Pyridine Synthesis

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Metal-Free *meta*-Selective Alkyne Oxyarylation with Pyridine *N*-Oxides: Rapid Assembly of Metyrapone Analogues

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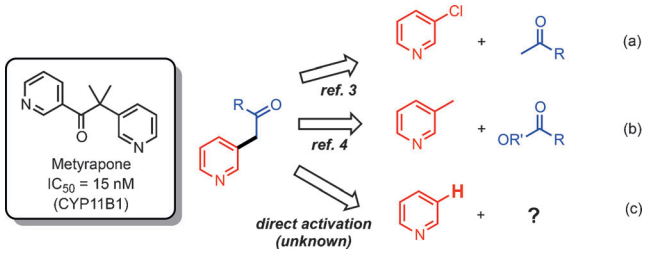
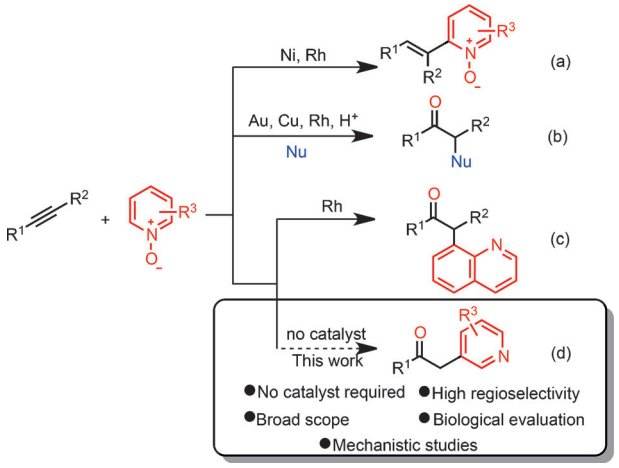
Abstract: *An efficient metal-free oxyarylation of electron-poor alkynes with pyridine N-oxides has been developed. This transformation affords meta-substituted pyridines analogous to the drug metyrapone in high regioselectivities. Density functional theory (DFT) calculations provided important insight into the mechanism. Evaluation of the inhibitory properties revealed the most active CYP11B1 inhibitor of these derivatives, with two-digit nanomolar inhibitory activity akin to that of metyrapone.*

Metyrapone and its analogues have attracted great attention in the treatment of Cushing's syndrome and in the diagnosis of adrenal insufficiency (Scheme 1). These compounds typically inhibit the 11β-hydroxylase CYP11B1.[1,2] Their synthesis, however, still remains largely underdeveloped. One typical approach relies on the catalytic monoarylation of methyl ketones with aryl chlorides (Scheme 1a).[3] Another strategy involves the acylation of 3-picoline with esters in the presence of a strong base (Scheme 1b).[4] Recently, the groups of Yu and Sanford developed elegant *meta*-C–H activation strategies to gain access to *meta*-substituted aryl compounds.[5] In spite of these promising precedents, we speculated whether the direct activation of the *meta* position of pyridine (or a derivative thereof) could be accomplished (Scheme 1c).



Scheme 1. Inhibition of 11β-hydroxylase by metyrapone (Ref. [2i]) and typical approaches to metyrapone and known analogues.

Pyridine *N*-oxides and derivatives[6] thereof have found wide applications in pharmaceutical[7] and organic chemistry[8] owing to their unique reactivity. In 2007, Hiyama and co-workers reported the nickel-catalyzed arylation of alkynes with pyridine *N*-oxides (Scheme 2a),[9] and in 2010, Zhang and co-workers published a pioneering method for the gold-catalyzed oxidation of alkynes with pyridine *N*-oxides. Since then, a series of catalytic alkyne difunctionalization reactions with pyridine *N*-oxides have been developed (Scheme 2b).[10] Despite this progress, pyridine *N*-oxides have been rarely employed as both oxygen source and aryl donor. Very recently, Li and co-workers successfully realized oxyarylation reactions of alkynes with quinoline *N*-oxides using a rhodium(III) catalyst (Scheme 2c).[11] Given our strong interest in the development of metal-free methods for oxyarylation reactions,[12] we herein report a metal-free oxyarylation of alkynes, where pyridine *N*-oxides enable the direct *meta*-regioselective preparation of metyrapone analogues (Scheme 2d).[13] We further report studies on the biological activity of the products and mechanistic studies.



Scheme 2. Reactions of pyridine *N*-oxides with alkynes.

Initially, the reaction of ethyl phenylpropynoate (**1a**) with lutidine *N*-oxide (**2a**) was investigated (Table 1). The desired oxyarylation product **3a** was obtained in 10% yield with 4% of the decarboalkoxylation product **4a** when the reaction mixture was stirred at 150°C (microwave irradiation) for 15 min (entry 1). Based on this preliminary result, we first investigated the impact of reaction time and found that the

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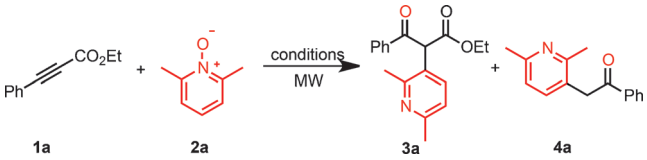
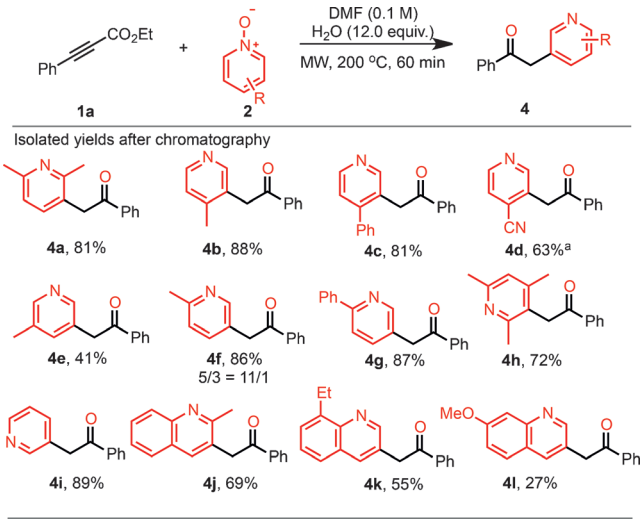
Table 1: Optimization of the reaction conditions.



1a 2a 3a 4a

Entry	Solvent	*T* [°C]	*t* [min]	Yield[a] [%] **3a**	**4a**
1	neat	150	15	10	4
2	neat	150	45	21	8
3	neat	150	120	45	19
4[b]	neat	150	60	ND	67
5[c]	neat	150	60	ND	77 (82)
6	DMF	150	60	3	20
7[d]	DMF	200	60	ND	83 (81)

[a] Determined by ^{1}H NMR analysis using mesitylene as an internal standard. Yields of isolated products given in parentheses. [b, c] After the indicated reaction time, DMF (2.0 mL) and H_2O (12 equiv) were added; then the mixture was stirred for 20 min at [b] 150 °C (MW) or [c] 200 °C (MW). [d] H_2O (12 equiv) added. ND = not detected.

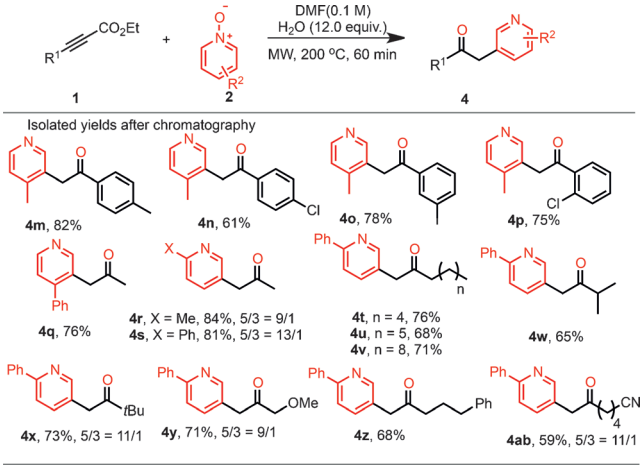


Scheme 3. Scope of pyridine *N*-oxides in the metal-free oxyarylation of alkynes. All reactions were carried out on 0.2 mmol scale. [a] The reaction was stirred at 150 °C for 1 h, then H_2O (12 equiv) was added, and the mixture was stirred in DMF at 200 °C (MW) for 20 min.

yields of the oxyarylation and decarboalkoxylation products could be improved by extending the reaction time (entries 1–3). We next turned our attention to enhancing the production of decarboalkoxylation product **4a**. The yield of **4a** indeed improved to 77 % upon increasing the temperature to 200 °C (entries 4 and 5). It should be noted that low yields were obtained in dry DMF (entry 6), and we therefore reasoned that traces of water play an important role in the decarboalkoxylation event. As expected, using wet DMF and raising the temperature to 200 °C led to a substantial increase in the decarboalkoxylation yield of **4a** (entry 7).[14]

With optimized reaction conditions in hand, the scope of the reaction was briefly investigated with respect to various pyridine *N*-oxides (Scheme 3). Pyridine *N*-oxides with electron-withdrawing or electron-donating substituents (4-Me, 4-Ph, and 4-CN) all reacted well and gave the desired products **4b**–**4d** in good yields. For **4d**, a lower temperature was beneficial for enhancing the product yield. Reactions of *ortho*-substituted nucleophiles also proceeded well, with lower yields observed with *meta* substitution (**4e**–**4g**). For nucleophiles with two non-equivalent *meta* positions, high selectivity for the less hindered position was observed (**4f**, 11:1 ratio). Notably, the reaction of a challenging 2,4,6-substituted substrate was also successful (**4h**). Several differently substituted quinoline *N*-oxides were also tested in the reaction, affording the desired products **4j**–**4l** in moderate yields.[15]

The scope of the reaction with respect to the alkyne coupling partner was also examined (Scheme 4). Aromatic alkynes with electron-withdrawing or electron-donating substituents (4-MeC_6H_4 and 4-ClC_6H_4) were well tolerated (**4m** and **4n**). Furthermore, *meta*- (3-MeC_6H_4) or *ortho*-substituted (2-ClC_6H_4) arene rings had no negative effect on the reaction (**4o** and **4p**). Aliphatic alkynes were also found to be suitable substrates, giving the desired products (**4q**–**4v**) in good yields. Both isopropyl- and *tert*-butyl-substituted alkynes reacted smoothly with pyridine *N*-oxide to afford the corresponding

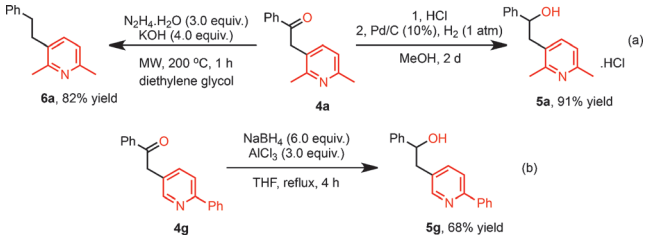


Scheme 4. Alkyne scope of the oxyarylation reaction. All reactions were carried out on 0.2 mmol scale.

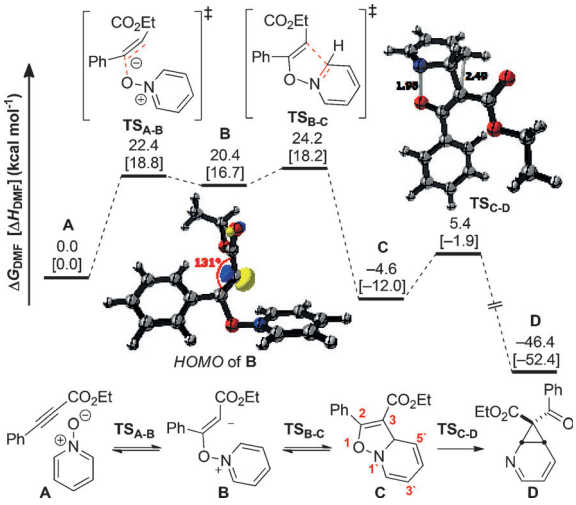
oxyarylation products in 65 % and 73 % yield with high regioselectivities (**4w** and **4x**). The method also tolerated a variety of functional groups, such as ethers, arenes, and nitriles (**4y**–**4ab**), and these reactions could also be conducted on gram scale (see the Supporting Information for details).

The products lend themselves to simple modifications (Scheme 5). For instance, alcohols **5a**/**5g** were easily obtained in good to very good yields by either hydrogenation or $NaBH_4$ reduction. Wolff–Kishner reduction is also possible (**6a**).

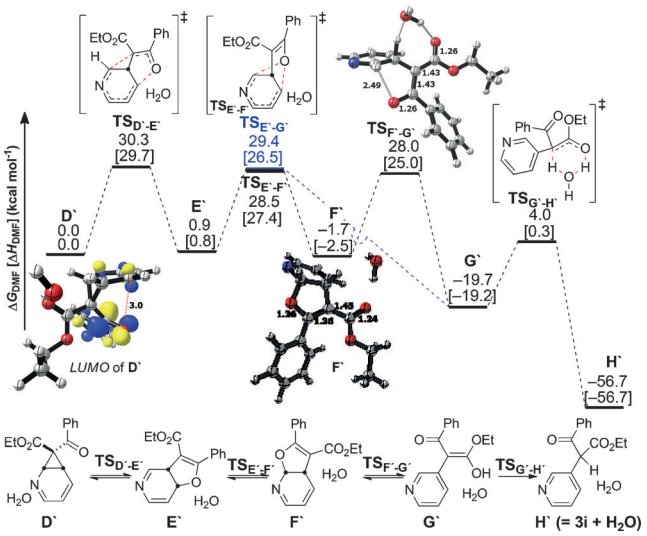
To gain insight into the factors determining the selectivity of this process, we conducted computational studies.[16] The parent substrate pyridine *N*-oxide (**2i**) and phenylacetylene (**1a**) were used as model substrates. As shown in Scheme 6, the formation of key cyclopropane **D** involves the generation of the formal (3+2) cycloadduct **C** and a subsequent pseudopericyclic reaction.[17] The initial process **A** → **D** is both highly feasible ($\Delta G^{\ddagger}_{max} = 22.4$ kcal mol^{-1}) and favorable ($\Delta G =$



Scheme 5. Derivatization of the oxyarylation products.



Scheme 6. Energy profile for the formation of key cyclopropane **D** through a [3,5] rearrangement of the formal (3+2) cycloaddition product **C**. The free enthalpies ΔG_{DMF} and enthalpies ΔH_{DMF} are given with respect to association complex **A**. Distances are given in Å.



Scheme 7. Energy profile for the generation of transient β-ketoester **3i** (see **H′**) in the presence of water. Free enthalpies ΔG_{DMF} and enthalpies ΔH_{DMF} are given with respect to association complex **D′** (= **D** + H_2O). Distances are given in Å.

−46.4 kcal mol^{-1}) under the reaction conditions, with the final step being irreversible (**C**→**D**). Interestingly, the (3+2) cycloaddition event proceeds via discrete vinyl anion **B**,[18] with the final concerted [3,5] rearrangement ($\mathbf{TS_{C\text{-}D}}$) being symmetry-allowed owing to the participation of the orthogonal oxygen lone pair.

The reaction pathway from **D** to β-ketoester **3i** is depicted in Scheme 7. The oxyarylation process was found to proceed more efficiently in the presence of both water and DMF (see Table 1), strongly suggesting that water may (re)actively participate in the reaction pathway leading to transient β-ketoester **3**. In accordance with this observation, we evaluated mechanistic scenarios in the absence and presence of explicit solvent molecules. Our computational data indeed suggest that water facilitates the formation of β-ketoester **3i** by acting as a proton shuttle (see $\mathbf{TS_{F'\text{-}G'}}$/$\mathbf{TS_{E'\text{-}G'}}$, Scheme 7).[19] Furthermore, the anticipated[14] direct cyclopropane opening/rearomatization sequence was found to be kinetically disfavored by $\Delta\Delta G = 4.9$ kcal mol^{-1} over yet another pseudopericyclic [3,5] rearrangement, which leads to dihydrofuran **E′** in the presence of water (Scheme 7). The preference of cyclopropane **D′** to undergo a [3,5] rearrangement ($\mathbf{TS_{D'\text{-}E'}}$) can also be deduced from an analysis of its LUMO.[20] This step ($\mathbf{TS_{D'\text{-}E'}}$) is rate-determining ($\Delta G^{\ddagger} = 30.3$ kcal mol^{-1}).

Once formed, dihydrofuran **E′** can undergo a water-mediated proton transfer/rearomatization sequence ($\mathbf{TS_{E'\text{-}G'}}$) affording ketene acetal **G′**, which is followed by exergonic water-assisted tautomerization ($\mathbf{TS_{G'\text{-}H'}}$) to generate ketoester **H′** (= **3i** and H_2O). Alternatively, an initial [1,5] sigmatropic rearrangement of dihydrofuran **E′** ($\mathbf{TS_{E'\text{-}F'}}$) followed by water-mediated proton transfer/rearomatization ($\mathbf{TS_{F'\text{-}G'}}$) also leads to **G′**. In light of the small energy difference between the two processes ($\mathbf{TS_{E'\text{-}G'}}$ vs. $\mathbf{TS_{E'\text{-}F'}}$: $\Delta\Delta G^{\ddagger} < 1.0$ kcal mol^{-1}), both pathways should be operative. Finally, hydrolysis and subsequent decarboxylation of β-ketoester **3i** give rise to ketone **4i**.[21]

Selected compounds were tested for inhibition of the human 11β-hydroxylase CYP11B1 and its isozyme CYP11B2 (aldosterone synthase, 93% sequence homology). Four compounds, namely **4b**, **4e**, **4n**, and **4o**, showed strong inhibition of both enzymes, with **4o** also displaying two-digit nanomolar inhibitory activity like metyrapone (Table 2).

Clearly, small electron-donating groups in the *meta* and *para* position to the heme-binding pyridyl nitrogen atom are important structural requirements for inhibition. Bulky moieties or substituents *ortho* to the pyridyl nitrogen atom lead to less active or inactive compounds. These compounds are good starting points for structural optimization to enhance CYP11B1 inhibition and the selectivity towards CYP11B2, in particular, as this enzyme must not be inhibited with similar potency to avoid side effects in the treatment of Cushing's syndrome.

In summary, we have developed a metal-free oxyarylation of alkynes with pyridine *N*-oxides, providing the corresponding *meta*-substituted pyridines in moderate to good yields with high regioselectivities. Metyrapone analogues were thus readily synthesized. Furthermore, computational studies have revealed that the oxyarylation proceeds through an unexpected elaborate rearrangement cascade involving rather unusual [3,5] pseudopericyclic reactions. The process developed herein resulted in a series of hit compounds as good

Table 2: Inhibition of the CYP11B isoenzymes 1 and 2 by selected compounds.

Compound	CYP11B1[b] % inhibition[a]	IC_{50} [nM]	CYP11B2[b] % inhibition[a]	IC_{50} [nM]
4b	100	120	100	85
4c	10	–	22	–
4d	11	–	14	–
4e	100	200	100	350
4f	0	–	12	–
4l	34	–	42	–
4n	100	110	100	12
4o	100	70	100	50
4v	6	–	21	–
5g	1	–	11	–
metyrapone	100	15	100	75

[a] At 10 μM. [b] From hamster fibroblasts expressing human CYP11B1 or CYP11B2; substrates for both enzymes: deoxycorticosterone (100 nM), mean values of at least two experiments, SD < 20% (for experimental details, see Ref. [2h]).

starting points for further optimization by common medicinal chemistry strategies.

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Keywords: 11β-hydroxylase (CYP11B1) · alkynes · density functional calculations · oxyarylations · pyridine *N*-oxides

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[20] The LUMO of cyclopropane **D′** features an orbital overlap between the carbonyl oxygen atom and the C4 carbon atom.

[21] The decarboxylation is delineated in the Supporting Information. The described transition state is in agreement with previous findings for β-keto acids; see: R. D. Bach, C. Canepa, *J. Org. Chem.* **1996**, *61*, 6346.

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Communications

Pyridine Synthesis

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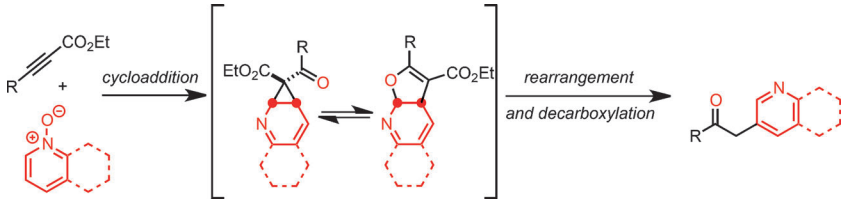
Metal-Free *meta*-Selective Alkyne Oxyarylation with Pyridine *N*-Oxides: Rapid Assembly of Metyrapone Analogues



New leads: The title reaction affords *meta*-substituted pyridines analogous to the drug metyrapone with high regioselectivities. DFT calculations revealed an elaborate rearrangement cascade involving unusual [3,5] pseudopericyclic reactions. Biological studies indicate that some of these products are active CYP11B1 inhibitors.