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Ethynyl Ketene-*S,S*-acetals: The Highly Reactive Electron-Rich Dienophiles and Applications in the Synthesis of 4-Functionalized Quinolines via a One-Pot Three-Component Reaction

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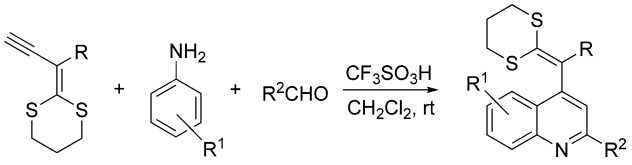

An efficient synthetic method for 4-functionalized quinoline derivatives, 4-((1,3-dithian-2-ylidene)methyl)quinolines, has been developed. Mediated by trifluoromethanesulfonic acid, ethynyl ketene-*S,S*-acetals can react in a one-pot procedure with various arylamines and aldehydes under mild conditions to give the corresponding quinoline derivatives in good to high yields via a consecutive arylimine formation, regiospecific aza-Diels−Alder (Povarov) reaction, and reductive amination.

Functionalized ketene dithioacetals, with the general structure **A** as shown in Figure 1, are versatile intermediates in organic synthesis[1−3] and α-EWG ketene dithioacetals (EWG = electron withdrawing group) have proven to be important building blocks in the construction of substituted aromatic[1,4] and heterocyclic compounds.[1,5] Some recent research has revealed that the coupling reaction at the α-carbon of functionalized ketene dithioacetals is reliable and incorporates a wide variety of functionalized ketene dithioacetals and carbon[6,7] or heteroatom electrophiles.[8] Recently, in a significant report, Beaton and co-workers described a novel approach to tetrahydroquinolines via the aza-Diels−Alder (Povarov) reaction of ketene dithioacetals **B** (Figure 1) with *N*-arylimines.[9]

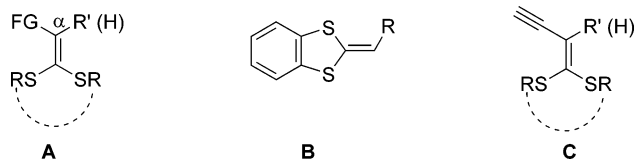

FIGURE 1. Structures of ketene dithioacetals.

During the course of our studies on the chemistry of functionalized ketene dithioacetals,[4a,b,5a−c,6,8,10] a series of α-ethynyl ketene-*S,S*-acetals, namely the alkylthio activated 1,3-enynes (Figure 1, **C**), were prepared in high yields via a consecutive Vilsmeier−Haack and dehydrochlorination reaction starting from easily available α-acetyl ketene dithioacetals[11] under mild conditions.[12] As synthetic applications of these electron-rich enynes, we have described the self-coupling reactions of the α-ethynyl ketene cyclic dithioacetals to the corresponding heteroatom-substituted expanded 1,3-dithiolan-[5]radialene[13a] and alkyne-spaced TTFs.[13b] Interestingly, when the addition reactions of carboxylic acids to α-ethynyl ketene dithioacetals were conducted in the absence of catalysts, the addition was found to occur at the carbon−carbon triple bond in a highly chemo- and regioselective manner.[14] The above results provided us with a more complete understanding of how to use the electron-rich carbon−carbon triple bond of the alkylthio activated 1,3-enynes. In this paper, the aza-Diels−

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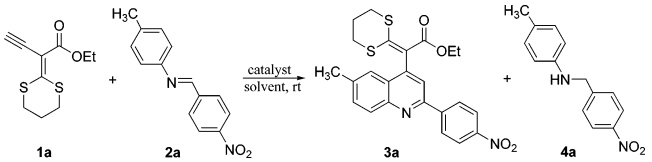
Alder (Povarov) reaction between α-ethynyl ketene dithioacetals and *N*-arylimines to provide functionalized quinolines is reported.

Quinoline derivatives represent a major class of heterocycles and the quinoline ring system occurs in various natural products possessing biological activity.[15,16] The synthetic methods for substituted quinolines commonly involve the elaboration of a quinoline ring,[17,18] the reactions of anilines with 1,3-dicarbonyl (Combes and Conrad−Limpach−Knorr synthesis)[17] or α,*β*-unsaturated compounds (Skraup−Doebner−Von Miller synthesis),[17,19] *o*-aminoaryl ketones/aldehydes with ketones (Friedländer synthesis),[17,20] *N*-arylimines with nucleophilic olefins or alkynes (Povarov reaction),[9,17,21] and some recently developed methods.[5f,22] It is noted that the [4+2] cycloaddition reaction of *N*-arylaldimines with dienophiles (Povarov reaction) has attracted increased attention and interest in recent years;[17,21,23b] however, these approaches are mainly limited to the synthesis of 4-alkyl-substituted quinolines. Other methods,[17−20,22] including those based on the Baylis−Hillman chemistry[23a] and the reactions of arylimines with 2-substituted acrylates and acrylamides,[23b] although could be considered the alternative approach to the corresponding 4-(substituted vinyl)quinolines and quinoline-4-carboxylic acid derivatives; however, they suffer from low product yields, multiple steps, or narrow scope for either aldehydes or arylimines. Herein we report an efficient synthetic method for 4-functionalized quinolines via a three-component one-pot procedure under mild conditions, which could allow for adequate diversity of aldehydes and arylamines and high regioselectivity (Table 3).

In the initial experiment, the aza-Diels−Alder reaction of enyne **1a** (1.0 equiv) with arylimine **2a** (1.0 equiv) was examined (Table 1). With dichloromethane as the solvent and mediated with $BF_3{\cdot}OEt_2$ (1.0 equiv), the reaction of **1a** with **2a** proceeded quickly (5 min) at room temperature and products **3a** and **4a** were obtained in 16% and 15% yield, respectively (Table 1, entry 1). The structure of **3a** was determined on the basis of its spectroscopic and analytical data and confirmed by X-ray crystal analysis.[24]

TABLE 1. Aza-Diels−Alder Reaction of Enyne 1a with Arylimine 2a under Various Reaction Conditions



entry	catalyst (equiv)	solvent	ratio (**1a**/**2a**)	time (min)	**3a** yield[a] (%)
1	$BF_3{\cdot}OEt_2$ (1.0)	CH_2Cl_2	1:1	5	16
2	CF_3SO_3H (1.0)	CH_2Cl_2	1:1	5	28
3	CF_3SO_3H(1.0)	CH_2Cl_2	1:2	5	60
4	CF_3SO_3H (1.0)	CH_2Cl_2	1:2.5	5	58
5	CF_3SO_3H (0.3)	CH_2Cl_2	1:2	10	11
6	PTSA (1.0)	CH_2Cl_2	1:2	180	41
7	HAC (1.0)	CH_2Cl_2	1:2	180	0
8	CF_3SO_3H (1.0)	DMF	1:2	5	13
9	CF_3SO_3H (1.0)	THF	1:2	5	18
10	CF_3SO_3H (1.0)	CH_3CN	1:2	5	17
11	CF_3SO_3H (1.0)	C_2H_5OH	1:2	15	14

[a] Isolated yields.

With quinoline **3a** at hand, next, the reaction conditions including solvents, catalysts, and the ratio of **1a** to **2a** were then optimized and the results are listed in Table 1. It was found that, with CF_3SO_3H (1.0 equiv) as the catalyst, **3a** could be produced in 28% yield by reacting **1a** (1.0 equiv) with arylimine **2a** (1.0 equiv) in dichloromethane for 5 min (Table 1, entry 2, along with 25% of amine **4a**). To our delight, under essentially the same conditions as above, the yield of **3a** could be increased to 60% by raising the ratio of **1a**/**2a** to 1:2 (Table 1, entry 3, along with 57% of **4a**). However, the yield of **3a** could not be increased by further raising the ratio of **2a**/**1a** (Table 1, entry 4) and the catalytic amount of CF_3SO_3H (0.3 equiv) led to lower yields of **3a** (Table 1, entry 5). Meanwhile, it was found that other catalysts tested, such as 4-methylbenzenesulfonic acid (PTSA) and acetic acid, were less effective than CF_3SO_3H (Table 1, entry 6) or ineffective (Table 1, entry 7). Among the solvents tested, dichloromethane seemed to be the best choice (Table 1, entry 3). Other solvents, for example, DMF, CH_3CN, THF, and ethanol, gave much lower product yields (Table 1, entries 8−11).

Prompted by the successful synthesis of quinoline **3a**, we then examined the scope of different arylimines **2** with electron-withdrawing or electron-donating groups on either the arylamine or arylaldehyde component. To our delight, under the optimized conditions (Table 1, entry 3), the arylimines **2** selected for this study gave strong evidence to suggest that this aza-Diels−Alder reaction tolerates a wide variety of arylimines **2** (Table 2). Comparatively, no desired aza-Diels−Alder products could be obtained by reacting arylimine **2a** with phenylacetylene and 1-pentyne, respectively, under essentially the same conditions as above.

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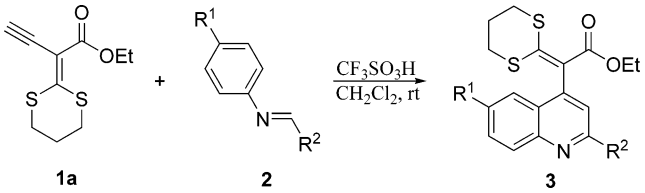
(24) Crystal data for **3a**: $C_{24}H_{22}N_2O_4S_2$, white crystal, $M = 466.58$, triclinic, $P\bar{1}$, $a = 9.616(4)$ Å, $b = 11.270(5)$ Å, $c = 11.587(5)$ Å, $\alpha = 69.052(7)°$, $\beta = 83.860(7)°$, $\gamma = 73.520(7)°$, $V = 1124.5(9)$ Å^3, $Z = 2$, $T = 273(2)$, $F_{000} = 488$, $R_1 = 0.0623$, $wR_2 = 0.1390$.

TABLE 2. CF_3SO_3H-Catalyzed Aza-Diels−Alder Reaction of Enyne 1a with Arylimines 2



1a 2 3

entry	R^1	R^2	time (min)	product	yield[a] (%)
1	CH_3	4-NO_2-C_6H_4	5	**3a**	60
2	CH_3	4-CH_3O-C_6H_4	5	**3b**	70
3	H	4-CH_3O-C_6H_4	5	**3c**	70
4	H	4-F-C_6H_4	5	**3d**	60
5	F	3,4-$CH_2O_2C_6H_3$	5	**3e**	63
6	F	4-NO_2-C_6H_4	5	**3f**	61

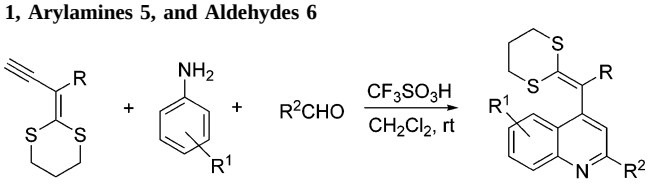
[a] Isolated yields.

Quinolines with the general structure **3** represent a new class of quinoline derivatives and are expected to have synthetic potential due to containing an α-oxo ketene-*S*,*S*-acetal functionality at the 4-position.[1] In addition, it should be emphasized that the aza-Diels−Alder reaction of enyne **1a** with arylimines **2** proceeded in a regiospecific manner since no other isomers of quinolines **3** were observed in our experiments. In consideration of the significant advantages of multicomponent reactions (MCRs),[25] we then focused our attention on the one-pot three-component reaction to construct 4-((1,3-dithian-2-ylidene)-methyl)quinolines **3** from structurally diverse aldehydes and arylamines. To our delight, the three-component reaction of enyne **1a** (R = CO_2Et), an arylamine **5**, and an aldehyde **6** (Table 3) also proceeded smoothly under otherwise identical conditions (Table 1, entry 3). Various aldehydes, such as aromatic aldehydes with either an electron-donating or an electron-withdrawing group on the benzene ring (Table 3, entries 1−14), heteroaromatic aldehydes (entries 15 and 16), olefinic aldehyde (entry 17), and aliphatic aldehydes (entries 18 and 19) served as suitable aldehyde components for the one-pot reaction to give the corresponding 4-functionalized quinoline derivatives (Table 3). Moreover, the yields of the above three-component reactions were comparable to those observed when the reaction was performed in two individual steps (Table 2). Additionally, under the identical conditions as above, the three-component aza-Diels−Alder reactions of enyne **1b** (R = CO_2H) and 4-methylbenzenamine with either 4-chlorobenzaldehyde or 4-nitrobenzaldehyde also proceeded quickly to give the corresponding 4-functionalized quinoline derivatives **3t** and **3u** in 65% and 70% yield, respectively (Table 3, entries 20 and 21).

On the basis of the above experimental results, the mechanism is proposed as a usual consecutive arylimine formation, aza-Diels−Alder (Povarov) reaction, followed by a reductive amination process (Scheme 1). However, unlike the related reports,[22a] it should be emphasized that in our experiments, we could not isolate the dihydroquinoline intermediate **8** and amines **4** were obtained in nearly the same yields as the corresponding quinolines **3** under identical conditions in all cases. Even under an N_2 atmosphere, the aza-Diels−Alder reactions of enyne **1a** (1.0 equiv) with arylimine **2a** (2.0 or 1.0 equiv) can also proceed quickly to give similar yields of product **3a** as those obtained under an air atmosphere (Table 1, entries 2 and 3) for 5 min at room temperature, along with the corresponding equimolar amount of amine **4a** without the formation of intermediate **8a**, which showed that the oxygen in the air was not an effective oxidant for aromatization of intermediate **8**. Consequently, the dihydroquinoline intermediate **8**, obtained by the [4+2] cycloaddition reaction of terminal alkyne **1** with arylimine **2**, was able to be immediately oxidized by iminium ion intermediate **9** to give quinoline **3** along with amine **4** (Scheme 1).[26]

In conclusion, we have demonstrated a novel and efficient three-component aza Diels−Alder reaction with the highly electron-rich dienophile, an α-ethynyl ketene-*S*,*S*-acetal **1**, an

TABLE 3. Three-Component Aza-Diels−Alder Reaction of Enynes 1, Arylamines 5, and Aldehydes 6

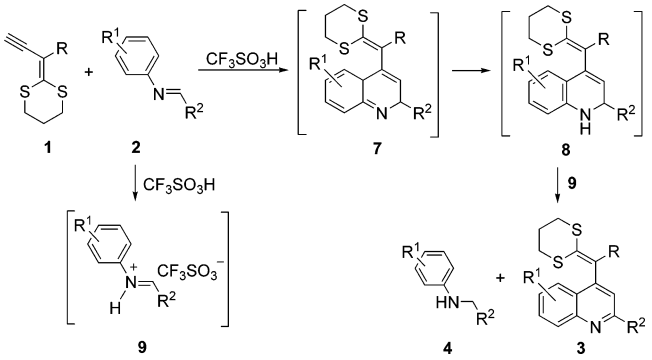


1 5 6 3

entry	R	R^1	R^2	time (min)	product	yield[a] (%)
1	COOEt	4-CH_3	4-NO_2-C_6H_4	5	**3a**	59
2	COOEt	4-CH_3	4-CH_3O-C_6H_4	5	**3b**	72
3	COOEt	H	4-CH_3O-C_6H_4	5	**3c**	71
4	COOEt	H	4-F-C_6H_4	5	**3d**	63
5	COOEt	4-F	3,4-$CH_2O_2C_6H_3$	5	**3e**	64
6	COOEt	4-F	4-NO_2-C_6H_4	5	**3f**	60
7	COOEt	4-CH_3	3,4-$CH_2O_2C_6H_3$	5	**3g**	58
8	COOEt	4-CH_3	4-F-C_6H_4	5	**3h**	63
9	COOEt	4-CH_3	4-Cl-C_6H_4	5	**3i**	68
10	COOEt	4-CH_3	C_6H_5	5	**3j**	69
11	COOEt	4-CH_3	3-NO_2-C_6H_4	5	**3k**	70
12	COOEt	3-CH_3	4-F-C_6H_4	5	**3*l***	56
13	COOEt	4-Cl	3,4-$CH_2O_2C_6H_3$	5	**3m**	59
14	COOEt	4-Cl	4-NO_2-C_6H_4	5	**3n**	57
15	COOEt	4-CH_3	4-pyridyl	5	**3o**	69
16	COOEt	4-CH_3	2-thienyl	5	**3p**	72
17	COOEt	4-CH_3	C_6H_5CH:CH	5	**3q**	72
18	COOEt	4-CH_3	$(CH_3)_3C$	5	**3r**	67
19	COOEt	4-CH_3	$PhCH_2$	5	**3s**	53
20	COOH	4-CH_3	4-Cl-C_6H_4	5	**3t**	65
21	COOH	4-CH_3	4-NO_2-C_6H_4	5	**3u**	70

[a] Isolated yields.

SCHEME 1. Proposed Mechanism for the Aza-Diels−Alder Reaction of Enynes 1 with Arylimines 2



1 2 7 8 9 4 3

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aldehyde, and an arylamine. This reaction provides a highly facile and efficient access to 4-functionalized quinolines and the advantages, such as mild reaction conditions, good to high yields, short reaction time, readily available or cheap starting materials, three-component, one-pot procedure, and wide arylamine and aldehyde components. Moreover, this aza Diels−Alder reaction extends the synthetic utility of versatile polarized ketene dithioacetals. Further research is in progress.

Experimental Section

General Procedure for Three-Component Aza-Diels−Alder Reaction of Terminal Alkynes 1, Arylamines 5, and Aldehydes 6 (3a for example). To a stirred solution of terminal alkyne **1a** (1.0 mmol, 228 mg), 4-nitrobenzaldehyde (2.0 mmol, 302 mg), and 4-methylbenzenamine (2.0 mmol, 214 mg) in CH_2Cl_2 (10 mL) was added CF_3SO_3H (1.0 mmol, 0.087 mL) in one portion. Then the reaction mixture was stirred for 5 min at room temperature. After **1a** was consumed (monitored by TLC), the reaction mixture was poured into water (50 mL), followed by basification with saturated aqueous $NaHCO_3$ solution to adjust the pH value of the solution to 8, and extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to yield the corresponding crude product, which was purified by silica gel chromatography (diethyl ether/hexane = 1/5, v/v) to give 275 mg (59%) of **3a** as a yellow crystal. Mp 182−183 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.04 (t, J = 7.0 Hz, 3H), 2.18−2.22 (m, 2H), 2.54 (s, 3H), 2.82−3.14 (m, 4H), 4.12 (q, J = 7.0 Hz, 2H), 7.50 (s, 1H), 7.59 (d, J = 8.5 Hz, 1H), 7.74 (s, 1H), 8.10 (d, J = 8.5 Hz, 1H), 8.37 (s, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.4, 22.2, 23.4, 29.3, 29.9, 61.0, 121.2, 122.1, 123.8, 124.3 (2C), 126.8, 128.5 (2C), 130.3, 132.7, 137.8, 144.9, 145.9, 147.6, 148.4, 153.6, 161.7, 164.6; IR (KBr, cm^{-1}) 669, 857, 1109, 1192, 1253, 1343, 1490, 1518, 1549, 1684; MS (ESI) m/z 467 $[(M + 1)]^+$. Anal. Calcd (found) for $C_{24}H_{22}N_2O_4S_2$: C, 61.78 (61.93); H, 4.75 (4.78); N, 6.00 (6.13).

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Supporting Information Available: Crystallographic data for **3a** (CIF), experimental procedures, NMR spectra, and characterization data for new compounds **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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