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New methodology for the synthesis of 2-pyridones using basic Al_2O_3 as catalyst

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Abstract

A novel series of 2-pyridones derivatives have prepared by new multi-component reaction (MCR) in excellent yields. The first step of this methodology is the reaction of methylcetones **1a-c** with N, N-dimethylformamide dimethyl acetal under microwave irradiation affords the corresponding enaminone **2a-c** which is the key intermediary of our synthetic method. The second step is one pot reaction of enaminones with ethyl 2-cyanoacetate in the presence of basic Al_2O_3 as catalyst without solvent. Structural assignments are based on spectroscopic data (IR, ^{1}H NMR, ^{13}C NMR, mass spectra). This method has the advantage of short time, high yields and being environmentally-friendly.

Keywords: 2-pyridones, enaminones, multicomponent reactions, green chemistry.

1. Introduction

2-pyridones derivatives have attracted considerable attention because this skeleton is present in many compounds that have been isolated from natural substances [1, 2], with various biological activities, such as antibacterial and antifungal agents [3, 4]. Several methods have been developed in the literature for the synthesis of this structural motif [5-13]. In our current studies on the synthesis of 3-cyano-2-pyridones, we have reported a simple and new multicomponent reaction in the eco-friendly "green chemistry" economical and environmental conditions.
Recently, mulicomponent reaction (MCR) coupling in a one pot operation has received considerable interest due to generate molecular diversity and complexity [14, 15]. This work describe a new efficient and convenient method for the synthesis of 2-pyridone from enaminones under solvent-free conditions. Solvent-free

reactions represent very powerful green chemical technology procedures from both the economical and synthetic point of view. They not only reduce the burden of organic solvent disposal, but also enhance the rate of many organic reactions [16, 17].

In addition catalysis remains represent an important fields of green chemistry by providing atom-economical, selective, and energy efficient solutions to many industrially important problems. In the last decades, organic reactions using catalytic processes induced by heterogeneous catalysts especially under solvent-free conditions, have attracted much attention because of their enhanced selectivity, milder reaction conditions and associated ease of manipulation [18]. Departing from the previous literature, and as part of our continuing interest in the development of new synthetic methods in heterocyclic chemistry in our laboratory, we started the development of a new preparative procedure for this class of heterocyclic scaffold compounds [19]. Herein, we describe such an extremely simple and efficient synthesis of 2-pyridones using commercially available aluminium oxide (basic alumina) as a key catalyst for this reaction. Many synthetic methods have recently been explored using the basic alumina in the synthesis of bioactive heterocyclic compounds [20].

2. Experimental

2.1. Materials and methods

The melting points were measured using a Bank Kofler HEIZBANK apparatus standard WME 50-260°C and were uncorrected. IR spectra were obtained with solids with a Fourier transform Perkin Elmer Spectrum One with ATR accessory. Only significant absorptions are listed. The ^{1}H NMR spectra were recorded at 400 MHz, on a Brüker AC 400 spectrometers and ^{13}C NMR spectra were recorded in the same spectrometers at 100.6 MHz. Samples were registered in $CDCl_3$ solutions using TMS as an internal standard. The chemical shifts are expressed in δ units (ppm) and quoted downfield from TMS. Microwave irradiation experiments use a domestic microwave. The reactions are below illustrated for some examples:

2.2. Synthesis

General procedure 1: Synthesis of enaminone

An equimolar mixture of carbonyl compound **1a-c** (1 mmol) and (1 mmol) of DMFDMA was irradiated under microwave conditions for 5 min. After cooling, a yellow crystalline precipitate was formed, that was filtered off, washed with Et_2O and dried to give enaminones as a yellow solid.

3-(dimethylamino)-1-phenylprop-2-en-1-one 2a.

The general procedure 1, using (1.20 g, 1 mmol) of **1a** and (1.19 g, 1 mmol) of DMFDMA, gave 88% of compound **2a** as yellow solid, mp 90°C. ^{1}H NMR (400 MHz, $CDCl_3$): 7.90-7.87 (2H, m), 7.80 (1H, d, J_{H-H} = 12.40 Hz), 7.45-7.37 (3H, m), 5.71 (1H, d, J_{H-H} = 12.4 Hz), 3.12 (s, 3H), 2.91 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$):187.72, 153.24, 139.53, 129.85, 127.10, 126.47, 91.24, 44.00, 36.27. IR (neat, cm^{-1}): 1633, 1582. LCMS: m/z 175 (M^+, 34%), 158 (84), 98 (100). EIMS m/z (% relative abundance) 176 (M+H, 36), 98 (54), 77 (28). (ES-QTOF) Calcd f or $C_{11}H_{13}NO$ M+H 176.1123 Found 176.1117.

***General procedure 2: Synthesis of 2-Pyridones* $3a_i$-b_i**

A mixture of enaminones **2a-b** (2 mmol), primary amine (2 mmol), ethyl 2-cyanoacetate (2 mmol) and catalytic amount of Al_2O_3 were heated for a few hours. After cooling, the solid obtained was washed several times with diethyl ether to give 2-pyridone derivatives **$3a_i$-b_i.**

1,2-dihydro-1-methyl-2-oxo-4-phenylpyridine-3-carbonitrile $3a_1$.

The general procedure 2, using (0.35 g, 2 mmol) of **2a** and (0.07 g, 2 mmol) of methylamine, gave 93% of compound **$3a_1$** as white solid, mp 110°C. ^{1}H NMR (400 MHz, $CDCl_3$): 7.55 (d, 1H, J_{H-H} = 6.7 Hz), 7.51-7.50 (m, 5H), 6.62 (d, 1H, J_{H-H} = 6.4 Hz), 3.62 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 159.82, 158.87, 134.46, 129.69-127.00, 114.57, 106.04, 101.42, 37.12. IR (neat, cm^{-1}): 2220, 1645, 1597. EIMS m/z (% relative abundance) 211 (M+H, 31), 181(46). (ES-QTOF) Calcd f or $C_{13}H_{10}N_2O$ M+H 211.102 Found 211.089.

1-allyl-1, 2-dihydro-2-oxo-4-phenylpyridine-3-carbonitrile $3a_2$.

The general procedure 2, using (0.35 g, 2 mmol) **2a** and (0.11g, 2 mmol) of allylamine, gave 89 %

of compound **3a$_2$** as white solid, mp 99-100°C. ^{1}H NMR (400 MHz, $CDCl_3$): 7.61 (d, 1H), 7.53-7.49 (m, 5H), 6.36 (d, 1H, J_{H-H} = 6.7 Hz), 6.02-5.92 (m, 1H), 5.37-5.30 (m, 2H), 4.64-4.62 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 160.20, 159.78, 140.41, 135.46, 131.29-128.03, 120.29, 115.55, 107.26, 102.76, 51.26. IR (neat, cm^{-1}): 2216, 1634, 1591. EIMS m/z (% relative abundance) 237 (M+H, 75), 221 (54). (ES-QTOF) Calcd f or $C_{15}H_{11}N_2O$ M+H 237.091 Found 237.123.

1-benzyl-2-oxo-4-phenyl-1,2-dihydropyridine -3-carbonitrile 3a$_3$.

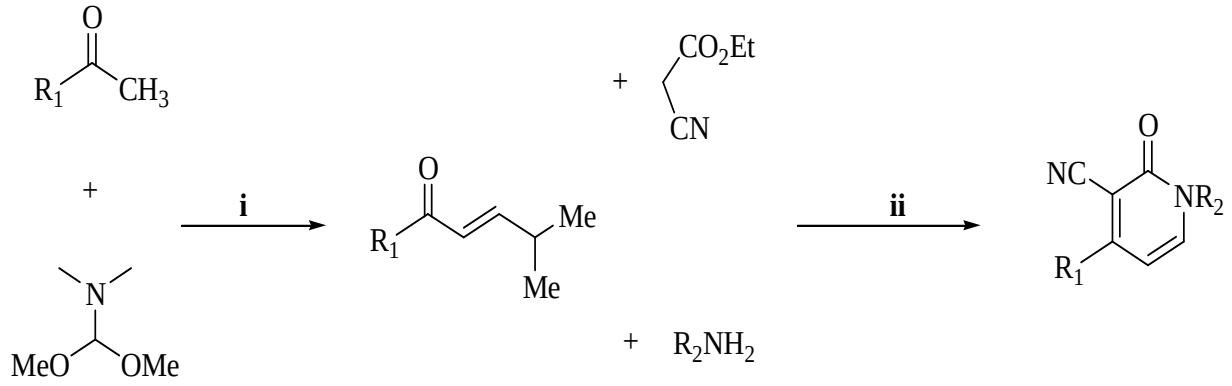
The general procedure 2, using (0.35 g, 2 mmol) **2a** and (0.22 g, 2 mmol) of benzylamine gave 96% of compound **3a$_3$** as white solid, mp 134°C. ^{1}H NMR (400 MHz, $CDCl_3$):7.60 (d, 1H, J_{H-H} = 7.2 Hz), 7.58-7.38(m, 2x5H), 6.31(d, 1H, J_{H-H} = 7.2 Hz), 5.19(s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$):160.55, 159.66, 140.44, 135.43, 134.96-128.71. IR (neat, cm^{-1}):2220, 1645, 1597. EIMS m/z (% relative abundance): 287 (M+H, 100), 91(65). HRMS (ES-QTOF) Calcd for $C_{19}H_{15}N_2O$ M+H 287.1184. Found 287.1189.

1-isopropyl-2-oxo-4-phenyl-1,2-dihydropyridine -3-carbonitrile 3a$_4$.

The general procedure 2, using (0.35 g, 2 mmol) **2a** and (0.22 g, 2 mmol) of (0.11g, 2 mmol) of isopropylamine gave 91% of compounds **3a$_4$** as white solid, mp 144°C. ^{1}H NMR (400 MHz, $CDCl_3$):7.57 (d, 1H, J_{H-H} = 6.8 Hz), 7.50-7.49 (m, 5H), 6.38 (d, 1H, J_{H-H} = 6.8 Hz), 5.31-5.24 (m, 1H), 1.42 (d, 6H, J_{H-H} = 7.2 Hz). NMR (100 MHz, $CDCl_3$): 160.27, 158.80, 136.85, 135.56-127.57, 115.86, 107.01, 102.34, 47.68, 21.78. IR (neat, cm^{-1}): 2219, 1640, 1592, 1571. EIMS m/z (% relative abundance): 239 (M+H, 86), 197 (100). HRMS (ES-QTOF) Calcd for $C_{15}H_{15}N_2O$ M+H 239.1184. Found 239.1192.

3. Result and discussion

Substituted 3-cyano-2-pyridones have been synthetized from enaminones by MCR using a catalytic amount of basic alumina (Al_2O_3), as figured in the following Scheme 1:



i: solvent-free, MW, (5-10 min) **ii: s**olvent-free, heat , 150 °C, (2-3 h)

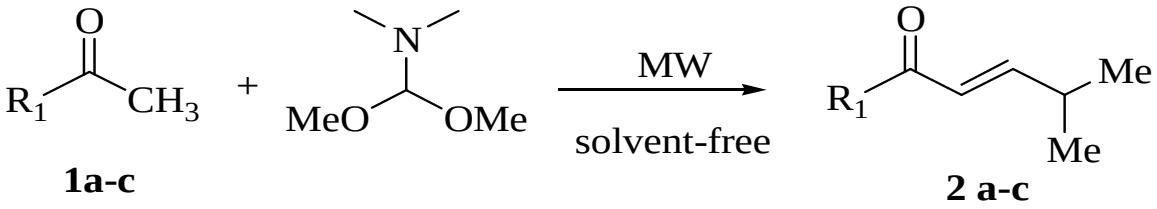
Scheme1. Synthesis of 2-pyridones

Enaminones are useful starting materials for the synthesis of heterocyclic compounds and their chemistry has recently received considerable attention [21-23]. Herein we have synthesized different enaminones by a clean procedure using MW irradiations (Scheme 2).

Firstly, enaminones **2a-c** were obtained from the reaction of methylcetones 1**a-c** with *N, N*-dimethylformamide-dimethylacetal (DMF-DMA) under solvent-free assisted by MW irradiations [24]. The yields obtained are very satisfactory 86-93% (Table 1).

These intermediates **2a-c** have been used as one of the key steps in the construction of the pyridone ring system. However, in second step of the synthesis of 2-pyridones we have developed a new MCR using Al_2O_3 as a clean catalyst; this reaction was shown in Scheme 3**.**

A mixture of enaminone **2a-c**, ethyl cyanoacetate, and primary amine in the presence of catalytic amount of basic Al_2O_3 was heated at 150°C for 2-3h for afforded the corresponding 2-pyridones in the excellent yields. The results of this reaction were showed in Table 2.



1a-c **2 a-c**

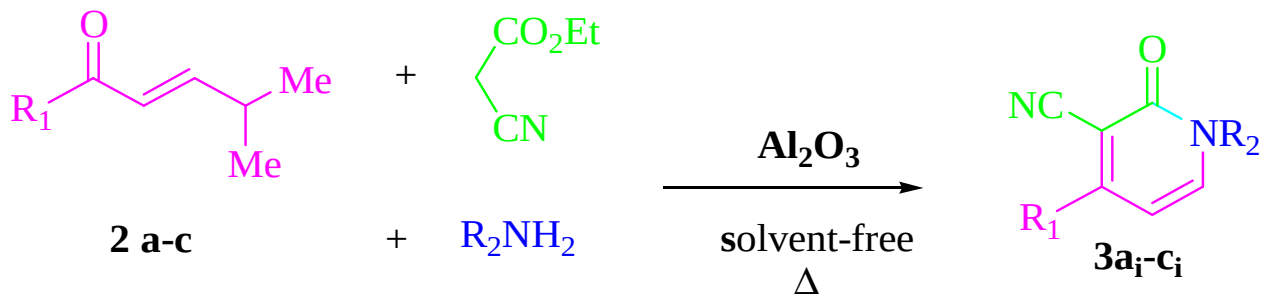
Scheme2. Synthesis of enaminones

Table 1: Synthesis of enaminones

Entry	R	Product	Yield (%)
1	C_6H_5-	**2a**	86
2	p-ClC_6H_4-	**2b**	93
3	p-$CH_3C_6H_4$-	**2c**	80

Table 2: Synthesis of 2-pyridones

Entry	Enaminone	R	Product	Yield (%)
4	**2a**	CH_3-	**$3a_1$**	93
5		CH_2=CH-CH_2-	**$3a_2$**	89
6		$C_6H_5CH_2$-	**$3a_3$**	96
7		$(CH_3)_2CH$-	**$3a_4$**	91
8	**2b**	CH_3-	**$3b_1$**	95
9		CH_2=CH-CH_2-	**$3b_2$**	93
10		$C_6H_5CH_2$-	**$3b_3$**	90
11		$(CH_3)_2CH$-	**$3b_4$**	98
12	**2c**	CH_3-	**$3c_1$**	88
13		CH_2=CH-CH_2-	**$3c_2$**	81
14		$C_6H_5CH_2$-	**$3c_3$**	85
15		$(CH_3)_2CH$-	**$3c_4$**	80



Scheme 3. The synthesis of pyridones using one-pot three components reaction

Conclusion

In conclusion, a simple and practical synthesis of 2-pyridones has been accomplished *via* the one-pot three component reaction in the presence of Al_2O_3 as catalyst. The reactions were carried out in neat and under solvent-free conditions to afford the expected products in good yields. The methodology provides an easy access to the synthesis of 2-pyridones from enaminones. Short reaction times, easy procedure and work up of the reactions, make this procedure a suitable method for this type of heterocyles. Our approach for the construction of pyridones ring system is novel and opens a new avenue for generation of molecular diversity, employing economical reagents without use of solvent.

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