KF/Al_2O_3: As a Solid Phase and Recyclable Basic Catalyst for Synthesis Mono and Bis Pyrimidine Derivatives

Abaszadeh, Mehdi*+

Pharmaceutics Research Center, Institute of Neuropharmacology, Kerman University of Medical Sciences, Kerman, I.R. IRAN

Seifi, Mohammad

Department of Chemistry, Faculty of Sciences, Najafabad Branch, Islamic Azad University, Najafabad, I.R. IRAN

ABSTRACT: *KF/Al_2O_3 as a green and efficient catalyst has been used for the synthesis of mono and bis pyrimidine derivatives via three-component reaction of amidines, malononitrile, and aldehydes in EtOH at reflux. The great advantage of this catalyst is the ease of handling. KF/Al_2O_3 can be used and removed by filtration, avoid cumbersome aqueous workups and decrease solvent waste handling issues. The additional benefit is achieved by taking advantage of the strongly basic nature of KF/Al_2O_3, which allows replacing organic bases in the reaction. A number of advantages are with this method such as no special handing necessity of catalyst, easy monitoring of reaction process, convenient workup procedure and high yields in short reaction times.*

KEYWORDS: *KF/Al_2O_3; Solid phase and recyclable basic catalyst; Mono and bis pyrimidine derivatives; Three-component reaction.*

INTRODUCTION

Recently, solid phase reagents have been preferred for carrying out various chemical transformations due to the good activation of adsorbed compounds, increase in reaction rate, selectivity, milder reaction conditions and easier workup [1]. Potassium fluoride on alumina is one of the most interesting of these reagents because it has surface properties which suggest that very rich organic reactions may occur there. KF/Al_2O_3 is an inexpensive and commercially available reagent which due to its strongly basic nature it has been used as a replacement for organic bases in a number of organic reactions, such as epoxidation [2], Michael addition [3], aldol condensation [4], rearrangement processes [5], cycloaddition reactions [6, 7], multicomponent reactions [8-11], for conversion of aldoximes into nitriles [12], α-phenylselenenylation of aldehydes and ketones [13] and synthesis of nitriles from aldehydes [14].

Multi-Component Reactions (MCRs) are efficient and effective methods to synthesis complex molecules with special synthetic yield, frequently with high stereoselectivity, easily accessible reactants [15-17]. The characteristic aspect of MCRs is that the final products contain almost all portions of substrates, generating almost no by-products, which make MCRs an extremely ideal and eco-friendly reaction system to produce many organic compounds [18-21].

It is not admiring that the synthesis of polyfunctionalized heterocyclic compounds has received substantial attention

* *To whom correspondence should be addressed.*
+ *E-mail: abaszadeh@kmu.ac.ir*
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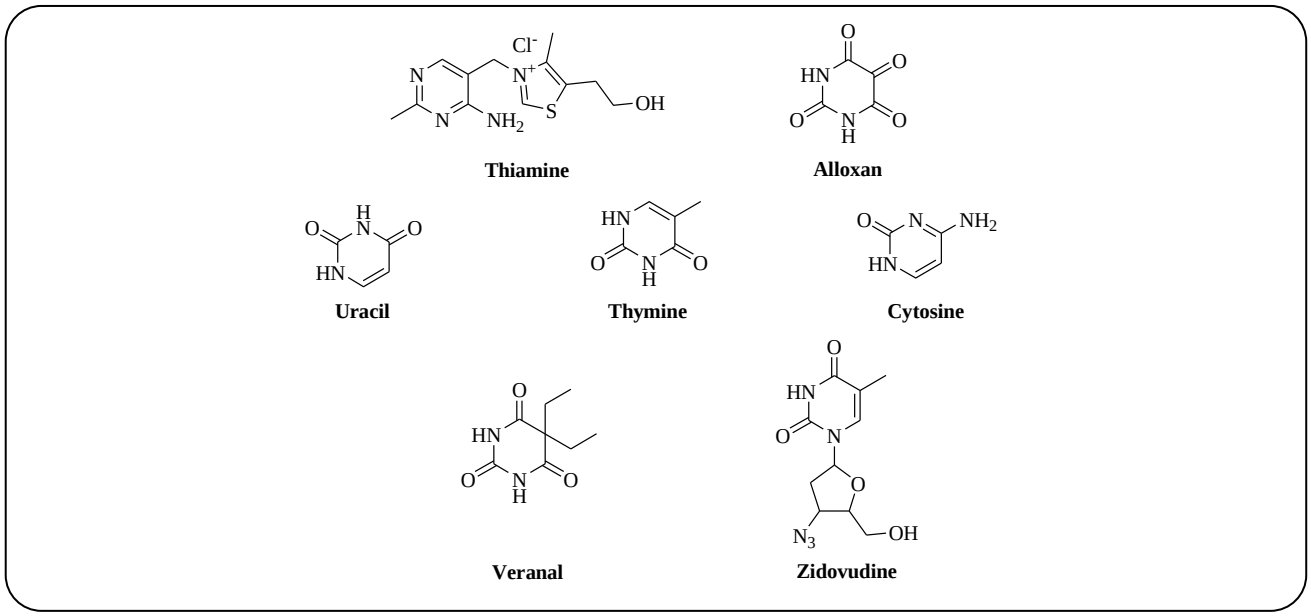


Scheme 1: Pyrimidine in nature and in synthetic compounds.

because polyfunctionalized heterocyclic compounds play important roles in the synthesis of a large number of biologically active molecules [22-25]. In recent years, a great deal of research in polyfunctionalized heterocyclic compounds paid to the synthesis of bis-heterocyclic compounds which show various biological activities, such as antibacterial, fungicidal, tuberculostatic, antiamoebic properties [26-28]. Among those, pyrimidine derivatives have recovered much attention in recent years due to their notable molecular structures and their important biological activities.

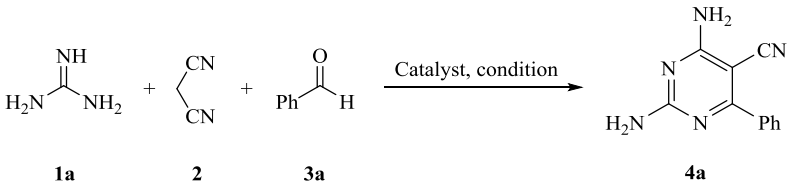
Pyrimidine is one of the most common *N*-heteroaromatic compounds containing two nitrogen atoms has widely appeared in nature as substituted and ring fused compounds and derivatives, including the thiamine (vitaminB1) and alloxan (Scheme 1) [29]. Several pyrimidines mainly uracil, thymine, and cytosine (Scheme 1) have been isolated from the nucleic acid hydrolyses [30]. It is also found in many synthetic compounds such as veranal which is used as hypnotics [31] and the HIV drug, zidovudine [32] (Scheme 1). In addition to this, pyrimidines ring demonstrate a diverse array of biological and pharmacological activities including, antibacterial [33], analgesics [34], antipyretics [35], anti-inflammatory [36], antifungal [37], and anticancer [38] properties.

There are various catalytic system to synthesis of pyrimidine derivatives by MCRs, such as sodium acetate [39, 40], potassium carbonate in the presence of tetrabutylammonium bromide (TBAB) [41], high surface area MgO (HSA-MgO) [42], copper oxide nanocatalyst [43] and $Bi(NO_3)_3.5H_2O$ and a catalytic amount of Et_3N [44]. But these systems have some disadvantage like the use of toxic organic solvents, costly catalysts, the existence of transition metals, time-consuming reaction, and low yield. Herein we used KF/Al_2O_3 as catalyst for the synthesis of 4-amino-5-pyrimidine-carbonitrile derivatives to remove the above-mentioned drawbacks. We consider the synthesis of compound 2,4-diamino-6-phenylpyrimidine-5-carbonitrile (**4a**) for a representative example to show the advantage of this work in comparison with previously reported procedures. As shown in Table 1, our catalyst produces compound **4a** with high yield in a short time than others. Also, KF/Al_2O_3 is a recyclable catalyst and ethanol was used as a green solvent. Moreover, KF/Al_2O_3 is more stable in air and non-toxic compared with other catalysts.

EXPERIMENTAL SECTION

Melting points were measured on a Electrothermal-9100 apparatus and are uncorrected. IR spectra were recorded on a Brucker FT-IR Tensor 27 infrared spectrophotometer. ^1H NMR and spectra were recorded on an Avance III 400 MHz Bruker spectrometer. ^{13}C NMR spectra were recorded on the same instruments at 100 MHz using TMS as an internal standard respectively.

Table 1: Comparison results of KF/Al_2O_3 with other catalysts reported in the literature for the synthesis of compound 4a.



1a **2** **3a** **4a**

Entry	Catalyst	Condition	Recyclability	Time (min)	Yield (%)
1	CH_3COONa	H_2O/C_2H_5OH, reflux	No	300	81 [39]
2	K_2CO_3/TBAB	H_2O, reflux	No	240	63 [41]
3	HSA-MgO	CH_3CN, reflux	No	15	88 [42]
4	Nano-CuO	H_2O, r.t.	Yes (5 cycles)	15	93 [43]
5	$Bi(NO_3)_3.5H_2O/Et_3N$	CH_3CN, reflux	No	4	83 [44]
6	KF/Al_2O_3	EtOH, reflux	Yes (4 cycles)	5	94 [This work]

Elemental analyses were performed using a Heracus CHN-O-Rapid analyzer.

Preparation of KF/Al_2O_3

A mixture of KF (5 mmol) and Al_2O_3 (5 mmol) was ground vigorously in a mortar to give the KF/Al_2O_3 reagent as a white powder (0.800 g) [45].

General procedure for the preparation of mono and bis 4-amino-5-pyrimidine-carbonitrile derivatives (4a-v)

A mixture of amidines (**1a-c**) (2 mmol), malononitrile (**2**) (2 mmol), aromatic aldehydes (**3a-g**) (2 mmol) (if terephthaldialdehyde or isophthaldialdehyde (**3h, 3i**) (1 mmol)), and KF/Al_2O_3 (30 mol%) in ethanol (10 mL) was refluxed for the time reported in Table 3 (the progress of the reaction being monitored by TLC and was used hexane/ethyl acetate as an eluent). After completion of the reaction, the catalyst was separated by a simple filtration from the reaction mixture. Then the reaction mixture was poured into ice-cold water; the crude product was filtered, dried, and recrystallized from ethanol.

2,4-Diamino-6-(furan-2-yl)pyrimidine-5-carbonitrile (4k)

Brown powders; IR (KBr, *v* max/cm^{-1}): 3392-3200 ($2NH_2$), 2192 (CN), 1619 (C=N), 1587 (C=C). ^{1}H NMR (400 MHz, DMSO-d_6): 8.11 (d, 1H, $^3J_{HH}$=8 Hz, CH-Ar), 8.01-7.59 (m, 4H, CH-Ar, NH_2), 7.37 (s, 2H, NH_2). ^{13}C NMR (100 MHz, DMSO-d_6): 170.14, 166.08, 163.58, 151.22, 142.35, 131.62, 126.14, 114.31 (CN), 84.69 (C5). Anal. calcd. for $C_9H_7N_5O$: C, 53.73; H, 3.51; N, 34.81 %. Found: C, 53.74; H, 3.33; N, 34.63 %.

4-Amino-6-(furan-2-yl)-2-phenylpyrimidine-5-carbonitrile (4l)

Orange powders; IR (KBr, *v* max/cm^{-1}): 3392, 3216 (NH_2), 2176 (CN), 1607 (C=N), 1593 (C=C). ^{1}H NMR (400 MHz, DMSO-d_6): 8.39 (d, 2H, $^3J_{HH}$=8 Hz, CH-Ar), 8.07 (d, 1H, $^3J_{HH}$=8 Hz, CH-Ar), 7.78-6.87 (m, 7H, CH-Ar, NH_2). ^{13}C NMR (100 MHz, DMSO-d_6): 170.69, 166.34, 164.27, 152.13, 141.47, 135.65, 132.27, 128.36, 127.25, 122.58, 121.44, 114.15 (CN), 85.47 (C5). Anal. calcd. for $C_{15}H_{10}N_4O$: C, 68.69; H, 3.84; N, 21.36 %. Found: C, 68.51; H, 3.66; N, 21.17 %.

4-Amino-6-(furan-2-yl)-2-methylpyrimidine-5-carbonitrile (4m)

Red powders; IR (KBr, *v* max/cm^{-1}): 3360, 3312 (NH_2), 2176 (CN), 1619 (C=N), 1584 (C=C). ^{1}H NMR (400 MHz, DMSO-d_6): 8.24 (d, 1H, $^3J_{HH}$=8 Hz, CH-Ar), 8.09-7.89 (m, 2H, CH-Ar), 7.59 (s, 2H, NH_2), 2.47 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): 170.02, 167.65, 163.58, 151.14, 136.20, 135.17, 128.11, 114.35 (CN), 84.78 (C5), 24.93 (CH_3). Anal. calcd. for

$C_{10}H_8N_4O$: C, 59.99; H, 4.03; N, 27.99 %. Found: C, 59.81; H, 3.85; N, 27.80 %.

2,4-Diamino-6-(thiophen-2-yl)pyrimidine-5-carbonitrile (4n)

Red powders; IR (KBr, *v* max/cm^{-1}): 3328-3200 ($2NH_2$), 2192 (CN), 1616 (C=N), 1590 (C=C). ^{1}H NMR (400 MHz, DMSO-d_6): 7.97-7.39 (m, 5H, CH-Ar, NH_2), 7.01 (s, 2H, NH_2). ^{13}C NMR (100 MHz, DMSO-d_6): 170.24, 165.88, 163.47, 141.40, 132.27, 129.25, 126.01, 113.89 (CN), 84.57 (C5). Anal. calcd. for $C_9H_7N_5S$: C, 49.76; H, 3.25; N, 32.24 %. Found: C, 49.56; H, 3.06; N, 32.25 %.

4-Amino-2-methyl-6-(thiophen-2-yl)pyrimidine-5-carbonitrile (4p)

Orange powders; IR (KBr, *v* max/cm^{-1}): 3344, 3232 (NH_2), 2176 (CN), 1607 (C=N), 1593 (C=C). ^{1}H NMR (400 MHz, DMSO-d_6): 8.01 (d, 1H, $^3J_{HH}$=8 Hz, CH-Ar), 7.92 (d, 1H, $^3J_{HH}$=8 Hz, CH-Ar), 7.68-7.35 (m, 3H, CH-Ar, NH_2), 2.27 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): 171.25, 166.98, 163.22, 144.75, 135.22, 129.67, 121.33, 114.25 (CN), 85.34 (C5), 25.12 (CH_3). Anal. calcd. for $C_{10}H_8N_4S$: C, 55.54; H, 3.73; N, 25.91 %. Found: C, 55.36; H, 3.55; N, 25.73 %.

6,6'-(1,4-Phenylene) bis(2,4-diaminopyrimidine-5-carbonitrile) (4q)

Orange powders; IR (KBr, *v* max/cm^{-1}): 3344-3200 ($2NH_2$), 2192 (CN), 1622 (C=N), 1580 (C=C). ^{1}H NMR (400 MHz, DMSO-d_6): 7.92-7.06 (m, 8H, $2NH_2$, CH-Ar), 6.53 (s, 4H, $2NH_2$). ^{13}C NMR (100 MHz, DMSO-d_6): 168.19, 164.77, 159.36, 137.28, 122.29, 115.07 (CN), 84.08 (C5). Anal. calcd. For $C_{16}H_{12}N_{10}$: C, 55.81; H, 3.51; N, 40.68 %. Found: C, 55.62; H, 3.33; N, 40.50 %.

6,6'-(1,3-Phenylene) bis(2,4-diaminopyrimidine-5-carbonitrile) (4t)

Yellow powders; IR (KBr, *v* max/cm^{-1}): 3344-3200 ($2NH_2$), 2192 (CN), 1616 (C=N), 1558 (C=C). ^{1}H NMR (400 MHz, DMSO-d_6): 7.89-7.23 (m, 8H, $2NH_2$, CH-Ar), 6.67 (s, 4H, $2NH_2$). ^{13}C NMR (100 MHz, DMSO-d_6): 168.10, 164.70, 159.94, 137.19, 126.63, 114.87 (CN), 84.13 (C5). Anal. calcd. For $C_{16}H_{12}N_{10}$: C, 55.81; H, 3.51; N, 40.68 %. Found: C, 55.63; H, 3.32; N, 40.50 %.

6,6'-(1,3-Phenylene) bis(4-amino-2-phenylpyrimidine-5-carbonitrile) (4u)

Yellow powders; IR (KBr, *v* max/cm^{-1}): 3360, 3216 (NH_2), 2176 (CN), 1619 (C=N), 1574 (C=C). ^{1}H NMR (400 MHz, DMSO-d_6): 8.45 (s, 4H, $2NH_2$), 7.79-7.12 (m, 14H, CH-Ar). ^{13}C NMR (100 MHz, DMSO-d_6): 168.69, 166.02, 162.35, 141.80, 136.58, 133.25, 129.07, 128.67, 126.38, 125.94, 121.25, 115.01 (CN), 84.20 (C5). Anal. calcd. For $C_{28}H_{18}N_8$: C, 72.09; H, 3.89; N, 24.02 %. Found: C, 71.90; H, 3.71; N, 23.83 %.

6,6'-(1,3-Phenylene) bis(4-amino-2-methylpyrimidine-5-carbonitrile) (4v)

Yellow powders; IR (KBr, *v* max/cm^{-1}): 3344, 3200 (NH_2), 2176 (CN), 1628 (C=N), 1545 (C=C). ^{1}H NMR (400 MHz, DMSO-d_6): 8.84 (s, 4H, $2NH_2$), 8.04-7.75 (m, 4H, CH-Ar), 2.47 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): 168.10, 164.77, 161.01, 139.97, 137.38, 128.54, 126.63, 114.49 (CN), 84.25 (C5), 26.49 (CH_3). Anal. calcd. For $C_{18}H_{14}N_8$: C, 63.15; H, 4.12; N, 32.73 %. Found: C, 62.96; H, 3.94; N, 32.54 %.

RESULTS AND DISCUSSION

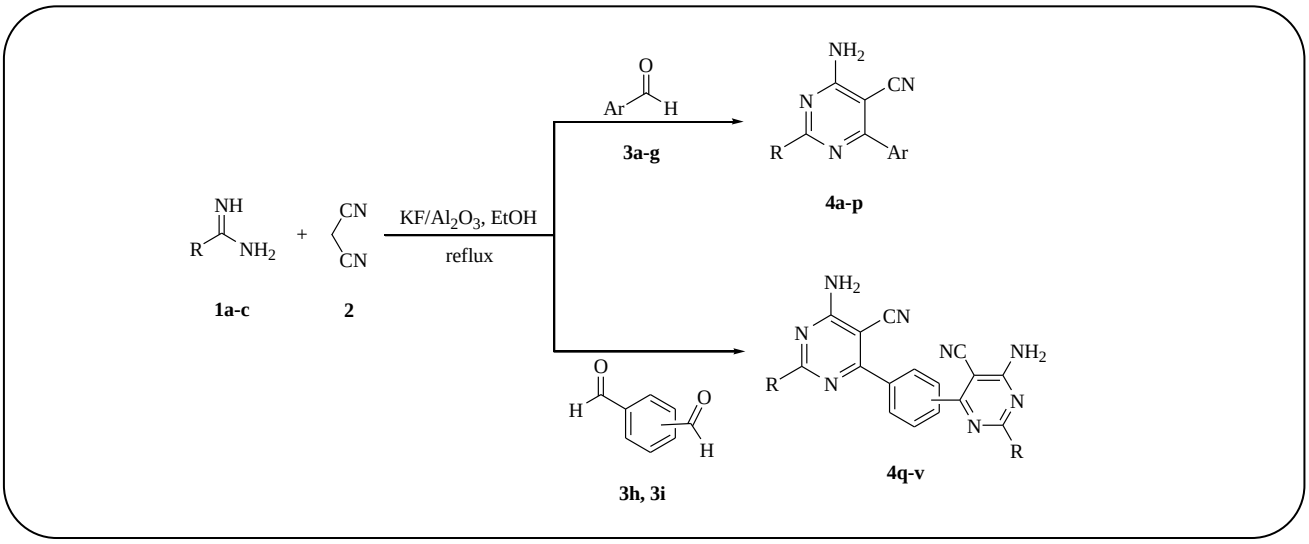
In continuation of our previous works on environmentally friendly multi-component reactions [46-49], we have synthesized a series of mono and bis 4-amino-5-pyrimidine-carbonitrile derivatives (**4a-v**) *via* three-component reaction of amidines (**1a-c**), malononitrile (**2**) and aldehydes (**3a-i**) in presence of KF/Al_2O_3 in EtOH at reflux (Scheme 2).

In order to optimize the reaction conditions, we used some polar and nonpolar solvents in the three-component reaction of guanidine **1a**, malononitrile **2** and benzaldehyde **3a** in the presence of 30 mol% KF/Al_2O_3 as model reactions to examine the effects of solvent for preparing compound **4a**. In each case, the substrates were mixed together with 30 mol% KF/Al_2O_3 agitated with 10 mL solvent under reflux. The results are shown in Table 2 (entry 1-4). The best results in terms of reaction time and yield of the desired product **4a** was obtained when the reaction was carried out in ethanol.

We also optimized the quantity of catalysts. The best results were obtained when the reactions were carried out in the presence of 30 mol% KF/Al_2O_3. The results are shown in Table 2 (entry 5-8).

Table 2: Optimization of the model reaction between guanidine 1a, malononitrile 2 and benzaldehyde 3a.

Entry	Solvent	Catalyst (mol %)	Time (min)	Yield (%)
1	EtOH*	30	5	94
2	CH_3CN	30	30	85
3	EtOAc	30	45	82
4	Toluene	30	60	55
5	EtOH	10	15	88
6	EtOH	20	10	90
7	EtOH	25	7	92
8	EtOH	35	5	94
9[a]	EtOH	30	7	92
10[b]	EtOH	30	10	91
11[c]	EtOH	30	15	90
12[d]	EtOH	30	15	88



Scheme 2: Synthesis of mono and bis 4-amino-5-pyrimidine-carbonitrile derivatives.

We also attempted to reuse the catalyst. After each cycle, the catalyst was recovered by simple filtration, washed with hot ethanol, dried and was used directly in the next cycle. As shown in Table 2 (entry 9-12) after the four cycle catalyst was still highly efficient.

According to the results obtained up to this point, we decided to apply this method for synthesis of mono and bis 4-amino-5-pyrimidine-carbonitrile derivatives (**4a-v**) *via* three-component reaction of amidines (**1a-c**), malononitrile (**2**) and aldehydes (**3a-i**) in the presence of 30 mol% KF/Al_2O_3 in EtOH at reflux (Table 3).

CONCLUSIONS

In this study, new applications of basic, solid phase KF/Al_2O_3 for the synthesis of mono and bis 4-amino-5-pyrimidine-carbonitrile derivatives *via* three-component

Table 3: The three-component reaction of amidines (1a-c), malononitrile (2) and aldehydes (3a-i).

Compd. No.	R	Ar	Time (min)	Yield (%)	M. P. observed (°C)	M. P. reported (°C)
4a	NH_2	C_6H_5	5	94	287-288	288-300 [39]
4b	Ph	C_6H_5	7	92	209-211	210-212 [39]
4c	NH_2	4-CH_3-C_6H_4	8	92	127-129	130 [39]
4d	Ph	4-CH_3-C_6H_4	10	91	209-211	210 [39]
4e	NH_2	4-CH_3O-C_6H_4	10	90	237-239	240 [41]
4f	Ph	4-CH_3O-C_6H_4	12	89	211-213	213 [39]
4g	NH_2	4-Cl-C_6H_4	4	95	227-230	229-231 [39]
4h	Ph	4-Cl-C_6H_4	5	93	220-222	222 [39]
4i	NH_2	4-Br-C_6H_4	5	95	237-239	>240 (dec.) [39]
4j	Ph	4-Br-C_6H_4	7	93	234-235	235-238 [39]
4k	NH_2	Furan-2-yl	10	91	>165 (dec.)	——
4l	Ph	Furan-2-yl	12	90	173-176	——
4m	CH_3	Furan-2-yl	12	90	>198 (dec.)	——
4n	NH_2	Thiophen-2-yl	10	90	125-128	——
4o	Ph	Thiophen-2-yl	12	89	197-198	200 [39]
4p	CH_3	Thiophen-2-yl	12	90	148-150	——
4q	NH_2	Terephthaldialdehyde	15	90	263 (dec.)	——
4r	Ph	Terephthaldialdehyde	18	89	>300	>300 [50]
4s	CH_3	Terephthaldialdehyde	18	90	>300	>300 [50]
4t	NH_2	Isophthaldialdehyde	15	89	248-250	——
4u	Ph	Isophthaldialdehyde	18	87	159-162	——
4v	CH_3	Isophthaldialdehyde	18	88	201-203	——

the reaction of amidines, malononitrile, and aldehydes are explained. KF/Al_2O_3 catalyst offers a simple, novel, and convenient method for this reaction. High yields, short reaction time, easy work-up and reusability of the catalyst are advantages of this procedure.

Acknowledgements

The authors express their great appreciation to Pharmaceutics Research Center, Institute of Neuropharmacology, Kerman University of Medical Sciences for supporting this investigation.

Received :Dec. 12, 2015 ; Accepted : Oct. 18, 2016

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