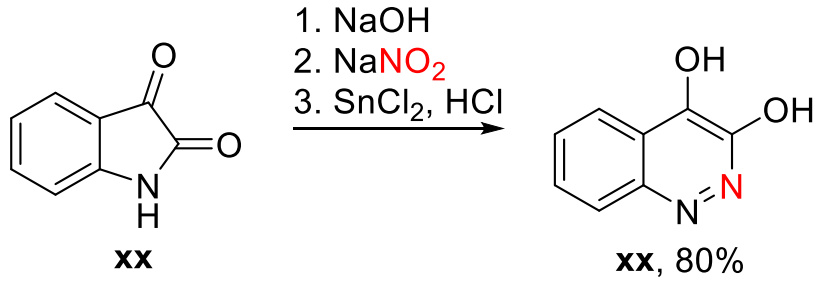


Noland, W. E.; Jones, D. A., *J. Org. Chem*. **1962**, *27*, 341.

Methods for synthesis of benzo[c]pyridazine

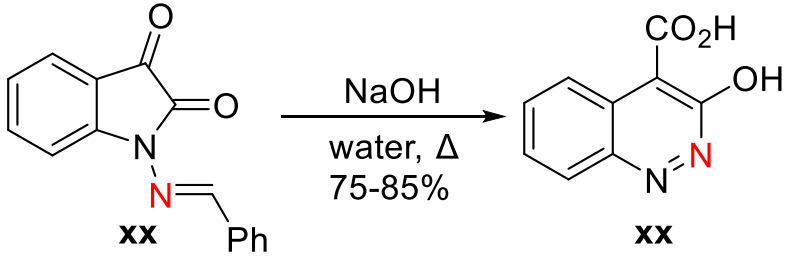


R. L. Zey, *J. Heterocycl. Chem*. **1972**, *9*, 1177.



Lora-Tamayo, M.; Marco, B.; Sender, C., *Org. Prep. Proced. Int.* **1978**, *10*, 298

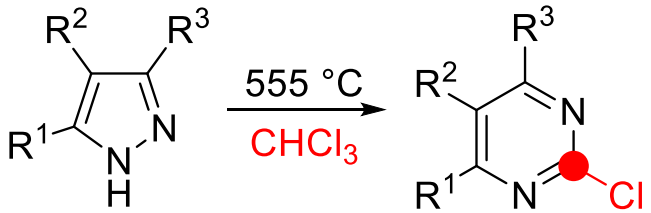
Stolle-Becker synthesis

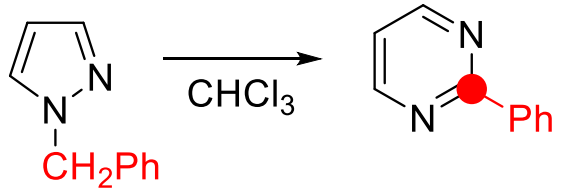


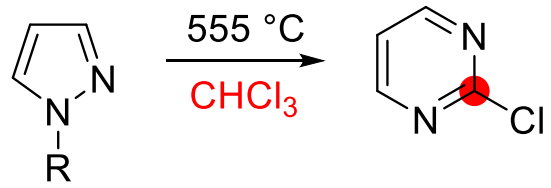
Stolle, R. and Becker, W., *Ber.,* **1924**, *57*, 1123.

Methods for synthesis of Pyrimidines/Quinazoline

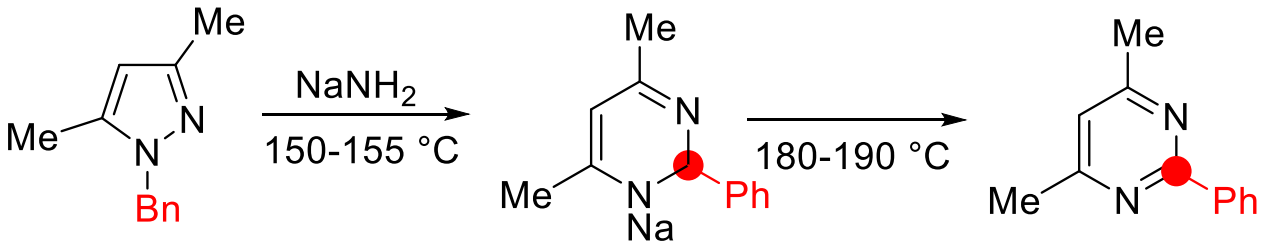
1A. Synthesis of Pyrimidines/Quinazoline by *N-N* insertion







R = Me, CH_2Ph, CPh_3

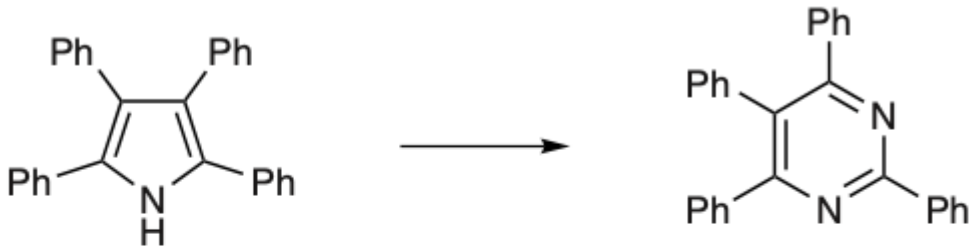


Journal of the Chemical Society, Perkin Transactions 1: Organic and Bio-Organic Chemistry (1972-1999), (11), 2786-8; 1979

Journal of the Chemical Society, Perkin Transactions 1: Organic and Bio-Organic Chemistry, (24), 3581-3586; 1997

Khimiya Geterotsiklicheskikh Soedinenii aka Chemistry of Heterocyclic compounds, (1), 119-20; 1981

1B. Synthesis of Pyrimidines/Quinazoline by C-N Insertion

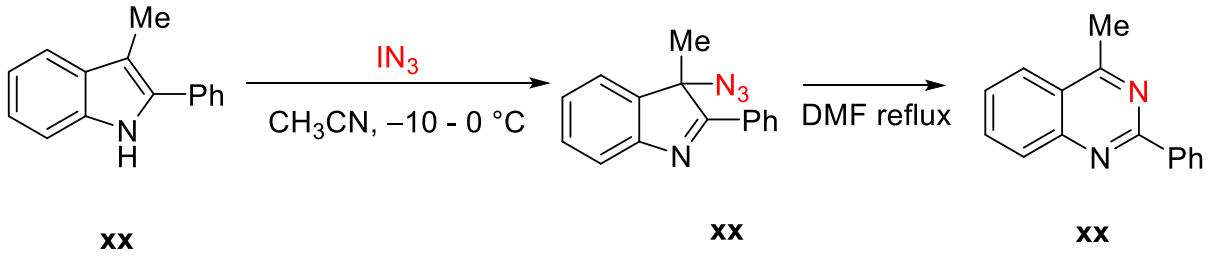


415

Conditions	Yield (%)	Ref
$(PhS)_3N$, CH_2Cl_2, reflux, 2 h	82	[565]
$2,4\text{-}(O_2N)_2C_6H_3SNH_2$, $Pb(OAc)_4$, CH_2Cl_2, rt, 40 min	48	[566]

J. Chem. Soc. Perkin I, **1973**, 1037

1B. Synthesis of Pyrimidines/Quinazoline by C-N Insertion



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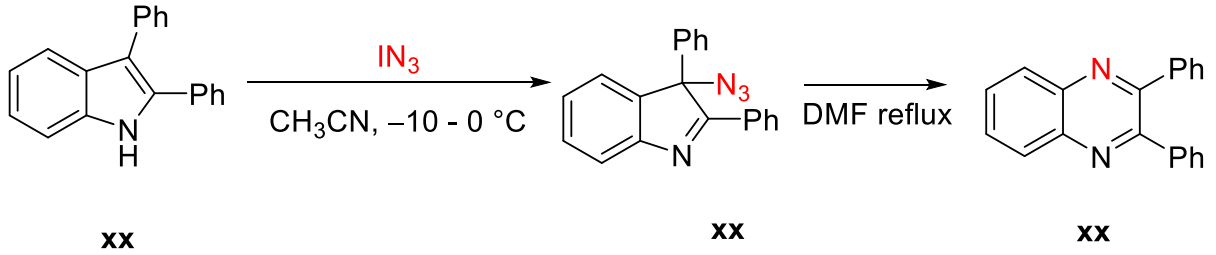

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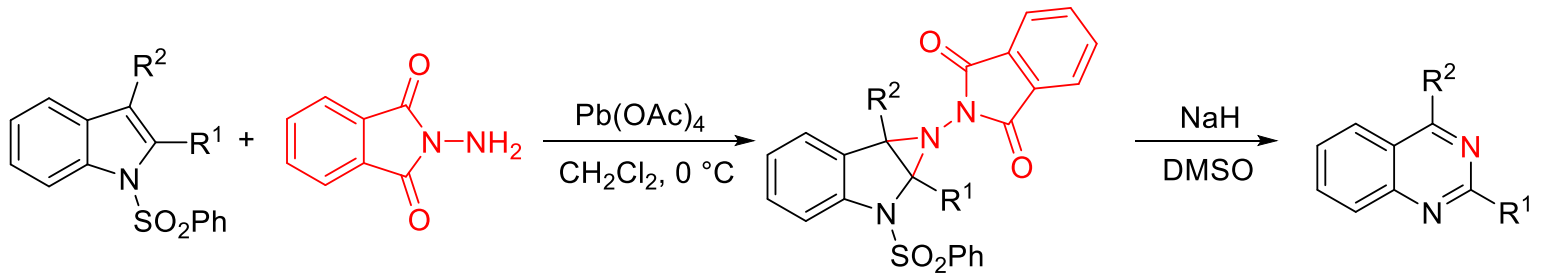
Tetrahedron Lett. **1976**, *27*, 2347-50



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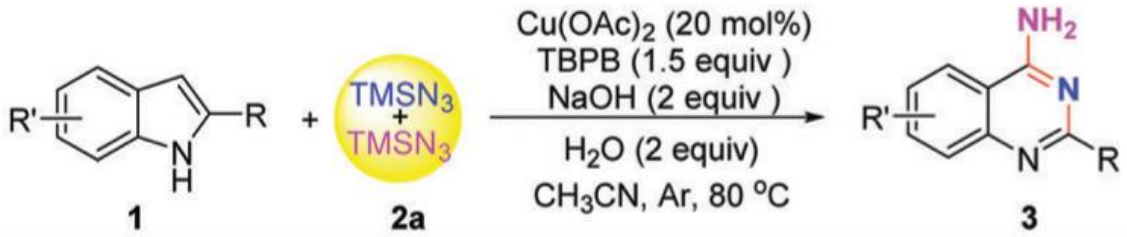
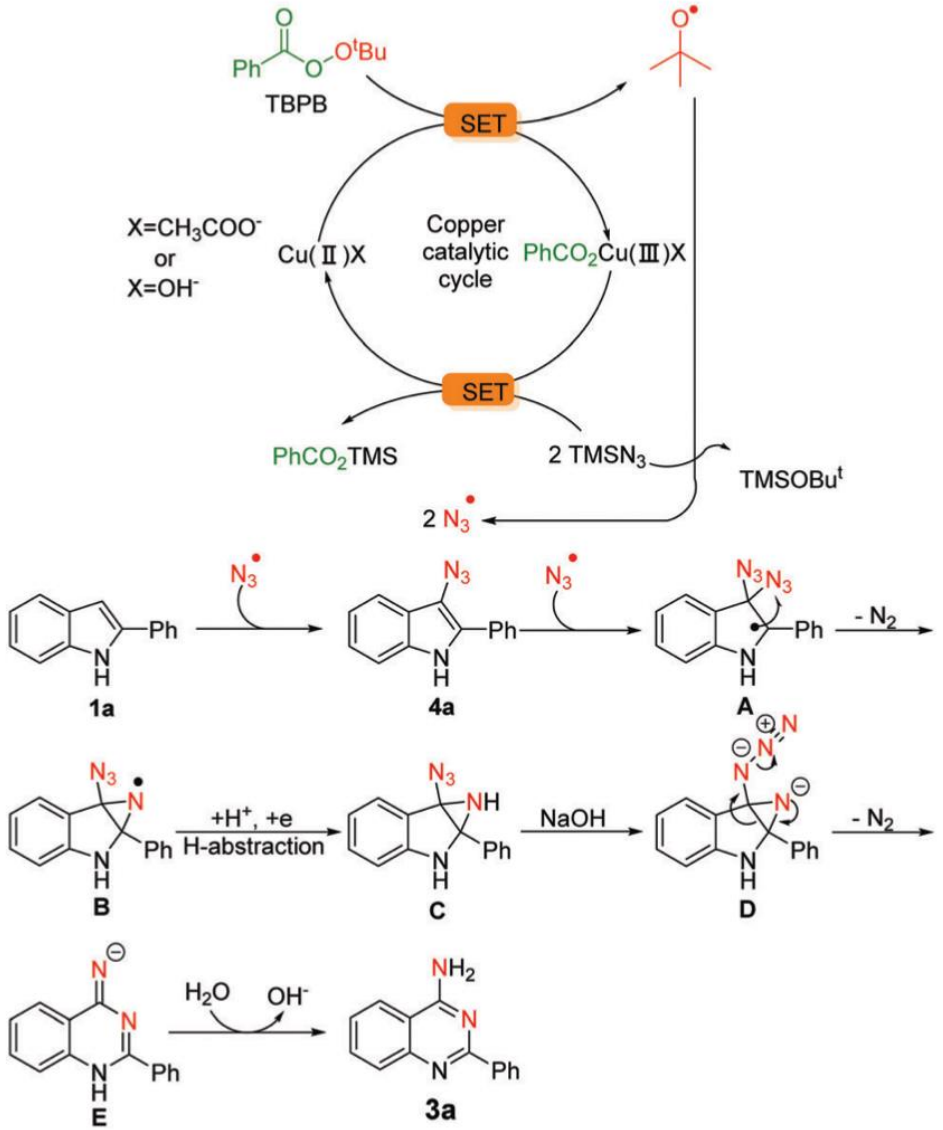
Kumar, P. R. Heterocycles 1987, 26, 1257.

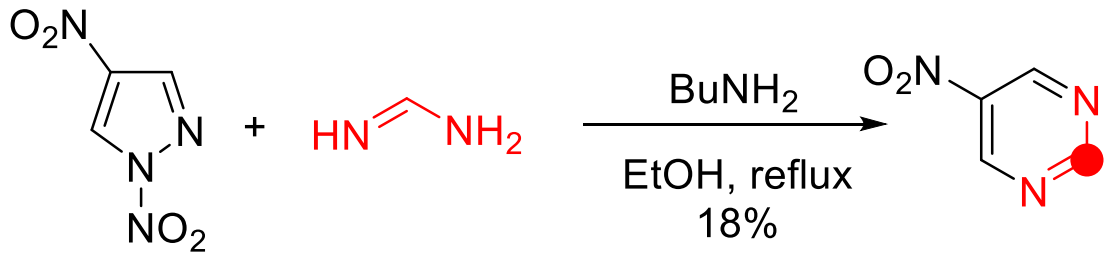
1B. Synthesis of Pyrimidines/Quinazoline by C-N Insertion



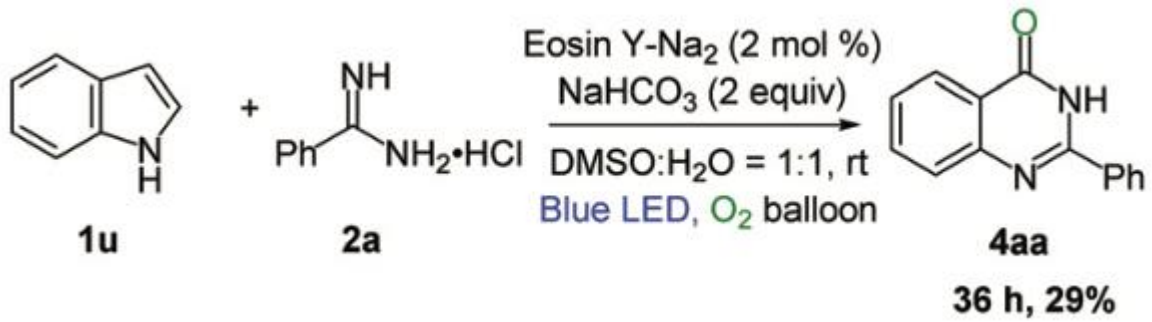


Meng-Meng Xu, Wen-Bin Cao, Xiao-Ping Xu* and Shun-Jun Ji Chem. Commun., 2018, 54, 12602--12605

1C. Synthesis of Pyrimidines/Quinazoline by Cleavage/Assembly

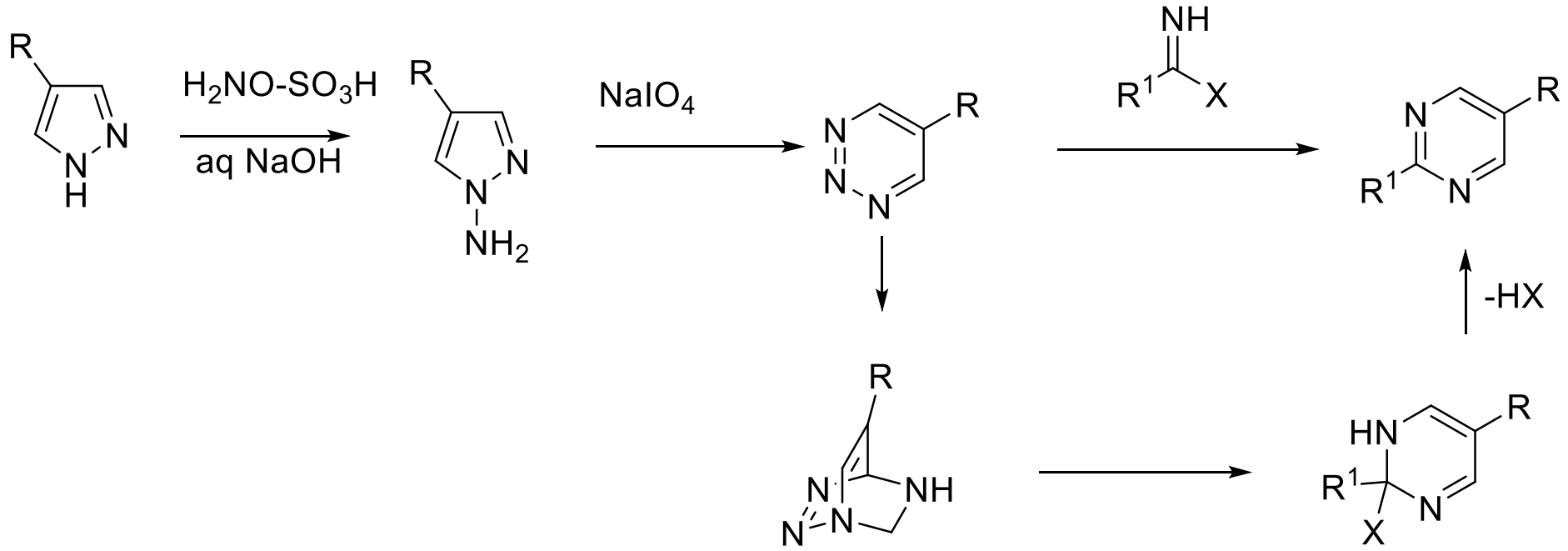


ARKIVOC (Gainesville, FL, United States), (6), 103-111; 2007



Ling-Ling Zhang, Wen-Bin Cao, Xiao-Ping Xu* and Shun-Jun Ji Org. Chem. Front., 2019, 6, 1787–1795

1C. Synthesis of Pyrimidines/Quinazoline by Cleavage/Assembly



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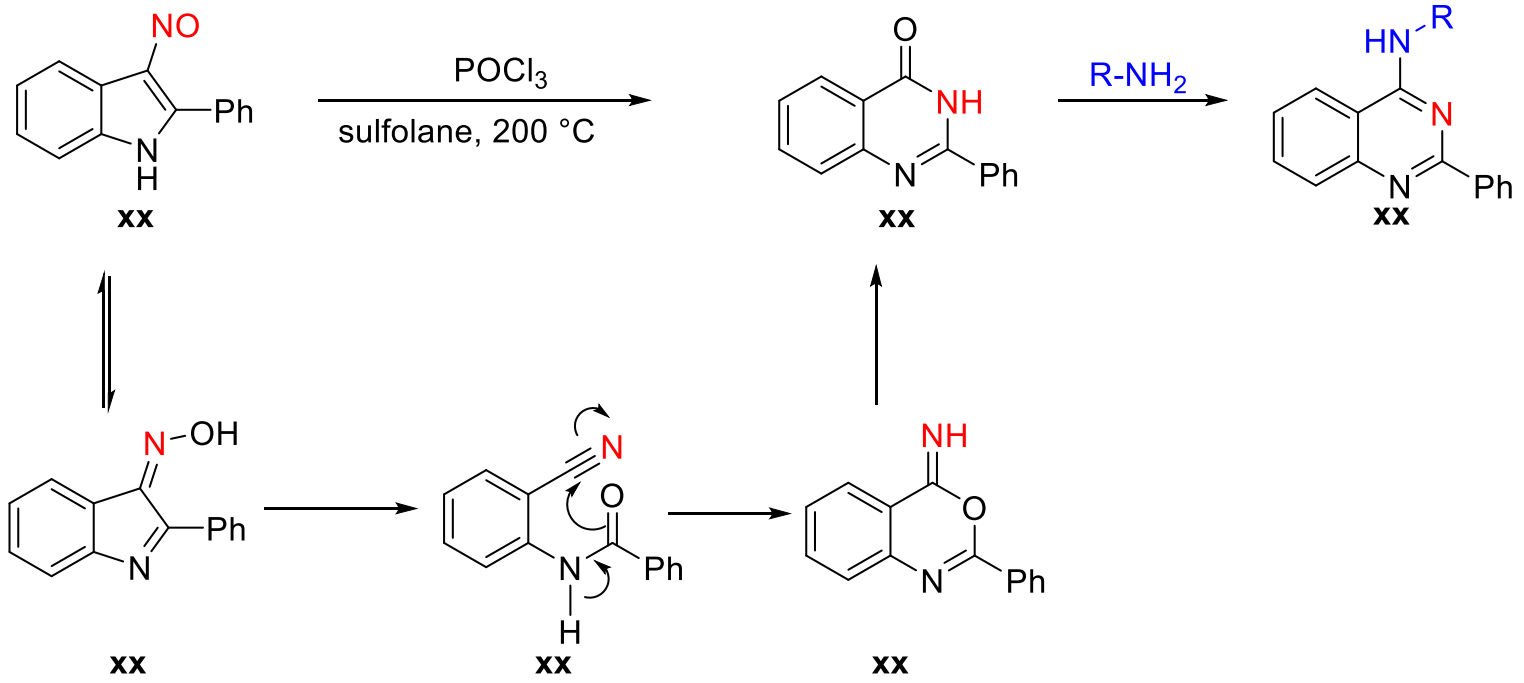
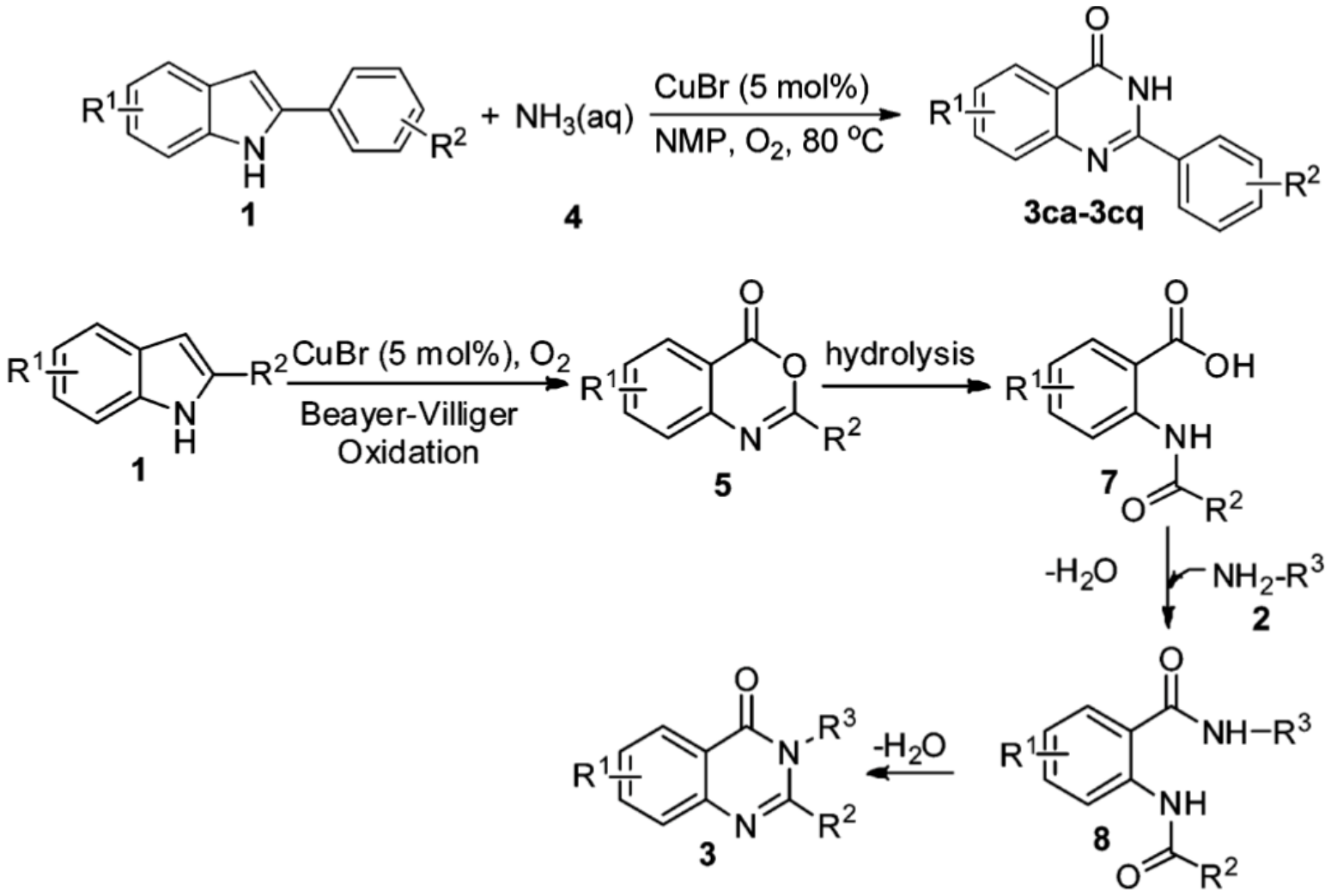


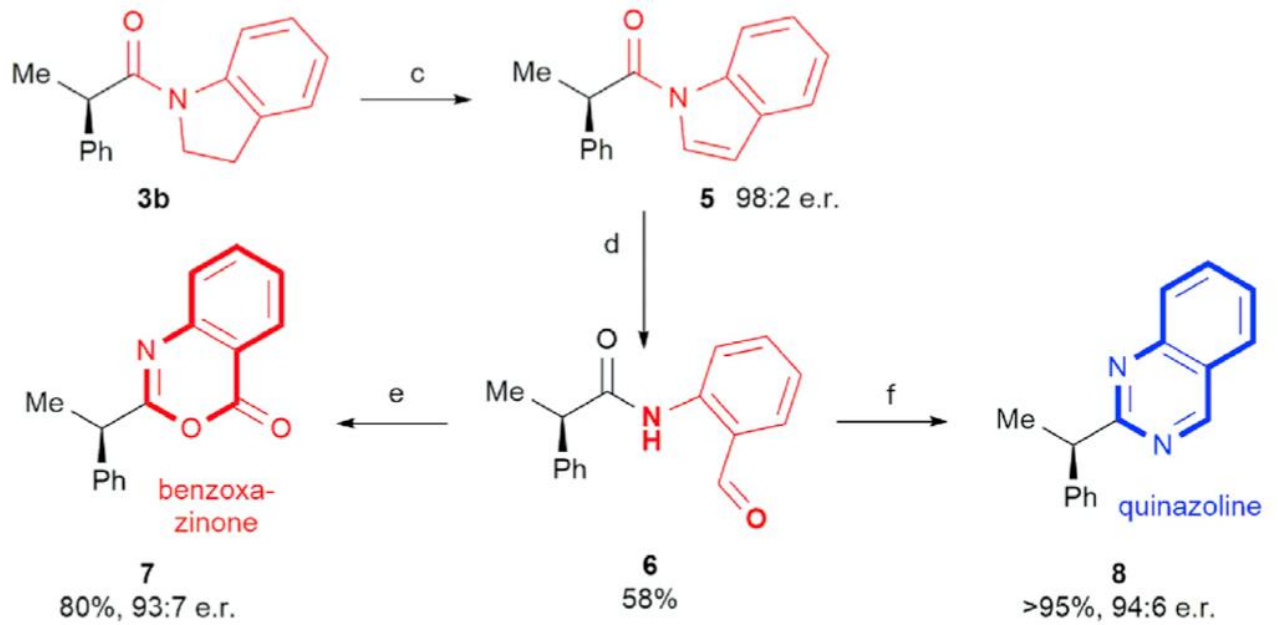
Fumio Yoneda, Masatsugu Higuchi and Reiko Nonaka TetrahedronLetters.No. 5, 359 - 360, 1973.

1C. Synthesis of Pyrimidines/Quinazoline by Cleavage/Assembly



Yadong Feng, Yudong Li, Guolin Cheng, Lianhui Wang, and Xiuling Cui J. Org. Chem. 2015, 80, 7099−7107

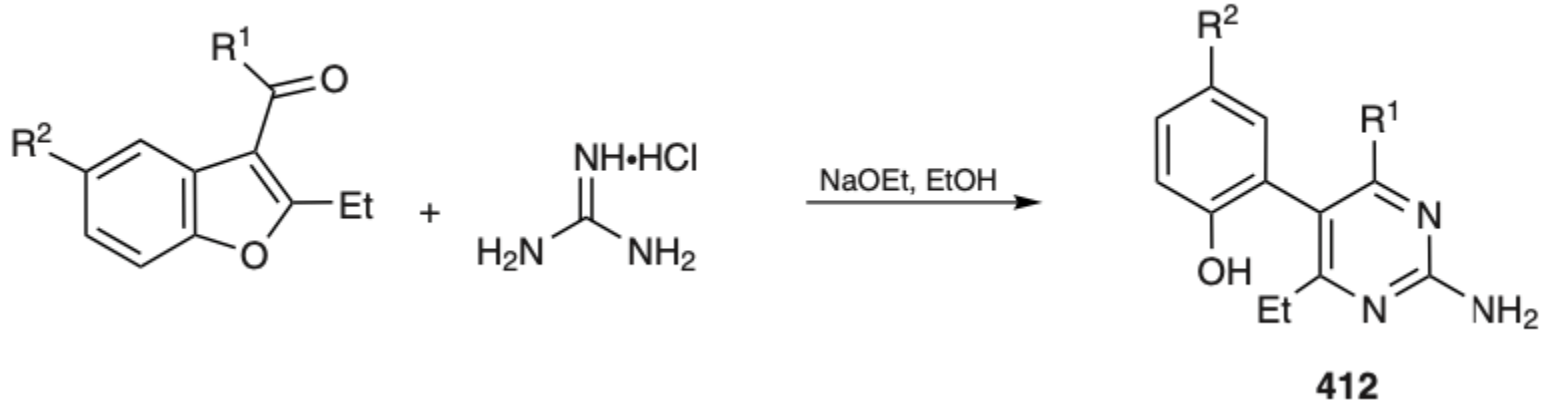
1C. Synthesis of Pyrimidines/Quinazoline by Cleavage/Assembly



(c) **3b** (1 equiv) and DDQ (2 equiv) in toluene at 80°C for 2 h.
(d) O_3, then Me_2S, and then K_2CO_3/MeOH.
(e) Pinnick oxidation, then Ac_2O for 1 h at 130°C.
(f) **6** (0.2 mmol) in EtOH (0.5 mL) + 25% NH_3 solution (0.5 mL) for 9 h were used.

Chem **2019**, *5*, 1883–1891

1A. Synthesis of Pyrimidines/Quinazoline by Cleavage/Assembly



412

R^1	R^2	Yield (%)	Ref
Me	Cl	76	[558]
Me	Br	85	[558]
Ph	Br	89	[558]

1C. Synthesis of Pyrimidines/Quinazoline by Cleavage/Assembly

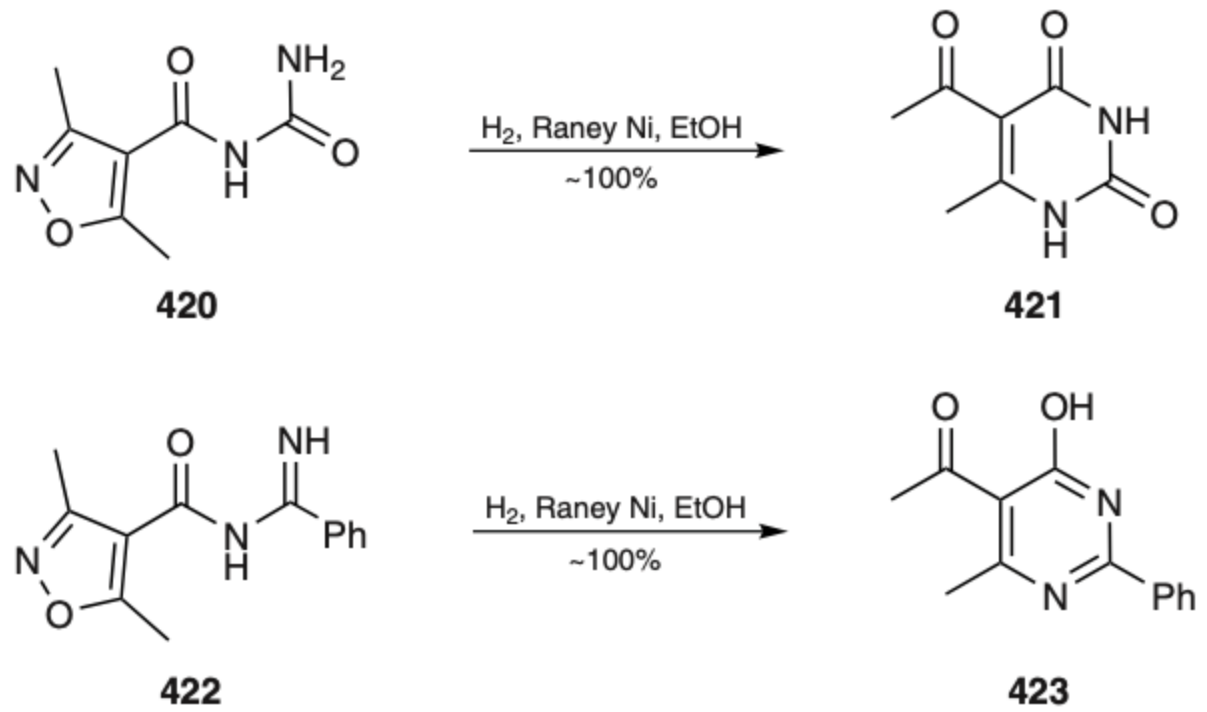
Scheme 233 Pyrimidin-4(3*H*)-ones by Deoxygenation and Rearrangement of 5-(Acylamino)isoxazoles[568–570]

418 **419**

R^1	R^2	R^3	Catalyst	Yield (%)	mp (°C)	Ref
Ph	H	Me	Raney Ni	86	238–240	[568]
Me	Me	H	Raney Ni	67	204–205	[569]
Me	Me	Bu	Raney Ni	74	120–121	[569]
Ph	H	CO_2Et	PtO_2	78	176–181	[570]

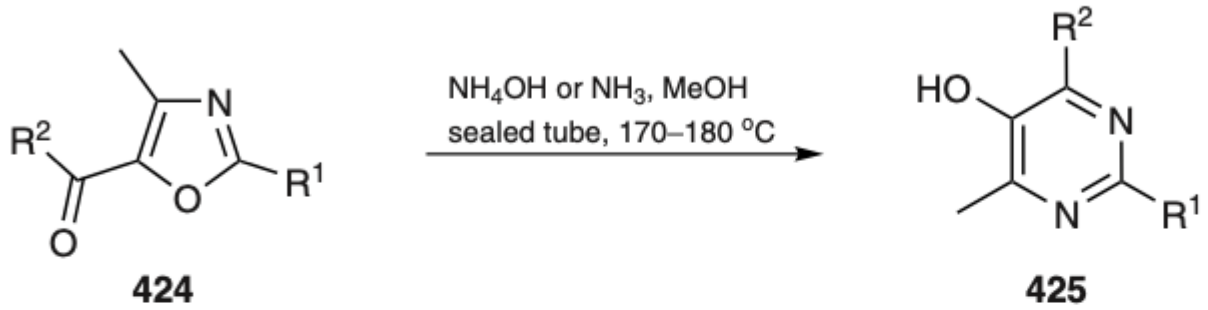
1C. Synthesis of Pyrimidines/Quinazoline by Cleavage/Assembly

Scheme 234 Pyrimidin-4(3*H*)-ones by Rearrangement of Isoxazoles[571]



1C. Synthesis of Pyrimidines/Quinazoline by Cleavage/Assembly

Scheme 235 Pyrimidin-5-ols by Rearrangement of 5-Acyloxazoles in the Presence of Ammonia[572–574]

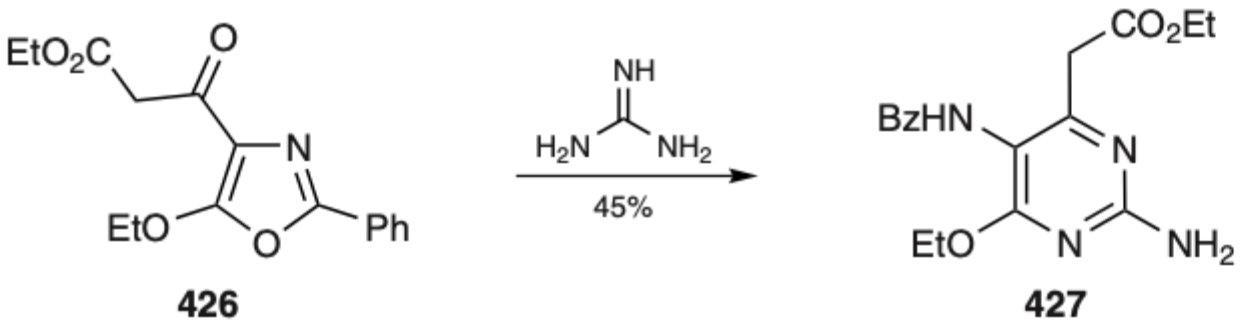


424 **425**

R^1	R^2	Yield (%)	mp (°C) or bp (°C/Torr)	Ref
H	Me	88	138	[572]
Me	Me	92	152–154	[572]
Ph	Me	91	152–153	[572]
H	CH_2OMe	36	55–57	[573]
H	CH_2OBn	61	155/0.1	[574]

1C. Synthesis of Pyrimidines/Quinazoline by Cleavage/Assembly

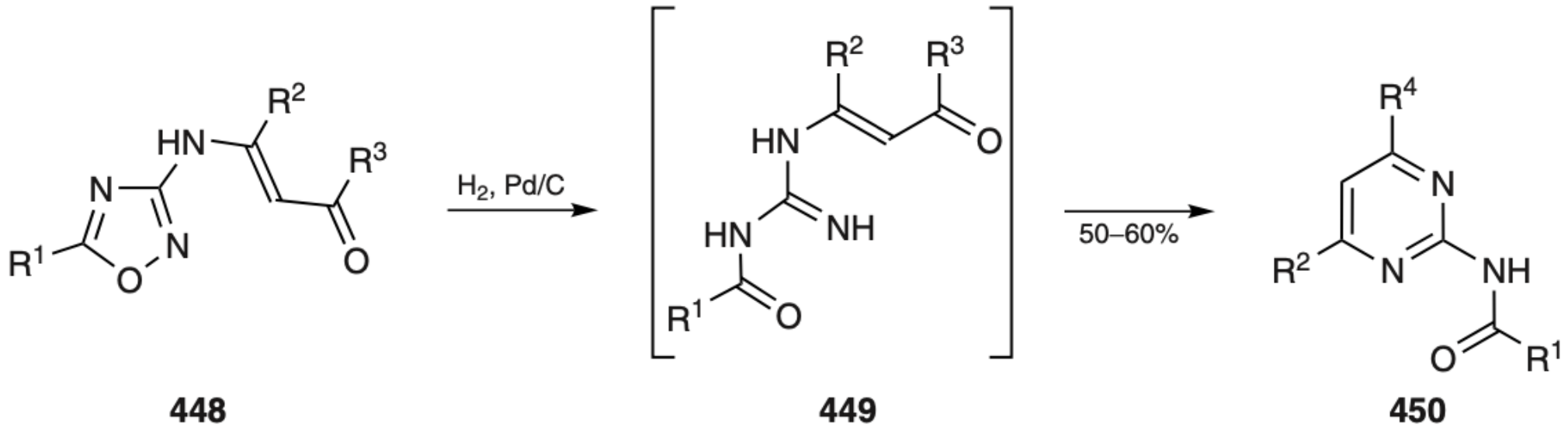
Scheme 236 Ethyl 2-Amino-5-(benzoylamino)-6-ethoxypyrimidin-4-acetate by Ring Enlargement of a 4-Acyloxazole[576]



426 **427**

1C. Synthesis of Pyrimidines/Quinazoline by Cleavage/Assembly

Scheme 248 2-(Acylamino)pyrimidines by Hydrogenation of 3-[(3-Oxoprop-1-enyl)amino)]-1,2,4-oxadiazoles[597]

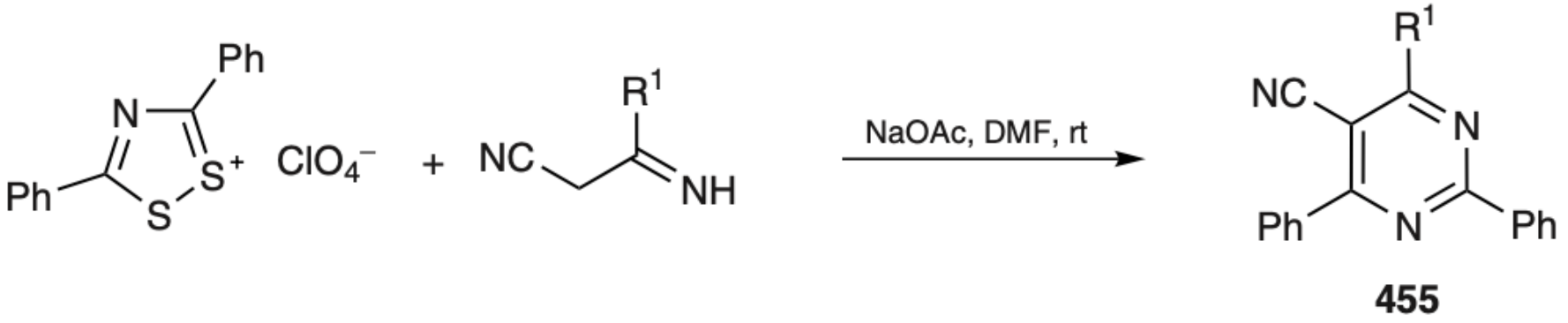


448 **449** **450**

$R^1 = R^2 = Me, Ph; R^3 = Me, Ph, OEt; R^4 = Me, Ph, OH$

1C. Synthesis of Pyrimidines/Quinazoline by Cleavage/Assembly

Scheme 251 2,6-Diphenylpyrimidines from 3,5-Diphenyl-1,2,4-dithiazol-1-ium Perchlorate and 3-Iminoalkanenitriles[601]

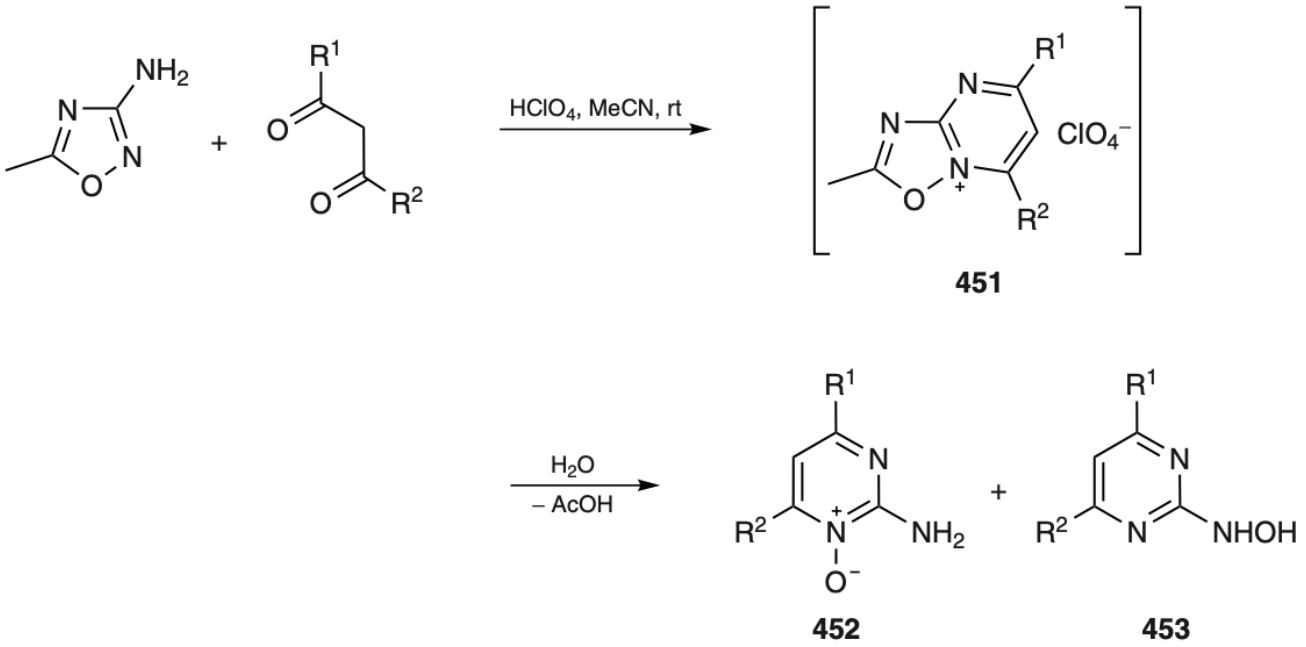


455

R^1	Yield (%)	Ref
OEt	86	[601]
Me	71	[601]

1C. Synthesis of Pyrimidines/Quinazoline by Cleavage/Assembly

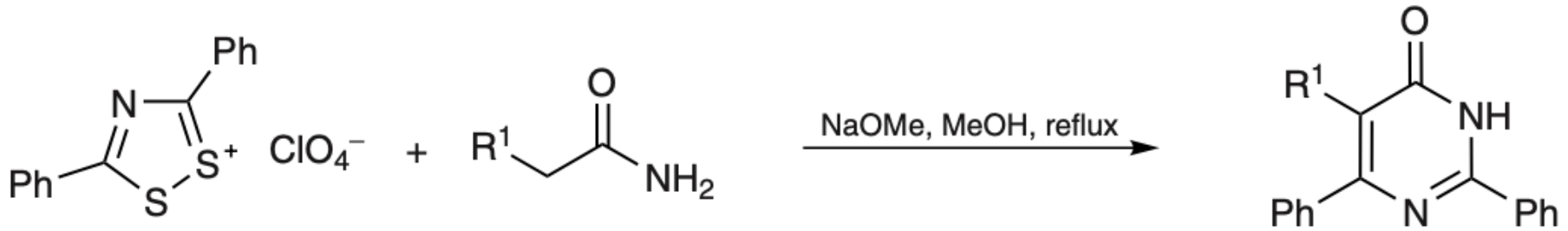
Scheme 249 Pyrimidin-2-amine 1-Oxides and 2-(Hydroxyamino)pyrimidines from 5-Methyl-1,2,4-oxadiazol-3-amine and β-Diketones[599]



R^1	R^2	Yield (%) of **452**	Yield (%) of **453**	Ref
Me	Me	92	0	[599]
Me	CF_3	50	12	[599]
CF_3	CF_3	21	39	[599]

1C. Synthesis of Pyrimidines/Quinazoline by Cleavage/Assembly

Scheme 250 2,6-Diphenylpyrimidines from 3,5-Diphenyl-1,2,4-dithiazol-1-ium Perchlorate and Amides[600]



454

R^1	Yield (%)	Ref
CN	92	[600]
Bz	38	[600]