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Multicomponent reactions under increased pressure: on the reaction of arylhydrazonals, aromatic aldehydes and malononitrile in Q-Tube

Kamal Usef Sadek [1,*], Maghraby Ali Selim [2], Abdul-Aziz Alnajjar [3], Mohamed Atallah [2] and Mohamed Hilmy Elnagdi [4]

[1] *Chemistry Department, Faculty of Science, Minia University, 61519, Minia, Egypt*
[2] *Chemistry Department, Faculty of Science at Qena, South Valley University, 83512, Qena, Egypt*
[3] *Applied Science Department, College of Technological Studies, Public Authority for Applied Education and Training, 13060, Safat, Kuwait*
[4] *Chemistry Department, Faculty of Science, Cairo University, 12613, Giza, Egypt*

** Corresponding author at: Chemistry Department, Faculty of Science, Minia University, 61519, Minia, Egypt.*
Tel.: +2.086.2364806. Fax: +2.086.2363011. E-mail address: kusadek@yahoo.com (K.U. Sadek).

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ABSTRACT

A novel multi-component reaction between arylhydrazonals, malononitrile and aromatic aldehydes under high pressure utilizing Q-tube was carried out. The reaction of arylhydrazonal (1j) with malononitrile and aromatic aldehydes afforded the corresponding biphenyl derivatives (4). However, compound 1h reacted with malononitrile and aromatic aldehydes (7) to afford pyridazino[5,4,3-*de*]1,6-naphthyridine-7-carbonitrile derivatives (8). In contrast, the arylhydrazonal (1k) at the same reaction conditions afforded the corresponding pyridazinoquinazoline derivative (22). A rationalization for the difference in behavior for reaction of compounds 1h-k with malononitrile and aromatic aldehydes was postulated. Based on these findings a mechanism to account for the formation of the reaction products is suggested excluding possible initial dimerization of malononitrile as has been previously reported.

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1. Introduction

For more than fifty years, we have emphasized on devising efficient syntheses for biologically relevant multifunctional hetero-aromatics. Our contributions have been recently surveyed [1]. We have also recently surveyed utility of multicomponent reactions in our area [2]. Since 1997, we investigated extensively utility of microwave to accelerate reaction rates [3-6]. As we became convinced that microwave techniques is very expensive to scale up and it is just allow reactions to proceed at higher temperature than that of the medium via formation of hot spots thus increasing the rate. It is well accepted that every 10 °C increase in temperature of reaction mixture duplicate the rate [7,8].

We recently turned to application of pressure as the latter also permit conducting reactions at temperatures higher than boiling point of the medium. In addition, the utility of high pressure in reactions with large negative volumes of activation (-*ve*) possess a rate accelerating effect [9,10]. Our first achievement in this area utilizing Q-tube as safe pressure reactor to enhance conducting reactions under high pressure in laboratory has very recently been reported [11,12]. In the present article, we report results of our investigation on the reported 3+3 atom combination for the synthesis of pyridazines and condensed pyridazines [13-15], under increased pressure. The work enabled defining the scope of this synthesis and enabled disclosing novel routes to naphthyridine, pyridazine and biphenyl derivatives.

In 2007, we reported what seemed to be a new general 3+3 atom combination synthesis of 6-amino-1,4-dihydro pyridazines (**3**) via reacting arylhydrazonals (**1a-e**) with α-substituted cinnamonitrile (**2a**) (Scheme 1) [15]. These were also obtained via reacting compounds **1a-e**, aromatic aldehydes (**7**) and active methylene nitriles (**6**). However, subsequent investigations indicated that the reaction product is depending on the nature of aryl substituent in compound **1**. Thus, compounds **1f,g** reacted with compound **2a** to yield compound **4** [16] whereas compound **1j** reacted with compound **2a** to yield compound **5** [13]. Recently, Abdelhamid *et al*. reported that pyrazolyl-azaenamines reacted with cinnamo nitrile derivatives yielding pyrazolo[4",3"-5,6]pyrimido[2,1-a]phthalazine-9-carbonitrile derivatives [17].

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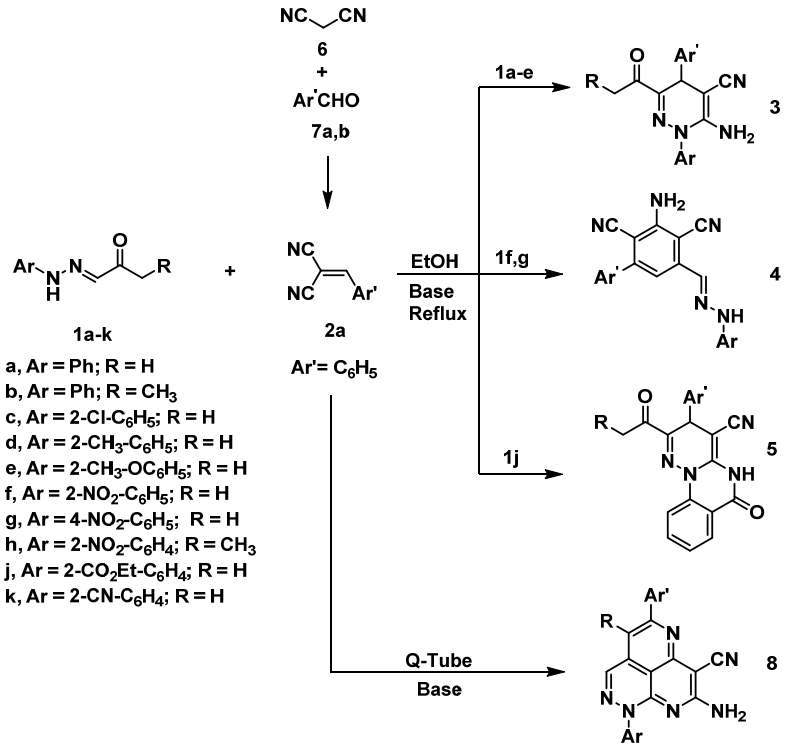


Scheme 1

Very recently, Moustafa *et al.* have developed a novel synthesis of tricyclic system **8** via reacting 2-phenylhydrazono derivatives with malononitrile (**6**) and aromatic aldehyde derivatives (**7**) in Q-Tube [18]. Also Abdelmoniem *et al.* [19] reported different synthetic routes for the synthesis of several pyridazine derivatives utilizing arylhydrazonals as starting materials as they possess an in vitro antitumor effect [20].

2. Experimental

2.1. Instrumentation

Melting points were recorded on a Griffin melting point apparatus and are reported uncorrected. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded at 25 °C using DMSO-d_6 as solvent with TMS as internal standard on a Bruker DPX 400 spectrometer. Chemical shift are reported in ppm. Mass spectra were performed using Shimadzu GMSS-Q-1000 Ex mass spectrometer with the EI (70 eV) mode. All reactions were monitored by using thin layer chromatography (TLC). Reactions were conducted under reduced pressure in Q-tube safe pressure reactor from Q-LabTech with a cap/sleeve, pressure adaptor (120 psi), needle adaptor, needle, borosilicate glass tube, Teflon septum and catch bottle.

2.2. Synthesis

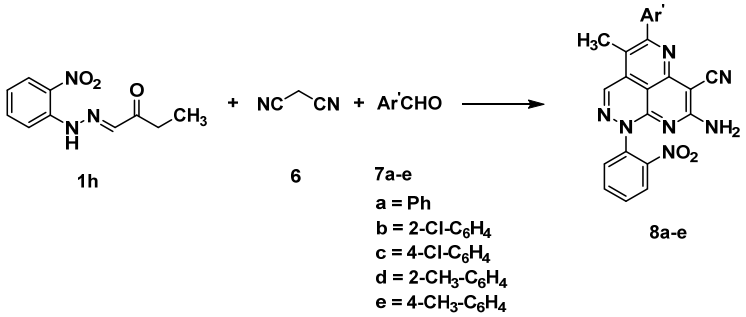
2.2.1. General procedures for Q-Tube-assisted synthesis of compounds 4, 8 and 22

Independed azaenamines derivative (**1h**-**k**) (0.01 mol), malononitrile (**6**) (0.02 mol) and aromatic aldehydes (**7a**-**e**) (0.01 mol) in dioxane (10 mL) and catalytic amount of either piperidine (1 mL) or zeolite (0.25 g) were sequentially added in a 35 mL Q-tube pressure tube, the mixture was heated in an oil bath at 150 °C. After about 60 min, the reaction mixture was monitored by TLC and stopped. The hot reaction mixture was cooled and poured into ice-water. The separated solid products obtained on standing at room temperature were collected by filtration and purified by column chromatography utilizing appropriate solvents mixture to give analytical pure products (Scheme 2).

8-Amino-5-phenyl-4-methyl-1-(2-nitrophenyl)-1H-pyridazino[5,4,3-de]1,6-naphthyridine-7-carbonitrile (**8a**): Recrystallized from acetic acid. Color: Brown. M.p.: 219-220 °C. Yield: 83 %. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.36 (s, 3H, CH_3), 7.0 (s, 2H, NH_2, D_2O exchangeable), 7.50-7.52 (m, 3H, Ar-H), 7.54-7.58 (m, 2H, Ar-H), 7.78-7.80 (m, 1H, Ar-H), 7.88-7.90 (dd, *J* = 0.8 Hz, 1H, Ar-H), 7.95-7.98 (m, 1H, Ar-H), 8.23-8.24 (dd, *J* = 0.8 Hz, 1H, Ar-H), 8.63 (s, 1H, pyridazine-H). MS (EI, *m/z* (%)): 422 (M^{+1}, 27.5), 421 (M^+, 100). Anal. calcd. for $C_{23}H_{15}N_7O_2$: C, 65.55; H, 3.59; N, 23.27. Found: 65.43; H, 3.55; N, 23.33%.

8-Amino-5-(2-chlorophenyl)-4-methyl-1-(2-nitrophenyl)-1H-pyridazino[5,4,3-de]1,6-naphthyridine-7-carbonitrile (**8b**): Recrystallized from acetic acid. Color: Yellow. M.p.: 240-241 °C. Yield: 71 %. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.49 (s, 3H, CH_3), 7.06 (s, 2H, NH_2, D_2O exchangeable), 7.46-7.54 (m, 4H, Ar-H), 7.77-7.99 (m, 3H, Ar-H), 8.23-8.25 (dd, *J* = 0.8 Hz, 1H, Ar-H), 8.63 (s, 1H, pyridazine-H). MS (EI, *m/z* (%)): 457 (M^{+2}, 40.3), 456 (M^{+1}, 28.7). Anal. calcd. for $C_{23}H_{14}ClN_7O_2$: C, 60.60; H, 3.10; N, 21.51. Found: C, 60.55; H, 3.22; N, 21.55 %.

8-Amino-5-(4-chlorophenyl)-4-methyl-1-(2-nitrophenyl)-1H-pyridazino[5,4,3-de]1,6-naphthyridine-7-carbonitrile (**8c**): Recrystallized from EtOH. Color: Yellow. M.p.: 275-276 °C. Yield: 68 %. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.35 (s, 3H, CH_3), 7.02 (s, 2H, NH_2, D_2O exchangeable), 7.57-7.61 (m, 4H, Ar-H), 7.77-7.80 (m, 1H, Ar-H), 7.87-7.88 (dd, *J* = 0.8 Hz, 1H, Ar-H), 7.93-7.95 (m, 1H, Ar-H), 8.22-8.24 (dd, *J* = 0.8 Hz, 1H, Ar-H), 8.62 (s, 1H, pyridazine-H). MS (EI, *m/z* (%)): 457 (M^{+2}, 37.2), 456 (M^{+1}, 38.3), 455 (M^+, 100). Anal. calcd. for $C_{23}H_{14}ClN_7O_2$: C, 60.60; H, 3.10, N, 21.51. Found: C, 60.62; H, 3.12, N, 21.49 %.



Scheme 2

8-Amino-5-(2-tolyl)-4-methyl-1-(2-nitrophenyl)-1H-pyridazino[5,4,3-de]1,6-naphthyridine-7-carbonitrile (**8d**): Recrystallized from dimethylformamide. Color: Orange. M.p.: 310-312 °C. Yield: 80 %. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.09 (s, 3H, CH_3), 2.14 (s, 3H, CH_3), 7.00 (s, 2H, NH_2, D_2O exchangeable), 7.21-8.24 (m, 8H, Ar-H), 8.60 (s, 1H, pyridazine-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 13.11, 19.08, 73.00, 108.10, 115.76, 116.78, 125.24, 125.65, 128.17, 128.22, 130.04, 130.10, 130.26, 130.46, 134.26, 134.82, 134.94, 137.95, 139.68, 137.95, 139.68, 144.60, 150.39, 152.17, 161.39, 166.42. MS (EI, *m/z* (%)): 435 (M^+, 50). Anal. calcd. for $C_{24}H_{17}N_7O_2$: C, 66.20; H, 3.94; N, 22.52. Found: C, 66.23; H, 3.88; N, 22.55 %.

8-*Amino-5-(4-tolyl)-4-methyl-1-(2-nitrophenyl)-1H-pyridazino[5,4,3-de]1,6-naphthyridine-7-carbonitrile* (**8e**): Recrystallized from acetic acid. Color: Orange. M.p.: 299-300 °C. Yield: 70 %. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.36 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 6.90 (s, 2H, NH_2, D_2O exchangeable), 7.34 (d, *J* = 5.2, 2H, Ar-H), 7.48 (d, *J* = 5.2, 2H, Ar-H), 7.77-7.80 (m, 1H, Ar-H), 7.88-7.89 (dd, *J* = 0.8 Hz, 1H, Ar-H), 7.96-7.98 (m, 1H, Ar-H), 8.23-8.24 (dd, *J* = 0.8 Hz, 1H, Ar-H), 8.61 (s, 1H, pyridazine-H). MS (EI, *m/z* (%)): 437 (M^{+2}, 28.2), 435 (M+, 100). Anal. calcd. for $C_{24}H_{17}N_7O_2$: C, 66.20; H, 3.94; N, 22.52. Found: C, 66.31; H, 3.88; N, 22.56 %.

Ethyl 2-(2-((5-amino-4,6-dicyano[1,1'-biphenyl]-3-yl)methylene)hydrazinyl)benzoate (**4a**): Recrystallized from dimethyl formamide. Color: Brown. M.p.: >350 °C. Yield: 80 %. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.35 (t, *J* = 4.8 Hz, 3H, CH_3), 4.32-4.35 (q, *J* = 4.8 Hz, 2H, CH_2) 6.73 (s, 2H, NH_2, D_2O exchangeable), 6.93 (m, 1H, Ar-H), 7.13 (s, 1H, hydrazinyl-CH), 7.53-7.56 (m, 4H, Ar-H), 7.58-7.60 (m, 2H, Ar-H), 7.80-7.81 (dd, *J* = 0.8 Hz, 1H, Ar-H), 7.86-7.88 (m, 1H, Ar-H), 8.31 (s, 1H, Ar-H), 11.45 (s, 1H, NH, D_2O exchangeable). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 14.56, 61.38, 91.72, 94.56, 111.54, 114.81, 116.14, 116.62, 120.01, 128.87, 129.21, 129.84, 131.11, 131.11, 135.20, 136.75, 138.12, 142.61, 146.01, 150.05, 154.66, 167.42. MS (EI, *m/z* (%)): 410 (M^{+1}, 4.8), 409 (M+, 65.6). Anal. calcd. for $C_{24}H_{19}N_5O_2$: C, 70.40; H, 4.68; N, 17.10. Found: C, 70.44; H, 4.70, N, 17.22 %.

Ethyl 2-(2-((5-amino-4-chloro-4,6-dicyano[1,1'-biphenyl]-3-yl)methylene)hydrazineyl)benzoate (**4b**): Recrystallized from dimethylformamide. Color: Dark Brown. M.p.: 291-292 °C. Yield: 72 %. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.35 (t, *J* = 7.2 Hz, 3H, CH_3), 4.33-4.36 (q, *J* = 4.8 Hz, 2H, CH_2), 6.78 (s, 2H, NH_2, D_2O exchangeable), 6.93-6.95 (m, 1H, Ar-H), 7.15 (s, 1H, hydrazinyl-CH), 7.53-7.62 (m, 5H, Ar-H), 7.81 (d, *J* = 5.6 Hz, 1H, Ar-H), 7.87-7.88 (dd, 1H, Ar-H), 8.33 (s, 1H, Ar-H), 11.47 (s, 1H, NH, D_2O exchangeable). ^{13}C NMR (400 MHz, DMSO-d_6, δ, ppm): 14.55, 61.37, 92.04, 94.35, 111.58, 114.86, 116.01, 116.49, 120.03, 129.27, 130.82, 131.11, 134.80, 135.18, 136.62, 139.91, 142.75, 145.97, 148.74, 154.61, 167.40. MS (EI, *m/z* (%)): 443 (M^+, 100). Anal. calcd. for $C_{24}H_{18}ClN_3O_2$: C, 64.94; H, 4.09; N, 15.78. Found: C, 64.96; H, 4.12; N, 15.88 %.

Ethyl 2-(2-((5-amino-4-nitro-4,6-dicyano[1,1-biphenyl]-3-yl)methylene)hydrazinyl)benzoate (**4c**): Recrystallized from acetic acid. Color: Brown. M.p.: 280-281 °C. Yield: 75 %. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.34 (t, *J* = 4.8 Hz, 3H, CH_3), 4.31-4.35 (q, *J* = 4.8 Hz, 2H, CH_2), 6.82 (s, 2H, NH_2, D_2O exchangeable), 6.93 (t, *J* = 4.8 Hz, 1H, Ar-H), 7.19 (s, 1H, hydrazinyl-CH), 7.52 (t, *J* = 4.8 Hz, 1H, Ar-H), 7.79-7.96 (m, 5H, Ar-H), 8.30 (s, 1H, Ar-H), 8.39 (s, 1H, Ar-H), 11.47 (s, 1H, NH, D_2O exchangeable). MS (EI, *m/z* (%)): 456 (M^{+2}, 17.2), 454 (M^+). Anal. calcd. for $C_{24}H_{18}N_6O_4$: C, 63.43; H, 3.99; N, 18.49. Found: C, 63.44; H, 3.88; N, 18.55 %.

2-Acetyl-6-amino-3-phenyl-3H-pyridazino[1,6-a]quinazoline-4-carbonitrile (**22**): Recrystallized from EtOH. Color: Green. M.p.: 285-286 °C. Yield: 83 %. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.48 (s, 3H, CH_3), 8.44 (s, 1H, pyridazin-H), 7.15-8.05 (m, 9H, Ar-H), 8.16 (s, 2H, NH_2, D_2O exchangeable). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 25.17, 37.50, 67.82, 111.99, 114.44, 120.58, 124.09, 124.68, 127.13, 127.35, 128.92, 134.42, 139.91, 142.30, 145.06, 147.26, 156.22. MS (EI, *m/z* (%)): 341 (M+, 45). Anal. calcd. for $C_{20}H_{15}N_5O$: C, 70.37; H, 4.43; N, 20.52. Found: C, 70.25; H, 4.32; N, 20.44 %.

3. Results and discussion

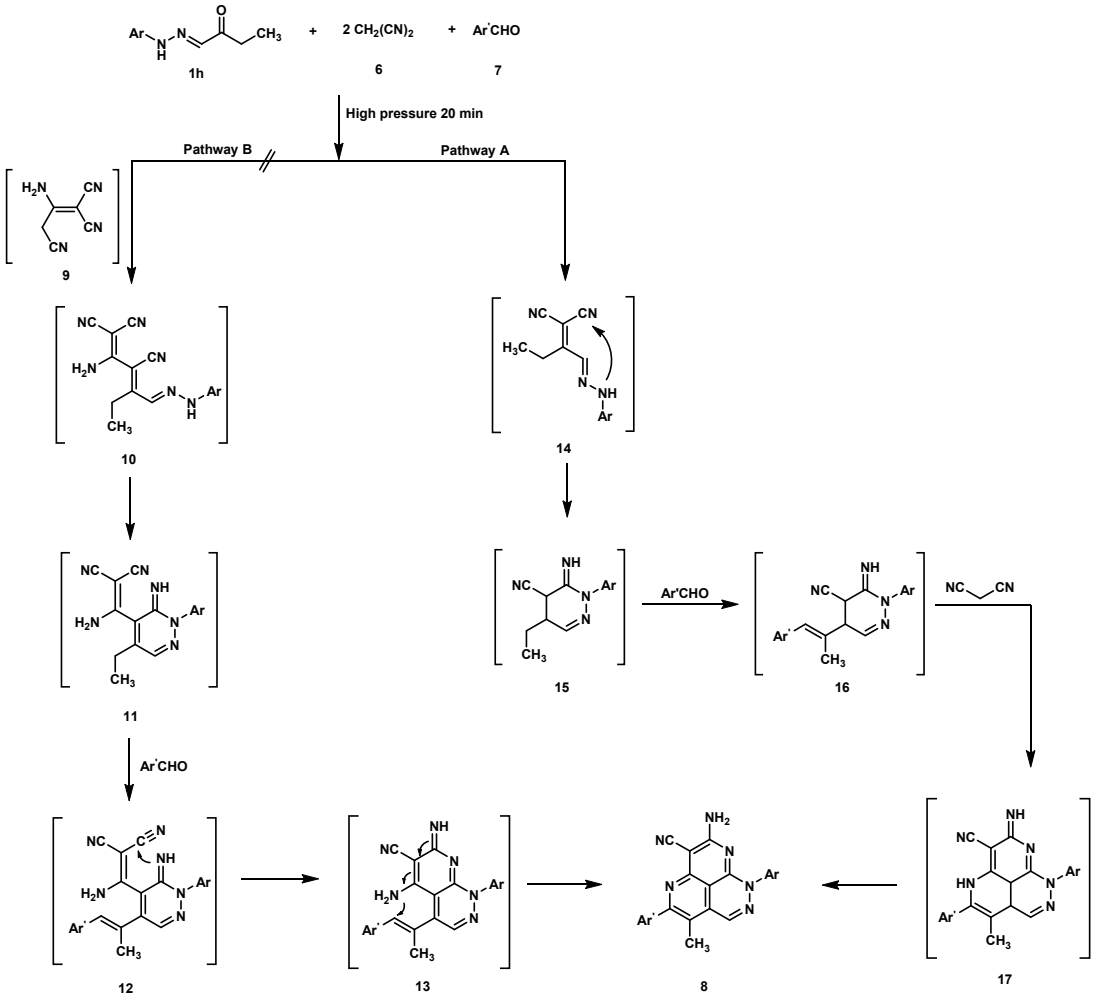
In conjunction to our interest in pyridazines and condensed pyridazines we report here on the reaction of arylhydrazonal derivatives (**1h-k**), malononitrile (**6**) and aromatic aldehyde derivatives (**7a-e**). We have found that arylhydrazonal derivative (**1h**) reacts with malononitrile (**6**) and aromatic aldehyde (**7a-e**) to yield the pyridazinonaphthyridine derivatives (**8a-e**) (Scheme 2).

Two routs can lead to the formed end product. Thus, initial condensation of compound **1h** with malononitrile (**6**) can afford compound **14** that then cyclized to compound **15** which reacted further with aromatic aldehydes to yield compound **16** that added further malononitrile molecule and cyclized then aromatized to yield compound **8** (Pathway A) (Scheme 3). Alternately initial formation of dimer **9** that condense with compound **1h** yielding compound **10** that afford compound **11** then compound **12** and finally compound **8** (Pathway B, Scheme 3) can also occur.

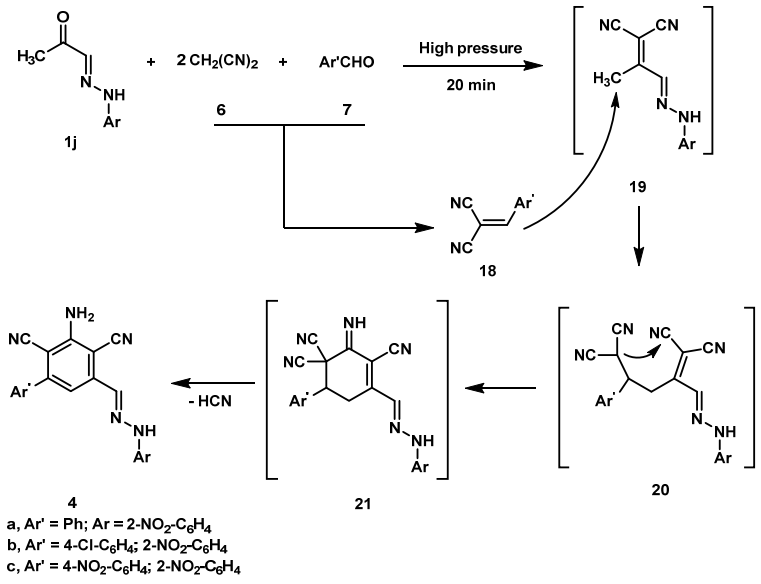
Under the same reaction condition, compound **1j** reacted with malononitrile (**6**) and aromatic aldehyde **7** to afford the benzene derivative **4** via sequence shown in Scheme 4 [16].

In contrast the arylhydrazonal **1k** reacted with malononitrile (**6**) and aromatic aldehyde **7a** at the same conditions to afford the pyridazine derivative **22** (Scheme 5).

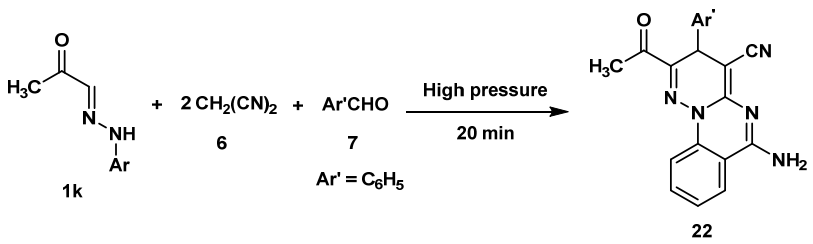
Although, in a previous article, Moustafa *et al.* [18] reported the formation of pyridazino[5,4,3-*de*][1,6]naphthyridine derivatives via reaction of ethyl 3-oxo-2-arylhydrazono butanoate, malononitrile and aromatic aldehydes under high pressure but they could not conclude exact mechanism of the process leading to the formation of the tricyclic system.



Scheme 3



Scheme 4



Scheme 5

In our efforts described above the reactions are also conducted in a Q-tube, as in more than one situation, products resulting from initial condensation with malononitrile as the case of compound **1j** and **1k** and subsequent reaction with arylidene malononitrile have been observed which decisively excluded the initial dimerization of malononitrile. It is almost certain that formation of the tricyclic system proceed in the same way operating in case of compound **1j**,**k** establishing route A for the reaction mechanism.

4. Conclusions

We do conclude that, 3+3 atom combination synthesis of dihydropyridazines is in fact very limited scope. Efficient electron donating substituents at the hydrazone aryl moiety renders hydrazone C-1 the most reactive center. Electron attracting substituents reverse the situation rendering the acyl carbonyl the most reactive center and the active methylene initially condense with yielding the corresponding ylidene derivative that react further with another of the reagent to yield biaryl derivatives (**4**) as with ortho-ester group, where hydrogen bonding of hydrazine NH with ester group enhances this process. If alternate cyclization products are either more stable or less soluble product, then another cyclization course took place. In case of compound **1k**, the produced enamino-nitrile is more reactive than the start and further reacted yielding the tricyclic system. Steric hindrance of the acyl carbonyl also plays a role in such reaction. In case of compound **1**, the propanoyl groups render the carbonyl group less reactive for further cyclization. Moreover, in a multicomponent reaction the active methylene reagent initially condense with acyl carbonyl moiety rather than initial formation of arylidene derivative that has the potentiality to add to aryl-hydrazonal C-1, establishing that initial dimerization of malononitrile does not occur.

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