Facile Regioselective Synthesis of Pyrazolo[5,1-*a*]isoquinolines via Ring-Opening Cyclization/Oxidation Reactions of Stable Aroyldiaziridines of 3,4-Tetrahydroisoquinoline with Alkynes

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Received 16 April 2007; revised 6 July 2007

Abstract: Newly prepared, stable aroyldiaziridines of 3,4-tetrahydroisoquinolines undergo regioselective cycloaddition reactions with a number of both mono and disubstituted alkynes, affording five-membered ring products which, after oxidative aromatization of the pyrazoline ring, lead to the efficient preparation of pyrazolo[5,1-*a*]isoquinolines. The overall transformation is base-catalyzed and occurs more rapidly in the presence of oxygen, in halogenated solvents and in dioxane.

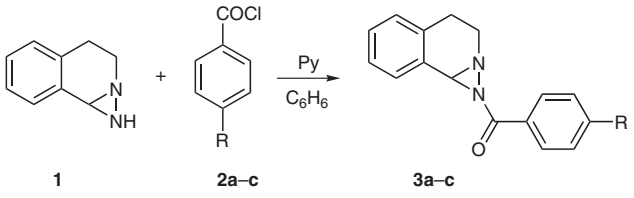
Key words: isoquinolines, diaziridines, cycloadditions, alkynes, oxidations

The employment of three-membered-ring heterocycles for the synthesis of five-membered-ring heterocycles has been widely used as a strategy for the preparation of a large number of compounds including some that are biologically active.[1] This approach was also used by our group for catalyzed[2–6] as well as uncatalyzed[6] reactions employing 1,2- and 1,2,3-substituted aziridines,[2] 2-vinyloxiranes,[3] 2-vinylaziridines,[4] 2-vinylthiiranes[5] and 1,2-diaroyldiaziridines.[6] As part of our ongoing interest in the study of three-membered-ring compounds containing two heteroatoms, we investigated the reaction of alkynes with new, stable aroyldiaziridines of 3,4-tetrahydroisoquinoline to form five-membered-ring compounds which, on oxidative aromatization of the pyrazoline ring, gave pyrazolo[5,1-*a*]isoquinolines.

Some pyrazoloisoquinolines and their derivatives are known to possess biological activity, such as antibiotics,[7] kinase inhibitors and anticonvulsants.[8,9]

Although there are some reports on the reaction of diaziridines with acetylenes,[10–13] the utility of this reaction for the synthesis of five-membered-ring heterocycles has not been fully described. Thus far, there are no publications on the reactions of alkynes with stable aroyldiaziridines of 3,4-tetrahydroisoquinoline leading to the regioselective formation of pyrazolo[5,1-*a*]isoquinolines.

Aroyldiaziridines of 3,4-tetrahydroisoquinoline **3** were prepared according to a slightly modified procedure[6] (Scheme 1). 1,2,3,7b-Tetrahydro-1,1a-diazacyclopropa[*a*]naphthalene (**1**)[14] reacts with aroyl chlorides **2** in pyridine–benzene to give the aroyldiaziridines of 3,4-tetrahydroisoquinoline **3**.

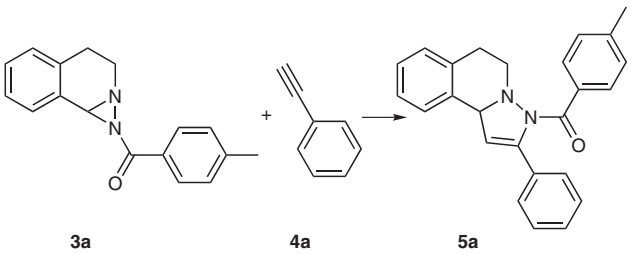


a, R = Me; **b**, R = OMe; **c**, R = NO_2

Scheme 1 Synthesis of aroyldiaziridines of 3,4-tetrahydroisoquinoline

To our knowledge, this is the first time that the aroyldiaziridines of 3,4-tetrahydroisoquinoline **3** have been synthesized as very stable, easy-to-handle, crystalline materials that do not decompose for months at room temperature.

We investigated the reaction of aroyldiaziridines of 3,4-tetrahydroisoquinoline **3** with alkynes **4** under a range of conditions (Scheme 2). We noted that the reaction was rather slow when employing equimolar amounts of reactants at room temperature; thus, we increased the temperature and the concentration of the alkyne **4a** in order to accelerate the formation of **5a**.



Scheme 2 Cycloaddition reaction of 3,4-tetrahydroisoquinoline (**3a**) with phenylacetylene (**4a**)

The structure of the cycloaddition product **5a** was confirmed by single-crystal X-ray diffraction (Figure 1).[15] During handling of the colorless crystals of **5a**, we noticed that some small but noticeable transformation to a light yellow compound was taking place. We realized that in the presence of air at room temperature, **5a** was easily transformed into the pyrazolo[5,1-*a*]isoquinoline **6a**.

SYNTHESIS 2007, No. 23, pp 3683–3691
Advanced online publication: 13.11.2007
DOI: 10.1055/s-2007-990888; Art ID: M12207SS

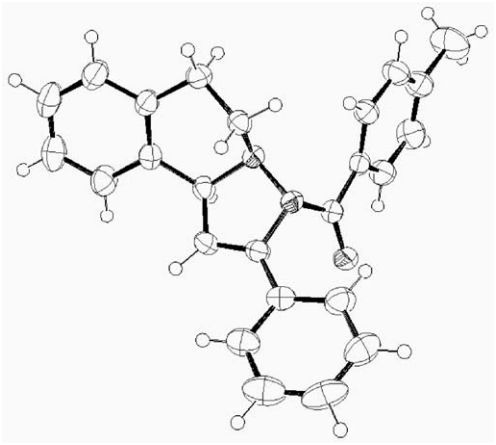
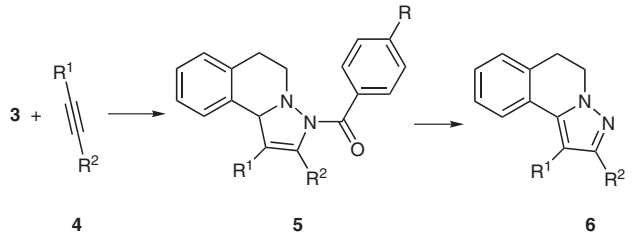


Figure 1 X-ray crystal structure of compound **5a**[15]

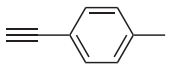
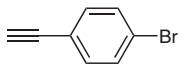
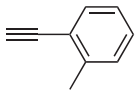
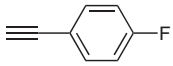
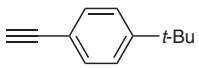


Scheme 3 Production of pyrazolo[5,1-*a*]isoquinolines **6**

We proceeded to optimize the reaction conditions in order to maximize the production of the pyrazolo[5,1-*a*]isoquinolines **6** (Scheme 3). Reaction optimization results are presented in Table 1.

Clearly, the reaction in chloroform (entry 8) gives rise to the highest conversion, together with a higher proportion of product **6**, by reaction in air for 24 hours. Under these conditions, the production of **5** appears to be optimal us-

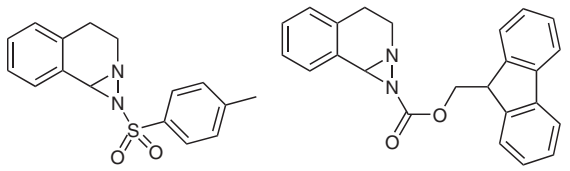
Table 1 Optimization of Reaction Conditions for the Reaction of **3a** with **4**[a]

Entry	Alkyne	Solvent	Time (h)	Atm	Conversion (%)[b]	Ratio of **5/6**[b]
1	**4a**	THF	24	air	87	94:6
2	**4a**	benzene	24	air	98	90:10
3	**4a**	MeOH	24	air	23	97:3
4	**4a**	EtOH	24	air	41	98:2
5	**4a**	CH_2Cl_2	24	air	100	93:7
6	 **4d**	CH_2Cl_2	24	air	92	99:trace
7	 **4f**	CH_2Cl_2	24	air	100	99:trace
8	**4a**	$CHCl_3$	24	air	100	77:23
9	**4a**	$CHCl_3$	12	air	76	99:trace
10	 **4b**	$CHCl_3$	48	N_2	100	57:43
11	 **4g**	$CHCl_3$	48	N_2	100	53:47
12	**4a**	dioxane	24	air	98	93:7
13	 **4k**[c]	$CHCl_3$	24	N_2	72	99:trace
14	**4k**[c]	$CHCl_3$	24	air	90	61:39
15	**4k**[c]	$CHCl_3$	24	O_2	100	0:100

[a] Reaction conditions: **3a** (0.087 mmol), **4** (0.87 mmol), solvent (2 mL), indicated gas (1 atm), 50 °C.
[b] Conversion (%) and the molar ratio were determined by ^{1}H NMR spectroscopy.
[c] **4k** (0.44 mmol) was used.

ing dichloromethane as the solvent for the reaction of a range of alkynes (entries 5–7).

Dioxane was also found to be a good solvent for the reaction in air (entry 12). However, the transformation of **5** to **6** can occur even in the absence of oxygen (entries 10 and 11) provided the reaction time is extended. The dramatic effect of increasing the amount of oxygen on the conversion, and on the ratio of **5**:**6** can be seen in the last three entries (entries 13–15). In the absence of oxygen (entry 13) only **5** is produced; while in an oxygen atmosphere (entry 15), **6** is formed with no detectable amounts of **5**.



7 **8**

Figure 2 Other stable diaziridines of 3,4-tetrahydroisoquinoline studied

In order to extend the scope of the present study, we synthesized compounds **7** and **8** (Figure 2) and studied them together with compounds **1** and **3a–c** (Table 2) in order to evaluate the effect of different substituent groups on diaziridines of 3,4-tetrahydroisoquinoline. However, contrary to our expectations, **7** and **8** were completely unreactive towards the formation of cycloaddition products with alkynes, even when, for example, **7** was stirred for several days at up to 100 °C in the presence of different alkyl and arylalkynes.

Table 2 Effect of the Substituent Group of Diaziridines of 3,4-Tetrahydroisoquinoline on the Conversion and Product Ratio[a]

Entry	Diaziridine	Conversion (%)	Ratio of **5**/**6**
1	**1**	0	–
2	**3a**	63	98:2
3	**3b**	78	92:8
4	**3c**	67	94:6
5	**7**	0	–
6	**8**	0	–

[a] Reaction conditions: diaziridine (0.087 mmol), **4a** (0.44 mmol), $CHCl_3$ (2 mL), O_2 (1 atm), 24 h, 50 °C.

The methoxy group of the aroyldiaziridine **3b** (entry 3) enhances conversion of **3** to **5** and **6**. However, the selectivity for **5** over **6**, using **3b** (R = OCH_3), is less than for both **3c** (R = NO_2) and **3a** (R = CH_3) (entries 4 and 2).

These results appear to indicate that the presence of an electron-withdrawing group on the diaziridine is helpful for the cycloaddition reaction. The lack of reactivity of **1** may be due to the absence of such a group. However, not all electron-withdrawing groups enhance the reaction, since neither the tosyl (**7**) nor the 9-fluorenylmethoxycarbonyl (**8**) substituted heterocycles are reactive, possibly because they substantially reduce the nucleophilicity of the nitrogen atom to which they are attached.

Having established that only the aroyldiaziridines (**3a–c**) of this study were reactive, we used several mono and disubstituted alkynes in reaction with them. Table 3 summarizes the very good results obtained. Fine yields of **6** resulted from using a variety of mono-substituted alkynes in reaction with **3**, and there was no substantive influence of the substituent on the reaction. As expected, the disubstituted alkynes were less reactive than their monosubstituted counterparts, probably due to steric effects (entries 10, 11).

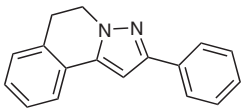
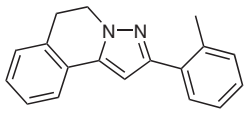
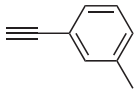
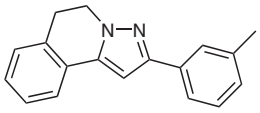
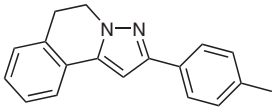
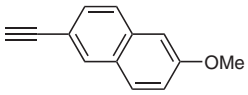
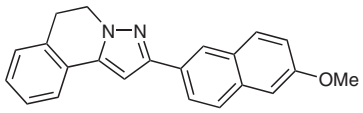
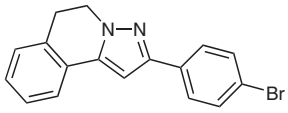
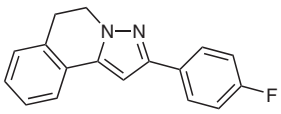
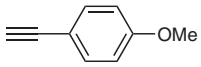
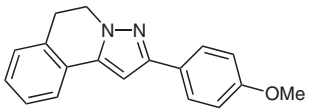
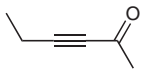
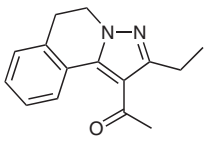
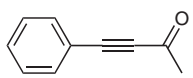
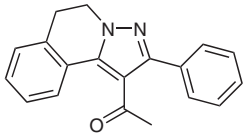
Relying upon the already established structure of **5a** (Figure 1), we assigned the structures of products **6a–h** as the ones shown (Table 3). Unfortunately, for products **6i** and **6j**, we could not obtain good enough crystals for X-ray crystallographic determinations and, therefore, we can only propose the shown structures. However, these proposed structures (**6i** and **6j**) are thought to be more likely, since they would originate from more stable arrangements of the partial charges thought to be present in the transition state during the cycloaddition reaction (Scheme 4).

In order to gain some insight into the mechanism of the overall reaction from **3** to **6**, we devised several additional experiments (Table 4). The transformation of **5** to **6** was inhibited in the presence of water (entries 1–3), however, in the presence of base, and in contrast to an acid, the reaction occurred and the total reaction time to obtain **6** was reduced (entries 4–6). Among the bases studied, the best was sodium bicarbonate (entry 11), which reduced the total reaction time to 12–15 hours less than in its absence (compare entry 17 of Table 4 with entry 1 in Table 3). Interestingly, the simultaneous presence of both base and oxygen was only slightly better than when the reaction was performed under nitrogen (entries 14 and 18) and this may mean that both the base and the oxygen compete for the same hydrogen atom abstraction in the last step of the mechanism proposed herein. When the reaction was run under nitrogen, essentially the same results were obtained whether pyridine or sodium bicarbonate was used as the base (entries 7 and 18).

In order to explain the conversion of **3** to **6a**, we propose the following mechanism (Scheme 4). In accord with previous contributions,[12,16,17] diaziridine **3** can ring open to form the azomethine imine **9**.[18] The latter can undergo reaction with the alkyne **4a** to produce the adduct **5a**, which oxidatively aromatizes with loss of a proton; this step being favored in the presence of base (Table 4).

Thus, aroyldiaziridines of 3,4-tetrahydroisoquinoline **3** undergo regioselective cycloaddition reactions with a number of alkynes **4**, affording five-membered ring products **5** which, after aromatization of the pyrazoline ring, lead to the efficient preparation of pyrazolo[5,1-*a*]isoquinolines **6**. By changing the reaction conditions, it is

Table 3 Reaction of Aroyldiaziridines of 3,4-Tetrahydroisoquinoline **3** with Mono- and Disubstituted alkynes **4**[a]

Entry	Diaziridine **3**	Alkyne	Solvent	Time (h)	Atm	Product	Yield (%)[b]
1	**3b**	**4a**	$CHCl_3$	48	O_2	 **6a**	84
2[c]	**3a**	**4a**	THF	144	N_2	**5a**	89
3	**3b**	**4b**	$CHCl_3$	48	O_2	 **6b**	80
4	**3b**	 **4c**	$CHCl_3$	48	O_2	 **6c**	78
5	**3b**	**4d**	$CHCl_3$	48	O_2	 **6d**	80
6	**3b**	 **4e**	$CHCl_3$	48	O_2	 **6e**	66
7	**3b**	**4f**	$CHCl_3$	48	O_2	 **6f**	77
8	**3b**	**4g**	$CHCl_3$	48	O_2	 **6g**	75
9	**3b**	 **4h**	$CHCl_3$	48	O_2	 **6h**	85
10	**3b**	 **4i**	$CHCl_3$	48	O_2	 **6i**	69
11[d]	**3a**	 **4j**	THF[d]	120/336[d]	N_2/air[d]	 **6j**	50

[a] Reaction conditions: **3** (0.087 mmol), **4** (0.44 mmol), solvent (2 mL), indicated gas (1 atm), 50 °C.
[b] Isolated yield.
[c] Reaction conditions: **3a** (0.25 mmol), **4a** (9.1 mmol), r.t.
[d] Reaction conditions: **3a** (0.25 mmol), **4j** (0.93 mmol), THF (4 mL), 50 °C, 5 d, N_2 then solvent exchanged to $CHCl_3$ (4 mL) and stirred under air for 2 weeks.

Table 4 Effect of Water, Base and Acid Additives on the Reaction of **3** with **4**[a]

Entry	3	4	Time (h)	Atm	Additive (mmol)	Conversion (%)[b]	Ratio of **5**:**6** [b]
1	**3a**	**4k**	24	air	none	90	61:39
2	**3a**	**4k**	24	air	H_2O (1.0)	81	99:trace
3	**3a**	**4k**	24	air	H_2O (22.0)	81	99:trace
4	**3b**	**4k**	16	N_2	Py (0.23)	100	11:89
5	**3a**	**4k**	16	N_2	Et_3N (0.23)	100	86:14
6	**3b**	**4k**	16	N_2	citric acid (0.021)	100	98:2
7	**3a**	**4a**	24	N_2	Py (0.23)	91	88:12
8	**3a**	**4a**	24	O_2	Py (0.23)	67	99:1
9	**3a**	**4a**	24	O_2	none	64	99:1
10	**3a**	**4a**	24	O_2	K_2CO_3 (0.23)	62	94:6
11	**3a**	**4a**	24	O_2	$NaHCO_3$ (0.23)	62	90:10
12	**3a**	**4a**	24	O_2	NaOAc (0.23)	75	99:trace
13	**3a**	**4a**	24	O_2	NH_4OH (0.23)	75	99:1
14	**3c**	**4a**	24	O_2	$NaHCO_3$ (0.05)	90	83:17
15	**3c**	**4a**	24	O_2	$NaHCO_3$ (0.025)	85	83:17
16	**3c**	**4a**	24	O_2	DTBMP[c] (0.025)	88	94:6
17	**3c**	**4a**	33	O_2	$NaHCO_3$ (0.05)	94	2:98
18	**3c**	**4a**	24	N_2	$NaHCO_3$ (0.05)	90	86:14

[a] Reaction conditions: **3** (0.087 mmol), **4** (0.44 mmol), solvent (2 mL), indicated gas (1 atm), 50 °C.
[b] Conversion (%) and the molar ratio of **5**:**6** were determined by ^{1}H NMR spectroscopy.
[c] DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine.

possible to direct the synthesis toward either product **5** or **6**. The overall transformation to **6** is base-catalyzed and occurs more rapidly in the presence of oxygen, in halogenated solvents, and in dioxane.

The present procedure can conveniently be employed for the synthesis of a variety of mono and disubstituted pyrazolo[5,1-*a*]isoquinolines **6**, expanding the scope and versatility over previous contributions which were either limited to monosubstituted compounds,[19] were not reactive with some phenylacetylenes[20] or involved a greater number of synthetic steps.[21] Therefore, a wide number of pyrazolo[5,1-*a*]isoquinolines **6**, which may have interesting biological properties, can now be conveniently synthesized in good yields following the present procedure.

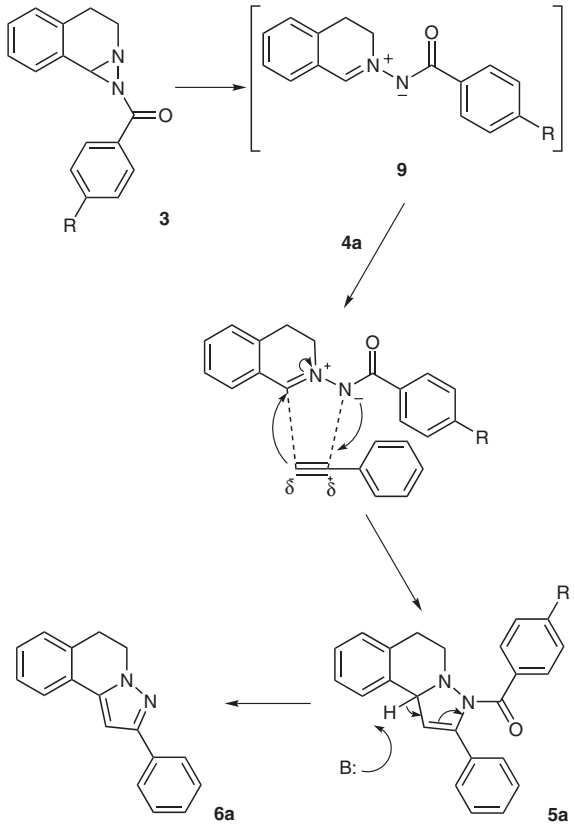
Unless otherwise indicated, all starting materials were obtained from commercial suppliers and were used without further purification. All solvents except for $CHCl_3$ and dioxane were dried and distilled under N_2 prior to use; other chemicals were used as received without further purification. Analytical thin-layer chromatography (TLC) was performed on E. Merck silica gel 60 F254 pre-coated plates (0.25 mm) and visualized with a 254 nm UV lamp. Before being used for separation of the reaction products, TLC plates were treated with a mix of hexanes–Et_3N, 50:50. Work-up of the reaction mixture consisted of reducing the solvent volume and subjecting it to preparative TLC (Et_2O–hexanes, 50:50). IR spectra were obtained with a Shimadzu FTIR 8400S spectrometer. Mass spectra were determined using a VG 7070E spectrometer. ^{1}H NMR and ^{13}C NMR were recorded in $CDCl_3$ on a Bruker Avance 300 MHz and/or a Bruker Avance 400 MHz spectrometer. Chemical shifts (δ) are reported in ppm with the solvent signal as reference, and coupling constants (*J*) are given in Hertz (Hz). Melting points are uncorrected.

1,2,3,7b-Tetrahydro-1,1a-diazacyclopropa[*a*]naphthalene (1)[14]

To a solution of NH_4OH (13 mL, 185 mmol) in MeOH (30 mL) at –20 °C was added, portion-wise, hydroxylamine-*O*-sulfonic acid (10 g, 84 mmol). After 30 min, a solution of 3,4 dihydroisoquinoline (11 g, 75 mmol)[22] in MeOH (30 mL) was added drop-wise and the mixture was stirred for 3 h. The reaction mixture was left overnight in a cold-bath then filtered and washed with Et_2O (3 × 50 mL). The filtrate and washings were evaporated to almost complete dryness without warming in a water bath. The residue was extracted with Et_2O (3 × 50 mL) and the combined organic layer was taken and dried (K_2CO_3). The solvent was evaporated and the residue was recrystallized (EtOH) to give **1**.

Yield: 6.70 g (58%); mp 93–95 °C (Lit.[14] 98–99 °C).

IR (film): 3209, 2959, 2943, 2932, 2916, 1497, 1080, 1057, 1014 cm^{-1}.



Scheme 4 Proposed mechanism for the formation of pyrazolo[5,1-*a*]isoquinolines **6** from base catalyzed cycloaddition reactions of aroyldiaziridines of 3,4-tetrahydroisoquinolines **3**. Example shown with phenylacetylene **4a**.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.31 (d, *J* = 4.2 Hz, 1 H, NH), 2.40–2.46 (dd, *J* = 3.6, 15.8 Hz, 1 H), 2.74–2.78 (m, 1 H, CH-Ar), 2.91–2.98 (m, 1 H, CH-Ar), 3.57–3.63 (dd, *J* = 6.3, 12.9 Hz, 1 H, CH-N), 4.09 (d, *J* = 8.4 Hz, 1 H, CH-N), 7.11–7.46 (m, 4 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.30, 46.67, 52.91, 126.69, 128.46, 128.52, 129.42, 132.24, 135.24.

MS (EI): *m*/*z* (%) = 117.1 (62), 146.1 (100) [M^+].

HRMS (EI): *m*/*z* [M^+] calcd for $C_9H_{10}N_2$: 146.08440; found: 146.08547.

(3,7b-Dihydro-2*H*-1,1a-diazacyclopropa[*a*]naphthalen-1-yl)-*p*-tolylmethanone (3a)[6]

To a two-necked round-bottomed flask, equipped with a condenser, was added diaziridine **1** (3.00 g, 20.3 mmol) dissolved in a mixture of pyridine (30 mL) and benzene (25 mL). A solution of *p*-toluoyl chloride (3 mL, 22.3 mmol) in benzene (15 mL) was added and the reaction mixture was slowly heated to 50–55 °C. After 30 min, a deep-red coloration developed and the reaction mixture was cooled by removing it from the bath. After pouring the contents into H_2O (200 mL), the aqueous phase was taken and washed with benzene (50 mL) and the organic extracts were washed with H_2O (60 mL) and then with Na_2CO_3 (5%, 50 mL). After drying ($MgSO_4$), the organic solvents were removed and the remaining red oil was dissolved in Et_2O to form a yellow solution. Yellow crystals appeared upon partial evaporation of the solvent overnight. Further addition of Et_2O to the remaining red oil with subsequent crystallization, was repeated several times to give the product **3a**.

Yield: 0.95 g (18%); yellow crystals; mp 155–156 °C.

IR (film): 3063, 3026, 2918, 1647, 1533, 1317, 1286, 984 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.37 (s, 3 H, CH_3), 3.23 (t, *J* = 7.6 Hz, 2 H, CH_2-Ar), 4.25 (dt, *J* = 0.8, 7.8 Hz, 2 H, CH_2-N), 7.18 (d, *J* = 7.9 Hz, 2 H, ArH), 7.27 (d, *J* = 7.4 Hz, 1 H, ArH), 7.34–7.50 (m, 3 H, ArH), 7.98 (dd, *J* = 1.6, 8.1 Hz, 2 H, ArH), 9.67 (s, 1 H, Ar-CH-N).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.49, 26.85, 54.91, 127.17, 127.67, 127.90, 128.05, 128.47, 128.65, 129.50, 132.89, 134.64, 134.58, 140.33, 170.94.

MS (EI): *m*/*z* (%) = 130.1 (41), 263.1 (100) [M^+ – 1].

HRMS (EI): *m*/*z* [M^+] calcd for $C_{17}H_{16}N_2O$: 264.12626; found: 264.12805.

(3,7b-Dihydro-2*H*-1,1a-diazacyclopropa[*a*]naphthalen-1-yl)-(4-methoxyphenyl)methanone (3b)

The procedure was essentially the same as described for the previous compound **3a**, only that the reaction solution became deep-red almost immediately after the addition of the aroyl chloride.

Yield: 1.1 g (28%); beige powder; mp 164–165 °C.

IR (film): 3007, 2995, 2962, 2833, 1643, 1605, 1589, 1537, 1502, 1246 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.27 (t, *J* = 7.7 Hz, 2 H, CH_2-Ar), 3.87 (s, 3 H, CH_3), 4.29 (dt, *J* = 0.9, 7.8 Hz, 2 H, CH_2-N), 6.93 (dt, *J* = 2.5, 9.0 Hz, 2 H, ArH), 7.31 (d, *J* = 7.3 Hz, 1 H, ArH), 7.36–7.52 (m, 3 H, ArH), 8.09 (dt, *J* = 2.5, 8.9 Hz, 2 H, ArH), 9.77 (s, 1 H, Ar-CH-N).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.86, 55.00, 55.30, 113.16, 127.15, 127.66, 128.05, 128.34, 129.48, 129.61, 130.02, 132.88, 133.58, 161.40, 170.71.

MS (EI): *m*/*z* (%) = 130.1 (49), 279.1 (100) [M^+ – 1].

HRMS (EI): *m*/*z* [M^+] calcd for $C_{17}H_{16}N_2O_2$: 280.12118; found: 280.12126.

(3,7b-Dihydro-2*H*-1,1a-diazacyclopropa[*a*]naphthalen-1-yl)-(4-nitrophenyl)methanone (3c)

Synthesized by the procedure described for **3a**; after 30 min heating, a dark-orange color developed.

Yield: 0.55 g (14%); bright-yellow crystals; mp 178–179 °C.

IR (film): 3099, 3065, 3043, 2837, 1568, 1558, 1508, 1309, 848 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.31 (t, *J* = 7.8 Hz, 2 H, CH_2-Ar), 4.33 (dt, *J* = 0.9, 7.7 Hz, 2 H, CH_2-N), 7.35 (d, *J* = 7.4 Hz, 1 H, ArH), 7.41–7.59 (m, 3 H, ArH), 8.23–8.30 (m, 4 H, ArH), 9.77 (s, 1 H, Ar-CH-N).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.74, 54.95, 123.12, 126.54, 127.83, 128.29, 128.91, 130.04, 133.68, 133.78, 143.91, 148.93, 150.14, 168.80.

MS (EI): *m*/*z* (%) = 130.1 (41), 294.1 (100) [M^+ – 1].

HRMS (EI): *m*/*z* [M^+] calcd for $C_{16}H_{13}N_3O_3$: 295.0957; found: 295.0945.

Reaction of Aroyldiaziridines 3a–c with Alkynes 4; General Procedure

To a test tube equipped with a stirring bar, **3a–c** (0.087 mmol), alkyne **4** (0.44 mmol) and $CHCl_3$ (2 mL) were added. The test tube was capped with a PTFE-covered rubber septum; if the reaction needed to be under N_2 or O_2, the required gas was bubbled through the contents of the test tube for at least 5 min. The tube was immersed in an oil bath at 50 °C and, after the reaction time (24–48 h), the reaction mixture was concentrated to be separated by means of preparative TLC.

(2-Phenyl-6,10b-dihydro-5*H*-pyrazolo[5,1-*a*]isoquinolin-3-yl)-*p*-tolylmethanone (5a)
Yield: 81 mg (89%); colorless crystals; mp 149–150 °C.

IR (film): 3007, 2930, 2856, 1659, 1647, 1605, 1493, 1323 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.36 (s, 3 H, CH_3), 2.71 (dt, *J* = 2.4, 16.0 Hz, 1 H, CH-N), 3.07 (dt, *J* = 4.1, 14.3 Hz, 1 H, CH-Ar), 3.22 (dt, *J* = 2.5, 11.9 Hz, 1 H, CH-Ar), 3.44 (dq, *J* = 2.2, 10.2 Hz, 1 H, CH-N), 5.40 (s, 1 H, CH-Ar), 5.97 (d, *J* = 1.8 Hz, 1 H, CH=C), 7.07 (d, *J* = 7.3 Hz, 1 H, ArH), 7.12–7.32 (m, 8 H, ArH), 7.47 (dd, *J* = 1.4, 6.8 Hz, 2 H, ArH), 7.75 (d, *J* = 8.1 Hz, 2 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.53, 28.42, 47.81, 66.96, 117.99, 125.52, 126.26, 126.48, 126.79, 126.95, 128.17, 128.28, 128.37, 128.45, 128.65, 128.93, 129.20, 130.21, 132.25, 132.36, 133.21, 134.07, 141.50, 143.69, 172.29.

MS (EI): *m*/*z* (%) = 247 (100), 366.2 (3) [M^+].

HRMS (EI): *m*/*z* [M^+] calcd for $C_{25}H_{22}N_2O$: 366.1732; found: 366.1741.

2-Phenyl-5,6-dihydropyrazolo[5,1-*a*]isoquinoline (6a)
Yield: 18 mg (84%); colorless solid; mp 83–84 °C (Lit.[9d] 88–89 °C).

IR (film): 3053, 2947, 2924, 2895, 2870, 1487, 1468, 1454, 1337, 1078 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.25 (t, *J* = 6.9 Hz, 2 H, CH_2-Ar), 4.43 (t, *J* = 6.9 Hz, 2 H, CH_2-N), 6.89 (s, 1 H, Ar-CH-N), 7.26–7.48 (m, 6 H, ArH), 7.63 (d, *J* = 7.2 Hz, 1 H, ArH), 7.88–7.91 (m, 2 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.60, 46.70, 98.01, 124.42, 125.91, 127.33, 127.84, 128.09, 128.58, 128.66, 129.08, 132.08, 133.90, 140.49, 151.71.

MS (EI): *m*/*z* (%) = 119.0 (19), 246.1 (100) [M^+].

HRMS (EI): *m*/*z* [M^+] calcd for $C_{17}H_{14}N_2$: 246.1157; found: 246.1149.

2-*o*-Tolyl-5,6-dihydropyrazolo[5,1-*a*]isoquinoline (6b)
Yield: 18 mg (80%); light-yellow oil.

IR (film): 3049, 2953, 2924, 2897, 2870, 1487, 1468, 1456, 1329, 953 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.52 (s, 3 H, CH_3), 3.25 (t, *J* = 5.2 Hz, 2 H, CH_2-Ar), 4.40 (t, *J* = 5.2 Hz, 2 H, CH_2-N), 6.68 (s, 1 H, Ar-CH-N), 7.22–7.33 (m, 6 H, ArH), 7.57–7.63 (m, 2 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.26, 29.24, 46.22, 100.75, 123.97, 125.82, 127.06, 127.40, 127.65, 128.06, 128.26, 129.24, 130.75, 131.69, 133.42, 135.98, 139.15, 151.60.

MS (EI): *m*/*z* (%) = 111.0 (38), 260.1 (100) [M^+].

HRMS (EI): *m*/*z* [M^+] calcd for $C_{18}H_{16}N_2$: 260.1314; found: 260.1302.

2-*m*-Tolyl-5,6-dihydropyrazolo[5,1-*a*]isoquinoline (6c)
Yield: 17 mg (78%); light-yellow oil.

IR (film): 3015, 2949, 2920, 2870, 1487, 1470, 1329, 1248, 1217, 1013 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.44 (s, 3 H, CH_3), 3.26 (t, *J* = 6.9 Hz, 2 H, CH_2-Ar), 4.43 (t, *J* = 6.9 Hz, 2 H, CH_2-N), 6.88 (s, 1 H, Ar-CH-N), 7.16 (d, *J* = 7.5 Hz, 1 H, ArH), 7.29–7.38 (m, 4 H, ArH), 7.61–7.74 (m, 3 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.92, 29.61, 46.68, 98.04, 123.08, 124.40, 126.52, 127.35, 127.82, 128.55, 128.65, 128.88, 128.97, 132.07, 133.74, 138.68, 140.43, 151.84.

MS (EI): *m*/*z* (%) = 115.1 (12), 260.1 (100) [M^+].

HRMS (EI): *m*/*z* [M^+] calcd for $C_{18}H_{16}N_2$: 260.1314; found: 260.1321.

2-*p*-Tolyl-5,6-dihydropyrazolo[5,1-*a*]isoquinoline (6d)
Yield: 18 mg (80%); light-yellow solid; mp 111–112 °C.

IR (film): 2945, 2920, 1470, 1458, 1439, 1331, 824 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.37 (s, 3 H, CH_3), 3.22 (t, *J* = 5.2 Hz, 2 H, CH_2-Ar), 4.38 (t, *J* = 5.2 Hz, 2 H, CH_2-N), 6.81 (s, 1 H, Ar-CH-N), 7.24–7.38 (m, 5 H, ArH), 7.58 (d, *J* = 5.6 Hz, 1 H, ArH), 7.73 (d, *J* = 6.1 Hz, 2 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.30, 29.23, 46.26, 97.39, 123.99, 125.41, 127.00, 127.40, 128.10, 128.23, 129.35, 130.69, 131.69, 137.41, 140.00, 151.41.

MS (EI): *m*/*z* (%) = 162.0 (14), 260.1 (100) [M^+].

HRMS (EI): *m*/*z* [M^+] calcd for $C_{18}H_{16}N_2$: 260.1314; found: 260.1305.

2-(6-Methoxynaphthalen-2-yl)-5,6-dihydropyrazolo[5,1-*a*]isoquinoline (6e)
Yield: 19 mg (66%); orange crystalline solid; mp 165–166 °C.

IR (film): 3001, 2953, 2945, 2930, 2899, 2870, 2837, 1632, 1607, 1497, 1391, 1215, 1030 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.28 (t, *J* = 6.9 Hz, 2 H, CH_2-Ar), 3.96 (s, 3 H, CH_3), 4.47 (t, *J* = 6.8 Hz, 2 H, CH_2-N), 6.98 (s, 1 H, Ar-CH-N), 7.16–7.20 (m, 2 H, ArH), 7.30–7.40 (m, 3 H, ArH), 7.65 (d, *J* = 7.3 Hz, 1 H, ArH), 7.80–7.84 (m, 2 H, ArH), 8.00 (dd, *J* = 1.8, 8.6 Hz, 1 H, ArH), 8.27 (d, *J* = 1.1 Hz, 1 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.22, 46.32, 55.34, 97.62, 105.80, 119.04, 123.94, 124.05, 124.52, 126.92, 127.14, 127.46, 128.23, 128.27, 128.73, 129.12, 129.73, 131.71, 134.23, 140.21, 151.42, 157.72.

MS (EI): *m*/*z* (%) = 283.1 (20), 326.1 (100) [M^+].

HRMS (EI): *m*/*z* [M^+] calcd for $C_{22}H_{18}N_2O$: 326.1419; found: 326.1398.

2-(4-Bromophenyl)-5,6-dihydropyrazolo[5,1-*a*]isoquinoline (6f)
Yield: 22 mg (77%); yellow crystalline solid; mp 104–105 °C.

IR (film): 3049, 2945, 2924, 2895, 2874, 1468, 1423, 1327, 1009, 953 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.26 (t, *J* = 7.0 Hz, 2 H, CH_2-Ar), 4.42 (t, *J* = 7.1 Hz, 2 H, CH_2-N), 6.85 (s, 1 H, Ar-CH-N), 7.29–7.40 (m, 3 H, ArH), 7.56 (dt, *J* = 2.2, 8.6 Hz, 2 H, ArH), 7.61 (dt, *J* = 1.2, 7.1 Hz, 1 H, ArH), 7.75 (dt, *J* = 2.2, 8.6 Hz, 2 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.16, 46.34, 97.56, 121.51, 124.02, 126.75, 127.05, 127.48, 128.28, 128.32, 131.66, 131.75, 132.49, 140.28, 150.22.

MS (EI): *m*/*z* (%) = 115 (31), 324 (100) [M^+].

HRMS (EI): *m*/*z* [M^+] calcd for $C_{17}H_{13}BrN_2$: 324.0262; found: 324.0269.

2-(4-Fluorophenyl)-5,6-dihydropyrazolo[5,1-*a*]isoquinoline (6g)
Yield: 17 mg (75%); yellow crystalline solid; mp 78–79 °C.

IR (film): 3053, 2923, 2870, 2851, 1526, 1468, 1439, 1217, 1153, 839 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.26 (t, *J* = 6.8 Hz, 2 H, CH_2-Ar), 4.42 (t, *J* = 6.8 Hz, 2 H, CH_2-N), 6.82 (s, 1 H, Ar-CH-N), 7.09–7.16 (m, 2 H, ArH), 7.29–7.39 (m, 3 H, ArH), 7.61 (dt, *J* = 1.1, 7.1 Hz, 1 H, ArH), 7.81–7.87 (m, 2 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.19, 46.28, 97.38, 115.54 (d, *J* = 21.6, 2 × C), 124.00, 126.84, 127.15 (d, *J* = 8.0 Hz, 2 × C), 127.45, 128.25, 128.27, 129.76 (d, *J* = 3.3 Hz), 131.67, 140.21, 150.46, 162.54 (d, *J* = 246.2 Hz).

MS (EI): *m*/*z* (%) = 263.1 (21), 264.1 (100) [M$^+$].

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{17}H_{13}BrN_2$: 264.1063; found: 264.1078.

2-(4-Methoxyphenyl)-5,6-dihydropyrazolo[5,1-*a*]isoquinoline (6h)

Yield: 20 mg (85%); colorless crystalline solid; mp 105–106 °C.

IR (film): 2957, 2924, 2851, 2835, 1529, 1472, 1435, 1246, 1175, 1032, 835 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.21 (t, *J* = 6.9 Hz, 2 H, CH_2-Ar), 3.82 (s, 3 H, CH_3), 4.37 (t, *J* = 6.8 Hz, 2 H, CH_2-N), 6.76 (s, 1 H, Ar-CH-N), 6.94 (dt, *J* = 2.5, 8.8 Hz, 2 H, ArH), 7.22–7.37 (m, 3 H, ArH), 7.57 (d, *J* = 7.4 Hz, 1 H, ArH), 7.77 (dt, *J* = 2.5, 8.9 Hz, 2 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.23, 46.22, 55.32, 97.08, 114.05, 123.97, 126.35, 126.76, 127.01, 127.39, 128.09, 128.23, 131.69, 140.02, 151.20, 159.34.

MS (EI): *m*/*z* (%) = 261.1 (32), 276.1 (100) [M$^+$].

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{18}H_{16}N_2O$: 276.12626; found: 276.12796.

1-(2-Ethyl-5,6-dihydropyrazolo[5,1-*a*]isoquinolin-1-yl)ethanone (6i)

Yield: 14 mg (69%); colorless crystalline solid; mp 106–107 °C.

IR (film): 2970, 2922, 1663, 1475, 773, 745 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.29 (t, *J* = 7.5 Hz, 3 H, CH_3), 2.51 (s, 3 H, CH_3), 2.83 (q, *J* = 7.5 Hz, 2 H, CH_2), 3.13 (t, *J* = 6.8 Hz, 2 H, CH_2-Ar), 4.22 (t, *J* = 6.9 Hz, 2 H, CH_2-N), 7.24 (s, 1 H, Ar-CH-N), 7.25–7.32 (m, 3 H, ArH), 7.77–7.81 (m, 1 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.75, 21.70, 29.59, 31.12, 46.24, 117.71, 126.29, 127.28, 127.35, 128.09, 129.19, 133.67, 139.43, 154.23, 196.46.

MS (EI): *m*/*z* (%) = 225.1 (100), 240.1 (33) [M$^+$].

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{15}H_{16}N_2O$: 240.12626; found: 240.12600.

1-(2-Phenyl-5,6-dihydropyrazolo[5,1-*a*]isoquinolin-1-yl)ethanone (6j)

Yield: 36 mg (50%); colorless crystalline solid; mp 147–148 °C.

IR (film): 2955, 2920, 1670, 1526, 1483, 1468, 1447, 1423, 1141, 1022 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.26 (s, 3 H, CH_3), 3.23 (t, *J* = 6.9 Hz, 2 H, CH_2-Ar), 4.40 (t, *J* = 6.7 Hz, 2 H, CH_2-N), 7.30–7.39 (m, 3 H, ArH), 7.43–7.50 (m, 3 H, ArH), 7.56–7.60 (m, 2 H, ArH), 8.09–8.14 (m, 1 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.52, 32.07, 46.62, 118.31, 126.16, 126.67, 127.56, 128.06, 128.61, 128.83, 129.38, 133.30, 133.45, 138.45, 151.84, 198.60.

MS (EI): *m*/*z* (%) = 273.1 (100), 288.1 (53) [M$^+$].

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{19}H_{16}N_2O$: 288.12626; found: 288.12676.

1-(Toluene-4-sulfonyl)-1,2,3,7b-tetrahydro-1,1a-diazacyclopropa[*a*]naphthalene (7)

The title compound was prepared following a modified published procedure.[12] To 1,2,3,7b-tetrahydro-1,1a-diazacyclopropa[*a*]naphthalene (**1**; 110 g, 6.4 mmol) dissolved in Et_3N (2.0 mL, 20 mmol) and cooled in an ice/salt bath, was added *p*-toluenesulfonyl chloride (1.24 g, 6.4 mmol) over a period of 5 min. After stirring for 3 h, the mixture was washed with $NaHCO_3$ (5%, 200 mL) and the crude product was filtered, washed with H_2O (2 × 10 mL) and recrystallized (EtOH) to give **7**.

Yield: 0.29 g (15%); light-beige crystals; mp 152–154 °C.

IR (film): 2932, 2875, 1169, 1089, 856, 814 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.39 (s, 3 H, CH_3), 3.32 (t, *J* = 5.2 Hz, 2 H, CH_2-Ar), 3.77 (t, *J* = 5.2 Hz, 2 H, CH_2-N), 7.18–7.31 (m, 6 H, ArH), 7.40 (s, 1 H, Ar-CH-N), 7.84 (d, *J* = 8.4 Hz, 2 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.63, 37.51, 48.51, 126.87, 128.36, 129.56, 129.76, 130.07, 130.32, 130.34, 133.73, 134.30, 144.24.

MS (EI): *m*/*z* (%) = 145.1 (100), 300.1 (20) [M$^+$].

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{16}H_{16}N_2O_2S$: 300.09325; found: 300.09052.

3,7b-Dihydro-2*H*-1,1a-diazacyclopropa[*a*]naphthalene-1-carboxylic Acid 9*H*-Fluoren-9-ylmethyl Ester (8)

To compound **1** (750 mg, 5.1 mmol), dissolved in Et_2O (30 mL) and cooled in an ice-bath, was added Fmoc chloride (1.5 g, 5.5 mmol), dissolved in Et_2O (15 mL), dropwise with stirring over a period of 20 min. After stirring for 1 h, the mixture was filtered, washed with H_2O (2 × 10 mL) and recrystallized (acetone) to give **8**.

Yield: 0.95 g (51%); colorless crystals; mp. 185–187 °C.

IR (film): 3062, 3039, 1701, 1450, 1417, 1398, 1274, 1201 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.20 (t, *J* = 4.4 Hz, 2 H, CH_2-Ar), 4.17 (t, *J* = 3.6 Hz, 2 H, CH_2-N), 4.39 (t, *J* = 7.7 Hz, 1 H, Ar-CH-Ar), 4.52 (d, *J* = 7.7 Hz, 2 H, CH_2-O), 7.23–7.24 (m, 1 H, ArH), 7.25–7.29 (m, 4 H, ArH), 7.39 (t, *J* = 7.4 Hz, 2 H, ArH), 7.46–7.50 (m, 1 H, ArH), 7.59 (s, 1 H, Ar-CH-N), 7.69 (d, *J* = 7.4 Hz, 2 H, ArH), 7.76 (d, *J* = 7.4 Hz, 2 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 37.25, 46.99, 47.06, 68.95, 119.99, 125.42, 126.87, 127.17, 127.78, 129.84, 130.96, 134.23, 141.17, 141.33, 143.46, 143.81, 154.59.

MS (EI): *m*/*z* (%) = 178.1 (100), 368.1 (1) [M$^+$].

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{24}H_{20}N_2O_2$: 368.15248; found: 368.14990.

Acknowledgment

We are grateful to the Natural Sciences and Engineering Research Council of Canada (NSERC) for support of this research.

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