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PII: S0040-4039(14)00515-2
DOI: http://dx.doi.org/10.1016/j.tetlet.2014.03.094
Reference: TETL 44416

To appear in: *Tetrahedron Letters*

Received Date: 21 February 2014
Revised Date: 15 March 2014
Accepted Date: 20 March 2014

Please cite this article as: Chen, W., Zheng, H., Pan, X., Xie, Z., Zan, X., Sun, B., Liu, L., Lou, H., A metal-free cross-dehydrogenative coupling of *N*-carbamoyl tetrahydroisoquinoline by sodium persulfate, *Tetrahedron Letters* (2014), doi: http://dx.doi.org/10.1016/j.tetlet.2014.03.094

## Graphical Abstract

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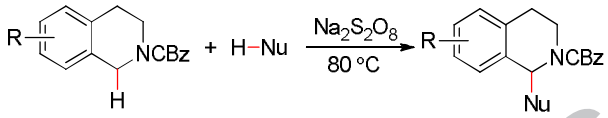


up to 83% yield

NuH = ketone, aldehyde, aryl ring

Tetrahedron Letters
journal homepage: www.elsevier.com

# A metal-free cross-dehydrogenative coupling of *N*-carbamoyl tetrahydroisoquinoline by sodium persulfate

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ARTICLE INFO

*Article history:*
Received
Received in revised form
Accepted
Available online

*Keywords:*
C–H functionalization
*N*-carbamoyl tetrahydroisoquinoline
Peroxydisulfate
Metal-free
Cross-dehydrogenative coupling

ABSTRACT

A metal-free cross-dehydrogenative coupling of *N*-carbamoyl tetrahydroisoquinoline with a variety of C–H nucleophiles mediated by $Na_2S_2O_8$ is developed. The reaction proceeds smoothly to give the coupled product in up to 83% yields. The nucleophile scope is broad, including simple ketones, aldehydes and aryl rings. The carbamoyl protecting group can be readily removed under mild condition. The use of $Na_2S_2O_8$ as the sole reagent for the CDC reaction is attractive based on economical and environmental factors.



The tetrahydroisoquinoline (THIQ) moiety is present in numerous structurally diverse natural products and pharmaceuticals.[1-3] In particular, THIQs bearing substituents like aryl and arylethyl groups at $C_1$ position are important not only as alkaloids themselves but also as valuable key intermediates in the synthesis and biosynthesis. For example, Solifenacin (trade name Vesicare), a $C_1$-phenyl substituted *N*-carbamoyl THIQ, is a competitive antagonist which is used in the treatment of overactive bladder.[2] As another example, almorexant, a $C_1$-arylethyl THIQ derivative as an orexin antagonist, was developed for the treatment of insomnia. Methopholine is an opioid analgesic used for the treatment of postoperative pain.[3] Therefore, a number of methodologies for the efficient preparation of such compounds have been developed.[4-5] However, the traditional protocols rely heavily on reactive functional group transformations, which usually require cumbersome synthetic routes.[6] Recently, direct functionalization of $sp^3$ C–H bonds adjacent to the nitrogen atom in THIQs presents a new synthetic strategy without prior installation of activating groups.[7] Among these, the cross-dehydrogenative coupling (CDC) reaction, namely, the direct coupling of two different C–H bonds between two reactants has attracted much interest in recent years.[8] During the past decade, a number of oxidation systems have been developed to efficiently promote the C–H functionalization of *N*-arylated THIQ substrates.[9] However, the *N*-aryl group can only be removed under very harsh conditions, resulting in poor functional group tolerance, and therefore, limits its synthetic utility.[10] In contrast, while the *N*-acyl protecting group can be easily removed under a variety of mild conditions,[11] such couplings with *N*-acyl THIQs are still less developed compared with those for *N*-arylated THIQs, probably due to the reduced reactivity of the former.[12] While moderate to good efficiency was achieved, almost all of these transformations require either the involvement of metal or strong acid. Moreover, relative expensive reagent was requisite for the coupling. For example, TEMPO oxoammonium salt is not a commercially available reagent, and needs to be prepared in the bench. TBHP in decane is moderately expensive, with a cost of about $273/mol according

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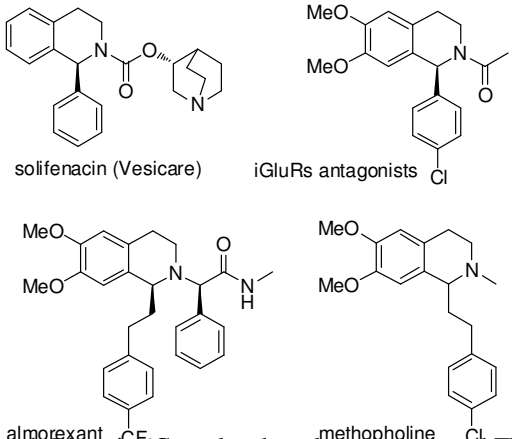



**Figure 1.** Bioactive $C_1$-aryl and -arylethyl substituted THIQs.

† These authors contributed equally to this work.

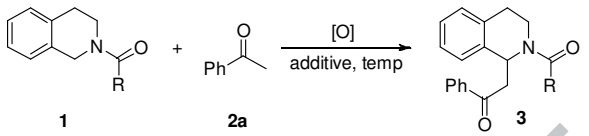
to the 2013-2014 Aldrich catalog, and can cause severe skin burns, eye damage, and an allergic skin reaction. Given the importance of THIQ moieties in pharmacology and that the concern of environmental issue of these CDC reactions are still far from satisfactory, the development of an economic and environmentally benign metal-free oxidation system is still an attractive project to pursue.

The use of peroxydisulfate ($S_2O_8^{2-}$) has long been known to oxidize the hydrocarbons initiated by a single electron transfer process.[13] The oxidant is inexpensive, less toxic, and easily handled. The price of peroxydisulfate salt like $Na_2S_2O_8$ is only \$8.3/mol, and the byproduct can be easily removed with a simple filtration over Celite or silica gel. To the best of our knowledge, such oxidation system has not yet been applied to CDC reactions of THIQs to date. Herein, we report a sodium persulfate mediated oxidative C–H functionalization of *N*-carbamoyl THIQs with a variety of C–H nucleophiles.

Our initial efforts were focused on the CDC of acetophenone and *N*-acyl THIQ using sodium persulfate as the oxidant. In the presence of $Na_2S_2O_8$ in $CH_3CN$ at 80 °C, a series of *N*-acyl and *N*-carbamoyl protected THIQs were examined. As shown in Table 1, methyl and benzyl carbamates proved to be good options (Table 1, entries 1-5). Considering that CBz moiety can be readily removed through mild hydrogenation, we selected benzyl carbamates for further optimization. Next the counter ion of peroxydisulfate was tested. While $K_2S_2O_8$ and $(NH_4)_2S_2O_8$ can also effect the coupling, $Na_2S_2O_8$ proved to be the best choice for the model reaction (entries 4, 6 and 7). The reaction was also highly dependent on the solvent choice. Solvents such as THF, hexane, $CH_2Cl_2$, ethanol, and 1,4-dioxane inhibited the reaction, and performing the coupling without any solvent provided the best result (entries 8 and 9). Since the majority of peroxydisulfate mediated oxidation employs metal additives, we also looked into the role of the metal additive in our transformation. A variety of metal catalysts were applied to the oxidation system. The results showed that the coupling was completely inhibited by copper(I) like CuCl and CuBr (entries 10 and 11). $AgNO_3$, $FeSO_4$ and copper(II) like $CuCl_2$ and $CuSO_4$ can mediate the CDC, with an inferior yield to that without any additive (entries 12-15). Therefore, we decided not to employ any catalyst for further studies for the concern of environmental issue and atom economy. Elevating the reaction temperature resulted in a reduced isolated yield (entries 9 and 16). The involvement of air did not bring down the reaction efficiency (entry 17). When 3 equiv of $Na_2S_2O_8$ was used, the reaction gave an 83% yield (entry 18). Addition of 1 equiv of a radical inhibitor TEMPO completely blocked the transformation (entry 19).

With the optimized CDC reaction conditions in hand, the scope of various C–H nucleophiles on the transformation was studied under air as shown in Scheme 1. A variety of electronically varied aromatic ketones were well compatible with the oxidation system to afford the desired product in good yields. The coupling efficiency was found to be sensitive to the electronic substituents. Electron-rich ketones provided products in slightly reduced yields relative to acetophenone (**6a** and **6b**, Scheme 1), while electron-deficient ones like 4'-bromoacetophenone **5c** afforded a better result (**6c**). In addition to aromatic ketones, cyclic aliphatic ketone like cyclohexanone **5d** and acyclic one like propiophenone **5e** were competent substrates for the transformation (**6d** and **6e**). Besides simple ketones, aldehydes also proved to be suitable coupling partners for the oxidative reaction. Both linear aldehyde **5f**, sterically hindered branched isobutyraldehyde **5g**, and phenylpropyl aldehyde **5h** reacted with *N*-methoxycarbonyl THIQ smoothly to give the corresponding products **6f-6h** in moderate yields.[14] Besides the simple carbonyl compounds, aromatic substrates like anisole **5i**, 2-methoxyanisole **5j** and 3-methoxyanisole **5k** were also tolerated with the oxidation to give the corresponding aryl substituted THIQ **6i-6k** in good yields. Heteroarenes like indole and thiophene are suitable substrates for the coupling, though low yields were isolated for the corresponding products **6l** and **6m**, respectively. After the exploration of the nucleophile scope of the CDC reaction, the substituent effect on the THIQ substructure was subsequently investigated. Both electron-withdrawing and electron-donating substituents were tolerated with the oxidation, though both of them provided a reduced yield relative to acetophenone (**6n** and **6o**).

**Table 1.** Reaction condition optimization[a]



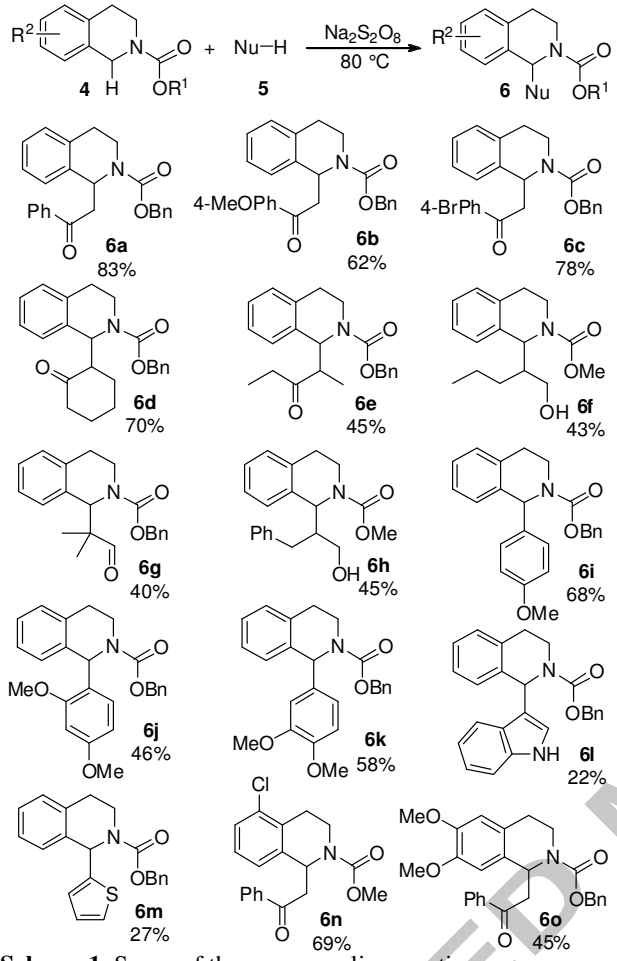

**1** **2a** **3**

| Entry | R | [O] | additive | Yield[b] (%) |
|---|---|---|---|---|
| 1 | Me | $Na_2S_2O_8$ | – | < 5 |
| 2 | Ph | $Na_2S_2O_8$ | – | < 5 |
| 3 | OMe | $Na_2S_2O_8$ | – | 30 |
| 4 | OBn | $Na_2S_2O_8$ | – | 32 |
| 5 | O$^t$Bu | $Na_2S_2O_8$ | – | 11 |
| 6 | OBn | $K_2S_2O_8$ | – | 16 |
| 7 | OBn | $(NH_4)_2S_2O_8$ | – | 22 |
| 8[c] | OBn | $Na_2S_2O_8$ | – | < 5 |
| 9[d] | OBn | $Na_2S_2O_8$ | – | 69 |
| 10[d] | OBn | $Na_2S_2O_8$ | CuCl | < 5 |
| 11[d] | OBn | $Na_2S_2O_8$ | CuBr | < 5 |
| 12[d] | OBn | $Na_2S_2O_8$ | $AgNO_3$ | 31 |
| 13[d] | OBn | $Na_2S_2O_8$ | $FeSO_4$ | 30 |
| 14[d] | OBn | $Na_2S_2O_8$ | $CuCl_2$ | 35 |
| 15[d] | OBn | $Na_2S_2O_8$ | $CuSO_4$ | 67 |
| 16[d,e] | OBn | $Na_2S_2O_8$ | – | 58 |
| 17[d,f] | OBn | $Na_2S_2O_8$ | – | 72 |
| 18[d,f,g] | OBn | $Na_2S_2O_8$ | – | 83 |
| 19[d,h] | OBn | $Na_2S_2O_8$ | – | < 5 |

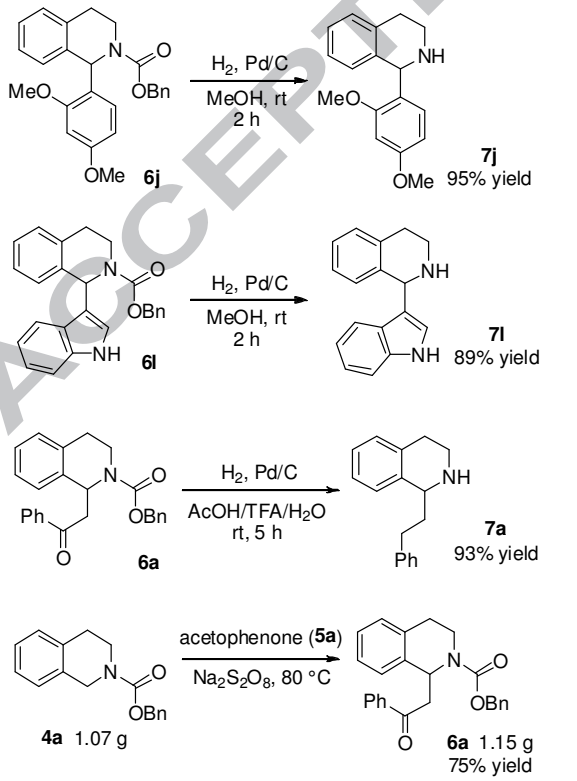
[a]General conditions: **1** (0.25 mmol), **2a** (1.0 mmol), oxidant (0.5 mmol), additive (0.05 mmol), $CH_3CN$ (1.0 mL) at 80 °C under $N_2$ for 24 h, unless stated otherwise.
[b]Isolated yield.
[c]THF, Hexane, $CH_2Cl_2$, Ethanol, and 1,4-dioxane.
[d]Reaction without solvent.
[e]Reaction at 100 °C.
[f]Reaction under air.
[g]0.75 mmol $Na_2S_2O_8$ employed.
[h]1 equiv of TEMPO added.

After the realization of the C–H functionalization of *N*-carbamoyl THIQs, we next investigated the potential synthetic application of above developed method. Given the significance of $C_1$-aryl and arylethyl substituted THIQs in both natural product chemistry and medicinal chemistry, compounds **6a**, **6j** and **6l** were selected as substrates for the deacylation study under mild conditions to distinguish this method from those for the C–H functionalization of *N*-aryl THIQ substrates. As shown in Scheme 2, compound **6j** was converted to **7j** in the presence of $H_2$ and Pd/C in 95% yield at room temperature in 2 h. Under the same condition, indole-based compound **6l** underwent deacylation process to produce THIQ **7l** in 89% yield. The keto

subunit in acetophenone-coupled product **6a** was efficiently reduced to a methylene together with the deacylation by a catalytic hydrogenation ($H_2$ and Pd/C) in the presence of AcOH



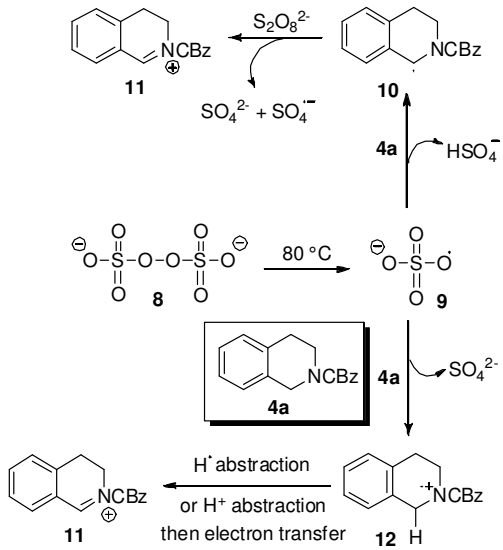

**Scheme 1**. Scope of the cross coupling reaction.




**Scheme 2**. Potential synthetic applications.

and trifluoroacetic acid in 5 h at room temperature. Previously the most frequently employed protocol to achieve such $C_1$-arylethyl THIQ was the hydrogenation of $C_1$-alkyne substructure generated through C–H alkynylation. The efficient manipulation of the ketone moiety provides an alternative strategy to access such compound. To demonstrate the practicability of the neat condition, a gram-scale reaction of *N*-CBz THIQ **4a** with acetophenone **5a** proceeded smoothly without any solvent to deliver **6a** in 75% yield.[15]

While the mechanism is not yet fully understood, radical intermediates should be involved in the reaction since stoichiometric amounts (1 equiv) of TEMPO completely blocked the transformation (entry 19, Table 1). A proposed mechanism for the CDC reaction is shown in Scheme 3 in which we envision that the acyliminium ion **11** might be the intermediate for the subsequent nucleophilic addition process. According to the literatures, persulfate **8** decomposes to generate 2 equiv of $SO_4^{\bullet-}$ (**9**) under thermal conditions.[13] Two mechanisms have been postulated for the generation of the carbocation **11** from **4a**. The first pathway proceeds through an initial benzylic hydrogen atom abstraction from **4a** to **9** to give free radical **10** together with 1 equiv of $HSO_4^-$. **10** then undergoes one electron oxidation to afford intermediate **11**. Alternatively, an initial electron transfer from **4a** to **9** to provide the radical cation **12** with $SO_4^{2-}$. Then **12** proceeds through a hydrogen atom abstraction or proton abstraction followed by a second electron transfer to generate cation **11**.




**Scheme 3**. The proposed mechanism.

In summary, we have developed an efficient oxidative cross-coupling reaction of *N*-carbamoyl THIQs with a variety of C–H nucleophiles employing the inexpensive reagent $Na_2S_2O_8$ as the sole reagent. The oxidant efficiently promotes the alkylation and arylation of *N*-carbamoyl THIQ with simple ketones, aldehydes, and aryl rings in good efficiency. The carbamoyl moiety can be readily removed through mild manipulations to afford $C_1$-aryl and -arylethyl substituted THIQ substructures, making the protocol applicable in the synthesis. The low cost, negligible toxicity and ease of handling of $Na_2S_2O_8$ combined with the absence of hazardous byproducts and the easy workup consisting of simple filtration are attractive. To the best of our knowledge,

this is the first example of the use of $Na_2S_2O_8$ to promote CDC reaction with carbamates, leading to C–C bond formation. The development of other peroxydisulfate-mediated oxidative coupling reactions is currently under investigation and will be disclosed in due course.

## Acknowledgments

Financial Support from the National Science Foundation of China (No. 21202093), Young Scientist Foundation Grant of Shandong Province (No. BS2013YY001) and Changjiang Scholars and Innovative Research Team (IRT13028) is greatly appreciated.

## Supplementary Material

The spectra of the products associated with this manuscript can be found in the supporting information.

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14. To facilitate the purifications, the obtained aldehydes were reduced by $NaBH_4$ in MeOH to afford alcohols **6f** and **6h**.
15. We thank the referee's suggestion on the demonstration of the gram-scale reaction.