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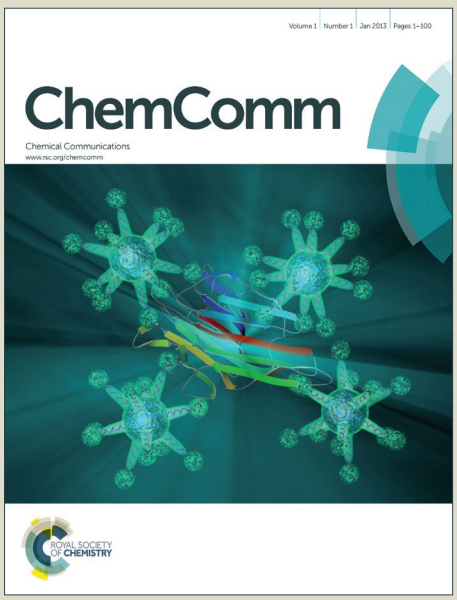

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Intermolecular Iodofunctionalization of Allenamides with indoles, pyrrole, and furan: Synthesis of iodine-substituted *Z*-enamides

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A new method was developed to synthesize iodine-substituted *Z*-enamides through *N*-iodosuccinimide-mediated intermolecular iodofunctionalization of allenamides with indoles, pyrrole, and furan. These reactions proceed rapidly and tolerate a broad scope of substrates. The conjugated sulfimide ion species probably acts as the key intermediate.

The regio- and stereo-controlled functionalization of carbon–carbon double bonds has enormous potential in organic synthesis.[1] Among them, allenamides have recently proven to be important synthetic intermediates, undergoing diverse interesting transformations.[2] In particular, this class of "electron-rich" π systems is receiving growing attention in organic synthesis through metal-assisted electrophilic activation.[3] The coordination of transition-metal complexes to the allenyl framework "C=C=C" affords positively charged intermediates **A** that can smoothly undergo condensation with a variety of nucleophilic agents both at the α or γ position (Figure 1, pathway **a**). However, few examples of the metal-free electrophilic activation of allenamides have been reported so far.[4] Recently, Bandini and co-workers reported a chiral Brønsted acid (BA)-assisted dearomatization of indoles (NuH) through the electrophilic activation of allenamides (Figure 1, pathway **b**).[5]

In the recent years, iodine reagents have received considerable attention as inexpensive, nontoxic, and readily available electrophiles for interactions with double bonds to create new stereogenic centers in an efficiently controlled manner (*reagent-controlled* stereoselective reactions),[6] or with alkynes to create vinyl iodides,[7] thus allowing diverse functionalization using metal-catalyzed coupling chemistry.[8] Iodine electrophile activates allenamides, however, still poses challenges with respect to low regioselectivity. Only a few

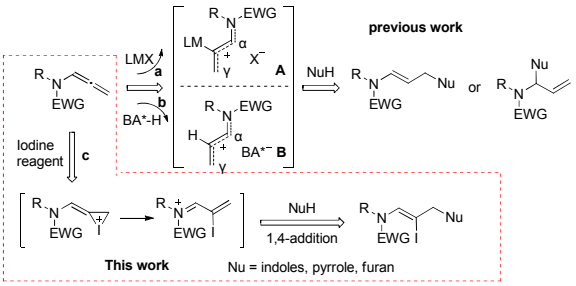

Fig. 1 Conventional (metal) and "unconventional" (metal-free) electrophilic activation of allenamides.

elegant examples of intramolecular cyclizations involving allenamides have been reported to date.[9]

Enamides[10] are an interesting class of substrates because of their use in the construction of heterocycles and chiral amines as well as their occurrence in several natural product frameworks.[11] Our research group has focused on the intermolecular cycloaddition[12] or nucleophilic addition[13] of allenamides via gold catalysis to afford the corresponding enamides. To the best of our knowledge, the iodine reagent mediated intermolecular nucleophilic addition of allenamides has not been reported. In this paper, we report the *N*-iodosuccinimide-mediated intermolecular iodofunctionalization of allenamides with indoles, pyrrole, and furan, providing iodine-substituted enamides. The reaction generates a new C–C bond at the γ-position of allenamides and affords iodine-substituted enamides with *Z*-configuration (Figure 1, pathway **c**).

Based on our previous results with respect to the catalyst-free addition of indoles to allenamides,[14] we began our studies by exploring the reaction between phenyl allenamide (**1a**) with 1-methylindole (**2a**). The optimization results are summarized in Table 1. The reaction afforded the desired product **4a** in 9% yield under the promotion with elemental Iodine electrophiles in DCM, along with significant amounts of degradation product 4-methyl-N-phenylbenzenesulfonamide (Table 1, entry 1). The use of NIS as the promoter afforded **4a** in 66% yield, along

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Electronic Supplementary Information (ESI) available: Experimental details, compound characterization, and NMR spectra. CCDC 1448325 for **7i** and CCDC 1479962 for **7l**. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/x0xx00000x

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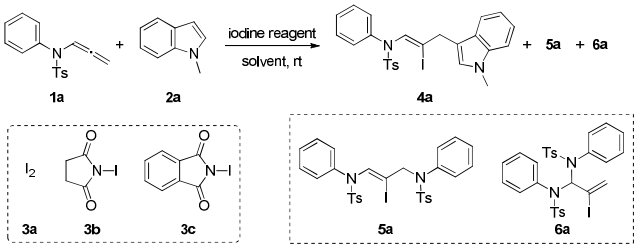
Table 1 Screening of optimal conditions[a]

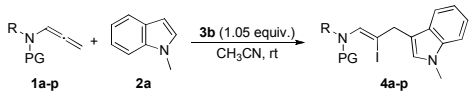


Entry	**1a**/**2a** (equiv.)	Iodine reagent (equiv.)/sol	Yield of **4a** (%)[c]	Yield of **5a** (%)[d]
1	1:3	**3a** (3)/DCM	9	ND
2	1:3	**3b** (3)/acetone	66	18
3	1:3	**3b** (2)/acetone	67	15
4	1:3	**3b** (1.05)/acetone	69	10
5	1:3	**3b** (1.05)/DCM	35	18
6	1:3	**3b** (1.05)/$CHCl_3$	40	18
7[b]	1:3	**3b** (1.05)/CCl_4	22	33
8	1:3	**3b** (1.05)/DCE	63	31
9	1:3	**3b** (1.05)/CH_3CN	86	8
10	1:3	**3b** (1.05)/toluene	26	29
11	1:3	**3a** (1.05)/CH_3CN	55	7
12	1:3	**3c** (1.05)/CH_3CN	70	14
13	1:2	**3b** (1.05)/CH_3CN	86	8
14	1:1.2	**3b** (1.05)/CH_3CN	78	9
15[e]	1:0	**3b** (1.05)/CH_3CN	0	31%/6%(**6a**)

[a] Unless noted, all the reactions were carried out at 0.1 mmol scale in 3 mL solvent at rt within 1 min. [b] **1a** was consumed within 5 min. [c] Yield of isolated product. [d] Yield of **5a** was determined by the ^{1}H NMR spectroscopy of the reaction mixture. [e] Yield of 4-methyl-*N*-phenylbenzenesulfonamide/**5a**/**6a** = 36%/31%/6%.

with **5a** as a by-product in 18% yield as determined from the ^{1}H NMR spectral data (Table 1, entry 2). A decrease in the iodine reagent loading to 2.0 equiv. led to a slightly increased reaction yield of 67% (Table 1, entry 3). Moreover, the yield of **4a** increased to 69% when the iodine reagent loading was reduced to 1.05 equiv. (Table 1, entry 4). Subsequent screening of the solvents led to an increase in the yield to 86% when CH_3CN was used as the solvent, whereas DCM, $CHCl_3$, CCl_4, DCE, and toluene were not as effective (Table 1, entries 5–10). Notably, 55% yield of **4a** could also be obtained when 1.05 equiv. of electrophile **3a** was used in CH_3CN (Table 1, entry 11). The process was also promoted with **3c** (Table 1, entry 12). Similar results were obtained when the amount of **2a** was reduced to 2.0 equiv. (Table 1, entry 13). The yield of **4a** decreased to 78% when the loading of **2a** was only 1.2 equiv. (Table 1, entry 14). In the control experiment, 4-methyl-*N*-phenylbenzenesulfonamide, **5a**, and **6a** were obtained in 36%, 31%, and 6% yields, respectively without **2a** as the nucleophile (Table 1, entry 15).

Table 2 Substrate scope of allenamides (**1**)[a]



Entry	Allenamide **1**	R	PG	Product **4** (%)[b]	**5** (%)[c]
1	**1a**	Ph	Ts	**4a** (86)	8
2	**1b**	4-MeC_6H_4	Ts	**4b** (84)	9
3	**1c**	2-MeC_6H_4	Ts	**4c** (89)	8
4	**1d**	4-$MeOC_6H_4$	Ts	**4d** (79)	8
5	**1e**	3-FC_6H_4	Ts	**4e** (79)	9
6	**1f**	4-FC_6H_4	Ts	**4f** (80)	8
7	**1g**	4-BrC_6H_4	Ts	**4g** (78)	8
8	**1h**	2,4-$(Me)_2C_6H_4$	Ts	**4h** (83)	8
9	**1i**	3,5-$(MeO)_2C_6H_4$	Ts	**4i** (84)	8
10	**1j**	Bn	Ts	**4j** (84)	<3
11	**1k**	4-$MeOC_6H_4CH_2$	Ts	**4k** (77)	<3
12	**1l**	4-$FC_6H_4CH_2$	Ts	**4l** (81)	<3
13	**1m**	$PhCH_2CH_2$	Ts	**4m** (81)	<3
14	**1n**	*n*-Bu	Ts	**4n** (86)	<3
15	**1o**	3,5-$(MeO)_2C_6H_4$	Ac	**4o** (82)	<3
16	**1p**	2-oxazolidinone		**4p** (71)	<3

[a] Conditions: **1** (0.1 mmol), **2a** (0.2 mmol), CH_3CN (3 mL), rt, within 1 min. [b] Yield of isolated product. [c] The yield of **5** was determined from the ^{1}H NMR spectral data.

Under the optimal conditions, the substrate scope of allenamides (**1**) was investigated in reactions with 1-methylindole (**2a**) (Table 2). Substrates **1** containing an aryl group substituted with an electron-donating or electron-withdrawing group, such as methyl, methoxy, fluoro, and bromo, efficiently reacted with **2a** to afford the desired products **4b–g** in 78–89% yields, exhibiting no obvious substituent effect (Table 2, entries 2–7). Both 2,4-dimethyl- and 3,5-dimethoxy-substituted phenyl allenamides efficiently reacted with **2a** to afford **4h** (83%) and **4i** (84%), respectively (Table 2, entries 8–9). Although benzyl allenamide **1j** and 4-fluoro-substituted benzyl allenamide **1l** were suitable for preparing **4j** and **4l** in 84% and 81% yields, 4-methoxy substituted benzyl allenamide **1k** gave the corresponding product **4k** in 77% yield (Table 2, entries 10–12). Furthermore, the reactivity of different aliphatic substituted allenamides was also investigated. Both phenethyl and *n*-butyl substituted allenamides produced products **4m** and **4n** in 81% and 86% yields, respectively (Table 2, entries 13 and 14). The reaction is also efficient with allenamides when acyl was used in the place of tosyl as the amino-protecting group. Thus, the reaction of 3,5-dimethoxy-substituted phenyl allenamide **1o** with an acyl substituent furnished **4o** in 82% yield, 2-oxazolidinone allenamide **1p** also provided the corresponding adduct **4p** in 71% yield (Table 2, entries 15 and 16). Notably, under the optimal conditions, the yields of the by-product **5** were <9%

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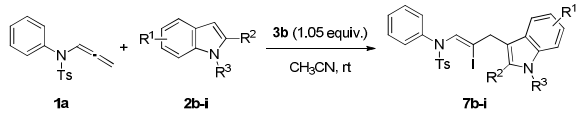
Table 3 Substrate scope of indole substrates (**2**)[a]



Entry	Indole **2**	R^1	R^2	R^3	Product **7** (%)	**5** (%)[c]
1	**2b**	H	H	H	**7b** (57)	18
2	**2c**	5-MeO	H	H	**7c** (77)	13
3[c]	**2d**	5-F	H	H	**7d** (43)	11
4[d]	**2e**	5-Br	H	H	**7e** (50)	25
5	**2f**	4-Me	H	H	**7f** (80)	10
6	**2g**	7-Me	H	H	**7g** (66)	19
7	**2h**	H	Me	H	**7h** (66)	15
8	**2i**	H	H	Bn	**7i** (70)	14

[a] Conditions: **1a** (0.1 mmol), **2** (0.2 mmol), CH_3CN (3 mL), rt, within 1 min.
[b] Yield of isolated product.
[c] The yield of **5** was determined from the ^{1}H NMR spectral data.
[d] Isolated yield after 24 h.

when 1-methylindole was used as the nucleophile.

Next, indole substrates **2** were investigated by reacting with phenyl allenamide (**1a**) (Table 3). Indole **2b** and 5-MeO-substituted indole derivative **2c** were successfully converted into **7b** and **7c** in 57% and 77% yields, respectively (Table 3, entries 1 and 2). The indole substrates with halo substituents, however, showed low reactivities. For example, 5-fluoroindole **2d** and 5-bromoindole **2e** afforded products **7d** and **7e** in only 43% and 50% yields, respectively, even after 24 h (Table 3, entries 3 and 4). Methyl substituents were also placed at different positions of the indolyl core (**2f–2h**), resulting in satisfactory yields. 4-Methylindole provided the C3-addition product **7f** in 80% yield (Table 3, entry 5), whereas 2-methylindole and 7-methylindole provided the C3-addition products **7g** and **7h** both in 66% yield (Table 3, entries 6 and 7). Indole bearing an *N*-benzyl group was also able to furnish **7i** in 70% yield, and the absolute configuration of the intermolecular nucleophilic addition products was further determined to be (*Z*) by the single-crystal diffraction study of **7i** (Fig. 2, left).[15] The yields of the by-products were in the 10–20% range according to their ^{1}H NMR spectral data.

In an attempt to extend this method, we explored the iodofunctionalization of other heterocyclic substrates, such as pyrrole **2j**, 2-methylfuran **2k**, and imidazole **2l**. As shown in scheme 1, C2-addition products **7j** and **7k** were successfully

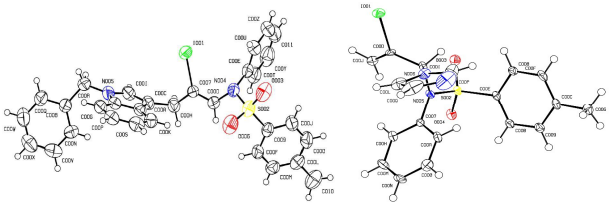
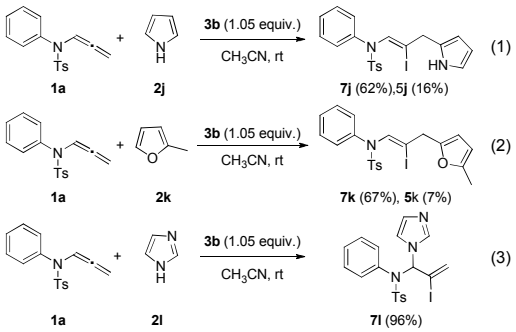


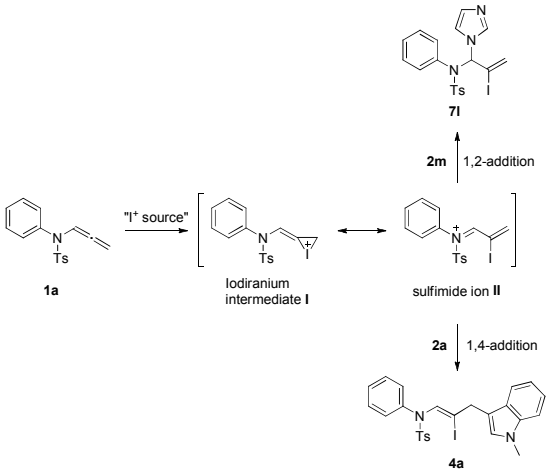
Fig. 2 X-ray structure of compound **7i** (left) and **7l** (right).



Scheme 1 Iodofunctionalization of other substrates.

obtained in 62% and 67% yields, whereas imidazole **2l** afforded the 1,2-addition product **7l** in 96% yield, providing the evidence of the reaction mechanism. Moreover, **7l** was a crystalline solid, and single-crystal X-ray analysis confirmed its structure (Fig. 2, right).[15]

Based on our experimental results and precedents in the literature,[9b,16] we propose a mechanism for the reaction as shown in Scheme 2. The first step of the reaction involves electrophilic halogenation via interaction between iodine electrophile and the π system of allenamide **1a** to form iodiranium intermediate **I**. This affords the key intermediate conjugated sulfimide ion species **II,** that undergoes a decyclization reaction through the delocalization of the nitrogen lone pair towards the alkene. Subsequently, **II** undergoes 1,4-addition with nucleophile **2a**, affording iodine-substituted enamide **4a**. The formation of 1,2-addition product **7l** indicates that the key intermediate is the conjugated sulfimide ion species **II**.



Scheme 2 Proposed reaction mechanism.

To prove the practicality of this iodine-promoted reaction, a gram-scale synthesis of the iodine-substituted enamide **4a** was performed. When 1.09 g of allenamide **1a** (4 mmol) was used, 1.63 g of the desired product **4a** was obtained in 85% yield within 1 min, indicating that this transformation is easy to scale up to gram scale without a loss in efficiency (Scheme 3). To further demonstrate the potential application of this protocol, **4a** was reacted with phenylboronic acid under Suzuki

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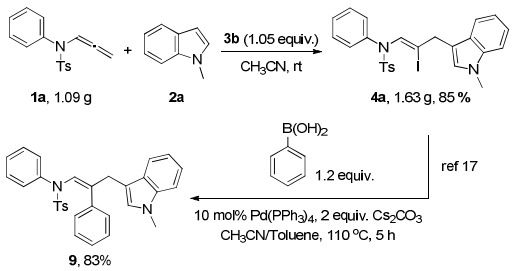

Scheme 3 Gram-scale synthesis and synthetic application.

cross-coupling conditions[17], the corresponding coupling product **9** was isolated in good yield.

In summary, a facile synthetic protocol for iodine-substituted *Z*-enamides was established through NIS-mediated intermolecular iodofunctionalization of allenamides with indoles, pyrrole, and furan, affording the desired 1,4-addition products in good yields under mild conditions. Moreover, when imidazole was used as the nucleophile, the corresponding 1,2-addition product was obtained in a good yield, indicating that the key intermediate was the conjugated sulfimide ion species. Importantly, the products of this reaction, iodine-substituted enamides, should facilitate diverse functionalization by metal-catalyzed cross-coupling chemistry. The potential utilization and extension of this interesting synthetic methodology are currently underway.

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