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Facile addition of alkynes to aza-aromatic systems: a new protocol for the preparation of 2-alkynyl-1,2-dihydroquinolines☆

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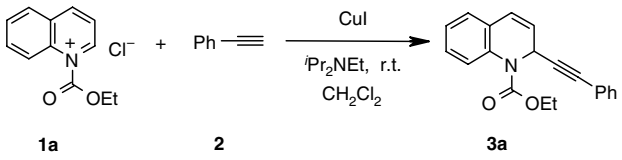
Abstract—1-Alkynes undergo smooth addition to activated quinolines, isoquinolines and pyridines in the presence of copper iodide/$^{i}Pr_2NEt$ under extremely mild conditions to afford 2-alkynyl-1,2-dihydroquinolines in excellent yields with high selectivity. This method is also useful for functionalization of monocyclic pyridines.

The addition of 1-alkynes to aldehydes and imines is an important carbon–carbon bond-forming reaction in organic synthesis.[1] Addition reactions of organometallic reagents to aza-aromatics activated by acyl chlorides are of great importance in organic synthesis, especially for the synthesis of a variety of biologically active nitrogen heterocycles.[2] The addition of alkynes to activated quinolines has attracted much attention for the synthesis of enediyne alkaloids such as dynemicin A.[3] In most cases, alkynyl Grignard reagents have been utilized to introduce alkynyl functionality into quinoline systems.[3–5] Subsequently, alkynyltin and alkynyl silanes were found to be useful for this conversion.[6] Iridium complexes have recently been utilized for the addition of ethynyltrimethylsilane to *N*-acylquinolinium ions via C–H activation.[7] However, most of these methods involve the use of expensive or toxic tin reagents which limits their use in large-scale synthesis. Furthermore, alkynyl Grignard reagents suffer from poor chemoselectivity leading to a mixture of 2- and 4-alkynyl quinolines. Herein, we wish to report the direct addition of alkynes to various quinolines, isoquinolines and pyridines activated by ethyl chloroformate to produce 2-alkynyl-1,2-dihydroheteroaromatics via C–H activation at room temperature. The alkynylation of *N*-acylated quinolinium ion **1a**, generated using ethyl chloroformate, with phenyl acetylene **2** in the presence of 0.5 equiv of copper iodide and



1a **2** **3a**

Scheme 1.

0.5 equiv of diisopropylethylamine was studied in dichloromethane. The reaction went to completion after 5 h and the product, 2-alkynyl-1,2-dihydroquinoline **3a** was obtained in 90% yield (Scheme 1). The solvent free reaction proceeded much faster than reactions in solution. For example, the reaction of **1a** with phenyl acetylene went to completion in 2.5 h under solvent-free conditions.

Several substituted quinolines were found to react smoothly with alkynes in solution to produce the corresponding 2-alkynyl-1,2-dihydroquinoline (Table 1).[8] This method is useful even for the addition of hydroxy substituted alkynes such as propargyl alcohol (entries c, f, g and j). No O–H addition product was observed in the case of propargyl alcohol. In all cases, the nucleophilic addition took place at the 2-position of the quinoline. Similarly, *N*-acylated isoquinolines underwent smooth addition with alkynes leading to the formation of 1-alkynyl-1,2-dihydroisoquinolines (Scheme 2, entries o, p, q and r).

Monocyclic pyridines also reacted readily with alkynes to give 2-substituted dihydropyridines (entries s, t and u). However, diazines failed to undergo nucleophilic

Keywords: Aza-aromatic compounds; Alkynylation; 2-Alkynyl quinolines.

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Table 1. CuI-promoted alkynylation of aza-aromatics

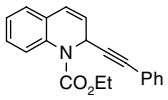
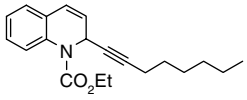
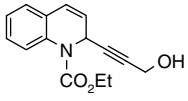
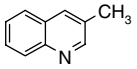
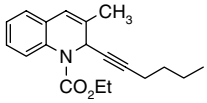
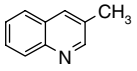
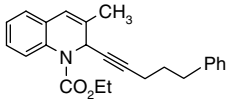
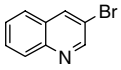
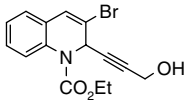
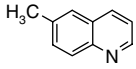
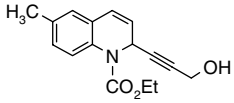
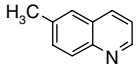
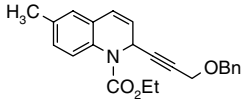
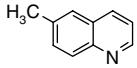
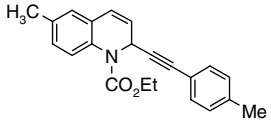
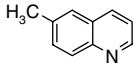
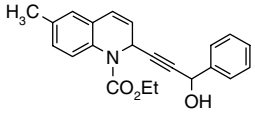
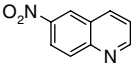
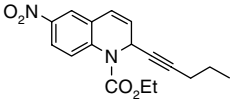
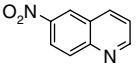
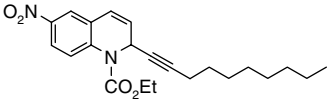
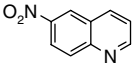
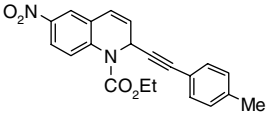
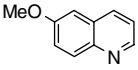
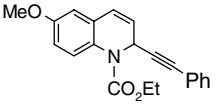
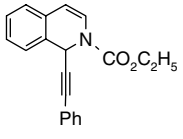
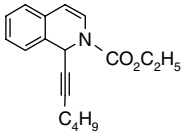
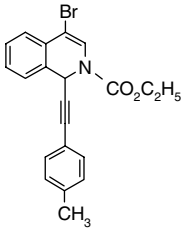
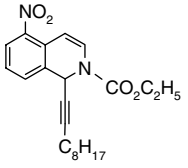
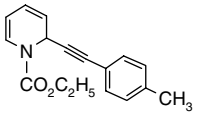
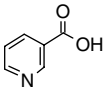
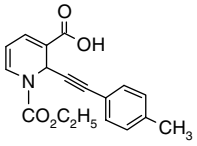
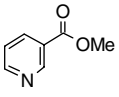
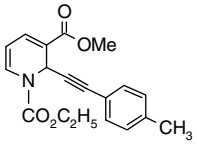
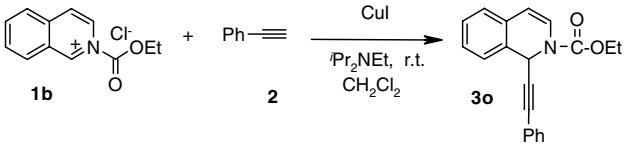
Entry	Quinolines	Product[a]	Yield[b] (%)	Time (h)
a			90	5.0
b			80	5.5
c			75	5.0
d			70	5.5
e			79	6.0
f			72	6.0
g			70	6.0
h			79	5.5
i			87	5.0
j			78	5.0
k			75	5.5
l			74	6.0
m			85	5.0
n			87	5.0
o			86	5.5

Table 1 (*continued*)

Entry	Quinolines	Product[a]	Yield[b] (%)	Time (h)
p			77	5.5
q			78	5.0
r			75	5.5
s			82	5.0
t			75	5.0
u			76	5.0

[a] All products were characterized by NMR, IR and mass spectroscopy.
[b] Isolated yields after purification.



Scheme 2.

addition with alkynes. No 4-substituted adduct was obtained from pyridines and quinolines. The products were characterized by ^{1}H NMR, IR and mass spectroscopy[9] and also by comparison with authentic compounds.[4,5] This method was useful for the alkynylation of both electron-rich and electron-deficient substrates. Although the reaction was also successful using the $Zn(OTf)_2$/Et_3N catalytic system, the products were obtained in comparatively low yields (60–70%) even after long reaction times (8–12 h). Thus, the combination of copper(I)iodide and diisopropylethylamine was the method of choice. No additives or acidic promoters were required for the reaction. The catalyst is readily available at low cost.

In summary, we have developed a simple and efficient method for the alkynylation of quinolines, isoquinolines and pyridines activated by ethyl chloroformate using the copper(I)iodide/diisopropylethylamine catalytic system. In addition to its efficiency, simplicity and mild reaction conditions, this method provides high yields of products with high selectivity and is a useful and attractive process for the preparation of alkynyl substituted dihydroquinolines, isoquinolines and pyridines.

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References and notes

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8. *General procedure*: To a stirred mixture of the alkyne (2 mmol), copper(I)iodide (0.5 mmol) and diisopropylethylamine (0.5 mmol) was added the *N*-acylquinolinium ion in dichloromethane (3 mL) generated from quinoline (1 mmol) and ethyl chloroformate (1.2 mmol). The resulting mixture was stirred at room temperature for the appropriate time (Table 1). After complete conversion, as indicated by TLC, the reaction mixture was quenched with water (10 mL) and extracted with dichloromethane (2×15 mL). The combined extracts were dried over anhydrous Na_2SO_4, and concentrated in vacuo. The product was purified by column chromatography on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 2:8) to afford 2-alkynyl-1,2-dihydroquinoline.
9. *Spectral data for selected products*: Compound **3a**: Liquid, IR (KBr): υ 2981, 2928, 2221, 1708, 1488, 1377, 1296, 1125, 1031, 947, 757, 692 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.72–7.65 (br s, 1H), 7.17–7.32 (m, 6H), 7.1 (t, 2H, $J = 7.4$ Hz), 6.55 (q, 1H, $J = 7.5$, 5.2 Hz), 6.1 (d, 2H, $J = 6.8$ Hz), 4.4–4.2 (m, 2H), 1.38 (t, 3H, $J = 6.8$ Hz); EIMS Mass: *m/z*: 303 M^+, 272, 257, 229, 201, 140, 127, 104, 97, 77, 61, 57, 43; HRMS calcd for $C_{20}H_{17}NO_2Na$: 326.1156. Found: 326.1146. Compound **3g**: Liquid, IR (KBr): υ 3439, 2923, 2219, 1701, 1495, 1379, 1296, 1260, 1113, 1029, 771 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.51–7.41 (br s, 1H), 7.02 (dd, 1H, $J = 8.3$, 1.51 Hz), 6.89 (d, 1H, $J = 1.51$ Hz), 6.44 (d, 1H, $J = 9$ Hz), 5.97 (dd, 1H, $J = 9$, 6 Hz), 5.86 (d, 1H, $J = 6$ Hz), 4.36–4.18 (m, 2H), 4.11 (d, 2H, $J = 1.51$ Hz), 2.32 (s, 3H), 1.35 (t, 3H, $J = 6.7$ Hz); EIMS Mass: *m/z*: 271 M^+, 242, 224, 198, 180, 168, 154, 143, 129, 97, 85, 71, 57, 43; HRMS calcd for $C_{16}H_{17}NO_3Na$: 294.1106. Found: 294.1102. Compound **3i**: Solid, mp 88–89 °C. IR (KBr): υ 2980, 2923, 2219, 1906, 1706, 1499, 1383, 1263, 1125, 1038, 818, 761 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.55–7.47 (br s, 1H), 7.17 (d, 2H, $J = 8.3$ Hz), 7.1 (d, 1H, $J = 9.8$ Hz), 7.0 (d, 2H, $J = 8.3$ Hz), 6.9 (s, 1H), 6.47 (q, 1H, $J = 7.5$, 5.2 Hz), 6.05 (d, 2H, $J = 6.8$ Hz), 4.36–4.21 (m, 2H), 2.32 (s, 3H), 2.29 (s, 3H), 1.36 (t, 3H, $J = 6.8$ Hz); FAB mass: *m/z*: 331 M^+, 302, 274, 258, 232, 216, 188, 172, 129, 97, 85, 71, 57, 43. Anal. Calcd for $C_{22}H_{21}NO_2$: C, 79.73; H, 6.39; N, 4.23. Found: C, 79.04; H, 5.97; N, 3.97. Compound **3l**: Solid, mp 64–65 °C. IR (KBr): υ 2922, 2850, 2215, 1710, 1519, 1483, 1384, 1305, 1270, 1234, 1137, 1042, 916, 831, 739 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.11 (dd, 1H, $J = 9$, 3 Hz), 8.0 (d, 1H, $J = 3$ Hz), 7.86 (d, 1H, $J = 9$ Hz), 6.55 (d, 1H, $J = 9.8$ Hz), 6.13 (dd, 1H, $J = 9$, 6 Hz), 5.8 (d, 1H, $J = 6$ Hz), 4.39–4.28 (m, 2H), 2.05 (dt, 2H, $J = 6.7$, 2.2 Hz), 1.38 (t, 5H, $J = 6.7$ Hz), 1.32–1.18 (m, 10H), 0.87 (t, 3H, $J = 6.7$ Hz); FAB mass: *m/z*: 384 M^+, 356, 311, 247, 175, 155, 136, 109, 95, 81, 69, 55. Anal. Calcd for $C_{22}H_{28}N_2O_4$: C, 68.73; H, 7.34; N, 7.29. Found: C, 67.33; H, 6.91; N, 7.13. Compound **3m**: Solid, mp 165–166 °C. IR (KBr): υ 2983, 2219, 1910, 1717, 1518, 1481, 1379, 1295, 1112, 1036, 911, 757 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.13 (dd, 1H, $J = 9$, 3 Hz), 8.01 (d, 1H, $J = 2.2$ Hz), 7.89 (d, 1H, $J = 9$ Hz), 7.16 (d, 2H, $J = 8.1$ Hz), 7.0 (d, 2H, $J = 7.4$ Hz), 6.61 (d, 1H, $J = 9.6$ Hz), 6.22 (dd, 1H, $J = 9$, 6 Hz), 6.07 (d, 1H, $J = 6$ Hz), 4.42–4.3 (m, 2H), 2.14 (s, 3H), 1.39 (t, 3H, $J = 6.7$ Hz); FAB mass: *m/z*: 362 M^+, 347, 333, 307, 289, 259, 247, 215, 203, 175, 136, 109, 95, 81, 69, 55. Anal. Calcd for $C_{21}H_{18}N_2O_4$: C, 69.60; H, 5.01; N, 7.73. Found: C, 70.06; H, 4.77; N, 7.03. Compound **3p**: Liquid, IR (KBr): υ 2959, 2221, 1712, 1639, 1455, 1376, 1335, 1293, 1236, 1125, 1019, 898, 769 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.22–7.08 (m, 3H), 7.02 (d, 1H, $J =$ 6.8 Hz), 6.85 (d, 1H, $J = 7.55$ Hz), 6.0 (d, 1H, $J =$ 7.55 Hz), 5.86 (br s, 1H), 4.37–4.28 (m, 2H), 2.09 (t, 2H, $J = 6.7$ Hz), 1.47–1.23 (m, 7H), 0.85 (t, 3H, $J = 6.7$ Hz); EIMS mass: *m/z*: 283 M^+, 253, 237, 209, 180, 166, 128, 115, 77, 41; HRMS calcd for $C_{18}H_{21}NO_2Na$: 306.1469. Found: 306.1483. Compound **3s**: Liquid, IR (KBr): υ 2924, 2220, 1719, 1590, 1460, 1376, 1308, 1257, 1216, 1113, 1022, 817, 759 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.31 (d, 2H, $J = 7.536$ Hz), 7.08 (d, 2H, $J = 8.373$ Hz), 6.81 (d, 1H, $J = 9.153$ Hz), 6.02 (dd, 1H, $J = 8.373$, 5.836 Hz), 5.75 (br d, 2H, $J = 9.354$ Hz), 5.37 (t, 1H, $J = 6.699$ Hz), 4.29 (m, 2H), 2.33 (s, 3H), 1.34 (t, 3H, $J = 6.699$ Hz); EIMS mass: *m/z*: 267 M^+, 238, 194, 191, 165, 152, 139, 115, 91, 78, 57, 41; HRMS calcd for $C_{17}H_{17}NO_2Na$: 290.1156. Found: 290.1146.