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Allylation and cyanation of aza-aromatics activated by chloroformate and a catalytic amount of iodine☆

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Abstract—Allyltrimethylsilane and trimethylsilyl cyanide undergo smooth addition to *N*-acylated quinolines in the presence of a catalytic amount of iodine to afford 2-allyl- and 2-cyano-1,2-dihydroquinoline derivatives, respectively in good yields with high chemo- and regioselectivity. A variety of functional groups such as alkyl, alkoxy, halo, and nitro functionalities are tolerated under the reaction conditions.
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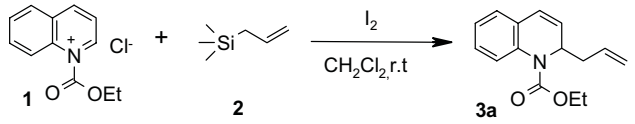
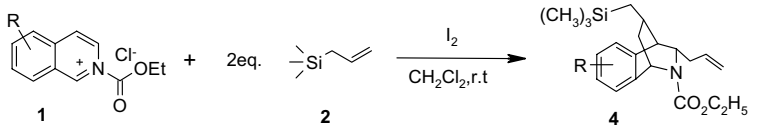
Addition reactions of organometallic reagents to activated aza-aromatics, generated in situ by chloroformates or acyl chlorides, are of great importance in organic synthesis, especially for the synthesis of biologically active alkaloids.[1] Among the methods used, allylation and cyanation of activated aza-aromatics are important methods for syntheses of quinoline and isoquinoline analogs.[2] Organometallic reagents such as allyltin, allylindium, and allylsilanes have been used extensively to introduce allylic functionality into these nitrogen heterocycles.[3–5] However, many of these methods involve the use of toxic tin compounds, expensive reagents, and require a stoichiometric amount or even an excess of the Lewis acid to obtain reasonable reaction rates and acceptable yields of products. Furthermore, allylindium or allylmagnesium reagents are reported to produce a mixture of α- and γ-allylated products.[6] There is still scope to develop a simple and efficient method for the allylation and cyanation of *N*-acylated aza-aromatics using less toxic and easily handled allylsilanes.



Scheme 1.

In continuation of our interest in catalytic applications of elemental iodine for organic transformations,[7] we report herein a mild and convenient method for the allylation of both activated quinolines and isoquinolines using elemental iodine as catalyst. Initially, we attempted the allylation of *N*-acylated quinoline **1**, generated by ethyl chloroformate, with allyltrimethylsilane **2** in the presence of 10 mol % of elemental iodine. The reaction went to completion in 2.5 h and the product, 2-allyl-1,2-dihydroquinoline **3a** was obtained in 85% yield (Scheme 1).



Scheme 2.

Keywords: Aza-aromatics; Iodine catalysis; Allylation; Cyanation.
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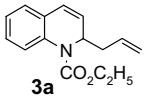
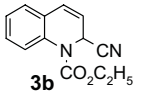
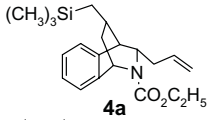
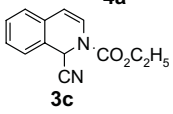
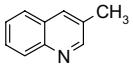
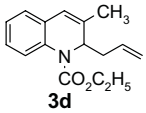
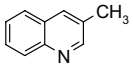
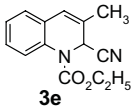
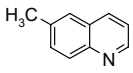
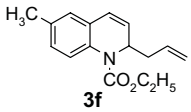
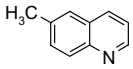
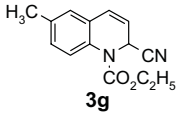
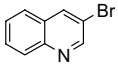
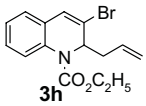
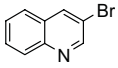
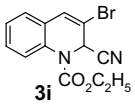
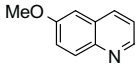
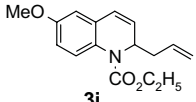
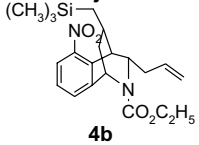
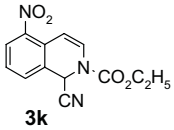
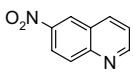
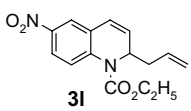
Table 1. I_2-Catalyzed allylation and cyanation of aza-aromatics activated by chloroformate

Entry	Quinolines	Product[a]	Yield (%)[b]	Time (h)	Refs.
(a)		 **3a**	84	2.5	4a
(b)		 **3b**	80	3.0	
(c)		 **4a**	75	2.5	4a
(d)		 **3c**	82	3.0	
(e)		 **3d**	80	2.5	4a
(f)		 **3e**	75	3.0	
(g)		 **3f**	81	2.5	
(h)		 **3g**	72	3.5	
(i)		 **3h**	70	2.5	4a
(j)		 **3i**	67	3.5	
(k)		 **3j**	79	3.5	4a
(l)		 **4b**	65	2.5	4a
(m)		 **3k**	72	4.0	
(n)		 **3l**	70	3.0	4a

[a] All products were characterized by ^{1}H NMR, IR, and mass spectroscopy.
[b] Isolated yields after purification.

Similarly, several substituted quinolines reacted smoothly with allyltrimethylsilane to produce the corresponding 2-allyl-1,2-dihydroquinoline derivatives. In all cases, the nucleophilic addition took place selectively at the 2-position of the quinoline whereas 2- and 4-allylated products are formed when allyl Grignards are used. Encouraged by the results obtained with quinolines, we turned our attention to isoquinolines. Interestingly, *N*-acylated isoquinolines underwent smooth addition with 2 equiv of allyltrimethylsilane leading to the formation of benzoisoquinuclidines[4a] as a 1:1 mixtures of invertomers (**4**) (Scheme 2).

The mono-allylated products were not observed by NMR. The formation of benzoisoquinuclidine from an isoquinoline was consistent with the literature.[4] Like allylsilane, trimethylsilyl cyanide (TMSCN) also reacted efficiently with *N*-acylated quinolinium and *N*-acylated isoquinolinium ions to give 2-cyano-1,2-dihydroquinoline and 1-cyano-1,2-dihydroisoquinoline derivatives, respectively (Table 1, entries b, d, f, h, j, and m). In all cases the reactions proceeded smoothly at ambient temperature with high regioselectivities. No 4-substituted adduct normally formed by Grignard reagents was obtained under these reaction conditions. The products were characterized by ^{1}H NMR, IR, and mass spectroscopy[9] and by comparison with authentic compounds.[4a] Dichloromethane is the solvent of choice. This method is useful for the allylation of both electron-rich and electron-deficient quinolines. The results of the allylation and cyanation of both quinolines and isoquinolines, are presented in Table 1.[8] Although the reaction was successful with a catalytic amount of TMSI, the products were obtained in comparatively low yields (50–65%) after longer reaction times (6–10 h). Thus, the combination of allyltrimethylsilane and iodine is better.

In summary, we have described in efficient method for the allylation and cyanation of quinolines and isoquinolines activated by ethyl chloroformate using elemental iodine as catalyst.

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8. *General procedure*: To a solution of quinoline (1 mmol), in CH_2Cl_2 (3 mL) was added $ClCO_2Et$ (1.5 mmol) and the mixture stirred at room temperature for 0.5 h. To the reaction was added iodine (0.1 mmol), and an allylic silane (1.2 mmol) under ice cooling and the reaction was stirred at rt for the appropriate time (Table 1). The reaction mixture was quenched with water (5 mL) and extracted with dichloromethane (3×10 mL) the combined extracts were washed with 15% solution of sodium thiosulfate, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The resulting product was purified by column chromatography on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 1:9) to afford pure product.
9. *Spectral data for selected products*: **3b**: Solid, mp 65–66 °C. IR (KBr): ν 2982, 2240, 1712, 1489, 1376, 1293, 1260, 1129, 1034, 920, 764 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.72 (d, 1H, J = 8 Hz), 7.35 (t, 1H, J = 8 Hz), 7.15 (m, 2H), 6.7 (d, 1H, J = 9 Hz), 6.1 (d, 1H, J = 6.4 Hz), 6.0 (dd, 1H, J = 9, 6.4 Hz), 4.4–4.2 (m, 2H), 1.4 (t, 3H, J = 7.4 Hz); EIMS Mass: m/z: 228 M$^+$, 184, 155, 129, 102, 77. Anal. Calcd for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.85; H, 5.28; N, 12.25. Compound **3c**: Solid, mp 83–84 °C. IR (KBr): ν 2959, 2239, 1712, 1639, 1455, 1376, 1335, 1293, 1236, 1125, 1019, 898, 769 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33 (dt, 1H, J = 6.8, 2.6 Hz), 7.26 (m, 2H), 7.13 (d, 1H, J = 6.8 Hz), 6.99 (d, 1H, J = 7.55 Hz), 6.31 (s, 1H), 5.98 (d, 1H, J = 7.55 Hz), 4.4–4.3 (m, 2H), 1.37 (t, 3H, J = 6.7 Hz); EIMS Mass: m/z: 228 M$^+$, 202, 184, 156, 129, 102, 77. Anal. Calcd for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.65, H, 5.55, N, 12.34. Compound **3e**: Solid, mp 79–80 °C. IR (KBr): ν 2930, 2240, 1702, 1377, 1324, 1251, 1029 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.52 (d, 1H, J = 8.1 Hz), 7.25 (t, 1H, J = 8.1 Hz), 7.1 (m, 2H), 6.4 (s, 1H), 5.7 (s, 1H), 4.45–4.20 (m, 2H), 2.1 (s, 3H), 1.4 (t, 3H, J = 7.4 Hz); EIMS Mass: m/z: 242 M$^+$, 214, 198, 170, 157, 144, 116, 78, 43. Anal. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.39; H, 5.62; N, 11.50. Compound **3f**: Liquid. IR (KBr): ν 2980, 1703, 1497, 1396, 1315, 1256, 1127, 1045, 916, 818, 763, 714 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39 (br s, 1H), 7.0 (d, 1H, J = 7.5 Hz), 6.84 (s, 1H), 6.4 (d, 1H, J = 9 Hz), 5.99 (dd, 1H, J = 9.8, 6 Hz), 5.80–5.65 (m, 1H), 5.07–4.9 (m, 3H), 4.3–4.15 (m, 2H), 2.31 (s, 3H), 2.2–2.06 (m, 2H), 1.31 (t, 3H, J = 6.77 Hz). EIMS Mass: m/z: 257 M$^+$, 217, 173, 145, 117, 90, 43. Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.38; H, 7.03; N, 5.02. Compound **3g**: Solid, mp 122–123 °C. IR (KBr): ν 2930, 2240, 1702, 1377, 1324, 1251, 1029 cm^{-1}; ^{1}H NMR(300 MHz, $CDCl_3$): δ 7.54

(d, 1H, J = 7.6 Hz), 7.12 (d, 1H, J = 8.4 Hz), 7.0 (br s, 1H), 6.7 (d, 1H, J = 9.3 Hz), 6.1 (d, 1H, J = 5.92 Hz), 5.98 (dd, 1H, J = 9.3, 5.92), 4.42–4.28 (m, 2H), 2.37 (s, 3H), 1.39 (t, 3H, J = 6.77 Hz); EIMS Mass: *m/z*: 242 M^+, 198, 169, 143, 115, 57, 43. Anal. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.42; H, 5.48; N, 11.32. Compound **3i**: Solid, mp 94–95 °C. IR (KBr): ν 2982, 2937, 2238, 1702, 1571, 1487, 1373, 1322, 1251, 1038, 918, 756 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.65 (d, 1H, J = 7.6 Hz), 7.36 (dt, 1H, J = 6.77, 2.5 Hz), 7.32 (m, 2H), 7.03 (s, 1H), 6.16 (s, 1H), 4.46–4.28 (m, 2H), 1.41 (t, 3H, J = 6.77 Hz). EIMS Mass: *m/z*: 308 (M^++2), 306, 235, 233, 209, 207, 155, 154, 128, 127, 101, 75, 51. Anal. Calcd for $C_{13}H_{11}N_2O_2$ Br: C, 50.84; H, 3.61; N, 9.12. Found: C, 50.66; H, 3.77; N, 9.22. Compound **3k**: Solid, mp 93–94 °C. IR (KBr): ν 2970, 2930, 2251, 1708, 1518, 1343, 1301, 1043, 747 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.06 (d, 1H, J = 9 Hz), 7.52 (br s, 1H), 7.41 (t, 1H, J = 7.5 Hz), 7.12 (d, 1H, J = 8.3 Hz), 6.83 (d, 1H, J = 8.3 Hz), 6.41 (s, 1H), 4.4 (m, 2H), 1.4 (t, 3H, J = 7.4 Hz). EIMS Mass: *m/z*: 273 M^+, 247, 174, 164, 146, 128, 116, 101, 91, 75, 57, 43. Anal. Calcd for $C_{13}H_{11}N_3O_4$: C, 57.14; H, 4.06; N, 15.38. Found: C, 57.12; H, 4.11; N, 15.22.