Solvent-controlled photocatalytic divergent cyclization of alkynyl aldehydes: access to cyclopentenones and dihydropyranols

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Abstract

Divergent synthesis is a powerful strategy for the fast assembly of different molecular scaffolds from the identical starting materials. We describe here a novel solvent-controlled photocatalytic divergent cyclization of alkynyl aldehydes with sulfonyl chlorides for the direct construction of highly functionalized cyclopentenones and dihydropyranols that widely exist in bioactive molecules and natural products. Density functional theory calculations suggest that an unprecedented $N,N$-dimethylacetamide-assisted 1,2-hydrogen transfer of alkoxy radicals is responsible for the cyclopentenone formation, whereas a C-C cleavage accounts for the selective production of dihydropyranols in acetonitrile. Given the simple and mild reaction conditions, excellent functional group compatibility, forming up to four chemical bonds, and tunable selectivity, it may find wide applications in synthetic chemistry.

Introduction

Nucleophilic addition to carbonyl groups represents one of the most classic reactions for accessing ubiquitous C-C bonds. The C-O double bonds accept the attack of nucleophiles to form an alkoxide intermediate, followed by protonation to afford alcohol products (Fig. 1a). In contrast, the radical addition to carboxyls can generate a more reactive and versatile alkoxy radical intermediate that may undergo a reduction, 1,2-hydrogen atom transfer (1,2-HAT), or $\beta$-fragmentation to produce structurally diverse products (Fig. 1b), such as alcohols$^{1-6}$, ketones$^{7-14}$, or aldehydes$^{15,16}$. In addition, the radical-mediated reaction usually occurs under mild, neutral conditions, thus tolerating many sensitive functional groups which are incompatible with the ionic reaction. Despite its apparent advantages, the addition of radicals to carbonyl compounds has been much less investigated due to the production of thermodynamically unfavorable alkoxy radicals$^{17}$. In this respect, we have established a new aldehyde-to-ketone methodology$^{7-10}$ with 1,2-HAT of alkoxy radicals as the key step. However, the known methods are limited to aryl or alkenyl aldehydes ($R^1 = \text{Ar, alkenyl}$), and the transformation of alkyl aldehydes ($R^1 = \text{alkyl}$) is still unknown owing to the lack of spin delocalization in the formed ketyl radical. Recently, Liu$^{15}$ and Zhu$^{16}$ reported an elegant intramolecular formyl migration reaction via $\beta$-scission of alkoxy radicals. Key to this transformation is the release of a much more stable radical ($R^1\cdot$), and therefore, it is a substrate-dependent process. So far, only $\alpha$-hydroxy aldehydes work for this reaction, and the migration of CHO group from the more common alkyl aldehydes remains unexplored.

As fundamental structural scaffolds, cyclopentenones$^{18-23}$ and dihydropyranones$^{24-29}$ widely exist in numerous natural products, biologically active compounds, and drugs, such as the antibiotics pentenomycins$^{18}$ and antitumor active (+)-altholactone$^{24}$ (Fig. 1c). Consequently, the development of efficient methods for assembling these two motifs is highly desirable. Pursuing our recent interests in the direct transformation of aldehydes to ketones$^{7-10}$, we envisioned that an intramolecular addition of alkenyl radicals to alkyl aldehydes would allow us to access the more reactive alkoxy radicals (Fig. 1d). If we could control the reaction pathways of the in situ generated alkoxy radicals, a divergent synthesis of cyclopentenones and dihydropyranols would be established. Herein, we disclose a visible light-induced
sulfonylative cyclization of alkynyl aldehydes using commercially available sulfonyl chlorides as the sulfonylation reagent\textsuperscript{30-34}. The reaction offers a facile access to various structurally diverse cyclopentenones, dihydropyranols, and dihydropyranones under mild conditions. Density functional theory (DFT) calculations provide insights into this unique solvent-controlled divergent transformation. Specifically, the cyclopentenone formation proceeds via a novel DMA-assisted 1,2-hydrogen transfer, while the β-scission of alkoxy radicals accounts for the selective production of dihydropyranols with MeCN as the solvent. In contrast to the existing photocatalysis divergent synthesis\textsuperscript{35-48} which is generally restricted to the substrate-\textsuperscript{35-41} or catalyst-controlled\textsuperscript{42-45} system, the solvent-controlled strategy developed here provides an operationally simple and highly efficient means for divergent synthesis.

Results

**Reaction optimization.** Initially, the alkynyl aldehyde **1a** and TsCl (**2a**) were chosen as model substrates for evaluating the reaction conditions. In the presence of 2 mol% of *fac*-Ir(ppy)$_3$ and 2.0 equiv of K$_2$CO$_3$, the 3-sulfonyl cyclopentenone **3a** was isolated in 66% yield after 5 h of irradiation with 15 W of blue LEDs in DMA at 25 °C (Table 1, entry 1). Base screening revealed that Na$_2$CO$_3$ was the most efficient choice, delivering **3a** in 76% yield (entries 2-5). Switching the solvent from DMA to MeCN led to **3a** in only 5% yield, and interestingly, the 4-sulfonyl dihydropyranol **4a** was isolated in 57% yield (entry 6). Encouraged by the result, we examined other bases and solvents for the dihydropyranol production, however, the reaction yields were not improved (entries 7-12). To our delight, running the reaction at 50 °C resulted in full conversion of **1a** and produced **4a** in 73% yield (entry 13).
Examination of substrate scope. With the optimized reaction conditions in hands, we set about evaluating the scope of this cyclopentenone formation protocol with DMA as the solvent (Fig. 2). In general, the transformation proceeded efficiently to form densely substituted cyclopentenones in moderate to high yields (3a-3w). A broad array of functional groups, such as F, Cl, Br, CN, Ac, OMe, quinoline, pyridine, and thiofuran, are well tolerated under the reaction conditions, which may be utilized for the downtown transformations. Although both the electron-rich and -deficient substituents were accommodated on the benzene ring of 1, relatively lower yields were observed for the latter cases (3g and 3h). In addition to arylalkynyl substrates (G = Ar), the thioalkynyl aldehyde 1o reacted with 2a as well to produce the desired product 3o in 73% yield. Direct construction of spirocyclopentenones was also feasible, as exemplified by the production of 3p. The reaction of 1r, a dicarbonyl substrate, took place uneventfully to afford 3r in 69% yield. Substitution at the propargyl position with two methyl groups led to 3u in a low yield, which may be attributed to the increased hindrance for the radical sulfonylation of C-C triple bonds.
After succeeding in synthesizing tetrasubstituted cyclopentenones, we then examined the feasibility of assembling tri- or disubstituted cyclopentenones. Starting from the α-secondary and α-primary aldehydes 1v and 1w, the 2,3,5-trisubstituted and 2,3-disubstituted cyclopentenones were successfully constructed (3v and 3w). The reaction was also amenable to the access of sulfonylated cyclohexenones, albeit in a moderate yield (3x). In the meantime, sulfonyl chlorides 2 were varied with 1i as the coupling partner. Pleasingly, various arylsulfonyl chlorides proved to be efficient substrates and produced the corresponding sulfonyl cyclopentenones in medium to high yields (3y-3zf). Unfortunately, MeSO₂Cl was not engaged in this reaction (3zg). The X-ray crystallographic analysis of 3g clearly indicated the structure of 3-sulfonyl cyclopentenones.

The generality of photoredox-catalyzed synthesis of dihydropyranols was then explored with MeCN as the solvent (Fig. 3). Alkynyl aldehydes bearing different substituents such as Me, F, Cl, Br, CN, Ac, and OMe served as competent substrates, delivering a variety of 4-sulfonyl dihydropyranols in moderate to high yields (4a-4i). The electron effects appeared to have an impact on the reaction efficiency. Specifically, the transformation of substrates 1g and 1h, having electron-withdrawing CN and Ac substituents on the benzene ring, produced the desired products 4g and 4h in 70% and 76% yield, respectively, while a moderate yield (42%) was observed in the case of 1i, bearing an electron-donating OMe group (4i). Substituents at the α-position of aldehydes were evaluated. In particular, α-tertiary aldehydes worked well for this reaction (4m-4q), whereas the α-secondary aldehyde failed to provide the corresponding product (4r), presumably due to the reduced stability of secondary alkyl radicals. Additionally, the scope with respect to sulfonyl chlorides was investigated. A wide range of arylsulfonyl chlorides, substituted by groups such as F, CF₃, Br, OMe, i-Pr, and CN, underwent the reaction smoothly to generate functionalized dihydropyranols in promising yields (4s-4z). Similarly, 2-furansulfonyl chloride served as an efficient sulfonylation reagent (4za). It’s noteworthy that four new chemical bonds are concurrently created under the reaction conditions, thus highlighting the high bond-forming efficiency of this method.

Meanwhile, the one-pot synthesis of polysubstituted dihydropyranones was explored (Fig. 4). As expected, the reaction furnished a set of sulfonylated dihydropyranones in medium to high yields with good functional group tolerance (5a-5e). The structure of 4-sulfonyl dihydropyranones was unambiguously identified by the X-ray crystallographic analysis of 5a.

**Synthetic applications.** To demonstrate the synthetic utility of this divergent transformation of alkynyl aldehydes, we carried out the derivatization of products (Fig. 5). Reduction of 3a with a combination of NaBH₄ and CeCl₃ produced the tetrasubstituted cyclopentenol 6a in 77% yield. Michael addition of BnSH to 3a followed by an elimination of sulfinate formed the benzylthiocylopentenone 6b in 86% yield. Following Orita’s protocol⁵⁰, photocatalytic desulfonylation of 3a and 5a occurred readily to give 6c and 6d in 81% and 84% yield, respectively. Bromination at the allylic position of 5a with NBS and BPO produced 6e in a good yield. Given the significant importance of tetrasubstituted alkenes in organic synthesis, the attempts to establish stereodefined tetrasubstituted alkenes were also performed.
Nucleophilic attack of MeMgCl to 5a delivered the tetrasubstituted (E)-alkene 6f in 82% yield. Furthermore, the (E)-enol 6g was selectively assembled in almost quantitative yield upon treatment of 5a with K₂CO₃ in MeOH at 55 °C for 10 h.

**Mechanistic investigations.** To gain insights into the reaction mechanism, some control experiments were performed, and the results are summarized in Fig. 6. In the presence of butylated hydroxytoluene (BHT, 2.0 equiv), neither 3a nor 4a could be obtained in a noticeable yield, and instead, the sulfonyl compound 7 was isolated in 11% and 48% yield, respectively. Likewise, adding 2,2,6,6-tetramethylpiperidinooxy (TMEPO, 2.0 equiv) to the standard conditions shut down the reaction (not shown). These results suggested a radical pathway. Additionally, the ¹⁸O isotope labeling experiments were conducted. With the addition of 5.0 equiv of H₂¹⁸O, 4a⁻¹⁸O was isolated in 69% yield with 89% ¹⁸O incorporation. In addition to the signal of [M+Na]⁺ ion of 4a⁻¹⁸O, a signal matched with [M+Na-H₂¹⁸O]⁺ ion was observed by the HRMS analysis, thus indicating that the hydroxy group of 4a is originated from water (see Supporting Information for details).

Based on the above results and previous reports, a mechanistic proposal for the divergent cyclization of 1a is summarized in Fig. 7. Initially, the single electron transfer (SET) between the excited photocatalysis Ir(III)* and TsCl affords a Ir(IV) species and sulfonyl radical Ts⁻. Radical sulfonylation of the C-C triple bond of 1a and a subsequent addition of vinyl radical I to the intramolecular CHO group produces a cyclopentenoxy radical II. It may undergo a 1,2-HAT to deliver the neutral ketyl radical III, followed by SET with Ir(IV) and deprotonation to provide 3a (path 1a). Alternatively, the β-C-C cleavage of II may take place to form a tertiary alkyl radical IV (path 1b), which can be converted into the oxonium ion VI via a 6-endo radical cyclization (path 2a)/SET oxidation sequence. Additionally, a radical oxidation to the cation VII (path 2b) followed by intramolecular nucleophilic attack may also lead to the generation of VI. Finally, the nucleophilic attack of VI by H₂O generates 4a as the product.

To shed light on the unique role of solvent in tuning the reaction pathways, we carried out computational studies using DFT calculations, and the results are presented in Fig. 8. As for the reaction performed in DMA, radical sulfonylation of 1a occurring via transition state TS1 requires an activation free energy of 14.3 kcal/mol, which is viable under the reaction conditions. Subsequently, radical addition to the intramolecular CHO group proceeds via a five-membered ring transition state TS2 to give the radical II. This step has a free energy barrier of 9.3 kcal/mol. Starting from II, an unprecedented DMA-assisted 1,2-hydrogen transfer via TS3-DMA, with a free energy of 7.6 kcal/mol) is favoured over the 6-endo radical cyclization (via TS5, with a free energy of 9.4 kcal/mol) by 1.8 kcal/mol, thus giving rise to the ketyl radical III. Formation of III is highly exergonic by 30.7 kcal/mol and is therefore an irreversible process. Followed by SET oxidation and deprotonation, 3a can be constructed together with the regeneration of photocatalysis Ir(III), which is strongly exergonic by 63.2 kcal/mol.

With MeCN as the solvent, the MeCN-assisted 1,2-hydrogen transfer of II (via TS3-NMe) has a higher energy barrier of 15.3 kcal/mol, which is unlikely to compete with the β-C-C cleavage/ 6-endo cyclization...
sequence. Moreover, the 6-endo radical cyclization of IV requiring a free energy barrier of 4.5 kcal/mol is
favoured over the SET oxidation, with a free energy barrier of 9.6 kcal/mol, by 5.1 kcal/mol. Therefore, a
stable allyl radical V that lies 25.8 kcal/mol lower in energy than IV is selectively formed. Spin
delocalization to the neighboring C-C double bond should be responsible for the increased stability of V,
which provides a driving force for the C-C bond cleavage and uncommon addition of alkyl radical to the
carbonyl oxygen atom\textsuperscript{62-64} in the 6-endo radical cyclization step. Subsequently, the radical V is oxidized
by Ir(IV) to form an oxonium ion intermediate VI, followed by nucleophilic attack of water to produce 4a,
which is strongly exergonic by 39.1 kcal/mol.

Discussion

In conclusion, a photocatalytic divergent coupling of alkynyl aldehydes with sulfonyl chlorides is
developed. The reaction provides a straightforward and highly selective method for the assembly of
structurally diverse cyclopentenones, dihydropyranols, and dihydropyranones that are important building
blocks in organic and medicinal chemistry. Up to four new chemical bonds are concurrently constructed
under mild reaction conditions, thus highlighting the high efficiency of this method. DFT calculations
reveal that an unprecedented DMA-assisted 1,2-HAT of alkoxy radicals is responsible for the production
of cyclopentenones, whereas a β-C-C cleavage followed by 6-endo radical cyclization to formyl group
accounts for the generation of dihydropyranols in MeCN. Tuneable selectivity for 1,2-HAT and β-
fragmentation of alkoxy radicals is realized for the first time, thus providing a novel strategy for the
selective activation of inert C-H and C-C bonds.

Methods

Procedure for the photocatalytic synthesis of cyclopentenones. To a mixture of \textit{fac}-Ir(ppy)\textsubscript{3} (2.6 mg,
0.004 mmol), Na\textsubscript{2}CO\textsubscript{3} (42.4 mg, 0.4 mmol), H\textsubscript{2}O (7.2 μL, 0.4 mmol), and 2a (57.0 mg, 0.3 mmol) in 2 mL
of DMA was added 1a (37.2 mg, 0.2 mmol) under a nitrogen atmosphere. After 5 h of irradiation at a
distance of ~5 cm from 15 W blue LEDs (BESTLLON\textsuperscript{\textregistered} lamps, 450 nm, 100% light intensity) at 25 °C, the
reaction mixture was quenched with water, extracted with EtOAc, washed with brine, dried over anhydrous
Na\textsubscript{2}SO\textsubscript{4}, and concentrated. The resulting residue was purified via column chromatography on silica gel to
afford the desired products.

Procedure for the photocatalytic synthesis of dihydropyranols. To a mixture of \textit{fac}-Ir(ppy)\textsubscript{3} (2.6 mg, 0.004
mmol), Na\textsubscript{2}CO\textsubscript{3} (42.4 mg, 0.4 mmol), H\textsubscript{2}O (7.2 μL, 0.4 mmol) and 2a (57.0 mg, 0.3 mmol) in 2 mL of dry
MeCN was added 1a (37.2 mg, 0.2 mmol) under a nitrogen atmosphere. After 5 h of irradiation at a
distance of ~5 cm from 15 W blue LEDs (BESTLLON\textsuperscript{\textregistered} lamps, 450 nm, 100% light intensity) at 50 °C, the
reaction mixture was quenched with water, extracted with EtOAc, washed with brine, dried over anhydrous
Na\textsubscript{2}SO\textsubscript{4}, and concentrated. The resulting residue was purified via column chromatography on silica gel to
afford the desired products.
Declarations

Data availability

Detailed experimental procedures and characterization of new compounds can be found in the Supplementary Information. Further relevant data are available from the authors upon request.

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Author contributions

G.Z. conceived the idea. H.Z., J.Z., J.F., L.K., and F.Z. conducted the experiments. H.Z., and X.X. conducted the DFT calculations. H.Z., H.Z., and J.Z. contribute equally to this paper. X.X., and G.Z. co-wrote the paper. All the authors discussed the results and commented on the manuscript.

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