Synthesis of Substituted Pyridines and Quinolines

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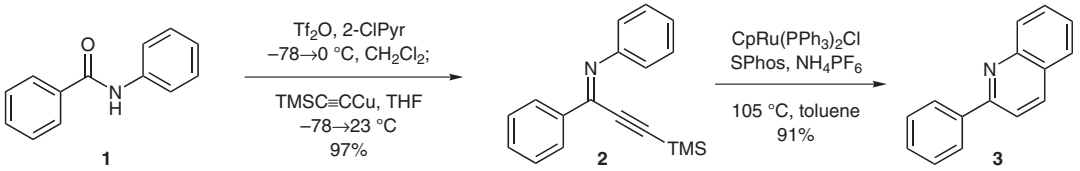
Abstract: A variety of *N*-vinyl and *N*-aryl amides were converted to the corresponding pyridine and quinoline derivatives, respectively. Amide activation and nucleophilic addition of copper(I) (trimethylsilyl)acetylide efficiently provided the desired alkynyl imines. Ruthenium-catalyzed protodesilylation and cycloisomerization of these imines gave the corresponding azaheterocycles.

Key words: amide, imine, pyridine, quinoline, vinylidene



Scheme 1

Introduction

Pyridines and quinolines are important classes of azaheterocycles and are found in many pharmaceuticals, natural products, and fine materials.[1,2] Their significance has inspired many synthetic methods for their synthesis and derivatization. Most syntheses of these azaheterocycles involve either condensation of amines and carbonyl derivatives or cycloaddition reactions.[3,4] Recent advances in cross-coupling chemistry enable the introduction of additional substituents to these azaheterocycles.[5] We describe an efficient two-step procedure for the synthesis of a variety of pyridine and quinoline derivatives from readily available *N*-vinyl and *N*-aryl amides, respectively.[6]

N-Vinyl and *N*-aryl amides serve as attractive starting materials due to their efficient preparation via convergent synthetic procedures.[7] Typical procedures for amide activation include reagents such as phosphorus pentachloride and phosphorus oxychloride.[8] Trifluoromethanesulfonic anhydride (Tf_2O) has been used in carbonyl activation enabling a wide range of valuable synthetic transformations.[9–11]

We found the use of Tf_2O and 2-chloropyridine (2-ClPyr) in CH_2Cl_2 to be the optimal reagent combination for activation of benzamide **1** and its direct conversion to the alkynyl imine **2** (Scheme 1).[6] Other base additives were found to be less effective in this single-step alkynyl imine synthesis (Table 1). The results of our mechanistic studies suggest a superb electrophilic activation of the amide substrates using this reagent combination[11c] that has enabled the use of a wide range of nucleophiles. Related to the chemistry at hand, these conditions have allowed the direct addition of copper(I) (trimethylsilyl)acetylide to a variety of amides to give the corresponding alkynyl imines in good yield.

Table 1 Conversion of Amide **1** to Alkynyl Imine **2**[a]

Entry	Base additive	Base (equiv)	Yield of **2**
1	pyridine	4	<10
2	2,6-lutidine	4	27
3	Et_3N	4	<4
4	DIPEA	4	<20
5	2-chloropyridine	4	97
6	2-chloropyridine	3	92
7	2-chloropyridine	2	65

[a] Reaction conditions: Amide **1** (1 equiv), Tf_2O (1.2 equiv), base, CH_2Cl_2, –78 → 0 °C; TMSC≡CCu (2.7 equiv), THF, –78 → 0 °C.

With an efficient synthesis of a variety of *N*-vinyl- and *N*-arylalkynyl imines at hand, we focused on the development of optimal reaction conditions for their conversion to the corresponding azaheterocycles. The chlorocyclopentadienylbis(triphenylphosphine)ruthenium complex [$CpRu(PPh_3)_2Cl$][12] was identified to be an excellent catalyst for the desired cycloisomerization following an in situ protodesilylation of the alkynyl imine substrates

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(Scheme 1). The intermediacy of a metal vinylidene intermediate enables a 6π-electrocyclization to the desired azaheterocycle. Introduction of 2-dicyclohexylphosphino-2′,6′-dimethoxy-1,1′-biphenyl (SPhos)[13] was found to provide for a more robust catalyst system. While the protodesilylated derivative of imine **2** could be used as the substrate for the cycloisomerization reaction to afford product **3**,[4c,6] this was found to be non-optimal due to the need for an additional desilylation step and reduced stability of the substrate. Toluene was found to be the optimal solvent and ammonium hexafluorophosphate was an effective additive allowing in situ protodesilylation of the substrates. These optimal reaction conditions allow the direct conversion of trimethylsilyl alkynyl imines to the corresponding azaheterocycles.

Scope and Limitations

A variety of amides were efficiently converted to the corresponding azadieneyne derivatives (Table 2). *N*-Aryl amides with electron-withdrawing or electron-donating groups were readily converted to the desired alkynyl imines (Table 2, entries 1–5). Aliphatic amides and a urea derivative provided the desired *C*-silylalkynyl imines (Table 2, entries 6–8). Unfortunately, *N*-aryl carbamates (e.g., ethyl and phenyl carbamates) did not provide the corresponding alkynyl imine derivatives (imidates) under the standard reaction conditions. Significantly, we were pleased to find that enamides, including acid sensitive derivatives, could be converted to the corresponding imines in moderate to excellent yield (Table 2, entries 9–16). For comparison, the use of existing methods for the synthesis of *N*-2-thienyl and *N*-dihydropyranyl alkynyl imines (Table 2, entries 13 and 15, respectively) gave none and <10% yield of the desired product, respectively.[8] These *C*-silylalkynyl imines, except that shown in entry 15 of Table 2, were found to be stable toward long-term storage. When necessary, the *C*-silylalkynyl imines could be efficiently desilylated with potassium carbonate in methanol (Table 2, entries 7 and 16).

Table 2 Pyridines and Quinolines Prepared

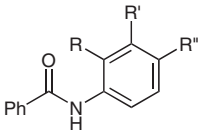
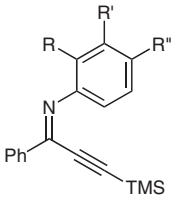
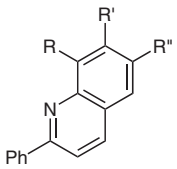
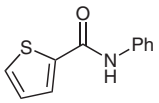
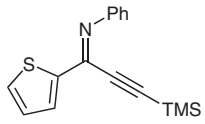
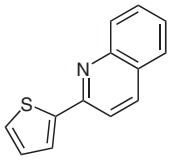
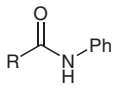
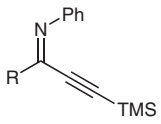
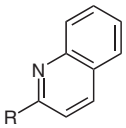
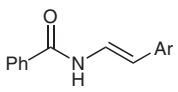
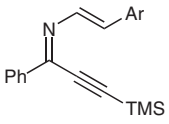
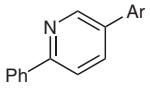
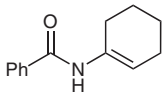
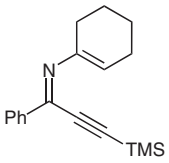
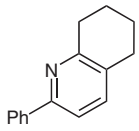
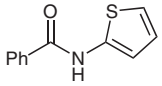
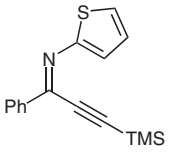
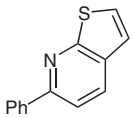
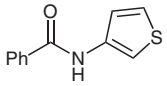
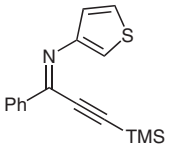
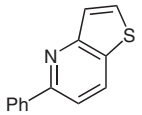
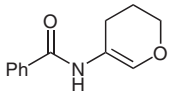
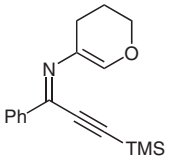
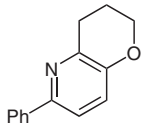
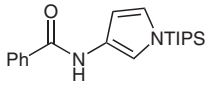
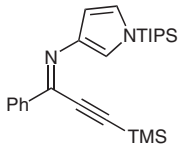
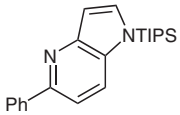
Entry	Amide	Yield (%)[a]	Yield (%)[a]
			
1	R = H, R′ = H, R″ = H (**1**)	97[b] (**2**)	91[b] (**3**)
2	R = H, R′ = H, R″ = OMe	89	92
3	R = OMe, R′ = H, R″ = H	96	91
4	R = H, R′ = CF_3, R″ = H	73, <10[c]	89
5		 81	 75
			
6	R = *c*-C_6H_{11}	85	69
7	R = *t*-Bu	83, 95[c]	69
8	R = $N(CH_2CH_2)_2O$	80	62
			
9	Ar = Ph	78	77
10	Ar = 1-naphthyl	86	83
11	Ar = 3,4-$(MeO)_2C_6H_3$	92	78

Table 2 Pyridines and Quinolines Prepared (continued)

Entry	Amide	Yield (%)[a]	Yield (%)[a]
12		 75	 73
13		 63[d]	 99
14		 98	 97
15		 99	 70
16		 82, 91[c]	 64[e]

[a] Isolated yields: all entries are average of two experiments. Optimum conditions used uniformly.
[b] Gram-scale experiments.
[c] Yield of the corresponding desilylated imine.
[d] Kept at –78 °C.
[e] 5 mol% of catalyst system was used.

The optimized reaction conditions described above for the conversion of azadienynes to the corresponding azaheterocycles provided a variety of pyridines and quinolines. Electron-rich and electron-deficient *N*-aryl derivatives gave the desired products in good yield (Table 2, entries 1–5). The use of aliphatic imines and a urea derivative led to the corresponding quinoline derivatives (Table 2, entries 6–8). We were pleased to find that a variety of *N*-vinyl/heteroaromatic imines could be used as substrates and gave the desired pyridine derivatives in moderate to excellent yield (Table 2, entries 9–16). In rare cases where the rate of the protodesilylation of the *C*-silylalkynyl imines was prohibitively slow, the use of the corresponding terminal alkyne derivatives was beneficial (Table 2, entries 7 and 16).

In conclusion, we have reported an efficient two-step synthesis of a wide range of pyridine and quinoline derivatives from readily available starting materials. Attractive features of this chemistry include the single-step synthesis of alkynyl imines from *N*-vinyl and *N*-aryl amides and the direct ruthenium-catalyzed protodesilylation and cycloisomerization of these products to the corresponding azaheterocycles.

Procedures

Herein we describe the efficient synthesis of alkynyl imines from *N*-aryl or *N*-vinyl amides and the Ru-catalyzed conversion of these alkynyl imines to the corresponding azaheterocycles.

4-Trimethylsilyl-*N*-phenyl-2-phenyl-1-azabut-1-en-3-yne (2); Typical Procedure

A flame-dried flask was charged with anhyd THF (40 mL), cooled to 0 °C, and vigorously stirred as (trimethylsilyl)acetylene (4.74 mL, 3.36 g, 34.2 mmol, 2.70 equiv) was added in one portion via syringe. *n*-BuLi (2.53 M, 13.5 mL, 34.2 mmol, 2.70 equiv) was added over 10 min and the mixture was kept at 0 °C for an additional 5 min before warming to r.t. After 40 min, the lithium (trimethylsilyl)acetylide solution was transferred via cannula over 5 min to a flame dried flask containing $CuBr{\cdot}SMe_2$ complex (7.03 g, 34.2 mmol, 2.70 equiv) and anhyd THF (20 mL) at –78 °C. The resulting bright-yellow solution was maintained at –78 °C for 5 min before it was warmed to 0 °C and maintained at that temperature for an additional 10 min prior to use. Separately, trifluoromethanesulfonic anhydride (2.51 mL, 15.2 mmol, 1.20 equiv) was added via syringe over 1 min to a well-stirred mixture of amide **1** (2.50 g, 12.7 mmol, 1 equiv), 2-chloropyridine (4.81 mL, 50.7 mmol, 4.00 equiv), and anhyd CH_2Cl_2 (25 mL) at –78 °C in a flame-dried and argon-purged Schlenk (Kjeldahl shape) flask. After 5 min, the mixture was warmed to 0 °C. After 20 min, the solution was cooled back down to –78 °C and the freshly prepared solution of copper(I) (trimethylsilyl)acetylide described above was added via cannula. The mixture was kept at –78 °C for 5 min and then warmed to 0 °C. After 10 min, the mixture was filtered through a column of Celite (2 cm diam × 3 cm length) and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (100% hexanes → 7:93 EtOAc–hexanes) to give the alkynyl imine **2** as a yellow oil; yield: 3.42 g (97%); R_f = 0.59 (EtOAc–hexanes, 20:80).

IR (film): 3063 (m), 3030 (w), 2960 (m), 1588 (s), 1565 cm^{-1} (s).

^1H NMR (500 MHz, $CDCl_3$): δ = 8.21–8.18 (m, 2 H), 7.51–7.45 (m, 3 H), 7.40–7.36 (m, 2 H), 7.17 (tt, *J* = 7.5, 1.1 Hz, 1 H), 7.14–7.11 (m, 2 H), 0.14 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 151.7, 150.1, 137.0, 131.4, 128.6, 128.5, 128.3, 125.0, 120.9, 105.4, 97.5, –0.5.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{18}H_{20}NSi$: 278.1360; found: 278.1365.

Anal. Calcd for $C_{18}H_{19}NSi$: C, 77.93; H, 6.90; N, 5.05. Found: C, 77.97; H, 6.87; N, 5.10.

2-Phenylquinoline (3); Typical Procedure

An oven-dried pressure vessel containing a magnetic stir bar was charged with anhyd ammonium hexafluorophosphate (587 mg, 3.60 mmol, 1.00 equiv), $CpRuCl(PPh_3)_2$ (262 mg, 0.35 mmol, 0.10 equiv) and SPhos (148 mg, 0.35 mmol, 0.10 equiv) under N_2 in a glove-box and the flask was sealed and brought out of the glove-box. Imine **2** (1.00 g, 3.60 mmol, 1 equiv) and anhyd toluene (18 mL) were sequentially added via syringe. The flask was flushed with argon, sealed, the contents were vigorously stirred, and placed in an oil bath at 105 °C. After 19 h, the reaction vessel was allowed to cool to r.t. and the mixture was transferred to a recovery flask using CH_2Cl_2 (20 mL). This solution was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (3:20 → 1:1 EtOAc–hexanes) to afford the quinoline **3** as a pale yellow solid; yield: 668 mg (91%); R_f = 0.51 (EtOAc–hexanes, 20:80); mp 79–80 °C.

IR (film): 3189 (s), 3055 (w), 2091 (s), 1617 (w), 1597 (s), 1491 (m), 1447 cm^{-1} (s).

^1H NMR (500 MHz, $CDCl_3$): δ = 8.25 (d, *J* = 8.5 Hz, 1 H), 8.21–8.16 (m, 3 H), 7.90 (d, *J* = 8.5 Hz, 1 H), 7.85 (d, *J* = 8.2 Hz, 1 H), 7.75 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1 H), 7.57–7.52 (m, 3 H), 7.48 (tt, *J* = 7.3, 1.2 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.5, 148.4, 139.8, 137.0, 129.9, 129.9, 129.5, 129.0, 127.8, 127.7, 127.3, 126.5, 119.2.

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{15}H_{11}N$: 205.0886; found: 205.0885.

Anal. Calcd for $C_{15}H_{11}N$: C, 87.77; H, 5.40; N, 6.82. Found: C, 87.81; H, 5.36; N, 6.88.

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