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Expedient Synthesis of 6-Acylindolo[1,2-*a*]quinoxalines

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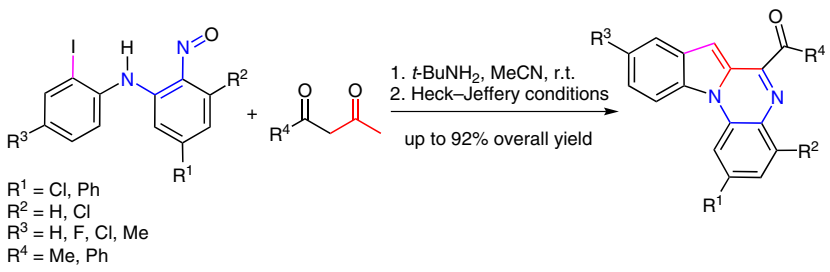

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Abstract A novel route leading to 6-acylindolo[1,2-*a*]quinoxalines involving condensation of *N*-(2-iodoaryl)-2-nitrosoanilines with β-diketones followed by Heck cyclization is described.

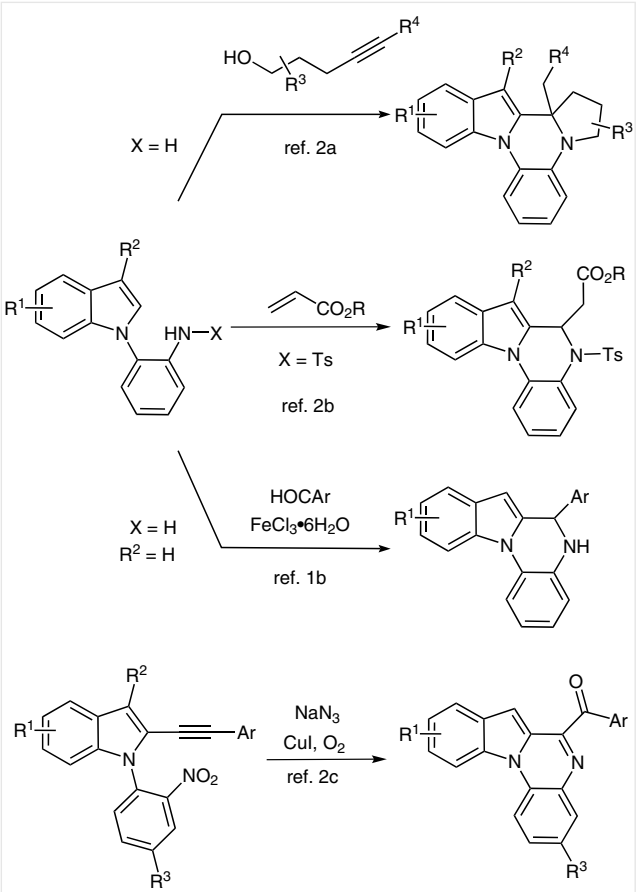
Key words cyclization, condensation, heterocycles, annulation, Heck reaction, indoles

The indolo[1,2-*a*]quinoxaline motif is present in many biologically active compounds exhibiting kinase receptor activity or antifungal activity.[1] Only a few strategies for the synthesis of such compounds have been reported (Scheme 1). All of them employ a suitably functionalized *N*-arylindole scaffold which in inter- or intramolecular mode undergoes annulation with the formation of the quinoxaline moiety.[1,2]

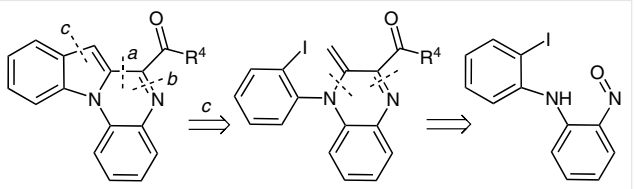
This approach requires more or less sophisticated indole derivatives as starting materials, and their synthesis from simpler substrates is not always short or easy. Particularly in the last example, a synthesis of indoloacetylene, the starting material for the synthesis of 6-aryoylindolo[1,2-a]-quinoxalines,[2c] requires at least five steps from available simple compounds. According to the literature data it is the only way to synthesize 6-aryloylindolo[1,2-*a*]quinoxalines.

An alternative approach for the synthesis of the title compounds which comprises formation of the indole five-membered ring by annulation of the suitable quinoxaline derivative can be, however, proposed (Scheme 2). The route to the latter can be founded on the basis of the results of our earlier works.

In 2007 a simple and efficient procedure for the synthesis of *N*-aryl-2-nitrosoanilines was found in our laboratory,[3] and its application in the synthesis of a variety of quinoxaline derivatives has been demonstrated.[4] We have also found lately that 2-methylene-1-aryl-1,2-dihydroquinoxalines, such as **3** in Scheme 3, can be synthesized directly from



Scheme 1 Reported strategies for the synthesis of indolo[1,2-*a*]quinoxalines



Scheme 2 Possible retrosynthetic routes to the title compounds

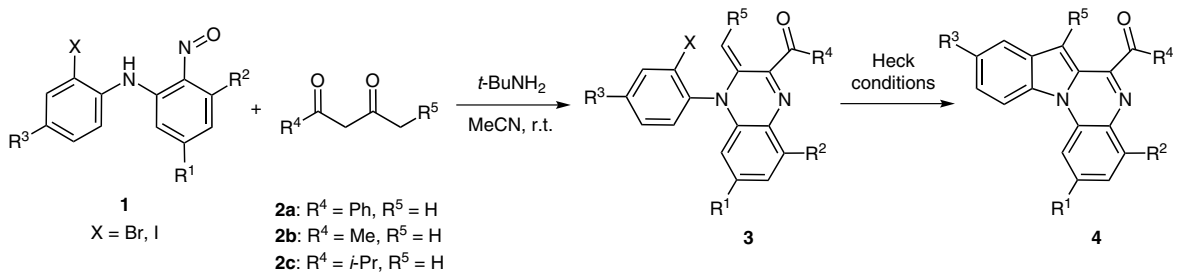
N-aryl-2-nitrosoanilines and 1,3-diketones.[5] The reaction proceeds efficiently only with nitrosoanilines bearing at least one *ortho* substituent in the *N*-aryl moiety. For the sake of this work Br or I at that position would provide the intermediate **3** suitable for subsequent Heck cyclization. The palladium-catalyzed arylation of olefins is widely used for the carbon–carbon bond formation in organic synthesis. The intramolecular variant of this reaction employing enamine or enamide double bonds has found numerous applications for the synthesis of fused heterocycles, principally indole derivatives.[6] To our knowledge the indolo[1,2-*a*]-quinoxaline scaffold has never been constructed in such a way.

The first step of the reaction sequence was optimized earlier.[5] Following on those results we decided to perform it in the *t*-$BuNH_2$/MeCN system; this turned out to be not the best regarding yields but easy for workup as it involved only volatile components.

In the test experiment *N*-(2-bromo-4-chlorophenyl)-5-chloro-2-nitrosoaniline (**1a**, R^1 = Cl, R^3 = Cl, X = Br) and benzoyl acetone (**2a**) in dry MeCN were treated with *t*-$BuNH_2$ and stirred at room temperature in a stoppered flask for four days. After that time the TLC control showed almost complete conversion of **1** and solely one product. The crude product **3aa** was heated in an ampoule in dry MeCN with addition of $Pd(OAc)_2$, Ph_3P, and Et_3N at 120 °C overnight. The orange solid of 6-benzoyl-2,9-dichloroindolo[1,2-*a*]-quinoxaline **4aa** was obtained in 48% overall yield from **1a**. The experiment was repeated starting from iodo derivative **1b** with similar final result of **4ba** = **4aa**. The product turned out to be practically insoluble at room temperature in any solvent but trifluoroacetic acid, which made its isolation and purification by column chromatography very inconvenient. On the other hand, due to its low solubility it could be easily isolated from the reaction mixture by simple filtering off the precipitate and washing it to yield practically pure product.

As the resulting yield was not fully satisfying we tried to isolate and purify the intermediate **3ba**. It was, however, moderately stable towards column chromatography and its efficient purification was very difficult. Thus, we tried to optimize the Heck-type cyclization step starting from crude **3aa** (X = Br) and **3ba** (X = I). Several attempts were made to optimize the cyclization step using $PdCl_2$, $Pd(OAc)_2$ with or without Ph_3P, with various amounts of Et_3N, Bu_3N, and DIPEA in MeCN, toluene, or DMF at 80–130 °C, varying the amount of the catalyst from 1–5%. In all cases, however, the results of the reaction were not reproducible. Finally, we tried the Jeffery protocol for the Heck reaction,[7] that is, relatively big load of $Pd(OAc)_2$ (10%), tetrabutylammonium chloride hydrate (TBACl·H_2O), and KOAc as a base in DMF. Under these conditions applied for crude **3ba**, which gave usually better results than **3aa**, the temperature of the reaction could be lowered to 60 °C, and the results became reproducible achieving 58% yield of **4ba** (Table 1, entry 1, column A).

The above conditions (method A) were then applied for the second step of the complete sequence **1** → **4** starting from several *N*-(2-iodoaryl)-2-nitrosoanilines **1b**–**g**, prepared analogously to the previously described procedures from nitroarenes and 2-iodoanilines.[3,8] The condensation step (**1** → **3**) was carried out by stirring the reagents in the *t*-$BuNH_2$/MeCN system until complete conversion was achieved (TLC monitoring), then the mixture was evaporated and directly subjected to the cyclization (**3** → **4**) in the same reaction vessel.[9] After the reaction was finished, the pure products were easily isolated by filtration as it was done in the test experiment. Contrary to the similar 6-acylindolo[1,2-*a*]quinoxalines described in the other work[2c] we found most of the products insoluble in almost any solvent. In the cases of the partially soluble products (Table 1, entries 15–17) column chromatography was used for their isolation. The analytical samples of **4** were obtained by succeeding recrystallization from DMF or hexane–EtOAc.



Scheme 3 One-pot, two-step synthesis of 6-acylindolo[1,2-*a*]quinoxalines **4**

Table 1 One-Pot, Two-Step Bisannulation of **1** (Scheme 3, X = I)[9,10]

Entry	R^1	R^2	R^3	Compd **1**	R^4	R^5	Compd **4**	Method A: total yield (%)[a]	Method B: total yield (%)[a]
1	Cl	H	Cl	**1b**	Ph	H	**4ba**	58	78
2					Me	H	**4bb**	36	81
3					Et	Me		0	0
4	Cl	H	H	**1c**	Ph	H	**4ca**	23	92
5					Me	H	**4cb**	20	–
6	Ph	H	Cl	**1d**	Ph	H	**4da**	56	–
7	Cl	H	Me	**1e**	Ph	H	**4ea**	38	82
8					Me	H	**4eb**	41	80
9					*i*-Pr	H	**4ec**	23[b]	–
10					Et	Me		0	–
11	Cl	H	F	**1f**	Ph	H	**4fa**	40	67
12					Me	H	**4fb**	25	–
13	Cl	Cl	Me	**1g**	Ph	H	**4ga**	26	62
14					Me	H	**4gb**	28	64
15	Cl	H	*t*-Bu	**1h**	Ph	H	**4ha**	74[b]	82[b]
16					Me	H	**4hb**	73[b]	–
17	H	H	H	**1i**	Ph	H	**4ia**	61[b]	72[b]

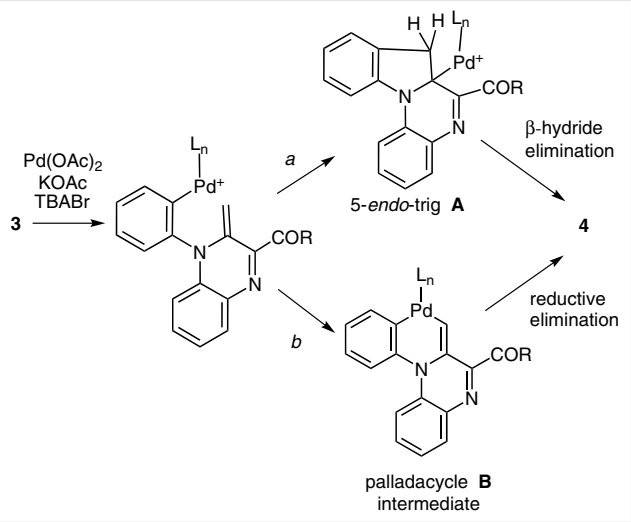
[a] Isolated yield of products separated by filtration.
[b] Isolated by column chromatography.

For relatively more stable **3**, the Heck cyclization seemed to be high-yielding. It was shown in the reaction of partially purified (of ca. 80% purity) **3ba** which, following method A, gave **4ba** in almost 80% yield, thus it appeared to be nearly quantitative. However, most of the intermediate **3**, which could not be isolated due to their instability, gave rather low yields of final products also in the one pot **1** → **4** sequence. Since it might be caused by some amount of water coming into the reaction mixture along with TBACl·H_2O, we decided to apply a more restricted procedure using anhydrous, nonhygroscopic bromide (TBABr, method B) instead. The overall yields of the two-step sequence grew up significantly up to 92% (Table 1, method B), most notably in cases when the condensation step was efficient.

The obtained results do not allow for discussing the detailed mechanistic scheme of this Heck-type cyclization. Although the generally preferred way of the five-membered ring formation in this type of reactions is the *exo*-mode cyclization, the intramolecular 5-*endo*-trig ring closure has been reported, particularly in the synthesis of indole skeleton.[6]

In fact, this process is often described as 'formal 5-*endo*-trig' cyclization as the real course of the reaction is rather obscured. In brief, possible routes of the cyclization of **3** under the Heck reaction conditions can be depicted as in Scheme 4. Parallel routes have been considered in numerous papers, although without firm conclusions.[6j–l] Path a which follows the typical course of intermolecular Heck reaction does not seem obvious. Any rotation of the intermediate **A** in order to reach *syn* conformation of the [Pd] substituent and β-hydrogen, requested for their elimination, is impossible due to the rigid ring configuration. Besides, there are no other suitable hydrogen atoms, neither at the nitrogen atom nor at the side chain/ring, which could play the role. This reasoning may vote for route B as the most likely. On the other hand, one can argue that conformation of the vicinal *cis* substituents in the pyrrolidine ring of **A** is in fact near to that of *syn* conformation in the open-chain intermediate, thus, one of the hydrogens of the methylene group can be eliminated without difficulty.

The results collected in Table 1 reveal scope and also some limitations of the reaction. The major one is its sensitivity to steric hindrance caused by the diketone substituents. In fact, only unsubstituted acetyl moieties (R^5 = H) were reactive enough to condense with the aniline nitrogen, thus to involve in the cyclization–dehydration process.[5] When both methyl groups of the diketone were substituted the reaction did not occur (Table 1, entries 3 and 10). As a result, the products collection is narrowed to those with 3-unsubstituted indole moiety. By contrast, the other published method[2c] for the synthesis of 6-acylindolo[1,2-*a*]quinoxalines (shown in Scheme 1), is apparently limited to compounds with R^4 = aryl. Moreover, the procedure reported there turned out to be tricky. In our hands it was difficult to reproduce, at least in the tested case of **4ia**. After some repetitions and modifications of the described proce-

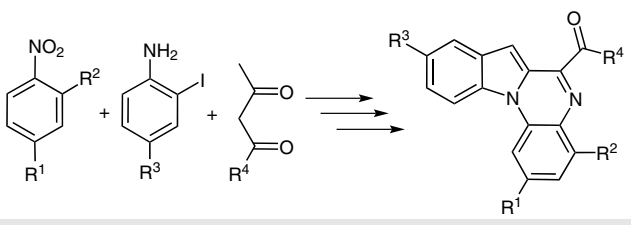


Scheme 4 Possible routes for the Heck-type cyclization

dure the yield varied from traces up to 37% [CuI (3 equiv = 300 mol%), 48 h] instead of reported 74% [CuI (5% mol), 16 h].[2c]

Taking the above into account, our method remains at the moment the best way to synthesize the title compounds. Moreover, after the reaction, most of the products could be separated without chromatography by simple filtration which is the great advantage of the protocol.

In conclusion, we have described a new, short synthesis of 6-acylindolo[1,2-*a*]quinoxalines **4**. Together with the efficient preparation of *N*-(2-iodoaryl)-2-nitrosoanilines from nitroarenes and 2-iodoanilines, the three-step method provides the title compounds in good overall yield, starting from mostly commercially available starting materials (Scheme 5).



Scheme 5 Three-step way for the synthesis of 6-acylindolo[1,2-*a*]quinoxalines from simple and available starting materials

Acknowledgment

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Supporting Information

Supporting information providing general experimental remarks and analytical data for the remaining new products, is available online at http://dx.doi.org/10.1055/s-0034-1380515.

References and Notes

(1) (a) Lin, P.-T.; Salunke, D. B.; Chen, L. H.; Sun, Ch. M. *Org. Biomol. Chem.* **2011**, *9*, 2925. (b) Xu, H.; Fan, L. L. *Eur. J. Med. Chem.* **2011**, *46*, 1919.

(2) (a) Patil, N. T.; Kavthe, R. D.; Shinde, V. S.; Sridhar, B. *J. Org. Chem.* **2010**, *75*, 3371. (b) Wang, L.; Guo, W.; Zhang, X.-X.; Xia, X.-D.; Xiao, W.-J. *Org. Lett.* **2012**, *14*, 740. (c) Samala, S.; Arigela, R. K.; Kant, R.; Kundu, B. *J. Org. Chem.* **2014**, *79*, 2491.

(3) (a) Wróbel, Z.; Kwast, A. *Synlett* **2007**, 1525. (b) Wróbel, Z.; Kwast, A. *Synthesis* **2010**, 3865.

(4) (a) Wróbel, Z.; Stachowska, K.; Kwast, A.; Gościk, A.; Królikiewicz, M.; Pawłowski, R.; Turska, I. *Helv. Chim. Acta* **2013**, *96*, 956. (b) Królikiewicz, M.; Cmoch, P.; Wróbel, Z. *Synlett* **2013**, *24*, 973. (c) Wróbel, Z.; Królikiewicz, M. *J. Heterocycl. Chem.* **2014**, *51*, 123. (d) Królikiewicz, M.; Błaziak, K.; Danikiewicz, W.; Wróbel, Z. *Synlett* **2013**, *24*, 1945.

(5) Trawczyński, A.; Wróbel, Z. *Synlett* **2014**, *25*, 2773.

(6) For representative intramolecular Heck reactions of enamines leading to indoles, see: (a) Baran, P. S.; Hafensteiner, B. D.; Ambhaikar, N. B.; Guerrero, C. A.; Gallagher, J. D. *J. Am. Chem. Soc.* **2006**, *128*, 8678. (b) Jia, J.; Zhu, J. *J. Org. Chem.* **2006**, *71*, 7826. (c) Fuwa, H.; Sasaki, M. *Org. Lett.* **2007**, *9*, 3347. (d) Ackermann, L.; Kaspar, L. T.; Gschrei, C. J. *Chem. Commun.* **2004**, 2824. (e) Kasahara, A.; Izumi, T.; Murakami, S.; Yanai, H.; Takatori, M. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 927. (f) Garcia-Cuadrado, D.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2007**, *129*, 6880. (g) Michael, J. P.; Chang, S.-F.; Wilson, C. *Tetrahedron Lett.* **1993**, 8365. (h) Barluenga, J.; Fernandez, M. A.; Aznar, F.; Valdes, C. *Chem. Eur. J.* **2005**, *11*, 2276. (i) Watanabe, T.; Arai, S.; Nishida, A. *Synlett* **2004**, 907. (j) Maruyama, J.; Yamashita, H.; Watanabe, T.; Arai, S.; Nishida, A. *Tetrahedron* **2009**, *65*, 1327. (k) Latham, E. J.; Stanforth, S. P. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2059. (l) Iida, H.; Yuasa, Y.; Kibayashi, C. *J. Org. Chem.* **1980**, *45*, 2938.

(7) (a) Jeffery, T. *Tetrahedron Lett.* **1985**, *26*, 2667. (b) Jeffery, T. *Tetrahedron* **1996**, *52*, 10113.

(8) **General Procedure for the Synthesis of *N*-(2-Iodoaryl)-2-nitrosoanilines 1a–i**
To a cooled solution of KO*t*-Bu (3,7 g, 30 mmol) in DMF (50 mL) was added dropwise at –60 °C a solution of the appropriate 2-iodoaniline (9.6 mmol) in DMF (3 mL) and the nitroarene (9.6 mmol) in DMF (8 mL). The mixture was stirred at –60 °C for 0.5 h then the temperature was raised slowly to –30 °C, and the reaction was continued for an additional 1 h, poured into sat. NH_4Cl solution (200 mL) and extracted with EtOAc. The extract was washed with H_2O, brine, and dried with Na_2SO_4. After evaporation, the crude product mixture was subjected to column chromatography (SiO_2, hexane–toluene). For analytical data, see the Supporting Information.

(9) **General Procedure for the Preparation of Compounds 4**
To a solution of the *N*-(2-iodoaryl)-2-nitrosobenzamine **1** (2 mmol) and an appropriate 1,3-diketone **2** (2 mmol) in dry MeCN (10 mL) was added *t*-$BuNH_2$ (4 mmol). The mixture was stirred at r.t. for 1–4 d (see the Supporting Information). The solvent and other volatile materials were then evaporated in

vacuo, and the crude product was used in the next step without purification. The reaction vial containing the crude product was charged with $Pd(OAc)_2$ (45 mg, 0.2 mmol), *n*-$Bu_4NCl{\cdot}H_2O$ (method A; 1050 mg, 3.5 mmol) or *n*-Bu_4NBr (method B; 1127 mg, 3.5 mmol) and KOAc (1000 mg, 10.2 mmol). The flask was purged with argon, then DMF (10 mL) was added, and argon was continuously bubbled via the reaction mixture for 20 min. The mixture was then heated under a positive argon pressure in an oil bath at 60–65 °C for 24 h. After cooling down some amount of H_2O (ca. 5 mL) was added. In the cases when a solid product precipitated it was filtered off and washed with EtOH, H_2O, and EtOAc repeatedly, to yield the product pure on TLC. Analytical sample was obtained by recrystallization from DMF. In the cases of soluble products (**4ec**,**ha**,**hb**,**ia**) the mixture was diluted with H_2O and extracted with EtOAc. The extract was thoroughly washed with H_2O, dried (Na_2SO_4), and the solvent was evaporated. The residue was separated by column chromatography (SiO_2, hexane–EtOAc). Analytical sample was recrystallized from hexane–EtOAc.

(10) **Analytical Data for the Selected 6-Acylindolo[1,2-*a*]quinoxalines 4**

Compound **4ba** (condensation time 4 d): orange crystals; mp 273–275 °C (DMF). ^{1}H NMR (500 MHz, CF_3CO_2D): δ = 7.59–7.64 (m, 2 H), 7.72 (d, *J* = 8.7 Hz, 1 H), 7.78 (s, 1 H), 7.84–7.92 (m, 2 H), 8.00–8.04 (m, 3 H), 8.10 (d, *J* = 8.7 Hz, 1 H), 8.52 (d, *J* = 9.4 Hz, 1 H), 8.74 (s, 1 H). ^{13}C NMR (125 MHz, CF_3CO_2D): δ = 115.17, 115.51, 116.38, 121.91, 123.23, 123.65, 125.72, 127.67, 129.44, 130.44, 130.62, 131.44, 132.93, 132.97, 134.90, 137.61, 140.74, 147.55, 161.34, 185.62. MS (EI): *m/z* (%) = 394 (13), 393 (18), 392 (68), 391 (36), 390 (100) [M$^{+\bullet}$], 389 (18), 364 (15), 363 (23), 362 (23), 261 (28), 357 (10), 355 (29), 327 (15), 250 (14), 177 (12). HRMS (EI): *m/z* calcd for $C_{22}H_{12}N_2OCl_2$: 390.0327; found: 390.0324.

Compound **4fa** (condensation time 1 d): orange crystals; mp 252–254 °C (DMF). ^{1}H NMR (500 MHz, CF_3CO_2D): δ = 7.54–7.94 (m, 7 H), 7.96–8.12 (m, 2 H), 8.14–8.26 (m, 1 H), 8.54–8.68 (m, 1 H), 8.77 (s, 1 H). ^{13}C NMR (125 MHz, CF_3CO_2D): δ =107.88 (d, J_{CF} = 24 Hz), 116.21, 121.92, 122.44 (d, J_{CF} = 28 Hz), 123.81, 125.91, 125.97, 127.56, 129.45, 130.83, 131.56, 131.65, 131.74, 131.78 (d, J_{CF} = 255 MHz), 133.63, 137.63, 140.71, 147.26, 185.80 (one C invisible). MS (EI): *m/z* (%) = 376 (37), 374 (100) [M$^{+\bullet}$], 373 (31), 348 (10), 347 (19), 346 (31), 345 (38), 234 (12), 105 (43), 77 (41). HRMS (EI): *m/z* calcd for $C_{22}H_{12}N_2OClF$: 374.0622; found: 374.0618.

Compound **4hb** (condensation time 1 d): orange crystals; mp 185–187 °C (hexane–EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.46 (s, 9 H), 2.79 (s, 3 H), 7.33 (dd, *J* = 8.8, 2.0 Hz, 1 H), 7.65 (dd, *J* = 9.2, 2.0 Hz, 1 H), 7.86–7.91 (m, 2 H), 7.92 (d, *J* = 2.0 Hz, 1 H), 8.17 (d, *J* = 9.2 Hz, 1 H), 8.30 (d, *J* = 2.0 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.3, 31.7, 35.0, 104.4, 113.78, 114.8, 119.0, 123.9, 124.3, 126.0, 130.4, 130.4, 132.0, 132.6, 133.2, 136.6, 146.6, 148.6, 199.4. MS (EI): *m/z* (%) = 352 (35), 351 (24), 350 (100) [M$^{+\bullet}$], 337 (30), 336 (20), 335 (87), 44 (32). HRMS (EI): *m/z* calcd for $C_{21}H_{19}N_2OCl$: 350.1186; found: 350.1190.