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Regio- and Stereoselective Synthesis of Ensulfonamides/Enamides via Catalyst-Free Intermolecular addition of Indoles/Pyrroles/Imidazole to Allenamides

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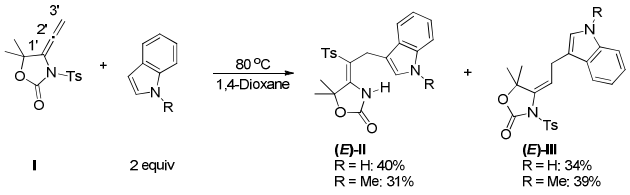
A Catalyst-free Intermolecular addition of indoles, pyrroles, and imidazole to allenamides is reported. The reaction proceeds smoothly at 80 °C and provides a series of (*E*)-ensulfonamide derivatives in high yields with excellent regioselectivity. Two enamides 3k and 3l can also abtained when using acyl in place of tosyl as an amino-protecting group of allenamides.

Sulfonamide functional groups have long been acclaimed as important structural motifs in drug discovery since the identification of a series of sulfonamide-containing drugs, such as sulfamethoxazole as an antibacterial agent, azosemide as a diuretic agent, sumatriptan as an antimigraine agent, and celecoxib as a COX-2 specific anti-inflammatory agent.[1] The introduction of a sulfonamide group is often a useful practice in medicinal chemistry for improving pharmacological potency and/or the absorption, distribution, metabolism, and excretion (ADME) properties of the lead compound. Moreover, they are also important protected intermediates of primary and secondary amines with interesting biological activities.[2] On the other hand, as the derivatives of sulfonamides, ensulfonamides are versatile building blocks that can be utilized in the heterocycle construction, asymmetric hydrogenation, and synthesis of bioactive molecules.[3] Consequently, the interest in ensulfonamides has been long standing and the effective synthesis of these motifs, especially the stereocontrolled version, is still in urgent need. So far, ensulfonamides can be assembled by palladium(II)-catalyzed vinyl transfer from vinyl ethers to sulfonamides,[4] Pd-catalyzed "Wacker-type" oxidative amidation of alkene,[5] the functionalization of ynamides[6] and Rhodium(II)-mediated transformations of N-sulfonyl-1,2,3-triazoles.[7] The functionalization of allenamides, [8]which contain the desired sp^2 carbon attached directly to the amide, stands out as an attractive alternative protocol for accessing ensulfonamides. Usual ly, the "electron-rich" π systems of allenamides are susceptible to electrophilic activation by transition metal[9] or Brønsted acid[10] providing zwitterionic intermediate, which can smoothly undergo condensation with a variety of nucleophilic agents. In contrast, they are robust to nucleophilic attack at the allene terminal carbons without catalyst. Yoshinao Tamaru and coworkers reported the first example that indole and Methylindole served as a C-nucleophile proceeds nucleophilic addition at the allene terminal carbons of N-tosyl-4-vinylidene-2-oxazolidinone **I** at 80 °C under neutral conditions, but they provided a mixture of (*E*)-II and (*E*)-III in comparable amounts because of an intramolecular migration of the sulfonyl group from N to C2′ (Equation 1). [11]



Equation 1 Intermolecular addition of indoles to N-tosyl-4-vinylidene-2-oxazolidinone

Our group have recently reported the gold catalyzed intermolecular [2+2] and [3+2] cycloaddition reaction of allenamides with olefins, azomethine imines and nitrones to provide multifunctional cyclobutanes, bipyrazolidin-1-one adducts and 4-Methyleneisoxazolidine derivatives.[12] In continuation of our program geared towards the functionalization of allenamides,[13] we describe here a catalyst-free intermolecular addition of indoles, pyrroles, and imidazole to allenamides, providing (*E*)-ensulfonamides/enamides in high yields with excellent regioselectivity.

Our initial studies focused on the reaction of tosyl N-allenamide (**1a**) with N-Methylindole (**2a**) for the optimization of reaction conditions (Table 1). Gratifyingly, the reaction outcome generally shows a regiochemical preference for the nucleophilic C3 attack by indole on the C3' position of the allenamide providing (*E*)-ensulfonamide **3a** as the only isomer in 54% yield together with minor amounts of C2-addition products of indole (>20 :1 ratio) at 120 °C in toluene after 25 h. Encouraged by these results, three other solvents, $CHCl_3$, CH_3CN, DCE were subsequently examined, and DCE showed the

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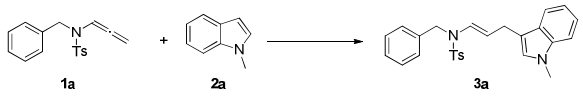
best reaction medium in terms of the yield (Table 1, entries 2-4). Variation of the number of equivalents of **2a** from 3.0 to 2.0 lowed the conversion of **3a** to 76% (Table 1, entry 5). The dramatically regio- and stereoselectivity was due to several reasons: Firstly, the thermodynamic stability of the product. Secondly, C3 position of indole shows stronger nuclephilicity. Lastly, C2' of the allenamide was to be nucleophilic centre because the electronic bias can be exerted through delocalization of the nitrogen lone pair of allenamide toward the allenic moiety. The structure and stereochemical identity of this adduct could be determined by the spectral analysis($J_{HC=CH}$ > 12 Hz). Morever, the structure of **3a** can be corroborated through **3k**(Table 2), which is consistent with literature.[14]

Table 1 Screening of the Optimal Conditions[a,b]



1a 2a 3a

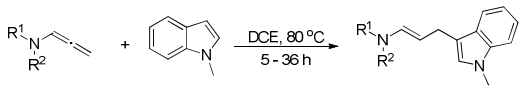
Entry	Solvent	Temp (℃)	Time (h)	Isolated yield (%)
1	toluene	120	25	54
2	$CHCl_3$	80	17	89
3	CH_3CN	80	24	69
4	DCE	80	5	92
5[c]	DCE	80	9	76

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.3 mmol) and solvent (anhydrous; 3 mL); [b] Only one isomer was observed by NMR(see S3-S5); [c] **1a** (0.1 mmol), **2a** (0.2 mmol).

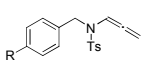
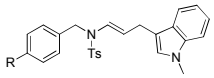
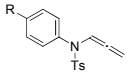
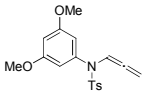
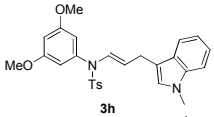
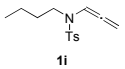
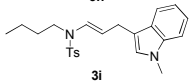
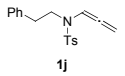
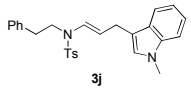
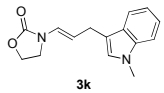
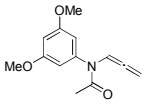
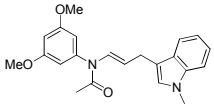
With the optimized reaction conditions in hand, we turned our attention to the scope of the intermolecular addition with respect to allenamides **1** and indoles **2** (Table 2 and 3). As shown in Table 2, we were pleased to find that a series of allenamides with different substitution patterns worked very well in this reaction. 4-F- or 4-MeO-substituted benzyl allenamides were suitable for accessing ensulfonamides **3b** and **3c** in 95% and 72% yield in the presence of N-Methylindole **2a**. Phenyl allenamide **1d** provided the desired ensulfonamide **3d** in 77% yield. Subsequently, the substitution effect on the aryl ring of aryl allenamide was examined. While allenamides **1e**, **1f** and **1g** bearing a 4-Me, 4-F or 4-Br group delivered **3e**, **3f** and **3g** in high yields, 3,5-dimethoxy substituted aryl allenamide **1h** gave the corresponding product **3h** in moderate yield. When n-butyl allenamide **1i** and phenethyl allenamide **1j** was utilized as the reactant, the addition products **3i** and **3j** were obtained in 96% and 93% yield, respectively. The reaction is also efficient with allenamides using acyl in place of tosyl as an amino-protecting group. Thus, 2-oxazolidinone allenamide **1k** and **1l** with an acyl substituent provided the corresponding adducts **3k** and **3l** in 80% yield and 50% yield respectively.

We next set out to explore the scope of indoles **2** in the presence of allenamide **1a** (Table 3). The optimal conditions were found to be applicable to a wide range of indole derivants **2b-m** and several substituents, such as Me, MeO, F, Br and benzyl on the indole ring were tolerated well. Indole **2b**, 5-MeO or 5-F-substituted indole derivatives **2c-d** were successfully converted into **4b-c** in high yield which suggests that the electronic effect of substituents on the aromatic ring of indole does not affect the intermolecular addition

Table 2 Variation of the allenamides **1**[a,b]



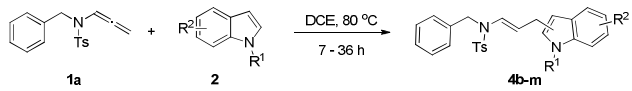
1 2a 3a-l

entry	allenamide, **1**	product, **3**	yield (%)[c]
1			
2	**1a**, R = H	**3a**	92
3	**1b**, R = F	**3b**	95
4	**1c**, R = MeO	**3c**	72
5			
6	**1d**, R = H	**3d**	77
7	**1e**, R = Me	**3e**	82
8	**1f**, R = F	**3f**	92
9	**1g**, R = Br	**3g**	90
10	 **1h**	 **3h**	62
11	 **1i**	 **3i**	96
12	 **1j**	 **3j**	93
13	 **1k**	 **3k**	80
14	 **1l**	 **3l**	50

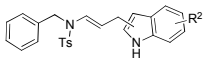
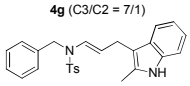
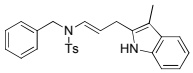
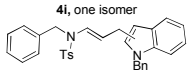
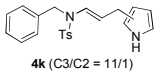
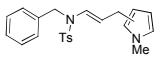
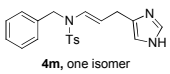
[a]Reagents and conditions: **1** (0.1 mmol), **2a** (0.3 mmol) and DCE (anhydrous; 3 mL) at 80 °C; [b]In all cases, only one isomer was observed by NMR (see S5-S11); [c]Isolated yield.

of allenamides. But 5-Bromoindole **2e** gave the corresponding products **4e** in moderate yield only when increasing the amount of **1a** to 3 eqivalent. 4-Methylindole and 7-Methylindole provided the C3- addition products in good yield together with minor amounts of C2-adducts which were unseparated.[15] Indoles bearing a 2-Me or N-benzyl were also viable to furnish **4h** and **4j** in 75% yield and 71% yield. Notably, 3-Methylindole **2i** could also provide the adduct **4i** at the C2-position of indole in 70% yield due to the migration of the allyl group from C3 to C2 of indole. Interestingly, the catalyst-free intermolecular addition protocol was extended to pyrrole leading to C2-addition product **4k** as the major isomer in 82% yield, [15]while N-Methylpyrrole provided C2-addition product **4l** in 80% yield together with isolated C3-adduct in 15% yield.[16] The regiochemical preference for the C2-position due to the more resonant type of the intermediate. Remarkably, imidazole is also an efficient nucleophile, which provided the C4-adduct **4m** as the only isomer. As expected, the use of indole, pyrroles, and imidazole as nucleophile provided the desired (*E*)-ensulfonamides in good yield and high regioselectivity.

Table 3 Variation of the indoles **2**[a,b]

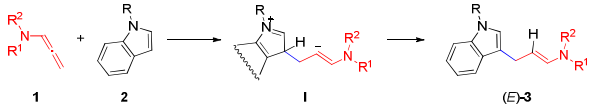


1a **2** **4b-m**

entry	indole, **2**	product, **4**	yield (%) [c]
1			
2	**2b**, R^2 = H	**4b** (C3/C2 = 20/1)	97
3	**2c**, R^2 = 5-OMe	**4c** (C3/C2 = 17/1)	90
4	**2d**, R^2 = 5-F	**4d** (C3/C2 = 16/1)	95
5 [d]	**2e**, R^2= 5-Br	**4e** (C3/C2 = 19/1)	61
6	**2f**, R^2 = 4-Me	**4f** (C3/C2 = 5/1)	75
7	**2g**, R^2 = 7-Me	**4g** (C3/C2 = 7/1)	70
8	 **2h**	 **4h,** one isomer	75
9	 **2i**	 **4i,** one isomer	70
10	 **2j**	 **4j** (C3/C2 = 33/1)	71
11	 **2k**	 **4k** (C3/C2 = 11/1)	82
12	 **2l**	 **4l** (C3/C2 = 1/5)	80
13	 **2m**	 **4m,** one isomer	81

[a]Reagents and conditions: **1a** (0.1 mmol), **2** (0.3 mmol) and DCE (anhydrous; 3 mL) at 80 °C. [b]The ratio was determined by NMR (see S11-S13). [c]Isolated yield of the major product. [d]**1a** (0.3 mmol)/**2** (0.1 mmol).

According to the report of Yoshinao Tamaru,[11] we gave a plausible mechanism for this transformation in Scheme 1. The the π* (C2'=C3')-δ*(N-SO_2) interaction makes the LUMO (C2'=C3') low in energy and the double bond an excellent electron acceptor. Thus the nucleophilic addition of indoles providing (*E*)-**3**, in a sense, might be regarded as electrophilic aromatic substitution of **1**; that is, despite the fact that **1** is a neutral species, it is even capable of undergoing the Friedel-Crafts type electrophilic aromatic substitution in the absence of any Lewis acid catalysts. Electrophilic addition of **1** to indoles and aromatization by deprotonation would provide (*E*)-**3**.



1 **2** **I** (*E*)-**3**

Scheme 1 Plausible mechanism.

Conclusions

In conclusion, we have developed a catalyst-free intermolecular addition of indole, pyrroles, and imidazole toward the distal double bond of allenamides. The reaction proceeds smoothly at 80 °C and provides a series of (*E*)-ensulfonamide/enamide derivatives in high yields with excellent regioselectivity. Further study of allenamides is currently ongoing in our laboratory.

Acknowledgements

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Graphical Abstract

A Catalyst-free Intermolecular addition of indoles, pyrroles, and imidazole to allenamides is reported. The reaction proceeds smoothly at 80 °C and provides a series of (*E*)-ensulfonamide derivatives in high yields with excellent regioselectivity. Two enamides **3k** and **3l** can also obtained when using acyl in place of tosyl as an amino-protecting group of allenamides.