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Synthesis of Pyrano[3,2-c]pyridines Derivatives

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An efficient and straightforward procedure for the synthesis of pyrano[3,2-c]pyridines derivatives has been reported through the one-pot condensation of malononitrile, ethylacetoacetate and aryl aldehydes in the presence of piperazine as catalyst under solvent-free media conditions by a microwave-assisted process.

Key Words: Multi-component reactions, Microwave-assisted, Heterocyclic chemistry, Pyrano[3,2-c]pyridines derivatives.

INTRODUCTION

Heterocyclic compounds are finding an increasing use as intermediates in organic synthesis. Currently a great deal of research in heterocyclic chemistry is concerned with the synthesis of new compounds and discovering new and more environmentally friendly methods in ring synthesis. Multi-component reactions (MCRs) are convergent reactions, in which three or more starting materials react through a one-pot process to form a new product that incorporates all or most of the contributed atoms[1].

There has been tremendous development in three-or four-component reactions which have further led to renaissance of multi-component reactions[2-8]. Foroughifar *et al*[9]. described the preparation of 4-semicarbazonoalkyl-2-naphthols by multi-component coupling reaction of two or three molecules of aldehydes with 2-naphthols and semicarbazide hydrochloride. They used TSA/NaOAc as an efficient catalyst system in THF at room temperature /or solvent-free conditions at elevated temperatures. This reaction occurs in a one-pot process in which three or four easily accessible components react to form a single product that incorporates essentially all the carbon atoms of the starting materials[9].

Using conventional heating usually involves the use of reflux, resulting in the loss of large amount of solvent (dependent on the reaction type) during the production process, which is not environmentally friendly. This problem can be addressed in the production of pyranopyridines[10] and cyclization of olefins containing aryls or alkenyl halides[11].

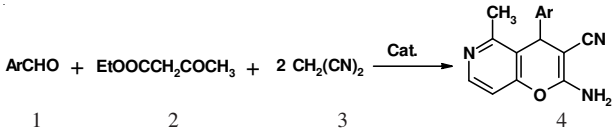
Pyranopyridines are chemically interesting molecules due to their structural similarity to quinolines, substituted pyridines and benzopyranes[12] and are important intermediates in the synthesis of biologically active compounds. Earlier methods for the preparation of DHPPs needed high reaction temperature or highly functionalized pyridine derivatives which cannot be easily prepared[10] .

Palladium-catalyzed cyclization of olefins containing aryl or alkenyl halide has also been widely applied to synthesize various heterocyclic which could not be easily synthesized by conventional methods[11]. Heck reactions have been used for the synthesis of fused pyridine derivatives due to possible formation of π-allyl complexes or metal complex with pyridine derivatives and various 6-amino-5-cyano-4-aryl-4H-pyrano[3,4-b]-pyridines were synthesized by the reaction of iodo-(3-butenyloxy) pyridine with LiCl mediate palladium catalyzed[12].

It is believed that the use of microwave heating in multi-component reactions would overcome the aforementioned problems and facilitate the multi-component reaction due to the higher efficiencies and yields obtained by this method.

In present work, we reported an efficient and eco-friendly three-component reaction protocol and describe our results on a new type of the multi-component reaction where four organic components react to form novel compounds by using a microwave-assisted process for the synthesis of pyrano-pyridines derivatives.

2-Amino-5-methyl-4-aryl-4H-pyrano [3,2-c] pyridine-3-carbonitrile (**4**) as final product was prepared by reaction between malononitrile (**1**), ethyl acetoacetate (**2**) and benzaldehyde (**3**) in the presence of a mediated catalyst, which consists of 5-10 % of a base with piperazine, as shown in Fig. 1.



1 2 3 4

Fig. 1. Synthesis of pyrano [3,2-c] pyridines derivatives

EXPERIMENTAL

Melting points were determined on an electrothermal digital melting point apparatus. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 300 MHz spectrometer. Reactions were monitored by thin layer chromatography. All commercial materials were used without purification. Reactions were performed in Samsung microwave oven of household with 230 v-50 HZ power source, 900 W output and 2450 MHz operating frequency.

0.2 g of piperazine powder was added to a mixture of ethyl acetoacetate (2 mmol), aldehyde (2 mmol), malononitrile (4 mmol) and mixed in a beaker vigorously. Then, the mixture was irradiated in a microwave for 90s with 50 % power. After irradiation the mixture was cooled down to the room temperature, an acidic aqueous solution (5 mL) was added to the beaker and the whole mixture was stirred for 5 min. Then, the precipitated solid was filtered and dried at room temperature and purified by ethanol.

2-Amino-5-methyl-4-(2,5-dimethoxyphenyl)-4H-pyrano[3,2-c]pyridine-3-carbonitrile (4a): Yellow solid, m.p. 222-225 ºC (EtOH); IR (KBr, ν_{max}, cm^{-1}): 3391(NH_2), 3209(NH_2), 3067(CH_{arom}), 2980(CH_{aliph}), 2202(CN), 1626. ^{1}H NMR (300 MHZ, DMSO-d_6): δ 8.61 (bs, 1H), 7.40 (d, 1H), 7.11 (d, 1H), 7.01(d, 1H), 6.94 (m, 1H), 5.88 (s, 1H), 3.74(d, 6H), 3.14(s, 3H). ^{13}C NMR (300 MHz, DMSO-d_6): δ 162 (C=C), 159 (C=C), 151 (C=C), 130 (C=C), 129, 122 (C=C), 120 (C=C), 117 (C=C), 106 (C=C), 100 (C=C), 98 (C=C), 78 (CN), 55 (OCH_3), 35 (CH), 23 (CH_3).

2-Amino-5-methyl-4-(2,4-dimethoxyphenyl)-4H-pyrano[3,2-c]pyridine-3-carbonitrile (4b): Yellow solid, m.p. 236-239 ºC (EtOH); IR (KBr, ν_{max}, cm^{-1}): 3344 (NH_2), 3212 (NH_2), 3051 (CH_{arom}), 2937 (CH_{aliph}), 2202 (CN), 1626. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.73 (bs, 1H), 7.37-7.50 (m, 2H), 7.03(d, 1H), 6.60(d, 1H), 5.85 (s, 1H), 3.86 (d, 6H), 3.27 (s, 3H). ^{13}C NMR (300 MHz, DMSO-d_6): δ 162(C=C), 158(C=C), 151(C=C), 135(C=C), 129(C=C), 127(C=C), 120(C=C), 117 (C=C), 101(C=C), 79(CN), 57(OCH_3), 38(CH), 20(CH_3).

2-Amino-5-methyl-4-(4-hydroxyphenyl)-4H-pyrano [3, 2c]pyridine-3-carbonitrile (4c): Yellow solid, m.p. 250-253 ºC (EtOH); IR (KBr, ν_{max}, cm^{-1}): 3443 (OH), 3344 (NH_2), 3194 (NH_2), 3043 (CH_{arom}), 2990 (CH_{aliph}), 2214 (CN), 1716 (C=C), 1606 (C=C). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.61 (bs, 1H), 7.40(d, 1H), 7.11(d, 1H), 7.01(d, 1H), 6.94 (m, 1H), 5.88 (s, 1H), 3.74(d, 6H), 3.14(s, 3H). ^{13}C NMR (300 MHz, DMSO-d_6): δ 162(C=C), 159(C=C), 155(C=C), 150(C=C), 135(C=C), 129(C=C), 127(C=C), 120(C=C), 117 (C=C), 101(C=C), 79(CN), 35(CH), 21(CH_3).

2-Amino-5-methyl -4-(4-methylphenyl)-4H-pyrano[3, 2-c]pyridine-3-carbonitrile (4d): White solid, m.p. 230-232 ºC (EtOH); IR (KBr, ν_{max}, cm^{-1}): 3391 (NH_2), 3209 (NH_2), 3067 (CH_{arom}), 2980 (CH_{aliph}), 2202 (CN), 1626. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.59 (bs, 1H), 7.43 (d, 1H), 7.11-7.14 (m, 5H), 4.84 (s, 1H), 2.53 (s, 3H), 2.34 (s, 3H). ^{13}C NMR (300 MHz, DMSO-d_6): δ 166 (C=C), 157 (C=C), 153 (C=C), 145 (C=C), 133, 130 (C=C), 128 (C=C), 126 (C=C), 120 (C=C), 118 (CN), 108 (C=C), 78 (C=C), 34 (CH), 21 (CH_3), 19 (CH_3).

2-Amino-5-methyl-4-(4-fluorophenyl)-4H-pyrano[3,2-c]pyridine-3-carbonitrile (4e): White solid, m.p. 239-241 ºC (EtOH); White solid, m.p. 222-225 ºC (EtOH); IR (KBr, ν_{max}, cm^{-1}): 3381 (NH_2), 3214 (NH_2), 3053 (CH_{arom}), 2986 (CH_{aliph}), 2212 (CN), 1626. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.57 (bs, 1H), 7.38(d, 1H), 7.21(d, 2H), 7.14(d, 1H), 7.12(d, 2H), 5.85 (s, 1H), 2.54(s, 3H). ^{13}C NMR (300 MHz, DMSO-d_6): δ 164(C=C), 158(C=C), 152(C=C), 143(C=C), 132, 130(C=C), 127(C=C), 125 (C=C), 121(C=C), 117(CN), 105(C=C), 76(C=C), 32(CH), 19(CH_3).

2-Amino-5-methyl -4-(4-chlorophenyl)-4H-pyrano[3, 2-c]pyridine-3-carbonitrile (4f): White solid, m.p. 242-245 ºC (EtOH); IR (KBr, ν_{max}, cm^{-1}): 3390 (NH_2), 3204 (NH_2), 3101 (CH_{arom}), 2991 (CH_{aliph}), 2214 (CN), 1636. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.59 (bs, 1H), 7.42(d, 1H), 7.33(d, 2H), 7.18(d, 2H), 7.12(d, 1H), 5.81(s, 1H), 2.58(s, 3H). δ 162(C=C), 158(C=C), 151(C=C), 141(C=C), 134, 130(C=C), 128(C=C), 124 (C=C), 120(C=C), 118(CN), 106(C=C), 77(C=C), 31(CH), 20(CH_3).

2-Amino-5-methyl-4-(2-chloro-4-fluorophenyl)-4H-pyrano[3,2-c]pyridine-3-carbonitrile (4g): White solid, m.p. 235-238 ºC (EtOH); IR (KBr, ν_{max}, cm^{-1}): 3391 (NH_2), 3209 (NH_2), 3067 (CH_{arom}), 2980 (CH_{aliph}), 2202 (CN), 1626. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.60 (bs, 1H), 7.70(d, 1H), 7.41(d, 1H), 7.14-7.17 (m, 2H), 6.94 (m, 1H), 5.78 (s, 1H), 2.58(s, 3H). ^{13}C NMR (300 MHz, DMSO-d_6): δ 164 (C=C), 157 (C=C), 153 (C=C), 150 (C=C), 131 (C=C), 129 (C=C), 122 (C=C), 120 (C=C), 117 (CN), 108 (C=C), 102 (C=C), 96 (C=C), 77 (C=C), 33 (CH), 23 (CH_3).

2-Amino-5-methyl-4-phenyl-4H-pyrano[3,2-c]pyridine-3-carbonitrile (4h): White solid, m.p. 216-219 ºC (EtOH); IR (KBr, ν_{max}, cm^{-1}): 3385 (NH_2), 3212 (NH_2), 3056 (CH_{arom}), 2985 (CH_{aliph}), 2209 (CN), 1636. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.62 (bs, 1H), 7.42(d, 1H), 7.20-7.28(m, 5H), 6.94 (d, 1H), 5.83 (s, 1H), 3.12(s, 3H). ^{13}C NMR (300 MHz, DMSO-d_6): δ 162 (C=C), 159 (C=C), 151 (C=C), 138 (C=C), 135 (C=C), 132 (C=C), 129 (C=C), 117 (CN), 106 (C=C), 101 (C=C), 78 (C=C), 35 (CH), 19 (CH_3).

2-Amino-5-methyl -4-(4-nitrophenyl)-4H-pyrano[3,2-c]-pyridine-3-carbonitrile (4i): Yellow solid, m.p. 248-250 ºC (EtOH); IR (KBr, ν_{max}, cm^{-1}): 3371 (NH_2), 3194 (NH_2), 3127 (CH_{arom}), 2990 (CH_{aliph}), 2212 (CN), 1646. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.63 (bs, 1H), 8.14(d, 2H), 7.49(d, 2H), 7.40(d, 1H), 7.14 (m, 1H), 5.74 (s, 1H), 3.3(s, 3H). ^{13}C NMR (300 MHz, DMSO-d_6): δ 162 (C=C), 157 (C=C), 154 (C=C), 144 (C=C), 129 (C=C), 123 (C=C), 120 (C=C), 117 (CN), 106 (C=C), 100 (C=C), 98 (C=C), 78 (C=C), 28 (CH), 19 (CH_3).

2-Amino-5-methyl-4-(2-methylphenyl)-4H-pyrano-[3,2-c]pyridine-3-carbonitrile (4j): White solid, m.p. 222-225 ºC (EtOH); IR (KBr, ν_{max}, cm^{-1}): 3391 (NH_2), 3209 (NH_2), 3067 (CH_{arom}), 2980 (CH_{aliph}), 2202 (CN), 1626. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.59 (bs, 1H), 7.40 (d, 1H), 7.34 (d,1H), 7.14 (m, 3H), 7.11 (d, 1H), 5.78 (s, 1H), 2.57 (s, 3H). ^{13}C NMR (300 MHz, DMSO-d_6): δ 161 (C=C), 158 (C=C), 147 (C=C), 138 (C=C), 136 (C=C), 130 (C=C), 125 (C=C), 124 (C=C), 119 (C=C), 118 (CN), 107 (C=C), 100 (C=C), 78 (C=C), 33 (CH), 21 (CH_3), 19 (CH_3).

2-Amino-5-methyl-4-(2-thionyl)-4H-pyrano[3,2-c]-pyridine-3-carbonitrile (4k): Yellow solid, m.p. 222-225 ºC

(EtOH); IR (KBr, ν_{max}, cm^{-1}): 3375 (NH_2), 3218 (NH_2), 3112 (CH_{arom}), 3105 (CH_{arom}), 2979 (CH_{aliph}), 2210 (CN), 1636. ^1H NMR (300 MHz, DMSO-d_6): δ 8.53 (bs, 1H), 7.48 (d, 1H), 7.42 (d, 1H), 7.11 (d, 1H), 6.93 (d, 1H), 6.83 (m, 1H), 5.74 (s, 1H), 2.6 (s, 3H). ^{13}C NMR (300 MHz, DMSO-d_6): δ 162 (C=C), 160 (C=C), 155 (C=C), 127 (C=C), 126 (C=C), 125 (C=C), 120 (C=C), 117 (CN), 106 (C=C), 68 (C=C), 29 (CH), 20 (CH_3).

2-Amino-5-methyl -4-(2-nitrophenyl)-4H-pyrano[3,2-c]pyridine-3-carbonitrile (4l): Yellow solid, m.p. 247-255 ºC (EtOH); IR (KBr, ν_{max}, cm^{-1}): 3391 (NH_2), 3209 (NH_2), 3067 (CH_{arom}), 2980 (CH_{aliph}), 2202 (CN), 1626. ^1H NMR (300 MHz, DMSO-d_6): δ 8.63 (bs, 1H), 7.96(d,1H), 7.44(d, 1H), 7.52(d, 1H), 7.49(d, 1H), 7.14 (d, 1H), 5.91 (s, 1H), 2.53(s, 3H). ^{13}C NMR (300 MHz, DMSO-d_6): δ 162 (C=C), 159 (C=C), 155, (C=C), 149 (C=C), 134 (C=C), 130 (C=C), 128 (C=C), 126 (C=C), 124, 122 (C=C), 120 (C=C), 116 (CN), 106 (C=C), 75 (C=C), 24 (CH), 18 (CH_3).

2-Amino-5-methyl-4-(3,4-dimethoxyphenyl)-4H-pyrano[3,2-c]pyridine-3-carbonitrile (4m): Yellow solid, m.p. 224-226 ºC (EtOH); IR (KBr, ν_{max}, cm^{-1}): 3378 (NH_2), 3234 (NH_2), 3054 (CH_{arom}), 2988 (CH_{aliph}), 2205 (CN), 1636. ^1H NMR (300 MHz, DMSO-d_6): δ 8.63 (bs, 1H), 7.43(d, 1H), 7.23 (d,1H), 6.99 (d, 1H), 6.91 (d, 1H), 6.72 (m, 1H), 5.87 (s, 1H), 3.84 (d, 6H), 2.59 (s, 3H). ^{13}C NMR (300 MHz, DMSO-d_6): δ 162 (C=C), 159 (C=C), 151 (C=C), 149 (C=C), 146 (C=C), 128 (C=C), 122 (C=C), 120 (C=C), 118 (CN), 108 (C=C), 102 (C=C), 75 (C=C), 55 (OCH_3), 35 (CH), 23 (CH_3).

RESULTS AND DISCUSSION

To evaluate the synthetic potential of the proposed procedure and to optimize the reaction conditions, the reaction of benzaldehyde, malononitrile and ethylactetoacetate was examined in different ratios under microwave irradiations. It was found that a slight excess of the malononitrile would be advantageous and therefore the molar ratio of benzaldyhe to ethylacetoacetate and malononitrile was kept at 1:1.1:2.1.

The reactions proceeded to completion almost instantaneously and the pure product was obtained by a simple purification using an acidic aqueous solution (0.1 N HCl), without using any chromatographic techniques. The products obtained from reaction between malononitrile, ethyl acetoacetate and other aromatic components are showed in Table-1. The maximum yield of 94 % was obtained for the product 4b. All the synthesized compounds were characterized by IR, ^1H and ^{13}C NMR.

TABLE-1
PYRANO[3,2-c]PYRIDINES DERIVATIVES, DHPPs (**4a-4m**)

Entrance	Ar	Yields (%)
4a	2,5-$(MeO)_2C_6H_3$	91
4b	2,4-$(MeO)_2C_6H_3$	94
4c	4-$(OH)C_6H_4$	90
4d	4-$(Me)C_6H_4$	85
4e	4-(F) C_6H_4	75
4f	4-$(Cl)C_6H_4$	78
4g	2-Cl-4-F-C_6H_4	73
4h	C_6H_5	86
4i	4-$(NO_2)C_6H_4$	81
4j	2-$(Me)C_6H_4$	65
4k	2-Thionyl	88
4l	2-$(NO_2)C_6H_4$	65
4m	3,4-$(MeO)_2C_6H_3$	88

Conclusion

The present study involved the synthesis of several new derivatives **4a-4m** by the direct condensation reaction of maleonitrile **3** with aldehyde **1** and ethylaceoacetate **2** by using a piperazine and solvent free system in microwave-assisted. The products were insoluble in various solvents such as H_2O, THF, *etc*.

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