Article

Application of *β*-(2-Chloroaroyl)thioacetanilide in Synthesis(III): An Efficient Three-Component Synthesis of Thiochromeno[2,3-*b*]pyridines Catalyzed by KF/Neutral Al₂O₃ Co-operated with PEG 6000 under Microwave Irradiation

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A series of new functionalized thiochromeno[2,3-*b*]pyridine derivatives have been synthesized via a sequence of Knoevenagel condensation, Michael addition, cyclization, and intramolecular nucleophilic substitution, which is first catalyzed by KF/neutral Al₂O₃ cooperated with PEG 6000 under microwave irradiation. Experimental results indicated that among the catalysts tested, KF/ neutral Al₂O₃ with PEG 6000 exhibits the best catalytic activity, which leads to a substantial improvement in the overall yield and purity of the desired final products and significantly shorter reaction time.

Introduction

In view of the recent trend in catalytic processes toward the development of clean and green chemical processes, the investigation for new and less hazardous catalysts has become a priority in synthetic organic chemistry. The use of environmentally friendly inorganic solids, as catalysts or reaction media, is rapidly increasing[1] because these reactions often involve milder conditions, an easier setup and workup, more rapid reaction rates, increased yield and higher selectivity, easy removal and decreased solvent handling issues.[2]

The utility of KF as a potential base in variety of synthetic reactions has been recognized because of the formation of a H-bond between a fluoride anion and an organic compound, which resulted in the transfer of electron density from the anion to the compound. This premise has been extensively explained by a variety of fluoride-promoted reactions.[3] Potassium fluoride on alumina (KF/Al₂O₃)[4] has been commonly used as an efficient and versatile basic catalyst in organic synthesis, which was developed by Ando et al. for alkylation reactions.[5] Over the past years, the application of KF/Al₂O₃ as a green catalytic system to organic synthesis has provided new methods for a wide array of organic reactions, such as elimination,[6] addition,[7] condensation,[8] epoxidation,[9] palladium-catalyzed coupling,[10] and the synthesis of heterocyclic compounds.[11] Moreover, phase-transfer catalysis is now a well-established method of organic

synthesis applied to the reactions of inorganic and organic anions or other active species with organic compounds. PEG, an inexpensive, thermally stable, nontoxic, widely applicable and environmentally friendly media for phase transfer catalysts, shows the high ability to form stable complexes with metal cations, which makes a valid alternative to more sophisticated crown ethers in solid−liquid phase-transfer reactions.[12]

To increase the molecular diversity of library and compound collections,[13] it is beneficial to investigate facile synthetic strategies used for the discovery of new biologically active chemical entities. Multicomponent reactions (MCRs)[14] are, for their intimate nature, extremely convergent, producing a remarkably high increase of molecular complexity in just one step. Therefore, especially when the components may be varied at will, they are very well suited for the generation of libraries. The coupling of microwave (MW) irradiation with the use of catalysts provides improved selectivity, enhanced reaction rates and manipulative simplicity.[15]

The interest in *N*,*S*-containing heterocycles[16] has been significantly surged since a wide range of biological activities has been identified. For example, the thiochromones[17] as important structural motifs exhibit interesting biological properties and have been tested and applied as drugs.[18] Apart from this, however, the study of pyridines fused to thiochromones has received little attention.

Our approach toward the development of new multicomponent procedures involves the use of building blocks that contain a number of chemically distinct functionalities, which

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Scheme 1. Possible Reaction Pattern of
ortho-Chloro-*β*-aroylthioamides

(a)

(b)
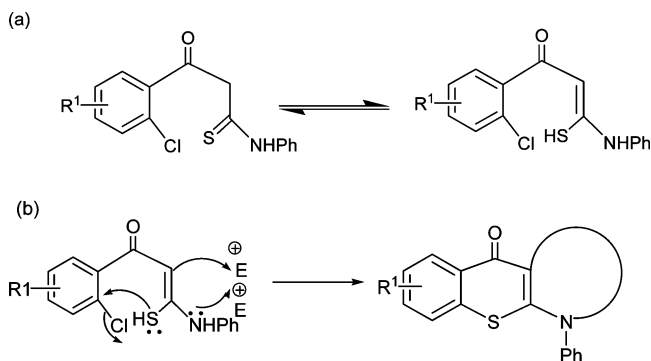
could be selectively reacted to generate diversity.[19] Thioa-mides,[20] referred to as ketene-(*N,S*)-acetals,[21] show promising structural features as versatile synthetic intermediates. For example, we have designed *ortho*-chloro-*β*-aroylthioamides in which four reactive centers are present (Scheme 1). Compared with a lot of the reports on the two-component reaction of *β*-aroylthioamides with various binucleophilic species,[22] to the best of our knowledge, there are very few reports about the three-component (3CR) reaction of *ortho*-chloro-*β*-aroylthioamides to synthesize thiochromeno[2,3-*b*]pyridine derivatives.[23]

As a research program aimed at the development of green organic synthesis, we herein report a simple and economical multi component reaction (MCR) consisting of *ortho*-chloro-*β*-aroyl thioamides **1a−c**, aldehydes and malononitrile catalyzed by KF/neutral Al$_2$O$_3$ cooperated with PEG 6000 under microwave irradiation (Scheme 2).

Results and Discussion

The increasing demand for clean and efficient eco-friendly chemical synthesis has increased our interest in solid catalysts and microwave irradiation. We first systematically examined the efficiency of various solid catalysts to this 3CR. The results are collected in Table 1.

The results showed that no reaction occurred without addition of any catalyst (Table 1, entry 1), and with KF as the catalyst, the yield of **4a** was only 35% (Table 1, entry 2), which may be attributed to the low solubility in organic solvents; when KF/PEG 6000[24] was used as catalyst, the reaction yield slightly increased (46%)(Table 1, entry 3), which suggested PEG 6000 can improve the yield of this reaction. When KF was adsorbed on various sorts of carriers,[25] including diatomite, MK-10, basic Al$_2$O$_3$, and neutral Al$_2$O$_3$ in ethanol (Table 1, entries 4−7), KF/neutral

Al$_2$O$_3$ exhibited better efficiency (56%) in this reaction. Encouraged by these results, we combined KF/ neutral Al$_2$O$_3$ and PEG 6000 as one catalyst. To our delight, the yield was enhanced to 68%. Surprisingly, after microwave irradiation (500 W) was employed under KF/neutral Al$_2$O$_3$ co-operated with PEG 6000 as catalyst, the yield was significantly reached up to 86%, the reaction time also reduced from 300 to 20 min. As can be seen from the results (Table 1), microwave irradiation exhibited several advantages over the conventional heating by not only significantly reducing the reaction time but also by improving the reaction yield and, in the process, eliminating the side reactions. It is obvious that the catalyst KF/neutral Al$_2$O$_3$ with PEG 6000 under microwave irradiation plays a very important role in this three-component reaction.

Solvent also has a significant impact on the reaction efficiency and yields (Table 1, entries 13−15). From these results, we can see that in the protic solvent such as EtOH or polar solvent such as CH$_3$CN the reaction can give desirable yields (86% or 70%), but in CH$_2$Cl$_2$, low yield was observed because of the formation of many byproducts (Table 1, entry 15). These results added further evidence toward protic solvent stabilized mechanism leading to molecular diversity.

Subsequently, the amount of catalyst plays a crucial role in the success of the reaction in terms of the rate and the yields. Increasing of the catalyst from 0.025 to 0.100 g resulted in accelerating the reaction yields from 35% to 86%; 0.100 g KF/neutral Al$_2$O$_3$ with PEG 6000 was sufficient to push the reaction to completion. Higher amounts of the catalyst (0.125 g), did not improve the results to a greater extent (the yield was 83%).

Under the optimized reaction conditions, namely, KF/ neutral Al$_2$O$_3$ with PEG 6000 as catalyst in EtOH at 80 °C under microwave irradiation, the reactions of different aldehydes, various *ortho*-chloro-*β*-aroylthioamides and ma-lononitrile were performed (Scheme 2). Initially, to test the scope of aldehyde substrates, 3-(2,4-dichlorophenyl)-3-oxo-*N*-phenylpropanethioanide **1a** and malononitrile were used as model substrates (Table 2, entries 1−13). The reactions showed remarkable flexibility, as the desired products were formed in excellent yields with various aromatic aldehydes, which were selected to have either electron-withdrawing or electron-donating properties (83−88% yields). The hetero aromatic aldehydes such as furfural (Table 2, entry 12) still displayed high reactivity under this standard condition. However, the yield for aliphatic aldehyde (Table 2, entry 13, 62% yield) is lower than that for aromatic aldehydes.
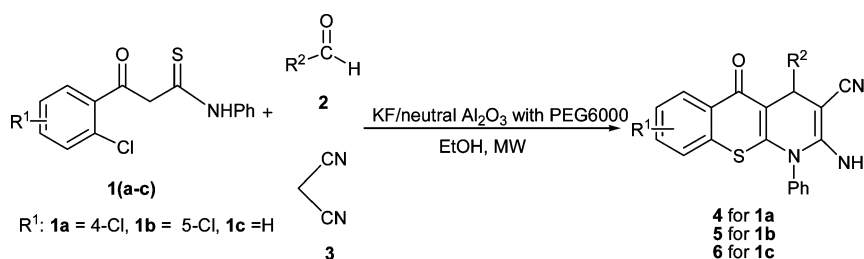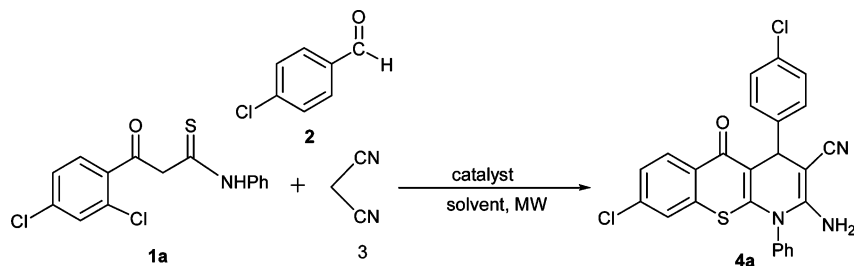
Scheme 2. Three-Component Reaction of *ortho*-Chloro-*β*-aroylthioamides to Synthesize Thiochromeno[2,3-*b*]pyridine Derivatives

Table 1. Tested Catalysts under Different Conditions[a]

entry	catalyst	solvent	time (min)	yield (%)[a]
1	none	EtOH (15 mL)	300[b] or 20[c]	none
2	KF	EtOH (15 mL)	300[b]	35
3	KF/PEG 6000	EtOH (15 mL)	300[b]	46
4	KF/ MK-10	EtOH (15 mL)	300[b]	41
5	KF/basic Al$_2$O$_3$	EtOH (15 mL)	300[b]	44
6	KF/neutral Al$_2$O$_3$	EtOH (15 mL)	300[b]	56
7	KF/diatomite	EtOH (15 mL)	300[b]	38
8	KF/neutral Al$_2$O$_3$ with PEG 6000	EtOH (15 mL)	300[b]	68
9	KF/ MK-10	EtOH (15 mL)	20[c]	49
10	KF/basic Al$_2$O$_3$	EtOH (15 mL)	20[c]	56
11	KF/PEG 6000	EtOH (15 mL)	20[c]	59
12	KF/neutral Al$_2$O$_3$	EtOH (15 mL)	20[c]	67
13	KF/neutral Al$_2$O$_3$ with PEG 6000	EtOH (15 mL)	20[c]	86
14	KF/neutral Al$_2$O$_3$ with PEG 6000	CH$_3$CN (15 mL)	20[c]	70
15	KF/neutral Al$_2$O$_3$ with PEG 6000	CH$_2$Cl$_2$ (15 mL)	20[d]	50
16	KF/neutral Al$_2$O$_3$ with PEG 6000	solvent-free	20[e]	49

[a] Isolated yield. General reaction condition: **1a** (1 mmol), **2** (1 mmol), **3** (1 mmol), catalyst (0.100 g). [b] Thermal heating, 80 °C. [c] MW 500 W, 80 °C. [d] MW 500 W, 40 °C. [e] MW 500 W, 100 °C.

This may be considered as a limitation for practical achievement in this reaction.

To further expand the scope of *ortho*-chloro-β-aroylthioamides substrates, we used **1b** (5-Cl) and **1c** (H) instead of **1a** (4-Cl) in this process. The results demonstrated that

Table 2. Synthesis of Products **4–6** Catalyzed by KF/Neutral Al$_2$O$_3$ Co-operated with PEG 6000 under Microwave Irradiation

entry	R^1	R^2	time (min)	yield (%)[a]
1	4-Cl	*p*-(Cl)C$_6$H$_4$	20	**4a** (86)
2	4-Cl	C$_6$H$_5$	20	**4b** (85)
3	4-Cl	*o*-(Cl)C$_6$H$_4$	20	**4c** (88)
4	4-Cl	2,4-Cl$_2$C$_6$H$_3$	20	**4d** (87)
5	4-Cl	*m*-(NO$_2$)C$_6$H$_4$	20	**4e** (87)
6	4-Cl	*m*-(OH)C$_6$H$_4$	21	**4f** (83)
7	4-Cl	*p*-(OH)C$_6$H$_4$	21	**4g** (82)
8	4-Cl	3,4-(OCH$_2$O)C$_6$H$_3$	20	**4h** (83)
9	4-Cl	*p*-(CH$_3$)C$_6$H$_4$	21	**4i** (83)
10	4-Cl	*p*-(OCH$_3$)C$_6$H$_4$	21	**4j** (83)
11	4-Cl	3,4-(OCH$_3$)$_2$C$_6$H$_3$	21	**4k** (83)
12	4-Cl	furfural	23	**4l** (80)
13	4-Cl	CH$_3$	35	**4m** (62)
14	5-Cl	*p*-(Cl)C$_6$H$_4$	22	**5a** (83)
15	5-Cl	2,4-Cl$_2$C$_6$H$_3$	22	**5b** (83)
16	5-Cl	*m*-(NO$_2$)C$_6$H$_4$	22	**5c** (82)
17	5-Cl	*p*-(OCH$_3$)C$_6$H$_4$	23	**5d** (79)
18	5-Cl	3,4-(OCH$_2$O)C$_6$H$_3$	23	**5e** (79)
19	5-Cl	3,4-(OCH$_3$)$_2$C$_6$H$_3$	23	**5f** (80)
20	5-Cl	*m*-(OH)C$_6$H$_4$	23	**5g** (80)
21	5-Cl	C$_6$H$_5$	22	**5h** (82)
22	H	*p*-(Cl)C$_6$H$_4$	25	**6a** (76)
23	H	*o*-(Cl)C$_6$H$_4$	25	**6b** (78)
24	H	2,4-Cl$_2$C$_6$H$_3$	25	**6c** (76)
25	H	*m*-(NO$_2$)C$_6$H$_4$	25	**6d** (77)
26	H	*p*-(OCH$_3$)C$_6$H$_4$	27	**6e** (73)
27	H	3,4-(OCH$_3$)$_2$C$_6$H$_3$	26	**6f** (74)
28	H	3,4-(OCH$_2$O)C$_6$H$_3$	27	**6g** (74)
29	H	*p*-(CH$_3$)C$_6$H$_4$	27	**6h** (75)

[a] Yields of the isolated products.

the reactions involving **1a** went smoothly, and the yields were all satisfactory. Compared to **5a** and **6a**, for example, the yield of **4a** was slightly higher and the reaction time was slightly shorter, which might be attributed to the presence and the site of R^1 (R^1= Cl) on the aromatic ring. Because the 4-chloro group meta to 2-Cl exists, there is an inductive effect as strong electron-withdrawing group leading to increase of electropositivity of C$_2$, whereas because the 5-chloro group para to 2-Cl exists, there is both an inductive effect and conjugate effect leading to decrease of electropositivity of C$_2$, so the 2-chloro group is more easily leaving in **1a** compared to that in **1b** and **1c** during nucleophilic aromatic substitution reaction.

After completion of the reaction, the catalyst of KF/Al$_2$O$_3$ with PEG 6000 could be reused through further treatment. For the reaction of **1a** with 4-chlorobenzaldehyde and malononitrile, over 50% yields for **4a** were obtained during the four recycling experiments (86%, 74%, 65%, and 53%).
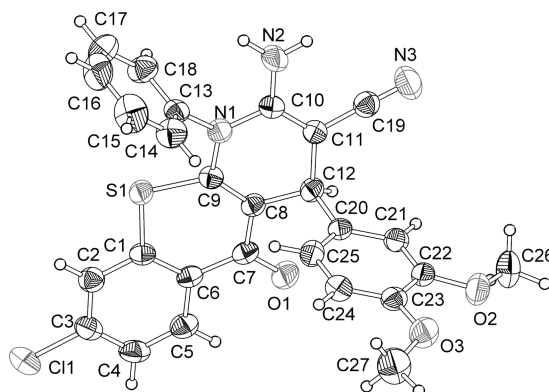
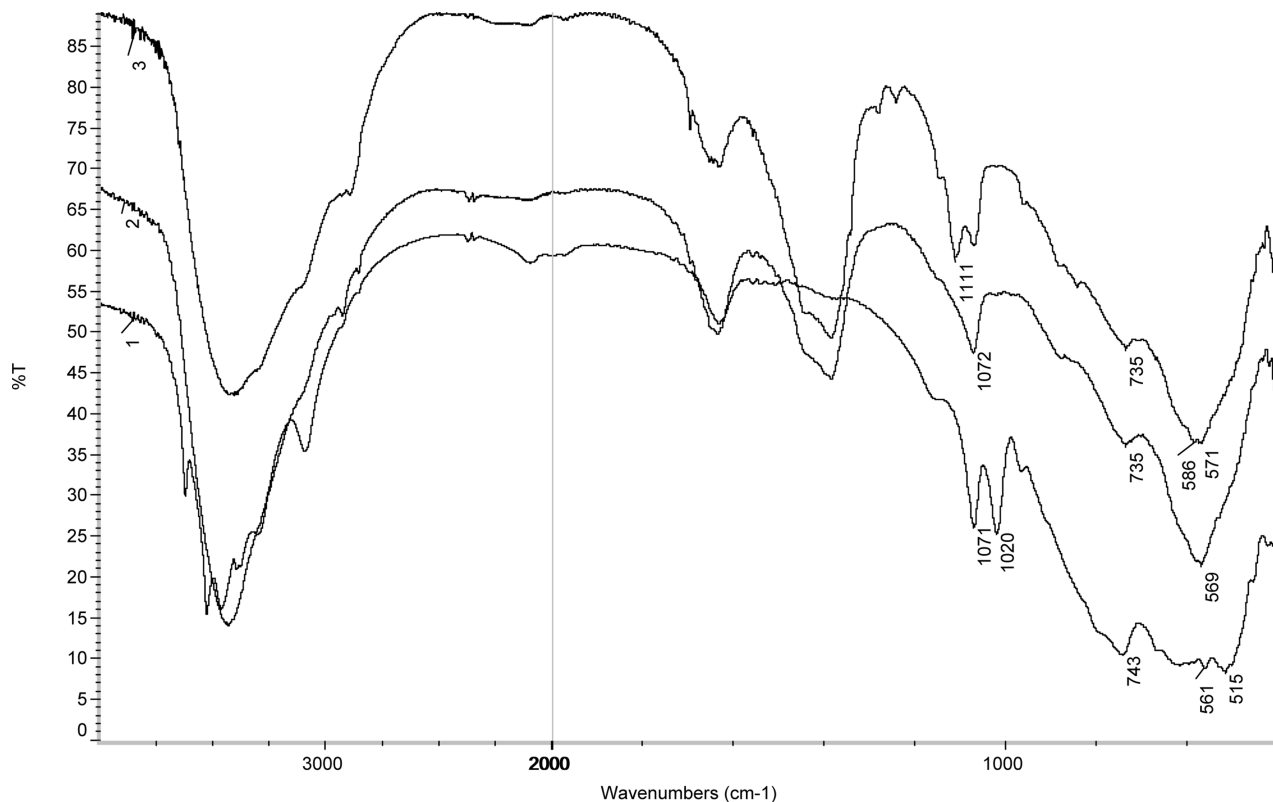
Figure 1. Molecular structure of **4k**.

Figure 2. FT-IR spectra of neutral Al_2O_3 (1), KF/neutral Al_2O_3 (2), and KF/neutral Al_2O_3 with PEG6000 (3).

It should be mentioned that the reaction under microwave irradiation was very clean, and only a yellow solid was obtained after a simple recrystallization. The products were characterized on the basis of their spectra and analytical data. The structure of **4k** was confirmed by X-ray single crystal diffraction analysis (Figure 1).

We primarily explored the co-operative mechanism of KF/ neutral Al_2O_3 and PEG 6000, where IR and XRD analysis were performed. The results are illustrated in Figures 2 and 3, respectively.

As shown in Figure 2, compared with 743 cm^{-1} band of Al−O bond in neutral Al_2O_3 (1), the Al−O bands of other two catalysts KF/ neutral Al_2O_3 (2), and KF/neutral Al_2O_3 with PEG 6000 (3) shift toward low wavenumber 735 cm^{-1}, which indicates that F$^-$ has the effect on the Al−O bonds. In addition, the appearance of two bands 586 and 571 cm^{-1} can verify K_3AlF_6 phase is formed.[26]

As can be seen from Figure 3, compared with that in KF/ neutral Al_2O_3, the diffraction peaks of AlO(OH) in KF/ neutral Al_2O_3 with PEG 6000 slightly decline, and meanwhile peaks of K_3AlF_6 apparently decrease. This may result from (1) the chelate of PEG and K$^+$ affects the formation of K_3AlF_6 or (2) the active F$^-$ from the chelate of PEG and KF replaces the −OH on the surface of Al_2O_3, which results in the decrease of AlO(OH). Compared with that in KF/ basic Al_2O_3, the peaks of KF in KF/basic Al_2O_3 with PEG 6000 apparently decrease, and meanwhile, the peaks of K_3AlF_6 hardly change. This possibly results from that a part of KF phase is destroyed with the chelate of PEG and K$^+$. It is worthy to note that the peaks of K_3AlF_6 in KF/neutral Al_2O_3 with PEG 6000 are lower than that in KF/basic Al_2O_3 with PEG 6000, but the catalytic activity of KF/neutral Al_2O_3
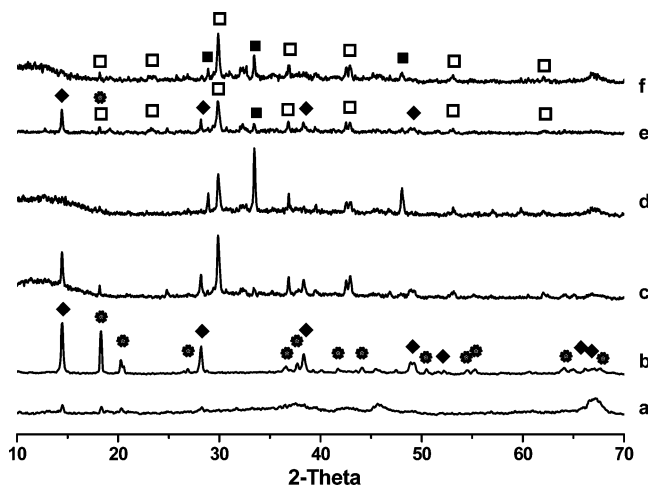

Figure 3. XRD patterns of (a) basic Al_2O_3, (b) neutral Al_2O_3, (c) KF/neutral Al_2O_3, (d) KF/basic Al_2O_3, (e) KF/neutral Al_2O_3/ PEG6000, and (f) KF/ basic Al_2O_3/ PEG6000. Legend: ◆ bohmite, AlO(OH); ■ carobblite, KF; * aluminum hydroxide, $Al(OH)_3$; □ potassium aluminum fluoride, K_3AlF_6.
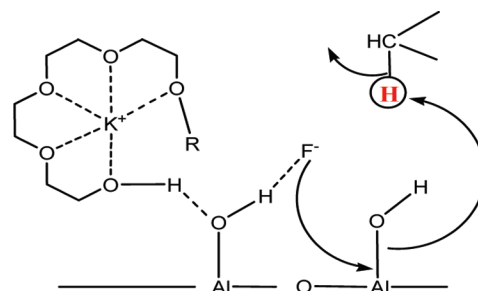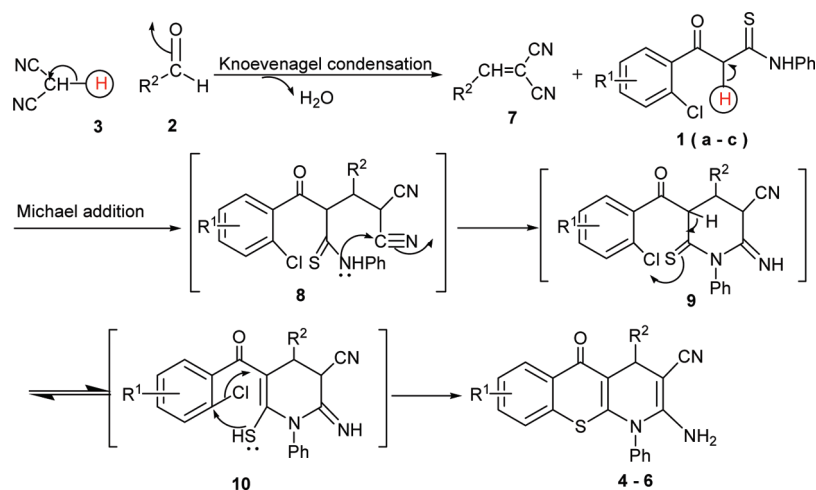

Figure 4. Plausible co-operative effect model of KF/neutral Al_2O_3 with PEG 6000.

Scheme 3. Possible Mechanism for the Synthesis of Products

with PEG 6000 is higher than that of KF/basic Al_2O_3 with PEG 6000. This suggests that K_3AlF_6 is not main catalyst species.

The mechanism of the appearance of the basicity of KF/Al_2O_3 remains a matter of debate in literatures. Weinstock et al.[27] have argued that KF/Al_2O_3 derives its basicity from the formation of KOH in the initial preparation of the solid supported material by reaction of KF with Al_2O_3. However, Ando et al.[28] have disputed that there are three basic species or mechanisms of the appearance of the basicity of KF/Al_2O_3: (a) the presence of active fluoride, (b) [Al−O$^-$] ions which generate OH$^-$ when water is present, and (c) cooperation of F$^-$ and [Al−OH].

Considering previous models[27,28] and our experimental results, a possible co-operative effect model of KF/neutral Al_2O_3 with PEG 6000 was proposed(Figure 4). It may be presumed that PEG 6000 adsorbed on surface of Al_2O_3 may chelated with K$^+$ forming the chelate cation, F$^-$ acts as balance ion. The three basic species generated through a co-operative action of KF on the surface Al_2O_3 and PEG 6000 would take part in nucleophilic reaction and display high catalytic activity.

On the basis of above results, the formation of thio-chromeno[2,3-b]pyridine derivatives could be explained by a possible reaction sequence presented in Scheme 3. Initially, Knoevenagel condensation occurs by attacking the carbonyl group of aldehydes **2** with the α-carbon atom of malononitrile **3**, leading to the formation of 2-arylidene malononitrile **7**. Then, Michael addition with concomitant cyclocondensation between **7** and **1(a−c)** would give **9**, in which the formation of a pyridine ring is involved. Finally, the product would be furnished by a nucleophilic aryl substitution (S$_N$Ar) reaction of the mercapto group attacking carbon atom linked to *ortho*-chloro on the phenyl ring of the intermediate **10** (Scheme 3).

The remarkable ability of microwaves to facilitate polar reactions has been well recognized.[29] Indeed, specific microwave effects can be observed for polar mechanisms when the polarity is increased during the reaction, from the ground state (GS) toward the transition state (TS).[30] In the present case, the TS for a sequence of Knoevenagel condensation, Michael addition, cyclization and intramolecular

nucleophilic substitution reactions involves loose ion pairs as a charge-delocalized anion, whereas the GS involves a neutral electrophile and a tighter ion pair. During the course of the reaction, ionic dissociation increases, and that way all the intermediates proposed in the mechanism are more polar[30] than the starting material. Thus, a favorable microwave effect can be observed. Further investigations regarding the elucidation of the precise mechanism are currently under progress.

Conclusions

In summary, we have presented a green and efficient reaction by using KF/neutral Al_2O_3 cooperated with PEG 6000 as an environmentally friendly, highly active catalyst under microwave irradiation that leads to the unusual thiochromeno [2,3-b]pyridine derivatives. In this one-pot, three-component reaction, seven different active sites are involved, and two C−C bonds, one C−S bond, one C−N bond, and two new rings are constructed with all reactants efficiently utilized via a sequence of reactions. Experimental results reveals that PEG 6000 adsorbed on surface of Al_2O_3 may chelated with K$^+$ forming the chelate cation, F$^-$ acts as balance ion. The three basic species generated through a co-operative action of KF on the surface Al_2O_3 and PEG6000 would take part in nucleophilic reaction and display high catalytic activity. By taking these points into consideration, new class of 3-CR studies catalyzed by KF/neutral Al_2O_3 cooperated with PEG 6000 will help to verify this proposition and will be reported in due course.

Supporting Information Available. Details of experimental procedures and analytical data (^{1}H NMR, ^{13}C NMR, IR, MS, EA), ^{1}H and ^{13}C NMR spectra and partial MS spectra of all new compounds, the surface area data of the

used catalysts, and the X-ray structure determination of compound **4k**. This material is available free of charge via the Internet at http://pubs.acs.org.

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