Mendeleev Communications

Mendeleev Commun., 2025, **35**, 648–650

C–H functionalization of highly electrophilic azolopyridines as a way to donor–acceptor conjugated indoles

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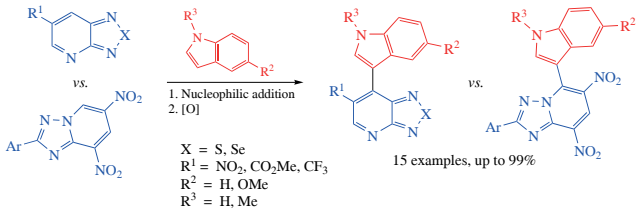
DOI: 10.71267/mencom.7793

The DDQ-assisted oxidative aromatization of 1,4-adducts of indoles to [1,2,5]chalcogenadiazolo[4,3-*b*]pyridines or 6,8-dinitro[1,2,4]triazolo[1,5-*a*]pyridines affords the corresponding new indole-type donor–acceptor compounds. Studying their photophysical properties revealed correlations between the substitution pattern and absorption spectra.

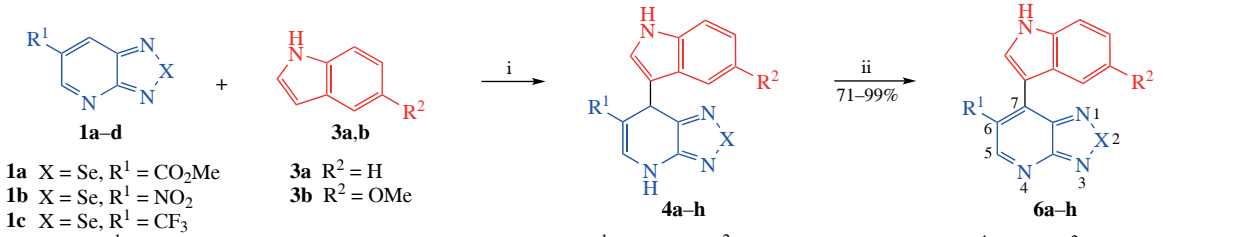


Keywords: azolopyridines, indoles, [1,2,5]thiadiazoles, [1,2,5]selenadiazoles, [1,2,4]triazolo[1,5-*a*]pyridines, C–H functionalization, nucleophilic addition, C-nucleophiles, UV-VIS spectroscopy.

Indole derivatives, of both natural and synthetic origin, exhibit a wide range of biological activity.[1–3] Indole is considered as a privileged motif in drug design and development.[4] Indole derivatives are used as fluorescent dyes,[5] energy storage (solar cells, fuel cells, batteries)[6–9] as well as photovoltaics.[10–13] Indole-type donor–acceptor molecules deserve particular attention since they are employed as components of dye-sensitized solar cells,[14] organic light emitting diodes,[15] organic field-effect transistors[16] and biological sensors.[17–20] Thus, the search for new functional indole derivatives is of significant fundamental and applied interest.

As one of the solutions for the implementation of the indicated task, we propose the use of C–H functionalization, a powerful synthetic tool that allows one to construct molecules of varying complexity and structural diversity.[21–25] We have previously reported on methods for the synthesis of highly electrophilic azolopyridines, namely, [1,2,5]thiadiazolo[4,3-*b*]pyridines[26–28] and [1,2,5]selenadiazolo[4,3-*b*]pyridines[29] of type **1** (Scheme 1) as well as 6,8-dinitro[1,2,4]triazolo[1,5-*a*]pyridines[30] of type **2** (Scheme 2) that exhibited high reactivity toward nucleophiles. These systems are capable to add a wide range of nucleophiles (including indoles **3**) giving rise to the corresponding azole-fused 1,4-dihydropyridines of type **4** and **5**, respectively. The advantage of these transformations is the mild conditions: room temperature, absence of a base or other initiators.

The development of a good method for the oxidative aromatization of adducts **4**, **5** should make it possible to access indole-type donor–acceptor molecules with potential useful properties. Herein, we chose compound **4a** as a model for optimization of oxidation conditions (see Scheme 1). It was found that the use of 30% aqueous hydrogen peroxide in CF_3COOH did not lead to the target product **6a** (Table 1, entry 1). Application of phenyliodine(III) diacetate (PIDA) as an oxidizer only caused the destruction of the starting material (entry 2). Electrochemical oxidation of **4a** at various oxidation potentials also did not afford the desired product **6a** while the starting compound decomposed during the reaction (entries 7, 8). Product **6a** with a moderate yield was isolated when ceric ammonium nitrate (CAN) was used (entry 3). Luckily, an equimolar amount of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) allows the reaction to properly proceed with almost complete conversion of **4a** (entries 4 and 5); with the application of 1.3 equiv. of DDQ 100% conversion was achieved to afford the target product in 92% yield (entry 6).



1a–d

1a X = Se, R^1 = CO_2Me
1b X = Se, R^1 = NO_2
1c X = Se, R^1 = CF_3
1d X = S, R^1 = CO_2Me

3a,b

3a R^2 = H
3b R^2 = OMe

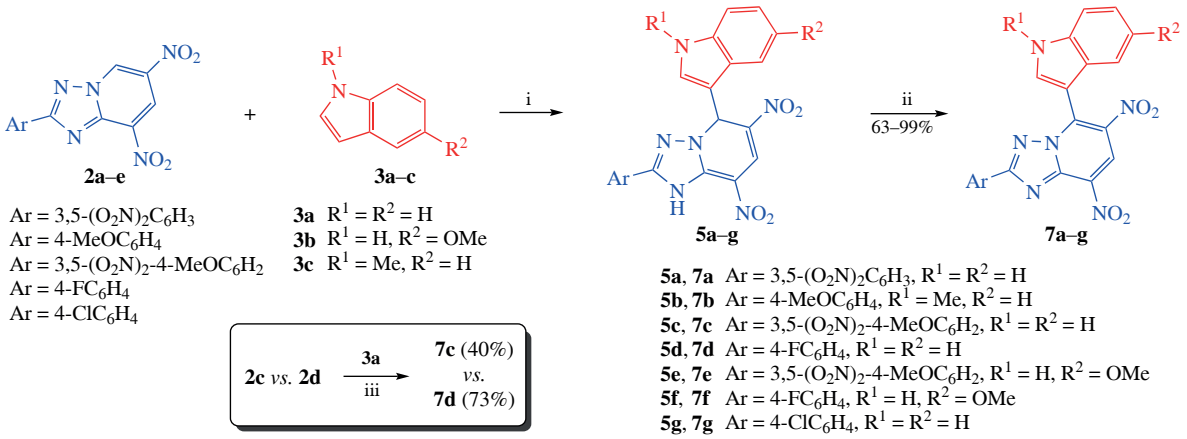
4a–h

4a, **6a** R^1 = CO_2Me, R^2 = H, X = Se
4b, **6b** R^1 = NO_2, R^2 = H, X = Se
4c, **6c** R^1 = CO_2Me, R^2 = OMe, X = Se
4d, **6d** R^1 = NO_2, R^2 = OMe, X = Se

6a–h

4e, **6e** R^1 = CF_3, R^2 = H, X = Se
4f, **6f** R^1 = CF_3, R^2 = OMe, X = Se
4g, **6g** R^1 = CO_2Me, R^2 = H, X = S
4h, **6h** R^1 = CO_2Me, R^2 = OMe, X = S

Scheme 1 *Reagents and conditions*: i, MeCN, room temperature; ii, DDQ, MeOH, room temperature, 1–24 h (optimum; for optimization with **4a**, see Table 1).



Scheme 2 *Reagents and conditions*: i, MeCN, room temperature; ii, DDQ, MeOH, room temperature, 1–24 h; iii, MeCN, room temperature, 24 h, then DDQ, room temperature, 24 h.

Table 1 Optimization of oxidation of 1,4-dihydro derivative **4a** into hetarene **6a**.

Entry	Oxidizer	Solvent	*T*/°C	*t*/h	Yield (%)
1	H_2O_2 (30%)	CF_3COOH	20	24	0
2	PIDA (1.25 equiv.)	AcOH	100	1.5	0
3	CAN (2 equiv.)	H_2O/MeCN	20	24	33
4	DDQ (1 equiv.)	MeOH	20	2	90[a]
5	DDQ (1 equiv.)	MeOH	20	24	90[a]
6	DDQ (1.3 equiv.)	MeOH	20	2	92
7	Electrochemical[b] oxidation (1600 mV)	MeCN	25	0.2	0
8	Electrochemical[b] oxidation (900 mV)	MeCN	25	0.2	0

[a] NMR conversion. [b] Pt working electrode, 0.1 M $NaClO_4$ in MeCN.

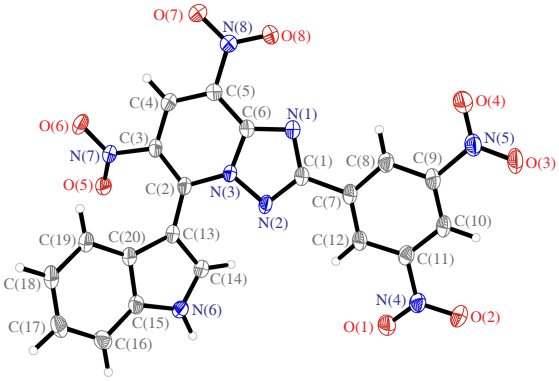


Figure 1 General view of the molecule **7a** in crystal in thermal ellipsoid representation (p = 50%).

The optimized conditions were extended to dihydropyridines **4b**–**h** annulated with selena- and thiadiazole rings. It was found that 1,4-adducts **4** of azolopyridine with various indoles underwent oxidative aromatization with the formation of target indole derivatives **6** in high yields (see Scheme 1). The structure of the synthesized compounds **6** was established based on spectral methods (^{1}H and ^{13}C NMR and HRMS). Compared to precursors **4**, in spectra of **6** two characteristic resonances for protons C^{7}H and N^{4}H of the initial adducts **4** in the regions of 4.5–6.0 and 12–13 ppm, respectively, disappeared. Moreover, resonance for the C^{5}H proton shifted from 8.3–8.4 (compounds **4**) to 9.2–9.4 ppm (compounds **6**).

Another type of highly electrophilic azolopyridines prone to the formation of adducts with nucleophiles are 2-R-6,8-dinitro[1,2,4]-triazolo[1,5-*a*]pyridines **2a**–**e** (see Scheme 2). These heterocycles under mild conditions form stable products **5** of nucleophilic addition of indoles **3** to the pyridine ring in yields up to 96%.[30] In this work, adducts **5** were involved in the oxidative aromatization reaction under the optimized conditions, which allowed for the preparation of new donor–acceptor indole-containing heterocycles **7a**–**g** in high yields. Their structure was established based on NMR spectroscopy and HRMS. In addition, the structure of solvate **7a**·(Me_2CO) was confirmed by X-ray diffraction (Figure 1).†

For 6,8-dinitro[1,2,4]triazolo[1,5-*a*]pyridines **2c**,**d**, the possibility of direct C–H functionalization under one-pot conditions was demonstrated. In fact, compounds **2c**,**d** were reacted with indole **3a** under standard conditions (see Scheme 2). After complete conversion (TLC monitoring) of the starting compounds **2**, 1.3 equiv. of DDQ was added to the reaction mixture, and finally products **7c**,**d** were obtained in reasonable yields.

It is known that donor–acceptor conjugated indoles have strong absorbance in the UV-VIS region.[31,32] We have studied photophysical properties of some synthesized compounds containing various substituents and their precursors (compounds **1a**, **1c**, **1d**, **2c**) for comparison. It was found that for all UV-VIS spectra of indole-containing donor–acceptor heterocycles in EtOH solution the absorption maxima are shifted towards visible region (400–550 nm). The replacement of CF_3-group with the CO_2Me-group in pyridine ring caused absorption growth and slight red shift (8 nm). The installation of OMe-group in indole ring also leads to significant increase in absorption and slight red shift (7 nm). On the other hand, changing a sulfur atom to selenium in a five-membered ring results in decrease in absorption and significant red shift (25 nm). It was concluded

† *Crystal data for* **7a**·(Me_2CO). $C_{23}H_{16}N_8O_9$ (M = 548.44), monoclinic, space group $P2_1/n$, a = 12.7454(3), b = 6.87168(18) and c = 27.0983(5) Å, β = 93.1454(19)°, V = 2369.76(9) Å^3, Z = 4, d_{calc} = 1.537 g cm^{-3}, $F(000)$ = 1128, T = 100 K, μ(CuKα) = 1.046 mm^{-1}, θ_{min} = 3.267°, θ_{max} = 81.693°, 27515 reflections measured, 5129 independent reflections (R_{int} = 0.0342), R_1 = 0.0447, wR_2 = 0.1204 for 4346 reflections with $I > 2\sigma(I)$; R_1 = 0.0527, wR_2 = 0.1266 for all data, 391 parameters and 52 restraints, GOF = 1.065, ρ_{max}/ρ_{min} = = 0.220/–0.298 ē Å^{-3}. The data were collected at 100 K on a four-circle Rigaku XtaLAB Synergy-S diffractometer equipped with a HyPix6000HE area-detector (kappa geometry, shutterless ω-scan technique, 0.5° step), using monochromatized CuKα-radiation (λ = 1.54184 Å). The intensity data were integrated and analytically corrected by the CrysAlisPro program (ver. 1.171.44.94a). The structure was solved by dual methods using SHELXT-2014/5 and refined by the full-matrix least-squares minimization method on F^2 using SHELXL-2018/3 in the OLEX2 program.

CCDC 2443088 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* https://www.ccdc.cam.ac.uk.

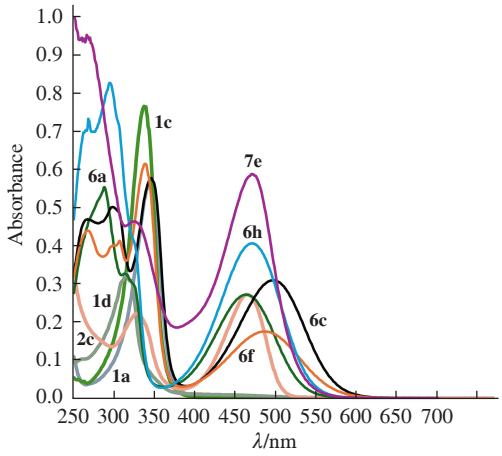


Figure 2 UV-VIS spectra of compounds **1a**, **1c**, **1d**, **2c**, **6a**, **6c**, **6f**, **6h**, **7e**. UV-VIS absorption spectra were recorded in EtOH (1×10^{-4} M) in standard $10\times10\times45$ mm quartz cuvettes on a Cary 60 UV-Vis spectrophotometer.

that substituents in indole ring, pyridine ring and also annulated five-membered ring in the corresponding molecules can be independently changed to predictably fine-tune absorption spectra of these compounds (Figure 2).

In summary, a method for direct C–H functionalization of a number of highly electrophilic azolopyridines was developed. It allows one to create the indole-containing donor–acceptor heterocycles with potent practically useful properties. Photophysical properties of synthesized heterocycles were assessed.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.7793.

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Received: 7th April 2025; Com. 25/7793