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# Synthesis of 3*H*-Pyrazolo[3,4-*c*]-isoquinolines and Thieno[3,2-*c*]-isoquinolines via Cascade Imination/ Intramolecular Decarboxylative Coupling

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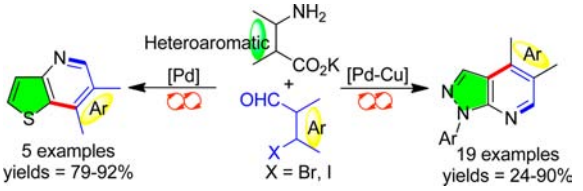
## ABSTRACT




**A general approach for the synthesis of 3*H*-pyrazolo[3,4-*c*]isoquinolines and thieno[3,2-*c*]isoquinolines is described involving the implementation of a cascade imination/intramolecular decarboxylative coupling between potassium 2-amino(hetero)benzoates and 2-haloarylaldehydes. The reactions of pyrazole-based substrates require a Pd−Cu bimetallic system for superior yields whereas the thienyl-based substrates afford the products in excellent yields with a Pd-catalyst only.**

The transition-metal based decarboxylative cross-coupling for the synthesis of biaryls is an expanding field of C−C bond forming reactions.[1] As compared to the conventional coupling reactions where expensive unstable organometallic reagents are required, the decarboxylative coupling employs readily available, diverse, cheap, and stable carboxylic acids as the nucleophilic partner, thereby obviating the need for sensitive organometallic reagents. Moreover the extrusion of carbon dioxide during such couplings, instead of toxic metallic waste, is environmentally benign. In general, the decarboxylative cross-coupling of aromatic carboxylic acids is realized either by the use of Pd−Cu[2] or Pd−Ag[3] bimetallic system or with Pd- or Cu-catalysts only.[4,5] Strikingly, the majority of these reactions are intermolecular in nature and only a few reports describe the intramolecular version. As a consequence, the intramolecular decarboxylative coupling in aromatic carboxylic acids is a subject of investigation. In this context, we have recently reported the synthesis of phenanthridine via a two-component reaction between potassium 2-aminobenzoate and 2-halobenzaldehyde which proceeded via a cascade imination/intramolecular decarboxylative

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coupling sequence.[6] However, the sequence operated only when a nitro group at the ortho-position to the carboxylate group in the arene ring was present, whereas, in the absence of the nitro group, the same catalytic condition drove the reaction via the imination/C−H activation sequence. This result was in line with Goossen's bimetallic approach which hypothesizes that due to its strong coordinating property, the presence of the nitro group ortho to the carboxylate in aromatic system enhances the copper-ligating quality of the carboxylate.[2b] In contrast, for heteroaromatic carboxylic acids, the decarboxylative coupling was shown to be successful with the Pd-catalyst only.[4a,c] Forgione et al. proposed that delocalization of the lone pair of electrons of the heteroatom in the ring induces nucleophilicity in the heteroaromatic partner which then undergoes a reaction with the in situ generated electrophile Ar−Pd(X)(L). This hypothesis gained support by the theoretical studies performed by Liu et al. toward understanding the Pd-catalyzed decarboxylative couplings.[7] With this background it became imperative to investigate the feasibility of transition-metal promoted tandem imination/decarboxylative coupling between potassium 2-amino-(hetero)benzoates and 2-haloarylaldehydes. Herein, we report results of our studies in this direction using potassium 5-amino-1-phenyl-1*H*-pyrazole-4-carboxylates and 3-aminothiophene-2-carboxylate as the heterocyclic substrates.

Pyrazoles are considered to be important heteroarenes due to their frequent presence in pharmaceuticals and herbicides.[8,9] In particular, the significance of pyrazole bi(heteroaryl) has resulted in the formulation of efficient protocols for direct C-3, C-4, and C-5 arylations of pyrazoles.[10] Arylations in pyrazoles can also be achieved via decarboxylative coupling, but to the best of our knowledge there is no previous report by this route. Therefore in order to investigate the implementation of cascade imination/decarboxylative coupling/arylation in pyrazoles for preparing fused pyrazoles,[11] we were prompted to initially establish the conditions for arylation in pyrazoles via decarboxylative coupling. In this context first we prepared 1-(2-chlorophenyl)-5-phenyl-1*H*-pyrazole-3-carboxylic acid **1** and 1,5-diphenyl-1*H*-pyrazole-4-carboxylic acid **3** and their respective potassium salts and subjected them to coupling with bromobenzene in the presence of a Pd-catalyst and $Cs_2CO_3$ as reported by Forgione et al. (condition ***A***) and in the presence of a Pd−Cu cocatalyst as reported by us (condition ***B***). It was gratifying to note that the reactions were successful under both conditions to afford the respective coupling products **2** and **4** in comparable yields (Scheme 1). Subsequently in a modification of condition ***A***, the reactions of potassium salts of **1** and **3** were performed in the presence of 1,10-phenanthroline in place of $Cs_2CO_3$ (condition ***C***). Under this condition though **2** was isolated in 58% yields, the yield of **4** increased to 92%. Thus it was apparent that as reported for other 5-member heterocyclic carboxylic acids, the decarboxylative coupling in pyrazole carboxylic acids can be achieved in the presence of the Pd-catalyst only.

Next in our objective to establish cascade imination/decarboxylative coupling in pyrazole-based substrates, we embarked on studying the reaction of potassium 5-amino-1-phenyl-1*H*-pyrazole-4-carboxylate (**5a**) with 2- bromobenzaldehyde (**6A**). Successful implementation of the protocol was anticipated to afford pyrazolo-fused-pyridine, a core unit represented in several bioactive compounds endowed with antidepressant, antianxiolytic, and platelet aggregation inhibitory activities.[12] Although the synthesis of such a system via a Pictet−Spengler reaction of 4-(3,4-dimethoxyphenyl)-5-aminopyrazoles with different aldehydes is reported,[13] its scope remains limited due to the necessity for the presence of electron donating groups on the aromatic ring. In a pilot experiment therefore, the reaction of **5a** with **6A** was investigated in the presence of $Pd(PPh_3)_2Cl_2$ (condition ***C***), but the required product **7aA** could be isolated in 47% yields only (Table 1, entry 1). Performing the same reaction in the presence of $Cs_2CO_3$ instead of 1,10-phenanthroline failed to yield any product (entry 2). This impelled us to screen other Pd-sources including $PdCl_2$, $Pd(TFA)_2$, and $Pd(OAc)_2$ for the reaction, but the yields of the product were only moderate (entries 3−6). To improve the yield of **7aA**, we next examined the Pd−Cu cocatalyst system (condition ***B***), and to our delight the yield improved to 90% (entry 7). Further we discovered that reducing the catalyst load to

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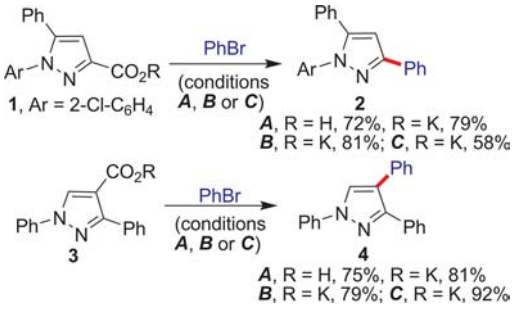
**Scheme 1.** Results of Decarboxylative Coupling in Pyrazole Derivatives[a] under Different Conditions[b]




[a] **1** (0.3 mmol), **3** (0.3 mmol), PhBr (0.3 mmol). [b] Condition ***A***: $PdCl_2$ (5 mol %), $PPh_3$ (10 mol %), $Cs_2CO_3$ (1.5 equiv), TBACl (1 equiv), DMF (2 mL), $\mu$W, 160 °C, 20 min. Condition ***B***: $Pd(PPh_3)_2Cl_2$ (1.5 mol %), $Cu_2O$ (1 mol %), 1,10-phen (6 mol %), TBAI (6 mol %), DMF (2 mL), $\mu$W, 160 °C, 15 min. Condition ***C***: $Pd(PPh_3)_2Cl_2$ (5 mol %), 1,10-phen (6 mol %), TBAI (15 mol %), DMF (2 mL), $\mu$W, 160 °C, 25 min.

1% of $Pd(PPh_3)_2Cl_2$ and ligand load to 2 mol % had no effect on the yield of **7aA** (entry 8). The reaction was successful even in the Pd−Ag cocatalyst system, though the yield was inferior as compared to the Pd−Cu system (entry 9).

Thus, the best conditions identified for the tandem reaction were $Pd(PPh_3)_2Cl_2$ (1.0 mol %), $Cu_2O$ (1.0 mol %), 1,10-phenanthroline (2.0 mol %), TBAI (6 mol %), and molecular sieves in DMF at 160 °C under microwave. With the optimized conditions in hand, we tested the scope of the protocol by introducing changes in the pyrazoles (**5a**−**e**) and the 2-bromobenzaldehyde (**6A**−**D**) units. It was satisfying to note that all substrates smoothly underwent the cascade reaction affording the respective products in excellent yields (Scheme 2). Installing substitutions on the phenyl ring in pyrazole (**5b**−**e**) did not influence the outcome. On the other hand substituting the phenyl ring in 2-bromobenzaldehyde (**6B**−**D**) afforded the products in good yields. Replacing 2-bromobenzaldehyde with 2-bromo-3-indolecarbaldehyde (**6E**) furnished the required product **3bE** in 62% yield. The scope of the protocol for the heterocyclic substrate was further enhanced by treating **5b** with 5-(4-chlorophenyl)-4-iodo-1-phenyl-3(1*H*)-pyrazolecarbaldehyde **6F** to obtain 3-(2-chlorophenyl)-7-(4-chlorophenyl)-8-phenyl-3,7-dihydrodipyrazolo[3,4-*b*:4′, 3′-*d*]pyridine **7bF** albiet in 24% yield only. It is worth mentioning that we also investigated the reactions of **5a** with 2-chlorobenzaldehyde and 2-iodobenzaldehyde but only moderate yields of **7aA** were isolated (see Supporting Information).

Mechanistically, we speculate that the presence of two nitrogens in pyrazole would result in weaker delocalization of electrons rendering them relatively less available for coordination with the Pd-catalyst. However in the presence of a bimetallic system, copper coordinates with the pyrazole thus increasing the ligating quality of carboxylate which results in the formation of the product in better yield (see SI).

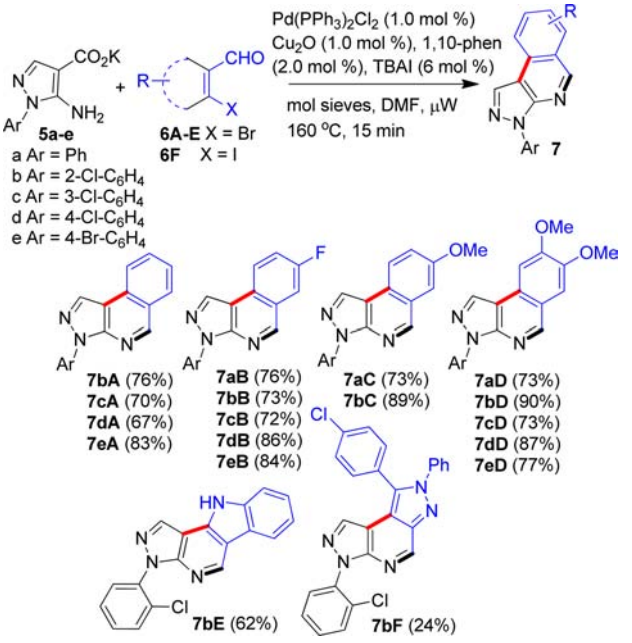
Next we turned our attention to an identical reaction of potassium 3-amino-thiophene-2-carboxylate because

**Table 1.** Result of the Optimization Study towards the Cascade Reaction of **5a** with **6A**[a]


| entry | [Pd] (mol %) | cocat. (mol %) | ligand/base (mol %) | **7aA** yield[b] (%) |
|---|---|---|---|---|
| 1 | $Pd(PPh_3)_2Cl_2$ (5.0) | – | 1,10-phen (6.0) | 47 |
| 2 | $Pd(PPh_3)_2Cl_2$ (5.0) | – | $Cs_2CO_3$ (1.5 equiv) | 0 |
| 3 | $PdCl_2$ (5.0) | – | 1,10-phen (6.0) | 13 |
| 4 | $PdCl_2$ (5.0) | – | $PPh_3$ (5.0) | 24 |
| 5 | $Pd(OAc)_2$ (5.0) | – | 1,10-phen (6.0) | 38 |
| 6 | $Pd(TFA)_2$ (5.0) | – | 1,10-phen (6.0) | 42 |
| 7 | $Pd(PPh_3)_2Cl_2$ (1.5) | $Cu_2O$ (1.0) | 1,10-phen (6.0) | 90 |
| 8 | $Pd(PPh_3)_2Cl_2$ (1.0) | $Cu_2O$ (1.0) | 1,10-phen (2.0) | 90 |
| 9 | $Pd(PPh_3)_2Cl_2$ (1.5) | $Ag_2CO_3$ (1.0) | – | 63 |

[a] Reaction conditions: **5a** (0.4 mmol), **6A** (0.4 mmol), DMF (2.0 mL). [b] Yield of **7aA** is the isolated yield in each entry.

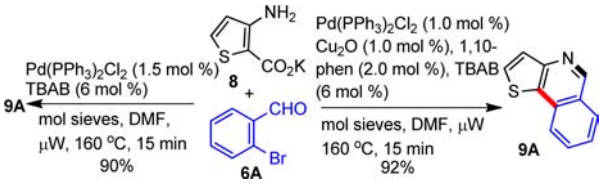
**Scheme 2.** Scope of [Pd−Cu]-Mediated Cascade Reaction[a] for the Synthesis of 3*H*-Pyrazolo[3,4-*c*]isoquinolines[b]




[a] Reaction conditions: **5** (0.4 mmol), **6** (0.4 mmol), DMF (2.0 mL). [b] Yields shown are the isolated yields.

(a) successful implementation of tandem imination/decarboxylative coupling would offer a general route to thieno[3,2-*c*]isoquinolines which are used in the synthesis of ER-NFkB inhibitors;[14] (b) thiophene 2-carboxylic acid

**Scheme 3.** Results of the Reaction[a] between **8** and **6a** in the Presence of [Pd−Cu] and Pd Only

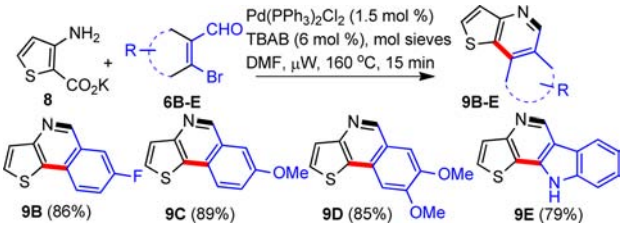



[a] Reaction conditions: **8** (0.4 mmol), **6A** (0.4 mmol), DMF (2.0 mL).

undergoes successful intermolecular decarboxylative coupling in the presence of the Pd-catalyst only.[4a,15] Initially therefore we carried out the reaction of potassium 3-amino-thiophene-2-carboxylate **8** with **6A** in the presence of a bimetallic catalyst system under microwave irradiation as optimized earlier.[6] The reaction was complete in 15 min to afford the product in 92% yield that was identified to be the tricyclic thieno[3,2-*c*]isoquinoline **9A** (Scheme 3). Next the same reaction was performed in the presence of $Pd(PPh_3)_2Cl_2$ (1.0 mol %), TBAB, and molecular sieves in DMF as the medium. We were delighted to note that the reaction furnished identical product **9A** in 80% yield. Increasing the catalyst load to 1.5 mol % furnished **9A** in comparable yields to those of the bimetallic system. This result inferred that as reported by Forgione and others, here the delocalization of the lone pair in the heterocyclic substrate assists the decarboxylation process efficiently. We speculate that the formation of thieno[3,2-*c*]-isoquinoline via a cascade process involving initial imine formation followed by decarboxylative coupling proceeds via the mechanism as proposed by Forgione et al. (see SI).[4a,15a]

Therefore the optimized conditions for the reaction were identified as $Pd(PPh_3)_2Cl_2$ (1.5 mol %), TBAB (6 mol %), and molecular sieves in DMF at 160 °C under microwave irradiation. The scope of the protocol was tested with several substituted 2-bromobenzaldehydes (**6B**−**D**), and the results are presented in Scheme 4. It was found that

**Scheme 4.** Scope of the Protocol[a] for the Synthesis of Substituted Thieno[3,2-*c*]isoquinoline[b]




[a] Reaction conditions: **8** (0.4 mmol), **6B**−**E** (0.4 mmol), DMF (2.0 mL). [b] Yields shown are the isolated yields.

the presence of substitutions on the phenyl ring in 2-bromobenzaldehyde did not have any significant impact on the reaction, as the respective products (**9B**−**D**) in each case were isolated in excellent yields. The reactions were successful even with heterocylic aldehyde **6E** to afford the corresponding product **9E** in 79% yield.

In conclusion we have disclosed the cascade imination/decarboxylative coupling of potassium 5-amino-1-phenyl-1*H*-pyrazole-4-carboxylates and 3-amino-thiophene-2-carboxylate with 2-haloarylaldehydes for the synthesis of a variety of fused-heterocyclic systems. Whereas the reactions of pyrazoles required a Pd−Cu cocatalyst system for better yields, identical reactions in thiophene were successful with Pd only. Besides, this study also established decarboxylative coupling as an alternative route to arylation in pyrazoles.

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**Supporting Information Available.** Mechanisms, experimental procedures, spectroscopic data, and copies of $^1H$ and $^{13}C$ NMR spectra for all compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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