Microwave-Enhanced Cadogan Cyclization: An Easy Access to the 2-Substituted Carbazoles and other Fused Heterocyclic Systems

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Abstract: A microwave-enhanced Suzuki–Miyaura cross-coupling reaction in combination with a microwave-assisted Cadogan reductive cyclization is presented as an easy access to a variety of 2-substituted carbazoles and other fused heterocyclic systems. Microwave irradiation was found very useful in minimizing the proto-deboronation issues in the cross-coupling reaction, and enhances the rate of reductive cyclization in a dramatic manner.

Key words: microwave-enhanced, Suzuki–Miyaura cross-coupling reaction, Cadogan reductive cyclization

Novel strategies for the synthesis of functionalized carbazole analogues recently have gained considerable interest, due to their widespread applications as light-emitting devices,[1] conjugate polymers,[2] dendrimers,[3] etc. There has also been much research done on the biological activities of the carbazole analogues in recent years and a great number of carbazole alkaloids has been isolated and synthesized.[4] Furthermore, the synthesis of aromatic fused systems like benzo- and indolocarbazoles, as well as heterocyclic fused systems such as α- and β-carbolines, thieno-indoles, etc. have found a rapidly increasing interest of the pharmaceutical industry due to their versatile and potent, though still scarcely explored, biological activities.[5] However, research carried out to improve the properties of these interesting carbazole analogues have mainly been restricted to the functionalizations of the 3,6- and 1,8-positions of the carbazole skeleton, owing to the relative inertness of the 2,7-positions towards electrophilic substitution. A large number of naturally occurring and biologically active carbazoles including mukonal, indizoline, glycozolidine and glycosinine[6] (Figure 1) as well as light-emitting devices features the 2- or 2,7-substitution pattern in their skeleton. However, a reliable, efficient and non-expensive strategy has scarcely been proposed in the literature for the synthesis of these highly interesting targets.

The majority of the work that has been performed concerning the synthesis of 2-substituted carbazoles is based on the phosphite-mediated Cadogan reductive cyclization[7] of the corresponding 2-nitro-biaryls. However, this nitrene-mediated reductive cyclization procedure often demands drastic conditions and long reaction times, making it a less-favored synthetic method. Even though there has been a large amount of literature on palladium-catalyzed cyclization strategies[8] as well as CO induced C-H activations[9] to serve the purpose, these methods often demand sensitive reaction conditions including high-pressure media, cause catalytic contamination of the products and often requires the use of expensive catalysts. Microwave irradiation has recently emerged as a valuable tool in organic synthesis, as is evident from the richness of the available literature.[10] Dramatic rate enhancements and superior yields are often observed when the reactions are carried out under focused microwave irradiation. As part of our research towards the microwave-assisted palladium-catalyzed Suzuki–Miyaura reactions of electron-poor boronic acids, we chose to develop a convenient, economic and general pathway for the synthesis of 2-substituted carbazoles. Our strategy was based on the generation of *ortho*-nitro-phenylboronic acid (**1**), in view to generate the required biaryl intermediates by Suzuki–Miyaura reaction with a suitable *para*-substituted aryl bromide. We envisaged that these biaryl intermediates, after the microwave-assisted Cadogan cyclization, would furnish the 2-substituted carbazoles, which are otherwise difficult to obtain.

Furthermore, this strategy enables us to carry out the cross-coupling reaction with a variety of cheap and commercially available heterocyclic halides, and these inter-

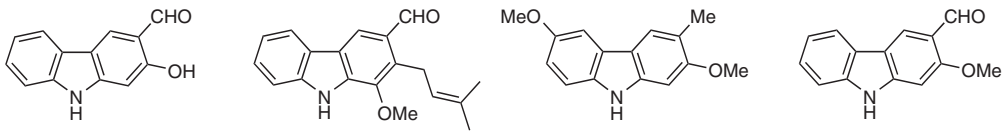

Figure 1 Some naturally occurring 2-substituted carbazole alkaloids.

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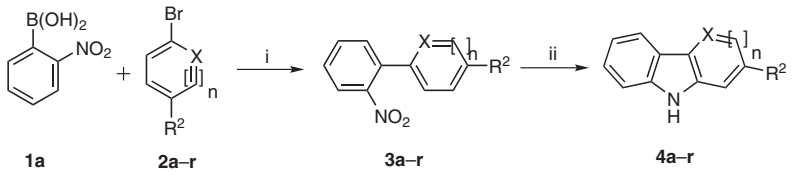


R^2 = H, Alk, OAlk, CN, Cl, NMe_2, COMe, etc. ; n = 0, 1; X = CH, N, S, etc.

Scheme 1 Synthesis of 2-substituted carbazoles and other indolo-fused systems. (i) Suzuki–Miyaura cross-coupling; (ii) Cadogan reductive cyclization.

mediates could easily be cyclized to a variety of fused heterocyclic systems with presumably interesting biological potentials. Even though the combination of Suzuki-type reactions with Cadogan reductive cyclization, albeit rarely, has been demonstrated in the literature[11] to generate the carbazoles and/or fused heterocyclic systems, these methods generally uses cross-coupling of an *ortho*-halogenated nitro compound with (hetero)arylboronic acids or stannanes that are expensive and rather difficult to generate.

Our initial task was the optimization of the Suzuki reactions between the *ortho*-nitro-phenylboronic acid (**1a**) and the halide, as this specific cross-coupling reaction imposes a challenge to the classical reaction conditions. It is a well-established fact from the recent literature that the presence of the electron-withdrawing nitro group in the *ortho*-position of the C-B bond makes it susceptible towards proto-deboronation,[12] thereby causing the yields to diminish. Most of the available literature advocates the use of non-aqueous, and thereby non-homogenous and slower reaction conditions as well as the use of bulky phosphine ligands that, besides having the apparent drawback of being expensive, demands sensitive reaction conditions.[13] We have recently demonstrated, using a number of 2-formyl boronic acids, that the undesired proto-deboronation can be considerably diminished if the cross-coupling reactions are carried out under microwave-enhanced conditions.[14] We therefore decided to extend our successful strategy towards the cross-coupling reactions of **1a** with a variety of (hetero)aryl bromides **2a**–**r** (Scheme 1).

The commercially available phenylboronic acid (**1**) was converted to the 2-nitro analogue according to the literature procedure,[15] using fuming HNO_3 as the nitrating agent in the presence of a catalytic amount of urea, and the product **1a** was isolated in good yield of 63% with an excellent *ortho*/*para* selectivity of (96:4). In order to optimize the cross-coupling parameters, we chose bromobenzene (**2a**), being the simplest case, as the initial coupling partner. In a typical procedure, the halide was sealed in a 10 mL sealed glass vial together with the boronic acid (1.3 equiv), Na_2CO_3 (3.0 equiv) and $Pd(Ph_3P)_4$ [5 mol%] in a 1:1 mixture of toluene and water (3 mL) and irradiated with a CEM-Discover[16] mono-mode microwave apparatus at 125 °C for 15 minutes, using a maximum power of 150 W. The reaction proceeded smoothly and the required biaryl compound **3a** was isolated in good yield of 70%, together with a minor amount of nitrobenzene being the proto-deboronated product. Further optimization studies to increase the yield of the biaryl compound as well as to minimize the proto-deboronation were performed, altering the base, catalyst, solvent and temperature. Best results were obtained when $NaHCO_3$ or Cs_2CO_3 were used as bases, in a 1:1 mixture of DMF and water at a pre-selected temperature of 150 °C for 15 minutes. After chromatographic purification, the product was isolated in excellent yields of 86% and 84%, respectively, while the proto-deboronated product was considerably minimized.

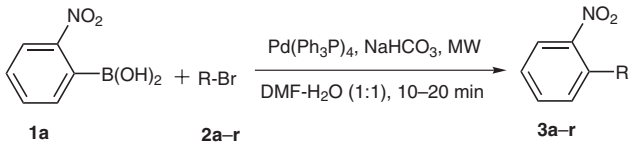
Thus, after optimizing the reaction parameters, our next goal was to extend our strategy by incorporating a wide variety of electron-rich, electron-poor and hetero(aryl) halides in view of generating a small library of biaryl nitro compounds so as to try the Cadogan cyclization at a later stage. The details of the cross-couplings carried out under microwave irradiation are presented in Table 1.

As can be viewed from Table 1, the reactions were found to proceed very smoothly, with very low extent of homo-coupling or proto-deboronation. Electron-rich halides **2b**–**d** were found to undergo the cross-coupling reaction in 15 minutes under microwave irradiation (Table 1, entries 2–4), and the corresponding biaryl compounds **3b**–**d** were isolated in yields of 84%, 89% and 79%, respectively. Electron-poor aryl halides **2e**–**h** were found to undergo the cross-coupling in only 10 minutes, owing to the fast oxidative addition of the catalyst to the C-X bond, and the products **3e**–**h** were isolated in good yields (Table 1, entries 5–8). The sterically hindered halide 1,4-dibromo-2,5-dihexyl-benzene (**2i**) underwent the cross-coupling reaction in 15 minutes, resulting in the formation of 2′,5′-dihexyl-2,2″-dinitro-[1,1′,4′,1″]-terphenyl (**3i**) in good yield of 87% (Table 1, entry 9). Bromonaphthalenes **2j** and **2k** were cross-coupled successfully according to the optimized conditions and the products, **3j** and **3k** were isolated in good yields (Table 1, entries 10, 11).

At this point, we decided to introduce heteroaryl moieties into our investigation. Our initial attempts were focusing on the indole skeleton, as a variety of indole containing compounds is well known for their biological activities. We decided to direct our explorations to the 4-, 5-, 6- and 7-analogues **2l**–**o**, as the cross-coupling reactions and subsequent manipulations at these centers are scarcely investigated compared to the well-explored 2- and 3-positions. We could successfully perform the cross-coupling reactions under microwave irradiation conditions in 20

minutes and the products, 4-(2-nitrophenyl)-1*H*-indole (**3l**), 5-(2-nitrophenyl)-1*H*-indole (**3m**), 6-(2-nitrophenyl)-1*H*-indole (**3n**) and 7-(2-nitrophenyl)-1*H*-indole (**3o**), were isolated in excellent yields (Table 1, entries 12–15). As expected, the unprotected nitrogen atom of the indole did not cause any complexation problem with the catalyst, and no substantial homo-coupling or proto-deboronation was observed during the reaction course. The 2- and 3-bromothiophenes as well as the 4-bromopyridine **2p–r** were successfully cross-coupled in the same manner in 15 minutes under microwave irradiation and the products **3p–r** were isolated in good yields (Table 1, entries 16–18).

Table 1 Suzuki–Miyaura Cross-Coupling Reactions of **1a** with Bromides **2a–r**[a,b]



R = aryl, heteroaryl

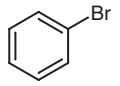
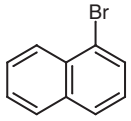
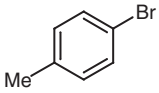
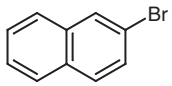
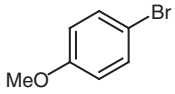
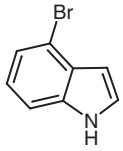
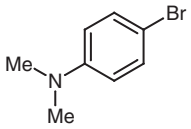
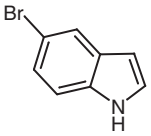
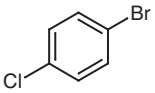
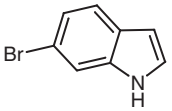
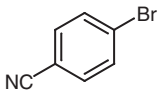
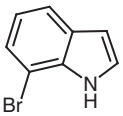
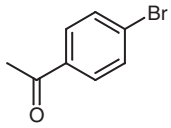
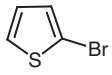
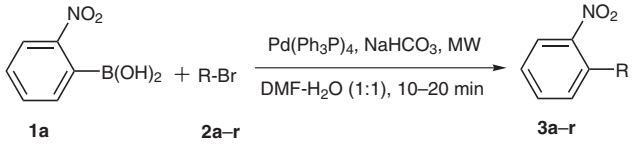
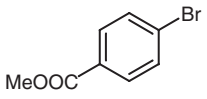
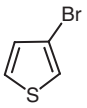
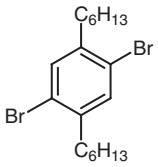
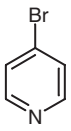
Entry	R	Time (min)	Yield (%)	Entry	R	Time (min)	Yield (%)
1	 **2a**	15	86	10	 **2j**	15	83
2	 **2b**	15	84	11	 **2k**	15	81
3	 **2c**	15	89	12	 **2l**	20	76
4	 **2d**	15	79	13	 **2m**	20	74
5	 **2e**	10	88	14	 **2n**	20	77
6	 **2f**	10	74	15	 **2o**	20	73
7	 **2g**	10	81	16	 **2p**	15	86

Table 1 Suzuki–Miyaura Cross-Coupling Reactions of **1a** with Bromides **2a–r**[a,b] (continued)



1a **2a–r** **3a–r**

R = aryl, heteroaryl

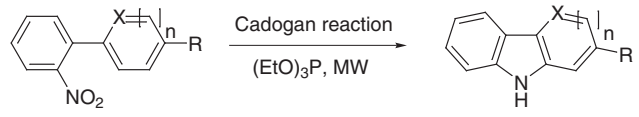
Entry	R	Time (min)	Yield (%)	Entry	R	Time (min)	Yield (%)
8	 **2h**	10	84	17	 **2q**	15	89
9	 **2i**	15	87	18	 **2r**	15	85

[a] All reactions were carried out on a 0.25 mmol scale with 1.3 equiv of boronic acid and 3.0 equiv of $NaHCO_3$ in 3 mL of DMF–H_2O (1:1) as solvent at a ceiling temperature of 150 °C and a maximum power of 150 W for the times indicated in Table 1. All yields are isolated yields.
[b] 2.5 Equiv of boronic acid and 5.0 equiv base were used.

Thus, after having synthesized all the needed biaryl nitro compounds, we decided to direct our attention towards the Cadogan reductive cyclization. Microwave irradiation was found to be extremely useful in this regard and the reactions were remarkably faster compared to conventional heating conditions. In a typical reaction, 0.25 mmol of the 2-nitro-biphenyl (**3a**) was suspended in 3 mL of triethyl phosphite in a 10 mL sealed glass vial and the reaction mixture was irradiated at 300 W maximum power with a pre-selected temperature of 210 °C. The reaction was found to be over in 15 minutes and after the usual acidic work-up to remove the phosphate by-products, the product **4a** was isolated in good yield (Table 2, entry 1). The fact that reaction times could be brought down from the order of hours to mere minutes clearly outlines the benefit of microwave irradiation. After further optimizations, we found that the best parameters for microwave irradiation were a maximum irradiation power of 300 W and a ceiling temperature of 210 °C. Even though the reaction proceeds also at a lower temperature of 180 °C, it was found to be slower, requiring a time of 25 minutes for the completion.

Our next aim was to explore the scope and limitations of the strategy and we decided to extend our investigation towards the entire range of 2-nitro-biaryls **3a–r** generated via the previously mentioned Suzuki–Miyaura cross-coupling reactions. The details of our experiments are summarized in Table 2.

Table 2 Microwave-Assisted Cadogan Cyclization of Nitro Compounds **3a–r**[a]



3a-r **4a-r**

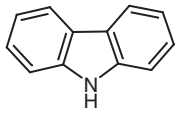
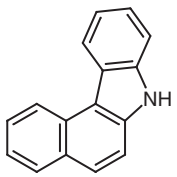
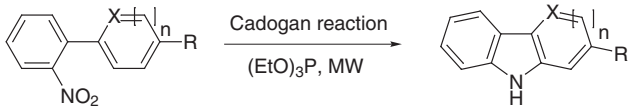
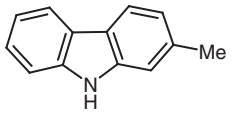
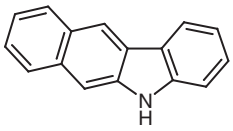
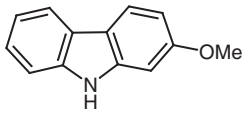
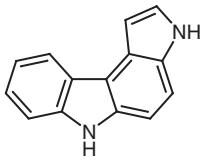
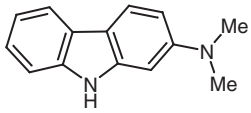
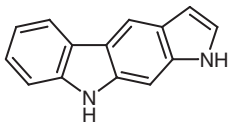
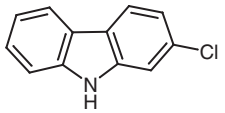
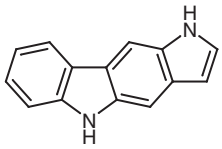
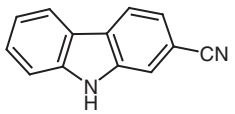
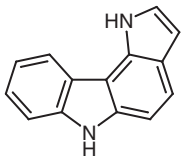
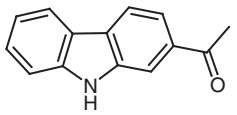
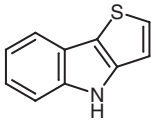
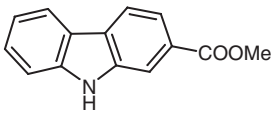
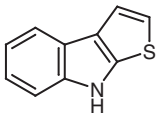
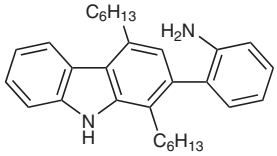
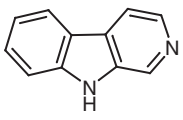
No.	R	Time (min)	Yield (%)	No.	R	Time (min)	Yield (%)
1	 **4a**	15	74	10	 **4j**	15	72

Table 2 Microwave-Assisted Cadogan Cyclization of Nitro Compounds **3a–r**[a] (continued)



3a-r **4a-r**

No.	R	Time (min)	Yield (%)	No.	R	Time (min)	Yield (%)
2	 **4b**	15	71	11	 **4k**	15	74
3	 **4c**	15	68	12	 **4l**	20	69
4	 **4d**	15	63	13	 **4m**	20	73
5	 **4e**	10	74	14	 **4n**	20	64
6	 **4f**	10	68	15	 **4o**	20	67
7	 **4g**	10	74	16	 **4p**	15	78
8	 **4h**	10	71	17	 **4q**	15	76
9	 **4i**	15	59	18	 **4r**	15	79

[a] All reactions were carried out on a 0.25 mmol scale, in 3 mL of triethyl phosphite at a ceiling temperature of 210 °C and a maximum irradiation power of 300 W for the times indicated in Table 2. All yields are isolated yields.

As can be viewed from Table 2, the reactions proceeded smoothly in 10–20 minutes, and the products were isolated in good yields. The reaction times were slightly longer (20 min) when electron-donating groups were present in the biaryl compounds, presumably due to the more difficult insertion of the in situ generated nitrene to the electron-rich ring system, and the products **4b**–**d** were isolated in acceptable yields (Table 2, entries 2–4). The synthesis of 2-methoxy-9*H*-carbazole (**4c**) was particularly interesting, as a variety of naturally occurring carbazole alkaloids contain one or more methoxy groups on their skeleton. When the biaryls were bearing electron-withdrawing groups, the reactions were found to proceed smoothly in 10 minutes and the products **4e**–**h** were isolated in good yields (Table 2, entries 5–8). These examples clearly show the usefulness of the methodology, as the usual way of synthesizing these molecules is often not straightforward and rather long reaction times are needed for the conversion.[17] In the case where the sterically hindered biaryl nitro compound **3i** was irradiated, only one of the nitro groups underwent Cadogan cyclization generating 2-(1,4-dihexyl-9*H*-carbazol-2-yl)aniline (**4i**) as the sole product (Table 2, entry 9). This can be due to the competitive overreduction of the nitrene, generating the amine phosphate as the by-product, which on acidic work-up sets free **4i**.

Following the same protocol, the naphthalene derivatives **3j** and **3k** were successfully ring-closed in 25 minutes at 210 °C into the corresponding 7*H*-benzo[*c*]carbazole (**4j**) and 5*H*-benzo[*b*]carbazole (**4k**) in good yields of 72% and 74%, respectively (Table 2, entries 10, 11). No side products of nitrene insertion at the alternative positions were isolated during the course of the reaction. Our next goal was the ring-closure of the indole analogues **3l**–**o**, and we started our explorations with **3l**, as this intermediate gives the possibility of two different Cadogan cyclization pathways, arising from the possible nitrene insertion at the C-3 or C-5 position of the indole ring. The reaction was finished in 20 minutes at 210 °C and the only product isolated was 3,6-dihydropyrrolo[2,3-*c*]carbazole (**4l**, Table 2, entry 12, 69%); no traces of C-3 insertion product were detected throughout the course of the reaction. The 5-(2-nitrophenyl)-1*H*-indole (**3m**) underwent Cadogan cyclization at the C-6 position of indole ring and the 1,9-dihydropyrrolo[2,3-*b*]carbazole (**4m**) was isolated in good yield of 73% (Table 2, entry 13). No trace of the isomer arising from the nitrene insertion at the C-4 position of the indole was observed. Similarly the 6- and 7-analogues **3n**,**o** underwent the reductive cyclization in 20 minutes generating the products 1,5-dihydropyrrolo[3,2-*b*]carbazole (**4n**) and 1,6-dihydropyrrolo[3,2-*c*]carbazole (**4o**) in moderate to good yields of 64% and 67%, respectively (Table 2, entries 14, 15). The thiophene derivatives **3p**,**q** and the pyridine analogues **3r** were similarly ring-closed in 15 minutes under microwave irradiation[18] at 210 °C and the products **4p**,**r** were isolated in good yields (Table 2, entries 16–18).

In conclusion, we have demonstrated a versatile, efficient and economical microwave-assisted pathway for the synthesis of 2-substituted carbazoles and other difficultly obtainable indolo-fused heterocyclic systems. Suzuki–Miyaura cross-coupling reactions of 2-nitro-phenylboronic acid provides an easy access to the biaryl compounds required for the Cadogan cyclization, avoiding the use of expensive and difficult to synthesize heterocyclic boronic acids or stannanes. Microwave irradiation was found to be highly effective in minimizing the proto-deboronation, a notoriously common problem associated with the cross-coupling of boronic acids bearing electron-poor groups in the *ortho*-position. The biaryl intermediates were then successfully ring-closed to the corresponding fused ring heterocycles under microwave-enhanced Cadogan cyclization conditions and dramatic increases of the reaction rates were observed. Further studies to extend this strategy towards a variety of novel heterocyclic skeletons are under current investigation.

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(18) **General Procedure for the Microwave-Enhanced Suzuki Reaction and Cadogan Cyclization – Synthesis of 8*H*-Thieno[2,3-*b*]indole (4q)**: 3-Bromothiophene (**2q**, 0.041 g, 0.25 mmol), 2-nitrophenylboronic acid (0.054 g, 0.325 mmol), $NaHCO_3$ (0.063 g, 0.75 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.015 g, 5 mol%) were suspended in DMF (1.5 mL) and H_2O (1.5 mL) in a 10 mL glass vial equipped with a small stirring magnet. The vial was sealed tightly with an aluminium-Teflon® crimp top and the mixture was irradiated in the cavity of a mono-mode CEM®-Discover machine for 15 min at a pre-selected temperature of 150 °C, using a maximum irradiation power of 100 W. After the reaction, the vial was cooled to 50 °C by gas jet cooling. The crude mixture was partitioned between Et_2O and H_2O (25 mL each) and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were dried on $MgSO_4$ and solvents were removed under vacuum to yield the crude product as yellow oil. Column chromatography [silica gel, heptane–EtOAc (9:1)] afforded the biaryl compound **3q** (0.046 g, 890%) as yellowish oily material.
The nitro compound **3q** was suspended in triethyl phosphate (3 mL) in a tightly sealed 10 mL glass vial and was irradiated at a maximum irradiation power of 300 W for 15 min at a pre-selected temperature of 210 °C. After the reaction, the vial was cooled to 50 °C by gas jet cooling and the contents were transferred to a 50 mL flask with the help of EtOAc (10 mL). This mixture was then heated to 80 °C with an excess of HCl (6 N, 10 mL) and maintained at the temperature for 3 h. After cooling to r.t., the mixture was partitioned between H_2O and EtOAc (20 mL each) and the aqueous layer was further extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and solvents were removed under reduced pressure, and further purification by column chromatography (silica gel, heptane–EtOAc, 9:1) afforded the thieno-indole **4q** (0.0296 g, 76%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.92 (d, 1 H, *J* = 5.2 Hz), 7.19–7.27 (m, 2 H), 7.36 (d, 1 H, *J* = 5.2 Hz), 7.41 (d, 1 H, *J* = 8.0 Hz), 7.81 (dd, 1 H, *J* = 7.6, 0.8 Hz), 8.22 (br s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 111.2, 117.1, 117.6, 119.3, 119.9, 122.2, 122.5, 125.6, 141.2, 142.2 ppm. DEPT-NMR (75 MHz, $CDCl_3$): δ = 111.2, 117.1, 117.6, 119.3, 122.5, 125.6 ppm. MS (EI): 173 [M^+]. HRMS (EI): *m/z* calcd for $C_{10}H_{07}NS$ [M^+]: 173.02992; found: 173.02986.