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A Rh-catalyzed regio- and stereoselective route to enamides: benzamides as assembling reagents†

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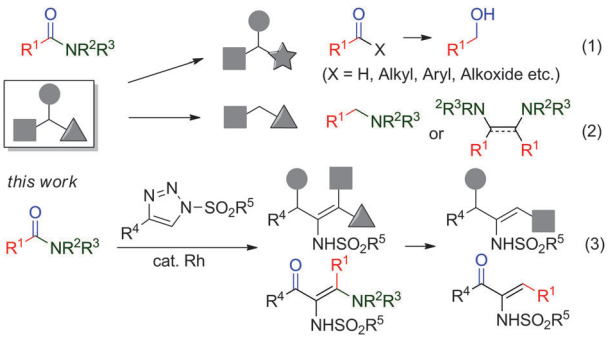
A new protocol for the synthesis of fully substituted enaminones has been achieved using a diverse range of benzamides and 1-sulfonyl-1,2,3-triazoles. Selective removal of the β-amino moiety of the obtained α-amido-enaminones to form *Z*-enamides was also demonstrated thus improving the synthetic value of benzamides for structural diversities in a minimum number of synthetic steps.

The strategy of pot, atom and step economy (PASE) provides a line of green trend and approach towards efficient tools to synthesize target molecules.[1] The beauty of the PASE concept is that it provides maximum structural complexity and diversity with the least number of synthetic steps and few or no by-products to assemble the compounds. In this regard, the 1,3-dipolar cyclization has become a powerful and widely used strategy as it ensures 100% atom economy with a single operation.[2] The proximity and conformational constraints between 1,3-dipoles and dipolarophiles often lead to regio- or stereoselectivity, and therefore the development of a straightforward method for dipolarophiles, selectively matched to 1,3-dipoles, is still in demand and need to be investigated.

Amides are one of the most common and reliable functional groups in all branches of chemistry because of their distinct features, such as high polarity, stability and conformational diversity.[3] These widespread amide bonds are present in all natural peptides and many pharmaceuticals. Also some of the amides serve as directing groups in the C–H activation reactions.[4] Thus, it is not surprising that the development of an organic method for the transformation of amides into other functional groups is of vital importance. Among many transformation reactions, synthesis of aldehydes, ketones, alcohols, (eqn (1)) and amines *via* selective reduction by alkali-metal hydrides, borohydrides, and transition metal catalyst has mainly been developed (eqn (2)).[5] Conversions from amides to enediamines, vicinal diamines or benzils have also been researched by a few groups.[6] Although established transformation methods are quite general, there are still remaining synthetic challenges from the perspective of atom and redox economy (Scheme 1).



Scheme 1 Transformation reactions of amides.

Herein, we demonstrate the atom-economic reaction of benzamides with 1-sulfonyl-1,2,3-triazoles to synthesize fully substituted enaminones (eqn (3)). Particularly, benzamides stereoselectively matched triazoles, which results in the formation of (*Z*)-α-amido-enaminones. Selective cleavage of the β-amino moiety of the obtained product is also reported.

Rh-Azavinyl carbene (Scheme 2, **A**), readily prepared from 1-sulfonyl-1,2,3-triazoles and a rhodium catalyst,[7] has electrophilic character in addition to its nucleophilic site because of the α-imino moiety. Thus, the Rh-azavinyl carbene (**A**) behaved as a 1,3-dipole to participate in cyclization reactions with dipolarophiles, including nitriles, alkynes, isocyanates, and allenes to form heterocycles.[8] It is noted that other 2π-moieties such as carbonyl could also undergo cyclization with such a dipole.[9] For example, cyclization reaction of Rh-azavinyl carbenes **A** with simple benzaldehyde to give 4-oxazolines was reported by Fokin and co-workers,[9a] and Murakami *et al.* reported that **A** reacted with α,β-unsaturated aldehydes leading to the production of *trans*-2,3-dihydropyrroles.[9b] We envisioned that benzamides could provide molecular complexities and structural diversities in the reaction with dipole **A** because of their variable substituents. Thus, the new reaction with benzamide as a partner of **A** meets

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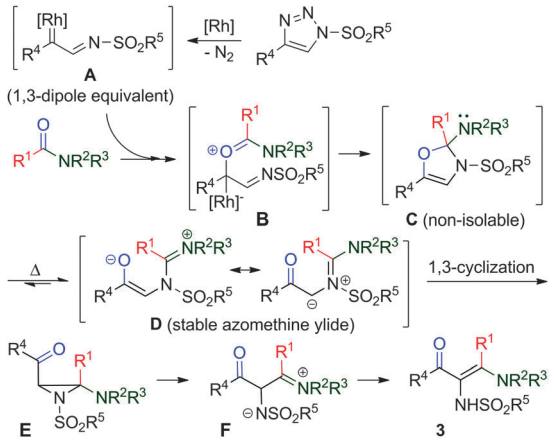
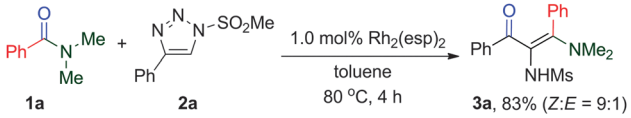


Scheme 2 Proposed mechanism.

the high demand of diversity-oriented synthesis (DOS). However, amides displayed very low reactivity in reactions with a dipole due to both electronic and steric factors as opposed to aldehydes. In our further studies, we observed that *N*,*N*-dimethylbenzamide (**1a**) reacted with 1-sulfonyl-1,2,3-triazole (**2a**) unexpectedly leading to the formation of the fully substituted α-amido-enaminone **3a**, a valuable building block of various medicinal compounds,[10] in 83% yield using $Rh_2(esp)_2$ as the catalyst in toluene at 80 °C (eqn (4)). Other Rh(II) catalysts including $Rh_2(OAc)_4$ and $Rh_2(Oct)_4$ were incompatible with the reaction of amides and no conversion was observed at room temperature even in the presence of $Rh_2(esp)_2$.

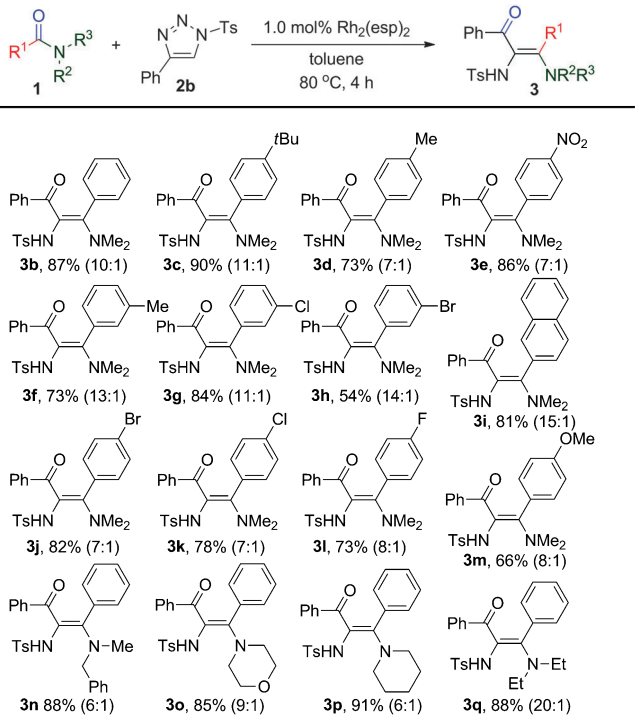


(4)

As shown in Scheme 2, a possible reaction pathway can be postulated that benzamide reacted with Rh-azavinyl carbene **A** to form unstable 4-oxazoline (**C**) *via* carbonyl ylide (**B**) at first. Then, the unstable 4-oxazoline (**C**) transformed the short-lived azomethine ylide (**D**) through ring-opening of **C**, a well-known thermal preparation method of azomethine ylide,[11] followed by the intramolecular 1,3-cyclization and subsequently the formation of aziridine (**E**) at an elevated temperature. Following ring-opening of **E**, zwitterionic intermediate **F** allowed the synthesis of the *Z*-selective enaminone **3** through proton rearrangement. The geometry of the double bond, presumably controlled by the shape of **D**, was assigned using single-crystal X-ray analysis.[12]

Reactions of various *N*,*N*-disubstituted benzamide derivatives (**1**) with **2b** were carried out under the reaction conditions to determine the scope of the present method (Table 1). It turns out that the variation of the *para*- or *meta*-substituent in benzamide does not alter the efficiency of the reactions. Nitro and halide functional groups were also tolerated under the reaction conditions. The reaction with *N*,*N*-dimethyl-2-naphthamide afforded the desired product (**3i**) in 81% isolated yield. However, the 3-bromo-*N*,*N*-dimethybenzamide substrate was slightly less reactive due to the steric effect and the desired product **3h** was isolated in 54% yield.

Table 1 Investigation of *N*,*N*-disubstituted benzamide scope[a,b,c]



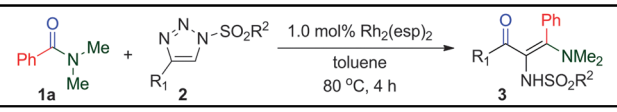
[a] Reaction conditions: **1** (3.0 equiv.), **2b** (0.5 mmol), $Rh_2(esp)_2$ (1.0 mol%) and toluene (5.0 mL) at 80 °C for 4 h. [b] Isolated yields. [c] The number in parentheses is the *Z*:*E* isomeric ratio of the product determined by ^{1}H NMR.

We were also pleased to find that 1-sulfonyl-1,2,3-triazoles reacted with other *N*,*N*-disubstituted benzamides in good to excellent yields, allowing for the introduction of a variety of amine groups (**3n–3q**). Notably, the benzyl group in **3n** can be cleaved to afford a secondary amine. Also, the synthesis of product **3** was performed on the gram scale without encountering any problems.[12] However, when *N*,*N*-dimethylacetamide was used instead of *N*,*N*-disubstituted benzamides, the corresponding adduct was not produced.

The reaction conditions were subsequently applied to a range of 1-sulfonyl-1,2,3-triazoles (Table 2). All types of 1-sulfonyl-1,2,3-triazole examined worked with high efficiency, affording the desired products in satisfactory yields. Electronic or steric variation of the C4-substituent on the triazoles exhibited small effects on the reaction efficiency, and the corresponding products were obtained in good yields. Not only aryl but also alkyl substituents on the sulfonyl group were readily employed resulting in comparable product yields.

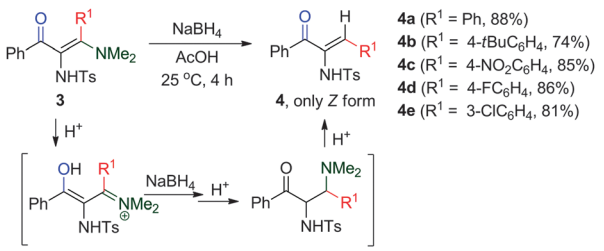
To demonstrate the synthetic utility of this reaction, we also performed the reduction of product α-amido-enaminones using $NaBH_4$. Surprisingly, compound **3** directly transformed to furnish the sterically less favourable *Z*-enamide (**4**),[13,14] which constitutes the core structure of many functional materials and natural products of biological significance (Scheme 3).[15] The reaction is thought to be initiated by $NaBH_4$ to form the α,β-diaminoketone intermediate followed by the stereoselective elimination to give the *Z*-enamide under the acidic reaction conditions,[16] however, we have no evidence supporting the intermediacy of this species. With this newly developed elimination conditions in hand, we examined the reactivity of representative substrates. Substrates possessing

Table 2 Examination of various 1-sulfonyl-1,2,3-triazoles[a,b]



Entry	R^1	R^2	Product **3**	Yield[c] (%)
1	4-*t*BuC_6H_4	4-MeC_6H_4	**3r**	86 (9 : 1)
2	4-MeOC_6H_4	4-MeC_6H_4	**3s**	88 (10 : 1)
3	4-BrC_6H_4	4-MeC_6H_4	**3t**	81 (11 : 1)
4	4-FC_6H_4	4-MeC_6H_4	**3u**	82 (8 : 1)
5	4-$CF_3C_6H_4$	4-MeC_6H_4	**3v**	79 (11 : 1)
6	3-MeC_6H_4	4-MeC_6H_4	**3w**	81 (9 : 1)
7	3-FC_6H_4	4-MeC_6H_4	**3x**	86 (11 : 1)
8	3-Thienyl	4-MeC_6H_4	**3y**	79 (7 : 1)
9	Ph	C_6H_5	**3z**	80 (8 : 1)
10	Ph	4-$CF_3C_6H_4$	**3aa**	64 (5 : 1)
11	Ph	4-MeOC_6H_4	**3ab**	92 (8 : 1)
12	Ph	*n*Bu	**3ac**	84 (7 : 1)

[a] Reaction conditions: **1a** (5.0 equiv.), **2** (0.2 mmol), $Rh_2(esp)_2$ (1.0 mol%) and toluene (2.0 mL) at 80 °C for 4 h. [b] Isolated yields. [c] The number in parentheses is the *Z* : *E* isomeric ratio of the product determined by ^{1}H NMR.



Scheme 3 Synthetic reactions of *Z*-enamides.

electron-donating or electron-withdrawing groups all smoothly reacted to provide the desired *Z*-enamides with high efficiency (**4a–4c**). When substrates having 4-fluoro and 3-chloro groups were subjected to reduction with $NaBH_4$, corresponding products **4d** and **4e** were obtained in 86% and 81% yields, respectively. Gratifyingly, the process can be successfully applied to a one-pot method starting from benzamides and 1-sulfonyl-1,2,3-triazole.[12]

In summary, the efficient synthetic reaction of 1-sulfonyl-1,2,3-triazoles with benzamides as sources of atom economic coupling partners is described herein. Various tertiary benzamides stereoselectively react with *in-situ* generated Rh-azavinyl carbenes to synthesize fully substituted α-amido-enaminones. The β-amino substituent of the obtained product could be selectively removed by treating with $NaBH_4$ to form *Z*-enamides. Considering its convenient reaction conditions and excellent stereoselectivity, this method presents a novel approach for the construction of multi-functionalized enaminones or enamides.

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