The First Indazolimine-Arylazobenzonitrile Rearrangement

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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 diazokalanes 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 anilide derivatives 2a–f in the presence of aluminum chloride as a catalyst (Scheme 1) and were fully characterized [14].

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].
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 1H NMR spectrum except for those of the aromatic protons with chemical shifts between δ = 7 and 8 ppm. Moreover, the 1H NMR spectrum showed the absence of the broad signals which correspond to the exchangeable protons (–NH2) of the starting materials. The 13C NMR spectra of

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Moreover, the 1H NMR spectrum showed the absence of the broad signals which correspond to the exchangeable protons (–NH2) of the starting materials. The 13C NMR spectra displayed signals close to δ ≈ 116.7 ppm for -C=N groups whose presence was confirmed by IR spectroscopy (ν = 2219–2231 cm⁻¹). The 1H and 13C 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 13C 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 1H,15N HMBC NMR experiments on 5c (Fig. 1). The 15N 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 cross-peaks with protons 2′,6′-H (δJNH), 3-H (δJNH) and 6-H (δJNH) (decreasing intensity in this order) and N_A with 2′,6′-H (δJNH, 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, Σ|Δδ|, relative to (E)-azobenzene is 18.6 ppm whereas it is much larger, 37.8 ppm, with respect to (Z)-azobenzene. As the 15N 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 (δJNH) with 6-H, the proton ortho to -C=N (δN = −151.3 ppm, δH = 7.86 ppm). This nitrogen chemical shift is atypical for aromatic nitriles, which usually occur between δ = −112 and −125 ppm [20]. However, only very few 15N shifts of ortho-substituted benzonitriles have been reported (δ = −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 1H,15N 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.

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

![Fig. 1. Details of the 2D 1H,15N HMBC NMR spectrum of 5c (in CDCl₃ at 500/51 MHz). The total 15N chemical shift range acquired was +170 to −230 ppm relative to external nitromethane (δN = 0 ppm).](image-url)
2-arylazonitrile 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'-arylazamidines 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. 1H NMR (300, 400 or 600 MHz) and 13C NMR (75, 101 or 151 MHz) spectra were recorded in CDCl3 on Bruker Avance II-300, Avance DRX-400 and Avance II-600 spectrometers with TMS (for 1H) or the solvent (for 13C, δC = 77.01 ppm) as the internal standards. 1H-15N HMBC spectra of 5c were obtained on a Bruker Avance III-500 spectrometer equipped with a broadband cryo-probehead at 500.1 MHz with the pulse program HMBCPNDQF (Bruker) was used for data acquisition. The 15N chemical shifts are referenced to neat external CH3NO2. Mass spectral measurements (EI, 70 eV) were performed using a Finnigan MAT 8430 spectrometer.

**General procedures**

2-Amino-N'-arylazamidines (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 MgSO4, the 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 MgSO4, the resulting solution was concentrated 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-Phenylazonitrile (5a) [22]

Blue powder (112 mg, 39 %), m. p.: 101–102 °C. – IR (KBr): ν = 2219 (C≡N), 1595, 1429 cm⁻¹. – 1H NMR (400 MHz, CDCl3): δ = 7.53–7.58 (m, 4 H, 5-, 3′, 4′, 5′-H), 7.70 (dd, J = 8.2, 7.4, 1.5 Hz, 1 H, 4-H), 7.85 (dd, J = 7.7, 1.5, 0.5 Hz, 1 H, 6-H), 7.90 (dd, J = 8.2, 1.2, 0.5 Hz, 1 H, 3-H), 8.02–8.07 (m, 2 H, 2′-H), – 13C NMR (101 MHz, CDCl3): 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), 150.94 (C, C-1′), 131.19 (CH, C-5), 132.60 (CH, 2 C, C-3′, 5′), 133.33 (CH, C-4′), 133.70 (CH, C-6), 150.94 (C, C-1′), 152.95 (C, C-2′). – MS: m/z (%) = 207 (40) [M]+, 178 (12), 151 (6), 130 (4), 105 (40), 92 (4), 77 (100), 57 (4). – C13H9N3 (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)azonitrile (5b)

Reddish-brown powder (112 mg, 39 %), m. p.: 101–102 °C. – IR (KBr): ν = 2231 (C≡N), 1590, 1421 cm⁻¹. – 1H NMR (300 MHz, CDCl3): 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), 7.88–7.91 (m, 2 H, 3-, 6-H), 7.92 (AA′XX′, N = 8.8 Hz, 2 H, 2′-, 6′-H). – 13C NMR (75 MHz, CDCl3): 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 (CH, 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+Br]+, 285 (40) [M79Br]+, 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). – C13H9BrN3 (286.13): calcd. C 54.57, H 4.28, N 14.5, found C 54.37, H 2.75, N 14.57.

2-(4-Chlorophenyl)azonitrile (5c)

Reddish-brown powder (113 mg, 47 %), m. p.: 75–76 °C. – IR (KBr): ν = 2231 (C≡N), 1590, 1409 cm⁻¹. – 1H NMR (600 MHz, CDCl3): 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 (dd, J = 8.2, 7.5, 1.5 Hz, 1 H, H-4), 7.85 (dd, J = 7.8,
8.2, 1.2, 0.5 Hz, 1 H, 3-H), 7.93 (AA′, J = 7.82 (ddd, d, H-3), 7.98 (C′N M R (51 MHz, CDCl₃)), δ = 113.31 (C, C-1), 116.75 (C, C=Н), 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). – 13C NMR (51 MHz, CDCl₃), chemical shifts (rel. to ext. CH₃NO₂) from the 2D HMBC spectrum: δ = 136.9 (Nα), 118.3 (N′), – 1.51 ppm (C=Н). – MS: m/z (%) = 243 (12) [M(37Cl)]⁺, 241 (36) [M(35Cl)]⁺, 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), – C₃H₃NCl₃ (241.68): calcd. C 66.41, H 3.34, N 17.39; found C 66.43, H 3.31, N 17.23.

2-(p-Toly)azobenzonitrile (5d)

Brown powder (98 mg, 44 %), m.p.: 90 – 93 °C. – IR (KBr): ν = 2229 (C=Н), 1600, 1411 cm⁻¹. – 1H NMR (300 MHz, CDCl₃): δ = 2.44 (s, 3 H, CH₃), 7.32 (AA’XX′, d, N = 8.3, J = 0.6 Hz, 2 H, 3′, 5′-H), 7.51 (dd, 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). – 13C NMR (75 MHz, CDCl₃): δ = 21.62 (CH₃), 112.90 (C, C-1), 116.91 (C, C=Н), 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), – C₁₀H₉N₃ (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 – 90 °C. – IR (KBr): ν = 2227 (C=Н), 1593, 1417 cm⁻¹. – 1H NMR (300 MHz, CDCl₃): δ = 2.39 (s, 3 H, 5′-CH₃), 2.72 (s, 3 H, 2′-CH₃), 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). – 13C NMR (75 MHz, CDCl₃): δ = 17.28 (2′-CH₃), 21.01 (5′-CH₃), 111.97 (CH), 116.24 (CH), 117.15 (C, C=Н), 118.31 (CH), 130.40 (CH), 131.29 (CH), 133.30 (CH), 133.51 (CH), 137.77 (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 (9), 118 (8), 105 (100), 91 (6), 77 (32). – C₁₅H₁₃N₃ (235.28): calcd. C 76.57, H 5.57, N 17.86; found C 76.41, H 5.54, N 17.71.

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