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# CONVENIENT ULTRASOUND-PROMOTED REGIOSELECTIVE SYNTHESIS OF FUSED 6-AMINO-3-METHYL-4-ARYL-1H-PYRAZOLO[3,4-b]PYRIDINE-5-CARBONITRILE

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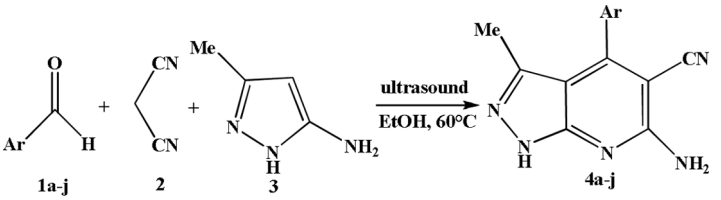
## GRAPHICAL ABSTRACT




**Ar = *2*-$NO_2C_6H_4$, *3*-$NO_2C_6H_4$,*4*-$NO_2C_6H_4$, *4*-$BrC_6H_4$,*4*-$ClC_6H_4$, etc.**

**Abstract** *A multicomponent, catalyst-free reaction for the synthesis of fused 6-amino-3-methyl-4-aryl-1H-pyrazolo [3,4-b] pyridine-5-carbonitrile from 3-amino-5-methylpyrazole, malononitrile, and substituted aldehydes under ultrasound irradiation in short reaction times (8–10 min) with good yields (85–98%) is reported.*

**Keywords** 3-Amino-5-methylpyrazole; fused 6-amino-3-methyl-4-aryl-1*H*-pyrazolo [3,4-*b*] pyridine-5-carbonitrile; malononitrile; multicomponent

## INTRODUCTION

Pyrazolopyridines have received much attention in recent years. Pharmaceutical research of this kind of compound has been reported, such as a potent cyclin dependent kinase 1 (CDK1) inhibitor,[1] HIV reverse transcriptase inhibitors,[2] CCR1 antagonists,[3] protein kinase inhibitors,[4] and inhibitors of cGMP degradation, together with several herbicidal and fungicidal activities.[5] Some derivatives exhibit potential antimalarial[6] and antiviral properties.[7,8] Others show intense fluorescence in the blue-green region and have been considered for applications as fluorescence

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standards and luminophores in organic light-emitting diodes.[9] Numerous methods for the synthesis of pyrazolopyridines in the past 20 years have been reported with respect to their different structures.[10]

The main disadvantages of most of these procedures are harsh reaction conditions, tedious workups, poor yields, long reaction times, multistep reactions, use of large quantities of volatile organic solvents, and poor regioselectivity. Therefore, development of an efficient and versatile method is still required.

Green chemistry has become a major driving force for organic chemists to develop environmentally benign routes for the preparation of organic compounds of synthetic and biological values. For example, the possibility of performing reactions under ultrasounic irradiation to enhance the reaction efficiency from both economical and ecological points of view has remarkable synthetic value and received great attention.[11]

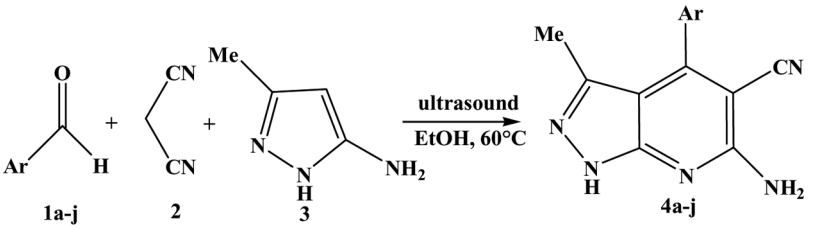
## RESULTS AND DISCUSSION

Recent developments in pyrazolopyridines chemistry and our continued interest in the development of efficient and environmentally friendly procedures for the synthesis of pharmaceutical compounds[12–16] triggered us to describe here an efficient method for the regioselective synthesis of new derivatives of pyrazolopyridines. Multicomponent reactions of 3-amino-5-methylpyrazole, aldehydes, and CH-acid compounds, forming different condensation products depending on the specific conditions, have recently attracted the interest of many chemists.[17]

In this report, we have devised an efficient one-pot, three-component reaction for the synthesis of novel fused derivatives of pyrazolopyridines (**4a**–**j**) from aldehydes (**1a**–**j**), malononitrile **2,** and 3-amino-5-methylpyrazole **3** under ultrasounic irradiation (Scheme 1).

Equimolar amounts of reactants **1** (Table 1, entries 6–10, 0.5 eq.), **2,** and **3** in ethanol were placed into a Pyrex open vessel and irradiated at 60 °C by ultrasound (45 kHz) to produce the desired pyrazolopyridine derivatives (**4a**–**j**) in 8–10 min with 85–98% yields (Table 1). A control reaction on substrates in refluxing ethanol, using the same ratio of the reactants, furnished the related pyrazolopyridines in lower yields and in much longer reaction times (5–6 h) (Table 1).

It is important to point out that when 3-amino-5-methylpyrazole **3**, malononitrile **2,** and substituted benzaldehyde **1** were irradiated for just 4–5 min, in all cases the

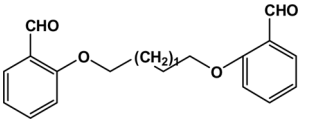
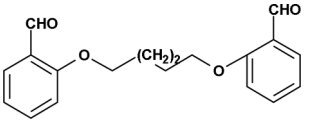
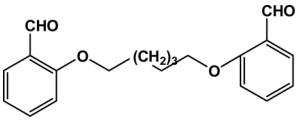
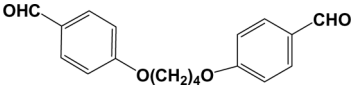
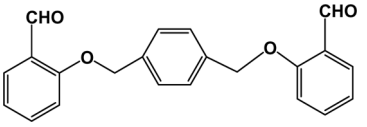



1a-j 2 3 4a-j

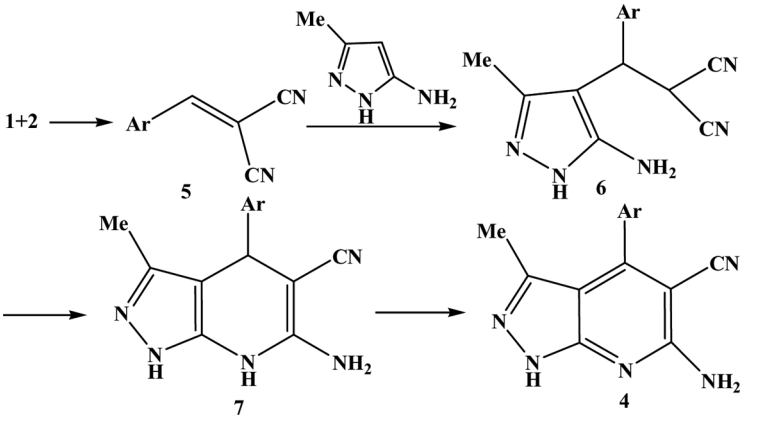
**Ar = *2*-$NO_2C_6H_4$, *3*-$NO_2C_6H_4$,*4*-$NO_2C_6H_4$, *4*-$BrC_6H_4$,*4*-$ClC_6H_4$, etc.**

**Scheme 1.** Synthesis of pyrazolopyridine derivatives (**4a–j**).

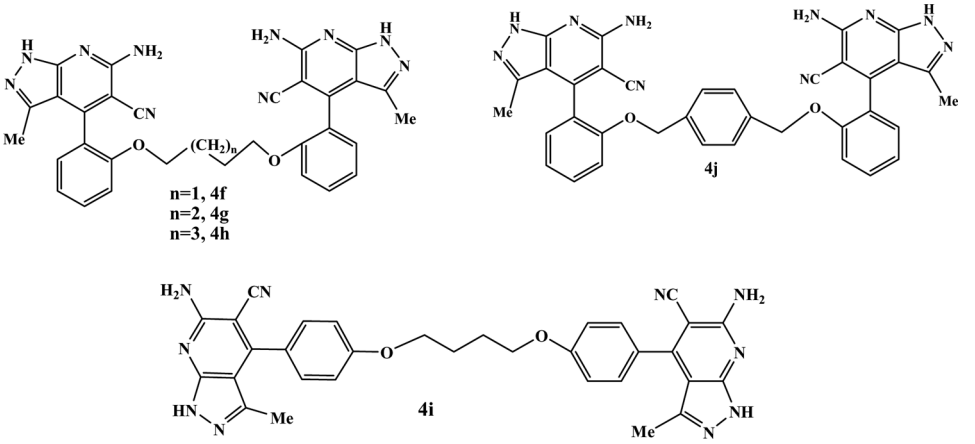
**Table 1.** Comparative studies of pyrazolopyridines synthesized under thermal and ultrasonic irradiation

| | | Thermal | | Ultrasound irradiation | |
|---|---|---|---|---|---|
| Entry | Aldehydes | Time (h) | Yield[a] (%) | Time (min) | Yield[a] (%) |
| a | 4-$NO_2$ $C_6H_4CHO$ | 6 | 50 | 10 | 85 |
| b | 3-$NO_2$ $C_6H_4CHO$ | 5.5 | 52 | 8.5 | 89 |
| c | 2-$NO_2$ $C_6H_4CHO$ | 5 | 61 | 8 | 92 |
| d | 4-Cl $C_6H_4CHO$ | 5 | 56 | 8.5 | 85 |
| e | 4-Br $C_6H_4CHO$ | 5 | 54 | 8 | 88 |
| f |  | 6 | 62 | 9 | 95 |
| g |  | 5.5 | 65 | 8.5 | 96 |
| h |  | 5.5 | 63 | 8 | 95 |
| i |  | 5 | 62 | 8.5 | 98 |
| j |  | 5 | 59 | 10 | 98 |

[a]Isolated yields.
[b]Identified by spectroscopic analysis (IR, $^1$H NMR) and elemental analysis.




**Scheme 2.** Mechanism of formation of **4a–j** via intermediates **6** and **7**.




**Scheme 3.** Synthesis of bispyrazolopyridines (**4f–j**).

reaction led to the formation of the stable intermediates **7**, which in one case were isolated and characterized. For this reason, we assume that the formation of **4** proceeds by a Michael-type addition from the free ring carbon atom in 3-amino-5-methylpyrazole **3** to the activated double bond of the compound **5** (formed in situ by a Knovenagel condensation between malononitrile **2** and substituted benzaldehyde **1**), which subsequently cyclizes the previously form Michael adduct **6** to give **7** (Scheme 2). When compound **7** is continuously irradiated (an additional 4–5 min), it yields pyrazolopyridine **4a–j**.

Interestingly, this multicomponent reaction also afforded an efficient protocol for the synthesis of bispyrazolopyridines **4f–j** in good yields and short reaction times.

All of compounds summarized in Table 1 were characterized by spectroscopic methods [infrared (IR) and $^1$H NMR] and elemental analysis. In the other efforts, when 37% formaldehyde was used instead of substituted benzaldehyde with refluxing the reaction mixture for 9 h or under ultrasounic irradiation, no product was observed.

## CONCLUSION

In conclusion, this one-pot, three component protocol under ultrasound irradiation provides a regioselective, fast, and practical method for the preparation of fused pyrazolo[3,4-*b*]pyridine carbonitriles from 5-amino-3-methylpyrazole, malononitrile, and various aryl aldehydes in short reaction times and in excellent yields, which pave the way for assessment of pharmacological activities of these novel pyrazolopyridine derivatives. The simplicity, high atom economy, easy excecution, east workup, and productivity, together with the use of inexpensive material and environmentally friendly procedure, are the remarkable features of this procedure.

## EXPERIMENTAL

Melting points were measured on an Electrothermal 9100 apparatus. For the ultrasounic 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. IR spectra were determined on a Shimadzo IR-470 spectrometer. $^1$H NMR spectra were recorded on a 500-MHz Bruker DRX-500 in dimethylsulfoxide (DMSO-$d_6$) as solvent and tetramethylsilane (TMS) as an internal standard. Chemicals were purchased from Merck and Fluka. Elemental analyses were done on a Carlo-Erba EA1110 CNNO-S analyser and agreed with the calculated values. All solvents used were dried and distilled according to standard procedures.

### General Procedure

**Thermal condition.** A solution of 5-amino-3-methylpyrazole **3** (1 mmol), malononitrile **2** (1 mmol), and aldehyde **1** (1 mmol) (Table 1, entries **1f–j**, 0.5 mmol) in EtOH (10 mL) were refluxed for the required reaction time. After completion of the reaction, the amount of solvent was reduced to a minimum under vacuum, to afford **4a–j** as crystalline products in 50–65% yields (Table 1).

**Ultrasounic irradiation.** A solution of 5-amino-3-methylpyrazole **3** (1 mmol), malononitrile **2** (1 mmol), and aldehyde **1** (1 mmol) (Table 1, entries **1f–j**, 0.5 mmol) in EtOH (10 mL) were placed into a Pyrex open vessel and irradiated in a water bath under silent conditions by ultrasound (45 kHz) at 60 °C for the required reaction times (Table 1). When the irradiation was stopped, the amount of solvent was reduced to a minimum under vacuum to afford **4a–j** as crystalline products in 85–98% yields (Table 1).

### Selected Data

**6-Amino-4,7-dihydro-3-methyl-4-(4-nitrophenyl)-1*H*-pyrazolo[3,4-*b*] pyridine-5-carbonitrile 7a.** Off-white solid; mp 310–312 °C; FT-IR (KBr, cm$^{-1}$): 3420, 3300, 2200, 1645, 1600, 1560, 1340, 1265. $^1$H NMR (DMSO, 500 MHz): 2.5 (s, 3H), 6.4 (s, 1H), 7.53 (d, $J = 7.2$ Hz, 2H), 7.84 (d, $J = 7.2$ Hz, 2H), 8.50 (s, br, 1H). Anal. calcd. for $C_{14}H_{12}N_6O_2$: C, 56.75; H, 4.08; N, 28.36. Found: C, 56.60; H, 3.82; N, 28.42.

**6-Amino-3-methyl-4-(3-nitrophenyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile 4b.** Off-white solid; mp 285–287 °C; FT-IR (KBr, cm$^{-1}$): 3369, 3313, 3236, 3099, 2925, 2187, 1600, 1517, 1352. $^1$H NMR (DMSO, 500 MHz): 2.04 (s, 3H), 7.42 (t, $J = 7.9$ Hz, 1H), 7.63 (d, $J = 7.7$ Hz, 1H), 8.01 (dd, $J = 8.1$ Hz, 1.32 Hz, 1H), 8.14 (t, $J = 1.86$ Hz, 1H), 8.65 (s, 1H). Anal. calcd. for $C_{14}H_{10}N_6O_2$: C, 57.14; H, 3.43; N, 28.56. Found: C, 57.25; H, 3.52; N, 28.93.

**6-Amino-3-methyl-4-(2-nitrophenyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile 4c.** Brown solid; mp 290–292 °C; FT-IR (KBr, cm$^{-1}$): 3404, 3132, 2935, 2202, 1623, 1585, 1496, 1434. $^1$H NMR (DMSO, 500 MHz): 2.46 (s, 3H), 7.48 (t, $J = 6.0$ Hz, 1H), 7.63 (d, $J = 8.4$ Hz, 1H), 7.81 (t, $J = 7.2$ Hz, 1H), 7.85 (d, $J = 8.2$ Hz, 1H). Anal. calcd. for $C_{14}H_{10}N_6O_2$: C, 57.14; H, 3.43; N, 28.56. Found: C, 57.36; H, 3.25; N, 28.65.

**6-Amino-4-(4-chlorophenyl)-3-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile 4d.** Off-white solid; mp 268–270 °C; FT-IR (KBr, cm$^{-1}$); 3433, 3311,

3234, 3172, 2925, 2212, 1580, 1554, 1087. $^1$H NMR (DMSO, 500 MHz): 2.4 (s, 3H), 7.59 (d, $J = 8.5$ Hz, 2H), 7.81 (d, $J = 8.5$ Hz, 2H), 8.82 (s, br, 2H). Anal. calcd. for $C_{14}H_{10}ClN_5$: C, 59.27; H, 3.55; N, 24.68. Found: C, 59.55; H, 3.59; N, 24.73.

**6-Amino-4-(4-bromophenyl)-3-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile 4e.** Off-white solid; mp 278–280 °C; FT-IR (KBr, cm$^{-1}$): 3600, 3100, 2900, 2200, 1600, 1590, 1460, 1100. $^1$H NMR (DMSO, 500 MHz): 2.45 (s, 3H), 8.04 (d, $J = 7.78$ Hz, 2H), 8.37 (d, $J = 7.78$ Hz, 2H), 8.92 (s, br, 2H). Anal. calcd. for $C_{14}H_{10}BrN_5$: C, 51.24; H, 3.07; N, 21.34. Found: C, 51.55; H, 3.24; N, 21.53.

**4,4′-((Butane-1,4-diylbis(oxy))bis(2,1-phenylene))bis(6-amino-3-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile) 4f.** Yellow solid; mp 210–212 °C; FT-IR (KBr, cm$^{-1}$): 3458, 3037, 2946, 2219, 1589, 1483, 1452, 1255. $^1$H NMR (DMSO, 500 MHz): 2.0 (s, br, 4H), 2.43 (s, br, 6H), 4.22 (s, br, 4H), 7.07 (s, br, 2H), 7.24 (s, br, 2H), 7.67 (s, br, 2H), 7.98 (s, br, 2H), 8.4 (s, br, 2H). Anal. calcd. for $C_{32}H_{28}N_{10}O_2$: C, 65.74; H, 4.83; N, 23.96. Found: C, 65.54; H, 4.64; N, 23.59.

**4,4′-((Pentane-1,5-diylbis(oxy))bis(2,1-phenylene))bis(6-amino-3-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile) 4g.** Light brown solid; mp 204–206 °C; FT-IR (KBr, cm$^{-1}$): 3434, 3230, 2937, 2194, 1639, 1602, 1242. $^1$H NMR (DMSO, 500 MHz): 1.4 (s, br, 2H), 2.0 (s, br, 4H), 2.5 (s, 3H), 4.20 (s, br, 4H), 7.14 (s, br, 2H), 7.23 (d, $J = 7.5$ Hz, 2H), 7.66 (s, br, 3H),7.97 (d, $J = 6.30$ Hz, 2H), 8.41(s, br, 1H). Anal. calcd. for $C_{33}H_{30}N_{10}O_2$: C, 66.21; H, 5.05; N, 23.40. Found: C, 66.24; H, 5.33; N, 23.48.

**4,4′-((Hexane-1,6-diylbis(oxy))bis(2,1-phenylene))bis(6-amino-3-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile) 4h.** Yellow solid; mp 166–168 °C; FT-IR (KBr, cm$^{-1}$): 3471, 3458, 3035, 2945, 2219, 1591, 1573, 1454, 1257. $^1$H NMR (DMSO, 500 MHz): 1.5 (s, br, 2H), 2.0 (s, br, 2H), 2.5 (s, 3H), 4.14 (s, br, 2H), 7.06 (s, br, 1H), 7.13 (s, br, 1H), 7.66 (s, br, 1H), 7.98 (s, br, 1H), 8.43 (s, br, 1H). Anal. calcd. for $C_{34}H_{32}N_{10}O_2$: C, 66.65; H, 5.26; N, 22.86. Found: C, 66.10; H, 5.91; N, 22.74.

**4,4′-((Butane-1,4-diylbis(oxy))bis(4,1-phenylene))bis(6-amino-3-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile) 4i.** Yellow solid; mp 200–202 °C; FT-IR (KBr, cm$^{-1}$): 3473, 3039, 2943, 2200, 1589, 1452, 1253. $^1$H NMR (DMSO, 500 MHz): 1.9 (s, br, 2H), 2.45 (s, 3H), 4.2 (s, br, 2H), 7.18 (d, $J = 8.04$ Hz, 2H), 7.96 (d, $J = 8.04$ Hz, 2H), 8.38 (s, 1H). Anal. calcd. for $C_{32}H_{28}N_{10}O_2$: C, 65.74; H, 4.83; N, 23.96. Found: C, 65.36; H, 4.95; N, 23.69.

**4,4′-(((1,4-Phenylenebis(methylene))bis(oxy))bis(2,1-phenylene))bis(6-amino-3-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile) 4j.** Yellow solid; mp 230–232 °C; FT-IR (KBr, cm$^{-1}$): 3446, 3029, 2936, 2225, 1593, 1483, 1456, 1299, 1244. $^1$H NMR (DMSO, 500 MHz): 2.5 (s, 3H), 5.3 (s, 2H), 7.17 (t, $J = 7.56$ Hz, 1H), 7.31 (d, $J = 8.5$ Hz, 1H), 7.57 (s, 2H), 7.66 (t, $J = 7.81$ Hz, 1H), 8.01 (d, $J = 7.78$ Hz, 1H), 8.5 (s, 1H). Anal. calcd. for $C_{36}H_{28}N_{10}O_2$: C, 68.34; H, 4.46; N, 22.14. Found: C, 68.62; H, 4.55; N, 22.07.

## ACKNOWLEDGMENT

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