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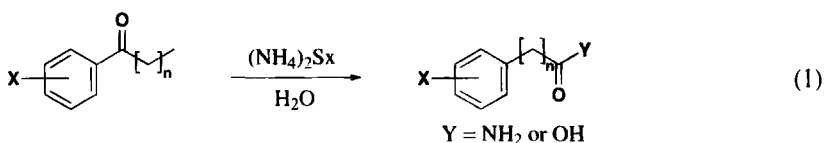
BASE CATALYSIS IN THE WILLGERODT-KINDLER REACTION

Jacques H. Poupaert*, Karim Bouinidane, Marc Renard, Didier M. Lambert, and Majed Isa†

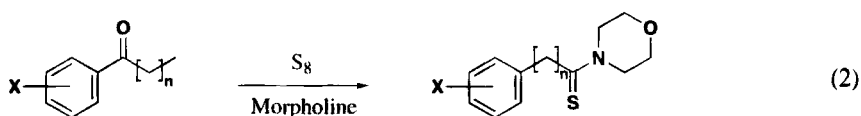
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The Willgerodt involved originally the reaction of arylalkylketones with ammonium polysulfide to yield chiefly amide derivatives (*Eq. 1*).¹ This reaction behaves as an auto-redox system in



which the carbonyl group of the ketone is reduced while the terminal methyl group is oxidized.² Some 25 years later, Kindler suggested a modification of Willgerodt's procedure using sulfur and an amine as oxido-reducing system to yield a thioamide (*Eq. 2*).³ The so-called Kindler modification of the Willgerodt reaction is now commonly named Willgerodt-Kindler (WK) reaction.⁴ Recently, sulfur has



been substituted by selenium.⁵ While the WK reaction is cited in most organic textbooks,⁶ and is of considerable synthetic interest, it has suffered from a rather poor reputation due to low yields and complex reaction mixtures generally encountered with multifunctional substrates.⁷ It is noteworthy that the yield drops sharply when the number of methylenes linking the carbonyl to the terminal methyl group increases.⁸ In practice, the reaction is useful only when the number of methylene groups is less than 3. Aromatic aldehydes and a variety of benzylic substrates such as benzylamine, benzyl cyanide, and benzyl halides, are converted to thiobenzamides under these conditions.⁹ The mechanism

itself remains also somewhat obscure. An evaluation of this complex and versatile reaction concluded that it cannot be described by a single mechanism.¹⁰ One of the drawbacks of the reaction is that the amine itself is often partially oxidized by sulfur.⁷ It is the reason for the popularity of morpholine as the amine partner due precisely to its greater resistance to oxidation.

In spite of the fact that the WK reaction has been extensively studied in the past (more than 600 papers had been published by the end of the 1960's),¹¹ little is known about the potential benefits of catalysis in this reaction.¹² Along this line, in an effort to improve the scope of the WK reaction, we initially explored the use of various acid or basic homogeneous or heterogeneous catalysts on a model reaction, *i.e.* the action of sulfur on 4'-methoxyacetophenone and morpholine (Eq. 3). This reaction

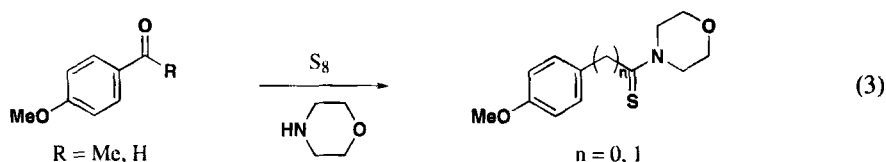


Table 1. WK Reaction of 4'-Methoxyacetophenone and 4'-Methoxybenzaldehyde with Morpholine and Sulfur (Eq. 3)

Entry	R	time (h)	T (°C)	Solvent/catalyst	Yield (%)
1	Me	6	135	Neat	31
2	Me	6	118	AcOH	<10
3	Me	6	100	Dioxane/ Al_2O_3 acid	<10
4	Me	6	135	Dioxane/ K_{10}	<10
5	Me	6	135	Dioxane/ SiO_2	<10
6	Me	6	100	Dioxane	18
7	Me	6	115	Pyridine	64
8	Me	6	115	N-methylmorpholine	61
9	Me	6	100	Et_3N	67
10	H	3	135	Neat	69
11	H	2	135	DMF	83
12	H	2	100	Et_3N	94
13	H	3	135	Neat/ K_{10}	79
14	H	3	135	Neat/ SiO_2	76
15	H	6	118	AcOH	42

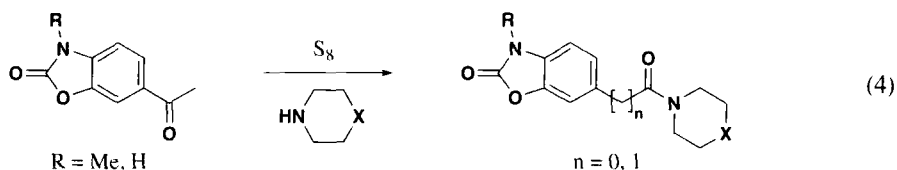
was selected as it gives a moderate yield (~30% of analytically pure material) using the procedure reported in Vogel's textbook.¹³ Our desire to investigate the role of acid/base catalysis in the WK reaction was motivated by the hypothesis that at an early stage of the reaction, an enamine is formed under acid/base catalysis. We therefore investigated the effect of various bases or acids and the effect

of adding 50% surface catalyst (w/w ratio vs. 4'-methoxyacetophenone) to the reaction mixture. With ketones, acidic conditions or solid acid catalysts were in general detrimental to the yield (Table 1, Entries 2-5). We confirmed this point in the aldehyde series which are known to react more easily than the corresponding acetophenones² where again substantially lower yields were obtained (Table 1, Entries 13-15).

Among the various conditions tried (Table 1) for the model reaction, the most interesting was the enhancement of the reaction when triethylamine (TEA) was added to the reaction mixture. Although pyridine and N-methylmorpholine behaved quite well, TEA is the most useful solvent because (1) a lower reaction temperature could be used with the benefit of azeotropic removal of water, (2) a cleaner reaction mixture was obtained at the end of the reaction and (3) the ease of recovery made higher yields possible. It should be stressed that sulfur insertion into C-H bond, a key step in the WK reaction, is indeed base-catalyzed.¹⁴

It is noteworthy that using Vogel's conditions (neat) we obtained only ~30% yield while ~80% yield of crude wet material is claimed.¹³ We found out that this material is badly contaminated with phenylglyoxalic thiomorpholide. The same problem was encountered when DMF was used as solvent. These findings were in full agreement with Carlson's studies.¹⁵

In view of the good results obtained above, we examined these conditions on more sensitive substrates such as 6-acetyl-2(3*H*)benzoxazolone and 3-methyl-6-acetyl-2(3*H*)benzoxazolone and various secondary amines such as morpholine, piperidine, 1-phenylpiperazine and 1-benzylpiperazine (Table 2). When 3-methyl-6-acetyl-2(3*H*)benzoxazolone was treated at 135° by an excess of morpholine and sulfur, sixteen hours were necessary to ensure complete transformation of the ketone and the



resulting thiomorpholide could be isolated in only 30% yield and with much difficulty from tarry material. The use of DMF as solvent improved the yield somewhat (42%). When the reaction was performed at reflux for 6 h with TEA added, the yield was considerably improved (Table 2, Entry 5).

Table 2. WK Reaction of 6-Acetyl-2(3*H*)-benzoxazolones using TEA

Entry	X	R	Yield (%)
1	O	Me	75
2	O	H	72
3	CH ₂	H	68
4	NC ₆ H ₅	H	70
5	NCH ₂ C ₆ H ₅	H	68

The experiments carried out suggest that the WK reaction is best performed using triethylamine as solvent. These conditions are now being used for the preparation of combinatorial chemistry libraries targeted toward σ -1 and σ -2 receptors.

EXPERIMENTAL SECTION

Melting points were determined using an Electrothermal melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 457 spectrometer using KBr pellets. Wave numbers are expressed in cm^{-1} . ^1H - and ^{13}C -NMR spectra were recorded at ambient temperature on a Bruker AC-300 spectrometer. Compounds were dissolved in DMSO-d_6 . Chemical shifts are expressed in the δ scale with TMS as internal standard. High performance reverse-phase thin layer chromatography conditions were: HPTLC plates RP-18 F-254 S (Merck), methanol:water (75/25, v/v). All surface catalysts were purchased from Aldrich. All solvents were of the A. C. S. reagent grade (Aldrich). Mass spectra (electron impact, 70 eV) were obtained by courtesy of Prof. G. K. E. Scriba (University of Münster, Germany). Only the molecular ion and the base peak are reported. Elemental analyses were obtained by courtesy of Prof. B. Masereel (FUNDP, Namur, Belgium). Triethylamine (TEA) was dried by refluxing over KOH for 1 h prior distillation at atmospheric pressure.

***N*-(4-Methoxyphenylthioacetyl)morpholine (Neat condition).**- A mixture of 21 g (0.14 mol) of 4'-methoxyacetophenone, 6.75 g (0.21 mol) of sulfur and 18 g (0.21 mol) of morpholine was stirred and heated in an oil bath at 135° for 6 h. The hot reaction mixture was allowed to cool overnight. On standing at room temperature for 12 h, the oil partially crystallized. The crystalline material was collected and washed with 50 mL of acetonitrile and then recrystallized from 100 mL of methanol. Overnight cooling in a refrigerator produced yellow crystals, which were collected and washed with 25 mL of diethyl ether to yield 9.56 g, mp $73\text{--}74^\circ$, *lit.* mp 71° ,¹³ also $73\text{--}74^\circ$.¹⁵ By reprocessing the mother liquors, an additional 1.37 g was obtained. The total yield was 31%. TLC: R_f 0.65. This material readily crystallizes in long needles from acetonitrile or from pyridine: water (50/50, v/v) though with high loss of material.

Anal. Calcd for $\text{C}_{13}\text{H}_{17}\text{NO}_2\text{S}$: C, 62.12; H, 6.81; N, 12.73; S, 12.75

Found: C, 62.22; H, 6.69; N, 12.79; S, 12.60

***N*-(4-Methoxythiobenzoyl)morpholine (Neat condition).**- A mixture of 26.23 g (0.2 mol) of 4'-methoxybenzaldehyde, 9.6 g (0.3 mol) of sulfur and 27 g (0.3 mol) of morpholine were stirred and heated in an oil bath at 135° for 3 h. The hot reaction mixture was diluted with 400 mL of ethanol. On standing at room temperature for 12 h, the mixture gave crystalline material that was collected and washed with 100 mL of diethylether to give 45 g of rough material. This material was recrystallized from ethanol to give pale yellow needles (32 g, 69%). mp $109\text{--}110^\circ$, *lit.*¹⁶ mp $109\text{--}111^\circ$. TLC: R_f 0.78.

Anal. Calcd for $\text{C}_{12}\text{H}_{15}\text{NO}_2\text{S}$: C, 60.73; H, 6.37; N, 5.90; S, 13.50

Found: C, 60.88; H, 6.21; N, 5.83; S, 13.45

***N*-(4-Methoxyphenylthioacetyl)morpholine (TEA condition).**- A solution of 42 g (0.28 mol) of 4'-methoxyacetophenone, 13.5 g (0.42 mol) of sulfur and 36.5 g (0.42 mol) of morpholine in 50 mL of dry TEA was stirred and refluxed for 2 h after which time the reflux condenser was replaced by a distillation head. Water and TEA were slowly distilled for 2 h. The reaction mixture was allowed to cool

overnight and solidified completely. It was recrystallized from 200 mL of methanol to yield long slightly yellow needles, which were collected and washed twice with 25 mL of diethyl ether to yield 40 g of material. By reprocessing the mother liquors, an additional amount (6.6) g was obtained. The total yield was 67%, mp 73-74°. TLC: R_f 0.65

3-Methyl-2(3H)-(benzoxazon-6-yl)acetothiomorpholide. General Procedure.- A mixture of 25 g (0.13 mol) of 3-methyl-6-acetyl-2(3H)benzoxazolone, 6.75 g (0.21 mol) of sulfur and 18 g (0.21 mol) of morpholine in 50 mL of dry TEA was stirred and refluxed for 4 h after which time the reflux condenser was replaced by a distillation head. Water and TEA were slowly distilled for 2 h. The hot reaction mixture was poured onto ice, acidified with 6N HCl. The resulting precipitate was filtered, dried and recrystallized from ethyl acetate to give the thiomorpholide in 75% yield. Mp 108-110° (*lit.* mp 108-110°¹⁷). ¹H-NMR and IR spectra were identical to the spectra obtained previously¹⁷.

Anal. Calcd for $C_{14}H_{16}N_2O_3S$: C, 60.84; H, 5.83; N, 10.13; S, 11.60

Found: C, 60.95; H, 5.71; N, 10.27; S, 11.75

2(3H)-(Benzoxazon-6-yl)acetothiomorpholide, mp 169-170°. IR: 3260, 1700, 1610, 1260 cm^{-1} . MS (m/z): 279 (M^{+1}), 278, 162. ¹H-NMR: δ 2.48 (s, 2H), 3.43 (t, 4H), 3.62 (t, 4H), 7.40-7.90 (m, 3H), 10.27 (broad, 1H). ¹³C-NMR: δ 26.22 (CH_2), 43.91 (CH_2), 65.75 (CH_2), 114.01, 119.55, 120.62, 131.49, 132.58, 146.50 (arom. C), 154.49 (C=O), 196.40 (C=S).

Anal. Calcd for $C_{13}H_{17}NO_3S$: C, 58.10; H, 5.07; N, 10.06; S, 11.51

Found: C, 58.22; H, 5.01; N, 10.26; S, 11.63

6-[(1-Piperidino)thiocarboxymethyl]-2(3H)benzoxazolone, mp 135-137°. IR: 3240, 1700, 1615, 1265 cm^{-1} . MS (m/z): 278 (M^{+1}), 277, 178. ¹H-NMR: δ 1.51-1.53 (m, 6H) 2.48 (s, 2H), 3.43 (t, 4H), 7.38-7.96 (m, 3H), 10.45 (broad, 1H). ¹³C-NMR: δ 23.75 (CH_2), 25.24 (CH_2), 26.26 (CH_2), 44.66 (CH_2), 114.29, 119.40, 120.62, 131.35, 132.93, 148.38 (arom. C), 154.17 (C=O), 196.37 (C=S).

Anal. Calcd for $C_{14}H_{16}N_2O_2S$: C, 60.84; H, 5.83; N, 10.13; S, 11.50

Found: C, 60.95; H, 5.81; N, 10.27; S, 11.75

6-[4-(1-Phenylpiperazino)thiocarboxymethyl]-2(3H)benzoxazolone, mp 173-175°. IR: 3240, 2900, 2815, 1700, 1625, 1270 cm^{-1} . MS (m/z): 354 (M^{+1}), 353, 120. ¹H-NMR: δ 2.50 (s, 2H), 3.46-3.50 (m, 8H), 7.28-7.98 (m, 8H), 10.29 (broad, 1H). ¹³C-NMR: δ 26.40 (CH_2), 43.68 (CH_2), 48.24 (CH_2), 114.27, 115.86, 119.29, 119.77, 120.77, 129.05, 131.66, 132.83, 146.74 (arom. C), 154.48 (C=O), 196.39 (C=S).

Anal. Calcd for $C_{19}H_{19}N_3O_2S$: C, 64.56; H, 5.41; N, 11.88; S, 9.07

Found: C, 64.72; H, 5.32; N, 12.01; S, 9.22

6-[4-(1-Phenylpiperazino)thiocarboxymethyl]-2(3H)benzoxazolone, mp 154-156°. IR: 3235, 2890, 2815, 1700, 1610, 1270 cm^{-1} . MS (m/z): 376, 91. ¹H-NMR: δ 2.50 (s, 2H), 3.19 (s, 2H), 3.50-3.62 (m, 8H), 6.79-8.08 (m, 8H), 10.25 (broad, 1H). ¹³C-NMR: δ 26.47 (CH_2), 43.91 (CH_2), 52.45 (CH_2), 62.04 (CH_2), 114.36, 119.71, 120.83, 127.17, 128.36, 129.05, 131.67, 132.97, 138.01, 146.72 (arom. C), 154.49 (C=O), 196.59 (C=S).

Anal. Calcd for $C_{20}H_{21}N_3O_2S$: C, 64.37; H, 5.76; N, 11.43; S, 8.72

Found: C, 64.52; H, 5.61; N, 11.73; S, 8.75

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