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Ahmed Chaambi, Gülbin Kurtay, Raoudha Abderrahim, Frédéric Robert, Yannick Landais.
Aryl Radical-Mediated Alkenylation of Alkyl Halides. *Helvetica Chimica Acta*, 2019, 102 (8),
10.1002/hlca.201900140 . hal-02988393

HAL Id: hal-02988393

<https://hal.science/hal-02988393>

Submitted on 8 Jan 2021

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Aryl radical-mediated Free-radical alkenylation of Alkyl Halides

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Free-radical alkenylation of a range of alkyl iodides has been carried out leading to the desired olefins in moderate to good yields under mild conditions. The process is initiated by an aryl radical which abstracts the iodide from the alkyl iodide to form a C-centered radical intermediate, the addition of which onto a vinylsulfone providing the final vinylsulfone. The aryl radical is generated *in situ* through a single-electron transfer from an electron donor-acceptor complex (EDA) formed between a diaryliodonium salt ($\text{Ph}_2\text{I}^+ \text{PF}_6^-$) and triethylamine.

Keywords: Aryl radical • alkenylation • diaryliodonium • Electron Donor-Acceptor • vinylsulfone

Introduction

Free-radical alkenylation (also called vinylation) of alkyl halides constitutes a powerful C-C bond forming process offering an access to a wide range of olefins.^[1-8] The reaction proceeds through the addition of a C-centered radical **IV**, generated from an alkyl halide precursor **I**, onto an olefinic acceptor **II**. This leads to a new radical intermediate **V**, affording the final unsaturated system **III** through β -elimination (Figure 1).^[1,4-7] Among the broad range of alkenyl acceptors (varying the Y substituent), sulfur derivatives,^[5,7,9-11] and in particular vinylsulfones,^[7,11-16] have attracted the most interest due to their easy accessibility and relative innocuousness. The generation of radical precursors **IV** from alkyl halides **I** generally implied the use of tin reagents such as R_3SnSnR_3 ($\text{R}=\text{Me}$, $n\text{Bu}$) to initiate the reaction.^[7] In this efficient process, the released sulfonyl radical ($\text{Y} = \text{SO}_2\text{R}'$) was shown to react with ditin, forming a new R_3Sn radical, which sustained the radical chain.^[1,7-8] However, due to the perceived toxicity of tin reagents and the contamination of final products with tin residues, alternative strategies have been developed using for instance the Pd/light-initiated radical reactions, as recently reported by Ryu and co-workers.^[17]

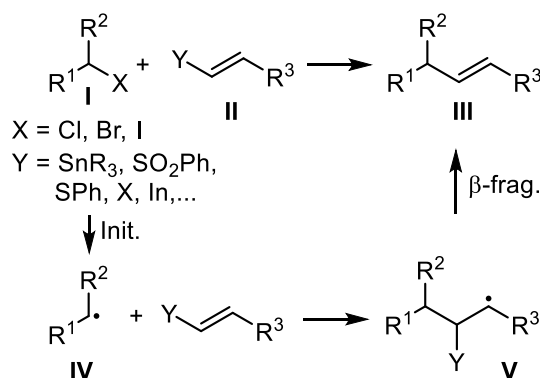


Figure 1. General free-radical alkenylation of alkyl halides.

In the course of our studies on multi-component olefin carbo-functionalization processes,^[7,11] we also devised recently a radical alkenylation of alkyl iodides, in which aryl radicals, generated *in situ* from boronic acids, were used as initiators.^[18] The highly reactive aryl radicals are known to abstract iodine atom from alkyl iodides with rate constant close to $k \sim 10^9 \text{ M}^{-1} \text{ s}^{-1}$,^[19] a fast process which outperforms all other competitive processes that might occur in the reaction medium. Using this method, carbo-cyanation of olefins and addition of alkyl iodides to vinylsulfones were carried out, affording respectively the desired nitriles and olefins in moderate to good yields. Although efficient, the generation of the aryl radical requires the use of an excess of the costly *t*-BuON=NOt-Bu (DTBHN), as the reaction is a non-chain process, the released PhSO₂ radical being unable to regenerate the aryl radical from phenylboronic acid. In the course of our search for a better source of aryl radicals, our attention was drawn by recent studies on electron donor-acceptor complexes (EDA) formed between diaryliodonium salts (Ph₂I⁺OTf⁻) and electron donors.^[20-24] Such complexes were shown to provide aryl radicals upon single electron transfer (SET) under thermal or photochemical activation (Figure 2).^[25-26] Lakhdar and co-workers elegantly illustrated the reactivity of these EDA complexes and the utility of aryl radicals for the generation of phosphinoyl radicals and their subsequent reaction with isonitriles.^[23] Earlier, Chatani et al described the arylation of pyrroles and the generation of aryl radicals through a charge transfer complex between a diaryliodonium salt and electron-rich pyrroles.^[22] Based on these premises, we devised an efficient modification of our aryl-mediated alkenylation of alkyl iodides, based on the generation of a phenyl radical from an EDA complex resulting from the association between PhI⁺PF₆⁻ and Et₃N. A scope and limitation of the methodology is provided and a mechanism based on literature precedent and isolation of by-products is proposed to rationalize the course of the reaction between alkyl halides **1** and bis-sulfone **2** (Figure 2).

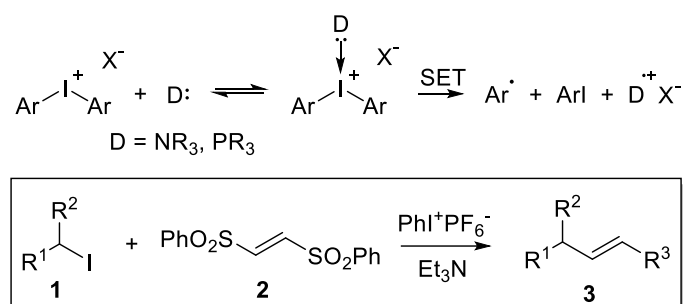


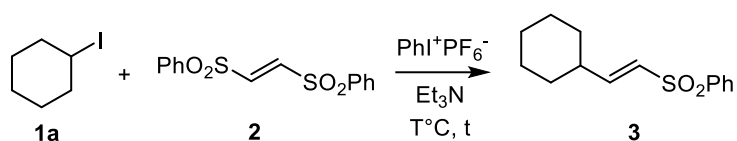
Figure 2. EDA complex and generation of aryl radicals. Application to the alkenylation of alkyl iodides.

Results and Discussion

Based on previous studies on the generation of aryl radicals from iodonium salts-Amine EDA complexes,^[21,23-24] we first optimized the process, using cyclohexyl iodide **1a** as an alkyl iodide model, bis-sulfone **2**, PhI⁺PF₆⁻ and Et₃N as the electron donor in DMF. Results are summarized in Table 1. The reaction was first performed at 65°C in the presence of 1.5 equiv. of PhI⁺PF₆⁻, and 2 equiv. of Et₃N, leading to the formation of the expected olefin **3a** in 52% isolated yield (Table 1, entry 1). When the reaction was repeated under similar conditions but in the absence of Et₃N, **3a** was not formed showing the importance of the amine for a smooth running of the reaction (Table 1, entry 2). The addition of a large excess of Et₃N led to a slight but not significant increase in yield (Table 1, entry 3). Under the same conditions, but under visible-light irradiation at room temperature, using a blue LED lamp at 433 nm, the reaction led to **3a** with the same yield (Table 1, entry 4). During reactions above, we also noticed the formation of various amount of PhSO₂Ph, likely arising from the reaction between the released PhSO₂ group from bis-sulfone **2** and PhI⁺PF₆⁻,^[27] indicating that a part of the iodonium reagent was consumed in undesired processes. The reaction was thus repeated using an excess of PhI⁺PF₆⁻ (3

equiv.) under thermal activation, which resulted in the formation of **3a** in a more satisfying 80% yield (Table 1, entry 5). These optimized conditions were then used in the following investigations.

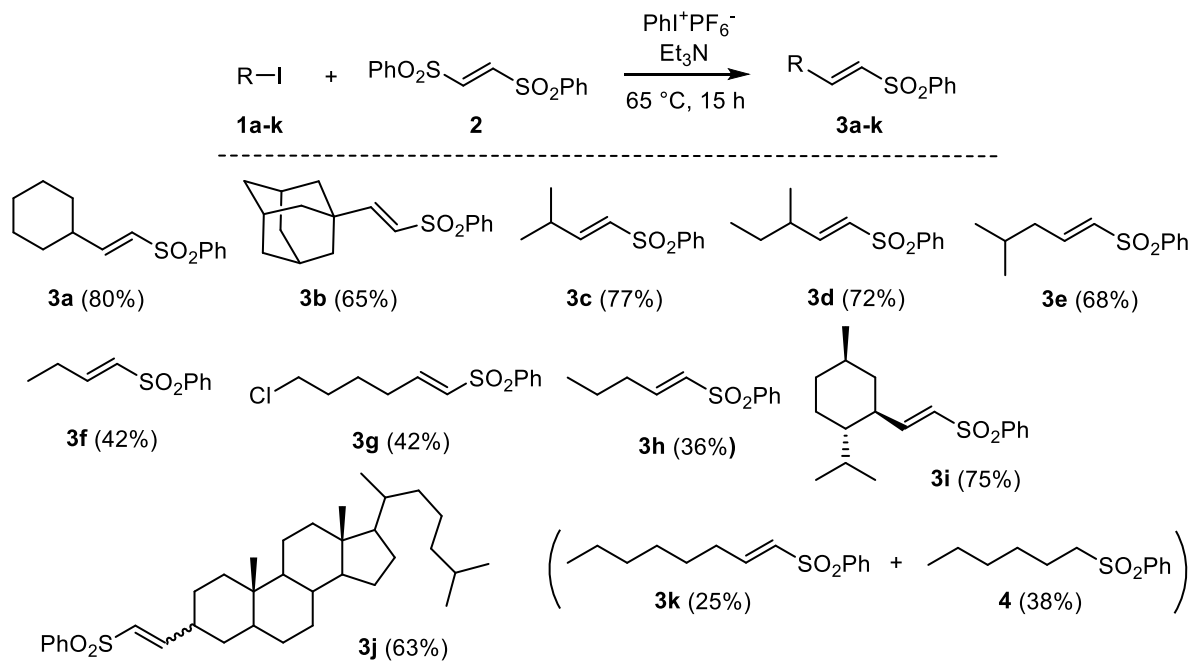
Table 1. Optimization of the alkyl iodides alkenylation process.



Entry ^[a]	Et ₃ N (equiv.)	Ph ₂ I ⁺ , ⁻ PF ₆ (equiv.)	T (°C)	time (h)	Yield
1	2	1.5	65	15	52
2	-	1.5	65	24	-
3	20	1.5	65	15	56
4 ^[b]	20	1.5	20	48	56
5	2	3.0	65	15	80

^[a] The reaction was carried out using **1a** (0.5 mmol), **2** (1 mmol) in DMF in the presence of Ph₂I⁺,⁻PF₆ and Et₃N under thermal conditions. ^[b] The reaction was performed under visible light irradiation (blue LED (433 nm)).

The optimized conditions of the alkenylation reaction were extended to several alkyl iodides **1b-k** leading to vinylsulfones **3b-k** with moderate to good yields (Scheme 1). Alkyl radicals, whether primary, secondary or tertiary, all react effectively with bis-sulfone **2**, although with slightly lower yields in general for the former. As mentioned before, in all reactions, PhSO₂Ph was also formed with yields ranging between 50-55%, but was easily discarded from the desired olefins, through silica gel chromatography. Starting from diastereomerically pure menthyl iodide **1k**, the corresponding olefin **3i** was obtained in good yield and high diastereocontrol, with the stereochemistry as shown. A 6:4 diastereomeric mixture of 3β-iodo-5α-cholestane **1j**,^[28] under similar conditions led to olefin **3j** as a 6:4 mixture of diastereomers. Finally, it is worth noticing in the case of n-hexyl iodide **1k**, the formation of hexylphenylsulfone **4**, along with the desired product **3k**. The isolation of such an alkylsulfone from primary iodide **1k** was not observed with secondary and tertiary iodides, pointing toward a S_N2 type reaction between iodide **1k** and a putative phenylsulfinate anion.^[29] The presence of the latter, tentatively rationalized below, could also explain the formation of PhSO₂Ph through reaction with excess Ph₂I⁺,⁻PF₆ (*vide infra*).^[27]



Scheme 1. Ph₂I⁺, PF₆⁻-Et₃N mediated alkenylation of alkyl halides.

Based on experimental evidences, and drawing on the studies of Lakhdar and co-workers,^[23] a mechanism for this radical alkenylation is proposed in Figure 3. The reaction likely begins with the association between Et₃N and Ph₂I⁺PF₆⁻, resulting in the corresponding strongly colored EDA complex **A** (eq. 1). Single-electron transfer from **A** under thermal activation likely generate the required phenyl radical. Absorption of the EDA complex in the visible region also allowed its activation and the SET process to occur using simple blue LEDs, albeit with generally lower yields and longer reaction time. The aryl radical then abstracts the iodine atom from the alkyl iodide **1** to form the alkyl radical **R** (eq. 2), which is trapped by the bis-sulfone **2**, affording the desired product **3** and the phenylsulfonyl radical (eq. 3).^[18] As mentioned above, the formation of both PhSO₂Ph and the alkylsulfone **4** may be rationalized by the formation at some stage of a phenylsulfinate anion (eq. 6 and 7 respectively). A putative recombination between n-hexyl or phenyl radicals and the PhSO₂ radical, is unlikely considering the low concentration of these radical species in the reaction medium. Several pathways maybe envisioned to explain the formation of PhSO₂[·]. Phenylsulfonyl radical is known for its ability to abstract allylic hydrogens to form PhSO₂H,^[30-31] then leading to the corresponding sulfinate in the presence of excess Et₃N. Hydrogen abstraction from vinylsulfone products **3** was ruled out due to the absence of clear evidence of isomerized products including allylsulfones in the medium. However, an alternative hydrogen transfer seemed more favorable considering the presence of the Et₃N^{·+} radical-cation **i** formed in the first step (eq. 1). Recent studies indicate that the C-H bond α to nitrogen in the aminium **i** is significantly weakened with a BDE estimated to ~42 kcal/mol.^[32] Such a weak bond and the expected high concentration of the aminium **i** in the medium would thus allow an hydrogen atom abstraction^[32-34] by the PhSO₂ radical, leading to iminium **ii** and PhSO₂H (eq. 4), then to the corresponding sulfinate **iii** through deprotonation by excess Et₃N (eq. 5). Although we were unable to isolate diethylamine and acetaldehyde resulting from the hydrolysis of iminium **ii** upon work-up, this route appears reasonable to explain the presence of PhSO₂Ph and sulfone **4** in large amount.

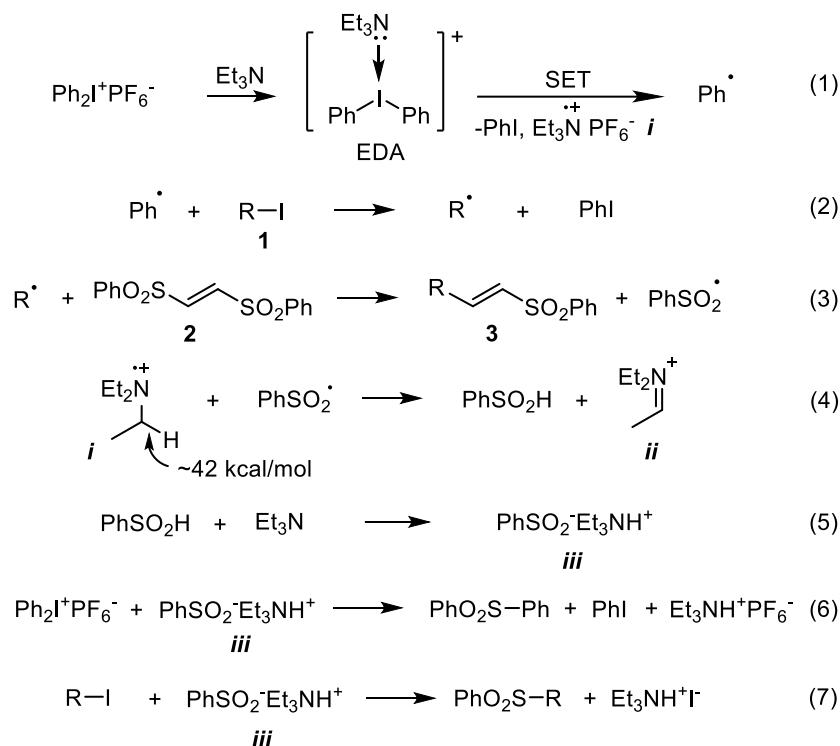


Figure 3. Mechanism of the aryl radical-mediated alkenylation of alkyl iodides.

Conclusions

In summary, we have reported a straightforward alkenylation of alkyl halides, mediated by aryl radicals. The latter are generated through a SET process from an EDA complex formed *in situ* between a diaryliodonium salt (acceptor) and Et₃N (electron-donor). An excess of both the iodonium salt and the amine are required to reach good yields of olefins, as a portion of the iodonium salt is consumed through a side-reaction involving a phenylsulfinate, generated during the reaction. The latter may thus react with more reactive primary iodides through a S_N process, explaining the lower yields in these cases as compared to those obtained with secondary and tertiary iodides. Despite the modest yields with primary iodides, good yields of olefins are obtained starting from commercially available reagents. Other sulfonyl acceptors,^[7] including cyanides, oximes and alkynes should react under these conditions, which are now studied in our laboratory and will be reported in due course.

Experimental Section

Diphenyliodonium hexafluorophosphate alkenylation of alkyl iodides - General procedure

A single-neck-round-bottomed flask was charged with the corresponding alkyl iodide **1** (0.5 mmol), the *E*-1,2-bis(phenylsulfonyl)ethylene **2** (1 mmol), the diphenyliodonium hexafluorophosphate (1.5 mmol), triethylamine (1 mmol) and DMF (0.2 M). The reaction mixture was degassed by three consecutive freeze/pump/thaw cycles. The flask was sealed under vacuum, and the reaction mixture was heated at 65°C for 15 to 24 h (depending on the completion of the reaction monitored by TLC) under an argon atmosphere. The reaction was then quenched with a 0.1M HCl solution (10 mL) then extracted with CH₂Cl₂ (3x20 mL). After separation of the aqueous layer, the organic layer was saturated with brine, dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The target compound **3** was finally obtained by column chromatography using the adequate petroleum ether: ethyl acetate mixtures as the eluent.

Author Contribution Statement

G. K. and A. C. contributed equally and performed the experiments and characterization of all materials. Y. L. and F. R. supervised the work and wrote the article. All authors commented on the manuscript.

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