Formation of 1,2-Dihydroquinoline-3-carboxylic Acid Derivatives from Methyl 3-(Arylamino)acrylates with Hydrogen Iodide

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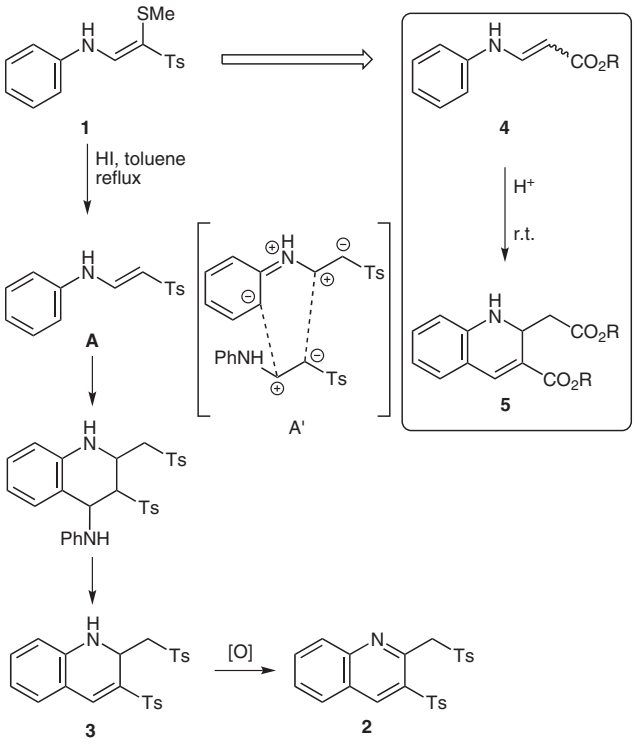
Abstract: The reaction of methyl 3-(arylamino)acrylates with hydrogen iodide gave 1,2-dihydroquinoline-3-carboxylic acid derivatives at room temperature. This reaction proceeds efficiently in alcoholic solvent; bulky *tert*-butyl alcohol is the best solvent to give the 1,2-dihydroquinoline derivatives. It is particularly interesting that hydrogen iodide is the most efficient acid to achieve this reaction in *tert*-butyl alcohol. Various substituents at the phenyl ring are applicable. Compounds bearing *meta*-substituted phenyl ring with electron-donating group led to the corresponding 1,2-dihydroquinoline derivatives in good yields.

Key words: cyclization, hydrogen iodide, heterocycles, solvent effects, substituent effects

Quinolines and hydroquinolines are important organic materials for synthesizing alkaloids, agrochemicals, dyes, and pharmaceuticals. Various synthetic methods of the 1,2-dihydroquinolines have been reported.[1–3] The reaction of quinoline derivatives with alkylmetal reagents or with reducing agents ($NaBH_4$, $LiAlH_4$, etc.) is an important method to form 1,2-dihydroquinoline derivatives.[4,5] However, it presents the limitation that quinoline derivatives bearing the reactive substituent interact with alkyl anion or hydride to give undesired products. To overcome this limitation, condensation type reactions were sought, which offer useful methods to produce 1,2-dihydroquinoline derivatives.[6] We reported earlier the formation of the 3-tosylquinoline derivatives **2** by the reaction of 2-(arylamino)-1-(methylthio)-1-tosylethenes **1** with hydrogen iodide in refluxing toluene.[7] In that report, the formation of 3-tosyl-1,2-dihydroquinoline derivatives **3** was described. In the proposed mechanism, the in situ formed 2-(arylamino)-1-tosylethene **A** was reacted bimolecularly (Scheme 1). A similar type of the formation of 2-methyl-1,2,3,4-tetrahydroquinolines from aniline and vinyl ethers with cerium ammonium nitrate was reported by Menéndez and co-workers.[8] They extracted the dihydroquinoline derivatives from the 4-alkoxy-2-methyl-1,2,3,4-tetrahydroquinolines through an additional reaction with hydrochloric acid. Their result relies upon the lesser leaving ability of the alkoxy group. In our system, the good arylamino leaving group under acidic conditions is attached in the cyclic system to effect the formation of the 1,2-dihydroquinoline structure **3**. Regarding the resonance structure **A′**, structure **A** has a good charge distribution to promote the cyclization reaction based on the electron-donating nitrogen atom and the electron-accepting tosyl group. When a carboxyl group is introduced instead of the tosyl group such as in **4**, the charge distribution will be retained and the reaction will yield 1,2-dihydroquinoline-3-carboxylic acid derivatives **5**. Few reports in the relevant literature describe the useful formation of 1,2-dihydroquinoline-3-carboxylic acid derivatives.[6d,f–h,9] Herein, we report the reaction of 3-(arylamino)acrylic esters with protic acid to give 1,2-dihydroquinoline-3-carboxylic acid derivatives at room temperature.



Scheme 1 Quinoline formation from **1** with HI and the application to **4**

Methyl 3-(arylamino)acrylates **4** were prepared easily from the reaction of methyl prop-2-ynoate and the corresponding aniline derivatives using a procedure reported by Isobe and co-workers.[10] Although the reaction of **4a** with hydrogen iodide was examined under the same conditions as for **1**,[7] it was not possible to initiate the reaction

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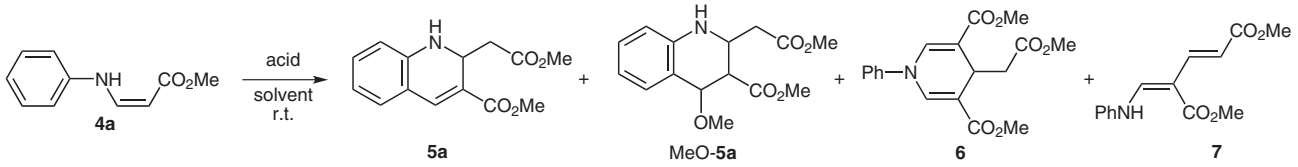
because of the lower solubility of **4a** in toluene. Therefore, a suitable solvent for the reaction was surveyed at first and the results are presented in Table 1. To a solution of **4a** was added 55% aqueous hydrogen iodide (1.0 equiv) under a nitrogen atmosphere. The reaction proceeded even at room temperature affording two or three products. Regarding the formation of dihydroquinoline derivatives, results show that the most promising solvent was a protic solvent such as methanol, which gave 21% yield of **5a** together with 33% yield of MeO-**5a** (Table 1, entry 4). The effect of an acid in this reaction was also studied. It was found that the reaction proceeded efficiently with hydrogen iodide or *p*-toluenesulfonic acid as an acid (entries 4 and 7) affording both **5a** and MeO-**5a**.[11] Furthermore, the formation of undesired compounds such as **6** and **7** was observed using other acids (entries 5–7).

An increase in the formation of **5a** was attempted by changing the protic solvent from methanol to *tert*-butyl alcohol to cease the formation of MeO-**5a**. The yield of **5a** improved to 34% when the reaction was conducted with hydrogen iodide (entry 8). However, the reaction with *p*-toluenesulfonic acid was inhibited (entry 9), revealing the importance of the counter anion as well as the solvent. The amount of hydrogen iodide was also controlled and found that it can be reduced to 0.6 equivalent to maintain the yield of **5a**, the slightly prolonged reaction time was necessary (entry 10). The reaction using a geometric isomer mixture of **4a** revealed no influence of geometric isomerism (entry 11).

The reaction pathway depicted in Scheme 2 is inferred based on the reaction of **1** with hydrogen iodide.[7] Hydrogen iodide combines with **4a** to produce the cationic intermediate **I** to promote the ring-closing reaction in cooperation with the proper charge distribution **B**. Intermediate **I** undergoes addition to another **4a** to give the intermediate **II**. In methanol, the cationic carbon of **II** is solvated to form the intermediate **III**; thereby, the reactivity of **II** will be decreased. Consequently, the intramolecular nucleophilic substitution occurred efficiently using the aromatic electron at the *ortho* position of the nitrogen atom to give the intermediate **IV**. The 1,2-dihydroquinoline derivative **5a** is formed by elimination of proton and aniline with the recovery of hydrogen iodide. When the attack from the phenyl ring occurs at the carbon of α-amino ether moiety in **III**, both **5a** (path *a*) and MeO-**5a** (path *b*) are obtained. Compared to the refluxing conditions in the reaction of **1**,[7] milder conditions such as room temperature will prevent oxidation to form the quinoline derivatives. However, in the case of the other solvents, the intermediate **III** cannot form. Therefore, the elimination will proceed to give **7** and its regioisomer **7′**. Subsequently, **7′** can add a proton to undergo another cyclization reaction. The detailed mechanism for the formation of **6** remains unclear. However, the regiospecific formation of **7** includes a hint; the proposed mechanism shown in

Table 1 Reaction of **4a** with Acid in Various Solvents

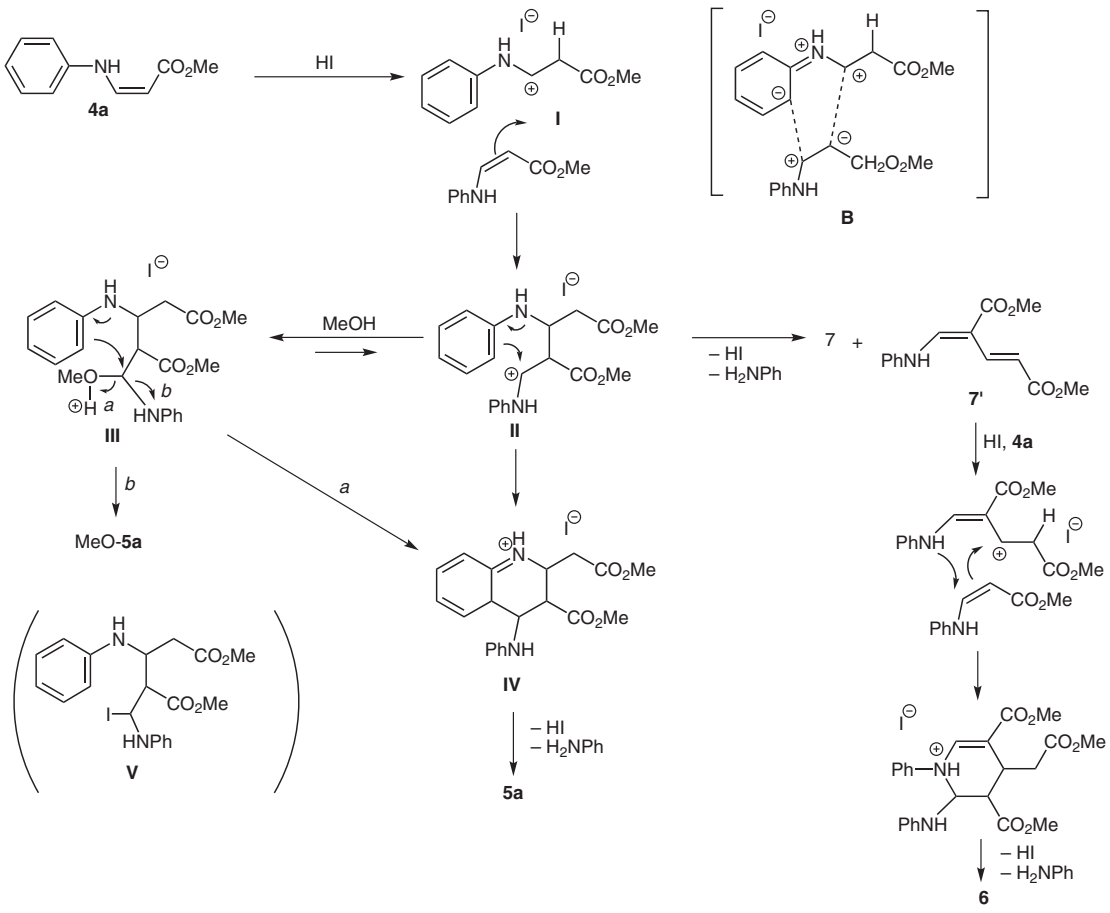


				Yield (%)			
Entry	Solvent	Acid (equiv)	Time (h)	**5a**	MeO-**5a**	**6**	**7**
1	$CHCl_3$	55% aq HI (1.0)	2	12	–	52	0
2	MeCN	55% aq HI (1.0)	2	9	–	43	0
3	THF	55% aq HI (1.0)	1	0	–	32	44
4	MeOH	55% aq HI (1.0)	1	21	33	0	0
5	MeOH	concd HCl (1.0)	1.5	10[a]	10	39	8
6	MeOH	CF_3CO_2H (1.0)	24	19	30	26	6
7	MeOH	$TsOH·H_2O$ (1.0)	1	34	21	14	10
8	*t*-BuOH	55% aq HI (1.0)	3	34[b]	–	0	3
9	*t*-BuOH	$TsOH·H_2O$ (1.0)	4	8	–	25	35
10	*t*-BuOH	55% aq HI (0.6)	4	38	–	0	18
11[c]	*t*-BuOH	55% aq HI (0.6)	4	41	–	0	19

[a] Quinoline derivative formed in 11% yield.
[b] Quinoline derivative formed in 10% yield.
[c] A geometric isomer mixture of **4a** (*E*/*Z* = 24:76) was used.

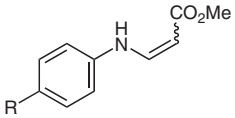
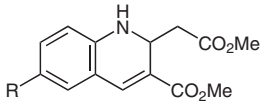
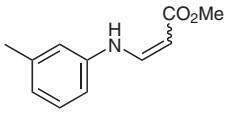
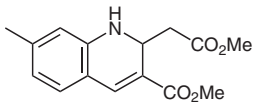
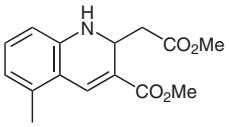
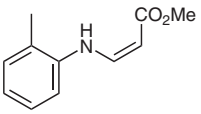
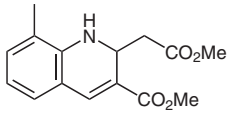
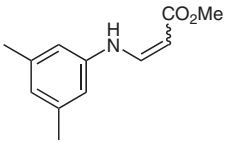
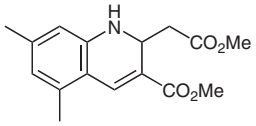
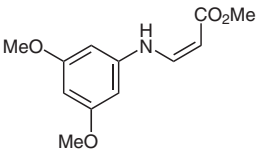
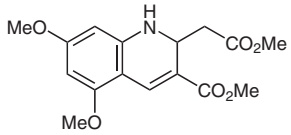
Scheme 2 is plausible. Additionally, an iodide ion possesses nucleophilicity.[12] Therefore, decrease of the reactivity of **II** will be realized by the addition of the iodide ion to form **V**. The effect of the iodide ion worked also efficiently in *tert*-butyl alcohol, although its ability is insufficient to strictly inhibit the formation of the side product **7**. This could be the reason for the decrease in the yield of **5a** in the case of using *p*-toluenesulfonic acid in *tert*-butyl alcohol (Table 1, entry 9).

The reaction of the compounds having various substituents at the phenyl ring was examined to give the corresponding 1,2-dihydroquinoline derivatives (Table 2) under the efficient reaction conditions using *tert*-butyl alcohol as a solvent with 0.6 equivalent of hydrogen iodide at room temperature. Introduction of the methyl group at the 4 position of the phenyl ring gave **5b** in 48% yield (Table 2, entry 1). When a more electron-donating substituent such as methoxy group was attached at that position, the yield of 1,2-dihydroquinoline derivative was decreased (5%), although the oxidized quinoline derivative of **5c** was obtained in 25% yield (entry 2). The reason is the substitution of the strong electron-donating group at the 4 position of the phenyl ring enhanced the oxidation ability of the formed 1,2-dihydroquinoline derivatives.[13] The compounds bearing the electron-withdrawing substituents at the 4 position of the phenyl ring, **4d** and **4e**, gave the corresponding 1,2-dihydroquinoline derivatives **5d** and **5e**, respectively, although it took a long period of the reaction time (entries 3 and 4). Based on the schematic proposal portrayed in Scheme 1, it would be reasonable to require longer reaction times in the cases of **4d** and **4e** because of the decreased nucleophilicity of the phenyl ring, especially at the *ortho* position from nitrogen atom, in the resonance structure **C** (Scheme 3). The influence of the substituents in the phenyl ring at 2 and 3 positions was also examined (entries 5 and 6). Consequently, **4f** gave the corresponding 1,2-dihydroquinolines **5f** and **5f′** in the highest yield (totally 60%) between the methyl substituted compounds (**5b**, 48%; **5g**, 48%). A good explanation might be that the cyclization reactions occurred at the *para* or *ortho* position from the electron-donating methyl group, which would enhance the nucleophilicity at the reaction site (see **D** in Scheme 3).[14] Based on these suggestions, **5i** was ultimately obtained in 71% yield by the reaction of **4i** that is doubly activated by two methoxy groups at the *meta* position of the phenyl ring from the nitrogen atom. It is also noteworthy that the methyl ester part and methoxy group are unchanged in these reaction conditions, although hydrogen iodide is well known as a demethylation reagent.[15] This is true because the present reaction conditions using 0.6 equivalent of hydrogen iodide at room temperature are too mild to cleave the O–Me bond.

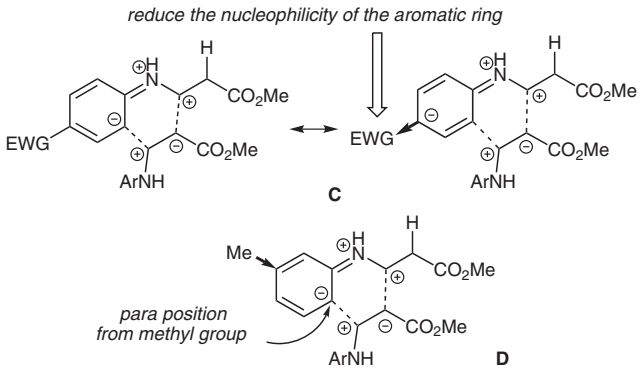


Scheme 2 Proposed reaction mechanism for the formation of **5a**, MeO-**5a**, and **6**

Table 2 Reaction of **4b–i** with HI[a]

Entry	Compound (*E*/*Z*)	Time (h)	Product	Yield (%)[b]
1	 **4b** (R = Me) (28:72)	2	 **5b**	48 (10)
2	**4c** (R = OMe) (27:73)	2	**5c**	5 (25)
3	**4d** (R = CO_2Me) (0:100)	48	**5d**	43
4	**4e** (R = Br) (28:72)	72	**5e**	40
5	 **4f** (26:74)	2	 **5f**	51 (13)
			 **5f′**	9
6	 **4g** (0:100)	2	 **5g**	48
7	 **4h** (5:95)	1	 **5h**	66 (12)
8	 **4i** (0:100)	1	 **5i**	71 (13)

[a] Reaction conditions: compound **4b–i** (1.0 mmol) and 55% aq HI (0.6 equiv) in *t*-BuOH.
[b] Values in parentheses show the yield of quinoline derivative.



Scheme 3 Electronic effect of the substituents

In summary, we have found that the reaction of methyl 3-(arylamino)acrylates **4** with hydrogen iodide gave 1,2-dihydroquinoline-3-carboxylic acid derivatives **5**. This reaction is applicable to various substituents at the phenyl ring. Furthermore, the results demonstrate that the addition of the electron-donating substituent(s) at the *meta* position of the phenyl ring from the nitrogen atom is an efficient means to increase the yield of **5**.

Melting points were determined with Yanaco MP-J3 and values are uncorrected. ^{1}H NMR measurement was performed on a Varian GEMINI 2000 (300 MHz) spectrometer. Chemical shifts (δ) of ^{1}H NMR were expressed in parts per million downfield from TMS as an internal standard (δ = 0 ppm). Multiplicities are indicated as s

(singlet), br s (broadened singlet), d (doublet), t (triplet), m (multiplet), br (broadened), and coupling constants (*J*) are reported in Hz. IR spectra were recorded on a JASCO FT/IR-350 or a JASCO FT/IR-460 plus spectrometers in KBr disk or on NaCl plates. Elemental analyses (EA) were carried out on a PerkinElmer 2400CHN in Analytical Chemical Center of Chiba University. Mass spectra were carried out on a JEOL JMS-AX500, a JMS-HX110, or a Thermo Scientific Exactive in Analytical Chemical Center of Chiba University. Analytical TLC was performed on glass plates pre-coated with silica gel (layer thickness 0.25 mm). Column chromatography was performed on 70–230 mesh silica gel. Methyl prop-2-ynoate, anilines, acids, and solvents were used as commercially available (Aldrich Chemical Co., Tokyo Kasei Chemical Industry Co., Wako Pure Chemical Co., Kanto Chemical Co., and Nacalai Tesque Inc.).

Methyl 3-(Arylamino)acrylates; (*Z*)-Methyl 3-(Phenylamino)acrylate (4a);[10] Typical Procedure

To a solution of aniline (0.376 g, 4.04 mmol) in MeOH (8.4 mL) was added methyl prop-2-ynoate (0.362 g, 4.31 mmol) at r.t. The mixture was stirred for 48 h and was concentrated under reduced pressure to give (*E*)- and (*Z*)-methyl 3-(phenylamino)acrylates (24:76). The residue was subject to column chromatography on silica gel ($CHCl_3$–EtOAc, 15:1) to give **4a**; yield: 0.633 g (3.57 mmol, 88%); colorless solid; mp 155.0–156.3 °C (hexane–EtOAc) (Lit.[10] mp 151–154 °C).

Methyl 3-(4-Tolylamino)acrylate (4b)[16]

Reaction time: 115 h; yield: 98% (*E*/*Z* = 28:72).

^{1}H NMR (300 MHz, $CDCl_3$): δ (*Z*-isomer) = 2.30 (s, 3 H), 3.71 (s, 3 H), 4.81 (d, *J* = 8.3 Hz, 1 H), 6.83 (d, *J* = 9.0 Hz, 2 H), 7.10 (d, *J* = 8.3 Hz, 2 H), 7.22 (dd, *J* = 8.3, 12.9 Hz, 1 H), 9.81 (br d, *J* = 12.6 Hz, 1 H).

^{1}H NMR (300 MHz, $CDCl_3$): δ (*E*-isomer, selected data) = 5.17 (d, *J* = 13.2 Hz, 1 H), 6.45 (br d, *J* = 12.7 Hz, 1 H), 7.89 (t, *J* = 13.2 Hz, 1 H).

Methyl 3-[(4-Methoxyphenyl)amino]acrylate (4c)[17]

Reaction time: 48 h; yield: ~100% (*E*/*Z* = 27:73).

^{1}H NMR (300 MHz, $CDCl_3$): δ (*Z*-isomer) = 3.71 (s, 3 H), 3.78 (s, 3 H), 4.79 (d, *J* = 8.4 Hz, 1 H), 6.84–6.93 (m, 4 H), 7.15 (dd, *J* = 8.3, 12.9 Hz, 1 H), 9.78 (br d, *J* = 12.7 Hz, 1 H).

^{1}H NMR (300 MHz, $CDCl_3$): δ (*E*-isomer, selected data) = 5.14 (d, *J* = 13.0 Hz, 1 H), 7.82 (t, *J* = 12.9 Hz, 1 H).

(*Z*)-Methyl 3-[(4-Methoxycarbonylphenyl)amino]acrylate (4d)

Reaction time: 125 h; yield: 23%; colorless solid; mp 128.7–129.5 °C (hexane–EtOAc).

IR (KBr): 3300, 1712, 1669, 1634, 1432, 1286, 1202 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.74 (s, 3 H), 3.89 (s, 3 H), 4.96 (d, *J* = 8.4 Hz, 1 H), 6.97 (d, *J* = 8.8 Hz, 2 H), 7.28 (dd, *J* = 8.4, 12.5 Hz, 1 H), 7.98 (d, *J* = 8.8 Hz, 2 H), 10.06 (br d, *J* = 11.5 Hz, 1 H).

Anal. Calcd for $C_{11}H_{13}NO_2$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.32; H, 5.47; N, 5.86.

Methyl 3-[(4-Bromophenyl)amino]acrylate (4e)

Reaction time: 54 h; yield: 85% (*E*/*Z* = 28:72).

Z-Isomer: colorless solid; mp 155.2–156.7 °C (hexane–$CHCl_3$).

IR (KBr): 3290, 1693, 1671, 1615, 1579, 1486, 1434, 1269, 1204, 1163, 1075, 973, 818 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.72 (s, 3 H), 4.88 (d, *J* = 8.3 Hz, 1 H), 6.84 (diffused d, *J* = 8.8 Hz, 2 H), 7.18 (dd, *J* = 8.4, 12.6 Hz, 1 H), 7.40 (diffused d, *J* = 8.8 Hz, 2 H), 9.88 (br d, *J* = 12.6 Hz, 1 H).

Anal. Calcd for $C_{10}H_{10}BrNO_2$: C, 46.90; H, 3.94; N, 5.47. Found: C, 46.64; H, 3.70; N, 5.29.

E-Isomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ (selected data) = 5.23 (d, *J* = 13.0 Hz, 1 H), 7.84 (t, *J* = 13.1 Hz, 1 H).

Methyl 3-(3-Tolylamino)acrylate (4f)

Reaction time: 48 h; yield: 98% (*E*/*Z* = 26:74).

Z-Isomer: colorless needles; mp 117.5–119.5 °C (hexane–EtOAc).

IR (KBr): 3290, 1698, 1619, 1586, 1275, 1141 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.34 (s, 3 H), 3.73 (s, 3 H), 4.84 (d, *J* = 8.3 Hz, 1 H), 6.77 (d, *J* = 7.6 Hz, 1 H), 6.80 (s, 1 H), 6.82 (d, *J* = 7.4 Hz, 1 H), 7.18 (t, *J* = 7.5 Hz, 1 H), 7.25 (dd, *J* = 8.4, 12.7 Hz, 1 H), 9.83 (br d, *J* = 12.5 Hz, 1 H).

Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 68.88; H, 6.84; N, 7.21.

E-Isomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ (selected data) = 5.19 (d, *J* = 13.1 Hz, 1 H), 7.93 (t, *J* = 13.3 Hz, 1 H).

(*Z*)-Methyl 3-(2-Tolylamino)acrylate (4g)

Reaction time: 54 h; yield: 85%; colorless needles; mp 64.4–65.8 °C (hexane–EtOAc).

IR (KBr): 3297, 1674, 1632, 1600, 1461, 1246, 1215 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.34 (s, 3 H), 3.74 (s, 3 H), 4.89 (d, *J* = 8.2 Hz, 1 H), 6.94 (t, *J* = 7.4 Hz, 1 H), 7.04 (d, *J* = 7.9 Hz, 1 H), 7.16–7.22 (m, 2 H), 7.33 (dd, *J* = 8.2, 12.5 Hz, 1 H), 10.20 (br s, 1 H).

Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 68.70; H, 6.83; N, 7.24.

Methyl 3-[(3,5-Dimethylphenyl)amino]acrylate (4h)

Reaction time: 120 h; yield: 99% (*E*/*Z* = 5:95).

Z-Isomer: brown oil.

IR (NaCl, neat): 3315, 2948, 1634, 1456, 1204, 1013, 909, 832, 789 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.28 (s, 6 H), 3.71 (s, 3 H), 4.81 (d, *J* = 8.3 Hz, 1 H), 6.60 (s, 2 H), 6.65 (s, 1 H), 7.24 (dd, *J* = 8.3, 12.8 Hz, 1 H), 9.75 (br d, *J* = 12.3 Hz, 1 H).

HRMS-ESI: *m*/*z* $[M + Na]^+$ calcd for $C_{12}H_{15}NO_2$ + Na: 228.0995; found: 228.0995.

E-Isomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ (selected data) = 5.17 (d, *J* = 13.1 Hz, 1 H), 7.91 (t, *J* = 13.2 Hz, 1 H).

(*Z*)-Methyl 3-[(3,5-Dimethoxyphenyl)amino]acrylate (4i)

Reaction time: 144 h; yield: 90%; yellow solid; mp 99.5–101.7 °C (hexane–$CHCl_3$).

IR (KBr): 3142, 2992, 1688, 1627, 1590, 1539, 1267, 1204, 1155, 818 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.72 (s, 3 H), 3.78 (s, 6 H), 4.85 (d, *J* = 8.3 Hz, 1 H), 6.12 (s, 3 H), 7.21 (dd, *J* = 8.4, 12.7 Hz, 1 H), 9.84 (br d, *J* = 13.7 Hz, 1 H).

HRMS-ESI: *m*/*z* $[M + Na]^+$ calcd for $C_{12}H_{15}NO_4$ + Na: 260.0892; found: 260.0893.

1,2-Dihydroquinoline Derivatives; 3-(Methoxycarbonyl)-2-[(methoxycarbonyl)methyl]-1,2-dihydroquinoline (5a); Typical Procedure

To a solution of methyl 3-(phenylamino)acrylate (**4a**; 0.177 g, 1.00 mmol) in *t*-BuOH (10 mL) was added aq 55% HI (0.136 g, 0.58 mmol) at r.t. and the mixture was stirred for 4 h. The mixture was then poured into sat. aq Na_2SO_3 (10 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with H_2O (5

mL) and dried (Na_2SO_4). After filtration and evaporation of the solvent, the residue was subjected to column chromatography on silica gel ($CHCl_3$–EtOAc, 15: 1) to give **5a**; yield: 53.0 mg (0.203 mmol, 41%); yellow needles; mp 61.4–63.4 °C (hexane–EtOAc).

IR (KBr): 3379, 2951, 1708, 1635, 1602, 1574, 1484, 1440, 1364, 1339, 1300, 1264, 1242, 987, 771, 743 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.43 (dd, *J* = 2.1, 16.7 Hz, 1 H), 2.78 (dd, *J* = 10.2, 16.8 Hz, 1 H), 3.66 (s, 3 H), 3.80 (s, 3 H), 4.91 (dd, *J* = 2.2, 10.3 Hz, 1 H), 4.93 (br s, 1 H), 6.51 (d, *J* = 8.1 Hz, 1 H), 6.64 (t, *J* = 7.3 Hz, 1 H), 7.04 (d, *J* = 7.2 Hz, 1 H), 7.09 (t, *J* = 8.1 Hz, 1 H), 7.46 (s, 1 H).

HRMS-ESI: *m*/*z* $[M + Na]^+$ calcd for $C_{14}H_{15}NO_4$ + Na: 284.0893; found: 284.0891.

6-Methyl-3-(methoxycarbonyl)-2-[(methoxycarbonyl)methyl]-1,2-dihydroquinoline (5b)
Yield: 48%; yellow needles; mp 99.0–101.3 °C (hexane–EtOAc).

IR (KBr): 3405, 2954, 1722, 1706, 1638, 1577, 1559, 1507, 1439, 1369, 1336, 1284, 1224, 1179, 1147, 808 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.02 (s, 3 H), 2.38 (dd, *J* = 1.7, 16.7 Hz, 1 H), 2.77 (dd, *J* = 10.2, 16.7 Hz, 1 H), 3.72 (s, 3 H), 3.80 (s, 3 H), 4.85 (br s, 1 H), 4.86 (dd, *J* = 2.2, 10.3 Hz, 1 H), 6.45 (d, *J* = 8.2 Hz, 1 H), 6.86 (s, 1 H), 6.92 (d, *J* = 10.0 Hz, 1 H), 7.43 (s, 1 H).

HRMS-FAB: *m*/*z* $[M]^+$ calcd for $C_{15}H_{17}NO_4$: 275.1158; found: 275.1140.

6-Methoxy-3-(methoxycarbonyl)-2-[(methoxycarbonyl)methyl]-1,2-dihydroquinoline (5c)
Yield: 5%; yellow needles; mp 115.1–116.3 °C (hexane–EtOAc).

IR (KBr): 3354, 2952, 1711, 1699, 1497, 1442, 1287, 1231, 1164, 1067, 1034, 822 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.36 (dd, *J* = 2.3, 16.6 Hz, 1 H), 2.77 (dd, *J* = 10.5, 16.7 Hz, 1 H), 3.68 (s, 3 H), 3.74 (s, 3 H), 3.80 (s, 3 H), 4.74 (br s, 1 H), 4.84 (dd, *J* = 2.4, 10.1 Hz, 1 H), 6.49 (d, *J* = 8.6 Hz, 1 H), 6.64 (d, *J* = 2.8 Hz, 1 H), 6.92 (dd, *J* = 2.8, 8.6 Hz, 1 H), 7.43 (s, 1 H).

HRMS-ESI: *m*/*z* $[M + Na]^+$ calcd for $C_{15}H_{17}NO_5$ + Na: 314.0999; found: 314.0997.

3,6-Di(methoxycarbonyl)-2-[(methoxycarbonyl)methyl]-1,2-dihydroquinoline (5d)
Yield: 43%; yellow needles; mp 138.3–140.3 °C (hexane–EtOAc).

IR (KBr): 3373, 2947, 1728, 1696, 1638, 1438, 1362, 1337, 1259, 1238, 1196, 1177, 881 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.55 (dd, *J* = 2.2, 17.1 Hz, 1 H), 2.76 (dd, *J* = 10.3, 17.0 Hz, 1 H), 3.70 (s, 3 H), 3.81 (s, 3 H), 3.85 (s, 3 H), 5.01 (d, *J* = 9.8 Hz, 1 H), 5.35 (s, 1 H), 6.47 (d, *J* = 8.4 Hz, 1 H), 7.46 (s, 1 H), 7.73–7.77 (m, 2 H).

HRMS-FAB: *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{18}NO_6$: 320.1134; found: 320.1121.

6-Bromo-3-(methoxycarbonyl)-2-[(methoxycarbonyl)methyl]-1,2-dihydroquinoline (5e)
Yield: 40%; yellow needle crystals; mp 130.3–132.1 °C (hexane–EtOAc).

IR (KBr): 3373, 2947, 1728, 1696, 1638, 1438, 1362, 1337, 1259, 1238, 1196, 1177, 881 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.43 (dd, *J* = 2.1, 16.7 Hz, 1 H), 2.75 (dd, *J* = 10.4, 16.9 Hz, 1 H), 3.69 (s, 3 H), 3.80 (s, 3 H), 4.90 (d, *J* = 10.0 Hz, 1 H), 4.96 (br s, 1 H), 6.41 (d, *J* = 8.5 Hz, 1 H), 7.18–7.14 (m, 2 H), 7.38 (s, 1 H).

Anal. Calcd for $C_{14}H_{14}BrNO_4$: C, 49.43; H, 4.15; N, 4.12. Found: C, 49.31; H, 3.78; N, 4.07.

7-Methyl-3-(methoxycarbonyl)-2-[(methoxycarbonyl)methyl]-1,2-dihydroquinoline (5f)
Yield: 51%; yellow needles; mp 80.1–82.0 °C (hexane–EtOAc).

IR (KBr): 3365, 2952, 1735, 1685, 1630, 1439, 1360, 1302, 1245, 1205 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.23 (s, 3 H), 2.41 (dd, *J* = 1.5, 16.3 Hz, 1 H), 2.77 (dd, *J* = 10.3, 16.7 Hz, 1 H), 3.69 (s, 3 H), 3.79 (s, 3 H), 4.90 (d, *J* = 11.1 Hz, 1 H), 4.94 (br s, 1 H), 6.35 (s, 1 H), 6.47 (d, *J* = 7.3 Hz, 1 H), 6.94 (d, *J* = 7.7 Hz, 1 H), 7.45 (s, 1 H).

HRMS-ESI: *m*/*z* $[M + Na]^+$ calcd for $C_{15}H_{17}NO_4$ + Na: 298.1050; found: 298.1049.

5-Methyl-3-(methoxycarbonyl)-2-[(methoxycarbonyl)methyl]-1,2-dihydroquinoline (5f′)
^1H NMR (300 MHz, $CDCl_3$): δ (selected data) = 2.16 (s, 3 H), 3.81 (s, 3 H), 6.38 (d, *J* = 8.1 Hz, 1 H), 6.49 (d, *J* = 7.7 Hz, 1 H), 6.98 (t, *J* = 7.5 Hz, 1 H), 7.70 (s, 1 H).

8-Methyl-3-(methoxycarbonyl)-2-[(methoxycarbonyl)methyl]-1,2-dihydroquinoline (5g)
Yield: 48%; yellow needles; mp 63.6–65.6 °C (hexane–EtOAc).

IR (KBr): 3409, 2955, 1725, 1706, 1441, 1360, 1249, 1217, 1173, 784, 745 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.09 (s, 3 H), 2.42 (dd, *J* = 2.2, 16.8 Hz, 1 H), 2.75 (dd, *J* = 10.1, 16.5 Hz, 1 H), 3.68 (s, 3 H), 3.80 (s, 3 H), 4.94 (br s, 1 H), 4.98 (br s, 1 H), 6.58 (t, *J* = 7.4 Hz, 1 H), 6.97 (d, *J* = 10.5 Hz, 1 H), 7.02 (d, *J* = 7.5 Hz, 1 H), 7.47 (s, 1 H).

HRMS-ESI: *m*/*z* $[M + Na]^+$ calcd for $C_{15}H_{17}NO_4$ + Na: 298.1050; found: 298.1047.

5,7-Dimethyl-3-(methoxycarbonyl)-2-[(methoxycarbonyl)methyl]-1,2-dihydroquinoline (5h)
Yield: 66%; yellow needles; mp 89.5–91.4 °C (hexane–EtOAc).

IR (KBr): 3365, 2947, 1741, 1685, 1632, 1609, 1441, 1371, 1251, 1221, 1197, 1076, 825, 774 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.19 (s, 3 H), 2.29 (s, 3 H), 2.37 (dd, *J* = 2.4, 16.7 Hz, 1 H), 2.75 (dd, *J* = 10.2, 16.7 Hz, 1 H), 3.68 (s, 3 H), 3.79 (s, 3 H), 4.85 (dd, *J* = 2.3, 10.5 Hz, 1 H), 4.87 (br s, 1 H), 6.21 (s, 1 H), 6.33 (s, 1 H), 7.67 (s, 1 H).

Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.55; H, 6.48; N, 4.87.

5,7-Dimethoxy-3-(methoxycarbonyl)-2-[(methoxycarbonyl)methyl]-1,2-dihydroquinoline (5i)
Yield: 71%; yellow needles; mp 134.8–136.5 °C (hexane–EtOAc).

IR (KBr): 3384, 2949, 1718, 1692, 1628, 1577, 1514, 1439, 1319, 1245, 1221, 1171, 1145, 993 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.39 (dd, *J* = 2.1, 16.8 Hz, 1 H), 2.76 (dd, *J* = 10.4, 16.9 Hz, 1 H), 3.69 (s, 3 H), 3.76 (s, 3 H), 3.77 (s, 3 H), 3.79 (s, 3 H), 4.85 (diffused d, *J* = 10.3 Hz, 1 H), 5.04 (br s, 1 H), 5.69 (d, *J* = 1.8 Hz, 1 H), 5.76 (d, *J* = 2.0 Hz, 1 H), 7.79 (s, 1 H).

Anal. Calcd for $C_{16}H_{19}NO_6$: C, 59.81; H, 5.96; N, 4.36. Found: C, 59.76; H, 5.70; N, 4.28.

Reaction of Methyl 3-(Phenylamino)acrylate (4a) with *p*-Toluenesulfonic Acid
To a solution of **4a** (0.886 g, 0.500 mmol) in MeOH (5.0 mL) was added *p*-toluenesulfonic acid monohydrate (94.9 mg, 0.499 mmol) at r.t. and the mixture was stirred for 1 h. The mixture was poured

into sat. aq $NaHCO_3$ (2 × 5 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with H_2O (5 mL), and dried (Na_2SO_4). After filtration and evaporation, the residue was subjected to column chromatography on SiO_2 (hexane–EtOAc, 5: 1) to give **5a** (22.3 mg, 0.0854 mmol, 34%), 4-methoxy-3-(methoxycarbonyl)-2-[(methoxycarbonyl)methyl]-1,2,3,4-tetrahydroquinoline (MeO-**5a**; 15.6 mg, 0.0854 mmol, 21%), 3,5-di(methoxycarbonyl)-4-[(methoxycarbonyl)methyl]-1-phenyl-1,4-dihydropyridine (**6**; 8.1 mg, 0.0235 mmol, 14%), and methyl (2*E*,4*Z*)-4-(methoxycarbonyl)-5-(phenylamino)penta-2,4-dienoate (**7**; 6.8 mg, 0.0260 mmol, 10%).

4-Methoxy-3-(methoxycarbonyl)-2-[(methoxycarbonyl)methyl]-1,2,3,4-tetrahydroquinoline (MeO-5a)
Colorless solid; mp 72.5–74.4 °C (hexane–EtOAc).

IR (KBr): 3384, 2953, 1749, 1725, 1668, 1498, 1435, 1271, 1189, 1173, 1071, 755 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.41 (dd, *J* = 9.6, 16.8 Hz, 1 H), 2.64 (dd, *J* = 2.9, 11.8 Hz, 1 H), 3.05 (dd, *J* = 2.4, 16.2 Hz, 1 H), 3.27 (s, 3 H), 3.73 (s, 3 H), 3.80 (s, 3 H), 4.17 (ddd, *J* = 2.4, 9.8, 11.9 Hz, 1 H), 4.49 (d, *J* = 3.0 Hz, 1 H), 4.93 (br s, 1 H), 6.59 (d, *J* = 8.1 Hz, 1 H), 6.64 (t, *J* = 7.4 Hz, 1 H), 7.08 (d, *J* = 7.5 Hz, 1 H), 7.13 (t, *J* = 7.9 Hz, 1 H).

HRMS-ESI: *m*/*z* $[M + Na]^+$ calcd for $C_{15}H_{19}NO_5$ + Na: 316.1155; found: 316.1151.

3,5-Di(methoxycarbonyl)-4-[(methoxycarbonyl)methyl]-1-phenyl-1,4-dihydropyridine (6)
Yellow oil.

IR (NaCl, neat): 2951, 1713, 1596, 1495, 1436, 1211, 1084, 755, 715, 696 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.60 (d, *J* = 5.0 Hz, 2 H), 3.59 (s, 3 H), 3.77 (s, 6 H), 4.26 (t, *J* = 5.0 Hz, 1 H), 7.23 (d, *J* = 7.4 Hz, 2 H), 7.27 (t, *J* = 7.4 Hz, 1 H), 7.40 (t, *J* = 7.8 Hz, 2 H), 7.59 (s, 2 H).

HRMS-ESI: *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{19}NO_6$ + Na: 368.1105; found: 368.1101.

Methyl (2*E*,4*Z*)-4-(Methoxycarbonyl)-5-(phenylamino)penta-2,4-dienoate (7)
Yellow solid; mp 117.1–118.5 °C (hexane–EtOAc) (Lit.[18] mp 118.9 °C; Lit.[19] mp 116.4–117.7 °C).

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