Efficient Introduction of Aryl Acetylenes to Quinolinium and Pyridinium Salts: Synthesis of 1-Acyl-1,2-dihydroquinolines and 1-Acyl-1,2-dihydropyridines

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Recently, we reported the alkynylation of *N*-tosylimines with aryl acetylenes promoted by $ZnBr_2$ and *N*,*N*-diisopropylethylamine (DIEA) in acetonitrile.[1] In the reaction, *in situ* generated zinc acetylide was added to *N*-tosylimine to afford the corresponding *N*-tosyl propargylamines in good yields.[1] As a continuing work we presumed that we could synthesize 1-acyl-1,2-dihydroquinolines and 1-acyl-1,2-dihydropyridines when we used 1-acylquinolinium salts or 1-acylpyridinium salts as the electrophile.

Synthesis of 1-acyl-1,2-dihydroquinolines and 1-acyl-1,2-dihydropyridines have received much attention due to the usefulness of them for the synthesis of natural products and as useful building blocks for alkaloid synthesis.[2,3] The most straightforward method for the synthesis of substituted dihydroquinolines and dihydropyridines is the addition of Grignard reagents to 1-acylquinolinium and 1-acylpyridinium salts.[4b,4c] Besides organomagnesium reagents, other organometallic reagents involving indium,[5a,5c] tin,[5b] silver,[4a] copper,[4d,6] and zinc[4e] were reported as the efficient reagents for the reaction. However, the addition of alkynyl moiety to 1-acylquinolinium or 1-acylpyridinium salts was rather limited.[4]

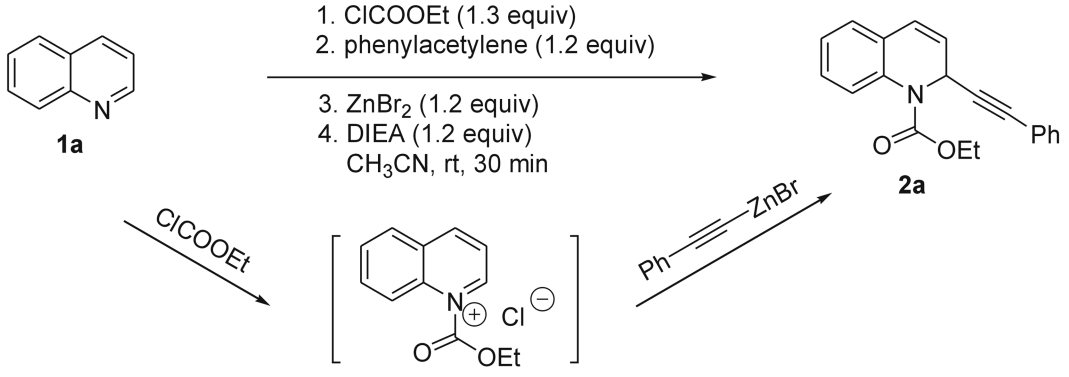
Initially, we tried the reaction of 1-ethoxycarbonylquinolinium chloride and phenylacetylene in acetonitrile in the presence of $ZnBr_2$ and DIEA (*N*,*N*-diisopropylethylamine, Hunig's base) as shown in Scheme 1. The starting material 1-ethoxycarbonylquinolinium chloride was generated *in situ* instantaneously by simply mixing quinoline (**1a**) and ethyl chloroformate in acetonitrile at room temperature. As expected we obtained 1-ethoxycarbonyl-1,2-dihydroquinoline derivative **2a** in 70% isolated yield.

Encouraged by the successful results we tried other entries as shown in Table 1 and obtained moderate to good yields of products. As the substrates, we examined quinoline (entries 1-4), pyridine (entries 5-6), and isoquinoline (entry 7). We used ethyl chloroformate (entries 1-3, 5, 7) and benzoyl chloride (entries 4 and 6) as the activators. As the acetylenes, we chose phenylacetylene (entries 1, 4-7), 4-ethynyltoluene (entry 2), and 1-ethynyl-4-methoxybenzene (entry 3) as the representative examples. As shown in Table 1, we obtained the desired products **2a**-**g** in 63-79% isolated yields. Identification of the structure of **2a**-**g** was carried out by their IR, ^1H and ^{13}C NMR spectra, mass, and/or by comparison with the reported data.[1,4a,4d,6] The ^1H and ^{13}C NMR spectra showed broad peaks in some cases presumably due to the line broadening effect of nitrogen atom as easily can be seen in a similar system.[1,6]

In summary, we disclosed in this paper that the combination of aryl acetylene, $ZnBr_2$, and DIEA could be used for the efficient introduction of acetylene moiety toward activated pyridines, quinolines, and isoquinolines.

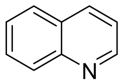
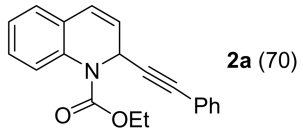
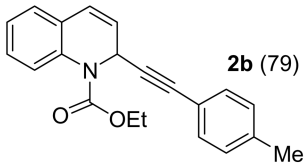
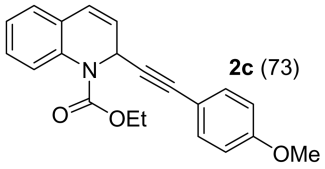
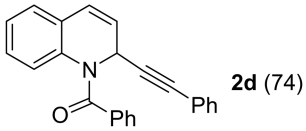
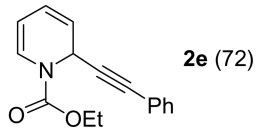
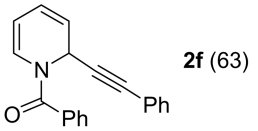
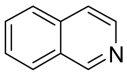
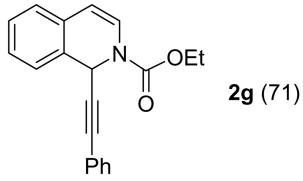
Experimental Section

Typical procedure for the synthesis of 1-ethoxycarbonyl-1,2-dihydroquinoline derivative 2a: To a stirred solution of quinoline (130 mg, 1 mmol) in CH_3CN (2 mL) was added ethyl chloroformate (141 mg, 1.3 mmol), phenylacetylene (122 mg, 1.2 mmol), $ZnBr_2$ (270 mg, 1.2 mmol),



Scheme 1

Table 1. Synthesis of dihydroquinolines, dihydropyridines, and dihydroisoquinolines

Entry	Substrates	Conditions	Products (%)
1	 **1a**	ethyl chloroformate (1.3 equiv) phenylacetylene (1.2 equiv) $ZnBr_2$ (1.2 equiv), DIEA (1.2 equiv) CH_3CN, rt, 30 min	 **2a** (70)
2	**1a**	ethyl chloroformate (1.3 equiv) 4-ethynyltoluene (1.2 equiv) $ZnBr_2$ (1.2 equiv), DIEA (1.2 equiv) CH_3CN, rt, 30 min	 **2b** (79)
3	**1a**	ethyl chloroformate (1.3 equiv) 1-ethynyl-4-methoxybenzene (1.2 equiv) $ZnBr_2$ (1.2 equiv), DIEA (1.2 equiv) CH_3CN, rt, 30 min	 **2c** (73)
4	**1a**	benzoyl chloride (1.3 equiv) phenylacetylene (1.2 equiv) $ZnBr_2$ (1.2 equiv), DIEA (1.2 equiv) CH_3CN, rt, 30 min	 **2d** (74)
5	 **1b**	ethyl chloroformate (1.3 equiv) phenylacetylene (1.2 equiv) $ZnBr_2$ (1.2 equiv), DIEA (1.2 equiv) CH_3CN, rt, 30 min	 **2e** (72)
6	**1b**	benzoyl chloride (1.3 equiv) phenylacetylene (1.2 equiv) $ZnBr_2$ (1.2 equiv), DIEA (1.2 equiv) CH_3CN, rt, 30 min	 **2f** (63)
7	 **1c**	ethyl chloroformate (1.3 equiv) phenylacetylene (1.2 equiv) $ZnBr_2$ (1.2 equiv), DIEA (1.2 equiv) CH_3CN, rt, 30 min	 **2g** (71)

and finally DIEA (155 mg, 1.2 mmol) successively at room temperature. After 30 min the reaction mixture was poured into cold water. After normal workup with ether, removal of solvent, flash column chromatographic purification (hexanes/ether, 40 : 1) we obtained the desired 1-ethoxycarbonyl-1,2-dihydroquinoline derivative **2a**, 213 mg (70%). The spectroscopic data of the synthesized compounds are as follows.

2a: 70%; clear oil; IR (KBr) 2222, 1705, 1489 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.34 (t, J = 7.2 Hz, 3H), 4.20-4.41 (m, 2H), 6.06-6.12 (m, 2H), 6.52-6.58 (m, 1H), 7.03-7.31 (m, 8H), 7.67 (d, J = 8.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.60, 44.72, 62.67, 83.54, 85.83, 122.63, 124.45, 124.53, 125.26, 126.05, 126.71, 126.72, 127.93, 128.19, 128.40, 131.93, 134.49, 153.94; Mass (70 eV) *m/z* (rel intensity) 76 (17), 114 (21), 128 (28), 202 (16), 230 (100), 274 (15), 303 (M^+, 8).

2b: 79%; clear oil; IR (KBr) 2218, 1705 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.33 (t, J = 7.2 Hz, 3H), 2.26 (s, 3H), 4.20-4.39 (m, 2H), 6.05-6.11 (m, 2H), 6.50-6.56 (m, 1H), 6.98-7.26 (m, 7H), 7.66 (d, J = 7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.63, 21.54, 44.81, 62.67, 83.71, 85.13, 119.59, 124.50, 124.52, 125.42, 125.96, 126.73, 126.77, 127.92, 128.98, 131.85, 134.55, 138.53, 153.99.

2c: 73%; clear oil; IR (KBr) 2218, 1705 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.34 (t, J = 7.2 Hz, 3H), 3.73 (s, 3H), 4.20-4.40 (m, 2H), 6.08-6.10 (m, 2H), 6.51-6.57 (m, 1H), 6.73 (d, J = 8.7 Hz, 2H), 7.06-7.15 (m, 2H), 7.18-7.27 (m, 3H), 7.66 (d, J = 8.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$ + 2 drops of DMSO-d_6) δ 14.57, 44.74, 55.28, 62.59, 83.41, 84.36, 113.80, 114.65, 124.41, 124.45, 125.45, 125.79, 126.65, 126.70, 127.84, 133.35, 134.46, 153.92, 159.68.

2d[1,4a]: 74%; clear oil; IR (KBr) 2218, 1651 cm^{-1}; ^1H NMR

(300 MHz, $CDCl_3$) δ 6.19-6.24 (m, 2H), 6.65-6.70 (m, 2H), 6.90 (t, J = 7.5 Hz, 1H), 7.05 (td, J = 7.5 and 1.2 Hz, 1H), 7.17-7.45 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 44.42, 83.66, 85.07, 122.38, 125.10, 125.61, 125.71, 126.13, 126.53, 126.84, 127.12, 127.98, 128.06, 128.25, 128.98, 130.58, 131.79, 134.94, 135.15, 169.38; Mass (70 eV) *m/z* (rel intensity) 77 (52), 105 (100), 129 (18), 230 (14), 306 (13), 335 (M^+, 7).

2e[4d]: 72%; clear oil; IR (KBr) 2221, 1716 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (t, J = 6.9 Hz, 3H), 4.28 (q, J = 6.9 Hz, 2H), 5.36 (m, 1H), 5.66-5.83 (m, 2H), 6.01 (ddt, J = 9.3, 5.7, and 0.9 Hz, 1H), 6.77-6.85 (m, 1H), 7.26-7.41 (m, 5H); Mass (70 eV) *m/z* (rel intensity) 43 (100), 55 (98), 77 (55), 115 (60), 128 (43), 167 (69), 202 (36), 230 (33), 252 (M^+-1, 27).

2f[4a,6]: 63%; clear oil; IR (KBr) 2222, 1720, 1639 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.43 (br s, 1H), 5.81 (br s, 1H), 6.07-6.12 (m, 2H), 6.46 (br s, 1H), 7.28-7.60 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 42.92, 82.99, 86.10, 106.72, 119.99, 122.31, 122.55, 126.64, 128.06, 128.28, 128.33, 128.63, 130.91, 131.89, 133.87, 169.42.

2g: 71%; clear oil; IR (KBr) 2218, 1716 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.23 (t, J = 6.9 Hz, 3H), 4.21 (q, J = 6.9 Hz, 2H), 6.05 (d, J = 7.8 Hz, 1H), 6.39 (s, 1H), 6.89 (d, J = 7.8 Hz, 1H), 7.14-7.41 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.69, 47.34, 62.88, 83.69, 87.40, 108.70, 122.70, 124.59, 125.97, 126.36, 127.50, 128.21, 128.42, 128.53, 129.73, 130.11, 131.98, 152.97; Mass (70 eV) *m/z* (rel intensity) 43 (39), 101 (32), 128 (40), 202 (23), 230 (100), 274 (11), 303 (M^+, 25).

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References and Notes

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