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ARTICLE TYPE

Metal-Free TBAI-Catalyzed Arylsulfonylation of Activated Alkenes with Sulfonylhydrazides

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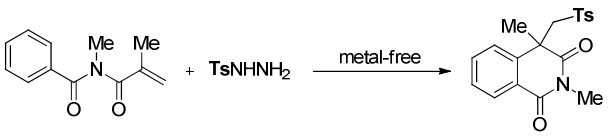
Efficient metal-free oxidative arylsulfonylation of α,β-unsaturated imides with sulfonylhydrazides leading to isoquinoline-1,3(2H,4H)-dione derivatives has been developed. The procedure involves the generation of sulfonyl radicals via cleavage of S-N bond of sulfonylhydrazides with sulfonylation and C–H functionalization. The protocol uses economical and environmentally friendly TBAI-TBHP catalytic system, and the corresponding isoquinoline-1,3(*2H,4H*)-diones with various functional groups were obtained in moderate to good yields.

Introduction

The strategy for free-radical-mediated difunctionalization of alkenes through direct C-H functionalization of arenes has drawn much attention in recent years.[1] Among them metal-free oxidative coupling/cyclization reactions represent one of the most economic and environmentally benign methods. In 2013, Li reported oxidative tandem coupling of activated alkenes with carbonyl C(sp^2)-H bonds and aryl C(sp^2)-H bonds using TBHP oxidation.[2] Duan and Liang independently described the oxidative hydroxyalkylarylation of activated alkenes by direct sp^3 C-H functionalization of alcohols.[3] Recently, Jiao and Yang developed the carbonitration of activated alkenes using *t*-BuONO and $NaNO_2$ as nitrated reagents, respectively.[4] Antonchick reported azidoarylation of alkenes using $TMSN_3$ as azidyl precuser in the presence of $PhI(OCOCF_3)_2$ as oxidant.[5] The Nevado and Liu research groups independently demonstrated that metal-free aryltrifluoromethylation of alkenes can be achieved with varies trifluoromethylated reagents, such as $TMSCF_3$ and Togni's reagent. [6] However, despite progress in this area, examples of metal-free carbon-sulfur functionalization of alkenes are quite rare.[1i,7] As part of the continuing efforts in our laboratory toward the development of novel free radical reactions using readily accessible hydrazides as free-radical precursors,[1i-j,8] herein we disclose an efficient and useful method to construct sulfonated isoquinolinediones via the metal-free TBAI-catalyzed arylsulfonylation of activated alkenes (Scheme 1). To the best of our knowledge, this work constitutes the first examples of six-member ring formation via metal-free carbon-sulfur functionalization of electron-deficient olefins.

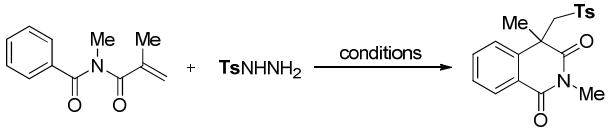


Scheme 1. Synthesis of isoquinoline-1,3(*2H,4H*)-diones via metal-free arylsulfonylation of activated alkenes

Results and discussion

Our investigation commenced with the reaction of α,β-unsaturated imide (**1a**) and $TsNHNH_2$ (**2a**) in DMF at 80 °C under air atmosphere. The desired isoquinoline-1,3(2H,4H)-dione derivative (3a) was isolated in 69% yield (Table 1, entry 1). Other iodine reagents, such as KI, NaI, I_2, were also examined, but they were not better than TBAI (Table 1, entries 2-4). Further investigation indicated that the metal catalysts, such as $Cu(OAc)_2$ and $FeCl_2•4H_2O$ plays no role in the reaction (Table 1, entries 5 and 6). A survey of solvents demonstrated that CH_3CN is the best choice, affording the desired product in 81% yield (Table 1, entries 7-9). Some representative oxidants were chosen for our studies, and it was confirmed that TBHP was a better choice for this transformation (Table 1, entries 10-12). Increasing the reaction temperature or changing the oxidant loading did not improve the yield further (Table 1, entries 13-14).

Table 1 Optimization of Reaction Conditions [a]



1a **2a** **3a**

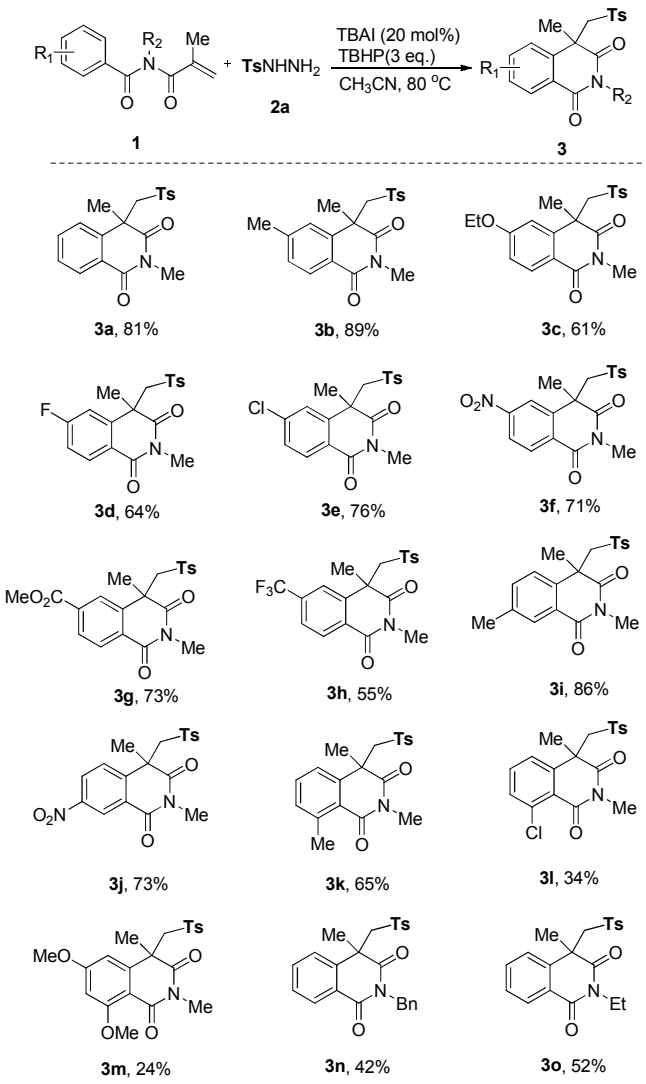
Entry	Catalyst	Oxidant	solvent	Yield % [b]
1 [a]	TBAI	TBHP	DMF	69
2	KI	TBHP	DMF	64
3	NaI	TBHP	DMF	59
4	I_2	TBHP	DMF	68
5	$Cu(OAc)_2$	TBHP	DMF	0
6	$FeCl_2•4H_2O$	TBHP	DMF	0
7	TBAI	TBHP	CH_3CN	81
8	TBAI	TBHP	H_2O	59
9	TBAI	TBHP	toluene	49
10	TBAI	DTBP	CH_3CN	Trace
11	TBAI	TBPB	CH_3CN	66

12	TBAI	H_2O_2	CH_3CN	Trace
13 [c]	TBAI	TBHP	CH_3CN	69
14 [d]	TBAI	TBHP	CH_3CN	79

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.6 mmol), oxidant (3eq), catalyst (0.06 mmol), solvent (2.0 mL), at 80 °C for 6 h. [b] isolated yield. [c] 100 °C. [d] 5.0 equiv of TBHP was used.

With the optimized conditions established, the substrate scope of this reaction was investigated (Table 2). Various substituted α,β-unsaturated imides (**1**) bearing electron-donating groups, such as Me, EtO and electron-withdrawing groups, such as F, Cl, NO_2, CO_2Me, CF_3 were well tolerated, thus giving the desired products in moderate to good yields (**3b-3l**). Notably, for *meta*-Me and NO_2 substituted methacryloyl benzamide (**1**), *para* was preferred to *ortho* benzannulation, as **3i** and **3j** was obtained as single products.[6a] Substrates bearing ortho substituents showed slightly lower reactivity due to the steric effect (products 3k and 3l). In contrast to aryltrifluoromethylation, arylsulfonylation of 2,4-dimethoxybenzamide delivered desired isoquinolinedione **3m** in 24% yield rather than spirobicyclic compound.[6a] Substrates with more sterically demanding group, such as Bn and Et on the nitrogen atom afforded the expected product **3n** and **3o** in slightly lower yields. In the cases with moderate to low yields, such as **3h**, **3l**, **3m**, **3n**, and **3o**, starting materials **1** were recovered with the formation of small amounts of inseparable side-products.

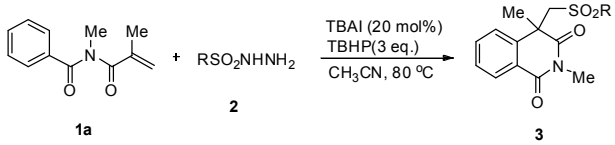
Table 2. Scope of the reaction [a,b]

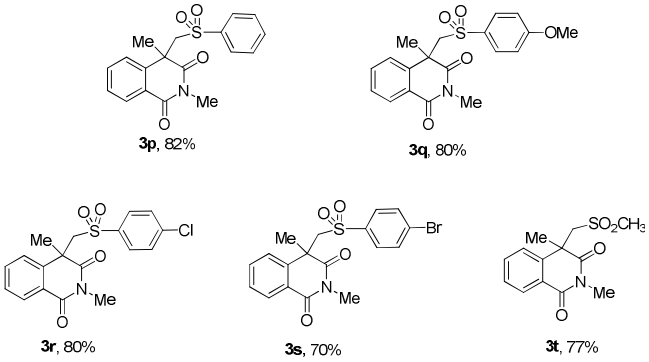


[a] Reaction conditions: **1** (0.3 mmol), **2** (0.6 mmol), TBAI (20 mol%), TBHP (3 equiv), CH_3CN (2mL) at 80 °C for 6 h. [b] isolated yield.

Furthermore, sulfonylhydrazides with different substituents were investigated to extend the reaction scope (Table 3). It was found that phenyl, *p*-methoxyphenyl, *p*-cholophenyl and *p*-bromophenyl substituted sulfonylhydrazides were all tolerated in the reaction to give the corresponding isoquinolinediones **3p-3s** in good yields. Preliminary study show that the reaction is not limited to aromatic sulfonyl hydrazides: methanesulfonyl hydrazide provided the isoquinolinedione **3t** in 77% yield.

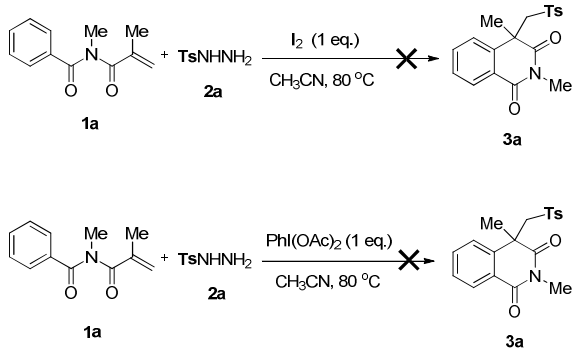
Table 3. Scope of the reaction [a,b]





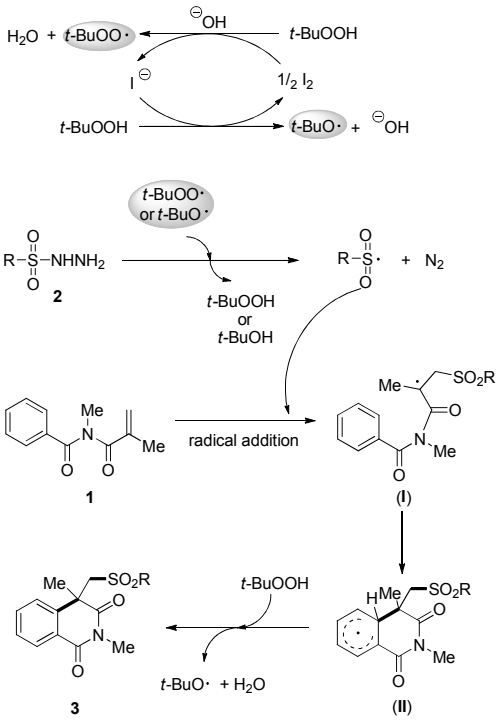
[a] Reaction conditions: **1** (0.3 mmol), **2** (0.6 mmol), TBAI (20 mol%), TBHP (3 equiv), CH_3CN (2mL) at 80 °C for 6 h. [b] isolated yield

Some control experiments were carried out to understand the details of the mechanism. No compound **3a** were formed when 1.0 equivalents of I_2 and $PhI(OAc)_2$ were added to the reaction in the absence of TBHP. The results exclude the possibility that the *in situ* generated I_2 or I^{3+} are involved in the oxidative N-S bond cleavage of sulfonylhydrazides in this transformation.



Scheme 2. control experiments

On the basis of these results and previously reported results, a plausible mechanism is proposed (Scheme 3). The transformation between I^- ans I_2 lead to the decomposition of TBHP and generation of the *tert*-butoxyl and *tert*-butylperoxy radicals.[9] Sulfonylhydrazides is readily transformed into sulfonyl radicals in the presence of the tert-butoxyl and tert-butylperoxy radicals.[1i,8] Addition of sulfonyl radicals to the C=C bond of α,β-unsaturated imides (**1**) results in the formation of radical intermediate (**I**),[8,10] which upon intramolecular cyclization with an aryl ring gives radical intermediate (**II**).[1] Finally, hydrogen abstraction of radical intermediate (**II**) by TBHP affords isoquinolinedione 3.[2]



Scheme 3. Proposed preliminary mechanisms

Conclusion

In summary, we have developed a novel metal-free radical arylsulfonylation of α,β-unsaturated imides with sulfonylhydrazides that provides straightforward access to isoquinolinediones. TBAI-catalyzed generation of sulfonyl radicals utilizing sulfonylhydrazides as precursor and TBHP as oxidant was involved. Further investigations of this reaction system are under way in our laboratory.

Experimental Section

General Methods: All reagents and solvents were purchased from commercial suppliers and used without purifications. NMR spectra were recorded on a 500 MHz or a 400 MHz NMR spectrometer, with TMS as the internal standard. Chemical shifts (δ) are expressed in ppm and coupling constants J are given in Hz. High resolution mass spectra (HRMS) were obtained on a TOF MS instrument with ESI source. Starting materials **1**[6a] and **2**[11] were prepared by the reported procedure.

*General procedure for the synthesis of isoquinolinediones **3**:* To a suspension of α,β-unsaturated imides **1** (0.3 mmol), sulfonylhydrazides **2** (0.6 mmol), and tetrabutylammonium iodide (0.06 mmol) in CH_3CN (2 mL) was added TBHP (70% aqueous solution) (0.9 mmol) and the mixture was stirred at 80 °C for 6 h. After the solvent was removed under reduced pressure, the residual was treated with silica gel chromatography (ethyl acetate/petroleum ether) to give isoquinolones **3**.

2,4-dimethyl-4-(tosylmethyl)isoquinoline-1,3(2H,4H)-dione(3a) ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 – 8.27 (m, 1H), 7.43 – 7.40 (m, 2H), 7.36 (d, J = 8.3 Hz, 2H), 7.21 – 7.19 (m, 1H), 7.16 (d, J = 8.1 Hz, 2H), 4.44 (d, J = 14.6 Hz, 1H), 3.88 (d, J = 14.6 Hz, 1H), 3.39 (s, 3H), 2.39 (s, 3H), 1.58 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.3, 163.8, 144.5, 139.2,

137.2, 133.4, 129.7, 129.3, 128.0, 127.7, 125.9, 124.8, 64.8, 45.4, 31.6, 27.5, 21.6. HRMS (ESI) calcd for $C_{19}H_{20}NO_4S$ (M + H)$^+$ 358.1108; found: 358.1109.

2,4,6-trimethyl-4-(tosylmethyl)isoquinoline-1,3(2H,4H)-dione(3b). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (d, J = 8.0 Hz, 1H), 7.29 – 7.26 (m, 2H), 7.17 (d, J = 7.9 Hz, 1H), 7.11 (d, J = 8.0 Hz, 2H), 6.80 (s, 1H), 4.45 (d, J = 14.7 Hz, 1H), 3.87 (d, J = 14.7 Hz, 1H), 3.39 (s, 3H), 2.38 (s, 3H), 2.17 (s, 3H), 1.56 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.4, 163.8, 144.3, 144.2, 138.9, 137.3, 129.5, 129.3, 129.0, 127.6, 126.4, 122.4, 64.8, 45.3, 31.6, 27.4, 21.6, 21.5. HRMS (ESI) calcd for $C_{20}H_{22}NO_4S$ (M + H)$^+$ 372.1264; found: 371.1265.

6-ethoxy-2,4-dimethyl-4-(tosylmethyl)isoquinoline-1,3(2H,4H)-dione(3c) ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (d, J = 8.8 Hz, 1H), 7.32 (d, J = 8.3 Hz, 2H), 7.13 (d, J = 8.0 Hz, 2H), 6.87 (dd, J = 8.8, 2.4 Hz, 1H), 6.47 (d, J = 2.4 Hz, 1H), 4.44 (d, J = 14.7 Hz, 1H), 3.96 – 3.84 (m, 2H), 3.82 (d, J = 14.7 Hz, 1H), 3.37 (s, 3H), 2.38 (s, 3H), 1.55 (s, 3H), 1.39 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.4, 163.5, 163.1, 144.3, 141.1, 137.4, 131.4, 129.5, 127.7, 117.6 114.5, 111.3, 64.9, 63.8, 45.6, 31.7, 27.4, 21.5, 14.6. HRMS (ESI) calcd for $C_{21}H_{24}NO_5S$ (M + H)$^+$ 402.1370; found: 402.1372.

6-fluoro-2,4-dimethyl-4-(tosylmethyl)isoquinoline-1,3(2H,4H)-dione(3d) ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (dd, J = 8.8, 5.8 Hz, 1H), 7.37 (d, J = 8.3 Hz, 2H), 7.18 (d, J = 8.0 Hz, 2H), 7.09 (td, J = 8.6, 2.4 Hz, 1H), 6.81 (dd, J = 9.2, 2.3 Hz, 1H), 4.43 (d, J = 14.7 Hz, 1H), 3.82 (d, J = 14.7 Hz, 1H), 3.40 (s, 3H), 2.40 (s, 3H), 1.57 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9, 165.8(J_{CF}=253.5 Hz), 162.9, 144.8, 142.1 (d, J = 8.6 Hz), 137.1, 132.3 (d, J = 9.6 Hz), 129.8, 128.6, 127.6, 121.3 (d, J = 2.6 Hz), 116.0(J_{CF}=23.1 Hz), 113.0(J_{CF}=23.3 Hz), 64.7, 45.6 (d, J = 1.4 Hz), 31.5, 27.6, 21.5. ^{19}F NMR (400 MHz, $CDCl_3$) δ -104.1 (dd, J = 14.6, 7.4 Hz). HRMS (ESI) calcd for $C_{19}H_{19}NO_4SF$ (M + H)$^+$ 376.1013; found: 376.1014.

6-chloro-2,4-dimethyl-4-(tosylmethyl)isoquinoline-1,3(2H,4H)-dione(3e) ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (d, J = 8.5 Hz, 1H), 7.33 (dd, J = 8.5, 1.8 Hz, 1H), 7.29 (t, J = 6.7 Hz, 2H), 7.14 (d, J = 8.1 Hz, 2H), 6.97 (d, J = 1.9 Hz, 1H), 4.44 (d, J = 14.8 Hz, 1H), 3.84 (d, J = 14.8 Hz, 1H), 3.42 (s, 3H), 2.39 (s, 3H), 1.57 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.7, 163.0, 144.8, 140.6, 140.1, 137.0, 130.8, 129.8, 128.6, 127.3, 126.2, 123.4, 64.7, 45.3, 31.3, 27.6, 21.6. HRMS (ESI) calcd for $C_{19}H_{19}NO_4SCl$ (M + H)$^+$ 392.0718; found: 392.0719.

2,4-dimethyl-6-nitro-4-(tosylmethyl)isoquinoline-1,3(2H,4H)-dione(3f) ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49 (d, J = 8.6 Hz, 1H), 8.21 (dd, J = 8.6, 2.1 Hz, 1H), 7.91 (d, J = 2.1 Hz, 1H), 7.33 (d, J = 8.3 Hz, 2H), 7.15 (d, J = 8.0 Hz, 2H), 4.51 (d, J = 14.8 Hz, 1H), 3.96 (d, J = 14.8 Hz, 1H), 3.48 (s, 3H), 2.36 (s, 3H), 1.67 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.3, 162.1, 150.4, 145.0, 140.7, 137.0, 131.0, 130.0, 129.6, 127.3 122.7, 121.6, 64.6, 45.6, 31.1, 27.9, 21.4. HRMS (ESI) calcd for $C_{19}H_{19}N_2O_6S$ (M + H)$^+$ 403.0958; found: 403.0960

methyl 2,4-dimethyl-1,3-dioxo-4-(tosylmethyl)-1,2,3,4-tetrahydroisoquinoline-6-carboxylate(3g) ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (d, J = 8.2 Hz, 1H), 7.99 (dd, J = 8.2, 1.4 Hz, 1H), 7.66 (d, J = 1.2 Hz, 1H), 7.29 – 7.23 (m, 2H), 7.08 (d, J = 8.0 Hz, 2H), 4.46 (d, J = 14.8 Hz, 1H), 3.97 (d, J = 14.8 Hz, 1H), 3.91 (s, 3H), 3.44 (s, 3H), 2.33 (s, 3H), 1.62 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9, 165.2, 163.1, 144.4, 139.0, 137.1, 134.2, 129.7, 129.4, 128.7, 128.2, 127.4, 127.3, 64.8, 52.5, 45.3, 31.2, 27.7, 21.4. HRMS (ESI) calcd for $C_{21}H_{22}NO_6S$ (M + H)$^+$ 416.1162; found: 416.1163.

2,4-dimethyl-4-(tosylmethyl)-6-(trifluoromethyl)isoquinoline-1,3(2H,4H)-dione(3h) ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (d, J = 8.2 Hz, 1H), 7.63 (d, J = 8.2 Hz, 1H), 7.29 – 7.24 (m, 3H), 7.11 (d, J = 8.1 Hz, 2H), 4.48 (d, J = 14.9 Hz, 1H), 3.92 (d, J = 14.9 Hz, 1H), 3.46 (s, 3H), 2.36 (s, 3H), 1.62 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6, 162.7, 145.09, 139.9, 136.9, 134.9(q, J_{CF} = 39.2 Hz), 130.1, 129.8, 127.9, 127.28, 124.9 (q, J_{CF} = 3.3 Hz), 123.0 (q, J_{CF} = 3.8 Hz), 123.0(q, J_{CF} = 273.1 Hz), 64.9, 45.4, 31.2, 27.9, 21.5. ^{19}F NMR (400 MHz, $CDCl_3$) δ -64.0 (s). HRMS (ESI) calcd for $C_{20}H_{19}NO_4SF_3$ (M + H)$^+$ 426.0981; found: 426.0983

2,4,7-trimethyl-4-(tosylmethyl)isoquinoline-1,3(2H,4H)-dione(3i) ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.34 (d, J = 8.3 Hz, 2H), 7.15 (t, J = 8.9 Hz, 3H), 7.05 (d, J = 8.0 Hz, 1H), 4.40 (d, J = 14.6 Hz, 1H), 3.86 (d, J = 14.6 Hz, 1H), 3.38 (s, 3H), 2.39 (d, J = 2.2 Hz, 6H), 1.56 (s, 3H).^{13}C NMR (125 MHz, $CDCl_3$) δ 174.5, 164.0 144.4, 138.1, 137.2, 136.2, 134.4, 129.6, 129.2, 127.7, 125.9, 124.5, 65.0, 45.1, 31.5, 27.5, 21.6, 21.0. HRMS (ESI) calcd for $C_{20}H_{22}NO_4S$ (M + H)$^+$ 372.1264; found: 371.1265.

2,4-dimethyl-7-nitro-4-(tosylmethyl)isoquinoline-1,3(2H,4H)-dione(3j) ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.08 (d, J = 2.5 Hz, 1H), 8.22 (dd, J = 8.6, 2.5 Hz, 1H), 7.48 (d, J = 8.6 Hz, 1H), 7.43 (d, J = 8.3 Hz, 2H), 7.21 (d, J = 7.9 Hz, 2H), 4.47 (d, J = 14.7 Hz, 1H), 3.92 (d, J = 14.6 Hz, 1H), 3.44 (s, 3H), 2.41 (s, 3H), 1.64 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1, 160.9, 146.6, 144.6, 144.3, 135.8, 128.9, 126.9, 126.6, 126.3, 125.4, 123.5, 63.5, 44.7, 30.0, 26.9, 20.6. HRMS (ESI) calcd for $C_{19}H_{19}N_2O_6S$ (M + H)$^+$ 403.0958; found: 403.0959

2,4,8-trimethyl-4-(tosylmethyl)isoquinoline-1,3(2H,4H)-dione(3k) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, J = 8.2 Hz, 2H), 7.27 (t, J = 7.7 Hz, 1H), 7.22 – 7.11 (m, 4H), 4.44 (d, J = 14.6 Hz, 1H), 3.88 (d, J = 14.6 Hz, 1H), 3.36 (s, 3H), 2.81 (s, 3H), 2.39 (s, 3H), 1.58 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.0, 164.3, 144.5, 142.9, 140.5, 137.4, 132.3, 132.0, 129.6, 127.7, 124.2, 123.0, 65.1, 45.5, 32.1, 27.5, 24.1, 21.6. HRMS (ESI) calcd for $C_{20}H_{22}NO_4S$ (M + H)$^+$ 372.1264; found: 371.1265.

8-chloro-2,4-dimethyl-4-(tosylmethyl)isoquinoline-1,3(2H,4H)-dione(3l) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (m, 3H), 7.34 (t, J = 7.9 Hz, 1H), 7.27 – 7.21 (m, 3H), 4.46 (d, J = 14.6 Hz, 1H), 3.85 (d, J = 14.6 Hz, 1H), 3.38 (s, 3H), 2.41 (s, 3H), 1.59 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.1, 161.5, 144.8, 142.4, 137.2, 136.7, 132.9, 132.2, 129.8, 127.8, 125.0, 122.0, 64.8, 45.9, 31.9, 27.9, 21.6. HRMS (ESI) calcd for $C_{19}H_{19}NO_4SCl$ (M + H)$^+$ 392.0718; found: 392.0719.

6,7-dimethoxy-2,4-dimethyl-4-(tosylmethyl)isoquinoline-1,3(2H,4H)-dione(3m) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.31 (d, J = 8.3 Hz, 2H), 7.13 (d, J = 8.0 Hz, 2H), 6.35 (s, 1H), 4.45 (d, J = 14.8 Hz, 1H), 3.99 (s, 3H), 3.80 (d, J = 6.9 Hz, 1H), 3.70 (s, 3H), 3.38 (s, 3H), 2.39 (s, 3H), 1.55 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5, 162.5, 152.5, 148.1, 143.6, 136.2, 131.9, 128.4, 126.7, 116.9, 109.0, 106.5, 64.1, 55.2, 54.8, 44.3, 30.6, 26.5, 20.5. HRMS (ESI) calcd for $C_{21}H_{24}NO_6S$ (M + H)$^+$ 418.1319; found: 418.1320

2-benzyl-4-methyl-4-(tosylmethyl)isoquinoline-1,3(2H,4H)-dione(3n) ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 – 8.26 (m, 1H), 7.47 – 7.16 (m, 12H), 5.22 (q, J = 14.1 Hz, 2H), 4.47 (d, J = 14.6 Hz, 1H), 3.92 (d, J = 14.6 Hz, 1H), 2.39 (s, 3H), 1.53 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.3, 163.6, 144.5, 139.5, 137.6, 137.0, 133.6, 129.7, 129.5, 128.4, 128.4, 128.0, 127.6, 127.3, 125.8, 124.8, 64.5, 45.9, 44.0, 31.8, 21.6. HRMS (ESI) calcd for $C_{25}H_{24}NO_4S$ (M + H)$^+$ 434.1421; found: 434.1422

2-ethyl-4-methyl-4-(tosylmethyl)isoquinoline-1,3(2H,4H)-dione(3o) ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (dd, J = 7.5, 1.6 Hz, 1H), 7.43 – 7.35 (m, 4H), 7.16 (t, J = 8.1 Hz, 3H), 4.45(d, J = 14.6 Hz, 1H), 4.07(q, J = 7.1 Hz, 2H), 3.89(d, J = 14.6 Hz, 1H), 2.38 (s, 3H), 1.56 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9, 163.3, 144.4, 139.3, 137.5 133.3, 129.7, 129.3, 128.0, 127.6, 125.8, 125.0, 64.8, 45.4, 36.1, 31.6, 21.6, 12.7. HRMS (ESI) calcd for $C_{20}H_{22}NO_4S$ (M + H)$^+$ 372.1264; found: 372.1265.

2,4-dimethyl-4-((phenylsulfonyl)methyl)isoquinoline-1,3(2H,4H)-dione(3p) ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (dd, J = 7.8, 1.1 Hz, 1H), 7.52 (t, J = 7.4 Hz, 1H), 7.46 (d, J = 7.4 Hz, 2H), 7.41 – 7.32 (m, 4H), 7.15 (d, J = 7.7 Hz, 1H), 4.46 (d, J = 14.7 Hz, 1H), 3.94 (d, J = 14.7 Hz, 1H), 3.41 (s, 3H), 1.59 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.3, 163.8, 140.2, 139.0, 133.5, 133.4, 129.2, 129.1, 128.1, 127.5, 125.9, 124.7, 64.8, 45.4, 31.5, 27.5. .HRMS (ESI) calcd for $C_{18}H_{18}NO_4S$ (M + H)$^+$ 344.0951; found: 344.0952.

4-(((4-methoxyphenyl)sulfonyl)methyl)-2,4-dimethylisoquinoline-1,3(2H,4H)-dione(3q) ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (dd, J = 6.1, 3.3 Hz, 1H), 7.43 – 7.40 (m, 2H), 7.38 (d, J = 8.9 Hz, 2H), 7.22 – 7.18 (m, 1H), 6.80 (d, J = 8.9 Hz, 2H), 4.43 (d, J = 14.6 Hz, 1H), 3.88 (d, J = 14.6 Hz, 1H), 3.83 (s, 3H), 3.39 (s, 3H), 1.58 (s, 3H).^{13}C NMR (125 MHz, $CDCl_3$) δ 174.3, 163.8, 163.6, 139.2, 133.4, 131.7, 129.8, 129.2, 128.1, 126.0, 124.8, 114.3, 65.0, 55.7, 45.4, 31.6, 27.5. HRMS (ESI) calcd for $C_{19}H_{20}NO_5S$ (M + H)$^+$ 374.1057; found: 374.1058.

4-(((4-chlorophenyl)sulfonyl)methyl)-2,4-dimethylisoquinoline-1,3(2H,4H)-dione(3r) ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (d, J = 7.8 Hz, 1H), 7.42 (t, J = 7.6 Hz, 1H), 7.37 (t, J = 8.3 Hz, 3H), 7.31 (d, J = 8.6 Hz, 2H), 7.14 (d, J = 7.8 Hz, 1H), 4.45 (d, J = 14.8 Hz, 1H), 3.96 (d, J = 14.8 Hz, 1H), 3.42 (s, 3H), 1.59 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.3, 163.7, 140.2, 138.9, 138.6, 133.5, 129.3, 129.2, 129.0, 128.2, 125.8, 124.8, 64.8, 45.4, 31.4, 27.6. HRMS (ESI) calcd for $C_{18}H_{17}NO_4SCl$ (M + H)$^+$ 378.0561; found: 378.0562.

4-(((4-bromophenyl)sulfonyl)methyl)-2,4-dimethylisoquinoline-1,3(2H,4H)-dione(3s) ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (dd, J = 7.8, 1.3 Hz, 1H), 7.48 (d, J = 8.6 Hz, 2H), 7.43-7.35 (m, 2H), 7.30 (d, J = 8.6 Hz, 2H), 7.14 (d, J = 7.7 Hz, 1H), 4.45 (d, J = 14.7 Hz, 1H), 3.94 (d, J = 14.7 Hz, 1H), 3.42 (s, 3H), 1.59 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.2, 163.7, 139.1, 138.9, 133.5, 132.3, 129.3, 129.1, 128.8, 128.2, 125.8,

124.8, 64.8, 45.4, 31.4, 27.6. HRMS (ESI) calcd for $C_{18}H_{17}NO_4SBr$ $(M + H)^+$ 422.0056; found: 422.0057.

2,4-dimethyl-4-((methylsulfonyl)methyl)isoquinoline-1,3(2H,4H)-dione (3t) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (dd, J = 7.9, 1.4 Hz, 1H), 7.67 (td, J = 7.6, 1.3 Hz, 1H), 7.48 (dd, J = 13.9, 7.7 Hz, 2H), 4.30 (d, J = 14.6 Hz, 1H), 3.81 (d, J = 14.6 Hz, 1H), 3.41 (s, 3H), 2.60 (s, 3H), 1.64 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 163.5, 139.8, 133.8, 129.6, 128.2, 125.1, 124.7, 63.4, 45.7, 43.9, 31.4, 27.6. HRMS (ESI) calcd for $C_{13}H_{16}NO_4S$ $(M + H)^+$ 282.0795; found: 282.0796.

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