Минобрнауки России
федеральное государственное бюджетное образовательное учреждение
высшего образования
«Санкт-Петербургский государственный технологический институт
(технический университет)»

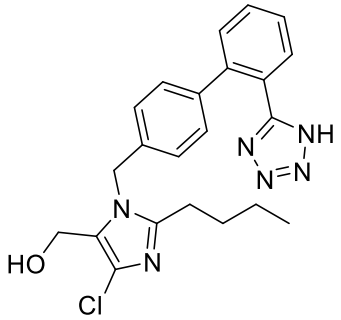
Тема: **Разработка общего метода синтеза 2,5-диарил(гетерил)тетразолов на основе реакции Чана-Эванса-Лама**

---

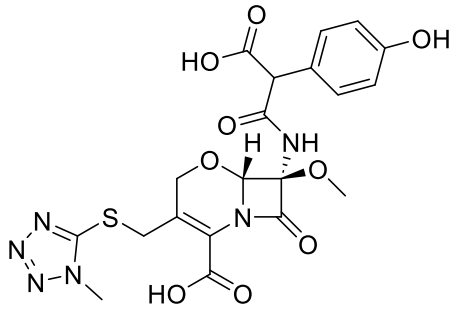
Аспирант 3-го года обучения
каф. ХТОСА СПбГТИ(ТУ)
Ершов Иван Станиславович

Научный семинар РХО им. Д.И. Менделеева
«Современные проблемы органической химии»
Санкт-Петербург, Российская Федерация 26 февраля 2026 года

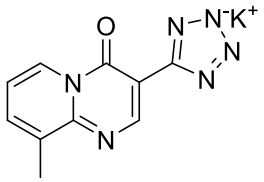
# Актуальность темы исследования



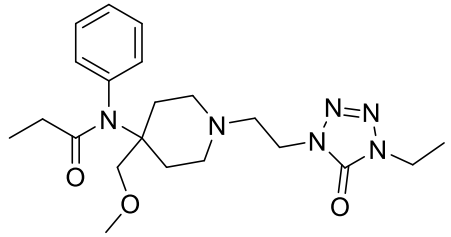
Losartane



Latamoxef

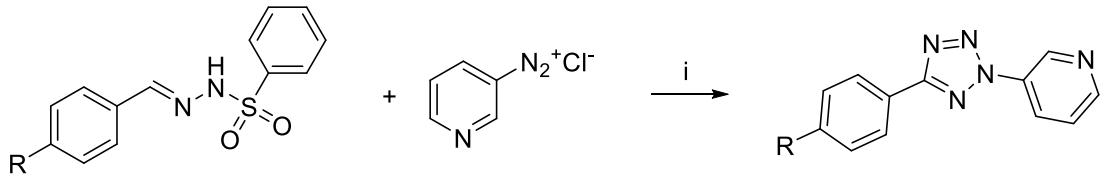


Pemirolast potassium



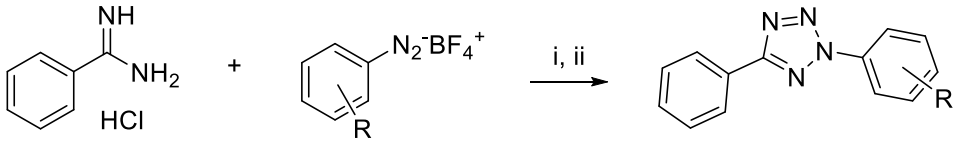
Alfentanil

# Получение 2,5-диарил(гетерил)тетразолов путем реакций циклизации



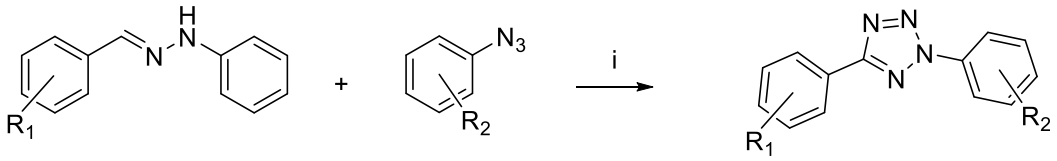

i: Pyridine, 0 °C, 40-50%
R: H, Me, MeO, OH, Cl, Br, $NO_2$

Shawali A.S., Fahmi A.A., Eweiss N.F. Azo coupling of benzenesulfonylhydrazones of heterocyclic aldehydes // *J. Heterocycl. Chem.* 1979. V. 16(1). Pp. 123-128. DOI: 10.1002/jhet.5570160123




i: $K_2CO_3$, DMSO, rt
ii: $I_2$, KI, rt, 51-82%
R: Alk, OAlk, SAlk, Ph, CN, etc.

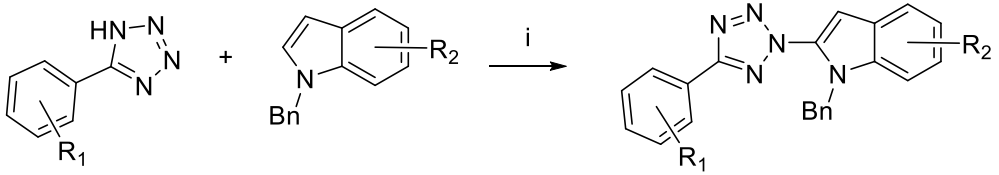
Ramanathan M., Wang Y., Liu S. One-Pot Reactions for Synthesis of 2,5-Substituted Tetrazoles from Aryldiazonium Salts and Amidines // *Organic Letters.* 2015. V. 17(23). Pp. 5886–5889. DOI: 10.1021/acs.orglett.5b03068




i: $MeOCH_2CH_2OH$, Na, reflux, 6-48%
$R_1$: Me, OMe, Cl, Br, CN
$R_2$: Me, OMe, Cl

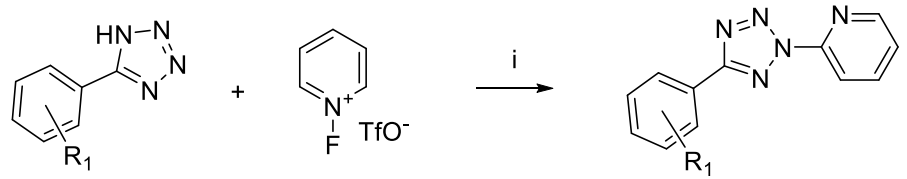
Hong S., Baldwin J. Cycloadditions—XIX. Kinetics of the thermal decomposition of 2,5-diaryltetrazoles // *Tetrahedron.* 1968. V. 24(10). Pp. 3787–3794. DOI: 10.1016/s0040-4020(01)92586-4

# Получение 2,5-диарил(гетерил)тетразолов путем арилирования NH-незамещенного тетразола



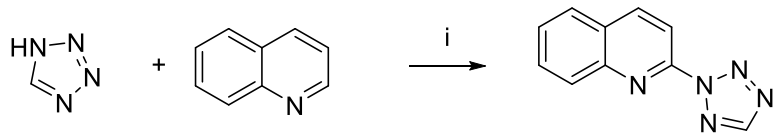

i: NIS, $K_2CO_3$, 1,4-dioxane, rt, 5 min, 70-98%
$R_1$: H, Alk, Ar, OAlk, OH, Hal, $NO_2$
$R_2$: H, Alk, Ar, OAlk, Hal, CHO, $NO_2$, BPin, etc.

Zhang H., Tian L., Li Q., Zheng H., Dai Y., Li J., Liu G., Zhu L.-L., Wang Y. N2-site-selective cross-couplings of tetrazoles with indoles // *Org. Biomol. Chem*. 2025. V. 23(31), Pp. 7270-7274. DOI: 10.1039/D5OB00914F.




i: MeOH, MeONa, -78°C, 3h
$R_1$: Cl, Br, CN

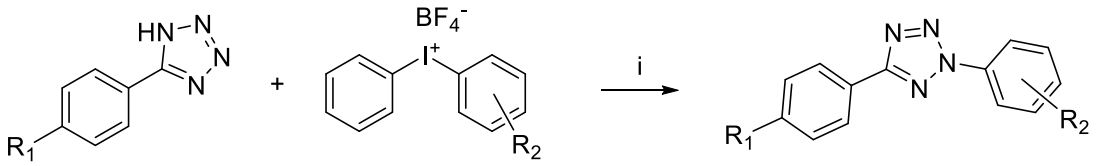
Pat. WO 2003029210A2 № US0231294W; Cosford N.D., Roppe J., Chen C., Smith N., Reger T. Heteroaryl substituted tetrazole modulators of metabotropic glutamate receptor-5: zayavl. 01.10.2002; opubl. 10.04.2003. 119 p.




i: MeCN, Selectfluor, rt, 82%

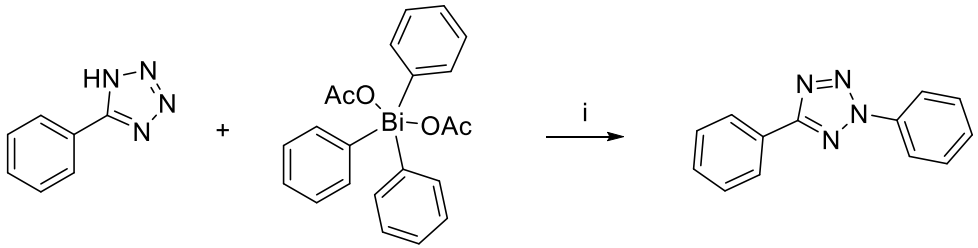
Xie L., Qu J., Peng S., Liu K., Wang Z., Ding M., Wang Y., Cao Z., He W. Selectfluor-mediated regioselective nucleophilic functionalization of N-heterocycles under metal- and base-free conditions // *Green Chem*. 2018. V. 20(3). Pp. 760-764. DOI: 10.1039/c7gc03106h.

# Получение 2,5-диарил(гетерил)тетразолов путем арилирования NH-незамещенного тетразола



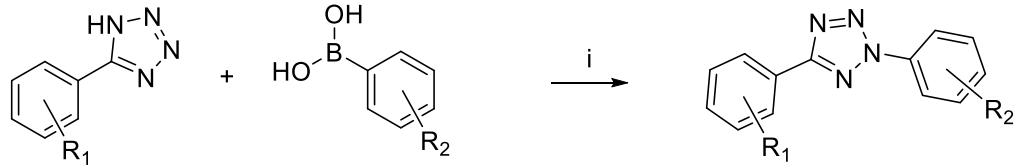

i:CuI, $K_2CO_3$, DMF, rt, 2-4h, 53-77%
$R_1$: H, Cl, OMe
$R_2$: H, Cl, Br, $NO_2$

Zhou T., Chen Z. Hypervalent iodine in synthesis 87: The synthesis of 2,5-diaryl-2H-tetrazoles // *Journal of Chemical Research*. 2004. V. 2004(6). Pp. 404–405. DOI:10.3184/0308234041423655




i: $Cu(OAc)_2$, TMG, THF, 50°C, 87%

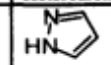
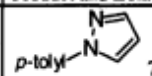
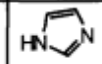
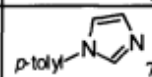
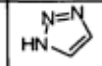
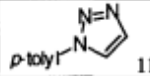
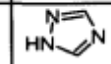
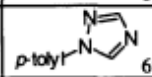
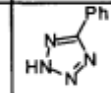
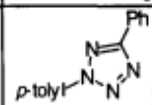
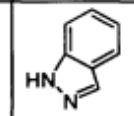
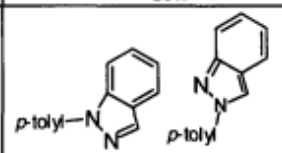
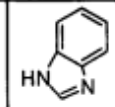
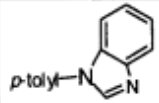
Fedorov A.Y., Finet J. N-Phenylation of azole derivatives by triphenylbismuth derivatives/cupric acetate // *Tetrahedron Letters*. 1999. V. 40(14). Pp. 2747–2748. DOI: 10.1016/s0040-4039(99)00287-7




i: $Cu_2O$ (5 mol.%), $O_2$, DMSO, 100°C, 4h, 53-77%
$R_1$: H, Cl, Br, $NO_2$, OMe
$R_2$: H, Alk, OMe, $NH_2$, OH, Cl, Br, $NO_2$, CHO, $CO_2Me$, etc.

- Li Y., Gao L., Han F. Efficient synthesis of 2,5-disubstituted tetrazoles via the Cu2O-catalyzed aerobic oxidative direct cross-coupling of N–H free tetrazoles with boronic acids // *Chem. Commun.* 2012. V. 48(21). Pp. 2719-2721. DOI: 10.1039/c2cc17894j
- Liu C., Li Y., Ding J., Dong D., Han F. The Development of Copper-Catalyzed Aerobic Oxidative Coupling of H-Tetrazoles with Boronic Acids and an Insight into the Reaction Mechanism // *Chem. Eur. J.* 2014. V. 20(8). Pp. 2373-2381. DOI: 10.1002/chem.201302857.

# Арилирование 5-фенил-1*H*-тетразола в литературе

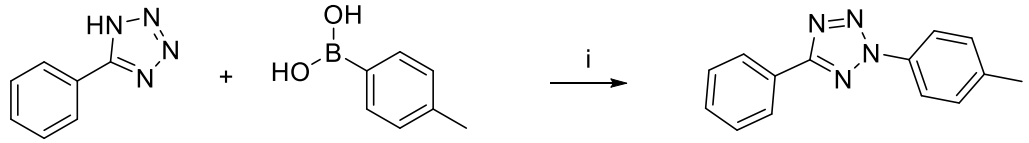
| Entry | Heteroarene substrate | Product and isolated yield |
|---|---|---|
| 1 |  |  76% |
| 2[b] |  |  72% |
| 3[c] |  |  11% |
| 4[c] |  |  6% |
| 5[c,d] |  |  26% |
| 6 |  |  9 : 2 88% |
| 7 |  |  67% |

[a]Conditions: 1.0 eq. heteroarene + 2.0 eq. *p*-tolylboronic acid + 2.0 eq. pyridine + 1.5 eq. anhydrous $Cu(OAc)_2$ + 4Å molecular sieves in methylene chloride. The spectral data for the new compounds are in accord with the structures assigned.

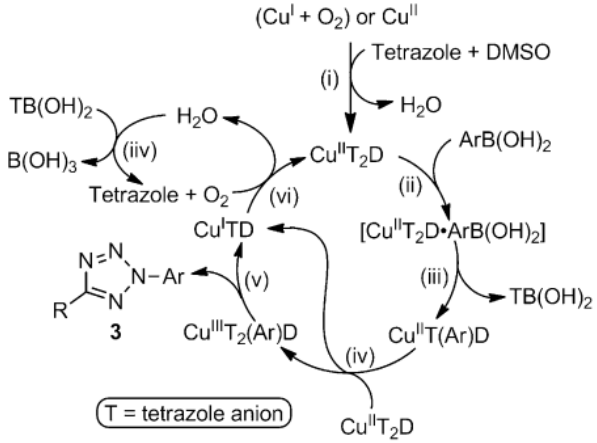
[b]Use of pyridine or triethylamine as base gives similar yields.

[c]Pyridine, triethylamine, N-methylmorpholine and 1,8-diazabicyclo[5.4.0]undecane were used as base. Pyridine gives the best yield. Regiochemistry was determined by nOe experiments.

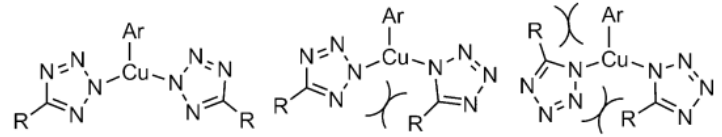
[d]Five equivalents of pyridine gave 24% yield.



i: $Cu_2O$ (5 mol.%), $O_2$, DMSO, 100°C, 95%




Possible $Cu^{III}T_2(Ar)$ intermediates:

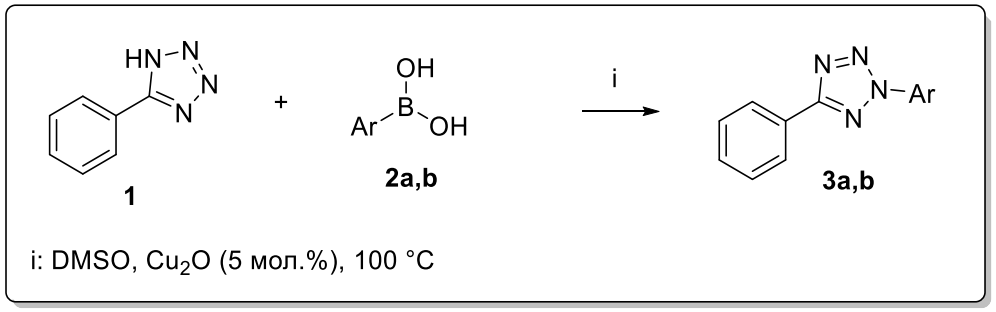


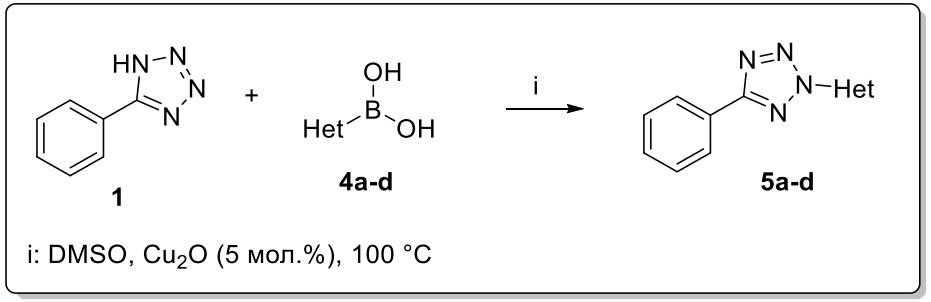
IN1 (favorable) IN2 (unfavorable) IN3 (unfavorable)

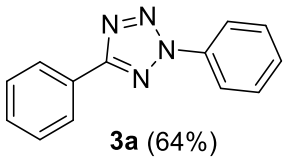
Lam P.Y., Clark C.G., Saubern S., Adams J., Winters M.P., Chan D.M., Combs A. New aryl/heteroaryl CN bond cross-coupling reactions via arylboronic acid/cupric acetate arylation // *Tetrahedron Lett*. 1998. V. 39(19). Pp. 2941-2944. DOI: 10.1016/s0040-4039(98)00504-8.

Liu C., Li Y., Ding J., Dong D., Han F. The Development of Copper-Catalyzed Aerobic Oxidative Coupling of H-Tetrazoles with Boronic Acids and an Insight into the Reaction Mechanism // *Chem. Eur. J.* 2014. V. 20(8). Pp. 2373-2381. DOI: 10.1002/chem.201302857.

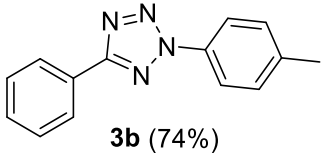
# Арилирование и гетарилирование 5-фенил-(1*H*)-тетразола при катализе Cu2O при 100°C



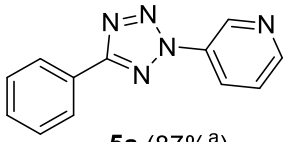



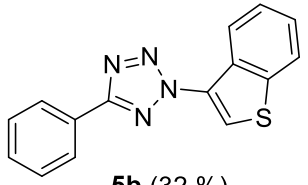
**3a** (64%)



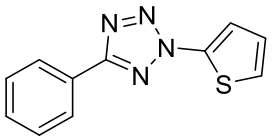
**3b** (74%)



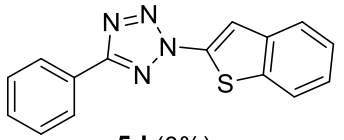
**5a** (87%[a])



**5b** (32 %)



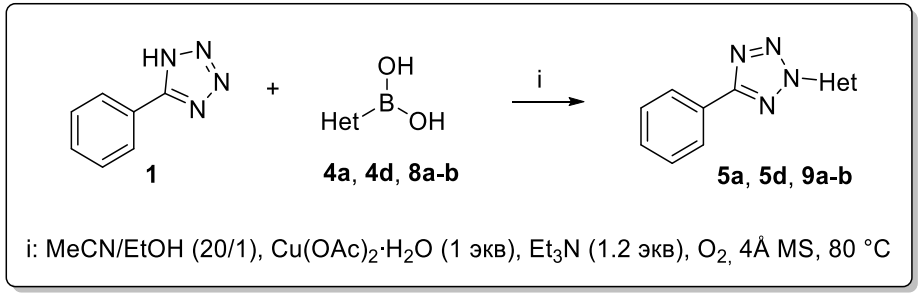
**5c** (0%)



**5d** (0%)

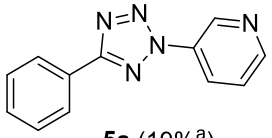
a - $O_2$ instead air

# Гетарилирование 5-фенил-(1*H*)-тетразола при катализе Cu(OAc)2 при 80°C

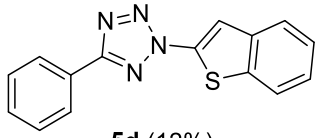



**1** **4a**, **4d**, **8a-b** **5a**, **5d**, **9a-b**

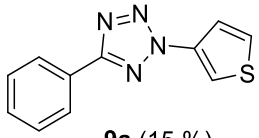
i: MeCN/EtOH (20/1), $Cu(OAc)_2 \cdot H_2O$ (1 экв), $Et_3N$ (1.2 экв), $O_2$, 4Å MS, 80 °C



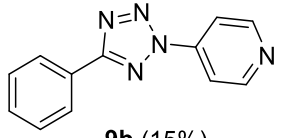
**5a** (19%[a])



**5d** (12%)



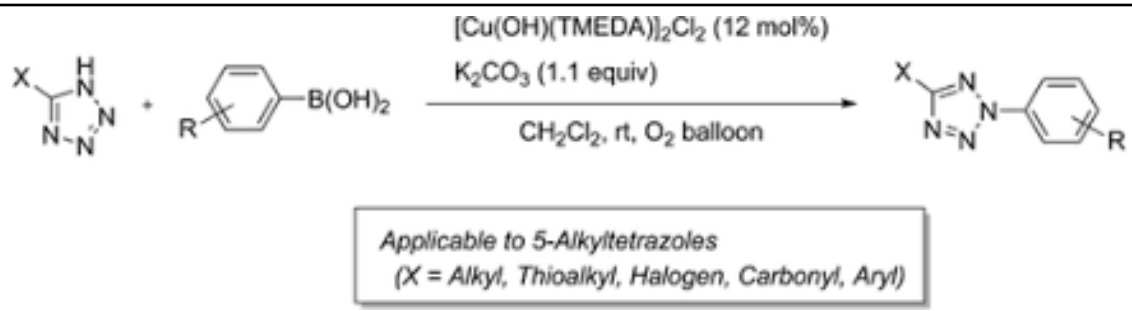
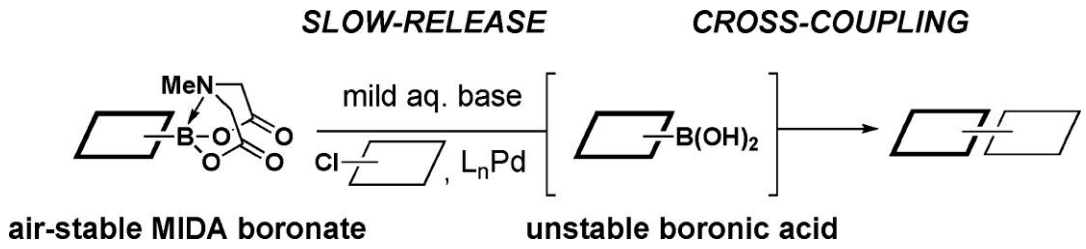
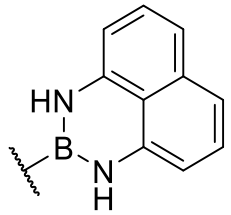
**9a** (15 %)



**9b** (15%)

a - pyridine instead Et3N

# Идеи для дальнейшей работы

| | |
|---|---|
| Дальнейшее снижение температуры реакции |  |
| Использование Het-BMIDA<br>Концепция медленного высвобождения |  |
| Использование Het-BDan |  |

# Спасибо за внимание!