Synthesis of (*Z*)-2-(2*H*-Isoquinolin-1-ylidene)acetamides by Iodine-Mediated Cyclization of (*Z*)-3-Amino-3-(2-vinylphenyl)propenamides

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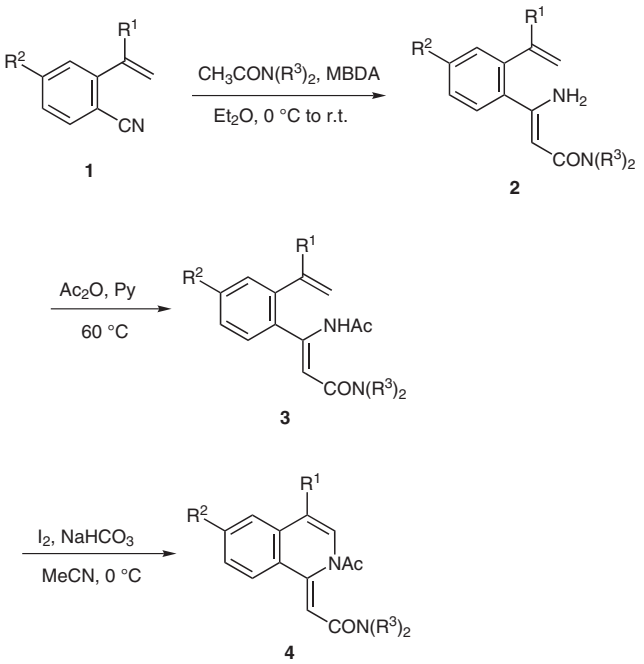
Abstract: (*Z*)-2-(2-Acetyl-2*H*-isoquinolin-1-ylidene)acetamides have been synthesized from 2-vinylbenzonitrile derivatives in three steps. The key step involves the iodine-mediated 6-*endo* cyclization of (*Z*)-3-acetylamino-3-(2-vinylphenyl)propenamides, which are prepared by the coupling of 2-vinylbenzonitriles with magnesium enolates of tertiary amides followed by N-acetylation.

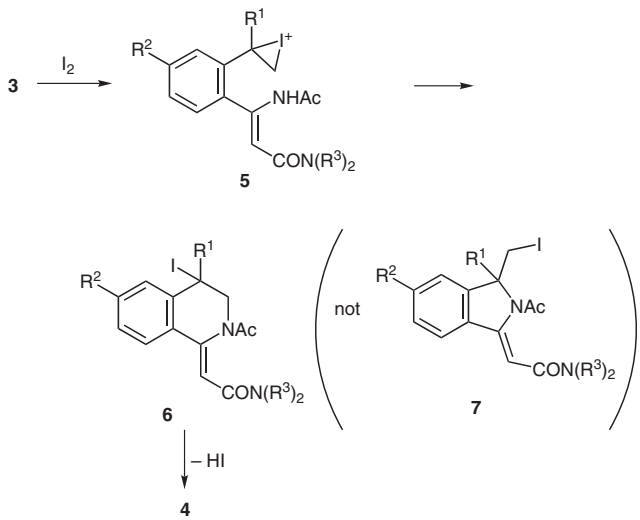
Key words: 6-*endo* cyclization, iodine, isoquinoline, magnesium amide, magnesium enolate

Recently, we have reported a few syntheses of nitrogen heterocycles utilizing iodoamination of styrene derivatives carrying a substituent including a NH moiety. Thus, 2-(arylamino)styrenes were allowed to react with iodine in the presence of sodium hydrogencarbonate to give the 5-*endo* cyclization products, 1-aryl-1*H*-indoles,[1] whereas a similar treatment of 2-(acylamino)styrenes gave the 4-*exo* cyclization products, 2-iodomethylbenzazetines.[2] We also found that secondary 2-vinylbenzamides gave the 5-*exo* cyclization products, 3-(iodomethyl)isoindolin-1-ones, on treatment with iodine.[3] In this paper we wish to report a synthesis of (*Z*)-2-(2-acetyl-2*H*-isoquinolin-1-ylidene)acetamides **4**. We have found that a 6-*endo* cyclization takes places by treating (*Z*)-3-acetylamino-3-(2-vinylphenyl)propenamides **3** with iodine to give **4**. Although a number of methods for the preparation of isoquinoline derivatives have been reported[4] because of their biological importance,[5] there have been few reports on the general synthesis of 2-(2*H*-isoquinolin-1-ylidene)acetic acid derivatives.[6]

In our previous paper,[7a] we reported on the formation of vinylogous urea derivatives by the magnesium bis(diisopropylamide) (MBDA)-mediated coupling reaction between tertiary amides and nitriles. As shown in Scheme 1, the first step of our sequence was this coupling reaction with 2-vinylbenzonitrile derivatives **1**, which could be easily prepared by conventional synthetic methods (see experimental section). The coupling products (*Z*)-3-amino-3-(2-vinylphenyl)propenamides **2** were obtained in good yields. Subsequent N-acetylation of these enamino amides **2** with acetic anhydride in pyridine afforded good yields of (*Z*)-3-acetylamino-3-(2-vinylphenyl)propenamide derivatives **3**, which cyclized on treatment with three molar amounts each of iodine and sodium hydrogencarbonate for one hour to give the corresponding (*Z*)-2-(2-acetyl-2*H*-isoquinolin-1-ylidene)acetamides **4** in 50–59% yields, via 6-*endo* iodoamination intermediates **6**; 5-*exo* cyclization products **7**, which have more strained structures, were not detected (Scheme 2). The results obtained



Scheme 1



Scheme 2

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Table 1 Preparation of 2-(2*H*-Isoquinolin-1-ylidene)acetamides **4** from 2-Vinylbenzonitriles **1**

Entry	**1**	$N(R^3)_2$ in amide	**2** (Yield, %)[a]	**3** (Yield, %)[a]	**4** (Yield, %)[a]
1	**1a** (R^1 = Ph, R^2 = H)	NMe_2	**2a** (91)	**3a** (73)	**4a** (51)
2	**1a**	NEt_2	**2b** (87)	**3b** (73)	**4b** (59)
3	**1a**	morpholin-4-yl	**2c** (83)	**3c** (70)	**4c** (56)
4	**1b** (R^1 = 4-ClC_6H_4, R^2 = H)	NMe_2	**2d** (87)	**3d** (78)	**4d** (55)
5	**1c** (R^1 = Me, R^2 = H)	NMe_2	**2e** (85)	**3e** (75)	**4e** (50)
6	**1d** (R^1 = Et, R^2 = H)	NMe_2	**2f** (90)	**3f** (60)	**4f** (58)
7	**1e** (R^1 = Ph, R^2 = OMe)	NMe_2	**2g** (80)	**3g** (77)	**4g** (53)

[a] Isolated yields.

from this sequence are summarized in Table 1. The use of less than three molar amounts each of iodine and sodium hydrogencarbonate did not give satisfactory results. For example, the reaction of **3a** with two molar amounts each of iodine and sodium hydrogencarbonate for a prolonged time (5 h) gave only 29% yield of the desired product **4a**, and a considerable amount (40%) of the starting material was recovered. The reaction of **3a** with iodine using potassium *tert*-butoxide as base in toluene gave a rather complex mixture of products, from which only 28% yield of the desired product **4a** was obtained. It should be noted that all attempts for direct conversion of **2** into the corresponding (isoquinolinylidene)acetamide derivatives were unsuccessful and resulted in the formation of intractable mixtures of products.

The stereochemistry of **2** and **3** were assigned to be *Z* in analogy with earlier results[7] on the basis of their spectral (IR and ^{1}H NMR) data (see experimental section). The *Z* preference is ascribed to intramolecular hydrogen bonding between the N-hydrogen and amide carbonyl. Unambiguous determination of the stereochemistry of **4** was carried out by NOE experiments. Thus, irradiation of the signal at δ = 5.33 assignable to the vinyl proton α to carboxamide of compound **4e** resulted in an enhancement (13%) of the signal at δ = 7.23 assignable to the proton at the 8-position of the isoquinoline ring.

In conclusion, (*Z*)-2-(2*H*-isoquinolin-1-ylidene)acetamide derivatives have been synthesized in three steps from 2-vinylbenzonitrile derivatives. Although total yields of the products were moderate, the present sequence may find some value in organic synthesis, because the reactions are simple to conduct and the starting materials are readily available.

The melting points were determined on a Laboratory Devices Mel-Temp II melting-point apparatus and are uncorrected. The IR spectra were recorded on a Shimadzu FTIR-8300 spectrometer. The ^{1}H NMR spectra were determined using $SiMe_4$ as an internal reference in $CDCl_3$ with a Jeol ECP500 FT NMR spectrometer operating at 500 MHz, a Jeol LA400 FT NMR spectrometer operating at 400 MHz, or a Jeol JNM-GX270 FT NMR spectrometer operating at 270 MHz. The ^{13}C NMR spectrum was determined using $SiMe_4$ as an internal reference with a Jeol ECP500 FT NMR spectrometer operating at 125 MHz in $CDCl_3$. Low-resolution mass spectra (EI) were recorded on a Jeol Automass 20 spectrometer (Center for Joint Research and Development, this University). TLC analyses were carried out on Merck Kieselgel 60 PF_{254}. Column chromatography was performed using Merck Kieselgel 60 (0.063–0.200 mm). All solvents were dried over appropriate drying agents and distilled under argon prior to use.

2-(1-Phenylvinyl)benzonitrile (**1a**),[8] 2-[1-(4-chlorophenyl)vinyl]benzonitrile (**1b**), and 4-methoxy-2-(1-phenylvinyl)benzonitrile (**1e**) were prepared by the procedure reported previously by us.[9] 2-Acetylbenzonitrile[10] and 1-(2-bromophenyl)propan-1-one[11] were prepared according to appropriate literature procedures. All other chemicals used in this study were commercially available.

2-(1-Methylvinyl)benzonitrile (1c)[12]

This compound was prepared by treating 2-acetylbenzonitrile[10] with methylenetriphenylphosphorane under the conditions reported by us for the preparation of **1a**;[9] yield: 64%; colorless liquid; R_f = 0.41 (CH_2Cl_2–hexane, 1:2).

IR (neat): 2224, 1638 cm^{-1}.

The ^{1}H NMR data for this compound were identical to those reported previously.[12]

2-Propanoylbenzonitrile

A mixture of 1-(2-bromophenyl)propan-1-one[11] (2.3 g, 11 mmol) in DMF (30 mL) containing CuCN (1.1 g, 13 mmol) was heated at reflux temperature for 30 min. Toluene and H_2O (50 mL each) were added to the cooled mixture and the precipitate was filtered through a Celite pad. The layers were separated and the organic layer was washed with H_2O (3 × 10 mL) and then brine (10 mL). After drying (Na_2SO_4), the solvent was evaporated. The residue was purified by column chromatography on silica gel (1:2 hexane–Et_2O) to give the title compound; yield: 0.88 g (52%); white solid; mp 45–48 °C (hexane–Et_2O).

IR (KBr): 2222, 1695 cm^{-1}.

^{1}H NMR (500 MHz): δ = 1.27 (t, *J* = 7.3 Hz, 3 H), 3.06 (q, *J* = 7.3 Hz, 2 H), 7.64 (ddd, *J* = 7.8, 7.3, 1.4 Hz, 1 H), 7.70 (ddd, *J* = 7.8, 7.3, 1.4 Hz, 1 H), 7.82 (dd, *J* = 7.8, 1.4 Hz, 1 H), 7.93 (dd, *J* = 7.8, 1.4 Hz, 1 H).

Anal. Calcd for $C_{10}H_9NO$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.41; H, 5.80; N, 9.00.

2-(1-Ethylvinyl)benzonitrile (1d)

This compound was prepared by treating 2-propanoylbenzonitrile with methylenetriphenylphosphorane under the conditions reported by us for the preparation of **1a**;[9] yield: 59%; colorless liquid; R_f = 0.33 (CH_2Cl_2–hexane, 1:2).

IR (neat): 2224, 1636 cm^{-1}.

^1H NMR (270 MHz): δ = 1.08 (t, *J* = 7.3 Hz, 3 H), 2.51 (qd, *J* = 7.3, 0.9 Hz, 2 H), 5.19 (d, *J* = 0.9 Hz, 1 H), 5.36 (q, *J* = 0.9 Hz, 1 H), 7.33 (d, *J* = 7.3 Hz, 1 H), 7.35 (td, *J* = 7.3, 0.9 Hz, 1 H), 7.54 (ddd, *J* = 7.8, 7.3, 1.4 Hz, 1 H), 7.66 (dd, *J* = 7.8, 0.9 Hz, 1 H).

Anal. Calcd for $C_{11}H_{11}N$: C, 84.04; H, 7.05; N, 8.91. Found: C, 83.64; H, 7.14; N, 9.13.

3-Amino-3-(2-vinylphenyl)propenamides 2; (*Z*)-3-Amino-*N*,*N*-dimethyl-3-[2-(1-phenylvinyl)phenyl]propenamide (2a); Typical Procedure

To a stirred turbid solution of MBDA at 0 °C, generated by treating diisopropylamine (1.8 g, 18 mmol) with EtMgBr (18 mmol, 3 M solution in Et_2O) in Et_2O (15 mL) at reflux temperature for 1 h, were added *N*,*N*-dimethylacetamide (0.76 g, 8.8 mmol) and **1a** (0.45 g, 2.2 mmol) successively. After stirring for 10 min at the same temperature, aq NH_4Cl (20 mL) was added and the mixture was extracted with Et_2O (3 × 20 mL). The combined extracts were washed with brine (20 mL), dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography on silica gel to give **2a**; yield: 0.46 g (91%); yellow oil; R_f = 0.31 (EtOAc–hexane, 1:3).

IR (neat): 3383, 3275, 1614 cm^{-1}.

^1H NMR (500 MHz): δ = 2.82 (br s, 6 H), 4.69 (s, 1 H), 5.30 (d, *J* = 1.4 Hz, 1 H), 5.69 (d, *J* = 1.4 Hz, 1 H), 6.0–7.0 (br, 2 H), 7.20–7.26 (m, 5 H), 7.31 (dd, *J* = 7.3, 1.8 Hz, 1 H), 7.35–7.42 (m, 2 H), 7.44 (dd, *J* = 7.3, 1.8 Hz, 1 H).

Anal. Calcd for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.89; N, 9.58. Found: C, 77.96; H, 6.91; N, 9.27.

(*Z*)-3-Amino-*N*,*N*-diethyl-3-[2-(1-phenylvinyl)phenyl]propenamide (2b)

Pale-yellow solid; mp 100–101 °C (hexane–Et_2O).

IR (KBr): 3381, 3273, 1616 cm^{-1}.

^1H NMR (500 MHz): δ = 1.04 (br s, 6 H), 3.08 (br s, 2 H), 3.31 (br s, 2 H), 4.65 (s, 1 H), 5.30 (d, *J* = 0.9 Hz, 1 H), 5.69 (d, *J* = 0.9 Hz, 1 H), 6.0–7.0 (br, 2 H), 7.20–7.26 (m, 5 H), 7.32 (dd, *J* = 7.3, 2.3 Hz, 1 H), 7.35–7.42 (m, 2 H), 7.45 (dd, *J* = 7.3, 1.8 Hz, 1 H).

Anal. Calcd for $C_{21}H_{24}N_2O$: C, 78.71; H, 7.55; N, 8.74. Found: C, 78.57; H, 7.73; N, 8.58.

(*Z*)-Amino-1-(morpholin-4-yl)-3-[2-(1-phenylvinyl)phenyl]propenone (2c)

White solid; mp 150–153 °C (hexane–Et_2O).

IR (KBr): 3402, 3292, 1614 cm^{-1}.

^1H NMR (500 MHz): δ = 3.1–3.5 (br, 4 H), 3.56 (br s, 4 H), 4.61 (s, 1 H), 5.28 (d, *J* = 0.9 Hz, 1 H), 5.71 (d, *J* = 0.9 Hz, 1 H), 6.0–7.0 (br, 2 H), 7.22–7.27 (m, 5 H), 7.34 (dd, *J* = 7.3, 1.4 Hz, 1 H), 7.36–7.45 (m, 3 H).

Anal. Calcd for $C_{21}H_{22}N_2O_2$: C, 75.42; H, 6.63; N, 8.38. Found: C, 75.38; H, 6.80; N, 8.21.

(*Z*)-3-Amino-3-{2-[1-(4-chlorophenyl)vinyl]phenyl}-*N*,*N*-dimethylpropenamide (2d)

Yellow viscous oil; R_f = 0.42 (EtOAc–hexane, 1:1).

IR (neat): 3383, 3275, 1614 cm^{-1}.

^1H NMR (500 MHz): δ = 2.84 (br s, 6 H), 4.63 (s, 1 H), 5.32 (d, *J* = 0.9 Hz, 1 H), 5.65 (s, 1 H), 6.0–7.0 (br, 2 H), 7.16 (d, *J* = 8.7 Hz, 2 H), 7.20 (d, *J* = 8.7 Hz, 2 H), 7.31 (dd, *J* = 8.7, 1.8 Hz, 1 H), 7.36–7.44 (m, 3 H).

Anal. Calcd for $C_{19}H_{19}ClN_2O$: C, 69.83; H, 5.86; N, 8.57. Found: C, 69.63; H, 5.92; N, 8.43.

(*Z*)-3-Amino-*N*,*N*-dimethyl-3-[2-(1-methylvinyl)phenyl]propenamide (2e)

Pale-yellow solid; mp 79–82 °C (hexane–Et_2O).

IR (KBr): 3381, 3275, 1614 cm^{-1}.

^1H NMR (500 MHz): δ = 2.07 (dd, *J* = 1.4, 0.9 Hz, 3 H), 2.99 (s, 6 H), 4.94 (s, 1 H), 5.06 (quint, 0.9 Hz, 1 H), 5.12–5.14 (m, 1 H), 6.0–7.0 (br, 2 H), 7.25 (dd, *J* = 7.3, 1.4 Hz, 1 H), 7.29 (ddd, *J* = 7.8, 7.3, 1.4 Hz, 1 H), 7.33 (td, *J* = 7.3, 1.4 Hz, 1 H), 7.39 (dd, *J* = 7.8, 1.4 Hz, 1 H).

Anal. Calcd for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.16. Found: C, 73.64; H, 8.03; N, 12.15.

(*Z*)-3-Amino-3-[2-(1-ethylvinyl)phenyl]-*N*,*N*-dimethylpropenamide (2f)

White solid; mp 75–77 °C (hexane–Et_2O).

IR (KBr): 3381, 3275, 1614 cm^{-1}.

^1H NMR (500 MHz): δ = 0.98 (t, *J* = 7.3 Hz, 3 H), 2.38 (q, *J* = 7.3 Hz, 2 H), 2.99 (s, 6 H), 4.93 (s, 1 H), 5.06 (d, *J* = 0.9 Hz, 1 H), 5.13 (d, *J* = 0.9 Hz, 1 H), 6.0–7.0 (br, 2 H), 7.21 (dd, *J* = 7.3, 1.8 Hz, 1 H), 7.29 (td, *J* = 7.3, 1.4 Hz, 1 H), 7.33 (td, *J* = 7.3, 1.8 Hz, 1 H), 7.39 (dd, *J* = 7.3, 1.4 Hz, 1 H).

Anal. Calcd for $C_{15}H_{20}N_2O$: C, 73.74; H, 8.25; N, 11.47. Found: C, 73.70; H, 8.35; N, 11.35.

(*Z*)-3-Amino-3-[4-methoxy-2-(1-phenylvinyl)phenyl]-*N*,*N*-dimethylpropenamide (2g)

Yellow viscous oil; R_f = 0.19 (EtOAc–hexane, 1:3).

IR (neat): 3385, 3277, 1614 cm^{-1}.

^1H NMR (400 MHz): δ = 2.81 (br s, 6 H), 3.83 (s, 3 H), 4.68 (s, 1 H), 5.30 (s, 1 H), 5.69 (s, 1 H), 6.0–7.0 (br, 2 H), 6.84 (d, *J* = 2.6 Hz, 1 H), 6.90 (dd, *J* = 8.4, 2.6 Hz, 1 H), 7.21–7.26 (m, 5 H), 7.38 (d, *J* = 8.4 Hz, 1 H).

Anal. Calcd for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.18; H, 6.89; N, 8.47.

3-Acetylamino-3-(vinylphenyl)propenamides 3; (*Z*)-3-Acetylamino-*N*,*N*-dimethyl-3-[2-(1-phenylvinyl)phenyl]propenamide (3a); Typical Procedure

A mixture of **2a** (0.41 g, 1.8 mmol), pyridine (1 mL), and Ac_2O (1 mL) was heated at 60 °C for 4 h. After removal of excess pyridine and Ac_2O under reduced pressure, the residue was purified by preparative TLC on silica gel to give **3a**; yield: 0.44 g (73%); yellow viscous oil; R_f = 0.48 (EtOAc–hexane, 1:1).

IR (neat): 3408, 1711, 1622 cm^{-1}.

^1H NMR (500 MHz): δ = 1.95 (s, 3 H), 2.74 (s, 3 H), 2.90 (s, 3 H), 5.05 (s, 1 H), 5.28 (d, *J* = 1.4 Hz, 1 H), 5.66 (d, *J* = 1.4 Hz, 1 H), 7.19–7.30 (m, 7 H), 7.32–7.39 (m, 2 H), 11.71 (br s, 1 H).

Anal. Calcd for $C_{21}H_{22}N_2O_2$: C, 75.42; H, 6.63; N, 8.38. Found: C, 75.37; H, 6.65; N, 7.99.

(*Z*)-3-Acetylamino-*N*,*N*-diethyl-3-[2-(1-phenylvinyl)phenyl]propenamide (3b)

Brownish-yellow viscous oil; R_f = 0.39 (EtOAc–hexane, 1:2).

IR (neat): 3402, 1711, 1622 cm^{-1}.

^1H NMR (500 MHz): δ = 0.94 (t, *J* = 7.3 Hz, 3 H), 1.09 (t, *J* = 7.3 Hz, 3 H), 1.96 (s, 3 H), 3.03 (q, *J* = 7.3 Hz, 2 H), 3.31 (q, *J* = 7.3 Hz, 2 H), 4.98 (s, 1 H), 5.29 (d, *J* = 1.4 Hz, 1 H), 5.66 (d, *J* = 1.4 Hz, 1 H), 7.19–7.30 (m, 7 H), 7.32–7.39 (m, 2 H), 11.83 (br s, 1 H).

Anal. Calcd for $C_{23}H_{26}N_2O_2$: C, 76.21; H, 7.23; N, 7.73. Found: C, 76.18; H, 7.40; N, 7.74.

(*Z*)-*N*-{3-(Morpholin-4-yl)-3-oxo-1-[2-(1-phenylvinyl)phenyl]propenyl}acetamide (3c)
Yellow viscous oil; R_f = 0.23 (EtOAc–hexane, 1:1).

IR (neat): 3402, 1713, 1622 cm^{-1}.

^1H NMR (500 MHz): δ = 1.97 (s, 3 H), 3.07 (br s, 2 H), 3.45–3.62 (m, 6 H), 4.96 (s, 1 H), 5.28 (d, *J* = 1.4 Hz, 1 H), 5.70 (d, *J* = 1.4 Hz, 1 H), 7.21–7.42 (m, 9 H), 11.54 (br s, 1 H).

Anal. Calcd for $C_{23}H_{24}N_2O_3$: C, 73.38; H, 6.43; N, 7.44. Found: C, 73.27; H, 6.71; N, 7.39.

(*Z*)-3-Acetylamino-3-{2-[1-(4-chlorophenyl)vinyl]phenyl}-*N*,*N*-dimethylpropenamide (3d)
Yellow oil; R_f = 0.22 (EtOAc–pentane, 1:2).

IR (KBr): 3404, 1709, 1622 cm^{-1}.

^1H NMR (500 MHz): δ = 1.95 (s, 3 H), 2.82 (s, 3 H), 2.93 (s, 3 H), 5.02 (s, 1 H), 5.30 (d, *J* = 0.9 Hz, 1 H), 5.62 (d, *J* = 0.9 Hz, 1 H), 7.20 (br s, 4 H), 7.27 (dd, *J* = 8.7, 2.3 Hz, 1 H), 7.33–7.40 (m, 3 H,), 11.75 (br s, 1 H).

Anal. Calcd for $C_{21}H_{21}ClN_2O_2$: C, 68.38; H, 5.74; N, 7.59. Found: C, 68.29; H, 5.77; N, 7.41.

(*Z*)-3-Acetylamino-*N*,*N*-dimethyl-3-[2-(1-methylvinyl)phenyl]propenamide (3e)
Pale-yellow viscous oil; R_f = 0.36 (EtOAc–hexane, 1:1).

IR (neat): 3402, 1713, 1622 cm^{-1}.

^1H NMR (500 MHz): δ = 2.02 (s, 3 H), 2.07 (s, 3 H), 3.02 (s, 3 H), 3.03 (s, 3 H), 4.99 (d, *J* = 0.9 Hz, 1 H), 5.09 (d, *J* = 0.9 Hz, 1 H), 5.33 (s, 1 H), 7.21–7.32 (m, 4 H), 11.92 (br s, 1 H).

Anal. Calcd for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.29. Found: C, 70.52; H, 7.40; N, 10.28.

(*Z*)-3-Acetylamino-3-[2-(1-ethylvinyl)phenyl]-*N*,*N*-dimethylpropenamide (3f)

Colorless viscous oil; R_f = 0.39 (EtOAc–hexane, 1:1).

IR (neat): 3402, 1713, 1622 cm^{-1}.

^1H NMR (500 MHz): δ = 1.00 (t, *J* = 7.3 Hz, 3 H), 2.06 (s, 3 H), 2.33 (q, *J* = 7.3 Hz, 2 H), 3.02 (s, 3 H), 3.03 (s, 3 H), 4.99 (s, 1 H), 5.08 (q, *J* = 1.4 Hz, 1 H), 5.34 (s, 1 H), 7.18 (dd, *J* = 7.3, 1.4 Hz, 1 H), 7.23 (dd, *J* = 7.3, 1.4 Hz, 1 H), 7.25 (td, *J* = 7.3, 1.4 Hz, 1 H), 7.30 (td, *J* = 7.3, 1.4 Hz, 1 H), 11.87 (br s, 1 H).

Anal. Calcd for $C_{17}H_{22}N_2O_2$: C, 71.30; H, 7.74; N, 9.78. Found: C, 71.28; H, 7.78; N, 9.53.

(*Z*)-3-Acetylamino-3-[4-methoxy-2-(1-phenylvinyl)phenyl]-*N*,*N*-dimethylpropenamide (3g)

Yellow viscous oil; R_f = 0.26 (EtOAc–hexane, 3:2).

IR (neat): 3410, 1709, 1622 cm^{-1}.

^1H NMR (400 MHz): δ = 1.94 (s, 3 H), 2.74 (s, 3 H), 2.89 (s, 3 H), 3.82 (s, 3 H), 5.04 (s, 1 H), 5.29 (d, *J* = 1.0 Hz, 1 H), 5.66 (d, *J* = 1.0 Hz, 1 H), 6.82 (d, *J* = 2.4 Hz, 1 H), 6.88 (dd, *J* = 8.2, 2.4 Hz, 1 H), 7.19–7.30 (m, 6 H), 11.65 (br s, 1 H).

Anal. Calcd for $C_{22}H_{24}N_2O_3$: C, 72.50; H, 6.64; N, 7.69. Found: C, 72.29; H, 6.68; N, 7.77.

2-(2*H*-Isoquinolin-1-ylidene)acetamides 4; (*Z*)-2-(2-Acetyl-4-phenyl-2*H*-isoquinolin-1-ylidene)-*N*,*N*-dimethylacetamide (4a); Typical Procedure
To a stirred solution of **3a** (0.25 g, 0.74 mmol) in MeCN (5 mL) containing $NaHCO_3$ (0.19 g, 2.2 mmol) at 0 °C, was added I_2 (0.56 g, 2.2 mmol) in portions and the mixture was stirred for 1 h at the same temperature. Aq 10% $Na_2S_2O_3$ was added until the color of I_2 had disappeared, and the mixture was extracted with Et_2O (3 × 15 mL). The combined extracts were washed with sat. aq $NaHCO_3$ (20 mL) and then brine (10 mL), and dried (K_2CO_3). Evaporation of the solvent gave a residue, which was purified by preparative TLC on silica gel to afford **4a**; yield: 0.13 g (51%); pale-yellow solid; mp 167–168 °C (hexane–CH_2Cl_2).

IR (KBr): 1664 cm^{-1}.

^1H NMR (500 MHz): δ = 2.26 (s, 3 H), 2.28 (s, 3 H), 2.62 (s, 3 H), 5.45 (s, 1 H), 6.36 (s, 1 H), 7.23 (td, *J* = 7.3, 1.4 Hz, 1 H), 7.31 (td, *J* = 7.3, 1.4 Hz, 1 H), 7.33 (d, *J* = 7.3 Hz, 1 H), 7.40–7.49 (m, 4 H), 7.59 (dd, *J* = 8.2, 1.4 Hz, 2 H).

MS: *m*/*z* (%) = 332 (7.3, [M$^+$]), 272 (18), 231 (87), 189 (100).

Anal. Calcd for $C_{21}H_{20}N_2O_2$: C, 75.88; H, 6.06; N, 8.43. Found: C, 76.00; H, 6.12; N, 8.32.

(*Z*)-2-(2-Acetyl-4-phenyl-2*H*-isoquinolin-1-ylidene)-*N*,*N*-diethylacetamide (4b)
Pale-yellow solid; mp 157–158 °C (hexane–CH_2Cl_2).

IR (KBr): 1661 cm^{-1}.

^1H NMR (500 MHz): δ = 0.73 (t, *J* = 7.3 Hz, 3 H), 0.84 (t, *J* = 7.3 Hz, 3 H), 2.28 (s, 3 H), 2.41 (dq, *J* = 15.3, 7.3 Hz, 1 H), 2.83–2.91 (m, 2 H), 3.37 (dq, *J* = 15.3, 7.3 Hz, 1 H), 5.37 (s, 1 H), 6.35 (s, 1 H), 7.20 (td, *J* = 7.3, 1.4 Hz, 1 H), 7.28 (ddd, *J* = 7.8, 7.3, 1.4 Hz, 1 H), 7.38–7.50 (m, 5 H), 7.59 (dd, *J* = 8.2, 1.4 Hz, 2 H).

MS: *m*/*z* (%) = 360 (6.2, [M$^+$]), 300 (11), 231 (100).

Anal. Calcd for $C_{23}H_{24}N_2O_2$: C, 76.64; H, 6.71; N, 7.77. Found: C, 76.31; H, 6.81; N, 7.39.

(*Z*)-2-(2-Acetyl-4-phenyl-2*H*-isoquinolin-1-ylidene)-1-(morpholin-4-yl)ethanone (4c)
Pale-yellow solid; mp 204–205 °C (hexane–CH_2Cl_2).

IR (KBr): 1670, 1655 cm^{-1}.

^1H NMR (500 MHz): δ = 2.28 (s, 3 H), 2.29–2.32 (m, 1 H), 2.61–2.65 (m, 1 H), 2.91–2.94 (m, 1 H), 2.99–3.09 (m, 2 H), 3.30–3.33 (m, 1 H), 3.51–3.54 (m, 1 H), 3.67–3.70 (m, 1 H), 5.37 (s, 1 H), 6.33 (s, 1 H), 7.27 (t, *J* = 7.3 Hz, 1 H), 7.33–7.40 (m, 2 H), 7.41–7.49 (m, 4 H), 7.57 (d, *J* = 8.2 Hz, 2 H).

^{13}C NMR: δ = 14.27, 41.71, 44.70, 65.49, 66.22, 78.71, 83.49, 121.28, 125.50, 127.02, 127.50, 128.78, 128.88, 128.99, 134.03, 135.12, 142.28, 144.86, 146.29, 165.56, 168.56.

MS: *m*/*z* (%) = 374 (6.4, [M$^+$]), 314 (15), 231 (83), 189 (100).

Anal. Calcd for $C_{23}H_{22}N_2O_3$: C, 73.78; H, 5.92; N, 7.48. Found: C, 73.86; H, 5.75; N, 7.18.

(*Z*)-2-[2-Acetyl-4-(4-chlorophenyl)-2*H*-isoquinolin-1-ylidene]-*N*,*N*-dimethylacetamide (4d)
Pale-yellow solid; mp 179–181 °C (hexane–CH_2Cl_2).

IR (KBr): 1658 cm^{-1}.

^1H NMR (500 MHz): δ = 2.24 (s, 3 H), 2.27 (s, 3 H), 2.62 (s, 3 H), 5.44 (s, 1 H), 6.36 (s, 1 H), 7.24 (td, *J* = 7.3, 0.9 Hz, 1 H), 7.32 (td, *J* = 7.3, 0.9 Hz, 1 H), 7.33 (d, *J* = 7.3 Hz, 1 H), 7.38 (d, *J* = 7.3 Hz, 1 H), 7.44 (d, *J* = 8.7 Hz, 2 H), 7.52 (d, *J* = 8.7 Hz, 2 H).

MS: *m*/*z* (%) = 366 (2.9, [M$^+$]), 306 (11), 265 (46), 189 (100).

Anal. Calcd for $C_{21}H_{19}ClN_2O_2$: C, 68.76; H, 5.22; N, 7.64. Found: C, 68.89; H, 5.37; N, 7.51.

(*Z*)-2-(2-Acetyl-4-methyl-2*H*-isoquinolin-1-ylidene)-*N*,*N*-dimethylacetamide (4e)
Pale-yellow solid; mp 123–127 °C (hexane–CH_2Cl_2).

IR (KBr): 1653 cm^{-1}.

^{1}H NMR (500 MHz): δ = 2.13 (d, *J* = 1.4 Hz, 3 H), 2.15 (s, 3 H), 2.23 (s, 3 H), 2.60 (s, 3 H), 5.33 (s, 1 H), 6.01 (q, 1.4 Hz, 1 H), 7.17 (td, *J* = 7.3, 0.9 Hz, 1 H), 7.19 (d, *J* = 7.3 Hz, 1 H), 7.23 (d, *J* = 7.3 Hz, 1 H), 7.30 (td, *J* = 7.3, 1.4 Hz, 1 H).

MS: *m*/*z* (%) = 270 (3.0, [M$^+$]), 198 (7.9), 183 (14), 169 (100).

Anal. Calcd for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 70.96; H, 6.82; N, 10.34.

(*Z*)-2-(2-Acetyl-4-ethyl-2*H*-isoquinolin-1-ylidene)-*N*,*N*-dimethylacetamide (4f)

Pale-yellow solid; mp 102–103 °C (hexane–Et_2O–$CHCl_3$).

IR (KBr): 1663 cm^{-1}.

^{1}H NMR (500 MHz): δ = 1.27 (t, *J* = 7.3 Hz, 3 H), 2.15 (s, 3 H), 2.24 (s, 3 H), 2.49–2.56 (m, 2 H), 2.60 (s, 3 H), 5.34 (s, 1 H), 6.01 (t, *J* = 1.4 Hz, 1 H), 7.16 (td, *J* = 7.3, 0.9 Hz, 1 H), 7.21 (d, 7.3 Hz, 1 H), 7.23 (d, *J* = 7.3 Hz, 1 H), 7.28 (td, *J* = 7.3, 0.9 Hz, 1 H).

MS: *m*/*z* (%) = 284 (2.9, [M$^+$]), 212 (9.0), 183 (100).

Anal. Calcd for $C_{17}H_{20}N_2O_2$: C, 71.81; H, 7.09; N, 9.85. Found: C, 71.73; H, 7.20; N, 9.73.

(*Z*)-2-(2-Acetyl-6-methoxy-4-phenyl-2*H*-isoquinolin-1-ylidene)-*N*,*N*-dimethylacetamide (4g)

Pale-yellow solid; mp 176–178 °C (hexane–CH_2Cl_2).

IR (KBr): 1668 cm^{-1}.

^{1}H NMR (500 MHz): δ = 2.26 (s, 3 H), 2.30 (s, 3 H), 2.66 (s, 3 H), 3.80 (s, 3 H), 5.42 (s, 1 H), 6.37 (s, 1 H), 6.74 (dd, *J* = 8.2, 2.3 Hz, 1 H), 6.97 (d, *J* = 2.3 Hz, 1 H), 7.23 (d, *J* = 8.2 Hz, 1 H), 7.40–7.49 (m, 3 H), 7.57 (dd, *J* = 8.2, 1.4 Hz, 2 H).

MS: *m*/*z* (%) = 362 (10, [M$^+$]), 317 (19), 290 (42), 261 (100).

Anal. Calcd for $C_{22}H_{22}N_2O_3$: C, 72.91; H, 6.12; N, 7.73. Found: C, 72.90; H, 6.10; N, 7.53.

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References

(1) Kobayashi, K.; Miyamoto, K.; Yamase, T.; Nakamura, D.; Morikawa, O.; Konishi, H. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 1580.
(2) Kobayashi, K.; Miyamoto, K.; Morikawa, O.; Konishi, H. *Bull. Chem. Soc. Jpn.* **2005**, *78*, 886.
(3) Kobayashi, K.; Hase, M.; Hashimoto, K.; Fujita, S.; Tanmatsu, M.; Morikawa, O.; Konishi, H. *Synthesis* **2006**, 2493.
(4) For recent reports, see: (a) Konno, T.; Chae, J.; Miyabe, T.; Ishihara, T. *J. Org. Chem.* **2005**, *70*, 10172. (b) Ichikawa, J.; Sakoda, K.; Moriyama, H.; Wada, Y. *Synthesis* **2006**, 1590. (c) Alonso, R.; Campos, P. J.; García, B.; Rodoríguez, M. A. *Org. Lett.* **2006**, *8*, 3521. For earlier reports, see pertinent references cited in these papers and ref. 9
(5) For recent reports on the biological activity of isoquinoline derivatives: (a) Barber, C. G.; Dickinson, R. P.; Fish, P. V. *Bioorg. Med. Chem. Lett.* **2005**, *14*, 3227. (b) Jiang, J.; Thomas, C. J.; Neumann, S.; Lu, X.; Rice, C. K.; Gershengorn, M. C. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 733. (c) Cui, W.; Iwasa, K.; Tokuda, H.; Kashihara, A.; Mitani, Y.; Hasegawa, T.; Nishiyama, Y.; Moriyasu, M.; Nishino, H.; Hanaoka, M.; Mukai, C.; Takeda, K. *Phytochemistry* **2006**, *67*, 70. (d) Markmee, S.; Ruchirawat, S.; Prachyawarakorn, W.; Ingkaninan, K.; Khorana, N. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2170. (e) Zhu, G.-D.; Gong, J.; Claiborne, A.; Woods, K. W.; Gandhi, V. B.; Thomas, S.; Luo, Y.; Liu, X.; Shi, Y.; Guan, R.; Magnone, S. R.; Klinghofer, V.; Johnson, E. F.; Bouska, J.; Shoemaker, A.; Oleksijew, A.; Stoll, V. S.; De Jong, R.; Olterdorf, T.; Li, Q.; Rosenberg, S. H.; Girranda, V. L. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3150.
(6) A synthesis of (2*H*-isoquinolin-1-ylidene)acetates by reactions of 2-alkyl-1-methylthioisoquinolinium salts with active methylene compounds has been reported: (a) Fujita, R.; Watanabe, N.; Tomisawa, H. *Chem. Pharm. Bull.* **2001**, *50*, 225. (b) Fujita, R.; Watanabe, N.; Tomisawa, H. *Heterocycles* **2001**, *55*, 435. For other reports on the synthesis of related compounds, see: (c) Stanovnik, B.; Drofenik, I.; Tisler, M.; Durst, T. *Heterocycles* **1987**, *26*, 1805. (d) Finke, J. A.; Huisgen, R.; Temme, R. *Helv. Chim. Acta* **2000**, *83*, 2363.
(7) (a) Kobayashi, K.; Kitamura, T.; Nakahashi, R.; Shimizu, A.; Morikawa, O.; Konishi, H. *Heterocycles* **2000**, *53*, 1021. (b) Hiyama, T.; Kobayashi, K.; Nishide, K. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 2127.
(8) Dordor, I. M.; Mellor, J. M. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1253.
(9) Kobayashi, K.; Shiokawa, T.; Omote, H.; Hashimoto, K.; Morikawa, O.; Konishi, H. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 1126.
(10) (a) Helberger, J. H.; von Rebay, A. *Liebigs Ann. Chem.* **1937**, *531*, 279. (b) Alan Aitken, R.; Fairhurst, I. M.; Ford, A.; Milne, P. E. Y.; Russell, D. W.; Whittaker, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3107.
(11) Wang, S.; Morrow, G. W.; Swenton, J. S. *J. Org. Chem.* **1989**, *54*, 5364.
(12) Peyroux, E.; Berthiol, F.; Doucet, H.; Santelli, M. *Eur. J. Org. Chem.* **2004**, 1075.