Tetrahedron 68 (2012) 4152–4158

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

# An efficient one-pot synthesis of 1,4-disubstituted 3-amino-2-pyridone derivatives via three-component reactions of alkynyl aldehydes and amines with ethyl 2-((diphenylmethylene)amino)acetate

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ARTICLE INFO

*Article history:*
Received 7 February 2012
Received in revised form 19 March 2012
Accepted 27 March 2012
Available online 30 March 2012

*Keywords:*
Alkynyl aldehyde
3-Amino-2-pyridone
Amine
Synthesis
Ethyl 2-((diphenylmethylene)amino)acetate

ABSTRACT

A facile and efficient one-pot synthesis of 1,4-disubstituted 3-amino-2-pyridone derivatives via three-component reactions of readily available alkynyl aldehydes, amines, and ethyl 2-((diphenylmethylene) amino)acetate has been developed. The alkynyl aldehyde substrates and the amine partners can be flexibly varied to achieve a range of 3-amino-2-pyridone derivatives, which could exert interesting chemical and biological properties. The reaction mechanism for the formation of 3-amino-2-pyridone derivatives is briefly explained.



## 1. Introduction

2-Pyridone ring represents an important structural motif occurring in many natural products and related congeners because many of the molecules containing this structural motif exhibit a wide range of biological activities.[1] For example, cytisine (1), which was extracted from the seeds of *Laburnum anagyroides* has been recognized as a partial agonist of nicotinic cholinergic receptors (nAChRs) with a nanomolar affinity and a high selectivity for the $\alpha_4\beta_2$ subtype;[2] farinosone (2), which was isolated from the entomopathogenic fungi *Paecilomyces farinosus* and *Paecilomyces militaris* induces and enhances neurite outgrowth in the PC-12 cell line;[3] apiosporamide (3), which was isolated from the fungus *Apiospora montagnei Saccardo* exhibits potent antifungal activity against the coprophilous fungus *Ascobolus furfuraceus* and shows antibacterial activity against *Bacillus subtilis* and *Staphylococcus aureus* (Fig. 1).[4] 2-Pyridone derivatives are also a versatile synthon for the preparation of a variety of other nitrogen-containing heterocycles, such as β-lactam, quinolizidine, pyridine, piperidine, and indolizidine alkaloids;[5] the diene portion of the molecule can undergo Diels–Alder cycloaddition reactions with a dienophile, or one double bond of the molecule may act as a dienophile to an added diene;[6] and they have been applied as a key synthetic intermediate to synthesize some complex natural products.[7] Consequently, a large number of methods have been developed for the synthesis of 2-pyridones and their derivatives.[8] The most common strategies involve the modification of the preconstructed heterocyclic ring and the construction of the heterocyclic skeleton from acyclic compounds. Due to the importance of 2-pyridone skeleton, to develop new and efficient methodologies for diversely functionalized construction of 2-pyridone is still highly desired.

Amino-2-pyridones are an important subset of 2-pyridones; they exhibit a wide range of interesting biological activities,[9] which includes as interleukin-2 inducible T-cell (Itk) inhibitor,[9a] glycogen synthase-3β inhibitor,[9b] insulin-like growth factor-1 receptor (IGF-1R) inhibitor,[9c] $EP_3$ receptor antagonist,[9d] selective tissue Factor VIIa inhibitor,[9e] and other medicinal properties.[9f,g] Among the syntheses of amino-2-pyridone derivatives, the most general approaches for accessing amino substituent on the 2-pyridones are reduction of the nitro group on the 2-pyridones[9f,10] or amination of halopyridines,[11] but each of them often suffers from significant limitations, such as multistep procedures, harsh conditions, low yields, or poor chemo- and regioselectivity. Recently, Rigo and coworkers reported the synthesis of 4-amino-2-pyridones by the reaction of amines with a dicarbonylallene;[12a] Schirok and coworkers developed the synthesis of 6-amino-2-pyridones by the reaction of acyclic ketene aminals with propiolic acid ester;[12b] Nan

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doi:10.1016/j.tet.2012.03.106

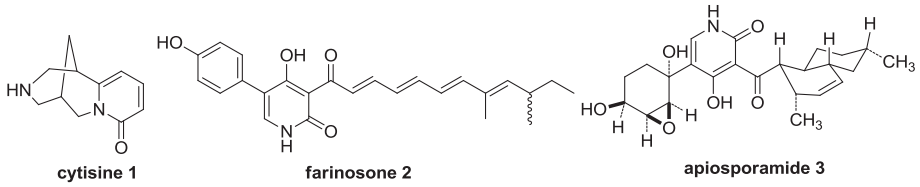



**Fig. 1.** Representative natural product containing 2-pyridone moiety.

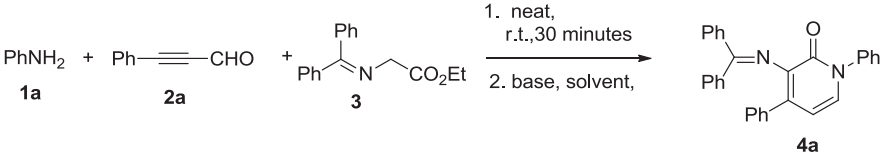
and co-workers described the synthesis of 3-amino-2-pyridone by the ring-closing metathesis reaction of α-amino acrylamide.[12c] Despite the plethora of these synthetic processes, there is a general lack of simple and effective procedures with which to synthesize 1,4-disubstituted 3-amino-2-pyridone derivatives from simple and readily available starting materials. Therefore, the search for an operational convenient, modular, and broadly applicable 1,4-disubstituted 3-amino-2-pyridone derivatives synthesis still represents a challenging research task. We have previously reported the synthesis of α,β-dehydroamino acid derivatives and 3-amino-2-pyrone derivatives from the reaction of alkynyl ketones with *N*-(diphenylmethylene)glycinates.[13] As continuation of these efforts in our laboratory, we wish to report herein an efficient and convenient one-pot synthesis of a variety of biologically interesting 3-amino-2-pyridone derivatives via three-component reactions of amines, alkynyl aldehydes and *N*-(diphenylmethylene)glycinates.

## 2. Results and discussion

At the outset of our study, we first chose aniline (**1a**), 3-phenylpropiolaldehyde (**2a**), and ethyl 2-((diphenylmethylene) amino)acetate (**3**) as the standard substrates to search for suitable reaction conditions for the synthesis 3-amino-2-pyridone derivatives, and the results are shown in Table 1. It was disappointing that no desired product was found by TLC when organic bases were used, such as triphenylphosphine ($Ph_3P$), triethylamine ($Et_3N$) (Table 1, entries 2 and 3). Both sodium carbonate ($Na_2CO_3$) and potassium carbonate ($K_2CO_3$) as Lewis bases afforded only trace amount of desired products (Table 1, entries 4 and 5). Fortunately, the reaction performed in the presence of sodium hydroxide (NaOH) at room temperature and afforded a yellow solid in 17% isolated yield in 24 h, and the product was characterized as **4a** by NMR and MS analysis (Table 1, entry 6). More gratifyingly, rapid reaction was observed to provide desired product **4a** in 84% isolated yield by using sodium hydride (NaH) at room temperature for 3 h (Table 1, entry 7). Other strong bases were also tested as the promoter in the reaction, such as sodium methanolate (MeONa), potassium 2-methylpropan-2-olate ($^t$BuOK), and they provided less satisfactory results (Table 1, entries 8 and 9). The amount of NaH employed had a significance effect on the reaction rate and the yield (Table 1, entries 7, 10–12). As shown in Table 1, the temperature had an effect on this reaction. When the reaction temperature decreased from room temperature to 0 °C, no desired product was found (Table 1, entry 13). Among the solvents we examined, dichloromethane, THF, and toluene were proved to be usable solvents for the reaction (Table 1, entries 10, 14, and 16). The choice of $Et_2O$ as the solvent gave the desired product **4a** in 71% isolated yield (Table 1, entry 15). Thus, the optimal reaction conditions for this one-pot reaction were determined to be 120 mol % sodium hydride as the promoter in dichloromethane at room temperature.

With these results in hand, we first screened several amines to explore the scope of the reaction, and the results are shown in Table 2. The electronic nature of the substituent on the phenyl moiety has an obvious influence on the activity of the reaction. Anilines with an electron-donating substituent afforded better yields than aniline (Table 2, entries 1, 6, and 7). Anilines with an

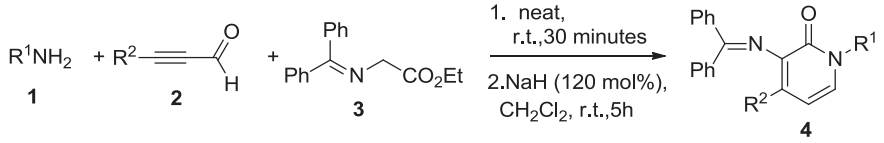
**Table 1**
Optimization of the reaction conditions of the three-component reactions of aniline (**1a**), 3-phenylpropiolaldehyde (**2a**), and ethyl 2-((diphenylmethylene) amin)acetate (**3**)[a]




| Entry | Base (mol %) | Solvent | Temp (°C) | Time (h) | Yield[b] (%) |
|---|---|---|---|---|---|
| 1 | None | $CH_2Cl_2$ | rt | 24 | 0 |
| 2 | $Et_3N$ (200) | $CH_2Cl_2$ | rt | 24 | 0 |
| 3 | $Ph_3P$ (200) | $CH_2Cl_2$ | rt | 24 | 0 |
| 4 | $Na_2CO_3$ (200) | $CH_2Cl_2$ | rt | 24 | Trace |
| 5 | $K_2CO_3$ (200) | $CH_2Cl_2$ | rt | 24 | Trace |
| 6 | NaOH (200) | $CH_2Cl_2$ | rt | 24 | 17 |
| 7 | NaH (200) | $CH_2Cl_2$ | rt | 3 | 84 |
| 8 | NaOMe (200) | $CH_2Cl_2$ | rt | 3 | 52 |
| 9 | $^t$BuOK (200) | $CH_2Cl_2$ | rt | 3 | 44 |
| 10 | NaH (120) | $CH_2Cl_2$ | rt | 5 | 92 |
| 11 | NaH (100) | $CH_2Cl_2$ | rt | 5 | 86 |
| 12 | NaH (50) | $CH_2Cl_2$ | rt | 5 | 52 |
| 13 | NaH (120) | $CH_2Cl_2$ | 0 | 5 | 0 |
| 14 | NaH (120) | THF | rt | 5 | 91 |
| 15 | NaH (120) | $Et_2O$ | rt | 5 | 71 |
| 16 | NaH (120) | Toluene | rt | 5 | 88 |

[a] All reactions were first carried out with **1a** (0.6 mmol) and **2a** (0.6 mmol) in the absence of solvent at rt for 30 min, then **3** (0.5 mmol), solvent (2.0 mL), and base were successively added and the resulting mixture was carried out at rt under nitrogen atmosphere.
[b] Isolated yield based on **3**.

**Table 2**
Reaction of amines, alkynyl aldehydes, and ethyl 2-((diphenylmethylene)amino)acetate[a]

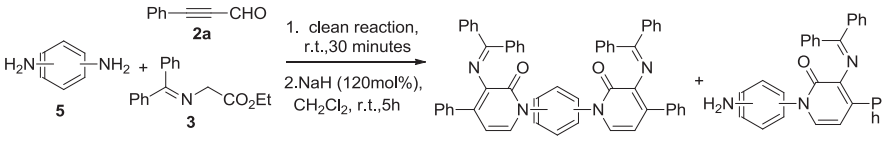



| Entry | $R^1$ | $R^2$ | Product | Yield[b] (%) |
|---|---|---|---|---|
| 1 | Ph, **1a** | Ph, **2a** | **4a** | 92 |
| 2 | 3-F–Ph, **1b** | Ph, **2a** | **4b** | 81 |
| 3 | 3-Cl–Ph, **1c** | Ph, **2a** | **4c** | 86 |
| 4 | 3-Br–Ph, **1d** | Ph, **2a** | **4d** | 92 |
| 5 | 3-MeO–Ph, **1e** | Ph, **2a** | **4e** | 96 |
| 6 | 4-Cl–Ph, **1f** | Ph, **2a** | **4f** | 97 |
| 7 | 4-MeO–Ph, **1g** | Ph, **2a** | **4g** | 95 |
| 8 | 4-$NO_2$–Ph, **1h** | Ph, **2a** | —[c] | — |
| 9 | 2,4-$Cl_2$–Ph, **1i** | Ph, **2a** | **4h** | 95 |
| 10 | 3,4-$Cl_2$–Ph, **1j** | Ph, **2a** | **4i** | 94 |
| 11 | 3-F-4-Cl–Ph, **1k** | Ph, **2a** | **4j** | 82 |
| 12 | $^t$Bu, **1l** | Ph, **2a** | —[c] | — |
| 13 | $PhCH_2$, **1m** | Ph, **2a** | —[c] | — |
| 14 | Ph, **1a** | 4-F-Ph, **2b** | **4k** | 97 |
| 15 | Ph, **1a** | 4-Cl-Ph, **2c** | **4l** | 94 |
| 16 | Ph, **1a** | 4-Me-Ph, **2d** | **4m** | 98 |
| 17 | Ph, **1a** | 4-MeO-Ph, **2e** | **4n** | 98 |
| 18 | Ph, **1a** | 3-Cl-Ph, **2f** | **4o** | 95 |
| 19 | Ph, **1a** | 3-Me-Ph, **2g** | **4p** | 97 |
| 20 | Ph, **1a** | $^n$Pr, **2i** | —[c] | — |

[a] All reactions were first carried out with **1** (0.6 mmol) and **2** (0.6 mmol) in the absence of solvent at rt for 30 min, then **3** (0.5 mmol), dichloromethane (2.0 mL), and sodium hydride (0.6 mmol) were successively added and the resulting mixture was carried out at rt for 5 h under nitrogen atmosphere.
[b] Isolated yield based on **3**.
[c] No desired product was found.

electron-withdrawing substituent such as 4-F aniline afforded a lower yield than aniline (Table 2, entries 1 and 2). Even aniline with a strong electron-withdrawing substituent such as 4-nitro aniline did not yield any desired product (Table 2, entry 8). The feasibility of employing aliphatic amines instead of aryl amines in the reaction was also investigated. Unfortunately, when 2-methylpropan-2-amine was used, no desired product was obtained (Table 2, entry 12). And the use of phenylmethanamine could not afford the expected product (Table 2, entry 13). It was noteworthy that when benzene-1,4-diamine and benzene-1,3-diamine were submitted to the reaction conditions, bis-3-amino-2-pyridone derivatives were formed besides the mono-3-amino-2-pyridone derivatives (Scheme 1). The reaction of benzene-1,4-diamine (0.6 mmol) and 3-phenylpropiolaldehyde (0.6 mmol) with ethyl 2-((diphenylmethylene)amino)acetate (0.5 mmol) performed at room temperature for 5 h under the optimal reaction conditions gave products **6a** (5%) and **7a** (79%). Alternately, treatment of benzene-1,3-diamine in the reaction provided products **6b** (7%) and **7b** (67%).

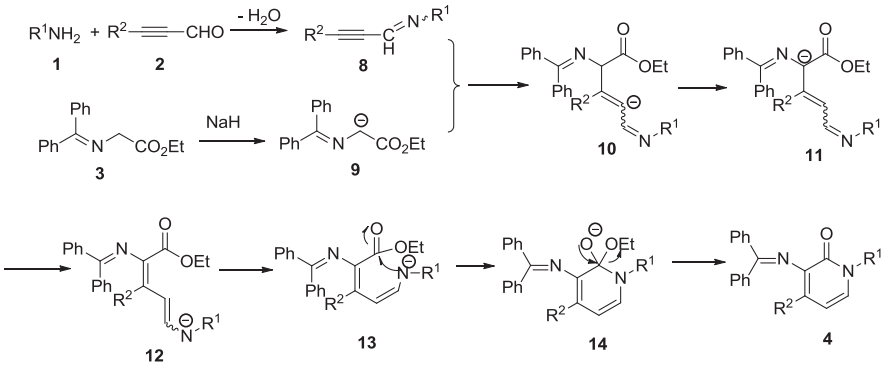
On the base of our results and previous works,[13,14] a plausible mechanism to account for the formation of the 3-amino-2-pyridone derivatives **4** is presented in Scheme 2 as follows: Sodium hydride deprotonates the active methylene proton of the ethyl 2-((diphenylmethylene)amino)acetate **3** to generate intermediate **9**. The intermediate **9** then undergoes conjugate addition to the alkynyl imine **8**,[15] which is formed by condensation of alkynyl aldehyde and amine to give **10**, followed by proton transfer to give compound **11**. The intermediate **11** would undergo double




**Scheme 1.**

A variety of alkynyl aldehydes were then submitted to the reaction; these results are summarized in Table 2. It was observed that the reactions proceeded smoothly under the optimized conditions to afford the corresponding products in good to excellent yields, when aromatic alkynyl aldehydes were examined under the reaction conditions; while no desired product was obtained, when aliphatic alkynyl aldehyde was tested under the reaction conditions. The substituents on the phenyl ring of the aromatic alkynyl aldehydes have no obvious effect on the yields of the reactions. For example, the reaction of 3-(4-fluorophenyl)propiolaldehyde or 3-(4-methoxyphenyl)propiolaldehyde, under the conditions described, gave the corresponding products **4k** and **4n** in 97% and 98% yields, respectively.

bond migration and the subsequent intramolecular aza-cyclization reaction of **13** would give the product 3-amino-2-pyridone derivatives **4**.



**Scheme 2.** Proposed mechanism for the formation of 3-amino-2-pyridone derivatives.

## 3. Conclusions

In summary, we have developed an efficient route to diverse 1,4-disubstituted 3-amino-2-pyridone derivatives **4** through a mild, room temperature, one-pot procedure by combining alkynyl aldehydes, amines, and ethyl 2-((diphenylmethylene) amino)acetate. A range of 3-amino-2-pyridone derivatives would be achieved because the alkynyl substrates and the amine partners can be flexibly varied. Owing to the interest of the amino-2-pyridone derivatives for the design of biologically relevant compounds, this methodology offers a route for the synthesis of diverse 1,4-disubstituted 3-amino-2-pyridone derivatives. The potential utilization and extension of the scope of the methodology and the examination of biological activity of the 3-amino-2-pyridone derivatives are currently under investigation in our laboratory.

## 4. Experimental section

### 4.1. General

All reactions were performed in anhydrous solvents under an $N_2$ atmosphere. THF, $Et_2O$, and toluene were distilled from K and Na metal, respectively. $CH_2Cl_2$ and acetone were distilled from $CaH_2$. PE refers to petroleum ether (boiling range 60–90 °C). Alkynyl aldehyde[16] and ethyl 2-((diphenylmethylene)amino)acetate[13a] were prepared following known procedures. Amines are commercially available without further purification. Reaction progress was monitored using thin layer chromatography (TLC), which was visualized by ultraviolet light (254 nm). Flash chromatography was conducted with silica gel 200–300 mesh. IR spectra were recorded on an FTIR-8400s spectrometer. Melting points were obtained on a Yanaco-241 apparatus and are uncorrected. $^1H$ and $^{13}C$ NMR spectra were recorded in DMSO-$d_6$ using a Bruker Avance 300 spectrometer or a Bruker Avance 500 spectrometer: chemical shifts ($\delta$) are given in parts per million, coupling constants ($J$) in hertz. High-resolution mass spectra were recorded on a Waters/Micromass QTOF MS spectrometer.

### 4.2. General procedure for the synthesis of 3-amino-2-pyridone derivatives

A mixture of alkynyl aldehyde (0.6 mmol) and amine (0.6 mmol) was stirred at room temperature for 30 min, and then ethyl 2-((diphenylmethylene)amino)acetate (0.5 mmol), dichloromethane (2 mL), and sodium hydride (0.6 mmol) were successively added. The resulting mixture was stirred at room temperature for 5 h under nitrogen atmosphere. Saturated aqueous $NaHCO_3$ (10 mL) was added to quench the reaction. The mixture was extracted with dichloromethane (3×10 mL). The combined organic layers were dried with sodium sulfate. The solvents were evaporated in vacuo and then the residue was purified by silica gel chromatography ($SiO_2$; ethylacetate/PE, 1:10–1:5) to afford 3-amino-2-pyridone derivatives **4a**–**p**, **6**, and **7**.

*4.2.1. 3-(Diphenylmethyleneamino)-1,4-diphenylpyridin-2(1H)-one (**4a**).* Yield 92%; yellow solid; mp 57–58 °C. IR (KBr): $\nu$=3059, 1724, 1647, 1612, 1591, 1491, 1444, 1398, 754, 694 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$): $\delta$=7.56–7.42 (m, 9H), 7.38–7.29 (m, 10H), 6.74 (d, $J$=6.6 Hz, 2H), 6.25 (d, $J$=7.2, 1H) ppm. $^{13}C$ NMR (75 MHz, DMSO-$d_6$): $\delta$=169.3, 156.0, 140.7, 139.1, 136.9, 133.6, 132.1, 130.9, 128.9, 128.89, 128.8, 128.7, 128.6, 128.4, 128.1, 128.0, 127.9, 127.7, 127.6, 126.7, 126.4, 106.6 ppm. HRMS (ESI): calcd for $C_{30}H_{23}N_2O$ $[M+H]^+$ 427.1805; found 427.1811.

*4.2.2. 3-(Diphenylmethyleneamino)-1-(3-fluorophenyl)-4-phenylpyridin-2(1H)-one (**4b**).* Yield 81%; yellow solid; mp 64–65 °C. IR (KBr): $\nu$=3032, 1747, 1645, 1618, 1599, 1487, 1398, 756, 694 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$): $\delta$=7.59–7.43 (m, 5H), 7.37–7.16 (m, 13H), 6.73 (d, $J$=6.0 Hz, 2H), 6.27 (d, $J$=7.2 Hz, 1H) ppm. $^{13}C$ NMR (75 MHz, DMSO-$d_6$): $\delta$=169.5, 163.3, 155.8, 142.0, 139.0, 137.7, 136.5, 133.8, 131.9, 130.9, 130.6, 130.5, 128.7, 128.3, 128.2, 128.0, 127.8, 127.6, 126.7, 122.6, 122.5, 115.0, 114.2, 106.8 ppm. HRMS (ESI): calcd for $C_{30}H_{22}FN_2O$ $[M+H]^+$ 445.1711; found 445.1710.

*4.2.3. 1-(3-Chlorophenyl)-3-(diphenylmethyleneamino)-4-phenylpyridin-2(1H)-one (**4c**).* Yield 86%; yellow solid; mp 65–66 °C. IR (DMSO): $\nu$=3080, 1649, 1610, 1587, 1489, 1475, 1446, 1292, 785, 758, 694 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$): $\delta$=7.58–7.42 (m, 7H), 7.40–7.36 (m, 7H), 7.33–7.28 (m, 4H), 6.74 (d, $J$=6.3 Hz, 2H), 6.27 (d, $J$=7.2 Hz, 1H) ppm. $^{13}C$ NMR (75 MHz, DMSO-$d_6$): $\delta$=169.5, 155.8, 141.7, 138.9, 137.7, 136.7, 133.9, 132.9, 131.8, 131.0, 130.9, 130.5, 128.8, 128.7, 128.4, 128.2, 128.1, 128.0, 127.8, 127.6, 126.8, 126.5, 125.2, 106.8 ppm. HRMS (ESI): calcd for $C_{30}H_{22}ClN_2O$ $[M+H]^+$ 461.1415; found 461.1420.

*4.2.4. 1-(3-Bromophenyl)-3-(diphenylmethyleneamino)-4-phenylpyridin-2(1H)-one (**4d**).* Yield 92%; yellow solid; mp 62–63 °C. IR (KBr): $\nu$=3016, 1656, 1639, 1627, 1398, 823, 761, 624 $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$): $\delta$=7.65–7.64 (m, 1H), 7.57–7.56 (m, 2H), 7.52–7.43 (m, 5H), 7.42–7.37 (m, 5H), 7.35–7.28 (m, 5H), 6.74 (d, $J$=7.0 Hz, 2H), 6.27 (d, $J$=7.0 Hz, 1H) ppm. $^{13}C$ NMR (125 MHz, DMSO-$d_6$): $\delta$=171.1, 157.2, 142.2, 140.6, 138.4, 137.4, 137.3, 134.5, 131.4, 131.0, 130.8, 130.5, 130.1, 129.9, 129.7, 128.9, 128.8, 128.3, 128.1, 128.0, 127.6, 125.3, 122.5, 108.1 ppm. HRMS (ESI): calcd for $C_{30}H_{22}BrN_2O$ $[M+H]^+$ 505.0910; found 505.0917.

*4.2.5. 3-(Diphenylmethyleneamino)-1-(3-methoxyphenyl)-4-phenylpyridin-2(1H)-one (**4e**).* Yield 96%; yellow solid; mp 66–67 °C. IR

(KBr): $\nu$=3055, 1647, 1608, 1489, 1292, 783, 756, 694 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$): $\delta$=7.58–7.21 (m, 15H), 7.02 (dd, $J_1$=8.4 Hz, $J_2$=2.1 Hz, 1H), 6.87 (d, $J$=8.4 Hz, 1H), 6.82 (d, $J$=2.1 Hz, 1H), 6.75 (d, $J$=6.6 Hz, 2H), 6.24 (d, $J$=7.2 Hz, 1H), 3.78 (s, 3H) ppm. $^{13}C$ NMR (75 MHz, DMSO-$d_6$): $\delta$=169.3, 159.4, 155.8, 141.8, 139.0, 136.9, 133.7, 132.1, 130.9, 129.7, 128.7, 128.6, 128.3, 128.1, 128.0, 127.7, 127.6, 127.5, 126.7, 118.4, 113.7, 112.2, 112.1, 106.5, 55.2 ppm. HRMS (ESI): calcd for $C_{31}H_{25}N_2O_2$ $[M+H]^+$ 457.1911; found 457.1916.

*4.2.6. 1-(4-Chlorophenyl)-3-(diphenylmethyleneamino)-4-phenylpyridin-2(1H)-one (**4f**).* Yield 97%; yellow solid; mp 149–150 °C. IR (KBr): $\nu$=3051, 1643, 1606, 1589, 1579, 1491, 1317, 1286, 1082, 754, 694 $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$): $\delta$=7.58–7.49 (m, 5H), 7.44–7.40 (m, 2H), 7.36–7.25 (m, 11H), 6.71 (d, $J$=7.2 Hz, 2H), 6.26 (d, $J$=7.5 Hz, 1H) ppm. $^{13}C$ NMR (125 MHz, DMSO-$d_6$): $\delta$=169.5, 156.0, 139.4, 139.0, 137.7, 136.8, 133.8, 132.5, 132.0, 131.0, 129.0, 128.9, 128.8, 128.7, 128.4, 128.3, 128.2, 128.1, 127.9, 127.6, 126.7, 106.9 ppm. HRMS (ESI): calcd for $C_{30}H_{22}ClN_2O$ $[M+H]^+$ 461.1415; found 461.1413.

*4.2.7. 3-(Diphenylmethyleneamino)-1-(4-methoxyphenyl)-4-phenylpyridin-2(1H)-one (**4g**).* Yield 95%; yellow solid; mp 178–179 °C. IR (KBr): $\nu$=3057, 1647, 1622, 1602, 1599, 1545, 1487, 1400, 756, 694 $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$): $\delta$=7.56 (d, $J$=7.0 Hz, 2H), 7.51 (d, $J$=7.5 Hz, 1H), 7.44 (d, $J$=7.0 Hz, 2H), 7.36–7.25 (m, 9H), 7.22 (d, $J$=9.0 Hz, 2H), 7.04 (d, $J$=9.0 Hz, 2H), 6.72 (d, $J$=7.0 Hz, 2H), 6.21 (d, $J$=7.5 Hz, 1H), 3.80 (s, 3H) ppm. $^{13}C$ NMR (125 MHz, DMSO-$d_6$) $\delta$=169.3, 158.5, 156.2, 139.0, 137.8, 136.9, 136.5, 133.6, 132.5, 130.9, 128.8, 128.7, 128.4, 128.2, 128.0, 127.7, 127.6, 127.4, 126.7, 126.4, 114.1, 106.4, 55.3 ppm. HRMS (ESI): calcd for $C_{31}H_{25}N_2O_2$ $[M+H]^+$ 457.1911; found 457.1916.

*4.2.8. 1-(2,4-Dichlorophenyl)-3-(diphenylmethyleneamino)-4-phenylpyridin-2(1H)-one (**4h**).* Yield 95%; yellow solid; mp 213–214 °C. IR (KBr): $\nu$=3076, 1647, 1622, 1606, 1581, 1479, 1442, 1400, 758, 698 $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$): $\delta$=7.85 (s, 1H), 7.61–7.49 (m, 4H), 7.44 (t, $J$=7.4 Hz, 2H), 7.37–7.23 (m, 10H), 6.71 (d, $J$=6.0 Hz, 2H), 6.27 (d, $J$=7.0 Hz, 1H) ppm. $^{13}C$ NMR (125 MHz, DMSO-$d_6$): $\delta$=169.6, 155.7, 139.2, 137.7, 137.5, 137.2, 136.7, 136.3, 134.2, 134.1, 131.9, 131.0, 130.8, 129.4, 128.9, 128.8, 128.5, 128.4, 128.2, 128.0, 127.9, 127.6, 126.9, 107.0 ppm. HRMS (ESI): calcd for $C_{30}H_{21}Cl_2N_2O$ $[M+H]^+$ 495.1025; found 495.1031.

*4.2.9. 1-(3,4-Dichlorophenyl)-3-(diphenylmethyleneamino)-4-phenylpyridin-2(1H)-one (**4i**).* Yield 94%; yellow solid; mp 123–124 °C. IR (KBr): $\nu$=3078, 1651, 1614, 1587, 1471, 1444, 1290, 1130, 756, 696 $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$): $\delta$=7.78 (d, $J$=9.0 Hz, 1H), 7.65 (d, $J$=2.5 Hz, 1H), 7.57 (d, $J$=7.0 Hz, 2H), 7.51–7.34 (m, 10H), 7.31–7.26 (m, 3H), 6.72 (d, $J$=7.0 Hz, 2H), 6.28 (d, $J$=7.5 Hz, 1H) ppm. $^{13}C$ NMR (125 MHz, DMSO-$d_6$): $\delta$=169.6, 155.8, 140.1, 138.9, 137.7, 136.7, 136.4, 134.0, 131.7, 131.1, 131.0, 130.8, 130.7, 128.9, 128.8, 128.7, 128.4, 128.2, 128.1, 127.9, 127.7, 126.9, 126.8, 107.0 ppm. HRMS (ESI): calcd for $C_{30}H_{21}Cl_2N_2O$ $[M+H]^+$ 495.1025; found 495.1023.

*4.2.10. 1-(4-Chloro-3-fluorophenyl)-3-(diphenylmethyleneamino)-4-phenylpyridin-2(1H)-one (**4j**).* Yield 82%; yellow solid; mp 147–148 °C. IR (KBr): $\nu$=3070, 1651, 1616, 1597, 1572, 1487, 1440, 1311, 759, 694 $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$): $\delta$=7.73 (t, $J$=8.5, 1H), 7.58 (d, $J$=6.0, 2H), 7.51 (dd, $J_1$=10.0 Hz, $J_2$=2.0 Hz, 2H), 7.49–7.22 (m, 12H), 6.72 (d, $J$=6.0 Hz, 2H), 6.27 (d, $J$=7.0 Hz, 1H) ppm. $^{13}C$ NMR (125 MHz, DMSO-$d_6$): $\delta$=169.6, 157.7, 155.7, 140.5, 140.4, 139.0, 137.7, 136.4, 133.9, 131.7, 131.0, 130.6, 128.8, 128.7, 128.4, 128.2, 128.0, 127.9, 127.6, 126.7, 123.9, 119.2, 115.8, 107.0 ppm. HRMS (ESI): calcd for $C_{30}H_{21}ClFN_2O$ $[M+H]^+$ 479.1321; found 479.1325.

*4.2.11. 3-(Diphenylmethyleneamino)-4-(4-fluorophenyl)-1-phenylpyridin-2(1H)-one (**4k**).* Yield 97%; yellow solid; mp 54–55 °C. IR (KBr): $\nu$=3014, 1703, 1647, 1543, 1508, 1398, 823, 759, 624 $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$): $\delta$=7.59 (d, $J$=7.0 Hz, 2H), 7.52–7.49 (m, 3H), 7.44–7.41 (m, 5H), 7.35–7.28 (m, 6H), 7.22–7.18 (m, 2H), 6.77 (d, $J$=6.5 Hz, 2H), 6.23 (d, $J$=7.0 Hz, 1H) ppm. $^{13}C$ NMR (125 MHz, DMSO-$d_6$): $\delta$=169.6, 162.3, 155.9, 140.7, 139.0, 137.7, 136.5, 133.2, 133.1, 132.7, 131.0, 130.5, 128.9, 128.8, 128.7, 128.2, 127.9, 127.6, 126.7, 126.3, 115.0, 106.4 ppm. HRMS (ESI): calcd for $C_{30}H_{22}FN_2O$ $[M+H]^+$ 445.1711; found 445.1716.

*4.2.12. 4-(4-Chlorophenyl)-3-(diphenylmethyleneamino)-1-phenylpyridin-2(1H)-one (**4l**).* Yield 94%; brown oil; IR (DMSO): $\nu$=3032, 1655, 1637, 1610, 1508, 1398, 823, 759 $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$): $\delta$=7.58 (d, $J$=7.5 Hz, 2H), 7.52 (m, 3H), 7.45–7.39 (m, 7H), 7.35–7.28 (m, 6H), 6.76 (d, $J$=7.5 Hz, 2H), 6.24 (d, $J$=7.2 Hz, 1H) ppm. $^{13}C$ NMR (125 MHz, DMSO-$d_6$): $\delta$=169.6, 155.8, 140.6, 139.1, 136.8, 135.6, 132.5, 132.4, 132.3, 130.2, 129.3, 128.9, 128.7, 128.5, 128.3, 128.2, 128.0, 127.9, 127.6, 126.6, 126.3, 106.2 ppm. HRMS (ESI): calcd for $C_{30}H_{22}ClN_2O$ $[M+H]^+$ 461.1415; found 461.1421.

*4.2.13. 3-(Diphenylmethyleneamino)-1-phenyl-4-p-tolylpyridin-2(1H)-one (**4m**).* Yield 98%; yellow solid; mp 76–77 °C. IR (KBr): $\nu$=3032, 1657, 1639, 1608, 1510, 1398, 821, 759, 623 $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$): $\delta$=7.59 (d, $J$=7.0 Hz, 2H), 7.51–7.40 (m, 6H), 7.32–7.26 (m, 8H), 7.18 (d, $J$=7.0 Hz, 2H), 6.76 (d, $J$=6.5 Hz, 2H), 6.23 (d, $J$=7.5 Hz, 1H), 2.28 (s, 3H) ppm. $^{13}C$ NMR (125 MHz, DMSO-$d_6$): $\delta$=169.2, 155.8, 140.7, 138.7, 137.8, 137.2, 136.5, 133.9, 133.8, 132.0, 131.4, 130.9, 129.1, 128.7, 128.6, 128.3, 128.2, 127.8, 127.5, 126.6, 126.3, 106.5, 20.6 ppm. HRMS (ESI): calcd for $C_{31}H_{25}N_2O$ $[M+H]^+$ 441.1961; found 441.1967.

*4.2.14. 3-(Diphenylmethyleneamino)-4-(4-methoxyphenyl)-1-phenylpyridin-2(1H)-one (**4n**).* Yield 98%; yellow solid; mp 66–67 °C. IR (KBr): $\nu$=3012, 1659, 1647, 1543, 1508, 1398, 1055, 823, 759, 624 $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$): $\delta$=7.60 (d, $J$=7.5 Hz, 2H), 7.53–7.47 (m, 3H), 7.45–7.41 (m, 3H), 7.40–7.38 (m, 2H), 7.35 (d, $J$=7.5 Hz, 1H), 7.30–7.24 (m, 5H), 6.95–6.92 (m, 2H), 6.79 (d, $J$=7.0 Hz, 2H), 6.25 (d, $J$=7.0H, 1H), 3.74 (s, 3H) ppm. $^{13}C$ NMR (125 MHz, DMSO-$d_6$): $\delta$=169.3, 158.8, 155.7, 140.8, 138.4, 137.9, 136.6, 133.7, 131.9, 130.9, 129.8, 129.1, 129.0, 128.9, 128.7, 128.6, 128.2, 127.8, 127.5, 126.7, 126.3, 113.5, 106.5, 55.0 ppm. HRMS (ESI): calcd for $C_{31}H_{25}N_2O_2$ $[M+H]^+$ 457.1911; found 457.1916.

*4.2.15. 4-(3-Chlorophenyl)-3-(diphenylmethyleneamino)-1-phenylpyridin-2(1H)-one (**4o**).* Yield 95%; yellow solid; mp 56–57 °C. IR (KBr): $\nu$=3030, 1646, 1608, 1589, 1564, 1491, 1444, 756, 692 $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$): $\delta$=7.57 (d, $J$=5.0 Hz, 2H), 7.53–7.50 (m, 3H), 7.45–7.43 (m, 3H), 7.40–7.29 (m, 10H), 6.73 (d, $J$=5.0 Hz, 2H), 6.25 (d, $J$=7.0 Hz, 1H) ppm. $^{13}C$ NMR (125 MHz, DMSO-$d_6$): $\delta$=169.6, 156.1, 140.6, 139.4, 138.8, 137.6, 136.3, 132.7, 132.4, 131.9, 131.1, 129.8, 128.9, 128.7, 128.6, 128.4, 128.2, 127.9, 127.7, 127.6, 126.9, 126.7, 126.3, 106.1 ppm. HRMS (ESI): calcd for $C_{30}H_{22}ClN_2O$ $[M+H]^+$ 461.1415; found 461.1421.

*4.2.16. 3-(Diphenylmethyleneamino)-1-phenyl-4-m-tolylpyridin-2(1H)-one (**4p**).* Yield 97%; yellow solid; mp 45–46 °C. IR (KBr): $\nu$=3032, 1655, 1647, 1610, 1508, 1400, 823, 759, 624 $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$): $\delta$=7.56 (d, $J$=6.5 Hz, 2H), 7.53–7.50 (m, 3H), 7.45–7.42 (m, 3H), 7.35–7.21 (m, 7H), 7.14–7.09 (m, 3H), 6.70 (d, $J$=6.5 Hz, 2H), 6.22 (d, $J$=7.0 Hz, 1H), 2.25 (s, 3H) ppm. $^{13}C$ NMR (125 MHz, DMSO-$d_6$): $\delta$=169.2, 156.1, 140.7, 139.1, 137.8, 137.0, 136.7,

136.4, 133.6, 132.0, 130.8, 129.1, 128.9, 128.7, 128.6, 128.2, 128.1, 127.9, 127.8, 127.5, 126.7, 126.3, 125.4, 106.6, 20.8 ppm. HRMS (ESI): calcd for $C_{31}H_{25}N_2O$ $[M+H]^+$ 441.1961; found 441.1966.

*4.2.17. 1,1′-(1,4-Phenylene)bis(3-((diphenylmethylene)amino)-4-phenylpyridin-2(1H)-one) (**6a**).* Yield 5%; yellow solid; mp 304–305 °C. IR (DMSO): $\nu$=3018, 1657, 1639, 1562, 1510, 823, 761, 624 $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$): $\delta$=7.58 (d, $J$=7.0 Hz, 4H), 7.53 (m, 2H), 7.46–7.41 (m, 10H), 7.39–7.35 (m, 10H), 7.32–7.28 (m, 6H), 6.73 (d, $J$=7.0 Hz, 4H), 6.2 9 (*d*, $J$=7.0 Hz, 2H) ppm. $^{13}C$ NMR (125 MHz, DMSO-$d_6$): $\delta$=169.5, 156.0, 140.0, 139.1, 136.8, 133.8, 131.9, 128.8, 128.7, 128.4, 128.3, 128.26, 128.21, 128.0, 127.8, 127.7, 127.6, 127.1, 126.7, 106.9 ppm. HRMS (ESI): calcd for $C_{54}H_{39}N_4O_2$ $[M+H]^+$ 775.3068; found 775.3053.

*4.2.18. 1-(4-Aminophenyl)-3-(diphenylmethyleneamino)-4-phenylpyridin-2(1H)-one (**7a**).* Yield 79%; yellow solid; mp 176–177 °C. IR (DMSO): $\nu$=3018, 1656, 1639, 1398, 823, 761, 624 $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$): $\delta$=7.56 (d, $J$=7.5 Hz, 2H), 7.50 (t, $J$=7.0 Hz, 1H), 7.43 (t, $J$=8.0 Hz, 2H), 7.36–7.23 (m, 8H), 7.22 (d, $J$=7.0 Hz, 1H), 6.91 (d, $J$=8.5 Hz, 2H), 6.70 (d, $J$=7.0 Hz, 2H), 6.62 (d, $J$=8.5 Hz, 2H), 6.15 (d, $J$=7.0 Hz, 1H), 5.32 (br s, 2H) ppm. $^{13}C$ NMR (125 MHz, DMSO-$d_6$): $\delta$=169.0, 156.3, 148.3, 138.9, 137.9, 137.0, 136.5, 133.2, 132.8, 130.8, 129.3, 128.7, 128.6, 128.3, 128.1, 127.9, 127.6, 127.5, 126.7, 126.6, 113.3, 106.0 ppm. HRMS (ESI): calcd for $C_{30}H_{24}N_3O$ $[M+H]^+$ 442.1914; found 442.1913.

*4.2.19. 1,1′-(1,3-Phenylene)bis(3-((diphenylmethylene)amino)-4-phenylpyridin-2(1H)-one) (**6b**).* Yield 7%; yellow solid ; mp 216–217 °C. IR (KBr): $\nu$=3026, 1647, 1612, 1591, 1489, 1315, 1290, 754, 694 $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$): $\delta$=7.64–7.50 (m, 7H), 7.42–7.27 (m, 25H), 6.74 (d, $J$=6.0 Hz, 4H), 6.31 (d, $J$=7.0 Hz, 2H) ppm. $^{13}C$ NMR (125 MHz, DMSO-$d_6$): $\delta$=169.5, 155.9, 140.9, 139.1, 137.8, 136.8, 136.5, 133.8, 132.0, 131.0, 129.3, 128.8, 128.7, 128.4, 128.2, 128.1, 127.9, 127.6, 126.8, 126.0, 124.3, 106.9 ppm. HRMS (ESI): calcd for $C_{54}H_{39}N_4O_2$ $[M+H]^+$ 775.3068; found 775.3070.

*4.2.20. 1-(3-Aminophenyl)-3-(diphenylmethyleneamino)-4-phenylpyridin-2(1H)-one (**7b**).* Yield 67%; yellow solid; mp 165–166 °C. IR (KBr): $\nu$=3012, 1658, 1643, 1626, 1545, 1512, 1400, 823, 759, 624 $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$): $\delta$=7.56 (d, $J$=7.5 Hz, 2H), 7.52 (t, $J$=6.9 Hz, 1H), 7.44 (t, $J$=7.3 Hz, 2H), 7.41–7.33 (m, 5H), 7.30–7.25 (m, 2H), 7.24 (d, $J$=7.0 Hz, 1H), 7.12 (t, $J$=8.0 Hz, 1H ), 6.70 (d, $J$=7.5 Hz, 2H), 6.61 (dd, $J_1$=8.0 Hz, $J_2$=1.5 Hz, 1H), 6.46 (m, 1H), 6.37 (dd, $J_1$=8.0 Hz, $J_2$=1.5 Hz, 1H), 6.17 (d, $J$=7.5 Hz, 1H), 5.35 (br s, 2H) ppm. $^{13}C$ NMR (125 MHz, DMSO-$d_6$): $\delta$=169.2, 156.0, 149.3, 141.6, 139.1, 137.8, 136.9, 133.3, 132.2, 130.9, 129.2, 128.8, 128.7, 128.6, 128.4, 128.2, 127.9, 127.6, 127.5, 126.6, 113.3, 113.2, 111.6, 106.1 ppm. HRMS (ESI): calcd for $C_{30}H_{24}N_3O$ $[M+H]^+$ 442.1914; found 442.1913.

## Acknowledgements

This work was financially supported by the National Natural Science Foundation of China (Grant No. 21102179) and Fundamental Research Funds for the Central Universities (No. JKZ2011011).

## Supplementary data

Copies of NMR spectra for all products related to this article can be found online at doi:10.1016/j.tet.2012.03.106.

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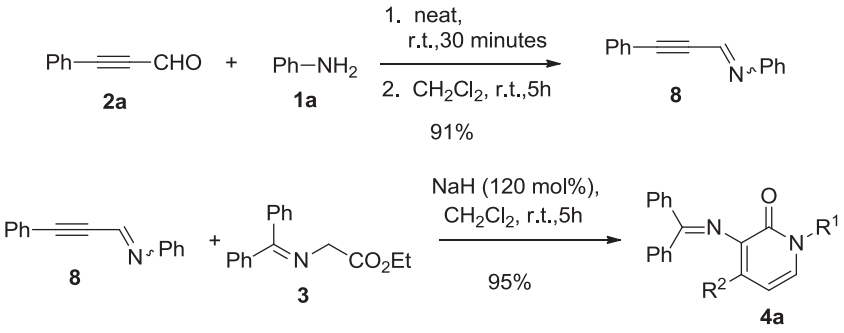
15. The alkynyl imine **8** was synthesized by the condensation of aniline **1a** and 3-phenylpropiolaldehyde **2a** (based on Ref. 14a). Then, the reaction of imine **8**, ethyl 2-((diphenylmethylene)amino)acetate **3**, and sodium hydride was carried out in dichloromethane (2.0 mL) at room temperature for 5 h under nitrogen atmosphere. The expected product **4a** was given in 95% isolated yield.




**2a** **1a** **8** **8** **3** **4a**

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