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ORIGINAL ARTICLE

Microwave and ultrasound promoted synthesis of substituted new arylhydrazono pyridinones

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Abstract A variety of arylhydrazonopyridinones **6a,b** were prepared *via* heating cyanoacetamide derivative with ethyl acetoacetate in the absence of solvent under reflux conventionally or ultrasound irradiation or in a microwave oven then coupling with heteroaromatic diazonium salts. Several attempts were made to synthesize corresponding aminothienopyridinones **7a,b** from **6a,b**. Also, attempts to add electron poor olefins to **6a,b** have failed and only arylhydrazonopyridinones recovered.

1. Introduction

Arylhydrazonopyridinones are now rapidly replacing arylazopyrazolones in classical dye industry. Moreover, reasonable solubility of these derivatives in lipophilic solvents gives these dyes high potential for utility in D^2T^2 (Dye Diffusion Thermal Transfer) printing. Although almost all commercial arylhydrazonopyridinones have an alkyl function utility of these pyridinones, synthesis of arylhydrazone condensed pyridinones have not interested researchers.

Moreover, to our knowledge, modern green synthetic methodologies have not yet been adopted for the synthesis of these pyridinones. Hence, there remains a demand for more efficious and safer green technologies (Hjeresen et al., 2000; Tundo et al., 2000; Lidstrom et al., 2001; Poliakoff et al., 2002; Bonrath, 2004; Al-Zaydi et al., 2009, 2007; Al-Zaydi, 2009, in press) for synthesis of alkyl azinylcarbonitriles as precursors to condensed azines.

We report here about an adoptation of green methodologies for the synthesis of heteroaromatic hydrazonopyridinones (Bougrin et al., 2005; Cravotto and Cintas, 2006; Heo et al., 2005; Cravotto et al., 2005; Disselkamp et al., 2005; Priego-Capote and Luque de Castro, 2007; Elnagdi et al., 1989; Elnagdi and Erian, 1990).

2. Experimental

2.1. General

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. ^{1}H NMR, ^{13}C NMR spectra

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were recorded in deuterated dimethylsulfoxide (DMSO) or deutrated chloroform ($CDCl_3$) at 200 MHz on a Varian Gemini NMR spectrometer and a Bruker DPX 400 MHz spectrometer using tetramethylsilane (TMS) as an internal reference. 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, 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 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 have been done using Perkin Elmer 2400 CHN Elemental analyzer flowchart.

3. General procedure for the preparation of *N*-benzyl-2-cyanoacetamide 3 (Al-Zaydi et al., 2009)

3.1. Method I (thermal)

Equimolar amounts (0.1 mol) of ethyl cyanoacetate and benzyl amine were stirred at room temperature for 60 min. The resulting solid product was recrystallized from ethanol.

3.2. Method II (microwave)

A mixture of ethyl cyanoacetate (0.1 mol) and benzyl amine (0.1 mol) were placed in the microwave oven and irradiated at 400 W for 1 min. Then left to cool to room temperature. The solid so-formed was filtered and recrystallized from ethanol.

3.3. Method III (ultrasound)

Equimolar amounts (0.1 mol) of ethyl cyanoacetate and the benzyl amine were mixed and the reaction mixture was heated under ultrasound irradiation at 40 °C for 2 min, and then left to cool to room temperature. The solid so-formed was filtered and recrystallized from ethanol.

3.4. Preparation of 1-benzyl-4-methyl-2,6-dioxo-1,2,5,6-tetrahydropyridine-3-carbonitrile (**4**)

3.4.1. Method I (thermal) (Al-Zaydi et al., 2009)

Ethyl acetoacetate (0.1 mol) was added to *N*-benzyl-2-cyanoacetamide (0.1 mol) (**3**). The reaction mixture was refluxed for 13 h. The reaction mixture was poured into ice-cold water and acidified with dilute HCl and then left to cool to room temperature. The solid so-formed was filtered and recrystallized from ethanol.

3.5. Method II (microwave)

A mixture of ethyl acetoacetate (0.1 mol) and *N*-benzyl-2-cyano-acetamide (0.1 mol) (**3**), was placed in the microwave oven and irradiated at 400 W for 20 min. The reaction mixture was poured into ice-cold water and acidified with dilute HCl and then left to cool to room temperature. The solid product so-formed was filtered and recrystallized from ethanol.

3.6. Method III (ultrasound)

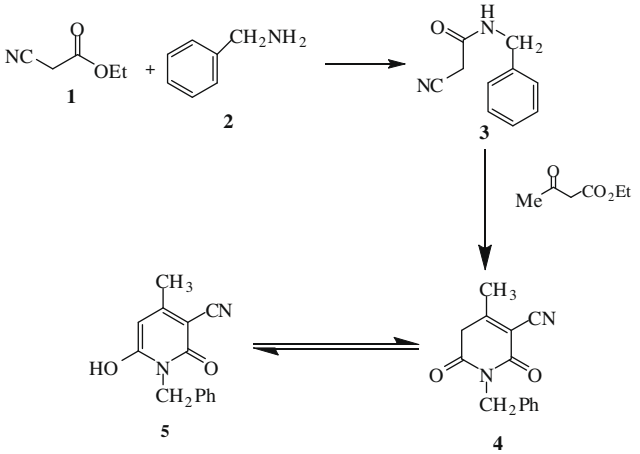
Ethyl acetoacetate (0.1 mol) was added to a mixture of amine derivative (0.1 mol) and ethyl cyanoacetate (0.1 mol) and the reaction mixture was catalyzed by 0.1 mol of ceric ammonium nitrate under ultrasound irradiation at 40 °C for 7 h. The reaction mixture was poured into ice-cold water and acidified with dilute HCl and then left to cool to room temperature. The solid product so-formed was filtered and recrystallized from ethanol.

3.7. Preparation of heterohydrazone compounds (**6a,b**) (Al-Zaydi et al., 2003, 2007)

A cold solution of arenediazonium salt (10 mmol) prepared by adding a solution of sodium nitrite (1 g in 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 arenediazonium was then added to a cold solution of **4** (0.1 mol) in ethanol (50 ml) containing sodium acetate (1 g in 10 ml H_2O). The mixture was stirred at room temperature for 1 h and the solid product so formed was collected by filtration and recrystallized from ethanol.

3.8. 1-Benzyl-4-methyl-2,6-dioxo-5[(2H-[1,2,4]triazol-3-yl)-hydrazono]-1,2,5,6-tetrahydro-pyridine-3-carbonitrile (**6a**)

m.p. 255 °C. IR (KBr): t = 3333 (2NH), 3032 (CH aromatic), 2924 (CH aliphatic), 2229 (CN) and 1685, 1639 (2C═O ring) - cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C, TMS): δ = 2.61 (s, 3H, C<u>H</u>$_3$), 5.02 (s, 2H, C<u>H</u>$_2$ph), 7.24–7.37 (m, 5H, ph-H), 8.63 (s, 1H, C<u>H</u> triazole ring), 14.30 (s, 1H, N<u>H</u> triazole ring) and 14.57 (s, 1H, N<u>H</u>) ppm; ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C, TMS): δ = 16.93 (<u>C</u>H$_3$), 43.50 (<u>C</u>H$_2$Ph), 102.90 (C-3), 115.23 (<u>C</u>N), 125.59, 127.87, 128.25, 128.93 (phenyl carbons), 136.69 (<u>C</u>-4), 146.20, 151.22 (triazole ring carbons), 159.40 (<u>C</u>-5) and 160.28, 160.48 (2C═O) ppm; MS: m/z = 335. Anal. For $C_{16}H_{13}N_7O_2$ (335.33) calcd. C57.31, H3.91, N29.24. Found C57.40, H3.82, N29.30.



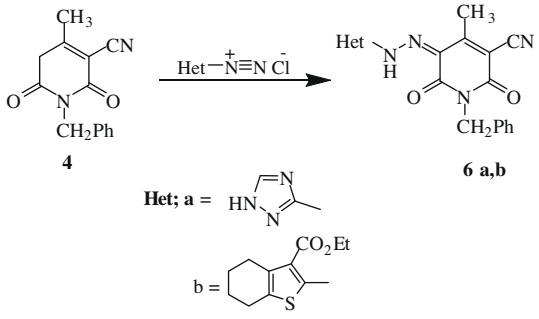
Scheme 1

Table 1 Time and yield of compounds 3, 4 by (Δ = thermal, MW = microwave irradiation and US = ultrasound).

No.	Time (min)			Yield (%)		
	Δ	MW	US	Δ	MW	US
3	60	1	2	89	93	90
4	780	20	420	72	93	88

*3.9. 2[N-(1-benzyl-5-cyano-4-methyl-2,6-dioxo-1,6-dihydro-2H-pyridine-3-ylidene)-hydrazino]-4,5,6,7-tetrahydro-benzo[b]thiophene-3-carboxylic acid ethyl ester (**6b**)*

m.p. 247 °C. IR (KBr): t = 3349 (br NH due to H-bond between O and NH), 3091 (CH aromatic), 2947 (CH aliphatic), 2223 (CN), 1670 (C═O ester) and 1624 (2C═O ring) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6, 25 °C, TMS): δ = 1.28 (t, 3H, $COOCH_2C\underline{H}_3$, J = 7 Hz), 1.64–2.59 (m, 8H, cyclohexene-H), 2.65 (s, 3H, $C\underline{H}_3$), 4.21-(q, 2H, $COOC\underline{H}_2CH_3$, J = 7 Hz), 5.03 (s, 2H, $C\underline{H}_2$ph), 7.06–7.14 (m, 5H, ph) and 14.21 (s, 1H, N$\underline{H}$) ppm; MS: m/z = 476. Anal. For $C_{25}H_{24}N_4O_4S$ (476.56) calcd. C63.01, H5.08, N11.76. Found C63.10, H5.13, N11.83.



Scheme 2

4. Results and discussion

The standard route to arylhydrazonopyridinones is coupling of **4**, prepared from **1** and benzyl amine **2**, with heteroaromatic diazonium salts. In our laboratory several cyanoacetamides **3** have been prepared *via* treatment of **1** with primary amines either at room temperature for a longer time or *via* irradiation with microwave for 1 min at 100 W or with ultrasound (US) for 2 min at 40 °C.

Compound **3** was reacted with an ethyl acetoacetate also either *via* a longer time using reflux of neat reagents and by a short time microwave or by US to afford product **4** which may be exist in another tautmeric form **5** (Scheme 1). In Table 1 yields as well as reaction times by the three methodologies are compared.

Coupling of **4** with heteroaromatic diazonium salts afforded the corresponding heteroaromatic hydrazones **6a,b** (Scheme 2).

The isolated products **6a,b** gave satisfactory elemental analyses and spectroscopic data (IR, ^1H NMR, ^{13}C NMR, MS) consistent with their assigned structures. Their IR spectra of the products showed presence of imino group (NH) absorption band. The mass spectra of the isolated product such as **6a** showed, a peak corresponding to the molecular ion at 335 (cf. Section 2).

As anticipated the heteroaromatic hydrazones **6a,b** reacted with elemental sulfur either by heating with microwave or by US and by conventional heating to the corresponding aminothienopyridinones **7a,b**. But several attempts were attained to synthesize corresponding aminothienopyridinones in presence of elemental sulfur using different conditions (changing temperature and time) under microwave irradiation, ultrasonic irradiation, and by conventional heating, the reaction did not takeplace (monitoring reaction by TLC).

Also, reaction of heteroaromatic hydrazones **6a,b** with acrylonitrile and methyl acrylate to afford isoquinoline derivatives did not occur using different conditions under microwave irradiation, ultrasonic irradiation, and by conventional heating as examined by TLC. In our opinion this may be due to a steric factor.

5. Conclusion

We have synthesized a variety of arylhydrazonopyridinors under microwave, sonication and classical conditions. In general, improvements in rates and yield of reactions are observed when reactions were carried out under microwave and sonication compared with classical condition.

It should be noted, however, that activation occurs at different temperatures with these techniques and, therefore strict comparisons will require a balance between effectiveness and energy costs.

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