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Rapid Access to Pyrazolo[3,4-*c*]pyridines via Alkyne Annulation: Limitations of Steric Control in Nickel-Catalyzed Alkyne Insertions

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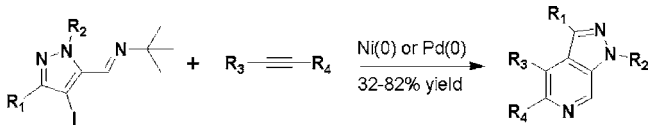
ABSTRACT



Polyfunctionalized pyrazolo[3,4-*c*]pyridines were readily prepared by the annulation of alkynes with *tert*-butyl 4-iodopyrazolocarboximines. The reaction was found to be catalyzed by both $NiBr_2(PPh_3)_2$/Zn or $PdCl_2(PhCN)_2$ to yield complex heterocycles in good to moderate yields. Annulation using nickel catalysis was found to be regio-random, implying that steric control in nickel-catalyzed alkyne insertion has limitations based on the character of the Ni–C bond in the pre-insertion complex.

Indoles are pervasive in the medicinal chemistry literature,[1] and some would argue that they constitute a "privileged structure".[2] However, while indoles can be made more polar and less prone to metabolic degradation by replacement with an indazole or a pyrrolopyridine, these ring systems have few ready replacements and also come with their own metabolic and synthetic limitations.

Pyrazolopyridines have found use as indole[3,4] and indazole[5] analogues — offering lower log *P* and enhanced water solubility (Figure 1) — but have not found widespread use due to a paucity of synthetic methods amenable to SAR work.

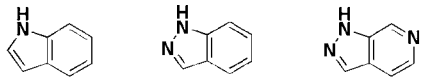


Figure 1. Log *P* of indole, indazole, and pyrazolo[3,4-*c*]pyridine: effect of additional nitrogens.[9]

Generally, the Huisgen indazole synthesis is applied to functionalized pyridines to yield pyrazolopyridines.[6] However, each functionalized pyridine must be prepared through multistep sequences. With this in mind, we set out to develop a versatile and efficient approach to the pyrazolopyridine scaffold in an effort to facilitate their use in drug development programs.

Larock has reported the synthesis of isoquinolines via an annulation process involving carbopalladation of alkynes.[7] This reaction allows for C−N bond formation as a terminal step by reductive elimination of a *tert*-butyliminium salt.[8]

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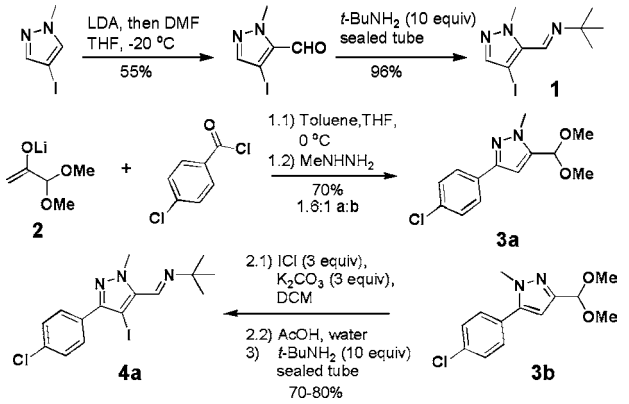
In light of this precedent, we considered the possibility that a functionalized pyrazole could be used as the parent ring in annulation, representing a synthon for more complex heterocycles.

Iodopyrazole **1** was prepared by regioselective lithiation of 4-iodo-1-methyl-(1*H*)-pyrazole followed by formylation with DMF (Scheme 1, top). The resulting aldehyde was condensed with *tert*-butylamine to yield **1**.[10]

Scheme 1. Synthesis of Pyrazolecarboximines **1**, **4a**, and **4b**

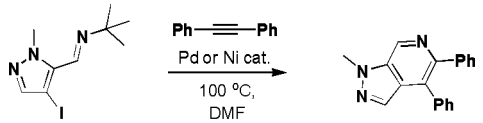


Substituted iodopyrazoles **4a** and **4b** were prepared according to Scheme 1 (bottom). Acylation of **2** with 4-chlorobenzoyl chloride followed by in situ condensation with methylhydrazine utilizing our previously described pyrazole synthesis[11] afforded the substituted pyrazole **3** as a regiomeric mixture that was separated by column chromatography. The pyrazole was iodinated with ICl and the acetal hydrolyzed to afford the pyrazolecarboxaldehyde in 70−80% yield over two steps. Without further purification, the aldehyde was condensed with *tert*-butylamine to give **4** in nearly quantitative yield.

With the desired pyrazole synthon in hand, we turned to the metal-catalyzed annulation of internal alkynes. We began our investigation with the traditional palladium-catalyzed annulation conditions reported by Larock but found that the transformation was sluggish and low-yielding (entries 1 and 2, Table 1). Varying the phosphine/palladium ratio from 2:1 to 1:1 had little effect. However, the use of tributylamine as the base significantly improved the efficiency of the reaction, potentially due to base solubility. When phosphine ligands were excluded, the yield of **5** from the annulation reaction increased to an acceptable 68% (entry 4, Table 1). In similar fashion, **16** and **17** could be prepared in 65 and 41% yields, respectively. However, **16** was obtained as a 1:1 mixture of regioisomers.

We then extended our catalyst screening beyond palladium since it has been reported that nickel[12] and cobalt[13] both

Table 1. Screening Annulation Conditions for the Synthesis of Pyrazolo[3,4-*c*]pyridines from Internal Alkynes[a]



1 5

entry	catalyst	ligand	base[b]/ additive	time (h)	yield (%)
1	$Pd(OAc)_2$	10% PPh_3	Na_2CO_3	20	33
2	$Pd(OAc)_2$	5% PPh_3	Na_2CO_3	16	26
3	$Pd(OAc)_2$	10% PPh_3	Bu_3N	10	55[b]
4	$PdCl_2(PhCN)_2$	–	Bu_3N	12	68[b]
5	$NiBr_2(PPh_3)_2$	–	Zn	2	82[c]
6	$NiBr_2$	5% dppe	Zn	3	65[c]

[a] Palladium-catalyzed reactions were run with 2 equiv of alkyne, and nickel catalysis was performed with 1.1 equiv of alkyne. [b] 1.1 equiv of base used. All reactions were performed with 5 mol % catalyst loading. [c] Reaction run at 80 °C in MeCN.

undergo similar transformations. Commercially available $NiBr_2(PPh_3)_2$ was found to produce **5** in 82% yield. The nickel-catalyzed transformation required the use of only 1.1 equiv of alkyne, whereas palladium required an excess, leading to the formation of several oligomeric side products.[14] We found that nickel catalysis also led to a small amount of these side products (vide infra). This side reaction became more significant as reaction time increased. Both palladium and nickel can efficiently catalyze this transformation, and it is advisable to empirically evaluate which metal is more appropriate for a given substrate since yields can be similar. We opted to study the nickel-catalyzed reaction further as reaction times were generally shorter.

In some cases, a large amount of deiodinated pyrazole was observed as a side product. We reasoned that reduction is a competitive process with insertion into the alkyne. In the case of sterically demanding TMS-functionalized alkynes or very sterically congested pre-insertion nickel complexes (Table 2, entries 12 and 13), reduction becomes a major outcome of the reaction. In these cases, the alkyne is oligomerized through metal catalysis; however, these products are only observed in small amounts when deiodination is suppressed. On the basis of these findings, we presume that oligomerization is substantially slower than addition to the pyrazole but becomes dominant when insertion is retarded (or impossible in the case of deiodination). In no case was the indenone arising from oxidative addition of the C−H bond and subsequent hydrolysis observed.[15]

Unsurprisingly, submission of very electron-poor alkynes such as diethyl acetylenedicarboxylate (entries 4 and 7) led to low yields of pyrazolo[3,4-*c*]pyridines as this class of alkynes is known to undergo rapid metal-catalyzed trimerization.[16] In these cases, nearly all iodoimine not converted to the pyrazolo[3,4-*c*]pyridine is deiodinated as judged by NMR analysis of the crude reaction mixture.

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Table 2. Scope of the Nickel-Catalyzed Annulation of Alkynes with 4-Iodopyrazolecarboximines

entry	pyrazole	alkyne	pyrazolo[3,4-*c*]pyridine[a]	time (h)	Yield (%)[b]
1	**1**	Ph—≡—Ph	**5**	2	82
2	**6**	Ph—≡—Ph	**7**	2	77
3	**1**	Ph—≡	**8a** 1.14:1 **8b**	3	75
4	**1**	EtOOC—≡—COOEt	**9**	4	38
5	**1**	Ph—≡—TMS	**10a** 1.9:1 **10b**	10	32
6	**1**	Ph—≡—COOEt	**11a** 9.8:1 **11b**	4	72
7	**1**	—≡—COOEt	**12**	5	35
8	**1**		**13**	3	50
9	**1**	Ph—≡—H	**14**	3	46
10	**1**	H—≡—	**15**	3	43
11	**4a**	Ph—≡	**16a** 0.92:1 **16b**	3	60
12	**4a**	Ph—≡—Ph	**17**	3	49
13	**4a**	Ph—≡—H	**18**	3	39
14	**4b**	Ph—≡—Ph	**19**	5	42[c]

[a] Isomeric ratios calculated from crude ^{1}H NMR, and structures were assigned by NOE NMR experimentation. [b] Isolated yields. [c] Reaction was performed at 0.025 M due to poor solubility of **4b**.

Annulation of unsymmetrical internal alkynes led to nearly 1:1 regiomeric mixtures, though the total yield of the reaction was generally acceptable. However, when ynoates were subjected to annulation, the reaction became highly regioselective, giving 4-carboxypyrazolopyridines such as **11a**.

Also of significance is the ability of dialkylalkynes to undergo the annulation reaction to give 4,5-dialkylpyrazolo[3,4-*c*]pyridines similar to **13** (Table 2, entry 8) as β-elimination is possible when these substrates are used in the presence of metal catalysts.[17] (2*H*)-Pyrazolo[3,4-*c*]pyridines such as **19** (Table 2, entry 14) can also be prepared by utilizing 3-imino-4-iodopyrazoles (Scheme 2). These compounds were previously hard to access due to the difficulty associated with functionalization at the 2- and 3-positions.

Encouraged by our results with internal alkynes, we decided to pursue the use of terminal alkynes in the nickel-

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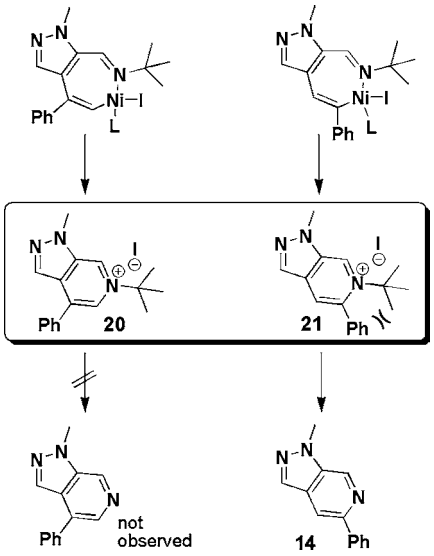
Scheme 2. Rationale for Observed Regioselectivity in the Annulation of **1** with Phenylacetylene



catalyzed pyrazolopyridine synthesis. Disappointingly, the yield of **14** was rather low, and we observed several side products, though no Sonogashira coupling product was isolated.[18]

LCMS analysis of the crude reaction mixture revealed a major peak corresponding to the *tert*-butyl pyrazolo[3,4-*c*]pyridinium salt. NMR of the crude mass confirmed this assignment.[19] Scheme 2 shows the two possible isomers formed from an annulation reaction. Both can form the *tert*-butyl pyrazolo[3,4-*c*]pyridinium salt, but the strain induced from the presence of a proximal phenyl group in **21** allows it to collapse to the pyrazolo[3,4-*c*]pyridine **14**, whereas **20** lacks this driving force and thus persists as a salt. A similar result and mechanistic explanation has been reported in the palladium catalyzed annulation-based preparation of carbolines.[20]

Though previous reports on the nickel-catalyzed annulation of terminal acetylenes with haloimines claim that the initial insertion step is regioselective,[12] the isolation of equal amounts of regioisomer from annulation reactions with 1-phenyl-1-propyne (Table 2, entries 3 and 11) along with the identification of **20**, a major side product in the annulation of phenylacetylene, implies that, in the context of heterocycles explored in this paper, regioselectivity of insertion breaks down.

To the best of our knowledge, the loss of regiochemical control during nickel-catalyzed alkyne insertion with aryl−alkyl alkynes has not been previously reported.[21] The regioselectivity of insertion into unsymmetrical alkynes is thought to be, with the exception of ynoates,[22] largely sterically controlled.[23] Later studies using DFT calculations supported this finding, also speculating that electron-rich systems may give different isomers due to a reversal of HOMO−LUMO interactions, but still be regioselective.[24]

In the present study, we have found experimental evidence supporting the concept that electronics can dictate the regiochemical outcome of nickel-catalyzed alkyne insertions. Comparison of annulations of 1-phenyl-1-propyne with **1** and **4a** strongly suggests that steric control is at least partially overcome in the reaction presented here. Since the isomeric ratios of entries 3 and 11 (Table 2) are nearly identical while the steric profile of the two parent systems vary dramatically, we believe that electronics dominate the selectivity. Specifically, the electron-rich parent ring is nucleophilic enough that steric preferences are overcome, and thus reorientation of the alkyne during the insertion event is not a significant factor in determining regioselectivity. While this may be deleterious for highly efficient annulations with electron-rich parent rings, these findings can help provide an understanding of the regioselective capacity of nickel catalysis.

Alternatively, competing mechanisms may exist that give rise to the observed regiochemical outcome, though at this time these mechanisms are not well understood. This possibility is suggested by the highly regioselective insertion of ynoates such as **11** and **12**. Cheng previously argued that a Michael-type attack on the activated alkyne by the proximal imine could explain the observed regiochemistry,[12] and this pathway may be preferred in the pyrazolic context as well. However, this mechanism is unlikely to occur with alkynes other than ynoates.

In summary, we have developed a nickel (or palladium)-catalyzed annulation of alkynes onto iodopyrazolecarboximines that allows for rapid access to polyfunctionalized pyrazolo[3,4-*c*]pyridines — a heterocycle that shows promise in medicinal chemistry. We also found that the regiochemistry of the reaction is influenced by the electronic nature of the carbon ligand arising from the iodide. Continued investigation into the mechanism of the nickel-catalyzed annulation, application to the pyrazolo[3,4-*d*]pyridine system, and further efficiency enhancement of the annulation will be presented in due course.

Acknowledgment. We thank Mark Holmes for NMR support.

Supporting Information Available: ^{1}H and ^{13}C NMR data and purification procedures for **1**−**19**, experimental details for catalysis reactions as well as the preparation of **1**, **4a**, **4b**, and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Assigned as **20** by comparison with the isolated *tert*-butylpyridinium bromide that was isolated by Larock; Zhang, H.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 5132.

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(21) For recent examples of highly regioselective nickel-catalyzed C−C bond forming transformations, see: (a) Intermolecular coupling of enones and alkynes: Herath, A.; Thompson, B. A.; Montgomery, J. *J. Am. Chem. Soc.* **2007**, *129*, 8712. (b) Allylcyanation of alkynes: Nakao, Y.; Yukawa, T.; Hirata, Y.; Oda, S.; Satoh, J.; Hiyama, T. *J. Am. Chem. Soc.* **2006**, *128*, 7116. (c) [3 + 2 + 2] Cocyclization of alkynes and cyclopropylidene acetate: Komagawa, S.; Saito, S. **2006**, *Angew. Chem., Int. Ed.* **2006**, *45*, 2446.

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