Studies with 2-Arylhydrazono-3-oxopropanals: A Novel Route to 4-Aroyl-2-aryl-1,2,3-triazoles, 3-Substituted 4-Arylazopyrazoles, 2-Substituted Glyxalonitrile and 3-Oxoalkanenitriles

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2-Arylhydrazono-3-oxopropanals \textsuperscript{1} react with hydroxylamine hydrochloride to yield the corresponding oximes \textsuperscript{3} that are cyclized into isoxazoles \textsuperscript{9} on reflux in acetic anhydride and are converted into 2-arylhydrazono-3-oxonitriles \textsuperscript{4} on treatment with pyridine. The reaction of \textsuperscript{1} with hydrazines afforded dihydrazones \textsuperscript{10} which were converted to arylazopyrazoles \textsuperscript{11} when treated with pyridine, whereas treatment with an acidic reagent resulted in the formation of 3-ary2-phenyl-1,2,3-triazoles \textsuperscript{12}.

Although the chemistry of 1,2,3-trione-2-arylhydrazones has been extensively investigated \cite{1-3}, only little attention has been focussed on the chemistry of structurally related 2-arylhydrazono-3-oxopropanals \textsuperscript{1} \cite{4-5}. The lack of efficient routes to 2-arylhydrazono-3-oxopropanals \textsuperscript{1} is probably behind the ignorance of their chemistry. In earlier work we reported the synthesis of \textsuperscript{1} via coupling the enaminoles \textsuperscript{2a, b} with aromatic diazonium salts and further studies on their utility as precursors for the preparation of pyridazinones, pyridazinimines and arylazopyranones \cite{4-6}. In view of the continued interest in the chemistry of these compounds, we report here the results of our investigations aiming to explore the synthetic potential of \textsuperscript{1}. The present report enables developing novel routes to 2-arylhydrazono-3-oxonitriles, 2-aryl-1,2,3-triazoles and of 3-substituted 4-arylazopyrazoles. Thus reacting \textsuperscript{1a-c} with hydroxylamine hydrochloride in aqueous sodium carbonate afforded the aldoximes \textsuperscript{3a-c}. Compounds \textsuperscript{3a-c} were also obtained by an alternative route by coupling the aldoximes \textsuperscript{5a-b} with one mole equivalent of aryl diazonium salts in ethanol/sodium acetate. Compounds \textsuperscript{3a-c} can be cyclized to the isoxazole \textsuperscript{9} or converted on the 3-oxoalkanenitriles \textsuperscript{4a-c} by the choice of the appropriate reaction conditions. Although aldoximes are expected to cyclize readily into isoxazoles in basic medium, initial attempted cyclization of \textsuperscript{3a-c} in refluxing pyridine failed and has resulted in the formation of the 3-oxoalkanenitriles \textsuperscript{4a-c}. The formation of \textsuperscript{4a-c} from \textsuperscript{3a-c} is believed to occur via initial protonation of the oxime oxygen followed by water elimination and proton loss facilitated by the solvent. Alternatively, compounds \textsuperscript{4a-c} have been directly obtained from the reaction of \textsuperscript{1a-c} with the reagent system hydroxylamine hydrochloride in refluxing pyridine. On the other hand, direct cyclization of \textsuperscript{3b} to yield the isoxazole \textsuperscript{9} can be achieved upon heating with acetic anhydride.

When compound \textsuperscript{5} was treated with two moles of the aryl diazonium salts in ethanol/sodium hydroxide, the formazanes \textsuperscript{6a, b} were obtained presumably via intermediacy of the bis(arylazo)aldoxime \textsuperscript{7} which undergoes Japp-Klingmann acyl group cleavage yielding \textsuperscript{8}, that dehydrates under the reaction conditions to give \textsuperscript{6}.

Compound \textsuperscript{1a} reacted with phenylhydrazine yielding the diphenylhydrazine \textsuperscript{10a} that could not be cyclized under a variety of conditions into pyrazoles. Similar treatment of \textsuperscript{1a, b} with hydrazine hydrate afforded the hydrazone \textsuperscript{10b, c} which when refluxed in pyridine afforded the pyrazoles \textsuperscript{11a, b}. However refluxing \textsuperscript{10b, c} in ethanol/hydrochloric acid resulted in the formation of 1,2,3-triazoles
12a, b that could be also formed from the reaction of 1a, b with hydrazine dihydrochloride.

In conclusion 3-oxo-2-arylhydrazonopropanals are useful starts and their chemistry is different than the established chemical reactivity pattern of 2-arylhydrazono-1,2,3-triones.

Experimental

All melting points are uncorrected. IR spectra were recorded in KBr with a FT IR-820 IPC spectrophotometer Shimadzu ($\nu$, cm$^{-1}$). $^1$H NMR and $^{13}$C NMR spectra were recorded on a Varian EM-390 spectrometer in $[^2]$D$_6$DMSO as solvent and TMS as internal reference; chemical shifts are reported in $\delta$ units (ppm). Mass spectra were measured on a Shimadzu GCMS-QP 1000 Ex mass spectrometer. At 70 eV. Microanalyses were performed on LECO CHNS-932. Microanalytical data were obtained from the Microanalytical Data Unit at Cairo University.

General procedure for the preparation of 3a–c

A warm solution of hydroxylamine hydrochloride (0.69 g, 10 mmol) and sodium carbonate (1.27 g, 12 mmol) in 10 ml water were added to a stirred solution of the arylhydrazonopropanals 1a–c (10 mmol) in ethanol (4 ml). The reaction mixture was
stirred at room temperature for one hour. The oximes soon separated as semisolid crystals that were solidified by cooling in crushed ice. The solid product, so formed, was collected by filtration and crystallized from ethanol.

**3-Phenyl-3-oxo-2-phenylhydrazonopropanal-1-oxime (3a):**

Yield: 2.13 g (80%); m.p. 202–206 °C. – IR (KBr): ν = 3240 (OH), 3145 (NH), 1624 cm⁻¹ (C=O). – MS (EI, 70 EV): m/z (%) = 153 [M⁺]. – ¹H NMR (300 MHz, DMSO): δ = 7.04–7.59 (m, 8H, arom. H), 7.81–7.93 (m, 2H, arom. H), 8.45 (s, 1H, 1-H), 11.95 (s, 1H, NH), 12.68 (s, 1H, oxime-H). – ¹³C{¹H} NMR (300 MHz, DMSO): δ = 164.02 (CO), 162.58 (C-1), 161.12 (C-2), 152.18, 140.90, 133.14, 127.18, 122.48, 119.30, 115.72, 87.81 (arom. C). – C₁₃H₁₁N₃O₂ (239.23): calcd. C 65.26, H 3.79, N 17.57; found C 65.39, H 3.62, N 17.46.

3-(2-Furyl)-2-(4-methoxyphenylhydrazono)-3-oxo-2-phenylhydrazonopropanal-1-oxime (3b):

Yield: 2.13 g (83%); m.p. 204–206 °C. – IR (KBr): ν = 3304 (OH), 3245 (NH), 1612 cm⁻¹ (C=O). – MS (EI, 70 EV): m/z (%) = 269 [M⁺]. – ¹H NMR (300 MHz, DMSO): δ = 6.74–6.75 (m, 1H, furyl 4-H), 7.14–7.73 (m, 6H, arom. H, furyl 3-H), 8.26 (s, 1H, furyl 5-H), 11.99 (s, 1H, NH). – C₁₃H₁₂N₂O₃ (269.25): calcd. C 72.27, H 4.45, N 16.86; found C 72.08, H 4.40, N 16.91.

3-(2-Furyl)-2-(4-methoxyphenylhydrazono)-3-oxo-propanitrile (4c):

Yield: 1.99 g (74%); m.p. 173–174 °C. – IR (KBr): ν = 3304 (OH), 2208 (CN), 1627 cm⁻¹ (C=O). – MS (EI, 70 EV): m/z (%) = 269 [M⁺]. – ¹H NMR (300 MHz, DMSO): δ = 6.74–6.75 (m, 1H, furyl 4-H), 7.05 (d, 2H, J = 8 Hz, arom. H), 7.56–7.63 (m, 3H, arom. H, furyl 3-H), 8.13 (s, 1H, furyl 5-H), 12.32 (s, 1H, NH). – C₁₃H₁₁N₂O₂ (269.25): calcd. C 62.45, H 4.12, N 16.34; found C 62.49, H 4.24, N 15.52.

**General procedure for the preparation of 4a-c:**

Each of compound 3a-c (10 mmol) was refluxed in pyridine for 1 h, then left to cool at r.t. The target nitriles separated as yellow crystals that were collected by filtration and crystallized from ethanol/dioxane (3:1 v/v).

3-Phenyl-3-oxo-2-phenylhydrazonopropanil-1-oxide (3a):

Yield: 1.66 g (67%); m.p. 134–135 °C. – IR (KBr): ν = 3240 (NH), 2210 (CN), 1630 cm⁻¹ (C=O). – MS (EI, 70 EV): m/z (%) = 249 [M⁺]. – ¹H NMR (300 MHz, DMSO): δ = 7.17–7.96 (m, 10H, arom. H), 14.23 (s, 1H, NH). – C₁₅H₁₃N₃O (249.26): calcd. C 72.27, H 4.45, N 16.86; found C 72.08, H 4.40, N 16.91.

3-(2-Furyl)-3-oxo-2-phenylhydrazonopropanitrile (4b):

Yield: 1.69 (71%); m.p. 161–162 °C. – IR (KBr): ν = 3245 (NH), 2190 (CN), 1612 cm⁻¹ (C=O). – MS (EI, 70 EV): m/z (%) = 239 [M⁺]. – ¹H NMR (300 MHz, DMSO): δ = 6.74–6.75 (m, 1H, furyl 4-H), 7.14–7.73 (m, 6H, arom. H, furyl 3-H), 8.26 (s, 1H, furyl 5-H), 11.99 (s, 1H, NH). – C₁₃H₁₂N₂O₂ (269.25): calcd. C 62.45, H 4.12, N 16.34; found C 62.49, H 4.24, N 15.52.

**General procedure for the preparation of 5a,b:**

Similar reaction condition as for compounds 3a-c but using the enamiones 2a,b (10 mmol). The target products 5a,b were crystallized from ethanol as yellow crystals, as for compound 5a it was obtained as semisolid compound.

3-(2-Furyl)-3-oxo-propanal-1-oxide (5b):

Yield: 1.16 g (76%); m.p. 123–124 °C. – IR (KBr): ν = 3304 (OH), 1665 cm⁻¹ (C=O). – MS (EI, 70 EV): m/z (%) = 153 [M⁺]. – ¹H NMR (300 MHz, DMSO): δ = 3.75–3.87 (m, 2H, CH₂), 6.68–6.75 (m, 1H, furyl 4-H), 6.97–6.99 (m, 1H, furyl 3-H), 7.47–7.53 (m, 1H, furyl 5-H), 8.00 (s, 1H, 1-H), 11.15 (s, 1H, oxime-H). – C₅H₇NO₃ (153.13): calcd. C 54.98, H 4.64, N 9.28.
General procedure for the preparation of 6a,b:

A cold solution of arenediazonium chloride (30 mmol), prepared as described earlier [1], was added to a cold solution of each of the oximes 5a,b (10 mmol) in ethanol (50 ml) containing sodium acetate (0.60 g). The reaction mixture was stirred at room temperature for one hour and the solid product, so formed, was collected by filtration and crystallized from ethanol.

2-Phenyldrazono-2-(phenylazo)acetonitrile (6a):

Yield: 1.54 g (62%); m.p. 95–97 °C. - IR (KBr): \(\nu = 3230 \text{ (NH)}, 2219 \text{ cm}^{-1} \text{ (CN).} \) - MS (EI, 70 EV): \(m/z\) (%) = 249 [M⁺]. - ¹H NMR (300 MHz, DMSO): \(\delta = 7.02-7.83 \text{ (m, 10H, arom. H), 12.50 (s, 1H, NH).} \) - C₁₅H₁₂N₄ (248.28): calcd. C 73.66, H 5.30, N 21.04; found C 73.64, H 5.31, N 21.08.

2-(4-Methoxyphenylhydrazono)-2-(phenylazo)acetonitrile (6b):

Yield: 1.97 g (64%); m.p. 175–176 °C. - IR (KBr): \(\nu = 3221 \text{ (NH)}, 2219 \text{ cm}^{-1} \text{ (CN).} \) - MS (EI, 70 EV): \(m/z\) (%) = 309 [M⁺]. - ¹H NMR (300 MHz, DMSO): \(\delta = 7.04-7.58 \text{ (m, 10H, arom. H), 12.60 (s, 1H, NH).} \) - C₁₆H₁₅N₅O₂ (309.32): calcd. C 62.12, H 4.89, N 21.87; found C 62.09, H 4.90, N 21.88.

5-(2-Furlyl)-4-(phenylazo)isoxazole (9):

Compound 3b (2.57 g, 10 mmol) was refluxed in acetic anhydride (10 ml) for 1 h, then left to cool at r.t. The solid product separated as pale yellow crystals that were collected by filtration and crystallized from ethanol. Yield: 1.60 g (67%); m.p. 159–160 °C. - MS (EI, 70 EV): \(m/z\) (%) = 299 [M⁺]. - ¹H NMR (300 MHz, DMSO): \(\delta = 6.80-6.81 \text{ (m, 1H, furyl 4-H), 7.19-7.22 (m, 1H, furyl 3-H), 7.44-7.61 (m, 6H, arom. H, furyl 5-H), 8.12 (s, 1H, isoxazolyl H).} \) - ¹³C[¹H] NMR (300 MHz, DMSO): \(\delta = 152.94 \text{ (C-5), 148.58 (C-3), 146.92 (C-4), 143.45, 141.89, 140.70, 129.99, 125.58, 121.77, 117.09, 113.10 (arom. carbons).} \) - C₁₃H₁₅N₅O₂ (239.23): calcd. C 65.26, H 3.79, N 20.85; found C 65.27, H 3.79, N 20.86.

1-Phenyl-2,3-bis(phenylhydrazono)-1-propanone (10a):

A mixture of compound 1a (2.52 g, 10 mmol) and phenyldrazine (1.08 g, 10 mmol) was refluxed in ethanol (10 ml) for 1 h. The solvent was removed and the residue cooled to deposit a solid, which was crystallized from ethanol. Yield: 2.56 g (75%); m.p. 240–242 °C. - IR (KBr): \(\nu = 3255 \text{ (NH), 1620 cm}^{-1} \text{ (C=O).} \) - MS (EI, 70 EV): \(m/z\) (%) = 342 [M⁺]. - ¹H NMR (300 MHz, DMSO): \(\delta = 7.04-7.58 \text{ (m, 13H, arom. H), 7.84-7.96 (m, 2H, arom. H), 8.39 (s, 1H, 3-H), 11.68 (s, 1H, NH).} \) - C₂₁H₁₈N₄O (342.39): calcd. C 73.66, H 5.30, N 16.36; found C 73.64, H 5.31, N 16.39.

General procedure for the preparation of 10b,c:

A mixture of compound 1a,b (10 mmol) and hydrazine monohydrate (0.60 g, 12 mmol) was refluxed in ethanol (10 ml) for 1 h. The solvent was removed and the residue cooled to deposit a solid, which was crystallized from ethanol.

3-Hydrazono-1-phenyl-2-phenyldrazono-1-propanone (10b):

Yield: 1.97 g (77%); m.p. 240–242 °C. IR (KBr): \(\nu = 3356 \text{ and 3220 (NH), 1613 cm}^{-1} \text{ (C=O).} \) - MS (EI, 70 EV): \(m/z\) (%) = 248 [M⁺-18]. - ¹H NMR (300 MHz, DMSO): \(\delta = 7.09-7.70 \text{ (m, 12H, arom. H, NH₂).} \) - C₁₅H₁₄N₅O₂ (266.29): calcd. C 67.65, H 5.30, N 21.04; found C 67.78, H 5.40, N 20.85.

1-(2-Furyl)-3-hydrazono-2-phenyldrazono-1-propanone (10c):

Yield: 1.97 g (77%); m.p. 145–146 °C. - IR (KBr): \(\nu = 3345 \text{ and 3210 (NH), 1593 cm}^{-1} \text{ (C=O).} \) - MS (EI, 70 EV): \(m/z\) (%) = 238 [M⁺-18]. - ¹H NMR (300 MHz, DMSO): \(\delta = 6.69-6.76 \text{ (m, 1H, furyl 4-H), 7.03-7.58 (m, 8H, arom. H, furyl 3-H, NH₂), 7.96-7.98 (m, 1H, furyl 5-H), 8.15 (s, 1H, 3-H).} \) - C₁₃H₁₂N₄O₂ (256.26): calcd. C 60.93, H 4.72, N 21.87; found C 60.99, H 4.72, N 21.60.

General preparation of 11a,b:

A solution of each of compound 10b,c (10 mmol) in pyridine (10 ml) was refluxed for 3 h. The resultant solution was poured in water. The solid product obtained was filtered off and crystallized from ethanol.

3-Phenyldrazono-4-(phenylazo)pyrazole (11a):

Yield: 1.78 g (72%); m.p. 240–242 °C. - IR (KBr): \(\nu = 3220 \text{ cm}^{-1} \text{ (NH).} \) - MS (EI, 70 EV): \(m/z\) (%) = 248 [M⁺]. - ¹H NMR (300 MHz, DMSO): \(\delta = 7.09-7.56 \text{ (m, 10H, arom. H).} \) - C₁₅H₁₃N₄O₂ (248.28): calcd. C 73.66, H 5.30, N 16.36; found C 73.64, H 5.31, N 16.39.
calcd. C 72.56, H 4.89, N 22.57; found C 72.39, H 4.73, N 22.62.

3-(2-Furyl)-4-(phenylazo)pyrazole (11b):

Yield: 1.53 g (69%); m.p. 210–212 °C. – IR (KBr): \( \nu = 3215 \text{ cm}^{-1} \) (NH). – MS (EI, 70 EV): \( m/z \) (%) = 222 [M⁺]. – \(^1\)H NMR (300 MHz, DMSO): \( \delta = 6.67–6.79 \) (m, 1H, furyl 4-H), 7.10–7.84 (m, 6H, arom. H, furyl 3-H), 7.96–7.98 (m, 1H, furyl 5-H), 8.64 (s, 1H, NH). – \( C_{13}H_{10}N_4 \) (222.24): calcd. C 70.25, H 4.54, N 25.21; found C 70.19, H 4.41, N 15.32.

General procedure for the preparation of 12a, b:

Method A: A solution of each of compound 10b, c (10 mmol) in HCl–EtOH (1 M, 10 ml) was refluxed for 1 h. The resultant solution was left to cool at r.t. The solid product obtained was filtered off and crystallized from ethanol. – Method B: A mixture of compound 1a, b (10 mmol) and hydrazine dihydrochloride (1.04 g, 10 mmol) was refluxed in ethanol (10 ml) for 1 h. The solvent was removed and the residue cooled to deposit a solid which was crystallized from ethanol.

4-Benzoyl-2-phenyl-1,2,3-triazole (12a):

Yield: 1.69 g (68%); m.p. 262–263 °C. – IR (KBr): \( \nu = 1629 \text{ cm}^{-1} \) (C=O). – MS (EI, 70 EV): \( m/z \) (%) = 249 [M⁺]. – \(^1\)H NMR (300 MHz, DMSO): \( \delta = 7.38–7.59 \) (m, 8H, arom. H), 7.86–7.94 (m, 2H, arom. H), 9.14 (s, 1H, H-5). – \(^13\)C\(^{1}\)H NMR (300 MHz, DMSO): \( \delta = 169.45 \) (CO), 158.63 (C-4), 144.20 (C-5), 142.01, 130.09, 129.69, 128.87, 127.94, 125.18, 116.33, 101.49 (arom. C). – \( C_{15}H_{11}N_3O \) (249.26): calcd. C 72.27, H 4.45, N 16.86; found C 72.18, H 4.62, N 16.85.

4-(2-Furyl)-2-phenyl-1,2,3-triazole (12b):

Yield: 1.74 g (73%); m.p. 260–261 °C. – IR (KBr): \( \nu = 1608 \text{ cm}^{-1} \) (C=O). MS (EI, 70 EV): \( m/z \) (%) = 239 [M⁺]. – \(^1\)H NMR (300 MHz, DMSO): \( \delta = 6.65–6.79 \) (m, 1H, furyl 4-H), 7.00–7.62 (m, 6H, arom. H, furyl 3-H), 7.96–7.98 (m, 1H, furyl 5-H), 9.15 (s, 1H, H-5). – \( C_{13}H_{10}N_2O_2 \) (239.23): calcd. C 65.26, H 3.79, N 17.57; found C 65.24, H 3.89, N 17.45.