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An efficient regioselective sonochemical synthesis of novel 4-aryl-3-methyl-4,5-dihydro-1*H*-pyrazolo[3,4-b]pyridin-6(7*H*)-ones

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Abstract

An efficient ultrasound-assisted preparation of a series of novel 4-aryl-3-methyl-4,5-dihydro-1*H*-pyrazolo[3,4-b]pyridin-6(7*H*)-ones *via* the reaction of 5-amino-3-methyl-1*H*-pyrazole, Meldrum's acid and various arylaldehydes using one-pot three-component approach is described. This rapid method produced the products in short reaction times (3–4 min) and excellent yields (87–95%).

Keywords: Pyrazolo[3,4-b]pyridin-6(7*H*)-one; Meldrum's acid; 5-Amino-3-methylpyrazole; One-pot; Ultrasonic irradiation; Three-component; Regioselective

Multi-component reactions (MCRs) in which three or more reactants are brought together in a highly convergent approach to rapidly build up molecular structure and complexity, high atom economy and environmentally benign procedures, have occupied a prominent and advantageous position in pharmaceutical and synthetic chemistry [1,2].

On the other hand, pyrazole and its derivatives are key substructures in a large variety of compounds and pyrazole-containing compounds have received considerable attention owing to their diverse biological activities and pharmacological properties [3–6], some pyrazoles have been implemented as antileukemic [7], antitumor [8] and anti-proliferative [9] agents. In addition combination of the pyrazole moiety with various heterocyclic ring systems have been resulted in interesting biological and pharmacological properties [10–13]. In particular pyrazolopyridines have attracted many interests in recent years as possible anti-viral agent [14,15], potent p38 kinase inhibitors [16], HIV reverse transcriptase inhibitors [17], and inhibitors of cGMP degradation [18,19]. Some derivatives exhibit potential antimalarial properties [20]. Others show intense fluorescence in the blue green region and have been considered for applications as fluorescence standards and luminophores in organic light emitting diodes [21], bactericidal activity [22], and also used as vasodilators [23] or evaluated for CCR1 antagonists and enzymatic inhibitory activities [24,25]. Therefore, extensive studies have been devoted to the synthesis and evaluation of activities of pyrazolopyridines [26]. However, most of these methods suffer from multi-step reactions, use of more expensive reagents, harsh reaction conditions, long reaction times, low yields of products and low regioselectivity, therefore, development of an efficient and versatile method is still required for the synthesis of pyrazolopyridines.

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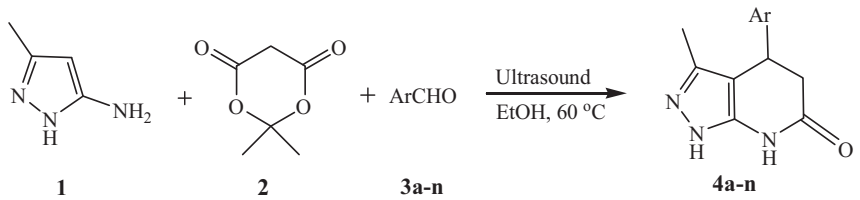
Recently, the use of ultrasonic irradiation as clean, green and environmentally benign route to activate organic reactions has attained greater value, compared to conventional heating. It has been used for a wide variety of organic reactions, such as oxidations, reductions, cleavage of epoxides, multicomponent reactions, synthesis of ionic liquids and *N*-heterocyclic compounds [27].

Our continued interests in heterocycles of potent medicinal values [27,28] and considering the great synthetic potentiality of ultrasound induced organic reactions triggered us to explore the use of this methodology in the synthesis of pyrazolopyridinones. In this report we have devised an efficient one-pot three-component reaction for the synthesis of novel derivatives of pyrazolo[3,4-b]pyridin-6(7*H*)-ones (**4a**–**n**) from 5-amino-3-methyl-1*H*-pyrazole (**1**), 6,6-dimethyl-1,3,5-trioxane-2,4-dione (Meldrum's acid) (**2**) and aryl aldehydes (**3a**–**n**) under ultrasonic irradiation (Scheme 1). Equimolar amounts of reactants **1**, **2** and **3** (Table 1, entry **n**, 0.5 equiv.) in ethanol were placed into Pyrex-glass open vessel and irradiated at 60 °C by ultrasound (45 kHz) to produce the desired pyrazolo[3,4-b]pyridin-6(7*H*)-one derivatives (**4a**–**n**) in 3–4 min with excellent yields (87–95%) (Table 1). The reaction under conventional heating using **4a** and **4b** as model compounds in refluxing ethanol, furnished the desired products in much longer reaction times (120–140 min) and lower yields (45–50%) (Table 1). The structures of all the products were fully characterized by spectroscopic (FT-IR, ^{1}H NMR, ^{13}C NMR) and elemental analyses.

The effect of several solvents (1,4-dioxane, CH_3CN, DMF, EtOH, H_2O) on the efficiency of the reaction was also examined by using synthesis of **4a** as model reaction. This study revealed that EtOH is the solvent of choice.

Interestingly this one-pot multicomponent approach also afforded an efficient protocol for the synthesis of bis-pyrazolo[3,4-b]pyridin-6(7*H*)-one (Fig. 1) in high yield (90%) (Table 1).

Mechanistically the formation of the products (**4a**–**n**) can be visualized by initial Knoevenagel condensation of arylaldehydes **3** and 6,6-dimethyl-1,3,5-trioxane-2,4-dione resulting in arylidene **5**, followed by a Michael type



1 **2** **3a-n** **4a-n**

Ar: 3-$NO_2C_6H_4$, 4-$MeOC_6H_4$, 4-$Me_2NC_6H_4$, furan-2-yl, 4-$NO_2C_6H_4$, C_6H_5, 4-ClC_6H_4, thiophen-2-yl, 2,4-$Cl_2C_6H_3$, 3,4-$(MeO)_2C_6H_3$, 4-FC_6H_4, 4-^{i}PrC_6H_4, pyridin-3-yl, 1,4-phenylene

Scheme 1. Synthesis of 4-aryl-3-methyl-4,5-dihydro-1*H*-pyrazolo[3,4-b]pyridin-6(7*H*)-ones **4a**–**n**.

Table 1
Synthesis of 4-aryl-3-methyl-4,5-dihydro-1*H*-pyrazolo[3,4-b]pyridin-6(7*H*)-one derivatives **4a**–**n**.

Entry	Ar	MP (°C)	Time (min)	Yield (%)[a,b]
a	3-$NO_2C_6H_4$	265–267	3 (120)[c]	95 (50)[c]
b	2-Thienyl	303–305	4 (140)[c]	95 (45)[c]
c	4-$Me_2NC_6H_4$	347–349	3	90
d	2-Furyl	>350	4	87
e	4-$NO_2C_6H_4$	>350	4	95
f	C_6H_5	304–306	3	95
g	4-ClC_6H_4	344–346	3	95
h	4-$MeOC_6H_4$	308–310	3	87
j	3,4-$(MeO)_2C_6H_3$	230–232	3	90
k	4-FC_6H_4	306–308	3	95
l	4-^{i}Pr C_6H_4	292–295	3	95
m	Pyridin-3-yl	302–305	4	90
n	1,4-phenylene	>350	4	90

[a] Isolated yields.
[b] Identified by spectroscopic (FT-IR, ^{1}H NMR, ^{13}C NMR) and elemental analyses.
[c] Classical method with heating in refluxing EtOH.

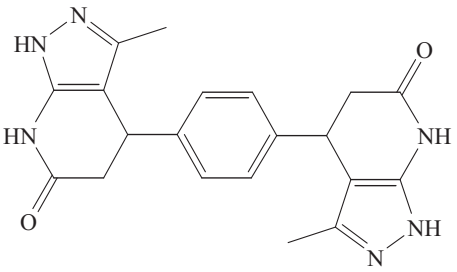
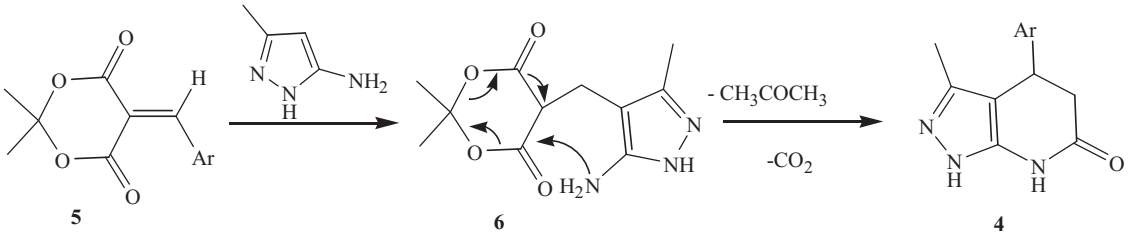


Fig. 1. Synthesis of bis-pyrazolo[3,4-b]pyridin-6(7*H*)-one.



Scheme 2. Plausible mechanism of formation of **4a**–**n**.

nucleophilic addition of C-4 of the pyrazole ring to the enone intermediate (**5**) and subsequent cyclodehydration to furnish the desired compounds (Scheme 2).

A comparison of the results obtained under ultrasonic irradiations with those of conventional heating in refluxing ethanol (Table 1) revealed that the reaction under ultrasonic irradiation proceeds in much lower reaction times and excellent yields. The rate acceleration using ultrasonic irradiations may be due to cavitation phenomena, in which the energy being transmitted more efficiently to the substrates [27a].

In summary, we have reported here a simple one-pot three component protocol under ultrasonic irradiation for the synthesis of pyrazolo[3,4-b]pyridin-6(7*H*)-ones without catalyst in short reaction times (3–4 min) and excellent yields (87–95%). The simplicity, easy workup, together with the use of inexpensive and environmentally friendly organic solvent and clean source of energy are the notable features of this protocol. Moreover this method is also extendable to the synthesis of bis-pyrazolo[3,4-b]pyridin-6(7*H*)-ones.

1. Experimental

Melting points were measured on an Electrothermal 9100 apparatus. For the ultrasound reactions, ultrasound apparatus Astra 3D (9.5 L, 45 kHz frequency, input power with heating, 305 W, number of transducers, 2) from TECNO-GAZ was used. FT-IR spectra were determined on a Shimadzo FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 500 MHz Bruker DRX-500 in DMSO as solvent and TMS as an internal standard. Elemental analyses were done on a Carlo-Erba EA1110 CNNO-S analyser and agreed with the calculated values. Chemicals were purchased from Merck and Aldrich. All solvents used were dried and distilled according to the standard procedures.

A solution of 5-amino-3-methyl-1*H*-pyrazole (1 mmol), 6,6-dimethyl-1,3,5-trioxane-2,4-dione (1 mmol) and aryl aldehydes (1 mmol) (Table 1, entry **n**, 0.5 mmol) were reacted in refluxing EtOH (7 mL) or placed into Pyrex glass open vessel and irradiated in a water bath under silent condition by ultrasound (45 kHz) at 60 °C for the required reaction times (Table 1). After completion of the reaction, which was checked by TLC the solvent was evaporated under vacuum and the residue was purified by recrystallization from a mixture of EtOH and H_2O to furnish the desired products (**4a**–**n**) (Table 1).

4a: Yellow solid, ^{1}H NMR (DMSO-d_6): δ 1.86 (s, 3H); 2.62 (dd, 1H); 2.89 (dd, 1H); 4.39 (t, 1H); 7.62 (t, 1H); 7.66 (d, 1H) 8.00 (s, 1H); 8.08 (dd, 1H); 10.40 (s, 1H, NH); 11.91 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 10.3, 34.3, 41.0, 101.8, 122.4, 122.6, 131.1, 134.8, 135.8, 147.0, 148.9, 149.7, 169.9 (C=O). FT-IR (KBr): ν 3200, 3150 cm^{-1} (NH),

1640 cm^{-1} (C=O). Anal. Calcd. for $C_{13}H_{12}N_4O_3$ (272.26): C, 57.35; H, 4.44; N, 20.58%; Found: C, 57.15; H, 4.28 N, 20.41%.

4b: White solid, ^{1}H NMR (DMSO-d_6): δ 2.02 (s, 3H); 2.64 (dd, 1H); 2.88 (dd, 1H,); 4.44 (dd, 1H,); 6.83 (d, 1H); 6.93 (dd, 1H); 7.32 (dd, 1H); 10.30 (s, 1H, NH); 11.86 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 10.2, 30.0, 41.7, 103.3, 124.5, 125.1, 127.8, 135.6, 149.0, 149.1, 170.0 (C=O). FT-IR (KBr): ν 3160, 3100 cm^{-1} (NH), 1650 cm^{-1} (C=O). Anal. Calcd. for $C_{11}H_{11}N_3OS$ (233.29): C, 56.63; H, 4.75; N, 18.01%; Found: C, 56.30; H, 4.61; N, 17.85%.

4c: White solid, ^{1}H NMR (DMSO-d_6): δ 1.83 (s, 3H), 2.49 (dd, 1H), 2.71 (dd, 1H), 2.83 (s, 6H), 4.0 (t, 1H), 6.65 (d, 2H), 6.97 (d, 2H), 10.22 (s, 1H, NH), 11.76 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 10.3, 33.9, 41.9, 103.4, 113.5, 128.3, 132.0, 135.4, 149.6, 150.1, 170.7 (C=O); FT-IR (KBr): 3180, 3160 cm^{-1} (NH), 1640 cm^{-1} (C=O). Anal. Calcd. for $C_{15}H_{18}N_4O$ (270.33): C, 66.65; H, 6.71; N, 20.72%; Found: C, 66.43; H, 6.51; N, 20.60%.

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