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General Acid - Base Catalysis in the Willgerodt-Kindler Reaction

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Summary: The reaction of acenaphthone with morpholine and sulfur was studied in order to assess the effects of adding a source of acid or base in the Willgerodt-Kindler (WK) reaction. Addition of a strong acid was found beneficial particularly with Montmorillonite K10 which proved to be the best agent for this purpose.
As the best conditions involved the use of a strong acid in the presence of an excess of morpholine (acting also as base), it can be inferred that general acid-base catalysis conditions are beneficial in the WK reaction.

Key words: acenaphthone, morpholine, Willgerodt-Kindler (WK), Montmorillonite K10

La catalyse générale acido-basique dans la réaction de Willgerodt-Kindler

Résumé: La réaction de l'acénaphtone avec la morpholine et les sulfures a été étudiée dans le but d'évaluer les effets des sources d'acide ou de base additionnée dans la réaction de Willgerodt-Kindler (WK). L'ajout d'un acide fort comme la Montmorillonite K10 (particulièrement bénéfique au cours de cette expérience) a montré que ce mélange est le meilleur réactif pour cette réaction.
Comme les meilleures conditions impliquent l'usage d'un acide fort en présence d'un excès de morpholine (utilisée aussi comme une base), on peut déduire qu'en général les conditions de la catalyse acido-basique favorisent la réaction de W.K.

Mots clés : acénaphthone, morpholine, Willgerodt-Kindler (WK), Montmorillonite K10

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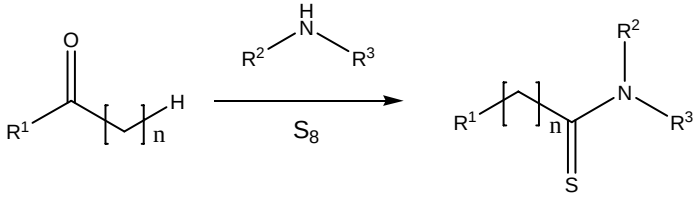
1. Introduction

The organic compounds maintain over the years vast interest not only for the development of innovative synthetic methods but also for their considerable potentialities in medicinal chemistry [1-3]. In recent years, there has been a resurgence of interest in sulfur chemistry. Particularly in synthetic organic chemistry, sulfur occupies a peculiar niche generating special structures in thionated functions (thioketones, thioamides, etc.) and abnormal reactivity behaviors when compared to their oxygenated counterparts. In many instances, difficult access to certain chemical classes of organic compounds devoid *per se* of sulfur atoms in their composition can be circumvented *via* a sulfur route. The most famous example is the "umpolung" reaction allowing the reversion in the polarity of a carbonyl group *via* intermediate conversion to a dithiane moiety [4].

Among the thioorganic compounds, thioamides are essential synthons for the elaboration of various biologically relevant heterocyclic scaffolds [5]. Although lots of synthetic approaches to prepare thioamides were reported previously in the literature [6], the three-component reaction of a carbonyl compound (either aldehyde or ketone), elemental sulfur and an amine (either primary or secondary, Scheme 1) continues to draw attention, despite the fact that this one-pot process was already disclosed in 1923 by Kindler [7]. This process, now known as the Willgerodt-Kindler (WK) reaction, allows for an easy introduction of chemical diversity into the thioamide backbone by simple variation of the aldone (R^1) and amine (R^2, R^3) components in the condensation step (Scheme 1). One of the fascinating features of this reaction resides in the fact that the system behaves as an auto-redox system in which the carbonyl gets reduced while the terminal methyl group gets oxidized into a thioamide [8]. As a large number of aldones and primary/secondary amines are marketed, a broad set of synthetically or pharmacologically useful thioamide products can be prepared in one step using this straightforward method. Despite its broad scope, the WK reaction has found so far only a limited field of application because of the high reaction temperatures and long reaction times usually required (120 – 130°C, several hours) [9,10]. The main synthetic application of the WK reaction resides in the transformation of an acetophenone or propiophenone using morpholine as amine partner into the corresponding thiomorpholide which is then further hydrolyzed to yield a carboxylic acid with the same number of carbons [11].



Scheme 1. Willgerodt-Kindler reaction

The WK reaction suffered in the past from a bad reputation because, in many instances, complex mixtures with several side-products were obtained, but recent improvements have rendered the reaction much more attractive. These improvements can be summarized as follows: (i) use of a dipolar aprotic solvent such as DMF; (ii) performing the reaction under base-catalyzed conditions (using TEA for example); and (iii) use of micro-wave activation [12]. It should be noted however that, as a general rule, aldehydes tend to react much more readily in the WK reaction than ketones. Furthermore, for the ketones the yield drops sharply when the number of methylenes (designated as "n" in the Scheme 1) linking the carbonyl to the

terminal methyl group increases [13]. The amine partner can be either primary or secondary [14].

Although there is no general accord as to the mechanism of the WK reaction, it can be conceived however that imine or immonium (in the case of aldehydes) or enamine formation (in the case of ketones) are the primary events taking place before any sulfurization takes place [15]. As these condensations between amines and aldones are all governed by generalized acid-base catalysis [16], it was anticipated that such a catalysis could be beneficial in the WK reaction. Therefore, in our continuing endeavour to improve the synthetic scope of the WK reaction, we explored the value of adding a catalytic amount of an acid in the reaction medium. We thus explored various reaction conditions using the WK reaction of acenaphthone (1-acetylnaphthalene) with morpholine and sulfur as benchmark reaction and leading to **1** (Figure 1).

2. Experimental Section

2.1 General Procedures. Melting points (uncorrected) were determined in open capillary tubes using a Büchi SMP 20 melting point apparatus. Infrared (IR) spectra were recorded using a dispersion of the product in potassium bromide disks by means of a Perkin-Elmer Model 297 spectrometer. Proton and Carbon-13 Nuclear Magnetic Resonance (^{1}H- and ^{13}C-NMR) spectra were recorded in $CDCl_3$ at ambient temperature using an AC 300 P Bruker spectrometer. Thin layer chromatography analyses were performed on Merck TLC plates (silica gel, 60 F 254, E. Merck, Darmstadt, ref. 5735). All the compounds reported here were found chromatographically homogenous in two standard solvents, *i. e.* acetone/toluene/cyclohexane (5:2:3, v/v/v) and methanol/chloroform equilibrated with ammonia (1:9, v/v). All reagents including Aluminum oxide (weakly acidic) and Montmorillonite K10 were purchased from Aldrich (Beerse, Belgium).

Table 1. WK reaction of acenaphthone with morpholine and sulfur[a]

Entry	T (°C)	Solvent/catalyst	Yield (%)
1	120	Neat	44
2	100	Dioxane	22
3	115	Pyridine	50
4	120	DMF	53
5	120	DMF/NMM.HCl	56
6	120	Neat/K10	58
7	microwave	Neat/K10	60
8	120	DMF/CH_3COOH	50
9	120	DMF/Pyridine.HCl	64
10	120	DMF/K10	72
11	120	DMF/PTSA	64
12	120	DMF/SiO_2	50
13	135	DMF/acidic Al_20_3	50
14	135	DMF/Na_2S	54
15	135	DMF/ Na_2S	56
16	microwave	DMF/K10	67

[a]All reactions were performed thermally and reaction times were all 6 hours except for entry 13 where the reaction time was 3 hours.

2.2 1-morpholino-2-(naphthalen-1-yl)ethanethione (entry 9)

A mixture of 5.1 g (30 mmol) of acenaphthone, 1.6 g (50 mmol) of sulfur, 8 g (92 mmol) of morpholine, 260 mg of Montmorillonite K10, and 5 ml of anhydrous DMF were stirred magnetically and heated at 120°C (silicone oil bath) for 6 h. After cooling overnight, the oily residue was washed first with 250 ml of 0.01 N sulfuric acid and then twice with 250 ml of distilled water. The red oily layer was then dissolved in 250 ml of boiling ethanol and the resulting suspension was filtered through a bed of charcoal. After standing 24 h in the refrigerator, a slightly yellowish crystalline material was collected. A second crystallization from ethanol afforded 72 % of the target compound, TLC-pure in all respects (m. p., IR, ^{1}H- and ^{13}C-NMR) similar to the one obtained in a previous study [12].

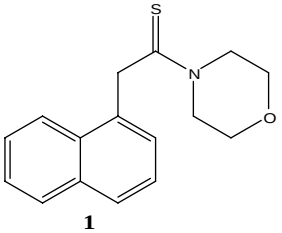
3. Results and Discussion

The idea of using an acidic catalyst is nothing new. In 1983, Amupitan [10b] treated benzaldehydes or acetophenones with sulfur and *N*,*N*-dimethylamine hydrochloride in the presence of sodium acetate to produce the expected *N*,*N*-dimethylthiobenzamides in good yields. More recently, Rolfs and Liebscher (1998) used *p*-toluenesulfonic [17] and Nooshabadi *et al.* [18] investigated H-Y zeolite as an acid catalyst.

The WK reaction of acenaphthone with morpholine and sulfur was chosen as benchmark reaction because of the ease of recovery of the resulting thiomorpholide (**1**). Under solvent-free conditions (entry 1), the thiomorpholide (**1**) was obtained after precipitation with diluted sulfuric acid and crystallization from ethanol in 44 % yield. The same procedure of isolation was used for all entries (see Table 1, entries 1 – 14).

As observed previously by many authors, DMF works well as solvent in the WK reaction (see entries 1-4); it was therefore used for our catalysis condition experiments. It should be noted however that the promotion of the WK reaction by DMF is less important for ketones than for aldehydes. As already noted by Carlson *et al.* [19] for the conversion of acetophenone with morpholine and sulfur into the corresponding thiomorpholide, when a high level of dilution by DMF is used, the proportion of a yellow impurity identified as 2-morpholin-4-yl-1-phenyl-2-thioethanone (**2**) tends to increase [19]. It is therefore crucial to maintain the proportion ketone/DMF low (after different trials, a ~1:1 ratio was established).

Different acid catalysts were investigated including: N-methylmorpholine hydrochloride (NMM.HCl, entry 5), acetic acid (entry 7), pyridinium chloride (entry 8), Montmorillonite K10 (entry 9), *p*-toluenesulfonic acid (PTSA, entry 10), and acid silica gel (entry 11). Silica gel and acetic acid were found ineffective but N-methylmorpholine hydrochloride, pyridinium chloride and p-toluenesufonic acid promoted the reaction. Montmorillonite K10 was found the most convenient, even improving the yield in solvent-free conditions (compare entries 1 and 6). Use of higher temperatures (135°C) along with shorter reaction time failed to improve the yield (not illustrated). Obviously strong acids (entries 5, 8, 9 and 10) were efficient while weak acids (entries 7 ,11, and 12) were found ineffective.



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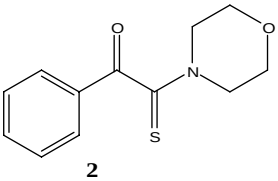

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Figure 1. Structures of the mentioned thiomorpholides

At the time of this research was in progress, we became aware of the interesting contribution of Klingele and Brooker [21] who used sodium sulphide as catalyst in the WK conversion of 2-methylpyridine to N-arylpyridine-2-thiocarboxamide and observed a significant increase of the yield when using this adjuvant. In our hands, addition of sodium sulphide (2% mol %) did not bring about a significant yield increase (entries 13 and 14). It should be noted that Klingele and Brooker [21] used much different reaction conditions: high temperatures (165°C), long reaction times (2 days) and huge excess of the 2-methylpyridine substrate (~50 times).

In view of the results obtained with entry 6 (which involves use of Neat/K10), we carried out the very same reaction under microwave activation under pulsed conditions as already reported in reference 12 and obtained a 60 percent yield. But in view of the excellent results obtained with entry 9 (which involves use of K10 as catalyst in DMF), we carried out the very same reaction under microwave activation under pulsed conditions as already reported in reference 12 and obtained a 67 percent yield after extensive column chromatography purification, the crude product being contaminated by a N,N-dimethylthioamide component possibly resulting from microwave-assisted transamidification from DMF. Obviously, further work will be required to improve this preliminary encouraging result.

4. Conclusion

In recent years, synthetic catalytic methods have generated intense research efforts in the quest to provide scientists with the tools required to perform carbon - heteroatom bond-forming reactions in an efficacious, atom-economical fashion. Such research efforts have created an extensive list of highly active catalysts that facilitate the synthesis of compounds of greater complexity and in fewer steps. As a consequence, the efficient constructive capacity found in recent catalyzed methodologies has been a determining factor in the process design of fine chemical and pharmaceutical building blocks and has resulted in the replacement of linearly designed organic transformations concise catalyst-mediated transformations. *Per se*, as mentioned in the introduction, the WK reaction has great potentials. If one considers for example that Friedel-Crafts acylation of an aromatic nucleus followed by WK reaction allows, in a two-step process, the creation of functionally rich molecules that would be otherwise cumbersome to assemble in a linear way. As the best conditions involved use of a strong acid in the presence of an excess of morpholine (acting also as base), we can infer that general acid-base catalysis is beneficial in the WK reaction. The present contribution opens new perspectives as to the scope of the WK reaction.

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