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Visible Light-promoted C(sp^3)-H α-Carbamoylation of Cyclic Ethers with Isocyanides

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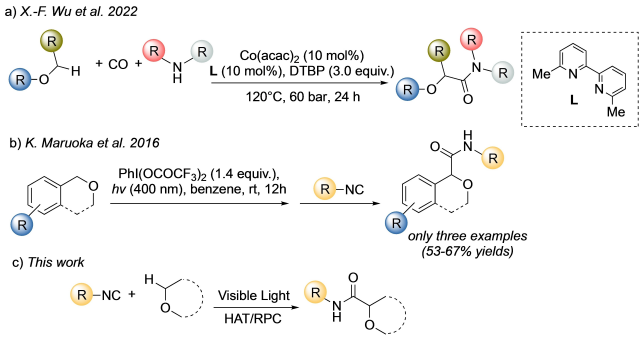
A protocol exploiting isocyanides as carbamoylating agents for the α-C(sp^3)-H functionalization of cyclic ethers has been optimized via a combined visible light-driven hydrogen atom transfer/Lewis acid-catalyzed approach. The isocyanide substrate scope revealed an exquisite functional group compatibility (18 examples, with yields up to 99%). Both radical and polar trapping, kinetic isotopic effect and real-time NMR studies support the mechanistic hypothesis and provide insightful details for the design of new chemical processes involving the generation of oxocarbenium ions.

Introduction

Ethers represent valuable functional groups in both organic and medicinal chemistry, where they appear in over two-thirds of FDA approved drugs.[1] Accordingly, the search for new general and green methods to achieve C(sp^3)-H functionalization is highly desirable.[2–8] To this end, α-C(sp^3)-H carbamoylation reactions represent a poor investigated field, except for a cobalt-catalyzed carbonylative coupling involving carbon monoxide and amines reported by X.-F. Wu (Scheme 1a).[9] Despite the use of a base-metal catalyst and a broad substrate scope both for the ether and the amine coupling partners, the need for high pressure (60 bar) and temperature (120 °C), along with an over-stoichiometric amount of di-*tert*-butyl peroxide (DTBP), partially limited the greenness of the process. An alternative approach relies on the addition of isocyanides to oxocarbenium ions, generated upon light-triggered oxidation of ethers with a hypervalent iodine (III) reagent (Scheme 1b).[10] However, this method is limited to benzylic ethers and, overall, only three examples have been reported by using either *tert*-butyl isocyanide or TosMIC (4 equiv. of isocyanide needed; 53–67% yields). As the results of our interests in the development of visible light-driven strategies involving isocyanides,[8,12] we engaged in the development of a light driven protocol for the C(sp^3)-H α-carbamoylation of ethers which would rely on a hydrogen atom transfer (HAT) event followed by a radical polar crossover (RPC) pathway, as proposed in Scheme 1c.[11]



Scheme 1. a) Cobalt-catalyzed aminocarbonylation of ethers; b) hypervalent iodine (III) promoted photolytic C(sp^3)-H functionalization of benzylic ethers; c) our proposal.

Results and Discussion

We initially focused on the preparation of amide **8** from tetrahydrofuran (that acts as both starting substrate and reaction medium) and 4-isocyano biphenyl as the model reaction, and a selection of the obtained results is available in Table 1 (See also Tables S1 and S2 in Supporting Information). Early efforts were based on the hypothesis of a radical addition of an α-oxyalkyl radical to the isocyanide. Thus, the test reactions reported in Table S1 (Supporting Information) were performed in the presence of a hydrogen atom transfer photocatalyst (PC_{HAT}) and a Lewis acid (LA) such as ytterbium triflate. The latter could activate the isocyanide as an electrophile thus favoring the addition of the nucleophilic α-oxyalkyl radicals).[13–15] Moreover, the Lewis acid could also stabilize the

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Table 1. Optimization of reaction conditions.

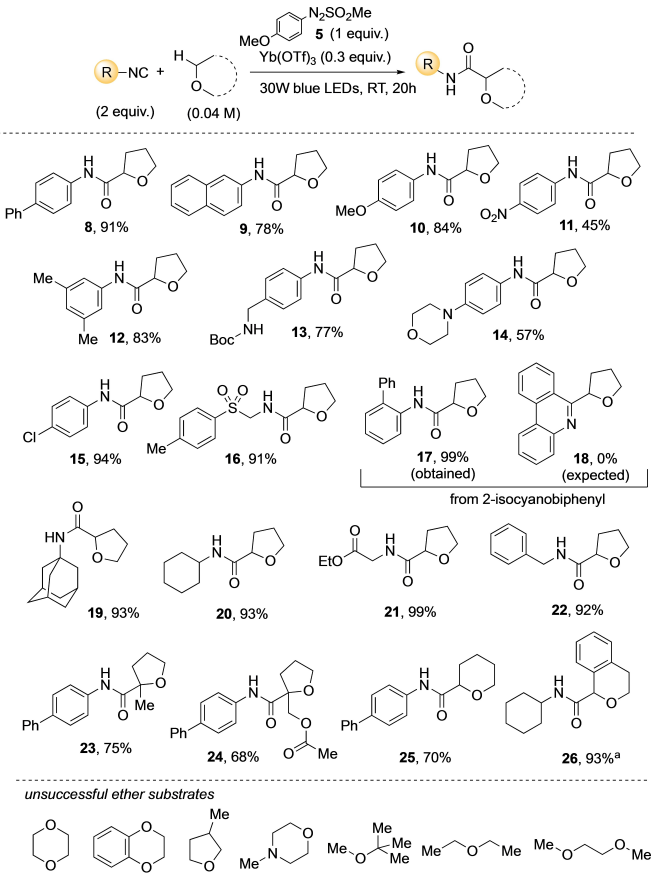
Entry	Isocyanide 1 (Equiv.)	THF 2	$Yb(OTf)_3$ (Equiv.)	Arylazo sulfones 3-7 (Equiv.)	Yield (NMR)
1	1	0.04M	0.6	**3**, *m*-Cl (1.5)	39%
2	1	0.04M	0.6	**4**, *m*-CN (1)	37%
3	1	0.04M	0.6	**5**, *p*-OCH_3 (1)	41%
4	1	0.04M	0.6	**6**, *o*-OCH_3 (1)	30%
5	1	0.04M	0.6	**7**, 3,4-di-Cl (1)	39%
6	1	0.04M	0.3	**5**, *p*-OCH_3 (1)	39%
7	2	10 equiv. in cyclo-hexane (0.1M)	0.3	**5**, *p*-OCH_3 (1)	ND
8	2	0.04M	0.3	**5**, *p*-OCH_3 (1)	90%

generated nucleophilic imidoyl radical intermediate, thus preventing a possible unproductive α-fragmentation pathway to give back the α-oxyalkyl radical and the isocyanide.[8] The use of traditional PC_{HAT} such as tetrabutylammonium decatungstate (TBADT), eosin Y (EY), and aromatic ketones (Table S1 in Supporting Information) in tetrahydrofuran (THF) as a solvent afforded the desired product in yields not exceeding the 40%, while any attempt to use THF as a reagent in different solvents (acetonitrile, dichloromethane, toluene, *N*,*N*-dimethylformamide, and *tert*-butanol, Table S1 in Supporting Information), led to detrimental outcomes due to hydrolysis of the Lewis-acid-activated isocyanide to its *N*-formamide analogue (23–72% depending on reaction conditions, due to adventitious water). On the other hand, the presence of the Lewis acid proved to be key to promote the reaction, since, in its absence, unreacted isocyanide remained detectable by TLC analysis. Other ytterbium sources (e.g., $Yb(OAc)_3$ and $YbCl_3 \bullet 6\ H_2O$) as well as different Lewis acids such as $Sm(OTf)_3$, $Cu(OTf)_2$, $La(OTf)_3$, $Y(OTf)_3$, and Ag(OTf) led to poorer yields. Based on these observations we reasoned that such results could be improved by promoting the formation of the α-oxyalkyl radical with a stoichiometric hydrogen abstraction promoter. Our attention thus turned on arylazo sulfones, visible light photoactive precursors of aryl radicals, which upon hydrogen abstraction from a suitable H-donor would form inert and volatile aryl derivatives.[16,17] Such reactants, indeed, were known to be efficient H-abstractors with a range of common organic solvents (acetonitrile, chloroform, dichloromethane, ethyl acetate, and acetone), but no reports were available about their ability to promote H-abstraction from ethers such as tetrahydrofuran (BDE (C–H) = 92.0 kcal mol^{-1}).[18–20] In this frame, we were encouraged by a test reaction involving isocyanide **1** (1 equiv.) and arylazo sulfone **3** (1.5 equiv.), in the presence of $Yb(OTf)_3$ (0.6 equiv.) in THF (0.04 M) which afforded the targeted amide **8** in 39% yield after 20 h of irradiation with blue light (30 W LED, Table 1).

We thus investigated different arylazo sulfones, as well as the effects of the molar ratio between the isocyanide and the arylazo sulfone, the catalyst loading, and the solvent medium (Table 1 and Table S2, Supporting Information). Whereas the substitution on the aryl ring of the azo sulfone with either electron-donor or electron-withdrawing groups had negligible effect on the yield, the best reaction conditions were found when 2 equivalents of isocyanide were used and by employing *p*-methoxy substituted arylazo sulfone **5** as the HAT agent (1 equiv.) and a Lewis acid catalyst loading of 0.3 equiv. (Table 1, Entry 8).

In order to explore the substrate scope of such conditions a library of nineteen amides **8–17** and **19–26** (Scheme 2) featuring both electron-rich (**8, 9, 10, 12–14**) and electron-poor (**11** and **15**) aromatic isocyanides, primary (**16**, **21**, **22**), secondary (**20**, **26**), and tertiary (**19**) aliphatic isocyanides and different 5- and 6-membered cyclic ethers (**23-26**) was prepared, with yields ranging from 45% to quantitative.

Functional group tolerance was good and involved aromatic ethers (**10**), methyl groups (**12**, **16, 23**), carbamate (**13**), amine (**14**), halogen (**15**), sulfonyl (**16**), and ester (**21**, **24**) functionalities. Interestingly, when using 2-isocyanobiphenyl as the coupling partner, the reaction afforded exclusively the desired



Scheme 2. Optimized reaction conditions and substrate scope (a: reaction run in the absence of both arylazo sulfone and light).

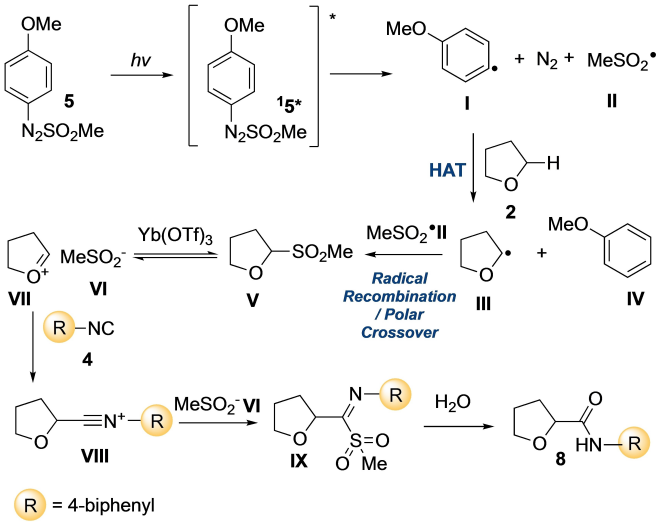
amide **17**, and no traces of phenanthridine derivative **18** were observed.[21] Unfortunately, the reaction with linear ethers such as diethyl ether and *tert*-butyl methyl ether did not afford the desired amide derivatives, and in this case the aromatic amide formed upon reaction between the isocyanide and the aryl radical from the arylazo sulfone was isolated in 26% yield.[22] Finally, the formation of **26** via α-carbamoylation of isochroman with cyclohexylisocyanide occurred even in the absence of the arylazo sulfone and light probably due to a non-light mediated oxidation of the benzylic ether.

These data led us to propose a mechanistic hypothesis relying on the combination of a HAT process and a Radical Polar Crossover (RPC) pathway as highlighted in Scheme 3.

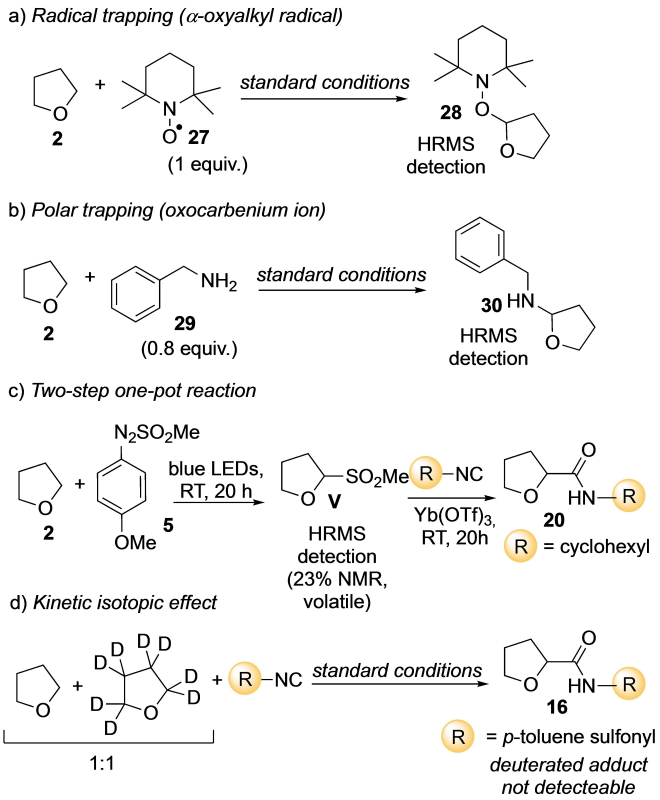
It is worth noting that oxocarbenium ions generation via visible light triggered methods involving a HAT/RPC sequence has been reported for the synthesis of alkylated azoles, requiring either over-stoichiometric amounts of oxidants (e.g., 3 equiv. of TBHP) or N–F reagents as HAT agents.[23–25] Scheme 3 reports a mechanism for the formation of amide **8**.

Under visible light irradiation arylazo sulfone **5** undergoes homolytic fragmentation from its singlet excited state ^{1}**5***, to release aryl radical **I**, nitrogen, and sulfinyl radical **II**. Aryl radical **I** abstracts a hydrogen from THF, thus forming α-oxyalkyl radical **III**, which in turn undergoes a radical recombination with sulfinyl radical **II**, forming the intermediate **V**. The latter is subjected to Lewis acid mediated heterolytic fragmentation to give the sulfinate anion **VI** and oxocarbenium ion **VII**, further intercepted by the isocyanide **1** to give a nitrilium ion **VIII**. Finally, hydrolysis of sulfonyl imidate **IX** affords the amide **8**.

Experimental support to this mechanistic hypothesis was provided by the formation of adduct **28** between 1,1,3,3-tetramethylpiperidine *N*-oxide **27** (TEMPO, 1 equiv.) and THF (Scheme 4a and Figure S1 in Supporting Information) as well as via formation of product **30** upon addition of benzylamine **29** (0.8 equiv.) to oxocarbenium ion **VII** as detected by means of HRMS (Scheme 4b and Figure S2 in Supporting Information).



Scheme 3. Mechanistic hypothesis for ethers' C(sp^3)-H α-carbamoylation via a HAT/RPC sequence.



Scheme 4. Experimental support to the mechanistic hypothesis.

Furthermore, to point out the role of $Yb(OTf)_3$ in promoting the formation of oxocarbenium ion **VII** via heterolytic fragmentation, two identical reactions were performed in a one-pot two-step sequence (Scheme 4c), by mixing at first arylazo sulfone **5** alone (i.e., in the absence of the Lewis acid) in THF under irradiation with blue LEDs. One of two reactions was stopped and the analyzed both via HRMS and NMR, confirming the formation of intermediate **V** (22% yield based on the NMR of the crude mixture, volatile; see Figures S3–S5 Supporting Information). To the second identical reaction, the addition of cyclohexyl isocyanide and $Yb(OTf)_3$ led the expected amide **20** in 45% yield (based on the NMR of the crude mixture, see Scheme 4c and Figure S4 Supporting Information), thus highlighting the superior performance of the one-pot protocol (93% isolated yield, compound **20** in Scheme 2). Additionally, a real-time NMR analysis of the reaction led to exclude the persistent formation of ytterbium-isocyanide complexes, as the chemical shift of THF, the isocyanide **1**, and toluene added as non-complexing reference were all similarly influenced by the paramagnetic effects of ytterbium (See Figures S6 and S7 in Supporting Information). This is in accordance with literature data indicating that a complexation of isocyanides arises from σ-donation from the isocyanide carbon lone pair to the transition metal d-orbitals, coupled with π-donation from the metal to the isocyanide π*-orbital. However, isocyanides are reported in literature as poor π-acceptor ligands (e.g., with respect to CO), thus leading to the formation of reversible complexes with metal ions possessing filled d-orbitals.[15,26,27]

Additionally, kinetic isotopic effects, observed by performing the reaction in a 1:1 THF/THF-d_8 solvent mixture and leading to no evident formation of deuterated adduct, proved that the rate limiting step was the hydrogen atom abstraction from THF (Scheme 4d).

Conclusions

In conclusion, the combination of an arylazo sulfone as a HAT agent and a Lewis acid to promote a radical/polar crossover pathway, proved to be a valuable visible-light driven approach enabling a smooth formation of oxocarbenium ions from cyclic ethers. The isocyanide substrate scope and the functional group tolerance proved here to be excellent, in contrast with the limited examples in literature.[10,11] This method interestingly provides a useful approach to amide derivatives by avoiding over-stoichiometric coupling agents and expand the chemical space of electrophilic species (i.e., oxocarbenium ions) suitable to react with isocyanides in a Passerini-like three-component reaction.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: C–H carbamoylation · Hydrogen atom transfer · Isocyanides · Lewis acid catalysis · Radical polar crossover

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