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# An Efficient Synthesis of Arylated Pyridines from Conjugated Acetylenes and Substituted Benzylamines Catalyzed by Base

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**Abstract:** An efficient base-catalyzed synthesis of arylated pyridines has been disclosed. This reaction involving conjugated acetylenes and substituted benzylamines proceeded smoothly, giving rise to tri-aryl substituted pyridines which are biologically relevant compounds in good to excellent yields in *N*,*N*-dimethylformamide (DMF) under air at 140 °C with $K_2CO_3$ as catalyst.

**Keywords:** arylated pyridines; synthesis; transition-metal-free; base; catalysis

## 1. Introduction

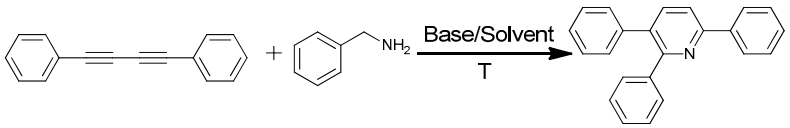
The importance of pyridine motif comes from its unique biological activity in natural products [1–3], pharmaceutical compounds [4–8] and agrochemicals [9]. In addition, pyridine derivatives are widely applied in organometallic chemistry [10,11], catalysis [12], material science [13–15] and supramolecular chemistry [16–18]. Therefore, the more efficient synthesis of pyridine derivatives is still an important topic [19,20]. However, there are only very few examples reported on this topic: in 1974, Chalk [21] reported a new pyridine synthesis from conjugated acetylenes and substituted methylamines, leading to 51% of 2-*p*-tolyl-3,6-diphenylpyridine and 38% of 2-*p*-tolyl-3,6-diphenylpyridine N-oxide at 145 °C under nitrogen with dimethylsulfoxide as solvent. In 2013, Shaand coworkers [22] disclosed a facile synthetic method for the preparation of trisubstituted pyridines with high regioselectivity through a three-component assembly strategy of arynes, isocyanides, and 3-bromo- or 3-acetoxypropynes, leading to 65% of 2-(4-fluorophenyl)-3,6-diphenylpyridine. In recent years, transition-metal-catalyzed C-C cross-coupling reaction has been applied to a diverse array of fields. Peter [3] recently reported the site-selective arylation of commercially available 2,3,5,6-tetrachloropyridine using the Suzuki–Miyaura reaction, allowing the selective synthesis of mono-, di-, tri- and tetraarylated pyridines in good to quantitative yields. In this context, based on the advantages of conjugated acetylenes, which are readily prepared by the catalytic oxidative coupling of terminal alkynes [23], studying more efficient synthesis of pyridine derivatives between conjugated acetylenes and substituted methylamines is still highly desirable and challenging.

## 2. Resultsand Discussion

Our interest in increasing the synthetic yield of arylated pyridines from conjugated acetylenes and substituted benzylamines under optimum conditions stemmed from the fact that Chalk's [24] work gave only a 70% yield of 2,3,6-triphenylpyridine fromsolutions of 1,4-diphenylbutadiyne in

benzylamine (1:6.13 mmol) after two to three hours at 180 °C under nitrogen. Initially, we tested the reaction of 1,4-diphenylbutadiyne **1** (1 mmol) and benzylamine **2** (6 mmol) in DMSO at 140 °C in the presence of $K_2CO_3$ (0.5 mmol) under air. To our delight, 2,3,6-triphenylpyridine **3c** was obtained in 85% isolated yield (Table 1, entry 3). Then, the effects of the ratio of starting materials **1**:**2** were examined (Table 1, entries 1–5). The yield of **3** improved to 96% with a **1**:**2** ratio of 1:8 or 1:10 (Table 1, entries 1–2). This result really encouraged us and extensive exploration of the conditions was further carried out. When the reaction temperature was dropped from 120 °C to 80 °C, 70% and 30% of the desired product **3** were obtained respectively (Table 1, entries 6–7). Subsequent solvent screening suggested that *N*,*N*-dimethylformamide (DMF) was the optimal one with 1,4-diphenylbutadiyne **1** (1 mmol) and benzylamine **2** (8 mmol) catalyzed by $K_2CO_3$ (0.5 mmol), and the desired product **3** was obtained in 99% isolated yield without any byproducts at 140 °C under air. It is worth noting that the reaction could proceed without a base, also as a catalyst, rendering the desired product in 38% isolated yield (Table 1, entry 11), which demonstrated that the yield of desired product **3** depends on the catalytic activity of the base. To demonstrate the catalytic value of a variety of bases, the synthetic reactions of 2,3,6-triphenylpyridine between 1,4-diphenylbutadiyne **1** (1 mmol) and benzylamine **2** (8 mmol) were carried out in DMF using different bases at 140 °C for 10 h with 0.5 mmol catalyst loading under air (Table 1, entries 12–20). The almost quantitative yield (99%) was obtained by using $K_2CO_3$ as the catalyst (Table 1, entry 8). Use of other bases, such as $Na_2CO_3$, NaOH, KOH and $KHCO_3$ also gave good yields (Table 1, entries 13–15, 17). Under similar reaction conditions, $Cs_2CO_3$, NaF, $NaH_2PO_4$, $KH_2PO_4$ and $CH_3COONa$ afforded only moderate yield (Table 1, entries 12, 16, 18–20). These resultsindicate that $K_2CO_3$ is very effective in promoting the synthesis of arylated pyridines from conjugated acetylenes and substituted benzylamines under facile conditions.

**Table 1.** Optimization of the reaction conditions [a].



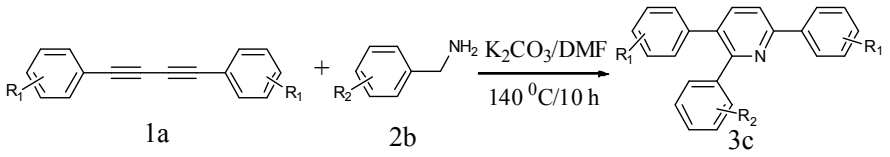

1 2 3

| Entry | Ratio of 1:2 | Temperature | Solvent | Catalyst | Yield(%) [b] |
|---|---|---|---|---|---|
| 1 | 1:10 | 140 °C | DMSO | $K_2CO_3$ | 96 |
| 2 | 1:8 | 140 °C | DMSO | $K_2CO_3$ | 96 |
| 3 | 1:6 | 140 °C | DMSO | $K_2CO_3$ | 85 |
| 4 | 1:5 | 140 °C | DMSO | $K_2CO_3$ | 80 |
| 5 | 1:4 | 140 °C | DMSO | $K_2CO_3$ | 70 |
| 6 | 1:8 | 120 °C | DMSO | $K_2CO_3$ | 70 |
| 7 | 1:8 | 80 °C | DMSO | $K_2CO_3$ | 30 |
| 8 | 1:8 | 140 °C | DMF | $K_2CO_3$ | 99 |
| 9 | 1:8 | 140 °C | DMAc | $K_2CO_3$ | 94 |
| 10 | 1:8 | 140 °C | PEG400 | $K_2CO_3$ | 50 |
| 11 | 1:8 | 140 °C | DMF | _ | 38 |
| 12 | 1:8 | 140 °C | DMF | $Cs_2CO_3$ | 65 |
| 13 | 1:8 | 140 °C | DMF | $Na_2CO_3$ | 81 |
| 14 | 1:8 | 140 °C | DMF | NaOH | 86 |
| 15 | 1:8 | 140 °C | DMF | KOH | 88 |
| 16 | 1:8 | 140 °C | DMF | NaF | 65 |
| 17 | 1:8 | 140 °C | DMF | $NaHCO_3$ | 87 |
| 18 | 1:8 | 140 °C | DMF | $NaH_2PO_4$ | 53 |
| 19 | 1:8 | 140 °C | DMF | $KH_2PO_4$ | 61 |
| 20 | 1:8 | 140 °C | DMF | $CH_3COONa$ | 63 |

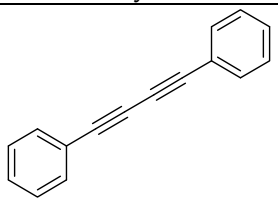
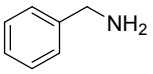
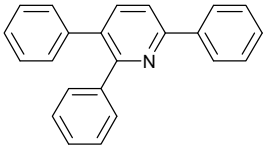
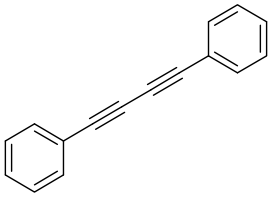
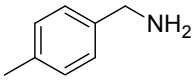
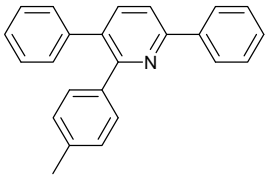
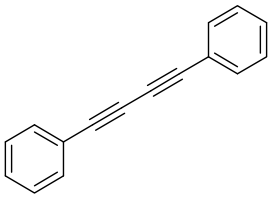
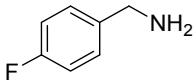
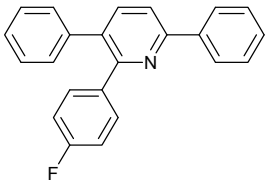
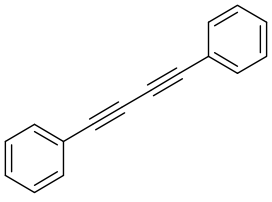
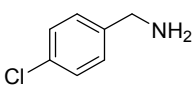
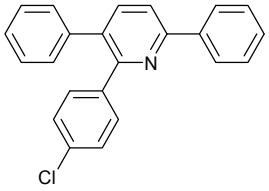
[a] The reactions were conducted with 1,4-diphenylbutadiyne and benzylamine, and base (0.5 mmol), solvent (0.5 mL), 10 h; [b] Isolated yield.

Under the optimized reaction conditions, the scope of this synthetic protocol was evaluated to test the compatibility of varying symmetrical 1,4-diarylbuta-1,3-diynes as starting materials (Table 2). The 1,4-diarylbuta-1,3-diyne bearing two methyl groups at the 1- and 4-position was easily converted to give the desired products with excellent yield (90%) in the synthesis of arylated pyridines using benzylamine (**3cbb**). However, 1,4-bis(4-butylphenyl)buta-1,3-diyne was slightly less reactive, giving the desired product with 60% yield under the same conditions, and this result clearly demonstrated that steric hindrance has an effect on the yield of desired product (**3cfb**). The reaction using sterically hindered 1,4-di-*o*-tolylbuta-1,3-diyne and 1,4-di-*m*-tolylbuta-1,3-diyne led to 77% and 78% yields, respectively (**3ccb**, **3cdb**).Investigations of substituted benzylamines in the synthesis of arylated pyridines using 1,4-diphenylbutadiyne were also conducted. The reaction with substituted benzylamine having an electron-donating group was carried out efficiently, affording almost quantitative yield (99%) (**3cac**).Various substituted benzylamines bearing electron-withdrawing groups, such as -F, -Cl, and -$CF_3$, provided the corresponding products in moderate to good yields (**3cad**, **3cae**, **3caf**). The steric and electronic effects of the substrate bearing electron-withdrawing substituent in the 3-position of benzylamine remarkably affected the reaction yield: upon using [3-(trifluoromethyl)phenyl]methanamine, product 3,6-diphenyl-2-[3-(trifluoromethyl)phenyl]pyridine was obtained in 50% yield (**3caf**).

**Table 2.** Synthesis of arylated pyridines from conjugated acetylenes and substituted benzylamines under optimized conditions. [a]




1a 2b 3c

| Entry | Acetylene | Benzylamine | Product | Yield(%) [b] |
|---|---|---|---|---|
| 1 |  |  |  **3cab** | 99 |
| 2 |  |  |  **3cac** | 99 |
| 3 |  |  |  **3cad** | 73 |
| 4 |  |  |  **3cae** | 62 |

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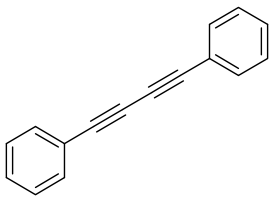
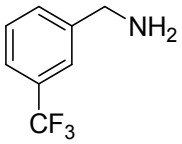
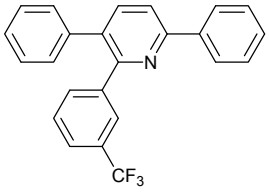
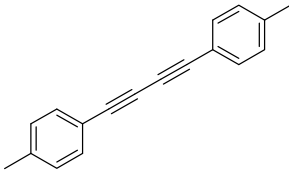
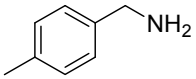
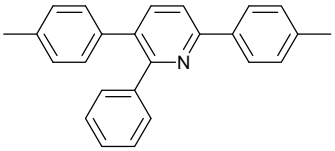
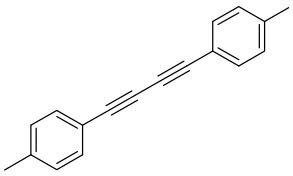
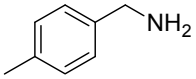
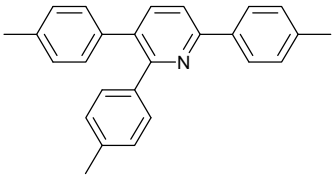
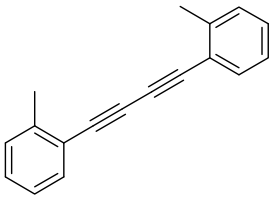
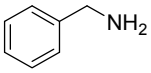
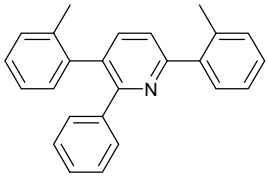
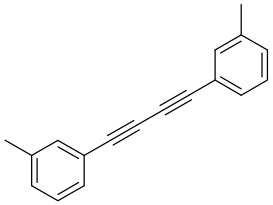
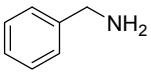
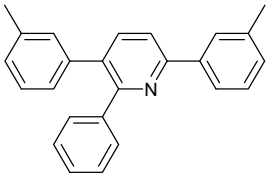
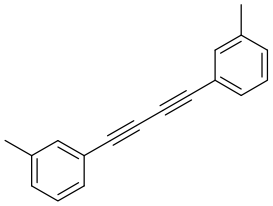
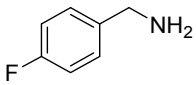
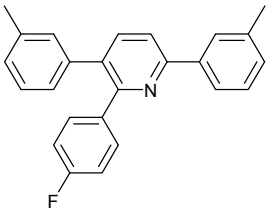
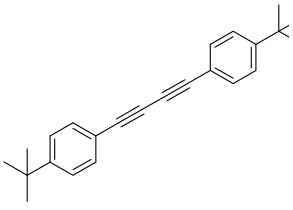
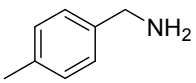
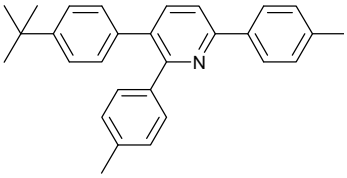
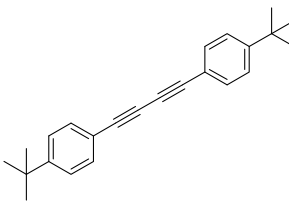
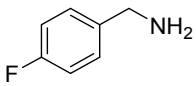
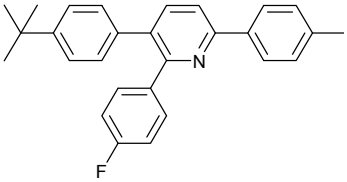
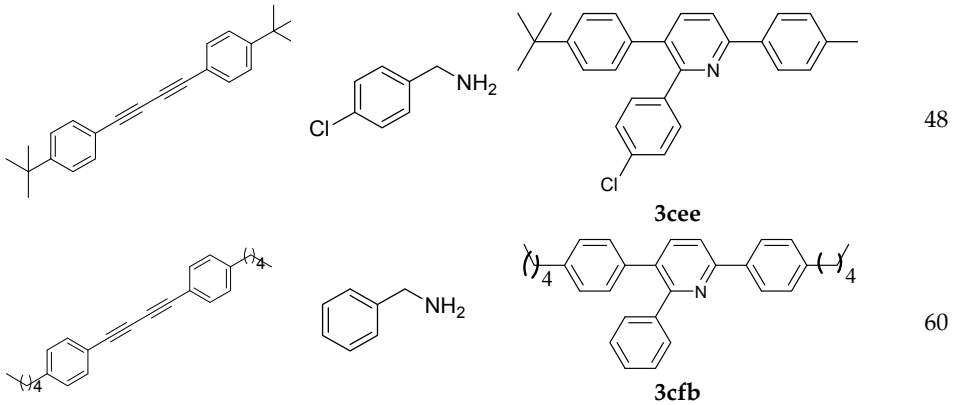
|---|---|---|---|---|---|
| 5 |  |  |  **3caf** | | 50 |
| 6 |  |  |  **3cbb** | | 90 |
| 7 |  |  |  **3cbc** | | 99 |
| 8 |  |  |  **3ccb** | | 77 |
| 9 |  |  |  **3cdb** | | 78 |
| 10 |  |  |  **3ccd** | | 63 |
| 11 |  |  |  **3cec** | | 65 |
| 12 |  |  |  **3ced** | | 45 |




[a] Reaction conditions: conjugated acetylene (**1a**) (0.25 mmol), substituted benzylamine (**2b**) (2.0 mmol), $K_2CO_3$ (0.5 mmol), DMF (0.5 mL), 140 °C, 10 h; [b] Isolated yield.

## 3. Materials and Methods

### *3.1. General Conditions*

All manipulations were performed under air. All reagents employed in the synthesis were analytical grade, purchased from J&K Scientific Ltd. (Shanghai, China) and used as received without any prior purification. The products were isolated by thin layer chromatography on silica gel using petroleum ether as the eluent. $^1$H-NMR, $^{13}$C-NMR spectra were recorded on a BrukerAvance III (400 MHz, Bruker Corporation, Billerica, MA, USA) spectrometer using tetramethylsilane as the internal standard and $CDCl_3$ as the solvent. Chemical shift values are expressed in ppm relative to external TMS (see supplementary).

### *3.2. General Procedure for the Preparation of Arylated Pyridines*

1,4-Disubstituted-1,3-diacetylene (0.25 mmol) and $K_2CO_3$ (0.5 mmol) were added, under air, to a solution of appropriate benzylamine (2.0 mmol) in DMSO (0.5 mL) previously heated at 140 °C. The resulting solution was stirred for 10 h at this temperature and washed with saturated aqNaCl, extracted with ethyl acetate (3 × 15 mL). The combined organic phase was dried with anhydrous $Na_2SO_4$, filtrated and concentrated under vacuum to yield the crude product. The crude product was purified by thin layer chromatography on silica gel with petroleum ether as eluent.

### *3.3. Analytical Data of Representative Products*

*2,3,6-Triphenylpyridine*: White crystals (m.p. = 110–111 °C, lit [24] 110.5–112 °C, lit [25] 111–112 °C). $^1$H-NMR (400 MHz, $CDCl_3$) δ 8.20 (d, 2H), 7.98–7.75 (m, 2H), 7.50 (dq, 5H), 7.30 (ddd, 8H).$^{13}$C-NMR (101 MHz, $CDCl_3$) δ 156.64, 155.68, 140.43, 140.01, 139.43, 139.10, 134.43, 130.23, 129.59, 129.01, 128.75, 128.37, 127.84, 127.18, 127.02, 118.59. lit [25]: $^1$H-NMR (400MHz, $CDCl_3$) δ 8.16–8.14 (m, 2H), 7.78–7.77 (m, 2H), 7.51–7.42 (m, 5H), 7.30–7.21 (m, 9H); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 156.6, 155.6, 140.4, 140.0, 139.4, 139.1, 134.4, 130.2, 129.5, 129.0, 128.7, 128.3, 127.8, 127.1, 127.0, 118.5. HRMS (EI) calcd. for $C_{23}H_{17}N$: 307.1361, found: 307.2.

*2-(4-Fluorophenyl)-3,6-diphenylpyridine*: White solid (m.p. = 115–117 °C, lit [22] 115–116 °C). $^1$H-NMR (400 MHz, $CDCl_3$) δ 8.19 (d, 2H), 7.82 (d, 2H), 7.52 (dd, 5H), 7.32 (d, 3H), 7.27 (d, 2H), 7.01 (d, 2H). $^{13}$C-NMR (101 MHz, $CDCl_3$) δ 162.53 ($J_{C-F}$ = 245.6 Hz), 155.73, 155.53, 139.81, 139.56, 138.95, 134.31 ($J_{C-F}$ = 4.3 Hz), 132.06, 131.97 ($J_{C-F}$ = 8.2 Hz), 129.55, 129.13, 128.82, 128.53, 127.34, 126.99, 118.70, 114.74($J_{C-F}$ = 21.5 Hz). lit [22]: $^1$H-NMR (400 MHz, $CDCl_3$): δ 8.13 (d, 2H), 7.77 (s, 2H), 7.51–7.42 (m, 5H), 7.31–7.29 (m, 3H), 7.22–7.20 (m, 2H), 6.94 (t, 2H); $^{13}$C-NMR (100 MHz, $CDCl_3$): 162.5 ($J_{C-F}$ = 245.6 Hz), 155.7, 155.5, 139.8, 139.5, 138.9, 136.4 ($J_{C-F}$ = 4.3 Hz), 134.2, 131.9 ($J_{C-F}$ = 8.2 Hz), 129.5, 129.0, 128.7, 128.4, 127.2, 126.9, 118.6, 114.7 ($J_{C-F}$ = 21.5Hz). HRMS (EI) calcd. for $C_{23}H_{16}FN$: 325.1267, found: 325.2.

## 4. Conclusions

In summary, an efficient protocol for arylated pyridines from conjugated acetylenes and substituted benzylamines catalyzed by base was developed, which gives a much more convenient approach to obtain arylated pyridines with good to excellent yields. Compared to the approachreported by Chalk [21], the advantages of this protocol are inthe absence ofbyproduct detected by GC-MS even if the reaction was carried out in the air. Efforts to understand this reaction mechanism are in progress in our laboratory.

**Supplementary Materials:** Supplementary materials are available online.

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**Conflicts of Interest:** The authors declare no conflict of interest.

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**Sample Availability:** Samples of the compounds are available from the authors.