



Original Paper

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Comparative study of acid and basic catalysis in microwave assistance of Willgerodt-Kindler reaction for thiobenzamides and derivatives synthesis

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ABSTRACT

Montmorillonite K-10 was used in the acid catalysis of the Willgerodt-Kindler's reaction (WK) under microwave heating for synthesis of thiobenzamides. Yields of 67% and 43% for the synthesis of morpholin-4-yl (phenyl) methanethione (1) and [4 - (dimethylamino) phenyl] (morpholin-4-yl) methanethione (2) respectively, showed that the mixture (aldehyde, sulfur, morpholine and K-10) is quite suitable for this reaction. This enables to deduce that the conditions of acid catalysis with the K-10 are favourable to the WK's reaction of carbonyl compounds. Furthermore, yields of 81% and 74% respectively for the synthesis of thioamides 1 and 2 in basic catalysis with 4-methylmorpholine allows to confirm that this reaction is more advantageous in basic catalysis. The structures of thioamides synthesized were characterized and confirmed by spectroscopy Infrared (IR), nuclear magnetic resonance (¹H and ¹³C NMR) and mass spectrometry (MS).

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Keywords: Montmorillonite K-10, 4-methylmorpholine, morpholin-4-yl(phenyl)methanethione, [4-(dimethylamino)phenyl](morpholin-4-yl)methanethione.

INTRODUCTION

Sulphur compounds in which there is stability of the functional groups with sulphur in different oxidation states are an interesting family of therapeutic molecules. These compounds are among other thioethers, thioamides, thiosemicarbazones etc. Thioamides, in particular thiobenzamide group, seems to be an interesting pharmacophore in medicinal chemistry, with

widespread applications, including the antifungal and antibacterial properties (Matysiak et al., 2000), inhibitors of aldose reductase (Sestani et al., 1984) and receptors of estrogens antagonists (Stauffer et al., 2000; Waisser et al., 2000).

Although many synthetic approaches to prepare thioamides have been previously reported in the literature (Schaumann et al., 1991), the condensation's reaction of the

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carbonyl compound with an amine in the presence of sulphur known as the Willgerodt-Kindler's reaction (Kindler, 1923; DeTar *et al.*, 1946) is the most used for the synthesis of thioamides (Amupitan, 1983) (Figure 1). One of the interesting characteristics of this reaction lies in the fact that the system behaves as an auto-redox system in which the carbonyl is reduced while the terminal methyl group is oxidized into a thioamide (Dauben *et al.*, 1957; Darabi *et al.*, 2004)

Considering its wide applications, the reaction continues to be the subject of several optimization works. Recently, Gbaguidi *et al.* (2010) showed that an acid catalyst such as Montmorillonite K-10 is also participated in optimum conditions during its use for the synthesis of 1-morpholino-2-(naphthalen-1-yl)ethanethione. The use of this strong acid in the presence of an excess of morpholine (also used as a base), concludes that acid-base catalysis conditions ameliorate the WK's reaction of ketone compounds. This condensation between amines and aldehydes is governed by the acid-base catalysis (Bruice *et al.*, 1963) which could be beneficial.

In our pursuit to improve the scope of the WK's reaction, we explored the value of the adding amount of an acid catalytic in heterogeneous phase as montmorillonite K-10 in the reaction (aldehyde, morphine and sulphur) under microwave heating for the synthesis of thiobenzamides and derivatives and its comparative study with base catalysis with 4-methylmorpholine.

MATERIALS AND METHODS

Reagents and catalysts

Substrates such as benzaldehyde, 4-(dimethylamino)benzaldehyde; reagents (sulphur, morpholine) were bought at the chemical PROLABO industries ACROS ORGANICS.

Montmorillonite K-10 and 4-methylmorpholine obtained from Sigma Chemical Corporation were used as catalysts during the reactions.

Montmorillonite K-10 is a commercial clay obtained by acidification of the natural Montmorillonite belonging to smectite group of the family of phyllosilicates of the formula $(\text{Na, Ca})_{0.3}(\text{Al, Mg})_2\text{Si}_4\text{O}_{10}(\text{OH})_2 \cdot n\text{H}_2\text{O}$ (Alas *et al.*, 1994; do Rego *et al.*, 2010).

Similarly, the 4-methylmorpholine is dried by reflux on KOH during 1 hour followed by distillation at atmospheric pressure.

General techniques

The synthesis was made under radiation heating in an oven microwave "Brandt type MB 18 T (940W, 2450 MHz)". The evolution of the reagents to products is assessed using a thin layer chromatography (TLC). This TLC was realized on the plates of silica (silica gel 60 F254 Merck TCL) with mobile phase which is a mixture of hexane and ethyl in proportion acetate (6v/4v) and then revealed to the ultraviolet (UV) light of wavelength $\lambda = 254$ nm.

The treatment of the reaction mixture was made with solutions of ethyl acetate, hydrochloric acid, ammonia chloride and distilled water. Indeed, the solubility of the product in ethyl acetate has allowed the elimination of excess sulphur by simple filtration before his treatment other solvents by decantation. The organic phase to ethyl acetate after drying on the crystals of MgSO_4 , was concentrated with a rotary evaporator at low pressure (pressure in tap water) type 4000 - efficient laborota Heidolph.

Thioamides synthesized after recrystallization in ethyl alcohol 95 °, were purified on column chromatography with mobile phase which is a mixture of hexane and ethyl in proportion acetate (6v/4v) and phase stationary silica (Silica gel 63-160 μm) marketed by PROLABO.

The melting point of synthesized and purified thioamides is made on a fusionometer of type electrothermal 1A 9000, before the characterization and confirmation of their structure by the spectral analysis methods (IR, NMR, MS). The infrared (IR) spectra have

been recorded using a spectrophotometer (Perkin - Elmer FTIR 286).

The different spectra of Nuclear Magnetic Resonance (NMR) were carried out and recorded using a Bruker 400 MHz for ^1H proton and 100 MHz for the carbon ^{13}C in CDCl_3 (deuterated chloroform). Regarding the mass spectra in direct introduction and LC/MS (liquid chromatography high performance coupled with mass spectrometry), they were made using a mass spectrometer equipped with an interface of chemical ionization atmospheric pressure (APCI) in positive mode. This technique allowed to determine molecular molar mass and to confirm the purity of synthetic products.

Method of synthesis

The synthesis of thioamides is made in acid catalysis with Montmorillonite K-10 and basic with 4-methylmorpholine (Figure 2).

Acid Catalysis: Montmorillonite K-10

In a mixture (5 mmol) of aldehyde and (7.5 mmol) of morpholine put under agitation, 15 mL of DMF (the solvent) are added. To the mixing under agitation, we are added 0.35 g of K-10 and 8 mmol of sulphur. The agitation continues until the obtaining a mixture of Brown colour which will be submitted to the microwave heating for about 10-15 minutes in a 10 sequences (01 min) spaced pulses of 1 minute 20 seconds.

After cooling to room temperature, the mixture is then poured in a solution of ethyl acetate for allowing the elimination of sulphur and K-10 by simple filtration. The filtrate obtained is treated with 100 mL of hydrochloric acid (0.1 M) to protonate the amine in excess, then with 100 mL of saturated NH_4Cl solution and finally washed with 2×100 ml of distilled water. The organic phase after drying over MgSO_4 is concentrated by evaporation.

The formed crystals have recrystallized in ethyl alcohol 95° before its purification on column to ensure the

elimination of sulphur and secondary products.

Basic Catalysis: 4-methylmorpholine (4-MM)

A mixture (5 mmol) of aldehyde (7.5 mmol) of morpholine, 8 mmol of sulfur and 0.5 mmol of 4-methylmorpholine in 25 mL of DMF (solvent) were thoroughly under agitation. The mixture was placed on the rotating plateau of an oven microwave during one minute then allows standing for three minutes. The reaction mixture is again subjected to microwave for approximately 25 sequences of irradiation of 1.5 minutes spaced 3 minutes until a brown colour.

After cooling to room temperature, the mixture is then poured in a solution of ethyl acetate for allowing the elimination of sulphur. The obtained filtrate is washed with 2×100 mL of distilled water. The organic phase after drying over MgSO_4 is concentrated by evaporation. Left to rest in fridge, the formed crystals have been recrystallized in ethyl alcohol 95° before its purification on column to ensure the elimination of sulphur and secondary products.

RESULTS

Two thioamides morpholin-4-yl(phenyl)methanethione (**1**) and [4-(dimethylamino) phenyl](morpholin-4-yl)methanethione (**2**) were synthesized with different yields according to the type of catalysis. Indeed, in acid catalysis with Montmorillonite K - 10, the thioamides **1** and **2** gave respectively 67% and 43%.

Similarly, the synthesis of thioamide **1** and **2** in basic catalysis with the 4-methylmorpholine gave 81% and 74% respectively (Table 1). The calculated molar mass of **1** and **2** are 207.07 g/mol and 250.11 g/mol, respectively. The physicochemical characteristics and spectrometric analyses of these thioamides give:

R_f (Hexane / ethyl acetate 6v/4v): 0.71

M.P (melting point): 137-138 °C

MS: 207.06 m/z

IR ν (KBr cm^{-1}): 3025.16; 3009.17; 2971.68 (C aromatic); 1594.11; 1574.71; 1495.25 (thioamide).

¹H NMR (CDCl₃, δ ppm): 7.3 (5H, m, aromatic); 4.4 (2H, t, C¹H₂); 3.85 (2H, t, C⁴H₂); 3.6 (4H, t, C²H₂, C³H₂).

¹³C NMR (CDCl₃, δ ppm): 140.6 (C¹ aromatic); 126.99 (C², C⁶ aromatic); 126.66 (C³, C⁵ aromatic); 123.99 (C⁴ aromatic); 199.15(C=S); 47.16 (C^{1'}); 64.64 (C^{2'}); 64.86 (C^{3'}); 50.63 (C^{4'}).

R_f (Hexane / ethyl acetate 6v /4v): 0.60

M.P: 149-150 °C

MS: 250.12 m/z

IR ν (KBr cm⁻¹): 3000.38; 3020.40 (C aromatic); 2962.64 (methyl); 3448.83 (amine); 1547.15; 1520.63; 1487.27 (thioamide)

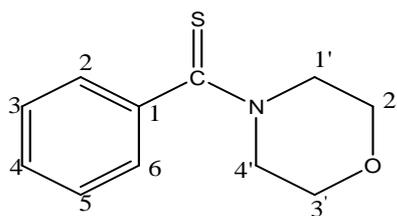
¹H NMR (CDCl₃, δ ppm): 7.3 (2H, t, C²H, C⁶H aromatic); 6.7 (2H, t, C³H, C⁵H aromatic); 4.4 (2H, t, C¹H₂); 3.8 (6H, t, C⁴H₂, C²H₂, C³H₂), 3 (6H, s, 2CH₃)

¹³C NMR (CDCl₃, δ ppm): 129.78 (C¹ aromatic); 128.72 (C², C⁶ aromatic); 111.1 (C³, C⁵ aromatic); 151.24 (C⁴ aromatic);

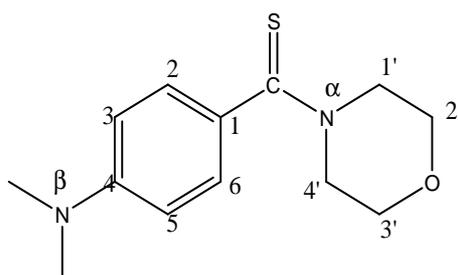
202.25 (C=S); 52.89 (C^{1'}, C^{4'}); 66.78 (C^{2'}, C^{3'}); 40.27 (2CH₃)

In infrared spectrometry, the aromatic ring of our thioamides vibrates between frequencies 2971.68–3025.16 cm⁻¹ for **1** and 3000.38–3020.4 cm⁻¹ for **2**.

Their corresponding thioamide group vibrates respectively between 1495.25 – 1594.11 and 1487.27 – 1547.15 cm⁻¹. The NMR ¹H analysis confirms the existence of the deblinded aromatic protons which usually appear around chemical shift δ ≈ 7 ppm. As the NMR ¹³C which allows us to determine different types of carbon forming the chains of thioamides, the group thioamide of **1** and **2** shows respectively a chemical shift of 199.15 and 202.25 ppm. In addition, the dimethylamino group bound to the aromatic nucleus of product **2** presents chemical shifts of δ = 3 ppm in the ¹H NMR and δ = 40.27 ppm ¹³C NMR.



1: Morpholin-4-yl (phenyl)methanethione.



2: [4-(dimethylamino) phenyl] (morpholin-4-yl) methanethione

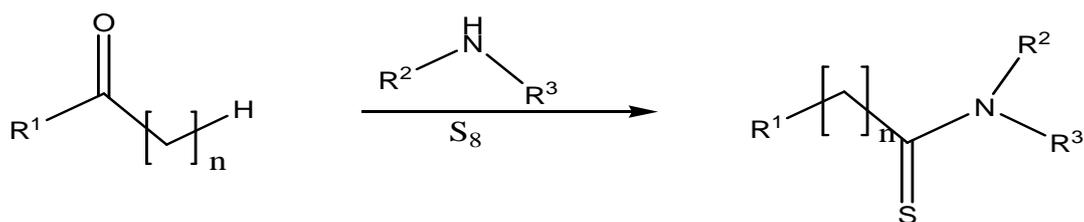


Figure 1: Reaction of Willgerodt-Kindler.

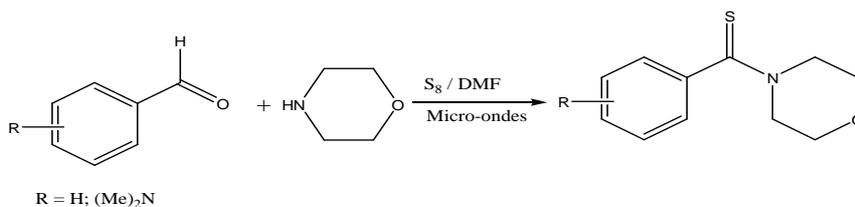


Figure 2: formation of thioamides by the WK's reaction.

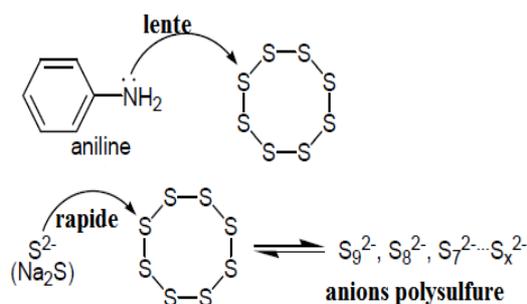


Figure 3: Kinetic of the initiation phase with a basic catalyst Na₂S·9H₂O (Okamoto et al., 2009).

Table 1: Yield of synthesized thioamides.

	Montmorillonite K-10	4-methylmorpholine
morpholin-4-yl(phenyl)methanethione (1)	67%	81%
[4-(dimethylamino)phenyl](morpholin-4-yl)methanethione (2)	43%	74%

DISCUSSION

The difference between the calculated molecular weight and the molecular weight obtained by mass spectrometry APCI each thioamide is generally of the order of 0.05% of the calculated mass which confirms

partially the structures of the suggested thioamides.

All the data spectrometric of the thioamides synthesized are in accordance with the structures suggested by thioamides **1** and **2**. Indeed, the frequencies of vibration of

thioamides in IR between 3030-3050 cm^{-1} and the chemical shifts in NMR ^1H (around $\delta \approx 7$ ppm) revealed the presence of an aromatic ring. Moreover the analysis in RMN ^{13}C presents a chemical shifts of $\delta = 199.15$ ppm and $\delta = 202.25$ ppm for the compound **1** and **2** respectively characterizing the group thioamide. These values including those of the group morpholino of our thioamides are quite similar to those obtained by chemdraw calculation and indicated in the literature (Daniel *et al.*, 2009).

The idea of using montmorillonite K-10 as acid catalyst is nothing new. Its use is justified not only by the possibility of the formation of an enamine and imine in acid medium, but also the ease of recycling by simple filtration. This appears as an advantage compared to homogeneous phase reactions. Through our work, this catalyst is suitable for the synthesis of thioamides morpholin-4-yl(phenyl)methanethione (**1**) and [4-(dimethylamino)phenyl](morpholin-4-yl)methanethione (**2**) using microwave heating. To our knowledge, montmorillonite K-10 had never been used to catalyze this synthesis.

The extension of the Willgerodt – Kindler's reaction of aldehyde compounds with the catalyst K-10 allows firstly the recovery of acid catalysis of this reaction of carbonyl compounds and from a comparative study between this catalysis and base catalysis. In effect, the work of Kioumars *et al.* (2007) revealed a high chemoselectivity of derivatives of benzaldehyde on those of acetophenones when using water as a solvent in the WK's reaction. This present work showed that the K-10 used as a catalyst in the reaction of WK for ketone compounds indicated in the work of Gbaguidi *et al.* (2010) can also be used for derivatives of benzaldehyde with interesting yield. So, with this catalyst K-10, benzaldehyde is the most reactive. It reacts quickly and leads to better performance ($> 60\%$). But this catalysis may influence the reactivity of the compounds

having an amino group bound to the nucleus aromatic **2** (43%).

A synthesis of thioamides **1** and **2** in DMF under microwave heating in the presence of another catalyst including a basic catalyst such as 4-methylmorpholine (4-MM) gives yields of 81% and 74% respectively. The choice of 4-MM was motivated by its appropriate boiling point and the fact that the tertiary amines by catalyzing the reaction are also subject in sulfuration completes on the methylene in nearby position of the basic nitrogen. This secondary reaction has been minimized during use of 4-MM. (Poupaert *et al.*, 2001, 2004).

A comparative analysis of both catalysts shows that in the presence of K-10, the yield is lowers that with the basic catalyst. The basic catalysis of WK's reaction to the course which takes place in a reaction between sulphur and the amine has been the subject of numerous studies although the behaviour and fate of sulphur in the intermediate reaction have not been elucidated.

Nevertheless, Davis *et al.* (1962) suggested the formation of anions polysulphides and related ions generated by nucleophilic attack of the amine on the ring of sulphur S_8 (Okamoto *et al.*, 2009). In addition, the work of Okamoto *et al.* (2009) showed that in the presence of a base catalysis, this initiation of nucleophilic cleavage of the ring of sulphur is fast and therefore promotes best performance (Okamoto *et al.*, 2009) (Figure 3). As against, acid catalysis may enhance the less nucleophilic attack of the amine on the ring by engaging S_8 because the amine is engaged in an acid-base reaction. This would explain the low yield of this acid catalysis.

Conclusion

In recent years, catalytic synthesis methods have generated intense research efforts in the quest to provide scientists the tools to perform a binding of carbon - heteroatom with interesting biological properties. These research efforts have created

a comprehensive list of highly active catalysts that facilitate the synthesis of compounds of greater complexity and reduced steps. Accordingly, the effective constructive ability found during the latest catalyzed methodologies has been a determining factor in the design of the fine chemicals and pharmaceutical building blocks. In itself, as mentioned in the introduction, the reaction of WK has a great potential.

The application to benzaldehyde and 4-(dimethylamino)benzaldehyde of the Willgerodt-Kindler's reaction under microwave heating in acid catalysis with Montmorillonite K-10 is valid despite having a less interesting yield than the basic catalysis with 4-methylmorpholine. The present contribution opens new perspectives on the scope of the WK's reaction under microwave heating in heterogeneous catalysis acid of carbonyl compounds.

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