Article

Multi Component Reactions under Increased Pressure: On the Mechanism of Formation of Pyridazino[5,4,3-de][1,6]naphthyridine Derivatives from Reaction of Malononitrile, Aldehyde and 2-Oxoglyoxalarylhydrazones in Q-Tubes

Majdah A. AL-Johani [1], Khadijah M. Al-Zaydi [1,*], Sameera M. Mousally [1], Norah F. Alqahtani [1] and Mohamed H. Elnagdi [2]

[1] Department of Chemistry, Faculty of Sciences - AL Faisaliah, King Abdulaziz University, Jeddah, P.O. Box 50918, Jeddah 21533, Kingdom Saudi Arabia; moon98.1@hotmail.com (M.A.A); smousally@kau.edu.sa (S.M.M); nfa14@case.edu (N.F.A)

[2] Emeritus Professor; Cairo University and Kuwait University and a free science writer; m.h.elnagdi@outlook.com

* Correspondence: kalzaydi@kau.edu.sa; Tel.: +00966505678719

Abstract: The considerable biological and medicinal activities of pyridazines has stimulated considerable research on efficient syntheses of these derivatives. In the last decade, microwave irradiation has generally been used for the energy source. As demonstrated in recent studies, pressure reactor "Q-tubes" may be used to accelerate several of these reactions in a more optimal and safer manner (compared to microwaves). In these studies there has been postulated a pathway for the formation of pyridazino[5,4,3-de][1,6]naphthyridine derivatives . In this paper we consider this pathway, and an alternate pathway, for several reactions. Contrary to the suggestion in these studies the pathway in which initial dimerization of malononitrile was postulated could be excluded based on chemical evidence. The reactions performed were the reaction of arylhydrazonals 1a,b with benzylidinemalononitrile which afforded in Q-tube the 3-acyl-4-aryl-1-phenyl-6-amino-1,4-dihydropyridazines, and the reaction of arylhydrazonals 1a,b, malononitrile 9 and aromatic aldehydes 10a-g in Q-tubes which afforded the tricyclic systems 12a-n whose structure could be established by X-ray crystal structure determination. In conclusion, we have added to the work of the recent studies by excluding a reaction pathway for one of their reaction products.

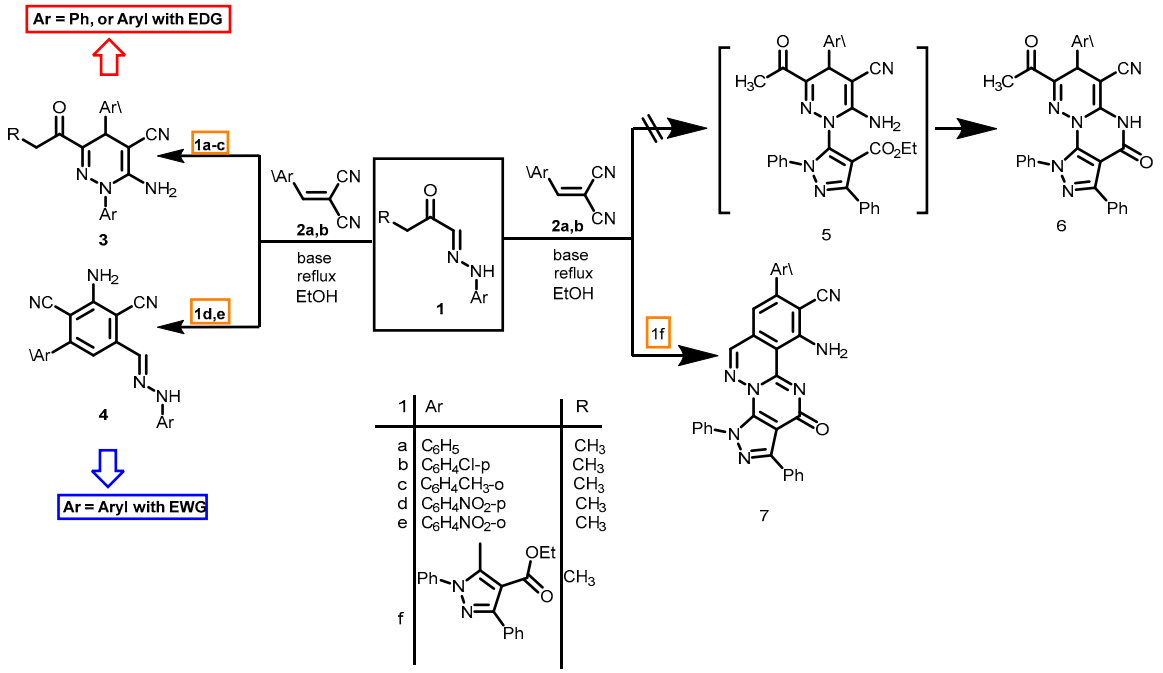
Keywords: X-ray; arylhydrazones; 2-amino-1,1,3-propenetricarbonitrile; pyridazines; rate enhance under pressure

1. Introduction

The considerable biological and medicinal activities of pyridazines stimulated considerable research on efficient syntheses of these derivatives in past years [1-4]. Some time ago we reported synthesis of 2-amino-1,4-dihydropyridazine, isoelectronic derivative of 1,4-dihydropyrimidines of established biological activities [5-8], via 3+3 atom combination of **1a** and **2** [9] (Scheme 1). Subsequent studies [10,11] however on this novel route revealed that it is of limited scope as reaction product proved dependent on the nature of reacting the aryl group in the aldehyde hydrazones and **4** were the sole product from reaction of aldehyde hydrazones **1a-c** with α,β-functionally substituted cinnamonitriles. In recent article Abdelhamid *et al.* [12] have reported that the reaction of arylhydrazone **1f** with α,β-unsaturated nitriles **2** form pyrazolo[4',3'-5,6]pyrimido[2,1-*a*]phthalazine-9-carbonitrile derivative **7,** rather than the expected product **6** (Scheme 1).

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 17 October 2017 doi:10.20944/preprints201710.0110.v1

Peer-reviewed version available at Molecules 2017, 22, 2114; doi:10.3390/molecules22122114

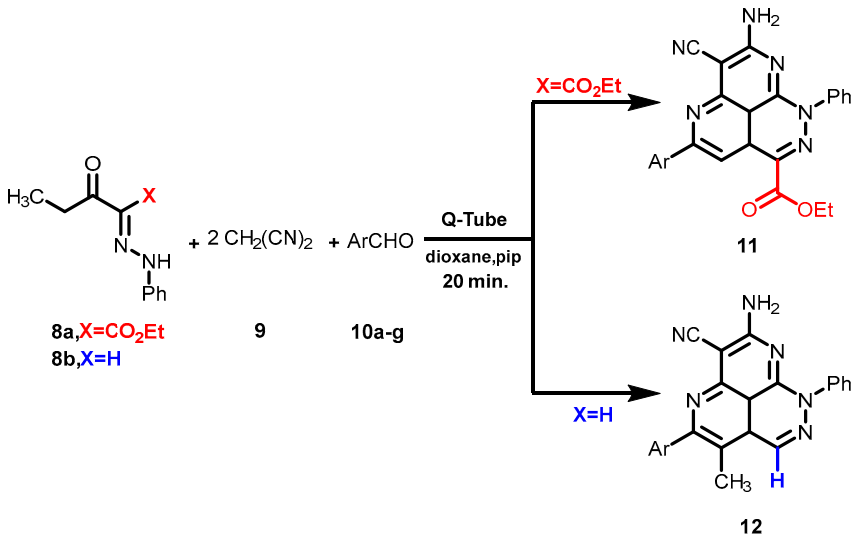


Scheme 1: The reactivity of aryl hydrazones **1** towards *α,β*-functionally substituted cinnamonitriles.

We in the last decades have generally utilized microwaves irradiations as energy source [13-16]. However, we noted that microwaves technology is expensive to scale up [17]. The technique that renders the organic reaction under pressure, can be easily scaled up utilizing presser reactor "Q-tubes" to accelerate several reactions in a more optimal and safer manner, compared to Microwaves [18].

We reported on the efficient synthesis of benzo[c]chromen-6-one and phenanthridin-6(5H)-one derivatives in a four-component reaction in Q-Tube [19].

Recently, Moustafa *et al.* have developed a novel synthesis of tricyclic system **11** via reacting ethyl-3-oxo-2-(2-phenylhydrazono) pentanoate **8a** with malononitrile **9** and aromatic aldehyde derivatives **10** in Q-Tube [20] (Scheme 2). Very recently Sadek and Elnagdi [21] reported the formation of **12** upon reacting arylhydrazonal with malononitrile and aromatic aldehydes in Q-tube but evidence for proposed structure looked debatable. In the present article, we report on the multicomponent reaction of aldehyde hydrazone **1**, aromatic aldehydes and malononitrile, where we observed that under pressure in a Q-tube the reaction products different than those conducted by conventional heating as a result of apparent volume effect on the first step transition state of this multicomponent reaction (Scheme 2).



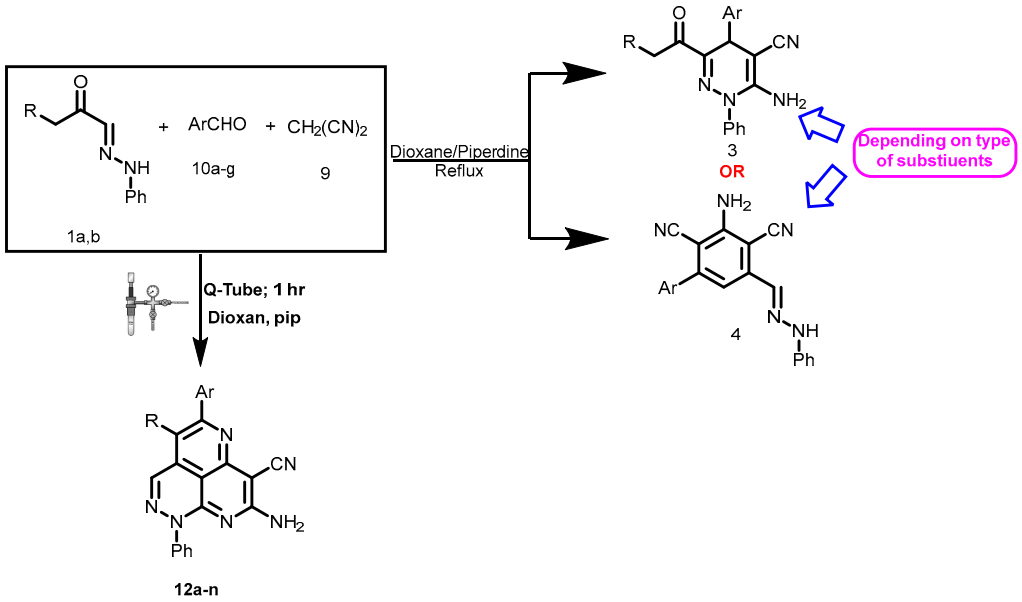
Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 17 October 2017 doi:10.20944/preprints201710.0110.v1

Peer-reviewed version available at Molecules 2017, 22, 2114; doi:10.3390/molecules22122114

Scheme 2: novel synthesis of tricyclic system **11** via reacting ethyl-3-oxo-2-(2-phenylhydrazono) pentanoate **8a** with malononitrile **9** and aromatic aldehyde derivatives **10** in Q-Tube

2. Results

Reacting **1a** with **2a** in Q-tube afforded **3**. Compound **3** has also been obtained earlier by Elnagdi et al [9]. However reaction of 2-oxo-2-arylhydrazonals **1a,b** with aromatic aldehydes **10a-g** and malononitrile **9** afforded in dioxane in presence of piperidine in Q-Tube (*cf.* Fig.1) at 150 °C and 20 psi, the tricyclic system **12** is formed in 72%-85 % yield (Scheme 3, Table 1).



Scheme 3 A new reaction path for aldehyde hydrazone with malononitril and aldehydes.

Table 1: Synthesis of pyridazino[5,4,3-de][1,6]naphthyridine derivatives **12a-n.**

Entry	R	Ar	Yield %	Time (min)
12a	H	Ph	85	60
12b	H	4-ClC_6H_4	75	60
12c	H	2-ClC_6H_4	80	120
12d	H	4-$CH_3C_6H_4$	77	60
12e	H	2-$CH_3C_6H_4$	73	120
12f	H	4-$O_2NC_6H_4$	82	60
12g	H	2-furyl	86	120
12h	CH_3	Ph	83	60
12j	CH_3	4-ClC_6H_4	78	60
12k	CH_3	4-$CH_3C_6H_4$	80	60
12l	CH_3	2-$CH_3C_6H_4$	72	120
12m	CH_3	4-$O_2NC_6H_4$	82	60
12n	CH_3	2-furyl	86	120

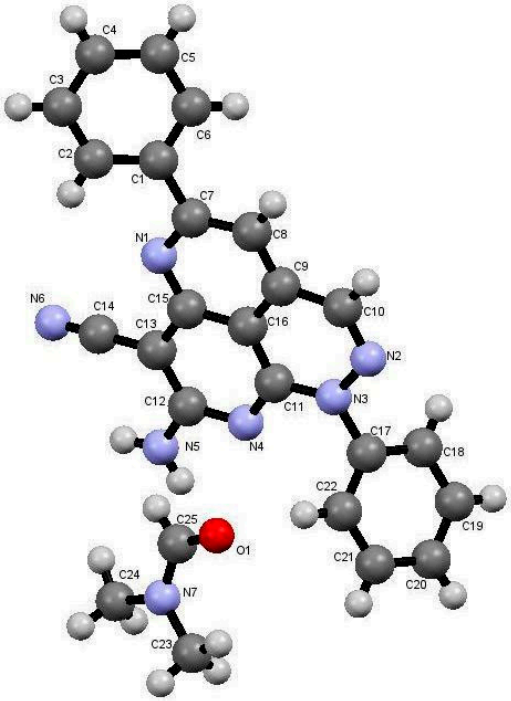


Fig. 1: X-ray crystallography of compound **12a [22].**

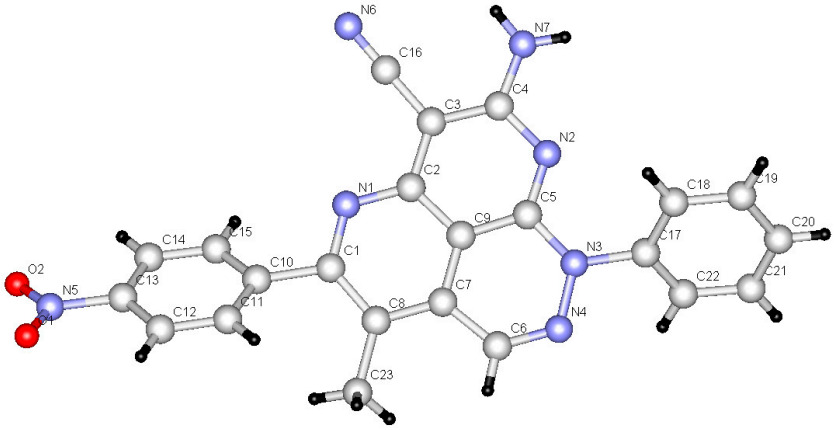


Fig. 2: X-ray crystallography of compound **12m [23].**

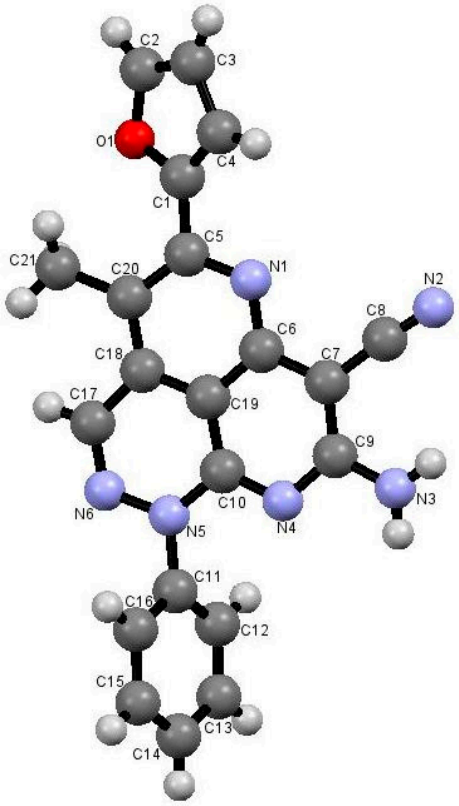


Fig. 3: X-ray crystallography of compound **12n [24].**

The structure of the reaction products could be established to be pyridazino[5,4,3-de][1,6]naphthyridine derivatives **12a-n** *via* X-ray crystal structure determination of products **12a**, **12m** and **12n** (Fig. 1-3).

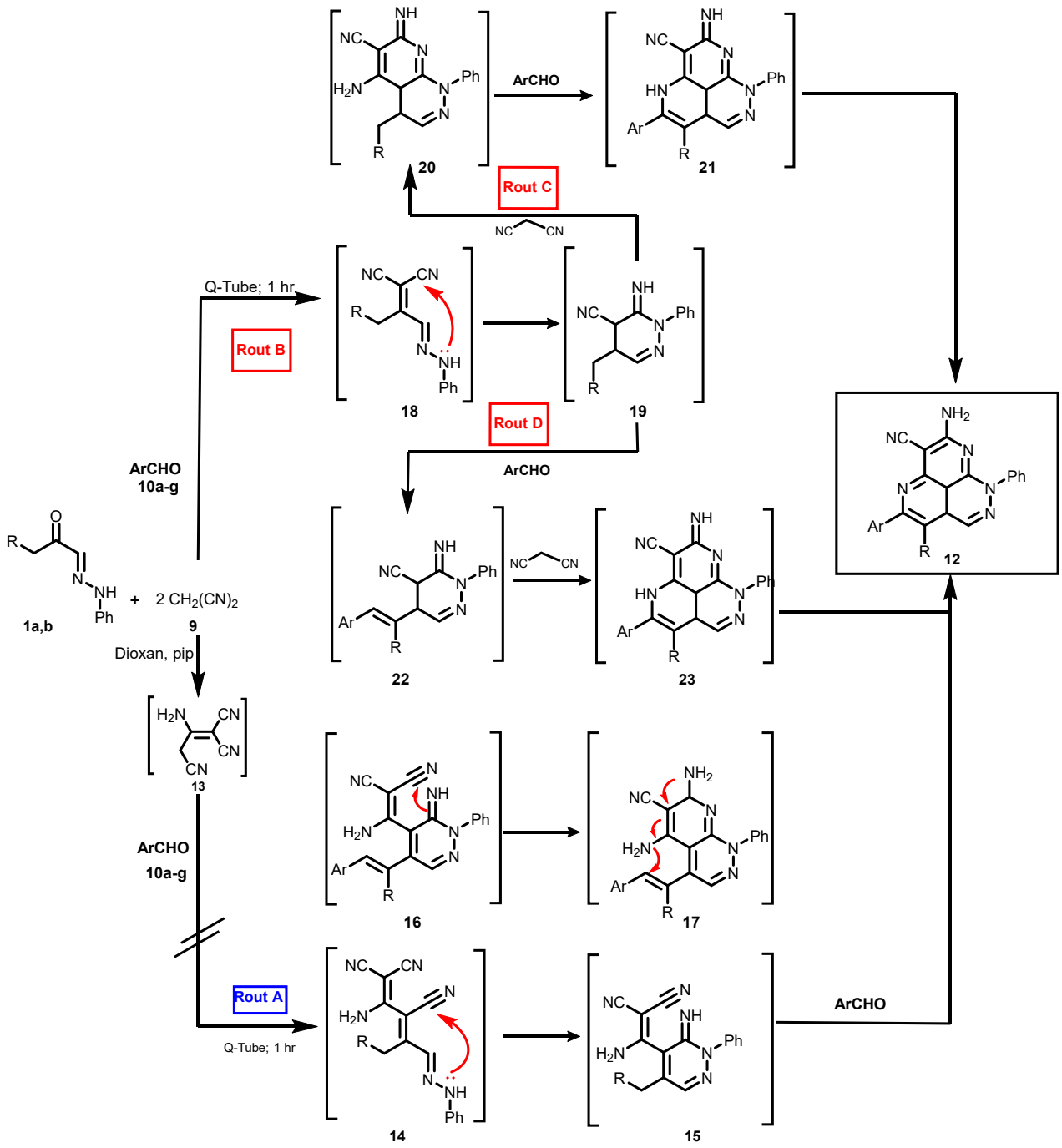
3. Discussion

Two mechanistic pathways seem possible (Scheme 4). Initial dimerization of malononitrile to yield **13** dimer, that then condense with the acyl carbonyl yielding **14** that cyclize to form **15** (rout A), as has been suggested by Moustafa *et al.* [20] could be readily eliminated. As in our hand arylhydrazonals **1a, b** did not condense with malononitrile dimer **13** under a variety of rustic conditions.

Moustafa *et al.* [20] also reported that the dimer **13** alone reacts with their arylhydrazone **1a,b** yielding pyridazino[5,4,3-de][1,6]naphthyridine derivatives, not condensed with pyridazine derivatives. Thus, it is almost certain that the initial step leading to formation of **12** is the condensation of malononitrile **9** with acyl carbonyl **18**. The product **19** can then either cyclize into **20** then **21** (rout C) or condense aromatic aldehyde to give **22** then **23**(rout D), neither rout (C, D) can be completely ruled out. Although we believe that aromatic aldehyde condenses initially with **19** then subsequent reaction leading to **22** and then react with malononitrile **9** to form **23** which cyclize to the final product **12** that taking place in rout D (Scheme 4).

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 17 October 2017 doi:10.20944/preprints201710.0110.v1

Peer-reviewed version available at Molecules 2017, 22, 2114; doi:10.3390/molecules22122114



Scheme 4: A suggested mechanism for the formation of pyridazino[5,4,3-de][1,6]naphthyridine derivatives **12a-n.**

4. Experimental Section

4.1 General

Q-tube assisted reactions were performed in a Q-tube safe pressure reactor from Q Labtech, equipped with a cap/sleeve, pressure adapter (120 psi), needle adapter/needle, borosilicate glass tube, Teflon septum, and catch bottle. All reactions were monitored by using TLC with 1:1 ethyl acetate-petroleum ether as eluent and were carried out until starting materials were completely consumed. Melting points are reported uncorrected and were determined with a Sanyo (Gallaenkamp) instrument. Infrared spectra were recorded using KBr pellets and a Jasco FT–IR 6300 instrument and

absorption bands are reported in cm^{-1}. ^1H- and ^{13}C-NMR spectra were determined by using a Bruker DPX instrument at 400 MHz or 600 MHz for ^1H-NMR and 100 MHz for ^{13}C-NMR and either $CDCl_3$ or DMSO-d6 solutions with TMS as internal standards. Chemical shifts are reported in ppm. Mass spectra and accurate mass measurements were made using a GCMS DFS Thermo spectrometer with the EI (70 EV) mode. X-ray crystallographic structure determinations were performed by using Rigaku Rapid II and Bruker X8 Prospector single crystal X-ray Diffractometers. All X-ray crystal structure data can be obtained free of charge from the Cambridge Crystallographic Data Centre [21-24] via www.ccdc.cam.ac.uk.

4.2 General Procedures for Q-Tube-Assisted Synthesis of 12a-n

2-oxo-2-arylhydrazonals (**1a,b**) (0.01 mol), aromatic aldehydes (**13a-g**) (0.01 mol) and malononitrile (**14**) (0.02 mol) in presence of piperidine (1 mL) and dioxin (20 mL) as solvent were sequentially added in a 35 mL Q-tube pressure tube, furnished by Q Labtech. A Teflon septum was placed on the top of the tube, and an appropriate cap was used. The mixture was heated in an oil bath at 150 °C. After about 60 min, the reaction mixture was monitored by TLC. The mixture was cooled and poured into ice-water. The solid was collected by filtration and purified by column chromatography utilizing appropriate solvents mixture to give crystals of compounds **12a-n**.

8-Amino-1,5-diphenyl-1H-pyridazino[5,4,3-de][1,6]naphthyridine-7-carbonitrile (12a)

Dark yellow crystals, Yield 85%; mp. 314-315 ºC; *Anal*. Calcd for $C_{22}H_{14}N_6$ (362.13): C, 72.92; H, 3.89; N, 23.19. Found: C, 72.83; H, 3.79; N, 23.25. EI-HRMS: *m/z* = 362.12 (MH^+); $C_{22}H_{14}N_6$ requires: *m/z* = 362.13 (MH^+); IR: 3467, 3449 (NH_2), 2199 (CN); ^1H NMR (400 MHz, DMSO-*d6*): δ = 7.06 (br, 2H, NH_2, D_2O exchangeable), 7.44-7.66 (m, 9H, Ph-H, CH), 8.19-8.22 (m, 2H, Ph-H), 8.38 (s, 1H, CH); ^{13}C NMR (100 MHz, DMSO-*d6*): δ = 162.0, 161.2, 154.5, 150.9, 141.7, 138.7, 137.8, 133.2, 130.3, 128.8 (2C), 128.7 (2C), 128.1, 127.1 (2C), 126.3 (2C), 116.8, 108.8, 104.6, 73.3. MS: *m/z* (%) 362.2 (M^+, 100), 334 (10), 181 (10), 77 (5).

8-amino-5-(4-chlorophenyl)-1-phenyl-1H-pyridazino[5,4,3-de][1,6]naphthyridine-7-carbonitrile (12b)

Green crystals, yield 75%; mp. 340-341 ºC; *Anal*. Calcd for $C_{22}H_{13}ClN_6$ (396.06): C, 66.59; H, 3.30; N, 21.18. Found: C, 66.70; H, 3.35; N, 21.20. EI-HRMS: *m/z* = 396.08 (MH^+); $C_{22}H_{13}N_6{}^{35}Cl$ requires: *m/z* 969= 396.06 (MH^+); IR: 3463, 3328 (NH_2), 2203 (CN); ^1H NMR (400 MHz, DMSO-*d6*): δ = 7.10 (br, 2H, NH_2, D_2O exchangeable), 7.45-7.66 (m, 8H, Ph-H, CH), 8.22-8.24 (m, 2H, Ph-CH), 8.38 (s, 1H, CH); ^{13}C NMR (100 MHz, DMSO-*d6*): δ = 162.1, 160.0, 154.6, 151.0, 141.7, 138.7, 136.7, 133.4, 130.3, 129.1 (2C), 128.9 (2C), 128.2, 126.6 (2C), 124.6 (2C), 118.0, 109.1, 104.6, 56.0. MS: *m/z* (%) 396.1 (M^+, 100), 368 (10), 198 (10), 166 (5), 77 (5).

8-amino-5-(3-chlorophenyl)-1-phenyl-1H-pyridazino[5,4,3-de][1,6]naphthyridine-7-carbonitrile (12c)

Green crystals, yield 80%; mp. 314-316 ºC; *Anal*. Calcd for $C_{22}H_{13}ClN_6$ (396.06): C, 66.59; H, 3.30; N, 21.18. Found: C, 66.57; H, 3.33; N, 21.12. EI-HRMS: *m/z* = 396.08 (MH^+); $C_{22}H_{13}N_6{}^{35}Cl$ requires: *m/z* = 396.06 (MH^+); IR: 3488, 3347 (NH_2), 2213 (CN); ^1H NMR (400 MHz, DMSO-*d6*): δ = 7.11 (br, 2H, NH_2, D_2O exchangeable), 7.27 (s, 1H, CH), 7.45-7.67 (m, 9H, Ph-H), 8.45 (s, 1H, CH); ^{13}C NMR (100 MHz, DMSO-*d6*): δ = 162.2, 162.0, 154.6, 151.1, 141.7, 138.8, 138.5, 132.4, 131.4, 131.0, 130.6, 129.9 (2C), 128.8, 128.2, 127.4, 126.4 (2C), 116.8, 108.9, 108.8, 73.1. MS: *m/z* (%) 396.1 (M^+, 100), 361 (15), 334 (5), 198 (10), 166 (5), 77 (5).

8-amino-1-phenyl-5-p-tolyl-1H-pyridazino[5,4,3-de][1,6]naphthyridine-7-carbonitrile (12d)

Faint green crystals, yield 77%; mp. 340-341 ºC; *Anal*. Calcd for $C_{23}H_{16}N_6$ (376.14): C, 73.39; H, 4.28; N, 22.33. Found: C, 73.34; H, 4.30; N, 22.28. EI-HRMS: *m/z* = 376.14 (MH^+); $C_{23}H_{16}N_6$ requires: *m/z* = 376.14 (MH^+); IR: 3470, 3343 (NH_2), 2199 (CN); ^1H NMR (400 MHz, DMSO-*d6*): δ = 2.39 (s, 3H, CH_3),

7.05 (br, 2H, NH_2, D_2O exchangeable), 7.34-7.65 (m, 8H, Ph-H, CH), 8.09-8.29 (m, 2H, Ph-H), 8.36 (s, 1H, CH); ^{13}C NMR (100 MHz, DMSO-*d6*): δ = 162.2, 161.2, 154.4, 150.9, 141.7, 140.2, 138.8, 135.1, 133.2, 129.4 (2C), 128.8 (2C), 128.1, 127.1 (2C), 126.3 (2C), 116.9, 108.7, 104.2, 73.3, 20.9. MS: *m/z* (%) 376.2 (M^+, 100), 348 (10), 188 (10), 77 (5).

8-amino-1-phenyl-5-m-tolyl-1H-pyridazino[5,4,3-de][1,6]naphthyridine-7-carbonitrile (12e)

Green crystals, yield 73%; mp. 280-281 ºC; *Anal*. Calcd for $C_{23}H_{16}N_6$ (376.14): C, 73.39; H, 4.28; N, 22.33. Found: C, 73.38; H, 4.27; N, 22.31. EI-HRMS: *m/z* = 376.14 (MH^+); $C_{23}H_{16}N_6$ requires: *m/z* = 376.14 (MH^+); IR: 3450, 3338 (NH_2), 2197 (CN); ^1H NMR (400 MHz, DMSO-*d6*): δ = 2.43 (s, 3H, CH_3), 7.07 (br, 2H, NH_2, D_2O exchangeable), 7.18 (s, 1H, CH), 7.34-7.66 (m, 9H, Ph-H), 8.40 (s, 1H, CH); ^{13}C NMR (100 MHz, DMSO-*d6*): δ = 165.2, 162.0, 154.3, 151.1, 141.7, 139.6, 138.7, 135.8, 133.7, 130.8, 129.3, 128.9, 128.2 (2C), 128.1, 126.3 (2C), 125.9, 116.9, 108.3, 108.2, 73.3, 20.3. MS: *m/z* (%) 376 (M^+, 50), 375 (100), 348 (10), 255 (10), 187 (10), 77 (5).

8-amino-5-(4-nitrophenyl)-1-phenyl-1H-pyridazino[5,4,3-de][1,6]naphthyridine-7-carbonitrile (12f)

Dark brown crystals, yield 82%; mp. 397-398 ºC; *Anal*. Calcd for $C_{22}H_{13}N_7O_2$ (407.11): C, 64.86; H, 3.22; N, 24.07. Found: C, 64.75; H, 3.10; N, 24.12. EI-HRMS: *m/z* = 407.11 (MH^+); $C_{22}H_{13}O_2N_7$ requires: *m/z* = 407.11 (MH^+); IR: 3433, 3334 (NH_2), 2199 (CN); ^1H NMR (400 MHz, DMSO-*d6*): δ = 7.18 (br, 2H, NH_2, D_2O exchangeable), 7.48-8.48 (m, 10H, Ph-H, CH), 9.20 (s, 1H, CH). MS: *m/z* (%) 407.2 (M^+, 100), 361 (20), 334 (10), 180 (10), 77 (5).

8-amino-5-(furan-2-yl)-1-phenyl-1H-pyridazino[5,4,3-de][1,6]naphthyridine-7-carbonitrile (12g)

Dark green crystals, yield 86%; mp. 345-346 ºC; *Anal*. Calcd for $C_{20}H_{12}N_6O$ (352.11): C, 68.18; H, 3.43; N, 23.85. Found: C, 68.21; H, 3.52; N, 23.77. EI-HRMS: *m/z* = 352.10 (MH^+); $C_{20}H_{12}O_1N_6$ requires: *m/z* = 352.11 (MH^+); IR: 3460, 3329 (NH_2), 2203 (CN); ^1H NMR (400 MHz, DMSO-*d6*): δ = 6.74-6.75 (m, 1H, furayl-H), 7.05 (br, 2H, NH_2, D_2O exchangeable), 7.24-7.97 (m, 8H, Ph-H, furyl-H, CH), 8.42 (s, 1H, CH); ^{13}C NMR (100 MHz, DMSO-*d6*): δ = 162.0, 154.6, 153.2, 152.7, 150.8, 145.6, 141.7, 138.6, 133.2, 128.8 (2C), 128.2, 126.3 (2C), 116.8, 112.7, 11.8, 108.6, 102.7, 73.0. MS: *m/z* (%) 352.1 (M^+, 100), 324 (5), 176 (10), 77 (5).

8-amino-4-methyl-1,5-diphenyl-1H-pyridazino[5,4,3-de][1,6]naphthyridine-7-carbonitrile (12h)

Yellow crystals, yield 83%; mp. 364-365 ºC; *Anal*. Calcd for $C_{23}H_{16}N_6$ (376.14): C, 73.39; H, 4.28; N, 22.33. Found: C, 73.35; H, 4.15; N, 22.41. EI-HRMS: *m/z* = 376.14 (MH^+); $C_{23}H_{16}N_6$ requires: *m/z* = 376.14 (MH^+); IR: 3482, 3341 (NH_2), 2198 (CN); ^1H NMR (400 MHz, DMSO-*d6*): δ = 2.34 (s, 3H, CH_3), 6.95 (br, 2H, NH_2, D_2O exchangeable), 7.45-7.66 (m, 10H, Ph-H, CH), 8.56 (s, 1H, CH); ^{13}C NMR (100 MHz, DMSO-*d6*): δ = 164.5, 161.6, 152.3, 150.6, 141.8, 140.0, 136.9, 131.0, 129.0 (2C), 128.8 (2C), 128.5, 128.2, 128.0 (2C), 126.3 (2C), 117.1, 114.1, 108.9, 72.6, 13.9. MS: *m/z* (%) 376.2 (M^+, 100), 368 (10), 348 (5), 255 (5), 188 (10), 97 (10), 57 (5).

8-amino-5-(4-chlorophenyl)-4-methyl-1-phenyl-1H-pyridazino[5,4,3-de][1,6]naphthyridine-7-carbonitrile (12j)

Dark yellow crystals, yield 78%; mp. 345-346 ºC; *Anal*. Calcd for $C_{23}H_{15}ClN_6$ (410.1): C, 67.24; H, 3.68; N, 20.45. Found: C, 67.27; H, 3.56; N, 20.45. EI-HRMS: *m/z* = 410.10 (MH^+); $C_{23}H_{15}N_6{}^{35}Cl$ requires: *m/z* = 410.1 (MH^+); IR: 3479, 3332 (NH_2), 2201 (CN); ^1H NMR (400 MHz, DMSO-*d6*): δ = 2.35 (s, 3H, CH_3), 6.90 (br, 2H, NH_2, D_2O exchangeable), 7.45-7.66 (m, 9H, Ph-H, CH), 8.58 (s, 1H, CH); ^{13}C NMR (100 MHz, DMSO-*d6*): δ = 163.8, 162.1, 156.4, 151.1, 142.3, 139.4, 137.3, 134.0, 132.5, 131.7, 131.3 (2C), 129.3 (2C), 128.6 (2C), 126.7 (2C), 117.2, 114.8, 109.7, 73.5, 14.3. MS: *m/z* (%) 410.1 (M^+, 100), 374 (10), 346 (5), 255 (5), 205 (5), 187 (10), 173 (5), 97 (5), 77 (5).

8-amino-4-methyl-1-phenyl-5-p-tolyl-1H-pyridazino[5,4,3-de][1,6]naphthyridine-7-carbonitrile (12k)

Dark orange crystals, Yield 80%; mp. 370-371 ºC; *Anal*. Calcd for $C_{24}H_{18}N_6$ (390.16): C, 73.83; H, 4.65; N, 21.52. Found: C, 73.88; H, 4.59; N, 21.60;. EI-HRMS: *m/z* = 390.15 (MH^+); $C_{24}H_{18}N_6$ requires: *m/z* = 390.16 (MH^+); IR: 3426, 3320 (NH_2), 2206 (CN); ^{1}H NMR (400 MHz, DMSO-*d6*): δ = 2.36 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 6.93 (br, 2H, NH_2, D_2O exchangeable), 7.34-7.67 (m, 9H, Ph-H, CH), 8.56 (s, 1H, CH); ^{13}C NMR (100 MHz, DMSO-*d6*): δ = 163.9, 161.6, 152.4, 150.7, 141.8, 140.2, 137.2, 129.0 (2C), 128.8 (2C), 128.6 (2C), 127.1, 126.3 (2C), 129.1, 124.5, 119.1, 114.8, 109.7, 72.6, 20.8, 14.0. MS: *m/z* (%) 390.2 (M^+, 100), 375 (5), 269 (5), 187 (5), 77 (5).

8-amino-4-methyl-1-phenyl-5-m-tolyl-1H-pyridazino[5,4,3-de][1,6]naphthyridine-7-carbonitrile (12l)

Yellow crystals, yield 72%; mp. 284-285 ºC; *Anal*. Calcd for $C_{24}H_{18}N_6$ (390.16): C, 73.83; H, 4.65; N, 21.52. Found: C, 73.81; H, 4.68; N, 21.55. EI-HRMS: *m/z* = 390.15 (MH^+); $C_{24}H_{18}N_6$ requires: *m/z* = 390.16 (MH^+); IR: 3489, 3336 (NH_2), 2200 (CN); ^{1}H NMR (400 MHz, DMSO-*d6*): δ = 2.08 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 6.96 (br, 2H, NH_2, D_2O exchangeable), 7.19-7.66 (m, 9H, Ph-H, CH), 8.53 (s, 1H, CH); ^{13}C NMR (100 MHz, DMSO-*d6*): δ = 165.5, 161.5, 152.4, 150.7, 141.8, 139.8, 136.9, 134.8, 130.6, 130.0, 128.9 (2C), 128.2 (2C), 126.3 (2C), 125.6 (2C), 117.1, 114.7, 109.0, 72.6, 19.0, 13.0. MS: *m/z* (%) 390.2 (M^+, 50), 375 (100), 346 (5), 255 (5), 195 (5), 187 (15), 173 (10), 129 (5), 77 (5).

8-amino-4-methyl-5-(4-nitrophenyl)-1-phenyl-1H-pyridazino[5,4,3-de][1,6]naphthyridine-7-carbonitrile (12m)

Dark yellow crystals, yield 82%; mp. 368-369 ºC; *Anal*. Calcd for $C_{23}H_{15}N_7O_2$ (421.13): C, 65.55; H, 3.59; N, 23.27. Found: C, 65.59; H, 3.63; N, 23.31. EI-HRMS: *m/z* = 421.12 (MH^+); $C_{23}H_{15}O_2N_7$ requires: *m/z* = 421.13 (MH^+); IR: 3464, 3350 (NH_2), 2198 (CN); ^{1}H NMR (400 MHz, DMSO-*d6*): δ = 2.37 (s, 3H, CH_3), 6.82 (br, 2H, NH_2, D_2O exchangeable), 7.47-8.38 (m, 9H, Ph-H, CH), 8.58 (s, 1H, CH). MS: *m/z* (%) 421.2 (M^+, 100), 390 (15), 374 (25), 348 (10), 255 (5), 187 (10), 77 (5).

8-amino-5-(furan-2-yl)-4-methyl-1-phenyl-1H-pyridazino[5,4,3-de][1,6]naphthyridine-7-carbonitrile (12n)

Dark green crystals, yield 86%; mp. 368-369 ºC; *Anal*. Calcd for $C_{21}H_{14}N_6O$ (366.12): C, 68.84; H, 3.85; N, 22.94. Found: C, 68.89; H, 3.78; N, 22.88. EI-HRMS: *m/z* = 366.12 (MH^+); $C_{21}H_{14}O_1N_6$ requires: *m/z* = 366.12 (MH^+); IR: 3470, 3330 (NH_2), 2203 (CN); ^{1}H NMR (400 MHz, DMSO-*d6*): δ = 2.50 (s, 3H, CH_3), 6.72-6.73 (m, 1H, furayl-H), 6.91 (br, 2H, NH_2, D_2O exchangeable), 7.19-7.97 (m, 7H, Ph-H, furyl-H), 8.52 (s, 1H, CH); ^{13}C NMR (100 MHz, DMSO-*d6*): δ = 161.6, 153.0, 152.4, 152.2, 150.4, 145.1, 141.8, 136.8, 131.8, 128.9 (2C), 128.2, 126.3 (2C), 117.0, 114.3, 113.2, 112.0, 108.8, 72.3, 13.2. MS: *m/z* (%) 366.1 (M^+, 100), 337 (5), 311 (5), 183 (5), 77 (10).

5. Conclusions

Under pressure MCRs change their sequence and initial steps change sequence as a result of preference of formation of products of least activation volume. Reactions under pressure can be more easily and much less expensively scaled up on it is thus recommend to expand this technique.

Ethics approval and consent to participate

The authors approve the ethics and consent to participate

Consent for publication

The authors approve publication.

Availability of data and material

The data and material are available in the Supplementary material and manuscript.

Supplementary material is attached as PDF format and submitted along with the manuscript.

Competing interests

The authors declare that they have no competing interests.

Funding

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

Authors' contributions

The main part of the work was carried out by Majdah A. AL-Johani and Sameera M. Mousally, with the direct supervision of Khadijah M. Al-Zaydi and Norah F.Alqahtani. Conceptually the work was designed by Mohamed H. Elnagdi, Khadijah M. Al-Zaydi and Norah F.Alqahtani .All authors read and approved the final manuscript.

Acknowledgements

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

References

1. Asif M. Some Recent Approaches of Biologically Active Substituted Pyridazine and Phthalazine Drugs. *Curr. Med. Chem.* **2012**, 19,2984-2991, DOI: 10.2174/092986712800672139
2. Singh, A. K.; Hegde, G.L.; Khanum, S.A.; Shashikanth, S. Synthesis and Pharmacological Activity of 4-Aryl-Thieno-(2, 3-d)-Pyridazines. *Indian J. Pharm. Sci.* **2005**, 67,210-215.
3. Tucaliuc, R. A.; Cotea, V. V.; Niculaua, M.; Tuchilus, C.; Mantu, D.; Mangalagiu, I. I. New pyridazine–fluorine derivatives: Synthesis, chemistry and biological activity. *Eur. J. Med. Chem.* **2013**, 67, 367-372. DOI: 10.1016/j.ejmech.2013.04.069
4. Gao, Q.; Zhu, Y.; Lian, M.; Liu, M; Yuan, J.; Yin, G.; Wu. A. Unexpected C–C Bond Cleavage: A Route to 3, 6-Diarylpyridazines and 6-Arylpyridazin-3-ones from 1, 3-Dicarbonyl Compounds and Methyl Ketones. *J. Org. Chem.* **2012**, 77, 9865–9870. DOI: 10.1021/jo301751e
5. Kessler, S. N.; Wegner. H. A. One-Pot Synthesis of Phthalazines and Pyridazino-aromatics: A Novel Strategy for Substituted Naphthalenes. *Org. Lett.* **2012**, 14(13), 3268-3271, **DOI:** 10.1021/ol301167q
6. Poschenrieder H.; Stachel, H-D. Synthesis of pyrrolo [3, 4-c] pyridazines. *J. Heterocyclic Chem.* 1995, 32, 1457-1460, DOI: 10.1002/jhet.5570320507
7. Behbehani, H.; Ibrahim. H. M. Microwave-Assisted Synthesis in Water: First One-Pot Synthesis of A Novel Class of Polysubstituted benzo[4,5]imidazo[1,2-b]pyridazines via Intramolecular SNAr. *RSC Adv.*, **2015**, 5, 89226-89237. DOI: 10.1039/C5RA17313B
8. . Elnagdi, M. H; Moustafa, M. S; Sadek. K. U. Green Synthesis of Biologically Relevant Azoles and Azines Derivatives. *Lap Lambert Acadimic Publishing*, **2014**.
9. Ghozlan, S. A.S.; Abdelhamid, I. A; Hassaneen, H. M.; Elnagdi. M. H. Studies with Enamines and Azaenamines: A novel Efficient Route to 6-amino-1, 4-dihydropyridazines and their Condensed Derivatives. *J. Heterocyclic Chem*. **2007**, 44, 105-108.
10. Al-Mousawi, S. M.; Moustafa, M. S.; Abdelhamid, I. A.; Elnagdi. M. H. Reassignment of the Structures of Condensation Products of α-keto α'-formylarylhydrazones with Ethyl Cyanoacetate: A Novel Route to ethyl 5-arylazo-2-hydroxynicotinates. *Tetrahedron Lett.* **2011**, 52(2), 202-204.
11. Elshalkamy, R. M.Sc. thesis Cairo University, **2008**.

12. Ghozlan, S. A. S.; Abdelmoniem, A. M.; Butenschon, H.; Abdelhamid. I. A. Discrepancies in The Reactivity Pattern of Azaenamines towards Cinnamonitriles: Synthesis of Novel aza-steroid Analogues. *Tetrahedron*. **2015**, 71, 1413-1418.
13. Al-Zaydi. K.M. Microwave Assisted Synthesis, Part 1: Rapid Solventless Synthesis of 3-Substituted Coumarins and Benzocoumarins by Microwave Irradiation of the Corresponding Enaminones. *Molecules*, **2003**, 8, 541-555.
14. Al-Zaydi, K. M.; Borik, R. M.; Elnagdi. M. H. Arylhydrazononitriles as Precursors to 2-Substituted 1, 2, 3-triazoles and 4-amino-5-cyano-pyrazole Derivatives Utilizing Microwave and Ultrasound Irradiation. *Green Chemistry Letters and Reviews*, **2012**, 5, 241-250.
15. Al-Zaydi, K. M.; Nhari, L. M.; Borik, R. M.; Elnagdi. M. H. Green Technologies in Organic Synthesis: Self-Condensation of Enamines, Enaminones and Enaminoesters Under Microwave Irradiation in Ionic Liquid. *Green Chemistry Letters and Reviews*, **2010**, 3, 93-99.
16. Al-Zaydi, K. M.; Borik, R. M.; Elnagdi. M.H. 2-Arylhydrazonopropanals as Building Blocks in Heterocyclic Chemistry: Microwave Assisted Condensation of 2-Aryl-hydrazonopropanals with Amines and Active Methylene Reagents. *Molecules*, **2003**, 8, 910-923. DOI: 10.3390/81200910
17. Kappe, C. O.; Stadler. A. Microwaves in Organic and Medicinal Chemistry. *Wiley-VCH, Weinheim*, **2005**.
18. Kappe, C. O.; Dallinger, D.; Murphree, S. S. Practical Microwave Synthesis for Organic Chemists—Strategies. *Instruments, and Protocols, Wiley-VCH, Weinheim*, **2009**.
19. Alzaydi, K. M.; Abojabal, N. S.; Elnagdi. M. H. Multicomponent Reactions in Q-Tubes™: One-Pot Synthesis of Benzo[c]chromen-6-one and phenanthridin-6(5H)-one Derivatives in a Four-Component Reaction. *Tetrahedron Letters*, **2016**, 57, 3596-3599. DOI10.1016/j.tetlet.2016.05.035
20. Moustafa, M. S.; Al-Mousawi, S. M.; Abdelhamid, I. A.; Elnagdi. M. H. Use of A Novel Multicomponent Reaction Under High Pressure for The Efficient Construction of A New Pyridazino[5,4,3-de][1,6]naphthyridine Tricyclic System. *RSC Adv.*, **2016**, 93, 90840-90845. DOI: 10.1039/C6RA19535K
21. Sadek, K. U.; Selim, M. A.; .Alnajjar, A.; Atallah, M.; Elnagdi. M. H. Multicomponent Reactions under Increased Pressure: On the Reaction of Arylhydrazonals, Aromatic Aldehydes and Malononitrile in Q-Tube. *Chem. Eur. J.*, **2016**, *7* (4), 468-472. DOI: http://dx.doi.org/10.5155/eurjchem.7.4.468-472.1508
22. A single crystal of compound **12a** was obtained by slow evaporation from a mixture of ethanol:DMF (2:1). The crystal structure was solved and refined using maxus (nonius, Deflt and MacScience, Japan). Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 1434604 Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union, Road, Cambridge CB2 1EZ, UK. [fax: 144 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
23. A single crystal of compound **12m** was obtained by slow evaporation from a mixture of ethanol:DMF (2:1). The crystal structure was solved and refined using maxus (nonius, Deflt and MacScience, Japan). Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as

supplementary publication number CCDC 1434605 Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union, Road, Cambridge CB2 1EZ, UK. [fax: 144 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

24. A single crystal of compound **12n** was obtained by slow evaporation from a mixture of ethanol:DMF (2:1). The crystal structure was solved and refined using maxus (nonius, Deflt and MacScience, Japan). Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 1493165 Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union, Road, Cambridge CB2 1EZ, UK. [Fax: 144 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].