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Palladium mediated regioselective intramolecular Heck reaction: synthesis of 1,3,4-trisubstituted pyrazolo[3,4-*b*]pyridines, 3*H*-pyrazolo[3,4-*c*]isoquinolines and 3*H*-pyrazolo[4,3-*f*][1,7]naphthyridines

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Abstract: An efficient method was developed for the synthesis of 1,3,4-trisubstituted pyrazolo[3,4-*b*]pyridines, 3*H*-pyrazolo[3,4-*c*]isoquinolines and 3*H*-pyrazolo[4,3-*f*][1,7]naphthyridines via intramolecular Heck reactions of imine derivatives of *β*-halovinyl/aryl aldehydes and 5-aminopyrazoles. This palladium acetate catalyzed reaction afforded good yields of these pyrazolo fused compounds under thermal condition in presence of xantphos as the ligand.

Introduction:

The pyrazolo[3,4-*b*]pyridine moieties are found as important building blocks in both natural and synthetic bioactive compounds.[1] They show wide range of biological activities such as anxiolytic, inhibitors of xanthine oxidases, kinase inhibitors of p38a, potent and selective inhibitors of A1 adenosine receptors, glycogen synthase kinase-3 (GSK-3) inhibitors, inhibitors of B-Raf^{V600E} and cholesterol formation.[2] Similarly, 3*H*-pyrazolo[3,4-*c*]isoquinoline and 3*H*-pyrazolo[4,3-*f*][1,7]naphthyridine derivatives are also known for their wide range of biological activities.[3]

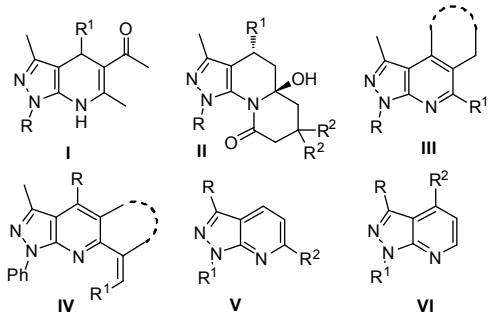
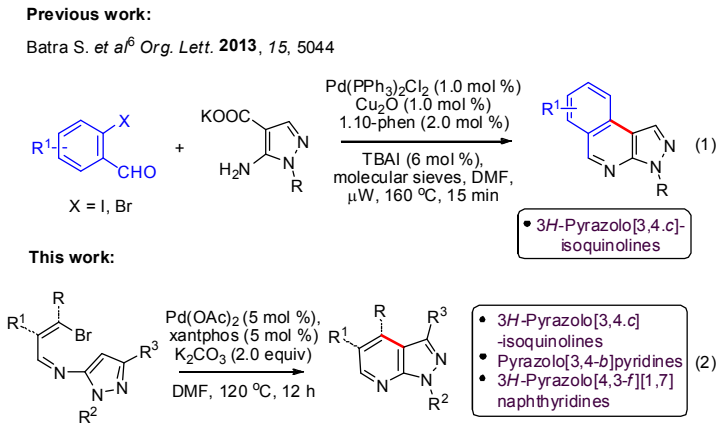


Figure 1. Pyrazolo[3,4-*b*]pyridines with different substituted patterns

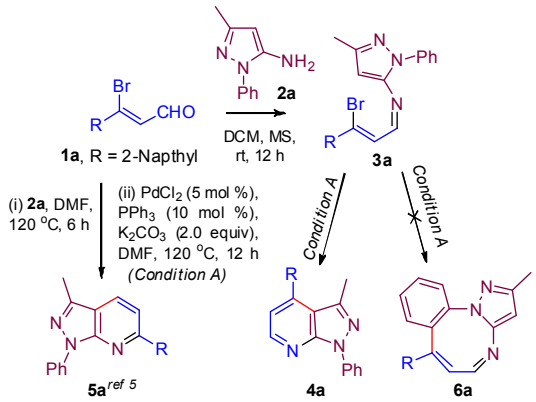
In view of the biological importance of these pyrazolo[3,4-*b*]pyridines, considerable attention has been focused on the synthesis of these fused heterocycles. There are various methods reported for the synthesis of pyrazolo[3,4-*b*]pyridines of types **I-IV** (Figure 1), using typically multi-component reactions.[4] Very recently, we reported the synthesis of pyrazolo[3,4-*b*]pyridines of type **V** (Figure 1) by the reaction of *β*-bromovinyl aldehyde with 5-aminopyrazole in the presence of palladium catalyst via cascade amination/imination/cycloaddition reactions.[5] In spite of various methods available for the construction of pyrazolo[3,4-*b*]pyridines with different substituent patterns, to the best of our knowledge, the synthesis of 1,3,4-trisubstituted pyrazolo[3,4-*b*]pyridines (**VI**, Figure 1) is not investigated so far in the literature. Our reported methodology for pyrazolo[3,4-*b*]pyridines **V**,[5] could not be applied for the synthesis of these pyrazolo[3,4-*b*]pyridines **VI**. Similarly, there are only few references known in the literature for the synthesis of 3*H*-pyrazolo[3,4-*c*]isoquinolines and 3*H*-pyrazolo[4,3-*f*][1,7]naphthyridine derivatives. The only metal catalyzed methodology for the synthesis of 3*H*-pyrazolo[3,4-*c*]isoquinolines was reported recently by Batra and co-workers using Pd-Cu catalyzed cascade imination/intramolecular decarboxylative coupling reaction, which required the presence of one acid group at δ-position of 5-amino pyrazoles (Scheme 1, eqn 1).[6] The methodology developed by Bogza and co-workers is limited to the syntheses of only 7,8-



Scheme 1: Metal catalyzed approaches for pyrazolo[3,4.*c*]-isoquinolines

dimethoxy-3*H*-pyrazolo[3,4-*c*]isoquinolines, which was performed by the reflux reaction of 4-(3,4-dimethoxyphenyl)-5-aminopyrazoles with aromatic aldehydes in strong acidic media.[3a,3d] Recently, Jiang and co-workers reported the synthesis of pyrazolo-fused 1,7-naphthyridines by the domino reactions of arylglyoxals with pyrazol-5-amine.[3b] In spite of the importance of these pyrazolo fused heterocycles, a general route for the synthesis of these novel heterocycles that have wide substrate scope is so far absent in the literature. Thus, the development of new routes to construct these pyrazolo skeletons is highly essential.

Intramolecular Heck reactions have become a powerful method for the construction of fused heteroaromatic compounds as well as cyclic natural products.[7] Palladium(II) catalyzed intramolecular Heck reactions have been using effectively by different research groups for the construction of different heterocycles such as isoquinolines, indolines, benzofurans etc.[8] Herein, we wish to report the first attempt of intramolelar Heck reaction of imine derivatives of *β*-bromovinyl/aryl aldehydes and 5-aminopyrazoles for the construction of different important pyrazole fused heterocycles such as 1,3,4-trisubstituted pyrazolo[3,4-*b*]pyridines, 3*H*-pyrazolo[3,4-*c*]isoquinolines and 3*H*-pyrazolo[4,3-*f*][1,7]naphthyridines.



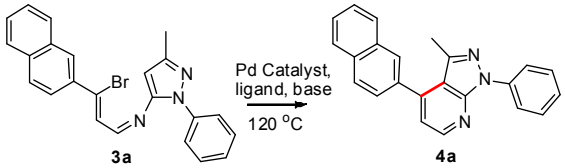
Scheme 2: Synthesis of pyrazolo[3,4-*b*]pyridines

Results and discussion

At the beginning, our attempt to perform the $PdCl_2$ catalyzed intramolecular coupling reaction of the *in situ* generated imine derivative of *β*-bromo-*β*-(2-napthyl)vinyl aldehyde (**1a**, 1.0 mmol) and 1-phenyl-3-methyl-5-aminopyrazole (**2a**, 1.0 mmol) in DMF, furnished only the previously reported pyrazolo[3,4-*b*]pyridine **5a**[5] (Scheme 2). Probably, the presence of water molecules helped the partial hydrolysis of the imines to generate the free amines, which in presence of the Pd catalyst affords compound **5a**, via previously reported cascade imination/coupling/cycloaddition reaction.[5] To overcome the formation of compound **5a**, then we tried the intramolecular coupling reaction of pure imine derivative **3a** (1.0 mmol), with $PdCl_2$ (5.0 mol%), PPh_3 (10.0 mol%) and K_2CO_3 (2.0 mmol) in DMF (Table 1). To our delight, after heating the reaction mixture for 12 hours at 120 ^oC, the reaction afforded pyrazolo[3,4-*b*]pyridine derivative **4a** in 34% yield (entry 1, Table 1). This pyrazolo[3,4-*b*]pyridine derivative **4a** was fully characterized by ^1H NMR, ^{13}C NMR and mass spectroscopy. Then, we studied some other palladium catalysts and ligands to determine the ideal reaction condition for the synthesis of compound **4a** which are shown in Table 1. Moreover, we screened some bases and solvents which were frequently used to perform the intramolecular Heck reactions (Table 1).[9] Screening of palladium catalysts such as $Pd(OAc)_2$, $PdCl_2(PPh_3)_2$ and $Pd(TFA)_2$ revealed $Pd(OAc)_2$ as the best catalyst to perform this reaction (entries 2−4). In absence of the catalyst, the reaction did not work (entry 5). In addition, screening of solvents disclosed DMF as the best solvent to perform this reaction (entries 2, 6-7). Further studies on bases revealed K_2CO_3 as the best base, although Cs_2CO_3 worked efficiently, the yield of **4a** did not exceed 68% (entries 2, 8-9). For further improvement of the yield, we next focused our attention on the ligands. In absence of the ligand, the reaction gave inferior result, whereas, the use of the monophosphine ligand P(*o*-tol)$_3$ provided the desired compound in 67% yield (entries 10-11). Then, we further

tested some bisphosphine ligands such as dppf and xantphos for optimization of the reaction (entries 12−13).

Table 1. Optimization of the reaction conditions[a]



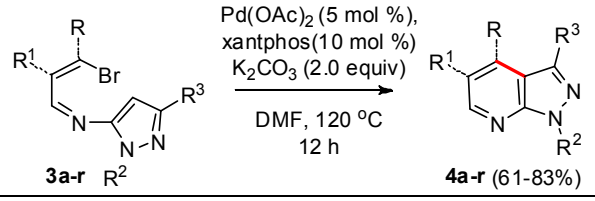
3a **4a**

Entry	Pd catalyst	Base	Ligand	Solvent	**4a** (%)[b]
1	$PdCl_2$	K_2CO_3	PPh_3	DMF	34
2	$Pd(OAc)_2$	K_2CO_3	PPh_3	DMF	70
3	$PdCl_2(PPh_3)_2$	K_2CO_3	PPh_3	DMF	49
4	$Pd(TFA)_2$	K_2CO_3	PPh_3	DMF	58
5	none	K_2CO_3	PPh_3	DMF	0
6	$Pd(OAc)_2$	K_2CO_3	PPh_3	MeCN	28
7	$Pd(OAc)_2$	K_2CO_3	PPh_3	DMSO	57
8	$Pd(OAc)_2$	Cs_2CO_3	PPh_3	DMF	68
9	$Pd(OAc)_2$	Ag_2CO_3	PPh_3	DMF	52
10	$Pd(OAc)_2$	K_2CO_3	none	DMF	15
11	$Pd(OAc)_2$	K_2CO_3	P(*o*-tol)$_3$	DMF	67
12	$Pd(OAc)_2$	K_2CO_3	dppf	DMF	54
13	$Pd(OAc)_2$	K_2CO_3	xantphos	DMF	79
14	$Pd(OAc)_2$	K_2CO_3	1,10-phen	DMF	44
15[c]	$Pd(OAc)_2$	K_2CO_3	xantphos	DMF	63
16[d]	$Pd(OAc)_2$	K_2CO_3	xantphos	DMF	77

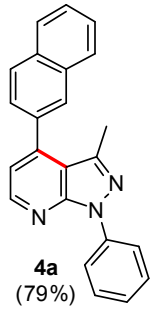
[a]*Reaction conditions:* **3a** (1.0 mmol), catalyst (5.0 mol %), base (2.0 equiv), ligand (10.0 mol %), solvent (3.0 mL), 120 °C, 12 h. [b]Isolated yield. [c]Using 2.5 mol % of catalyst. [d]Using 7.5 mol % of catalyst

Gratifyingly, xantphos (4,5-*bis*(diphenylphosphino)-9,9-dimethyl xanthene) was found to be the most effective ligand to afford **4a** in 79% yield (entry 13). Further exploration of bidentate ligand, such as 1,10-phen provided poor yield of **4a** (entry 14). Next, the effect of catalyst loading was investigated and we found that reduction of the catalyst to 2.5 mol % led to decreased product yield (entry 15). The use of higher catalyst loading could not further increase the yield of **4a** (entry 16, Table 1). Our attempt to perform the optimized reaction of purified

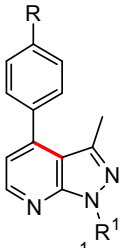
Table 2. Intramolecular Heck reactions for the synthesis of pyrazole fused heterocycles[a]



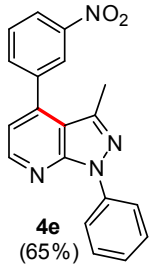
3a-r **4a-r** (61-83%)



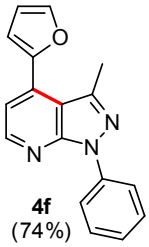
4a (79%)



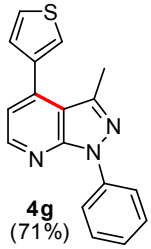
4b, R = Me, R^1 = Ph (83%)
4c, R = Cl, R^1 = Me (67%)
4d, R = Cl, R^1 = Ph (72%)



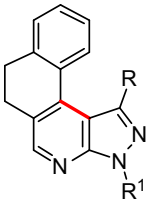
4e (65%)



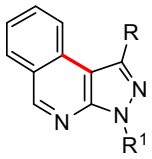
4f (74%)



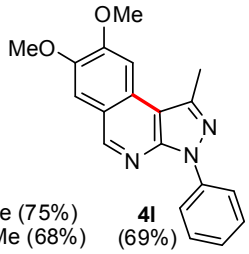
4g (71%)



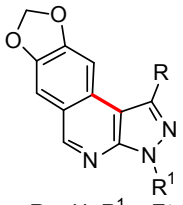
4h, R = Me, R^1 = Me (75%)
4i, R = Me, R^1 = Ph (78%)



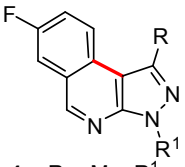
4j, R = Me,R^1 = Me (75%)
4k, R = Ph, R^1 = Me (68%)



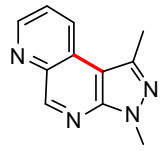
4l (69%)



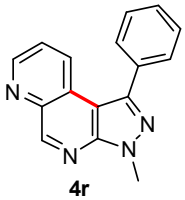
4m, R = H, R^1 = Et (72%)
4n, R = Me, R^1 = Ph (75%)



4o, R = Me, R^1 = Me (61%)
4p, R = Ph, R^1 = Me (64%)



4q (69%)



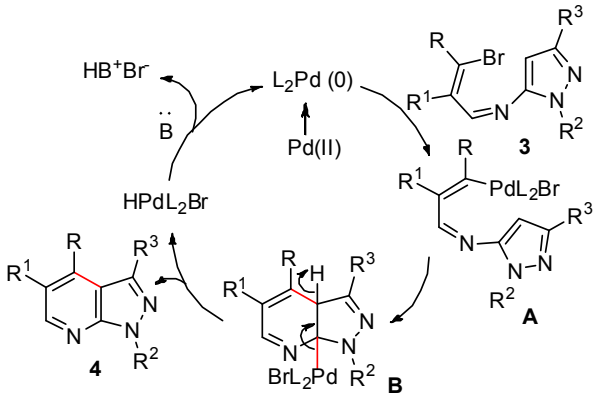
4r (68%)

[a]*Reaction conditions:* Imine **1** (1.0 mmol), $Pd(OAc)_2$ (5 mol%), PPh_3 (10 mil%), K_2CO_3 (3.0 mmol) in DMF (3.0 mL) was heated at 120 °C for 12 h; Isolated yields.

imine derivative **3a** in presence of one equivalent of water afforded the pyrazolo[3,4-*b*]pyridine **5a**.

Using the optimized reaction condition (entry 13, Table 1), we evaluated the scope of the reaction by using different acyclic imines **3b-e** (Table 2). As shown in table 2, various acyclic *β*-bromovinyl imines that have *β*-substituents such as 4-methylphenyl, 4-chlorophenyl and 3-nitrophenyl groups underwent the above coupling reaction smoothly to give 1,3,4-trisubstituted pyrazolo[3,4-*b*]pyridines **4b-e** in 65-83% yields. Notably, chloro and nitro groups were compatible with the reaction conditions, though they provided slightly less yields. In addition, the coupling reaction of *β*-bromovinyl imines having *β*-heterocycles proceeded efficiently to afford 71-74% yields of 4-heterocycle substituted pyrazolo[3,4-*b*]pyridines **4f-g**. Similar intramolecular coupling reactions of cyclic *β*-bromovinyl imines that have *N*-alkyl/aryl substituents, under the optimized condition, afforded tetrahydronaphthalene ring fused pyrazolo[3,4-*b*]pyridine derivatives **4h-i** in 75-78% yields. Finally, we explored the scope of this Heck reaction by using different aromatic imines **3j-p** under the optimized conditions. The aromatic imines (**3j-p**) with functional groups such as methoxy, 1,3-dioxole and fluoro groups on the aromatic ring were compatible with the reaction condition to afford 3*H*-pyrazolo[3,4-*c*]isoquinolines (**4l-p**) in 61-75% yields. The formation of compound **4** was finally proved by comparison of spectral and physical data with those reported in the literature for compound **4l**.[3a] Moreover, the Heck reaction of pyridyl imine derivatives **3q-r** proceeded smoothly under the optimized reaction conditions to give the corresponding 3*H*-pyrazolo[4,3-*f*][1,7]naphthyridines in 68-69% yields. It was worth noting that this intramolecular coupling reaction is highly regioselctive. Although there was a possibility for the formation of nitrogen containing eight membered heterocycle **6a** (Scheme 2), it failed to afford it probably, due to the inherent strain of the eight membered ring **6a**.

On the basis of the above observations and literature reports,[10] a plausible reaction mechanism for the Pd-catalyzed formation of compound **4** is shown in Scheme 3. First, oxidative addition of the Pd(0) species to compound **3** forms Pd(II) intermediate **A**. Then, intramolecular coordination of the olefin of the pyrazole part to the palladium center, followed by migratory insertion of the alkene into the carbon-palladium bond provides intermediate **B**. The subsequent *β*-hydride elimination provides compound **4** and a palladium(II)-hydrido complex $HPdL_2Br$, which is reduced by base to afford PdL_2 to complete the catalytic cycle.[11]



Scheme 3. Plausible mechanism

Conclusions

In conclusion, we have demonstrated an efficient new approach for the synthesis of biologically important 1,3,4-trisubstituted pyrazolo[3,4-*b*]pyridines, tetrahydronaphthalene ring fused pyrazolo[3,4-*b*]pyridines, 3*H*-pyrazolo[3,4-*c*]isoquinolines and 3*H*-pyrazolo[4,3-*f*][1,7]naphthyridines via an intramolecular Heck reaction. A wide variety of imine derivatives of *β*-bromovinyl/aryl aldehydes and 5-aminopyrazoles undergo this regioselective reaction to afford good yields of these heterocycles.

Acknowledgements

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Supplementary Material

General experimental procedure, characterization data, copies of ^{1}H and ^{13}C NMR spectra for compounds **4a-r**, **3a**, **3d**, **3g**, **3i**, **3k**, **3m**, **3o** and **3r**.

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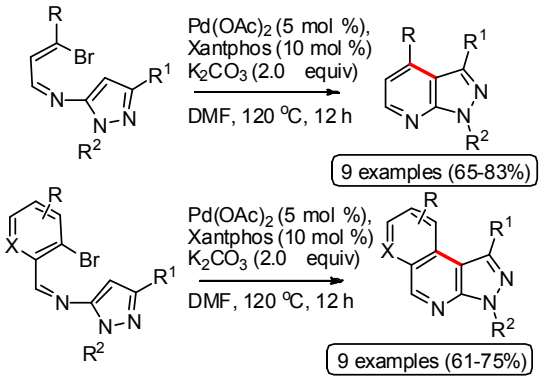

A new approach for the synthesis of 1,3,4-trisubstituted pyrazolo[3,4-*b*]pyridines, 3*H*-pyrazolo[3,4-*c*]isoquinolines and 3*H*-pyrazolo[4,3-*f*][1,7]naphthyridines via an intramolecular Heck reaction is described.