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KF/Al_2O_3 AS A RECYCLABLE BASIC CATALYST FOR 1,3-DIPOLAR CYCLOADDITION REACTION: SYNTHESIS OF INDOLIZINE-1-CARBONITRILE DERIVATIVES

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Abstract: KF/Al_2O_3 as a green and efficient catalyst has been used for synthesis of indolizine-1-carbonitrile derivatives. It can be proceeded by using 1,3-dipolar cycloaddition reaction of 1-alkyl-2-chloropyridinium bromides, malononitrile and benzaldehyde in ethanol, at reflux. The great advantage of this catalyst is the ease of handling. KF/Al_2O_3 can be used and removed by filtration, avoiding cumbersome aqueous workups and decreasing solvent waste handling issues. High conversions, short reaction times and a cleaner reaction profiles are some of the outstanding advantages of this method.

***Keywords*:** KF/Al_2O_3, indolizine-1-carbonitrile derivatives, 1,3-dipolar cycloaddition reaction, 1-alkyl-2-chloropyridinium bromides.

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

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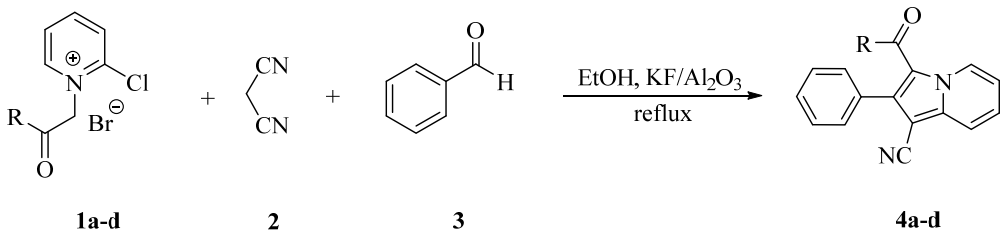
and easier workup.[1] Potassium fluoride on alumina is one of the most interesting of these reagents because it has surface properties which suggest that very rich organic reactions may occur there. KF/Al_2O_3 is an inexpensive and commercially available reagent which due to its strongly basic nature 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]

Biological and pharmacological applications of numerous and diverse indolizine derivatives have made them as of interest heterocyclic compounds to work on.[8-10]

Many substituted indolizine derivatives have shown biological activities such as anti-inflammatory,[11] antioxidant,[12] anticancer,[13] antitubercular,[14] antimicrobial,[15] analgesic[16] activities *etc*. In addition, a group that synthesizes indolizine derivatives, used these compounds for production of organic fluorescent substances,[17] dyes[18] and so on. Recently, synthesis of indolizine derivatives has received lots of attention leading to numerous synthetic pathways including chichibabin reaction,[19] multicomponent reactions[20] and acetic acid-assisted intramolecular annulations.[21] 1,3-Dipolar cycloaddition reactions of pyridinium ylides with activated alkenes[22] and alkynes[23] are one of the most important methods for constructing indolizine derivatives.

Due to the increasing use of the indolizine derivatives in the organic, medicinal and pharmaceutical chemistry, an efficient developed method for the synthesis of these compounds have often been noted. Here, we have investigated a two-step tandem reaction for the synthesis of mono indolizine-1-carbonitrile derivatives (**4a-d**) by using 1,3-dipolar cycloaddition reaction of 1-alkyl-2-chloropyridinium bromides (**1a-d**),

malononitrile (**2**) and benzaldehyde (**3**) at reflux, in the presence of KF/Al_2O_3 in ethanol (Scheme **1**).



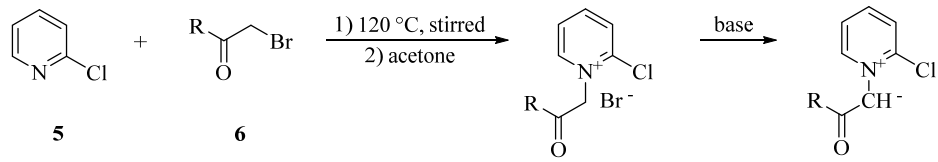
1a-d **2** **3** **4a-d**

a: R= C_6H_5
b: R= 4-Br-C_6H_4
c: R= OCH_3
d: R= 4-OCH_3-C_6H_4

Scheme 1. Synthesis of indolizine-1-carbonitrile derivatives.

Results and Discussion

First, 1-alkyl-2-chloropyridinium bromides (**1a-d**) which were produced by reaction of 2-chloropyridine (**5**) with halogenated reagent (**6**), have found applications as reagents in the organic synthesis of other classes of substances. The most striking examples are 1-alkyl-2-chloropyridinium bromides (**1a-d**), readily forming ylides (**Ia-d**) with bases, to undergo 1,3-dipolar cycloaddition reactions (Scheme **2**).



5 **6** **1a-d** **Ia-d**

Scheme 2. Synthesis of 1-alkyl-2-chloropyridinium bromides and forming ylides.

Then, the reaction between 2-chloro-1-(2-oxo-2-phenylethyl)pyridin-1-ium bromide (**1a**), malononitrile (**2**) and benzaldehyde (**3**) was chosen as a

model to optimize the reaction conditions. This reaction was carried out in different solvents such as ethanol, acetonitrile and dichloromethane (Table **1**, entries 1-9), in the presence of KF/Al_2O_3, triethylamine and potassium carbonate as base (Table**1**, entries 1-9). When tandem reaction was carried out at reflux, in the presence of KF/Al_2O_3 in ethanol, the 3-benzoyl-2-phenylindolizine-1-carbonitrile (**4a**) was obtained in 93 % yield within 25 min (Table**1**, entries 1).

Table 1. Optimization of the model reaction between 2-chloro-1-(2-oxo-2-phenylethyl)pyridin-1-ium bromide (**1a**), malononitrile (**2**) and benzaldehyde (**3**).

Entry	Solvent	Base	Time (min)	Yield (%)
1	EtOH	KF/Al_2O_3	25	93
2	EtOH	Et_3N	35	89
3	EtOH	K_2CO_3	40	87
4	CH_3CN	KF/Al_2O_3	35	90
5	CH_3CN	Et_3N	42	87
6	CH_3CN	K_2CO_3	48	86
7	CH_2Cl_2	KF/Al_2O_3	40	88
8	CH_2Cl_2	Et_3N	48	83
9	CH_2Cl_2	K_2CO_3	60	80

We have done previously synthesis of indolizines by using 1,3-dipolar cycloaddition reaction of 2-chloropyridinium bromides (**1a-c**) with 2-benzylidenemalononitrile (**II**) under ultrasound irradiation at room temperature in the presence of triethylamine in acetonitrile.[24] But for the synthesis of further derivatives of these compounds and fix problems, we developed this method and used reaction of 1-alkyl-2-chloropyridinium

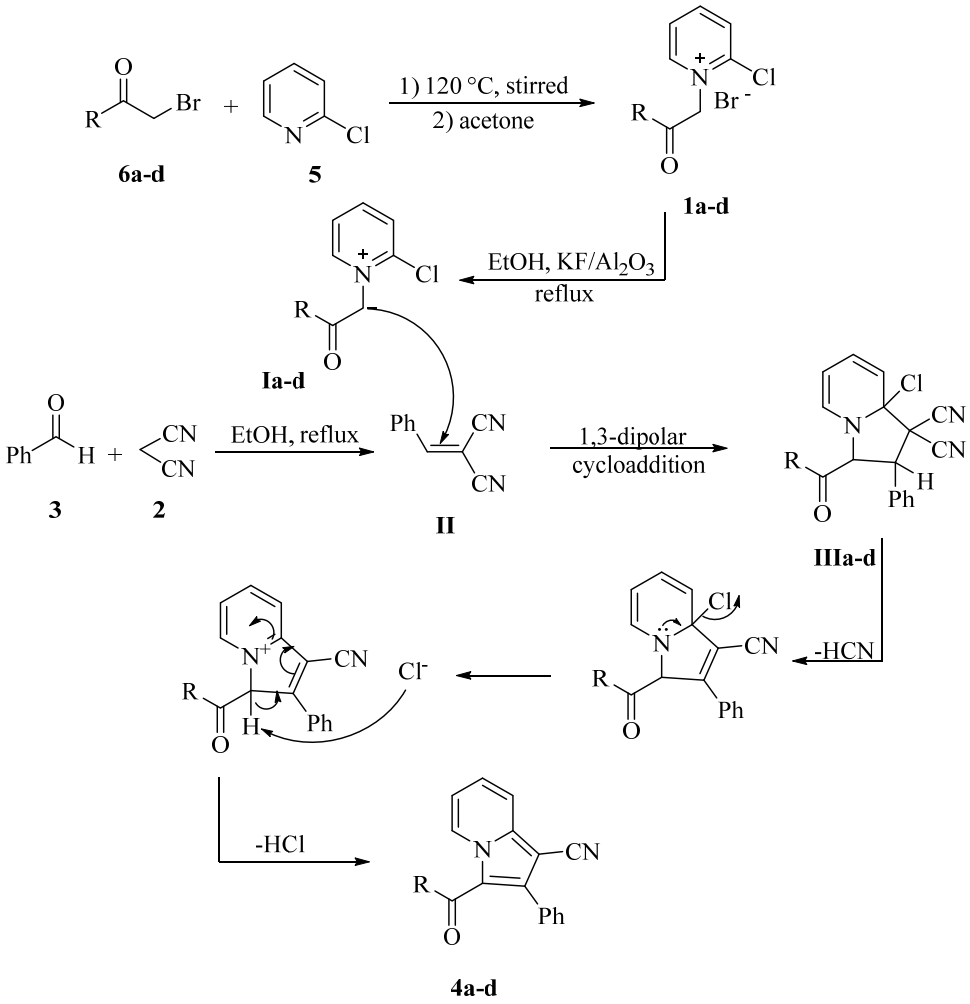
bromides (**1a-d**), malononitrile (**2**) and benzaldehyde (**3**) at reflux, in the presence of KF/Al_2O_3 in ethanol (Scheme **1**).

According to the results obtained up to this point, we decided to apply this method for synthesis of mono indolizine-1-carbonitrile derivatives (**4a-d**) by using 1,3-dipolar cycloaddition reaction of 1-alkyl-2-chloropyridinium bromides (**1a-d**), malononitrile (**2**) and benzaldehyde (**3**) at reflux, in the presence of KF/Al_2O_3 in ethanol (Table **2**).

Table 2. 1,3-Dipolar cycloaddition reaction of 1-alkyl-2-chloropyridinium bromides (**1a-d**), malononitrile (**2**) and benzaldehyde (**3**).

Compd.No.	R	Time (min)	Yield (%)	M. P. observed (°C)	M. P. reported (°C)
4a	C_6H_5	25	93	223-225	223-225 [24]
4b	4-Br-C_6H_4	28	92	180 (dec.)	180 (dec.) [24]
4c	OCH_3	30	92	160-162	160-162 [24]
4d	4-OCH_3-C_6H_4	25	91	195 (dec.)	-

To explain the mechanism of this one-pot two-step tandem reaction, we propose a plausible reaction mechanism which is illustrated in Scheme **3**. In the first step the 1-alkyl-2-chloropyridinium bromides (**1a-d**) converts to ylides (**Ia-d**) by deprotonation using KF/Al_2O_3. The second step, which is a Knoevenagel condensation, takes place to form the 2-benzylidenemalononitrile (**II**). The reaction was performed in ethanol at reflux for about 5 min. The third step is a 1,3-dipolar cycloaddition involving ylides (**Ia-d**) and 2-benzylidenemalononitrile (**II**) to afford the intermediate (**IIIa-d**), followed by the elimination of HCN and HCl to yield the desired indolizine-1-carbonitrile derivatives (**4a-d**).



Scheme 3. Plausible mechanism for synthesis of indolizine-1-carbonitrile derivatives.

Experimental

General

Melting points were measured on an Electrothermal-9100 apparatus and are uncorrected. IR spectra were recorded on a Brucker FT-IR Tensor 27 infrared spectrophotometer. ^{1}H NMR spectra were recorded on a Brucker Avance III 300 MHz spectrometer. ^{13}C NMR spectra were recorded on the same instruments at 75 MHz using TMS as an internal standard

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

Typical procedure for the preparation of 1-alkyl-2-chloropyridinium bromides **(1a-d):**

A solution of 2-chloropyridine (**5**) (10 mmol) and halogenated reagent (**6**) (10 mmol) was stirred at 120 °C for 240 min. Then, the reaction mixture was cooled and 30 mL acetone was added and the resulting precipitate was collected by filtration.

2-Chloro-1-(2-oxo-2-phenylethyl)pyridin-1-ium bromide **(1a):**

White powders; yield: 75%. mp 187 °C; IR (KBr, ν_{max}/cm^{-1}): 1695 (C=O), 1632 (C=N), 1593 (C=C). ^{1}H NMR (300 MHz, D_2O) δ_{ppm}: 9.19 (d, 1H, J=6Hz, Ar), 9.04-7.20 (m, 8H, Ar), 6.30 (s, 2H, CH_2).

1-(2-(4-Bromophenyl)-2-oxoethyl)-2-chloropyridin-1-ium bromide **(1b):**

White powders; yield: 77%. mp 194 °C; IR (KBr, ν_{max}/cm^{-1}): 1688 (C=O), 1619 (C=N), 1593 (C=C). ^{1}H NMR (300 MHz, D_2O) δ_{ppm}: 9.08 (d, 1H, J=6Hz, Ar), 8.89-7.38 (m, 7H, Ar), 6.29 (s, 2H, CH_2).

2-Chloro-1-(2-methoxy-2-oxoethyl)pyridin-1-ium bromide **(1c):**

White powders; yield: 72%. mp 194 °C; IR (KBr, ν_{max}/cm^{-1}): 1697 (C=O), 1633 (C=N), 1591 (C=C). ^{1}H NMR (300 MHz, D_2O) δ_{ppm}: 9.04 (d, 1H, J=6Hz, Ar), 8.89-7.97 (m, 3H, Ar), 6.27 (s, 2H, CH_2) 3.59 (s, 3H, OCH_3).

2-Chloro-1-(2-(4-methoxyphenyl)-2-oxoethyl)pyridin-1-ium bromide **(1d):**

White powders; yield: 70%. mp 171 °C; IR (KBr, ν_{max}/cm^{-1}): 1688 (C=O), 1632 (C=N), 1593 (C=C). ^{1}H NMR (300 MHz, D_2O) δ_{ppm}: 9.06 (d, 1H, J=6Hz, Ar), 8.79-7.48 (m, 7H, Ar), 6.29 (s, 2H, CH_2), 3.56 (s, 3H, OCH_3).

Typical procedure for the preparation of indolizine-1-carbonitrile derivatives **(4a-d):**

A solution of 1-alkyl-2-chloropyridinium bromides (**1a-d**) (2 mmol), malononitrile (**2**) (2 mmol) and benzaldehyde (**3**) (2 mmol) and KF/Al_2O_3 (1 mmol) in ethanol (10 mL) was refluxed for the time reported in Table **2** (the progress of the reaction was monitored by TLC using hexane/ethyl acetate as eluents). The reaction mixture was filtered and diluted with 50 mL of water and the resulting precipitate was collected by filtration.

3-Benzoyl-2-phenylindolizine-1-carbonitrile **(4a):**

Yellow powder; IR (KBr, ν_{max}/cm^{-1}): 2208 (CN), 1648 (C=O), 1593, 1571 (C=C). ^1H NMR (300 MHz, DMSO-d_6) δ_{ppm}: 7.99-7.90 (m, 3H, Ar), 7.84 (t, 1H, J=6Hz, Ar), 7.72 (t, 1H, J=3Hz, Ar), 7.64-7.22 (m, 8H, Ar), 6.98 (t, 1H, J=6Hz, Ar). ^{13}C NMR (75 MHz, DMSO-d_6) δ_{ppm}: 190.07 (C=O), 154.74, 147.87, 144.89, 141.72, 140.54, 135.79, 135.30, 132.52, 132.28, 130.55, 130.51, 129.62, 129.50, 128.60, 120.94, 118.07, 114.74 (CN). Anal. calcd. for $C_{22}H_{14}N_2O$: C, 81.97; H, 4.38; N, 8.69%. Found: C, 81.80; H, 4.22; N, 8.52%.

3-(4-Bromobenzoyl)-2-phenylindolizine-1-carbonitrile **(4b):**

Yellow powder; IR (KBr, ν_{max}/cm^{-1}): 2192 (CN), 1648 (C=O), 1616, 1580 (C=C). ^1H NMR (300 MHz, $CDCl_3$) δ_{ppm}: 7.95 (t, 1H, J=3Hz, Ar), 7.93 (t, 1H, J=3Hz, Ar), 7.81 (s, 1H, Ar), 7.72 (t, 1H, J=3Hz, Ar), 7.70 (t, 1H, J=3Hz, Ar), 7.53-7.22 (m, 6H, Ar), 7.15 (t, 1H, J=3Hz, Ar), 6.64-6.60 (m, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ_{ppm}: 188.71 (C=O), 156.08, 145.20, 141.66, 140.34, 137.96, 136.48, 134.49, 132.71, 132.13, 131.48, 130.73, 130.20, 129.74, 127.93, 122.51, 117.63, 113.35 (CN). Anal. calcd. for $C_{22}H_{13}BrN_2O$: C, 65.85; H, 3.27; N, 6.98%. Found: C, 65.67; H, 3.13; N, 6.79%.

Methyl 1-cyano-2-phenylindolizine-3-carboxylate **(4c):**

Yellow powder; IR (KBr, ν_{max}/cm^{-1}): 2192 (CN), 1731 (C=O), 1628, 1542 (C=C). ^1H NMR (300 MHz, DMSO-d_6) δ_{ppm}: 8.07 (d, 1H, J=3Hz, Ar), 7.79-7.45 (m, 6H, Ar), 7.28 (d, 1H, J=3Hz, Ar), 6.90 (t, 1H, J=3Hz, Ar), 3.70 (s, 3H, OCH_3). ^{13}C NMR (75 MHz, DMSO-d_6) δ_{ppm}: 161.37 (C=O), 156.08, 145.89, 142.38, 139.89, 131.47, 130.95, 130.51, 129.92, 129.52, 127.81, 120.21, 118.51, 113.39 (CN), 52.75 (OCH_3). Anal. calcd. for $C_{17}H_{12}N_2O_2$: C, 73.90; H, 4.38; N, 10.14%. Found: C, 73.71; H, 4.20; N, 9.93%.

3-(4-Methoxybenzoyl)-2-phenylindolizine-1-carbonitrile **(4d):**

Yellow crystals; IR (KBr, ν_{max}/cm^{-1}): 2195 (CN), 1643 (C=O), 1616, 1543 (C=C); ^1H NMR (300 MHz, DMSO-d_6) δ_{ppm}: 8.00-7.92 (m, 4H, Ar), 7.84 (t, 1H, J=4Hz, Ar), 7.55-7.15 (m, 7H, Ar), 6.96 (t, 1H, J=4Hz, Ar), 3.90 (s, 3H, O-CH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ_{ppm}: 188.92 (C=O), 163.42, 155.39, 144.44, 142.43, 140.95, 135.93, 132.74, 132.51, 131.25, 130.92, 129.95, 128.46, 121.44, 118.57, 115.17, 114.50 (CN), 56.10 (O-CH_3); Anal. calcd. for $C_{23}H_{16}N_2O_2$: C, 78.39; H, 4.58; N, 7.95%. Found: C, 78.20; H, 4.41; N, 7.77%.

Conclusions

In summary, we have reported an efficient procedure for tandem 1,3-dipolar cycloaddition of 1-alkyl-2-chloropyridinium bromides, malononitrile and benzaldehyde at reflux, in the presence of KF/Al_2O_3 in ethanol. The procedure offers several advantages including high yields, operational simplicity, reactions proceed in mild conditions and separation process is very simple which makes it a useful practical process for the synthesis of these compounds.

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