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Acetylenic Ester Promoted Tandem Ring Opening of Dienyl Thiazolidin-4-ones and Cyclizations: A Facile and Chemoselective Synthesis of Functionalized Pyridine-2-carboxylates

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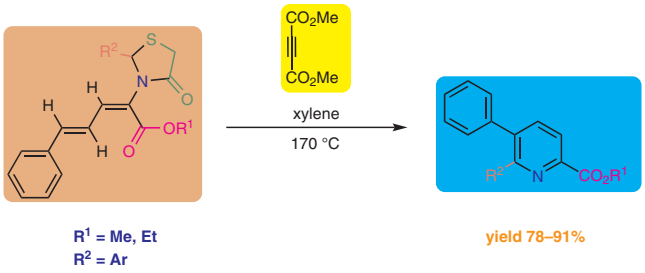

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Abstract Acetylenic ester promoted ring opening of dienyl-thiazolidin-4-ones and subsequent electrocyclization affords 5-phenyl-6-aryl pyridine-2-carboxylates in good to excellent yields.

Key words pyridine-2-carboxylate, dienyl-thiazolidin-4-one, acetylenic ester, cyclization, 5,6-diarylpyridine

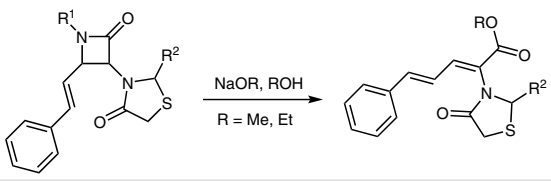
Functionalized pyridines having ester substituents at their 2-position i.e., pyridine-2-carboxylates, are prominent in biologically active molecules.[1–3] Functionalized pyridine-2-carboxylates have been identified as cholecystokinin (CCK1) receptors, cannabinoid receptor type 1 (CB1), and telomerase inhibitors.[4] Similarly, 5,6-diaryl-2-pyridine-carboxamides have been used as urotensin II receptor antagonists and sphingosine-1-phosphate (S1P) receptor agonists.[5,6]

Traditionally, [4+2] cycloadditions of acyclic 2-azadienes have been used as a versatile method for the formation of functionalized pyridines, dihydropyridines, and tetrahydropyridines.[7–11] Barluenga et al. have explored the synthesis of functionalized pyridines utilizing ethoxycarbonyl 2-aza-1,3-butadienes as starting materials.[12] Meurer et al. have reported the synthesis of different 5,6-diarylpyridine carboxylates and carboxamides via cycloaddition of azadiene phosphazene moieties and subsequently studied their human CB1 inverse agonist activity.[13] However, most 2-azadienes are found to be quite unstable and their synthesis requires cumbersome experimental procedures. Moreover, synthesis and cycloadditions of conjugated 2-azadienes have been little explored.

Thiazolidin-4-ones represent an important class of heterocyclic compounds due to their diverse biological activities.[14] Thiazolidin-4-ones have activity profiles, acting as inhibitors of COX-1,[15] HIV-RT,[16] aldose reductase,[17,18] bacterial enzyme MurB and YycG histidine kinase,[19,20] as well as having antidiabetic activity,[21] antitubercular, antifungal, and antihelmintic activities.[21] Thiazolidin-4-ones have also been explored as useful organic synthons of different heterocycles.[22]

There are numerous reports on the acetylenic ester-mediated synthesis of thiazolidin-4-ones using a variety of thioamides and thioureas.[22] However, there are few reports exploring acetylenic ester mediated ring opening/transformations of 4-thiazolidinones. The present manuscript demonstrates acetylenic ester mediated synthetic transformations of dienyl-thiazolidinones[23] leading to a facile synthesis of functionalized pyridine-2-carboxylates. In this transformation, the dienyl-thiazolidinones **1a–h** behave as masked conjugated 2-azadienes and afford a facile and chemoselective formation of pyridine-2-carboxylates mediated by acetylenic esters in good to excellent yields.

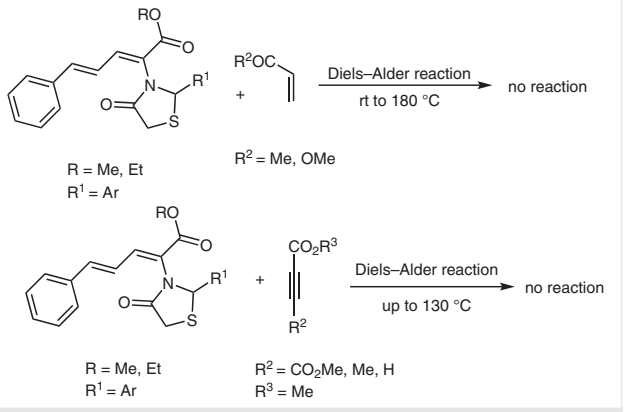
The dienyl thiazolidin-4-ones **1a–h** were prepared by amidiolytic ring opening of 2-azetidinones-3-thiazolidin-4-ones with sodium alkoxide in the corresponding alcohols (Scheme 1).[23] Crystallography data for **1a** established the *trans* conformation of the dienyl thiazolidin-4-one moiety.[23]



Scheme 1 Synthesis of dienyl thiazolidin-4-ones[23]

We started our investigations by attempting Diels–Alder reactions of dienyl thiazolidin-4-one **1a** with electron-deficient dienophiles (such as methyl acrylate, methyl vinyl

ketone, maleic anhydride, *N*-phenyl maleimides) as well as electron-rich dienophiles (such as ethyl vinyl ether, tetrahydropyram, enamines etc.) in different solvents at different temperatures (rt to 180 °C). However, all attempts to achieve the desired reaction proved unsuccessful. Attempts to use activated acetylenes with dienyl thiazolidin-4-one **1a** were also unsuccessful and resulted in the recovery of starting material, even at elevated temperatures (up to 130 °C; Scheme 2). However, reaction of dienyl thiazolidin-4-one **1a** with different acetylenic esters at high temperature (170 °C and above) resulted in the formation of 6-(2,5-dimethylphenyl)-5-phenylpyridine-2-carboxylate (**3a**) in good yield (Scheme 3, Table 1; entry 3).



Scheme 2 Attempted Diels–Alder cycloadditions of dienyl thiazolidin-4-ones

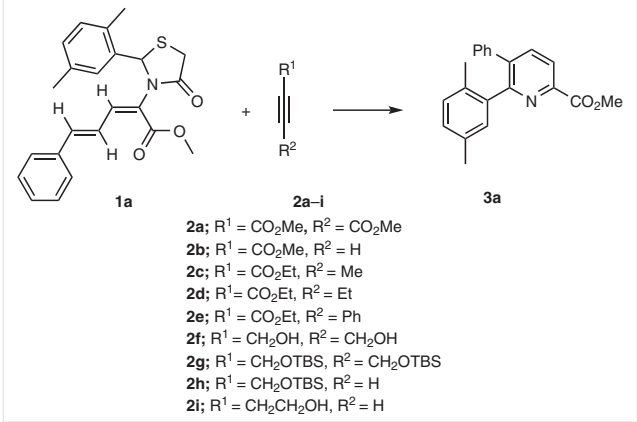
With this encouraging outcome, we concentrated on finding optimal reaction conditions. Several acetylenes were found to be ineffective or less effective for tandem ring opening and electrocyclization reaction leading to low yields of pyridine ester **3** (Table 1, entries 6–8). Starting material **1a** did not afford any functionalized pyridine **3a** using unactivated acetylenes such as butyne-1,4-diol and propargyl alcohol (entries 9–12). The reaction of dienyl thiazolidin-4-one **1a** with methyl propiolate **2b** was also not successful (entry 5). However, the reaction of dienyl thiazolidin-4-one **1a** with activated acetylenes such as DMAD, ethyl but-2-enoate, or ethyl-2-pentenoate resulted in the formation of 5,6-diaryl pyridine-2-carboxylate **3a** in fair to good yields (entries 3–8). Best results in terms of yield for the synthesis of 5,6-diaryl pyridine-2-carboxylate **3a** were observed with the use of DMAD as the activated acetylene in xylene (entries 3 and 4). The reaction gave poor yields at low temperature or with the use of other solvents such as dioxane, 1,2-dichloroethane (DCE) etc. (entries 13 and 14).

The synthesis of 5,6-diaryl pyridine-2-carboxylate (**3a**) is proposed to involve a ring opening of the functionalized dienyl thiazolidin-4-one, resulting in generation of the functionalized conjugated 2-azadeine in situ, which undergoes subsequent electrocyclization to yield final product **3a** at high temperature. The possible by-product of this reaction, the acetylenic ester thioglycolic complex, was never isolated, probably due to its unstable nature at elevated temperature.

Table 1 Optimization of Reaction Conditions for the Synthesis of Methyl 6-(2,5-Dimethylphenyl)-5-phenylpyridine-2-carboxylate (**3a**)

Entry	Alkynes	Solvent	Temp. (°C)	Time (h)[a]	Yield (%)[b]
1	–	toluene	150	24	0
2	–	xylene	180	24	0
3	**2a**	xylene	170	16	91
4	**2a**	xylene	150	24	40
5	**2b**	xylene	190	36	0
6	**2c**	xylene	180	24	39
7	**2d**	xylene	180	24	52
8	**2e**	xylene	180	24	48
9	**2f**	xylene[c]	180	24	0
10	**2g**	xylene[c]	180	24	0
11	**2h**	xylene[c]	180	24	0
12	**2i**	xylene[c]	180	24	0
13	**2a**	dioxane[c]	180	24	5
14	**2a**	DCE[c]	180	24	8

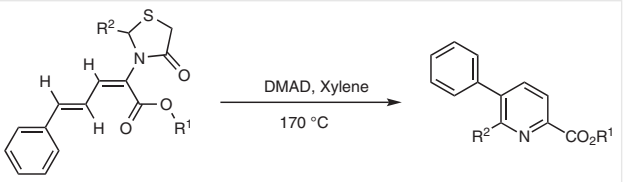
[a] Sealed tube was used.
[b] Isolated yield after purification.
[c] Starting material was recovered unreacted.



Scheme 3 Synthesis of methyl 6-(2,5-dimethylphenyl)-5-phenylpyridine-2-carboxylate **3a**

After optimization of the reaction conditions, these tandem ring opening and electrocyclizations were further explored by employing dienyl-thiazolidin-4-ones with different substituents such as 4-methoxyphenyl, phenyl, 2-furyl and 2 pyridyl at C-5 using DMAD and xylene as solvent at 170 °C (Scheme 4).[24] All the reactions resulted in the formation of pyridine-2-carboxylates **3a–h** in good yields (Table

2). The acetylenic ester promoted tandem ring opening and electrocyclization was found to be well tolerated by a variety of substituents on the dienyl thiazolidin-4-one. The reaction of 2-[2-(2,5-dimethylphenyl)-4-oxo-thiazolidin-3-yl]-5-phenyl-penta-2,4-dienoic acid methyl ester (**1a**) gave the best yield of pyridine-2-carboxylate **3a** (entry 1). 2-[(Furyl/pyridyl)-4-oxo-thiazolidin-3-yl]-5-phenyl-penta-2,4-dienoic acid methyl and ethyl esters **1d/1h** on reaction with DMAD afforded 6-furan-2-yl-5-phenyl-pyridine-2-carboxylic acid alkyl ester (**3d**) and 3-phenyl[2,2′]bipyridinyl-6-carboxylic acid alkyl ester (**3h**), respectively, in good yields (entries 4 and 8).



1a; R^1 = Me, R^2 = 2,5-$Me_2C_6H_3$
1b; R^1 = Me, R^2 = PhNO
1c; R^1 = Me, R^2 = 4-$MeOC_6H_4$
1d; R^1 = Me, R^2 = 2-furyl
1e; R^1 = Et, R^2 = 2,5-$Me_2C_6H_3$
1f; R^1 = Et, R^2 = PhNO
1g; R^1 = Et, R^2 = 4-$MeOC_6H_4$
1h; R^1 = Et, R^2 = pyridyl

3a; R^1 = Me, R^2 = 2,5-$Me_2C_6H_3$
3b; R^1 = Me, R^2 = PhNO
3c; R^1 = Me, R^2 = 4-$MeOC_6H_4$
3d; R^1 = Me, R^2 = 2-furyl
3e; R^1 = Et, R^2 = 2,5-$Me_2C_6H_3$
3f; R^1 = Et, R^2 = PhNO
3g; R^1 = Et, R^2 = 4-$MeOC_6H_4$
3h; R^1 = Et, R^2 = pyridyl

Scheme 4 Synthesis of 5,6-diaryl pyridine-2-carboxylate **3a–h**

Table 2 Synthesis of 5,6-Diaryl Pyridine-2-carboxylates **3a–h**

Entry	S	R_1	Ar	Product[a]	Yield (%)[b]
1	**1a**	Me	2,5-dimethyl phenyl	**3a**	91
2	**1b**	Me	phenyl	**3b**	78
3	**1c**	Me	*p*-methoxy Phenyl	**3c**	83
4	**1d**	Me	2-furyl	**3d**	80
5	**1e**	Et	2,5-dimethyl phenyl	**3e**	87
6	**1f**	Et	phenyl	**3f**	80
7	**1g**	Et	*p*-methoxy Phenyl	**3g**	82
8	**1h**	Et	2-pyridyl	**3h**	81

[a] Xylene was used as solvent, reaction time 16 hours.
[b] Isolated yield after purification.

The functionalized 5,6-disubstituted pyridine-2-carboxylates **3a–h**, thus obtained were characterized on the basis of spectroscopic analysis. For example, 6-(2,5-dimethylphenyl)-5-phenylpyridine-2-carboxylate (**3a**), showed a molecular ion at *m*/*z* 318 in its mass spectrum.[25] The ^{1}H NMR (300 MHz) spectrum of **3a** showed two characteristic doublets (*J* = 7.8 Hz) at δ = 7.88 and 8.19 ppm corresponding to H3 and H4 of the pyridine ring. A singlet at δ = 4.00 ppm corresponded to the methyl ester, and two singlets at δ = 2.25 and 1.83 ppm where assigned to the methyl protons of the 2,5-dimethylphenyl group. ^{13}C NMR analysis demonstrated the presence of a carbonyl carbon at δ = 166.0 ppm (CO of ester) and three aromatic carbons at δ = 140.1, 146.2, and 158.6 ppm corresponding to C-4, C-2 and C-5 of the pyridine ring, respectively, as well as resonances corresponding to the methyl ester at δ = 52.9 ppm and two methyl carbons at δ = 19.1 and 20.8 ppm corresponding to the 2,5-dimethylphenyl group (Figure 1).[24–26]

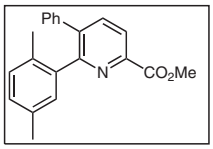
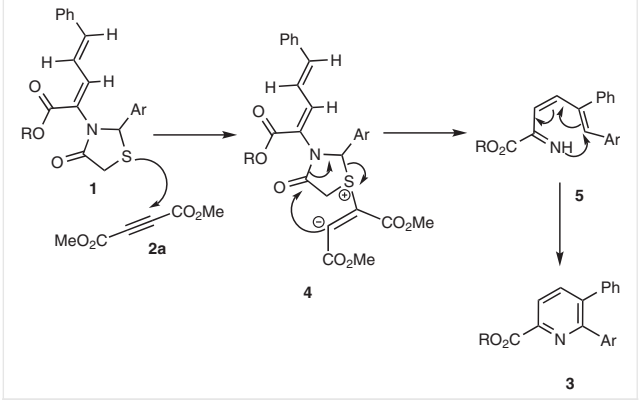


Figure 1 6-(2,5-Dimethylphenyl)-5-phenylpyridine-2-carboxylate (**3a**)

A plausible mechanism for the formation of alkyl 5,6-disubstituted pyridine-2-carboxylates **3a–h** is proposed to involve an initial thia-Michael addition of sulfur from the thiazolidin-4-one ring onto the acetylenic ester to provide a dipolar complex **4**. This is followed by an intramolecular amidolytic ring opening of the thiazolidinone ring by nucleophilic attack of the carbanion generated by initial thia-Michael addition reaction and then a rearrangement to yield the corresponding conjugated 2-azadiene **5**. The conjugated 2-azadiene **5** subsequently undergoes electrocyclic ring closure reaction at high temperature to yield pyridines-2-ester **3** (Scheme 5).



Scheme 5 Plausible mechanisms for the formation of 5,6-diaryl pyridine-2-carboxylate **3a–h**

In conclusion, we have demonstrated the acetylenic ester promoted tandem ring opening and electrocyclization of dienyl-thiazolidin-4-ones for the synthesis of pyridine-2-carboxylates in good to excellent yields. The present methodology represents a facile, chemoselective and metal-free synthesis of substituted pyridines

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591721.

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(24) **General procedure for the preparation of alkyl 6-(aryl)-5-phenylpyridine-2-carboxylate (3a–h)**: To a solution of compound **1** (0.1 g, 0.2544 mmol, 1 equiv) in xylene (10 mL), DMAD (3 equiv) was added and the reaction mixture was heated to 170 °C for 16 h. Progress of the reaction was monitored by TLC taking **1** as the limiting reactant. After completion of reaction, the solvent was removed under reduced pressure. The crude product was purified by column chromatography, using a 20–25% mixture of ethyl acetate in hexane as eluent to obtain **3** as the pure product.

(25) Methyl 6-(2,5-dimethylphenyl)-5-phenylpyridine-2-carboxylate (**3a**): White solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.83 (s, 3 H), 2.25 (s, 3 H), 4.00 (s, 3 H), 6.91 (d, *J* = 7.8 Hz, 1 H), 6.98 (dd, *J* = 7.8, 1.2 Hz, 1 H), 7.04 (s, 1 H), 7.10–7.15 (m, 2 H), 7.20–7.23 (m, 3 H), 7.88 (d, *J* = 7.8 Hz, 1 H), 8.19 (d, *J* = 7.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$): δ = 19.1, 20.8, 52.9, 123.7, 127.7, 128.1, 128.9, 129.1, 129.9, 130.9, 132.6, 134.9, 138.4, 139.0, 140.1, 146.2, 158.6, 166.0; LRMS: *m*/*z* = 318.2 [M+1]; HRMS: *m*/*z* calcd for $C_{21}H_{20}NO_2$ [MH^+]: 318.1494; found: 318.1490.

(26) Ethyl 6-(2,5-dimethylphenyl)-5-phenylpyridine-2-carboxylate (**3e**): Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (t, *J* = 7.8 Hz, 3 H), 1.85 (s, 3 H), 2.22 (s, 3 H), 4.23 (q, *J* = 7.8 Hz, 2 H), 6.94–7.05 (m, 3 H), 7.13–7.25 (m, 5 H), 7.89 (d, *J* = 7.5 Hz, 1 H), 8.16 (d, *J* = 7.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$): δ = 15.5, 18.9, 20.8, 60.5, 123.7, 127.8, 128.3, 128.7, 129.9, 130.4, 131.0, 132.6, 135.2, 138.4, 139.1, 139.9, 146.2, 158.4, 165.7; LRMS: *m*/*z* = 332 [M+1]; HRMS: *m*/*z* calcd for $C_{22}H_{22}NO_2$ [MH^+]: 332.1651; found: 332.1655.