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ARTICLE TYPE

## Interception Of Benzyne With Thioethers: A Facile Access To Sulfur Ylides In Mild Conditions

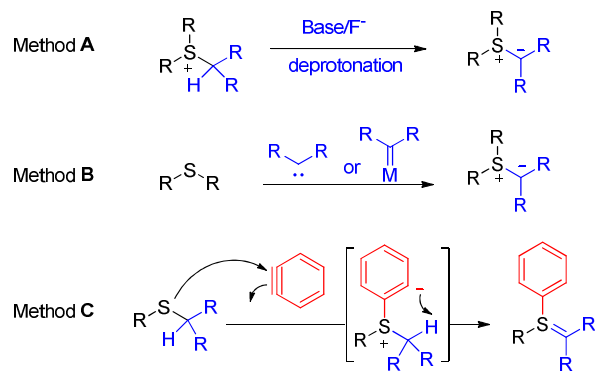
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Reactive benzyne generated from *o*-(trimethylsilyl)phenyl triflate under the action of CsF has been trapped in situ by thioethers to give sulfonium ylides, which in turn have been intercepted by isatins to give rise to corresponding spiroepoxy oxindoles in moderate to high yields. This reaction provides a facile and efficient synthesis of spiroepoxy oxindoles.

Since discovered in 1930,<sup>1</sup> Sulfonium ylides have been involved in various transformations, such as epoxidation of aldehydes/ketones,<sup>2</sup> aziridination of imines,<sup>3</sup> cyclopropanation of conjugated enones/enoates and their congeners,<sup>2c,4</sup> as well as 2,3-Wittig rearrangement of allylic/propagyl sulfonium ylides,<sup>5</sup>

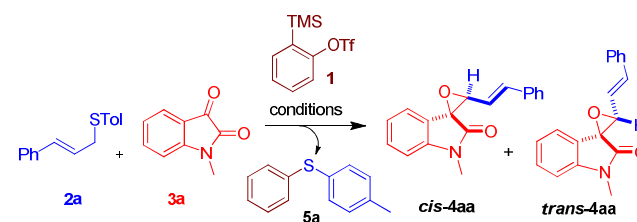


providing invaluable synthetic methods. Recently, Aggarwal group has made great advances in sulfonium ylide mediated catalytic asymmetric epoxidation,<sup>6</sup> Tang laboratory has also achieved a series of excellent asymmetric Michael addition/cyclization cascades triggered by sulfonium ylides;<sup>4c,7</sup> moreover Xiao and colleagues have disclosed several efficient heterocyclic synthesis featuring formal [4+1] cycloaddition on sulfonium ylides.<sup>8</sup> Although there exist a handful of methods for sulfonium ylide formation,<sup>9</sup> deprotonation of corresponding sulfonium salts constitutes the major avenue to the ylide formation due to their inherent benefits (Method A, Figure 1).<sup>10</sup> Reaction of thioethers with carbenes/metal carbenoids constitutes a second consequential approach which has found broad applications (Method B, Figure 1).<sup>10a,11</sup> Another elegant yet undeveloped strategy for sulfonium ylide formation, namely, nucleophilic attack of alkyl thioether on benzyne followed by an intramolecular 1,4-proton shift (Method C, Figure 1)<sup>12</sup> has been almost totally neglected Since its debut, wherein the *o*-fluorophenylmagnesium bromide was employed as the benzyne

precursor, as few further investigations have been followed up.<sup>13</sup> The poor compatibility of these protocols with some common functional groups seriously limited their applications.

Recent flourishing advances in the area of aryne chemistry have brought new reactivities and applications to these highly reactive intermediates.<sup>14</sup> This resurgence in aryne chemistry is attributed largely to the introduction of *o*-(trimethylsilyl)aryl triflates, by Kobayashi et al, as convenient and efficient aryne precursors that require only very mild conditions (weakly basic fluoride anion source and ambient temperature) to promote the in situ formation of corresponding arynes.<sup>15</sup> We therefore decided to use *o*-(trimethylsilyl)aryl triflate to revisit the thioether/benzyne strategy of sulfonium ylide formation, hoping to develop new synthetic processes. Here we report a convenient one-pot synthesis of epoxyoxindoles<sup>16</sup> via this thioether/benzyne strategy.

Table 1. Optimization of Reaction Condition<sup>a</sup>



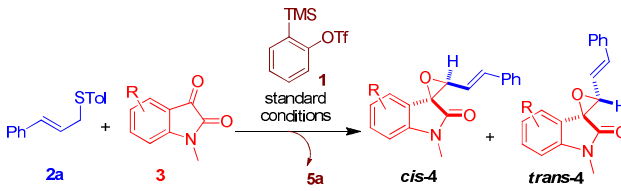
entry	1/2a/3a/CsF	T (°C)	Yield <sup>b</sup> (%)	Dr <sup>c</sup> (cis/trans)
1	1.2/1.5/1.0/3.0	25	68	56/44
2	1.2/1.5/1.0/3.0	40	87	44/56
3	1.2/1.5/1.0/3.0	60	65	35/65
4	1.2/1.5/1.0/3.0	80	41	21/79
5	1.0/1.0/1.6/3.0	40	68 <sup>d</sup>	27/73

<sup>a</sup> All reactions were performed on 0.25 mmol of *N*-methyl isatin **3a** with *o*-(trimethylsilyl)aryl triflate **1**, thioether **2a**, and CsF in anhydrous acetonitrile. <sup>b</sup> sum of isolated yields of *cis*-**4aa** and *trans*-**4aa** after column chromatography, based on the isatin. <sup>c</sup> Determined by the isolated yields of two isomers. <sup>d</sup> yield based on **1**.

We chose cinnamyl *p*-tolyl sulfide (**2a**) and *N*-methyl isatin (**3a**) as benzyne interceptor and sulfonium ylide interceptor respectively to test this strategy.<sup>17</sup> Thus a mixture of **1**, **2a**, and **3a** with cesium fluoride (1/2a/3a/CsF: 1.2/1.5/1.0/3.0) in anhydrous acetonitrile was vigorously stirred overnight at room temperature. A pair of diastereoisomers (*cis*-**4a** and *trans*-**4a**) was isolated in 25% yield, and the by-product phenyl tolyl thioether **5a** was also

collected and identified. These observations confirmed our proposal. Brief screening of solvents quickly distinguished acetonitrile as a better reaction medium than other solvents such as Tetrahydrofuran, ethyl acetate, *N,N*-dimethylformamide and dichloromethane. Further optimization was carried out in acetonitrile and the results were shown in table 1. When the reaction mixture was stirred overnight at 40 °C, the epoxide isomers **4aa** was obtained in 87% yield (entry 2), much higher than both at 25 °C (entry 3, 68%) and at 80 °C (entry 4, 41%). With the Isatin **3a** as limiting reagent, the reaction gave diastereomers **4aa** in 68% yield at 40 °C (entry 5). Interestingly, the modest *dr* value obtained at room temperature improved toward the *trans*-product evidently as the reaction temperature increased (entries 1-4).

Table 2. Substituent Effects on Isatin Aromatic Ring<sup>a</sup>



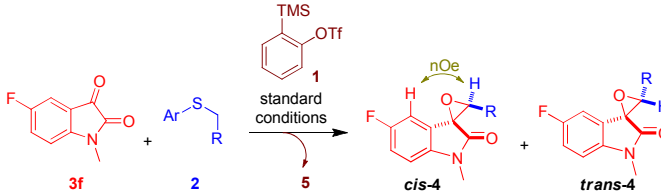
Entry	Isatin 3, R	Product 4, yield <sup>b</sup> (%)	<i>Dr</i> <sup>c</sup> ( <i>cis:trans</i> )
1	<b>3a</b> , H	<b>4aa</b> , 87	44:56
2	<b>3b</b> , 5-CH <sub>3</sub>	<b>4ab</b> , 50	54:46
3	<b>3c</b> , 5-OMe	<b>4ac</b> , 32	59:41
4	<b>3d</b> , 5-Br	<b>4ad</b> , 36	53:47
5	<b>3e</b> , 5-Cl	<b>4ae</b> , 58	43:57
6	<b>3f</b> , 5-F	<b>4af</b> , 93	33:67
7	<b>3g</b> , 5-NO <sub>2</sub>	<b>4ag</b> , 84	45:55
8	<b>3h</b> , 4-Br	<b>4ah</b> , 64	76:24
9	<b>3i</b> , 6-Cl	<b>4ai</b> , 42	45:55
10	<b>3j</b> , 6-F	<b>4aj</b> , 31	43:57
11	<b>3k</b> , 7-Cl	<b>4ak</b> , 70	49:51

<sup>a</sup> All reactions were performed on 0.25 mmol of isatins **3** with *o*-(trimethylsilyl)aryl triflates **1** (1.2 equiv), thioether **2a** (1.5 equiv), and CsF (3.0 equiv) in anhydrous acetonitrile at 40 °C overnight. <sup>b</sup> Sum of isolated yields of *cis*-**4** and *trans*-**4** after column chromatography, based on the isatin. <sup>c</sup> Determined by the isolated yields of two isomers.

At this stage, the optimal conditions in table 1 were set as standards (conditions for entry 2 table 1) for further studies. A number of substituted isatins **3b-3k** were subjected to the standard conditions to test the substitution effects on isatin aromatic ring (table 2). These data demonstrated that the electronic property undoubtedly exerts profound effects on the reactions, notably manifested by the yields of the corresponding 5-substituted spiroepoxy oxindoles **4**, which roughly parallel with the donating/withdrawing abilities of their 5-substituents (entries 1-6). Strong electron donating 5-Methoxyl group gave **4ac** in a yield as low as 32%, while strong electron withdrawing 5-NO<sub>2</sub> and 5-F groups delivered **4ag** and **4af** in 84% and 93% yields respectively; Isatins **3b**, **3d** and **3e** bearing relatively weaker electron donating groups on 5-position resulted in moderate yields. 7-Cl isatin **3k** under standard conditions achieved better yield (entry 11) than its 5- and 6-congeners (entries 5 and 9); and 4-Br isatin **3h** showed a less negative impact on the yield in comparison to its 5-epimer (entry 8 vs 4), yet still less than the parent isatin **4a** (entry 1). The impressive electronic and

positional effects, though lacking concrete rationale at this time, may indicate that the epoxidation of isatin proceeded stepwise with the first step, namely, the nucleophilic attack of ylide on the isatin carbonyl group, as the rate limiting step. Overall, this tandem reaction is fairly non-diastereoselective, even though the steric effect at 4-position favours the *cis*-isomer more than the anti-isomer as exhibited by the highest *cis/trans* ratio of 76/24 presented in table 2 entry 8 probably due to steric effect.

Table 3. The Substrate Scope of Thioethers<sup>a</sup>



entry	Sulfide 2, Ar, R	Product 4 yield <sup>b</sup> (%)	<i>Dr</i> <sup>c</sup> ( <i>cis:trans</i> )
1	<b>2a</b> , p-MePh, Z-PV	<b>4af</b> , 93	33:67
2	<b>2b</b> , p-MePh, 2-NO <sub>2</sub> Ph	<b>4bf</b> , 99	31:69 <sup>d</sup>
3	<b>2c</b> , p-MePh, 2-CIPh	<b>4cf</b> , 74	57:43 <sup>d</sup>
4	<b>2d</b> , p-MePh, 3-FPh	<b>4df</b> , 89	74:26
5	<b>2e</b> , p-MePh, 3-CIPh	<b>4ef</b> , 83	81:19
6	<b>2f</b> , p-MePh, 4-CIPh	<b>4ff</b> , 92	70:30
7	<b>2g</b> , p-MePh, CHCH <sub>2</sub>	<b>4gf</b> , 73	46:56
8	<b>2h</b> , Ph, Ph	<b>4hf</b> , 83	61:39
9	<b>2i</b> , Ph, Me	<b>4if</b> , 85	47:53

<sup>a</sup> All reactions were performed on 0.25 mmol of isatins **3a** with *o*-(trimethylsilyl)aryl triflates **1** (1.2 equiv), thioether **2a** (1.5 equiv), and CsF (3.0 equiv) in anhydrous acetonitrile at 40 °C overnight. <sup>b</sup> Sum of isolated yields of *cis*-**4** and *trans*-**4** after column chromatography, based on the isatin. <sup>c</sup> Estimated on the isolated yield. <sup>d</sup> determined via the <sup>1</sup>H NMR of the crude product. Z-PV = Z-phenylvinyl.

With isatin **3f** as epoxidation acceptor, a series of thioethers **2** were examined under standard conditions, the results are charted in table 3. allylic, benzylic and simple alkyl aryl thioethers all give good to excellent yields. As previously observed, the diastereoselectivities are normally low and steric bulkiness seems to be an important factor which favours *cis*-isomers over their *trans*-counterparts. More sterically demanding benzylic thioethers **2c-2f** reversed the *cis/trans* ratio with an exception of 2-NO<sub>2</sub> benzylic sulfide **4bf** whose strong dipolar nature may be involved to some extent in the transition state.

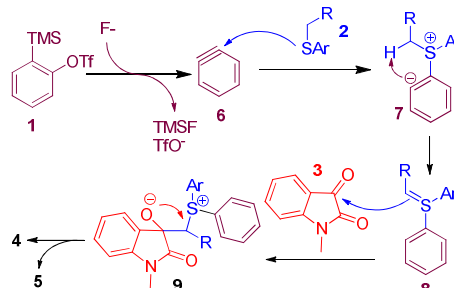


Figure 1. Proposed Mechanism for the Cascade of Benzyne Formation, Sulfonium Ylide Formation and Epoxidation

The structure of these spiroepoxides has been established by NMR spectra and high resolution mass spectra. Specifically, four pairs of representative diastereoisomers of **4af**, **4ag**, **4ff** and **4gf** were each submitted to acquire 2D <sup>1</sup>H-<sup>1</sup>H NOESY spectrum. The

presence of cross-peaks at the 4-H next to the fluoride atom and the epoxide H set a key diagnosis interactions which distinguished the *cis*-configuration from its *anti*-counterpart without doubt (refer to the NOESY spectra in SI). The relative stereochemistry of the others was assigned by analogy to those four pairs.

A possible mechanism for this process has been outline in Figure 1. *O*-(trimethylsilyl)aryl triflate **1** is converted to the reactive benzyne **6**, which is attacked by thioether **2** delivering intermediate zwitterion **7**. Immediate intramolecular 1,3-proton shift from the alkyl carbon onto the aromatic carbon produces sulfonium ylide **8**. Reaction of **8** with isatin **3** gives the spiroepoxide **4** via intermediate **9**.

## Conclusions

In summary, we have established a one pot process to spiro epoxyoxindoles. This method features two successive *in situ* capturing steps of reactive intermediates in very mild conditions. The use of *o*-(trimethylsilyl)aryl triflate as benzyne source upon a fluoride activation is the base for this improved protocol.

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## Notes and references

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† Electronic Supplementary Information (ESI) available: general experimental information, detailed procedures, characterize data of compounds, Copies of <sup>1</sup>H and <sup>13</sup>C NMR spectra for selected compounds. See DOI: 10.1039/b000000x/

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Fluoride anion kicks off the generation of a high energetic species benzyne which enables two successive trapping reactions.

