The First Indazolimine-Arylazobenzonitrile Rearrangement

Kamal M. El-Shaieb[a], Ludger Ernst[b], and Rainer Kerssebaum[c]

[a] Chemistry Department, Faculty of Science, Minia University, El-Minia, Egypt
[b] Chemistry Department, NMR Laboratory, Technische Universität Braunschweig, Hagenring 30, 38106 Braunschweig, Germany
[c] Bruker BioSpin GmbH, Silberstreifen 4, 76287 Rheinstetten, Germany

Reprint requests to Dr. Kamal M. El-Shaieb. Fax: +2-086-2363011. E-mail: kmelshaieb@yahoo.com

Z. Naturforsch. **2012**, *67b,* 238 – 242; received January 28, 2012

A series of 2-arylazobenzonitriles (**5a – f**) have been obtained through a novel indazolimine-arylazobenzonitrile rearrangement. The products **5a – f** were fully characterized and their structure elucidated on the basis of spectroscopic and analytical data. The mechanism of formation of **5a – f** is discussed.

Key words: Aminobenzamidine, Chlorination, Indazolimine, Arylazobenzonitrile, Rearrangement

Introduction

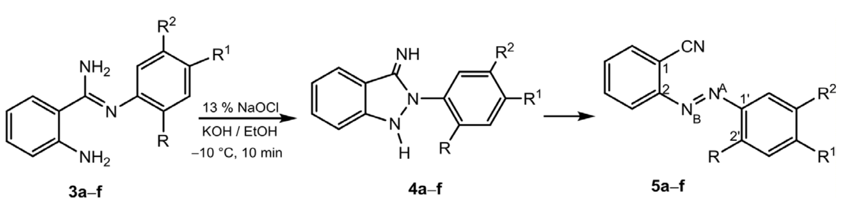
Indazole, also called benzopyrazole or isoindazone, is a heterocyclic aromatic organic compound that is rare in Nature. Indazole derivatives were found to exhibit many biological activities including anti-inflammatory [1], antifungal [2], antimicrobial [3], and antitumor activities [4]. Some indazole analogs were also used as novel antiplatelet agents [5]. The synthesis of indazole derivatives from the reaction of diazoalkanes with some benzo- and naphthoquinones has been investigated [6 – 9]. Similarly, the analogous Michael addition of *N*-2 substituted hydrazones, which can be regarded as azaenamines, to 1,4-naphthoquinone, followed by ring closure, gave indazole derivatives [10]. Much less attention has been given to the synthesis of indazole derivatives from the reaction of thiosemicarbazides with benzoquinones [11 – 13]. In this study 2-amino-*N*′-arylbenzamidines **3a – f** were prepared in good yields by treatment of 2-aminobenzonitrile (**1**) with aniline derivatives **2a – f** in the presence of aluminum chloride as a catalyst (Scheme 1) and were fully characterized [14].

a: R = R^1 = R^2 = H; **b**: R = R^2 = H, R^1 = Br; **c**: R = R^2 = H, R^1 = Cl;
d: R = R^2 = H, R^1 = CH_3; **e**: R^1 = H, R = R^2 = CH_3;
f: R^2 = H, R = R^1 = CH_3

Scheme 1. Synthesis of 2-amino-*N*′-arylbenzamidines **3a–f**.

Results and Discussion

We have shown earlier that 4,15-diaminoparacyclophane is oxidized by NaOCl in EtOH to give 4,15-azoparacyclophane [15], and that 2-aminothiophenol is transformed into 2-[(2-aminophenyl)-dithio]aniline by the same oxidant [16]. Therefore, we felt encouraged to apply this reaction to 2-amino-*N*′-arylbenzamidines **3a – f**, aiming to obtain indazole derivatives **4a – f**. However, the products which we isolated from this experiment were identified as 2-arylazobenzonitriles **5a – f**, (Scheme 2). A compound having structure **4a** (*E*/*Z* isomers at the imine nitrogen) has been described in the literature, but its spectroscopic data are different from those of our product **5a** [17].



Scheme 2. Reaction of 2-amino-*N*′-arylbenzamidines **3a – f** with NaOCl.

The synthesis of indazole derivatives has been described several times in the literature, but a rearrangement of indazolimines to 2-arylazobenzonitriles has not been known as yet.

Products **5a–f** were fully characterized and their structures secured on the basis of spectroscopic and analytical data. Detailed spectroscopic data are given in the Experimental Section, and only the salient features are discussed here. Compounds **5a–f** did not show any characteristic signals in the ^{1}H NMR spectrum except for those of the aromatic protons with chemical shifts between δ = 7 and 8 ppm. Moreover, the ^{1}H NMR spectrum showed the absence of the broad signals which correspond to the exchangeable protons (-NH_2) of the starting materials. The ^{13}C NMR spectra displayed signals close to $\delta \approx 116.7$ ppm for -C≡N groups whose presence was confirmed by IR spectroscopy (ν = 2219–2231 cm^{-1}). The ^{1}H and ^{13}C NMR spectra of **5c** were fully assigned by 1D and 2D NMR methods (DEPT-135, H-H NOESY, H-C HSQC, H-C HMBC). Assignments of the ^{13}C NMR spectra of **5a**, **5b** and **5d** were derived from those of **5c** by appropriate chemical shift increment calculations. The presence of the azo group, which in general is difficult to prove by IR spectroscopy [18], was confirmed by ^{1}H-^{15}N HMBC NMR experiments on **5c** (Fig. 1). The ^{15}N chemical shifts of the azo group were found to be 136.9 ppm (N_A, for atom labeling see Scheme 2) and 118.3 ppm (N_B). N_B showed crosspeaks with protons 2′,6′-H ($^4J_{NH}$), 3-H ($^3J_{NH}$) and 6-H ($^4J_{NH}$) (decreasing intensity in this order) and N_A with 2′,6′-H ($^3J_{NH}$, very strong). The nitrogen chemical shift of azobenzene has been reported to be 146.5 and 129.0 ppm for the (*Z*)- and (*E*)-isomer, respectively [19]. This indicates that **5c** is the (*E*)-isomer: the sum of the absolute shift differences, $\Sigma|\Delta\delta|$, relative to (*E*)-azobenzene is 18.6 ppm whereas it is much larger, 37.8 ppm, with respect to (*Z*)-azobenzene. As the ^{15}N chemical shifts of azo groups are very characteristic with no other functional groups absorbing in the same range, the NMR experiments give definite proof of the presence of the azo group in compounds **5a–f**. The nitrogen nucleus of the nitrile group in **5c** gave a weak crosspeak ($^4J_{\mathrm{NH}}$) with 6-H, the proton *ortho* to -C≡N ($\delta_N = -151.3$ ppm, $\delta_H = 7.86$ ppm). This nitrogen chemical shift is atypical for aromatic nitriles, which usually occur between $\delta = -112$ and -125 ppm [20]. However, only very few ^{15}N shifts of *ortho*-substituted benzonitriles have been reported ($\delta = -107.4$ to -116.4 ppm) [21] and none of the substituents in these compounds had characteristics comparable to an azo group. As we have measured the ^{1}H-^{15}N HMBC spectrum using different chemical shift ranges we are sure that we observed the true chemical shifts and not those of aliased crosspeaks. Both mass spectra and elemental analyses confirm the molecular formulae of **5a–f**.

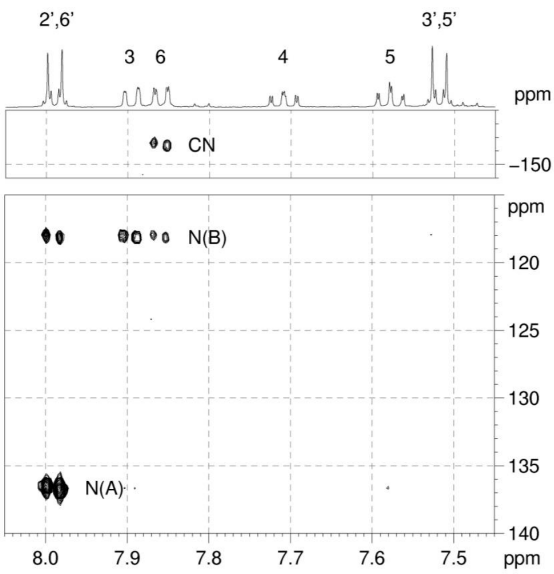
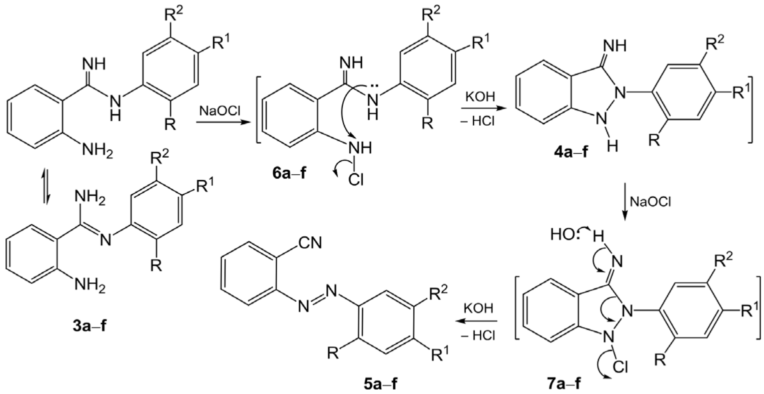


Fig. 1. Details of the 2D ^{1}H-^{15}N HMBC NMR spectrum of **5c** (in $CDCl_3$ at 500/51 MHz). The total ^{15}N chemical shift range acquired was +170 to −230 ppm relative to external nitromethane (δ_N = 0 ppm).

To explain the formation of products **5a–f**, we tentatively propose that the reaction begins with the chlorination of the aromatic amino group of reactants **3a–f** by NaOCl to yield the intermediates **6a–f**. These lose HCl under the influence of KOH to yield indazole intermediates **4a–f**. Chlorination of the indazole -NH group in **4a–f** by NaOCl furnishes chloro-indazole derivatives **7a–f**. The final products, arylazobenzonitriles **5a–f**, are obtained by the loss of HCl from intermediates **7a–f** (Scheme 3). Thus, the simple sequence of chlorination, HCl elimination, chlorination, HCl elimination can account for the observed rearrangement but this still has to be verified by suitable experiments.

Conclusion

In summary, we report a new procedure for the one-pot preparation of 2-aryl-azobenzonitriles from commercial or easily prepared reagents. It entails the unprecedented rearrangement of an indazolimine to a



Scheme 3. A proposed mechanism for the formation of **5a – f**.

2-arylazobenzonitrile under the influence of hypochlorite and alkali.

Experimental Section

General. All reagents were purchased from Alfa Aesar or Fluka and were used without further purification. 2-Amino-N'-arylbenzamidines **3a – f** were prepared according to ref. [14]. Melting points were measured in capillary tubes using a Büchi 530 melting point apparatus and are uncorrected. IR spectra were measured using a Bruker Tensor 27 instrument. ^{1}H NMR (300, 400 or 600 MHz) and ^{13}C NMR (75, 101 or 151 MHz) spectra were recorded in $CDCl_3$ on Bruker Avance II-300, Avance DRX-400 and Avance II-600 spectrometers with TMS (for ^{1}H) or the solvent (for ^{13}C, δ_C = 77.01 ppm) as the internal standards. ^{1}H-^{15}N HMBC spectra of **5c** were obtained on a Bruker Avance III-500 spectrometer equipped with a broadband cryo-probehead at 500.1 (^{1}H)/50.7 (^{15}N) MHz with the $^nJ(^{15}N,^1H)$ evolution delay optimized for a coupling constant of 3.0 Hz. The pulse program HMBCGPNDQF (Bruker) was used for data acquisition. The ^{15}N chemical shifts are referenced to neat external CH_3NO_2. Mass spectral measurements (EI, 70 eV) were performed using a Finnigan MAT 8430 spectrometer.

General procedures

2-Amino-N'-arylbenzamidines (**3a – f**, 0.2 mmol) were added to a solution of potassium hydroxide (0.2 g, 4 mmol) in ethanol (95 %). The reaction mixture was cooled to 0 °C, and a freshly prepared aqueous sodium hypochlorite solution (15 mL) was added. After 20 min of stirring at this temperature, the mixture was poured into 100 mL of ice-cold water. The product was extracted with dichloromethane, the organic phases were combined and dried with $MgSO_4$, the solvent was evaporated under reduced pressure, and the remaining solid was purified by silica gel chromatography with dichloromethane. Recrystallization from dichloromethane gave **5a – f** as reddish-brown to blue powders in 39 – 47 % yield.

*2-Phenylazobenzonitrile (**5a**)* [22]

Blue powder (81 mg, 39 %), m. p.: 59 – 61 °C. – IR (KBr): ν = 2219 (C≡N), 1595, 1429 cm^{-1}. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53 – 7.58 (m, 4 H, 5-, 3′-, 4′-, 5′-H), 7.70 (ddd, J = 8.2, 7.4, 1.5 Hz, 1 H, 4-H), 7.85 (ddd, J = 7.7, 1.5, 0.5 Hz, 1 H, 6-H), 7.90 (ddd, J = 8.2, 1.2, 0.5 Hz, 1 H, 3-H), 8.02 – 8.07 (m, 2 H, 2′,6′-H). – ^{13}C NMR (101 MHz, $CDCl_3$): δ = 113.15 (C, C-1), 116.84 (C, C≡N), 117.10 (CH, C-3), 123.70 (CH, 2 C, C-2′,-6′), 129.26 (CH, 2 C, C-3′,-5′), 130.85 (CH, C-5), 132.46 (CH, C-4′), 133.33 (CH, C-4), 133.60 (CH, C-6), 152.24 (C, C-1′), 153.17 (C, C-2). – MS: m/z (%) = 207 (40) [M]$^+$, 178 (12), 151 (6), 130 (4), 105 (40), 92 (4), 77 (100), 57 (4). – $C_{13}H_9N_3$ (207.23): calcd. C 75.35, H 4.38, N 20.28; found C 75.17, H 4.35, N 20.11.

*2-(4-Bromophenyl)azobenzonitrile (**5b**)*

Reddish-brown powder (112 mg, 39 %), m. p.: 101 – 102 °C. – IR (KBr): ν = 2231 (C≡N), 1590, 1421 cm^{-1}. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.58 (td, J = 7.5, 1.2 Hz, 1 H, 5-H), 7.66 (AA′XX', N = 8.8 Hz, 2 H, 3′-, 5′-H), 7.68 – 7.74 (m, 1 H, 4-H), 7.84 – 7.91 (m, 2 H, 3-, 6-H), 7.92 (AA'XX′, N = 8.8 Hz, 2 H, 2′-, 6′-H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 113.34 (C, C-1), 116.76 (C, C≡N), 117.10 (CH, C-3), 125.10 (CH, 2 C, C-2′,-6′), 127.22 (C, C-4′), 131.19 (CH, C-5), 132.60 (CH, 2 C, C-3′,-5′), 133.39 (CH, C-4), 133.70 (CH, C-6), 150.94 (C, C-1′), 152.95 (C, C-2). – MS: m/z (%) = 287 (39) [M(^{81}Br)]$^+$, 285 (40) [M(^{79}Br)]$^+$, 219 (2), 206 (16), 193 (2), 185 (62), 183 (64), 177 (12), 157 (96), 155 (100), 151 (16), 130 (8), 111 (8), 102 (40), 81 (8), 76 (36). – $C_{13}H_8BrN_3$ (286.13): calcd. C 54.57, H 2.82, N 14.69; found C 54.37, H 2.75, N 14.57.

*2-(4 Chlorophenyl)azobenzonitrile (**5c**)*

Reddish-brown powder (113 mg, 47 %), m. p.: 75 – 76 °C. – IR (KBr): ν = 2231 (C≡N), 1590, 1409 cm^{-1}. – ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.51 (AA′XX', N = 8.8 Hz, 2 H, H-3′,-5′), 7.57 (td, J = 7.6, 1.2 Hz, 1 H, H-5), 7.70 (ddd, J = 8.2, 7.5, 1.5 Hz, 1 H, H-4), 7.85 (ddd, J = 7.8, 1.5, 0.4 Hz, 1 H, H-6), 7.89 (ddd, J = 8.2, 1.1, 0.4 Hz, 1 H, H-3), 7.98 (AA'XX$'$, N = 8.8 Hz, 2 H, H-2$'$,-6$'$). – ^{13}C NMR (151 MHz, $CDCl_3$): δ = 113.31 (C, C-1), 116.75 (C, C≡N), 117.09 (CH, C-3), 124.92 (CH, 2 C, C-2$'$,-6$'$), 129.58 (CH, 2 C, C-3$'$,-5$'$), 131.13 (CH, C-5), 133.36 (CH, C-4), 133.67 (CH, C-6), 138.59 (C, C-4$'$), 150.59 (C, C-1$'$), 152.94 (C, C-2). – ^{15}N NMR (51 MHz, $CDCl_3$), chemical shifts (rel. to ext. CH_3NO_2) from the 2D HMBC spectrum: δ = 136.9 (N_B), 118.3 (N_A), −151.3 ppm (C≡N). – MS: m/z (%) = 243 (12) [M(^{37}Cl)]$^+$, 241 (36) [M(^{35}Cl)]$^+$, 219 (2), 206 (16), 193 (2), 185 (62), 183 (64), 177 (12), 157 (96), 155 (100), 151 (16), 130 (8), 111 (8), 102 (40), 81 (8), 76 (36). – $C_{13}H_8ClN_3$ (241.68): calcd. C 64.61, H 3.34, N 17.39; found C 64.43, H 3.31, N 17.23.

*2-(p-Tolyl)azobenzonitrile (**5d**)*

Brown powder (98 mg, 44 %), m. p.: 90 – 93 °C. – IR (KBr): ν = 2229 (C≡N), 1600, 1411 cm^{-1}. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.44 (s, 3 H, CH_3), 7.32 (AA$'$XX$'$ × d, N = 8.3, J = 0.6 Hz, 2 H, 3$'$-, 5$'$-H), 7.51 (ddd, J = 7.7, 7.4, 1.2 Hz, 1 H, 5-H), 7.67 (ddd, J = 8.2, 7.4, 1.5 Hz, 1 H, 4-H), 7.82 (ddd, J = 7.7, 1.5, 0.5 Hz, 1 H, 6-H), 7.87 (ddd, J = 8.2, 1.2, 0.5 Hz, 1 H, 3-H), 7.93 (AA$'$XX$'$, N = 8.3 Hz, 2 H, 2$'$-, 6$'$-H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.62 (CH_3), 112.90 (C, C-1), 116.91 (C, C≡N), 117.05 (CH, C-3), 123.72 (CH, 2 C, C-2$'$,-6$'$), 129.90 (CH, 2 C, C-3$'$,-5$'$), 130.50 (CH, C-5), 133.26 (CH, C-6), 133.52 (CH, C-4), 143.36 (C, C-4$'$), 150.45 (C, C-1$'$), 153.31 (C, C-2). – MS: m/z (%) = 221 (24) [M]$^+$, 205 (12), 191 (20), 177 (32), 157 (16), 155 (20), 151 (6), 130 (8), 111 (8), 102 (40), 81 (8), 76 (36). – $C_{14}H_{11}N_3$ (221.26): calcd. C 76.00, H 5.01, N 18.99; found C 75.87, H 4.93, N 18.81.

*2-(2,5-Dimethylphenyl)azobenzonitrile (**5e**)*

Brown powder (94 mg, 40 %), m. p.: 67 – 9 °C. – IR (KBr): ν = 2227 (C≡N), 1593, 1417 cm^{-1}. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.39 (s, 3 H, 5$'$-CH_3), 2.72 (s, 3 H, 2$'$-CH_3), 7.2 – 7.3 (m, 2 H, 3$'$-, 4$'$-H), 7.54 (ddd, J = 7.7, 7.4, 1.2 Hz, 1 H, 5-H), 7.63 (br. s, 1 H, 6$'$-H), 7.70 (ddd, J = 8.1, 7.4, 1.4 Hz, 1 H, 4-H), 7.84 (ddd, J = 7.7, 1.4, 0.5 Hz, 1 H, 6-H), 7.87 (ddd, J = 8.1, 1.2, 0.5 Hz, 1 H, 3-H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.28 (2$'$-CH_3), 21.01 (5$'$-CH_3), 111.97 (C), 116.24 (CH), 117.15 (C, C≡N), 118.31 (CH), 130.40 (CH), 131.29 (CH), 133.30 (CH), 133.51 (CH), 133.77 (CH), 136.36 (C), 136.87 (C), 150.15 (C), 153.77 (C). – MS: m/z (%) = 235 (34) [M]$^+$, 234 (92), 219 (4), 206 (16), 191 (4), 179 (4), 165 (6), 133 (10), 118 (8), 105 (100), 91 (6), 77 (32). – $C_{15}H_{13}N_3$ (235.28): calcd. C 76.57, H 5.57, N 17.86; found C 76.41, H 5.54, N 17.71.

*2-(2,4-Dimethylphenyl)azobenzonitrile (**5f**)*

Brown powder (99 mg, 42 %), m. p.: 73 – 74 °C. – IR (KBr): ν = 2225 (C≡N), 1591, 1419 cm^{-1}. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.39 (s, 3 H, 4$'$-CH_3), 2.73 (s, 3 H, 2$'$-CH_3), 7.08 (dd, J = 8.3, 1.9 Hz, 1 H, 5$'$-H), 7.16 (br. s, 1 H, 3$'$-H), 7.51 (ddd, J = 7.7, 7.4, 1.2 Hz, 1 H, 5-H), 7.67 (ddd, J = 8.2, 7.4, 1.4 Hz, 1 H, 4-H), 7.77 (d, J = 8.3 Hz, 1 H, 6$'$-H), 7.82 (dd, J = 7.7, 1.4 Hz, 1 H, 6-H), 7.86 (dd, J = 8.2, 1.2 Hz, 1 H, 3-H). – ^{13}C NMR (101 MHz, $CDCl_3$): δ = 17.62 (2$'$-CH_3), 21.55 (4$'$-CH_3), 111.98 (C, C-1), 116.10 (CH, C-6$'$), 117.19 (C, C≡N), 118.16 (CH, C-3), 127.48 (CH, C-5$'$), 130.20 (CH, C-5), 132.01 (CH, C-3$'$), 133.23 (CH, C-4), 133.68 (CH, C-6), 139.81 (C, C-2$'$), 143.36 (C, C-4$'$), 148.51 (C, C-1$'$), 153.80 (C, C-2). – MS: m/z (%) = 235 (46) [M]$^+$, 234 (28), 219 (8), 206 (6), 191 (14), 179 (4), 165 (2), 133 (30), 118 (18), 105 (60), 91 (16), 77 (32). – $C_{15}H_{13}N_3$ (235.28): calcd. C 76.57, H 5.57, N 17.86; found C 76.41, H 5.54, N 17.69.

Acknowledgements

K. M. El-Shaieb deeply thanks Prof. H. Hopf (Institute of Organic Chemistry, TU Braunschweig, Germany) for the provision of laboratory facilities and valuable discussions, and the Egyptian Government for a post-doctoral fellowship and financial support.

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