# Simple Indole Synthesis by One-Pot Sonogashira Coupling–NaOH-Mediated Cyclization

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Dedicated to Prof. Dr. Josep Font on the occasion of his 70th birthday.

**Abstract:** Coupling of *o*-iodoanilines with terminal alkynes under standard Sonogashira conditions, and further treatment with NaOH under conventional heating or microwave irradiation, afford 2-substituted indoles in usually high yields. Functionalities such as halides, nitro, and cyano groups are tolerated under the reaction conditions.

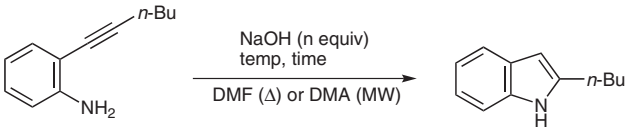
**Key words:** indoles, cyclizations, alkynes, microwave irradiation

The indole ring system is a prominent structural unit frequently found in numerous natural products and pharmaceutically active compounds.[1] The synthesis and functionalization of indoles has been a major challenge for synthetic organic chemists, and numerous methods for their preparation have been developed.[2] The implementation of practical, safe, and scalable methods for the large-scale preparation of indoles is of interest and so, the development of practical methodologies that allow the synthesis of a great variety of substituted indoles is a current objective in organic synthesis. Among the many methods for indole-ring synthesis, the cyclization reactions of 2-alkynylaniline derivatives are some of the most useful procedures for the construction of the indole nucleus.[3] In this field, an interesting access to 2-substituted indoles makes use of a metal-alkoxide-mediated cyclization of 2-alkynylaniline derivatives. Several examples of this methodology typically involved the use of NaOEt[4] or KO*t*-Bu[5] with N-substituted anilines, usually carbamates. In this context, Knochel reported a milder procedure which relied on the use of *N*-methyl-2-pyrrolidone (NMP) as the reaction solvent and KH or KO*t*-Bu as bases.[6] This strategy has also been employed by other authors for the preparation of azaindoles,[7] 2-alkynylindoles,[8] as well as amino and nitroindoles.[9] Most of these methods suffer from drawbacks like high temperatures, long reaction times, low yields, and the use of moisture-sensitive bases.[10] During the last years we have been interested in the development of suitable methodologies for the synthesis of functionalized indoles.[11] Herein, we report a new method for the one-pot synthesis of 2-substituted indoles from *o*-iodoanilines using a NaOH-mediated 5-*endo-dig* cyclization of *o*-alkynylanilines as the key step. This base-mediated cyclization takes place under conventional heating, or more conveniently, under microwave irradiation.

Our studies started with the model reaction of *o*-hex-1-ynylaniline (**1a**) with finely powdered NaOH in DMF as solvent under different conditions. As shown in Table 1, the cyclization does not take place at room temperature using a high excess of NaOH (entry 1), and after some experimentation we determined that the reaction must be conducted at 140 °C with 3 equivalents of base to get complete conversion of the starting aniline **1a** to 2-butylindole (**2a**, Table 1, entry 2). Due to the fact that microwave heating has emerged as a versatile method to speed up many chemical processes, getting cleaner reactions, and delivering high yields in a few minutes,[12] we decided to try our reaction under microwave irradiation (Table 1, entries 3 and 4). Under these conditions *N*,*N*-dimethylacetamide (DMA) gave cleaner results than DMF and, in this way, complete cyclization of **1a** under optimized conditions took place in 8 minutes with only 1.5 equivalents of NaOH at 170 °C, affording **2a** in high yield (Table 1, entry 4).

Having established the best reaction conditions for cyclization of **1a**, both under conventional heating and microwave irradiation, we then explored the scope of this indole synthesis with respect to the substituent at the C2-

**Table 1** Sodium hydroxide Mediated Cyclization of *o*-Hex-1-ynylaniline (**1a**)[a]




**1a** **2a**

| Entry | NaOH (equiv) | Heating | Temp (°C) | Time (min) | Ratio[b] **2a**/**1a** | Yield (%)[c] |
|---|---|---|---|---|---|---|
| 1 | 6 | Δ | 20 | 120 | 0:1 | –[d] |
| 2 | 3 | Δ | 140 | 150 | 1:0 | 85 |
| 3 | 6 | MW | 140 | 10 | 6:1 | –[d] |
| 4 | 1.5 | MW | 170 | 8 | 1:0 | 89 |

[a] All reactions were carried out with **1a** (0.5 mmol) in anhyd DMF or DMA (2 mL).
[b] Determined by $^1$H NMR analysis of the crude product.
[c] Isolated yield of **2a** after column chromatography.
[d] Not determined.

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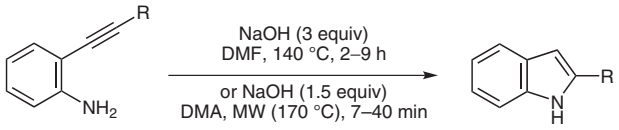
position in the final indole **2**. As shown in Table 2, 2-substituted indoles **2b–f** were synthesized in usually high yields. In general, slightly better yields were obtained under microwave irradiation (Table 2, entries 2, 4, 6, and 8), although the most important fact was the significant reduction in reaction time, from several hours to typically 10–20 minutes.

**Table 2** 2-Substituted-1*H*-indoles **2b–f** by NaOH-Mediated Cyclization of *o*-Alkynylanilines **1**[a]



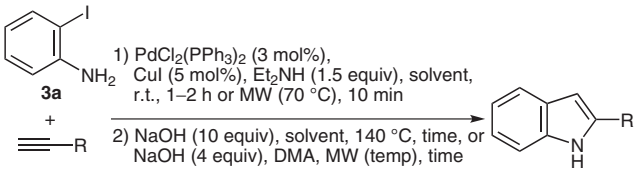

**1** **2**

| Entry | Starting aniline | R | Heating | Time | Product | Yield (%)[b] |
|---|---|---|---|---|---|---|
| 1 | **1b** | Ph | Δ | 9 h | **2b** | 74 |
| 2 | **1b** | Ph | MW | 20 min | **2b** | 81 |
| 3 | **1c** | *c*-$C_6H_9$[c] | Δ | 2 h | **2c** | 87 |
| 4 | **1c** | *c*-$C_6H_9$[c] | MW | 7 min | **2c** | 91 |
| 5 | **1d** | 3-Th[d] | Δ | 6 h | **2d** | 77 |
| 6 | **1d** | 3-Th[d] | MW | 40 min | **2d** | 78 |
| 7 | **1e** | *c*-$C_6H_{11}$ | Δ | 5 h | **2e** | 72 |
| 8 | **1e** | *c*-$C_6H_{11}$ | MW | 20 min | **2e** | 76 |
| 9 | **1f** | *n*-$C_5H_{11}$ | Δ | 2.5 h | **2f** | 83 |

[a] Reactions were carried out with **1** (1 mmol) in anhyd DMF (4 mL) under conventional heating or with **1** (0.5 mmol) in anhyd DMA (2 mL) under microwave irradiation.
[b] Isolated yield of indoles **2** after column chromatography.
[c] 1-Cyclohexenyl.
[d] 3-Thienyl.

Although the starting anilines **1** were easily synthesized by the Sonogashira cross-coupling of 2-iodoaniline **3a** with 1-alkynes,[13] at this point we wondered if 2-substituted indoles **2** could be prepared by a one-pot, two step procedure from **3a**. To this end, **3a** was first treated with 1-hexyne under standard Sonogashira conditions at room temperature and then, excess of NaOH (10 equiv) was added to the mixture and heated to 140 °C for several hours. Gratifyingly, indole **2a** was obtained in 78% overall yield without isolation of intermediate **1a** (Table 3, entry 1).[14] In addition, this one-pot procedure for the synthesis of 2-substituted indoles **2a–k** from 2-iodoaniline **3a** could also be carried out under microwave irradiation. In this case, Sonogashira couplings took place in 10 minutes,[15] and for the cyclization step the microwave irradiation allowed the use of a lesser amount of NaOH (4 equiv), as well as the reaction times were reduced from several hours to 10–40 minutes (Table 3). As shown in Table 3, different 1-alkynes bearing aliphatic (entries 1, 2, 8, and 9), alkenyl (entries 5 and 6), aryl (entries 3, 4, and 11), heteroaryl (entries 7 and 10), and functionalized aryl (entries 12–14) substituents were appropriate substrates for this methodology. In general, satisfactory to high yields were obtained and, moreover, this one-pot procedure is amenable for the gram-scale synthesis of 2-substituted indoles **2**.[16]

**Table 3** 2-Substituted-1*H*-indoles **2** by One-Pot Sonogashira Coupling–NaOH-Mediated Cyclization of *o*-Iodoaniline **3a** with Terminal Alkynes[a,17]



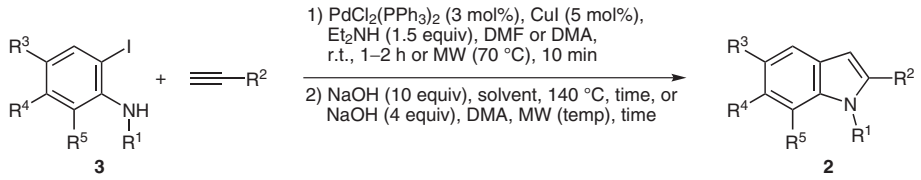

**2**

| Entry | Alkyne (R) | Solvent | Heating (temp) | Time | Prod. | Yield (%)[b] |
|---|---|---|---|---|---|---|
| 1 | *n*-Bu | DMF | Δ (140 °C) | 3.5 h | **2a** | 78 |
| 2 | *n*-Bu | DMA | MW (170 °C) | 10 min | **2a** | 81 |
| 3 | Ph | DMA | Δ (140 °C) | 6 h | **2b** | 76 |
| 4 | Ph | DMA | MW (190 °C) | 20 min | **2b** | 77 |
| 5 | *c*-$C_6H_9$[c] | DMF | Δ (140 °C) | 2 h | **2c** | 82 |
| 6 | *c*-$C_6H_9$[c] | DMA | MW (170 °C) | 10 min | **2c** | 88 |
| 7 | 3-Th[d] | DMA | MW (180 °C) | 40 min | **2d** | 60 |
| 8 | *c*-$C_6H_{11}$ | DMA | Δ (140 °C) | 6 h | **2e** | 69 |
| 9 | *n*-$C_5H_{11}$ | DMF | Δ (140 °C) | 4.5 h | **2f** | 68 |
| 10 | 2-Py[e] | DMF | Δ (140 °C) | 2.5 h | **2g** | 76 |
| 11 | 4-Me$C_6H_4$ | DMA | Δ (140 °C) | 4 h | **2h** | 70 |
| 12 | 2-$NH_2C_6H_4$ | DMA | MW (180 °C) | 50 min | **2i** | 40 |
| 13 | 4-F-3-Me$C_6H_3$ | DMA | MW (180 °C) | 40 min | **2j** | 71 |
| 14 | 3-Cl$C_6H_4$ | DMA | MW (180 °C) | 40 min | **2k** | 74 |

[a] Reactions were carried out with **3a** (1 mmol) in anhyd DMF or DMA (5 mL) under conventional heating or with **3a** (0.5 mmol) in anhyd DMA (2 mL) under microwave irradiation.
[b] Isolated yield of indoles **2** after column chromatography.
[c] 1-Cyclohexenyl.
[d] 3-Thienyl.
[e] 2-Pyridyl.

Once we had established the generality of this one-pot procedure for the synthesis of 2-substituted indoles **2** with respect to the alkyne counterpart, we decided to explore the scope of this synthetic strategy with regard to the *o*-iodoaniline moiety (Table 4). Again, reactions could be performed under conventional heating or under microwave irradiation. First, we observed that *N*-acetyl-2-iodoaniline (**3b**) behaves as a synthetic equivalent of 2-iodoaniline (**3a**) since N-deacetylation occurred under the basic conditions (Table 4, entries 1–3). This methodology is not restricted to N-unsubstituted starting anilines and

**Table 4** Functionalized Indoles **2** by One-Pot Sonogashira Coupling–NaOH-Mediated Cyclization of *o*-Iodoanilines **3**[a,17]

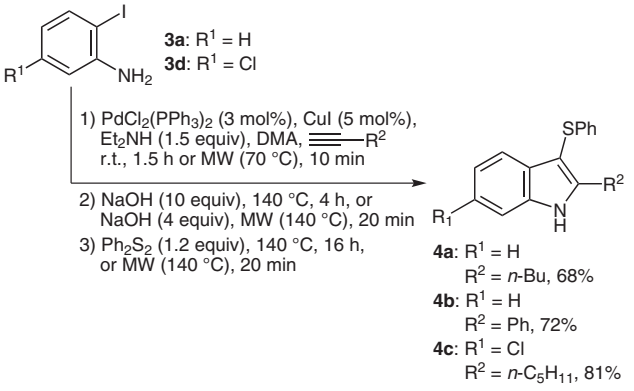



| Entry | Starting aniline | $R^1$ | $R^3$ | $R^4$ | $R^5$ | Alkyne ($R^2$) | Solvent | Heating (temp) | Time | Product | Yield (%)[b] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | **3b** | COMe | H | H | H | *n*-Bu | DMF | Δ (140 °C) | 2.5 h | **2a** $R^1$ = H | 89 |
| 2 | **3b** | COMe | H | H | H | *c*-$C_6H_9$[c] | DMF | Δ (140 °C) | 3.5 h | **2c** $R^1$ = H | 75 |
| 3 | **3b** | COMe | H | H | H | *n*-$C_5H_{11}$ | DMA | MW (180 °C) | 20 min | **2f** $R^1$ = H | 74 |
| 4 | **3c** | Bn | H | H | H | *n*-Bu | DMF | Δ (140 °C) | 3.5 h | **2l** | 80 |
| 5 | **3c** | Bn | H | H | H | *c*-$C_6H_9$[c] | DMA | MW (170 °C) | 20 min | **2m** | 75 |
| 6 | **3d** | H | H | Cl | H | *n*-Bu | DMF | Δ (140 °C) | 3 h | **2n** | 88 |
| 7 | **3d** | H | H | Cl | H | *c*-$C_6H_9$[c] | DMF | Δ (140 °C) | 3 h | **2o** | 75 |
| 8 | **3e** | H | H | F | H | *n*-Bu | DMF | Δ (140 °C) | 3 h | **2p** | 74 |
| 9 | **3e** | H | H | F | H | Ph | DMA | MW (180 °C) | 40 min | **2q** | 66 |
| 10 | **3e** | H | H | F | H | *c*-$C_6H_9$[c] | DMF | Δ (140 °C) | 3 h | **2r** | 61 |
| 11 | **3f** | H | Cl | H | Cl | *c*-$C_6H_9$[c] | DMF | Δ (140 °C) | 2.5 h | **2s** | 68 (66)[d] |
| 12 | **3f** | H | Cl | H | Cl | *n*-$C_5H_{11}$ | DMF | Δ (140 °C) | 2.5 h | **2t** | 78 |
| 13 | **3g** | H | Cl | H | F | Ph | DMA | Δ (140 °C) | 3 h | **2u** | 81 |
| 14 | **3g** | H | Cl | H | F | *n*-$C_5H_{11}$ | DMF | Δ (140 °C) | 3 h | **2v** | 83 |
| 15 | **3h** | H | CN | H | H | Ph | DMA | Δ (140 °C) | 3 h | **2w** | 85 |
| 16 | **3i** | H | $NO_2$ | H | H | *n*-Bu | DMA | MW (180 °C) | 20 min | **2x** | 79 |

[a] Reactions were carried out with **3** (1 mmol) in anhyd DMF or DMA (5 mL) under conventional heating or with **3** (0.5 mmol) in anhyd DMA (4 mL) under microwave irradiation.
[b] Isolated yield of indoles **2** after column chromatography.
[c] 1-Cyclohexenyl.
[d] Yield in brackets refers to the reaction carried out under microwave irradiation.

so, *N*-benzyl-2-iodoaniline (**3c**) afforded the corresponding *N*-benzyl indole derivatives **2l** and **2m** in high yields (Table 4, entries 4 and 5). Furthermore, halo-2-iodoanilines **3d**,**e** and dihalo-2-iodoanilines **3f**,**g** allowed the synthesis of regioselectively halogenated indole derivatives **2n**–**v** in usually high yields (Table 4, entries 6–14). Finally, 2-iodoanilines **3h** and **3i** bearing cyano and nitro functionalities, respectively, also afforded the corresponding functionalized indoles **2w**–**x** (Table 4, entries 15 and 16), showing that several functional groups are tolerated under the reaction conditions.

Interestingly, by using this methodology it is also possible to prepare 3-arylthio-2-substituted indoles **4**, due to the fact that the arylthio group could be selectively introduced at C-3 under the basic conditions required for the cyclization step (Scheme 1).[18] Again, this one-pot, three-step procedure could be carried out under conventional thermal heating or under microwave irradiation.[19] In the last




**Scheme 1** Synthesis of 3-arylthio-2-substituted-1*H*-indoles **4** from *o*-iodoanilines **3**

case, shorter reaction times were required. As shown in Scheme 1, highly functionalized indole derivatives **4a**–**c** were obtained in moderate to high yields from commercially available starting materials **3a**,**d**.

In summary, we have developed an efficient route to 2-substituted indoles using a NaOH-mediated 5-*endo-dig* cyclization of *o*-alkynylanilines as the key step. The reaction can be performed from 2-iodoanilines and alkynes in a one-pot process that involves an initial Sonogashira coupling followed by the cyclization. This one-pot procedure is compatible with the presence of several important functional groups onto the benzenoid moiety, and also it does work with N-unsubstituted anilines as well as with substituted ones. Moreover, an arylthio group can also be selectively introduced at the C-3 position without isolation of any intermediate. In addition, all the reactions can be carried out under conventional heating or under microwave irradiation with considerable reduction of reaction times.

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(14) However, when this one-pot procedure was applied to phenylacetylene, as terminal alkyne counterpart, 2-(2-phenylethyl)aniline was generated along with the expected indole derivative **2b**. This side reaction due to hydrogenation of intermediate 2-alkynylaniline **1b** was easily avoided using DMA instead of DMF. Under the reaction conditions an ammonium formate derivative is probably generated, which is known to act as a source of hydrogen. See, for instance: Nacario, R.; Kotakonda, S.; Fouchard, D. M. D.; Viranga Tillekeratne, L. M.; Hudson, R. A. *Org. Lett.* **2005**, *7*, 471.

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(16) The amount of 2.31 g of indole **2a** (67% isolated yield) were easily prepared in one batch from 4.38 g (20 mmol) of 2-iodoaniline **3a**.

(17) **Typical Procedure for the One-Pot Synthesis of 2-Substituted Indoles 2 from *o*-Iodoanilines 3 under Conventional Heating – Synthesis of 2-Cyclohex-1-enyl-1*H*-indole (2c; Table 3, Entry 5)**
A mixture of 2-iodoaniline (**3a**, 219 mg, 1 mmol), 1-ethynylcyclohexene (159 mg, 1.5 mmol), $PdCl_2(PPh_3)_2$ (21 mg, 0.03 mmol), CuI (9.5 mg, 0.05 mmol), and $Et_2NH$ (110 mg, 1.5 mmol) in anhyd DMF (3 mL) was stirred under $N_2$ at r.t. for 1.5 h (the consumption of the starting material was monitored by GC-MS). Then, DMF (2 mL) and freshly powdered NaOH (400 mg, 10 mmol) were added to the reaction mixture, and it was heated at 140 °C for 2 h (the end of the cyclization was monitored by GC-MS). The reaction was cooled to r.t. and then, $CH_2Cl_2$ (15 mL) and HCl aq (20 mL of a 0.5M solution) were added. The separated aqueous phase was extracted with $CH_2Cl_2$ (2 × 15 mL), and the combined organic layers were washed with $H_2O$ (3 × 50 mL). The organic phase was dried ($Na_2SO_4$) and concentrated under reduced pressure. The crude product was purified by column chromatography on $SiO_2$ (hexane–EtOAc, 10:1) to afford **2c** (162 mg, 82%) as a white solid; mp 137–139 °C (lit.[20] mp 140–141 °C). $^1$H NMR (300 MHz, $CDCl_3$): δ = 8.06 (br s, 1 H), 7.66 (d, *J* = 7.8 Hz, 1 H), 7.35 (dd, *J* = 7.8, 1.2 Hz, 1 H), 7.29–7.14 (m, 2 H), 6.53 (d, *J* = 1.7 Hz, 1 H), 6.15–6.09 (m, 1 H), 2.57–2.48 (m, 2 H), 2.36–2.27 (m, 2 H), 1.92–1.82 (m, 2 H), 1.82–1.72 (m, 2 H). $^{13}$C NMR (75.4 MHz, $CDCl_3$): δ = 139.6 (C), 136.2 (C), 129.1 (C), 129.0 (C), 122.7 (CH), 122.0 (CH), 120.4 (CH), 119.8 (CH), 110.5 (CH), 98.7 (CH), 26.1 ($CH_2$), 25.6 ($CH_2$), 22.6 ($CH_2$), 22.3 ($CH_2$). LRMS (EI): *m*/*z* (%) = 197 (100) [$M^+$], 182 (13), 168 (58), 130 (33). HRMS: *m*/*z* calcd for $C_{14}H_{15}N$: 197.1204; found: 197.1199.

(18) For the reaction of indoles with $Ar_2S_2$, see: Atkinson, J. G.; Hamel, P.; Girard, Y. *Synthesis* **1988**, 480.

(19) **Typical Procedure for the One-Pot Synthesis of 3-Arylthio-2-Substituted Indoles 4 from *o*-Iodoanilines 3 under Microwave Irradiation – Synthesis of 6-Chloro-2-pentyl-3-phenylsulfanyl-1*H*-indole (4c)**
A mixture of 5-chloro-2-iodoaniline (**3d**, 127 mg, 0.5 mmol), 1-heptyne (72 mg, 0.75 mmol), $PdCl_2(PPh_3)_2$ (10.5 mg, 0.015 mmol), CuI (4.8 mg, 0.025 mmol), and $Et_2NH$ (55 mg, 0.75 mmol) in DMA (2 mL) was charged under air in a 35 mL thick-walled glass sealed tube and irradiated, under stirring, at 70 °C in the microwave cavity for 10 min (CEM Focused Microwave System, Discover S-Class). Temperature measurements were conducted using an IR sensor located below the microwave-cavity floor, and reaction times refer to the total hold time at the indicated temperature. The maximum wattage supplied was 70–80 W). After cooling, freshly powdered NaOH (80 mg, 2 mmol) was added to the reaction mixture and it was heated at 180 °C in the microwave cavity for 20 min. The reaction mixture was cooled to r.t. and then, $Ph_2S_2$ (131 mg, 0.6 mmol) was added to the mixture, and it was heated at 140 °C in the microwave cavity for 20 min. The reaction was cooled to r.t. and then, $CH_2Cl_2$ (15 mL) and HCl aq (20 mL of a 0.5 M solution) were added. The separated aqueous phase was extracted with $CH_2Cl_2$ (2 × 15 mL), and the combined organic layers were washed with $H_2O$ (3 × 50 mL). The organic phase was dried ($Na_2SO_4$) and concentrated under reduced pressure. The crude product was purified by column chromatography on $SiO_2$ (hexane–EtOAc, 15:1) to afford **4c** (133 mg, 81%) as a light brown oil; $R_f$ = 0.27 (hexane–EtOAc, 15:1). $^1$H NMR (300 MHz, $CDCl_3$): δ = 8.37 (br s, 1 H), 7.47 (d, *J* = 8.4 Hz, 1 H), 7.32 (d, *J* = 1.7 Hz, 1 H), 7.22–7.15 (m, 2 H), 7.15–7.02 (m, 4 H), 2.89 (t, *J* = 7.5 Hz, 2 H), 1.71–1.60 (m, 2 H), 1.36–1.25 (m, 4 H), 0.86 (t, *J* = 6.9 Hz, 3 H). $^{13}$C NMR (75.4 MHz, $CDCl_3$): δ = 146.4 (C), 139.2 (C), 135.9 (C), 128.9 (C), 128.8 (2 × CH), 128.0 (C), 125.5 (2 × CH), 124.7 (CH), 121.4 (CH), 120.0 (CH), 111.0 (CH), 99.2 (C), 31.5 ($CH_2$), 29.2 ($CH_2$), 26.5 ($CH_2$), 22.4 ($CH_2$), 14.0 ($CH_3$). LRMS (EI): *m*/*z* (%) = 331 (37) [$M^+$ + 2], 329 (92) [$M^+$], 272 (57), 236 (100), 204 (38), 164 (60). IR (neat): 3411, 2931, 1582, 1454, 808, 740, 690 $cm^{-1}$. HRMS: *m*/*z* calcd for $C_{19}H_{20}ClNS$: 329.1005; found: 329.1004.

(20) Kano, S.; Sugino, E.; Shibuya, S.; Hibino, S. *J. Org. Chem.* **1981**, *46*, 3856.