Facile, mild and efficient synthesis of azines using phosphonic dihydrazide

Rizk E. Khidre[a,b], Hanan A. Mohamed[c,d], Benson M. Kariuki[e], and Gamal A. El-Hiti[f]

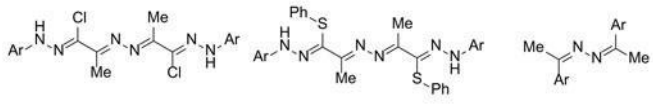
[a]Chemical Industries Division, National Research Centre, Dokki, Giza, Egypt; [b]Chemistry Department, Faculty of Science, Jazan University, Jazan, Saudi Arabia; [c]Applied Organic Chemistry Department, National Research Center, Dokki, Giza, Egypt; [d]Department of Chemistry, College of Science and Humanities, Shaqra University, Duwadimi, Saudi Arabia; [e]School of Chemistry, Cardiff University, Cardiff, UK; [f]Department of Optometry, College of Applied Medical Sciences, King Saud University, Riyadh, Saudi Arabia

ABSTRACT

Several bis(N' -arylpropanehydrazonoyl chlorides) were synthesized in good yields from condensation reactions of hydrazonoyl chlorides and phosphonic dihydrazide. Under the conditions employed, none of the expected phosphorylhydrazines were isolated. Nucleophilic substitution of bis(N' -arylpropanehydrazonoyl chlorides) with thiophenol, sodium phenylsulfinate, hydroxyl amine, and piperidine afforded the corresponding azines. Similarly, 1,2-bis(heteroaryl)ethylidene)hydra-zines were produced from reaction of phosphonic dihydrazide and heteroaryl methyl ketones. The structures of the products were confirmed by NMR and IR spectral data along with X-ray crystal structure determination and their purities were confirmed by the elemental analyses.

KEYWORDS Phosphonic dihydrazide; azines; nucleophilic substitution reaction; heterocycles; bis(N'-arylpropanehydrazonoyl chlorides); X-ray crystallography

GRAPHICAL ABSTRACT



Introduction

Azines or 2,3-diaza-1,3-butadienes, (R_2C ¼ N–N ¼ CR_2), are important compounds in various synthetic transforma-tions.[1–4] They have unique chemical structures compared to simple 1,3-butadienes and therefore can produce five-membered heterocycles via 1,3-dipolar cycloadditions.[5–8] For example, one-pot reaction of azines and benzylidenemalononitriles, via copper-catalyzed tandem cyclization, gave 1,2,4-triazolo[1,5-a]pyridines.[9] Azines exhibit various pharmacological activities[10] and act as antitumor,[11] anti-convulsant,[12] antioxidant,[13] and antimicrobial agents.[14] In addition, they have interesting industrial applications and can be used as optical materials,[15] conductive media,[16] organic sensors,[17] and semiconductors.[18]

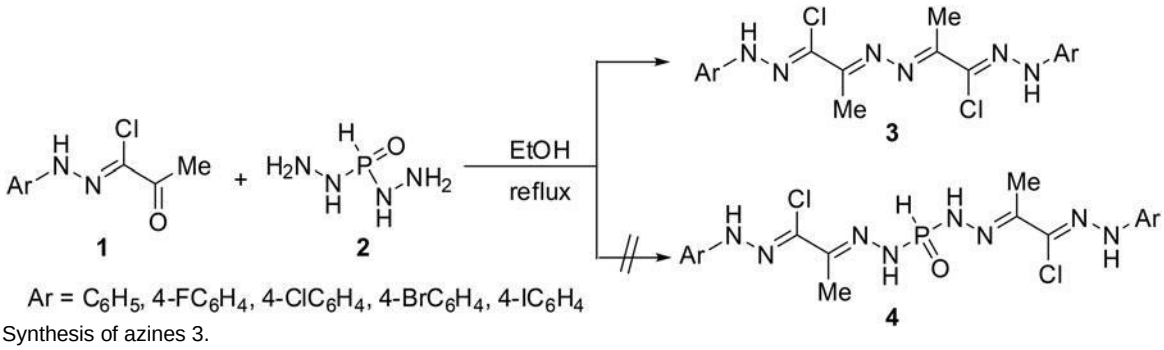
The synthesis of azines involves the condensation reaction of carbonyl compounds and hydrazines such as hydrazine hydrate, hydrazine sulfate or hydrazinium carboxylate.[19] Also, they can be synthesized from the copper-catalyzed dimerization of imines,[20] and homo-coupling of ketoximes.[21] In addition, azines can be directly synthesized from reaction of alcohols and hydrazine hydrate in the presence of ruthenium[22] or nickel complexes.[23] Recently, the reaction of 3-hydrazonobutan-2-one oxime and aromatic aldehydes has been reported to produce the corresponding 1,2-bis(arylidene)hydrazines in high yields.[24] In the current work, a novel series of azines was produced by simple and efficient synthetic procedures from phosphonic dihydrazide, as part of our research program on the synthesis of novel heterocycles.[25–29]

Results and discussion

Condensation of a 2:1 mixture of 2-oxo-N'-arylpropanehydrazonoyl chlorides 1 and phosphonic dihydrazide (2) in boiling ethanol for 3 h gave bis(N'-arylpropanehydrazonoyl chlorides) 3 in good yields rather than the expected products, (2,2^{U}-phosphoryl)bis(hydrazin-2-yl-1-ylidene))bis(N^{U}-arylpropanehydrazonoyl chlorides) 4 (Scheme 1). The ^{1}H NMR spectra of 3 showed exchangeable singlets that resonated within the 10.32–10.47 ppm region corresponding to the NH protons. The ^{13}C NMR spectra of 3 showed all the expected carbons. Moreover, IR and ^{13}C NMR spectra of 3 indicated the absence of a carbonyl group. The X-ray crystal structures of 3c and 3d are shown in Figures 1 and 2, respectively.

No evidence was found to prove that products 4 were formed under the condition attempted. When an equimolar reaction of 1 and 2 was attempted, only products 3 were

CONTACT Gamal A. El-Hiti gelhiti@ksu.edu.sa Department of Optometry, College of Applied Medical Sciences, King Saud University, P.O. Box 10219, Riyadh 11433, Saudi Arabia.



Scheme 1. Synthesis of azines 3.

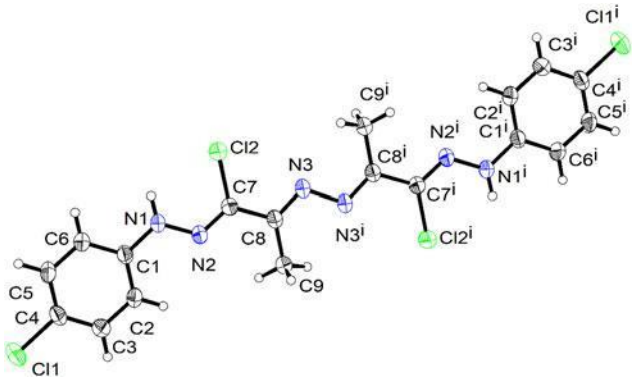


Figure 1. Ortep representation of the molecular structure of 3c showing 50% probability ellipsoids.

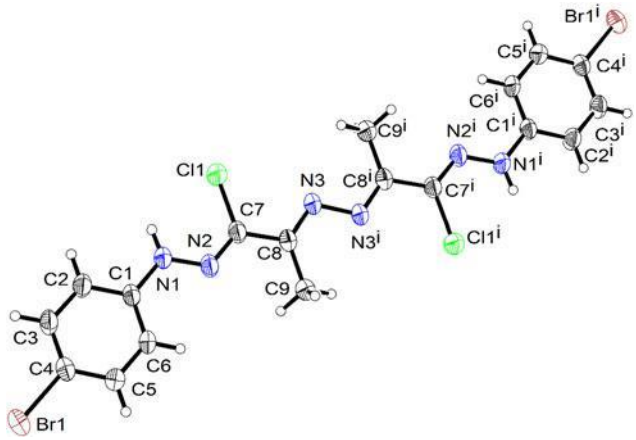


Figure 2. Ortep representation of the molecular structure 3d showing 50% probability ellipsoids.

produced in low yields along with 1. Such results are not in agreement with the reported ones.[30,31] Two reports, by the same author(s), showed that reactions of a 2:1 mixture of compounds of the type of 1 and 2 in EtOH for 1–4 h, in the presence or absence of sulfuric acid, gave 4 in 46–91% yields.[30,31] However, an early report that investigated the reactions between carbonyl compounds and dihydrazides of phosphonothioic acid showed that products either of the type 3 or 4 or a mixture of both could be produced based on the substituents attached to the carbonyl group.[32] For example, the reaction of 4-methylbenzaldehyde with the dihydrazide of phosphonothioic acid gave the corre-sponding product of type 3 as the only product in 78% yield.[32] A proposed mechanism for the formation of 3 from reaction of 1 (two mole equivalents) and 2 is shown in Scheme 2. Based on an early report,[32] it is believed that the nucleophilic attack of the nitrogen of the amino group in 2 at the carbonyl carbon of 1 would lead to intermediate A which on reaction with 1 would give cyclic intermediate B. Hydrolysis of B would give 3 and hydrazinylphosphinic acid as a side product.

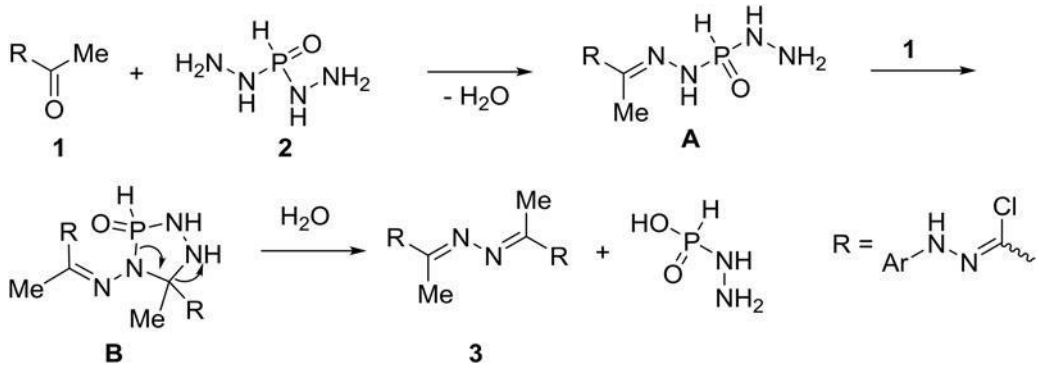
The utility of 3 in organic synthesis has been tested on reactions with nucleophiles. Reactions of 3c,d and thiophenol, sodium phenylsulfinate, hydroxylamine hydrochloride and piperidine in boiling ethanol afforded the corresponding azines 5–8 (Scheme 3) in good yields. The reactions proceeded via replacement of the two chlorine atoms in compounds 3c,d. Similar related reactions have been reported.[33–35] The X-ray crystal structure of compound 5b is shown in Figure 3.

Reaction of methyl ketones 9 and 2 in boiling ethanol for 2–3 h furnished the corresponding azines 10a–e (Scheme 4) in good yields. The structures of 10a and 10b were confirmed by X-ray crystallography as shown in Figures 4 and 5, respectively. The spectral data for 10a,b were in agree-ment with those reported.[36,37]

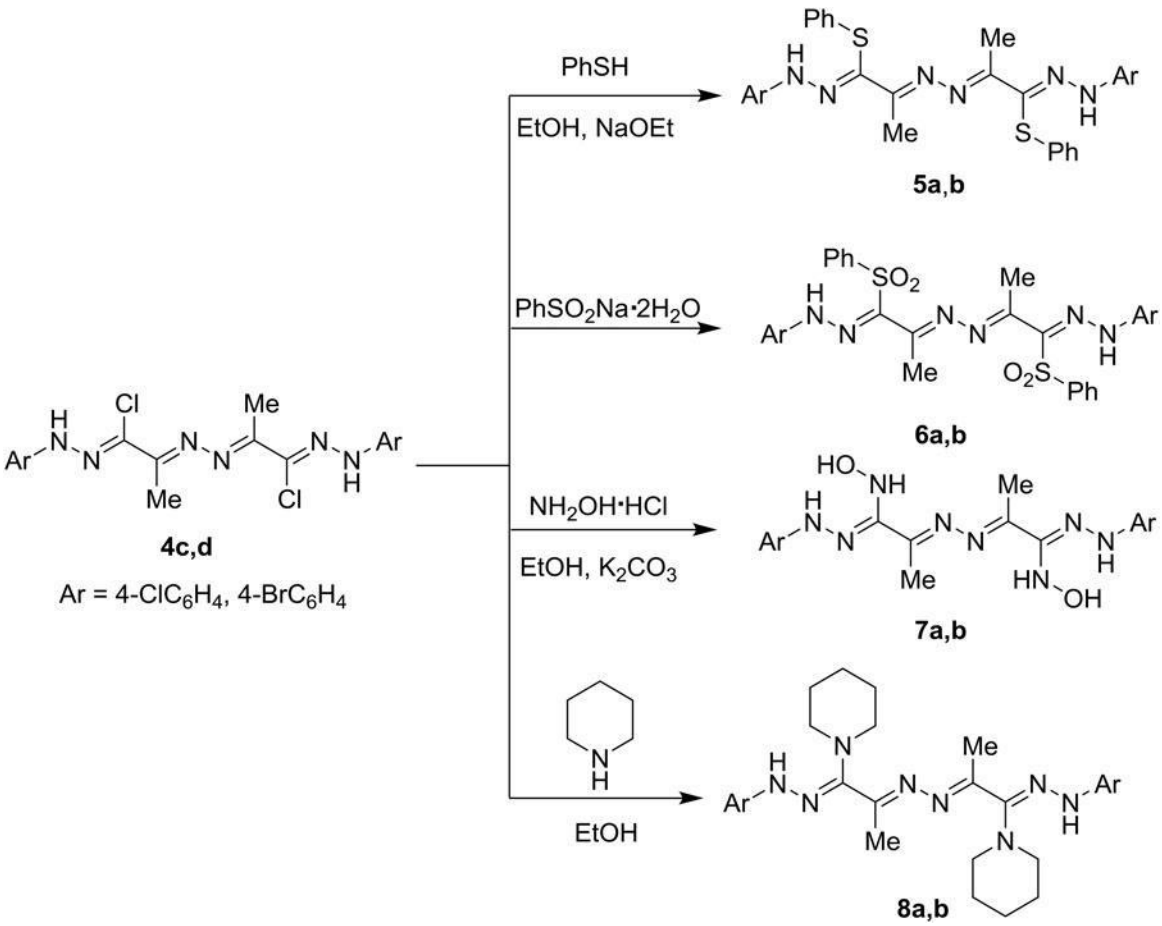
Similarly, reaction of isatin (11) and 2 in ethanol under reflux for 3 h afforded (3Z,3'E)-3,3'-(hydrazine-1,2-diylidene)bis(indolin-2-one) (12) in 85% yield (Scheme 5). The X-ray crystal structure of 12 is shown in Figure 6. The spectral data for 12 were in agreement with those reported.[38] For example, the IR spectrum showed a strong absorption peak at 1725 cm ^{1} which is attributed to the carbonyl group. The carbonyl carbon appeared at 164.1 ppm in the ^{13}C NMR spectrum. In addition, the ^{1}H NMR spectrum showed the presence of exchangeable singlets that appeared at 10.61 ppm due to the two NH protons.

Discussion of molecular structures

Data refinement parameter, bond lengths and angles obtained by single crystal diffraction are shown in Tables S1–S12. The molecule of 3c has inversion symmetry and, apart from the methyl hydrogen atoms, is planer with a maximum deviation of 0.11(1) Å from the least squares plane through the atoms Figure 1). The molecule of 3d also has inversion symmetry and is planer apart from the methyl hydrogen atoms with a maximum deviation of 0.11(1) Å from the least squares plane (Figure 2). The molecule of 5b has inversion symmetry and,



Scheme 2. Possible pathway for the formation of azines 3.



Scheme 3. Synthesis of azines 5–8.

with the exception of the phenyl group and methyl hydrogen atoms, is planar with a maximum deviation of 0.105(2) Å from the least squares plane (Figure 3).

In 10a, the separate dihydrobenzofuranyl ethanimine fragments of the molecule are planer (apart from the methyl hydrogen atoms) with a maximum deviation of 0.192(2) Å from their least squares planes (Figure 4). The twist angle between the two fragments of the molecule is 55.66(3) . For 10b, the molecule has pseudo-inversion symmetry in the crystal (Figure 5). In contrast to 10a, the molecule is essentially planar with a maximum deviation of 0.268(2) Å from the least squares plane of the molecule (apart from the methyl hydrogen atoms). Molecule 12 has inversion sym-metry and is planer with a maximum deviation of ±0.0706 (14) from the least squares plane through the atoms (Figure 6).

The planar geometry and inversion symmetry generally observed for these materials (except for 10a) is akin to that observed for 3,3^0-(hydrazine-1,2-diylidenedieth-1-yl-1-ylidene)bis(1H-pyrazole).[39]

Experimental

General

Melting points were recorded on a Gallenkamp melting point apparatus. The IR spectra (KBr disks) were obtained using PerkinElmer GX Spectrometer. The NMR spectra

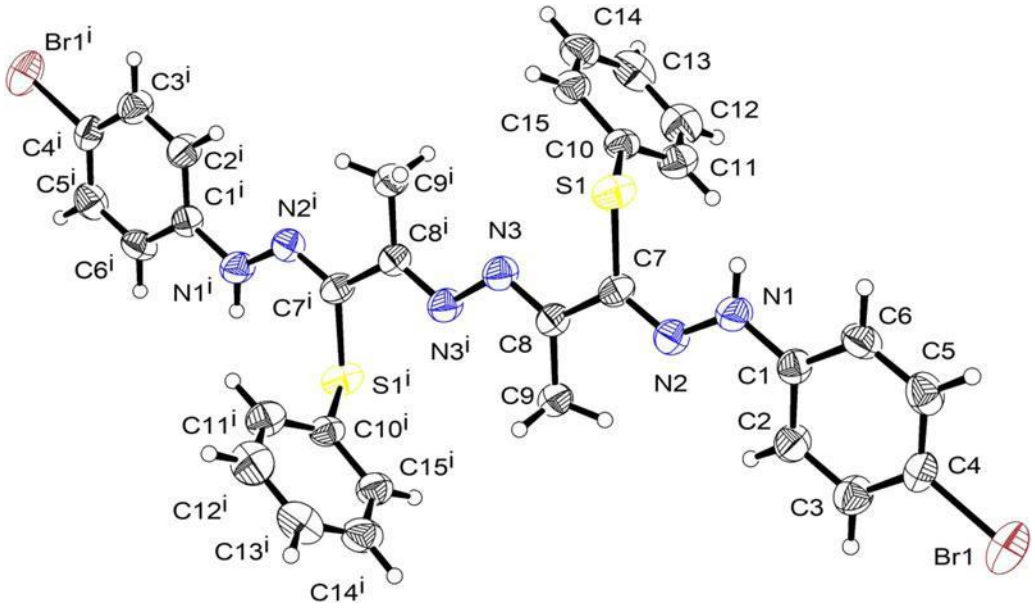
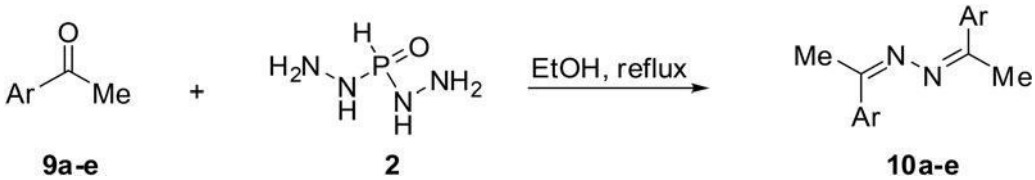


Figure 3. Ortep representation of the molecular structure of 5b showing 50% probability ellipsoids.



Scheme 4. Synthesis of azines 10a-e.

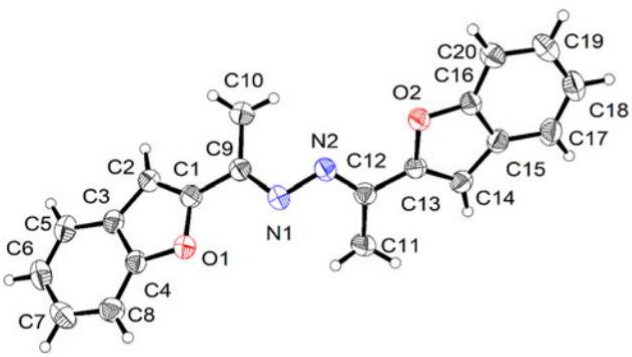


Figure 4. Ortep representation of the molecular structure of 10a showing 50% probability ellipsoids.

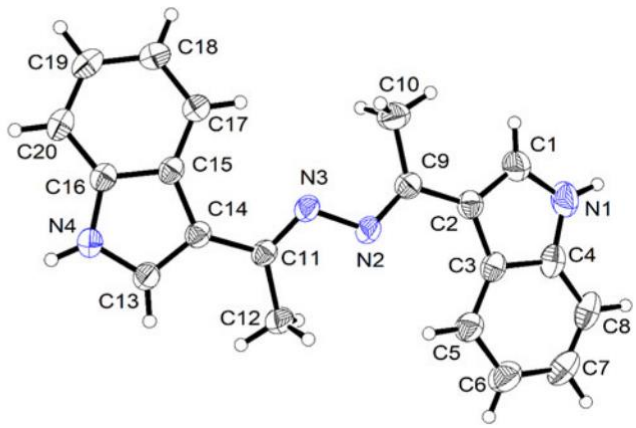
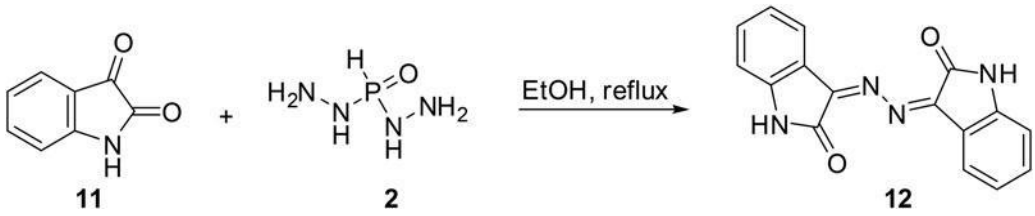


Figure 5. Ortep representation of the molecular structure of 10b showing 50% probability ellipsoids.

were carried out on JEOL 500 MHz spectrometer (TMS; d in ppm and J in Hz) at 500 MHz for ^{1}H and 125 MHz for ^{13}C NMR, in DMSO-d_6 unless otherwise indicated. The crystallographic data for compounds 3c, 3d, 5b, 10a, 10b, and 12 were deposited at the Cambridge Crystallographic Data Center with CCDC reference numbers 1861134–1861139. Phosphonic dihydrazide 2 was produced based on a literature procedure.[40] The Supplemental Materials contains sample ^{1}H and ^{13}C NMR spectra for products 3, 5, and 6 (Figures S1 – S11).

Synthesis of 3a–e: A mixture of 1 (10.0 mmol) and 2 (0.55 g, 5.0 mmol) in EtOH (20 mL) was refluxed for 3 h. The solid formed on cooling was filtered and recrystallized from EtOH to give pure 3.

(1Z,1^{0}Z,2E,2^{0}E)-2,2^{0}-(Hydrazine-1,2-diylidene)bis(N^{0}-phenylpropanehydrazonoyl chloride) (3a): m.p., 197–198 C, brown, yield, 85%; IR (max, cm ^{1}): 3319 (NH), 1602 (C ¼ N), 1541, 1508 (C ¼ C). ^{1}H NMR (d_H, ppm): 2.25 (s, 6 H, 2Me), 6.93 (t, J ¼ 8.5 Hz, 2 H, H-4 of 2Ph), 7.30 (t, J ¼ 8.5 Hz, 4 H, H-3/H-5 of 2Ph), 7.36 (d, 4 H, $_{13}$J ¼ 8.5 Hz, H-2/H-6 of 2Ph), 10.32 (s, exch., 2 H, 2NH). C NMR (d_C, ppm): 14.6 (Me), 114.0, 123.2, 129.2, 143.4, 153.9 (C-Cl), 155.7 (C-Me). Anal. Calcd. for $C_{18}H_{18}Cl_2N_6$ (389.28): C, 55.54; H, 4.66; N, 21.59, Found: C, 55.21; H, 4.42; N, 21.44%.



Scheme 5. Synthesis of (3Z,3'E)-3,3'-(hydrazine-1,2-diylidene)bis(indolin-2-one) (12).

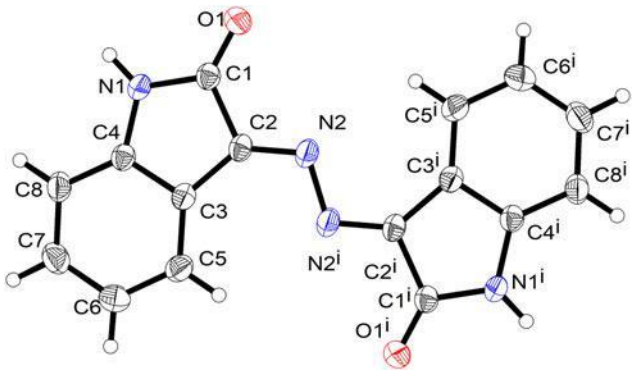


Figure 6. Ortep representation of the molecular structure of 12 showing 50% probability ellipsoids.

(1Z,1^{0}Z,2E,2^{0}E)-2,2^{0}-(Hydrazine-1,2-diylidene)bis(N-(4-flu-orophenyl)propanehydrazonoyl chloride) (3 b): m.p., 193–194 C, red, yield, 89%; IR ($_{max}$, cm ^{1}): 3329 (NH), 1600 (C ¼ N), 1541, 1510 (C ¼ C). ^{1}H NMR (d$_{H}$, ppm): 2.24 (s, 6 H, 2Me), 7.34 (d, 4 H, J ¼ 8.4 Hz, H-2/H-6 of 2Ar), 7.37 (d, ^{4} $_{13}$ J ¼ 8.4 Hz, H-3/H-5 of 2Ar), 10.34 (s, exch., 2 H, 2NH). C NMR (d$_{C}$, ppm): 14.6 (Me), 114.3, 116.5, 131.8, 143.4, 153.9 (C-Cl), 156.4 (C-Me). Anal. Calcd. for $C_{18}H_{16}Cl_2F_2N_6$ (425.26): C, 50.84; H, 3.79; N, 19.76, Found: C, 50.59; H, 3.57; N, 19.63%.

(1Z,1^{0}Z,2E,2^{0}E)-2,2^{0}-(Hydrazine-1,2-diylidene)bis(N^{0}-(4-chlorophenyl)propanehydrazonoyl chloride) (3c): m.p., 217–218 C, brown, yield, 90%; IR ($_{max}$, cm ^{1}): 3325 (NH), 1595 (C ¼ N), 1552, 1500 (C ¼ C). ^{1}H NMR (d$_{H}$, ppm): 2.26 (s, 6 H, 2Me), 7.30 (d, 4 H, J ¼ 8.1 Hz, H-2/H-6 of 2Ar), 7.37 (d, 4 H, J ¼ 8.1 Hz, H-3/H-5 of 2Ar), 10.45 (s, exch., 2 H, 2NH). ^{13}C NMR (d$_{C}$, ppm): 14.6 (Me), 115.0, 123.5, 129.8, 142.2, 153.4 (C-Cl), 155.9 (C-Me); Anal. Calcd. for $C_{18}H_{16}Cl_4N_6$ (458.17): C, 47.19; H, 3.52; N, 18.34, Found: C, 46.97; H, 3.35; N, 18.19%.

(1Z,1^{0}Z,2E,2^{0}E)-2,2^{0}-(Hydrazine-1,2-diylidene)bis(N^{0}-(4-bromophenyl)propanehydrazonoyl chloride) (3d): m.p., 227–228 C, brown, yield, 87%; IR ($_{max}$, cm ^{1}): 3325 (NH), 1591 (C ¼ N), 1552 s, 1497 s (C ¼ C); ^{1}H NMR (d$_{H}$, ppm): 2.21 (s, 6 H, 2Me), 7.36 (d, 4 H, J ¼ 8.0 Hz, H-2/H-6 of 2Ar), 7.63 (d, 4 H, $_{13}$ J ¼ 8.0 Hz, H-3/H-5 of 2Ar), 10.43 (s, exch., 2 H, 2NH); C NMR (d$_{C}$, ppm): 14.6 (Me), 115.0, 116.0, 132.5, 143.2, 153.4 (C-Cl), 156.0 (C-Me); Anal. Calcd. for $C_{18}H_{16}Br_2Cl_2N_6$ (547.08): C, 39.52; H, 2.95; N, 15.36, Found: C, 39.37; H, 2.79; N, 15.18%.

(1Z,1^{0}Z,2E,2^{0}E)-2,2^{0}-(Hydrazine-1,2-diylidene)bis(N^{0}-(4-iodophenyl)propanehydrazonoyl chloride) (3e): m.p., 230–231 C, red, yield, 80%; IR ($_{max}$, cm ^{1}): 3323 (NH), 1590 (C ¼ N), 1552, 1496 (C ¼ C). ^{1}H NMR (d$_{H}$, ppm): 2.19 (s, 6 H, 2Me), 7.28 (d, 4 H, J ¼ 7.9 Hz, H-2/H-6 of 2Ar), 7.67 (d, 4 H, J ¼ 7.9 Hz, H-3/H-5 of 2Ar), 10.47 (s, exch., 2 H, 2NH). ^{13}C NMR (d$_{C}$, ppm): 14.6 (Me), 87.0, 116.0, 135.6, 143.2, 154.0 (C-Cl), 156.5 (C-Me). Anal. Calcd. for $C_{18}H_{16}Cl_2I_2N_6$ (641.08): C, 33.72; H, 2.52; N, 13.11, Found: C, 33.64; H, 2.43; N, 13.02%.

Synthesis of 5a,b: A mixture of thiophenol (0.22 g, 2.0 mmol) and 3c or 3d (1.0 mmol) was added to dry EtOH (30 mL) containing sodium (46 mg, 2.0 mmol). The mixture was refluxed for 6 h and the solid formed on cooling was isolated by filtration, washed with EtOH, dried and recrys-tallized from EtOH to give 5a or 5 b, respectively.

(1Z,1^{0}Z,2E,2^{0}E)-Diphenyl 2,2^{0}-(hydrazine-1,2-diylidene) bis(N^{0}-4-chlorophenylpropanehydrazono-thioate) (5a): m.p., 158–159 C, red, yield, 85%; IR ($_{max}$, cm ^{1}): 3270 (NH), 1590, 1578 (C ¼ N), 1510, 1475 (C ¼ C). ^{1}H NMR (d$_{H}$, ppm): 1.82 (s, 6 H, 2Me), 7.32–7.37 (m, 18 H, 2Ph and 2Ar), 10.6 (s, exch., 2 H, 2NH). ^{13}C NMR (d$_{C}$, ppm): 13.87 (Me), 112.7, 116.2, 126.0, 127.5, 129.3, 131.7, 133.9, 135.8, 142.8 (C-S), 155.2 (C-Me). Anal. Calcd. for $C_{30}H_{26}Cl_2N_6S_2$ (605.60): C, 59.50; H, 4.33; N, 13.88, Found: C, 59.32; H, 4.15; N, 13.67%.

(1Z,1^{0}Z,2E,2^{0}E)-Diphenyl 2,2^{0}-(hydrazine-1,2-diylidene) bis(N^{0}-4-bromophenylpropanehydrazono-thioate) (5 b): m.p., 160–161 C, red, yield, 86%; IR ($_{max}$, cm ^{1}): 3269 (NH), 1591, 1575 (C ¼ N), 1510, 1475 (C ¼ C). ^{1}H NMR (d$_{H}$, ppm): 1.82 (s, 6 H, 2Me), 7.17–7.28 (m, 10 H, 2Ph), 7.37 (d, 4 H, J ¼ 8.0 Hz, H-2/H-6 of 2Ar), 7.51 (d, ^{4} $_{13}$ H, J ¼ 8.0 Hz, H-3/H-5 of 2Ar), 10.60 (s, exch., 2 H, 2NH). C NMR (d$_{C}$, ppm): 13.9 (Me), 112.7, 116.2, 126.0, 127.5, 129.3, 131.7, 133.9, 135.8, 142.8 (C-S), 155.2 (C-Me). Anal. Calcd. for $C_{30}H_{26}Br_2N_6S_2$ (694.51): C, 51.88; H, 3.77; N, 12.10, Found: C, 51.67; H, 3.62; N, 11.92%.

Synthesis of 6a,b: A mixture of 3c or 3d (1.0 mmol) and sodium benzenesulfinate dihydrate (0.80 g, 4.0 mmol) in EtOH (30 mL) was heated under reflux for 2 h. The solid produced on cooling was filtered, washed with EtOH, dried and recrystallized from EtOH to give 6a or 6 b, respectively.

(1E,2E)-1,2-bis((Z)-1-(2-(4-Chlorophenyl)hydrazono)-1-(phenylsulfonyl)propan-2-ylidene)hydrazine (6a): m.p., 219–220 C, brown, yield, 89%; IR ($_{max}$, cm ^{1}): 3325 (NH), 1597 (C ¼ N), 1552, 1500 (C ¼ C). ^{1}H NMR (d$_{H}$, ppm): 2.22 (s, 6 H, 2Me), 7.32–7.37 (m, 18 H, 2Ph and 2Ar), 10.45 (s, exch. 2 H, 2NH). ^{13}C NMR (d$_{C}$, ppm): 14.6 (Me), 115.5, 116.2, 124.0, 125.0, 129.0, 142.4, 145.8 (C-S), 153.2 (C-Me). Anal. Calcd. for $C_{30}H_{26}Cl_2N_6O_4S_2$ (669.60): C, 53.81; H, 3.91; N, 12.55, Found: C, 53.69; H, 3.78; N, 12.39%.

(1E,2E)-1,2-bis((Z)-1-(2-(4-Bromophenyl)hydrazono)-1-(phenylsulfonyl)propan-2-ylidene)hydrazine (6 b): m.p., 252–253 C, brown, yield, 90%; IR ($_{max}$, cm ^{1}): 3325 (NH), 1591 (C ¼ N), 1552, 1496 (C ¼ C). ^{1}H NMR (d$_{H}$, ppm): 1.87

(s, 6 H, 2Me), 7.27–7.32 (m, 10 H, 2Ph), 7.39 (d, 4 H, J ¼ 8.0 Hz, H-2/H-6 of 2Ar), 7.55 (d, 4 H, J ¼ 8.0 Hz, H-3/H-5 of 2Ar), 10.63 (s, exch., 2 H, 2NH). ^{13}C NMR (δ_C, ppm): 13.9 (CH_3), 112.7, 116.2, 126.0, 127.5, 129.3, 131.7, 133.9, 137.8, 142.8 (C-S), 155.9 (C-Me). Anal. Calcd. for $C_{30}H_{26}Br_2N_6O_4S_2$ (758.50): C, 47.50; H, 3.46; N, 11.08, Found: C, 47.36; H, 3.29; N, 10.89%.

Synthesis of 7a,b: Hydroxylamine hydrochloride (0.14 g, 2.0 mmol) and anhydrous potassium carbonate (0.28 g, 2.1 mmol) was added to a solution of 3c or 3d (1.0 mmol) in dry EtOH (30 mL). The mixture was refluxed for 3 h and the solid formed on cooling was filtered and recrystallized from EtOH to give 7a or 7b, respectively.

(1Z,1′Z,2E,2′E)-2,2′-(Hydrazine-1,2-diylidene)bis(N′-(4-chlorophenyl)-N-hydroxypropane-hydrazonamide) (7a): m.p., 235–236 C, red, yield, 83%; IR (ν_{max}, cm^{-1}): 3392 (OH), 3244 (NH), 1597 (C ¼ N), 1496 (C ¼ C). ^{1}H NMR (δ_H, ppm): 2.22 (s, 6 H, 2Me), 7.18 (d, 4 H, J ¼ 8.0 Hz, H-2/ H-6 of 2Ar), 7.32 (d, 4 H, J ¼ 8 Hz, H-3/H-5 of 2Ar), 7.70 (s, exch., 2 H, 2OH), 7.80 (s, exch., 2 H, 2NH), 10.46 (s, exch., 2 H, 2NH). ^{13}C NMR (δ_C, ppm): 13.9 (Me), 113.6, 116.0, 126.0, 131.9, 143.8 (C-NH), 152.7 (C-Me). Anal. Calcd. for $C_{18}H_{20}Cl_2N_8O_2$ (451.31): C, 47.90; H, 4.47; N, 24.83, Found: C, 47.76; H, 4.31; N, 24.67%.

(1Z,1′Z,2E,2′E)-2,2′-(Hydrazine-1,2-diylidene)bis(N′-(4-bromophenyl)-N-hydroxypropane-hydrazonamide) (7 b): m.p., 254–255 C, brown, yield, 87%; IR (ν_{max}, cm^{-1}): 3400 (OH), 3325 (NH), 1591 (C ¼ N), 1552, 1500 (C ¼ C). ^{1}H NMR (δ_H, ppm): 2.22 (s, 6 H, 2Me), 7.30 (d, 4 H, J ¼ 9.0 Hz, H-2/H-6 of 2Ar), 7.45 (d, 4 H, J ¼ 9.0 Hz, H-3/H-5 of 2Ar), 7.70 (s, exch., 2 H, 2OH), 7.90 (s, exch., 2 H, 2NH), 10.46 (s, exch., 2 H, 2NH). ^{13}C NMR (δ_C, ppm): 14.6 (Me), 112.8, 116.0, 124.0, 131.9, 142.7 (C-NH), 153.7 (C-Me). Anal. Calcd. for $C_{18}H_{20}Br_2N_8O_2$ (540.22): C, 40.02; H, 3.73; N, 20.74, Found: C, 39.92; H, 3.61; N, 20.56%.

Synthesis of 8a,b: A mixture of 3c or 3d (1.0 mmol) in dry EtOH (30 mL) containing piperidine (0.34 g, 4.0 mmol) was then refluxed for 6 h. The solid formed on cooling was filtered and recrystallized from EtOH to yield 8a or 8 b, respectively.

(1E,2E)-1,2-bis((Z)-1-(2-(4-Chlorophenyl)hydrazono)-1-(piperidin-1-yl)propan-2-ylidene)hydrazine (8a): m.p., 228–229 C, red, yield, 82%; IR (ν_{max}, cm^{-1}): 3310 (NH), 1601 (C ¼ N), 1562, 1510 (C ¼ C). ^{1}H NMR (δ_H, ppm): 1.58–1.62 (m, 12 H, H-3/H-4/H-5 of 2 piperidinyl), 2.26 (s, 6 H, 2Me), 3.16 (m, 8 H, H-2/H-6 of 2 piperidinyl), 7.28 (d, 4 H, J ¼8 Hz, H-2/H-6 of 2Ar), 7.36 (d, 4 H, J_{13} ¼ 7.5 Hz, H-3/H-5 of 2Ar), 10.45 (s, exch., 2 H, 2NH). ^{13}C NMR (δ_C, ppm): 14.6 (Me), 23.7 (C-4 of piperidinyl), 25.3 (C-3/ C-5 of piperidinyl), 48.7 (C-2/C-5 of piperidinyl), 115.0, 124.5, 129.8, 142.21, 153.4 (C-piperidinyl), 155.8 (C-Me). Anal. Calcd. for $C_{28}H_{36}Cl_2N_8$ (555.55): C, 60.54; H, 6.53; N, 20.17, Found: C, 60.36; H, 6.33; N, 20.02%.

(1E,2E)-1,2-bis((Z)-1-(2-(4-Bromophenyl)hydrazono)-1-(piperidin-1-yl)propan-2-ylidene)hydrazine (8 b): m.p., 236–237 C, red, yield, 80%; IR (ν_{max}, cm^{-1}): 3295 (NH), 1597 (C ¼ N), 1560, 1490 (C ¼ C). ^{1}H NMR (δ_H, ppm): 1.57–1.63 (m, 12 H, H-3/H-4/H-5 of 2 piperidinyl), 2.26 (s, 6 H, 2Me), 3.16 (m, 8 H, H-2/H-6 of 2 piperidinyl), 7.35 (d, 4 H, J ¼ 8 Hz, H-2/H-6 of 2Ar), 7.476 (d, 4 H, J ¼ 8.5 Hz, H-3/H-5 of 2Ar), 10.55 (s, exch., 2 H, 2NH). ^{13}C NMR (δ_C, ppm): 14.6 (Me), 23.0 (C-4 of piperidinyl), 25.5 (C-3/C-5 of piperidinyl), 48.7 (C-2/C-6 of piperidinyl), 116.0, 117.0, 131.8, 142.2, 153.4 (C-piperidinyl), 154.7 (C-Me). Anal. Calcd. for $C_{28}H_{36}Br_2N_8$ (644.46): C, 52.18; H, 5.63; N, 17.39, Found: C, 52.01; H, 5.45; N, 17.21%.

Synthesis of 10a–e: A mixture of ketones 9 (20 mmol) and 2 (1.10 g, 10 mmol) in EtOH (20 mL) was refluxed for 2–3 h. The solid produced on cooling was filtered, dried and recrystallized from EtOH to give 10.

(1Z,2Z)-1,2-bis(1-(Benzofuran-2-yl)ethylidene)hydrazine (10a): m.p., 163–165 C (lit. m.p. 163–164 C[36]), red, yield, 88%. The spectral data for 10a was in agreement with those reported.[36]

(1Z,2Z)-1,2-bis(1-(1H-Indol-3-yl)ethylidene)hydrazine (10 b): m.p., 280–281 C (lit. m.p. 280–282 C [37]), red, yield, 80%. The spectral data for 10b was in agreement with those reported.[37]

(1Z,2Z)-1,2-bis(1-(5-Methyl-1-phenyl-1H-1,2,3-triazol-4-yl)ethylidene)hydrazine (10c): m.p., 260–261 C, yellow, yield, 82%; IR (ν_{max}, cm^{-1}): 1614, 1598 (C ¼ N), 1500 (C ¼ C). ^{1}H NMR ($CDCl_3$; δ_H, ppm): 2.47 (s, 6_{H}, 2Me), 2.70 (s, 6 H, 2Me), 7.25–7.30 (m, 10 H, 2Ph). ^{13}C NMR ($CDCl_3$; δ_C, ppm): 10.5 (Me), 21.34 (Me), 115.0, 125.0, 131.1, 133.1, 139.6, 144.4, 160.0 (C-Me). Anal. Calcd. for $C_{22}H_{22}N_8$ (398.47): C, 66.31; H, 5.57; N, 28.12, Found: C, 66.13; H, 5.39; N, 27.98%.

(1Z,2Z)-1,2-bis(1-(1-(4-Fluorophenyl)-5-methyl-1H-1,2,3-triazol-4-yl)ethylidene)hydrazine (10d): m.p., >300 C, pale yellow, yield, 81%; IR (ν_{max}, cm^{-1}): 1614 (C ¼ N), 1514 (C ¼ C). ^{1}H NMR ($CDCl_3$; δ_H, ppm): 2.47 (s, 6 H, 2Me), 2.70 (s, 6 H, 2Me), 7.35 (d, 4 H, J ¼ 8 Hz, H-2/H-6 of 2Ar), 7.38 (d, 4 H, J ¼ 8 Hz, H-3/H-5 of 2Ar). ^{13}C NMR ($CDCl_3$; δ_C, ppm): 10.8 (Me), 21.3 (Me), 116.0, 124.7, 132.5, 135.3, 141.5, 145.2, 161.2 (C-Me). Anal. Calcd. for $C_{22}H_{20}F_2N_8$ (434.45): C, 60.82; H, 4.64; N, 25.79, Found: C, 60.67; H, 4.51; N, 25.57%.

(1Z,2Z)-1,2-bis(1-(5-Methyl-1-(4-tolyl)-1H-1,2,3-triazol-4-yl)ethylidene)hydrazine (10e): m.p., 285–286 C, yellow, yield, 86%; IR (ν_{max}, cm^{-1}): 1612 (C ¼ N), 1552, 1520 (C ¼ C). ^{1}H NMR ($CDCl_3$; δ_H, ppm): 2.47 (s, 6 H, 2Me), 2.68 (s, 6 H, 2Me), 2.75 (s, 6 H, 2Me), 7.26–7.39 (m, 8 H, 2Ar). ^{13}C NMR ($CDCl_3$; (δ_C, ppm): 11.5 (Me), 21.3 (Me), 27.9 (Me), 125.0, 125.2, 130.14, 130.2, 140.4, 144.0, 157.0 (C-Me). Anal. Calcd. for $C_{24}H_{26}N_8$ (426.53): C, 67.58; H, 6.14; N, 26.27, Found: C, 67.45; H, 5.97; N, 26.07%.

Synthesis of (3Z,3′E)-3,3′-(hydrazine-1,2-diylidene)diindolin-2-one (12): A mixture of 11 (1.47 g, 10 mmol) and 2 (0.55 g, 5 mmol) in EtOH (20 mL) was refluxed for 3 h. The solid obtained on cooling was filtered, dried and recrystallized from EtOH to give 12 as red crystals, yield 2.58 g (89%), m.p. 293–294 C (lit. m.p. > 300 C[38]). The spectral data was in agreement with those reported.

Crystal structure determination

Single-crystal XRD data were collected on an Agilent SuperNova Dual Atlas diffractometer with a mirror

monochromator using either Cu (k ¼ 1.5418 Å) or Mo (k ¼ 0.7107 Å) radiation. Crystal structures were solved using SHELXS [41] and refined using SHELXL. [42] Non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were inserted in idealized positions, and a riding model was used with U_{iso}(H) set at 1.2 or 1.5 times the value of U_{eq}(C/N). Data collection and refinement parameters are shown in Tables S1–S12 (Supplemental Materials).

Conclusions

New, simple and efficient procedures have been developed for the synthesis of symmetrical azines in high yields from phosphonic dihydrazide and commercially avail-able reagents.

Acknowledgements

The authors extend their appreciation to the College of Applied Medical Sciences Research Center and the Deanship of Scientific Research at King Saud University for their funding of this research.

Disclosure statement

No potential conflict of interest was reported by the authors.

ORCID

Gamal A. El-Hiti http://orcid.org/0000-0001-6675-3126

References

[1] Nanjundaswamy, H. M.; Pasha, M. A. Rapid, Chemoselective and Facile Synthesis of Azines by Hydrazine/I_2. Synth. Commun 2007, 37, 3417–3420. DOI: 10.1080/00397910701483837.

[2] Manikannan, R.; Venkatesan, R.; Muthusubramanian, S.; Yogeeswari, P.; Sriram, D. Pyrazole Derivatives from Azines of Substituted Phenacyl Aryl/Cyclohexyl Sulfides and Their Antimycobacterial Activity. Bioorg. Med. Chem. Lett 2010, 20, 6920–6924. DOI: 10.1016/j.bmcl.2010.09.137.

[3] Goodall, G. W.; Hayes, W. Advances in Cycloaddition Polymerizations. Chem. Soc. Rev 2006, 35, 280–312. DOI: 10.1039/B507209N.

[4] Xiong, Y.; Yao, S.; Driess, M. Unusual [3 þ 1] Cycloaddition of a Stable Silylene with a 2,3-Diazabuta-1,3-Diene versus [4 þ 1] Cycloaddition toward a Buta-1,3-Diene. Organometallics 2010, 29, 987–990. DOI: 10.1021/om901034w.

[5] Safari, J.; Gandomi-Ravandi, S. Structure, Synthesis and Application of Azines: A Historical Perspective. RSC Adv 2014, 4, 46224–46249. DOI: 10.1039/C4RA04870A.

[6] Shridevi, D. D.; Ningaiah, S.; Kuduva, N. U.; Yhya, R. K.; Lokanatha Rai, K. M. Solvent-Free Green Synthesis of Azines and Their Conversion to 2,5-Disubstituted-1,3,4-Thiadiazoles. Synth. Commun 2015, 45, 2869–2875. DOI: 10.1080/00397911. 2015.1113297.

[7] Safari, J.; Gandomi-Ravandi, S.; Ghotbinejad, M. Ultrasound-Promoted Synthesis of Novel Fused Heterocycles by Criss-Cross Cycloaddition. J. Saudi Chem. Soc 2016, 20, 20–23. DOI: 10.1016/j.jscs.2012.02.009.

[8] Alahakoon, S. B.; Thompson, C. M.; Nguyen, A. X.; Occhialini, G.; McCandless, G. T.; Smaldone, R. A. An Azine-Linked Hexaphenylbenzene Based Covalent Organic Framework. Chem. Commun. 2016, 52, 2843–2845. DOI: 10.1039/C5CC10408D.

[9] Lv, J.; He, Z.; Zhang, J.; Guo, Y.; Han, Z.; Bao, X. One-Pot Synthesis of [1,2,4]Triazolo[1,5-a]Pyridines from Azines and Benzylidenemalononitriles via Copper-Catalyzed Tandem Cyclization. Tetrahedron 2018, 74, 3996–4004. DOI: 10.1016/j.tet.2018.06.002.

[10] Kuznetsova, Y. A.; Romakh, V. B. Syringaldazine. Appl. Biochem. Biotechnol. 1996, 61, 205–209. DOI: 10.1007/BF02785703.

[11] Bondock, S.; Gieman, H.; El-Shafei, A. Selective Synthesis, Structural Studies and Antitumor Evaluation of Some Novel Unsymmetrical 1-Hetaryl-4-(2-Chloroquinolin-3-yl)Azines. A. J. Saudi Chem. Soc 2016, 20, 695–702. DOI: 10.1016/j.jscs.2015.01. 005.

[12] Gul, H. I.; Calis, U.; Vepsalainen, J. Synthesis of Some Mono-Mannich Bases and Corresponding Azine Derivatives and Evaluation of Their Anticonvulsant Activity. Aranelm.-Forach./Drug Res. 2004, 54, 359–364. DOI: 10.1055/s-0031-1296984.

[13] Gurkok, G.; Coban, T.; Suzen, S. Melatonin Analogue New Indole Hydrazide/Hydrazone Derivatives with Antioxidant Behavior: Synthesis and Structure-Activity Relationships. J. Enzyme Inhib. Med. Chem. 2009, 24, 506–515. DOI: 10.1080/ 14756360802218516.

[14] Kurteva, V. B.; Simeonov, S. P.; Disheva, M. S. Symmetrical Acyclic Aryl Aldazines with Antibacterial and Antifungal Activity. PP. 2011, 2, 1–9. DOI: 10.4236/pp.2011.21001.

[15] Tang, W.; Xiang, Y.; Tong, A. Salicylaldehyde Azines as Fluorophores of Aggregation-Induced Emission Enhancement Characteristics. J. Org. Chem. 2009, 74, 2163–2166. DOI: 10.1021/jo802631m.

[16] Wu, C.-Y.; Chen, Y.; Jing, S.-Y.; Lee, C.-S.; Dinda, J.; Hwang, W.-S. Reactions of Diiron Nonacarbonyl with Pyrrolyl-, Pyridyl- and Thienyl-Substituted Azines: N-N Bond Cleavage, Cyclometallation and C ¼ N r and p-Bonding. Polyhedron 2006, 25, 3053–3056. DOI: 10.1016/j.poly.2006.04.031.

[17] Chen, G. S.; Wilbur, J. K.; Barnes, C. L.; Glaser, R. Stereochemistry and Stereoelectronic Stereoelectronics of Azines. 5. Push-Pull Substitution versus Intrinsic or Packing Related N-N Gauche Preferences in Azines. Synthesis, Crystal Structures and Packing of Asymmetrical Acetophenone Azines. J. Chem. Soc., Perkin Trans 1995, 2, 2311–2317. DOI: 10.1039/ P29950002311.

[18] Hong, W.; Guo, C.; Sun, B.; Li, Y. (3Z,3^0Z)-3,3^0-(Hydrazine-1,2-Diylidene)Bis(Indolin-2-One) as a New Electron-Acceptor Building Block for Donor–Acceptor p-Conjugated Polymers for Organic Thin Film Transistors. J. Mater. Chem. C 2015, 3, 4464–4470. DOI: 10.1039/C5TC00447K.

[19] Laouiti, A.; Rammah, M. M.; Rammah, M. B.; Marrot, J.; Couty, F.; Evano, G. Copper-Catalyzed Oxidative Alkynylation of Diaryl Imines with Terminal Alkynes: A Facile Synthesis of Ynimines. Org. Lett. 2012, 14, 6–9. DOI: 10.1021/ol2032152.

[20] Zhao, M.-N.; Liang, H.; Ren, Z.-H.; Guan, Z.-H. Copper-Catalyzed N–N Bond Formation by Homocoupling of Ketoximes via N–O Bond Cleavage: facile, Mild, and Efficient Synthesis of Azines. Synthesis 2012, 44, 1501–1506. DOI: 10. 1055/s-0031-1290779.

[21] Lee, B.; Kang, P.; Lee, K. H.; Cho, J.; Nam, W.; Lee, W. K.; Hur, N. H. Solid-State and Solvent-Free Synthesis of Azines, Pyrazoles, and Pyridazinones Using Solid Hydrazine. Tetrahedron Lett 2013, 54, 1384–1388. DOI: 10.1016/j.tetlet.2012.12.106.

[22] Bauer, J. O.; Leitus, G.; Ben-David, Y.; Milstein, D. Direct Synthesis of Symmetrical Azines from Alcohols and Hydrazine Catalyzed by a Ruthenium Pincer Complex: effect of Hydrogen Bonding. ACS Catal. 2016, 6, 8415–8419. DOI: 10.1021/acscatal. 6b02946.

[23] Chakraborty, M.; Sengupta, D.; Saha, T.; Goswami, S. Ligand Redox-Controlled Tandem Synthesis of Azines from Aromatic Alcohols and Hydrazine in Air: one-Pot Synthesis of Phthalazine. J. Org. Chem. 2018, 83, 7771–7778. DOI: 10.1021/acs.joc.8b00661.

[24] Sumran, G.; Aggarwal, R.; Hooda, M.; Sanz, D.; Claramunt, R. M. Unusual Synthesis of Azines and Their Oxidative Degradation to Carboxylic Acid Using Iodobenzene Diacetate. Synth. Commun 2018, 48, 439–446. DOI: 10.1080/00397911. 2017.1407791.

[25] Abdel-Megeed, M. F.; Badr, B. E.; Azaam, M. M.; El-Hiti, G. A. Antimicrobial Activities of a Series of Diphenyl (4'-(Aryldiazenyl)Biphenyl-4-Ylamino)(Pyridin-3-yl)Methylphosphonates. Phosphorous Sulfur Silicon Relat. Elem 2012, 187, 1201–1206. DOI: 10.1080/10426507.2012.680084.

[26] Abdel-Megeed, M. F.; Badr, B. E.; Azaam, M. M.; El-Hiti, G. A. Synthesis and Antimicrobial Activities of Diphenyl (Arylamino)(1-Phenyl-3-(Pyridin-2-yl)-1H-Pyrazol-4-yl)Methylphosphonates. Phosphorous Sulfur Silicon Relat. Elem. 2012, 187, 1462–1468. DOI: 10.1080/10426507.2012.690117.

[27] Abdel-Megeed, M. F.; El-Hiti, G. A.; Badr, B. E.; Azaam, M. M. Synthesis of a Series of Diphenyl (Arylamino)(Pyridin-3-yl)Methylphosphonates as Potential Antimicrobial Agents. Phosphorous Sulfur Silicon Relat. Elem 2013, 188, 879–885. DOI: 10.1080/10426507.2012.717141.

[28] Baashen, M. B.; Abdel-Wahab, B. F.; El-Hiti, G. A. A Simple Procedure for the Synthesis of Novel 3-(Benzofur-2-yl)Pyrazole-Based Heterocycles. Chem. Pap. 2017, 71, 2159–2166. DOI: 10. 1007/s11696-017-0209-5.

[29] Smith, K.; Alshammari, M. B.; El-Hiti, G. A. Unravelling Factors Affecting Directed Lithiation of Acylamino Aromatics. Synthesis 2018, 50, 3634–3652. DOI: 10.1055/s-0036-1591954.

[30] Ali, T. E.-S. Synthesis and Characterization of Novel Bis-(a-Aminophosphonates) with Terminal Chromone Moieties. ARKIVOC 2008, 2008, 71–79. DOI: 10.3998/ark.5550190.0009.209.

[31] Abdel-Aziz, S. A.-G.; Ali, T. E.-S.; El-Mahdy, K. M.; Abdel-Karim, S. M. Synthesis and Antimicrobial Activities of Some Novel Bis-Pyrazole Derivatives Containing a Hydrophosphoryl Unit. Eur. J. Chem. 2011, 2, 25–35. DOI: 10.5155/eurjchem.2.1. 25-35.208.

[32] Grapov, A. F.; Mikhailova, O. B.; Melnikov, N. N. Einig Reaktionen Der Dihydrazide Von Thiosauren Des Phosphors. Zh. Obshch. Chem. 1977, 47, 1704–1711.

[33] Abdelhamid, A. O.; Gomha, S. M.; Shawali, A. S. Utility of N-Aryl 2-Aroylhydrazono-Propanehydrazonoyl Chlorides as Precursors for Synthesis of New Functionalized 1,3,4-Thiadiazoles with Potential Antimicrobial Activity. J. Adv. Res. 2015, 6, 885–893. DOI: 10.1016/j.jare.2014.08.007.

[34] Radini, I. A. M. Convenient Synthesis of New 7-Methyltetrazolo[1,5-a]Quinoline-4 Carbaldehyde Derivatives. Eur. Chem. Bull. 2016, 5, 232–237. DOI: 10.17628/ECB.2016.5. 232.

[35] Khidre, R. E.; Radini, I. A. M.; Abdel-Wahab, B. F. Synthesis of New Heterocycles Incorporating 3-(n-Phthalimidomethyl)-1,2,4-Triazole as Antimicrobial Agents. Egypt J. Chem. 2016, 59, 731–744.

[36] Gatta, F.; Settimj, G. Reaction of 2-Acyl-3-Aminobenzofurans with Hydrazines. J. Heterocycl. Chem. 1984, 21, 937. DOI: 10. 1002/jhet.5570210401.

[37] Alberti, C. Transformations of Indolyl Methyl Ketones into Homologs of Indole. III. A Transformation of 3-Acyl-Substituted Indoles. Gazzetta Chim. Italiana 1947, 77, 398–415.

[38] Ibrahim, H. S.; Abdelhad, S. R.; Hatem, A.; Abdel-Aziz, H. A. Hydrolysis and Hydrazinolysis of Isatin-Based Ald- and Ketazines. J. Chem. 2015, 2015, 1. DOI: 10.1155/2015/826489.

[39] Kats, S. V.; Varzatskii, O. A.; Penkova, L. V.; Vologzhanina, A. V. V.; Novikov, A. V.; Lebed, E. G.; Voloshin, Y. Z. On a Way to New Types of the Hybrid Polyazomethine-Pyrazolate Metal Pseudomacrobicyclic Complexes: The Synthesis and Structure of Their Ligand Synthones. Mhc. 2014, 7, 34–39. DOI: 10.6060/mhc140485v.

[40] Shukla, J. S.; Zaidi, M. G. H. Synthesis of Some Newer Polyhydrazides Containing Hydrazinophosphite Linkage. Asian J.Chem. 1993, 5, 253–260.

[41] Sheldrick, G. M. A Short History of SHELX. Acta Crystallogr. A Found. Crystallogr. 2008, 64, 112–122. DOI: 10.1107/ S0108767307043930.

[42] Sheldrick, G. M. Crystal Structure Refinement with SHELXL. Acta Crystallogr. C Struct. Chem. 2015, 71, 3–8. DOI: 10.1107/ S2053229614024218.