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Photoinduced α-Alkenylation of Katritzky Salts: Synthesis of β,γ-Unsaturated Esters

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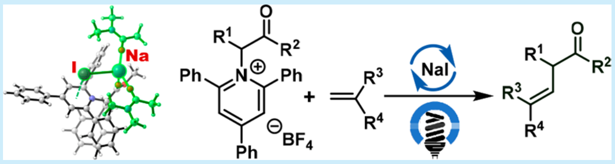
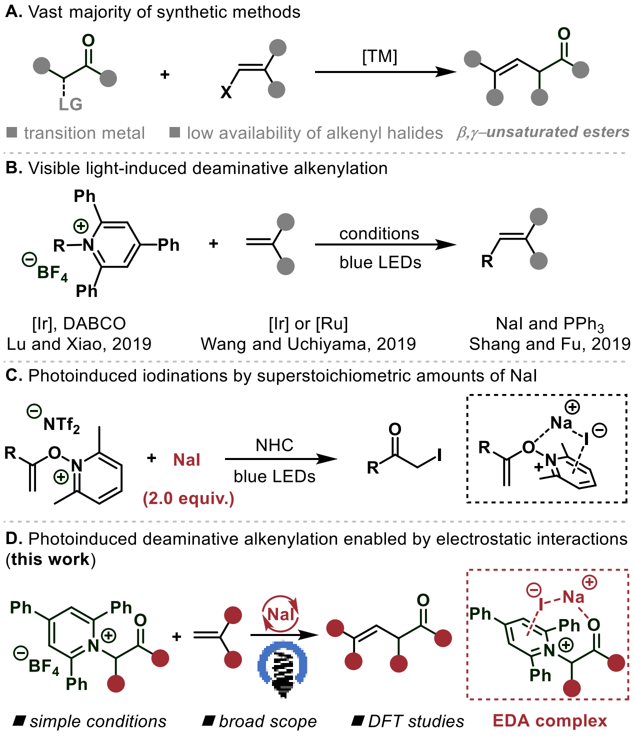
ABSTRACT: β,γ-Unsaturated esters are building blocks in biologically important compounds, pharmaceuticals, and natural products. Because the current synthetic methods often require transition-metal catalysts or lack general variants, we herein describe a simple NaI-involved photoinduced deaminative alkenylation for their synthesis in the absence of photocatalysts and additives. The density functional theory study unveils that the electrostatic interaction of NaI with Katritzky salts is the key to forming the photoactive electron donor−acceptor complex, thus leading to the alkyl radicals for the alkenylation.



The search for efficient strategies to synthesize carbonyl compounds starting from cheap and readily available materials has always been a central goal in modern organic synthesis. In particular, β,γ-unsaturated carbonyl compounds display privileged activity features and find wide applications as valuable synthetic building blocks.[1] Several elegant strategies exist for the synthesis of β,γ-unsaturated esters,[2] including the nickel- or palladium-catalyzed cross-coupling of enolates and alkenyl halides, triflates, and tosylates,[3] the nickel-catalyzed cross-coupling of α-bromo esters with alkenyl bromides,[4] silanes, and Grignard reagents[5] and the one-pot C−H zincation and copper-catalyzed cross-coupling of alkenyliodonium salts,[6] but most require transition-metal catalysis or lack general variants (Scheme 1A). The development of new synthetic routes allowing greater practicality and scope from readily available starting materials is thus highly desirable.

Recently, primary amines, which are abundant natural feedstocks, have emerged as powerful reagents for the generation of alkyl radicals.[7] In 2017, Watson and coworkers first reported the Suzuki−Miyaura cross-coupling of aryl boronic acids, employing Katritzky salts as C-centered radical precursors.[8] The visible-light-induced generation of alkyl radicals has been successfully realized by Glorius and coworkers.[9] In 2019, Lu and Xiao reported an elegant deaminative alkyl-Heck-type reaction for alkene synthesis.[10] Wang and Uchiyama achieved good E/Z selectivity of this transformation by choosing Ir- or Ru-based photocatalysts.[11] Later, Shang and Fu also realized this type of reaction by using the electron donor−acceptor (EDA) concept,[12] where both NaI and PPh_3 were necessary for the generation of alkyl radicals (Scheme 2B).[13] In our previous study, we found that the electrostatic interaction of an alkali metal cation and oxygen enabled the creation of a photoactive EDA complex for the iodination of N-alkenoxypyridiniums[14] (Scheme 2C) and N-hydroxyphthalimide esters.[15] As such, we envisioned that if

Scheme 1. Motivation and Synthetic Strategy



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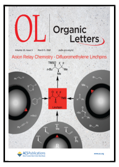

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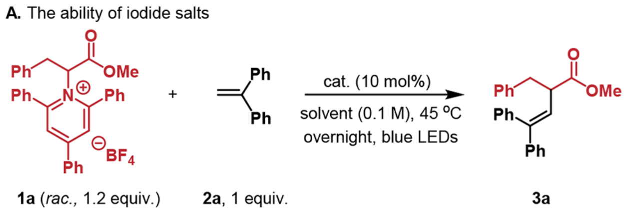
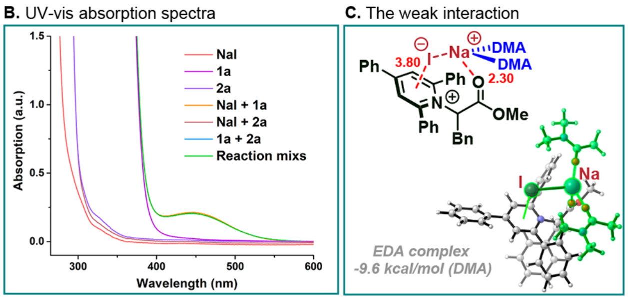
Scheme 2. Optimization of the Reaction Conditions



Entry	Cat.	Solvent	Yield of **3a** (%)[a]
1	NaI	acetone	67
2	NaI	DCM	50
3	NaI	DMSO	74
4	NaI	DMA	86
5	ZnI_2	DMA	70
6	CsI	DMA	81
7	N^nBu_4I	DMA	83
8[b]	LiI	DMA	90
9[b]	KI	DMA	88
10[b]	**NaI**	**DMA**	**95 (81)**
11[c]	NaI	DMA	ND
12[d]	--	DMA	ND



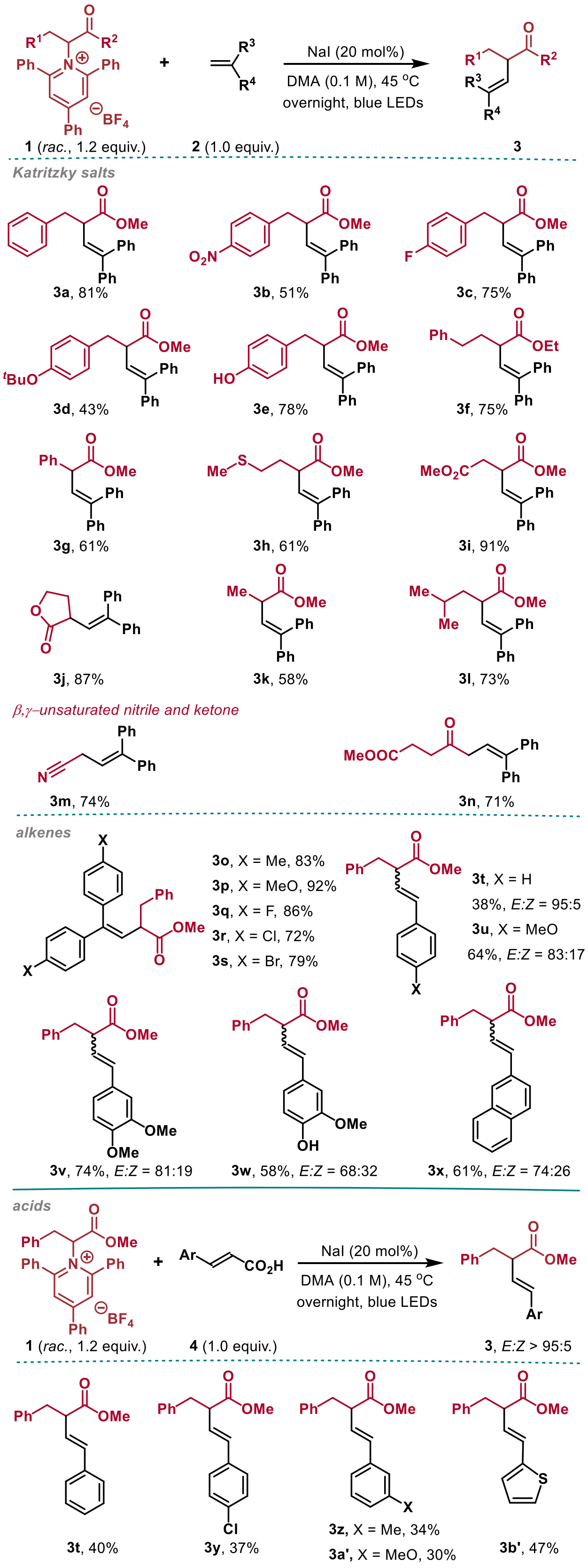
[a]GC yield using *n*-hexadecane as an internal standard. Isolated yield in parentheses. [b]20 mol % of NaI was used. [c]No irradiation. [d]No NaI.

it were possible to form the EDA complex between NaI and Katritzky salts bearing a carbonyl group, then a much simpler method for the generation of alkyl radicals would be unleashed without using expensive external photocatalysts or any additives. We therefore set out to develop a method to access diverse *β*,*γ*-unsaturated carbonyl compounds by using only NaI and readily available Katritzky salts.

Initially, the reaction of the Katritzky salt **1a** and 1,1-diphenylethylene **2a** was investigated (Scheme 2A). We were pleased to find that the reaction with a catalytic amount of NaI under the irradiation of blue light furnished the desired alkenylation product **3a** in 67% yield (entry 1). After optimization (entries 2−10), the yield was increased to 95% when the reaction was carried out in DMA with 20 mol % of NaI (entry 10). Control experiments showed that no reaction was observed without irradiation or NaI (entries 11 and 12).

To confirm our above conjecture (Scheme 1D), we investigated the involvement of the EDA complex. Whereas the Katritzky salt **1a**, **2a**, and NaI individually showed no significant UV−vis absorption in the visible region of the spectra, an obvious red shift of absorption could be observed in the spectrum of the reaction mixture and the mixture of **1a** and NaI. These experiments indicate the formation of a visible-light-active EDA complex (Scheme 2B). Furthermore, using density functional theory (DFT) calculations (see the SI for computational details), we were able to locate the EDA complex with a complexation free energy of 9.6 kcal/mol (Scheme 2C). The optimized structure of the complex with

Scheme 3. Reaction Scope[a]



[a]Yield of isolated products **3** after chromatography.

Na···O=C (2.30 Å) and I⁻···pyridine ring (3.80 Å) distances indicates that the EDA complex is stabilized by the $Na^{\sigma+}\cdots O^{\sigma-}$

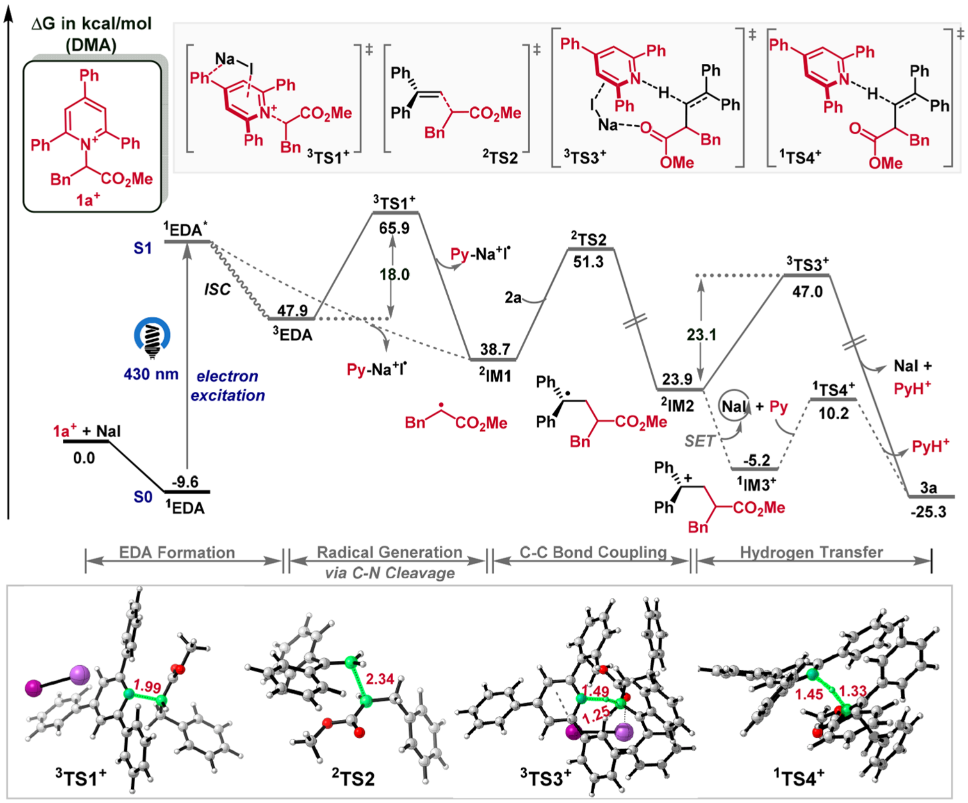


Figure 1. Free-energy profiles (in kcal/mol) for the reaction of **1a** with **2a** in dimethylacetamide.

electrostatic interaction and the I$^{\sigma-}\cdots\pi$ anion−π interaction. The complex was predicted to feature an absorption peak at 430 nm, which is in agreement with the UV−vis spectrum of NaI and **1a**. The absorption originates from excitation from the iodine lone pair to the π^* orbital of the pyridine ring.

With the optimized conditions in hand, we then investigated the generality of this protocol (Scheme 3). A series of phenylalanine-derived Katritzky salts bearing electron-donating or electron-withdrawing substituents (4-$NO_2C_6H_4$, 4-FC_6H_4, 4-*t*$BuOC_6H_4$, and 4-HOC_6H_4) reacted smoothly and gave the corresponding products **3a**−**e** in 43−81% yields. This was also true for the homophenylalanine- and phenylethylamine-derived Katritzky salts, giving rise to products **3f** and **3g**. Moreover, the method tolerated a variety of functional groups, such as thioether, esters, ketone, and nitrile (**3h**−**n**). The effect of alkenes was examined as well. Both electron-donating (4-Me and 4-MeO) and electron-withdrawing (4-F, 4-Cl, and 4-Br) groups on the phenyl ring of 1,1-diphenylethylenes were tolerable and afforded the desired products **3o**−**s** in good yields. Notably, the reaction of the styrene gave the corresponding β,γ-unsaturated product **3t** with excellent diastereomeric ratios, albeit in somewhat decreased yield. In addition, substituted styrenes were also suitable reaction partners, whereas a decrease in *E*/*Z* selectivity was observed (**3u**−**x**).

The reaction scope of this protocol was further demonstrated by using widely available carboxylic acids as starting materials. Various substituted cinnamic acids were readily reacted under the standard reaction conditions, and the corresponding products (**3t** and **3y**−**b′**) were obtained with high *E*/*Z* ratios.

To understand the reaction mechanism, we performed DFT calculations to construct the free-energy profile for the photoinduced NaI-catalyzed reaction of **1a**$^+$ and 1,1-diphenylethylene (**2a**). According to the computational results, we propose a plausible mechanism, as illustrated in Figure 1.

Starting with the electron donor−acceptor complex (namely, ^{1}**EDA**), the blue light first excites the singlet ground state ^{1}**EDA** to the first singlet excited state ^{1}**EDA***. Subsequently, ^{1}**EDA*** undergoes homolytic C−N bond cleavage to generate the alkyl radical through two possible mechanisms. It may take place on the first singlet excited state, directly giving the ^{2}**IM1** radical. Previously, we have shown that the first singlet excited state of an EDA complex could undergo homolytic bond cleavage without an apparent barrier.[14] Alternatively, ^{1}**EDA*** may convert to the triplet ^{3}**EDA** via intersystem crossing; then ^{3}**EDA**, breaks the C−N bond via ^{3}**TS1**$^+$ to give the ^{2}**IM1** radical with a barrier of 18.0 kcal/mol. It is not certain which pathway is preferred, but it is certain that the ^{2}**IM1** radical can be generated. After the radical generation, the resultant radical ^{2}**IM1** attacks the terminal carbon of **2a** via ^{2}**TS2** to form the C−C bond with a low barrier of 12.6 kcal/mol, leading to ^{2}**IM2**. We considered two mechanisms to convert ^{2}**IM2** to the final product **3a**. On the one hand, the radical Py−Na$^+$I$^\bullet$ released from radical generation abstracts a hydrogen atom from ^{2}**IM2** via ^{3}**TS3**$^+$ with a barrier of 23.1 kcal/mol to afford **3a**. The regeneration of the NaI catalyst is achieved via intramolecular electron transfer from the PyH fragment and Na$^+$I$^\bullet$, with the byproduct PyH$^+$ being stabilized by the counteranion (BF_4^-). On the other hand, Py−Na$^+$I$^\bullet$ and ^{2}**IM2** first undergo intermolecular single-electron transfer (SET) to regenerate the catalyst NaI, giving ^{1}**IM3**$^+$ and Py. Then, Py deprotonates ^{1}**IM3**$^+$ via ^{1}**TS4**$^+$ with a barrier of 15.4 kcal/mol, giving **3a** and PyH$^+$. Overall, the reaction has accessible kinetic barriers with gradually downhill thermodynamics, rationalizing the occurrence of the reaction.

In summary, we herein developed a much simpler method for the synthesis of β,γ-unsaturated compounds by using only the weak interactions of NaI. The DFT studies depicted that the weak interaction of Katritzky salt and NaI hastens the formation of the EDA complex and revealed a comprehensive mechanistic understanding of the radical reaction process. The method is characterized by operational simplicity, generality, no need for the use of transition-metal catalysts or any additives, and easily accessible starting materials. In light of the promising properties of β,γ-unsaturated compounds as well as the potential applications of weak interactions, we anticipate that the presented strategy will facilitate the pharmaceutical and photochemical synthesis arenas.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c04287.

Experimental details, DFT calculations, characterization data, and spectra (PDF)

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Notes

The authors declare no competing financial interest.

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