ISSN 1070-3632, Russian Journal of General Chemistry, 2020, Vol. 90, No. 4, pp. 710–719. © Pleiades Publishing, Ltd., 2020.

Reactions under Pressure: Synthesis of Functionally Substituted Arylhydrazonal Derivatives as Precursors of Novel Pyridazines and Nicotinates

K. M. Al Zaydi[a,b,*], M. A. Al-Johani[a,c], N. F. Alqahtani[a,b], S. M. Mousally[a,b], and N. Hilmy Elnagdi[d]

[a] *Department of Chemistry, Faculty of Sciences–AL Faisaliah, King Abdulaziz University, Jeddah, 21533 Saudi Arabia*
[b] *Chemistry Department, Faculty of Sciences, University of Jeddah, Jeddah, 21589 Saudi Arabia*
[c] *College of Science at Yanbu–Taibah University, Almadinah Almunawarah, Almadinah, 41477 Saudi Arabia*
[d] *Faculty of Pharmacy, Modern University for Technology and Information, Cairo, 11571 Egypt*
**e-mail: kmalzaydi@uj.edu.sa*

Received February 17, 2020; revised April 3, 2020; accepted April 10, 2020

Abstract—Q-tube assisted multicomponent synthesis of novel arylhydrazonals, pyridazines and nicotinates has been explored. The target molecules have been prepared via one pot reaction of arylhydrazonals with activated methylene nitriles in either ethanolic piperidine, dimethyl acetylene dicarboxylate (DMAD), 1,4-diazobicyclo[2.2.2]-octane (DABCO), or Ph_3P under pressure. Such conditions make reaction time much shorter and yields higher as compared with those conducted under conventional conditions. The structures of products have been determined by X-ray crystallography and spectroscopic methods.

Keywords: arylhydrazonals, Q-tubes, pyridazines, nicotinates, reactions under pressure, green chemistry

DOI: 10.1134/S1070363220040234

INTRODUCTION

Reactions under pressure in Q-tubes have proven to be a faster and cleaner approach to chemical transformations thus addressing most of the green chemistry principles [1]. To date, there are more than 50 papers devoted to the successful use of high pressure processes in Q-tubes [2]. In this study, we have developed a new general approach to synthesis of functionally substituted 2-arylhydrazonals **3** as precursors for biologically active pyridazine and nicotinate derivatives utilizing Q-tubes. Their reactivity with malononitrile, ethyl 2-cyanoacetate and 3-oxo-3-phenylpropanenitrile under pressure in ethanol/piperidine and dimethylacetylenedicarboxylate (DMAD) in the presence of DABCO or Ph_3P is studied. The products formed under pressure have been compared with those formed upon conventional heating, microwave or ultrasound irradiation.

EXPERIMENTAL

Melting points were measured on a Gallenkamp Electrothermal melting point apparatus and are uncorrected. IR spectra were recorded on an 80486-pc FTIR Shimadzu spectrophotometer using KBr pellets. NMR spectra were measured on a Varian Mercury VX-300 NMR spectrometer using $CDCl_3$ or DMSO-d_6 as solvents. Chemical shifts were referenced to the solvent signals. IR and NMR spectral data were collected at the Micro analytical Center, Cairo University, Egypt. Elemental analysis was carried out on a Perkin–Elmer 2400 Analyzer. Mass spectra were measured on a MS-5988 GS-MS Hewlett–Packard spectrometer, EI technique at 70 eV. Elemental analysis and MS were carried out at the Regional Center for Mycology and Biotechnology, Al-Azhar University, Cairo, Egypt. X-ray crystallography analysis was carried out on a Kappa CCD Enraf Nonius FR 590 diffractometer at the National Research Center, Dokki, Cairo, Egypt. Microwave irradiation experiments were carried out using a Monowave 300 single-mode Anton Paar GmbH microwave reactor. Ultrasonication was carried out with a microprocessor controlled-2004, high-intensity ultrasonic processor (750 W). Q-Tube-assisted reactions were performed in a Q-tube-safe pressure reactor, Q Labtech.

General procedure for arylhydrazonals 3j, 3k, 3l, 3m. Cold solutions (0–5°C) of compounds **2a**–**2d** were prepared by adding cold solution of sodium nitrite (1 g in 10 mL of H_2O) to cold solution of 10 mmol of aryl amine **2Aa**–**2Ad** in 5 mL of conc. HCl upon stirring.

The corresponding crude product was added to cold solution of (10 mmol, 1.32 g) 4,4-dimethoxybutanone **16** in ethanol–sodium acetate mixture (50 mL EtOH, added to 1 g sodium acetate dissolved in 10 mL H_2O). The mixture was stirred at room temperature for 1 h, and the solid precipitate was filtered off and crystallized from EtOH to give the corresponding pure product.

3-Oxo-2-(2-phenylhydrazono)butanal (3j). Yield 62%, mp126–127°C. IR spectrum, ν cm^{-1}: 3439 (NH), 3025 (CH, aromatic), 2929 (CH aliphatic), 2865 (CH, aldehyde), 1668 (C=O aldehyde), 1641 (C=O ketone). ^{1}H NMR spectrum, δ, ppm: 2.31, 2.33, 2.39 (6H, $2CH_3$), 7.24–7.56 (4H, Ar-H), 9.44, 9.92 (1H, CHO), 14.13, 14.4 (1H, NH). ^{13}C NMR spectrum, δC, ppm: 116.61, 116.72, 120.68, 120.72, 125.98, 126.11, 129.48, 132.14, 141.25, 186.90, 189.56, 196.19. Found, %: C, 63.10; H, 5.35; N, 14.70. $C_{10}H_{10}N_2O_2$. Calculated, %: C, 63.15; H, 5.30; N, 14.73. *M* 190.20.

3-Oxo-2-[2-(4-methylphenyl)hydrazono]butanal (3k). Yield 62%, mp 112–113°C. IR spectrum, ν, cm^{-1}: 3435 (NH), 3019 (CH, aromatic), 2922 (CH, aliphatic), 2856 (CH, aldehyde), 1666 (C=O, aldehyde), 1634 (C=O, ketone). ^{1}H NMR spectrum: δ, ppm: 2.31, 2.33, 2.39 (6H, $2CH_3$), 7.28–7.55 (4H, Ar-H), 9.44, 9.91 (1H, CHO), 14.2, 14.5 (1H, NH). Found, %: C 64.70; H 5.89; N 13.69. $C_{11}H_{12}N_2O_2$. Calculated, %: C 64.69; H 5.92; N 13.72. *M* 204.23.

2-[2-(4-Nitrophenyl)hydrazono]-3-oxobutanal (3l). Yield 91%, mp 172°C. IR spectrum, ν, cm^{-1}: 3441 (NH), 3079 (CH, aromatic), 2924 (CH, aldehyde), 1671 (C=O, aldehyde), 1601 (C=O, ketone). ^{1}H NMR spectrum: δ, ppm: 2.35, 2.44 (3H, CH_3), 7.28–8.31 (4H, Ar-H), 9.49, 9.96, 11.82 (1H, CHO), 13.89, 14.1 (1H, NH). ^{13}C NMR spectrum, δ, ppm: 24.17, 113.00, 116.71, 125.24, 125.75, 138.57, 140.70, 148.82, 187.52, 196.43. Found, %: C 51.12; H 3.80; N 17.9. $C_{10}H_9N_3O_4$. Calculated, %: C 51.07; H 3.86; N 17.87. *M* 235.20.

2-[2-(4-Chlorophenyl)hydrazono]-3-oxobutanal (3m). Yield 32%, mp 130°C. IR spectrum, ν, cm^{-1}: 3444 (NH), 3081 (CH, aromatic), 2884 (CH, aldehyde), 1666 (C=O, aldehyde), 1634 (C=O, ketone). ^{1}H NMR spectrum: δ, ppm: 2.40, 2.513 (3H, CH_3), 7.48–7.70 (4H, Ar-H), 9.43, 9.93 (1H, CHO), 14.3 (1H, NH). Found, %: C 53.51; H 4.2; Cl 15.70; N 12.36. $C_{10}H_9ClN_2O_2$. Calculated, %: C 53.47; H 4.04; Cl 15.78; N 12.47. *M* 224.13.

General procedure of the reaction of arylhydrazonals 3 with activated methylene nitriles 8a–8c. A mixture of 10 mmol of the appropriate arylhydrazonal derivative **3a**–**3g** with 10 mmol of an activated methylene nitrile derivative **8a**–**8c**, piperidine (5 drops) and 10 mL of EtOH was added into a 35-mL pressure Q-tube furnished by Q Labtech. A Teflon septum was placed on top of the tube, and the tube was capped. The mixture was heated in an oil bath at 160°C for 0.5–3 h. The solid product formed was filtered off and crystallized from EtOH.

6-Benzoyl-3-oxo-2-(4-methylphenyl)-2,3-dihydropyridazine-4-carbonitrile (17b). Yield 99%, mp 106°C. IR spectrum, ν cm^{-1}: 2220 (CN), 1659, 1590 (C=O). ^{1}H NMR spectrum: δ, ppm: 2.34 (3H, CH_3), 7.29–8.02 (9H, Ar-H), 8.56 (1H, pyridazine H-5). Found, %: C 71.9; H 4.2; N 13.4. $C_{19}H_{13}N_3O_2$. Calculated, %: C 72.37; H 4.16; N 13.33. *M* 315.33.

6-(4-Chlorobenzoyl)-3-oxo-2-phenyl-2,3-dihydropyridazine-4-carbonitrile (17g). Yield 97%, mp 210–212°C. IR spectrum, ν, cm^{-1}: 2235 (CN), 1690, 1651 (C=O). ^{1}H NMR spectrum, δ, ppm: 7.49–8.04 (9H, Ar-H), 8.76 (1H, pyridazine H-5). ^{13}C NMR spectrum, δ, ppm: 113.58, 115.19, 125.58, 128.56, 128.92, 129.24, 132.32, 133.44, 138.43, 138.61, 140.44, 141.27, 156.12, 186.99. Found, %: C 64.30; H 3.98; Cl 11.01; N 12.32. $C_{18}H_{10}ClN_3O_2$. Calculated, %: C 64.39; H 3.00; Cl, 10.56; N 12.52. *M* 235.74.

2-Oxo-6-phenyl-5-(phenyldiazenyl)-1,2-dihydropyridine-3-carbonitrile (18a). Yield 98%, mp 119–120°C. IR spectrum, ν, cm^{-1}: 3434 (NH), 2229 (CN), 1635(C=O). ^{1}H NMR spectrum, δ, ppm: 7.54–7.86 (10H, 9Ar-H and NH), 8.51 (1H, pyridine H-4). ^{13}C NMR spectrum, δ, ppm: 114.64, 120.65, 122.84, 127.91, 129.52, 130.10, 131.21, 131.84, 132.61, 136.05, 139.51, 151.87, 157.97, 162.85. Found, %: C 71.87; H 4.2; N 17.98. $C_{18}H_{12}N_4O$. Calculated, %: C 71.99; H 4.03; N 18.66. *M* 300.31.

2-Oxo-6-(thiophen-2-yl)-5-[4-methylphenyl)diazenyl]-1,2-dihydropyridine-3-carbonitrile (18e). Yield 96, mp 190–192°C. IR spectrum, ν, cm^{-1}: 3433 (NH), 2225 (CN), 1629 (C=O). ^{1}H NMR spectrum, δ, ppm: 2.4 (3H, CH_3), 7.21–8.16 (7H, 4Ar-H, 3H-thiophene and NH), 8.39 (1H, pyridine H-4). Found, %: C 63.23; H 4.05; N 17.67. $C_{17}H_{12}N_4OS$. Calculated, %: C 63.73; H 3.78; N 17.49. *M* 320.37.

6-(4-Chlorophenyl)-2-oxo-5-(phenyldiazenyl)-1,2-dihydropyridine-3-carbonitrile (18g). Yield 98%, mp 161–162°C. IR spectrum, ν cm^{-1}: 3438 (NH), 2234 (CN), 1636 (C=O). ^{1}H NMR spectrum, δ, ppm: 7.59–7.91 (10H, 9Ar-H and NH), 8.55 (1H, pyridine H-4). Found,

%: C 63.23; H 4.31; Cl 11.03; N 17.21%. $C_{18}H_{11}ClN_4O$. Calculated, C 64.58; H 3.31; Cl 10.59; N 16.74. *M* 334.76.

3-Benzoyl-5-(phenyldiazenyl)-6-(thiophen-2-yl)-pyridin-2(1*H*)-one (19d). Yield 99%, mp 277–278°C. IR spectrum, ν, cm^{-1}: 3433 (NH), 1652, 1661 (2C=O). ^1H NMR spectrum, δ, ppm: 7.29–8.00 (14H, 10Ar-H, 3H-thiopheneand NH), 8.20 (1H, pyridine H-4). Found, %: C 68.40; H 4.05; N 11.04. $C_{22}H_{15}N_3O_2S$. Calculated, %: C 68.55; H 3.92; N 10.90. *M* 385.44.

3-Benzoyl-6-(thiophen-2-yl)-5-[(4-methylphenyl)-diazenyl]pyridin-2(1*H*)-one (19e). Yield 99%, mp 162–163°C. IR spectrum, ν, cm^{-1}: 3434 (NH), 1664, 1587 (2C=O). ^1H NMR spectrum, δ, ppm: 2.4 (3H, CH_3), 7.28–7.95 (13H, 9Ar-H, 3H-thiopheneand NH), 8.18 (1H, pyridine H-4). Found, %: C 69.87; H 3.99; N 11.04. $C_{23}H_{17}N_3O_2S$. Calculated, %: C 69.15; H 4.29; N 10.52. *M* 399.46.

3-Benzoyl-6-(4-chlorophenyl)-5-(phenyldiazenyl)-pyridin-2(1*H*)-one (19g). Yield 98%, mp 148–149°C. IR spectrum, ν, cm^{-1}: 3429 (NH), 1649, 1583 (2C=O). ^1H NMR spectrum, δ, ppm: 7.56–7.96 (15H, Ar-H and NH), 8.24 (1H, pyridine H-4). Found, %: C 68.98; H 4.05; Cl 8.98; N 10.04. $C_{24}H_{16}ClN_3O_2$. Calculated, %: C 69.65; H 3.90; Cl 8.57; N 10.15. *M* 413.86.

General procedure for the reaction of arylhydrazonal derivatives 3 with DMAD. *Method 1 (Δ).* A mixture of 10 mmol of Ph_3P (2.6 mL) or DABCO (1.12 mL) with 10 mmol of an appropriate compound **3b**, **3c**, **3g**, **3h** in CH_2Cl_2 (10 mL) was stirred in a stoppered flask for 2 h at room temperature, then 10 mmol of DMAD (1.24 mL) in CH_2Cl_2 (10 mL) were added, and the mixture was stirred for 24-48 h at room temperature. The solvent was evaporated, and the resulting solid product was filtered off, washed with EtOH, dried and crystallized from EtOH to give the corresponding pure compound **27b**, **27c**, **27g**, **27h**.

Method 2 (ultrasound). A mixture of 10 mmol of an appropriate compound **3b**, **3c**, **3g**, or 3**h** with 10 mmol of Ph_3P (2.6 mL) or DABCO (1.12 mL) and 10 mmol of DMAD (1.24 mL) in 50 mL of CH_2Cl_2 was heated under US at 40°C for 3 h and then cooled down to room temperature. The solid product was filtered off and crystallized from EtOH.

Method 3 (Q-tube). A mixture of 10 mmol of a compound **3b**, **3c, 3g**, **3h** with 10 mmol of Ph_3P (2.6 mL) or DABCO (1.12 mL) and 10 mL of CH_2Cl_2 was added into a 35-mL pressure Q-tube furnished by Q Labtech. A teflon septum was placed on top of the tube and it was capped. The mixture was heated in an oil bath at 160°C for 1 h. The solid product was filtered off and crystallized from EtOH.

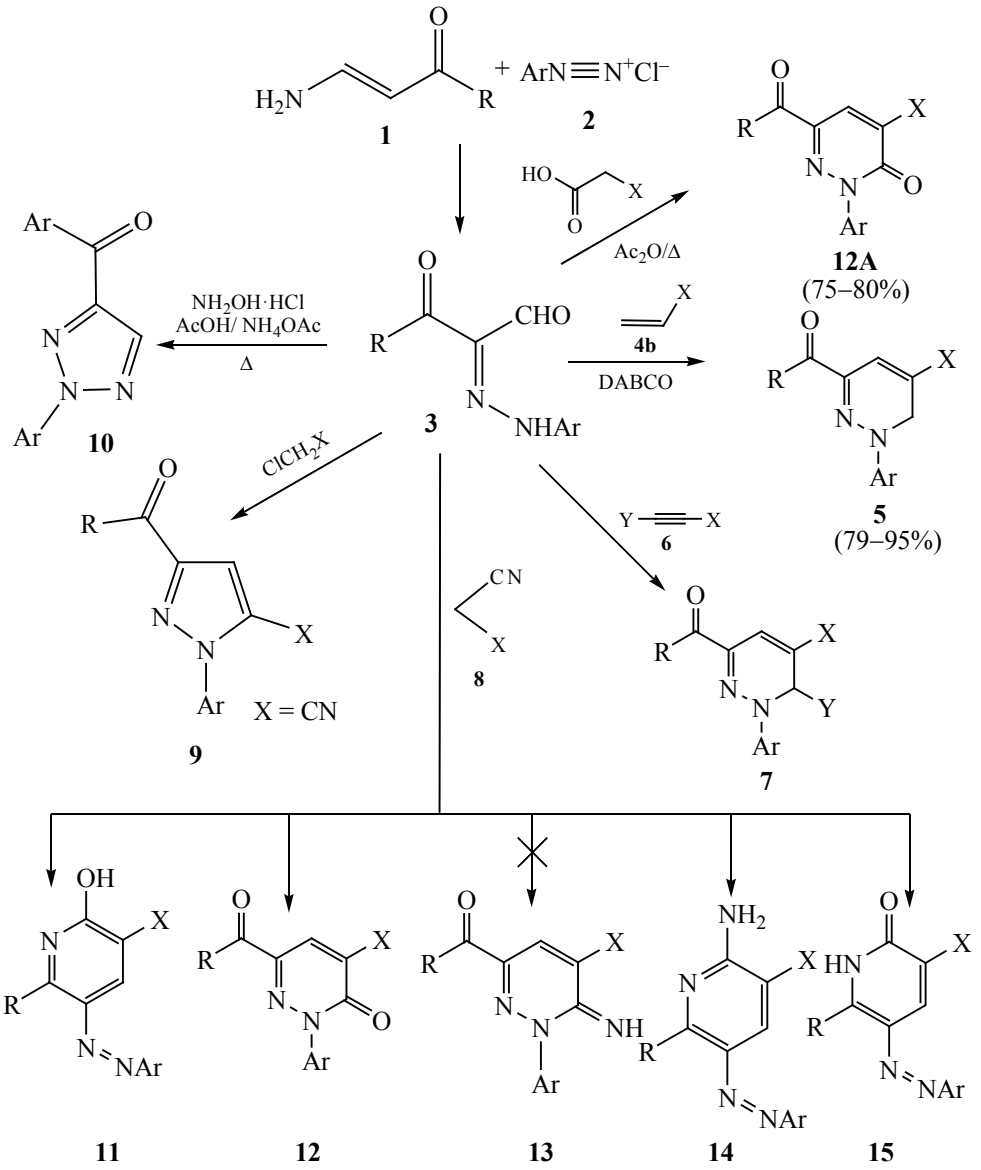
Dimethyl 6-benzoyl-2-(4-methylphenyl)-2,3-dihydropyridazine-3,4-dicarboxylate (27b) *(method 3)*. Yield 89%, mp 148–150°C. IR spectrum, ν, cm^{-1}: 3066 (CH aromatic), 2951 (CH aliphatic), 1757, 1704 (2C=O ester), 1630 (C=O ketone). ^1H NMR spectrum, δ, ppm: 2.30 (3H, CH_3), 3.66, 3.84 (3H, $2OCH_3$), 6.22 (1H, pyridazine H-3), 7.22–7.91 (9H, Ar-H), 7.60 (1H, pyridazine H-5). ^{13}C NMR spectrum, δ, ppm: 20.33, 52.60, 53.15, 116.84, 118.11, 121.65, 128.09, 129.82, 129.98, 132.37, 135.17, 136.67, 139.27, 141.84, 164.29, 168.15, 184.20. Found, %: C 67.44; H 4.95; N 7.88. $C_{22}H_{20}N_2O_5$. Calculated, %: C 67.34; H 5.14; N 7.14. *M* 392.40.

Dimethyl-6-benzoyl-2-(4-nitrophenyl)-2,3-dihydropyridazine-3,4-dicarboxylate (27c) *(method 3)*. Yield 80%, mp 172–174°C. IR spectrum, ν, cm^{-1}: 3081 (CH aromatic), 2953 (CH aliphatic), 1740, 1713 (2C=O ester), 1637 (C=O ketone). ^1H NMR spectrum, δ, ppm: 3.67, 3.87 (3H, $2OCH_3$), 6.38 (1H, pyridazine H-3), 7.58–8.29 (10H, Ar-H and H-5 pyridazine). Found, %: C 60.04; H 3.98; N 8.21. $C_{21}H_{17}N_3O_7$. Calculated, %: C 59.57; H 4.05; N 9.93. *M* 423.38.

Dimethyl-6-(4-chlorobenzoyl)-2-phenyl-2,3-dihydropyridazine-3,4-dicarboxylate (27g) *(method 3)*. Yield 87%, mp 171–172°C. IR spectrum, ν, cm^{-1}: 3024 (CH aromatic), 2954 (CH aliphatic), 1744, 1707 (2C=O ester), 1642 (C=O ketone). ^1H NMR spectrum, δ, ppm: 3.66, 3.85 (3H, $2OCH_3$), 6.28 (1H, pyridazine H-3), 7.27–7.94 (10H, Ar-H and H-5 pyridazine). ^{13}C NMR spectrum, δ, ppm: 20.33, 52.60, 53.15, 116.84, 118.11, 121.65, 128.09, 129.82, 129.98, 132.37, 135.17, 136.67, 139.27, 141.84, 164.29, 168.15, 184.20. Found, %: C 61.56; H 4.43; Cl 8.43; N 6.98. $C_{21}H_{17}ClN_2O_5$. Calculated, %: C 61.10; H 4.15; Cl 8.59; N 6.79. *M* 412.82.

Dimethyl-6-(4-chlorobenzoyl)-2-(4-methylphenyl)-2,3-dihydropyridazine-3,4-dicarboxylate (27h) *(method 3)*. Yield 92%, mp 124-–25°C. IR spectrum, ν, cm^{-1}: 3080 (CH aromatic), 2955 (CH aliphatic), 1742, 1715 (2C=O ester), 1631 (C=O ketone). ^1H NMR spectrum, δ, ppm: 2.31 (3H, CH_3), 3.66, 3.84 (3H, $2OCH_3$), 6.22 (1H, pyridazine H-3), 7.24–7.92 (9H, Ar-H and H-5 pyridazine). Found, %: C 62.02; H 4.39; Cl 8.89; N 6.78. $C_{22}H_{19}ClN_2O_5$. Calculated, %: C 61.90; H 4.49; Cl 8.31; N 6.56. *M* 426.85.

Scheme 1. Reported reactions of 2-arylhydrazonals **3** as precursors for preparation of heterocyclic compounds.

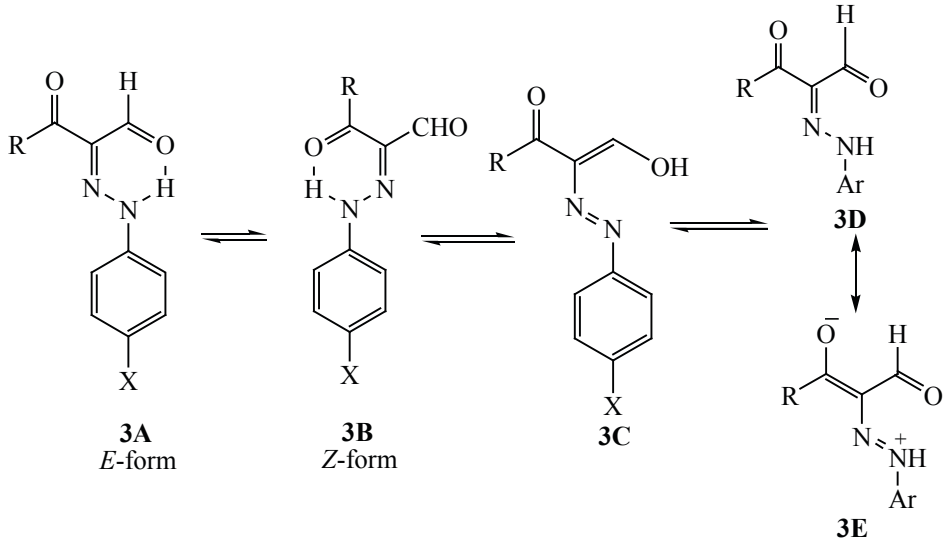


R = CH_3 (**1**, **3**, **5**, **7**, **9**, **11**–**15**); Ar = C_6H_5 (**2**, **3**, **5**, **7**, **9**, **10**, **11**–**15**);
X = COOEt (**4a**, **5a**, **11a**–**15a**), CN (**4b**, **5b**, **8b**, **9**, **11b**–**15b**), COOMe (**6**, **7**, **8a**);
Y = COOMe (**6**, **7**).

RESULTS AND DISCUSSION

Al-Awadi et al. [3] prepared 6-aroylpyridazine **5** by heating arylhydrazonals **3** with acrylonitrile or methyl vinyl ketone in the presence of DABCO utilizing MW irradiation without solvents (Scheme 1). It was previously suggested that the compound **13** could be formed upon treatment of **3** with ethyl cyanoacetate in the presence of a mixture of acetic acid and ammonium acetate [4]. Later, this assumption was found to be false, as actually pyridazinones **12** or arylazonicotinates **15** were formed under the mentioned reaction conditions [5]. A subsequent article [6] proved that compound **9** was formed in the reaction of **3** with activated methylene nitriles. The structure of the product was based on its X-ray crystallography [6]. It was suggested that compound **12** was formed upon the reaction carried out in the presence of an excess of NH_4OAc [7]. All these approaches confirmed that the reaction of arylhydrazonal derivatives **3** with activated methylenes was highly dependent on the process conditions. This has encouraged us to explore

Scheme 2. Possible conformations of arylhydrazonals **3** (**3A**: *E*-form, **3B**: *Z*-form, **3C**: enol form, **3D** and **3E**: two tautomeric forms of the anti-structure).



R = CH_3 (**3A**–**3E**); Ar = C_6H_5 (**3D**, **3E**); X = COOEt, CN (**3A**–**3C**).

chemical processes of arylhydrazonal derivatives **3** under specific conditions under pressure in Q-tubes.

To develop a new general approach to synthesis of functionally substituted 2-arylhydrazonals **3** utilizing green and economically sound methods as precursors for biologically active pyridazines and nicotinate derivatives, we first explored 4,4-dimethoxybutan-2-one or 3,3-dimethoxy-1-phenylpropan-1-one **16** as starting materials instead of enaminones **1a**–**1c**. Thus, coupling of **16** with aromatic diazonium salts **2a**–**2d** afforded compounds **3j**–**3m** in moderate yields (Scheme 3). The obtained coupling products were characterized by IR, ^{1}H and ^{13}C NMR spectra. Crystal structure of **3b** was approached by X-ray analysis. Although compounds **3a**–**3m** had been previously mentioned (Fig. 1) as intermediates in equilibrium between **3A** and **3B**, ^{1}H NMR spectra of compounds **3j**, **3k**, **3m** in DMSO-d_6 demonstrated two signals at 9.9 and 9.4 ppm with the total integration of one proton, which indicated an equilibrium mixture between *E*- (**3A**) and *Z*-forms (**3B**) for these compounds, accordingly (Scheme 2). Their ^{1}H NMR spectra demonstrated a signal at 14.13–14.4 ppm for NH proton. Two singlets at 2.48 and 2.51 ppm with a total integration of 3H indicated presence of the CH_3 group in the equilibrium between *Z*- and *E*-forms.

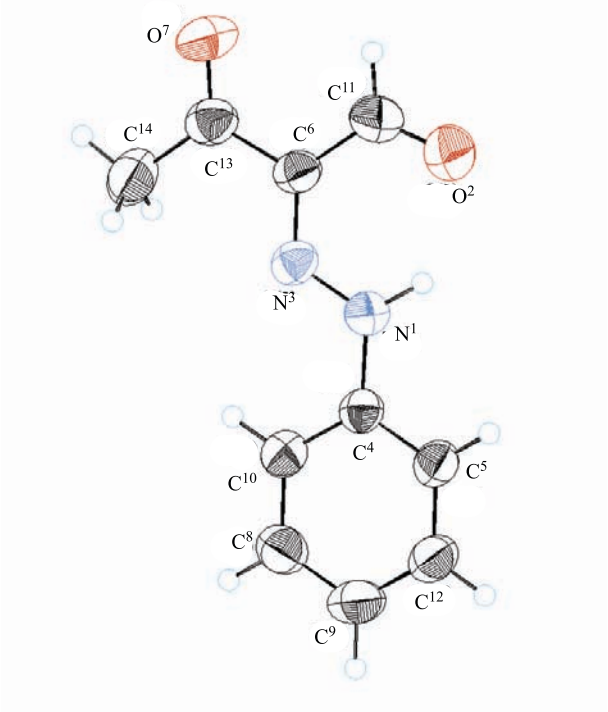
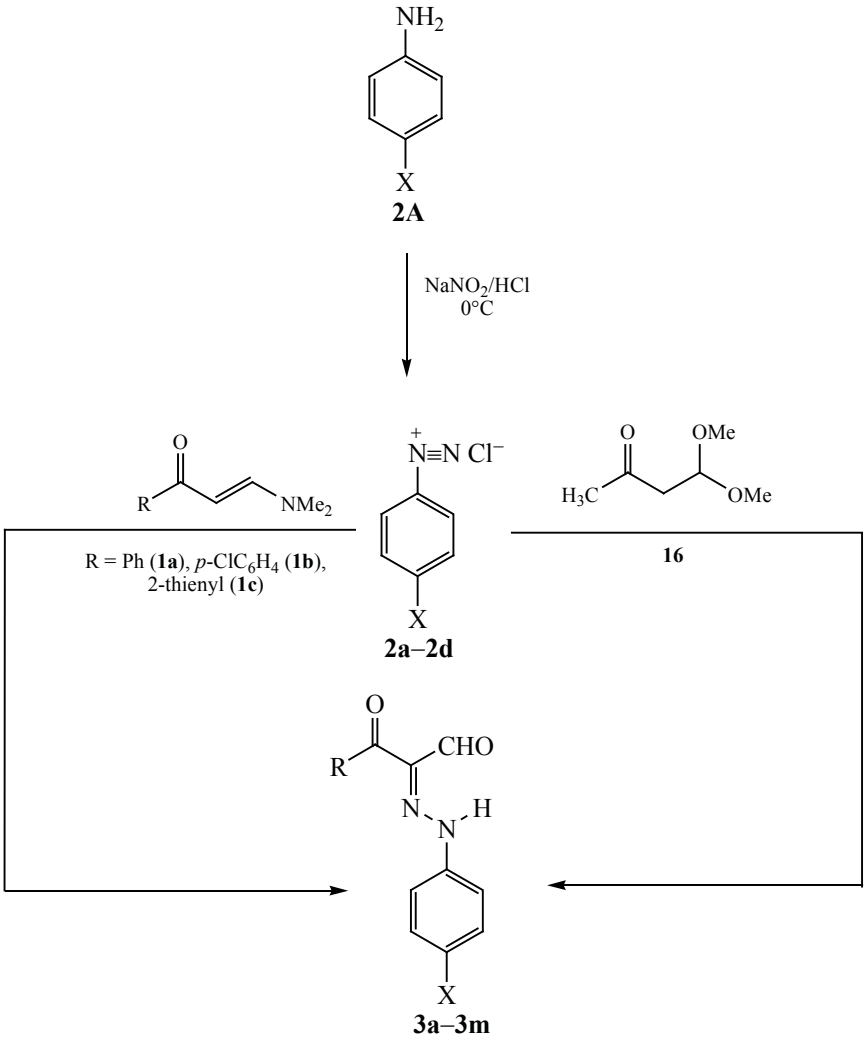


Fig. 1. X-Ray structure of (*E*)-3-oxo-2-(2-phenylhydrazono)-butanal (**3j**) [8].

On the other hand, ^{1}H NMR spectrum of compound **3l** contained three signals at 9.4, 9.9, and 11.8 ppm with total integration of 1H indicating an equilibrium mixture of the *E*- (**3A**), *Z*- (**3B**) and the enol forms (**3C**), accordingly. Energy measurements for these compounds suggested that the direct transformation of structure *E* into *Z* required rotation around the double bond, which was almost impossible. The indirect transformation from *E* to *Z* could be possible via three steps starting

Scheme 3. Synthesis of substituted 2-arylhydrazonals **3j**–**3m**.



2A: X = H (**a**), CH_3 (**b**), NO_2 (**c**), Cl (**d**); **3**: X = H (**a**, **d**, **g**, **j**), CH_3 (**b**, **e**, **h**, **k**), NO_2 (**c**, **f**, **i**, **l**); R = Ph (**a**–**c**), 2-thienyl (**d**–**f**), *p*-ClC_6H_4 (**g**–**i**), CH_3 (**j**–**m**).

with proton shift to structure **3C** with an energy barrier of –8.786 kcal/mol, which was higher than the thermal barrier of free rotation, followed by two other rotations around the single bonds. These results indicated that the solid crystalline form could have only one conformer, either *E* or *Z*, but not a mixture. X-Ray crystal study of the compound demonstrated that the anti-structure (**3D**) was the sole product of that reaction. In fact, the above was supported by stereoelectronic requirements that could be met only that way.

The bond lengths indicated nitrogen lone pair delocalization. The bond angles of N^2, N^4, C^{10}, C^6, and O^1 suggest their hybridization close to sp^2 (Table 1).

The next stage of the study was devoted to reactivity of arylhydrazonal derivatives **3** toward malononitrile, ethyl acetoacetate and malononitrile in Q-tubes. According to the accumulated data, under pressure the reaction was directed either to formation of the product **12** or **15** depending on the type of active methylene reagent **8**.

Compound **3** could be condensed with malononitrile in a Q-tube that made it possible to carry out various types of accelerated reactions that appeared to be more favorable than MW or conventional heating (Scheme 4). The products obtained in a Q-tube were different from those obtained in the reactions at ambient pressure (Table 2). The reaction of compounds **3** with benzoylacetonitrile afforded products **19** that were

Table 1. Selected bond lengths and angles for **3b**

Bond	*d*, Å	Angle	φ, deg
O^1–C^6	1.228	N^4–N^2–C^{11}	119.7
N^2–N^4	1.309	N^2–N^4–C^{10}	120.4
N^2–C^{11}	1.418		
O^3–C^{18}	1.221		
N^4–C^{10}	1.320		

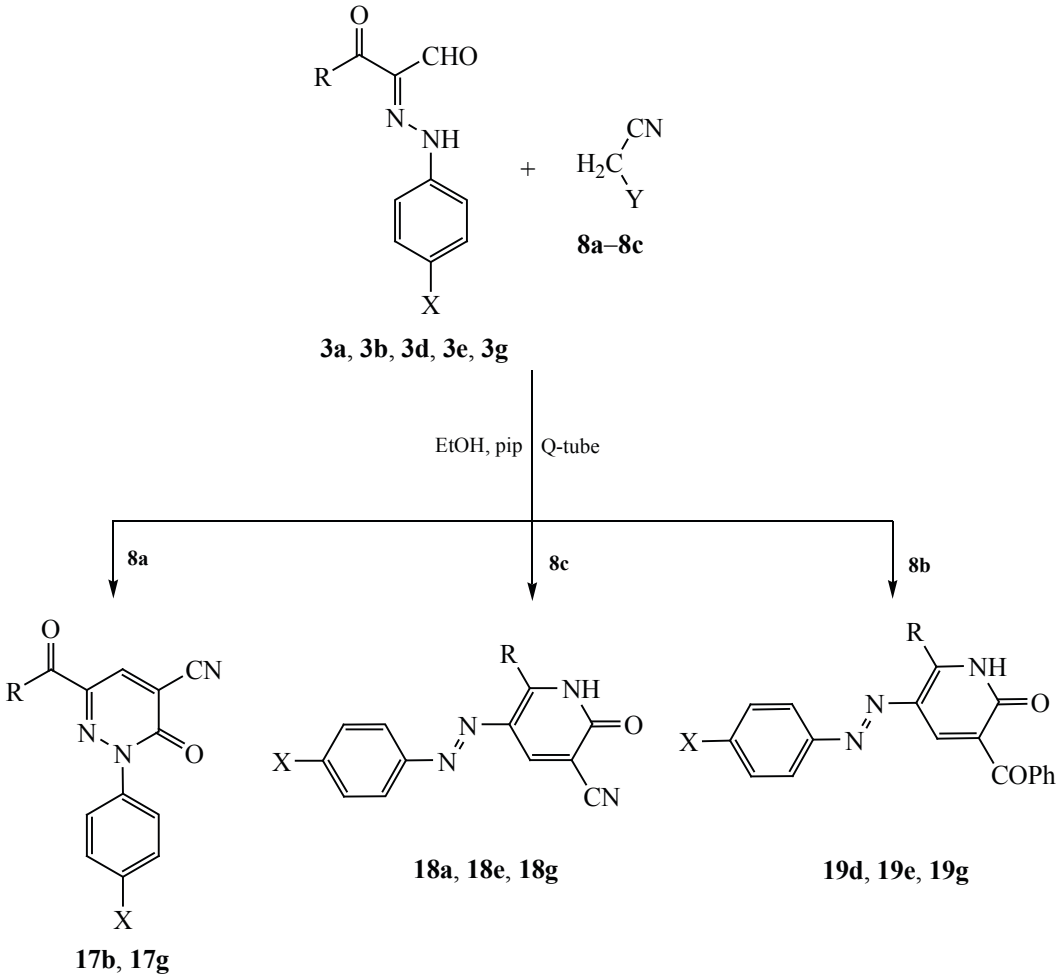
different from the products obtained by Bahbahani (**12A**) upon heating [10]. According to X-ray crystallography of compounds **17**, despite the sterical congestion of the conformation, the product again adopted the structure that followed the stereoelectronic requirements [9]. Scheme 5 presents a suggested mechanism of the reaction of **3** with activated methylene reagents **8** under pressure in Q-tubes.

Table 2. High pressure synthesis data of compounds **17**–**19**

Compound	Time, min	Yield, %
17b	60	75
17g	30	73
18a	60	88
18e	60	86
18g	60	88
19d	60	89
19e	60	89
19g	60	88

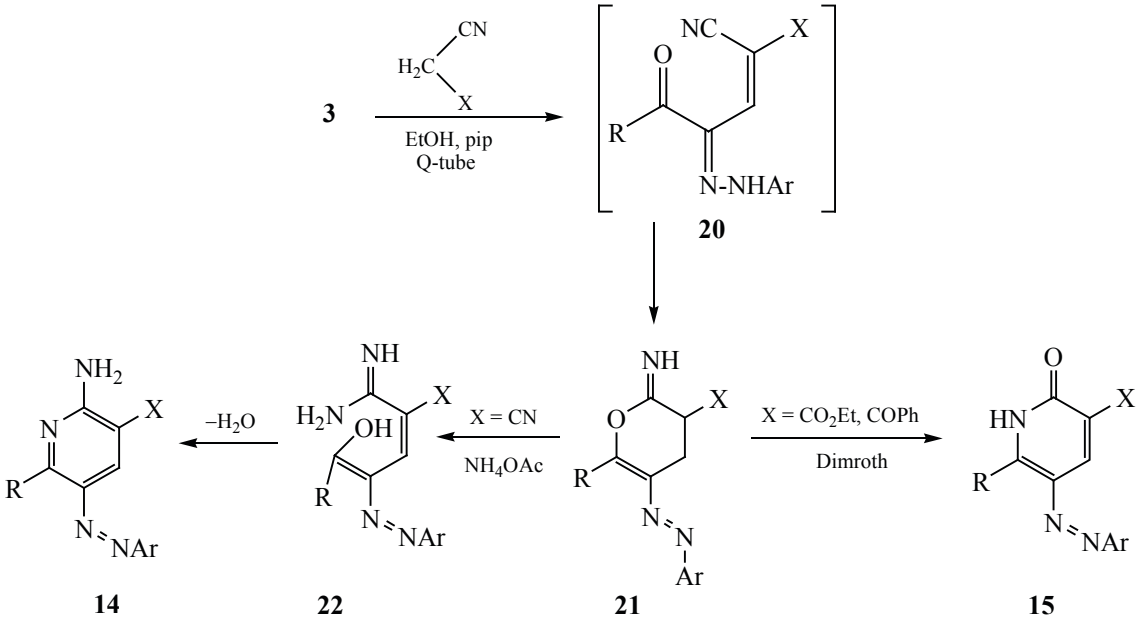
The reaction of 2-arylhydrazonal derivatives **3b**, **3c**, **3g**, **3h** with DMAD carried out in the presence of Ph_3P or DABCO as a catalyst in CH_2Cl_2 at room temperature for 24–48 h, or under ultrasonication or in Q-tube afforded the

Scheme 4. Syntheses of arylazonicotinates **18a**, **18e**, **18g**, pridazinones **17b**, **17g** and arylazonicotinates **19d**, **19e**, **19g** under high pressure.



Y = COOEt (**8a**), COPh (**8b**), CN (**8c**); R = Ph (**3a**, **3b**, **17b**, **18a**), 2-thienyl (**3d**, **3e**, **18e**, **19d**, **19e**), *p*-ClC_6H_4 (**3g**, **17g**, **18g**, **19g**); X = H (**3a**, **3d**, **3g**, **17g**, **18a**, **18g**, **19d**, **19g**), CH_3 (**3b**, **3e**, **17b**, **18e**, **19e**).

Scheme 5. A suggested mechanism of the reaction of **3** with active methylene reagents **8** under pressure.



X = CN (**14**, **22**), COOEt, COPh (**15**), H (**20**, **21**).

corresponding 2,3-dihydropyridazine-3,4-dicarboxylates **27b**, **27c**, **27g, 27h**. We believe that the reaction proceeded via the initial addition of Ph_3P to DMAD with formation of **23** followed by attack at the formyl carbonyl group of **24**, cyclization of which via intermediates **25** and **26** gave the end product (Scheme 6). The above speculations supported the fact that application of US and a Q-tube played a decisive role in the rapid synthesis of dihydropyridazine-3,4-dicarboxylates **27b**, **27c**, **27g**, **27h** (Table 3). The structures of these compounds were elucidated from their spectral data. The same reaction under US irradiation at 70°C proceeded faster (3 h) than under conventional method. The same compounds were also synthesized in a Q-tube at 160°C in only 1 h.

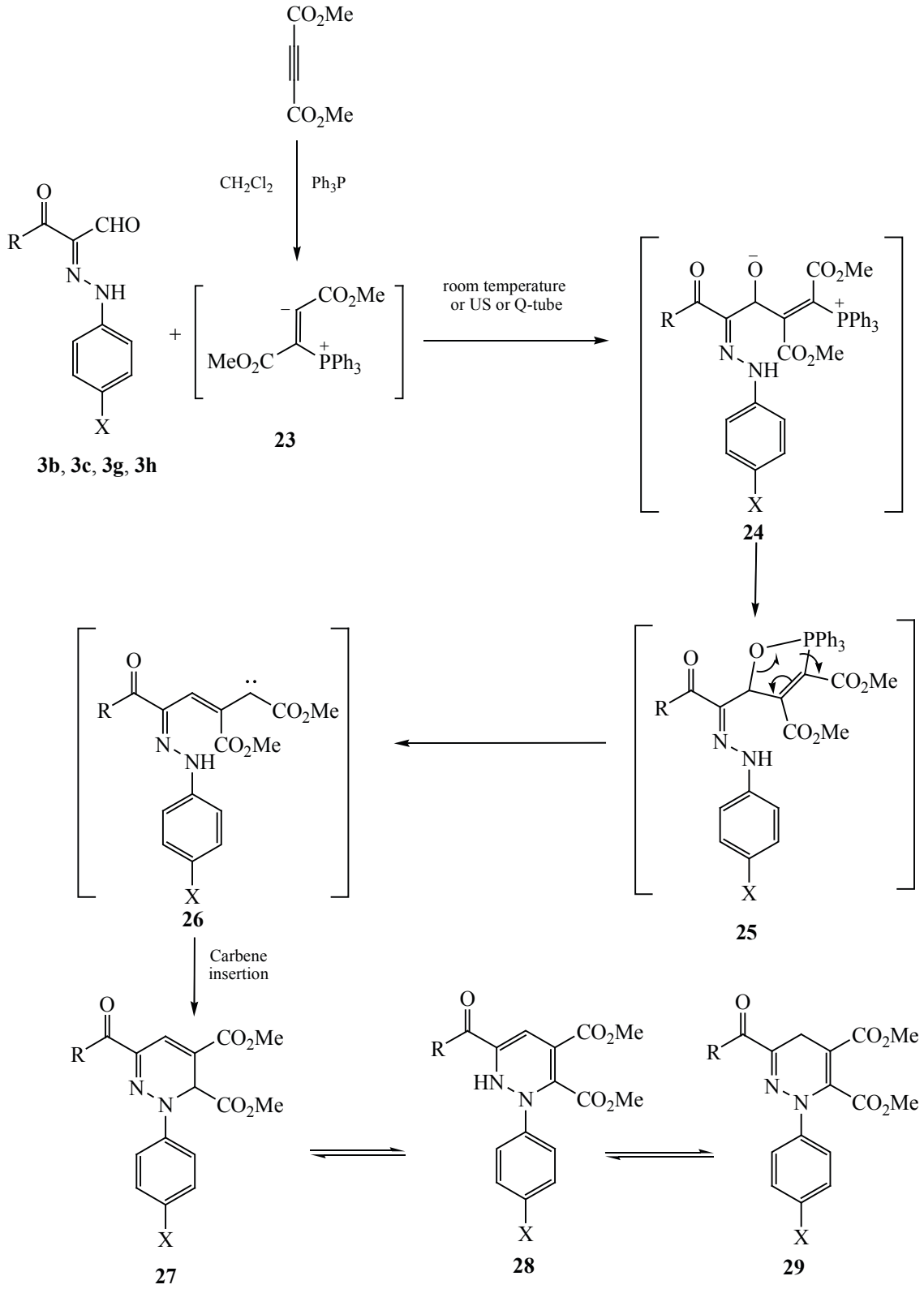
CONCLUSIONS

Condensation of aryl hydrazonal derivatives **3** with malononitrile, ethyl cyanoacetate and benzoyl acetonitrile under pressure generally proceeds much faster and/or with higher yields than under conventional heating or upon ultrasonication. Pressure favors formation of transition states corresponding to the lowest activation volumes. Products of condensation of benzoylacetonitrile and malononitrile with **3** under pressure are different from those accumulated under conventional heating in open tubes. The approach to the reaction of 2-arylhydrazonals **3** with DMAD in the presence of Ph_3P or DABCO at room temperature either upon ultrasonication or under

Table 3. Comparison of synthesis of compounds **27b**, **27c**, **27g**, **27h** under conventional heating, ultrasonication and in a Q-tube

Product	Conventional method (room temperature)				Ultrasonication (70°C)				Q-tube (160°C)	
	$Ph_3{}^{32}P$		DABCO		Ph_3P		DABCO		Ph_3P or DABCO	
	time, h	yield, %	time, h	yield, %	time, h	yield, %	time, h	yield, %	time, h	yield, %
27b	24	50	30	54	3	60	3	79	1	89
27c	24	60	44	83	3	75	3	80	1	80
27g	24	77	48	98	3	69	3	89	1	87
27h	24	92	48	98	3	70	3	90	1	92

Scheme 6. Probable mechanism of 2-arylhydrazonal derivatives **3b**, **3c**, **3g**, **3h** reaction with DMAD in the presence of Ph_3P or DABCO in a Q-tube.



R = Ph (**3b**, **3c**), *p*-ClC_6H_4 (**3g**, **3h**); X = CH_3 (**3a**, **3h**), NO_2 (**3b**), H (**3c**).

pressure confirms higher efficiency of the latter factor in the synthesis of substituted dihydropyridazine derivatives.

FUNDING

This project was funded by the Deanship of Scientific Research (DSR) at King Abdulaziz University, Jeddah, under grant no. 2-363-36-RG. The authors, therefore, acknowledge with thanks DSR technical and financial support.

CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

REFERENCES

1. Nacca, F.G., Merlino, O., Mangiavacchi, F., Krasowska, D., Santi, C., and Sancineto, L., *Current Green Chem.*, 2017, vol. 4, no. 2, p. 58. https://doi.org/10.2174/2213346104666170908160741
2. Sancineto, L., Monti, B., Merlino, O., Rosati, O., and Santib, C., *Arkivos*, 2018, p. 270. https://doi.org/10.24820/ark.5550190.p010.506
3. Al-Awadi, N.A., Ibrahim, M.R., Abdelhamid, I.A., and Elnagdi, M.H., *Tetrahedron*, 2008, no. 35, vol. 64, p. 8202. https://doi.org/10.1016/j.tet.2008.06.026
4. Zaky, O.S., Moustafa, M.S., Selim, M.A., El-Maghraby, A.M., and Elnagdi, M.H., *Molecules*, 2012, vol. 17, no. 5, p. 5924. https://doi.org/10.3390/molecules17055924
5. Moustafa, M.S., Al-Mousawi, S.M., and Elnagdi, M.H., *RSC Adv.*, 2016, vol. 6, p. 90840. https://doi.org/10.1039/C6RA19535K
6. Al-Mousawi, S.M. and El-Apasery, M.A., *Molecules*, 2012, vol. 17, no. 6, p. 6547. https://doi.org/10.3390/molecules17066547
7. Ashkar, A., El-Apasery, M.A., Touma, M., and Elnagdi, M.H., *Eur. J. Chem.*, 2013, vol. 4, no. 3, p. 245. https://doi.org/10.5155/eurjchem.4.3.245-249.820
8. CCDC 1590189.
9. CCDC 1590188.
10. Ibrahim, H.M. and Behbehani, H., *Molecules*, 2014, vol. 19, no. 2, p. 2637. https://doi.org/10.3390/molecules19022637