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Dielectrophilic Approach to Sequential Heterofunctionalization of Ethylene from Vinylthianthrenium Salt

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Dedicated to Prof. Marco Bandini for his 50th Birthday.

Vinyl thianthrenium salt is a compound with interesting electrophilic properties capable of reacting with two distinct nucleophiles. By using β-keto esters as one of the reaction partners, it is possible to insert a chain of two carbon atoms with a further functionalization under mild conditions. We have studied this new methodology which involves the stepwise formation of a C–C and a C–X bond (with X = N, O, etc.) in one step without the use of metals. Depending on the reaction conditions and the starting ketoester, a varied reactivity has been observed and described.

Introduction

The introduction of two functionalities to π bonds is a highly effective and straightforward method to providing molecular complexity and diversity using easily accessible starting materials. Several different strategies have emerged in recent years for the 1,2-difunctionalization of alkenes, enabling the simultaneous incorporation of two functional groups across the C=C double bond.[1] However, the heterofunctionalization of alkenes, which involves the addition of two distinct groups to the double bond, is still an area of ongoing development.[2] One potential approach involves the activation of the π bond using hypervalent iodine[3] or by the conversion of the functional group into a 1,2-dielectrophile, such as a halonium ion or 1,2-dihalide.[4] Subsequently, these species can be selectively attacked by a first nucleophile followed by a second one (Figure 1, A). This approach has been proven to yield satisfactory outcomes using bifunctional nucleophiles or in intramolecular reactions where the arrangement of nucleophiles within the molecule facilitates the desired regioselectivity suppressing the double attack from the same nucleophile. However, the intermolecular variant of this approach encounters peculiar challenges including uncontrolled sequential addition of the same nucleophiles, poor regioselectivity and potential elimination reactions.

In a groundbreaking study, Mukaiyama[5] made a significant discovery regarding alkenyl diphenyl sulfonium salts,[6] identifying these substrates as a 1,2-dielectrophilic double bond. Aggarwal reported the synthesis of morpholines, thio-morpholines, and piperazines from the corresponding β-amino alcohols, thiols or amines using a simply accessed diphenyl vinyl sulfonium triflate.[7] Additionally, compounds containing an activated methylene group, primary amines, or sulfonamides undergo reactions with vinyl sulfonium salts to yield cyclopropane[8] or aziridine[9] derivatives.

Alkenyl thianthrenium salts were a suitable alternative to the corresponding acyclic derivatives for multiple nucleophilic attack[10] and recent research studies have unveiled a range of diverse and distinct electrophilic reactivity stemming from C(sp^2)- and C(sp^3)-thianthrenium salts.[11] Interestingly, dicationic thianthrenium and dithianthrenium salts, obtained through oxidative conditions, exhibit dielectrophilic properties (Figure 1, B). These salts are intriguing capable of undergoing site-selective intermolecular attack by C– or N– nucleophiles in the presence of a base, without the assistance of transition metals. This synthetic strategy allows the synthesis of allylic amines,[12] aziridines,[13] and cyclopropanes[14] from alkenes via their thianthrenium salts utilizing secondary and primary amines, as well as carbon pronucleophiles, respectively. Additionally, Wickens demonstrated the utility of these salts in a highly regioselective substitution reaction with phthalimide anions, resulting in the formation of a monosulfonium salt (Figure 1, C).[15] This key intermediate can then be further substituted with various nucleophiles, enabling the synthesis of diverse mole-

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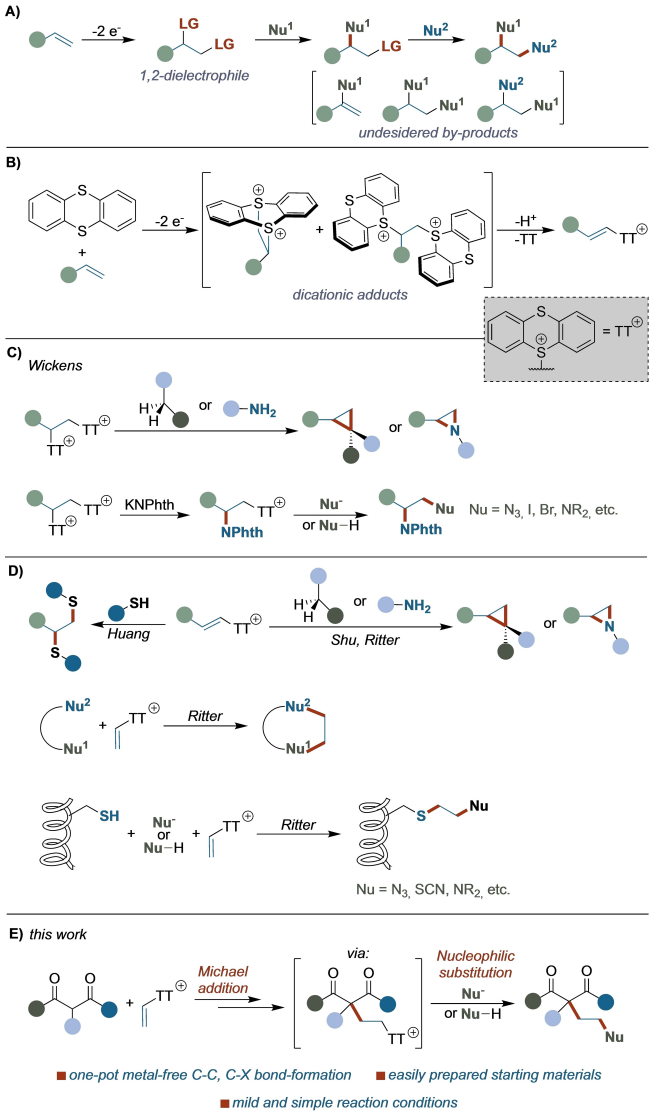

Figure 1. 1,2-Difunctionalization of alkenes.

cules with vicinal functionalization and exceptional regioselectivity.

In these studies, an alkenyl thianthrenium salt, obtained by the action of a base from the dicationic adducts, was suggested as the key intermediate (Figure 1, B).[14] In 2020, Ritter explored the reactivity of alkenyl thianthrenium salts introducing an easy preparation of these substrates simply obtained from unactivated olefins and thianthrene oxide by a direct and regioselective C–H thianthrenation reaction.[16] The utility of alkenyl thianthrenium compounds as alkenylating reagents was demonstrated in various palladium-[14,17] and rhodium[18]-catalyzed cross-coupling reactions, and in ruthenium-based catalysis.[14] These compounds were silylated or borylated by copper-catalyzed reactions[19] and used in the Heck-type reaction with different nucleophiles for the formation of C–C, C–N, C–P, and C–S bonds.[20] Furthermore, alkenyl thianthrenium salts were employed in the metal-free allylic C–H nitrogenation, oxygenation, and carbonation of alkenes.[21] Recently, Soós developed a Kornblum/Ganem-like oxidation method using alkenyl thianthrenium salts to obtain α,β-unsaturated carbonyl compounds.[22] Similar to dicationic thianthrenium adducts, alkenyl thianthrenium salts serve as useful 1,2-dielectrophile for the intermolecular metal-free cyclopropanation and aziridination of alkenes with XH_2 (X = N, C)[23] and for the preparation of 1,2-dithioalkanes by action of the arylthiols (Figure 1, D).[24]

Vinyl thianthrenium salt, simply obtained from ethylene gas at atmospheric pressure,[25] or from vinyl silane[25] has proven to be a highly practical and versatile reagent for vinylation. Interestingly, the utility of this reagent spans various areas. As noted by Aggarwal with diphenyl vinyl sulfonium salt,[7] the corresponding thianthrenium derivative can be employed in the annulation chemistry towards the synthesis of (hetero)-cycles (Figure 1, D).[25] Furthermore vinyl thianthrenium salt find application in the *N*-vinylation of heterocyclic compounds,[25] and in the palladium-catalyzed cross-coupling reactions.[26] It has been elegantly utilized as 1,2-dielectrophile in the bioconjugation of proteins (Figure 1, D).[27] In fact, forming *in situ* an episulfonium intermediate between cysteine moiety of the protein and vinyl thianthrenium, conjugation with a diverse array of bioorthogonal nucleophiles can be achieved in a single step.

The key aspect shared by the cited reactions is the ability of vinyl thianthrenium to act as a dielectrophile alongside suitable nucleophiles. Additionally, using acidic nucleophiles, strongly basic conditions are avoided, and alkylations are taking place in mild conditions. In this context, we wondered to understand if the reactivity of vinyl thianthrenium salt could be extended to the selective and sequential introduction of two different nucleophiles to the double bond employing carbon- and heteronucleophiles (Figure1, E). Following our idea, the procedure allows the introduction of a functionalized two carbon chain to a nucleophilic carbon center. Moreover, our proposition is to leverage the distinctive reactivity exhibited by alkenyl thianthrenium salts in comparison to other Michael acceptors. Specifically, upon the Michael addition of the C-nucleophile and subsequent protonation, the formation of alkyl thianthrenium salts occurs. This species can act as a reactive electrophile versus other nucleophiles present in solution. To ensure the optimal outcome of the reaction, it is necessary to prevent elimination reactions and nucleophilic attack by the same nucleophile on both electrophilic positions of the vinyl thianthrenium. To address this target, we focused on simple 2-alkyl-1,3-ketoesters, to prevent the formation of previously described cyclopropanes, conducting a systematic investigation by varying ketoesters and heteronucleophiles. Quite surprisingly, the outcome of the reaction depended on the specific ketoester employed and yields different products based on the nature of the nucleophiles and on the reaction conditions. In this paper, we report the results of our studies and investigations.

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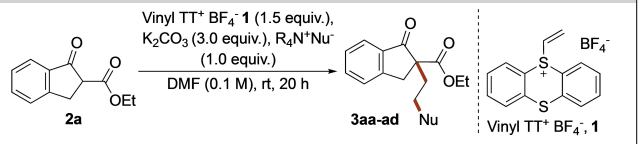
Results and Discussion

The investigation started examining the reaction between the readily prepared and stable vinylthianthrenium tetrafluoroborate[25] **1** and the ethyl indanone-2-carboxylate **2a** as pro-nucleophile (Table 1). The reaction was conducted in *N*,*N*-dimethylformamide (DMF) with potassium carbonate (K_2CO_3) serving as base to generate the nucleophilic enolate. Additionally, a second nucleophilic anion was used in the form of tetraalkylammonium salt. After 20 hours, the exclusively formation of the product resulting from the 1,2-heterofunctionalization of the ethylene moiety (**3aa**–**ad**) was observed in satisfactory yields, without any homofunctionalization or elimination products being detected. The presence of the tetraalkylammonium cation (R_4N^+) is mandatory in the transformation. In fact, when NaN_3 was used under reaction conditions, significant reductions in yield were observed (see Supporting Information). Due to the limited solubility of potassium carbonate in the reaction solvent, the amphiphilic cation (R_4N^+) has the potential to serve as a phase transfer catalyst (PTC),[28] facilitating the transfer of the carbonate anion from the solid phase to the liquid one.[29]

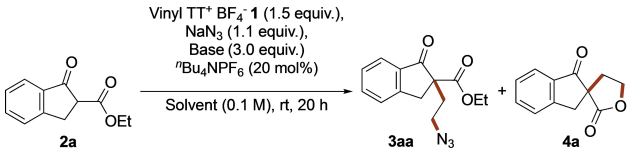
Table 1. Reaction of **2a** with **1** and different nucleophilic ammonium salts.



Entry[a]	$R_4N^+Nu^-$	Product	Yield%[b]
1	$Et_4N^+N_3^-$	**3aa**	86
2	$BnEt_3N^+Cl^-$	**3ab**	73
3	$^nBu_4N^+Br^-$	**3ac**	68
4	$^nBu_4N^+I^-$	**3ad**	81

[a] Reaction was performed on 0.1 mmol scale. [b] Isolated yield after chromatographic purification.

Table 2. Condition screening for functionalization of **1** with **2a** and NaN_3.



Entry[a]	Solvent	Base	Yield% **3aa**[b]	Yield% **4a**[b]
1	DMF	K_2CO_3	83 (72)[c]	3
2	**CH_3CN**	**K_2CO_3**	**92 (85)**[c]	**0**
3	DMSO	K_2CO_3	90 (78)[c]	0
4	DCM	K_2CO_3	34	57
5[d]	CH_3CN	KOH	41	10
6	CH_3CN	Cs_2CO_3	80 (61)[c]	0
7[e]	CH_3CN	K_2CO_3	66 (58)[c]	0
8[e]	DMSO	K_2CO_3	84 (72)[c]	0
9[f]	CH_3CN	K_2CO_3	–	82 (73)[c]
10[f]	DCM	K_2CO_3	–	93 (75)[c]

[a] Reaction was performed on 0.05 mmol scale. [b] ^{1}H-NMR yield determined with trichlorethylene as internal standard. [c] Isolated yield after purification by flash column chromatography. [d] Decomposition of **2a** was observed. [e] Reaction performed in absence of $^nBu_4NPF_6$. [f] Reaction performed in absence of NaN_3.

Based on the promising results obtained, we investigated the feasibility of employing various nucleophiles in the form of simple metal salts, in presence of a phase transfer catalyst. Starting from the conditions reported above, the nucleophilic tetraethylammonium azide was substituted with a catalytic amount of tetrabutylammonium hexafluorophosphate ($^nBu_4NPF_6$, 20 mol%) and 1.1 equiv. of NaN_3 (Table 2). Under these reaction conditions the desired product **3aa** was successfully isolated in good yields in different solvents (Table 2, entries 1–3). Interestingly, employing DCM as solvent led to the unexpected formation of spiro lactone **4a** as the main product (Table 2, entry 4). Remarkably, the same structure was obtained exclusively even in the absence of sodium azide (Table 2, entries 9 and 10). The formation of **4a** could be ascribed to the intramolecular attack of the ester's oxygen to the alkylsulfonium salt intermediate, followed by subsequent hydrolysis (see Infra). Moreover, the use of nonpolar solvents results in a lower concentration of the azido ion in solution, favoring the intramolecular attack over the intermolecular one, thereby enhancing the formation of **4a**. The relevance of the base and nucleophile concentrations in solution became evident when the reaction was conducted without the phase transfer catalyst (Table 2, entries 7 and 8). In both cases, a decrease in reaction yields was observed compared to the standard conditions, although the effect was less pronounced with DMSO. To finalize the evaluation of the various reaction parameters, Cs_2CO_3 and KOH were tested (Table 2, entries 5 and 6) with poor results; in particular, the use of strong KOH base resulted in the decomposition of compound **2a**. Any attempts to use chiral ammonium salts and chiral bases to perform an enantioselective synthesis of the spiro lactone **4a** was unsuccessful (see Supporting Information).

After the systematic evaluation of all reaction parameters and although the reaction proceeds with satisfactory yield in different solvents, for practical considerations, further investigations will be carried out specifically in CH_3CN and DMF. Therefore, compound **2a** was coupled with different nucleophiles in the two solvents (Scheme 1). Halogen anions have proven to be suitable nucleophiles, yielding the desired products (**3ab**–**3ad**) in good yields, particularly when CH_3CN was used as solvent. Notably, the formation of the by-product **4a** was not observed. On the other hand, less reactive nucleophile,[30] such as carboxylate ion, exhibited slightly lower result, leading to the formation of both product **3ae** and the lactone **4a**. Moreover, employing an over-stoichiometric amount of ethanol (60 equiv.) it was possible to isolate the ether **3af** in 81% of yield. This excess is essential in promoting the intermolecular nucleophilic attack over the intermolecular one. In fact, when only 1.1 equivalents of ethanol were used, only the product **4a** was observed (see Supporting Information). Furthermore, acid phenols and thiols were found to react

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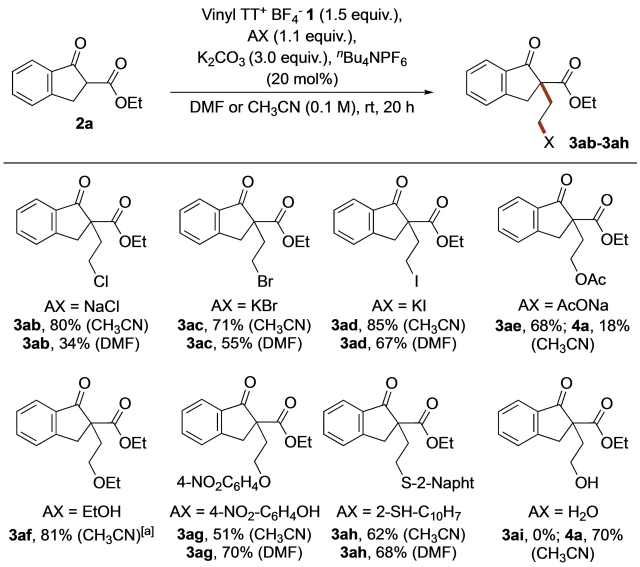


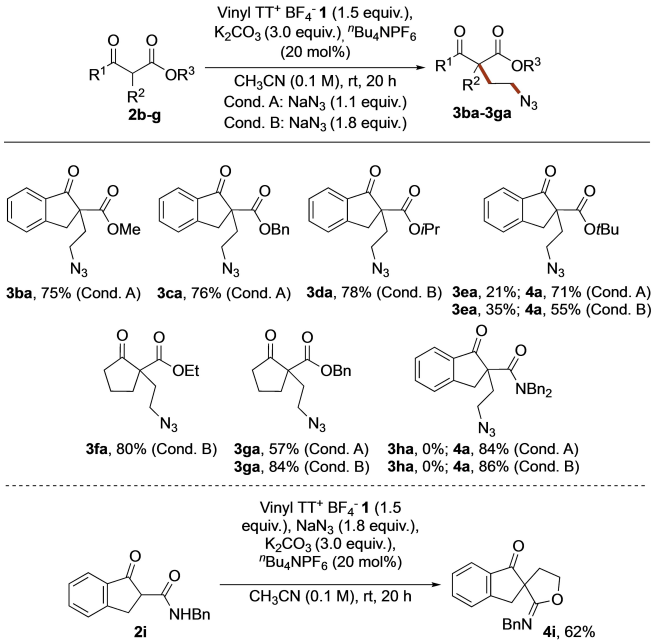
Scheme 1. Reaction of **2a** with **1** in presence of different nucleophiles. [a] 60 equiv. of EtOH were used in the reaction.

effectively, yielding the desired products (**3ag** and **3ah**) in good yields. For these specific nucleophiles, DMF was identified as the optimal solvent. Finally, when water was tested as potential nucleophile only the formation of the lactone **4a** was observed. C-nucleophiles as silyl-enol ethers and stannanes were also tested in the reaction with poor results and the lactone **4a** was the only product observed (see Supporting Information).

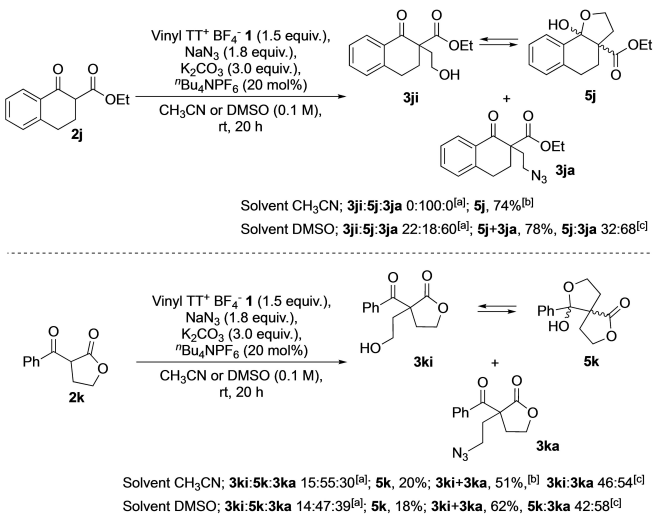
To demonstrate the feasibility of the method, various keto esters were investigated in the presence of NaN_3 as hetero-nucleophile, as depicted in Scheme 2. By increasing the steric hindrance on the ester moiety, a more favorable formation of lactone **4a** was observed. For the bulky *tert*-butyl ester (**2e**) only 21% of the desired product (**3ea**) was isolated, in comparison to the 71% obtained for **4a**. However, increasing the amount of NaN_3 to 1.8 equiv. the yields for demanding substrates were increased and the hetero-difunctionalized products were obtained in good yields. A diverse behavior was observed for the amide derivatives obtained from secondary and primary amines. Amide **3h**, which carried the *N*-dibenzylamino moiety, exclusively produced lactone **4a** even when an excess of NaN_3 was used. On the other hand, amide **2i** yielded the imidate **4i** in good yields, that rapidly undergoes hydrolysis to form lactone **4a**. The reaction was also investigated using various acyclic malonates, acetoacetates, and 1,3-ketoesters. Disappointingly, it was observed that these compounds exhibited complete inertness under the given reaction conditions (see Supporting Information).

Moreover, tetralone derivative **2j** unexpectedly produced the cyclic hemiacetal **5j** as single diastereoisomer[31] in acetonitrile (Scheme 3) and formation of **3ja** was not observed. The isolated hemiacetal **5j**, purified through column chromatography on silica, is in equilibrium with hydroxyketone **3ji**.

The same product was observed for the reaction conducted in absence of NaN_3 (see Supporting Information) suggesting that the attack of the oxygen of the keto group on the monosulfonium intermediate was responsible for the observed product. When a more polar solvent was used (e.g., DMSO), the reaction proceeded towards the formation of the azide derivative **3ja**, which was isolated in a 78% yield along with **5j**. Similar behavior was observed for the lactone **2k**. For this substrate, the product **3ka** was obtained in CH_3CN and was isolated as mixture with **3ki**. Furthermore, the cyclic hemiacetal **5k** was isolated in 20% yield. The utilization of DMSO as a solvent does not enhance the yield of the product **3ka**.



Scheme 2. Reaction of different 1,3-dicarbonylic compounds with **1** in the presence of NaN_3.



Scheme 3. Heterofunctionalization of vinyl thianthrenium salt with **2j** and **2k**.[a] Determined by ^1H NMR analysis of the reaction crude. [b] Yield determined after chromatographic purification. [c] Yield determined after chromatographic purification as inseparable mixture of products; ratio determined by ^1H NMR analysis.

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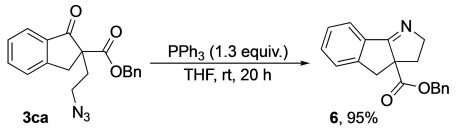
Attempts to use substituted alkenyl thianthrenium salts results in the formation of a mixture of products, with poor stereoselectivity. The increased sterical hindrance of the thianthrene salts favored the intramolecular attack of the C=O moieties of the substrate (see Supporting Information). Lastly, to highlight the synthetic utility of the compound prepared with this methodology, we decided to reduce the azido derivative **3 ca** by Staudinger reaction (Scheme 4).[32] Reduction reaction proceeded smoothly towards the formation of the corresponding cyclic ketimine **6**,[33] by a Staudinger-Aza-Wittig reaction,[34] which was successfully isolated with 95 % yield.

Following previous reports,[15,20,21,24,27] a plausible mechanism for the reaction is proposed (Figure 2). Initially, the pro-nucleophile 2-alkyl-1,3-ketoester undergoes deprotonation in presence of the carbonate anion. The resulting enolate exclusively attacks the β-position of **1** due to the high electron deficiency of the TT^+ group,[35] resulting in the formation of a stabilized sulfur ylide **I**. Protonation of **I** occurs via HCO_3^-, generated during the first deprotonation step, or by the pro-nucleophile, yielding the monosulfonium salt product **II**. The subsequent pathway can vary depending on the specific nature of the 1,3-ketoester and nucleophile employed. If a second nucleophile such as N_3^-, X^-, etc. is introduced, nucleophilic attack occurs displacing the TT^+ and leading to the 1,2-hetero difunctionalized product (Figure 2, Pathway A) with concomitant formation of thianthrene, that could be easily recovered by column chromatography. In the case of five-member ketoester or ketoamide, intramolecular nucleophilic attack by the C=O moiety[33,36] of the ester/amide group onto intermediate **II** results in the formation of the cationic imidate or an oxonium ion **III** (Figure 2, Pathway B). The hydrolysis of this intermediate **III** leads to the formation of lactone **4 a** as the reaction product. For the secondary amide **2 i**, deprotonation of the cationic imidate intermediate lead to the product **4 i**. In the case of the substrates **2 j** and **2 k**, the keto carbonyl group acts as the nucleophile in a substitution reaction with intermediate **II** (Figure 2, Pathway C), which, upon hydration, yields hemiacetal products **5 j** and **5 k**.



Scheme 4. Staudinger-Aza-Wittig reduction of the compound **3 ca**.

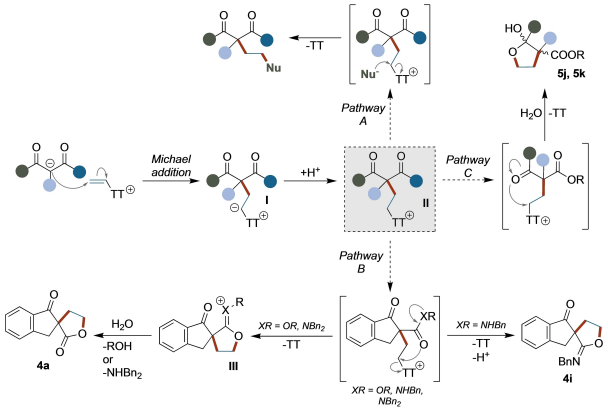


Figure 2. Proposed reaction mechanism for the formation of the different compounds in the reaction of pro-nucleophiles with **1**.

Conclusions

In summary, we have developed a one-pot procedure for the heterofunctionalization of ethylene using vinylthianthrenium salts. The unique dielectrophilic properties of this sulfonium ion allow for the addition of two different nucleophiles onto the masked ethylene molecule. This method enables the alkylation of carbon pronucleophiles using a functionalized two-carbon chain. The key step in this process involves the sequential formation of a C–C and a C–X bond. It is important to note that this methodology is dependent on the specific substrates and nucleophiles, and it has been observed to result in the formation of intriguing spirolactone or bicyclic-fused hemiacetal compounds.

Supporting Information

General experimental procedures, product isolation and characterization. Spectroscopic data and copies of NMR spectra. Reaction optimization studies. Tests for the enantioselective version of the spirocyclization reaction. The authors have cited additional references within the Supporting Information (Ref. [37–44]).

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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 in the supplementary material of this article.

Keywords: vinylthianthrenium · ketoester · thianthrenium salt · ethylene · alkenes

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