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Three-Component Approach to Pyridine-Stabilized Ketenimines for the Synthesis of Diverse Heterocycles

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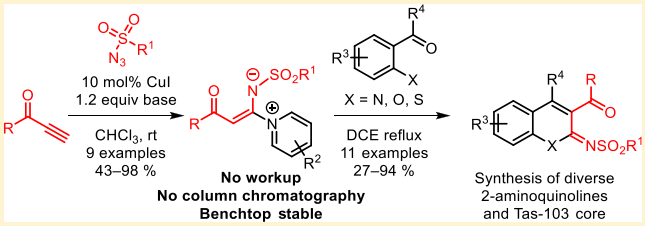
Supporting Information

ABSTRACT: Ketenimines are versatile synthetic intermediates capable of performing novel transformations in organic synthesis. They are normally generated in situ due to their inherent instability and high level of reactivity. Herein, we report pyridine-stabilized ketenimine zwitterionic salts, which are prepared through click chemistry from readily accessible alkynes and sulfonyl azides. To demonstrate their synonymous reactivity to ketenimines, these salts have been utilized in a cascade sequence to access highly functionalized quinolines including the core structures of an antiprotozoal agent and the potent topoisomerase inhibitor Tas-103.



INTRODUCTION

Ketenimines are reactive species exhibiting a diverse array of synthetic applications parallel to their isoelectronic cousins, ketenes and allenes.[1] Because of the inherent instability and reactivity, ketenimines are normally generated in situ for their applications in organic synthesis.[2] Current methods to prepare ketenimines include couplings,[3a] eliminations,[3b] rearrangements,[3c] and click chemistry (Scheme 1a−d).[3d]

There are also methods to access ketenimines, which are stable enough to isolate. However, they often require highly reactive starting materials, multistep processes, and chromatographic purification to obtain the desired ketenimine synthons (Scheme 2a).[4] Despite all of these methods, ketenimine chemistry is still at its infancy due to the lack of a stable ketenimine precursor. Therefore, the development of a stable precursor to such reactive intermediates could be attractive to the synthetic community. Herein, we report a bench-top stable ketenimine salt with synonymous reactivity to its unstable, traditional form (Scheme 2b).

RESULTS AND DISCUSSION

While pursuing the substrate scope of our previously developed carbene cascade,[5] we attempted to synthesize ethyl 1-tosyl-1*H*-1,2,3-triazole-4-carboxylate via the well-established click chemistry. To our surprise, instead of isolating the expected triazole, we exclusively observed a uniquely masked form of ketenimine stabilized as a zwitterionic adduct with 2,6-lutidine. The structure of organic salt 3a was further confirmed by X-ray diffraction (Scheme 3).[6]

These click-chemistry conditions described above were also performed at the gram scale successfully (Figures 1 and 3a). Encouraged by these findings, we then looked into the substrate scope and screened a variety of nitrogen bases used in click chemistry. As expected, the reaction proceeded in very high yield with 4-dimethylaminopyridine, but also proceeded in moderate yield with pyridine as a base (Figures 1 and 3b,c). We then screened non-nucleophilic triethyl amine and 2,6-di-*tert*-butyl-4-methylpyridine but did not observe the formation of ketenimine salt. These results indicate that nucleophilic pyridine bases with less steric crowding around the nitrogen of the pyridine ring were necessary for salt formation. We then turned our attention to the alkyne fragment in the click reaction. The reaction tolerated alkynes bearing the amide and ketone functionalities, albeit in diminished yields. We also attempted the reaction using phenylacetylene, although we exclusively isolated the triazole product. Finally, we screened a variety of sulfonyl azides. To our delight, the reaction accommodated electron-rich and sterically encumbered mesitylene in good yield (Figures 1 and 3f). Highly electron-withdrawing *p*-nitrobenzenesulfonyl azide also provided the salt in excellent yield (Figures 1 and 3g). The reaction also worked with functionalized aryl azides such as 4-acetamidobenzenesulfonyl azide (*p*-ABSA) even in the presence of unprotected N−H functionality (Figures 1 and 3h). In addition to benzenesulfonyl azides, ketenimine salt formation also happened in good yield with mesyl azide (Figures 1 and 3i).

To identify the key structural features necessary to stabilize these ketenimine salts, we used differential scanning calorimetry (DSC), a well-established tool for the characterization of small molecule thermal behavior[7] to perform structure exothermic relationships with our synthesized ketenimine salts and a well-known coupling reagent EDC, which is sold and distributed as the hydrochloric acid ammonium salt. During our analysis, we encountered very subtle exothermic events and much more defined endothermic maxima; so, we decided to compare our ketenimine salts and EDC in regard to their maximum heat flow

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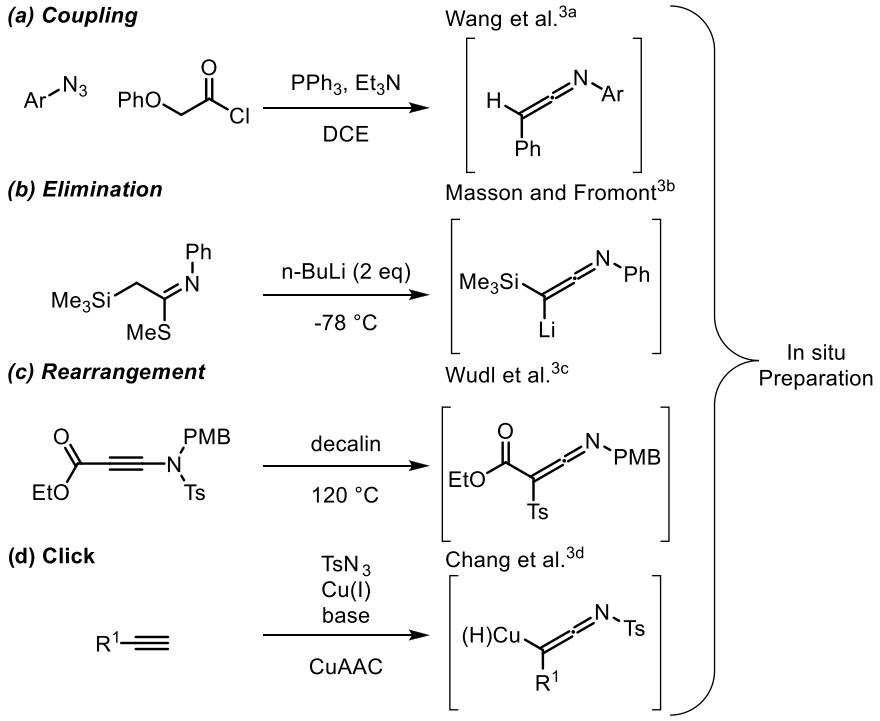
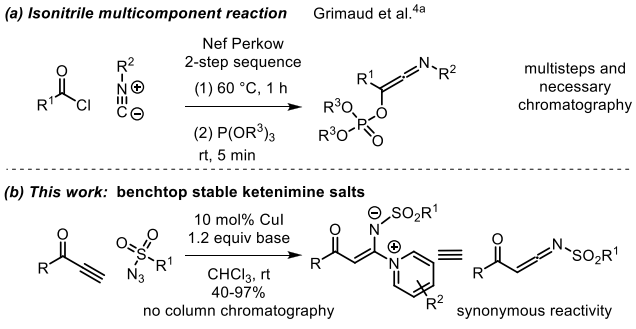
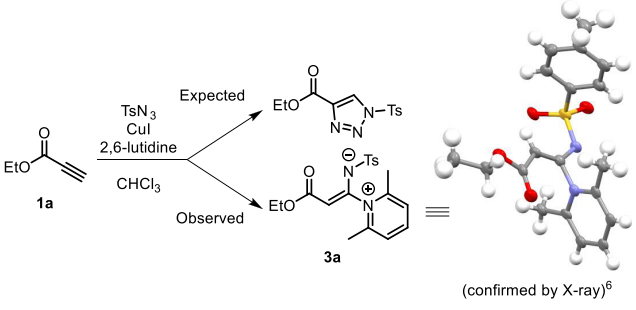
Scheme 1. In Situ Preparatory Methods for Ketenimine Synthons



Scheme 2. Synthesis of Stable Ketenimine Synthons



Scheme 3. Synthesis of Bench-Top Stable Ketenimine Salt via Click Chemistry



temperature. To our delight, the heat traces of **3a**–**c** in comparison to EDC suggest that these salts exhibit higher thermal stability (Figure 2).

Encouraged by these results, we then analyzed the influence of carbonyl functionality on the stability of the ketenimine salts. Although the yields of salts **3d** and **3e** were less compared to that of **3a**, their endothermic maxima still occurred at higher temperatures than EDC and were similar to **3a** (Figure 3).

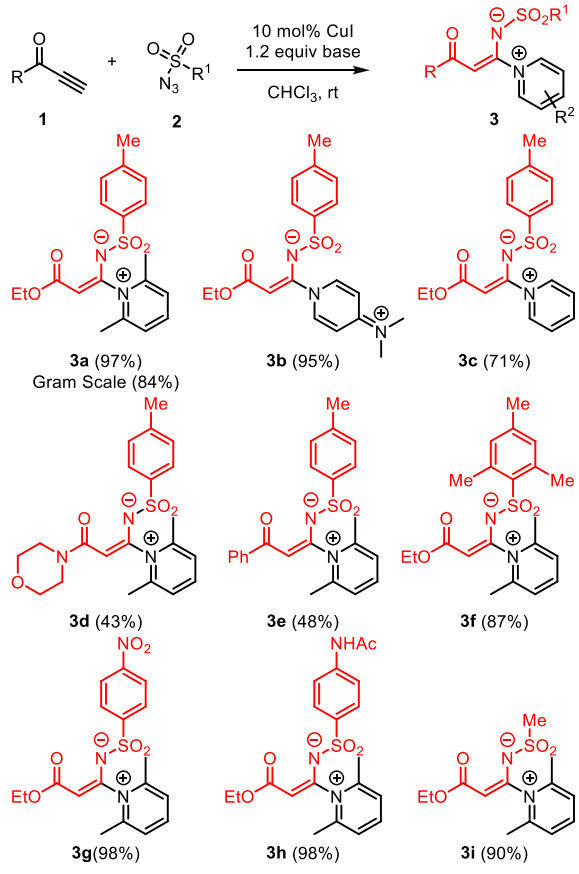


Figure 1. Scope of ketenimine salt formation; reactions were performed by adding pyridine-type bases (1.2 equiv) to a 0.2 M solution of **1** (0.10 mmol, 1.0 equiv), **2** (0.10 mmol, 1.0 equiv), and CuI in chloroform at 0 °C (see the Supporting Information for more details).

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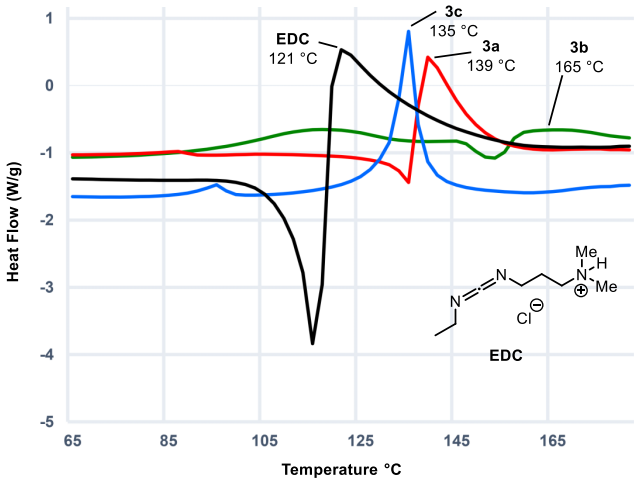


Figure 2. DSC traces for ketenimine salts **3a–c** and 1-ethyl-3–(3-dimethylaminopropyl) carbodiimide (EDC).

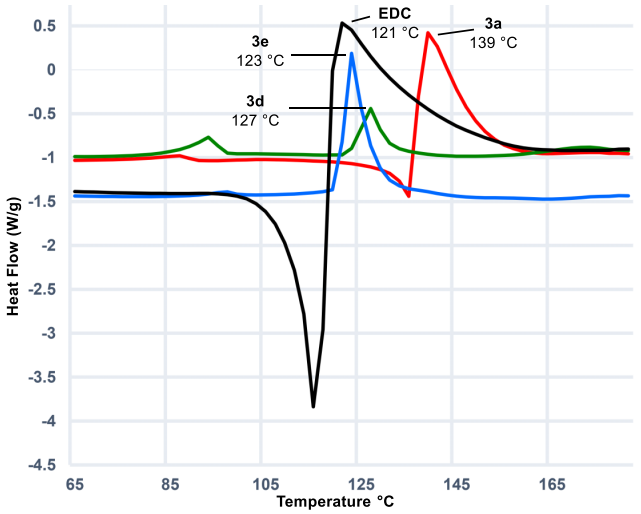


Figure 3. Differential scanning calorimetry (DSC) traces for ketenimine salts **3a**, **3d–e**, and EDC.

It was determined from the DSC traces that electron-rich ketenimine salts such as **3f** were significantly destabilized as compared to parent compound **3a**. The DSC trace of **3i** also suggests similar destabilizing effects due to the less stable mesyl group. Surprisingly, *p*-ABSA-derived salt **3h** was the least stable, presumably due to its unprotected acetamide functional group. To our delight, the *p*-nitrobenzene derivative **3g** exhibited significantly higher stability in comparison to our parent compound **3a** and EDC (Figure 4). This suggests that more electron-withdrawing sulfonyl groups provide a higher stabilizing effect.

The ketenimine salts presumably form synonymous to previous reports of multicomponent coupling reactions utilizing click chemistry. The mechanism begins with triazole formation following a stepwise copper(I)-catalyzed alkyne–azide cycloaddition.[8] These reactions are believed to incorporate multiple copper atoms, but one is shown for simplicity.[9,10] During these initial stages of the mechanism, copper acetylide formation provides intermediate **A**, which can coordinate with the sulfonyl azide to subsequently form adduct **B**, which then stepwise cyclizes to yield triazole **C**. This triazole then performs a ring-opening rearrangement to form a reactive ketenimine copper

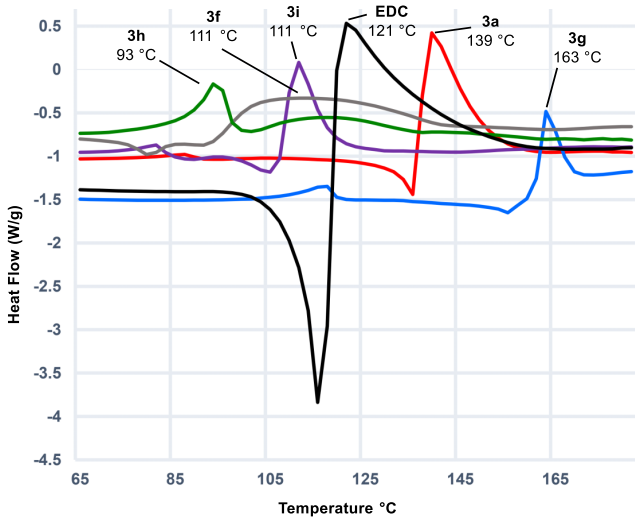
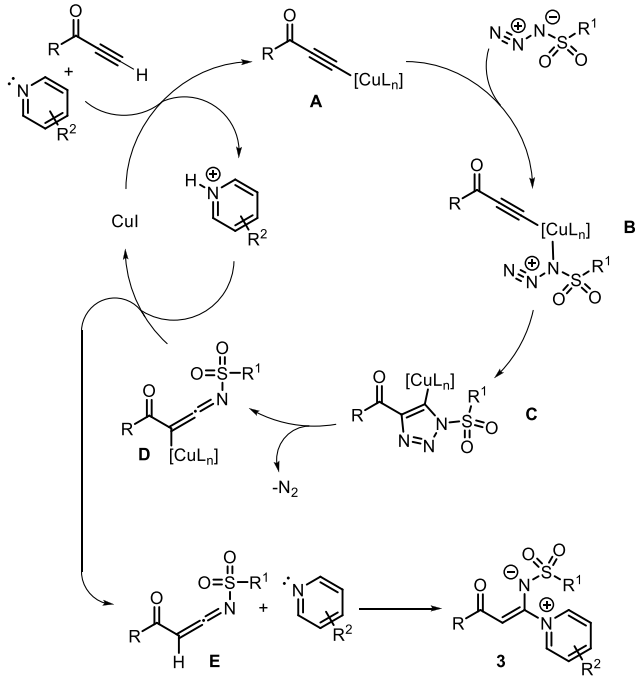


Figure 4. DSC traces for ketenimine salts **3a**, **3f–i**, and EDC.

species **D**,[11] which then undergoes protodemetalation to form unstable ketenimine intermediate **E**. The pyridine base then performs a nucleophilic addition to the electrophilic ketenimine **E** yielding the stabilized zwitterionic salt **3** (Scheme 4).

Scheme 4. Plausible Mechanism of Ketenimine Salt Synthesis



After the successful synthesis of several bench-top stable ketenimine precursors, we looked into their synonymous reactivity compared to in situ-generated ketenimine synthons. There are mainly five types of reactions known with ketenimines: nucleophilic additions,[12] radical additions,[13] cycloadditions,[14] electrocyclic ring-closure reactions,[15] and σ rearrangements.[16] We decided to go with nucleophilic addition reactions as previously reported by Wang et al.[17] for the synthesis of bioactive 2-aminoquinolines.[18]

We began our optimization using model substrates 2′-aminoacetophenone and ketenimine salt **3a**. As expected, our initial attempts using acetonitrile and 1,2-dichloroethane

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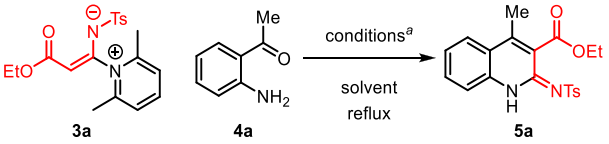
(DCE) as a solvent afforded the synthesis of 2-aminoquinoline **5a** in very high yield (Table 1, entries 1 and 2). The structure of

Table 1. Optimization of 2-Aminoquinoline Synthesis



entry	solvent	temp. (°C)[a]	5a yield[b]
1	MeCN	82	89
2	DCE	83	91
3	dioxane	101	73
4	toluene	111	72
5	DCE	60	49[c]
6	neat	90	96

[a]All optimization reactions were performed by refluxing a 0.2 M solution of **3a** (39.0 mg, 0.1 mmol, 1.0 equiv) and **4a** (14.0 mg, 0.1 mmol, 1.0 equiv) for 3 h. [b]Yields of **5a** obtained after column chromatography. [c]Reaction was performed under sonication. MeCN = acetonitrile; DCE = 1,2-dichloroethane.

5a was confirmed by X-ray crystallography (Figure 5).[19] We did not observe any significant improvement using high boiling point solvents, sonication conditions, and neat heating (entries 3−5). Therefore, we decided to perform the substrate scope using DCE reflux conditions.

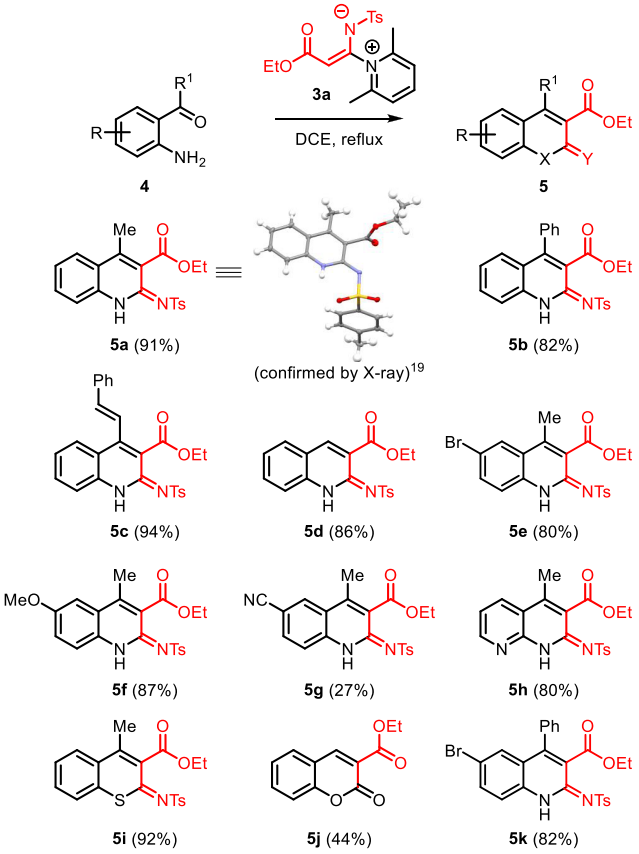


Figure 5. Scope of 2-aminoquinoline synthesis; all reactions were performed by refluxing a 0.2 M solution of **3a** (39.0 mg, 0.10 mmol, 1.0 equiv) and **4** (0.10 mmol, 1.0 equiv) in DCE for 3 h.

With optimized conditions in hand, we decided to explore the substrate scope of these ketenimine precursors. As expected, the reaction proceeded in high yield in the presence of a phenyl ketone and chalcone motifs (Figure 5b,c). This reaction also accommodated aldehyde functionality to provide the unsubstituted 2-aminoquinoline (Figure 5d). The reaction also tolerated the presence of electron-donating and -withdrawing substituents including a pyridine ring on the 2′-aminoacetophenone fragment (Figure 5e−h). The reaction also accommodated other nucleophiles such as phenols and thiophenols (Figure 5i,j). Interestingly, phenols performed the reaction only with aldehydes, and the product formed was the lactone generated by hydrolysis of the sulfonamide functionality (Figure 5j).

Finally, *N*-tosyl group was deprotected in quantitative yield under acidic conditions to provide medicinally relevant 2-aminoquinolines (Figure 6a). For example, molecules such as

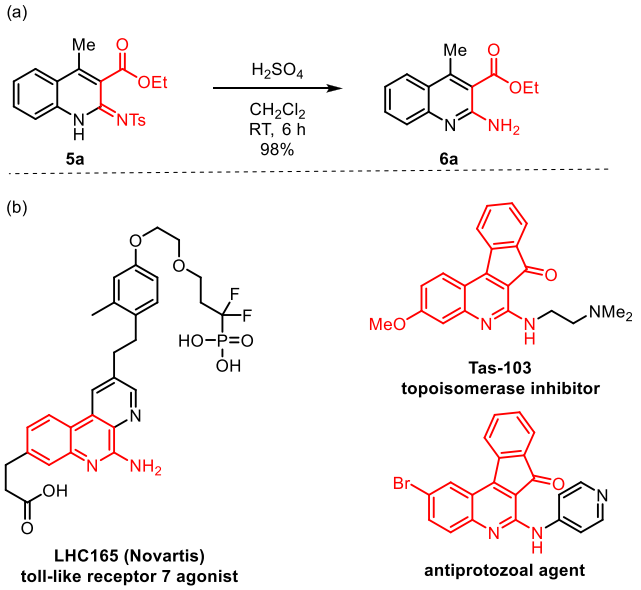


Figure 6. (a) Selective tosyl deprotection of **5a**, (b) medicinally relevant 2-aminoquinoline cores and 6-amino-7*H*-indeno[2,1-*c*]-quinolin-7-one cores.

LHC165 by Novartis were recently disclosed to be a potent Toll-like receptor 7 agonist.[20] In addition, 6-amino-7*H*-indeno[2,1-*c*]quinoline-7-ones are relevant bioactive cores and are present in potent topoisomerase inhibitor Tas-103[21] and antiprotozoal agent[22] shown in Figure 6b.

To further demonstrate the utility, we then decided to employ the ketenimine salt **3a** for the synthesis of a biologically relevant core scaffold such as Tas-103, a potent topoisomerase inhibitor. Our strategy involved a one-pot procedure to afford the Tas-103 core **7a**, which has previously been accessed in multiple steps (Scheme 5a).[23]

The low yield in our one-pot procedure is attributed to the presence of an electron-rich ketone in **4h**, which may be less susceptible to aldol cyclization. Therefore, we performed a stepwise procedure to synthesize a core scaffold of an antiprotozoal agent. The two-step procedure afforded compound **7b** in good yield as shown in Scheme 5b. The structure of product **7b** was confirmed by single-crystal X-ray diffraction.[24]

We propose that the mechanism of our ketenimine salt cascade is initiated by the liberation of 2,6-lutidine from **1**

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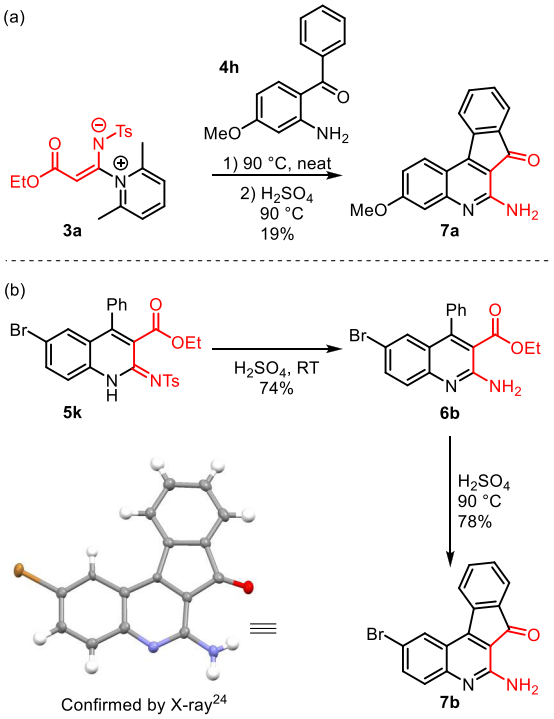
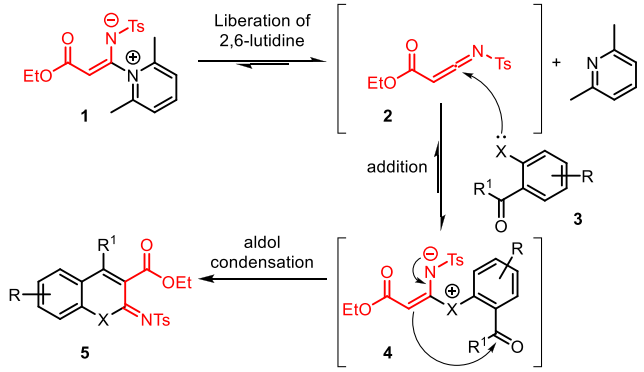
Scheme 5. Synthesis of 6-amino-7*H*-indeno[2,1-*c*]quinolin-7-one cores[1]



[1](a) One-pot procedure for the synthesis of Tas-103 core **7a**, (b) stepwise synthesis of antiprotozoal agent core **7b**.

producing a significantly electrophilic ketenimine **2**; this undergoes a nucleophilic addition to produce intermediate **4** (Scheme 6). This sort of ammonium exchange sequence is

Scheme 6. Plausible Mechanism of 2-Aminoquinoline Synthesis



known in the literature.[25] Then, intermediate **4** performs an intramolecular aldol condensation reaction to provide the 2-aminoquinoline product **5**.

CONCLUSIONS

In conclusion, we have synthesized a bench-top stable ketenimine precursor having the potential for commercialization. We also investigated the structure exothermic relationship of these ketenimine salts with DSC to identify the key structural features necessary for their stability. In addition, we explored the synthetic utility of these salts to access a variety of diverse heterocycles including the core structures of an antiprotozoal agent and a potent topoisomerase inhibitor Tas-103. New transformations incorporating these stable ketenimine precursors are being explored and will be communicated in due course.

EXPERIMENTAL SECTION

Materials and Methods. All reactions were performed in flame-dried glassware under positive N_2 pressure with magnetic stirring unless otherwise noted. Reagents and solvents were obtained from Sigma-Aldrich, Chem-Impex, VWR International, and Acros Organics and used without further purification unless otherwise indicated. Dichloromethane was distilled over CaH_2 under N_2 unless otherwise indicated. Tetrahydrofuran was distilled over Na under N_2 with benzophenone indicator. Thin-layer chromatography (TLC) was performed on 0.25 mm E. Merck silica gel 60 F254 plates and visualized under UV light (254 nm) or by staining with potassium permanganate ($KMnO_4$), cerium ammonium molybdate, phosphomolybdic acid, and ninhydrin. Silica flash chromatography was performed on a Sorbtech 230−400 mesh silica gel 60. Sonication was performed using a Bransonic Ultrasonic Cleaner (Model: M5800H). IR spectra were recorded on a Shimadzu IRAffinity-1 FTIR or a Nicolet 6700 FTIR spectrometer with peaks reported in cm^{-1}. NMR spectra were recorded on a Varian VNMRS 400 and 600 MHz NMR spectrometer in $CDCl_3$ unless otherwise indicated. Chemical shifts are expressed in ppm relative to solvent signals: $CDCl_3$ (1H, 7.26 ppm, 13C, 77.0 ppm); coupling constants are expressed in hertz. NMR spectra were processed using Mnova (www.mestrelab.com/software/mnova-nmr). Mass spectra were obtained at the OU Analytical Core Facility on an Agilent 6538 high-mass-resolution QTOF mass spectrometer and an Agilent 1290 UPLC. X-ray crystallography analysis was carried out at the University of Oklahoma using a Bruker APEX ccd area detector and graphite-monochromated Mo Kα radiation (λ = 0.71073 Å) source and a D8 Quest diffractometer with a Bruker Photon II cmos area detector and an Incoatec Iμs microfocus Mo Kα source (λ = 0.71073 Å). Crystal structures were visualized using CCDC Mercury software (http://www.ccdc.cam.ac.uk/products/mercury/). For further information regarding X-ray structures, see the Supporting Information.

*Synthesis of Alkynes **1b−c**.* 1-Morpholinoprop-2-yn-1-one (**1b**) was prepared using known literature protocol.[26]

1-Phenylprop-2-yn-1-one (**1c**) was prepared using known literature protocol.[27]

*Synthesis of Sulfonyl Azides **2a−e**.* 4-Methylbenzenesulfonyl azide (**2a**) was prepared using known literature protocol.[28]

2,4,6-Trimethylbenzenesulfonyl azide (**2b**) was prepared using known literature protocol.[29]

4-Nitrobenzenesulfonyl azide (**2c**) was prepared using known literature protocol.[30]

4-Acetamidobenzenesulfonyl azide (**2d**) was prepared using known literature protocol.[28]

Methanesulfonyl azide (**2e**) was prepared using known literature protocol.[31]

*General Procedure 1 for the Synthesis of Ketenimine Salts **3a−i**.* To a stirring solution of alkyne 1 (0.68−1.53 mmol, 1.2 equiv), sulfonyl azide 2 (0.57−1.27 mmol, 1.0 equiv) and CuI (10 mol %) in anhydrous chloroform (0.2 M) at 0 °C were added to corresponding pyridine reagent (0.68−1.53 mmol, 1.2 equiv). The reaction was allowed to stir at this temperature until the consumption of azide 2; reaction times ranged from 3 to 6 h. Then, the chloroform was removed by a rotoevaporator to yield a viscous oil. At this point, approximately 5−10 mL of ethyl acetate was added followed by brief sonication to mix. Crude residue would solubilize momentarily and be subsequently followed by immediate precipitation of stabilized ketenimine salt. The organic salt was isolated as a solid by decanting and further purified by trituration with ethyl acetate and hexane. Solid product obtained was removed of residual solvent by high vacuum to yield stabilized ketenimine salts **3a−i** without the need for further purification.

*(Z)-(1-(2,6-Dimethylpyridin-1-ium-1-yl)-3-ethoxy-3-oxoprop-1-en-1-yl)(tosyl)amide (**3a**).* White solid (465.5 mg, 97%, mp 146−149 °C). TLC: R_f 0.19 (9:1 EtOAc/MeOH). IR (neat): 3066, 2969, 1685, 1570, 1261, 1118. ^{1}H NMR (600 MHz) δ 8.01 (t, J = 7.9 Hz, 1H),

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7.97−7.83 (m, 2H), 7.45 (d, J = 7.9 Hz, 2H), 7.28 (d, J = 7.9 Hz, 2H), 5.54 (s, 1H), 3.85 (q, J = 7.1 Hz, 2H), 2.63 (s, 6H), 2.41 (s, 3H), 1.13 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (151 MHz) δ 166.8, 154.8, 152.6, 143.4, 141.8, 129.5, 129.0 (2C), 128.6, 127.2 (2C), 125.7 (2C), 86.2, 59.1, 21.5, 20.0 (2C), 14.3. High-resolution mass spectrometry (HRMS; ESI) m/z calcd for $C_{19}H_{23}N_2O_4S$ ($[M + H]^+$) 375.1379; found 375.1381. Preparation of ketenimine salt **3a** was also performed on gram scale without any modification of general procedure 1.

*(Z)-(1-(4-(Dimethyliminio)pyridin-1(4H)-yl)-3-ethoxy-3-oxoprop-1-en-1-yl)(tosyl)amide (**3b**).* Light brown solid (493.3 mg, 95%, mp 145−147 °C). TLC: R_f 0.15 (9:1 EtOAc/MeOH). IR (neat): 3076, 2928, 1640, 1567, 1121, 1080. ^1H NMR (500 MHz) δ 7.93 (d, J = 7.2 Hz, 2H), 7.86 (d, J = 8.0 Hz, 2H), 7.24 (d, J = 7.9 Hz, 2H), 6.67 (d, J = 7.1 Hz, 2H), 5.32 (s, 1H), 3.89 (q, J = 7.1 Hz, 2H), 3.23 (s, 6H), 2.38 (s, 3H), 1.14 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (75 MHz) δ 166.3, 156.6, 156.5, 155.6, 141.0, 140.7 (2C), 139.0, 128.5 (2C), 126.4 (2C), 105.5 (2C), 58.3, 40.0 (2C), 20.9, 13.9. HRMS (ESI) m/z calcd for $C_{19}H_{24}N_3O_4S$ ($[M + H]^+$) 390.1488; found 390.1472.

*(Z)-(3-Ethoxy-3-oxo-1-(pyridin-1-ium-1-yl)prop-1-en-1-yl)(tosyl)-amide (**3c**).* Pale yellow solid (313.2 mg, 71%, mp 123−125 °C). TLC: R_f 0.19 (9:1 EtOAc/MeOH). IR (neat): 3117, 2980, 1692, 1593, 1269, 1125. ^1H NMR (400 MHz) δ 8.57 (d, J = 5.5 Hz, 2H), 8.41 (tt, J = 7.8, 1.4 Hz, 1H), 7.91−7.86 (m, 4H), 7.29−7.26 (m, 2H), 5.44 (s, 1H), 3.86 (q, J = 7.1 Hz, 2H), 2.41 (s, 3H), 1.14 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (151 MHz, CD_2Cl_2) δ 166.0, 145.4, 143.4, 141.7, 129.1, 128.8 (2C), 128.0, 126.5 (2C), 126.1 (2C), 84.1, 58.9, 20.9, 13.7, 13.4. HRMS (ESI) m/z calcd for $C_{17}H_{19}N_2O_4S$ ($[M + H]^+$) 347.1066; found 347.1066.

*(Z)-(1-(2,6-Dimethylpyridin-1-ium-1-yl)-3-morpholino-3-oxoprop-1-en-1-yl)(tosyl)amide (**3d**).* Gray/white solid (102.1 mg, 43%, mp 120−123 °C). TLC: R_f 0.04 (9:1 EtOAc/MeOH). IR (neat): 3065, 2840, 1616, 1557, 1270, 899. ^1H NMR (600 MHz) δ 7.97 (t, J = 7.9 Hz, 1H), 7.87 (d, J = 7.9 Hz, 2H), 7.42 (d, J = 7.9 Hz, 2H), 7.25 (d, J = 7.7 Hz, 2H), 5.77 (s, 1H), 3.64−3.49 (m, 4H), 3.48−3.29 (m, 4H), 2.62 (s, 6H), 2.39 (s, 3H). $^{13}C\{^1H\}$ NMR (151 MHz) δ 164.8, 154.7 (2C), 151.1, 143.3, 141.8, 128.9 (2C), 127.1 (2C), 125.4 (2C), 121.7, 85.5, 66.8 (2C), 22.7, 21.4 (2C), 20.2 (2C). HRMS (ESI) m/z calcd for $C_{21}H_{26}N_3O_4S$ ($[M + H]^+$) 416.1644; found 416.1641.

*(Z)-(1-(2,6-Dimethylpyridin-1-ium-1-yl)-3-oxo-3-phenylprop-1-en-1-yl)(tosyl)amide (**3e**).* Gray/white solid (168.1 mg, 48%, mp 115−117 °C). TLC: R_f 0.29 (9:1 EtOAc/MeOH). IR (neat): 3066, 2969, 1625, 1521, 1135, 906. ^1H NMR (500 MHz) δ 8.05 (t, J = 7.9 Hz, 1H), 7.97 (d, J = 8.4 Hz, 2H), 7.80−7.75 (m, 2H), 7.48 (dd, J = 11.1, 7.7 Hz, 3H), 7.39 (t, J = 7.5 Hz, 2H), 7.30 (d, J = 7.9 Hz, 2H), 6.77 (s, 1H), 2.63 (s, 6H), 2.41 (s, 3H). $^{13}C\{^1H\}$ NMR (151 MHz) δ 186.0, 154.6, 152.8, 143.4, 142.4, 139.5, 131.8, 129.2 (2C), 128.6, 128.5, 128.4 (2C), 127.6 (2C), 127.3 (2C), 125.8 (2C), 91.5, 21.5, 20.1 (2C). HRMS (ESI) m/z calcd for $C_{23}H_{23}N_2O_3S$ ($[M + H]^+$) 407.1429; found 407.1426.

*(Z)-(1-(2,6-Dimethylpyridin-1-ium-1-yl)-3-ethoxy-3-oxoprop-1-en-1-yl)(mesitylsulfonyl)amide (**3f**).* Pale yellow solid (421.2 mg, 87%, mp 91−94 °C). TLC: R_f 0.31 (9:1 EtOAc/MeOH). IR (neat): 2980, 2933, 1689, 1577, 1107, 1039. ^1H NMR (300 MHz) δ 8.02 (t, J = 7.9 Hz, 1H), 7.48 (d, J = 7.9 Hz, 2H), 6.92 (s, 2H), 5.30 (s, 1H), 3.85 (q, J = 7.1 Hz, 2H), 2.78 (s, 6H), 2.77 (s, 6H), 2.28 (s, 3H), 1.11 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (75 MHz) δ 166.7, 154.6 (2C), 152.7, 143.5, 140.5, 138.4, 137.0, 131.8, 131.4 (2C), 125.7 (2C), 85.8, 58.9, 22.9 (2C), 20.8, 20.0 (2C), 14.3. HRMS (ESI) m/z calcd for $C_{21}H_{27}N_2O_4S$ ($[M + H]^+$) 403.1692; found 403.1679.

*(Z)-(1-(2,6-Dimethylpyridin-1-ium-1-yl)-3-ethoxy-3-oxoprop-1-en-1-yl)((4-nitrophenyl)sulfonyl)amide (**3g**).* Pale yellow solid (506.3 mg, 98%, mp 148−149 °C). TLC: R_f 0.29 (9:1 EtOAc/MeOH). IR (neat): 3101, 2983, 1687, 1601, 1351, 1133. ^1H NMR (500 MHz, CD_2Cl_2) δ 8.32 (d, J = 8.8 Hz, 2H), 8.13 (d, J = 8.9 Hz, 2H), 8.08 (t, J = 7.9 Hz, 1H), 7.52 (d, J = 7.9 Hz, 2H), 5.51 (s, 1H), 3.84 (q, J = 7.1 Hz, 2H), 2.59 (s, 6H), 1.11 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, CD_2Cl_2) δ 165.4, 154.0 (2C), 151.5, 148.9, 148.2, 143.7, 127.7 (2C), 125.6 (2C), 123.4 (2C), 87.6, 58.9, 19.4 (2C), 13.6. HRMS (ESI) m/z calcd for $C_{18}H_{20}N_3O_6S$ ($[M + H]^+$) 406.1073; found 406.1053.

*(Z)-((4-Acetamidophenyl)sulfonyl)(1-(2,6-dimethylpyridin-1-ium-1-yl)-3-ethoxy-3-oxoprop-1-en-1-yl)amide (**3h**).* Pale yellow solid (521.3 mg, 98%, mp 127−130 °C). TLC: R_f 0.10 (9:1 EtOAc/MeOH). IR (neat): 3341, 3099, 2984, 1687, 1265, 1122. ^1H NMR (500 MHz) δ 8.51 (s, 1H), 8.01 (t, J = 7.9 Hz, 1H), 7.85 (d, J = 8.3 Hz, 2H), 7.68 (d, J = 8.3 Hz, 2H), 7.45 (d, J = 7.9 Hz, 2H), 5.47 (s, 1H), 3.84 (q, J = 7.1 Hz, 2H), 2.57 (s, 6H), 2.19 (s, 3H), 1.12 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (75 MHz) δ 169.6, 166.2, 154.3 (2C), 152.1, 143.8, 141.8, 135.9, 127.8 (2C), 125.8 (2C), 119.0 (2C), 87.1, 59.3, 24.5, 19.8 (2C), 14.2. HRMS (ESI) m/z calcd for $C_{20}H_{24}N_3O_5S$ ($[M + H]^+$) 418.1437; found 418.1418.

*(Z)-(1-(2,6-Dimethylpyridin-1-ium-1-yl)-3-ethoxy-3-oxoprop-1-en-1-yl)(methylsulfonyl)amide (**3i**).* Yellow solid (310.5 mg, 90%, mp 98−100 °C). TLC: R_f 0.15 (9:1 EtOAc/MeOH). IR (neat): 3068, 2979, 1678, 1578, 1260, 1093. ^1H NMR (400 MHz) δ 8.06 (t, J = 7.9 Hz, 1H), 7.53 (d, J = 7.9 Hz, 2H), 5.57 (s, 1H), 3.90 (q, J = 7.1 Hz, 2H), 3.03 (s, 3H), 2.87 (s, 6H), 1.16 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (75 MHz) δ 166.5, 154.3 (2C), 153.0, 143.8, 125.8 (2C), 85.9, 59.0, 38.9, 20.0 (2C), 14.2. HRMS (ESI) m/z calcd for $C_{13}H_{19}N_2O_4S$ ($[M + H]^+$) 299.1066; found 299.1058.

*Synthesis of Starting Materials **4a**−**h**.* (2-Aminophenyl)(phenyl)-methanone (**4a**) was prepared using known literature protocol.[32]

(*E*)-1-(2-Aminophenyl)-3-phenylprop-2-en-1-one (**4b**) was prepared using known literature protocol.[33]

2-Aminobenzaldehyde (**4c**) was prepared using known literature protocol.[34]

1-(2-Amino-5-bromophenyl)ethan-1-one (**4d**) was prepared using known literature protocol.[35]

1-(2-Amino-5-methoxyphenyl)ethan-1-one (**4e**) was prepared using known literature protocol.[36]

3-Acetyl-4-aminobenzonitrile (**4f**) was prepared using known literature protocol.[37]

1-(2-Mercaptophenyl)ethan-1-one (**4g**) was prepared using known literature protocol.[38]

*(2-Amino-4-methoxyphenyl)(phenyl)methanone (**4h**).* To a stirring solution of commercially available 4-methoxy-2-nitrobenzaldehyde (300 mg, 1.66 mmol, 1.0 equiv, 0.2 M) in tetrahydrofuran was added phenylmagnesium bromide solution (608 μL, 1.1 equiv, 3.0 M) at 0 °C. The reaction was stirred at this temperature for 3 h and quenched at 0 °C with saturated ammonium chloride solution. Crude alcohol was extracted three times with ethyl acetate and dried over sodium sulfate. The crude product was concentrated to volume and redissolved in 30 mL of dichloromethane (0.05 M). To this solution was added MnO_2 (2.16 g, 24.88 mmol, 15 equiv) at room temperature, and the reaction was allowed to stir for 6 h, upon which the crude reaction was filtered over celite and concentrated to volume. This crude residue was then redissolved in methanol (0.3 M), Pd/C (20.1 mg, 10 mol %) was added, and the reaction was purged under hydrogen atmosphere (1 atm with H_2 balloon). After 3 h of stirring at room temperature, the crude reaction was filtered over celite and concentrated to volume. The crude residue was immediately purified by flash column chromatography eluting with a 2:5 EtOAc/hexane gradient to 2:1 EtOAc/hexane affording (2-amino-4-methoxyphenyl)(phenyl)methanone (**4h**) as a pale yellow solid (291.7 mg, 78%, mp 111−113 °C). TLC: R_f 0.28 (2:3 hexanes/EtOAc). IR (neat): 3474, 3344, 3016, 2975, 1608, 1225. ^1H NMR (300 MHz) δ 7.63−7.55 (m, 2H), 7.52−7.34 (m, 4H), 6.38 (s, 2H), 6.20−6.13 (m, 2H), 3.79 (s, 3H). $^{13}C\{^1H\}$ NMR (75 MHz) δ 197.6, 164.4, 153.6, 140.6, 136.9, 130.4, 128.6 (2C), 128.0 (2C), 112.2, 104.0, 99.2, 55.2. Low-resolution mass spectrometry (LRMS; ESI) m/z calcd for $C_{14}H_{14}NO_3$ ($[M + H_2O]^-$) 244.1; found 244.0. Values match literature known values.[39]

*General Procedure 2 for the Synthesis of Products **5a**−**k**.* To a 4 mL scintillation vial were added ketenimine salts **3** (0.05−0.27 mmol, 1.0 equiv) and **5** (0.05−0.27 mmol, 1.0 equiv) and anhydrous DCE (0.2 M). The reaction was stirred at 90 °C with a heating block until complete consumption of **5**. Reaction times ranged from 6 to 12 h. The crude reaction mixture was concentrated and then purified using flash column chromatography eluting with a 1:10 ethyl acetate/hexane gradient to 3:7 EtOAc/hexanes affording products **5a**−**k**.

*Ethyl (Z)-4-Methyl-2-(tosylimino)-1,2-dihydroquinoline-3-carboxylate (**5a**).* White solid (18.4 mg, 91%, mp 146−149 °C). TLC: R_f 0.19 (7:3 hexanes/EtOAc). IR (neat): 3237, 3068, 2976, 1733, 1622,

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1272. ^{1}H NMR (500 MHz) δ 11.89 (s, 1H), 7.84 (d, J = 7.8 Hz, 2H), 7.75 (d, J = 8.2 Hz, 1H), 7.59 (t, J = 8.4, 1H), 7.35 (t, J = 8.3 Hz, 1H), 7.33−7.29 (m, 1H) 7.21 (d, J = 8.1 Hz, 2H), 4.38 (q, J = 7.2 Hz, 2H), 2.47 (s, 3H), 2.35 (s, 3H), 1.30 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz) δ 165.3, 150.7, 146.2, 142.4, 140.1, 135.1, 132.5, 132.1, 129.3, 129.1, 126.4, 125.9, 125.0, 124.8, 120.8, 117.1, 61.9, 21.3, 16.3, 14.0. (Due to possible resonance and equilibrium forms of this molecule, the S/N ratio of some aromatic peaks was drastically reduced.) HRMS (ESI) m/z calcd for $C_{20}H_{21}N_2O_4S$ ([M + H]$^+$) 385.1222; found 385.1220.

*Ethyl (Z)-4-Phenyl-2-(tosylimino)-1,2-dihydroquinoline-3-carboxylate (**5b**).* White solid (19.3 mg, 82%, mp 65−68 °C). TLC: R_f 0.35 (7:3 hexanes/EtOAc). IR (neat): 3244, 2923, 1618, 1597, 1271, 1132. ^{1}H NMR (600 MHz) δ 12.13 (s, 1H), 7.88 (s, 1H), 7.63 (s, 1H), 7.47 (s, 3H), 7.41 (s, 1H), 7.35 (d, J = 8.2 Hz, 2H), 7.27 (d, J = 7.9 Hz, 5H), 4.04 (s, 2H), 2.39 (s, 3H), 0.95 (s, J = 8.7 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz) δ 164.9, 150.5, 142.8, 139.4, 134.1, 132.1, 129.1, 129.0, 128.9, 128.6, 128.3, 127.7, 126.6, 124.8, 121.4, 61.5, 21.4, 13.4. (Due to possible resonance and equilibrium forms of this molecule, the S/N ratio of some aromatic peaks was drastically reduced.) HRMS (ESI) m/z calcd for $C_{25}H_{23}N_2O_4S$ ([M + H]$^+$) 447.1379; found 447.1374.

*Ethyl (Z)-4-((E)-styryl)-2-(tosylimino)-1,2-dihydroquinoline-3-carboxylate (**5c**).* Pale yellow solid (23.5 mg, 94%, mp 73−75 °C). TLC: R_f 0.31 (7:3 hexanes/EtOAc). IR (neat): 3244, 2978, 1616, 1595, 1075, 667. ^{1}H NMR (400 MHz) δ 12.02 (s, 1H), 7.91−7.85 (m, 2H), 7.65 (t, J = 7.7 Hz, 1H), 7.53−7.49 (m, 2H), 7.43−7.34 (m, 5H), 7.28−7.21 (m, 4H), 7.15−7.04 (m, 1H), 4.31 (q, J = 7.1 Hz, 2H), 2.39 (s, 3H), 1.22 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz) δ 165.0, 151.2, 146.1, 142.5, 140.1, 139.5, 135.6, 132.3, 129.4, 129.2, 128.9, 128.4, 127.1, 126.4, 126.0, 124.8, 120.1, 117.2, 62.0, 21.5, 14.1. (Due to possible resonance and equilibrium forms of this molecule, the S/N ratio of some aromatic peaks was drastically reduced.) HRMS (ESI) m/z calcd for $C_{27}H_{25}N_2O_4S$ ([M + H]$^+$) 473.1535; found 473.1519.

*Ethyl (Z)-2-(Tosylimino)-1,2-dihydroquinoline-3-carboxylate (**5d**).* White solid (16.8 mg, 86%, mp 187−190 °C). TLC: R_f 0.46 (7:3 hexanes/EtOAc). IR (neat): 3194, 2923, 1679, 1444, 1157, 1079. ^{1}H NMR (400 MHz) δ 10.77 (s, 1H), 8.75 (s, 1H), 8.21 (d, J = 8.1 Hz, 2H), 7.83 (d, J = 8.4 Hz, 1H), 7.75−7.69 (m, 2H), 7.40 (t, J = 8.2 Hz 1H), 7.29 (d, J = 8.1 Hz, 2H), 4.46 (q, J = 7.1 Hz, 2H), 2.38 (s, 3H), 1.45 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz) δ 166.4, 148.5, 143.9, 142.2, 137.2, 132.8, 129.2 (2C), 128.9 (3C), 128.8, 127.7, 125.4, 123.7, 110.8, 62.3, 21.6, 14.2. HRMS (ESI) m/z calcd for $C_{19}H_{19}N_2O_4S$ ([M + H]$^+$) 371.1066; found 371.1061.

*Ethyl (Z)-6-Bromo-4-methyl-2-(tosylimino)-1,2-dihydroquinoline-3-carboxylate (**5e**).* White solid (49.6 mg, 80%, mp 160−162 °C). TLC: R_f 0.36 (7:3 hexanes/EtOAc). IR (neat): 3197, 2992, 1732, 1621, 1591, 1075. ^{1}H NMR (600 MHz) δ 11.97 (s, 1H), 7.91 (s, 1H), 7.83 (s, 1H), 7.71 (dd, J = 8.5, 2.1 Hz, 1H), 7.26 (s, 4H), 4.39 (s, 2H), 2.47 (s, 3H), 2.39 (s, 3H), 1.31 (s, 3H).^{13}C{^{1}H} NMR (151 MHz) δ 165.1, 150.4, 145.0, 142.8, 139.6, 134.9, 134.2, 129.1, 127.5, 126.1, 122.4, 118.8, 117.9, 62.1, 21.4, 14.0. (Due to possible resonance and equilibrium forms of this molecule, the S/N ratio of some aromatic peaks was drastically reduced.) HRMS (ESI) m/z calcd for $C_{20}H_{20}BrN_2O_4S$ ([M + H]$^+$) 463.0327; found 463.0318.

*Ethyl (Z)-6-Methoxy-4-methyl-2-(tosylimino)-1,2-dihydroquinoline-3-carboxylate (**5f**).* White solid (48.4 mg, 87%, mp 119−122 °C). TLC: R_f 0.12 (7:3 hexanes/EtOAc). IR (neat): 3185, 2985, 1734, 1600, 1251, 824. ^{1}H NMR (600 MHz) δ 11.97 (s, 1H), 7.84 (s, 1H), 7.33−7.22 (m, 5H), 7.14 (d, J = 2.5 Hz, 1H), 4.41 (s, 2H), 3.89 (s, 3H), 2.49 (s, 3H), 2.37 (s, 3H), 1.33 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz) δ 165.7, 156.7, 145.6, 142.4, 129.1, 126.1, 121.5, 106.3, 62.0, 55.7, 21.4, 16.6, 14.0. (Due to possible resonance and equilibrium forms of this molecule, the S/N ratio of some aromatic peaks was drastically reduced.) HRMS (ESI) m/z calcd for $C_{21}H_{23}N_2O_5S$ ([M + H]$^+$) 415.1328; found 415.1325.

*Ethyl (Z)-6-Cyano-4-methyl-2-(tosylimino)-1,2-dihydroquinoline-3-carboxylate (**5g, major isomer**).* Pale yellow solid (30.0 mg, 27%, mp 179−181 °C). TLC: R_f 0.16 (7:3 hexanes/EtOAc). IR (neat): 3192, 2901, 2227, 1733, 1608, 1073. ^{1}H NMR (600 MHz) δ 12.06 (s, 1H), 8.09 (s, 1H), 7.82 (d, J = 7.9 Hz, 4H), 7.43 (d, J = 8.5 Hz, 1H), 7.27 (s, 1H), 4.39 (d, J = 7.5 Hz, 2H), 2.50 (s, 3H), 2.40 (s, 3H), 1.30 (t, J = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz) δ 164.6, 150.7, 143.4, 139.2, 137.8, 134.1, 130.4, 129.6, 129.3, 129.2, 128.7, 126.4, 126.2, 125.5, 118.3, 108.6, 108.5, 62.3, 21.5, 14.0, 14.0. (Due to possible resonance and equilibrium forms of this molecule, the S/N ratio of some aromatic peaks was drastically reduced.) HRMS (ESI) m/z calcd for $C_{21}H_{20}N_3O_4S$ ([M + H]$^+$) 410.1175; found 410.1176.

*Ethyl (Z)-4-Methyl-2-(tosylimino)-1,2-dihydro-1,8-naphthyridine-3-carboxylate (**5h**).* Pale orange solid (34.5 mg, 80%, mp 124−126 °C). TLC: R_f 0.28 (7:3 hexanes/EtOAc). IR (neat): 3212, 2980, 1719, 1619, 1076. ^{1}H NMR (300 MHz) δ 11.91 (s, 1H), 8.63 (dd, J = 4.8, 1.6 Hz, 1H), 8.08 (ddd, J = 8.1, 1.7, 0.7 Hz, 1H), 7.90−7.80 (m, 2H), 7.34 (ddd, J = 8.1, 4.7, 0.7 Hz, 1H), 7.25−7.22 (m, 2H), 4.38 (qd, J = 7.1, 0.7 Hz, 2H), 2.46 (d, J = 0.7 Hz, 3H), 2.37 (s, 3H), 1.30 (td, J = 7.1, 0.7 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz) δ 164.9, 152.4, 142.8, 133.7, 129.2, 126.2, 120.7, 62.1, 21.5, 15.8, 14.0. (Due to possible resonance and equilibrium forms of this molecule, the S/N ratio of some aromatic peaks was drastically reduced.) HRMS (ESI) m/z calcd for $C_{19}H_{20}N_3O_4S$ ([M + H]$^+$) 386.1175; found 386.1176.

*Ethyl (Z)-4-Methyl-2-(tosylimino)-2H-thiochromene-3-carboxylate (**5i**).* White solid (40.9 mg, 92%, mp 139−140 °C). TLC: R_f 0.24 (7:3 hexanes/EtOAc). IR (neat): 2983, 1727, 1597, 1425, 1280, 1083. ^{1}H NMR (400 MHz) δ 7.91 (d, J = 8.0 Hz, 1H), 7.89−7.85 (m, 2H), 7.60−7.48 (m, 3H), 7.28−7.25 (m, 2H), 4.31 (q, J = 7.1 Hz, 2H), 2.51 (s, 3H), 2.39 (s, 3H), 1.23 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz) δ 166.2, 165.1, 145.8, 143.5, 137.6, 133.6, 130.5, 130.5, 129.2 (2C), 127.9, 127.6, 127.0 (2C), 126.8, 126.4, 62.0, 21.5, 19.1, 13.9. HRMS (ESI) m/z calcd for $C_{20}H_{20}NO_4S_2$ ([M + H]$^+$) 402.0834; found 402.0836.

*Ethyl 2-Oxo-2H-chromene-3-carboxylate (**5j**).* Amber grease (10.3 mg, 44%). TLC: R_f 0.41 (7:3 hexanes/EtOAc). IR (neat): 3110, 2979, 1755, 1605, 1209, 1037. ^{1}H NMR (400 MHz) δ 8.52 (d, J = 0.7 Hz, 1H), 7.68−7.56 (m, 2H), 7.40−7.30 (m, 2H), 4.42 (q, J = 7.1 Hz, 2H), 1.41 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz) δ 163.1, 156.7, 155.2, 148.6, 134.3, 129.5, 124.8, 118.4, 117.9, 116.8, 62.0, 14.2. LRMS (ESI) m/z calcd for $C_{12}H_{11}O_4$ ([M + H]$^+$) 241.0; found 240.4. Matches literature known values.[40]

*Ethyl (Z)-6-Bromo-4-phenyl-2-(tosylimino)-1,2-dihydroquinoline-3-carboxylate (**5k, Major Isomer**).* White solid (46.6 mg, 82%, mp 157−160 °C). TLC: R_f 0.52 (7:3 hexanes/EtOAc). IR (neat): 3243, 3060, 2980, 1733, 1617, 1074. ^{1}H NMR (600 MHz) δ 12.12 (s, 1H), 8.21 (s, 1H), 7.85 (d, J = 26.5 Hz, 1H), 7.71 (d, J = 7.6 Hz, 1H), 7.48 (d, J = 6.3 Hz, 4H), 7.30 (s, 4H), 7.18 (s, 1H), 4.00 (s, 2H), 2.40 (s, 3H), 1.00−0.67 (m, 3H). ^{13}C{^{1}H} NMR (151 MHz) δ 167.5, 163.9, 151.7, 150.7, 149.0, 147.6, 145.8, 144.1, 142.7, 139.8, 137.1, 137.1, 136.4, 135.1, 130.0, 129.4, 129.4, 129.2, 128.6, 126.9, 126.1, 119.0, 118.5, 61.8, 31.6, 22.6, 21.5. (Due to possible resonance and equilibrium forms of this molecule, the S/N ratio of some aromatic peaks was drastically reduced. Some peaks from both isomers could not be differentiated as well causing an excess number of carbon peaks.) HRMS (ESI) m/z calcd for $C_{25}H_{22}BrN_2O_4S$ ([M + H]$^+$) 525.0484; found 525.0473.

*Selective Deprotection of **5a** To Synthesize **6a**. Ethyl 2-Amino-4-methylquinoline-3-carboxylate (**6a**).* To a stirring solution of **5a** (20.9 mg, 0.05 mmol, 0.02 M) in CH_2Cl_2 at 0 °C was added three drops of concentrated H_2SO_4. The ice bath was removed, and the reaction was allowed to stir at room temperature for 7 h. Then, the reaction mixture was basified with a saturated $NaHCO_3$ solution. The organic layer was separated, and the aqueous layer was extracted three times with dichloromethane. The combined organic layers were dried over sodium sulfate and concentrated to volume. The crude ethyl 2-amino-4-methylquinoline-3-carboxylate (**6a**) was isolated as a pure white solid without the need for further purification (12.3 mg, 98%, mp 133−136 °C). TLC: R_f 0.70 (7:3 hexanes/EtOAc). IR (neat): 3428, 3127, 2991, 1705, 1234, 1094. ^{1}H NMR (500 MHz) δ 7.89 (ddd, J = 8.4, 1.4, 0.7 Hz, 1H), 7.65−7.56 (m, 2H), 7.29 (ddd, J = 8.3, 6.6, 1.6 Hz, 1H), 5.74 (s, 2H), 4.47 (q, J = 7.2 Hz, 2H), 2.73 (s, 3H), 1.44 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz) δ 168.3, 154.6, 147.4, 131.2, 126.2, 124.7, 123.3, 123.0, 114.4, 61.7, 16.8, 14.2. HRMS (ESI) m/z calcd for $C_{13}H_{15}N_2O_2$ ([M + H]$^+$) 231.1134; found 231.1137.

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*One-Pot Procedure for the Synthesis of **7a**. 6-Amino-3-methoxy-7H-indeno[2,1-c]quinolin-7-one (**7a**).* Ketenimine salt **3a** (39.4 mg, 0.11 mmol, 1 equiv) and aniline **4h** (24.0 mg, 0.11 mmol, 1 equiv) were heated neat at 90 °C with a heating block in a scintillation vial for 2 h. The homogeneous oil was then cooled down to room temperature, and 0.5 mL of concentrated H_2SO_4 was added. The reaction was then heated at 90 °C for 3 h. The reaction was then cooled to 0 °C and basified with a saturated $NaHCO_3$ solution. The quenched reaction was then extracted three times with ethyl acetate, and the combined organic layers were filtered over sodium sulfate and concentrated to volume yielding a red powder solid. The crude solid was then purified by flash column chromatography eluting with a 3:10 ethyl acetate/hexane gradient to 2:3 hexanes/ethyl acetate affording 6-amino-3-methoxy-7H-indeno[2,1-*c*]quinolin-7-one (**7a**) as an orange solid (5.5 mg, 19%). TLC: R_f 0.28 (2:3 hexanes/EtOAc). IR (neat): 3406, 3286, 2952, 1685, 1637, 1272. ^{1}H NMR (600 MHz) δ 8.15 (d, J = 9.2 Hz, 1H), 8.00 (d, J = 7.5 Hz, 1H), 7.70 (d, J = 7.2 Hz, 1H), 7.58−7.53 (m, 1H), 7.45 (t, J = 7.4 Hz, 1H), 7.02 (s, 1H), 6.99 (dd, J = 9.2, 2.5 Hz, 1H), 6.11 (s, 2H), 3.94 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz) δ 193.8, 163.9, 155.6, 154.1, 153.0, 141.6, 134.8, 133.7, 130.7, 126.4, 124.5, 123.6, 117.3, 114.8, 109.6, 105.6, 55.6. HRMS (ESI) m/z calcd for $C_{17}H_{13}N_2O_2$ ([M + H]$^+$) 277.0977; found 277.0970.

*Stepwise Procedure for the Synthesis of **7b**. Ethyl 2-Amino-6-bromo-4-phenylquinoline-3-carboxylate (**6b**).* To a 4 mL scintillation vial containing **5k** (46.6 mg, 0.09 mmol) prepared from general procedure 2 was added H_2SO_4 (443 μL, 0.2 M). This was allowed to stir at room temperature for 3 h. Once the starting material was consumed on TLC, the reaction was cooled to 0 °C and basified with a saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 three times. The combined organic layers were dried over sodium sulfate and concentrated to volume yielding ethyl 2-amino-6-bromo-4-phenylquinoline-3-carboxylate (**6b**) as a pale yellow solid (24.1 mg, 73%, mp 154−156 °C) without the need for further purification. TLC: R_f 0.68 (7:3 hexanes/EtOAc). IR (neat): 3460, 3297, 3155, 1698, 1638, 1090. ^{1}H NMR (600 MHz) δ 7.64 (dd, J = 8.9, 2.2 Hz, 1H), 7.53 (dd, J = 8.9, 1.4 Hz, 1H), 7.47 (td, J = 3.8, 3.3, 1.7 Hz, 4H), 7.29−7.25 (m, 2H), 5.91 (s, 2H), 3.92 (q, J = 7.2 Hz, 2H), 0.73 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz) δ 167.9, 155.2, 150.6, 147.2, 136.9, 134.5, 129.3, 128.8 (2C), 128.3, 128.3 (2C), 127.8, 124.1, 116.1, 113.9, 61.3, 13.1. HRMS (ESI) m/z calcd for $C_{18}H_{16}BrN_2O_2$ ([M + H]$^+$) 371.0395; found 371.0388.

*6-Amino-2-bromo-7H-indeno[2,1-c]quinolin-7-one (**7b**).* To a 4 mL scintillation vial containing **6b** was added (21.5 mg, 0.06 mmol) H_2SO_4 (579 μL, 0.1 M). This was set to stir at 90 °C with a heating block for 3 h. Once the starting material was consumed on TLC, the reaction was cooled to 0 °C and basified with a saturated $NaHCO_3$ solution and extracted with ethyl acetate three times. The combined organic layers were dried over sodium sulfate and concentrated to volume yielding a red solid. This crude solid was washed with a 1:1 mixture of dichloromethane and hexane. The solvent was decanted, and the residual solvent was removed via high vacuum providing pure 6-amino-2-bromo-7H-indeno[2,1-*c*]quinolin-7-one (7b) as an orange solid (14.6 mg, 78%, mp 254−257 °C). TLC: R_f 0.72 (7:3 hexanes/EtOAc). IR (neat): 3432, 3104, 2923, 1692, 1641, 745. ^{1}H NMR (600 MHz) δ 8.40 (s, 1H), 8.03 (d, J = 7.5 Hz, 1H), 7.73 (s, 2H), 7.62 (s, 1H), 7.56 (d, J = 8.8 Hz, 1H), 7.49 (s, 1H), NH_2 signal is absent. ^{13}C{^{1}H} NMR (151 MHz) δ 136.1, 134.4, 131.1, 127.2, 124.6, 124.1. (Due to poor solubility in deuterated solvents, ^{1}H NMR signals were broadened and effective ^{13}C spectra were not obtained; so, the structure was also confirmed by X-ray crystallography.) HRMS (ESI) m/z calcd for $C_{16}H_{10}BrN_2O$ ([M + H]$^+$) 324.9977; found 324.9986.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.9b01906.

X-ray crystallography data; sample preparation; displacement ellipsoids were drawn at the 50% probability level; crystal data and structure refinement (PDF)

Crystallographic data and relevant spectra for **5a** (CIF)

Crystallographic data and relevant spectra for **3a** (CIF)

Crystallographic data and relevant spectra for **7b** (CIF)

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Notes

The authors declare no competing financial interest.

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