Synthesis of 3,3-Disubstituted Isoindolin-1-ones via Iodoamination of α-Substituted Secondary 2-Vinylbenzamides

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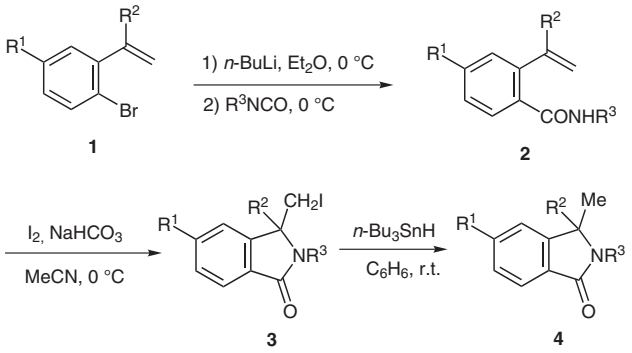
Abstract: A new and simple method for the preparation of 3,3-disubstituted isoindolin-1-ones from α-substituted 2-bromostyrenes is described. Construction of the isoindolin-1-one skeleton was accomplished by treating α-substituted secondary 2-vinylbenzamides, easily obtainable from the reaction of α-substituted 2-lithiostyrenes with isocyanates, with iodine to afford 3-substituted 3-iodomethylisoindolin-1-ones.

Key words: iodocyclization, isocyanate, isoindoline, 2-lithiostyrene, secondary benzamide

A number of synthetic methods for 3-substituted isoindolin-1-ones have been reported,[1] mainly on account of their biological interest.[2] For example, the alkylation of 2-substituted 3-lithioisoindolin-1-ones, first reported by Couture et al.,[1b] is one of the most efficient methods for preparing this class of compounds. However, there have been few reports on the synthesis of 3,3-disubstituted derivatives in literature.[3] In this paper we wish to demonstrate that the intramolecular iodoamination[4] of α-substituted secondary 2-vinylbenzamides provides a simple and convenient method for the synthesis of 3,3-disubstituted isoindolin-1-one derivatives.[5]

Our synthesis of 3,3-disubstituted isoindolin-1-one derivatives was conducted as outlined in Scheme 1. Thus, the bromine–lithium exchange between readily available α-substituted 2-bromostyrenes **1** and butyllithium in diethyl ether at 0 °C for one hour generated the corresponding α-substituted 2-lithiostyrenes. Almost complete generation of 1-(2-lithiophenyl)-1-phenylethene from **1a** was confirmed by obtaining 1,1-diphenylethene almost quantitatively after quenching with aqueous ammonium chloride. Then, these lithium products were allowed to react with isocyanates to give the α-substituted secondary 2-vinylbenzamides **2** in the yields summarized in Table 1. It indicates that aliphatic isocyanates (entries 3 and 4) gave poorer results than aromatic isocyanates (entries 1, 2, 5, and 6). The moderate yields of **2** may be ascribed to the liability of isocyanates to oligomerization.

The regioselective intramolecular iodoamination of these amides **2** proceeded smoothly on treatment with iodine in the presence of sodium hydrogen carbonate in acetonitrile



Scheme 1

at 0 °C to give the 3-iodomethylisoindolin-1-one derivatives **3** in fair to good yields. Reduction of the iodo moiety of **3** with tributyltin hydride smoothly proceeded in benzene at room temperature to afford the 3-methylisoindolin-1-one derivatives **4** in fair to good yields. These results are also summarized in Table 1.

We attempted the nucleophilic substitution reactions of **3a** with sodium thiolates; however, this resulted in the formation of intractable mixtures of products.

In conclusion, we have shown that 3,3-disubstituted isoindolin-1-ones can be synthesized in two steps from readily available α-substituted 2-bromostyrenes and under milder reaction conditions. This method may find some value in synthesis because of its simplicity.

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 or a JEOL LA400 FT NMR spectrometer operating at 400 MHz. Low-resolution mass spectra were recorded on a JEOL AUTOMASS 20 spectrometer (Center for Joint Research and Development, this University). TLC was carried out on Merck Kieselgel 60 PF_{254}. All of the solvents used were dried over appropriate drying agents and distilled under argon prior to use. All the reactions were carried out under argon.

1-Bromo-2-(1-phenylethenyl)benzene (**1a**),[6] 1-bromo-2-(1-methylethenyl)benzene (**1b**),[7] and 1-bromo-4-methoxy-2-(1-methylethenyl)benzene (**1c**)[8] were prepared by the appropriate reported methods. All other chemicals used in this study were commercially available.

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Table 1 Preparation of Isoindolin-1-one Derivatives **3** and **4** via **2**

Entry	2-Bromostyrene **1**	R^3	Yield of **2** (%)[a]	Yield of **3** (%)[a]	Yield of **4** (%)[a]
1	**1a** (R^1 = H, R^2 = Ph)	Ph	**2a** (53)	**3a** (85)	**4a** (75)
2	**1a**	4-ClC_6H_4	**2b** (57)	**3b** (80)	**4b** (82)
3	**1a**	*n*-Bu	**2c** (41)	**3c** (75)	**4c** (58)
4	**1a**	*t*-Bu	**2d** (43)	**3d** (71)	**4d** (57)
5	**1b** (R^1 = H, R^2 = Me)	Ph	**2e** (65)	**3e** (69)	**4e** (81)
6	**1c** (R^1 = OMe, R^2 = Me)	4-ClC_6H_4	**2f** (64)	**3f** (64)	**4f** (79)

[a] Isolated yield.

2-Vinylbenzamide Derivatives 2; *N*-Phenyl-2-(1-phenylethenyl)benzamide (2a); Typical Procedure

To a stirred solution of **1a**[6] (0.52 g, 2.0 mmol) in Et_2O (7 mL) at 0 °C was added dropwise *n*-BuLi (1.5 M in hexane, 2.0 mmol). After 1 h, phenyl isocyanate (0.24 g, 2.0 mmol) was added and stirring was continued for an additional 1 h before the reaction was quenched by adding sat. aq NH_4Cl (20 mL). The layers were separated and the aqueous layer was extracted with Et_2O (2 × 15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and evaporated. The residual solid was recrystallized from Et_2O–CH_2Cl_2 to give **2a**; yield: 0.32 g (53%); white solid; mp 134–135 °C.

IR (KBr): 3240, 1653 cm^{-1}.

^{1}H NMR (500 MHz): δ = 5.45 (1 H, s), 5.85 (1 H, s), 7.05 (1 H, tt, *J* = 7.3, 1.4 Hz), 7.17 (2 H, d, *J* = 7.8 Hz), 7.21–7.30 (7 H, m), 7.41 (1 H, dd, *J* = 7.3, 0.9 Hz), 7.49 (1 H, td, *J* = 7.3, 1.4 Hz), 7.53 (1 H, dd, *J* = 7.3, 1.4 Hz), 7.56 (1 H, br s), 7.82 (1 H, dd, *J* = 7.3, 1.4 Hz).

Anal. Calcd for $C_{21}H_{17}NO$: C, 84.25; H, 5.72; N, 4.68. Found: C, 84.22; H, 5.90; N, 4.60.

***N*-(4-Chlorophenyl)-2-(1-phenylethenyl)benzamide (2b)**

White solid; mp 163–164 °C (hexane–CH_2Cl_2).

IR (KBr): 3236, 1655 cm^{-1}.

^{1}H NMR (500 MHz): δ = 5.45 (1 H, s), 5.85 (1 H, s), 7.11 (2 H, d, *J* = 8.7 Hz), 7.18 (2 H, d, *J* = 8.7 Hz), 7.21–7.25 (5 H, m), 7.42 (1 H, d, *J* = 7.3 Hz), 7.49 (1 H, ddd, *J* = 7.8, 7.3, 1.4 Hz), 7.53–7.57 (2 H, m), 7.80 (1 H, dd, *J* = 7.8, 1.4 Hz).

Anal. Calcd for $C_{21}H_{16}ClNO$: C, 75.56; H, 4.83; N, 4.20. Found: C, 75.55; H, 5.07; N, 4.24.

***N*-Butyl-2-(1-phenylethenyl)benzamide (2c)**

Purified by preparative TLC on silica gel; colorless oil; R_f 0.05 (Et_2O–hexane, 1:2).

IR (neat): 3288, 1645 cm^{-1}.

^{1}H NMR (500 MHz): δ = 0.82 (3 H, t, *J* = 7.3 Hz), 1.12–1.27 (4 H, m), 3.06 (2 H, td, *J* = 7.3, 6.0 Hz), 5.38 (1 H, d, *J* = 0.9 Hz), 5.82 (1 H, d, *J* = 0.9 Hz), 5.84 (1 H, br s), 7.25–7.31 (5 H, m), 7.32 (1 H, dd, *J* = 7.3, 1.4 Hz), 7.42 (1 H, td, *J* = 7.3, 1.4 Hz), 7.46 (1 H, td, *J* = 7.3, 1.4 Hz), 7.71 (1 H, dd, *J* = 7.3, 1.4 Hz).

Anal. Calcd for $C_{19}H_{21}NO$: C, 81.68; H, 7.58; N, 5.01. Found: C, 81.53; H, 7.81; N, 5.00.

***N*-*tert*-Butyl-2-(1-phenylethenyl)benzamide (2d)**

Purified by preparative TLC on silica gel; colorless oil; R_f 0.23 (Et_2O–hexane, 1:2).

IR (neat): 3420, 3317, 1651 cm^{-1}.

^{1}H NMR (500 MHz): δ = 1.08 (9 H, s), 5.37 (1 H, d, *J* = 0.9 Hz), 5.78 (1 H, br s), 5.88 (1 H, d, *J* = 0.9 Hz), 7.24–7.31 (6 H, m), 7.40–7.47 (2 H, m), 7.73 (1 H, dd, *J* = 7.3, 1.4 Hz).

Anal. Calcd for $C_{19}H_{21}NO$: C, 81.68; H, 7.58; N, 5.01. Found: C, 81.58; H, 7.81; N, 4.94.

2-(1-Methylethenyl)-*N*-phenylbenzamide (2e)

White solid; mp 100–101 °C (hexane–Et_2O).

IR (KBr): 3261, 1643 cm^{-1}.

^{1}H NMR (500 MHz): δ = 2.10 (3 H, s), 5.21 (1 H, s), 5.33 (1 H, s), 7.15 (1 H, t, *J* = 7.3 Hz), 7.28 (1 H, d, *J* = 7.3 Hz), 7.31–7.45 (4 H, m), 7.58 (2 H, d, *J* = 7.8 Hz), 7.79 (1 H, d, *J* = 7.3 Hz), 7.96 (1 H, br s).

Anal. Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 80.94; H, 6.36; N, 5.90.

***N*-(4-Chlorophenyl)-4-methoxy-2-(1-methylethenyl)benzamide (2f)**

White solid; mp 139–140 °C (hexane–Et_2O).

IR (KBr): 3227, 1647 cm^{-1}.

^{1}H NMR (500 MHz): δ = 2.08 (3 H, s), 3.87 (3 H, s), 5.24 (1 H, s), 5.36 (1 H, s), 6.76 (1 H, d, *J* = 2.7 Hz), 6.91 (1 H, dd, *J* = 8.7, 2.7 Hz), 7.31 (2 H, d, *J* = 8.7 Hz), 7.53 (2 H, d, *J* = 8.7 Hz), 7.83 (1 H, d, *J* = 8.7 Hz), 8.10 (1 H, br s).

Anal. Calcd for $C_{17}H_{16}ClNO_2$: C, 67.66; H, 5.34; N, 4.64. Found: C, 67.59; H, 5.48; N, 4.60.

3-Iodomethylisoindolin-1-one Derivatives 3; 3-Iodomethyl-2,3-diphenylisoindolin-1-one (3a); Typical Procedure

To a stirred mixture of **2a** (0.28 g, 0.94 mmol) and $NaHCO_3$ (0.24 g, 2.8 mmol) in MeCN (8 mL) at 0 °C was added I_2 (0.71 g, 2.8 mmol) portionwise. After 1 h, 10% aq $Na_2S_2O_3$ was added until the color of I_2 disappeared. The organic solvent was evaporated and the resulting mixture was extracted with Et_2O (2 × 15 mL). The combined extracts were washed with sat. aq $NaHCO_3$ and brine, dried (Na_2SO_4), and evaporated. The residue was purified by preparative TLC on silica gel to give **3a**; yield: 0.34 g (85%); colorless viscous oil; R_f 0.56 (EtOAc–hexane, 1:3).

IR (neat): 1686 cm^{-1}.

^{1}H NMR (400 MHz): δ = 3.98 (1 H, d, *J* = 11.5 Hz), 4.03 (1 H, d, *J* = 11.5 Hz), 7.15 (1 H, tt, *J* = 7.3, 1.4 Hz), 7.29–7.41 (5 H, m), 7.44–7.52 (5 H, m), 7.54 (1 H, ddd, *J* = 7.8, 7.3, 0.9 Hz), 7.60 (1 H, ddd, *J* = 7.8, 7.3, 0.9 Hz), 7.99 (1 H, d, *J* = 7.8 Hz).

MS: *m*/*z* (%) = 425 (16, [M$^+$]), 284 (100).

Anal. Calcd for $C_{21}H_{16}INO$: C, 59.31; H, 3.79; N, 3.29. Found: C, 59.26; H, 3.90; N, 3.02.

2-(4-Chlorophenyl)-3-iodomethyl-3-phenylisoindolin-1-one (3b)
White solid; mp 41–46 °C (hexane–Et_2O).

IR (neat): 1686 cm^{-1}.

^1H NMR (500 MHz): δ = 3.97 (1 H, d, *J* = 11.5 Hz), 4.05 (1 H, d, *J* = 11.5 Hz), 7.32–7.41 (7 H, m), 7.47 (2 H, dd, *J* = 7.8, 1.8 Hz), 7.51 (1 H, d, *J* = 7.3 Hz), 7.55 (1 H, td, *J* = 7.3, 0.9 Hz), 7.62 (1 H, td, *J* = 7.3, 0.9 Hz), 7.96 (1 H, d, *J* = 7.3 Hz).

MS: *m*/*z* (%) = 459 (79, [M^+]), 318 (100).

Anal. Calcd for $C_{21}H_{15}ClINO$: C, 54.87; H, 3.29; N, 3.05. Found: C, 54.64; H, 3.26; N, 3.13.

2-Butyl-3-iodomethyl-3-phenylisoindolin-1-one (3c)
Colorless viscous oil; R_f 0.44 (EtOAc–hexane, 1:3).

IR (neat): 1699 cm^{-1}.

^1H NMR (500 MHz): δ = 0.99 (3 H, t, *J* = 7.3 Hz), 1.49 (2 H, sext, *J* = 7.3 Hz), 1.70–1.78 (2 H, m), 3.59–3.77 (2 H, m), 3.91 (1 H, d, *J* = 11.0 Hz), 4.02 (1 H, d, *J* = 11.0 Hz), 7.33 (1 H, tt, *J* = 7.3, 1.4 Hz), 7.38 (2 H, t, *J* = 7.3 Hz), 7.43–7.48 (3 H, m), 7.49–7.54 (2 H, m), 7.83 (1 H, dd, *J* = 7.8, 0.9 Hz).

MS: *m*/*z* (%) = 405 (48, [M^+]), 207 (100).

Anal. Calcd for $C_{19}H_{20}INO$: C, 56.31; H, 4.97; N, 3.46. Found: C, 56.28; H, 4.97; N, 3.56.

2-*tert*-Butyl-3-iodomethyl-3-phenylisoindolin-1-one (3d)
Pale-yellow oil; R_f 0.54 (EtOAc–hexane, 1:2).

IR (neat): 1699 cm^{-1}.

^1H NMR (400 MHz): δ = 1.51 (9 H, s), 3.88 (1 H, d, *J* = 11.0 Hz), 4.04 (1 H, d, *J* = 11.0 Hz), 7.31 (1 H, tt, *J* = 7.3, 1.1 Hz), 7.35–7.41 (3 H, m), 7.42 (1 H, ddd, *J* = 7.6, 7.3, 1.3 Hz), 7.48 (1 H, ddd, *J* = 7.6, 7.3, 1.3 Hz), 7.52 (2 H, dd, *J* = 6.9, 1.1 Hz), 7.79 (1 H, d, *J* = 7.6 Hz).

MS: *m*/*z* (%) = 406 (0.42), 405 (0.10, [M^+]), 391 (100).

Anal. Calcd for $C_{19}H_{20}INO$: C, 56.31; H, 4.97; N, 3.46. Found: C, 56.55; H, 4.87; N, 3.56.

3-Iodomethyl-3-methyl-2-phenylisoindolin-1-one (3e)
White solid; mp 102–104 °C (hexane–Et_2O).

IR (KBr): 1701 cm^{-1}.

^1H NMR (400 MHz): δ = 1.82 (3 H, s), 3.60 (1 H, d, *J* = 10.5 Hz), 3.68 (1 H, d, *J* = 10.5 Hz), 7.11–7.14 (1 H, m), 7.34–7.39 (5 H, m), 7.54 (1 H, t, *J* = 7.3 Hz), 7.59 (1 H, t, *J* = 7.3 Hz), 7.96 (1 H, d, *J* = 7.3 Hz).

MS: *m*/*z* (%) = 363 (100, [M^+]).

Anal. Calcd for $C_{16}H_{14}INO$: C, 52.91; H, 3.89; N, 3.86. Found: C, 52.87; H, 4.13; N, 3.86.

2-(4-Chlorophenyl)-3-iodomethyl-5-methoxy-3-methylisoindolin-1-one (3f)
Pale-yellow solid; mp 121–123 °C (pentane–Et_2O).

IR (KBr): 1697, 1611 cm^{-1}.

^1H NMR (400 MHz): δ = 1.80 (3 H, s), 3.55 (1H, d, *J* = 11.0 Hz), 3.65 (1 H, d, *J* = 11.0 Hz), 3.91 (3 H, s), 6.80 (1 H, d, *J* = 2.2 Hz), 7.05 (1 H, dd, *J* = 8.4, 2.2 Hz), 7.29 (4 H, s), 7.83 (1 H, d, *J* = 8.4 Hz).

MS: *m*/*z* (%) = 427 (100, [M^+]).

Anal. Calcd for $C_{17}H_{15}ClINO_2$: C, 47.74; H, 3.54; N, 3.28. Found: C, 47.62; H, 3.51; N, 3.26.

3-Methylisoindolin-1-one Derivatives 4; 3-Methyl-2,3-diphenylisoindolin-1-one (4a);[3a] Typical Procedure
A solution of 3a (0.33 g, 0.78 mmol) and Bu_3SnH (0.42 g, 1.6 mmol) in benzene (4 mL) was stirred for 10 h at r.t. After evaporation of benzene, the residue was purified by column chromatography on silica gel to give 4a; yield: 0.18 g (75%); white solid; mp 175–176 °C (hexane–Et_2O) (Lit.[3a] mp 174–176 °C).

IR (KBr): 1693 cm^{-1}.

^1H NMR (500 MHz): δ = 2.02 (3 H, s), 7.11 (1 H, tt, *J* = 7.3, 1.4 Hz), 7.28 (1 H, tt, *J* = 7.3, 1.4 Hz), 7.32–7.36 (5 H, m), 7.41 (2 H, dd, *J* = 8.7, 1.4 Hz), 7.45 (2 H, dd, *J* = 8.7, 1.4 Hz), 7.48 (1 H, td, *J* = 7.3, 0.9 Hz), 7.53 (1 H, tt, *J* = 7.3, 1.4 Hz), 7.97 (1 H, dd, *J* = 7.3, 1.4 Hz).

MS: *m*/*z* (%) = 299 (100, [M^+]).

Anal. Calcd for $C_{21}H_{17}NO$: C, 84.25; H, 5.72; N, 4.68. Found: C, 84.25; H, 5.77; N, 4.60.

2-(4-Chlorophenyl)-3-methyl-2-phenylisoindolin-1-one (4b)
White solid; mp 88–89 °C (hexane–Et_2O).

IR (KBr): 1682 cm^{-1}.

^1H NMR (500 MHz): δ = 2.02 (3 H, s), 7.28–7.31 (3 H, m), 7.32–7.37 (5 H, m), 7.41 (2 H, dd, *J* = 8.2, 1.4 Hz), 7.49 (1 H, ddd, *J* = 7.8, 7.3, 0.9 Hz), 7.54 (1 H, ddd, *J* = 7.8, 7.3, 1.4 Hz), 7.95 (1 H, dd, *J* = 7.8, 0.9 Hz).

MS: *m*/*z* (%) = 333 (100, [M^+]).

Anal. Calcd for $C_{21}H_{16}ClNO$: C, 75.56; H, 4.83; N, 4.20. Found: C, 75.36; H, 5.00; N, 4.12.

2-Butyl-3-methyl-3-phenylisoindolin-1-one (4c)
Colorless oil; R_f 0.38 (THF–hexane, 1:3).

IR (neat): 1693 cm^{-1}.

^1H NMR (500 MHz): δ = 0.96 (3 H, t, *J* = 7.3 Hz), 1.44 (2 H, sext, *J* = 7.3 Hz), 1.66–1.73 (2 H, m), 1.99 (3 H, s), 3.59 (2 H, t, *J* = 6.9 Hz), 7.29 (2 H, d, *J* = 7.3 Hz), 7.34 (2 H, t, *J* = 7.3 Hz), 7.39 (1 H, td, *J* = 7.3, 0.9 Hz), 7.41–7.47 (3 H, m), 7.83 (1 H, d, *J* = 7.3 Hz).

MS: *m*/*z* (%) = 279 (65, [M^+]), 208 (100).

Anal. Calcd for $C_{19}H_{21}NO$: C, 81.68; H, 7.58; N, 5.01. Found: C, 81.64; H, 7.59; N, 5.01.

2-*tert*-Butyl-3-methyl-3-phenylisoindolin-1-one (4d)
Pale-yellow oil; R_f 0.51(THF–hexane, 1:5).

IR (neat): 1699 cm^{-1}.

^1H NMR (500 MHz): δ = 1.45 (9 H, s), 1.98 (3 H, s), 7.24 (1 H, d, *J* = 7.8 Hz), 7.27 (1 H, tt, *J* = 7.3, 1.4 Hz), 7.34 (2 H, dd, *J* = 7.8, 7.3 Hz), 7.36 (1 H, ddd, *J* = 7.8, 7.3, 0.9 Hz), 7.41 (1 H, ddd, *J* = 7.8, 7.3, 1.4 Hz), 7.43 (2 H, dd, *J* = 7.8, 1.4 Hz), 7.79 (1 H, d, *J* = 7.8 Hz).

MS: *m*/*z* (%) = 279 (0.4, [M^+]), 264 (54), 207 (100).

Anal. Calcd for $C_{19}H_{21}NO$: C, 81.68; H, 7.58; N, 5.01. Found: C, 81.53; H, 7.82; N, 5.13.

3,3-Dimethyl-2-phenylisoindolin-1-one (4e)
Pale-yellow oil; R_f 0.28 (EtOAc–hexane, 1:9).

IR (neat): 1681 cm^{-1}.

^1H NMR (500 MHz): δ = 1.64 (6 H, s), 7.08–7.12 (1 H, m), 7.30–7.36 (5 H, m), 7.47 (1 H, t, *J* = 7.3 Hz), 7.54 (1 H, t, *J* = 7.3 Hz), 7.93 (1 H, d, *J* = 7.3 Hz).

MS: *m*/*z* (%) = 237 (100, [M$^+$]).

Anal. Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 80.92; H, 6.40; N, 5.51.

2-(4-Chlorophenyl)-5-methoxy-3,3-dimethylisoindolin-1-one (4f)

Pale-yellow solid; mp 116–118 °C (hexane–CH_2Cl_2).

IR (KBr): 1668, 1620 cm^{-1}.

^{1}H NMR (500 MHz): δ = 1.62 (6 H, s), 3.90 (3H, s), 6.75 (1 H, d, *J* = 1.8 Hz), 7.00 (1 H, dd, *J* = 8.7, 1.8 Hz), 7.25 (2 H, d, *J* = 9.2 Hz), 7.28 (2 H, d, *J* = 9.2 Hz), 7.81 (1 H, d, *J* = 8.7 Hz).

MS: *m*/*z* (%) = 301 (100, [M$^+$]).

Anal. Calcd for $C_{17}H_{16}ClNO_2$: C, 67.66; H, 5.34; N, 4.64. Found: C, 67.60; H, 5.66; N, 4.38.

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