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Synthesis of 3-quinolinecarboxylic acid esters from the Baylis–Hillman adducts of 2-halobenzaldehyde *N*-tosylimines

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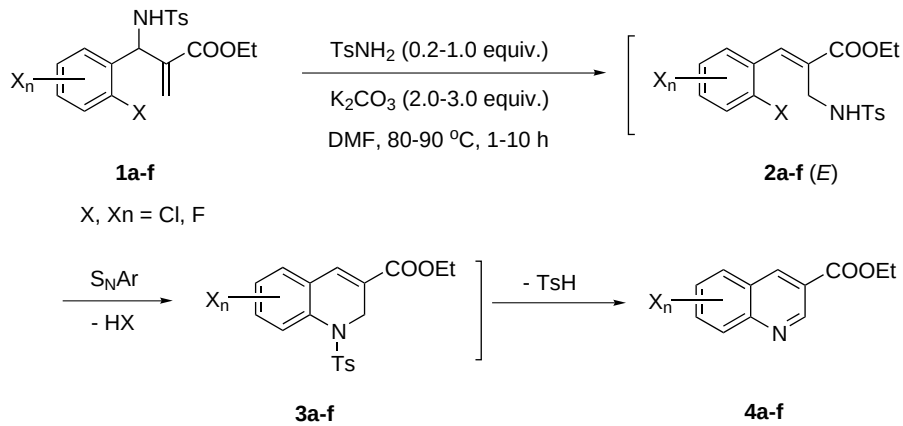
Abstract—3-Quinolinecarboxylic acid ethyl esters **4** were prepared from **1**, the Baylis–Hillman adducts of *o*-halobenzaldehyde *N*-tosylimines, in a one-pot reaction.

The Baylis–Hillman reaction is one of the most powerful carbon–carbon bond-forming methods in organic synthesis.[1] The Baylis–Hillman adducts, which are allylic alcohol or allylic amine derivatives, can be formed most often by the reaction of activated vinyls and carbonyl compounds or *N*-tosylimines.[1] Besides the usefulness of these Baylis–Hillman adducts themselves, further derivatization with various nucleophilic reagents toward synthetically useful compounds has been studied in depth by us and other groups.[2] Some papers reported on the formation of heterocyclic compounds, including quinoline from the Baylis–Hillman adducts.[3]

Quinolines and their derivatives occur in numerous natural products.[4] Many quinolines display interesting physiological activities and have found attractive applications as pharmaceuticals and agrochemicals, as well as being general synthetic building blocks.[4b] Many synthetic methods have been developed for the preparation of quinolines,[5] but due to their great importance, the development of novel synthetic methods remains an active research area.[6]

Recently, we reported on the synthesis of 4-hydroxy-3-ethoxycarbonylquinoline *N*-oxide derivatives from the Baylis–Hillman adducts of 2-nitrobenzaldehydes.[3a] As a continuation of our work, we intended to examine the possibility of transforming the Baylis–Hillman adducts of *o*-halobenzaldehyde *N*-tosylimines **1** into the corresponding quinolines.

The choice of the Baylis–Hillman adducts **1** as substrates was based on the following assumptions: (1)



Scheme 1.

Keywords: 3-quinolinecarboxylic acid ethyl esters; Baylis–Hillman adducts.

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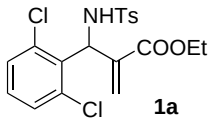
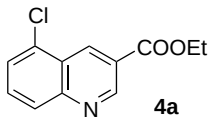
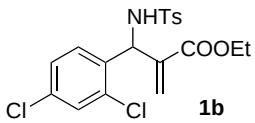
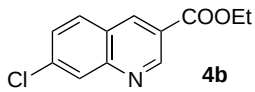
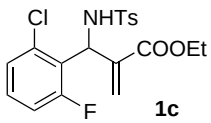
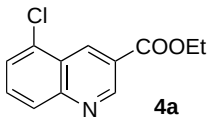
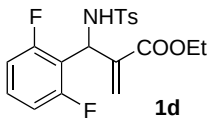
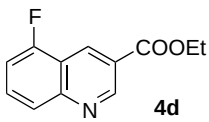
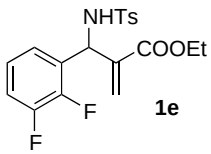
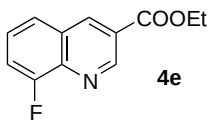
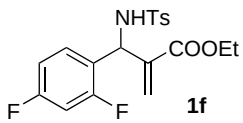
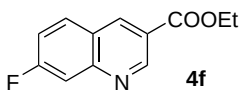
catalytic amounts of tosylamide might effect the rearrangement of **1** toward the thermodynamically more stable rearranged tosylamide derivatives **2**; (2) nucleophilic aromatic substitution reaction can be easily conducted at the *ortho* position; and (3) elimination of *p*-toluenesulfinic acid is possible to give the quinolines **4** directly in a one-pot reaction, as shown in Scheme 1.

Reaction of the Baylis–Hillman adduct **1a** in *N*,*N*-dimethylformamide in the presence of potassium carbonate (2.0 equiv.) and tosylamide (0.2 equiv.) at 80–90°C afforded the desired quinoline **4a** in 76% yield in a short time.[7] The reaction conditions and yields of products for the representative examples are shown in Table 1. In some cases, when we used catalytic amounts of tosylamide in the reaction, long reaction times were needed to obtain appreciable amounts of products. In such cases (entries c, d, and f in Table 1), we used 0.5–1.0 equiv. of tosylamide.

However, reaction of **1g** under the reaction conditions gave the 1,2-dihydroquinoline derivative **3g** in 81% yield instead of the expected quinoline **4g**. Elimination of *p*-toluenesulfinic acid was not efficient under the reaction conditions even after a long reaction time. Synthesis of quinoline **4g** was realized by the reaction of **3g** and DBU in THF in 69% yield (Scheme 2). As we already stated in other cases, **3a**–**f**, elimination of *p*-

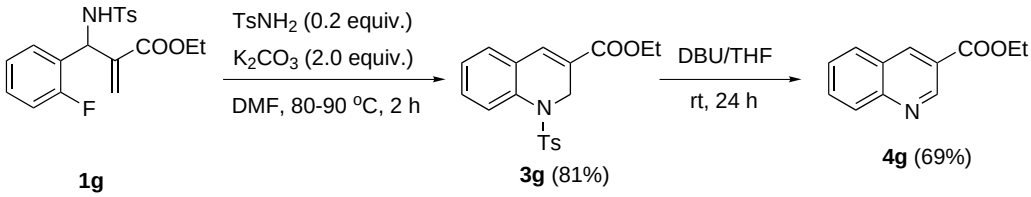
Table 1. One-pot synthesis of 3-ethoxycarbonylquinolines **4**

Entry	B-H adducts (**1**)	Conditions	Quinolines (**4**)	Yield (%)
a	 **1a**	$TsNH_2$ (0.2 equiv.) K_2CO_3 (2.0 equiv.) 1 h	 **4a**	76[a]
b	 **1b**	$TsNH_2$ (0.2 equiv.) K_2CO_3 (2.0 equiv.) 7 h	 **4b**	79[b]
c	 **1c**	$TsNH_2$ (0.5 equiv.) K_2CO_3 (3.0 equiv.) 2 h	 **4a**	77
d	 **1d**	$TsNH_2$ (1.0 equiv.) K_2CO_3 (3.0 equiv.) 7 h	 **4d**	75
e	 **1e**	$TsNH_2$ (0.2 equiv.) K_2CO_3 (3.0 equiv.) 5 h	 **4e**	75
f	 **1f**	$TsNH_2$ (1.0 equiv.) K_2CO_3 (3.0 equiv.) 10 h	 **4f**	71[c]

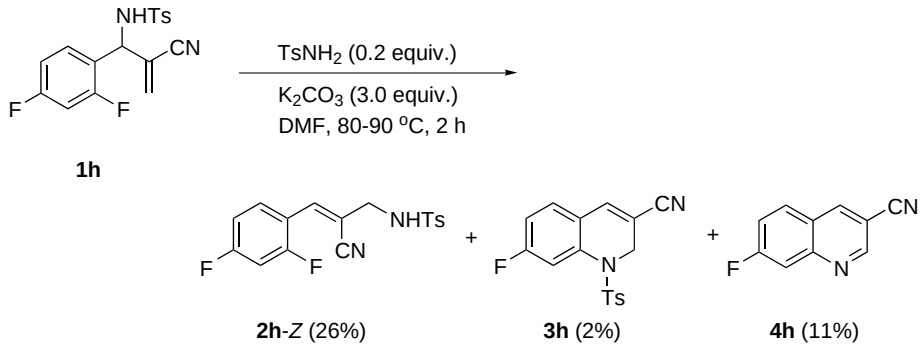
[a] *N*-(*p*-Toluenesulfonyl)-3-ethoxycarbonyl-5-chloro-1,2-dihydroquinoline (**3a**) was obtained in 8% yield.

[b] *N*-(*p*-Toluenesulfonyl)-3-ethoxycarbonyl-7-chloro-1,2-dihydroquinoline (**3b**) was obtained in 10% yield.

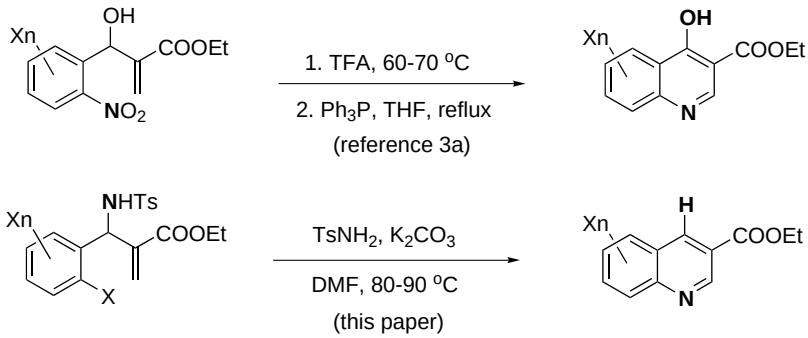
[c] *N*-(*p*-Toluenesulfonyl)-3-ethoxycarbonyl-7-flouro-1,2-dihydroquinoline (**3f**) was obtained in 6% yield. 3-Ethoxycarbonyl-7-(*p*-toluenesulfonamido)quinoline (**5f**) was also isolated in 11% yield.



Scheme 2.



Scheme 3.



Scheme 4.

toluenesulfinic acid occurred readily under the reaction conditions to give the corresponding quinolines **4a**–**f** in a one-pot reaction. The discrepancy between **1g** and **1a**–**f** might be due to the subtle difference in the acidity of the proton at the 2-position of the corresponding dihydroquinolines **3g** and **3a**–**f**. Depending on the substrate, we could isolate low yields of **3** and/or other compounds, such as **5f** (see footnotes a–c in Table 1). Quinoline **5f** was generated from the initially formed **4f** by successive S_NAr reactions with tosylamide at the 7-position.

The reaction mechanism is shown in Scheme 1 (vide sufra) and is as follows: (1) tosylamide catalyzed successive S_N2' type reactions of **1a**–**f** to form the primary rearranged allylic tosylamides **2a**–**f** (selective formation of the *E*-isomer);[2a–c] (2) S_NAr reaction with the aid of potassium carbonate to produce dihydroquinolines **3a**–**f**; and, finally, (3) elimination of *p*-toluenesulfinic acid gave quinolines **4a**–**f**.

The nitrile substituted Baylis–Hillman adduct **1h** produced low yields of dihydroquinoline **3h** (2%) and quinoline **4h** (11%). Instead, we could obtain the rearranged tosylamide derivative **2h** (*Z*-form) as the major product,[2a–c] which cannot undergo the requisite S_NAr reaction (Scheme 3).

It is interesting to compare these results with our previous paper.[3a] As shown in Scheme 4, 4-hydroxy-3-ethoxycarbonylquinolines can be synthesized from the Baylis–Hillman adducts of *o*-nitrobenzaldehydes,[3a] whereas 3-ethoxycarbonylquinolines can be prepared from the Baylis–Hillman adducts of *o*-halobenzaldehyde *N*-tosylimines.

Acknowledgements

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7. Typical procedure for the synthesis of **4a** and some selected spectroscopic data were as follows: A stirred solution of **1a** (860 mg, 2 mmol),[8] tosylamide (70 mg, 0.4 mmol), and K_2CO_3 (552 mg, 4 mmol) in *N*,*N*-dimethylformamide (5 mL) was heated at 80–90°C for 1 h. After cooling to room temperature, the reaction mixture was poured into a cold HCl solution and extracted with ether. After the usual work-up process, column chromatographic purification (hexane/ether, 8:2) gave **4a** as a white solid, 360 mg (76%); mp 97–98°C; IR (KBr): 3299, 2987, 1724, 1279 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.48 (t, $J=7.2$ Hz, 3H), 4.51 (q, $J=7.2$ Hz, 2H), 7.66–7.78 (m, 2H), 8.09 (dt, $J=8.1$ and 1.2 Hz, 1H), 9.22 (dd, $J=2.1$ and 0.9 Hz, 1H), 9.48 (d, $J=2.1$ Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 14.33, 61.75, 124.10, 125.26, 127.45, 128.63, 131.38, 132.68, 135.44, 150.41, 150.70, 164.99; MS (70 eV) m/z (rel. int.): 99 (38), 162 (66), 190 (100), 192 (35), 207 (54), 235 (M^+, 60), 237 (M^++2, 20).
8. For the preparation of the Baylis–Hillman adducts **1a**–**h**, see Refs. 2b and 2c.