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Pressure as effective green technology for synthesis of polyfunctionally substituted heteroaromatics : Synthesis of a variety of pyrazolo[1,5-a]pyrimidines

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ABSTRACT

Pyrazole molecules are in the forefront of organic chemistry due to their various encompass substituents, which have many biological activity sequence. The biological and medicinal activities of pyrazolo[1,5-a]pyrimidines have received considerable interest in this regard. We reported here a comparison between reaction of 4-phenylazo-3,5-diaminopyrazole (4) with ethyl propiolate (15), dimethylacetylene dicarboxylate (20), diethyl fumarate (25) and benzylidenemalononitrile (11) in the presence of catalytic amount of piperidine. We initially followed literature procedure (method A), then utilizing ultrasound irradiation (method B), microwave heating (method C) and in a Q-tube (method D). We confirmed the structure of the product by analytical spectroscopic methods. Method (D) gave a good yield with a record reaction time.

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1. Introduction

4-Arylazopyrazole-3,5-diamines (**4**), first synthesized by Elnagdi and Abdulla [1] have found plenty of applications initially as hair dyes [2], antibacterial agent [3] and recently as efficient cyclin-dependent kinases (CDK) inhibitors [4]. Elnagdi *et. al*. [5-8] have reported that while 4-arylazo-pyrazole-3,5-diamines react with acrylonitrile and ethyl acrylate (**5a**,**b**) to yield 4-(3,5-diamino)-4-(phenyldiazenyl)-1*H*-pyrazol-1-yl)butanenitrile or ethyl(3,5-diamino-4-(phenyl diazenyl)-1*H*-pyrazol-1-yl)butanoate (**6a**,**b**) that could be cyclized into 2-amino-3-(phenyldiazenyl)pyrazolo[1,5-a]pyrimidin-5(4*H*)-one (**7**) upon reflux in AcOH (Scheme 1). Similarly, 4-arylazopyrazole-3,5-diamines reacted with phenyl isothiocyanate (**8**) to afford 3,5-diamino-*N*-phenyl-4-(phenyl diazenyl)-1*H*-pyrazole-1-carbothioamide (**9**). Attempted cyclisation of compound **9** via refluxing in AcOH afforded the *N*,*N'*(4-phenyldiazenyl)-1*H*-pyrazole-3,5-diyl)diacetamide (**10**). On other hand, reaction of 4-arylazopyrazole-3,5-diamines with arylidene malononitrile (**11**) and enaminones (**13**) in refluxing pyridine has been reported to afford 2,7-diamino-5-phenyl-3-(phenyldiazenyl)pyrazolo[1,5-a]pyrimidine-6-carbonitrile (**12**) and 7-aryl-3-(phenyldiazenyl)pyrazolo[1,5-a]pyrimidine (**14**) via initial attack at exocyclic amino function and cyclization (Scheme 1).

Because of potential utility of the chemistry in Scheme 1 in fine chemical industry it looked of value to optimize reaction conditions and confirmed concluded structures as only few pyrazolo[1,5-a]pyrimidine derivatives have been reported in the literature [9-17]. Although several pyrazolopyrimidine-7-ones have been synthesized and tested for a variety of activities, only few isomeric-5-ones have ever been synthesized. In this article, we will examine if terminal alkynes will react initially with 4-arylazopyrazole-3,5-diamines (**4**) to yield ring *N*-alkylated derivatives that can be cyclized into the corresponding 5-ones thus developing a route for preparing such derivatives as only Elnagdi has claimed ring alkylation in cyanoethylation [14].

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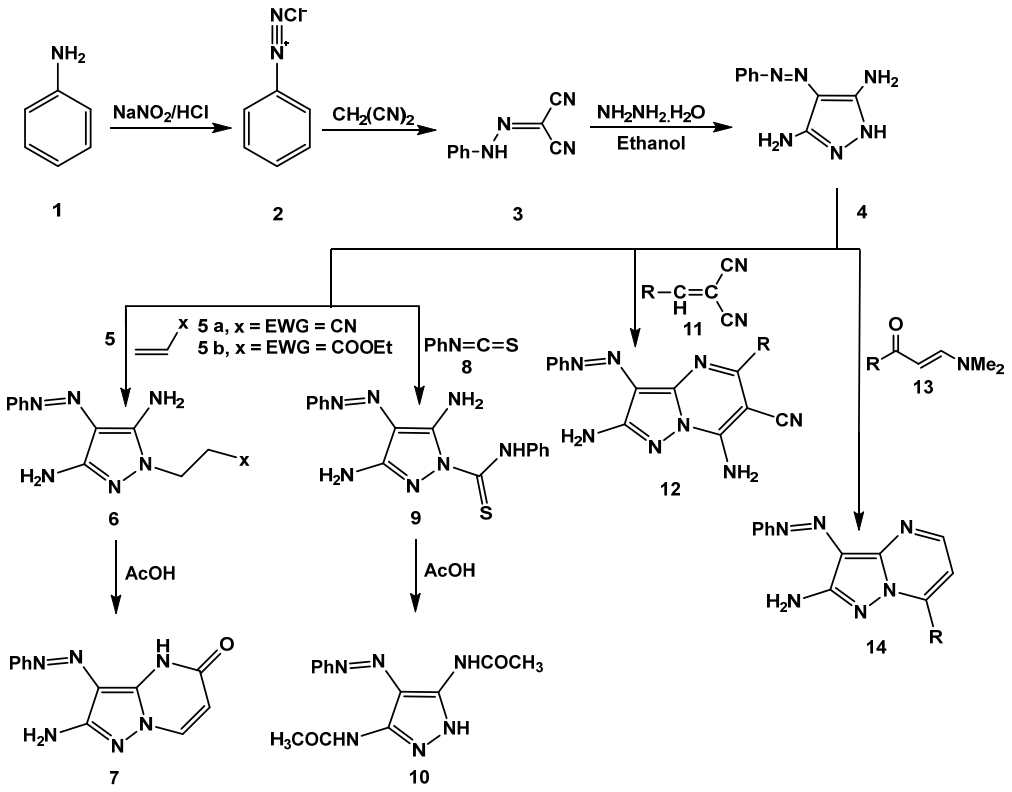


Scheme 1

2. Experimental

2.1. Instrumentation

Infrared spectra were recorded using dry KBr pellets and a Jasco vacuum 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 or 150 MHz for ^{13}C NMR and either deuterated chloroform ($CDCl_3$) or deuterated dimethyl sulphoxide (DMSO-d_6) solutions with tetramethylsilane (TMS) as internal standards. Chemical shifts are reported in part per million (ppm). Mass spectra and accurate mass measurements were made using a GC-MS DFS Thermo spectrometer with the EI (70 eV) mode. All reactions were monitored by using thin layer chromatography (TLC) with 1:1 ethyl acetate:petroleum ether as eluent and were carried out until starting materials were completely consumed. Sonication was performed in MKC6, Guyson ultrasonic bath (Model-MKC6, operating frequency 38 kHz +/- 10% and an output power of 110 Watts) with digital timer (6 sec. to 100 min.) and heater allows solution heating to be set from 20 to 80 °C in 1 °C increments. The inside tank dimensions are 150×300×150 mm (length × width × depth) with a fluid capacity of 6 liters. 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.

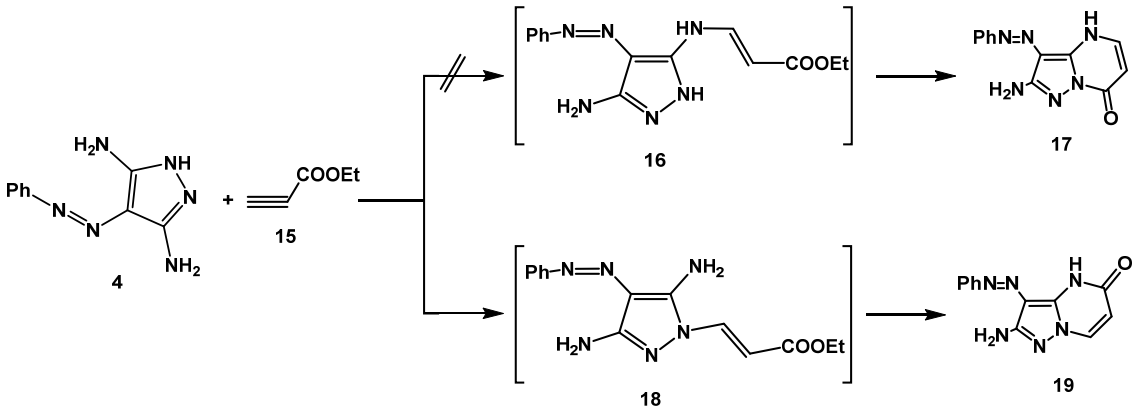
2.2. Synthesis

2.2.1. Synthesis of 2-(phenyl-hydrazono)-malononitrile (3)

Phenylamine (Aniline) (**1**) (9.3 g, 0.10 mol) added to 100 g ice and 100 mL water in 500 mL beaker and then slowly added around 10 mL of 33% hydrochloric acid with stirring. Prepared a solution of sodium nitrite (6.9 g, 0.10 mol) by dissolved in less amount of water. Slowly added the sodium nitrite solution to the phenylammonium chloride solution with continual cooling so that the temperature of the reaction never goes above 10 °C. Leaving it, in the ice bath at all times to keep the reaction mixture as cold as possible. Prepared a solution of malononitrile (6.6 g, 0.10 mol) in roughly amount of ethanol with 4.0 g of sodium hydroxide and poured it into a stirred solution of benzenediazonium chloride (**2**). The resulting precipitate was collected by filtration and washed with water, then air-dried. Purification was achieved by using extraction in ethanol and gave the pure desired product (Scheme 1). Color: Yellow powder. Yield: 95%. M.p.: 153-156 °C. FT-IR (KBr, ν, cm^{-1}): 3195 (NH), 2231, 2210 (CN), 1603 (C=N). ^1H NMR (600 MHz, DMSO-d_6, δ, ppm): 7.19 (t, 1H, *J* = 7.2 Hz, Ar-H), 7.40 (t, 2H, *J* = 8.4 Hz, Ar-H), 7.45 (d, 2H, *J* = 8.4 Hz, Ar-H) 13.05 (br. s, 1H, NH). ^{13}C NMR (150 MHz, DMSO-d_6, δ, ppm): 83.95, 111.09, 115.62, 117.20, 126.17, 129.93, 143.02 (Ar-C and CN). MS (EI, *m/z* (%)): 171 (M+1, 5), 170 (M+, 60), 77 (100). HRMS (EI, *m/z*) calcd. for $C_9H_6N_4$, 170.0587; found 170.0587.

2.2.2. Synthesis of 4-phenylazo-1H-pyrazole-3,5-diamine (4)

To a stirred 2-(phenyl-hydrazono)-malononitrile (**3**) (3.0 g, 17.50 mmol) in absolute ethanol (50 mL) was added hydrazine hydrated (1.0 g, 20 mmol) at room temperature for 1 h. The reaction mixture was monitored by TLC. The solid product was collected by filtration and washed with ethanol. Color: Free-flowing bright yellow powder (Scheme 1). Yield: 98%. M.p.: 260-264 °C. FT-IR (KBr, ν, cm^{-1}): 3291, 3183 (NH_2), 3392 (NH). ^1H NMR (600 MHz, DMSO-d_6, δ, ppm): 6.10 (br. s, 4H, NH_2), 7.20 (t, 1H, *J* = 7.2 Hz, Ar-H), 7.38 (t, 2H, *J* = 8.4 Hz, Ar-H), 7.62 (d, 2H, *J* = 8.4 Hz, Ar-H), 10.73 (br. s, 1H, NH).



Scheme 2

^{13}C NMR (150 MHz, DMSO-d_6, δ, ppm): 114.16, 120.41, 126.51, 128.71, 153.50. MS (EI, *m/z* (%)): 203 (M+1, 11), 202 (M+, 100), 125 (M, 68). HRMS (EI, *m/z*) calcd. for $C_9H_{10}N_6$, 202.0961; found 202.0961.

2.3. General procedure synthesis of pyrazolo[1,5-a] pyrimidine derivatives

2.3.1. Method A (Thermal heating)

Independent mixture of 4-phenylazo-1*H*-pyrazole-3,5-diamine (**4**) (0.5 g, 2.5 mmol) and 2.5 mmol of benzylidene malononitrile, ethyl propiolate, dimethylacetylene dicarboxylate, diethyl fumarate or diethylacetylene dicarboxylate was dissolved in 30 mL absolute ethanol in the presence of catalytic amount 1 mL of piperidine and was then refluxed for 6 h. After cooling, solid mixture was collected and recrystallized from ethanol. The %yield and melting point were calculated for the solid dry product.

2.3.2. Method B (Ultrasound irradiation)

Independent mixture of same reaction components was dissolved in 30 mL absolute ethanol, in the presence of catalytic amount 1 mL of piperidine and then the reaction mixture was sonicated in MKC6, Guyson ultrasonic bath (Model-MKC6, operating frequency 38 kHz +/- 10% and an output power of 110 Watts) for 3 hr at 80 °C. The hot reaction mixture was filtrated and washed with ethanol. The filtrate was concentrated and the solid product was collected and recrystallized from ethanol.

2.3.3. Method C (Microwave heating)

Microwave-assisted reactions were performed on a domestic 80 P instrument. The same procedure as described in method A and B was repeated under neat condition and was set for 2-5 min. The solid product was collected after cooling and crystallization from ethanol while the %yield was calculated and compared with the previous methods.

2.3.4. Method D (Q-tube)

The same procedure as described in method A and B were sequentially added in a 35 mL Q-tube pressure tube under neat condition, furnished by Q Labtech. A teflon septum was placed on the top of the tube, and an appropriate cap and pressure adapter were used. The mixture was heated in an oil bath at 140 °C. After about 10 min, the reaction mixture was monito-red by TLC and GC/MS and stopped. The hot reaction mixture was filtrated and washed with ethanol and crystallization from ethanol while the %yield was calculated and compared with the previous methods (Scheme 2).

2-Amino-3-(phenyldiazenyl)pyrazolo[1,5-a]pyrimidin-5-(4H)-one (**19**): Color: Yellow. % Yields: Method A (85), Method B (82), Method C (60), and Method D (90). M.p.: 268-270 °C. FT-IR (KBr, ν, cm^{-1}): 3416, 3277 (NH_2), 3179 (NH), 1651 (CO). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 5.96 (d, 1H, *J* = 7.6 Hz, C*H*5), 6.64 (s, 2H, NH_2), 7.36 (t, 1H, *J* = 7.2 Hz, Ar-H), 7.48 (t, 2H, *J* = 8.0 Hz, Ar-H), 7.90 (d, 2H, *J* = 7.6 Hz, Ar-H), 8.26 (d, 1H, *J* = 8.0 Hz, C*H*6), 12.90 (br. s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 104.31, 112.34, 121.49, 128.65, 128.92, 138.57, 150.84, 152.84, 160.20. MS (EI, *m/z* (%)): 255 (M+1, 15), 254 (M+, 100), 177 (43). HRMS (EI, *m/z*) calcd. for $C_{12}H_{10}N_6O$, 254.0911; found 254.0914.

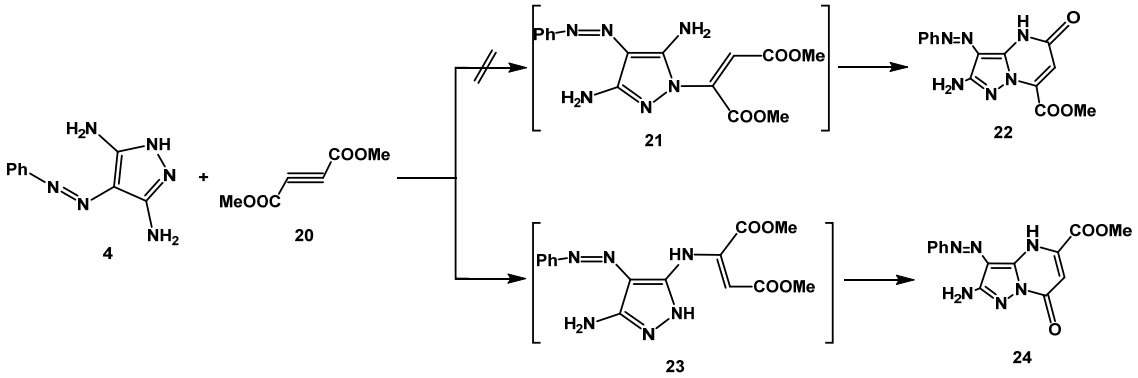
Methyl 2-amino-7-oxo-3-(phenyldiazenyl)-4,7-dihydropyrazolo[1,5-a]pyrimidine-5-carboxylate (**24**): Color: Brown. % Yields: Method A (75), Method B (84), Method C (55), and Method D (80). M.p.: 250-252 °C. FT-IR (KBr, ν, cm^{-1}): 3423, 3271 (NH_2), 3184 (NH), 1659 (CO), 1726 (COOH). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 3.94 (s, 3H, OCH_3), 6.33 (s, 1H, C*H*6), 6.80 (s, 2H, NH_2), 7.38 (t, 1H, *J* = 6.8 Hz, Ar-H), 7.49 (t, 2H, *J* = 8.0 Hz, Ar-H), 7.92 (d, 2H, *J* = 7.6 Hz, Ar-H), 13.175 (br. s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 53.63, 104.17, 112.29, 120.66, 121.64, 128.81, 128.98, 139.56, 150.88, 152.71, 160.09. MS (EI, *m/z* (%)): 313 (M+1, 18), 312 (M+, 100), 77 (67). HRMS (EI, *m/z*) calcd. for $C_{14}H_{12}N_6O_3$, 312.0965; found 312.0965.

Ethyl 2-amino-7-oxo-3-(phenyldiazenyl)-4,7-dihydropyrazolo[1,5-a]pyrimidine-5-carboxylate (**29**): Color: Brown. % Yields: Method A (70), Method B (78), Method C (66), and Method D (80). M.p.: 285-286 °C. FT-IR (KBr, ν, cm^{-1}): 3392, 3291 (NH_2), 3182 (NH), 1733 (COOH), 1616 (CO). ^{1}H NMR (600 MHz, DMSO-d_6, δ, ppm): 1.39 (t, 3H, *J* = 7.2 Hz, CH_3), 4.39 (q, 2H, *J* = 7.2 Hz, CH_2), 6.31 (s, 1H, C*H*6), 6.77 (s, 2H, NH_2), 7.37 (t, 1H, *J* = 7.2 Hz, Ar-H), 7.49 (t, 2H, *J* = 8.4 Hz, Ar-H), 7.91 (d, 2H, *J* = 7.8 Hz, Ar-H), 13.14 (br. s, 1H, NH). ^{13}C NMR (150 MHz, DMSO-d_6, δ, ppm): 62.81, 112.26, 121.59 128.92, 139.71, 150.85, 152.67, 159.45. MS (EI, *m/z* (%)): 327 (M+1, 17), 326 (M+, 100), 249 (40). HRMS (EI, *m/z*) calcd. for $C_{15}H_{14}N_6O_3$, 326.1122; found 326.1122.

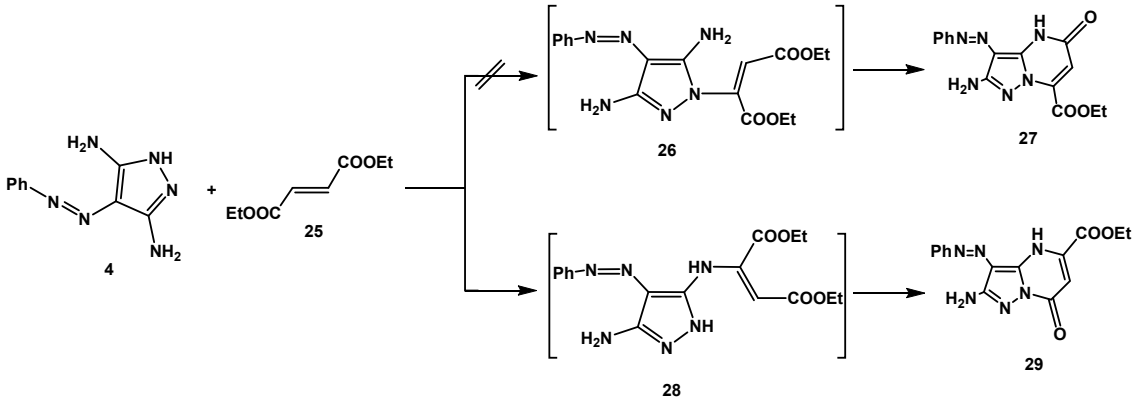
2,7-Diamino-5-phenyl-3-(phenyldiazenyl)pyrazolo[1,5-a]pyrimidine-6-carbonitrile (**33**): Color: Dark orange. % Yields: Method A (68), Method B (73), Method C (65), and Method D (76). M.p.: 230-232 °C. FT-IR (KBr, ν, cm^{-1}): 3465, 3438 (NH_2), 3324, 3289 (NH_2), 2218 (CN), 1642 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 7.13 (s, 2H, NH_2), 7.38 (t, 1H, *J* = 7.2 Hz, Ar-H), 7.50 (t, 2H, *J* = 7.6 Hz, Ar-H), 7.57-7.60 (m, 3H, Ar-H), 7.81 (d, 2H, *J* = 7.6 Hz, Ar-H), 7.88-7.89 (m, 2H, Ar-H), 8.61 (br. s, 2H, NH_2).

Table 1. The % yield products and the reaction time of pyrazolo[1,5-a]pyrimidine derivatives by using different methods.

Method	Product (19)		Product (24)		Product (29)		Product (33)	
	Time	Yield%	Time	Yield%	Time	Yield%	Time	Yield%
A	6 hr	85	7 hr	75	7 hr	70	5 hr	68
B	3 hr	82	4 hr	84	4 hr	78	3 hr	73
C	1 min	60	1 min	55	4 min	66	2 min	65
D	5 min	90	10 min	80	30 min	80	5 min	76



Scheme 3



Scheme 4

^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 75.45, 116.15, 116.53, 121.25, 128.31, 128.66, 128.86, 129.12, 130.28, 137.22, 146.21, 148.87, 152.09, 152.79, 160.93. MS (EI, *m/z* (%)): 355 (M+1, 20), 354 (M+, 100), 277 (48). HRMS (EI, *m/z*) calcd. for $C_{19}H_{14}N_8$, 354.1336; found 354.1337.

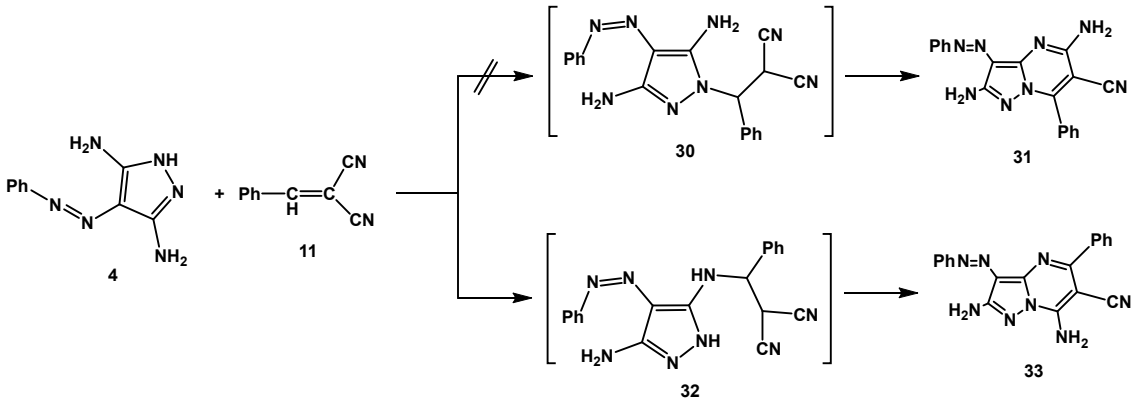
3. Results and discussion

Compound **4** reacted with ethyl propiolate (**15**) utilizing either conventional heating (method A), ultrasound (method B), microwave heating (method C), or heating at 140 °C in Q-tube (method D). The same product was obtained in each case and reaction times as well as yields are listed in Table 1. The Mass spectra of the product indicated that addition followed by ethanol elimination occurred. Thus, structure **19** or isomeric **17** maybe postulated. However, ^{1}H NMR of the product leads to exclude formation of isomeric **17**. It showed pyrimidine protons at δ 7.90 and δ 8.29 ppm appeared as two doublets with *J* = 7.6, 8.0 Hz. If the product was isomeric **17** then one of their pyrimidine protons should have appeared as quartet (Scheme 2).

Reacting compound **4** with dimethylacetylene dicarboxylate (**20**) afforded compound **24** rather than isomeric **22**. It is assumed that initially adduct compound **21** or **23** is formed and cyclize to compound **22** or **24**. Possible formation of compound **22** was also excluded. Based on ^{1}H NMR that revealed proton at C-6 as singlet at δ 6.33 ppm. If the product is isomeric **22**, it should appear at a lower field (≈ 7.9 ppm) (Scheme 3).

Similarly, reaction of compound **4** with ethyl fumarate (**25**) afforded compound **29** rather than compound **27** via intermediacy of compound **28** (Scheme 4). Again, results of utilizing methods (A-D) are tabulated in Table 1.

Compound **4** were reacted with benzylidenemalononitrile (**11**) initially following literature procedure (method A), then utilizing ultrasound irradiation (method B), microwave heating (method C) and in a Q-tube (method D) were gave us compound **33** rather than compound **31** (Scheme 5). We confirm the structure of compound **33** for the reaction product, based on ^{1}H NMR spectra, that revealed the amino function at C-7 at δ = 8.61 ppm which is downfield shifted by the anisotropic effect of pyrazole ring nitrogen. If the product is compound **31** it will appear at δ ≃ 5.8 ppm and (method D) gave a good yield with a record reaction time (Table 1).



Scheme 5

4. Conclusions

1. As regards in new rout of green chemistry, using new technique (Q-tube), it is a logical outcome after several researches and comparison with several old methods, that an improvement of the reactions yields with a record time was achieved.
2. Pyrazole compounds can provide privileged scaffolds for the generation of target compounds for biological and pharmacological activities.
3. Utility of Q-tube compering to microwaves, and ultrasound irradiation as green energy routes offers advantageous features such as good yield.
4. The method of Q-tube represents a promising benign route to replace many conventional basic methods which can encounter many environmental problems.
5. Utility of Q-tube method showed acceleration of several reactions in better way compared to microwave (MW) and ultrasound (US) methods.
6. Sealed tube is the key for all benefits (like short reaction time). Microwave is just a heating source, no impact on reactions.
7. For sealed tube, oil bath provided better results than microwave. Oil bath provides uniform heating while microwave could cause over heating due to its nature, which results in dark decomposed reaction mixture.

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References

[1]. Elnagdi, M. H.; Abd Allah, S. O. *J. Prakt. Chem.* **1973**, *315*, 1009-1016.
[2]. Braun, H. J. *Ger. Offen.* **1998**, DE 1996143059.
[3]. Sener, N.; Sener, I.; Yavuz, S.; Karci, F. *Asian J. Chem.* **2015**, *27(8)*, 3003-3012.
[4]. Jonas, C.; Karthik, K.; Aleksandras, S.; Asta, J.; Deividas, V.; Algirdas, K.; Mindaugas, V. *Cancers* **2014**, *6(4)*, 2224-2242.
[5]. Elkholy, A.; Al-Qalaf, F.; Elnagdi, M. H. *Arkivoc* **2008**, *14*, 124-131.
[6]. Elnagdi, M. H.; Kandeel, E. M.; Elmoghayar, M. R. H. *Z. Natureforsch. B* **1977**, *32*, 307-310.
[7]. Anwar, H. F.; Fleita, D. H.; Kolshorn, H.; Meier H.; Elnagdi, M. H. *Arkivoc* **2006**, *15*, 133-141.
[8]. Behbehani, H.; Ibrahim H. M.; Makhseed, S. *Arkivoc* **2010**, *2*, 267-282.
[9]. Abbas-Temerik, H. H.; Abo-Bakr, A. M. *Eur. J. Chem.* **2016**, *7(1)*, 107-114.
[10]. Vaquero, J. J.; Fuentes, L.; Castillo, J. C. D.; Perez, M. I.; Garcia, J. L.; Soto, J. L. *Synthesis* **1987**, *1*, 33-35.
[11]. Ried, W.; Aboul-Fetouh, S. *Tetrahedron* **1988**, *44(23)*, 7155-7162.
[12]. Konda, S.G. *Eur.J. Chem.* **2014**, *5(4)*, 676-680.
[13]. Chen-Tsai, P.; Wang, I. *Dyes Pigments* **2005**, *64(3)*, 259-264.
[14]. Elnagdi, M. H. *Tetrahedron* **1974**, *30(16)*, 2791-2796.
[15]. Karci, F.; Demircali, A. *Dyes Pigments* **2007**, *74(2)*, 288-297.
[16]. Tsai, P.; Wang, I. *Dyes Pigments* **2007**, *74(3)*, 578-584.
[17]. Al-Sehemi, A. G.; Irfan, A.; Fouda, A. M. *Spectrochim. Acta A* **2013**, *111*, 223-229.