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Synthesis of *N*-substituted 1,4-dihydroquinolines from the Baylis–Hillman acetates via the successive S_N2'–S_NAr isomerization strategy

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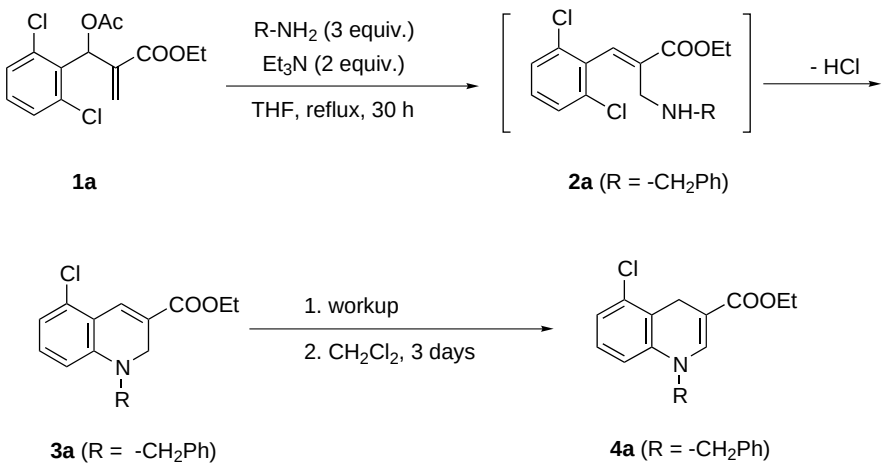
Abstract—1,4-Dihydroquinolines **4a**–**e** were prepared from the reaction of the Baylis–Hillman acetates of *ortho*-halobenzaldehydes and benzylamine or cyclohexylamine via the successive S_N2'–S_NAr isomerization strategy.

The Baylis–Hillman reaction provides a simple atom economic synthesis of β-hydroxy-α-methylene esters, ketones, nitriles, etc.[1] The versatility of the functionality have made these adducts valuable synthetic intermediates.[1] Besides the usefulness of these Baylis–Hillman adducts themselves, further derivatization with various nucleophiles toward synthetically useful compounds has been studied in depth by us and other groups.[2,3] Some papers have been reported on the formation of heterocyclic compounds including quinolines and dihydroquinolines from the Baylis–Hillman adducts.[2b,3] Quinolines and dihydroquinolines are important entries in medicinal and pharmaceutical chemistry.[4–6]

1,2-Dihydroquinolines have received substantial attention due to their potential biological activities arising from their antioxidative properties[7] as well as their usefulness as precursors of some other biologically active compounds.[8] However, synthetic methods of 1,2-dihydroquinolines are limited.[9,10] Dihydroquinolines can be prepared most often by the addition reac-



Scheme 1.

Keywords: dihydroquinoline; isomerization; Baylis–Hillman reaction.

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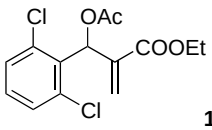
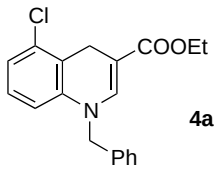
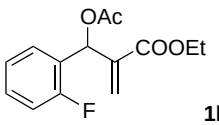
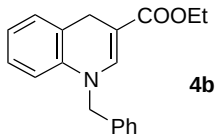
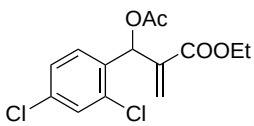
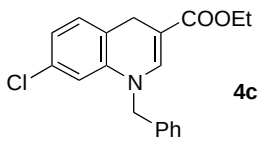
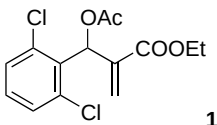
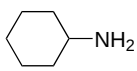
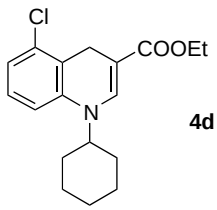
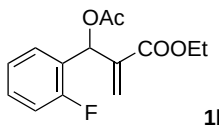
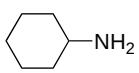
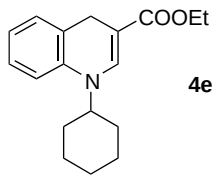
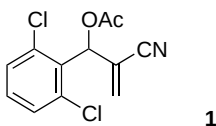
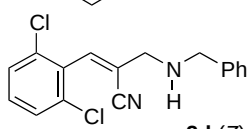
tion of nucleophiles to the quinolinium salts, which was studied deeply by Grignon-Dubois et al.[10]

The reaction of Baylis–Hillman acetates and benzylamine was reported by Foucaud to give the corresponding cinnamylamine derivatives.[11] We thought that if the aromatic moiety of the Baylis–Hillman acetate has an *ortho*-halogen substituent, we could obtain 1,2-dihydroquinoline via the following S_NAr reaction of the cinnamylamine derivative. And eventually, the 1,4-dihydro analog can be prepared via the appropriate isomerization reaction as reported.[10a–c,12] Thus, if possible, our synthetic method might become a good entry for the synthesis of dihydroquinolines. We examined the reaction of the Baylis–Hillman acetates of 2-halobenzaldehydes and benzylamine or cyclohexylamine and wish to report herein the results on the facile preparation method of 1,2-dihydroquinolines and their isomerization to 1,4-dihydroquinolines.

The reaction of the Baylis–Hillman acetates **1a** and benzylamine gave the 1,2-dihydroquinoline **3a** as expected in good yield (Scheme 1). The reaction might proceed via the initial allylic substitution (S_N2') of benzylamine[11] and the following S_NAr reaction of the allylic amine derivative **2a**. However, the yellow solid **3a** was very unstable. During the separation, **3a** was converted slowly to the 1,4-dihydro analog **4a**. We could isolate **3a** in the pure state by rapid column chromatography (75%), however, in other cases separation of **3** in the pure state is difficult (vide infra). Thus, we converted **3** into **4** by dissolving the crude organic extracts of the reaction mixtures in methylene chloride for 3 days at room temperature. Column chromatography gave pure **4**, and the results are summarized in Table 1.

1,2-Dihydroquinoline **3a** was quite stable in solid state at room temperature (no appreciable isomerization to

Table 1. Synthesis of *N*-substituted 1,4-dihydroquinolines **4**

entry	B-H acetates	R-NH_2	products	yield (%)
1	 **1a**	$PhCH_2NH_2$	 **4a**	72
2	 **1b**	$PhCH_2NH_2$	 **4b**	71
3	 **1c**	$PhCH_2NH_2$	 **4c**	63
4	 **1a**		 **4d**	52
5	 **1b**		 **4e**	58
6	 **1d**	$PhCH_2NH_2$	 **2d** (*Z*)	68

4a was observed after 10 days), however, it was isomerized completely in methylene chloride within 3 days to the 1,4-dihydroquinoline **4a** (72%). The isomerization process could be monitored by ^{1}H NMR spectroscopy. Conversion of **3a** to **4a** over 3 days was checked in $CDCl_3$. ^{1}H NMR spectrum of **3a** showed two singlets at 4.36 ppm (methylene protons at the 2-position) and 4.56 ppm (benzyl protons). After 24 h in $CDCl_3$, small peaks were observed at 3.83 ppm (methylene protons at the 4-position) and 4.74 ppm (benzyl protons). After 3 days, complete conversion to **4a** was observed. Thus, in other cases we did not isolate the 1,2-dihydro analogs **3** as mentioned before. Such isomerization was reported in some dihydropyridine and dihydroquinoline systems.[10a–c,12]

The structures of **3a** and **4a** were confirmed from various spectroscopic data. In the ^{1}H NMR spectrum, the methylene protons of **3a** at the 2-position appeared at 4.36 ppm, while the methylene protons of **4a** at the 4-position 3.83 ppm.[10,12] As shown in Fig. 1, NOE experiments provided unequivocal evidence for the structures of **3a** and **4a**. In IR spectrum, the carbonyl absorption of **4a** (1657 cm^{-1}) appeared at the lower frequency in about 50 cm^{-1} than that of **3a** (1707 cm^{-1}) due to the contribution of the resonance structure as shown in Fig. 2.

A typical procedure for the synthesis of **3a** and **4a** is as follows: A stirred solution of **1a** (634 mg, 2.0 mmol), benzylamine (642 mg, 6.0 mmol) and triethylamine (405 mg, 4.0 mmol) in THF (20 mL) was heated to reflux for 30 h. After usual workup process and rapid column chromatography, **3a** was isolated as a yellow solid (492 mg, 75%).[13] **3a** (164 mg, 0.5 mmol) was dissolved in CH_2Cl_2 (20 mL) and stirred at room temperature for 3 days. During the isomerization period, the yellow color of the reaction mixture turned colorless. Removal of solvent and column chromatographic purification gave analytically pure **4a** (118 mg, 72%) as a white solid.[13]

The S_NAr reaction proceeded slowly at room temperature. For the reaction of **1a** and benzylamine (3 equiv.) at room temperature after 20 h, as an example, there were observed rearranged cinnamyl amine derivatives **2a** (*E+Z*) and a trace amount of 1,2-dihydroquinoline **3a**. Cyclohexylamine gave similar results as shown (entries 4 and 5). When we used the Baylis–Hillman acetate of acrylonitrile (entry 6), the first S_N2' reaction gave the *Z*-form product **2d** as the major,[2] which could not undergo the next S_NAr reaction. The mechanism and the driving force for the isomerization of 1,2-dihydroquinolines to 1,4-dihydro analogs are currently underway.

In this report we disclosed the formation of 1,2-dihydroquinolines from the reaction of Baylis–Hillman acetates and benzylamine or cyclohexylamine. Eventually, the reaction provided a convenient method for the preparation of 1,4-dihydroquinoline derivatives.

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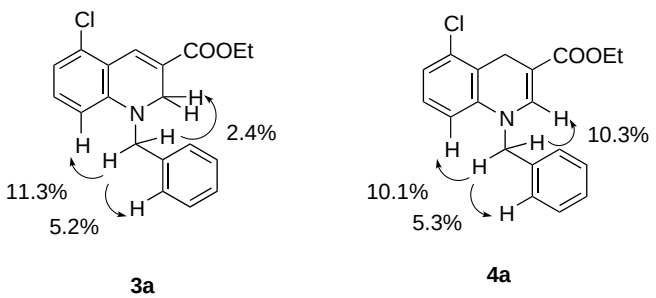

Figure 1.

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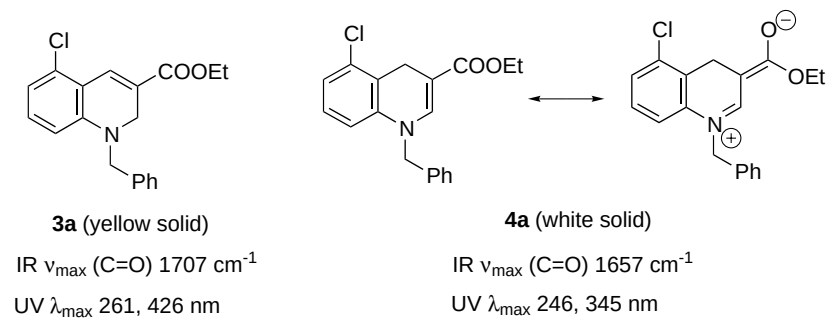

Figure 2.

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13. Some representative spectroscopic data of **3a** and **4a** are as follows.

3a: 75%; yellow solid; mp 105–107°C; IR (KBr) 1707, 1643, 1448, 1377, 1271, 1200 cm^{-1}; UV (CH_2Cl_2) $\lambda_{max}=$ 426 ($\varepsilon=7070$), 261 ($\varepsilon=32500$); ^1H NMR ($CDCl_3$) δ 1.32 (t, $J=7.2$ Hz, 3H), 4.25 (q, $J=7.2$ Hz, 2H), 4.36 (s, 2H), 4.56 (s, 2H), 6.38 (d, $J=8.4$ Hz, 1H), 6.62 (d, $J=8.4$ Hz, 1H), 6.94 (t, $J=8.4$ Hz, 1H), 7.23–7.36 (m, 5H), 7.81 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.30, 49.09, 54.40, 60.73, 109.64, 117.69, 117.85, 122.23, 126.89, 127.24, 128.77, 131.29, 131.79, 134.39, 136.22, 147.88, 165.23; mass (70 eV) m/z (rel. intensity) 91 (100), 92 (8), 298 (12), 327 (M^+, 4). Anal. calcd for $C_{19}H_{18}ClNO_2$: C, 69.62; H, 5.53; N, 4.27. Found: C, 69.44; H, 5.59; N, 4.32.

4a: 72%; white solid; mp 169–171°C; IR (KBr) 1657, 1591, 1462, 1396, 1296, 1261, 1217 cm^{-1}; UV (CH_2Cl_2) $\lambda_{max}=345$ ($\varepsilon=15300$), 246 ($\varepsilon=20300$); ^1H NMR ($CDCl_3$) δ 1.31 (t, $J=7.2$ Hz, 3H), 3.83 (s, 2H), 4.22 (q, $J=7.2$ Hz, 2H), 4.74 (s, 2H), 6.43–7.34 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 14.55, 25.35, 55.30, 59.80, 98.80, 111.85, 122.04, 123.44, 126.08, 127.56, 127.70, 128.99, 135.49, 136.21, 139.71, 142.23, 167.52. Anal. calcd for $C_{19}H_{18}ClNO_2$: C, 69.62; H, 5.53; N, 4.27. Found: C, 69.53; H, 5.58; N, 4.37.