March 2015  Synthesis and Tautomeric Structure of Tris(arylazo) Derivatives of Novel 1H-Bis-imidazo[1,2-b:2′,1′-e]pyrazole Ring System

Ahmad Sami Shawali,a* Thoraya A. Farghaly,a Mohamed R. Shehata,a and Shadia M. Hussein a

Department of Chemistry, Faculty of Science, University of Cairo, Giza 12613, Egypt
*E-mail: as_shawali@mail.com
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An efficient and convenient synthesis of tris(arylazo) derivatives of novel heterocyclic ring system, namely, 1H-bis-imidazo[1,2-b:2′,1′-e]pyrazole, is described. The structures of the compounds prepared and their tautomeric structure were elucidated on the basis of their elemental analyses and spectral data in addition to correlation of their acidity constants by Hammett equation. The mechanism of the studied reactions and their site selectivity are discussed.


INTRODUCTION

The chemistry of aryl- and heteroaryl-azo derivatives of aromatic and heterocyclic compounds has been the subject of interest of many research groups all over the world. This is because such coloring materials have found many applications in various fields such as dyeing of textiles and plastics, biological-medical studies, printing, electronic photography, laser technology, and solar energy conversion [1]. Furthermore, hydrazonoyl halides of the general formula, R-C(X) = NNHR, proved useful for the synthesis of numerous heterocyclic compounds. At present, there are several review articles by Shawali et al. [2–13] and by others [14] covering the chemistry and applications of such halides. In the light of these facts and in conjunction with our previous studies of synthesis of aryazo heterocycles [9], it was thought interesting to explore the utility of hydrazonoyl halides in the synthesis of tris-arylazo compounds that have not been reported hitherto. Here, we wish to report the synthesis of tris(arylazo) derivatives of novel heterocyclic ring system, namely, 1H-bis-imidazo[1,2-b:2′,1′-e]pyrazole using hydrazonoyl halides as precursors (Scheme 1). In addition, as the target azo compounds can theoretically have three possible tautomeric structures (Chart 1), their spectral data were also studied, and their acidity constants were determined and correlated by Hammett equation in order to explore their actual tautomeric structure.

RESULTS AND DISCUSSION

When each of the amines 1a–e was refluxed with two molar equivalents of the appropriate hydrazonoyl chloride 2 in dioxane in the presence of triethylamine, it gave in each case one isolable product as evidenced by TLC analysis of the crude product. The isolated products were identified on the basis of their spectral (IR, 1H NMR, and MS) and elemental analyses data (see Experimental) as the corresponding 2,7-dimethyl-3,6,9-tris(arylazo)-1H-bis-imidazo[1,2-b:2′,1′-e]pyrazoles 6 (Scheme 1). For example, their IR spectra revealed in each case an absorption band in the region ν 3360–3435 cm⁻¹ because of NH stretching vibration. Also, their 1H NMR spectra showed, in addition to aromatic proton signals, three characteristic signals in the regions δ 2.13–2.37, 2.38–2.50, and 14.03–14.50 ppm assignable to the resonances of the protons of the groups 2-CH₃, 7-CH₃, and 1-NH, respectively.

To account for the formation of the latter products, it is suggested, as indicated in Scheme 1, that the reaction starts with the formation of the addition intermediate 3 via nuleophilic addition of 1 to the nitrilimine, generated in situ from the base catalyzed dehydrochlorination of 2. The initially formed intermediate 3 then undergoes dehydrative cyclization to give 4. The latter, under the employed reaction conditions, undergoes further reaction with 2 to give 5 that in turn cyclizes to afford the corresponding tris(arylazo) derivative of 1H-bis-imidazo [1,2-b:2′,1′-e]pyrazole 6 as end product (Scheme 1). This suggested pathway was confirmed by the isolation of the intermediate 3 and its conversion into 6. Thus, when a mixture of 1 and 2 in molar ratio 1:1 was refluxed in dioxane in the presence of triethylamine, the corresponding product 4 was isolated in 65–70% yield. Treatment of the latter with one molar equivalent amount of 2 under the reaction conditions furnished products that proved...
identical in all respects (mp, mixed mp, IR, $^1$H NMR, and MS) with those obtained from direct reaction of 1 with two molar equivalents of 2 (Scheme 1).

The assigned site selectivity for the studied reactions is also compatible with literature reports that revealed that reactions of N-aryl C-acylhydrazonoyl chlorides with 5-amino-1H-pyrazoles furnished the arylazoimidazo[1,2-b]pyrazole derivatives [15–18].

Next, as the products 6 can theoretically have three possible tautomeric structures, namely, 6A–C (Chart 1), it was interesting to elucidate their actual tautomeric structure. To fulfill this objective, their electronic absorption spectra were first examined. The results are given in Table 1. As shown, the electronic absorption spectra of compounds 6 in dioxane showed, in each case, two absorption bands in the regions 421–476 and 332–380 nm. This absorption pattern is analogous to that reported for the azo chromophore [9]. Also, the electronic absorption spectra of compound 6c, taken as a typical example of the series prepared, in different solvents showed little, if any, shift (Table 1). This result, although it indicates that the studied compounds exist only in one tautomeric azo structure.

Table 1

<table>
<thead>
<tr>
<th>Compound no.</th>
<th>$\lambda_{\text{max}}$ (log ε)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6a</td>
<td>446 (4.31), 349 (4.53)</td>
</tr>
<tr>
<td>6b</td>
<td>435 (4.38), 380 (4.22)</td>
</tr>
<tr>
<td>6c</td>
<td>465 (4.18), 334 (4.44)</td>
</tr>
<tr>
<td>6d</td>
<td>443 (4.70), 370 (4.60)</td>
</tr>
<tr>
<td>6e</td>
<td>449 (4.10), 370 (4.18)</td>
</tr>
<tr>
<td>6f</td>
<td>421 (4.70), 335 (3.38)</td>
</tr>
<tr>
<td>6g</td>
<td>437 (3.75), 375 (3.59)</td>
</tr>
<tr>
<td>6h</td>
<td>476 (4.67), 337 (4.20)</td>
</tr>
<tr>
<td>6i</td>
<td>460 (4.55), 381 (4.26)</td>
</tr>
</tbody>
</table>

$\lambda_{\text{max}}$ (log ε): acetonitrile 468 (4.27), 332 (4.11); chloroform 469 (4.2), 339 (4.02); ethanol 474 (4.22), 341 (4.11); methanol 469 (4.46), 343 (3.99).
form, it cannot distinguish between the three tautomeric structures 6A–C.

To provide an unambiguous evidence for the actual tautomeric structure of compounds 6, their acid dissociation constants (pKₐ) were determined potentiometrically in 80% dioxane–water mixture at ionic strength (KNO₃) of 0.1 and 25 ±0.1°C, and their correlation with the Hammett equation was examined. The results are summarized in Table 2. As shown, the data indicate that the acidity constants of compounds 6 are influenced by the ring substituents, being increased by electron-withdrawing substituents and decreased by electron-donating substituents. Correlation of the pKₐ data of the two series 6a–e and 6c, f–i each with Hammett substituent constant σₛ using the least squares method resulted in the following equations, respectively:

\[
pKₐ (6a-e) = 10.190-1.670σₛ; \quad r = 0.994; \quad (1)
\]

\[
pKₐ (6c, f-i) = 10.023-1.644σₛ; \quad r = 0.996; \quad (2)
\]

where \( r \) and \( s \) are the correlation coefficient and standard deviation, respectively. These excellent correlations indicate that all of the studied compounds exist in one tautomeric form, namely, the tris-arylazo form 6A (Chart 1). This is because the \( ρ \) values (1.670 and 1.644) for the two series 6a–e and 6c, f–i are very similar. This similarity provides evidence that the bridges between the substituent and the acidic site (NH) in both series are of the same length and this is fulfilled by structure 6A. Also, the degree of conjugation in structure 6A, being more than that in 6B or 6C, renders it more stable than the latter two structures. On the basis of this finding, the other possible hydrazone tautomeric structures 6B–C were discarded.

**EXPERIMENTAL**

All melting points were determined on an electrothermal Gallenkamp apparatus and are uncorrected. Solvents were generally distilled and dried prior their use. The IR spectra were measured on a Pye-Unicam SP300 instrument in potassium bromide discs. The ¹H NMR spectra were recorded on a Varian Mercury VXⅢ-300 spectrometer (300 MHz for ¹H NMR), and the chemical shifts were related to that of the solvent DMSO-d₆. The mass spectra were recorded on a GCMS-Q1000-EX Shimadzu and GCMS 5988-A HP spectrometers, and the ionizing voltage was 70 eV. Elemental analyses of the products were carried out at the Microanalytical Center of Cairo University, Giza, Egypt. Hydrazonoyl halides 2 [19] and 3,5-diamino-4-phenylazo-pyrazole 1 [20–22] were prepared following literature procedures.

**Synthesis of 2,7-dimethyl-3,6,9-triarylazo-1H-bis-imidazo[1,2-b:2',1'-e]pyrazoles (6a–t)**

Method A: To a mixture of the aminopyrazole derivatives 1a–e (5 mmol) and the appropriate hydrazonoyl chlorides 2a–e (10 mmol) in dioxane (30 mL), triethylamine (1.4 mL) was added. The reaction mixture was refluxed for 20 h. The solvent was evaporated under vacuum. The solid left was collected and crystallized from the appropriate solvent to give the corresponding compounds 6a–t.

Method B: To a mixture of the aminimidazopyrazole derivatives 4a, b, d, e (5 mmol) and the appropriate hydrazonoyl chlorides 2 (5 mmol) in dioxane (20 mL), triethylamine (0.7 mL) was added. The reaction mixture was refluxed for 10–20 h (examined by TLC). The solvent was evaporated under vacuum. The solid left was collected and crystallized from the appropriate solvent to give the corresponding compounds 6a, b, d, e.

The compounds 6a–t prepared by the foregoing two methods together with their physical constants are listed in the following sections.

**2,7-Dimethyl-3,6-di-(phenylazo)-9-(4-methoxyphenylazo)-1H-bis-imidazo[1,2-b:2',1'-e]pyrazole (6a).** Dark red solid (80% yield), mp 216–218°C (EtOH/Dioxane), IR (KBr) νmax 3435 (NH) cm⁻¹. ¹H NMR (DMSO-d₆): δ 2.13 (s, 3H, CH₃), 2.17 (s, 3H, CH₃), 2.39 (s, 3H, CH₃), 3.85 (s, 3H, MeO), 7.00–7.87 (m, 14H, Ar-H), 14.42 (s, 1H, NH), MS m/z (%): 516 (M⁺, 12), 515 (M⁺ + 1, 12), 515 (9), 498 (13), 477 (15), 429 (14), 279 (11), 203 (18), 187 (14), 178 (16), 172 (23), 161 (16), 127 (21), 118 (42), 108 (61), 91 (69), 77 (100). Anal. calcd for C₂₈H₂₄N₁₀O (516.56): C, 67.10; H, 4.95; N, 27.98. Found: C, 67.10; H, 4.95; N, 27.98.

**2,7-Dimethyl-3,6-di-(phenylazo)-9-(4-methylphenylazo)-1H-bis-imidazo[1,2-b:2',1'-e]pyrazole (6b).** Dark orange solid (80% yield), mp 254–256°C (EtOH/Dioxane), IR (KBr) νmax 3413 (NH) cm⁻¹. ¹H NMR (DMSO-d₆): δ 2.31 (s, 3H, CH₃), 2.36 (s, 3H, CH₃), 2.38 (s, 3H, CH₃), 7.24–7.82 (m, 14H, Ar-H), 14.39 (s, 1H, NH), MS m/z (%): 500 (M⁺, 0.01), 236 (15), 125 (11), 109 (11), 86 (28), 83 (35), 80 (100), 71 (42). Anal. calcd for C₂₈H₂₂N₁₀O (500.56): C, 67.19; H, 4.83; N, 27.98. Found: C, 67.10; H, 4.95; N, 27.70.

**2,7-Dimethyl-3,6,9-tri-(phenylazo)-1H-bis-imidazo[1,2-b:2',1'-e]pyrazole (6c).** Brown solid (78% yield), mp 180–182°C (EtOH/Dioxane), IR (KBr) νmax 3421 (NH) cm⁻¹. ¹H NMR (DMSO-d₆): δ 2.35 (s, 3H, CH₃), 2.41 (s, 3H, CH₃), 7.42–7.92 (m, 15H, Ar-H), 14.41 (s, 1H, NH), MS m/z (%): 487 (M⁺ + 1, 29), 486 (M⁺, 39), 473 (44), 395 (46), 325 (48), 297 (40), 184 (56), 92 (50), 77 (20), 73 (100). Anal. calcd for C₂₉H₂₄N₁₀ (486.53): C, 66.65; H, 4.56; N, 28.79. Found: C, 66.54; H, 4.41; N, 28.59.

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*In dioxane–water (1:1 v/v) solution at 25°C, μ = 0.10 and standard deviation, s = ±0.03 – 0.05.*
2,7-Dimethyl-3,6-di-(phenylazo)-9-(4-chlorophenylazo)-1H-bis-imidazo[1,2-b:2,1′-e]pyrazole (6d). Pale brown solid (85% yield), mp 210–212°C (EtOH/Dioxane), IR (KBr) νmax3413 (NH) cm⁻¹. 1H NMR (DMSO-d6): δ 2.34 (s, 3H, CH3), 2.41 (s, 3H, CH3), 7.27–7.95 (m, 14H, Ar-H), 14.42 (s, 1H, NH). MS m/z (%): 521 (M⁺, 1, 0.09), 520 (M⁺, 0.01), 490 (1), 464 (2), 454 (2), 449 (1), 382 (4), 330 (1), 302 (100), 191 (60), 163 (44), 111 (57), 77 (9). Anal. calcd for C₂₇H₂₀Cl₂N₁₀O₄ (555.42): C, 58.20; H, 3.62; N, 25.43. Found: C, 58.39; H, 3.63; N, 25.71.

2,7-Dimethyl-3,6-di-(4-methoxyphenylazo)-9-phenylazo-1H-bis-imidazo[1,2-b:2,1′-e]pyrazole (6e). Dark brown solid (80% yield), mp 240–242°C (EtOH/Dioxane), IR (KBr) νmax3360 (NH) cm⁻¹. 1H NMR (DMSO-d6): δ 2.25 (s, 3H, CH3), 2.50 (s, 3H, CH3), 3.57 (s, 3H, OCH3), 3.73 (s, 3H, OCH3), 7.16–7.92 (m, 12H, Ar-H), 14.42 (s, 1H, NH). MS m/z (%): 547 (M⁺, 94), 546 (M⁺, 58), 547 (94), 511 (89), 446 (89), 398 (95), 283 (99), 222 (100), 103 (31). Anal. calcd for C₂₇H₂₀N₁₂O₄ (546.58): C, 63.73; H, 4.79; N, 25.63. Found: C, 63.58; H, 4.65; N, 25.43.

2,7-Dimethyl-3,6-di-(4-methoxyphenylazo)-9-phenylazo-1H-bis-imidazo[1,2-b:2,1′-e]pyrazole (6f). Dark brown solid (80% yield), mp 240–242°C (EtOH/Dioxane), IR (KBr) νmax3360 (NH) cm⁻¹. 1H NMR (DMSO-d6): δ 2.17 (s, 3H, CH3), 2.31 (s, 3H, CH3), 2.34 (s, 3H, CH3), 2.43 (s, 3H, CH3), 7.11–7.91 (m, 13H, Ar-H), 14.41 (s, 1H, NH). MS m/z (%): 514 (M⁺, 54), 480 (66), 435 (73), 395 (80), 357 (97), 351 (74), 234 (95), 203 (100), 193 (66), 173 (74), 129 (60), 111 (100), 88 (66), 77 (71). Anal. calcd for C₂₇H₂₂N₁₀O₄ (546.58): C, 67.69; H, 5.09; N, 27.13. Found: C, 67.40; H, 5.16; N, 27.03.

2,7-Dimethyl-3,6-di-(4-chlorophenylazo)-9-phenylazo-1H-bis-imidazo[1,2-b:2,1′-e]pyrazole (6g). Dark brown solid (75% yield), mp 214–216°C (EtOH/Dioxane), IR (KBr) νmax3421 (NH) cm⁻¹. 1H NMR (DMSO-d6): δ 2.17 (s, 3H, CH3), 2.31 (s, 3H, CH3), 2.34 (s, 3H, CH3), 2.43 (s, 3H, CH3), 7.16–7.97 (m, 13H, Ar-H), 14.40 (s, 1H, NH). MS m/z (%): 514 (M⁺, 54), 555 (M⁺, 1), 550 (94), 546 (8), 537 (11), 450 (5), 496 (10), 527 (11), 386 (56), 339 (11), 297 (24), 120 (31), 71 (54), 57 (100). Anal. calcd for C₂₇H₂₁Cl₂N₁₀O₄ (555.42): C, 58.39; H, 3.63; N, 25.22. Found: C, 58.20; H, 3.50; N, 25.17.

2,7-Dimethyl-3,6-di-(4-nitrophenylazo)-9-phenylazo-1H-bis-imidazo[1,2-b:2,1′-e]pyrazole (6h). Dark brown solid (80% yield), mp 230–232°C (EtOH/Dioxane), IR (KBr) νmax3429 (NH) cm⁻¹. 1H NMR (DMSO-d6): δ 2.23 (s, 3H, CH3), 2.25 (s, 3H, CH3), 2.36 (s, 3H, CH3), 2.46 (s, 3H, CH3), 7.51–7.93 (m, 12H, CH3), 14.40 (s, 1H, NH). MS m/z (%): 550 (M⁺, 2, 2), 549 (M⁺, 1, 2), 548 (M⁺, 7), 518 (8), 516 (7), 507 (9), 448 (9), 412 (12), 374 (10), 257 (24), 253 (25), 207 (12), 97 (100), 96 (49), 83 (60), 69 (89). Anal. calcd for C₂₇H₂₃Cl₂N₁₀O₄ (549.03): C, 56.44; H, 4.59; N, 25.21. Found: C, 63.25; H, 4.29; N, 25.31.

2,7-Dimethyl-3,6,9-tri-(4-chlorophenylazo)-1H-bis-imidazo[1,2-b:2,1′-e]pyrazole (6i). Dark brown solid (68% yield), mp 234–236°C (EtOH/Dioxane), IR (KBr) νmax3427 (NH) cm⁻¹. 1H NMR (DMSO-d6): δ 2.35 (s, 3H, CH3), 2.41 (s, 3H, CH3), 7.16–7.94 (m, 12H, Ar-H), 14.03 (s, 1H, NH). MS m/z (%): 589 (M⁺, 24), 405 (26), 397 (30), 360 (32.53), 332 (35), 274 (28), 256 (42) 170 (59), 156 (64), 90 (100), 84 (88), 77 (68). Anal. calcd for C₂₇H₂₃Cl₂N₁₀O₄ (589.88): C, 54.98; H, 3.25; N, 27.33. Found: C, 54.77; H, 3.48; N, 23.58.

2,7-Dimethyl-3,6-di-(4-chlorophenylazo)-9-(4-methylphenylazo)-1H-bis-imidazo[1,2-b:2,1′-e]pyrazole (6j). Dark brown solid (82% yield), mp >300°C (EtOH/Dioxane), IR (KBr) νmax3432 (NH) cm⁻¹. 1H NMR (DMSO-d6): δ 2.36 (s, 3H, CH3), 2.41 (s, 3H, CH3), 7.49–7.95 (m, 12H, Ar-H), 14.43 (s, 1H, NH). MS m/z (%): 610 (M⁺, 4), 373 (4), 360 (5), 327 (5), 232 (4), 190 (43), 138 (14), 123 (23), 97 (74), 96 (44), 85 (34), 74 (57), 55 (50). Anal. calcd for C₂₃H₁₈Cl₂N₁₀O₄ (528.61): C, 68.16; H, 5.34; N, 26.50. Found: C, 68.0; H, 5.24; N, 26.36.
1H-bis-imidazo[1,2-b:2′,1′-e]pyrazole (6g). Dark red solid (67% yield), mp 244–246°C (EtOH/Dioxane), IR (KBr) vmax 3428 (NH) cm⁻¹. 1H NMR (DMSO-d6): δ 7.03 (s, 2H, CH3), 7.11 (s, 2H, CH3), 8.36 (m, 12H, Ar-H), 14.48 (s, 1H, NH). MS m/z (%): 591 (M⁺, 8), 590 (2), 577 (41), 491 (41), 393 (45), 326 (41), 186 (46) 159 (46), 150 (60), 77 (100), 69 (28). Anal. calcd for C29H25N11O4 (609.59): C, 53.11; H, 3.02; N, 27.34%.

1H-bis-imidazo[1,2-b:2′,1′-e]pyrazole (4b). Dark brown solid (70% yield), mp 260–262°C (EtOH/Dioxane), R (KBr) vmax 3425 (NH2), 3180 (NH) cm⁻¹. 1H NMR (DMSO-d6): δ 2.31 (3H, CH3), 2.39 (3H, CH3), 2.40 (br.s, 2H, NH2), 7.28–7.32 (2m, 9H, Ar-H), 7.19–7.21 (2m, 9H, Ar-H), 14.39 (s, 1H, NH). MS m/z (%): 358 (M⁺, 9), 347 (67), 338 (76), 314 (78), 292 (84), 277 (90), 200 (74), 87 (100), 70 (84). Anal. calcd for C19H18N8O (96): C, 52.24; H, 4.95; N, 31.26. Found: C, 53.60; H, 4.99; N, 31.14%.

REFERENCES AND NOTES