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Indium-promoted butenolide synthesis through consecutive C–C and C–O bond formations in aqueous tetrahydrofuran enabled by radicals†

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An indium-promoted lactonization of (indol-3-yl)-2-oxoacetaldehydes, which allows the synthesis of substituted γ -methylenebutenolides in an aqueous environment, has been accomplished. This process is in clear contrast with the established metal-mediated reactivity of unsaturated organic halides and carbonyls. The use of an aqueous medium and the facile purification profile make our protocol a convenient and sustainable synthetic strategy. A plausible reaction pathway has been proposed with the help of density functional theory calculations.

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Introduction

Multi-step protocols and large volumes of organic solvents are normally required in organic synthesis. Achieving sustainable chemical strategies is highly desirable for meeting green chemistry principles.¹ In this context, the utilization of abundant and environmentally friendly water is a cheaper and greener alternative to the use of petroleum-derived solvents.² Indium is an air- and moisture-stable non-toxic metal which has gained recent importance for the formation of carbon–carbon bonds.^{3,4} The indium-mediated reaction between carbonyls and allyl or propargyl bromides resulted in the formation of allylic (Scheme 1a)⁵ or allenic/propargylic alcohols (Scheme 1b),⁶ respectively. On the other hand, butenolide-based structures have received considerable interest. γ -Methylenebutenolides are a relevant subclass because of their interesting biological activity⁷ and versatility as synthetic intermediates.⁸ However, despite remarkable examples such as a palladium-catalyzed cyclocarbonylation of aryl halides with acetylenes (Scheme 1c)^{9b} and a gold-catalyzed synthesis starting from pro-

pargyl diazoacetates (Scheme 1d),^{9c} the preparation of butenolides bearing the *exo*-methylene moiety is less explored.⁹ Despite the merits of previous protocols, all of them used transition metals and pollutant organic solvents, and required heating. Herein, we reveal how by just using arylglyoxals¹⁰ we can deflect the conventional indium-mediated reactivity of organic halides and carbonyls, enabling a simple and green access to γ -methylenebutenolides (Scheme 1e).

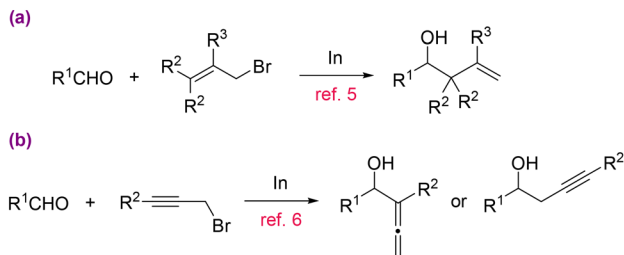
Results and discussion

 γ -Methylenebutenolide forming reaction

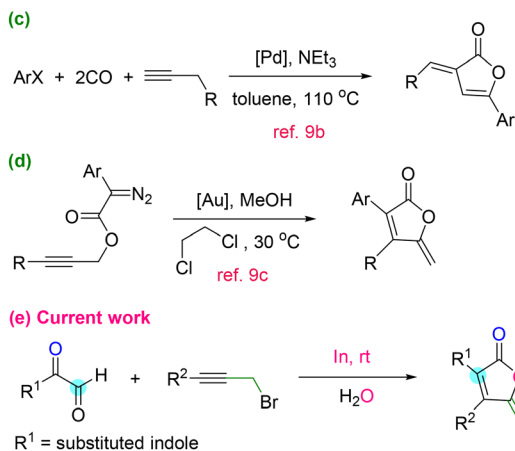
In the course of a project directed to study the chemistry of unsaturated systems, an unexpected result attracted our attention. An indium-mediated reaction between 2-(1*H*-indol-3-yl)-2-oxoacetaldehyde **1a** and 1-bromobut-2-yne **2a** in H₂O/THF (1 : 1) afforded γ -methylenebutenolide **3aa** bearing the cyclic butenolide nucleus in 53% yield instead of the expected allene product (Scheme 2).¹¹ This molecular transformation should include a rearrangement of the carbon chain. The reaction did not take place in pure organic solvents such as acetonitrile or DMF and proceeded poorly in aqueous ethanol. The reaction in pure water did not proceed due to the insolubility in the reaction medium of the starting glyoxal, which was recovered unaltered. Here we found that the best-suited solvent, namely, NH₄Cl (aq satd)/THF (5 : 1), brought about an improved yield of **3aa** (62%). In agreement with previous reports, the ionic strength enhancement in the reaction solvent provided by the presence of ammonium chloride may improve the yield and speed up the conversion rate.¹² Control experiments confirmed that the indium metal was critical for this reaction, because

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Previous work: Established metal-mediated reactivity of unsaturated organic halides and carbonyls

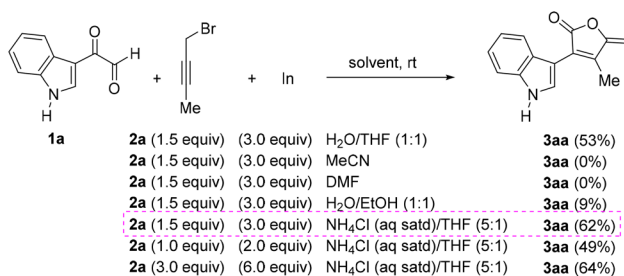


Previous work: Synthesis of γ -methylenebutenolides (transition metals, organic solvents, heating)



ligand-free; safe solvent; low energy consumption; easy purification

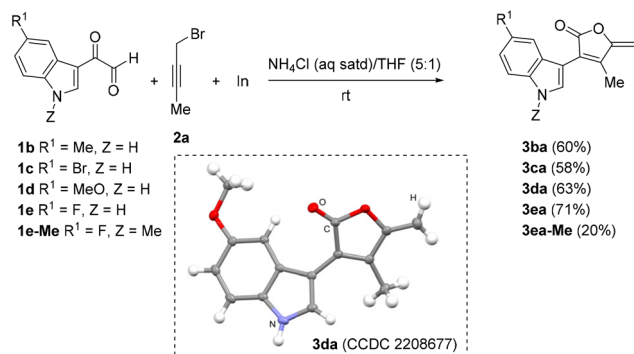
Scheme 1 State-of-the-art and current work.



Scheme 2 Impact of the reaction solvent on the formation of γ -methylenebutenolide **3aa**.

the use of Sn, Fe, or Zn instead of In resulted in no formation of **3aa** (*vide infra*). The yield decreased to 49% on using a **1a**/**2a**/In ratio of 1 : 1.0 : 2.0 and it was slightly improved to 64% on using an excess of indium. Thus, we resolved to use a three-fold excess of the indium metal for the next study on the substrate scope.

With the optimized conditions in hand, the scope of this rearrangement/heterocyclization reaction sequence was initially investigated through the incorporation of substituents in the indole nucleus. Several functional groups including both electron-withdrawing (Br and F) and electron-donating (Me and MeO) substituents were well-accommodated to deliver



Scheme 3 Controlled synthesis of γ -methylenebutenolides **3ba–ea**.

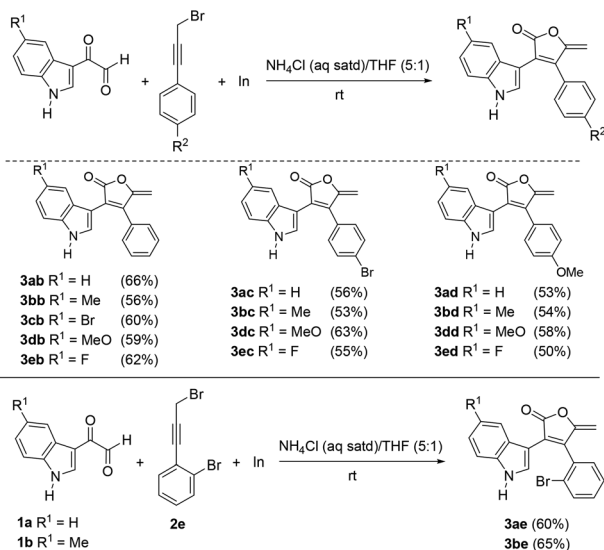
the required oxacycle **3**. As shown in Scheme 3, the reactions of 2-oxoacetaldehydes **1b–e** with 1-bromobut-2-yne **2a** resulted in the clean formation of methyl-substituted γ -methylenebutenolides **3ba–ea** in reasonable yields. When *N*-methyl indole **1e-Me** was used to further expand the migration of the indole nucleus under these indium-mediated conditions, the formation of the corresponding butenolide **3ea-Me** was observed. However, the heterocyclic product **3ea-Me** was less crystalline than its *NH*-counterpart **3ea**, making the purification by crystallization difficult and giving rise to poor-quality NMR spectra after recrystallization. The preparation of the *N*-methoxycarbonyl analogue was not feasible because a messy reaction was observed. The structure of compound **3da** was confirmed from single-crystal X-ray diffraction study, proving that the γ -methylenebutenolide structure was newly generated during the reaction.¹³ The indium-mediated reaction of 2-furylglyoxal with 1-bromobut-2-yne **2a** resulted in a complicated mixture, which pointed to the use of the *NH*-indole nucleus as the heteroarene of choice.

Next, variations of propargyl bromides as the coupling partner were also investigated. (3-Bromoprop-1-yn-1-yl)benzene **2b** and its derivatives **2c–e** bearing electron-rich or electron-poor aryl rings such as methoxyphenyl and bromophenyl groups were totally compatible with the above protocol. As illustrated in Scheme 4, the oxacycle formation demonstrated to be general and γ -methylenebutenolides **3ab–ed** were smoothly delivered. Gratifyingly, the 2-bromophenyl group performed well and the corresponding butenolides **3ae** and **3be**, which have a sterically more congested 1,2-diaryl structure, were formed in slightly better yields.

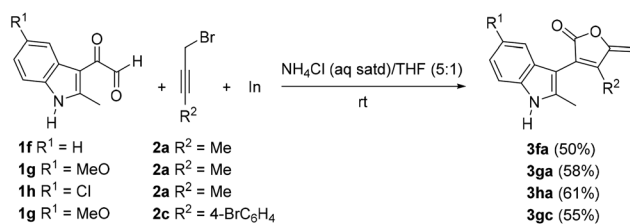
It is noteworthy that 2-(2-methyl-1*H*-indol-3-yl)-2-oxoacetaldehydes **1f–h**, where the C2 position of the indole moiety is substituted, still served as effective reaction substrates to yield butenolides **3fa–ha** conveniently (Scheme 5).

From the above results (Schemes 3–5), it may be inferred that this butenolide formation reaction which may run overnight is general for alkyl- and aryl-substituted alkynes. Moreover, the successful formation of the products bearing a bromine atom on the indole or benzene nuclei may provide opportunities for further functionalization. The mild reaction conditions allowed the nitrogen atom of the indole moiety to





Scheme 4 Controlled synthesis of γ -methylenebutenolides **3ab–be**.



Scheme 5 Controlled synthesis of γ -methylenebutenolides **3fa–ha**.

be not protected. Besides, water dilution followed by filtration allowed the isolation of the γ -methylenebutenolide products, which could be conveniently purified by crystallization, making our protocol a more appealing and sustainable synthetic strategy.¹⁴

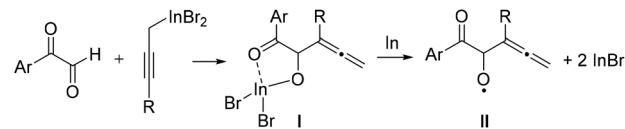
To gain some insight into the mechanism of this transformation, some control studies were conducted. The reaction of glyoxal **1a** with 1-bromobut-2-yne **2a** was carried out under otherwise optimal conditions, but under an argon atmosphere. In the reaction, the resulting γ -methylenebutenolide **3aa** was obtained in a poor yield of 21%, suggesting the involvement of molecular oxygen from air in this transformation. Either omitting the indium(0) or replacing it by a different metal source (Sn, Zn, and Fe) caused total suppression of γ -methylenebutenolide formation, highlighting the key role of indium in this cascade sequence. The reaction of labelled 2-(1*H*-indol-3-yl)-2-oxoacetaldehyde-*d* [D]-**1a**, which was prepared using tributyltin deuteride (D source) instead of tributyltin hydride, with 1-bromobut-2-yne **2a** furnished non-deuterated butenolide **3aa** which may support the release of the deuterium atom as HDO without reintegration in the target product. Importantly, by adding 3 equiv. of TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl) to the reaction mixture, complete inhibition of butenolide generation was observed (Scheme S1, please see

the ESI⁺). This fact supports that the reaction pathway should include radical-mediated processes. In order to detect any trapped TEMPO radical derivatives, the indium-mediated reaction of 2-oxoacetaldehyde **1a** with 1-bromobut-2-yne **2a** in the presence of TEMPO was analysed by HRMS, but the obtained information was inconclusive.

Theoretical studies for the reaction pathway

The present molecular transformation should include the rearrangement of the carbon chain in the allenic intermediate **I** (Scheme 6), which is generated by the reaction of the glyoxal substrate with propargylic indium(III) dibromide.^{15,6b} However, the following reaction paths for this reaction are not easily explained. To obtain a reliable understanding of the reaction path, we conducted DFT calculations for the reaction of **1d** with **2a** at the PCM(H₂O)-UM06-2X/6-31+G(d,p) level of theory. Here, we started the theoretical analysis from radical intermediate **II** (INT-1 in Scheme 6), which may be generated by a disproportionation reaction between **I** and indium(0) remaining in the reaction system through a single electron transfer (SET).

Isomerization of the oxygen-centred radical to the carbon-centred radical through a formal 1,2-H shift is well documented and a recent theoretical study has revealed that water accelerates this process through a cyclic transition state involving two water molecules.¹⁶ As shown in Fig. 1, in our case from radical INT-1 with two water molecules (INT-1-2H₂O), the cyclic transition state TS-1-2H₂O with an activation barrier



Scheme 6 Rationalization for the formation of γ -methylenebutenolides **3**.

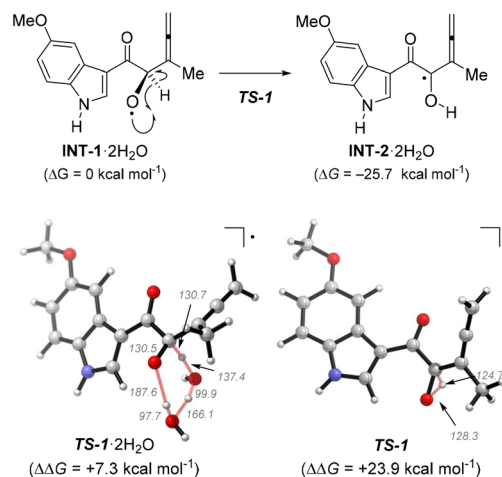


Fig. 1 DFT computation of the radical H shift step. In the chemical formula, water molecules have been omitted for clarity. Interatomic distances are shown in pm.



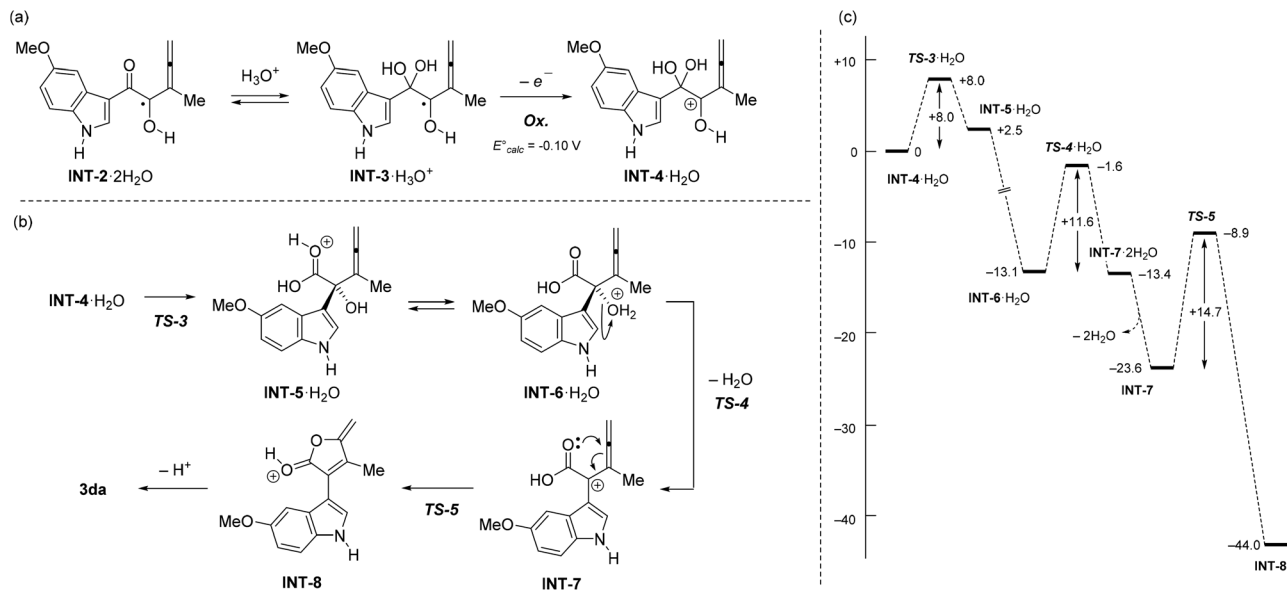


Fig. 2 (a) Considered precursors for the 1,2-Ar migration step. (b) Reaction path from **INT-4**. (c) Free energy profile for the steps from **INT-4** to **INT-8**.

$\Delta\Delta G$ of only +7.3 kcal mol⁻¹ was found. In contrast, a much higher activation energy (+23.9 kcal mol⁻¹) is required for the 1,2-H shift of the isolated radical species (**TS-1**). This result well agrees with our experimental observation that the use of an aqueous medium is essential for obtaining the γ -methylenebutenolide products.

As the following 1,2-Ar migration step, we considered three possibilities: two radical paths from **INT-2** bearing a ketone moiety and **INT-3** bearing a hydrate moiety, which may be generated through acid-catalysed hydration of the thermodynamically stabilised captodative radical **INT-2** ($\Delta\Delta G = 2.1$ kcal mol⁻¹), and one cation-mediated path from cationic hydrate **INT-4** (Fig. 2a). Among these, both radical mechanisms have been ruled out due to the requirement of too high activation energies (please see the ESI†). On the other hand, we successfully found an energetically acceptable path *via* the cationic intermediate **INT-4**·H₂O (Fig. 2b and c). That is, the 1,2-Ar migration with a low activation barrier ($\Delta\Delta G = +8.0$ kcal mol⁻¹) followed by proton-mediated dehydrative lactonization provides the desired γ -methylenebutenolide product **3da**. Here, considering the calculated standard redox potential E_{calc}° between **INT-3**·H₂O and **INT-4**·H₂O (-0.10 V, also see the ESI†), it is most likely that molecular oxygen in the air atmosphere serves as an oxidant for the radical intermediate **INT-3**. Protonated carboxylic acid **INT-5**·H₂O easily isomerizes to more stable oxonium species **INT-6**·H₂O, which can undergo an exergonic dehydrative lactonisation reaction.¹⁷

Conclusions

To sum up, the indium-mediated reaction between (indol-3-yl)-2-oxoacetaldehydes and 1-bromoprop-2-yne in an aqueous

environment resulted in an unexpected formation of γ -methylenebutenolides, which diverts from the conventional metal-mediated reactivity of organic halides and carbonyls. The products are isolated as solids by filtration and purified by simple recrystallization. The current protocol tolerates structural diversity in indole and alkyne moieties and greatly improves the synthetic efficiency of previous methods. DFT calculations provide further support to the involvement of radicals in this chemo- and regio-selective addition/rearrangement process.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

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