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Cycloisomerization

Access to Highly Functionalized Sulfonated Cyclopentanes by Acid-Promoted Rauhut–Currier Reaction with Sulfinamides

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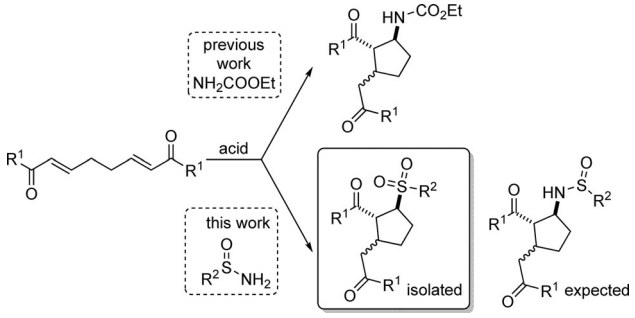
Abstract: An unexpected acid-mediated cascade reaction induced by conjugate addition of sulfinamides to dienediones has been developed. This highly efficient Rauhut–Currier reaction enables the rapid, high-yielding construction of sulfonated cyclopentanes with three contiguous stereogenic centers in a single operation starting from simple sulfinamides. This process constitutes the first example of sulfinamide-promoted cycloisomerization.

In recent years, much effort has been devoted toward designing highly selective strategies giving straightforward access to new and original frameworks starting from simple and easy available reagents.[1] Based on this strategy, the concept of diversity-oriented synthesis (DOS) was introduced by Schreiber in 2000 with the aim to rapidly generate new collections of drug-like small molecules and to find potential new therapeutic agents for incurable diseases.[2] Cascade reactions are thus an attractive method by which to prepare these new compound libraries.[3] Multiple stereocenters can be then created in a single-pot operation via both diversified and step-economical approaches.

In our continuing interest in the development of *Lobelia* alkaloid analogues for studying nicotinic acetylcholine receptor (nAChR) allosteric rearrangements,[4] we very recently reported an original example of a switchable aza-Michael-induced ring closure (aza-MIRC) by an "on/off" catalyst effect allowing the selective synthesis of cyclopentanes or pyrrolidines.[5] A range of polyfunctionalized aminocyclopentanes were selectively prepared through the acid-mediated conjugate addition of deactivated primary amines (Scheme 1). Similarly, Seo and co-workers recently depicted an elegant synthesis of 1,2,3-trisubstituted aminocyclohexanes based on an indium triflate-catalyzed aza-MIRC, this time using secondary amines.[6]



Scheme 1. Design of acid-mediated cascade reactions.

Initially, the objective of the present study was to extend the synthetic potential of our previous methodology in the Rauhut–Currier (RC) reaction by using deactivated *N*-nucleophiles bearing easily removable amine-protecting group such as the *tert*-butanesulfinyl moiety (Scheme 1).[7] Indeed, due to their useful synthetic applications, sulfinamide reagents are often involved in a wide array of reactions. However, to our knowledge, they have never been used as RC promoters.[8] Surprisingly, we found that the addition of sulfinamides to octa-2,6-diene-1,8-diones under acidic conditions serendipitously led to cyclopentylsulfones.

As the sulfone moiety (–SO_2–) is often encountered in pharmaceuticals,[9] agrochemicals,[10] and, materials,[11] this step-economical metal-free process constitutes an interesting alternative strategy to access valuable sulfonated scaffolds. In addition, sulfones are also involved in a number of useful chemical transformations for the preparation of olefins, such as the Julia[12] and Ramberg–Bäcklund[13] reactions, making them key building blocks in organic synthesis. For this reason, several methods for their preparation have been successfully developed, but they mainly suffer from limitations due to the harsh conditions or multistep strategies required.[14] In this context, a new straightforward pathway for the synthesis of sulfones is still highly appealing, especially if environmental considerations are taken into account. Herein, we report a totally new method of sulfone synthesis through an original metal-free thia-MIRC cascade involving sulfinamides.

We first selected the octadienedione **1a** and the *tert*-butylsulfinamide **2a** as substrates to test the viability of our reaction (Table 1). In the absence of catalyst activation, none of the expected five-membered ring compound was isolated, even under solvent-free conditions and thermal and/or ultrasonic activation: the starting material was recovered unchanged or de-

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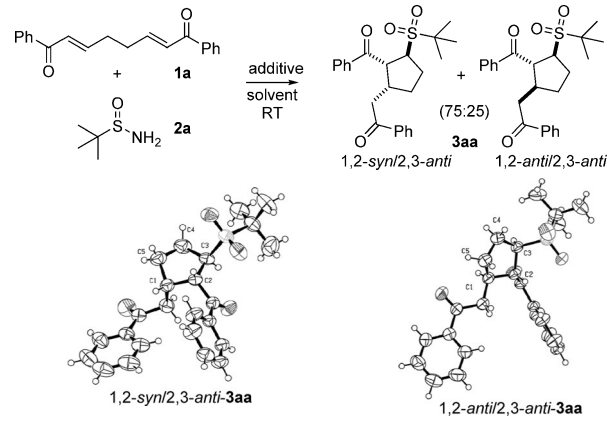
Table 1. Discovery of the sulfonated cyclopentane.

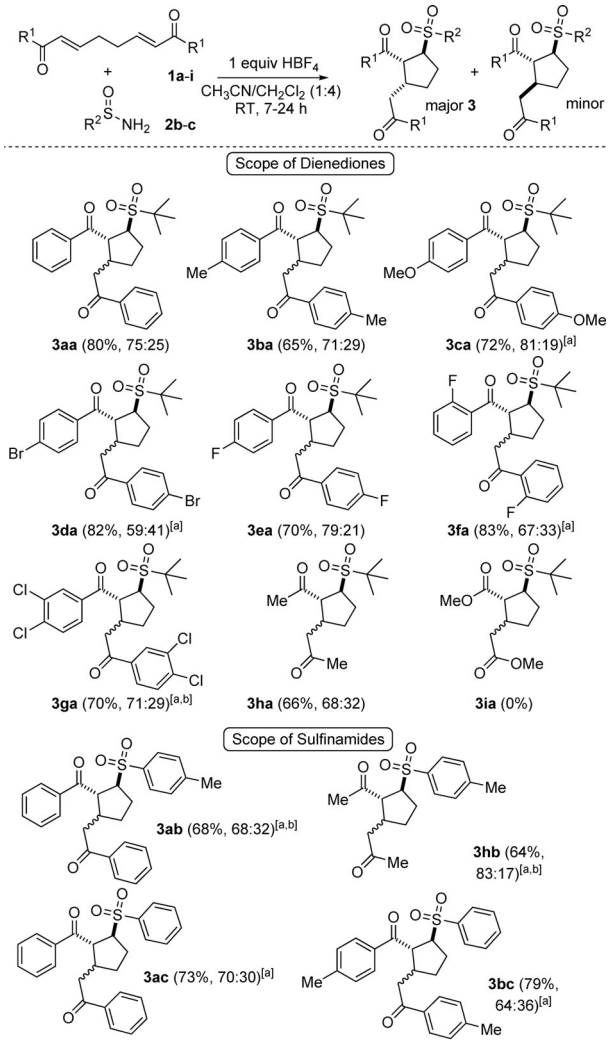


1,2-*syn*/2,3-*anti*-**3aa**

1,2-*anti*/2,3-*anti*-**3aa**

Entry[a]	Additive (equiv)	Solvent	**2a** [equiv]	Time [h]	Yield [%][b]
1	HBF_4 (0.3)	CH_3CN	1.2	24	17
2	HBF_4 (1)	CH_3CN	1.2	24	42
3	HBF_4 (1.2)	CH_3CN	1.2	24	42
4	HBF_4 (1)	CH_3CN	1.2	9	41
5	HBF_4 (1)	CH_3CN	1.6	9	61
6	HBF_4 (1)	CH_3CN	0.8	9	41
7	HBF_4 (1)	CH_3CN	2	9	70
8[c]	HBF_4 (1)	CH_3CN	1.6	9	60
9	TMSOTf (1)	CH_3CN	1.6	24	14
10	$BF_3{\cdot}Et_2O$ (1)	CH_3CN	1.6	24	40
11	TfOH (1)	CH_3CN	1.6	24	18
12	HBF_4 (1)	CH_2Cl_2	1.6	24	58
13	HBF_4 (1)	CH_3CN/CH_2Cl_2 (4:1)	1.6	6	61
14	HBF_4 (1)	CH_3CN/CH_2Cl_2 (1:1)	1.6	7	63
15	HBF_4 (1)	CH_3CN/CH_2Cl_2 (1:4)	1.6	7	85 (80)[d]

[a] Reaction conditions, unless otherwise stated: Diene **1a** (0.20 mmol), $c = 0.4$ mol L^{-1}; [b] NMR yield using 1,4-dimethoxybenzene as internal standard; [c] $c = 0.2$ mol L^{-1}; [d] yields refer to isolated products.



Scheme 2. Substrate scope of the reaction. Unless otherwise noted, reaction conditions were as follows: **1** (1 equiv), **2** (1.6 equiv), HBF_4 (1 equiv) in CH_3CN/CH_2Cl_2 (1:4, $c = 0.4$ mol L^{-1}) at RT for 7–24 h. Yields refer to isolated products. Diastereomeric ratio determined by NMR from the purified products. [a] $c = 0.2$ mol L^{-1}; [b] **2** (2 equiv), HBF_4 (1.5 equiv).

graded by high temperatures. Driven by our experiences in activation of aza-Michael reaction with deactivated primary amines,[5] we studied the influence of aqueous tetrafluoroboric acid (HBF_4; Table 1, entries 1–8). To our delight, although the reaction rate was sluggish with a catalytic amount of HBF_4, the reaction sequence proceeded more efficiently by using 1 equivalent of HBF_4. Two new cycloisomerized compounds were formed and separated by flash column chromatography on silica gel (Table 1, entries 1–3). Their diastereomeric relative configuration was easily assigned by nOesy experiments, but single-crystal X-ray diffraction analysis was required to allow us to clearly elucidate the exact structures of the two unanticipated sulfones **3aa**.[15] To our knowledge, this study represents the first example of the synthesis of a $-SO_2-$ unit starting from a simple sulfinamide. Encouraged by this result, we demonstrated that **3aa** could be prepared in 70% yield by using two equivalents of sulfinamide in a shorter reaction time (Table 1, entries 4–8). A variety of Lewis acids or acid promoters were then examined. Although $Bi(OTf)_3$ and $In(OTf)_3$ proved inefficient, $BF_3{\cdot}Et_2O$, TMSOTf, or TfOH were not more active than HBF_4 (Table 1, entries 9–11). Finally, we focused on the effect of the solvent. Although the concentration of the solution did not affect the efficiency of the reaction (Table 1, entry 8), a mixture of CH_3CN and CH_2Cl_2 in a 1:4 ratio dramatically increased the yield of the cascade reaction to 80% (Table 1, entries 12–15). Indeed, this weakly polar solvent system provided the best compromise between the conversion, the reaction time, and the amount of byproducts.[16]

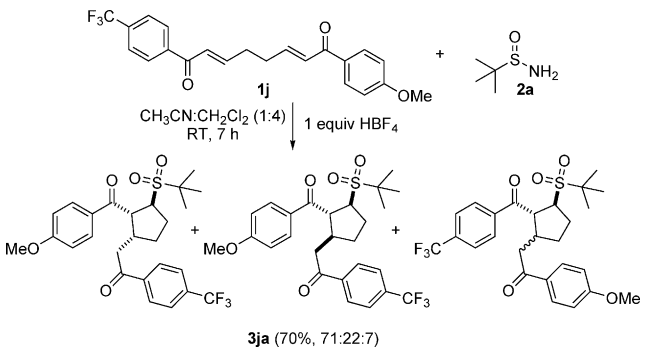
With the optimized conditions in hand, we next set out to examine the scope and the limitations of this original reaction (Scheme 2). Except in the case of **3aa** and **3da**, the generated cyclopentanes were rapidly isolated as a diastereomeric mixture without endeavoring to separate the two isomers. The reactivity of various dienediones was first investigated. Electron-rich *para*-substituents on the aromatic core did not affect the reaction and allowed access to the corresponding cyclopentanes **3ba** and **3ca** in 65 and 72% yield, respectively, and good diastereoselectivities up to 81:19 always in favor of the

1,2-*syn*/2,3-*anti* isomer.[17] Similar results were obtained for **3da**, **3ea**, **3fa** and **3ga** starting from dienediones substituted in variable positions by deactivating groups, demonstrating the generality of the process. However, neither the diastereoselectivity nor the yield of the cascade could be correlated with the electronic properties of the arenes. When applied to the methyl ketone **1h**, the reaction proceeded smoothly to give the corresponding cyclopentane derivative **3ha** in 64% yield and similar diastereomeric ratio. In contrast, the ester moiety was not electrophilic enough to promote the thia-MIRC reaction and the starting alkene **1i** was recovered.

Given that a range of sulfinamides are commercially available and that several simple, efficient, and innovative methods have been developed for their preparation,[18] we also surveyed the reactivity of various arylsulfinamides to synthesize structurally diversified sulfones (Scheme 2). We found that arylsulfinamides **2b** and **2c** were easily accommodated, leading to the corresponding cyclopentyl arylsulfones in good yields and diastereopreferences (d.r. up to 83:17). Finally, an enantioselectivity experiment was attempted starting from (*R*)-*tert*-butanesulfinamide but, as expected in the presence of an acid bearing a non-nucleophilic counter ion, the chirality of the sulfinyl group was not preserved.[19]

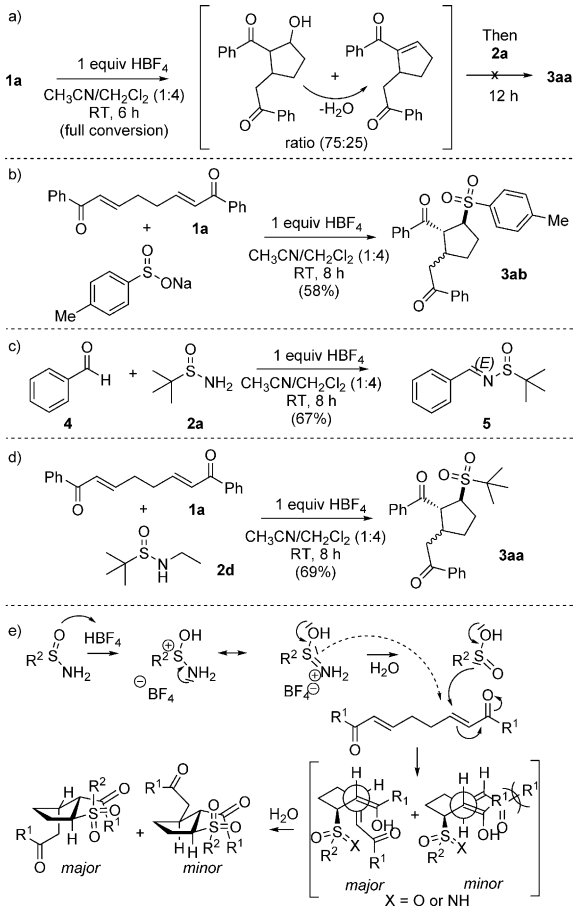
After the successful synthesis of cyclopentanes starting from symmetrical dienediones, diversification was also introduced by evaluating the reactivity of the unsymmetrical scaffold **1j** (Scheme 3). Even if a complex mixture of isomers could be forecasted starting from unsymmetrical substrates, we were pleased to find that a synthetically useful selectivity was obtained in the formation of **3ja**: the regioselectivity of the sequence was in favor of the isomer resulting from the initial thia-Michael addition onto the less electrophilic alkene moiety of **1j**.

These results immediately raised questions about the exact mechanism of this transformation (Scheme 4). Even if dienediones are known to undergo RC cyclization in the presence of a nucleophilic catalyst,[7,20] this reaction has never been reported starting from sulfinyl derivatives. Therefore, we postulated that the reaction might be initiated by the sulfinamide nucleophilic attack, leading a transient enol intermediate. To test this hypothesis, the reaction was first carried out in the absence of sulfinamide: two cyclic products resulting from the water-induced RC reaction were isolated (Scheme 4a). No evolution of



3ja (70%, 71:22:7)

Scheme 3. Reactivity of unsymmetrical scaffold **1j**.



Scheme 4. Experimental investigation of reaction mechanism.

the reaction mixture was detected when the sulfinamide was subsequently added, clearly demonstrating that the sequence is initiated by a usual hetero-Michael addition, leading to the expected five-membered ring.[21] To evaluate a possible preliminary sulfinamide hydrolysis into sulfinic acid prior to the nucleophilic attack,[22] the reaction was carried out, under similar reaction conditions, starting from an equimolar mixture of sodium *p*-toluenesulfinate and HBF_4 (Scheme 4b). The RC product **3ab** was isolated in a lower yield compared to the use of the corresponding sulfinamide. Although these experiments indicated that our acid-induced RC procedure can be extended to include the use of sulfinate derivatives,[23] they don't exclude a preliminary sulfinamide hydrolysis step. That was confirmed when the reaction was performed in the presence of 3 Å molecular sieves. The reaction rate was dramatically affected, only affording trace amount of the expected cyclopentane **3aa**. However, when the reaction was performed under similar reaction conditions and reaction time in the presence of benzaldehyde **4**, used as a hard electrophile (Scheme 4c), the corresponding imine **5** was then isolated in a very clean reaction, calling into question the sulfinamide's hydrolytic stability. The aforementioned results reveal the ambident nucleophilicity of the sulfinamide moiety that could display both hard (amide nitrogen) and soft (sulfinyl sulfur) nucleophilic additions in the presence of hard (aldehyde) and soft

electrophiles (enone), respectively. Finally, as the mechanism might be suspected to proceed via a transient sulfoximine intermediate,[15] we attempted to isolate a hydrolytically more stable sulfoximine species by condensing the *N*-ethyl sulfinamide **2d** with the dienedione **1a**. However, the sulfone **3aa** was the sole product delivered (Scheme 4d).

For these reasons, even if the formation of a nucleophilic sulfoximine intermediate cannot be totally ruled out, all the previous observations seem to suggest that the transformation might be initiated by sulfinamide hydrolysis to give the corresponding sulfinic acid before the thia-Michael addition (Scheme 4e). Moreover, the regioselectivity obtained from the unsymmetrical dienedione **1j** seems to corroborate this proposed mechanism: the *S*-nucleophile reacts preferentially on the least positively charged β-carbon of the two electron-deficient olefins, which is the softest electrophilic site.

In summary, we have discovered an elegant metal-free approach to the construction of a series of structurally novel sulfonated cyclopentanes bearing three contiguous stereogenic centers through an unusual RC cascade reaction. This easy-to-handle process is an original synthetic strategy for the rapid access to sulfones starting from simple sulfinyl derivatives under mild reaction conditions.

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Keywords: carbocycles · cascade reactions · cycloisomerization · Michael addition · sulfinamides

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[15] HRMS analysis of the initially isolated RC compounds matched with the expected sulfinyl cyclopentane structure (*m/z* $[M+H_2O+H]^+$ 430.2061). However, new HRMS analyses made on crystals used for the X-ray analyses indicated a different molecular mass matching with the sulfone structure **3aa** (*m/z* $[M+Na]^+$ 435.1504). We then hypothesized that a highly hydrolyzable sulfoximine might be a transient intermediate.

[16] The exchange of CH_3CN for MeOH dramatically affected the reaction, providing only the degradation of the starting material. Using water as solvent allowed the recovery of the unmodified starting materials **1a** and **2a**, probably due to the insolubility of the dienedione.

[17] The relative configuration of each diastereomeric RC product was established by analogy with the ^{1}H NMR data obtained for the isolated diastereoisomers of **3aa**, respectively.

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