

## The thiophene connection

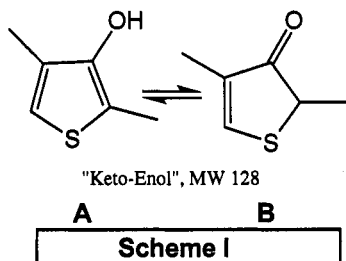
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### Abstract

The preparation of 3-hydroxy-2,4-dimethylthiophene **A** was critical to the successful commercial manufacture of the heterocyclic chloroacetamide herbicide Frontier™. Several different approaches were tried utilizing the readily available alkylsulfenyl chlorides or the sulfur mono and dichlorides. This technology provided several unexpected results as well as a successful route to the desired compound **A**. **A** has many interesting and potentially unique physical and chemical properties some of which were briefly studied.

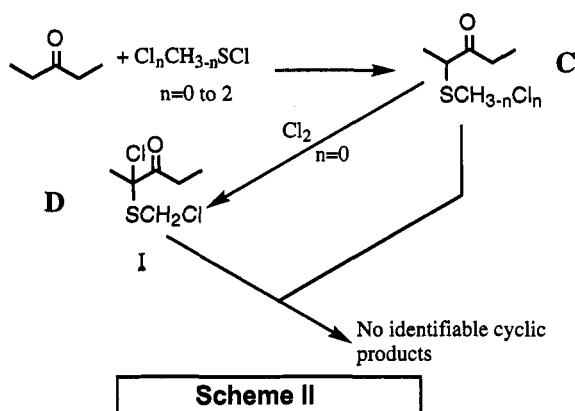
The preparation of 3-hydroxy-2,4-dimethylthiophene **A** (Scheme I)



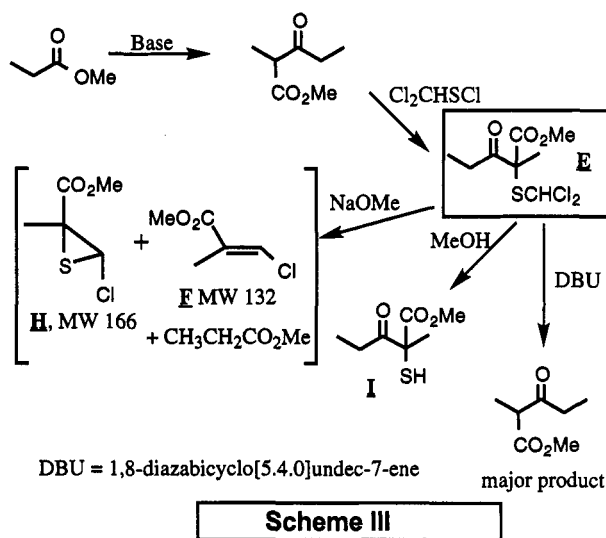
as an intermediate to the important herbicide Frontier®, i.e., 2-chloro-N-(2,4-dimethyl-3-thienyl)-N-(2-methoxy-1-methylethyl) acetamide, was a very exciting challenge. This material could easily be made by a variety of routes if the cost of its manufacture was not such a significant issue. However, due to the very competitive environment that commercial corn herbicides find themselves; the lowest cost possible was required for compound **A/B** preparation. Classical graduate chemists have developed great skills in understanding how to change chemicals' functionality; how to construct novel spatial arrangements or develop procedures for preparing intricate ring systems. However, this is just the first step in the requirement to become a valued process chemist. On top of these skills, the process chemist needs to understand how to utilize low cost commodity-type raw materials or at least how to have available easily prepared raw materials at the lowest cost from reliable suppliers; must consider all the environmental health concerns and safety issues of handling the components of the process and, along with these concerns, have a thorough understanding of how all the waste streams will be handled, including recycling as much of the components of the process streams as is possible. In addition to the cost of the major components of the system, catalyst used, and the need for low cost equipment is necessary. The influence of utility cost, depreciation and labor cost are all important in the development of a valued process. Finally, to make sure that all this gets done and is available to those who need it in its most useful form, an information system which provides the data in a reliable fashion is required. When a good chemist has mastered all of the above, they then become good process chemists. This normally requires about five years of diligent effort.

The first approach to prepare Intermediate **A/B** was to look for low cost ketones and olefins with the required carbon backbone and to find simple reagents which would add the required sulfur and allow for the required oxidation state.

Diethyl ketone was selected and allowed to react with  $\text{Cl}_n\text{CH}_3\text{-}_n\text{SCI}$  ( $n=0$  to 2) (Scheme II) under several different conditions.



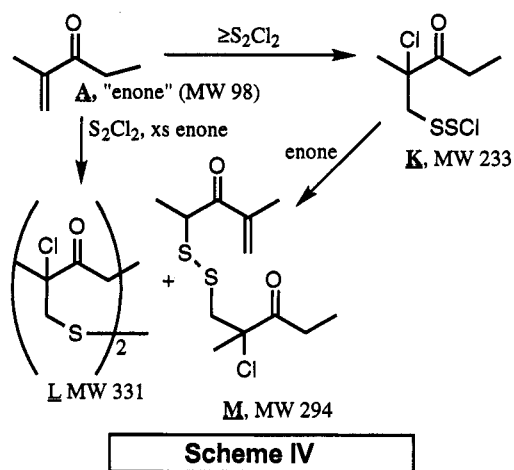
The  $n=0$  product of this system was the  $\alpha$ -thioether **C**. This could be cleanly chlorinated to the  $\alpha$ -chloro- $\alpha$ -thioether **D** ( $n=0$ ). No conditions could be found to cause cyclization of **D** to the thiophene ring structure. When  $\text{Cl}_2\text{CHSCI}$  was allowed to react with the Claisen condensation of methyl propionate, i.e. **E** in Scheme III followed by attempts to cyclize this new thioether with  $\text{NaOMe}$ ,  $\text{MeOH}$  or  $\text{DBU}$  (1,8-bicyclo [5.4.0] undec-7-ene).



No cyclized thiophene rings were prepared, but the system did provide several interesting by-products. Attack of the methoxide anion on the carbonyl of **E** gave methyl propionate plus methyl-2-methyl-3-chloroacrylate **F** and 2-methyl-3-chloro-2-methoxycarbonyl - thioepoxide **H**.

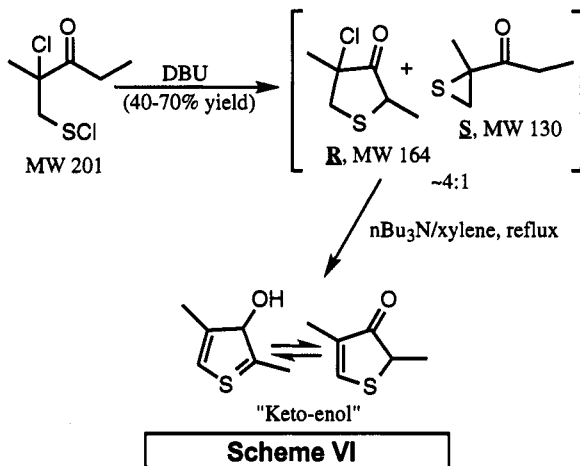
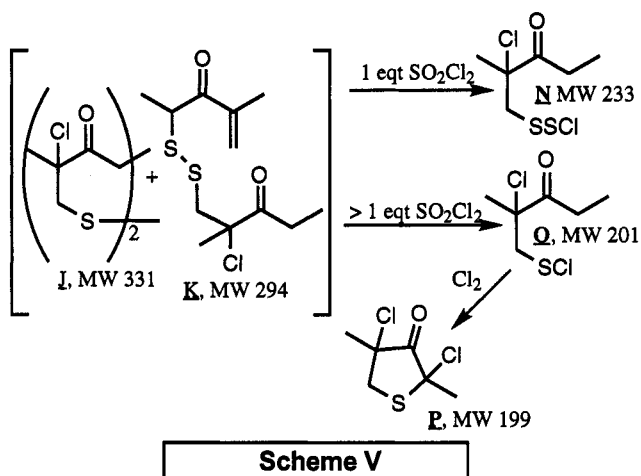
The next effort was to address the sulfur monochloride ( $\text{S}_2\text{Cl}_2$ ) addition to an active olefin, 2-methyl-3-ketopent -1-ene (enone)(Scheme IV).

Whether the enone was in excess or equivalency made a difference as to the product mixture. Excess enone provided a single product **L** which was the addition of 2 moles enone to one mole of  $\text{S}_2\text{Cl}_2$ , while excess  $\text{S}_2\text{Cl}_2$  initially gave the monochlorodithiochloride adduct **K** which subsequently reacted with another enone at the  $\alpha$ -hydrogen to yield **M**. When these dimeric intermediates were treated with either the equivalent or excess of sulfuryl chloride (Scheme V),



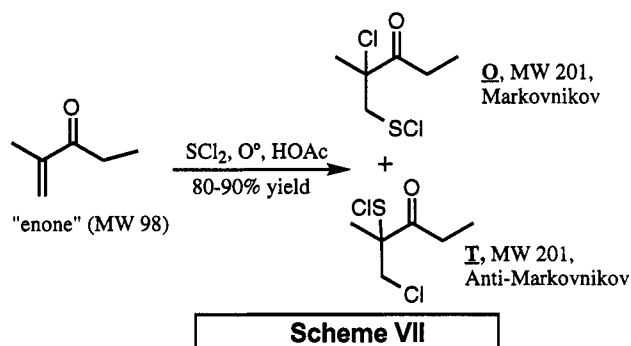
either the chlorothiochloride adduct **O** or the chlorodithiochloride adduct **N** were prepared.

Addition of chlorine to product **O** resulted in the preparation of 2,4-dichloro-3-keto tetrahydrothiophene. When this intermediate was treated with DBU two products (**R** & **S**) in a 4 to 1 ratio were prepared (Scheme VI).



The 4-chlorothiophene derivative is easily converted to the desired product. The fate of this thioepoxide of this system is not known. In addition, methanol caused simple methanolysis to **I** and DBU gave the Claisen product **J**.

This system did not prove to be useful for a commercial process. Therefore, the sulfur dichloride addition to the same enone was investigated. In this case the two products produced were the Markovnikov **O** and the anti-Markovnikov **T** addition product (Scheme VII).



The reactivity (Scheme IX) of intermediates of the chlorothiochloride with DBU was described. This process is thought to start by DBU forming a complex with **O** and then further reaction with DBU with the complex gives **R** and **S**, which yields the desired **A**. Na methoxide in MeOH displaces the 4-chloro function to yield the corresponding 4-methoxy derivative **U**. **U** does not cyclize to **A**.

The ratio of these products was strongly dependent upon conditions (Scheme VIII).

Expt	Change	Yield (%)	Markov/Anti
Standard*	1 M SCl <sub>2</sub>	87	52/48
a	0.25 M SCl <sub>2</sub>	86	69/31
b	Simultaneous addn	83	74/26
c	Inverse addn	81	89/11
d	EtOAc	80	85/15
e	5% HOAc	84	78/22
f	Chlorobenzene	77	98/2
g	xylene	20	99/1
h	large scale, 1-1.2 ratio	70	85/15

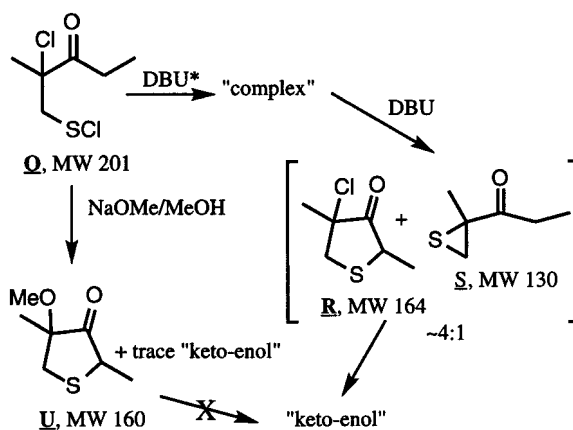
\*Enone to SCl<sub>2</sub> (1 to 2), CH<sub>2</sub>Cl<sub>2</sub>, 1 M, 0-5 C

**Scheme VIII**

Another interesting feature of working in an agricultural pesticide system is the fact that even as little as 0.1% yield of an intermediate is an initially encouraging result. It means that you are within 2 to 4 kcal of success. It is a difficult road to take 0.1% to over 90% yield, but the fact is that it takes less energy to do this than increasing a liter of water's temperature from 20 to 24°C.

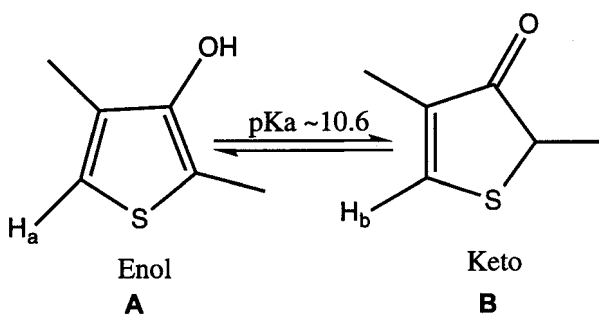
When you have at least a small quantity of what you are looking for, you are within the range of possibility. If you don't see anything at all you may be close to an area where there absolutely no possibility of success.

The 3-hydroxy-2,4-dimethyl thiophene system, **A/B**, is an equilibrium mixture which includes the keto form **B** (Scheme X).



\*Reaction using recovered DBU - poor results

**Scheme IX**



**Scheme X**

The ratio of these forms is very sensitive to conditions. An NMR study was undertaken (Scheme XI)

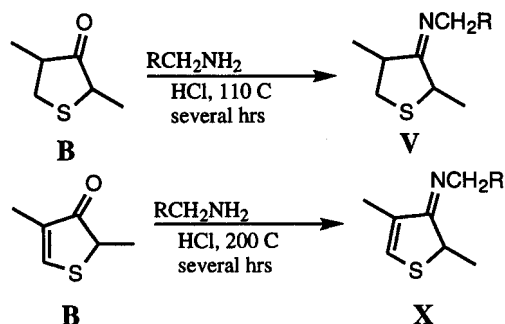
	Enol (NMR %)	Keto (NMR %)
1 M sln, no additive	40	60
1 M RNH <sub>2</sub>	64	36
2 M RNH <sub>2</sub>	77	23
3 M RNH <sub>2</sub>	85	15
1 M RNH <sub>2</sub> -HCl	63	37
0.2 M ZnCl <sub>2</sub>	32	68
1 M RNH <sub>2</sub> -HCl + 0.2 M ZnCl <sub>2</sub>	52	48
1 M TFA	28	72
2 M TFA	10	90
2 M TFA + 2 M RNH <sub>2</sub>	46	54
2 M TFA + 3 M RNH <sub>2</sub>	67	33

**Scheme XI**

and it showed how sensitive this system was. One can go from an 85% to 15% (E to K ratio) with 3 moles of a primary amine to 10% to 90% (E to K) with 2 moles of trifluoroacetic acid.

It requires hydrochloric acid as a catalyst plus 200°C for several hours to form the amine of the KE structure. The saturated system, i.e., tetrahydroalcohol equivalent, requires only 110°C to obtain the same yield at about the same rate.

The reactivity of this KE molecule is described by Scheme XII.



The reactivity of the KE may be dependent upon the actual form that it represents itself under the reaction conditions. Scheme XIII suggests that the difficulty may lie in the formation of a zwitterion, i.e.: as the principal electron distribution structure. Some examples of chemical shifts of analogous structures indicate this presentation of A/B may be useful.

H <sub>a</sub>	6.55	7.95
H <sub>b</sub>	2.17	1.85
H <sub>c</sub>	8.45	3.68
H <sub>d</sub>	2.30	1.55
Zwitterions		

**Scheme XIII**

\* Assisting these lead professionals were several others: L. Stach, W. Lipa and S. Jenkins.