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Metal-Free C-2-H Alkylation of Quinazolin-4-ones with Alkanes via Cross-Dehydrogenative Coupling

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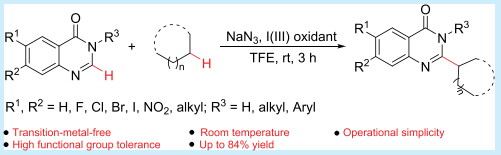
Supporting Information

ABSTRACT: A practically useful approach for the cross-dehydrogenative coupling of quinazolin-4-one with simple nonactivated alkanes is reported. The products were smoothly formed under mild reaction conditions, within short reaction time at ambient temperature. The formation of new Csp^3-Csp^2 bonds occurred at the electron-poor C-2 position of quinazolin-4-one. The approach has the potential to be an important tool for the late-stage functionalization of advanced synthetic intermediates and may find many applications in medicinal chemistry.



As a significant subclass of quinazoline derivatives, 2-alkylquinazolin-4-ones are widely found in bioactive natural products, synthetic drugs, pharmaceuticals, and agrochemicals (Figure 1).[1] Traditional strategies to synthesize the

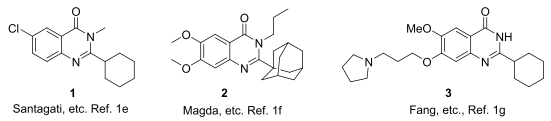
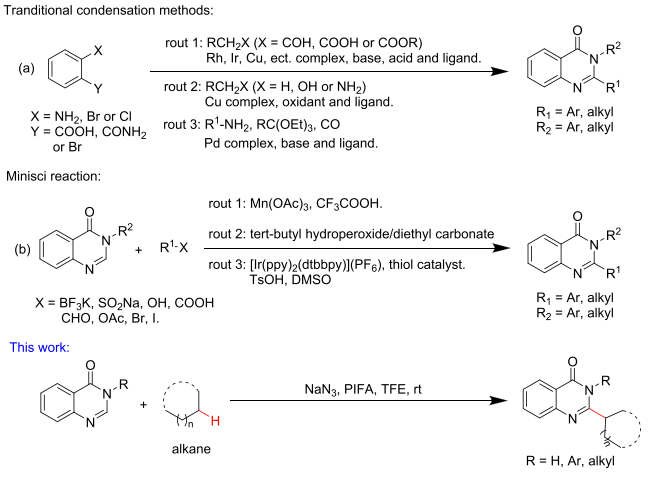


Figure 1. Selected representatives of bioactive 2-alkylquinazolin-4-ones.

molecules involve the acid/base-promoted condensation reactions of aldehydes, esters, or carboxylic acids with amides under harsh conditions (Scheme 1a, route 1).[2] However, despite of recent notable advance (Scheme 1a, routes 2 and 3),[3] they generally suffer from one or more drawbacks such as using expensive and toxic catalysts, needing complex homogeneous catalytic systems or expensive feedstocks, the presence of transition metals as trace impurities in the final products, and unsuitability for the synthesis of 2-alkylquinazolinones. Therefore, there is still a need for an efficient and economical method to synthesize 2-alkylquinazolinones. Directive late-stage modification of quinazolinones is of great value and significance for rapid synthesis of selective 2-alkyl quinazolin-4-ones under mild reaction conditions.[4,5]

Indeed, by the Minisci reaction, radical approaches have been developed as a strategy to carry on alkylation of quinazolinones, where an alkyl radical is coupled with a quinazolinone under oxidizing and acidic conditions to assemble the functionalized product (Scheme 1b). However, the limitation of the method is that the functionalized alkyl substrates such as carboxylic acids,[6a,b] halides,[6c] aldehydes,[6d,e]

Scheme 1. Approaches to 2-Substituted Quinazolin-4-one



boronic acids,[6f,g] organic peroxides,[6h] alkyltrifluoroborates,[6i] and sulfinate salts[6j,l] are required as radical precursors. In addition, an excess of the radical precursor, high temperature, strong oxidant, stoichiometric amounts of expensive metal salts or photocatalyst are required to obtain good yields.[6h,i,7−9] Thus, development of efficient C-2 alkylation of quinazolinones remains attractive to organic chemists. Recently, direct methods of Csp^3-C bonds by cross-dehydrogenative coupling (CDC) have been developed as a versatile and efficient technique for complex molecule syntheses.[10] Alkylation of quinazolinones is increasingly attractive as a C−C bond formation methodology, offering a powerful alternative to

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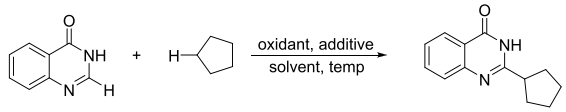
standard cross coupling reactions. To the best of our knowledge, C-2-H alkylation of quinazolin-4-ones with simple alkanes via CDC reaction is rarely reported.[11] Herein, we report the selective formation of Csp^3-Csp^2 bonds by CDC of simple unfunctionalized alkanes with quinazolin-4-ones under mild reaction conditions.

Following our effort for the construction of a broad range of substituted quinazolines as potential inhibitors of kinases,[12,13] and in connection to our continued interest in developing efficient metal-free functionalization strategies,[14] herein we decided to investigate the use of hypervalent iodine reagents for the direct alkylation of quinazolin-4-ones with unfunctionalized alkanes. Initially, we evaluated various reaction conditions for the direct coupling of quinazolin-4-one (**1a**) with cyclopentane (**2a**). To our delight, when we used Kita's methods,[15] the cross-coupling occurred in the presence of (bis(trifluoroacetoxy)iodo)benzene (PIFA) and trimethylsilyl azide ($TMSN_3$) at ambient temperature in 1,1,1,3,3,3-hexafluoro-2-propanol ($(CF_3)_2CHOH$) to product **3a** with a yield of 21% (Table 1, entry 1). However, product **3a** was not formed in the absence of either $PhI(OCOCF_3)_2$ or NaN_3. A variety of polar and nonpolar solvents were then employed (entries 1−5). The best yield (36% of **3a**) was achieved with 2,2,2-trifluoroethanol (TFE) as the solvent. In addition, we tested different additives. Changing the additive from $TMSN_3$ to NaN_3 resulted in increased yield to 48% (entry 6). The use of other sources of azide or iodine did not lead to formation of the product (entries 7−8). Next, we examined the influence of various oxidants (entries 9−17). The use of Koser's reagent (PhI(OH)OTs) or (bis(trifluoroacetoxy)iodo)-pentafluorobenzene (entries 10 and 11) provided lower yield of **3a** than $PhI(OCOCF_3)_2$ (entry 9). Other oxidizing agents, such as IBX, $PhI(OAc)_2$, DMP, $Na_2S_2O_8$, DTBP, TEMPO, *t*-BuOOH, and m-CPBA, did not initiate the transformation. With the optimized oxidant and additive, we investigated the relative ratio of reactants (entries 18−19). We also observed that the conversion remained incomplete, even though the reaction time was prolonged. To overcome this problem, we intended to add PIFA and NaN_3 in small batches. When a total of three equivalents of $PhI(O_2CCF_3)_2$ and NaN_3 was added with a 0.5 equiv batch-mode every 0.5 h, the isolated yield reached 79% (entries 18−19).

Table 1. Optimization of Reaction Conditions[a]



1a **2a** **3a**

entry	oxidant (equiv)	additive (equiv)	solvent	*t* (h)	yield (%)[b]
1	PIFA (2)	$TMSN_3$ (2)	HFIP	8 h	21
2	PIFA (2)	$TMSN_3$ (2)	CH_2Cl_2	8 h	15
3	PIFA (2)	$TMSN_3$ (2)	TFE	8 h	36
4	PIFA (2)	$TMSN_3$ (2)	CH_3CN	8 h	n.d.
5	PIFA (2)	$TMSN_3$ (2)	toluene	8 h	n.d.
6[c]	PIFA (2)	NaN_3 (2)	TFE	3 h	48
7	PIFA (2)	$(nBu)_4NN_3$ (2)	TFE	8 h	n.d.
8	PIFA (2)	I_2 (2)	TFE	8 h	n.d.
9[d]	PIFA (2)	NaN_3 (2)	TFE	3 h	46
10	PhI(OH)OTs (2)	NaN_3 (2)	TFE	3 h	24
11	F_5−PIFA (2)	NaN_3 (2)	TFE	3 h	41
12	IBX (2)	NaN_3 (2)	TFE	12 h	n.d.
13	$PhI(OAc)_2$ (2)	NaN_3 (2)	TFE	12 h	n.d.
14	DMP (2)	NaN_3 (2)	TFE	12 h	n.d.
15	$Na_2S_2O_8$ (2)	NaN_3 (2)	TFE	12 h	n.d.
16	DTBP (2)	NaN_3 (2)	TFE	12 h	n.d.
17	TEMPO (2)	NaN_3 (2)	TFE	12 h	n.d.
18[e]	PIFA (3)	NaN_3 (3)	TFE	3 h	79
19[e]	PIFA (4)	NaN_3 (4)	TFE	5 h	80

[a]Reaction conditions: Unless otherwise noted, the reaction was carried out with **1a** (0.2 mmol), **2a** (1.0 mmol), oxidant (0.4 mmol), additive (0.4 mmol) in solvent (4 mL) under air atmosphere at ambient temperature. [b]Isolated yields. [c]34% of quinazolin-4-ones was recovered. [d]Under argon (1 atm) atmosphere. [e]Oxidant and additive were added in batches of 0.5 equiv in 0.5 h in tervals. PIFA= [Bis(trifluoroacetoxy)iodo] benzene, TEMPO = (2,2,6,6-Tetramethylpiperidin-1-yl) oxyl, PIDA = (Diacetoxyiodo)benzene, DTBP = *tert*-Butyl peroxide, IBX= 2-iodoxybenzoic acid.

After obtaining the optimized reaction conditions (Table 1, entry 18), we explored the scope of this hypervalent iodine-mediated cross-dehydrogenative coupling of quinazolin-4(3*H*)-one with cyclopentane. First of all, the variation in the cycloalkane part of the reaction was studied. The reaction was found to work well with a range of cycloalkanes of various ring sizes. Cyclopentane reacted to give the corresponding product **2a** in 79% yield (Scheme 2). Similarly, cyclohexane, cycloheptane, and cyclooctane also underwent smooth coupling to form products **2c**, **2d**, and **2e** in 67%, 68%, and 71% yields, respectively. After studying the scope of alkanes in cross-coupling, we turned our attention toward substituted quinazolin-4(3H)-one. Substrates bearing either an electron-withdrawing group (**3e**−**3l**) or electron-donating (**3m** and **3n**) space on C5-, C6-, or C7-positions of the quinazoline rings all reacted smoothly to afford the desired products in good to excellent yields. Quinazolin-4(3H)-one substituted with various functional groups, such as Me, OMe, F, Cl, Br, I, and NO_2, at C6- or C7-positions were well-tolerated in the reaction system and provided the possibility for further functionalization of the polysubstituted quinazolin-4(3H)-one, enabling these products to be used as core structures for drug. Additionally, substrates bearing either two electron-donating or electron-withdrawing groups on C6-, and C7-positions of the quinazoline rings all reacted smoothly to afford the desired products in good yields (**3o**−**3t**). We examined the efficiency of inhibition of human A549 cells in vitro and found that the inhibition rate increased with increasing cycloalkane size, and compound **3t** caused >80% inhibition at 10 μM (Supporting Information). It is noteworthy that compound **3t** was obtained in 67% yield from a large-scale reaction (5 mmol of **1t**). To further investigate the functional group tolerance, next, we investigated N^3-substituted quinazolin-4-ones as starting materials.

Gratifyingly, a range of aryl- and alkylquinazolin-4(3H)-ones **1u**−**1y** was found to be suitable substrates and underwent the C−H cycloalkylation to give **3u**−**3y** with good efficiencies. However, in the cases of 4-quinazolinamine derivatives **1z**, messy results were observed based on ^1H NMR of the crude mixture (**3z**). Linear alkanes, such as *n*-hexane and isopentane, were also suitable substrates and afforded the corresponding products in moderate yields (**3aa**, 62% and **3ab**, 72%). C2-substituted product **3aa** was formed along with C3-substituted analog in the ratio of 4:1 when *n*-hexane was the substrate.

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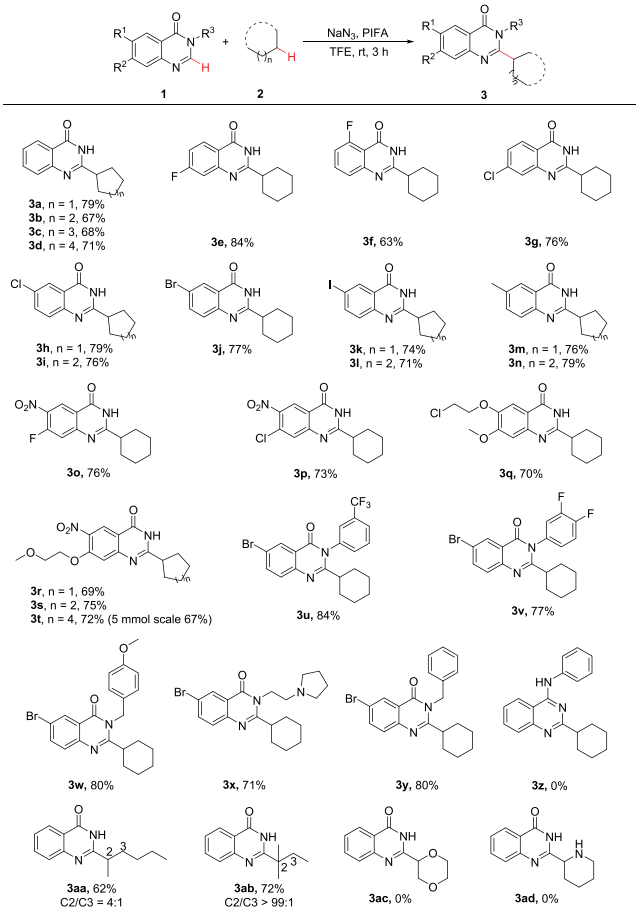
Scheme 2. Substrate Scope for Alkylation of Quinazolin-4-ones[a,b]

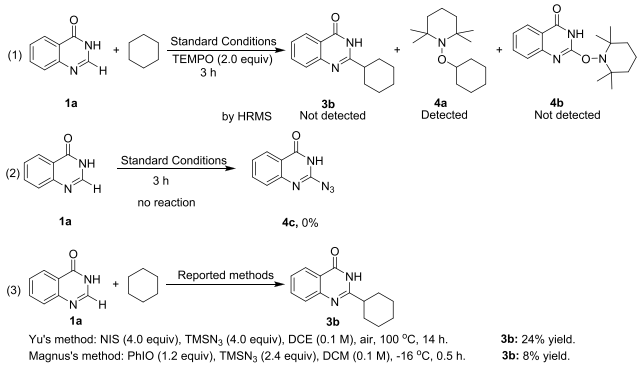


[a]Scope of alkanes in cross-dehydrogenative coupling. Reaction conditions: quinazolin-4-ones **1** (0.2 mmol), alkane (10 equiv), $PhI(O_2CCF_3)_2$ (3 equiv), and NaN_3 (3 equiv) in TFE (4 mL) at rt. [b]Isolated yield.

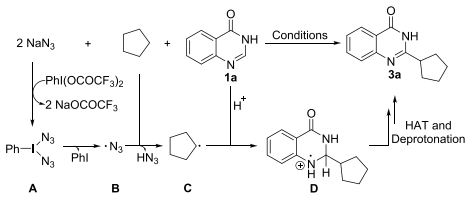
Likewise, alkylation at the 3° site over the 2° site was more preferred (C2/C3 > 99:1) for the branched isopentane. However, heterocyclic alkanes, such as 1,4-dioxane and piperidine, were inert under these conditions (**3ac** and **3ad**).

After exploring the scope of the cross-dehydrogenative coupling of quinazolin-4-ones and alkanes, we turned our attention to explore the mechanism of the coupling. A radical-trapping experiment was carried out. The radical trapping reagent TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) was introduced into the standard reaction system (Scheme 3, eq 1). As expected, the reaction was totally suppressed with formation of only the TEMPO−cyclohexane adduct **4a** (detected by HRMS analysis, see page 6 in the Supporting Information). This fact clearly points to the involvement of radicals in the reaction. In addition, a control experiment without the use of alkane resulted in no products (Scheme 3, eq 2). These results indicate that the alkane is first initiated relative to the quinazoline. Subsequently, we used our substrates in methods reported for generating azidyl radicals,[16] and we remain detected desired product (**3b**), albeit at a lower yield (Scheme 3, eq 3). This experiment shows that the process is also initiated by azidyl radicals. On the basis of these facts, a possible radical-chain mechanism is proposed in Scheme 4. At first, $PhI(O_2CCF_3)_2$ reacts with NaN_3 through

Scheme 3. Control Experiments for Mechanistic Study



Scheme 4. Plausible Mechanistic Pathway



ligand exchange of trifluoroacetate for azide to form the highly reactive $PhI(N_3)_2$ **A**,[17] which decomposes into PhI and the azidyl radical **B**. The azide radical **B** abstracts a hydrogen atom from alkane to generate the alkyl radical **C** and hydrazoic acid.[18] The alkyl radical **C** attacks the protonated quinazolin-4-one at the most electrophilic C2 position to generate a radical cation **D**. Subsequently, hydrogen-atom transfer (HAT) followed by deprotonation gives the final product **3a**.[19]

In conclusion, a highly selective direct oxidative transition-metal-free protocol for cross-coupling of quinazolin-4-ones with simple nonfunctionalized alkanes was developed. This methodology provides a simple and feasible method to predictably functionalize unactivated Csp^3-H bonds with biologically important quinazolin-4-ones under mild conditions. The protocol features a highly efficient synthetic process, wide substrate scope, and high functional-group tolerance. Because of the importance of quinazolinone scaffold in medicinal chemistry, the method can be easily used for the modular synthesis of bioactive quinazolin-4-one libraries. Detailed mechanical research and study of antitumor activity are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00638.

Methods, procedures, optimization of reaction conditions, antitumor activity research, synthesis of **3t**, control experiments, compound characterization, spectral data (PDF)

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⊥S.M. and K.L. contributed equally.

Notes

The authors declare no competing financial interest.

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