Ultrasonics Sonochemistry 16 (2009) 805–809

Contents lists available at ScienceDirect

Ultrasonics Sonochemistry

journal homepage: www.elsevier.com/locate/ultsonch

A simplified green chemistry approaches to synthesis of 2-substituted 1,2,3-triazoles and 4-amino-5-cyanopyrazole derivatives conventional heating versus microwave and ultrasound as ecofriendly energy sources

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ARTICLE INFO

Article history:
Received 20 January 2009
Received in revised form 17 February 2009
Accepted 18 February 2009
Available online 27 February 2009

Keywords:
Ecofriendly energy sources
Green chemistry
2-Arylhydrazonocyano acetamides
1,2,3-Triazole
Triazolopyrimidine
Pyrazol-4-amine
Microwave irradiation
Ultrasound irradiation

ABSTRACT

Cyanoacetamides **3** were prepared *via* reacting ethyl cyanoacetate with benzylamine. Yields and reaction times needed for reaction completion at room temperature, by microwaves ($\mu\omega$) heating and under ultrasound (US) irradiations are compared. The formed cyanoacetamides were coupled with aromatic diazonium salts and the formed arylhydrazones were used as precursors to title triazoles and pyrazoles *via* reacting the former with hydroxylamine and chloroacetonitrile. Yields of products formed *via* conventional heating are compared with those of $\mu\omega$ and US irradiation.

1. Introduction

Recently, many papers have been published dealing with 2-arylhydrazononitriles as precursors to heteroaromatics [1–6]. El-nagdi et al. [7–10] have reported efficient synthetic approaches to functionally substituted pyrazoles and 1,2,3-triazoles utilizing arylhydrazononitrile precursors. There is a clear tendency to replace existing synthetic procedures with more green and sustainable ones. It needs to be combined with more environmentally friendly technologies.

In the light of our recent interest, we adopt green synthetic methodologies for the synthesis of functionally substituted heteroaromatics utilizing microwaves heating and ultrasound irradiation [11–21]. We aimed in this work to report the synthesis and utility of cyanoacetamides as precursors to novel 1,2,3-triazoles and 4-amino-pyrazole-3-carboxamides which considered potential precursors to Zaprinast and Viagra analogues.

2. Results and discussion

Ethyl cyanoacetate (**1**) was reacted with benzylamine (**2**) either at room temperature, microwave heating or under ultrasound activation to yield **3**. Product yields and reaction times are reported in experimental part. Although the reaction completion required 1 h at room temperature, it needed only one minute for completing reactions under microwave irradiation and 2 min utilizing ultrasound irradiation at 40 °C (Scheme 1).

Compounds **3** coupled readily with aromatic diazonium salts to yield the corresponding arylhydrazononitriles **4a,b**. The structural formula of the resulting compounds was demonstrated by the study of elemental analysis and spectral methods. The study of ^{1}H NMR spectra of the compounds **4a,b** showed a singlet signal at δ = 12 ppm corresponding to the hydrazone (NH) proton, and a triplet signal at δ = 8 ppm corresponding to the amide group proton (Scheme 2).

Parallel to the recent literature data [22–24] compounds **4a,b** react with hydroxylamine hydrochloride in the presence of sodium acetate to yield amidoximes **5a,b**, respectively. It has been found that the reaction completion time was 1 h in refluxing ethanol while it needed 2 min by microwave heating, and 30 min utilizing ultrasound irradiation at 40 °C. The structures of the new amidoximes **5a,b** have been elucidated by elemental analyses, ^{1}H NMR and ^{13}C NMR spectroscopic measurements. The ^{1}H NMR spectra of compound **5** revealed the amino group protons at δ = 6 ppm and also showed a signal at δ = 14 ppm corresponding to the (OH) proton. The IR spectra of compound **5** showed a vibrational absorption band at 3587 cm^{-1} attributable to OH group. The two vibrational bands at 3456 and 3420 cm^{-1} were assigned to the

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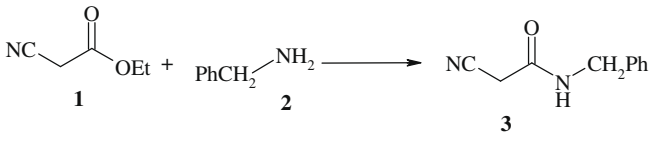
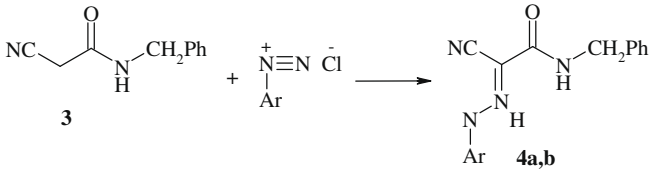
doi:10.1016/j.ultsonch.2009.02.007



Scheme 1.



4 a, Ar= $C_6H_4CO_2Me$-*o*
b, Ar= $C_6H_4NO_2$-*p*

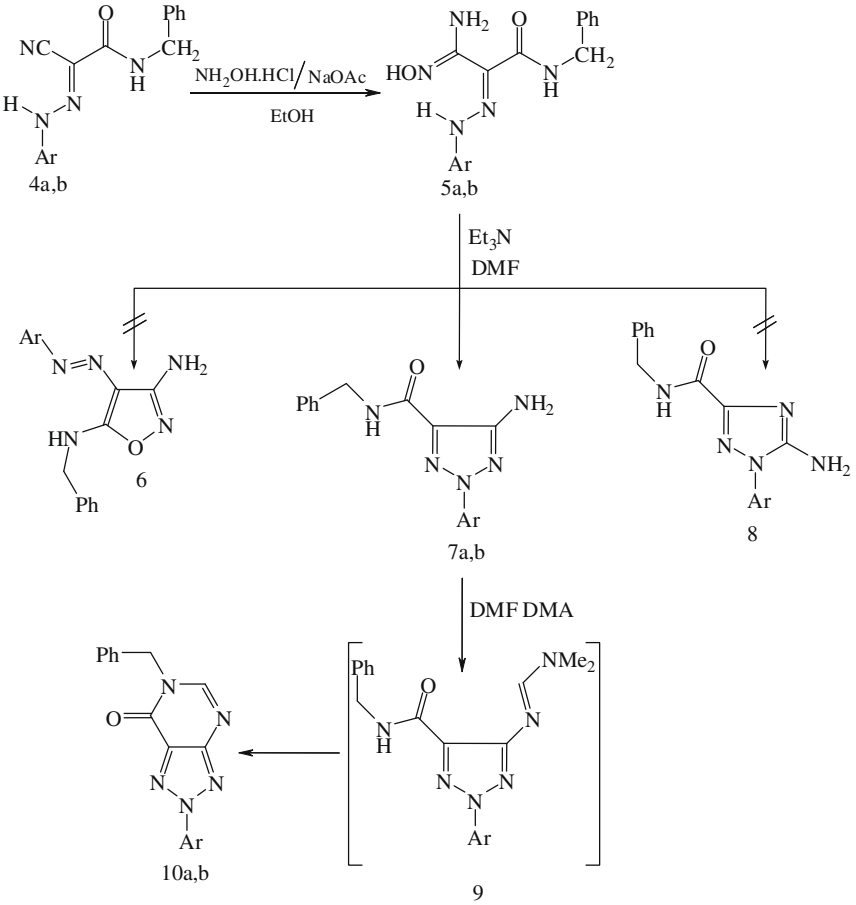
Scheme 2.

asymmetric and symmetric stretching vibration bands of the NH_2 group respectively (Scheme 3).

Upon cyclizing **5b** in refluxing dimethylformamide (DMF) and triethylamine, only 5 min were needed for completing reactions under microwave irradiation and 1 h was required to complete the reaction utilizing ultrasound irradiation at 40 °C, products of self cyclization *via* water elimination was formed. Theoretically, the three structures **6, 7** and **8** are possible. Earlier it has been established that amido oxims cyclises into triazoles under similar conditions [24]. Thus the isoxazole structure **6** seems least likely. The structural formula of compounds **7** or **8** resulting from this reaction has been confirmed utilizing elemental analyses and spectral methods. The ^{13}C NMR of this product revealed the (C=O) at $\delta = 165.67$ ppm, also the ^1H NMR revealed the (NH_2) proton at $\delta = 6.18$ ppm, and the IR spectra showed a vibrational band at 3344 cm^{-1} attributable to ν_{NH} group and another two vibrational band appeared at 3492, 3386 cm^{-1} for asymmetric and symmetric vibrations of the amino group.

As it has been reported earlier that arylhydrazonoamidoximes of similar structure cyclise either into 1,2,3-triazoles **7** or 1,2,4-triazoles **8** *via* a Tiemann like rearrangement looking into this possibility has seemed mandatory (*cf.* structures 7 and 8 in Scheme 3). It has been found, however, that reaction product reacts with *DMF–DMA* to yield **10** that can result only from **7** *via* **9**.

We have found that **4a,b** reacted with chloroacetonitrile to yield the corresponding acyclic non-isolable intermediates **12a,b** which undergo cyclization into the final products pyrazol-4-amines **13a,b**. Yields and reaction times under conventional heating, microwave irradiation and sonication were undertaken (*cf.* Table 1). Generally, less time and little yield improvements are observed by applying microwave and ultrasound irradiation (Scheme 4). The structural formula of **13a,b** resulting from this reaction has been demonstrated by elemental analyses and spec-



4-10 = a: Ar = C_6H_4-COOMe-*o*
b: Ar = C_6H_4-NO_2-*p*

Scheme 3.

Table 1
Formation of compounds 3–12 by (Δ = thermal, $\mu\omega$ = microwave irradiation and US = ultrasound).

Number	Time (min)			Yield (%)			Temperature °C		
	Δ	$\mu\omega$	US	Δ	$\mu\omega$	US	Δ	$\mu\omega$	US
3	60	1	2	85	93	90	RT	100–105	35–40
5a	180	2	30	46	84	88	80		
5b	180	5	30	46	90	85			
7a	60	5	60	52	90	80	130		
7b	60	5	60	42	80	78			
10a	420	2	–	78	95	–			
10b	420	2	–	62	88	–			
13a	30	2	30	52	80	75	100		
13b	30	2	30	67	88	79			

troscopic data. The ^{1}H NMR spectra of compound **13** revealed the (NH_2) protons at δ = 6.21 ppm, and also showed a triplet signal at δ = 8.89 ppm corresponding to the amide (NH) proton. The IR of the compound **13** showed an absorption band at 3299 cm^{-1}of the stretching vibration of (NH) group, a band at 2225 cm^{-1} due to the stretching vibration of the (CN) group and a band at 1644 cm^{-1} due to ν (C=O) group.

Table 1 shows yield as well as reaction times by the three methodologies are compared.

3. Conclusion

We have synthesized a novel substituted 2-aryl-1,2,3-triazoles and 4-aminopyrazoles from arylhydrazononitriles under microwave, sonication and classical conditions. In general, improvements in rates and yield of reactions are observed by carrying out the reactions under the influence of microwave and ultrasound irradiations. It should be noted, however, that reactions occur at different temperatures with these techniques and, therefore strict comparisons will require a balance between effectiveness and energy costs.

4. Experimental

4.1. Materials and methods

All melting points were measured on a Gallenkamp electrothermal melting point apparatus and are uncorrected. The IR absorption spectra were measured on a Nicolet Magna 520FT IR spectrophotometer. NMR spectra were recorded at Bruker DPX 400 MH_Z spectrometer using tetramethylsilane (TMS) as an internal reference, ^{1}H spectra were run at 400 MHz and ^{13}C spectra were run at 100 MHz in deuterated chloroform ($CDCl_3$) or dimethyl sulphoxide (DMSO–d_6). Mass spectra were performed on a Shimadzu GCMS-QP 1000 EX mass spectrometer at 70 eV. Microwave irradiation was carried out using the commercial microwave oven (SGO 1000 W), a thermocouple used to monitor the temperature inside the vessel, during the reactions, it was found that ≈105–110 °C.

Ultrasound, microprocessor controlled-2004, high intensity ultrasonic processor with temperature controller (750 W), the ultrasonic frequency of the cleaning bath used equal 25 KHz. The reaction temperature was stabilized at 35–40 °C even after more than 1 h by addition or removal of water in ultrasonic bath to keep the required temperature. Elemental analyses were measured by means of Perkin Elmer 2400 CHN Elemental analyzer flowchart.

4.2. Typical procedure for reactions

4.2.1. General procedure for the preparation of N-benzyl-2-cyano-acetamide (3)

Method I (Δ)*:* Equimolar amounts (0.1 mol) of both ethyl cyanoacetate and the benzylamine were stirred at room temperature for 1 h and the resulting solid product was crystallized from ethanol.

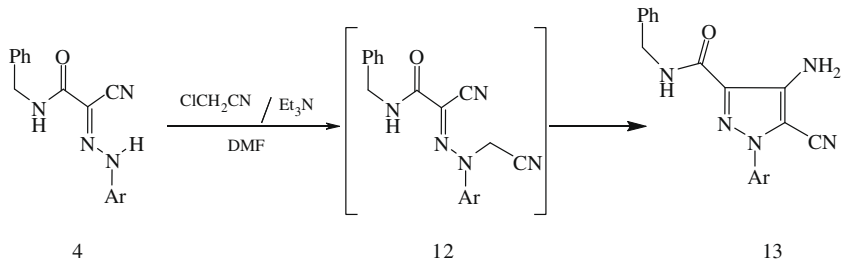
Method II ($\mu\omega$)*:* A mixture of ethyl cyanoacetate (0.1 mol) and the appropriate amount of amine compounds (0.1 mol) was placed in the microwave oven and irradiated at 460 W for one min. and then left to cool to room temperature. The solid product so-formed was filtered and crystallized from ethanol.

Method III (US): Equimolar amounts (0.1 mol) of both ethyl cyanoacetate and the amine compounds were mixed and the reaction mixture was irradiated with ultrasound irradiation at 35 °C for 2 min, and then the solid product so-formed was filtered and crystallized from ethanol.

N-benzyl-2-cyano-acetamide (3); brown crystals from ethanol; m.p. 124 °C; IR (KBr): υ = 3295 (NH), 3091 (CH aromatic), 2923 (CH aliphatic), 2220 (CN) and 1640 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, DMSO–d_6, 25 °C, TMS): δ = 3.71 (s, 2H, CH_2CN), 4.30 (d, 2H, $PhCH_2$, J = 5 Hz), 7.29–7.34 (m, 5H, ph–H) and 8.74 (d, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO–d_6, TMS): δ = 25.76, 39.28, 116.89, 126.35, 126.52, 126.99, 135. 85, 166.22; MS: M$^+$ 174; Anal. Calcd. For $C_{10}H_{10}N_2O$ (174.20) C, 68.95; H, 5.79; N, 16.08; Found: C, 68.90; H, 5.67; N, 16.20.

4.2.2. Preparation of arylhydrazone compounds ***(4a,b)***

A cold solution of aryldiazonium salt (10 mmol), [prepared by adding a solution of sodium nitrite (1 g into 10 mL H_2O) to a cold solution of aryl amine hydrochloride or aryl amine nitrate (10 mmol) with stirring as described earlier]. The resulting solution of the aryldiazonium was then added to a cold solution of *N*-b*enzyl*-2-cyano-acetamide (0.1 mol) in ethanol (50 mL) containing sodium acetate (1 g into 10 mL H_2O).The mixture was stirred at



4 12 13

4,13 =a,Ar=C$_6$H$_4$-CO$_2$Me-*o*
b,Ar=C$_6$H$_4$-NO$_2$-*p*

Scheme 4.

room temperature for 1 h and the solid product, so formed, was collected by filtration and crystallized from ethanol.

4.2.3. 2-[N′-(Benzylcarbamoyl-cyano-methylene)-hydrazino]-benzoic acid methyl ester (4a)

Yellow crystals from ethanol; yield 89%, m.p. 196 °C; IR (KBr): υ = 3387 (2NH), 3029 (CH aromatic), 2949 (CH aliphatic), 2210 (CN), 1693 (C=O ester) and 1664 (C=O amide) cm^{-1}; ^1H NMR (400 MHz, DMSO–d_6, 25 °C, TMS): δ = 3.91(s, 3H, $COOCH_3$), 4.45 (d, 2H, CH_2ph, *J* = 5 Hz), 7.24–7.33 (m, 5H, Ph–H), 7.18 (t, 1H, C_6H_4–CO_2Me H-5, *J* = 7 Hz), 7.66 (t, 1H, C_6H_4–CO_2Me H-4, *J* = 7 Hz), 7.97 (d, 1H, C_6H_4–CO_2Me H-6, *J* = 8 Hz), 8.16 (d, 1H, C_6H_4–CO_2Me H-3, *J* = 8 Hz), 9.15 (t, 1H, O=C–NH, *J* = 5 Hz) and 12.33 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO–d_6, TMS): δ = 42.90 (CH_2ph), 53.33 ($COOCH_3$), 111.15, 112.75, 113.59, 123.68, 131.22, 135.46 ($C_6H_4COOCH_3$-*o*), 116.54 (CN), 127.42, 127.79, 128.86, 139.75 (phenyl carbons), 143.61 (C=N–NH) and 160.36, 168.13(2C=O) ppm; MS: M^+ 336; Anal. Calcd. For $C_{18}H_{16}N_4O_3$ (336.35) C, 64.28; H, 4.79; N, 16.66; Found: C, 64.20; H, 4.96; N, 16.85.

4.2.4. N′-benzyl-2-cyano-2-[(4-nitro-phenyl)-hydrazono]-acetamide (4b)

Dark brown crystals from ethanol; yield 95%, m.p. 186 °C; IR (KBr): υ = 3343 (2NH), 3099 (CH aromatic), 2951 (CH aliphatic), 2219 (CN) and 1649 (C=O amide) cm^{-1}. ^1H NMR (400 MHz, DMSO–d_6, 25 °C, TMS): δ = 4.28 (d, 2H, CH2ph, *J* = 5 Hz), 7.25–7.73 (m, 5H, Ph–H), 7.82 (d, 2H, Ar, H-2, H-6, *J* = 8 Hz), 8.19 (d, 2H, Ar, H-3, H-5, *J* = 8 Hz), 9.10 (t, 1H, O=C–$NHCH_2$, *J* = 5 Hz) and 12.20 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO–d_6, TMS): δ = 43.61 (CH_2ph), 111.33, 112.23, 125.77, 143.20 (C_6H_4–NO_2-*p*), 127.40, 128.02, 129.12, 138.80 (phenyl carbons), 116.76 (CN), 148.25 (C=N–NH) and 160.71 (C=O) ppm; MS: (M^+-1) 322; Anal. Calcd. For $C_{16}H_{13}N_5O_3$ (323.31) C, 59.44; H, 4.05; N, 21.66; Found: C, 59.50; H, 4.00; N, 21.62.

4.2.5. General method for reaction of hydrazono-2-cyanoacetamide compounds (4a,b) with hydroxyl amine hydrochloride

Method I (Δ): 1-Hydroxylamine hydrochloride (0.1 mol) was added to a solution of hydrazono-2-cyanoacetamide derivative **4a,b** (0.1 mol) in (50 mL) ethanol, then 0.1 mol of anhydrous sodium acetate was added and the reaction mixture was refluxed for 1 h and then left to cool to room temperature. The solid product so-formed was filtered and crystallized from ethanol.

2-A solution of hydroxylamine hydrochloride (0.1 mol) in (30 mL) water was added to a solution of hydrazono-2-cyanoacetamide derivative **4a,b** (0.1 mol) in (100 mL ethanol), then 10 g of anhydrous sodium acetate was added and the reaction mixture was refluxed for 3 h. The reaction mixture was poured into ice-cold water. The solid product so-formed was filtered and crystallized from ethanol.

Method II (μω): A mixture of hydroxylamine hydrochloride (0.1 mol) and hydrazono-2-cyanoacetamide derivative **4a,b** (0.1 mol), was irradiated under microwave irradiation at 460 W in presence of 0.1 mole anhydrous sodium acetate, and drops of ethanol, for 2–5 min till no starting materials present as examined by TLC in 1 min intervals The reaction mixture was left to cool to room temperature. The solid product so-formed was filtered and crystallized from ethanol.

Method III (US): A mixture of hydroxylamine hydrochloride (0.1 mol) and hydrazono-2-cyanoacetamide derivative **4a,b** (0.1 mol) in (50 mL) ethanol, then (0.1 mol) of anhydrous sodium acetate was added and irradiated under ultrasound irradiation at 40 °C for 30 min till no starting materials present as examined by TLC. The solid product so-formed was filtered and crystallized from ethanol.

4.2.6. 2-(N′-[benzylcarbamoyl-(N-hydroxycarbamimidoyl)-methylene]-hydrazino)-benzoic acid methyl ester (5a)

Light brown crystals from ethanol; m.p. 103 °C; IR (KBr): υ = 3493(br OH), 3402, 3347 (NH_2), 3390 (2NH), 3090 (CH aromatic), 2923 (CH aliphatic), 1697 (C=O ester) and 1648 (C=O amide) cm^{-1}; ^1H NMR (400 MHz, DMSO–d_6, 25 °C, TMS): δ = 3.86 (s, 3H, $COOCH_3$), 5.79 (d, 2H, phCH_2, *J* = 5 Hz), 6.47 (s, 2H, NH_2), 7.02–8.17(m, 5H, Ph-H), 7.34 (t, 1H, Ar H-5, *J* = 7 Hz), 7.58 (t, 1H, Ar H-4, *J* = 7 Hz), 7.89 (d, 1H, Ar H-3, *J* = 8 Hz), 8.06 (d, 1H, Ar H-6, *J* = 8 Hz), 9.94 (t, 1H, O=C–$NHCH_2$, *J* = 5 Hz), 13.69 (s, 1H, NH) and 14.27 (s, 1H, OH) ppm; MS: M^+ 369; Anal. Calcd. For $C_{18}H_{19}N_5O_4$ (369.38) C, 58.53; H, 5.18; N, 18.96; Found: C, 58.50; H, 5.39; N, 18.82.

4.2.7. N-benzyl-2-(N-hydroxycarbamimidoyl)-2-[(4-nitro-phenyl)-hydrazono]-acetamide (5b)

Brown crystals from ethanol; m.p. >300 °C; IR (KBr): υ = 3595(OH), 3482, 3451 (NH_2), 3301 (2NH), 3086 (CH aromatic), 2904 (CH aliphatic) and 1644 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 4.46 (d, 2H, CH_2ph, *J* = 5 Hz), 6.48 (s, 2H, NH_2), 7.32–7.89 (m, 5H, Ph–H), 7.55 (d, 2H, Ar, H-2, H-6, *J* = 8 Hz), 8.29 (d, 2H, Ar, H-3, H-5, *J* = 8 Hz), 9.60 (t, 1H, O=C–$NHCH_2$, *J* = 5 Hz), 13.34 (s, 1H, NH) and 14.40 (s, 1H, OH) ppm; MS: M^+ 356; Anal. Calcd. For $C_{16}H_{16}N_6O_4$ (356.34) C, 53.93; H, 4.53; N, 23.58; Found: C, 53.70; H, 4.62; N, 23.47.

4.2.8. General method for reaction of compounds (5a,b) with triethylamine

Method I (Δ): A mixture of equimolar amount of compound **5** and triethylamine in (10 mL) dimethylformamide DMF was heated under reflux for 1 h. The reaction mixture was left to cool to room temperature. The solid product so-formed was filtered and crystallized from ethanol.

Method II (μω): A mixture of (0.1 mol) compound **5** and (0.1 mol) triethylamine was placed in a tightly closed tube, and subjected to a microwave irradiation for 1–5 min until completion of the reaction (monitored by TLC). The reaction mixture was left to cool to room temperature. The solid product so-formed was filtered and crystallized from ethanol.

Method III (US): Triethylamine (0.1 mol) was added to a solution of compounds **5** (0.1 mol) in (10 mL) dimethylformamide DMF under ultrasound irradiation at 40 °C for 1 h. The solid product so-formed was filtered and crystallized from ethanol.

4.2.9. 2-(4-Amino-5-benzylcarbamoyl-[1,2,3]triazole-2-yl)-benzoic acid methyl ester (7a)

Brown crystals from ethanol; m.p. >300 °C; IR (KBr): υ = 3480, 3438 (NH_2), 3370 (NH), 3088 (CH aromatic), 2950 (CH aliphatic) 1697 (C=O ester) and 1648 (C=O) cm^{-1}; ^1H NMR (400 MHz, DMSO–d_6, 25 °C, TMS): δ = 3.88 (s, 3H, $COOCH_3$), 4.52 (s, 2H, NH_2), 5.22 (d, 2H, CH_2Ph, *J* = 5 Hz), 7.31–8.17 (m, 9H, Ar–H), and 8.86 (t, 1H, O=C–NH, *J* = 5 Hz) ppm; MS: M^+351; Anal. Calcd. For $C_{18}H_{17}N_5O_3$ (351.36) C, 61.53; H, 4.88; N, 19.93; Found: C, 61.68; H, 4.55; N, 19.77.

4.2.10. 5-Amino-2-(4-nitro phenyl)-2H-[1,2,3]triazole-4-carboxylic acid benzyl amide (7b)

Brown crystals from ethanol; m.p. >300 °C; IR (KBr): υ = 3482, 3439 (NH2), 3379 (NH), 3083 (CH aromatic), 2950 (CH aliphatic) and 1697 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 4.52 (s, 2H, NH_2), 5.26 (d, 2H, CH_2Ph, *J* = 5 Hz), 7.31–8.31 (m, 9H, Ar–H), and 8.46 (t, 1H, O=C–NH, *J* = 5 Hz) ppm; MS: M^+338; Anal. Calcd. For $C_{16}H_{14}N_6O_3$ (338.33) C, 56.80; H, 4.17; N, 24.84; Found: C, 56.58; H, 4.25; N, 24.79.

4.2.11. General method to reaction of triazole compound 7 with dimethylformamide dimethylacetal (DMF DMA)

Method I (Δ): An equimolar amount of compounds **7** (5 mmol), dimethylformamide dimethylacetal (DMF DMA) in (20 mL) dry xylene was refluxed for 30 min. The reaction mixture was left to cool to room temperature, and then poured into ice-cold water. The solid product so-formed was filtered and crystallized from ethanol.

Method II ($\mu\omega$): A mixture of compounds **7** (0.1 mol) and (0.1 mol) of dimethylformamide dimethylacetal (DMF DMA) were placed in a tightly closed tube, and subjected to a microwave irradiation for 2–5 min until completion of the reaction (monitored by TLC). The reaction mixture was left to cool to room temperature, then poured into ice-cold water .The solid product so-formed was filtered and crystallized from ethanol.

4.2.12. 2-(6-Benzyl-7-oxo-6,7-dihydro-[1,2,3]triazolo[4,5-d]pyrimidin-2-yl)-benzoic acid methyl ester (10a)

Brown crystals from ethanol; m.p. 282 °C; IR (KBr): υ = 3092 (CH aromatic), 2939 (CH aliphatic), 1701 (C=O ester) and 1650 (C=O) cm^{-1}; ^1H NMR (400 MHz, DMSO–d_6, 25 °C, TMS): δ = 3.88 (s, 3H, $COOCH_3$), 5.25 (d, 2H, CH_2Ph, J = 5 Hz), 7.48 (s, 1H, pyrimidine ring) and 7.31–8.16 (m, 9H, Ar–H), ppm; MS: M^+361; Anal. Calcd. For $C_{19}H_{15}N_5O_3$ (361.12) C, 63.15; H, 4.18; N, 19.38; Found: C, 63.26; H, 4.29; N, 19.57.

4.2.13. 6-Benzyl-2-(4-nitrophenyl)-2,6-dihydro-[1,2,3]triazolo-[4,5-d]pyrimidin-7-one (10b)

Brown crystals from ethanol; m.p. 192 °C; IR (KBr): υ = 3092(CH aromatic), 2939 (CH aliphatic), and 1670 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 5.25 (d, 2H, CH_2Ph, J = 5 Hz, 7.50 (s, 1H, pyrimidine ring), 7.31 (d, 2H, Ar, H-2, H-6, J = 8 Hz) and 7.65 (d, 2H, Ar, H-3, H-5, J = 8 Hz), 7.32–7.89 (m, 5H, Ph–H) ppm; MS: M^+ 348; Anal. Calcd. For $C_{17}H_{12}N_6O_3$(348.10) C, 58.62; H, 3.47; N, 24.13; Found: C, 58.52; H, 3.64; N, 24.38.

*4.2.14. General method for reaction of aryl-hydrazono2-cyano acetamide compounds (**4a,b**) with chloroacetonitrile*

Method I (Δ): A solution of (0.1 mol) of each of compounds **4a,b** in (20 mL) triethylamine and chloroacetonitrile (0.1 mol) was refluxed for 30 min. The reaction mixture was left to cool to room temperature, and then poured into ice-cold water. The solid product so-formed was filtered and crystallized from ethanol.

Method II ($\mu\omega$): A mixture of compounds **4a,b** (0.1 mol) and (0.1 mol) chloroacetonitrile in 20 mL triethylamine were placed in a tightly closed tube, and subjected to a microwave irradiation for 2 min until completion of the reaction (monitored by TLC). The reaction mixture was left to cool to room temperature, then poured into ice-cold water. The solid product so-formed was filtered and crystallized from ethanol.

Method III (US): Chloroacetonitrile (0.1 mol) was added to a solution of compounds **4a,b** (0.1 mol) in (20 mL) triethyl amine Et_3 N, under ultrasound irradiation at 40 °C for 30 min. The reaction mixture poured into ice-cold water. The solid product so-formed was filtered and crystallized from ethanol.

4.2.15. 2-(4-Amino-3-benzyl carbamoyl-5-cyano-pyrazol-1-yl)-benzoic acid methyl ester (13a)

Dark brown crystals from ethanol; m.p.129 °C, IR (KBr): υ = 3480, 3434 (NH_2), 3386 (NH), 3160 (CH aromatic), 2950 (CH aliphatic), 2211 (CN), 1693 (C=O ester) and 1665 (C=O amide) cm^{-1}; ^1H NMR (400 MHz, DMSO–d_6, 25 °C, TMS): δ = 3.93 (s, 3H, $COOCH_3$), 4.57 (d, 2H, CH_2ph, J = 5 Hz), 6.84 (s, 2H, NH_2), 7.06–8.00 (m, 9H, Ar), 12.64 (t, 1H, O=C–$NHCH_2$, J = 5 Hz) ppm; ^{13}C NMR (100 MHz, DMSO–d_6, TMS): δ = 43.62(CH_2Ph), 52.89($COOCH_3$), 115.03 (CN), 110.15, 112.56, 113.94, 123.31, 127.84, 127.90, 128.89, 131.42, 134.77, 137.78 (aromatic carbons), 143.15, 147.99, 159.78 (pyrazole carbons) and 167.93 (C=O) ppm; MS: M^+ 375; Anal. Calcd. For $C_{20}H_{17}N_5O_3$ (375.39) C, 63.99; H, 4.56; N, 18.66; Found: C, 63.81; H, 4.75; N, 18.43.

4.2.16. 4-Amino-5-cyano-1-(4-nitro phenyl)-1H-pyrazole-3-cyclohexylic acid benzyl amide (13b)

Brown crystals from ethanol; m.p.99 °C; IR (KBr): υ = 3445, 3425 (NH_2), 3302 (NH), 3036 (CH aromatic), 2962 (CH aliphatic), 2256 (CN) and 1647 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 4.41 (d, 2H, CH_2ph, J = 5 Hz), 6.73 (s, 2H, NH_2), 7.90–8.33 (m, 9H, Ar–H) and 8.79 (t, 1H, O=C–$NHCH_2$, J = 5 Hz) ppm; ^{13}C NMR; non soluble; MS: M^+ 362; Anal. Calcd. For $C_{18}H_{14}N_6O_3$ (362.35) C, 59.67; H, 3.89; N, 32.19; Found: C, 59.43; H, 3.28; N, 23.43.

References

[1] S.A. Ghozlan, K.O. Badahdah, I.A. Abdelhamid, Belistien Journal of Organic Chemistry 3 (2007) 15.
[2] S.S.M. Al-Mousawi, M.S. Moustafa, Belistien Journal of Organic Chemistry 3 (2007) 12.
[3] K. Gewald, M. Rehwald, H. Mueller, P. Bellmann, H. Schaefer, Monatshefte Fur Chemie 126 (1995) 341.
[4] E. Sotelo, R. Mocelo, M. Suarez, A. Loupy, Synthetic Communications 27 (1997) 2419.
[5] A.S. Shawali, M.H. Abdelkader, F.M. Attalbawy, Tetrahedron 58 (2002) 2875.
[6] S. Al-Mousawi, A. Elassar, M.A. El-Apasery, Phosphate, Sulfur and Silicon and the Related Elements 181 (2006) 1755.
[7] B. Al-Saleh, M.A. El-Apasery, M.H. Elnagdi, Journal of Chemical Research (2004) 578–580.
[8] O.M.E. El-Dusouqui, M.M. Abdelkhalik, N.A. Al-Awadi, H.H. Dib, B.J. George, M.H. Elnagdi, Journal of Chemical Research (2006) 295–302.
[9] S.M. Riyadh, I.A. Abdelhamid, H.M. Ibrahim, H.M. Al-Matar, M.H. Elnagdi, Heterocycles 71 (12) (2007) 2545–2586.
[10] A.A. Elassar, H.H. Dib, N.A. Al-Awadi, M.H. Elnagdi, ARKIVOC (ii) (2007) 272–315.
[11] K.M. Al-Zaydi, R.M. Borik, M.H. Elnagdi, Ultrasonics Sonochemistry, in press.
[12] K.M. Al-Zaydi, R.M. Borik, Molecules 12 (2007) 2061.
[13] K.M. Al-Zaydi, R.M. Borik, M.H. Elnagdi, J. Heterocyclic 44 (5) (2007) 1187.
[14] R.S. Varma, Green Chemistry (1999) 43–55.
[15] P. Lidstrom, J. Tierney, B. Wathey, J. Westman, Tetrahedron 57 (2001) 9225–9283.
[16] A. Rehorek, M. Tauber, G. Gubitz, Ultrasonics Sonochemistry 11 (2004) 177–182.
[17] K.M. Al-Zaydi, R.M. Borik, M.H. Elnagdi, Molecules 9 (2003) 910–923.
[18] W. Bonrath, Ultrasonics Sonochemistry 11 (2004) 1–4.
[19] T.S. Saleh, N.M. Abd El-Rahman, Ultrasonics Sonochemistry 16 (2009) 237–242.
[20] K. Bougrin, A. Loupy, M. Soufiaoui, Journal of Photochemistry & Photobiology C: Photo Chemistry Reviews 6 (2005) 139–167.
[21] H.F. Anwar, N.H. Metwally, H. Gaber, M.H. Elnagdi, Journal of Chemical Research (2005) 29–31.
[22] R.M. Abdel-Motaleb, A.A. Makloof, H.M. Ibrahim, M.H. Elnagdi, Journal of Heterocyclic Chemistry 43 (2006) 931–934.
[23] H.M.E. Hassaneen, Synthetic Communications 37 (2007) 3579–3588.
[24] H.M. AL-Matar, S.M. Riyadh, M.H. Elnagdi, ARKIVOC (xiii) (2007) 53–62.