Synthesis and Photoluminescent Properties of 2-(3-Carboxymethylindazol-1-yl)anilines

A. A. Shetnev\textsuperscript{a,*}, V. A. Panova\textsuperscript{a}, P. M. Kutuzova\textsuperscript{b}, M. V. Tarasenko\textsuperscript{a}, M. V. Zhmykhova\textsuperscript{c}, S. V. Baykov\textsuperscript{c}, and S. I. Filimonov\textsuperscript{d}

\textsuperscript{a} K.D. Ushinsky Yaroslavl State Pedagogical University, Yaroslavl, 150000 Russia  
\textsuperscript{b} P.G. Demidov Yaroslavl State University, Yaroslavl, 150003 Russia  
\textsuperscript{c} Institute of Chemistry, St. Petersburg State University, 198504 Russia  
\textsuperscript{d} Yaroslavl State Technical University, Yaroslavl, 150023 Russia  
\textsuperscript{*}e-mail: a.shetnev@yspu.org

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Abstract—A two-stage method for the preparation of 2-(3-carboxymethylindazol-1-yl)anilines using the N-arylation reaction of 3-carboxymethylindazoles with o-nitrohaloarenes and subsequent reduction of nitro-containing intermediates with tin(II) chloride was developed. The experimental results showed that the use of the synthesized compounds as fluorophores in the visible region of the spectrum is promising.

Keywords: heterocycles, N-arylation, reduction, photoluminescence

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\textit{N}-Substituted indazole derivatives have attracted considerable interest of researchers for a long time. They have been found among the alkaloids of black cumin [1, 2]. These compounds are used as antiemetics (granisetron, tropisetron) [3], anticancer drugs (niraparib, pazopanib) [4], anti-inflammatory agents (benzadac, benzydamine) [5, 6]. Biological activity of \textit{N}-substituted indazole derivatives have been reviewed in detail in [7–9].

In addition, a wide range of useful photophysical properties of \textit{N}-substituted indazoles should be noted. They are used in lighting technology, for light-emitting devices production, as well as in study of biochemical processes in living systems using fluorescent trackers [10–13].

Due to great practical importance of \textit{N}-arylated indazoles, over the past two decades methods for their design have been studied in detail and developed using both base and transition metal catalysis [14–19]. \textit{N}-Arylation reactions of 1\textit{H}-indazoles can proceed at both nitrogen atoms [14–16]. However, as a rule, the reaction proceeds regioselectively at the N\textsubscript{1} atom of the indazole ring [17–19]. At the same time, despite a significant data on this topic, only a single publication is devoted to the reaction of \textit{N}-arylation of indazole-3-carboxylates [20].

Earlier, we have found unusual regioselectivity in the \textit{N}-arylation reaction of pyrazole-3-carboxylates when using \textit{O}-nitro-substituted haloarenes [21]. Under the reaction conditions, a predominant nucleophilic substitution at the N\textsubscript{2} atom of the pyrazole ring was observed. Subsequent reduction of the nitro derivative with tin(II) chloride and other reagents [22] in all cases gave \textit{N}-hydroxyquinoxalines as the products of reductive cyclization. The obtained compounds showed the properties of potent and selective inhibitors of human monoamine oxidase [23]. Herein, we attempted to apply this approach to the synthesis of fused systems containing indazole and quinoxaline rings.

To accomplish this task, methyl indazole-3-carboxylate was reacted with a number of electron-deficient \textit{O}-nitrohaloarenes in absolute DMF in the presence of anhydrous potassium carbonate as a deprotonating agent (Scheme 1). However, it was found that the \textit{N}-arylation of indazole-3-carboxylates proceeds at the N\textsubscript{1} atom of the indazole ring to give the corresponding \textit{N}-aryl derivatives \textbf{3a–3h}.
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The obtained series of nitro derivatives 3a–3h was converted into the corresponding amines 4a–4h using the previously developed method for the reduction of N-nitroarylpyrazole-3-carboxylates with tin(II) chloride in ethanol in the presence of hydrochloric acid [21] (Scheme 2). Compounds 4a–4h were obtained in yields of 58–88%.

A series of heterocyclic amines 4a–4h containing various functional groups was investigated for the presence of photoluminescence in the solid state at room temperature using a Fluorolog 3 fluorescence spectrometer. The found emission spectral maxima (\(\lambda_{\text{em}}^{\text{max}}\)), the excited state lifetime (\(\tau\)) and the chromaticity diagram parameters (CIE [\(x; y\)]) are given in Table 1. The emission spectra recorded upon irradiation with light \(\lambda_{\text{em}}\) 450 nm are shown in Fig. 1.

The obtained data showed that compounds 4a–4h possess strong yellow-green photoluminescence in the solid state. The emission spectra are mainly represented by a wide band. Luminescence maxima are in the range

with yields up to 97%. Despite attempts to vary the reaction conditions (temperature, solvent), the use of deprotonating agents of different nature (potassium tert-butoxide, triethylamine, 4-\(N,N\)-dimethylaminopyridine) failed to detect the formation of isomeric compounds 2.

\[\text{Scheme 1.}\]

\[
\begin{array}{c}
\text{R = H, X = C (a, 93%); R = CN, X = C (b, 93%); R = 4-NO}_2, X = C (c, 97%); R = 4-COOEt, X = C (d, 82%); R = 4-CF}_3, X = C (e, 90%); R = 4-
\end{array}
\]

\[\text{Scheme 2.}\]

\[
\begin{array}{c}
\text{R = H, X = C (a, 84%); R = CN, X = C (b, 59%); R = 4-NH}_2, X = C (c, 61%); R = 4-COOEt, X = C (d, 88%); R = 4-CF}_3, X = C (e, 58%); R = 4-
\end{array}
\]
from 487 to 540 nm. The largest shift of the maximum occurs when hydrogen (4a) is replaced by a nitrile group (4e) at position 4. The lifetimes of the excited state for compounds 4b, 4d–4h do not differ from each other and are in the range from 0.4 to 4.4 nsec. A sharp difference is observed for compounds 4a and 4c, for which the excited state lifetime is 653 and 518 ns, respectively. Such a sharp increase in the excited state lifetime may be explained by more dense molecular packing due to the strong intermolecular dipole-dipole interaction [24, 25].

In conclusion, a series of new 2-(3-carboxymethyl-indazol-1-yl)anilines was synthesized by a two-step method, including N-arylation of 3-carboxymethylindazoles with o-nitrohaloarenes followed by the reduction of nitro-containing intermediates. The proposed approach provides the overall yield of the target amino derivatives in 62–78% range. The obtained compounds are of interest as organic fluorophores with emission in the yellow-green spectral region.

### EXPERIMENTAL

Organic, inorganic reagents and solvents were obtained from commercial sources (Aldrich, Vekton, Ekros) and were used without additional purification. The reaction progress was monitored by thin layer chromatography (TLC) on silica gel on Silufol UV aluminum plates eluting with a mixture of ethyl acetate and petroleum ether (1 : 1). NMR spectra were recorded on a Varian XL-400 instrument (400 MHz) in DMSO-d$_6$ solutions at 25°C. Melting points were determined on a Büchi M-560 melting point and boiling point apparatus. High-resolution mass spectra were recorded on a Bruker Daltonics MicrOTOF-II instrument, the ionization method was electrospray ionisation (ESI), the temperature of the ionization source was 180°C, the eluent was methanol. Photoluminescence spectra, excited state lifetimes were obtained on a Fluorolog 3 fluorescence spectrometer (Horiba Jobin Yvon).

**General procedure for the synthesis of methyl 1-(2-nitroaryl)-1H-indazole-3-carboxylate 3a.** To a solution of 1H-indazole-3-carboxylate (1 mmol) in DMF (1.5 mL) was added the corresponding O-nitrohaloarene (1 mmol) and K$_2$CO$_3$ (1.3 mmol). The reaction mixture was stirred at 70–100°C for 12 h. After the reaction completed, the resulting suspension was diluted with 7 mL of distilled water, the precipitate was filtered off and washed with 2 mL of water. The resulting product was purified by recrystallization from an ethanol–DMF mixture.

### Table 1. Photoluminescent characteristics of compounds 4a–4h

| Comp. no. | $\lambda_{\text{em}}^\text{max}$, nm | $\tau$, ns | CIE [x;y] |
|-----------|-----------------|--------|----------|
| 4a        | 540             | 653    | 0.40; 0.58 |
| 4b        | 487, 520        | 0.4    | 0.35; 0.62 |
| 4c        | 535             | 518    | 0.41; 0.56 |
| 4s        | 515             | 4.4    | 0.37; 0.60 |
| 4e        | 530             | 3.9    | 0.39; 0.59 |
| 4f        | 515             | 4.2    | 0.38; 0.60 |
| 4g        | 512             | 3.3    | 0.35; 0.62 |
| 4h        | 530             | 2.8    | 0.43; 0.56 |

**Methyl 1-(2-nitrophenyl)-1H-indazole-3-carboxylate (3a).** Yield 0.276 g (93%), pale yellow crystals, mp 163–165°C. $^1$H NMR spectrum, δ, ppm: 3.97 s (3H, CH$_3$), 7.49 d. t (1H, Ar, J 8.4, 2.0 Hz), 7.61 d. d (2H, Ar, J 4.0, 2.0 Hz), 7.87 d. t (1H, Ar, J 8.8, 2.0 Hz), 7.93–8.07 m (2H, Ar), 8.22 d (1H, Ar, J 8.4 Hz), 8.27 d (1H, Ar, J 8.4 Hz). $^{13}$C NMR spectrum, δC, ppm: 52.06, 110.43, 121.68, 123.01, 124.26, 125.92, 128.50, 128.55, 130.64, 130.70, 134.61, 137.18, 140.78, 145.04, 161.81. Mass spectrum, m/z: 320.0643 [M + Na]$^+$ (calcd for C$_{15}$H$_{11}$N$_3$NaO$_4$: 320.0642).

**Methyl 1-(4-cyano-2-nitrophenyl)-1H-indazole-3-carboxylate (3b).** Yield 0.299 g (93%), pale yellow powder, mp 230–232°C. $^1$H NMR spectrum, δ, ppm: 3.97 s (3H, CH$_3$), 7.53 s (1H, Ar), 7.66 s (1H, Ar), 7.76 s (1H, Ar), 8.23 d (1H, Ar, J 8.0 Hz), 8.31 d (1H, Ar, J 8.4 Hz), 8.49 d (1H, Ar, J 8.4 Hz), 8.87 s (1H, Ar). $^{13}$C NMR spectrum, δC, ppm:

![Fig. 1. Photoluminescence spectra of compounds 4a–4h.](image-url)
Methyl 1-(2,4-dinitrophenyl)-1H-indazole-3-carboxylate (3c). Yield 0.322 g (82%), yellow powder, mp 186–189°C. 1H NMR spectrum, δ ppm: 3.89 s (3H, CH3), 7.54 t (2H, Ar, J 7.6 Hz), 7.68 t (1H, Ar, J 7.6 Hz), 7.78 d (1H, Ar, J 8.0 Hz), 8.24 d (1H, Ar, J 7.6 Hz), 8.37 d (1H, Ar, J 8.8 Hz), 8.75 d (1H, Ar, J 8.4 Hz), 9.00 s (1H, Ar). 13C NMR spectrum, δ ppm: 52.28, 110.66, 121.80, 122.00, 123.34, 124.85, 128.85, 129.08, 135.22, 138.57, 140.44, 144.26, 146.65, 161.49. Mass spectrum, m/z: 365.0493 [M + Na]+ (calcd for C16H10N3NaO4: 365.0493).

Methyl 1-[2-amino-4-cyanophenyl]-1H-indazole-3-carboxylate (3f). Yield 0.229 g (77%), pale yellow crystals, mp 159–162°C. 1H NMR spectrum, δ ppm: 3.96 s (3H, CH3), 7.54 t (1H, Ar, J 7.6 Hz), 7.65 t (1H, Ar, J 7.6 Hz), 7.76 d (1H, Ar, J 8.0 Hz), 8.24 d (1H, Ar, J 8.0 Hz), 8.32 d (1H, Ar, J 8.4 Hz), 8.39 d (1H, Ar, J 8.4 Hz), 8.47 d (1H, Ar, J 8.4 Hz), 8.65 s (1H, Ar). 13C NMR spectrum, δ ppm: 52.37, 117.90, 121.80, 123.53, 125.25, 137.53, 138.74, 139.08, 139.64, 141.44, 161.32. Mass spectrum, m/z: 398.9705 [M + Na]+ (calcd for C14H9BrN4NaO4: 398.9699).

General procedure for the synthesis of methyl 1-(2-aminoaryl)-1H-indazole-3-carboxylates 4a–4h. To a mixture of SnCl2 (3.5 mmol) in conc. HCl (2 mL) and ethanol (2 mL) was added the corresponding 1-(2-aminoaryl)-1H-indazole-3-carboxylate (3g). Yield 0.312 g (83%), orange crystals, mp 159–162°C. 1H NMR spectrum, δ ppm: 3.96 s (3H, CH3), 7.54 t (1H, Ar, J 7.2 Hz), 7.69 t (1H, Ar, J 8.0 Hz), 8.21 d (1H, Ar, J 8.4 Hz), 8.25 d (1H, Ar, J 8.8 Hz), 9.02 s (1H, Ar), 9.07 s (1H, Ar). 13C NMR spectrum, δ ppm: 52.37, 117.90, 121.80, 123.53, 125.25, 137.53, 138.74, 139.08, 139.64, 141.44, 161.32. Mass spectrum, m/z: 398.9705 [M + Na]+ (calcd for C14H9BrN4NaO4: 398.9699).
δC, ppm: 51.91, 111.14, 112.44, 118.67, 118.83, 119.27, 121.52, 123.18, 123.77, 125.89, 127.78, 128.86, 136.55, 140.73, 145.07, 162.20. Mass spectrum, m/z: 315.0856 [M + Na]+ (calcd for C16H12N4NaO2: 315.0852).

Methyl 1-(2,4-diaminophenyl)-1H-indazole-3-carboxylate (4c). Yield 0.173 g (61%), white powder, mp 176–180°C. 1H NMR spectrum, δ, ppm: 3.97 s (3H, CH3), 4.67 s (2H, NH2), 7.28 d (1H, Ar, J 7.2 Hz), 7.53 t (1H, Ar, J 7.6 Hz), 7.61 s (1H, Ar), 8.20 d (1H, Ar, J 8.0 Hz). 13C NMR spectrum, δC, ppm: 2.98 s (4H, Alk), 3.68 s (4H, Alk), 3.98 s (3H, CH3), 5.75 s (2H, NH2), 7.00 d (1H, Ar, J 8.0 Hz), 7.35 s (1H, Ar), 7.41–7.57 m (4H, Ar), 8.21 d (1H, Ar, J 7.6 Hz). 13C NMR spectrum, δC, ppm: 45.93, 51.86, 65.35, 111.25, 114.21, 115.00, 121.47, 123.15, 123.73, 125.65, 127.70, 128.52, 135.70, 136.47, 140.78, 145.02, 162.21. Mass spectrum, m/z: 349.0735 [M + Na]+ (calcd for C19H14F3N3O2: 349.0734).

Methyl 1-(3-aminopyridin-2-yl)-1H-indazole-3-carboxylate (4g). Yield 0.183 g (68%), beige powder, mp 145–149°C. 1H NMR spectrum, δ, ppm: 3.99 s (3H, CH3), 5.96 s (2H, NH2), 7.20–7.31 m (1H, Ar), 7.40 d (1H, Ar, J 8.0 Hz), 7.46 t (1H, Ar, J 7.2 Hz), 7.57 t (1H, Ar, J 7.6 Hz), 7.86 d (1H, Ar, J 4.4, 2.0 Hz), 8.10 d (1H, Ar, J 8.4 Hz), 8.21 d (1H, Ar, J 8.0 Hz). 13C NMR spectrum, δC, ppm: 51.97, 113.86, 121.19, 122.80, 124.17, 124.24, 124.74, 127.81, 135.16, 136.21, 137.91, 140.29, 162.01. Mass spectrum, m/z: 291.0854 [M + Na]+ (calcd for C14H11BrN3NaO2: 291.0852).

Methyl 1-(3-amino-5-bromopyridin-2-yl)-1H-indazole-3-carboxylate (4h). Yield 0.264 g (76%), yellow powder, mp 176–180°C. 1H NMR spectrum, δ, ppm: 3.99 s (3H, CH3), 6.23 s (2H, NH2), 7.47 t (1H, Ar, J 7.6 Hz), 7.54–7.65 m (2H, Ar), 7.92 s (1H, Ar), 8.09 d (1H, Ar, J 8.0 Hz), 8.21 d (1H, Ar, J 7.6 Hz). 13C NMR spectrum, δC, ppm: 52.01, 113.76, 119.06, 121.26, 122.80, 124.32, 125.85, 128.00, 134.74, 135.04, 135.55, 139.34, 140.23, 161.87. Mass spectrum, m/z: 368.9960 [M + Na]+ (calcd for C14H11BrN3NaO2: 368.9958).

AUTHOR INFORMATION

A.A. Shetnev, ORCID: http://orcid.org/0000-0002-4389-461X
V.A. Panova, ORCID: http://orcid.org/0000-0002-4775-5326
M.V. Tarasenko, ORCID: http://orcid.org/0000-0001-5720-2664
M.V. Zhmykhova, ORCID: http://orcid.org/0000-0001-9716-1203
S.V. Baykov, ORCID: http://orcid.org/0000-0002-8912-5816
S.I. Filimonov, ORCID: http://orcid.org/0000-0001-9903-4099

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CONFLICT OF INTEREST

No conflict of interest was declared by the authors.
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