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Two-step synthesis of indeno[1,2-*b*]furazanopyrazines through combination of the S_N^H and Heck reactions

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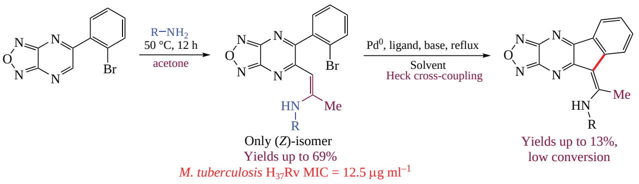
Enamines generated *in situ* from aliphatic amines and acetone react with 5-(2-bromophenyl)furazano[3,4-*b*]pyrazines *via* the nucleophilic substitution of hydrogen atom of the pyrazine ring. A representative of 9*H*-indeno[1,2-*b*]furazanopyrazin-9-ylidene ring system has been accessed by exploiting the intramolecular Heck cyclization of the obtained S_N^H-product. Several compounds derived from the S_N^H reaction, namely, *N*-alkyl-1-[6-(2-bromophenyl)furazano[3,4-*b*]pyrazin-5-yl]prop-1-en-2-amines, proved to exhibit a bacteriostatic activity *in vitro* against *Mycobacterium tuberculosis* $H_{37}Rv$.

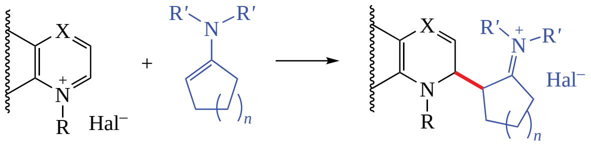


Keywords: furazanopyrazines, [1,2,5]oxadiazolo[3,4-*b*]pyrazines, intramolecular Heck reaction, C–H functionalization, S_N^H reactions, antimycobacterials, indeno[1,2-*b*][1,2,5]oxadiazolo[3,4-*e*]pyrazines.

Dedicated to Academician of the Russian Academy of Sciences M. P. Egorov on the occasion of his 70th birthday.

Furazano[3,4-*b*]pyrazines ([1,2,5]oxadiazolo[3,4-*b*]pyrazines) attract a growing attention as a family of compounds promising for both materials science[1] and medicinal chemistry.[2] 5-(Het)-aryl-substituted furazanopyrazines are of particular interest as plausible organic components for non-linear optical,[3] semiconductor[4] and sensor materials, as well as biologically active compounds exhibiting pronounced antitumor[5] and antibacterial activities.[6] One of modern approaches to modify the structure of furazanopyrazines is direct functionalization of the C–H bond through the metal-free nucleophilic aromatic substitution of hydrogen (the so-called S_N^H reactions).[1(*a*)]

It has been well-established that enamines are good C-nucleophiles for functionalization of pyrazines, quinoxalines and other diazines and triazines.[7] However, it is worth noting that preliminary activation of the pyrazine ring by putting a positive charge through the preparation of the corresponding *N*-alkyl- or *N*-acylazinium salts is often required to promote C–C coupling reactions of 1,4-diazines with enamines (Scheme 1).

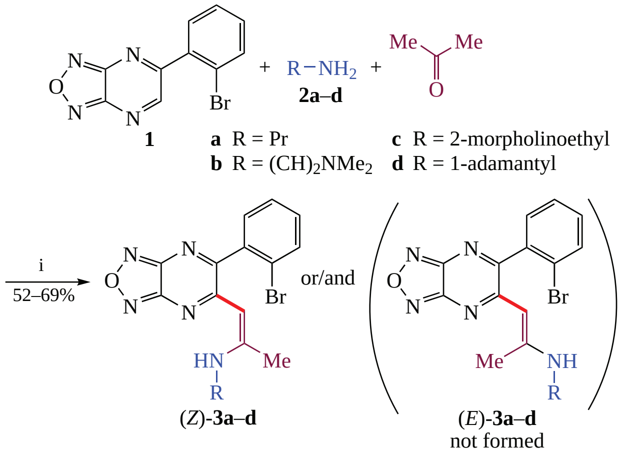


R = Me, Et, PhC(O); R′ = alkyl
n = 1–3; X = CH, N

Scheme 1

As a part of our ongoing research on modification of [1,2,5]-oxadiazolo[3,4-*b*]pyrazines, in this communication we wish to describe the reaction of non-activated 5-(2-bromophenyl)-furazanopyrazine with enamines (generated *in situ* from aliphatic amines and acetone), and to present the data on elucidation of an opportunity for further intramolecular transformation of the obtained S_N^H products into indeno[1,2-*b*]-fused pyrazines.

We used 5-(2-bromophenyl)[1,2,5]oxadiazolo[3,4-*b*]pyrazine **1** as the starting material for the S_N^H reactions with enamines, taking in account an opportunity for further transformation of the S_N^H products due to the presence of the *ortho*-positioned bromine



Scheme 2 *Reagents and conditions*: i, 50 °C, 12 h.

atom in the phenyl substituent. In fact, compound **1** reacted with alkyl amines **2a–c** or adamantan-1-amine **2d** on heating in acetone for 12 h in the contact with air oxygen, thus giving the corresponding 1-[6-(2-bromophenyl)[1,2,5]oxadiazolo[3,4-*b*]pyrazin-5-yl]-*N*-alkylprop-1-en-2-amines **3a–d**, as a result of the S_N^H reaction of **1** with *in situ* generated enamines (Scheme 2).

The structures of compounds **3a–d** have been confirmed by the ^1H and ^{13}C NMR data. The proton and carbon-13 resonance signals were assigned on the basis of 2D $^1H–^{13}C$ HSQC and HMBC experiments. *Z*-Configuration of the S_N^H products **3a–d** has been determined from 2D NOESY spectra, in which correlations between vinyl protons and both CH_3 and aromatic protons have been observed. It is worth noting that HMBC experiments revealed long-range spin–spin couplings over four bonds between the vinyl proton H(1″) and both C(3a) and NCH_2 (or NC for **3d**) carbons, apparently, due to the conjugation of aromatic system and double bond that corroborated by X-ray results. The 2D HSQMBC experiments were used to measure coupling constants $^4J_{H(1''),C(3a)} = 2.3$ Hz and $^4J_{H(1''),NC} = 1.1–1.9$ Hz.

In addition, the structure of (*Z*)-1-[6-(2-bromophenyl)[1,2,5]-oxadiazolo[3,4-*b*]pyrazin-5-yl]-*N*-propylprop-1-en-2-amine **3a** has been proved unequivocally by X-ray crystallography analysis (Figure 1).†

For S_N^H products **3a–d**, the formation of both *Z*- and *E*-isomers is possible (see Scheme 2). However, the reaction proceeded selectively, resulting in the formation of the only *Z*-isomer, whereas *E*-isomers in the reaction mixture were not detected. The proposed mechanism is shown in Scheme 3. We believe that one of the key factors determining the formation of the only *Z*-isomer is an opportunity to form an intramolecular hydrogen bond between the amino group of the enamine fragment and N(4) atom of the pyrazine ring.

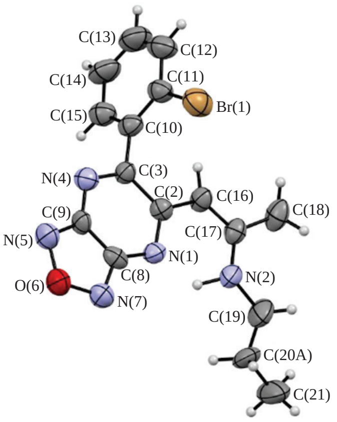
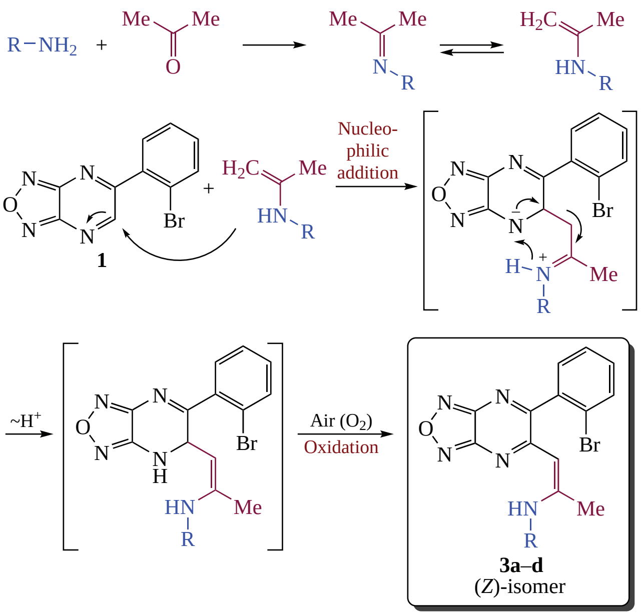
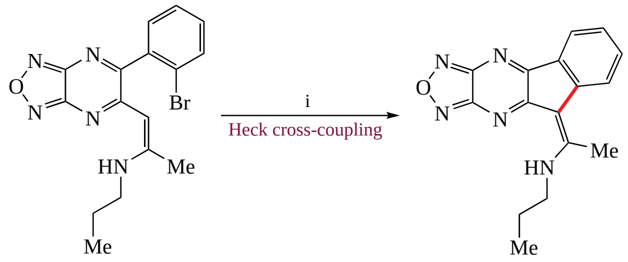


Figure 1 ORTEP representation of the X-ray crystal structure of **3a** with thermal ellipsoids of 50% probability.



Scheme 3

It is worth noting that 9*H*-indeno[1,2-*b*][1,2,5]oxadiazolo[3,4-*e*]pyrazine ring system is an important structural unit used in the design of new anticancer agents.[5,8] In this regard, we have considered an opportunity of obtaining such derivatives from compounds **3** by exploiting the intramolecular Heck reaction. Therefore, representative compound **3a** was chosen to optimize the intramolecular Heck cross-coupling conditions (Scheme 4, Table 1). Unfortunately, the conditions for this intramolecular reaction providing high conversion have so far not been found. The best results were observed with the use of



3a **4**

Scheme 4 *Reagents and conditions*: i, Pd^0, ligand, base, reflux, solvent.

Table 1 Optimization of the intramolecular Heck cross-coupling of compound **3a**.

Entry	Catalyst (equiv.)	Ligand[a] (0.2 equiv.)	Base (2.5 equiv.)	Solvent	Yields **4**/**3a** (%)
1	$Pd(PPh_3)_4$ (5 mol%)	–	K_3PO_4	toluene	5/75
2	$Pd(OAc)_2$ (10 mol%)	Xantphos[a]	K_3PO_4	toluene	13/59
3	$Pd(OAc)_2$ (10 mol%)	PCy_3	K_3PO_4	toluene	0/78
4	$Pd(PPh_3)_2Cl_2$ (10 mol%)	Xantphos	K_3PO_4	toluene	11/60
5	$Pd(OAc)_2$ (10 mol%)	Xantphos	K_3PO_4	1,4-dioxane	9/68
6	$Pd(OAc)_2$ (10 mol%)	P(*o*-Tol)$_3$	K_3PO_4	toluene	0/85
7	$Pd(OAc)_2$ (10 mol%)	Xantphos	K_2CO_3	toluene	7/71

[a] Xantphos is 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene; PCy_3 is tricyclohexylphosphine; P(*o*-Tol)$_3$ is tri(*o*-tolyl)phosphine.

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† *Crystallographic data for* **3a**: crystals of $C_{16}H_{16}BrN_5O$ (M = 374.25) are orthorhombic, space group *P*2*c*-2*n*, at 295 K: $a = 27.120(3)$, $b = 5.0120(7)$ and $c = 12.0341(11)$ Å, $\alpha = \beta = \gamma = 90.00°$, $V = 1635.7(3)$ Å^3, $Z = 4$, $d_{calc} = 1.520$ g cm^{-3}, $F(000) = 760$. 3250 reflections were measured, and 1848 independent reflections ($R_{int} = 0.1137$) were used in the further refinement. The refinement converged to $wR_2 = 0.1696$ and GOF = 1.016 for all independent reflections [$R_1 = 0.0587$ was calculated against F for 1848 observed reflections with $I > 2\sigma(I)$]. The measurements were made on an Xcalibur 3 diffractometer with graphite-monochromated MoKα radiation ($\lambda = 0.71073$ Å).

CCDC 2282840 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

palladium(II) acetate with Xantphos as a ligand. However, yields of the target polycyclic product **4** did not exceed 13%, while the starting compound **3a** was recovered in 59% yield (see Table 1, entry 2). Nevertheless, we have shown the principal opportunity of obtaining 9*H*-indeno[1,2-*b*][1,2,5]oxadiazolo[3,4-*e*]pyrazines by employing the intramolecular Heck reaction. As expected, the *Z*-configuration of the C–C double bond is retained during cyclization, which is confirmed by the NOESY experiment performed for product **4**.

Compounds **3a–d** were screened for their antimicrobial activity *in vitro* against *M. tuberculosis* $H_{37}Rv$ by applying the aerobic resazurin microplate assay (REMA).[9] It follows from experimental results that only two tested compounds **3b**,**c** have a moderate activity at minimal inhibitory concentration MIC = 12.5 μg ml^{-1}.

In summary, we have demonstrated an opportunity of reacting 5-(2-bromophenyl)furazanopyrazine with enamines (generated *in situ* from aliphatic amines and acetone) to afford the corresponding S_N^H products as well as the first example of intramolecular transformation of the latter through the Heck cross-coupling reaction, thus leading to indeno[1,2-*b*]-annulated furazanopyrazine ring system.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2023.10.004.

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