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Iodothiocyanation/Nitration of Allenes with Potassium Thiocyanate/Silver Nitrite and Iodine

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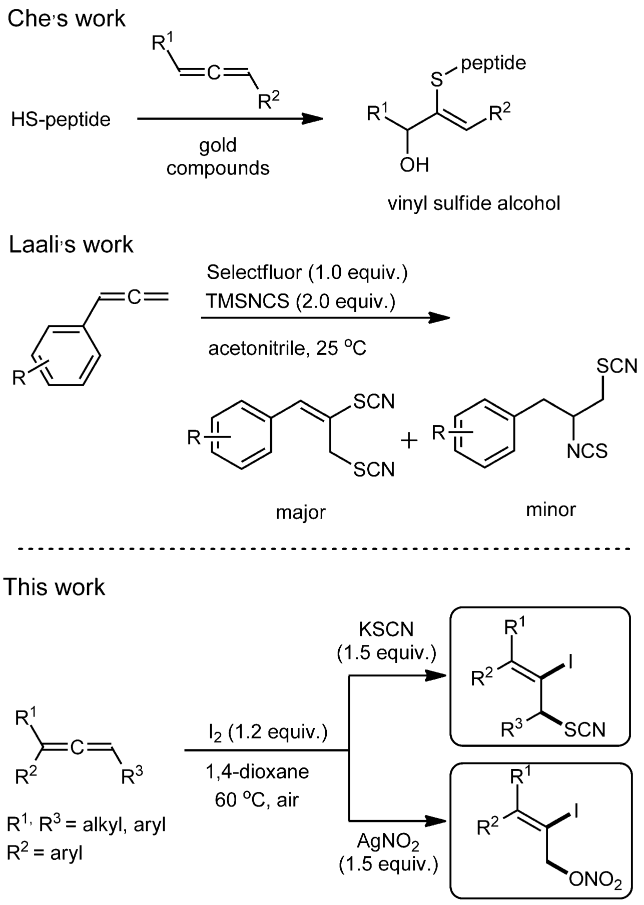
Abstract: Direct strategies for the iodothiocyanation and iodonitration of allenes have been developed. In this process, potassium thiocyanate/silver nitrite and molecular iodine are used as the source of SCN, ONO_2 and iodine to provide the desired products in moderate to good yields with high stereoselectivity.

Keywords: allenes; iodonitration; iodothiocyanation

Modern synthetic organic chemistry benefits tremendously from the advances in the difunctionalization of allenes providing for the rapid and straight-forward access to synthetically complex molecules in a single procedure.[1] A variety of different difunctional strategies have been elegantly demonstrated on olefins, such as diamination, aminooxygenation, dioxygenation, cyanotrifluoromethylation, fluoroamination, phosphonofluorination and oxysulfonylation.[2] With the development of difunctionalization, allene as a special and potential substrate had received much attention in difunctionalization for its unique chemical property.[3] In the past years, some excellent and significant works on the difunctionalization of allenes were reported by the group of Ma.[4] In 2013, the group of Che reported a new approach for the selective difunctionalization of cysteine-containing peptides through a gold-mediated oxidative allene-thiol coupling reaction (Scheme 1).[5] Recently, Laali reported a selectfluor-mediated difunctionalization of allenes with TMSX and NH_4SCN.[6] Although significant progress has been reported in the difunctionalization of allenes, the scope was mainly restricted to hydroxythiolation and dithiocyanation simultaneously in a one-pot process. In the light of sustainable chemistry, the development of a strategy for the difunctionalization of allenes with readily accessible reagents to achieve the transformations of iodothiocyanation and iodonitration is highly desirable.



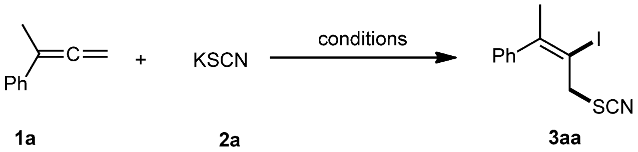
Scheme 1. The difunctionalization of allenes.

Organosulfur compounds have served as building blocks to generate bioactive and pharmaceutical molecules.[7] Especially, the iodothiocyanted allene has found ready use in the synthesis of macromolecular organosulfur compounds by way of the Negishi cross-coupling reaction.[8]

Commerically available potassium thiocyanate, as an ideal thiolating reagent, has been widely used to construct the C–S bond for its stability.[9] Similarly, simple iodine is also widely used in organic synthesis and iodo-organic compounds have a broad transformation ability to other functional groups.[10] As part of our investigations on the utilization of iodine in organic chemistry, herein, we report an iodine-promoted iodothiocyanation and iodonitration of allene with potassium thiocyanate/silver nitrite.

Firstly, buta-2,3-dien-2-ylbenzene (**1a**) and potassium thiocyanate (**2a**) were chosen as model substrates to perform test the reaction in the presence of iodine in 1,4-dioxane at 60 °C. To our delight, the reaction occurred and the product (*Z*)-(3-iodo-4-thiocyanato-but-2-en-2-yl) benzene (**3aa**) was isolated in 86% yield. The structure of **3aa** was confirmed unambiguously with NOE experiments. To further improve the yield, various solvents were tested and these studies demonstrated that the reaction could be performed most efficently in 1,4-dioxane (Table 1, entries 2–9). By optimizing the reaction temperature, we found that the reaction at 60 °C led to an improvement in yield (Table 1, entries 10–12). On extensive evaluating of additives such as AgF, CuI, $ZnCl_2$ and trifluoroacetic acid (TFA), only lower yields of **3aa** were obtained. The optimized conditions were thus established as **1a** (0.5 mmol), **2a** (0.75 mmol) and iodine (0.6 mmol) in 1,4-dioxane at 60 °C.

Table 1. Optimization of the reaction conditions.[a]



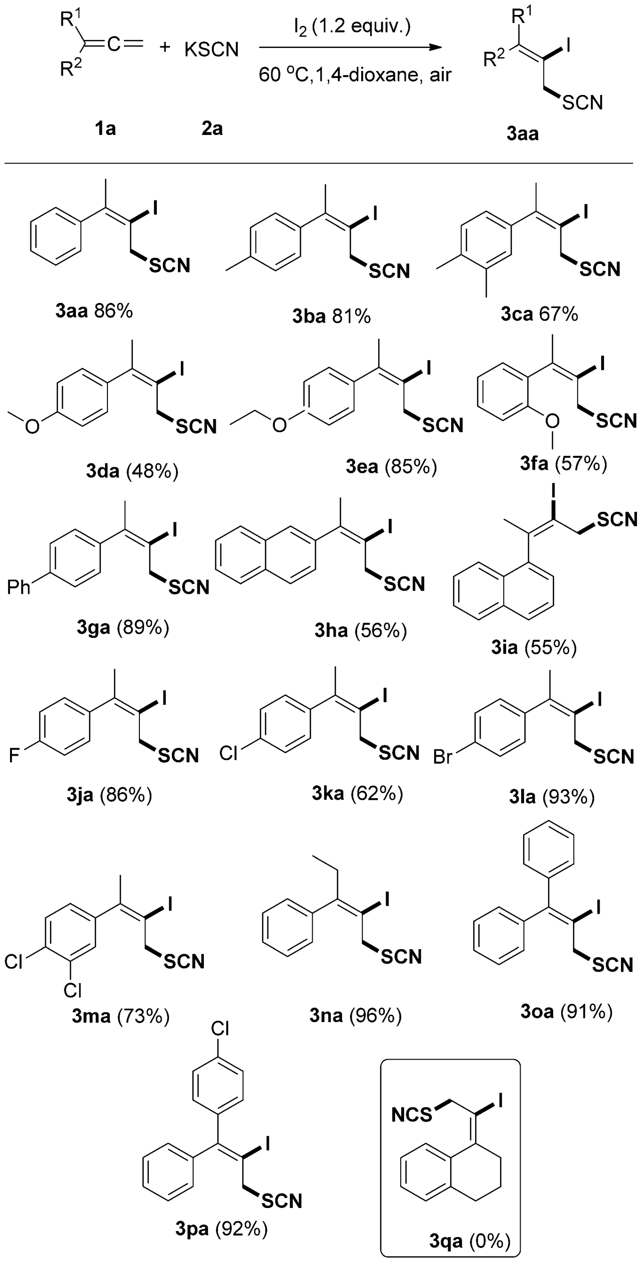
Entry	Additive (mol%)	*T* [°C]	Solvent	Yields [%][b]
1	**none**	**60**	**1,4-dioxane**	**86**
2	none	60	DMF	35
3	none	60	DMSO	26
4	none	60	NMP	–
5	none	60	DCE	53
6	none	60	EtOH	47
7	none	60	THF	61
8	none	60	toluene	22
9	none	60	MeCN	36
10	none	r.t.	1,4-dioxane	–
11	none	80	1,4-dioxane	75
12	none	100	1,4-dioxane	68
13[c]	none	60	1,4-dioxane	85
14	$ZnCl_2$ (10)	60	1,4-dioxane	71
15	TFA (10)	60	1,4-dioxane	77
16	AgF (10)	60	1,4-dioxane	66
17	CuI (10)	60	1,4-dioxane	43

[a] *Reaction conditions:* **1a** (0.5 mmol), **2a** (0.75 mmol), iodine (0.6 mmol) solvent (2 mL), 60 °C.

[b] Yields of isolated products.

[c] Under N_2. The entry in bold type highlights the optimized reaction conditions, and the reaction time was monitored by TLC. DMF = *N*,*N*-dimethylformamide, DMSO = dimethyl sulfoxide, NMP = *N*-methylpyrrolidone.

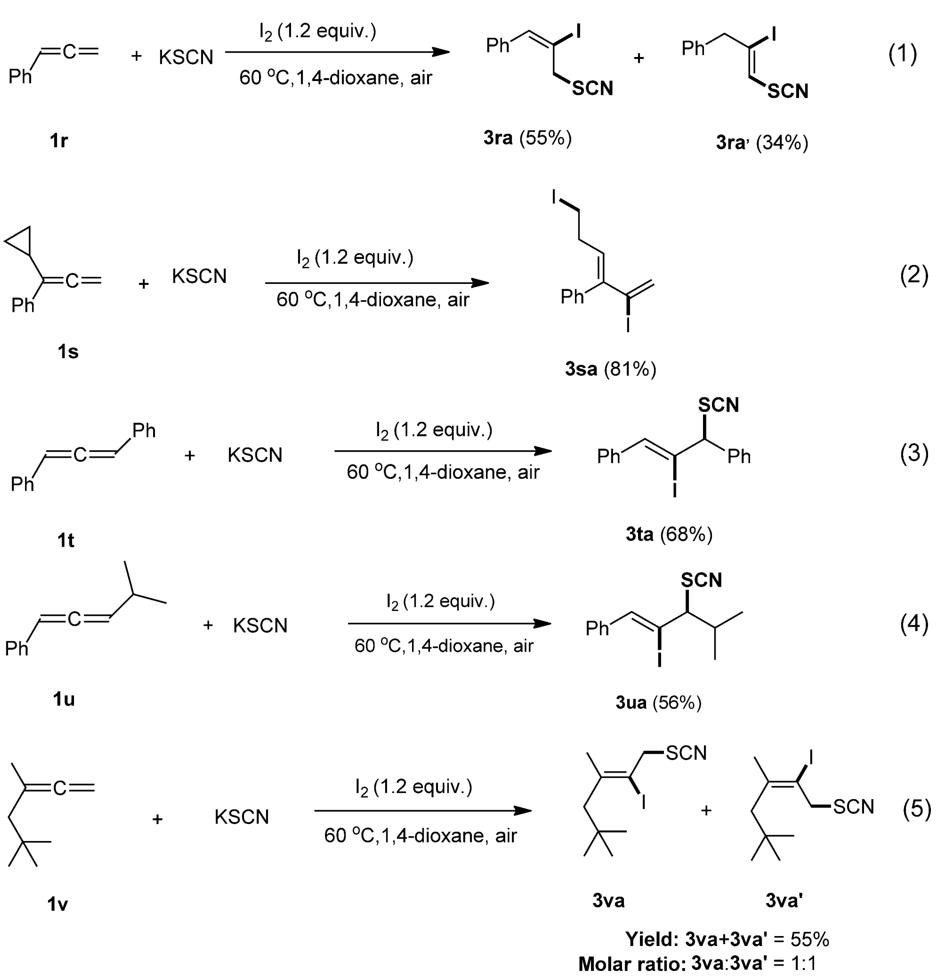
Table 2. The reactions of substituted allenes and potassium thiocyanate.



With the optimized conditions in hand, the scope of the substrate allenes was examined and the results are shown in Table 2. A number of allenes smoothly underwent this iodothiocyanation and the desired products were afforded in moderate to excellent yields with high regioselectivity. As shown in Table 2, the reactions were less affected by the nature of the groups on the aromatic ring of allenes. The substrates **3h** and **3i** were employed for this transformation, and the desired products **3ha** and **3ia** were obtained in 56% and 55% yields. Even on changing R^1 from alkyl to aryl, the desired products **3oa** and **3pa** were also generated in excellent yields. Nevertheless, the reaction was incompatible with 1-vinylidene-1,2,3,4-tetrahydronaphthalene, and failed to give the desired product **3qa**.

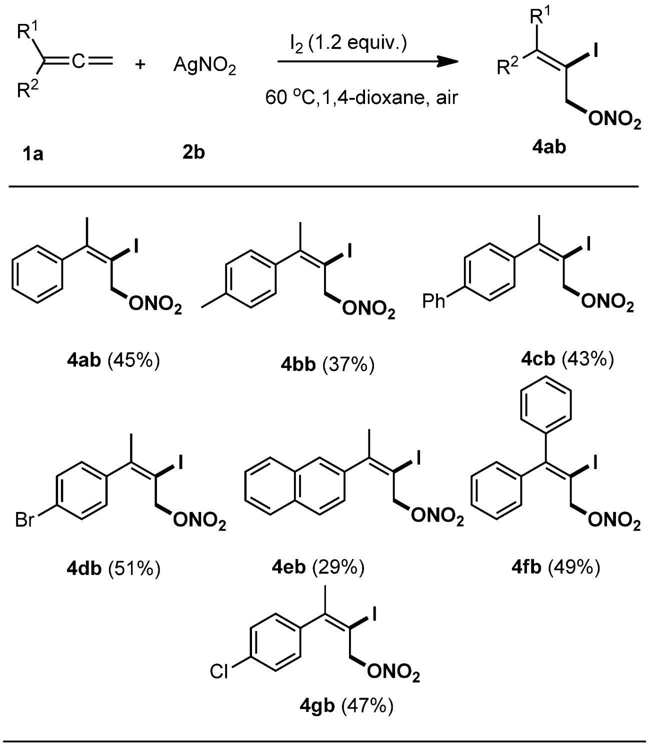
It is worth mentioning that when propa-1,2-dien-1-ylbenzene **1r** and KSCN were subjected to the optimized conditions, the products **3ra** and **3ra′** were obtained in 55% and 34% yields [Scheme 2, Eq. (1)]. Interestingly, an unexpected product **3sa** was isolated in 81% yield when (1-cyclopropylpropa-1,2-dien-1-yl)-benzene **1s** was employed as the substrate [Scheme 2, Eq. (2)].[11] Further investigation disclosed that poly-substituted allenes, such as **1t** and **1u**, were transformed under the standard conditions and the target products **3ta** and **3ua** were isolated in 68% and 56% yield, respectively [Scheme 2, Eqs. (3) and (4)]. The substrate **1v** with only alkyl substituents was also tolerated in this process, the total yield of **3va** and **3va′** was 55% and the molar ratio of isolated **3va**:**3va′** was approximately 1:1 [Scheme 2, Eq. (5)].

In order to enlarge the scope of this transformation, further experiments were conducted with more substrates, such as $AgNO_2$, $AgNO_3$, $NaSO_2Ph$, AgOTf, $NaNO_2$, AgF. It was gratifying to find that $AgNO_2$ was compatible with this process and gave the product (*E*)-2-iodo-3-phenylbut-2-en-1-yl nitrate **4ab** in 45% yield. After screening the parameters of temperature, acids and solvents, no better results were achieved. However, it is a facial method for the iodonitration of allenes.[12] The scope of this reaction was further investigated and the results are illustrated in Table 3. Generally, the reaction between substituted allenes and $AgNO_2$ proceeded smoothly and afforded the corresponding products in moderate yields. Similarly, the nature of the substituent on the aromatic



Scheme 2. The reactions of substituted allenes and potassium thiocyanate.

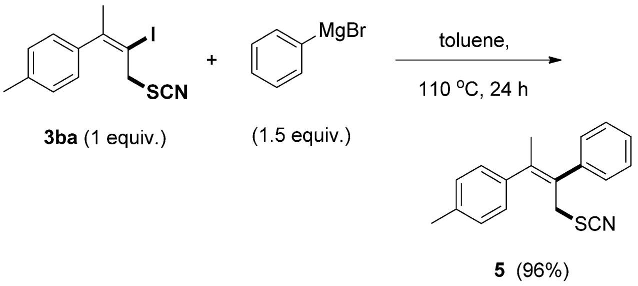
Table 3. The reaction of substituted allenes and $AgNO_2$.



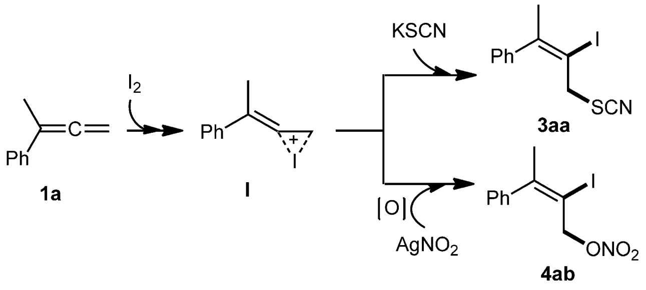
rings of the allenes again did not significantly affect the yields in this reaction.

The versatility of the product **3ba** is shown in Scheme 3 by further transformations into a valuable product. The product **3ba** reacted with phenylmagnesium bromide smoothly under mild conditions, thus yielding (*Z*)-1-methyl-4-(3-phenyl-4-thiocyanatobut-2-en-2-yl)benzene **5** in good yield.

To gain insight into the reaction mechanism, several mechanistic experiments were carried out. The radical scavengers TEMPO (2,2,6,6,-tetramethylpiperidine 1-oxyl) and BHT (butylated hydroxytoluene) were also employed in this transformation, but no influence was detected. This result suggests that this reaction does not follow a radical pathway. On the basis of the above results, a plausible mechanism is depicted in Scheme 4. The transformation of substrates **1a** and **2a**/**2b** occurs by similar pathways. firstly, iodine attacks the central carbon of allene to form iodonium intermediate **I**. For the trasformation of **1a** and **2a**, SCN^- quickly combines with **I** to form **3aa** *via* nucleophilic addition. For **1a** and **2b**, similarly, **4ab** is generated by oxidation and nucleophilic addition with $AgNO_2$.



Scheme 3. Transformation of the product **3ba**.



Scheme 4. Proposed mechanism.

In summary, we have successfully developed an efficient method for iodothiocyanation and iodonitration of allenes. The procedure, using iodine and $KSCN/AgNO_2$, provides a simple and practical approach to generate the desired products in moderate to high yields.

Experimental Section

General Procedure for Iodothiocyanation of Allenes with Iodine and Potassium Thiocyanate

The allene (**1a**, 0.5 mmol), potassium thiocyanate (**2a**, 0.75 mmol), and iodine (0.6 mmol) were mixed in 1,4-dioxane (2 mL) and this mixture was heated under air at 60 °C for 3 h. The reaction mixture was cooled to room temperature and quenched with water. Then the mixture was washed with saturated $Na_2S_2O_4$ solution and extracted with ethyl acetate (15 mL × 3). The combined organic phase was dried with anhydrous Na_2SO_4. The solvent was evaporated under vacuum and the crude product was purified by column chromatography, eluting with petroleum ether/EtOAc (20:1) to afford the desired product (*Z*)-(3-iodo-4-thiocyanatobut-2-en-2-yl)benzene (**3aa**).

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