EurJOC
European Journal of Organic Chemistry

Communications
doi.org/10.1002/ejoc.202100060

Chemistry Europe
European Chemical Societies Publishing

Synthesis of Isatin-Hydrazones from 3-Diazo Oxindoles and Sulfoxonium Ylides under Catalyst- and Additive-Free Conditions

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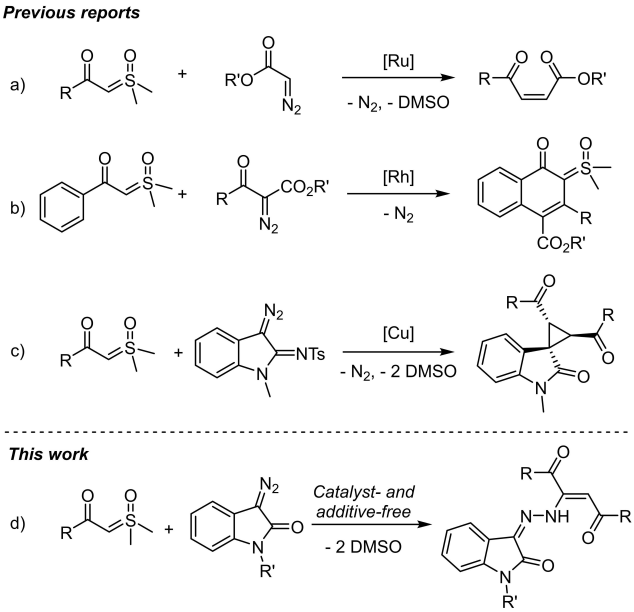
A facile synthesis of isatin-hydrazones from 3-diazo oxindoles and sulfoxonium ylides under catalyst- and additive-free conditions is described. A plausible reaction pathway is proposed for the transformation, in which diazo compounds play as electrophiles to react with nucleophilic sulfoxonium ylides. The reaction mechanism is supported by the experimental evidence.

Sulfoxonium ylides have been investigated as carbene precursors to undergo a large array of transformations.[1] Relying on their easy accessibility, moisture-/air-stability, and low explosibility, sulfoxonium ylides are considered as promising substitutes of diazo compounds. For example, distinct achievements have been gained in the transition-metal-catalyzed C–H and X–H functionalizations by using sulfoxonium ylides, instead of diazo compounds, as carbene precursors.[2] Generally, compared to diazo compounds, sulfoxonium ylides are more nucleophilic and show lower decomposition rates to form metal carbenes. These differences offer chemists opportunities to design new reactions that are generally difficult to achieve. For example, the cross-olefination of carbene precursors is challenging due to the competing homocouplings. In 2018, Maulide et al. devised a strategy to overcome this problem.[3] Sulfoxonium ylides and diazoesters were subjected to a ruthenium complex. Owing to the intrinsic difference in the reactivity, a metal carbene was generated faster from the diazoester, which was then attacked by the more nucleophilic sulfoxonium ylide, resulting in the generation of olefin products with high *Z* selectivity. Both N_2 and DMSO were eliminated in the reaction (Scheme 1a). Interestingly, the substituents adjacent to the carbanion of the diazo dramatically affected the reactivity of the diazo compounds. In 2019, Fan[4] and Wang[5] individually reported the Rh(III)-catalyzed cascade reactions of sulfoxonium ylides with α-diazo-β-ketoesters, which afforded naphthalenone derivatives bearing a β-ketosulfoxonium ylide unit. Only N_2 was eliminated in this reaction (Scheme 1b). Switching the diazo compound to a 3-diazoindolin-2-imines, in 2019 Lu and Wang



Scheme 1. Reactions of sulfoxonium ylides with diazo compounds.

successfully realized the synthesis of spiro[cyclopropane-1,3′-indolin]-2′-imines under copper catalysis. The reaction released both N_2 and DMSO as by-products (Scheme 1c).[6] Our group also engages in the carbene transfer reactions. For example, we have reported the gold-catalyzed dimerization of 3-diazo oxindoles[7] and the gold-catalyzed cross-coupling of 3-diazooxindoles with diazoesters,[8] respectively. During our investigation on the cross-olefination of 3-diazo oxindoles[9] with sulfoxonium ylides, we surprisingly found that isatin-hydrazones were formed. A literature screening showed that isatin-hydrazones are important compounds possessing antimicrobial,[10] antibacterial,[11] leucine-rich repeat kinase 2 (LRRK2) inhibiting[12] and β-amyloid aggregation inhibiting activities.[13] Giving the importance of isatin-hydrazones, herein we want to report their synthesis from 3-diazo oxindoles and sulfoxonium ylides under catalyst- and additive-free conditions (Scheme 1d).

In our first entry, we were aiming to realize the cross-olefination of sulfoxonium ylide **1a** with 3-diazo oxindole **2a** in the presence of XPhosAuCl/$AgPF_6$. To our surprise, isatin-hydrazone **3a** rather than a cross-olefination product, 3-alkylideneoxindole, was obtained (Table 1, entry 1). A control experiment revealed that the gold catalyst was not essential for this transformation. The yield of **3a** even slightly increased (entry 2). The product was generated from one 3-diazo oxindole

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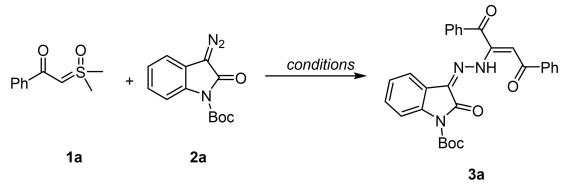
Supporting information for this article is available on the WWW under https://doi.org/10.1002/ejoc.202100060

Table 1. Optimization of the Reaction Conditions.[a]



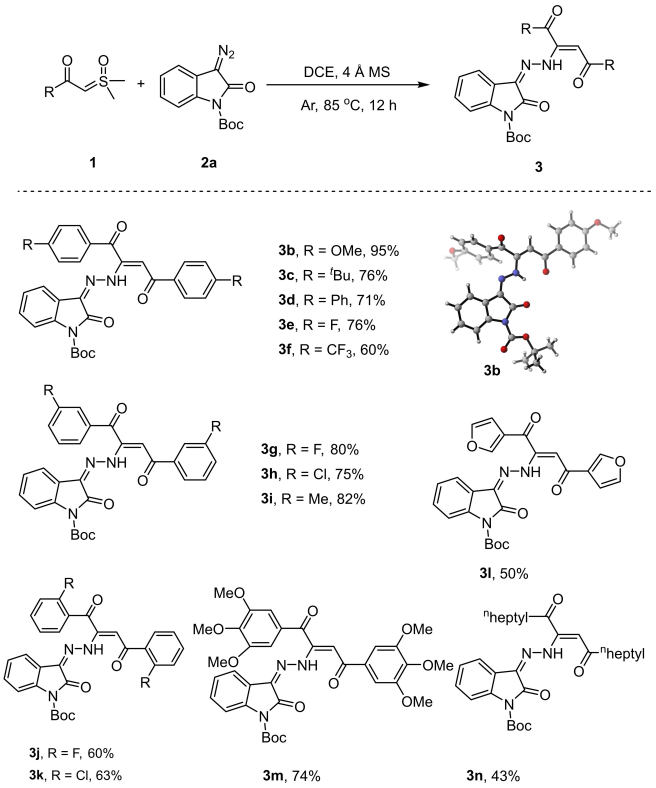
Entry	Ratio of **1a**/**2a**	Solvent	Yield [%][b]
1[c]	2:1	DCM	50
2	2:1	DCM	58
3	3:1	DCM	75
4	3:1	DCE	86
5	1:1	CH_3CN	70
6	3:1	THF	71
7	3:1	DMF	35
8	3:1	EtOH	trace
9[d]	3:1	DCE	86

[a] Unless otherwise noted, the reaction was conducted with **1a** (0.20 or 0.30 mmol), **2a** (0.10 mmol) and 4 Å molecular sieve (30 mg) in 3 mL of solvent at 50 °C under an argon atmosphere for 36 h, [b] Yields for isolated **3a**. [c] The reaction was conducted in the presence of 5 mol% of $XPhosAuCl/AgPF_6$, [d] The reaction was carried out at 85 °C for 12 h.

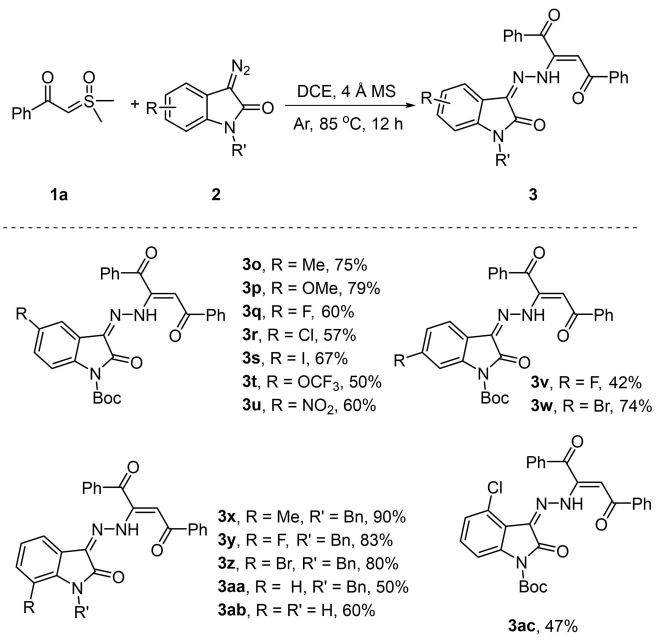
and two sulfoxonium ylide molecules, thus increasing the equivalent of **1a** would logically improve the yield of **3a**. Indeed, when 3 equiv. of **1a** were added, the yield of **3a** increased dramatically (entry 3). When the reaction was conducted in 1,2-dichloroethane (DCE), the yield of **3a** was obviously increased to 86% (entry 4). Further solvent screening revealed that the strong polar solvents such as MeCN, THF, and DMF were less efficient for this transformation (entries 5–7). Notably, when the reaction was carried out in a protic solvent, only trace amount of **3a** was observed (entry 8). When conducting at 85 °C, the reaction was completed in a relatively shorter time without reducing the yield of **3a** (entry 9).

With the optimized conditions in hand, the generality of this reaction was then investigated. The scope of sulfoxonium ylide was firstly explored (Scheme 2). It was found that sulfoxonium ylides **1** bearing aromatic substituents reacted smoothly with **2a** to afford the corresponding isatin-hydrazones in good yields (benzene ring, **3b**–**3m**; and thiophene ring, **3l**). Generally, sulfoxonium ylides bearing electron-donating groups on the benzene ring delivered the corresponding isatin-hydrazones in relatively higher yields (**3b**, **3c**, and **3i**) than those with electron-withdrawing groups (**3e**, **3f**, **3j**, and **3k**). The structure of **3b** was confirmed by a single-crystal X-ray structure analysis.[14] Besides aromatic groups, an aliphatic sulfoxonium ylide was also examined, which delivered **3n** in a relatively lower yield (43%).

The scope of 3-diazooxindoles was also investigated (Scheme 3). In analogy to sulfoxonium ylides, the relatively electron-enriched 3-diazooxindoles (**3o**, **3p**, and **3x**) generally afforded the corresponding isatin-hydrazones in better yields over the relatively electron-poor 3-diazooxindoles (**3q**, **3u**, and **3v**). **3ac** bearing a substituent on the 4-position of 3-diazooxindole was also obtained, even the yield is moderate (**3ac**, 47%). The relatively lower yield of **3ac** might be explained by the steric hindrance of the chloro group on the 4-position.



Scheme 2. The scope of sulfoxonium ylide. [a] Reactions were performed with **1** (0.60 mmol), **2a** (0.20 mmol), and 4 Å molecular sieve (30 mg) in 3 mL of DCE at 85 °C under an argon atmosphere for 12 h; the yields given are yields of isolated products.

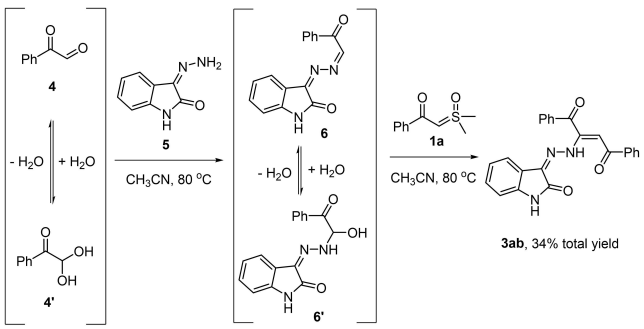


Scheme 3. The scope of sulfoxonium ylide. [a] Reactions were performed with **1** (0.60 mmol), **2a** (0.20 mmol), and 4 Å molecular sieve (30 mg) in 3 mL of DCE at 85 °C under an argon atmosphere for 12 h; the yields given are yields of isolated products.

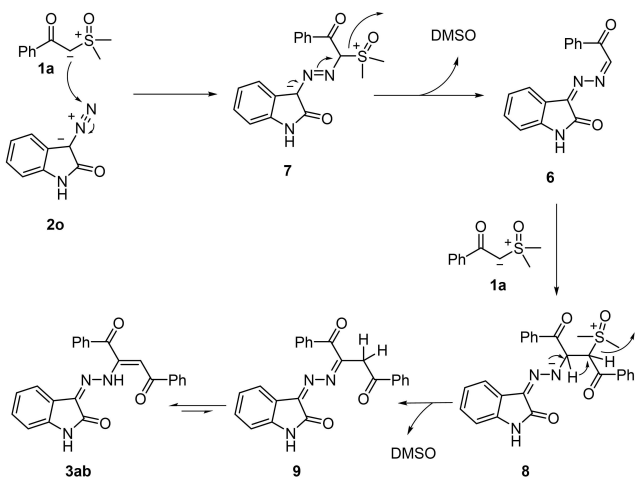
We next explored the mechanism of this transformation (Scheme 4). Compound **6** was proposed as a plausible intermediate. To examine the hypothesis, we attempted to prepare **6** through the reaction of phenylglyoxal **4** with 3-hydrazonoindolin-2-one 5. As a result, the corresponding hydrated species **6′** was afforded due to the instability of **6**.[15] After that, sulfoxonium ylide **1a** was added in a one-pot reaction. As we expected, the reaction afforded **3ab** in 34% total yield. An attempt to observe the plausible intermediate **6** and **6′** by ^{1}H NMR experiments failed, probably due to the fast reaction rate between **1a** and **6**/**6′**. However, when the reaction mixture was analyzed by high-resolution mass spectra (HRMS), both **6** and **6′** were observed (see the supporting information).

Based on the experimental results and literature reports, a plausible mechanism was proposed using the reaction of **1a** with **2o** as an example (Scheme 5). Firstly, 3-diazooxindole as electrophile[16] to react with the nucleophilic sulfoxonium ylide, forming a zwitterionic intermediate **7**. Subsequently, in analogy to the Japp-Klingemann reaction,[17] elimination of a dimethyl sulfoxide (DMSO) from **7** results in the formation of intermediate **6**. After that, the nucleophilic attack of sulfoxonium ylide to **6** generates a zwitterionic intermediate **8**. The following 1,2-hydride migration and the elimination of DMSO afford intermediate **9**, which finally gives the more stable **3ab** as a product via the enamine-imine tautomerization.

In conclusion, we have developed a facile synthesis of isatin-hydrazones from 3-diazooxindoles and sulfoxonium ylides. The reaction proceeded smoothly under catalyst- and additive-free conditions. A plausible mechanism was proposed and was supported by the experimental evidence. In this process, diazo compounds played as an electrophile to react with nucleophilic sulfoxonium ylides. Further investigation on the biological activity of isatin-hydrazones is underway in our laboratory.



Scheme 4. One-pot synthesis of **3aa** starting from phenylglyoxal.



Scheme 5. Plausible mechanism for the formation of isatin-hydrazones.

Acknowledgements

Financial support by the Natural Science Foundation of Shaanxi Province (2019JQ-323, 2018JM2049), the Fundamental Research Funds for the Central Universities (GK202103039), and the young top-notch talent of "Special Support Plan for High-Level Talents in Shaanxi Province" are greatly appreciated.

Conflict of Interest

The authors declare no conflict of interest.

Keywords: Hydrazones · Oxindoles · Ylides · Synthetic methods

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Manuscript received: January 20, 2021
Revised manuscript received: January 26, 2021
Accepted manuscript online: January 27, 2021