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Regioselective rhodium-catalyzed intermolecular [2+2+2] cycloaddition of alkynes and isocyanates to form pyridones

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ABSTRACT

A highly regioselective rhodium-catalyzed intermolecular [2+2+2] cycloaddition of terminal alkynes with a variety of isocyanates to provide 2- and 4-pyridones has been developed. This reaction proceeds in good to excellent yields and overcomes the problem of dimerization and trimerization through the use of phosphoramidite ligands. A CO migration in the metallacycle is proposed to account for the formation of 4-pyridone.

1. Introduction

Pyridones display a variety of interesting biological properties including anticancer, antiviral, and antibacterial activity.[1] Pyridones can be synthesized in a variety of ways; the most common strategies are transformations from other heterocycles, often pyridines, and condensation reactions.[1b] Most of these strategies allow for regiocontrolled syntheses of pyridones, but often require multiple transformations to reach the desired product. Cycloadditions using three π-components are a rapid and efficient route to heterocycles. This reaction manifold has been applied to the synthesis of pyridones and a variety of other heterocycles.[2]

Yamazaki and Hoberg pioneered metal-catalyzed pyridone formation from 2 equiv of alkyne and 1 equiv of isocyanate. Yamazaki used cobalt to catalyze the [2+2+2] cycloaddition of methyl phenylpropiolate and methyl isocyanate to form a mixture of pyridone isomers.[3] Use of methyl propiolate, a terminal alkyne, in the reaction provided hydantoin products instead of pyridones. Hoberg used a nickel catalyst to synthesize pyridones from symmetrical and unsymmetrical alkynes and isocyanates (Scheme 1).[4] Using stoichiometric nickel, these workers were able to isolate metallacycles presumably involved in the catalytic cycle. In addition to these studies, it was demonstrated that pyrimidine-diones could be synthesized from 2 equiv of isocyanate and 1 equiv of alkyne.[4] Vollhardt developed a regioselective partially intermolecular cobalt-catalyzed cycloaddition by tethering an alkyne to either another alkyne or an isocyanate (Scheme 1).[5] This strategy surmounts the problem associated with multiple regioisomers and this methodology was applied toward the synthesis of the natural product camptothecin. Flynn initially demonstrated rhodium's ability to catalyze pyridone formation, but substituted benzenes[6] were the major product.[7] Terminal alkynes present another issue when attempting metal-catalyzed cycloadditions, because they are known to undergo metal-catalyzed dimerization to produce enynes.[8]

Several researchers have expanded on these initial results by examining different metals and tethered substrates. Itoh has demonstrated ruthenium's ability as an efficient cycloaddition catalyst of α,ω-diynes and exogenous isocyanates to afford pyridones (Scheme 1).[9] Louie has shown that nickel complexes modified with a carbene or phosphorous ligand provide catalysts that are selective for either pyrimidine-diones or pyridones.[10] Kondo improved on Flynn's initial work with rhodium to form both pyridones and pyrimidine-diones using symmetrical alkynes.[11] In an effort to incorporate three different π-components, Takahashi developed a highly regioselective method to synthesize pyridones and other heterocycles that overcame the problem with regioisomers and allowed for the incorporation of three π-components, but uses stoichiometric amounts of zirconium and nickel.[12]

Recently, Tanaka has used cationic rhodium modified by enantioenriched ligands to synthesize pyridones containing axial chirality from tethered diynes (Scheme 1).[13] Tanaka is also one of the few who reports metal-catalyzed cycloadditions with terminal alkynes and isocyanates.[4a,13a,14] These researchers observed formation of multiple regioisomers when 1-dodecyne and benzyl isocyanate were subjected to their reaction conditions using cationic rhodium (Scheme 2). Better selectivity was observed with different alkynes: cyclohexenylacetylene furnished primarily 4,5-subsitituted pyridone and trimethylsilylacetylene furnished only 3,5-substituted pyridone (Scheme 2).

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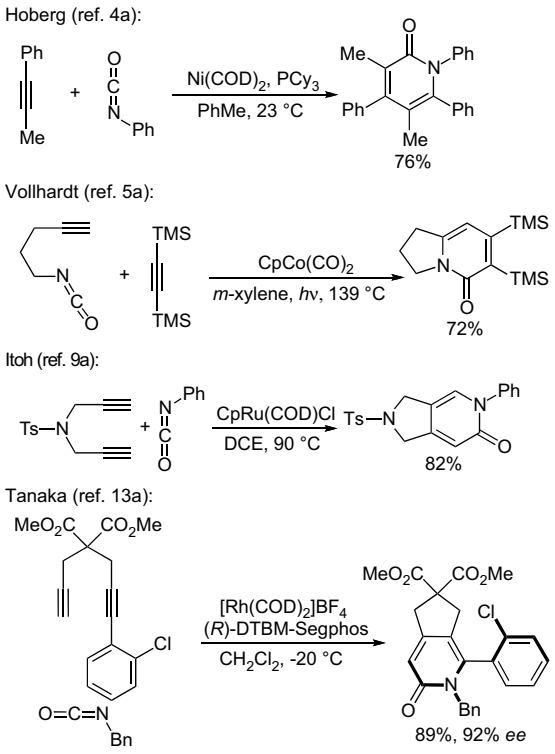
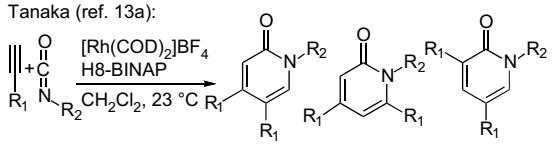
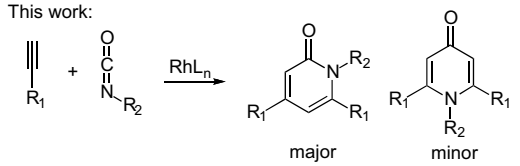


Scheme 1. Precedent for metal-catalyzed [2+2+2] pyridone forming cycloadditions.

Our interest in pyridone synthesis was piqued by its errant formation in our studies on enantioselective rhodium-catalyzed [2+2+2] cycloadditions of alkynes with an isocyanate tethered to an alkene.[15] We investigated this reaction further to determine its scope, and were pleased to find this [2+2+2] cycloaddition proceeds smoothly with terminal alkynes without issues of dimerization or trimerization. More importantly, this reaction proves highly regioselective furnishing exclusively 4,6-substituted pyridones despite a range of electronically and sterically different alkynes (Scheme 2). During the course of our investigation, we were surprised to isolate 4-pyridones generated from an apparent CO migration, the formation of which is unprecedented in [2+2+2] cycloadditions of alkynes and isocyanates (Scheme 2). Herein, we describe the rhodium-catalyzed [2+2+2] cycloaddition of terminal alkynes with various isocyanates to afford novel 2- and 4-pyridones



R_1	R_2		yield	
n-Dec	Bn	31%	30%	<5%
	Bn	47%	1%	-
TMS	*n*-Bu	-	-	65%



Scheme 2. Rhodium-catalyzed [2+2+2] pyridone forming cycloadditions with terminal alkynes.

in good to excellent yields in a regioselective manner using phosphoramidite ligands.

2. Results and discussion

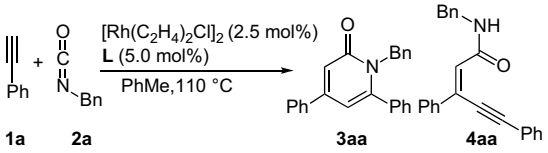
2.1. Ligand screen

We initially found that $[Rh(C_2H_4)_2Cl]_2$ (2.5 mol %) and triphenylphosphine (5 mol %) catalyze the reaction between phenyl acetylene **1a** and benzyl isocyanate **2a** to yield 2-pyridone **3aa** in poor yield along with an undesired enynamide **4aa** (Table 1, entry 1).[16] An attempt to optimize reaction conditions using different ligands was undertaken. Use of electron-deficient and electron-rich triaryl phosphine ligands gives marginally better yields of both **3aa** and **4aa**, but yields of the desired product remain low (entries 2 and 3). We observe an increase in desired product and a decrease in undesired product by using MonoPhos, *rac*-**L1**, as a ligand (entry 4). Excited by this dramatic improvement, additional phosphoramidites were screened; these ligands prove better than the triaryl phosphine ligands in both yield and selectivity for the desired product with *rac*-**L2** being the optimal (entry 5).

2.2. Alkyne scope

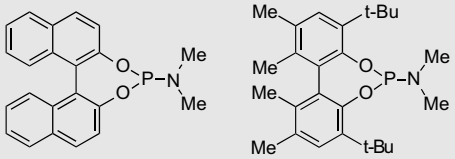
The alkyne scope was examined using benzyl isocyanate **2a** and is summarized in Table 2. Use of the electron-deficient alkyne **1b** gives a moderate yield, while the electron-rich alkyne **1c** affords an excellent yield of **3** (entries 2 and 3). Methoxy substitution on various positions on the aromatic ring affords the corresponding 2-pyridones smoothly (entries 4 and 5). A slightly lower yield at the *meta* position can be attributed to methoxy being electron-withdrawing at this position and a lower yield at the *ortho* position can be attributed to sterics. Other conjugated alkynes, **1f** and **1g**, provide excellent yields (entries 6 and 7). Alkyl alkynes show a lower overall reactivity, while benzyl alkyne **1i** promotes the formation of **4ia** (entries 8 and 9). Ethynyl ethers are tolerated in the reaction, but produce a yield similar to alkyl alkynes (entry 10). The use of diynes in the reaction does not provide pyridone product; dipropargyl ether produces the arene dimer and 1,6-heptadiyne affords a mixture of inseparable products. The electron-deficient alkyne

Table 1
Ligand screen[a]



1a **2a** **3aa** **4aa**

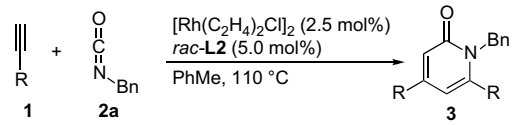
Entry	**L**	2-Pyridone[b]	Enynamide[b]
1	PPh_3	5%	13%
2	$P(4\text{-MeO-}C_6H_4)_3$	11%	18%
3	$P(4\text{-}CF_3\text{-}C_6H_4)_3$	22%	12%
4	*rac*-**L1**	39%	—
5	***rac*-L2**	**68%**	**6%**

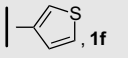
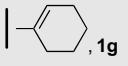


rac-**L1** *rac*-**L2**

[a] Conditions: **1** (3 equiv), **2**, Rh catalyst (2.5 mol %), **L** (5 mol %) in PhMe reflux for 12 h.
[b] Isolated yield.

Table 2
Terminal alkyne scope[a]

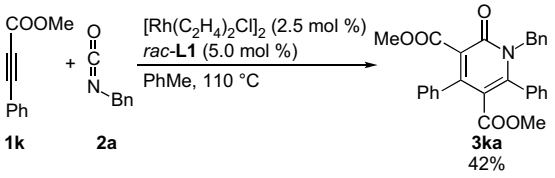


Entry	R	Product	Yield[b]
1	Ph, **1a**	**3aa**	68%
2	*m*-F-C_6H_4, **1b**	**3ba**	46%
3	*p*-MeO-C_6H_4, **1c**	**3ca**	88%
4	*m*-MeO-C_6H_4, **1d**	**3da**	73%
5	*o*-MeO-C_6H_4, **1e**	**3ea**	54%
6	 **1f**	**3fa**	80%
7	 **1g**	**3ga**	92%
8	*n*-Hex, **1h**	**3ha**	38%
9	Bn, **1i**	**3ia**	19%[c]
10	OEt, **1j**	**3ja**	38%

[a] See Table 1.
[b] See Table 1.
[c] Isolated 16% of enynamide **4ia**.

methyl propiolate fails to yield any pyridone product. It is significant to note that all terminal alkynes provide the same single regioisomer and products from trimerization and dimerization of either isocyanates or alkynes are not observed.[17,18]

Efforts to incorporate internal alkynes such as diphenyl acetylene, 5-decyne, and dimethyl acetylenedicarboxylate were unsuccessful. Despite screening a variety of ligands, these alkynes do not yield pyridone products under these conditions. One internal alkyne that affords pyridone is methyl phenylpropiolate **1k** with *rac*-**L1** as a ligand (Eq. 1). The more sterically hindered ligand, *rac*-**L2**, does not provide product. We assigned the regioisomer through comparison to a similar pyridone in the literature.[3a] Saponification of the ester groups and subsequent decarboxylation of the resulting acids produced pyridone **3aa** confirming our original assignment.



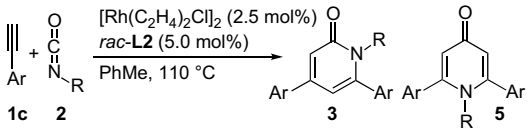
(1)

2.3. Isocyanate scope

We found that reacting 4-methoxyphenyl acetylene **1c** and benzyl isocyanate **2a** provides an excellent yield of pyridone; this alkyne was chosen to explore the scope of isocyanates that could be used in this system (Table 3). During the exploration with different isocyanates, it was found that a CO migration could occur giving 4-pyridone **5** in addition to 2-pyridone **3**. Benzyl isocyanate and PMB-isocyanate both give excellent yields of 2-pyridone with only trace amounts of 4-pyridone (entries 1 and 2). Aryl isocyanates afford good combined yields of pyridone (entries 3–5). As the electron-withdrawing ability of the aryl isocyanates increases, an increase in the amount of 4-pyridone is observed. Despite this trend, *para*-trifluoromethyl phenyl isocyanate only provides a ~1:1 ratio of 2-pyridone/4-pyridone. Alkyl isocyanates afford good combined yields (entries 6 and 7).

The proposed mechanism for pyridone formation is shown in Scheme 3. Both products can be formed from metallacycle ***A*** where

Table 3
Isocyanate scope[a]

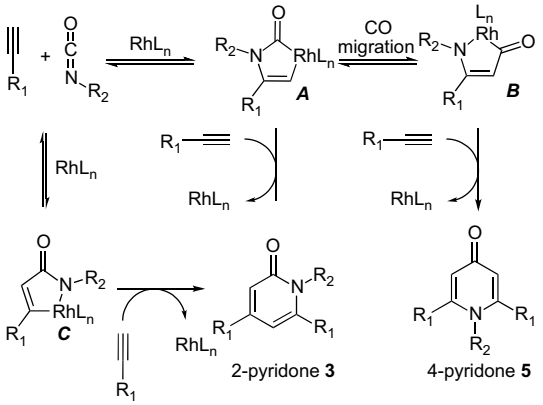


Ar = *p*-MeO-C_6H_4

Entry	R	Product	Yield **3**[b]	Yield **5**[b]
1	Bn, **2a**	**ca**	88%	4%
2	PMB, **2b**	**cb**	79%	4%
3	Ph, **2c**	**cc**	37%	20%
4	*p*-MeO-C_6H_4, **2d**	**cd**	43%	19%
5	*p*-CF_3-C_6H_4, **2e**	**ce**	34%	30%
6	*n*-Hex, **2f**	**cf**	52%	18%
7	Cy, **2g**	**cg**	55%	12%

[a] See Table 1.
[b] See Table 1.

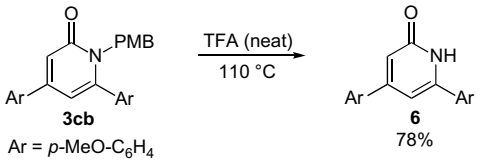
carbon–nitrogen bond formation occurs first. Addition of a second equivalent of alkyne and reductive elimination of the rhodium catalyst would provide 2-pyridone **3**. CO migration in metallacycle ***A*** to furnish metallacycle ***B*** and subsequent alkyne addition followed by reductive elimination would afford 4-pyridone **5**. This pathway is consistent with our previous results using alkenyl isocyanates and alkynes.[15] The formation of **5** is most pronounced when R_2 is electron-deficient (see Table 3). Although this pathway accounts for both products, an alternate route to 2-pyridones cannot be ruled out. Formation of metallacycle ***C***, where carbon–carbon bond formation is the first step, can be followed by alkyne insertion and reductive elimination to afford 2-pyridone.[19] This metallacycle would not be able to furnish 4-pyridone and thus suggests that metallacycle ***A*** from carbon–nitrogen bond formation occurring first is more probable.



Scheme 3. Proposed mechanism.

2.4. PMB deprotection

As seen in Table 3, pyridone **3cb** was synthesized in good yield. The PMB-protected amide of this pyridone can be cleaved in neat TFA to afford free pyridone **6** (Eq. 2).[20] Free pyridones have been reacted with triflic anhydride to make triflated pyridines, which have been successfully subjected to a variety of coupling reactions and reduced to the pyridine.[21]



(2)

3. Conclusion

In conclusion, we have shown that 2- and 4-pyridones can be accessed in a highly regioselective manner in good to excellent yields using a rhodium-catalyzed [2+2+2] cycloaddition. These catalytic conditions do not promote dimerization or trimerization of terminal alkynes. A variety of isocyanates and alkynes participate in this reaction and conjugated alkynes provide the best yields. This catalytic system provides a regioselective method to synthesize 4,6-substituted 2-pyridones from readily available precursors.

4. Experimental

4.1. General

All reactions were carried out under an atmosphere of argon in oven-dried glassware with magnetic stirring. Toluene was degassed with argon and passed through one column of neutral alumina and one column of Q5 reactant. Column chromatography was performed on Silicycle Inc. silica gel 60 (230–400 mesh). Thin layer chromatography was performed on Silicycle Inc. 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light (254 nm), potassium permanganate, and/or ceric ammonium nitrate.

^{1}H NMR and ^{13}C NMR spectra were obtained in $CDCl_3$ at ambient temperature and chemical shifts are expressed in parts per million (δ, ppm). Proton chemical shifts are referenced to 7.26 ppm ($CHCl_3$) and carbon chemical shifts are referenced to 77.0 ppm ($CDCl_3$). Data reporting uses the following abbreviations: s, singlet; br s, broad singlet; d, doublet; dd, doublet of doublets; t, triplet; m, multiplet; and *J*, coupling constant in hertz.

Alkynes **1a**–**1j**, isocyanates **2a**, **2c**–**2g**, triphenylphosphine, tris(4-methoxyphenyl)phosphine, and TFA were purchased from Aldrich Chemicals Co. and used without further purification. $[Rh(C_2H_4)_2Cl]_2$ and tris(4-trifluoromethylphenyl)phosphine were purchased from Strem Chemical, Inc. and used without further purification. Isocyanate **2b** was synthesized by converting 4-methoxyphenylacetic acid to the acyl azide with diphenylphosphoryl azide and gentle heating of the acyl azide neat to afford the isocyanate as described in previous work.[15c] *rac*-**L2** was synthesized as described in the literature.[22]

4.2. Typical pyridone reaction

To an oven-dried round bottom flask, $[Rh(C_2H_4)_2Cl]_2$ (2.3 mg, 0.006 mmol) and *rac*-**L2** (5.1 mg, 0.012 mmol) were added and an oven-dried reflux condenser was fitted in an inert atmosphere (N_2) glove box. After removal from the glove box, 1 ml of toluene was added via syringe and allowed to stir for 15 min at 23 °C under Ar flow. To this solution, a solution of alkyne **1** (0.720 mmol) and isocyanate **2** (0.240 mmol) in 1 ml toluene was added via syringe. After rinsing the condenser with additional 6 ml toluene, the solution was heated to 110 °C in an oil bath and maintained at reflux for 12 h. The reaction mixture was allowed to cool to 23 °C, concentrated in vacuo, and purified by flash chromatography (gradient elution typically 1:1 hex/EtOAc, difficult separations used 95:5 CH_2Cl_2/EtOAc, and 4-pyridones required elution with 10:1 EtOAc/MeOH). Evaporation of solvent afforded the analytically pure compounds.

4.3. Deprotection of PMB-protected pyridone

Compound **3cb** (19.6 mg, 0.046 mmol) was dissolved in neat TFA and added to an oven-dried pressure tube. The reaction vessel was sealed and heated to 110 °C for 12 h. The resulting solution was allowed to cool to 23 °C, concentrated in vacuo, and purified with flash chromatography (gradient elution 10:1 EtOAc/MeOH). The isolated salt was dissolved in concd aq NaOH solution and extracted three times with EtOAc. The resulting solution was dried and concentrated in vacuo to afford **6** (78%).

4.4. Characterization of 2-pyridones

*4.4.1. 1-Benzyl-4,6-diphenyl-2-pyridone (**3aa**)*

^{1}H NMR δ 7.62 (m, 2H), 7.43 (m, 4H), 7.34 (m, 2H), 7.19 (m, 5H), 6.94 (m, 3H), 6.40 (d, *J*=2.1 Hz, 1H), 5.22 (s, 2H). ^{13}C NMR δ 163.5, 150.6, 149.8, 137.2, 137.1, 135.2, 129.4, 129.1, 128.8, 128.6, 128.2, 127.0, 126.8, 126.7, 115.6, 107.8, 48.4. R_f=0.24 (2:1 hex/EtOAc). IR (NaCl, $CHCl_3$) 3053, 3027, 2996, 1650, 1603, 1583, 1532, 1486, 748, 723, 697. HRMS (ESI) $[C_{24}H_{20}NO]^+$ calcd 338.15002, found 338.15438.

*4.4.2. 1-Benzyl-4,6-bis(3-fluorophenyl)-2-pyridone (**3ba**)*

^{1}H NMR δ 7.41 (m, 2H), 7.31 (m, 2H), 7.21 (m, 3H), 7.13 (m, 2H), 6.96 (m, 1H), 6.91 (m, 3H), 6.86 (m, 1H), 6.33 (d, *J*=2.1 Hz, 1H), 5.20 (s, 2H). ^{13}C NMR δ 164.2, 163.4, 163.3, 161.8, 160.9, 149.4, 148.7, 139.4, 139.4, 136.9, 136.8, 130.6, 130.5, 130.1, 130.0, 128.4, 127.2, 126.8, 124.5, 122.4, 116.5, 116.3, 116.2, 116.0, 113.9, 113.6, 107.5, 48.5. R_f=0.24 (2:1 hex/EtOAc). IR (NaCl, $CHCl_3$) 3063, 3027, 3001, 2955, 1660, 1588, 1537, 1475, 1265, 784, 692. HRMS (ESI) $[C_{24}H_{18}F_2NO]^+$ calcd 374.13118, found 374.13546.

*4.4.3. 1-Benzyl-4,6-bis(4-methoxyphenyl)-2-pyridone (**3ca**)*

^{1}H NMR δ 7.58 (m, 2H), 7.21 (m, 3H), 7.10 (m, 2H), 6.96 (m, 4H), 6.87 (d, *J*=2.1 Hz, 1H), 6.85 (m, 2H), 6.38 (d, *J*=2.1 Hz, 1H), 5.21 (s, 2H), 3.84 (s, 3H), 3.82 (s, 3H). ^{13}C NMR δ 163.7, 160.7, 160.0, 150.0, 149.6, 137.3, 130.0, 129.4, 128.2, 128.0, 127.7, 126.9, 126.7, 114.2, 114.1, 113.6, 107.8, 55.2, 48.4. R_f=0.23 (1:1 hex/EtOAc). IR (NaCl, $CHCl_3$) 3063, 3032, 2960, 2838, 1650, 1608, 1511, 1250, 1030, 830, 728. HRMS (ESI) $[C_{26}H_{24}NO_3]^+$ calcd 398.17115, found 398.17577.

*4.4.4. 1-Benzyl-4,6-bis(3-methoxyphenyl)-2-pyridone (**3da**)*

^{1}H NMR δ 7.36 (t, *J*=8.0 Hz, 1H), 7.29–7.14 (m, 6H), 6.96 (m, 4H), 6.92 (d, *J*=2.1 Hz, 1H), 6.81 (m, 1H), 6.60 (m, 1H), 6.40 (d, *J*=2.1 Hz, 1H), 5.20 (s, 2H), 3.85 (s, 3H), 3.56 (s, 3H). ^{13}C NMR δ 163.6, 160.0, 159.1, 150.6, 149.8, 138.8, 137.4, 136.4, 130.0, 129.5, 128.4, 127.0, 126.8, 120.8, 119.1, 115.8, 115.7, 115.1, 113.6, 112.1, 107.6, 55.3, 55.0, 48.7. R_f=0.26 (95:5 CH_2Cl_2/EtOAc). IR (NaCl, $CHCl_3$) 3063, 3027, 3001, 2955, 2827, 1654, 1588, 1532, 1491, 1286, 1030, 733, 702. HRMS (ESI) $[C_{26}H_{24}NO_3]^+$ calcd 398.17115, found 398.17625.

*4.4.5. 1-Benzyl-4,6-bis(2-methoxyphenyl)-2-pyridone (**3ea**)*

^{1}H NMR δ 7.33 (m, 3H), 7.10 (m, 3H), 6.95 (m, 3H), 6.86 (m, 5H), 6.29 (d, *J*=2.0 Hz, 1H), 5.44 (d, *J*=14.8 Hz, 1H), 4.71 (d, *J*=14.8 Hz, 1H), 3.78 (s, 3H), 3.60 (s, 3H). ^{13}C NMR δ 163.7, 156.6, 156.4, 149.0, 145.5, 137.4, 131.0, 130.8, 130.2, 130.1, 127.9, 127.5, 127.0, 126.7, 124.5, 120.7, 120.3, 118.7, 111.2, 110.5, 55.5, 55.1, 48.2. R_f=0.28 (1:1 hex/EtOAc). IR (NaCl, $CHCl_3$) 3063, 3006, 2966, 2827, 1650, 1603, 1573, 1245, 1020. HRMS (ESI) $[C_{26}H_{24}NO_3]^+$ calcd 398.17115, found 398.17582.

*4.4.6. 1-Benzyl-4,6-di(thiophen-3-yl)-2-pyridone (**3fa**)*

^{1}H NMR δ 7.61 (dd, *J*=2.7, 1.6 Hz, 1H), 7.39 (m, 2H), 7.32 (dd, *J*=5.0, 3.0 Hz, 1H), 7.22 (m, 3H), 7.16 (dd, *J*=3.0, 1.3 Hz, 1H), 6.98 (m, 2H), 6.91 (dd, *J*=5.0, 1.3 Hz, 1H), 6.89 (d, *J*=2.0 Hz, 1H), 6.45 (d, *J*=2.1 Hz, 1H), 5.22 (s, 2H). ^{13}C NMR δ 163.7, 145.1, 144.6, 138.6, 137.2, 135.4, 128.4, 127.8, 127.0, 126.9, 126.5, 126.2, 125.9, 125.6, 123.9, 114.6, 107.6, 48.5. R_f=0.13 (2:1 hex/EtOAc). IR (NaCl, $CHCl_3$) 3104, 3083, 3022, 3001, 2950, 1660, 1578, 1552, 851, 789, 728. HRMS (ESI) $[C_{20}H_{15}NOS_2]^+$ calcd 350.06286, found 350.06775.

*4.4.7. 1-Benzyl-4,6-dicyclohexenyl-2-pyridone (**3ga**)*

^{1}H NMR δ 7.21 (m, 2H), 7.14 (m, 1H), 7.07 (m, 2H), 6.44 (d, *J*=2.0 Hz, 1H), 6.33 (m, 1H), 6.07 (d, *J*=2.1 Hz, 1H), 5.54 (m, 1H), 5.15

(s, 2H), 2.26 (m, 2H), 2.16 (m, 2H), 1.98 (m, 2H), 1.89 (m, 2H), 1.69 (m, 2H), 1.57 (m, 6H). ^{13}C NMR δ 164.1, 151.4, 150.8, 137.9, 133.9, 133.6, 130.5, 129.4, 128.2, 126.8, 126.6, 112.6, 103.7, 47.9, 29.6, 26.0, 25.9, 24.9, 22.6, 22.3, 21.8, 21.4. R_f=0.17 (2:1 hex/EtOAc). IR (NaCl, $CHCl_3$) 3068, 3022, 2930, 2853, 2827, 1644, 1568, 1521, 1429, 748, 687. HRMS (ESI) $[C_{24}H_{28}NO]^+$ calcd 346.21262, found 346.21702.

*4.4.8. 1-Benzyl-4,6-dihexyl-2-pyridone (**3ha**)*

^{1}H NMR δ 7.28 (m, 2H), 7.21 (m, 1H), 7.10 (m, 2H), 6.38 (s, 1H), 5.91 (d, J=1.7 Hz, 1H), 5.32 (s, 2H), 2.47 (t, J=7.8 Hz, 2H), 2.41 (t, J=7.6 Hz, 2H), 1.58 (m, 2H), 1.51 (m, 2H), 1.27 (m, 12H), 0.88 (t, J=6.8 Hz, 3H), 0.86 (t, J=6.9 Hz, 3H). ^{13}C NMR δ 164.0, 155.0, 149.3, 136.9, 128.6, 127.1, 126.2, 115.4, 107.8, 46.2, 35.3, 32.8, 31.5, 31.4, 29.1, 28.8, 28.5, 22.5, 22.4, 14.0, 13.9. R_f=0.22 (4:1 hex/EtOAc). IR (NaCl, $CHCl_3$) 3063, 3027, 2960, 2930, 2853, 1665, 1588, 1547, 1450, 728. HRMS (ESI) $[C_{24}H_{36}NO]^+$ calcd 354.27522, found 354.27904.

*4.4.9. 1,4,6-Tribenzyl-2-pyridone (**3ia**)*

^{1}H NMR δ 7.35–7.20 (m, 11H), 7.11 (m, 2H), 7.04 (m, 2H), 6.42 (s, 1H), 5.87 (d, J=1.8 Hz, 1H), 5.18 (s, 2H), 3.78 (s, 2H), 3.77 (s, 2H). ^{13}C NMR δ 164.1, 153.0, 147.1, 137.9, 136.7, 136.2, 129.1, 129.0, 128.8, 128.7, 128.1, 127.2, 127.1, 126.7, 126.1, 117.1, 110.1, 46.2, 41.3, 39.2. R_f=0.12 (95:5 CH_2Cl_2/EtOAc). IR (NaCl, $CHCl_3$) 3058, 3022, 2996, 1660, 1588, 1542, 1486, 723, 692. HRMS (ESI) $[C_{26}H_{24}NO]^+$ calcd 366.18132, found 366.18559.

*4.4.10. 1-Benzyl-4,6-diethoxy-2-pyridone (**3ja**)*

^{1}H NMR δ 7.26 (m, 5H), 5.69 (d, J=2.0 Hz, 1H), 5.21 (br s, 3H), 3.97 (m, 4H), 1.36 (m, 6H). ^{13}C NMR δ 168.3, 163.6, 156.8, 137.5, 128.2, 128.0, 127.1, 89.9, 79.6, 65.3, 63.9, 43.8, 14.3, 14.0. R_f=0.24 (1:1 hex/EtOAc). IR (NaCl, $CHCl_3$) 3063, 3032, 2976, 2935, 2894, 1660, 1593, 1547, 1255, 1189, 1112, 738. HRMS (ESI) $[C_{16}H_{20}NO_3]^+$ calcd 274.13985, found 274.14439.

*4.4.11. Dimethyl 1-benzyl-2-oxo-4,6-diphenyl-1,2-dihydropyridine-3,5-dicarboxylate (**3ka**)*

^{1}H NMR δ 7.44–7.31 (m, 8H), 7.21 (m, 3H), 7.11 (m, 2H), 6.90 (m, 2H), 5.15 (s, 2H), 3.64 (s, 3H), 3.05 (s, 3H). ^{13}C NMR δ 166.1, 165.9, 159.3, 149.4, 148.4, 136.0, 135.5, 132.0, 129.8, 128.8, 128.8, 128.3, 128.2, 128.1, 127.4, 127.3, 127.2, 124.3, 116.0, 52.3, 51.8, 49.3. R_f=0.38 (2:1 hex/EtOAc). IR (NaCl, $CHCl_3$) 3063, 3032, 2950, 1736, 1644, 1532, 1486, 1429, 1250, 1214, 1132, 764, 697. HRMS (ESI) $[C_{28}H_{24}NO_5]^+$ calcd 454.16098, found 454.16491.

*4.4.12. 1-(4-Methoxybenzyl)-4,6-(4-methoxyphenyl)-2-pyridone (**3cb**)*

^{1}H NMR δ 7.57 (m, 2H), 7.11 (m, 2H), 6.96 (m, 2H), 6.88 (m, 4H), 6.83 (d, J=2.1 Hz, 1H), 6.74 (m, 2H), 6.34 (d, J=2.1 Hz, 1H), 5.14 (s, 2H), 3.84 (s, 6H), 3.75 (s, 3H). ^{13}C NMR δ 163.7, 160.6, 160.0, 158.4, 149.8, 149.5, 130.0, 129.5, 128.3, 127.9, 127.8, 114.2, 113.5, 107.6, 55.2, 55.0, 47.7. R_f=0.18 (1:1 hex/EtOAc). IR (NaCl, $CHCl_3$) 3063, 3001, 2955, 2832, 1650, 1608, 1506, 1245, 1030, 820, 748. HRMS (ESI) $[C_{27}H_{26}NO_4]^+$ calcd 428.18171, found 428.18407.

*4.4.13. 4,6-Bis(4-methoxyphenyl)-1-phenyl-2-pyridone (**3cc**)*

^{1}H NMR δ 7.62 (m, 2H), 7.26 (m, 3H), 7.11 (m, 2H), 7.05 (m, 2H), 6.99 (m, 2H), 6.85 (d, J=2.0 Hz, 1H), 6.69 (m, 2H), 6.50 (d, J=2.0 Hz, 1H), 3.86 (s, 3H), 3.73 (s, 3H). ^{13}C NMR δ 163.8, 160.8, 159.4, 150.7, 149.1, 138.7, 130.3, 129.7, 129.0, 128.7, 128.2, 128.1, 127.8, 114.6, 114.4, 113.3, 107.2, 55.4, 55.1. R_f=0.68 (2:1 hex/EtOAc). IR (NaCl, $CHCl_3$) 3063, 3037, 2960, 2935, 2838, 1655, 1603, 1506, 1250, 1025, 820, 728. HRMS (ESI) $[C_{25}H_{22}NO_3]^+$ calcd 384.15550, found 384.16035.

*4.4.14. 1,4,6-Tris(4-methoxyphenyl)-2-pyridone (**3cd**)*

^{1}H NMR δ 7.62 (m, 2H), 7.07 (m, 2H), 7.02 (m, 2H), 6.98 (m, 2H), 6.84 (d, J=2.0 Hz, 1H), 6.79 (m, 2H), 6.71 (m, 2H), 6.48 (d, J=2.0 Hz, 1H), 3.86 (s, 3H), 3.75 (s, 3H), 3.74 (s, 3H). ^{13}C NMR δ 164.0, 160.7, 159.3, 158.6, 150.5, 149.4, 131.3, 130.3, 129.9, 129.7, 128.3, 128.0, 114.4, 114.3, 114.0, 113.3, 107.1, 55.3, 55.2, 55.1. R_f=0.40 (EtOAc). IR (NaCl, $CHCl_3$) 3037, 2996, 2960, 2838, 1650, 1608, 1506, 1250, 1030, 825, 723. HRMS (ESI) $[C_{26}H_{24}NO_4]^+$ calcd 414.16606, found 414.17046.

*4.4.15. 4,6-Bis(4-methoxyphenyl)-1-(4-(trifluoromethyl)phenyl)-2-pyridone (**3ce**)*

^{1}H NMR δ 7.62 (m, 2H), 7.55 (m, 2H), 7.25 (m, 2H), 7.01 (m, 4H), 6.84 (d, J=1.9 Hz, 1H), 6.71 (m, 2H), 6.54 (d, J=1.9 Hz, 1H), 3.86 (s, 3H), 3.75 (s, 3H). ^{13}C NMR δ 163.8, 161.2, 159.9, 151.4, 148.8, 142.1, 130.5, 130.2, 129.9, 129.6, 128.4, 127.8, 126.1, 126.0, 114.7, 114.6, 113.8, 108.0, 55.6, 55.4. R_f=0.19 (2:1 hex/EtOAc). IR (NaCl, $CHCl_3$) 3063, 3001, 2955, 2832, 1660, 1598, 1501, 1250, 1117, 825, 723. HRMS (ESI) $[C_{26}H_{21}F_3NO_3]^+$ calcd 452.14288, found 452.14608.

*4.4.16. 1-Hexyl-4,6-bis(4-methoxyphenyl)-2-pyridone (**3cf**)*

^{1}H NMR δ 7.53 (m, 2H), 7.29 (m, 2H), 6.95 (m, 4H), 6.74 (d, J=2.0 Hz, 1H), 6.29 (d, J=2.0 Hz, 1H), 3.88 (t, J=7.9 Hz, 2H), 3.86 (s, 3H), 3.82 (s, 3H), 1.56 (m, 2H), 1.14 (m, 6H), 0.79 (t, J=7.0 Hz, 3H). ^{13}C NMR δ 163.5, 160.6, 160.0, 149.5, 149.2, 129.9, 129.7, 128.1, 127.9, 114.2, 113.8, 107.4, 55.3, 55.2, 45.4, 31.0, 28.6, 26.3, 22.3, 13.9. R_f=0.12 (2:1 hex/EtOAc). IR (NaCl, $CHCl_3$) 3037, 3001, 2955, 2925, 2853, 2827, 1660, 1614, 1592, 1511, 1301, 1245, 1178, 1030, 825, 723. HRMS (ESI) $[C_{25}H_{30}NO_3]^+$ calcd 392.21810, found 392.22287.

*4.4.17. 1-Cyclohexyl-4,6-bis(4-methoxyphenyl)-2-pyridone (**3cg**)*

^{1}H NMR δ 7.52 (m, 2H), 7.27 (m, 2H), 6.97 (m, 2H), 6.93 (m, 2H), 6.65 (d, J=2.2 Hz, 1H), 6.23 (d, J=2.2 Hz, 1H), 3.87 (s, 3H), 3.82 (s, 3H), 3.80 (m, 1H), 2.79 (m, 2H), 1.74 (m, 2H), 1.61 (m, 2H), 1.50 (m, 1H), 1.22 (m, 1H), 0.96 (m, 2H). ^{13}C NMR δ 164.4, 160.5, 159.9, 149.8, 148.8, 129.6, 129.4, 129.2, 127.9, 116.1, 114.2, 113.8, 107.6, 61.8, 55.3, 28.6, 26.1, 24.9. R_f=0.22 (2:1 hex/EtOAc). IR (NaCl, $CHCl_3$) 3042, 2996, 2925, 2848, 1650, 1603, 1511, 1245, 1168, 1025, 820, 743. HRMS (ESI) $[C_{25}H_{28}NO_3]^+$ calcd 390.20245, found 390.20656.

*4.4.18. 4,6-Bis(4-methoxyphenyl)-2-pyridone (**6**)*

^{1}H NMR δ 7.69 (m, 2H), 7.60 (m, 2H), 7.01 (m, 4H), 6.66 (m, 2H), 3.88 (s, 3H), 3.87 (s, 3H). ^{13}C NMR δ 165.1, 161.1, 160.8, 153.2, 146.1, 130.4, 128.2, 127.9, 126.2, 114.6, 114.4, 103.6, 55.5, 55.4. R_f=0.51 (10:1 EtOAc/MeOH). IR (NaCl, $CHCl_3$) 3078, 2955, 2904, 1639, 1603, 1234, 1024, 809. HRMS (ESI) $[C_{19}H_{18}NO_3]^+$ calcd 308.12420, found 308.12806.

4.5. Characterization of enynamides

*4.5.1. (Z)-N-Benzyl-3,5-diphenylpent-2-en-4-ynamide (**4aa**)*

^{1}H NMR δ 7.73 (m, 2H), 7.64 (s, 1H), 7.44–7.24 (m, 11H), 7.13 (m, 2H), 6.69 (s, 1H), 4.64 (d, J=5.3 Hz, 2H). ^{13}C NMR δ 165.0, 137.8, 137.0, 131.6, 129.5, 129.0, 128.8, 128.7, 128.5, 128.3, 128.1, 127.6, 126.9, 121.2, 101.6, 85.8, 44.1. R_f=0.31 (95:5 CH_2Cl_2/EtOAc). IR (NaCl, $CHCl_3$) 3247, 3058, 3022, 2914, 1639, 1526, 1230, 989. HRMS (ESI) $[C_{24}H_{20}NO]^+$ calcd 338.15002, found 338.15405.

*4.5.2. (Z)-N,3-Dibenzyl-6-phenylhex-2-en-4-ynamide (**4ia**)*

^{1}H NMR δ 7.40 (s, 1H), 7.37–7.14 (m, 13H), 7.05 (m, 2H), 6.09 (s, 1H), 4.42 (d, J=5.5 Hz, 2H), 3.57 (s, 2H), 3.53 (s, 2H). ^{13}C NMR δ 164.8, 138.0, 137.0, 135.2, 130.4, 129.6, 129.2, 128.7, 128.6, 128.5, 127.8, 127.4, 126.9, 100.5, 80.3, 44.9, 43.6, 25.7. R_f=0.28 (95:5 CH_2Cl_2/EtOAc). IR (NaCl, $CHCl_3$) 3283, 3058, 3022, 2996, 2914, 1644, 1485, 1450, 697. HRMS (ESI) $[C_{26}H_{24}NO]^+$ calcd 366.18132, found 366.18552.

4.6. Characterization of 4-pyridones

*4.6.1. 1-Benzyl-2,6-bis(4-methoxyphenyl)-4-pyridone (**5ca**)*

^{1}H NMR δ 7.17 (m, 4H), 7.11 (m, 3H), 6.85 (m, 4H), 6.49 (m, 2H), 6.41 (s, 2H), 4.93 (s, 2H), 3.81 (s, 6H). ^{13}C NMR δ 179.0, 160.3, 153.7, 137.0,

130.0, 128.4, 127.5, 125.7, 120.6, 113.9, 55.3, 53.8. R_f=0.12 (10:1 EtOAc/MeOH). IR (NaCl, $CHCl_3$) 3068, 3001, 2925, 2838, 1619, 1496, 1250, 1173, 1020, 830. HRMS (ESI) $[C_{26}H_{24}NO_3]^+$ calcd 398.17115, found 398.17478.

*4.6.2. 1-(4-Methoxybenzyl)-2,6-bis(4-methoxyphenyl)-4-pyridone (**5cb**)*

^{1}H NMR δ 7.18 (m, 4H), 6.86 (m, 4H), 6.62 (m, 2H), 6.41 (s, 2H), 6.38 (m, 2H), 4.87 (s, 2H), 3.81 (s, 6H), 3.72 (s, 3H). ^{13}C NMR δ 178.9, 160.3, 158.8, 153.8, 130.0, 128.8, 127.5, 127.0, 120.5, 113.9, 113.8, 55.3, 55.2, 53.4. R_f=0.33 (10:1 EtOAc/MeOH). IR (NaCl, $CHCl_3$) 3006, 2925, 2832, 1619, 1496, 1245, 1173, 1020, 835. HRMS (ESI) $[C_{27}H_{26}NO_4]^+$ calcd 428.18171, found 428.18501.

*4.6.3. 2,6-Bis(4-methoxyphenyl)-1-phenyl-4-pyridone (**5cc**)*

^{1}H NMR δ 7.03 (m, 3H), 6.98 (m, 4H), 6.80 (m, 2H), 6.66 (m, 4H), 6.49 (s, 2H), 3.72 (s, 6H). ^{13}C NMR δ 179.0, 159.4, 152.4, 139.9, 130.5, 129.8, 128.4, 127.9, 127.7, 119.6, 113.3, 55.1. R_f=0.14 (10:1 EtOAc/MeOH). IR (NaCl, $CHCl_3$) 3058, 3001, 2925, 2832, 1629, 1501, 1296, 1250, 1173, 1025, 830, 728. HRMS (ESI) $[C_{25}H_{22}NO_3]^+$ calcd 384.15550, found 384.16090.

*4.6.4. 1,2,6-Tris(4-methoxyphenyl)-4-pyridone (**5cd**)*

^{1}H NMR δ 6.98 (m, 4H), 6.68 (m, 6H), 6.51 (m, 2H), 6.48 (s, 2H), 3.74 (s, 6H), 3.65 (s, 3H). ^{13}C NMR δ 178.9, 169.7, 159.4, 158.5, 152.7, 132.7, 130.6, 130.5, 127.9, 119.5, 113.4, 113.3, 55.2, 55.2. R_f=0.11 (10:1 EtOAc/MeOH). IR (NaCl, $CHCl_3$) 3053, 3001, 2930, 2832, 1624, 1501, 1557, 1434, 1255, 1030, 825, 733. HRMS (ESI) $[C_{26}H_{24}NO_4]^+$ calcd 414.16606, found 414.17067.

*4.6.5. 2,6-Bis(4-methoxyphenyl)-1-(4-(trifluoromethyl)phenyl)-4-pyridone (**5ce**)*

^{1}H NMR δ 7.30 (m, 2H), 6.94 (m, 6H), 6.67 (m, 4H), 6.52 (s, 2H), 3.72 (s, 6H). ^{13}C NMR δ 179.1, 160.0, 152.3, 143.2, 130.7, 130.5, 127.2, 125.8, 125.7, 120.0, 113.8, 55.4. R_f=0.28 (10:1 EtOAc/MeOH). IR (NaCl, $CHCl_3$) 3058, 3001, 2935, 2832, 1629, 1501, 1245, 1178, 1020, 835, 723. HRMS (ESI) $[C_{26}H_{21}F_3NO_3]^+$ calcd 452.14288, found 452.14620.

*4.6.6. 1-Hexyl-2,6-bis(4-methoxyphenyl)-4-pyridone (**5cf**)*

^{1}H NMR δ 7.33 (m, 4H), 6.98 (m, 4H), 6.34 (s, 2H), 3.86 (s, 6H), 3.70 (t, J=7.8 Hz, 2H), 1.13 (m, 2H), 0.98 (m, 2H), 0.77 (m, 4H), 0.68 (t, J=7.3 Hz, 3H). ^{13}C NMR δ 178.7, 160.3, 153.0, 130.0, 127.8, 120.5, 114.0, 55.4, 50.2, 30.6, 29.8, 25.5, 22.0, 13.7. R_f=0.16 (10:1 EtOAc/MeOH). IR (NaCl, $CHCl_3$) 3001, 2955, 2935, 2853, 1619, 1552, 1501, 1250, 1178, 1035, 830. HRMS (ESI) $[C_{25}H_{30}NO_3]^+$ calcd 392.21810, found 392.22238.

*4.6.7. 1-Cyclohexyl-2,6-bis(4-methoxyphenyl)-4-pyridone (**5cg**)*

^{1}H NMR δ 7.33 (m, 4H), 6.95 (m, 4H), 6.27 (s, 2H), 3.87 (s, 6H), 3.85 (m, 1H), 1.67 (m, 2H), 1.50 (m, 2H), 1.29 (m, 3H), 0.74 (m, 2H), 0.58 (m, 1H). ^{13}C NMR δ 178.4, 160.2, 154.2, 130.4, 129.1, 121.6, 113.6, 66.1, 55.3, 33.9, 26.6, 24.8. R_f=0.09 (10:1 EtOAc/MeOH). IR (NaCl, $CHCl_3$) 3001, 2930, 2858, 1624, 1501, 1245, 1025, 830, 733. HRMS (ESI) $[C_{25}H_{28}NO_3]^+$ calcd 390.20245, found 390.20633.

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