Organic & Biomolecular Chemistry

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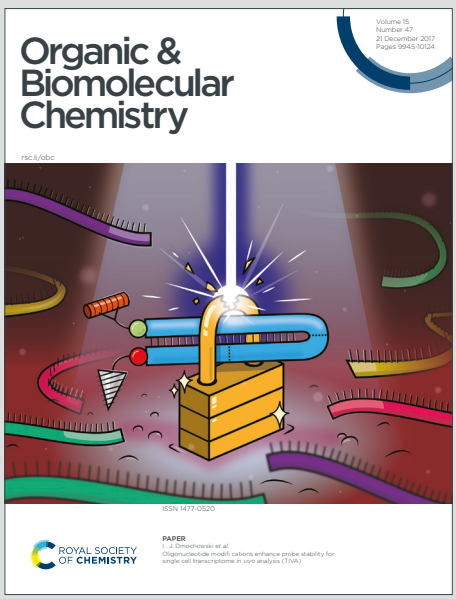

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DOI: 10.1039/C9OB01123D

COMMUNICATION

An Organocatalytic Method for Constructing Pyrroles via Cycloisomerisation of *Z*-1-Iodo-4-N-Methylbenzenesulfonyl-1,6-Enynes

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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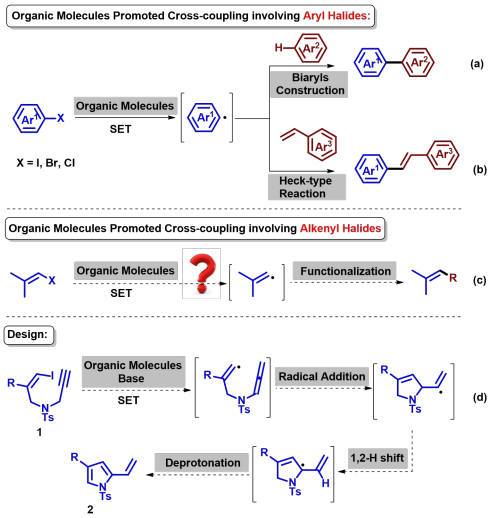
A new cycloisomerisation of *Z*-1-iodo-4-N-methylbenzenesulfonyl-1,6-enynes to functionalized pyrroles was realized in the presence of organomolecule (4,4'-bis(1,1-dimethylethyl)-2,2'-bipyridine) and KOtBu. The transformations performed efficiently to produce kinds of functionalized pyrroles within 10 min. This is the first example that organomolecule promotes methodology with vinyl iodides from non-aromatic system to aromatic system, which offers an excellent option toward establishing a new horizon for cross-coupling reactions of vinyl halides. Preliminary mechanistic studies were performed and a crude radical pathway was proposed.

Construction of C-C bond is of great importance in synthetic chemistry.[1] During the past decades, transition-metal-catalyzed C-C bond construction is emerging as a valuable and efficient alternative in the construction of cyclic compounds.[2] In pharmaceutical chemistry, to remove transition-metal impurities from products is necessary and difficult, hence to develop alternative routes is extremely worthwhile.

Organic halides (Csp^2-X) is an important category of intermediates in organic synthesis.[3] In addition to stoichiometric metalation or transition-metal catalysis,[4] organic molecules promoted C-X bond activation has attracted great attention in recent years. Since the pioneering work from the research groups of Shi,[5] Shirakawa/Hayashi,[6] and Kwong/Lei[7] on the cross-coupling between aryl halides and arenes with the aid of organo-catalysts, the electron-induced catalysis has been extensive investigated.[8] So far, a variety of organic molecules, such as 1,10-phenanthrolines,[5,6,9,10] 1,2-diamines,[7,9f,10] 1,2-diols,[11] amino acid,[12] hydrazine derivatives,[13] *N*-heterocyclic carbenes,[14] and *N*-methylanilines[11b,15] had been applied to promote the activation of haloarene with the assistance of strong base, which was considered as base-promoted homolytic aromatic substitution(BHAS).[8,16] The previous mechanistic studies revealed that the new mode of carbon-halogen bond activation is realized through organic molecules, which is transformed into a " super electron donor " to initiates the cleavage of the C-X bond by single electron transfer (SET).[17,19] Obviously, these organic molecules are thermostable and distinct from conventional radical initiators, while they could enable an efficiently unprecedented initiation system for radical chain reactions with new advances.



Scheme 1 Organic Molecules Promoted Carbon – Halogen Bond Activation and Transformation.

Notably, the reported examples are mainly focusing on cross-coupling between aryl halides and arenes to form biaryls (a, scheme 1), and Heck-type reaction between aryl halides and olefins to form aryl-substituted alkenes (b, scheme 1). However, there are rare examples for the coupling of vinyl iodides via organocatalytic method.

Pyrrole derivates are not only prevalent in a wide variety of important natural products and pharmaceuticals, but also used as building blocks in organic synthesis.[21] For the synthesis of pyrroles, Vessally and co-workers have contributed two elegant review recently, during which *N*-propargylamines as a building block are introduced.[22] However, the requirement of

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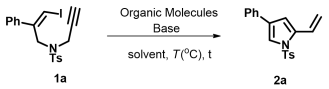
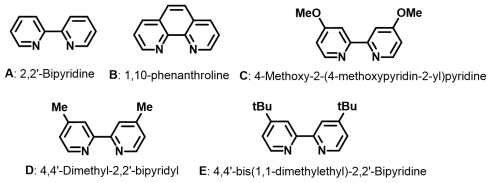
expensive metal catalysts or by the production of harmful waste streams limits their applications.

On the basis of our research interesting on halides,[18] we suppose vinyl iodides could also proceed via single electron transfer mechanism in the presence of organic molecules (c, scheme 1). With this conception in mind, we design the substrate **1** bearing vinyl iodide and *N*-propargylamine to synthesize pyrroles. We also proposed a possible transformation to multi-substituted pyrrole **2** via cascade SET C-I bond cleavage/allene formation, radical addition, 1,2-H shift and deprotonation (d, scheme 1).

Table 1 Optimization of the reaction conditions for Cycloisomerisation of *Z*-1-iodo-4-*N*-methylbenzenesulfonyl-1,6-enynes[a]



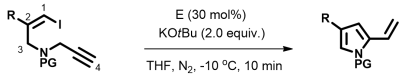
Entry	Organic Molecules	Base (equiv.)	Solvent	T (°C)	t (min)	Yield (%)[b]
1	**A** (20 mol%)	KO*t*Bu (1.2)	THF	rt	30	10
2	**A** (20 mol%)	KO*t*Bu (1.2)	THF	0	30	12
3	**A** (20 mol%)	KO*t*Bu (1.2)	THF	-10	30	22
4	**A** (20 mol%)	KO*t*Bu (2.0)	THF	-10	30	35
5	**A** (20 mol%)	KO*t*Bu (2.0)	THF	-20	30	30
6	**A** (20 mol%)	KO*t*Bu (2.0)	THF	-10	10	54
7	**B** (20 mol%)	KO*t*Bu (2.0)	THF	-10	10	ND
8	**C** (20 mol%)	KO*t*Bu (2.0)	THF	-10	10	32
9	**D** (20 mol%)	KO*t*Bu (2.0)	THF	-10	10	39
10	**E** (20 mol%)	KO*t*Bu (2.0)	THF	-10	10	62
11	**E (30 mol%)**	**KO*t*Bu (2.0)**	**THF**	**-10**	**10**	**77**
12	**E** (40 mol%)	KO*t*Bu (2.0)	THF	-10	10	70
13	**E** (30 mol%)	LiO*t*Bu (2.0)	THF	-10	10	ND
14	**E** (30 mol%)	NaO*t*Bu (2.0)	THF	-10	10	ND
15	**E** (30 mol%)	KO*t*Bu (2.0)	THF:tBuOH(10:1)	-10	10	23
16	**E** (30 mol%)	KO*t*Bu (2.0)	THF:tBuOH(1:1)	-10	10	17
17	**E** (30 mol%)	KO*t*Bu (2.0)	MeCN	-10	10	ND
18	**E** (30 mol%)	KO*t*Bu (2.0)	Anisole	-10	10	ND
19	**E** (30 mol%)	KO*t*Bu (2.0)	Dioxane	-10	10	ND
20	-	KO*t*Bu (2.0)	THF	-10	10	Decomposed

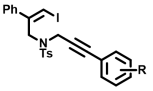
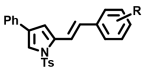


[a]Reaction Conditions: 1a (0.2 mmol), Organic Molecules, base, solvent (2.0 mL), N_2. [b]Isolated yields.

To investigate our deduction on the radical chain transformation of vinyl iodide derivates, (*Z*)-N-(3-iodo-2-phenylallyl)-4-methyl-N-(prop-2-yn-1-yl)benzenesulfonamide **1a** was synthesized and subjected to conditions as 2,2'-bipyridine (20 mol%), KOtBu (1.2 equiv.) in THF at room temperature for 30 min. The desired product was isolated in 10% yield, while no starting material was recovered (Entry 1, table 1). When the reaction temperature was lowered down to -10 °C, the yield was slightly increased to 22% (Entries 2 and 3). To increase the amount of KOtBu to 2.0 equivalents could improve the yield to 35% (Entry 4). However, there was no improvement to the reaction was obtained by lowering the temperature to -20 °C (Entry 5). When the reaction time was shortened to 10 min, the yield was increased to 54% dramatically. Subsequently, some organic molecules were investigated. The results showed that 1,10-phenanthroline **B** could not promote this transformation (Entry 7), and 4,4'-bis(1,1-dimethylethyl)-2,2'-bipyridine **E** gave better yield than 4-methoxy-2-(4-methoxypyridin-2-yl)pyridine **C** and 4,4'-dimethyl-2,2'-bipyridyl **D**. If 4,4'-bis(1,1-dimethylethyl)-2,2'-bipyridine **E** was used 30 mol%, the desired product was produced in 77% yield (Entries 11). We also screened different bases and solvents, however, no better yields were obtained (Entries 13-19). Without the addition of organic molecules, the starting materials will decomposed rapidly, indicating that the additive is essential to this transformation (entry 20). So 30 mol% **E** with 2.0 equiv. KOtBu in THF at -10 °C for 10 min were chosen as the optimized conditions. In all cases, no starting material wasrecovered.

Table 2 Substrates scope[a,b]



1(R)	2	Yeild
		
1a (R=C_6H_5)	**2a**	
PG = Ts		77%
Ns,Ms,Boc		ND
1b (R=4-Me-C_6H_5)	**2b**	75%
1c (R=4-Et-C_6H_5)	**2c**	51%
1d (R=4-iPr-C_6H_5)	**2d**	71%
1e (R=4-nBu-C_6H_5)	**2e**	44%
1f (R=3-Me-C_6H_5)	**2f**	50%
1g (R=4-MeO-C_6H_5)	**2g**	69%
1h (R=4-F-C_6H_5)	**2h**	79%
1i (R=Et)	**2i**	62%
1j (R=n**Bu**)	**2j**	52%
		
1k, R=(H,4-Cl,4-F,4-Bu)	**2k**	Complex
		
1l	**2l**	ND
		
1m	**2m**	ND

[a]Reaction Conditions: **1** (0.2 mmol), 30mol% **E**, KOtBu 2 equiv, THF, N_2, -10°C, 30min. [b]Isolated yields.

Having established the optimized conditions for the organocatalytic cycloisomerisation of *Z*-1-iodo-4-N-methylbenzenesulfonyl-1,6-enynes (Table 1, entry 11), we set out to investigate the substrate scope of this reaction (Table 2). First, we explored different protecting group of the nitrogen, however, only substrate with tosylate protected amine could give the desired products, and substrates bearing nosylate, mesylate and boc groups, decomposed under the standard conditions. The phenyl group at C2 position were screeninged, and we found that kinds of alkyls could afford the corresponding products in moderate to good yields (**2b**-**2f**). The substrate bearing electron donating group methoxy could deliver 4-(4-methoxyphenyl)-1-tosyl-2-vinyl-1*H*-pyrrole **2g** in 69% yield. The substrate with electron withdrawing group fluoro performed very well, providing **2h** in 79% yield. We also investigated alkyl substitutions at C2 position, and moderate yields were obtained (**2i** and **2j**). Subsequently, we tested

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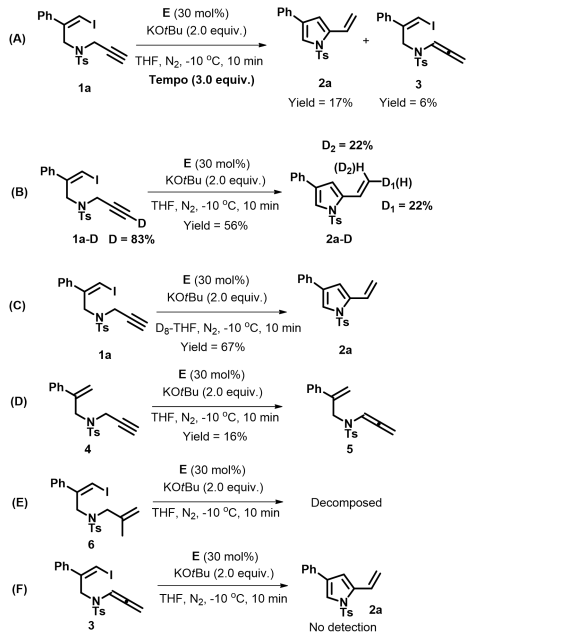
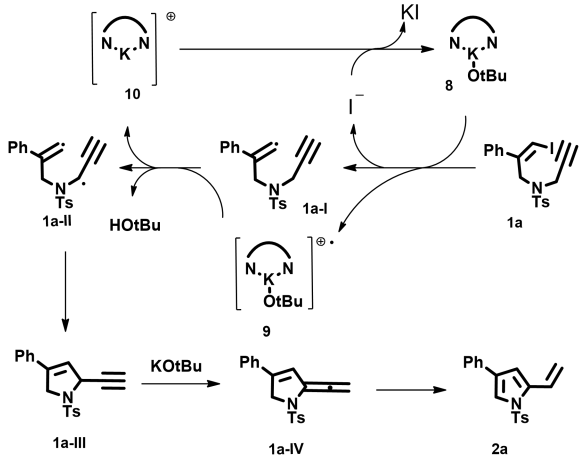
several examples bearing substitutions at C4, however, we could only isolate a complex including two compounds which could not be determined by NMR and GCMS (**2k**). The substrate with two substitutions at C1 and C2 produced allene derivate, but no product **2l** detected. The oxygen tethered 1m was synthesized and examined under the standard conditions, while neither starting material nor product **2m** was observed.



Scheme 2 Control Experiments.

While the substrate scope is not so satisfactory, we are deeply attracted by the reaction mechanism. To shed a light on the mechanism of this organic molecules promoted cycloisomerization, we conducted a series of control experiments (Scheme 2). First of all, radical scavenger TEMPO (3.0 equiv.) was added to test if the reaction was a radical process or not (Scheme 2A). This transformation was partially inhibited, delivering cyclization product **2a** in 17% yield and allene derivate **3** in 6% yield. The result indicated this reaction might undergo a radical pathway. A deuterated substrate **1a-D** (D = 83%) was synthesized and examined under the standard conditions (Scheme 2B). The reaction worked smoothly to provide **2a-D** in 56% yield, however, only 44% deuterium was transformed into the products **2a-D**. Compared to 83% deuterium, the loss of deuterium might due to de-protonation of Csp-D in the presence of strong base KOtBu. The reaction was also carried out in D8-THF, and the desired product **2a** was isolated in 67% without deuterium erosion (Scheme 2C). Subsequently, we designed 1,6-enyne compound **4** to investigate if the iodine atom was necessary or not to this reaction (Scheme 2D). The results showed no cyclization product was detected, but only the allenamide **5** was obtained, indicating iodine atom was essential to this transformation. According to our design in Scheme 1, the reaction might be initiated from the iodine atom, which inspired us to capture the proposed vinyl radical intermediate with alkene **6**. However, it decomposed under the standard conditions, and no adducts was detected even with TEMPO (**2E**). As proposed in scheme 1, allene **3** might be a key intermediate for the transformation, however, when allene **3** was subjected to the standard conditions, no desired product was obtained but only decomposition was detected, indicating this transformation did not go through allene intermediate (Scheme 2G).

The radical initiation mechanism of this kind of reactions still remains elusive, and only limited experimental efforts have been made to investigated this issue.[17a,b,d,19] Generally, the organic additive either generates an electron donor or directly functions as an electron donor, which then undergoes electron transfer to halides to produce the initiator radical (Scheme 3). On the basis of our experimental results and the previous reports, we proposed a radical-type mechanism for this cycloisomerisation of *Z*-1-iodo-4-N-methylbenzenesulfonyl-1,6-enynes, but the initiation mechanism was not revealed in sufficient detail.[8a,17c,20,23] As shown in scheme 3, firstly, the starting materials **1a** generates vinyl radical **1a-I**, iodide anion and complex **9** via homolytic cleavage of C-I in the presence of complex **8**. Then, the complex **9** abstracts a hydrogen from **1a-I** at propargylic position to form a double radical **1a-II**. Subsequently, the intramolecular coupling of the **1a-II** provides **1a-III**, which might isomerize to the allenamide **1a-IV** in the presence of KOtBu and produce the corresponding product via aromatization. On the other hand, complex **10** accepts iodide anion and release catalyst **8**. Finally, double bond migration to the pyrrole form **2a**, with aromatization as the driving force. Although the mechanism is proposed as below, there are still a lot of issues which could not be explained for this stage. Such as the deprotonation of propargylic CH_2 group followed by endo-cyclization and iodide elimination, and tautomerization might also lead to the product, while the affection of organocatalyst could not be explained. Further investigations will be kept on in the future.



Scheme 3 Proposed Mechanism.

In summary, we have developed a new cycloisomerisation of *Z*-1-iodo-1,6-enynes in the absence of any transition-metal catalyst. The using of organomolecule (4,4'-bis(1,1-dimethylethyl)-2,2'-bipyridine) and KOtBu are adequate to

promote the cycloisomerisation to an array of privileged pyrroles from non-aromatic system to aromatic system. The transformations worked efficiently to produce kinds of functionalized pyrroles within 10 min. To the best of our knowledge, such transformations has not been demonstrated previously. It represents a conceptual breakthrough in performing cycloisomerisation of non-aromatic system halides using an organomolecule. It offers an excellent option toward establishing a new horizon for cross-coupling reactions of vinyl halides. We are continuously investigating further cases, detailed kinetic and mechanism, and will be reported in due course.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank the Shandong Provincial Natural Science Foundation (ZR2018MB008, ZR2018MB012), the National Natural Science Foundation of China (21671121), the Shandong Provincal Key Research and Development program of China (2017GGX20131).

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DOI: 10.1039/C9OB01123D

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