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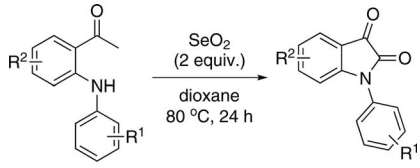
SHORT COMMUNICATION

Oxidative Amidation

An efficient method for the synthesis of *N*-arylisatins from 2-(arylamino)acetophenones by using SeO_2 as an oxidant under transition-metal-free conditions is described. The reaction proceeds smoothly in dioxane at 80 °C and gives the corresponding products in high yields. The reaction tolerates a wide range of functionalities.



Keywords: Nitrogen heterocycles / Fused-ring systems / Amidation / Selenium / Oxidation

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Selenium-Promoted Intramolecular Oxidative Amidation of 2-(Arylamino)-acetophenones for the Synthesis of *N*-Arylisatins

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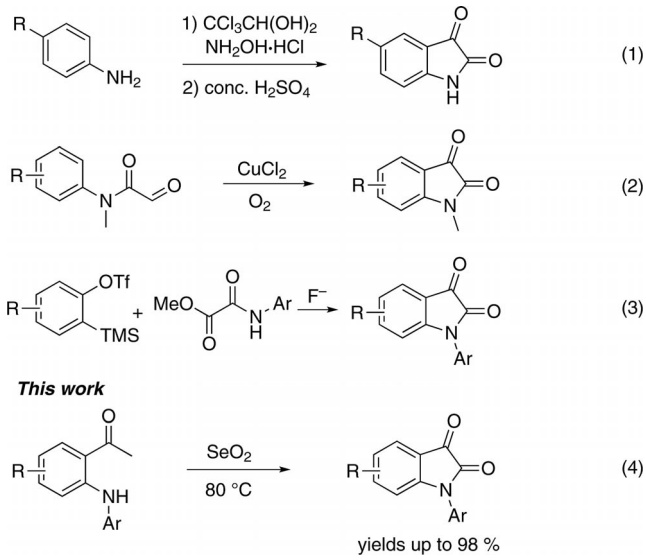
Keywords: Nitrogen heterocycles / Fused-ring systems / Amidation / Selenium / Oxidation

A convenient method for the synthesis of *N*-arylisatins from 2-(arylamino)acetophenones by using SeO_2 as an oxidant is described. Various substituted *N*-arylisatins were selectively obtained in good to excellent yields. The reaction tolerates a wide range of functionalities.

Introduction

Isatins (indoline-2,3-diones) are an important class of heterocycles and are commonly found in many natural compounds, pharmaceuticals, and dyes.[1] The higher reactivity of the C3 ketone carbonyl in isatins can be exploited to further introduce functionalization for the preparation of 3-substituted oxindoles, and this makes isatins versatile synthetic building blocks in organic synthesis.[2] Consequently, the development of efficient methods for the rapid construction of isatins has stimulated considerable interest. Conventional methods for the synthesis of these important compounds mainly involve the strong acid (often H_2SO_4) or base-mediated condensation of aniline with diethyl ketomalonate (Martinet procedure),[3] oxalyl chloride (Stollé procedure),[4] or chloral hydrate [Sandmeyer procedure, see Eq. (1) in Scheme 1].[5] Isatin is commercially available in large quantities and readily undergoes aromatic substitution reactions at C-5 and *N*-alkylation via an anion; thus, direct functionalization of unsubstituted isatin can provide an alternative approach for the preparation of substituted isatins.[6] Although these methods provided useful access to substituted isatins,[7] there are noticeable drawbacks associated with them, such as harsh reaction conditions, limited substrate scope, and the need for an excess amount of acid or base. Transition-metal-catalyzed cross-coupling reactions have proved to be very useful tools for constructing substituted heterocycles. In 2010, Li et al. reported a protocol for the synthesis of *N*-substituted isatins through the copper-catalyzed intramolecular C–H acylation of formyl-*N*-arylformamides by using oxygen as an oxidant [see Eq. (2) in Scheme 1].[8] Various *N*-alkylisatins were synthesized under relatively mild reaction conditions.



Scheme 1. Different strategies for the formation of substituted isatins.

N-Alkylisatins can be easily prepared, but in contrast, *N*-arylisatins remain underexplored partly because there is a limited number of methods available for their preparation, and most of those methods suffer from poor yields and limited scope.[9] The direct arylation of free *N*-H isatins with aryl boronic acids is a useful approach for the preparation of *N*-arylisatins.[10] However, this method suffers from low yields and only *para*- and *meta*-substituted aryl boronic acids work well in most cases. More recently, Larock et al. developed a F^--promoted reaction of arynes with methyl 2-oxo-2-(arylamino)acetates to afford various *N*-arylisatins in good yields [see Eq. (3) in Scheme 1].[11] Because *N*-arylisatins have exhibited impressive biological properties and because they can be readily used as key intermediates for the

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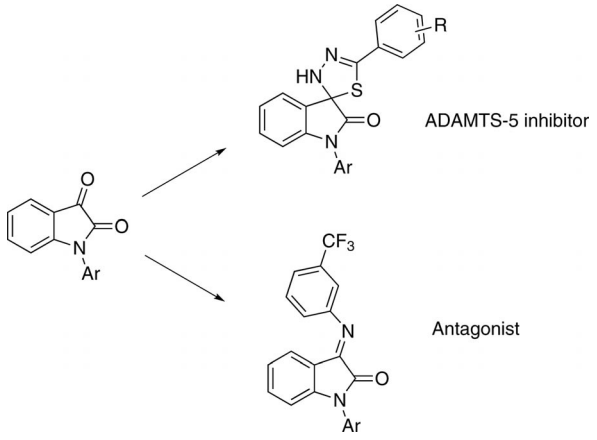
synthesis of potent drugs (Scheme 2),[10c,10d] the design of general and direct approaches for the preparation of *N*-arylisatins is highly desirable. In recent years, the transition-metal-catalyzed oxidative amidation of aldehydes (or from alcohols by dehydrogenation) with amines has proved to be a powerful and environmentally benign strategy for the preparation of amides.[12] Other carbonyl-containing compounds such as α-carbonyl aldehydes[13] and acetophenones[14] (the methyl group adjacent to the carbonyl group was oxidized in situ) were also successfully employed for this kind of transformation and afforded α-ketoamides in high yields. Peroxides and even molecular oxygen can act as an efficient oxidant for this kind of amidation reaction between amines and carbonyl compounds. Inspired by these discoveries, herein we report the SeO_2-promoted intramolecular oxidative amidation of 2-(arylamino)acetophenones to afford various *N*-arylisatins in high yields under mild reaction conditions.

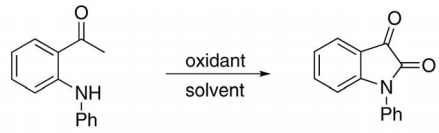


Scheme 2. *N*-Arylisatins as key intermediates for drug synthesis.

Results and Discussion

Our investigation began with the reaction of 1-[2-(phenylamino)phenyl]ethanone (**1a**) under oxidative reaction conditions in 1,4-dioxane. As the screening of transition metal catalysts did not improve the reaction yield, we focused our investigation on transition-metal-free conditions, and the results are summarized in Table 1. Organic and inorganic oxidants such as benzoyl peroxide (BPO), dicumyl peroxide (DCP), di-*tert*-butyl peroxide (DTBP), 1,4-benzoquinone (BQ), $PhI(OAc)_2$, 2,2,6,6-tetramethylpiperidyl-1-oxyl (TEMPO), and $K_2S_2O_8$ were tested for this transformation, but the desired 1-phenylindoline-2,3-dione (**2a**) product was not formed, as determined by GC–MS and ^1H NMR spectroscopy (Table 1, entries 1–8). To our delight, the desired product was obtained in 98% yield if SeO_2 (2 equiv.) was used as the oxidant in air at 80 °C (Table 1, entry 9). Solvents played an important role, and the use of solvents other than dioxane led to much lower yields (Table 1, entries 10–16). The use of 2 equiv. of SeO_2 is necessary to achieve a satisfactory yield, and the reaction yield decreased to 59% when 1 equiv. of SeO_2 was used (Table 1, entry 18). Temperature also played an important role, and the reaction yield decreased to 53% if the reaction temperature was decreased to 50 °C (Table 1, entry 19). A high yield could be achieved if the reaction was carried out under an atmosphere of argon (Table 1, entry 20).

Table 1. Optimization of the reaction conditions.[a]



1a **2a**

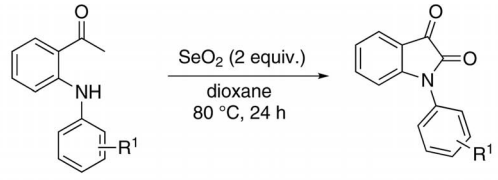
Entry	Oxidant	Solvent	*T* [°C]	Yield [%][b]
1	BPO	dioxane	80	trace
2	DCP	dioxane	80	trace
3	DTBP	dioxane	80	trace
4	BQ	dioxane	80	trace
5	$PhI(OAc)_2$	dioxane	80	trace
6	TBHP	dioxane	80	trace
7	TEMPO	dioxane	80	trace
8	$K_2S_2O_8$	dioxane	80	trace
9	SeO_2	dioxane	80	98
10	SeO_2	diglyme	80	88
11	SeO_2	toluene	80	5
12	SeO_2	DMF	80	31
13	SeO_2	anisole	80	28
14	SeO_2	PhCl	80	13
15	SeO_2	NMP	80	54
16	SeO_2	H_2O	80	trace
17	SeO_2 (0.5 equiv.)	dioxane	80	21
18	SeO_2 (1 equiv.)	dioxane	80	59
19	SeO_2	dioxane	50	53
20[c]	SeO_2	dioxane	80	98

[a] Reaction conditions: **1a** (0.5 mmol), solvent (1 mL), 24 h in air unless otherwise noted. NMP = *N*-methylpyrrolidone. [b] GC yield. [c] Under an atmosphere of argon.

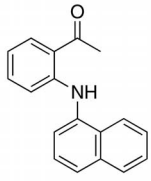
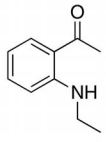
With the optimized reaction conditions in hand, we then explored the scope and generality of this transformation. The effect of different substituents on the *N*-aryl ring is listed in Table 2. Substrates bearing electron-donating groups such as methyl and methoxy groups on the aromatic ring could be selectively converted into the corresponding products in excellent yields (Table 2, entries 2 and 3). Halogens such as fluoro, chloro, bromo, and iodo were well tolerated under the optimized reaction conditions, and the desired products were obtained in high yields (Table 2, entries 5–8). Functional groups such as trifluoromethyl and ester were tolerated, and desired products **2i** and **2j** were obtained in 95 and 93% yield, respectively (Table 2, entries 9 and 10). The position of the substituents on the phenyl ring affected the reaction yield slightly. Good to excellent yields were obtained if 1-[2-(*o*-tolylamino)phenyl]-

ethanone (**1k**) and 1-[2-(*m*-tolylamino)phenyl]ethanone (**1l**) were used as starting materials (Table 2, entries 11 and 12). More sterically congested substrates such as 1-[2-(naphthalen-1-ylamino)phenyl]ethanone (**1m**) also efficiently coupled to give desired product **2m** in 79% yield (Table 2, entry 13). Notably, this method is also suitable for the preparation of *N*-alkylisatins without further optimization of the reaction conditions. When 1-[2-(ethylamino)phenyl]ethanone (**1n**) was used as the starting material, corresponding product **2n** was obtained in 78% yield (Table 2, entry 14).

Table 2. SeO_2-promoted formation of *N*-arylisatins.[a]



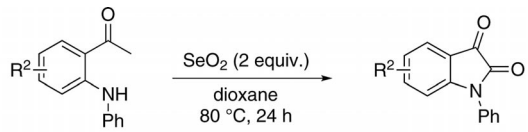
1 **2**

Entry	Substrate		Product	Yield [%][b]
1	R^1 = H	**1a**	**2a**	98
2	R^1 = 4-Me	**1b**	**2b**	97
3	R^1 = 4-OMe	**1c**	**2c**	96
4	R^1 = 4-Ph	**1d**	**2d**	95
5	R^1 = 4-F	**1e**	**2e**	96
6	R^1 = 4-Cl	**1f**	**2f**	97
7	R^1 = 4-Br	**1g**	**2g**	98
8	R^1 = 4-I	**1h**	**2h**	93
9	R^1 = 4-CF_3	**1i**	**2i**	95
10	R^1 = 4-COOMe	**1j**	**2j**	93
11	R^1 = 2-Me	**1k**	**2k**	85
12	R^1 = 3-Me	**1l**	**2l**	93
13		**1m**	**2m**	79
14		**1n**	**2n**	78

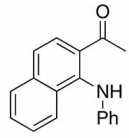
[a] Conditions: **1** (0.5 mmol), dioxane (1 mL), SeO_2 (1.0 mmol), 80 °C, 24 h in air. [b] Isolated yield.

To explore the scope of the reaction further, a number of substituted acetophenone derivatives were employed under the optimized conditions (Table 3). A series of functional groups including methyl, methoxy, fluoro, chloro, and bromo were well tolerated under the optimal reaction conditions (Table 3, entries 1–5). However, a trifluoromethoxy substituent dramatically decreased the reaction yield, and desired product **2t** was obtained in only 56% yield (Table 3, entry 6). The position of the substituents on the aromatic ring of acetophenone significantly affected the reaction yield (Table 3, entries 7 and 8).

Table 3. Substituent effect on acetophenone ring.[a]

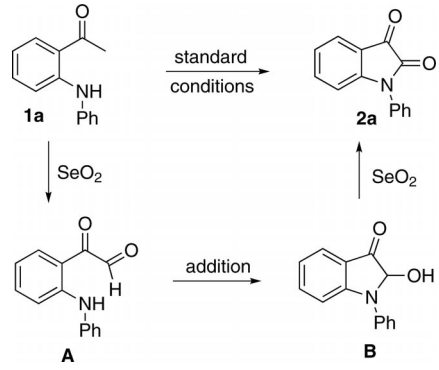


1 **2**

Entry	Substrate		Product	Yield [%][b]
1	R^2 = 5-Me	**1o**	**2o**	87
2	R^2 = 5-OMe	**1p**	**2p**	71
3	R^2 = 5-F	**1q**	**2q**	85
4	R^2 = 5-Cl	**1r**	**2r**	87
5	R^2 = 5-Br	**1s**	**2s**	86
6	R^2 = 5-OCF_3	**1t**	**2t**	56
7	R^2= 3-Me	**1u**	**2u**	78
8		**1v**	**2v**	73

[a] Conditions: **1** (0.5 mmol), dioxane (1 mL), SeO_2 (1.0 mmol), 80 °C, 24 h in air. [b] Isolated yield.

On the basis of observations by others[13,14] and ourselves, a tentative mechanism to rationalize this transformation is illustrated in Scheme 3. The methyl group in **1a** is oxidized into the corresponding carbonyl group in the presence of SeO_2 and generates intermediate **A**.[15] The addition of the glyoxal group with amine generates hemiaminal intermediate **B**. Subsequently, intermediate **B** is oxidized by SeO_2 to produce **2a**.



Scheme 3. Proposed reaction pathway.

Conclusions

In summary, we have developed an efficient method for the synthesis of *N*-arylisatins from 2-(arylamino)acetophenones by using SeO_2 as an oxidant under transition-metal-free conditions. The reaction proceeds smoothly in dioxane at 80 °C and gives the corresponding products in high yields. Functional groups such as methyl, methoxy, fluoro, chloro, bromo, iodo, and ester were all tolerated under the optimized reaction conditions. This method affords

an efficient alternative for the synthesis of *N*-arylisatins with a wide substrate scope and good functional group tolerance. The scope, mechanism, and synthetic applications of this reaction are under investigation.

Experimental Section

General Procedure: A 25 mL, oven-dried reaction vessel was charged with 1-[2-(phenylamino)phenyl]ethanone (**1a**, 0.5 mmol, 106 mg), SeO_2 (1 mmol, 110 mg), and 1,4-dioxane (1 mL). The resulting solution was stirred at 80 °C for 24 h in air. After cooling to room temperature, the volatiles were removed under vacuum, and the residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate = 5:1) to give **2a** as a red solid (109 mg, yield 98%).

Supporting Information (see footnote on the first page of this article): Experimental details and copies of the ^{1}H NMR and ^{13}C NMR spectra.

Acknowledgments

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