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Title: Rhodium(II) Acetate-Catalysed Cyclization of Pyrazol-5-amine and 1,3-Diketone-2-diazo Compounds using N,N-Dimethylformamide as a Carbon-Hydrogen Source: Access to Pyrazolo[3,4-b]pyridines

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COMMUNICATION

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Rhodium(II) Acetate-Catalysed Cyclization of Pyrazol-5-amine and 1,3-Diketone-2-diazo Compounds using *N,N*-Dimethylformamide as a Carbon-Hydrogen Source: Access to Pyrazolo[3,4-*b*]pyridines

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Abstract. Access to pyrazolo[3,4-*b*]pyridines through a rhodium-catalysed intermolecular cyclization of pyrazol-5-amine and cyclic 1,3-diketone-2-diazo compounds, has been developed. A methyl carbon of *N,N*-dimethylformamide (DMF) performed as a carbon-hydrogen source for the construction of the pyridine ring. Various pyrazolo[3,4-*b*]pyridine derivatives were obtained under mild conditions using air as the terminal oxidant.

Keywords: Rhodium; *N,N*-dimethylformamide; Pyrazolo[3,4-*b*]pyridines; C-H activation; Diazo compounds

As a class of fused, nitrogen-containing heterocycles, pyrazolo[3,4-*b*]pyridines are ubiquitous in synthetic bioactive compounds.[1] A number of complex molecules containing pyrazolo[3,4-*b*]pyridine motifs have been designed and synthesized, and their bioactivities have been evaluated (Figure 1). For example, compound **I** was found to be an efficient GSK-3b inhibitor.[2] Ding and co-workers developed compound **II** as an EGFR and B-Raf inhibitor.[3]

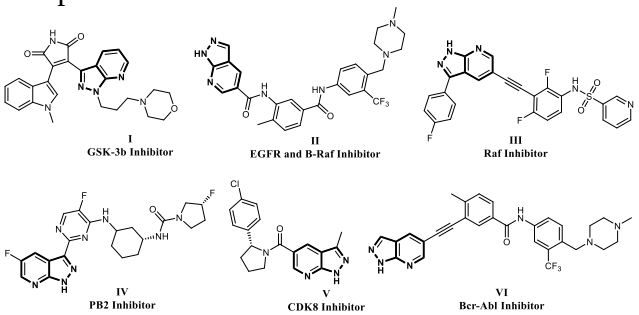
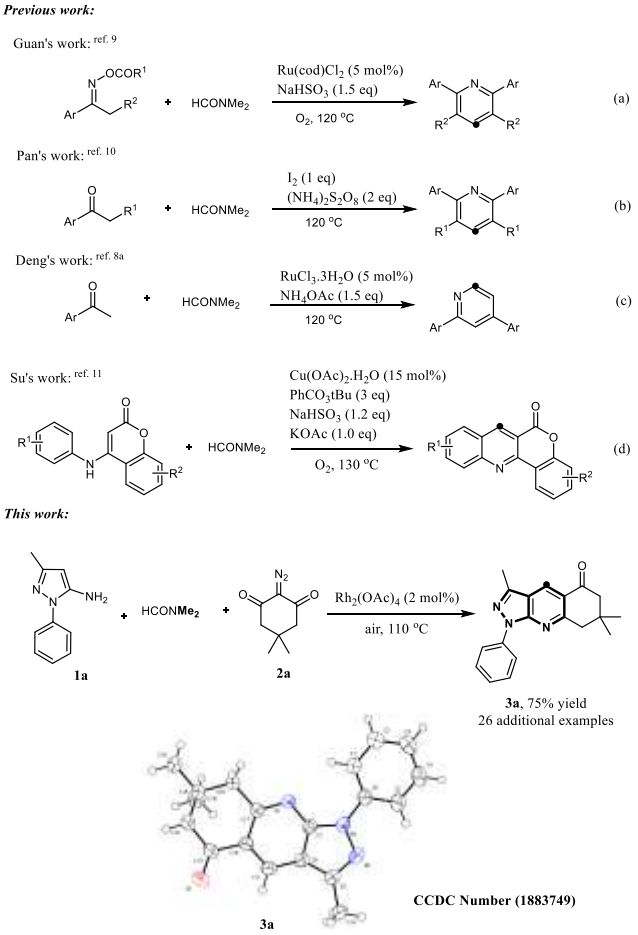


Figure 1. Representative Molecules Containing the Pyrazolo[3,4-*b*]pyridine Moiety.

By switching the linker to a pyrazolo[3,4-*b*]pyridine and the aminocarbonyl phenyl group from an amide to an alkyne, they obtained **VI**, which is an excellent Bcr-Abl inhibitor.[4] Other relevant compounds, **III-V** containing pyrazolo[3,4-*b*]pyridines, have been reported to be effective Raf, PB2 and CDK8 inhibitors, respectively.[5] Traditional preparations of such polycyclic compounds suffer from requiring starting materials that can only be obtained from multi-step procedures or requiring harsh reaction conditions.[1,6] Thus, developing general and efficient methods for the construction of pyrazolo[3,4-*b*]pyridine derivatives remains an attractive synthetic task.

N,N-Dimethylformamide (DMF) is one of the most commonly used polar solvents due to its unique ability to dissolve polar reactants. In addition to its dissolution properties, it can participate in a variety of transformations and serve as a source of building blocks.[7] DMF can be used as a reagent in formylation, amination, aminocarbonylation, amidation, and cyanation reactions and as a source of nitrogen or carbon for other reactions. In these processes, different sites on DMF are activated, resulting in the donation of one or more atoms in the construction of the new target molecule. Various methods have been developed for the synthesis or functionalization of heterocycles based on the ability of DMF to serve as a C1 source.[8] For example, Guan and co-workers reported a ruthenium-catalysed cycloaddition of ketoximes for the synthesis of symmetrical tetra-substituted pyridines using a methyl group of DMF as a CH fragment (Scheme 1a).[9] Later, Pan's group developed a transition-metal-free iodine and persulfate-promoted [2+2+1+1] cycloaddition for the construction of multi-substituted pyridines from arones (Scheme 1b).[10] An efficient

synthetic method leading to 6H□chromeno[4,3□*b*]quinolin-6-ones, in which two C(sp2)-H bond functionalizations were realized using DMF as a CH source, was reported by Su and co-workers (Scheme 1d).[11]

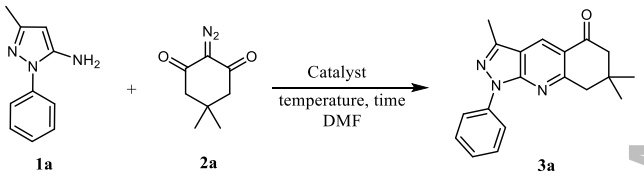


Scheme 1. Construction of 6-Membered *N*-Heterocycles using DMF as a C1 Sources.

Transition-metal-catalysed carbene insertion reactions have been well studied, and a number of synthetic methods have been developed based on their high and diverse reactivities.[12] Specifically, 1,3-dicarbonyl-2-diazo compounds are typically used as C2 building blocks in the construction of cyclic compounds due to their propensity toward undergoing transition-metal-catalysed carbene insertion and subsequent condensation cyclization reactions.[13] Based on our long-standing research interests in this field,[14] we designed a free amino-directed Rh-catalysed carbene insertion reaction with 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**1a**) and 2-diazo-5,5-dimethylcyclohexane-1,3-dione (**2a**) as the substrates. However, an unexpected product, 3,7,7-trimethyl-1-phenyl-1,6,7,8-tetrahydro-5*H*-pyrazolo[3,4-*b*]quinolin-5-one (**3a**), was generated when using $Rh_2(OAc)_2$ as the catalyst and DMF as the solvent. The structure of **3a** was confirmed by the single crystal structure using X-ray crystallography.[15] Herein, we report the Rh-catalysed synthesis of pyrazolo[3,4-*b*]pyridines *via* a formal [3+2+1] cyclization reaction under mild conditions. A methyl group of DMF provided one carbon for the formation of the pyridine ring, and air was the only oxidant in this reaction.

The investigations were begun with 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**1a**) and 2-diazo-5,5-dimethylcyclohexane-1,3-dione (**2a**) as model substrates with $Rh_2(OAc)_4$ as the catalyst at 110 °C. The product, 3,7,7-trimethyl-1-phenyl-1,6,7,8-tetrahydro-5*H*-pyrazolo[3,4-*b*]quinolin-5-one (**3a**), was fortunately obtained in 41% yield (Table 1, entry 1). A screening of other catalysts and solvents showed none of the desired product was generated under these alternative conditions (entries 2-10). The yield was improved to 75% when the amount of starting material **2a** was increased to 2 equivalents (entry 11). The reaction showed less efficient at both lower and higher temperatures (entries 12-13). The results were not improved by changing the catalyst loadings (entries 14-15). And the reaction was totally supressed in the absence of catalyst (entry 16).

Table 1. Optimization of the Reaction Conditions[a]



Entry	Catalyst	Solvent	Yield (%)[b]
1	$Rh_2(OAc)_4$	DMF	41
2	$[RhCp^*Cl_2]_2$	DMF	0
3	$[IrCp^*Cl_2]_2$	DMF	0
4	$Pd(PPh_3)_2Cl_2$	DMF	0
5	CuI	DMF	0
6	$AgNTf_2$	DMF	0
7	$Rh_2(OAc)_4$	EtOH	0
8	$Rh_2(OAc)_4$	toluene	0
9	$Rh_2(OAc)_4$	dioxane	0
10	$Rh_2(OAc)_4$	DMSO	0
11[c]	$Rh_2(OAc)_4$	DMF	75
12[c, d]	$Rh_2(OAc)_4$	DMF	64
13[c, e]	$Rh_2(OAc)_4$	DMF	73
14[c, f]	$Rh_2(OAc)_4$	DMF	51
15[c, g]	$Rh_2(OAc)_4$	DMF	75
16[c]		DMF	0

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.1 mmol), 1 mL of solvent, 110 °C, air.

[b] Isolated yields.

[c] **1a**/**2a**=0.1 mmol/0.2 mmol.

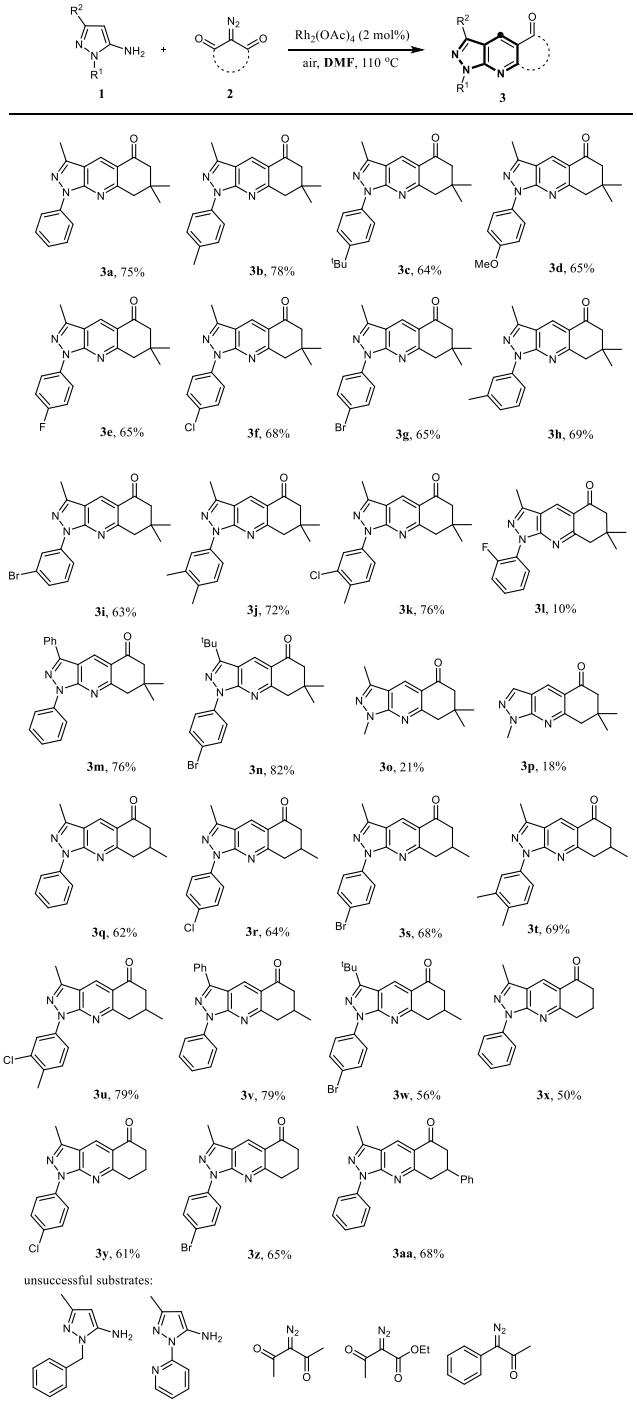
[d] 100 °C.

[e] 120 °C.

[f] 1 mol% of catalyst.

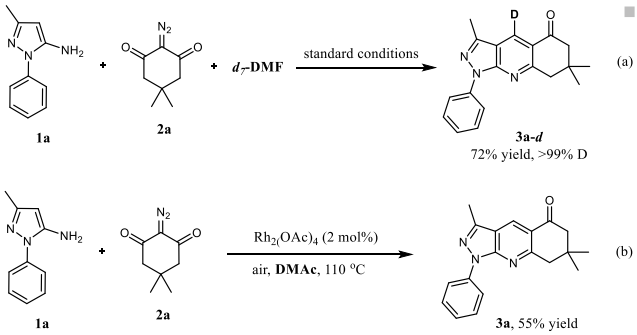
[g] 3 mol% of catalyst.

With the optimized conditions in hand, the substrate scope of 1-phenyl-1*H*-pyrazol-5-amine derivatives was investigated first with 2-diazo-5,5-dimethylcyclohexane-1,3-dione (**2a**) as the reaction partner (Scheme 2). Substituents such as Me, ^{t}Bu, OMe, F, Cl and Br on the aromatic rings were well tolerated under the optimal conditions, generating the corresponding products in moderate to good yields (**3b**-**3g**).



Scheme 2. Substrate Scope. Reaction conditions: **1** (0.1 mmol), **2** (0.2 mmol), $Rh_2(OAc)_4$ (0.002 mmol, 2 mol%), 1 mL of DMF, 110 °C, air. Isolated yields.

Halogens such as bromide, which are convenient for further transformations, were tolerated, and the reactions proceeded smoothly. Meta-substituted and disubstituted phenyl products were obtained in good yields as well (**3h**-**3k**). However, ortho-substituted phenyl product **3l** was generated with much lower efficiency, indicating the hindrance sensitivity of the reaction. Substituents on the pyrazole ring were then investigated. 3-Phenylated and alkylated products were generated in 76% and 82% yields, respectively (**3m**-**3n**). Changing the *N*-substitution of pyrazole to methyl group could generate the corresponding product in relatively lower yields (**3o**-**3p**).



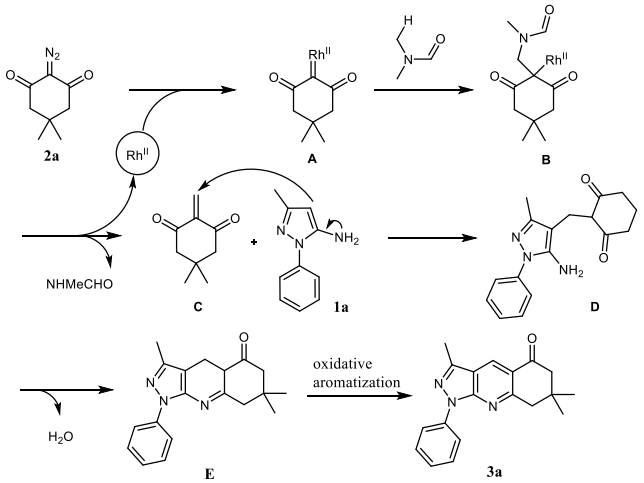
Scheme 3. Mechanistic Studies

Next, the scope of diazo substrates **2** was evaluated under the standard conditions. When methyl, phenyl, and unsubstituted cyclic diazo compounds were used as reactants, products **3q**-**3aa** were generated in moderate to good yields (Scheme 2). Unfortunately, acyclic 1,3-diketone-2-diazo compounds were not tolerated under the reaction conditions.

To elucidate the formation of the unexpected pyrazolo[3,4-*b*]pyridines, a deuteration study, shown in Scheme 3a, was performed. When DMF-d_7 was applied as the solvent, one hundred percent of product **3b** was deuterated at the para position of the pyridine ring, indicating that the para carbon of the pyridine came from *N,N*-dimethylformamide. The possibility that the labelled carbon of **3a** came from the carbonyl group of DMF could be ruled out by the experiment in which the solvent was changed from DMF to its analogue DMAc (*N,N*-dimethylacetamide) as the product could only be obtained in 55% yield (Scheme 3b).

Based on these experimental results and previous literature reports, a plausible mechanism was proposed, as shown in Scheme 4. It is believed that the reaction was initiated by the coordination of diazo compound **2a** to the Rh^{II} centre, generating rhodium-carbene species **A**. Insertion of rhodium carbenoid **A** into a methyl C-H bond of DMF generated intermediate **B**. A beta-nitrogen elimination reaction

delivered compound **C**, which was detected by GC-MS. Rhodium^{II} was released to complete the catalytic cycle. 3-Methyl-1-phenyl-1*H*-pyrazol-5-amine (**1a**) underwent a subsequent Friedel-Crafts-type nucleophilic addition to **C** to generate **D**, which then underwent an intramolecular condensation to give **E**. The title product (**3a**) was obtained by an oxidation pathway driven by aromatization.



Scheme 4. Proposed Mechanism.

In conclusion, we have developed a novel and practical method for the synthesis of fused pyrazolo[3,4-*b*]pyridine derivatives *via* an unexpected rhodium-catalysed cyclization of pyrazol-5-amines and 1,3-diketone-2-diazo compounds. A formal [3+2+1] cyclization reaction employing a methyl carbon of DMF as the source of a CH fragment in the formation of the pyridine ring was realized under mild conditions. Dioxygen in air acted as the terminal oxidant in this transformation. A broad range of fused *N*-heterocycles with challenging substitution patterns were obtained.

Experimental Section

General procedure for the synthesis of the Pyrazolo[3,4-*b*]pyridines 3

A mixture of 5-amino pyrazole **1** (0.1 mmol), cyclic 2-diazo-1,3-diketone **2** (0.2 mmol) and $Rh_2(OAc)_4$ (0.002 mmol) in DMF (1 mL) was heated to 110 °C in an oil bath. After the reaction was complete (as determined using TLC), the reaction mixture was cooled to room temperature and quenched with H_2O, and the mixture was then extracted with ethyl acetate (3 × 10 mL). The organic layers were combined and dried over Na_2SO_4. After removal of the solvent under vacuum, the residue was purified using flash column chromatography (ethyl acetate : petroleum ether = 1:10, v/v) to give desired product

Acknowledgements

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[15] CCDC 1883749 (**3a**) contains the supplementary csystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.carn.ac.uk/data_request/cif.

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