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"Pd-catalyzed selective C(sp^3)-H acetoxylation of quinazolinones"

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ABSTRACT

An efficient Pd-catalyzed selective C (sp^3)-H acetoxylation of 8-methylquinazolinones was reported. Due to the versatility of organic acetates, the route provides facile access to various C8-acetoxylated quinazolinones. The approach is significant because of its features like mild reaction conditions, decent tolerance of functional groups, and wide substrate scope. The monoselective acetoxylation established here may find significant claims in the area of C–H activation.

1. Introduction

One of the significant classes of heterocyclic compounds that are frequently found in many natural products and medicinal molecules is the quinazolinone family [1]. Due to its wide range of biological and therapeutic properties, such as anticancer, antimalarial, antidiabetic, antihypertensive, anticonvulsant, anti-inflammatory, anti-tussive, diuretic, and hypnotic effects, synthetic quinazolinone has caught the attention of organic and medicinal chemists. Numerous alkaloids also have quinazoline motifs. The β/γ hydroxy functional group is present in many of these alkaloids, including vasicine, balaglitazone, and (−) serantrypinone [2]. (Fig. 1).

By using an oxidative metal-catalyzed and directed C–H activation method, it may be possible to produce quinazolinones that contain such hydroxy functional groups. Similar to this, the C–H bond activation methods not only avoid the pre-functionalizing of starting materials but also assists in minimizing the number of steps. It can be difficult to activate C–H bonds with such regioselectivity since organic compounds contain a variety of C–H bonds. Utilizing a directing group, which can chelate with a metal catalyst to bring it close to a certain C–H bond is one of the finest approaches to deal with the problem of regioselectivity [3]. Due to its simplicity, C (sp^2)-H bond functionalization is the main focus of the major reports in the field of C–H activation. Due to the-stabilizing interaction with a metal catalyst to produce a strong olefin/aryl metal bond, C (sp^2)-H bonds like arene/olefin are easy to activate. In contrast to arenes/olefins, which have access to such stabilizing interactions with metal centres, C (sp^3)-H bond activation is still difficult and underdeveloped [2]. However, there have been some notable advancements in the area of C (sp^3)-H bond activation, where several directing groups, including mono- and bidentate groups, have been subjected to the C (sp^3)-H bond functionalization [2,4]. For C (sp^3)-H bond functionalization, a variety of metal catalysts have been utilized, including Pd, Rh, Ir, Ru, Co, Cu, and Fe. Arylation, alkylation, alkynylation, alkoxylation, acetoxylation, amination, hydroxylation, halogenation and olefination are some of the functionalization's, that were used for C (sp^3)-H functionalization by transition-metal catalysis [5,6]. Although the quinazolinone scaffolds have been involved in metal-catalyzed C (sp^2)-H activation approaches, specially, Sanford et al. , Daugulis and Shabashov , Yu et al. , and other groups have independently developed elegant C (sp^3)-H arylation and other C–C ,

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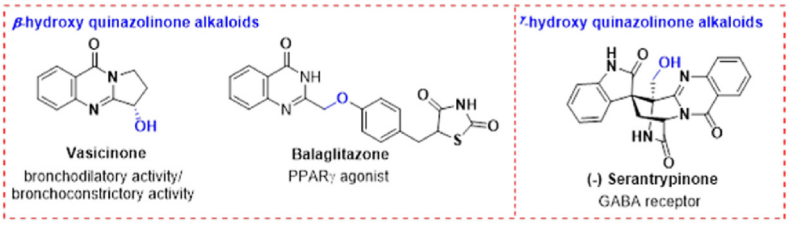
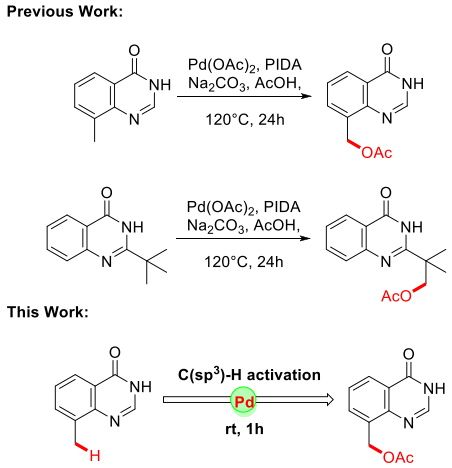


Fig. 1. Selected quinazolinone alkaloids containing β or γ-hydroxy functional group.



Scheme 1. Comparison between previous and this study.

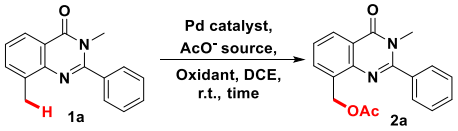
C–N , C–O , or C–Si bond formations of 8-Methylquinoline 7. To the best of our knowledge, Mhaske et al. reported a single protocol for C (sp^3)-acetoxylation of quinazolinone directed by a quinazolinone scaffold [8]. We predicted that the quinazolinone scaffold might be used as an intrinsic directing group for the C (sp^3)H acetoxylation as a continuation to our earlier work on the development of new methodologies [8] and literature reports. Almost all the previous report suffers from prolonged heating at higher temperatures [7,9] in this context, herein we report quinazolinone-directed diverse C (sp^3)-acetoxylation's, in presence of an oxidant and Pd catalyst, at ambient temperature (Scheme 1).

2. Results and discussion

We began optimization of the envisioned protocol carried on substrate **1a** (Table 1). We initially attempted the commonly used reaction conditions for C (sp^3)-acetoxylation by using $Pd(OAc)_2$ catalyst and phenyl iodonium diacetate (PIDA) in acetic acid at 60 °C, unfortunately, we did not observe the expected product **2a** formation (entry 1). Adding 2.0 equivalent of oxidant $K_2S_2O_8$ in the reaction yielded desired product in trace (entry 2).

But this result encouraged us to further optimize the reaction condition. When we changed the catalyst to Pd $(dba)_3$ without oxidant we did not observe any conversion. But on adding an oxidant to the reaction, we observed product **2a** in 80% yield. (Entries 3 & 4). Further changing the oxidant to $Na_2S_2O_8$, $(NH_3)_2S_2O_8$ and $Cu(OAc)_2$ did not improve the product yield (entries 5, 6 & 7). To our delight, we used acetic acid and acetic anhydride as a source of acetate anion but this change resulted in no product formation (entries 8 & 9). These results indicated that the PIDA is essential for the reaction to obtain product **2a**. It is interesting that when the reaction is performed at room temperature surprising increase in the yield of the product is observed (entry

Table 1
Optimization Studies[a].

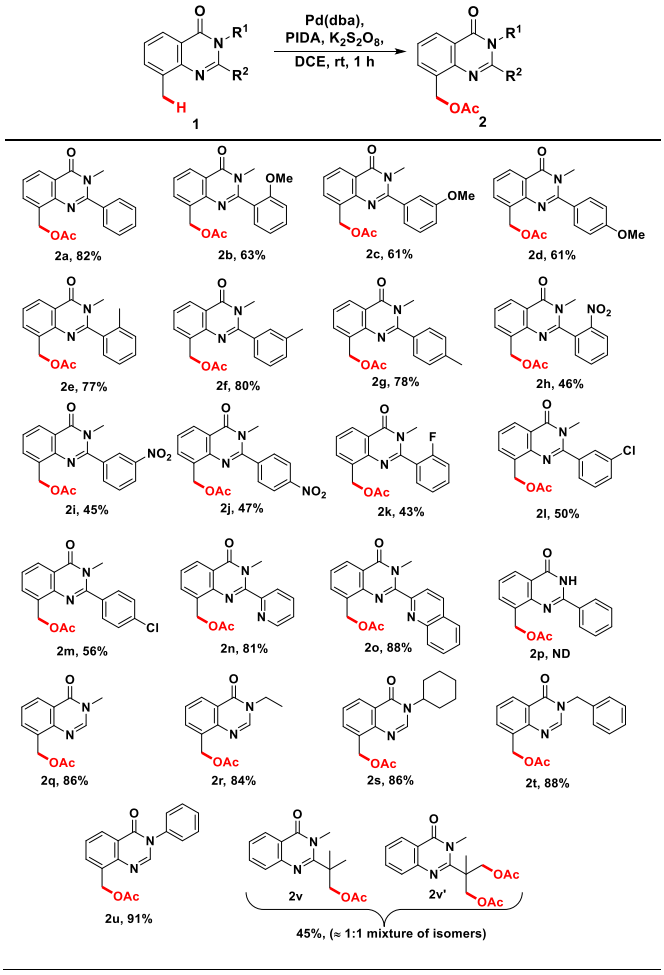


Entry	Catalyst (10 mol %)	$[AcO]^-$ Source	Oxidant	% Yield[b]
1	$Pd(OAc)_2$	$PhI(OAc)_2$	–	32
2	$Pd(OAc)_2$	$PhI(OAc)_2$	$K_2S_2O_8$	55
3	Pd_2 $(dba)_3$	$PhI(OAc)_2$	–	trace
4	Pd_2 $(dba)_3$	$PhI(OAc)_2$	$K_2S_2O_8$	80
5	Pd_2 $(dba)_3$	$PhI(OAc)_2$	$Na_2S_2O_8$	36
6	Pd_2 $(dba)_3$	$PhI(OAc)_2$	$(NH_3)_2S_2O_8$	41
7	Pd_2 $(dba)_3$	$PhI(OAc)_2$	$Cu(OAc)_2$	53
8	Pd_2 $(dba)_3$	AcOH	$K_2S_2O_8$	NR
9	Pd_2 $(dba)_3$	$(AcO)_2O$	$K_2S_2O_8$	NR
10[c]	**$Pd_2(dba)_3$**	**$PhI(OAc)_2$**	**$K_2S_2O_8$**	**82**
10[d]	Pd_2 $(dba)_3$	$PhI(OAc)_2$	$K_2S_2O_8$	59
11[e]	Pd_2 $(dba)_3$	$PhI(OAc)_2$	$K_2S_2O_8$	NR
12[f]	Pd_2 $(dba)_3$	$PhI(OAc)_2$	$K_2S_2O_8$	27
12	–	AcOH	$PhI(OAc)_2$	11
13	–	$(AcO)_2O$	$PhI(OAc)_2$	17

[a] **Reaction conditions:** 1a (0.5 mmol), Catalyst (10 mol %), OAc- Source (0.5 mmol), Oxidant (1.0 mmol), Solvent = DCE (5.0 mL) at room temperature for 1 h.
[b] Isolated yields.
[c] Solvent = 1,4-dioxane.
[d] Solvent = THF.
[e] Solvent = Toluene.
[f] Solvent = $CHCl_3$.

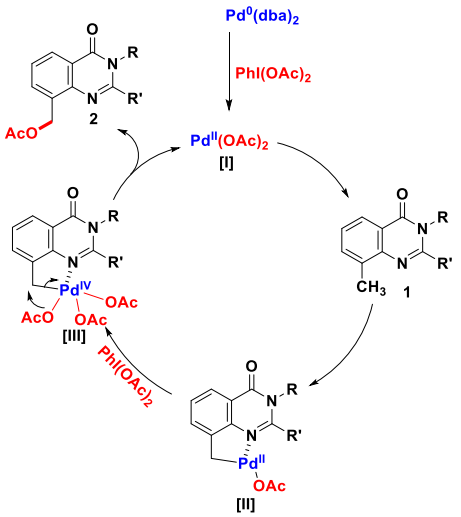
10). In the next optimization studies, the solvent was changed but further improvement in the yields of product **2a** was not seen (entries 11,12) For our delight when the reaction is performed without Pd-catalyst reaction did not move forward or gave yields <20% (entry 13 and 14).

After getting the optimized reaction conditions in hand we next identified the substrate scope of the reaction concerning the variation in the substituent and their positions on quinazolinones (Scheme 2). In the beginning, N–Me substituted quinazolinone ring was used and the effect of variation at the second position of the quinazolinone ring was studied. As mentioned in Scheme 2, phenyl ring substituent at the second position of quinazolinone provided product **2a** in very good yield, whereas ortho, meta, and *para*-OMe substituted benzene at the second position provided moderate yields of the product (**2b-2d**). This might be attributed to the interference of lone pair of electrons on -OMe group in the metal coordination. Substitution of benzene at the second position of quinazolinone ring with -Me group yielded in product with very good yields (**2e-2g**). When the benzene ring is substituted with electron-withdrawing groups like nitro and halo substitution provided moderate yields of the expected acylated product (**2h to 2m**). Thus, it might be drawn that (C-sp^3)-acetoxylation of



Scheme 2. Palladium-Catalyzed Benzylic Acetoxylation of Various Quinazolinones.

quinazolinone rings with electron-withdrawing substitution on the benzene ring at the second position might reduce the yields of acetoxylation products in the moderate yield range. Pleasingly, heterocyclic substituents at the second position of the quinazolinones produced expected products **2n** and **2o** in very good yields. Probably the heteroatoms of these heterocyclic substituents coordinate with the metal catalyst more effectively, and substrates behave like a bidentate directing group hence increase in the yields of the product was seen. For our curiosity when the N–H-free quinazolinone, was subjected to acetoxylation under the developed protocol, it ended up in the complex reaction mixture, and no expected product formation **2p** was observed. Furthermore, the scope of the reaction concerning N-substituent variation without substitution at the second position was studied. When N–Me substituted quinazolinones without substitution at the second position was subjected under the developed conditions the respective expected product **2q** was observed in a very good yield of 86%. Use of aliphatic substitution was used instead of -Me group on –N of quinazolinone the expected product was detected in very good yields (**2r**). N-cyclohexyl substituted derivative also provides a very good yield of product (**2s**). Interestingly, N-benzyl and N-Phenyl substituted derivatives without substitution at the second position of quinazolinone yielded the respective product in very good to excellent yields (**2t** and **2u**). Surprisingly, when substituent with ^{t}-butyl-substitution at the second position of quinazolinone was subjected under the developed protocol, the expected mono



Scheme 3. A plausible mechanism of the reaction.

acylated product was formed in a trace amount (22%) along with the formation of other di-C (sp^3)-acetoxylation (**2v** and **2v'** in 23% yield). In this reaction, tri-acylated product formation was not observed.

3. A plausible mechanism of the reaction

A plausible mechanism for the developed protocol is depicted in Scheme 3. According to the reported literature analogy [9], we trust that in the first step Pd2 $(dba)_3$ gets oxidized by $PhI(OAc)_2$ to generate a Pd(II) species **I**, which undergoes quinazolinone-directed palladation to generate cyclopalladated complex **II**. Note that Pd(II) compound $Pd(OAc)_2$ in Table 1, (entries 1 and 2) provided lower yields of product, which may be probably due to in situ generated fresh Pd(II) species possessing higher catalytic activity. The oxidative addition of cyclopalladated complex **II** with IOAc, which can be generated during the first step of the mechanism and $PhI(OAc)_2$ [10–13], gives rise to Pd(IV) species **III** which yields the acetoxylation product **2** and then Pd(II) catalyst regeneration by a subsequent reductive elimination.

4. Conclusion

A palladium-catalyzed regioselective C (sp^3)-H acetoxylation of N-protected 8-methylquinazolinones has been developed. The developed protocol features mild reaction conditions, decent tolerance of functional groups, and wide substrate scope. Thus, monoselective acetoxylation established here may find significant claims in the area of C–H activation. Application of the proctored methodology in the synthesis of bioactive natural products and their congeners is ongoing in our laboratory.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2023.133405.

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