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SOME ASPECTS OF THE WILLGERODT–KINDLER REACTION AND CONNECTED REACTIONS

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Abstract – This review presents a discussion, in near chronological order, of the course of Willgerodt–Kindler reactions that occur under different experimental conditions. It is possible to isolate the various intermediates postulated in our initial working hypotheses of these reactions, allowing us to clarify *inter alia* the course of the isomerization process. Of note, we show that room temperature reactions follows the same reaction pathway as those synthesized under more severe experimental conditions, and this observation allows us to comprehend the chemism of the initial steps of the process.

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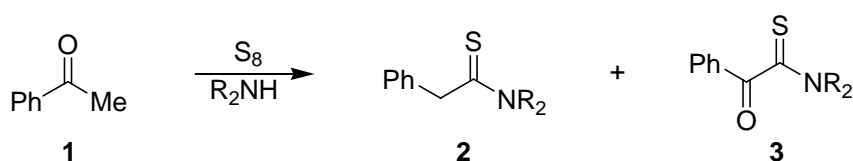
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INTRODUCTION

The reaction of sulfur at high temperatures with organic compounds that have reactive groups, and in particular, a carbonyl and an alkyl group, in the presence of a secondary amine is known as the Willgerodt–Kindler reaction.^{1,2} An example of this type of reaction involves acetophenone (**1**)



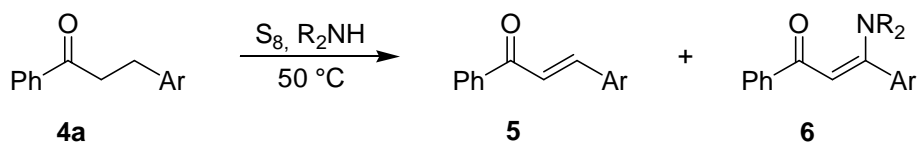
and therefore the reaction (if complete) formally includes

- a) the thionation of an alkyl group, and
- b) the reduction of a carbonyl group.

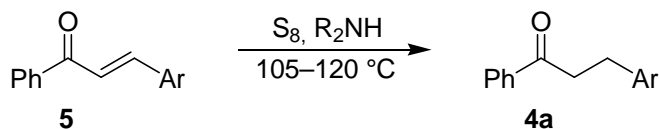
However, during the course of the research carried out in this field, the formation of additional compounds different from thioamides and ketothioamides, (for example, the formation of cyclic compounds), has been observed by some groups.^{5–10}

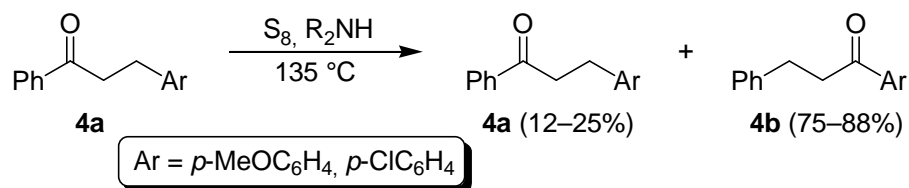
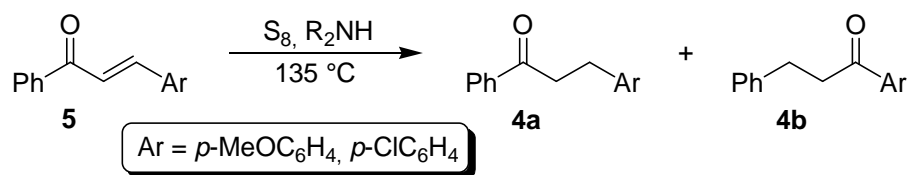
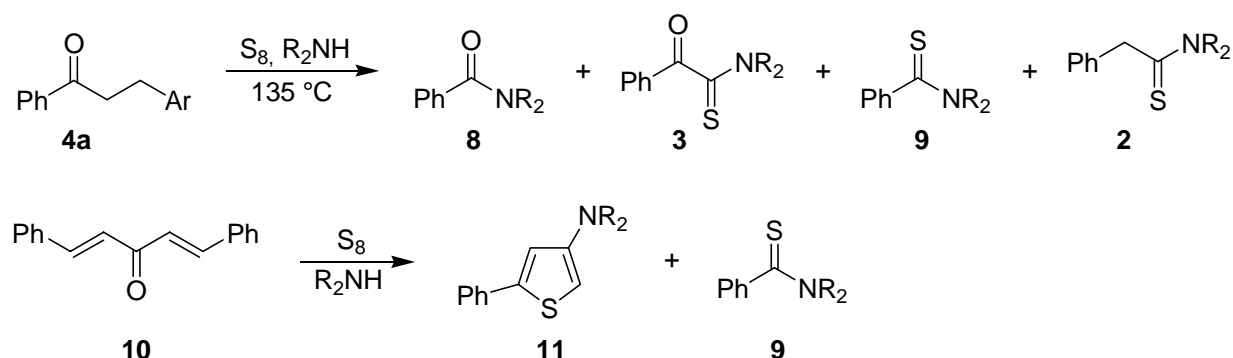
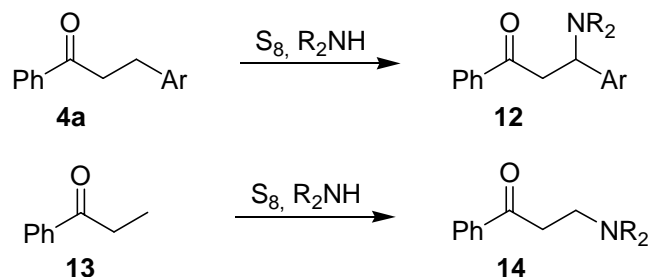
The following examples highlight the most significant processes observed working under different experimental conditions with mono or bis-aryl-alkylketones (saturated or unsaturated) containing two to five (but sometimes more) carbon atoms in the chain. Other reactions can occur either together with, or in place of, the two processes discussed above. It should be noted that not all of these have been previously revealed in this type of reaction. Some are to be considered normal, but transient, states of the reaction, the products of which are not easy to isolate. Others are produced only in particular cases.

- a) The formation of unsaturated compounds^{11–13} (either with or without a carbonyl group).

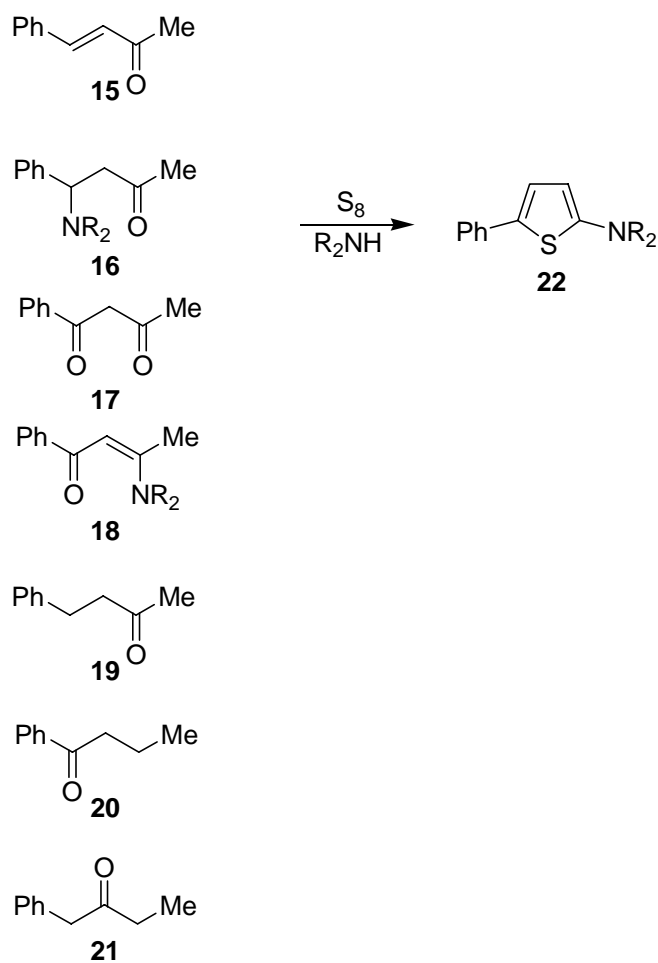


- b) The reduction of double bonds.¹⁴



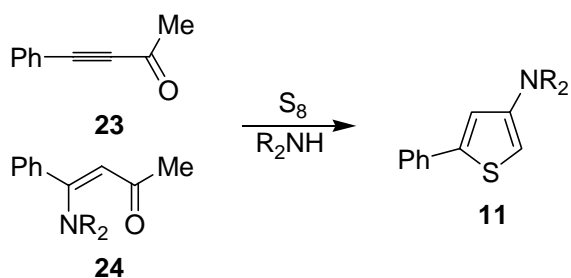
c) Isomerization.^{14,15}d) Reduction and isomerization.¹⁴e) Fragmentation.^{12,14,16,17}f) Formation of β-aminoketones.¹⁴

g) Formation of cyclic compounds. This particularly occurs for long chains of carbon atoms. These compounds are either stable or transient, depending on the cycle stability. For example, from **15–21**, the thiophene derivative (**22**)^{5,8} is obtained as the main product⁵ (Scheme 1) (Slater and Heywood⁶ and Bacchetti *et al.*⁷ reported on the reaction of **15**, and the reaction of **19** and its isomers (**20** and **21**), was reported by Asinger *et al.*⁸

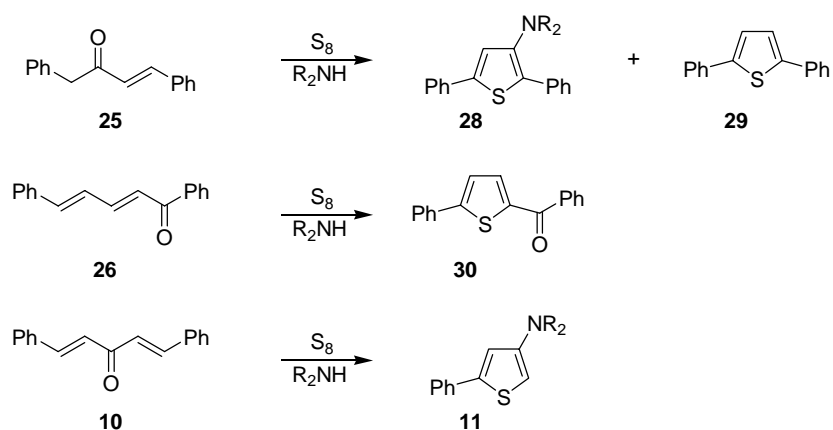


Scheme 1

In contrast, in the case of the compounds (**23** and **24**), the isomer compound (**11**)⁹ is the major product. (An interpretation of this particular case of isomerism is reported in the chapter dealing with thiophene derivatives.)

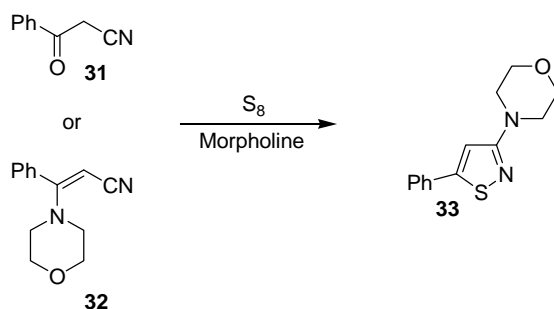


Thiophene derivatives are also obtained starting from benzyl styryl ketone (**25**)¹⁰ from cinnamylideneacetophenone (**26**)¹⁶ and dibenzylideneacetone (**10**)¹⁶ (Scheme 2).

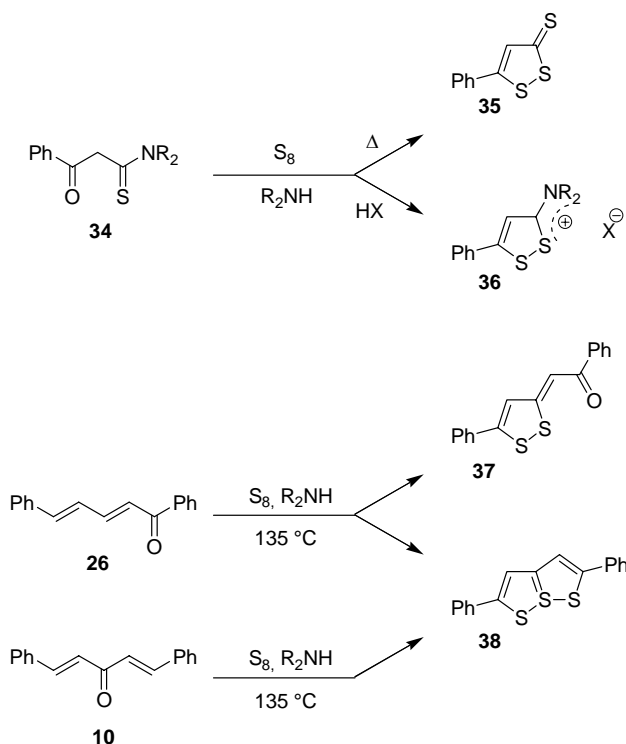


Scheme 2

When cyanoacetophenone (**31**) and β -cyanostyryl- α,N -morpholine (**32**) (where Ar = Ph) react with sulfur and morpholine, the 3-morpholine-5-phenylisotiazole (**33**)¹⁷ is obtained.

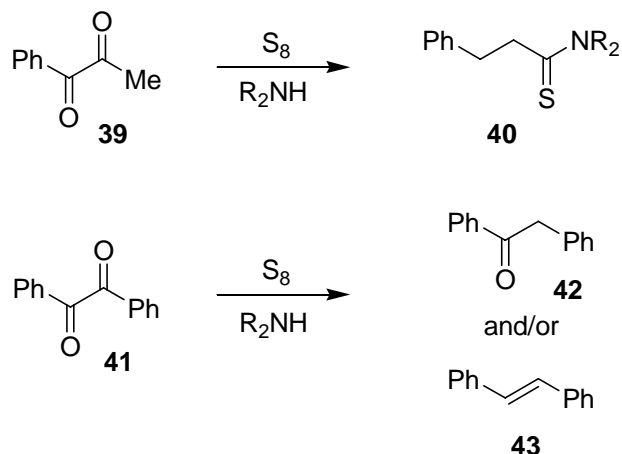


Of particular interest for evaluating the proposed pattern of the reaction course is the formation of 1,2-dithiole derivatives, such as compounds (**35–38**)^{16,19} starting from **34**, **26**, or **10** (Scheme 3).



Scheme 3

If a compound contains several identical groups then they can all be involved in the reaction (Scheme 4).^{11,18}



Scheme 4

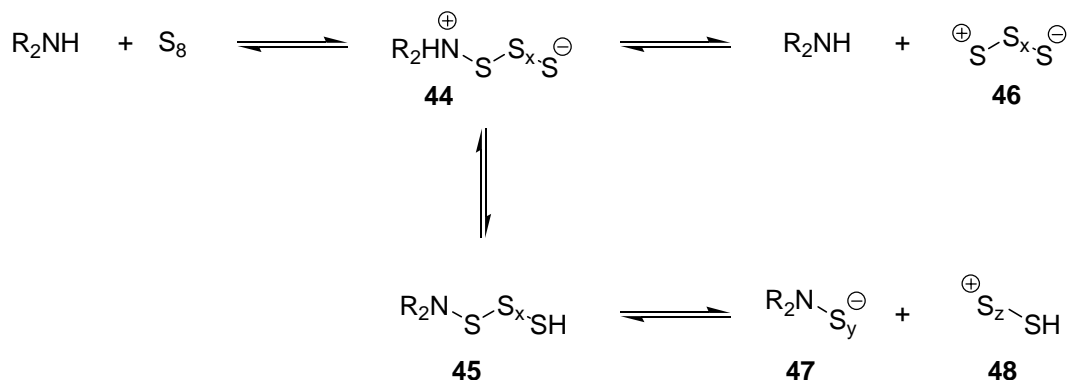
Finally, it is possible to grade the attack according to the experimental conditions adopted (i.e., the nature of the reagents, and the reaction temperature and time). Reactions carried out with the addition of a particular reagent (*e.g.*, PbO or H₂S) are interesting, as well as those in which, instead of sulfur and an amine, polythioamine alone or in the presence of hydrogen sulfide is used. This means that these chemicals can be considered¹² the forerunners of the sulfur species involved in the reaction and/or their prototypes.¹⁹ By using polythioamine and hydrogen sulfide, it is possible to obtain thioamides and/or ketothioamides, depending on the experimental conditions used.^{19,20}

In summary, when an organic compound reacts with sulfur in the presence of a *sec*-amine, it can undergo a series of electrophilic and nucleophilic attack (involving all its functional groups, *e.g.* CH-acids, activated vinyls, and carbonyl and cyano groups), i) from the sulfur species formed by the reaction between the sulfur and the amine, or ii) from the amine itself. Therefore, the resulting reaction products will be a combination of all the processes that would have occurred, according to the nature of the reactant, the reactivity of the groups present within it, and the order in which they are connected with each other.

As previously stated, the selection of the appropriate experimental conditions is very important. Reactions carried out at room temperature have proven to be particularly important, because they enable us to: i) isolate the first intermediates of the process; ii) evaluate their stability; and iii) follow their evolution in the formation of other compounds up to the final stable products. This brief summary attempted to provide a comprehension of the nature of all the observed synthetic processes. These are further illustrated in the following text on the reactions of an appropriately functionalized organic compound with sulfur and an amine under various experimental conditions.

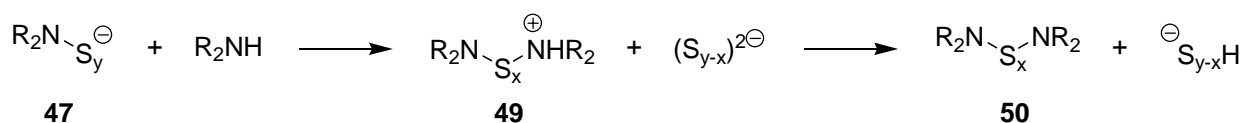
1. NATURE OF THE REAGENTS

In the literature, there have been a few reports on the nature of the species that are active in the course of the Willgerodt–Kindler reaction with sulfur and an amine. According to Davis and Nakshbendi,²¹ the following reactions occur between sulfur and an amine at room temperature (Scheme 5).



Scheme 5

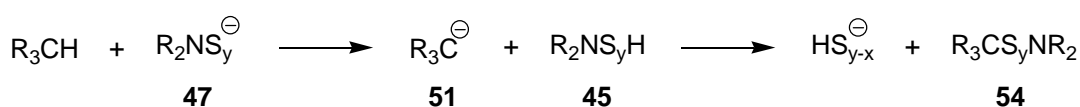
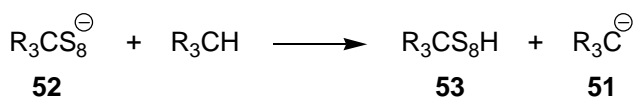
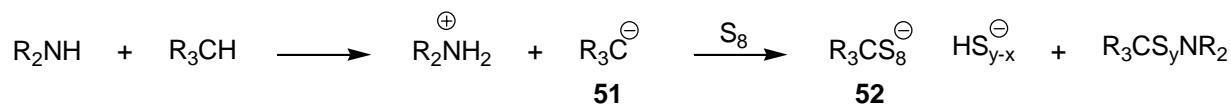
It is possible to isolate the polythiodiamine (**50**),²² the formation of which leads to the supposition that the $\text{R}_2\text{-N-S}_y^{\ominus}$ species, a weak base, can undergo a further nucleophilic attack along the chain of sulfur atoms.



(When working in the presence of lead oxide, the process becomes irreversible because of the formation of lead sulfide.)

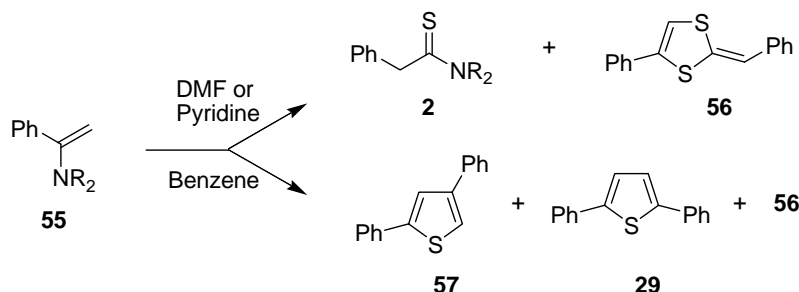
1.1. ELECTROPHILIC ACTION OF THE SULFUR-CONTAINING SPECIES

When a compound containing a CH acid is placed in contact with sulfur and a secondary amine, the carbanionic species formed by the action of the amine can itself determine the opening of the sulfur ring.^{23–25}



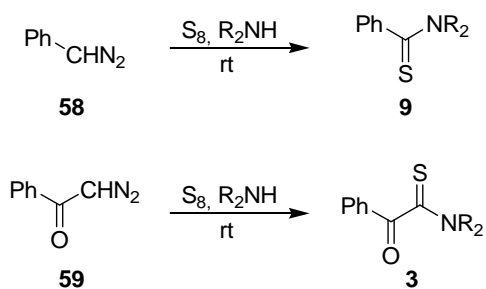
The formation of polythiodiamides at $T = 40\text{--}50\text{ }^{\circ}\text{C}$ indicates that, in the case of secondary amines, hydrogen sulfide is formed by reaction of the hydrogen atoms bound to the nitrogen atoms rather than by the reaction of the hydrogen atoms of the amine methylene groups. Compounds with a high nucleophilic

strength, such as the styrylamine (**55**) react with sulfur (in DMF or in pyridine) to afford the thioamide **2**, together with a small yield of the 1,3-dithiole derivative (**56**).^{26,27} In benzene, both the dithiole derivative and the thiophene derivatives (**57** and **29**)²⁷ are formed in high yields (Scheme 6).

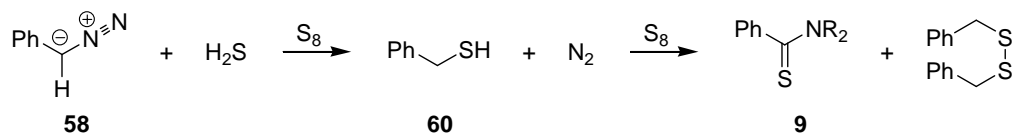


Scheme 6

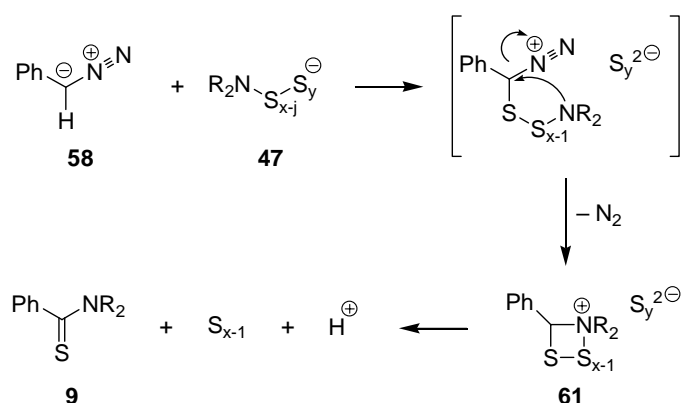
Compounds such as the diazoalkane (**58**)²⁸ and diazoketone (**59**)²⁹ react at room temperature with sulfur and a secondary amine to form thioamides (**9** and **3**), respectively.



Here, it appears that the reaction begins with an interaction between the nucleophilic carbon and the sulfur-bearing species, $\text{R}_2\text{N}-\text{S}_x^-$ (**47**). If this is true, then hydrogen sulfide should react with the diazo derivatives to afford benzyl mercaptan (**60**) as an intermediate, which, through a reaction with sulfur and morpholine at room temperature, gives thiobenzomorpholide (**9**).³⁰

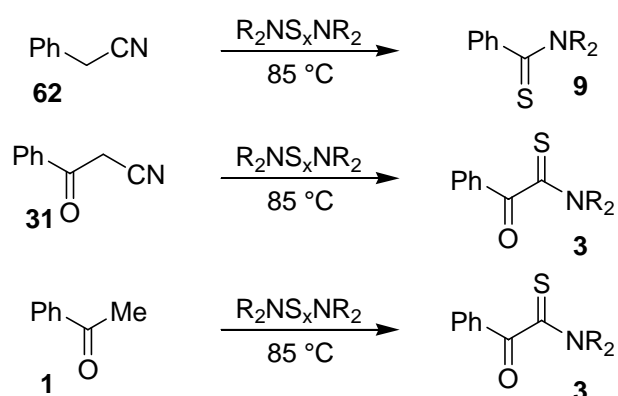


Therefore, the reaction of **58** can be formulated, for example, as follows.

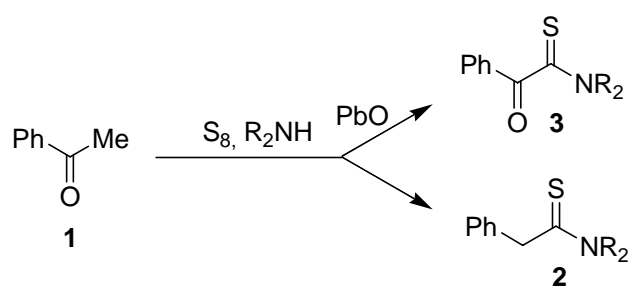


In the case of ketomethylene compounds, the thiation of the electrophilic species can also occur at room

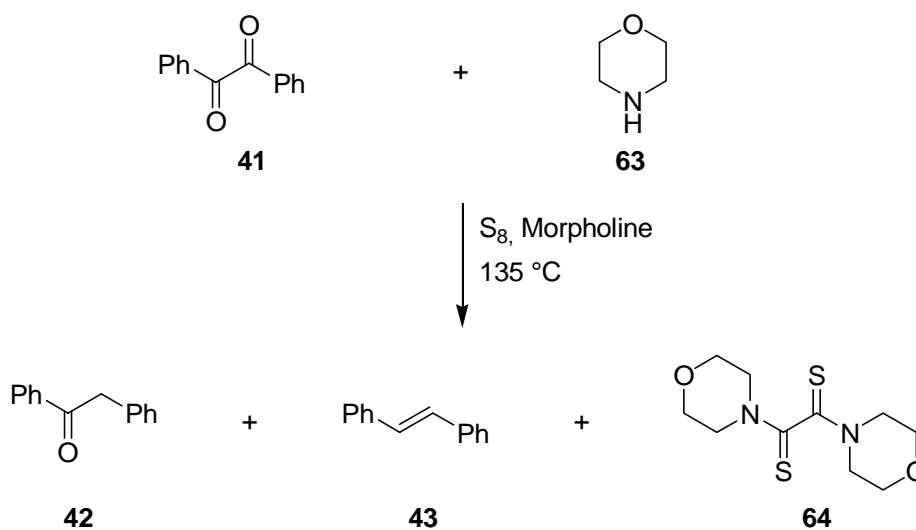
temperature, but it becomes consistent from 50 °C,^{6,8} and remains practically the only type of attack carried out by the sulfur species at 80 °C.²⁰ The thiation of CH acids can also be carried out by the polythiodiamine (**50**), but it is less active; and the presence of the second basic residue evidently makes the polythiol chain more stable towards the nucleophiles. However, polythiodiamines can react with diazo compounds at room temperature,³¹ while in the case of arylalkyl ketones and of α -methylenenitrile, a significant reaction is shown at 80 °C. In the temperature interval 80–120 °C, polythioamines show a selective electrophilic action on these compounds.



It is interesting to note that keto thioamide (**3**) is formed when a keto-methylene compound reacts with a sulfur/*sec*-amine mixture, especially if in the presence of a compound that is able to extract the nucleophilic species (for a full comparison of the action of different test reagents, compare Tables 1 and 2).



The tendency of the sulfur species formed by sulfur and the amine to react even with a low-reactivity methylene group is evident in the case where a compound, such as benzyl (**41**), which does not contain any CH acids, is treated with sulfur and morpholine. Together with compounds (**42** and **43**), quite unexpectedly, the formation of a discrete yield of dithioxaldimorpholide (**64**) has been observed. Compound (**64**) arises from the action of the sulfur species on the morpholine (**63**) itself (Scheme 7).



Scheme 7

In this case, the methylene groups involved are those of morpholine that usually, because of the presence of more acidic CH groups, are either little or not involved at all in the reaction. This is evidence of the high electrophilic reactivity of the sulfur species.

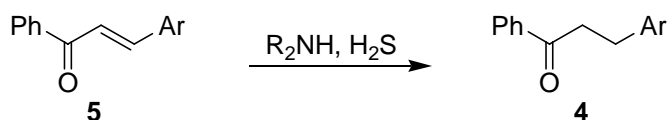
1.2. NUCLEOPHILIC ACTION OF THE SULFUR-CONTAINING SPECIES

The production of nucleophilic sulfur-containing species in the course of a Willgerodt–Kindler reaction is indicated by the formation of hydrogen sulfide. The influence of the hydrogen sulfide on the course of the action is clear from examination of Table 1, Entries 1 and 2. It can be seen that, if hydrogen sulfide is subtracted from the reaction mixture (e.g., by working in the presence of lead oxide), then the prevailing yield is the formation of the non-reduced compound (Table 1, Entries 1–3). In contrast, if hydrogen sulfide is added to the reaction mixture of the ketomethylene compound with the polythiodiamine (**50**), then the formation of thioamides, and not of the ketothioamides, is observed (Table 1, Entries 4 and 5). Therefore, the combined action of the polythioamine and hydrogen sulfide leads to the same products obtained as when sulfur reacts with a secondary amine.

The case involving nitriles is significant. In the absence of a sulfur nucleophilic species, an attack on the reactive methylene takes place, and is followed by substitution of the cyano group with an amine residue (Table 2, Entries 1, 4–9, and 12–15). In the presence of a nucleophilic reagent, such as hydrogen sulfide (added or formed *in situ* by the sulfur and amine) at a sufficiently high temperature, the nitrile pairs with the hydrogen sulfide, resulting in formation of thioamides with an equal number of carbon atoms as the substrate (Table 2, Entries 2,3, and 10).^{17,32} The observation that when a keto methylene compound is treated with polythiodiamine in the presence of hydrogen sulfide at 85 °C, the thioamide is obtained instead of the keto thioamide, accounts for the influence of the nucleophilic agent. It also induces one to think that the relatively high temperatures adopted for the Willgerodt–Kindler reaction are mainly required for the formation of more consistent yields of the nucleophilic sulfur species.

The addition of hydrogen sulfide has also proven to be influential in the case of reactions carried out with sulfur and a secondary amine.^{9,17} However, the sulfur nucleophilic species, even before they react with the carbonyl group, can react with the ethylene group of α,β -unsaturated ketones³³ and β -enamino ketones, which are both intermediates of the Willgerodt–Kindler reaction. In the case of unsaturated ketones, the reaction with hydrogen sulfide competes with that of the amine. The latter is more significant for the course of the reaction, and leads to the formation of β -thio derivatives. From the desulfuration of these derivatives, probably due to the amine, the saturated ketones are formed once again. A similar reaction for α -mercapto ketones has been also reported by Asinger et al.³⁴

In accordance with this, the chalcone (**5**) reacts with hydrogen sulfide in the presence of morpholine to give the ω -phenylpropiophenone (**4**).^{13,15}



β -Enamino ketones are more sensitive to the action of the hydrogen sulfide.^{13,15,35} On one hand, these reactions account for the rapid formation of saturated ketones when unsaturated ketones react with sulfur and a secondary amine, and on the other hand, they account for the low availability of the nucleophilic sulfur species at low temperatures, as the attack on the carbonyl group can also occur then, even with low performance.

Table 1.

Entry	Compound	Reactant	Solvent	Temp (°C)	Time (h)	Product	Yield (%)
1	1	S ₈ , MoH ^a	—	85	6	2	40.9
2	1	S ₈ , MoH, PbO	—	85	6	3	20.8
3	1	S ₈ , MoH, PbO	—	145	6	3 2	10.4 21.5
4	1	Mo ₂ S ₃	Pyridine	85	12	3	20.4
5	1	Mo ₂ S ₃ , H ₂ S	Pyridine	85	12	2	41.2
6	1	Mo ₂ S ₃ , MoH	—	85	12	3 2	26.6 3.4

^aMoH = morpholine.

Table 2.

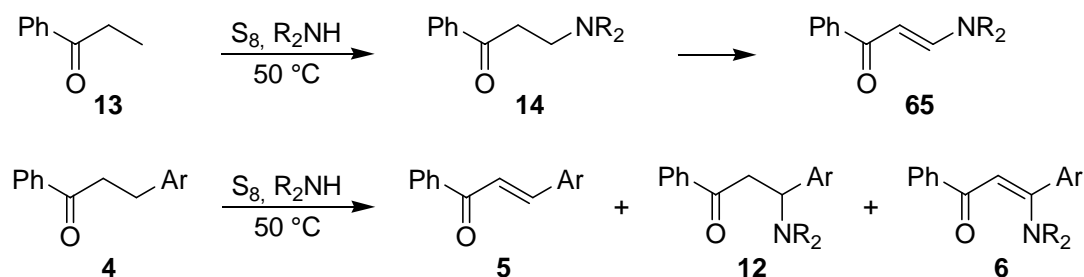
Entry	Compound	Reactant	Temp (°C)	Time (h)	Product	Yield (%)
1	62	S ₈ , MoH ^a	105	4	9	43.5
2	62	S ₈ , MoH	120	4	9 2	31.2 8.2
3	62	S ₈ , MoH, H ₂ S	120	4	9 2	25.2 31.3
4	62	Mo ₂ S	105	6	9	14.3
5	62	Mo ₂ S	120	6	9	26.2
6	62	Mo ₂ S ₂	80	12	—	—
7	62	Mo ₂ S ₂	105	6	9	19.0
8	62	Mo ₂ S ₂	120	4	9	28.6
9	62	Mo ₂ S ₃	105–120	4	9	35.7
10	62	Mo ₂ S ₂ , H ₂ S	110	2	9 2 PhCO₂H 33	16.7 7.0 8.7 6.7
11	31	S ₈ , MoH	125	3	103 40 3	11.8 4.0 2.5
12	31	Mo ₂ S	110	4	3	14.9
13	31	Mo ₂ S ₂	80	10	3	12.8
14	31	Mo ₂ S ₂	120	10	3	23.4
15	31	Mo ₂ S	80	10	3	21.2
16	31	Mo ₂ S	120	3	3	32.0

^aMoH = morpholine

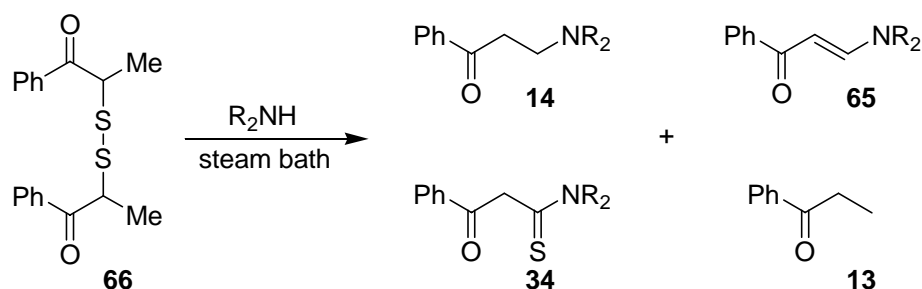
1.3. AMINES

The *sec*-amines present in the reaction mixture have several functions that involve the various phases of the entire process:

- They determine the formation of the reactive species (carbanions and sulfur species).
- They add to the unsaturated compounds initially present as reagents or formed as intermediates, according to previous postulation,¹⁴ and later verification.¹² Therefore, they promote the reactive functions lying towards the extremity of the chain.

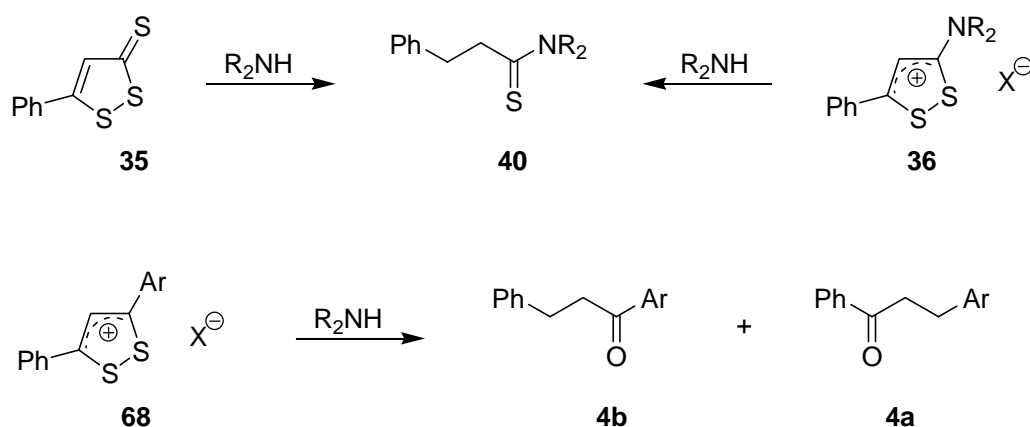


c) They react with di- and polysulfides present in the reaction mixture. At this point, it is interesting to report the case of the disulfide (**66**). The reaction of this compound with morpholine alone (at a temperature of about 100 °C) leads to the formation of the same species obtained when propiophenone reacts with sulfur and morpholine in the temperature range 50–80 °C:¹³



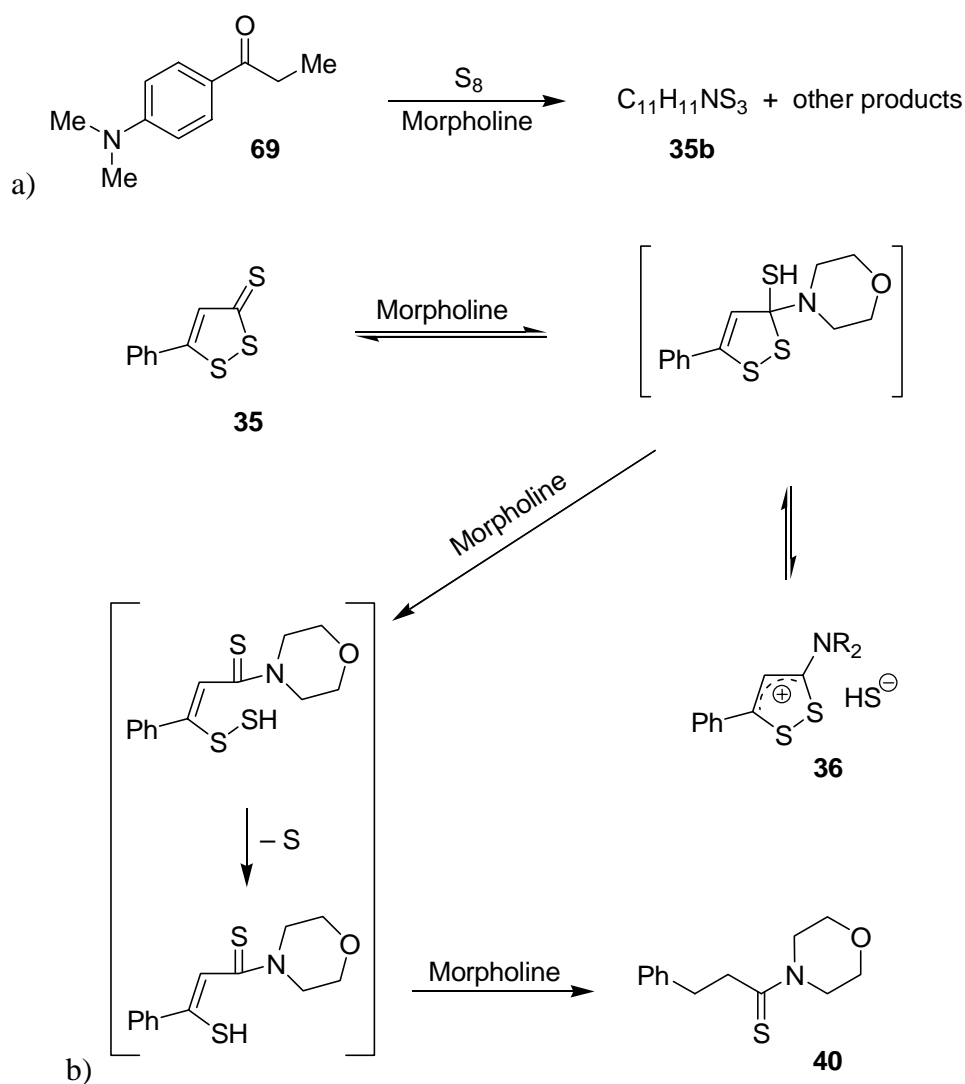
It appears evident that, from the reaction between the disulfide and amine, sulfur species are originated that allow the process to proceed up to the formation of the thioamide. (For the formulation of the reaction, see Scheme 13.) There is no doubt that the high reactivity of the disulfide and compounds that are initially formed because of the action of the amine is due to the presence of the carbonyl group. (β -Phenethyl disulfide ($\text{PhCH}_2\text{CH}_2\text{S-})_2$ (**67**) under the same conditions remains unaltered).³⁰

d) Finally, they play an important role in the reduction of the carbonyl group. The impossibility of the amines participating directly in this process has been verified repeatedly in the course of our research. One of their prominent actions consists of determining the degradation of the adduct (the dithiole derivative) formed between the organic compound and the reactive sulfur species. Except in cases where the dithiole system is not stabilized by conjugation with an electron-donating group (as in the case of compound (**35**)) or by resonance (as in the case of compounds (**35–38**)), it is very sensitive towards the action of nucleophiles (Scheme 8). This usually does not allow for dithiole isolation among the products of these reactions.



Scheme 8

When dithiolenes are heated with *sec*-amines, they are transformed into benzylacetophenones (**4**),³⁶ if α,ω -bis-aryl substituted, or into the corresponding thioamides (**40**), if monoaryl substituted¹⁹ (Scheme 8). In the former case, isomerism is manifested.



Scheme 9

In this way, the same final compounds are found in the reaction of the propiophenone (**13**)¹⁹ (the reaction of **13** under mild temperature conditions is reported in Scheme 12) and of benzylacetophenone (**4**) with sulfur

and morpholine at high temperatures.¹⁵ This hypothesis has been verified with the finding, among the reaction products of the *p*-dimethylaminopropiophenone (**69**), of a compound having the composition C₁₁H₁₁NS₃,³⁵ which was identified as the *p*-dimethylaminophenyl-1,2-dithiole-3-thione (**35b**).¹⁰ This species, through the action of morpholine, is transformed into **40** (Scheme 9) in accordance with the role given to the dithiole derivatives of intermediate species both in the reduction of the carbonyl group and in the isomerization process.

2. COURSE OF THE REACTION

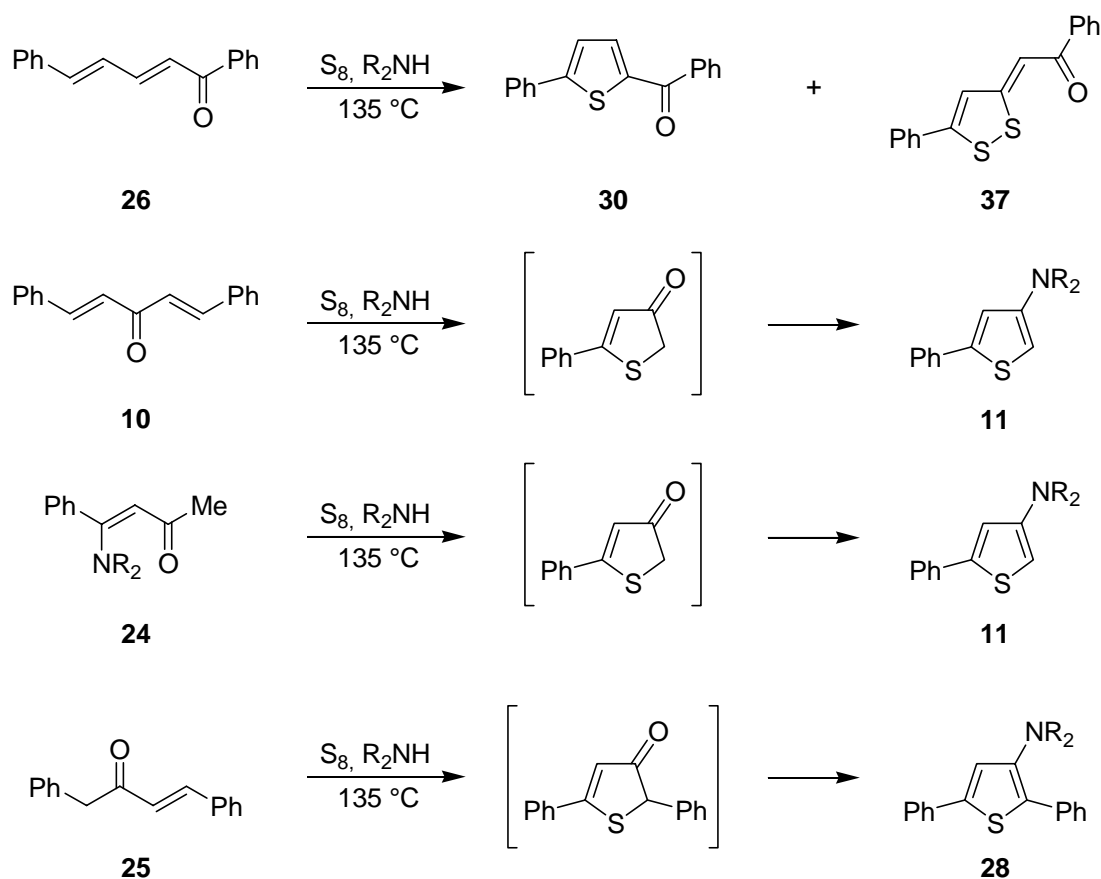
2.1. POINT OF THE INITIAL ATTACK

We have previously shown that, in the temperature range 20–100 °C, the reaction of CH acids with sulfur species takes place in conditions in which the carbonyl group contained in the CH acid molecule has little or no involvement in the reaction. There is enough evidence to postulate that the attack on a CH acid constitutes the first stage of the reaction, even when working at a usual reflux temperature. It has been found that, at these temperatures, even for very brief reaction times, the same compounds (still containing the unreacted carbonyl) are isolated as when working at lower temperatures.¹⁶ A confirmation of the priority¹⁶ of the reaction of the alkyl chain is the preferred formation of cyclic compounds when the length of the chain allows for this. In addition, in this case, the carbonyl group either remains unaltered, or is found as an enamine derivative^{9,16} (see Scheme 10).

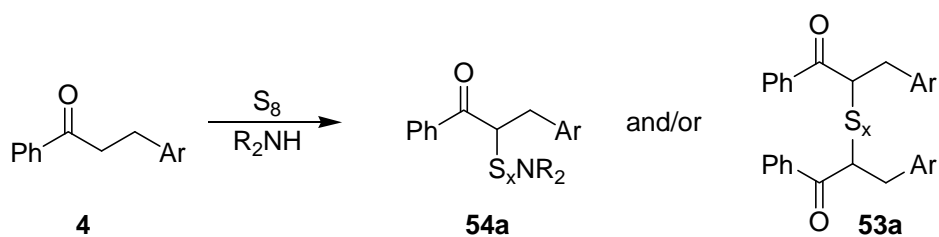
This finding verifies the assumption of the formation of unsaturated compounds as intermediates of Willgerodt–Kindler reactions,¹⁵ and allows reassessment of a process that previously had not been correctly interpreted;³⁷ e.g., in the synthesis of sulfur heterocyclic, the use of unsaturated ketones and more reactive and more easily obtainable ketones, such as benzyl styryl ketone (**25**),¹⁰ cinnamylidene acetophenone (**26**)¹⁶ and benzylidene acetone (**15**).

The conclusions of other researchers are in accordance with this assumption.³⁸ In particular, Asinger *et al.*³⁴ have shown that reactions between carbonyl compounds, sulfur, and ammonia lead to the formation of thiazoline and imidazolinethiones. In this last type of reaction, carried out at room temperature, the thiation of the CH acids leads to α -mercapto ketones, which are intermediates of the cyclic compounds. However, in no case does the carbonyl group undergo a reduction process, which instead, occurs at higher temperatures than those at which the Willgerodt–Kindler reactions are carried out. The thiation process, when performed under Willgerodt–Kindler reaction conditions, must preferentially lead to the formation of a polysulfide derivative; i.e., polysulfonamide (**54**) and polysulfide (**53**). The α -mercapto ketones eventually formed react mercaptan-like with sulfur (even at room temperature) in the presence of amine to give disulfides.³⁰ Owing to the action of the amine, these in turn produce polysulfonamides and thioles,³⁷

which go back into circulation (Scheme 13).



The intermediate formation of polysulfonamides has been postulated also by other researchers.³⁴

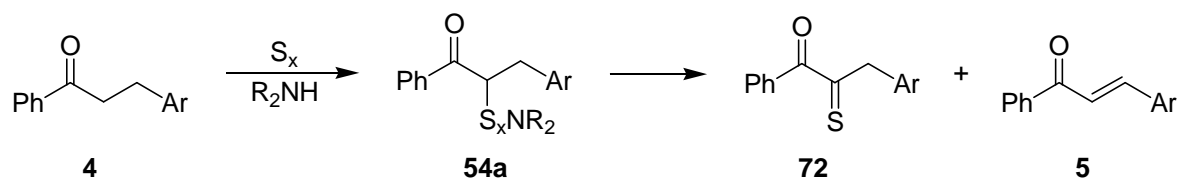


In particular, the evident instability of polysulfonamides of this type (i.e., polysulfonamides containing α or β hydrogen atoms) accounts for the ease with which, starting from this stage, the process proceeds, even in under mild conditions.¹² After the formation of intermediates (54) and/or (53), the reaction may follow different pathways (expulsion or sum of the reagents and formation of stable or unstable cyclic compounds) mainly according to the length of the chain and the experimental conditions (temperature and time of the reaction and the stoichiometric ratio of the reagents).

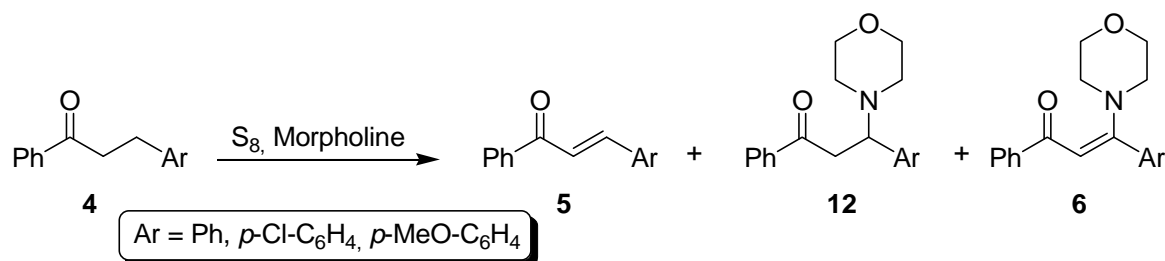
2.2. FURTHER COURSE OF THE ATTACK

The case of longer chain ketones can be excluded, because of experimental evidence that the ensuing

intermediate stage of thiation proceeds *via* an attack on the carbonyl group, for which more extreme conditions are required. The reaction of the unstable intermediate (formulated as sulfenamide (**54a**)) can bring about the formation of an α -thio diketone (**72**), or an unsaturated ketone (**5**).

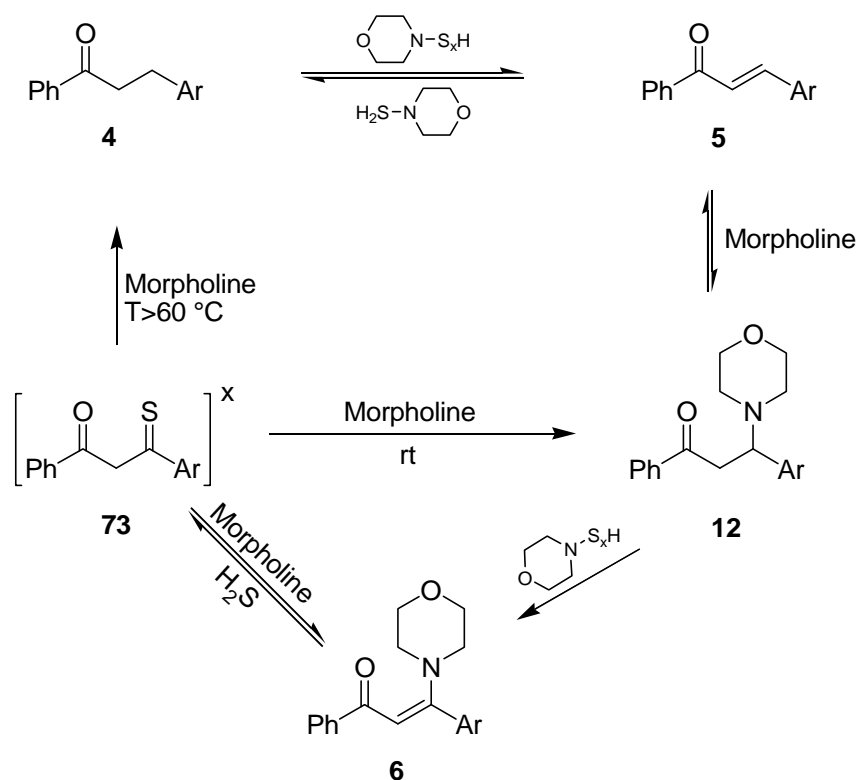


However, the thioketone (**72**), if formed, would react vigorously with any nucleophiles present in the reaction mixture (e.g., amines or hydrogen sulfide), and at usual reaction temperatures would form the saturated ketone (**4**),^{19,34} and, therefore, the reaction would not be significant. In accordance with predictions, 1,3-diarylpropanones at 55–75 °C allowed the isolation for the first time of the corresponding unsaturated ketone (**5**), postulated to be among the first intermediates^{12,38} of the Willgerodt–Kindler reaction. Along with the chalcone (**5**), the β -amino ketone (**12**), and the enamino ketone (**6**)¹³ were obtained.



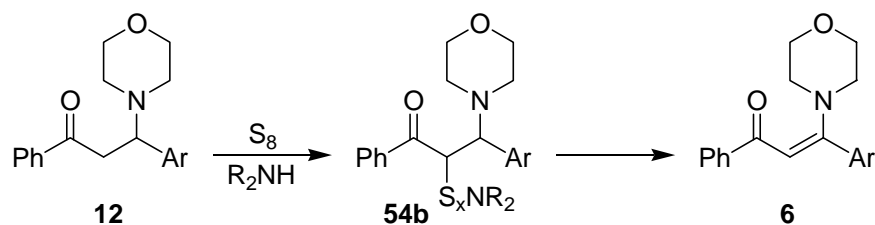
Under the same experimental conditions, the unsaturated ketone (**5**) reacts with sulfur and morpholine to give compounds (**4**, **12**, and **6**). The β -amino ketone (**12**) and enamino ketone (**6**) in turn form a mixture of three other compounds. In each case, there was always an unaltered part of the initial compound.¹³

Therefore, starting with any one of compounds (**5**, **4**, **12**, and **6**), a cyclic process occurs on reaction with sulfur and a *sec*-amine (Scheme 11). The isolated components of this cycle are the four above compounds. (A fifth compound, postulated as being an intermediate in the process, the monothio diketone (**73**), is too reactive³⁹ to be isolated in the example in which it is formed.) A sixth compound is also formed, the dithiol salt, which is stable enough to be isolated only when the substrate has an electron-rich substituent. The saturated ketone (**4**) and β -amino ketone (**12**) are sensitive to electrophilic attack by sulfur species.¹³ From the reaction of these two compounds, the unsaturated ketone (**5**) and enamino ketone (**6**) are formed (Scheme 11). The latter compounds instead react with the nucleophiles present in the reaction mixture. Thus, from compound (**5**), through the action of the amine, the amino ketone (**12**) is formed.

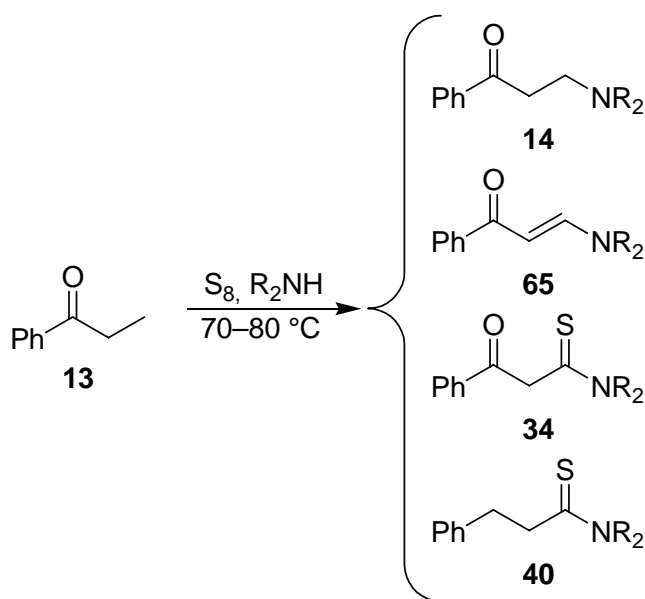


The chalcone (**5a**) itself on the other hand, is partly reduced to ω -phenylpropiophenone (**4a**) during the course of the reaction. The same reduction has been obtained by bubbling hydrogen sulfide in a pyridine solution of chalcone (**5a**) in the presence of morpholine.¹² It is then possible to think that, like the addition of amines¹² and the thiation of the Mannich base (**12**) formed in this way, this would lead to the enamino ketone (**6**). Therefore, the addition of hydrogen sulfide and the consequent desulfuration of the corresponding β -mercapto ketone in a basic environment leads to saturated ketones, in spite of the presence of water (Scheme 11).¹²

The involvement of the enamino ketones in the Willgerodt–Kindler reaction now appears to be the primary, and not a secondary consideration, as was previously thought when working at high temperatures.¹⁴ These compounds are formed by the thiation of β -amino ketones and the consequent expulsion of the sulfur species. The β -amino ketone can undergo thiation at the α position of the amine group⁴⁰ as well as at the α position carbonyl group. However, a higher reactivity of methylene at the α carbonyl group is confirmed using NMR spectrometry.⁴¹



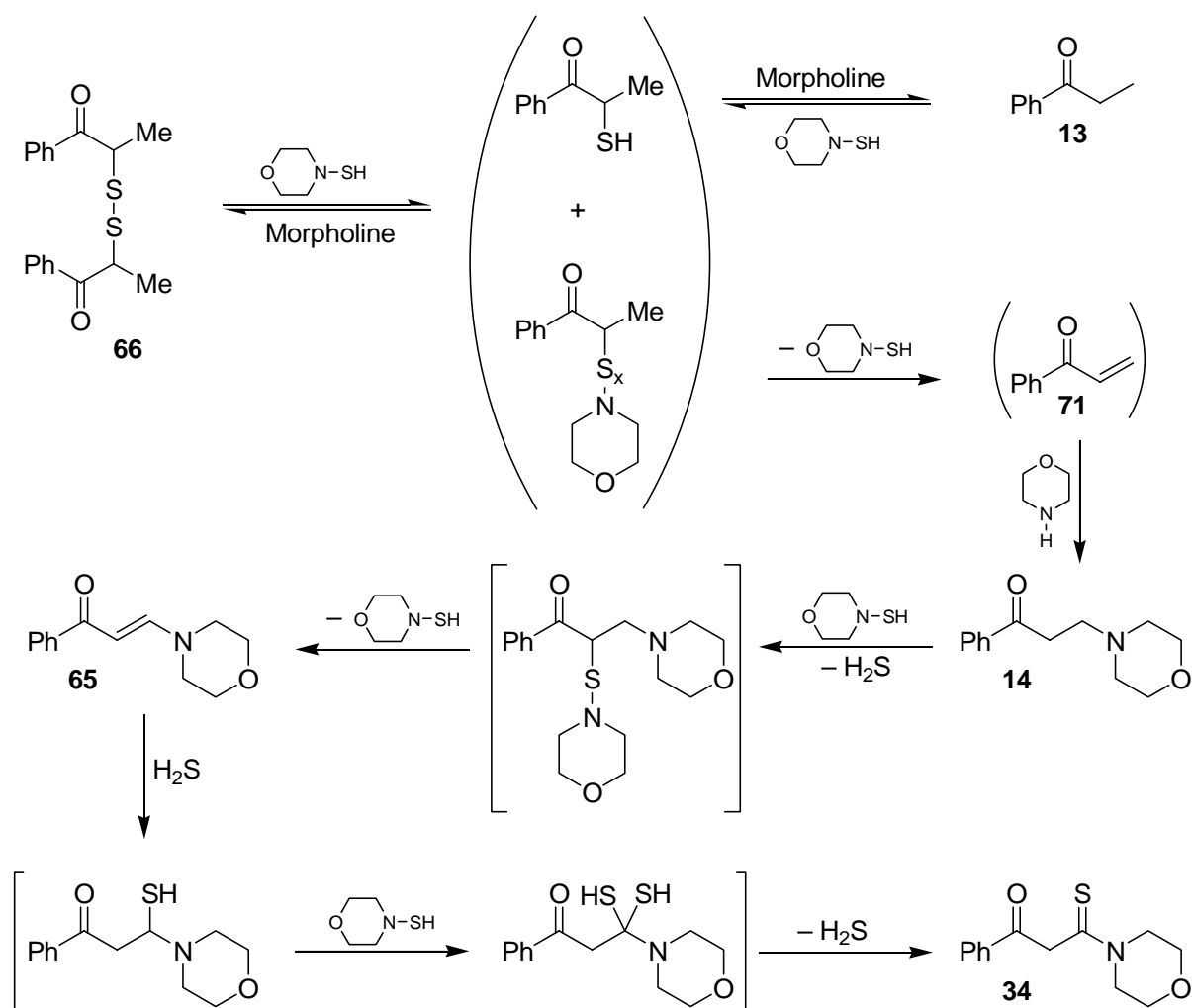
It is not possible to form thioamides from the 1,3-bisaryl substituted enamino ketone (**6**). This is in contrast to what happens in the case of the enamino ketone monoaryl substituted **65** (see later). The β -thio diketone (**73**) (see Scheme 11) reacts vigorously with nucleophiles, because its thione group is not assisted, as it is in the case of thioamides. In addition, this reaction affords compounds (**5**, **4**, **12**, and **6**), which are the other components of the cycle^{13,39} (Scheme 11), made possible by the reactivity of the thione component (**73**), which is not assisted in this case by a nucleophile. In non-extreme conditions ($T = 55\text{--}95\text{ }^\circ\text{C}$), the prevailing compounds by far in the system are the saturated ketone (**4**) and the enamino ketone (**6**).¹³ Therefore, in the course of the process, the sulfur electrophilic (denoted by $\text{R}_2\text{-N-S}_x\text{H}$) and nucleophilic (denoted by H_2S) species are alternately used and then recuperated. As the time of the reaction is prolonged, the fragmentation of the propanoic chain becomes increasingly consistent. This is determined separately by the enamino ketone (**6**), the quantity of which diminishes until it disappears.¹³ Working with deficient sulfur and amine, when the reagent is exhausted only the saturated ketone (**4**) is present among the four possible components (**5**, **4**, **12**, and **6**).¹³



Scheme 12

Similarly, by the reaction of the propiophenone (**13**) with sulfur and morpholine under mild temperature conditions, the β -morpholinopropiophenone (**14**), benzoylmorpholinoethylene (**65**), benzoylthioacetomorpholide (**34**), and phenylthiopropionmorpholide (**40**) are obtained (Scheme 12). (For the reaction of **13** at high temperatures, see Section 2.4, Scheme 19.)

For complete accordance with what has been discussed so far, the reaction of the disulfide (**66**) with morpholine has a particular relevance. It is significant that this reaction forms the same compounds that are formed when the propiophenone reacts with sulfur and morpholine. Therefore, Scheme 13 also serves to illustrate the course of the reaction of propiophenone and its derivatives with sulfur and morpholine.



Scheme 13

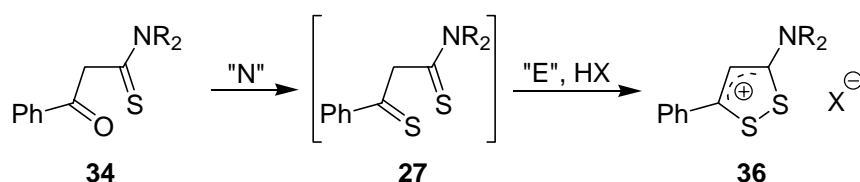
The α -mercapto ketone (**52**) is in part reoxidized into disulfide by the thiolating species³⁰ (denoted by R₂NSH), and, in part, is desulfurated into propiophenone (**13**), which is found among the reaction products.⁴² The sulfenamide that is also obtained⁴³ is decomposed into the transient vinyl ketone (**71**), from which the Mannich base (**14**) is rapidly formed. The insufficient quantity of thiolating agent that, in this case, only comes from the reaction of the disulfide with the morpholine, facilitates in the isolation of **14**. The benzoylthioacetomorpholide (**34**) is formed from the reaction of the enamino ketone (**65**) (Scheme 13). Under usual conditions (*i.e.*, high temperatures and excess reagent), the benzoylthioacetomorpholide (**34**) reacts further to give the phenylthiopropionmorpholide (**40**).

2.3. REDUCTION OF THE CARBONYL GROUP

One of the most interesting aspects of the Willgerodt–Kindler reaction is that related to the carbonyl reduction into a methylenic group. The experimental data show that a) the reaction of the lone polythioamine (**50**) with a ketomethylenic moiety leads to the formation of ketothioamide (**3**); b) the addition of hydrogen sulfide to the same mixture causes an abrupt change, and the formation of the thioamide (**2**) as the major product is observed; c) conversely, a reaction mixture of a ketomethylenic

compound with sulfur and a secondary amine, under the usual experimental conditions, leads to the thioamide (**2**); and d) if a hydrogen sulfide acceptor is added (*e.g.*, lead oxide), then the carbonyl group remains unaltered and the formation of the corresponding ketothioamide (**3**) is observed.

From the above evidence, it turns out that different species take part in the process: a) a compound bearing the carbonyl function, b) a nucleophilic species of sulfur [*e.g.*, hydrogen (poly-)sulfide or similar species, ($R_2N-S_x^-$)] (indicated in Scheme 14 as N), which gives rise to carbonyl group thionation, and c) $R_2N-S_x^+$ species (indicated in Scheme 14 as E), which is the oxidizing agent leading to the formation of open or cyclic species. In the same period, other groups hypothesized on this cascade of reactions, but no experimental evidence was presented by them.^{37,38}



Scheme 14

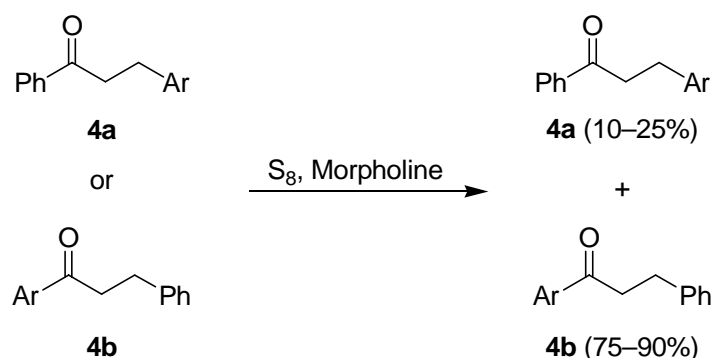
On the other hand, the possibility that, in the course of the reduction of the carbonyl group, a thiocarbonyl compound can be formed as an intermediate has been considered by many researchers.^{34,39,43–45} In particular, compounds containing a thiocarbonyl group in the place of the original carbonyl have been isolated among the products of the reaction with sulfur and *sec*-amine of compounds containing electron donor groups, such as tetramethyldiaminobenzophenone (**76**),⁴⁵ *p*-dimethylaminoacetophenone (**77**),³⁵ and *p*-dimethylaminopropiophenone (**78**).³⁵ In all these cases, the presence of a strong basic group in the conjugated aryl chain stabilizes the thiocarbonyl group to nucleophilic attack ("vinylogue" thioamides), and allows for the isolation of the thiocarbonyl compound. When the chain length allows, the dithiole derivatives can be isolated (Scheme 15).

The thionation products (**79** and **80**), owing to the conjugation with the amine groups, are stable enough to be isolated. In the case of compound (**78**), the formation of compound (**35a**) allows us to consider intermediate (**81**) as the first product of the reaction that, owing to the suitable 1,3 position of the two thiocarbonyl moieties, evolves towards the formation of the 1,2-dithiole derivatives. On the other hand, the fact that carbonyl reduction proceeds through the formation of sulfur-containing cyclic compounds is also evident. It has been found that, because of the reaction of the base of Mannich (**14**) and of the ketothioamide (**34b**) with sulfur and morpholine (deficient), the corresponding 5-aryl-1,2-dithiol-3-thione (**35**) can be obtained (Scheme 16). In the case of the *p*-methoxy derivative (**34c**), it is possible to isolate the dithiolium salt (**36c**)¹⁹ (Scheme 16).

function of the nature of the substituent (Scheme 8). For those compounds that have sufficiently long chains and are resistant to the action of nucleophiles, the formation of the 1,2-dithiole derivatives can be a usual stage in the reaction with sulfur and *sec*-amine, in accordance with the repeated isolation of the latter compounds among the products of Willgerodt–Kindler type reactions.⁴⁶ This is the case for compounds (35–38) (Scheme 3), which are obtained under normal experimental conditions. All of this evidence allows us to insert the symbol of the dithiole system in Scheme 11, which is now related to the cyclic process that is produced during the course of the reaction. This cyclic process is therefore responsible, under the auspices of a new component having a 1,2-dithiole structure, for the reduction of the carbonyl group, and the isomerization and fragmentation processes.

2.4. ISOMERIZATION

When an α,ω -diaryl propanone (**4a** or **4b**) reacts with sulfur and morpholine at $T = 105\text{--}130\text{ }^\circ\text{C}$, a mixture of the same compounds is the usual result, in which the ratio between the two compounds is about 75–90/25–10 in favor of isomer (**4b**), which contains a carbonyl group conjugated with an aryl electron-donor group as a substituent (Scheme 17).^{14,15}

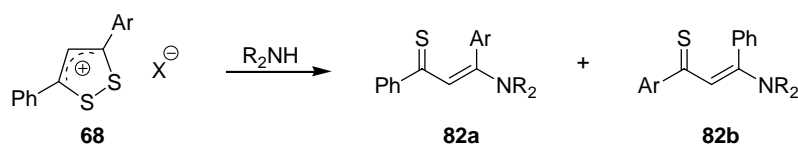


Scheme 17

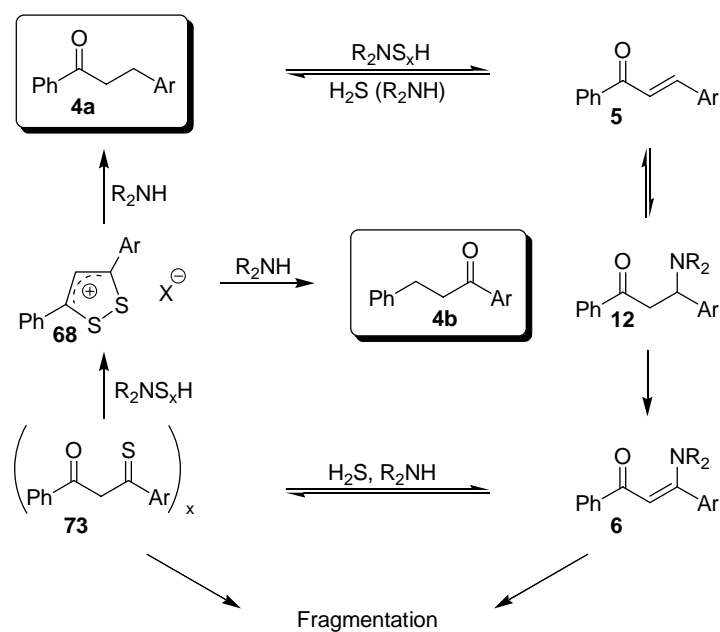
Isomerization has been observed in the course of Willgerodt–Kindler reactions. Bible⁴⁷ has reported that the reaction of methyl *O*-methyl-7-propionylpodocarpato with sulfur and morpholine affords a 10% yield of the methyl ketone isomer, along with the expected thiomorpholide. Asinger and coworkers⁴² have found that sulfur and primary amine determine the isomerization of aryl and alkyl ketones, and predicted the possible formation of intermediates in the thiirane and aziridine cycles. The isomerization of enamine in the presence of sulfur has also been reported.²⁵ Carmack and Berchtold²⁴ have observed this phenomenon with some α,ω -bis-aryl-1,2-substituted ketones. according to these Authors,²⁴ the process of isomerization can proceed *via* three different schemes, two of which require monomolecular cyclization, and a third scheme involving the interaction of two units. Of the three proposed sequences, the second (intramolecular cyclization) was the only one that was accompanied by experimental evidence; *i.e.*, the isolation of the phenylsathiocanes. Furthermore, this is in accordance with the predicted behavior of

α -mercaptoketones.⁴⁸ As discussed in Section 2.2 on the systematic studies on the reaction of alkanones and alkenones substituted with sulfur and an amine, it has been found that, in the case of α,ω -diaryl-propanones having different terminal functions, isomerization occurs in the course of decomposition of the intermediate cyclic structure, which suggests the formation of intermediates containing a dithiole nucleus (with the particular characteristic of being very sensitive to the action of a nucleophile) (Schemes 18 and 19).

This is in agreement with what is known about the behavior of the salt 3,5-bisaryl-1,2-dithiole. Compound (**68**) reacts with morpholine under mild conditions to yield enamino thiones (**82a** and **82b**).⁴¹ However, if the reaction takes place at the reflux temperature of the amine, then the final product is a mixture of the two benzylacetophenones (**4a** and **4b**). These are found in the same ratio in which they are obtained when starting from one of components (**76**, **77**, and **78** and **79**, **80**, and **81**), owing to the reaction with sulfur and amine. This confirms the hypothesis on the formation of dithiole derivatives as intermediates of the reaction with sulfur and amine. Owing to the symmetry of the dithiole ring, two isomers can be formed from the decomposition of the dithiole (Schemes 1 and 6).



Scheme 18

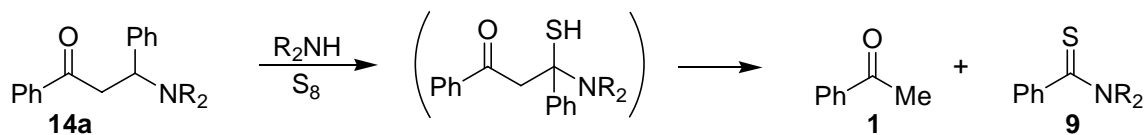


Scheme 19

2.5. FRAGMENTATION

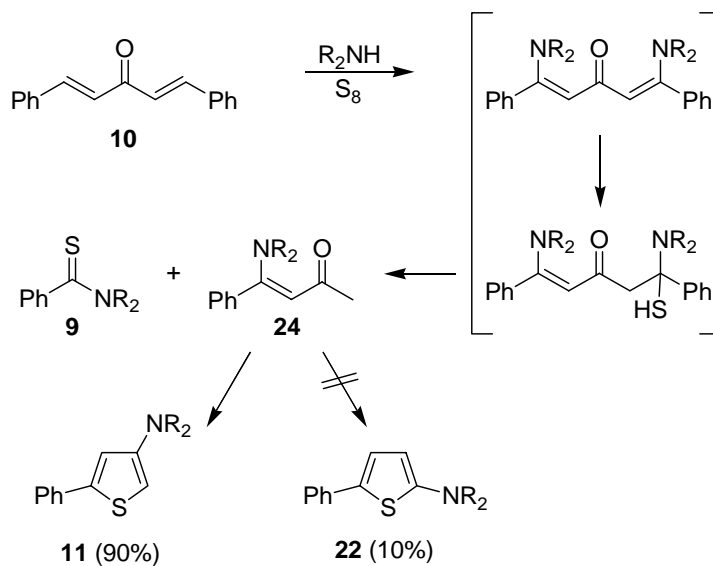
Research into the Willgerdt–Kindler reaction carried out on bis-aryl-propanones has provided an increase in knowledge about the course of the fragmentation collateral process. Reactions carried out with

α,ω -bisaryl derivatives must be considered general in nature, and they can occur even in the case of monoarylic derivatives. Therefore, among the reaction products of propiophenone is acetophenone (**1**), which could be related to a retro-Mannich type reaction⁴⁹ starting from the β -amino ketone (**12**) and one of the products of its reaction, phenylthioglyoxylmorpholide (**3**) (Scheme 20).



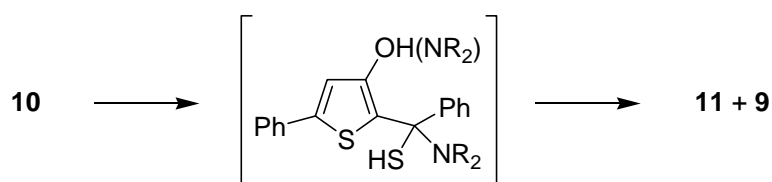
Scheme 20

In the case of α,ω -bis-aryl substituted compounds, a retro aldol reaction seems to govern the fragmentation process. The nature of the fragmentation compounds can be a useful indicator of the course of the reaction itself. For example, in the case of dibenzylideneacetone (**10**), the 2-phenyl-4-*N*-morpholinothiophene (**11**)¹⁶ is formed, along with the thiobenzomorpholide (**9**), as a second product of fragmentation. The formation of compound (**11**) in place of the isomer (**22**) allows us to exclude the possibilities that the fragmentation was determined by the dibenzylideneacetone (**10**) itself or that the formation of intermediate benzylideneacetone (**15**) occurs in any case, because, when starting from this compound or most of its derivatives, compound (**22**) is predominantly formed. The fragmentation process can afford 1-phenyl-1-*N*-morpholino-2-acetylene (**24**), which by reaction with sulfur and morpholine gives compound (**11**). In this case, the isomer compound (**22**)¹⁹ should be formed, even in a small yield, but no evidence of compound (**22**) has been found¹⁶ (Scheme 21).



Scheme 21

In particular, the experimental conditions (*e.g.*, humidity and temperature) of the fragmentation process can prevail. An examination of the fragmentation processes reported shows that scission generally occurs at the location of a carbonyl function. (See for example, the quoted case of benzylacetophenones (**4**),^{12,36b} benzylideneacetophenone (**5**),¹⁵ dibenzylideneacetone (**10**),¹⁶ phenylbenzyl diketone (**83**), dibenzoyl methane (**84**),¹⁸ phenylacetonitrile (**85**), and dithiolium salts (**68**)).



Scheme 22

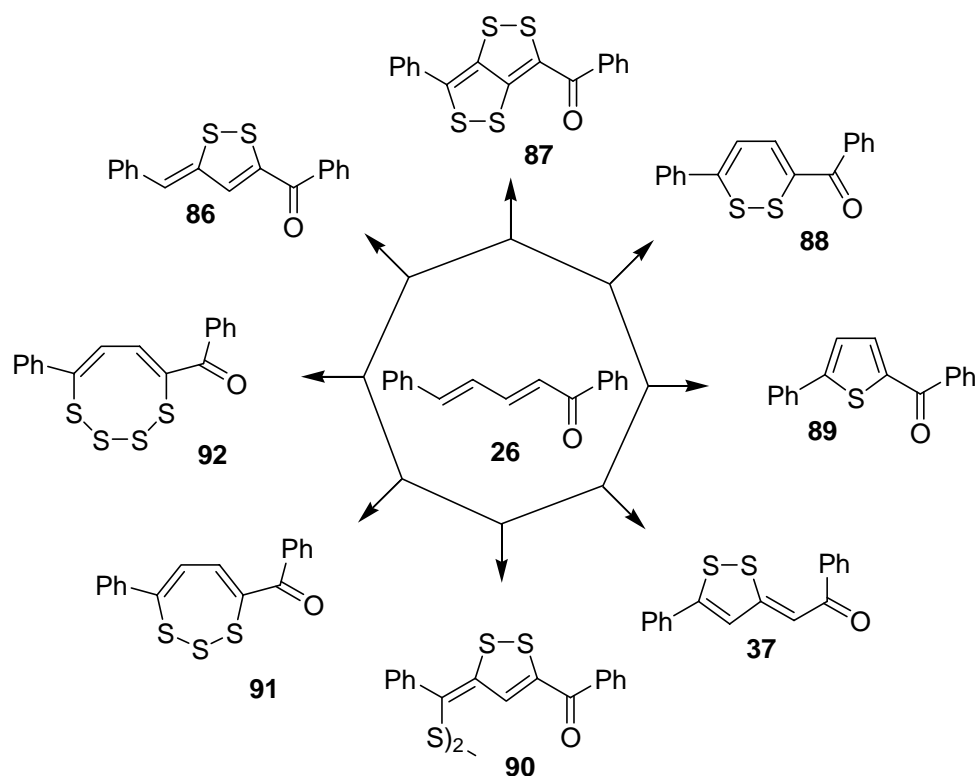
3. REACTIONS CARRIED OUT AT ROOM TEMPERATURE

Experience has shown that the thiation process of non-carbonyl carbon atoms can also occur at room temperature. In contrast, an attack on the carbonyl group by the nucleophilic species requires temperatures of at least 80 °C. Reactions of organic compounds with electrophilic species in mild conditions have been carried out in our laboratory using alogen-derivatives,⁴⁸ diazocompounds,^{28,29,31} and ketomethylene compounds.^{47,50,51} In all cases, the substitution of a non-sulfonated outgoing group with a group containing sulfur has been observed.

A remarkable extension of knowledge in this field has come about by examining the reactions of unsaturated carbonyl systems, which were postulated as being intermediates in the reaction of ketomethylene systems.¹²⁻¹⁴ The chalcones were allowed to react at room temperature with activated sulfur in contact with triethylamine (TEA) in the presence of non-protic solvents, such as the amine, to impede forming stable bonds with the enones. The obtained data indicate that, under these conditions, the process leading to the formation of the compounds begins immediately. The presence and quantity of the compounds in the reaction mixture varies according to the nature of the solvent chosen and of the duration of the reaction.

3.1. COURSE OF THE REACTION

Compounds that have been isolated and characterized starting from the cinnamylideneacetophenone (**26**) are shown in Scheme 23. Surprisingly, as far as the chemism of the process is concerned, it has been found that compound (**86**) is generally formed initially; *i.e.*, that it clearly derives from an attack of the electrophilic species of sulfur (“E”) on the 2 and 4 positions of the enone.



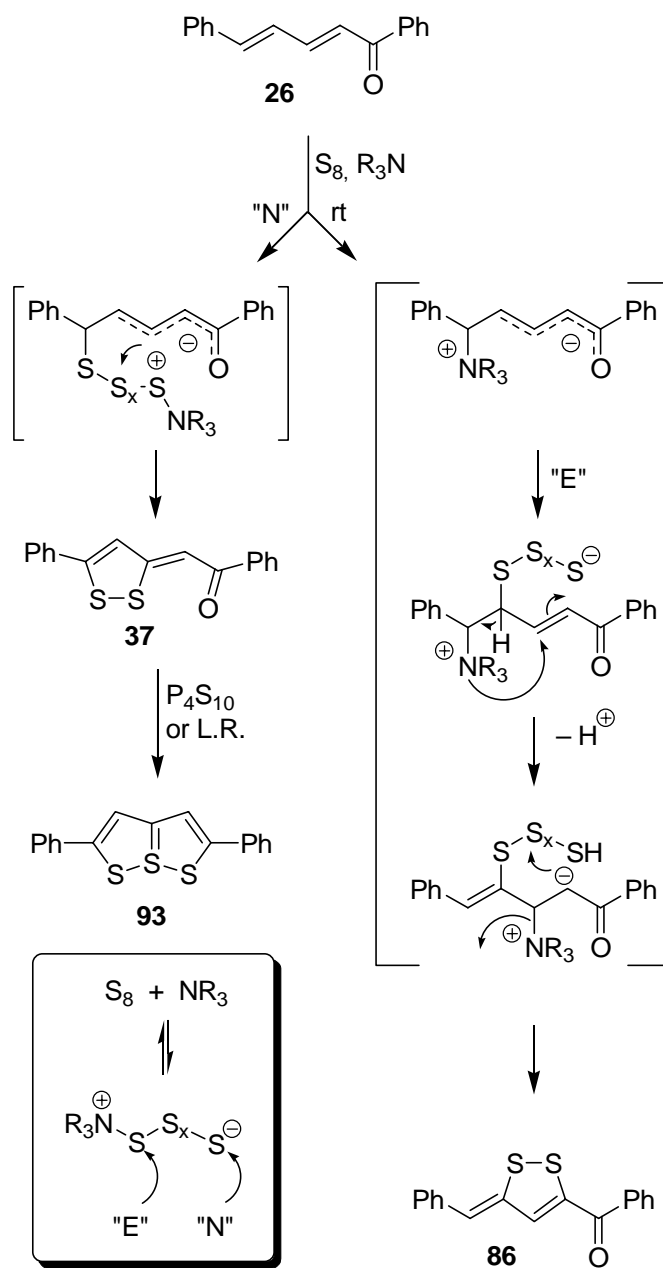
Scheme 23

The higher yield of compound (**86**) is conceivably due to the attack on the 3 and 5 the positions of TEA, which behaves as a stronger nucleophilic agent than the sulfur species.

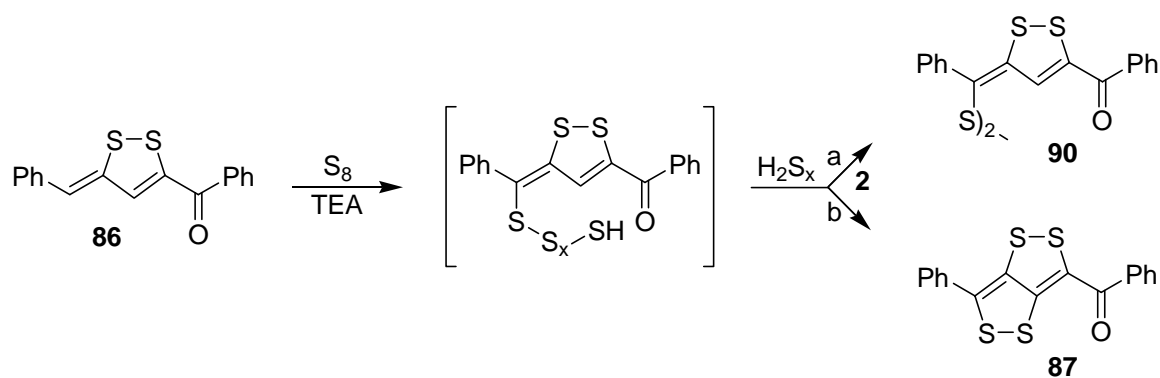
The interaction between the 3 and 5 positions of the enone and TEA promotes the nucleophilicity of the 2 and 4 positions, which then react with the electrophilic species. In accordance with this hypothesis, it has been found that, when using the more encumbering triisobutylamine (TIBA) as a solvent instead of TEA, the formation of the dithiole (**86**) is no longer observed.

Isomer (**37**) is more stable, because of the low nucleophilicity of its 2 and 4 positions, and because of the stabilization of its 3 and 5 positions, which form the dithiole nucleus. In contrast, dithiole (**86**) easily reacts with the nucleophilic species in the 5 position and the 3 and 5 positions, which are directly conjugated with the carbonyl group to give compounds (**90** and **87**), respectively (Scheme 25).

In the reaction conditions used, the disulfide (**90**), in contrast to the stable dithiolodithiole (**87**), undergoes a reduction to form the dithiolothione (**91**). Starting with this intermediate, a series of reactions can be originated, such as intramolecular cycloaddition, retro electrocycling, and the addition and/or extrusion of sulfur, with the consequent formation of compounds (**88**, **89**, **91**, and **92**) (Schemes 26 and 27). The existence of this process indicates that compound (**90**) undergoes an opening of the dithiole ring with the probable formation of thiosulfine (**96**), from which, through an electrocyclical closure, trithiepine^{6,7,15} can be formed.

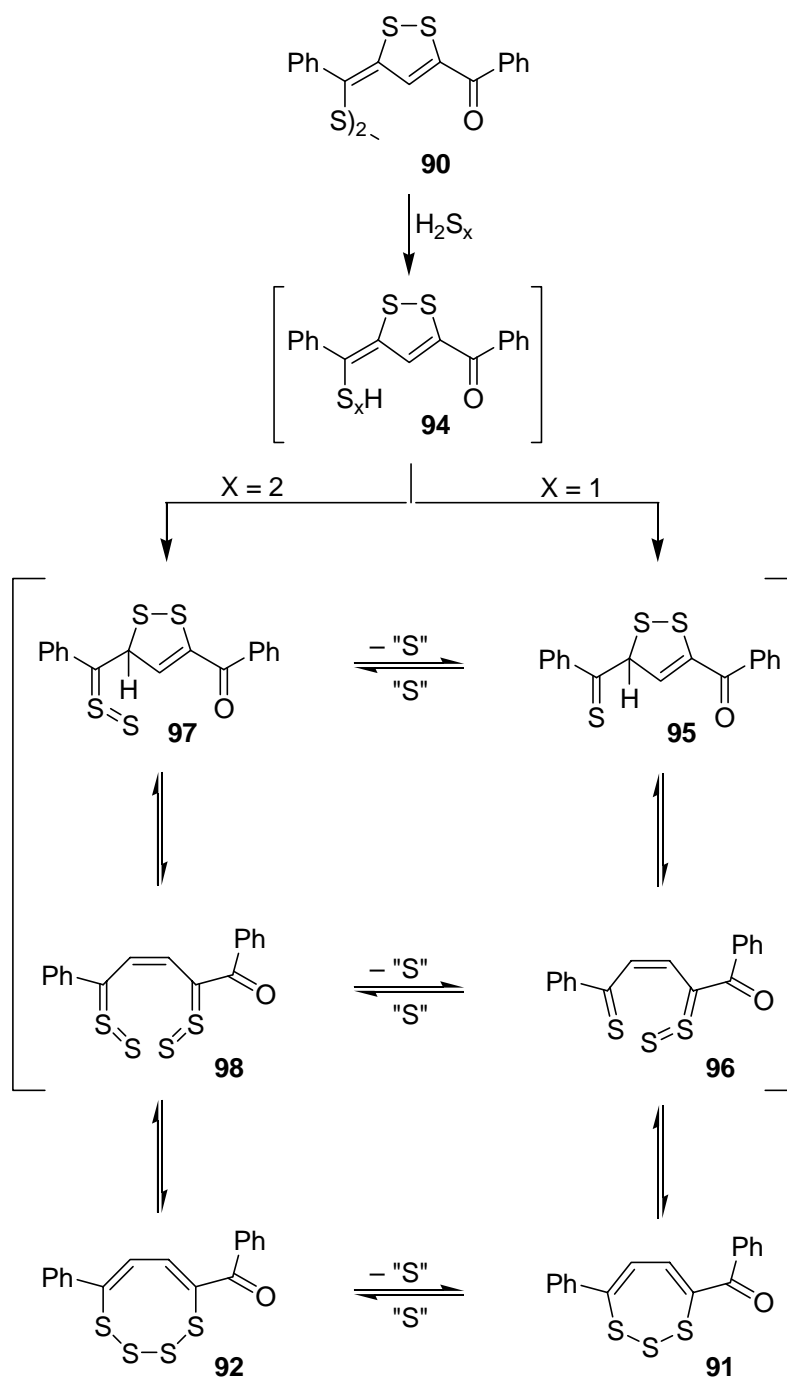


Scheme 24



Scheme 25

However, it is not possible to exclude a preliminary division of the C-S bond, with the formation of compound (**97**), and therefore compound (**98**), in addition to compounds (**86** and **87**) (Scheme 26).



Scheme 26

The antiaromatic character of compounds (**88** and **92**) accounts for their instability, which determines the exclusion of sulfur with the formation of **89** and **91**. This latter compound is also unstable, and therefore the thiophene derivative (**89**) appears as the final main product along with a minor yield of compound (**37**), from the process that begins with compound (**26**) when it is made to react with sulfur and TEA at room temperature and at 135 °C.¹⁶

Retirement from active university duties has now caused a suspension of my studies on the reactions of organic compounds with sulfur and secondary and tertiary amines. I intend to publish my proposed structure of the highest molecular weight compound obtained from the spectral of

1,9-diphenylnonatetraen-5-one, as deduced from mass spectrometry, UV, IR, and NMR spectral experiments (Figure 1).

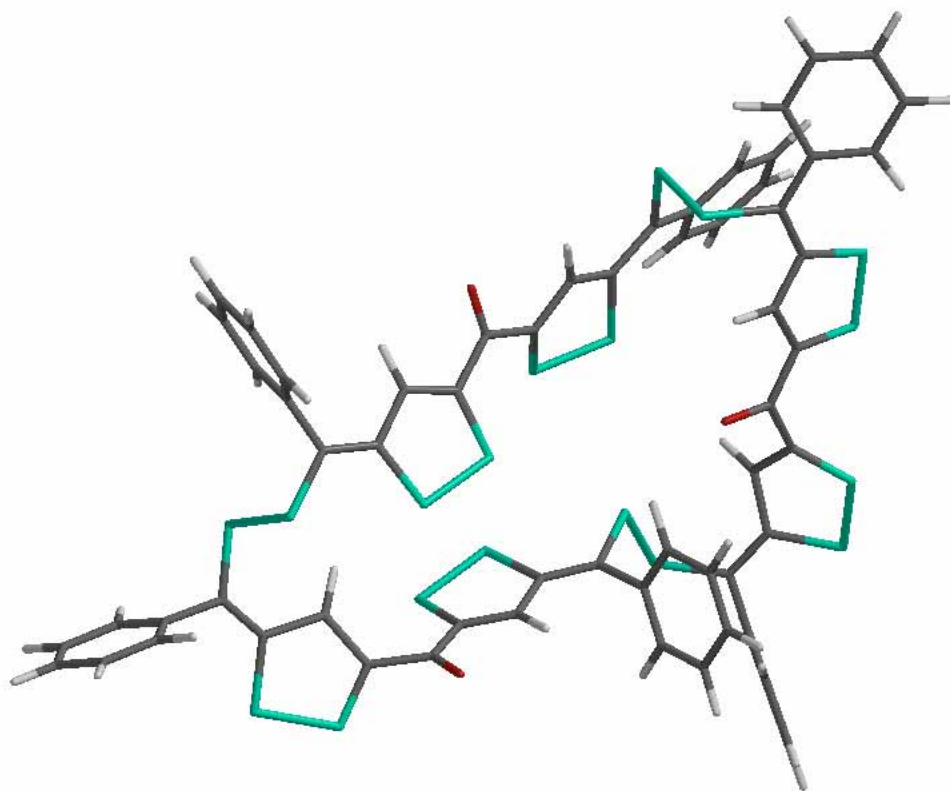
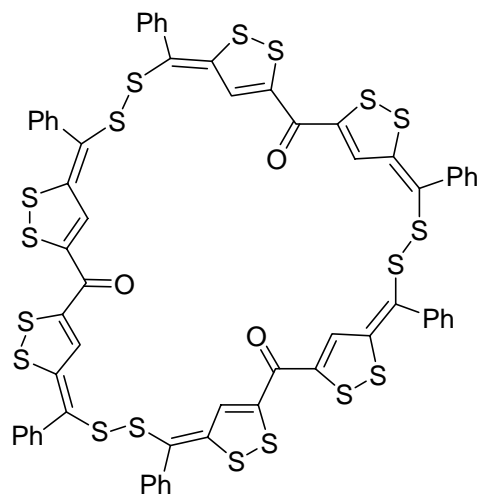
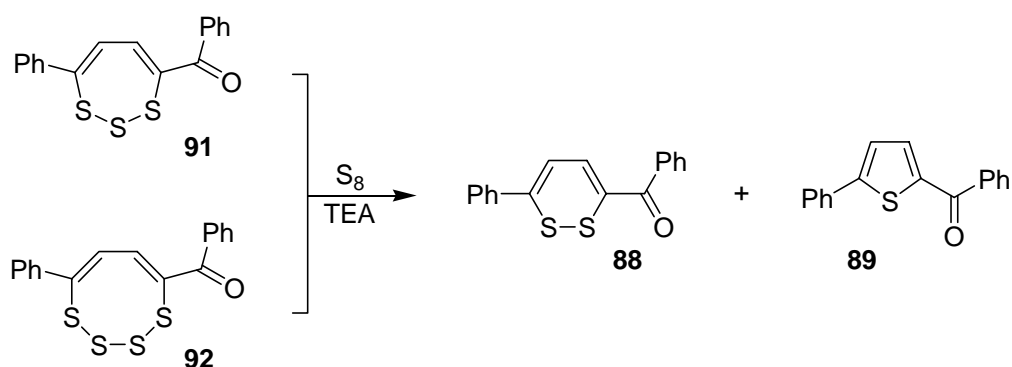


Figure 1: Schematic drawn of the proposed structure of the highest molecular weight compound obtained from the reaction of 1,9-diphenylnonatetraen-5-one.



Scheme 27

4. FORMATION OF CYCLIC COMPOUNDS

In the course of research carried out on the Willgerodt–Kindler reaction, the tendency of intermediate compounds to cyclize with inter- or intramolecular processes is clear, with the consequent formation of 1,2-dithiophene, 1,3-dithiophene, isothiazole, and thiophene derivatives. Intramolecular cyclization with the formation of thiophene derivatives and 1,3-dithiophenes occurs in the reactions of styrylamines with sulfur. Thiophene compounds formed by these reactions have been obtained by Willgerodt on reaction of acetophenone with ammonium polysulfide.

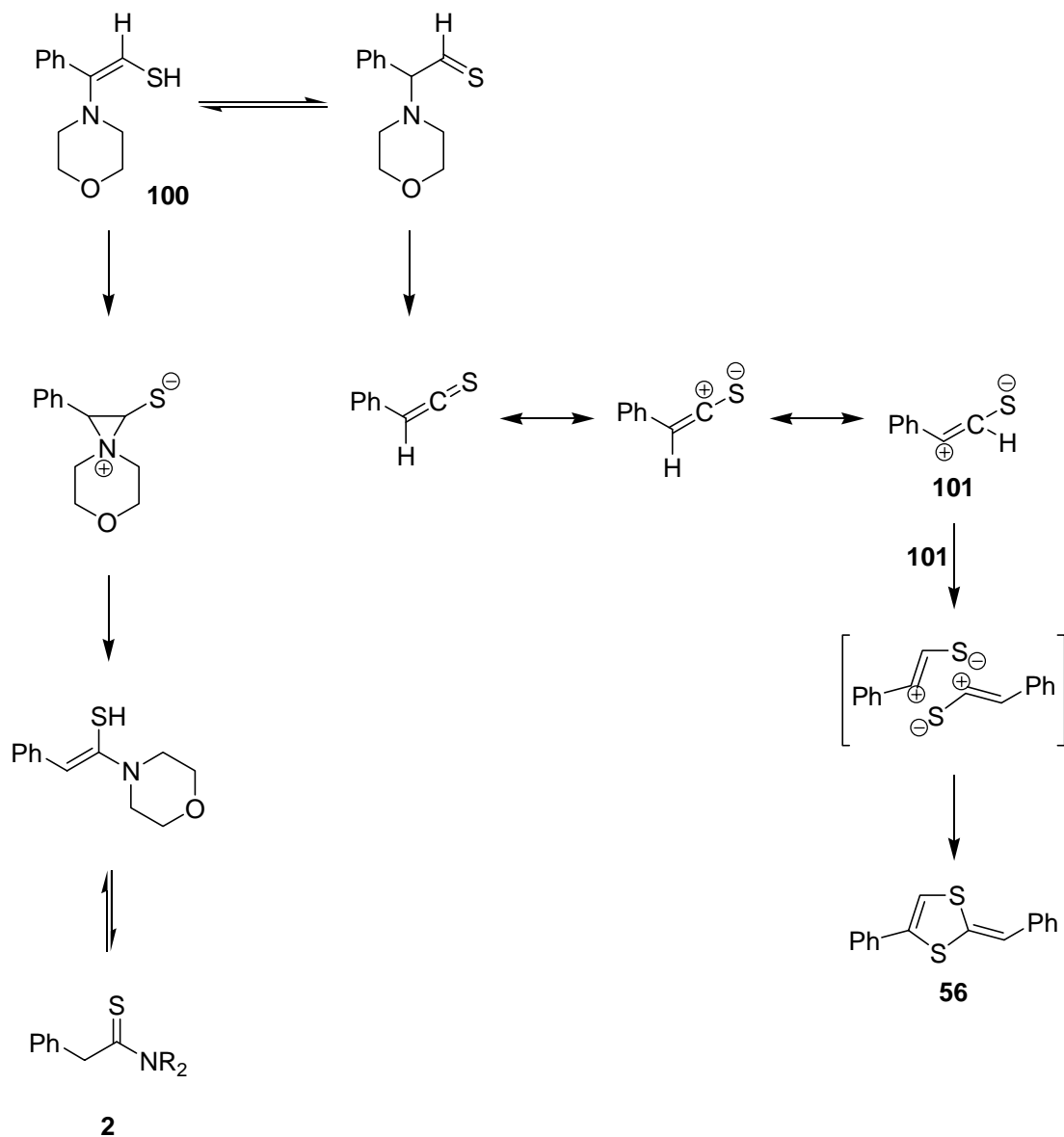
4.1. 1,2-DITHIOLE DERIVATIVES

The presence of 1,2-dithiophene derivatives among the products of the Willgerodt–Kindler reaction was recognized only after *p*-dimethylamino-1,2-dithiophene-3-thione (**37**) was isolated by Barret³⁵ (Scheme 8), and identified in our laboratory.¹⁹ These 1,2-dithiophene derivatives are extremely sensitive to the action of nucleophilic agents, and this makes it difficult to isolate them, but also renders them useful intermediates for the syntheses of other rings. Furthermore, they can play a relevant role in isomerization processes. Stable 1,2-dithiophene derivatives have been isolated by allowing the cinnamylidenacetophenone (**26**) and dibenzylideneacetone (**10**) to react with sulfur and morpholine.⁹ The reactions of these compounds is a clear example of the variety of processes that can be produced in the course of the reaction with sulfur and a secondary amine, according to the structure of the organic compound used.

The conjugation between the dithiophene nucleus and the carbonyl group in compound (**37**) protects both from attack by nucleophiles. Compound (**37**) does not react further with sulfur and morpholine in a basic environment to form 2,5-diphenylthiathioptene (**38**), the formation of which must therefore follow another path.¹⁶ Compounds (**37** and **38**), along with 2-phenyl-5-benzothiothiophene (**30**), are also obtained by reaction of **26** and **10** with sulfur alone.⁵² The thionation of the carbonyl group must therefore occur at a stage of the process in which it is not conjugated with an unsaturated system.

4.2. 1,3-DITHIOLE DERIVATIVES

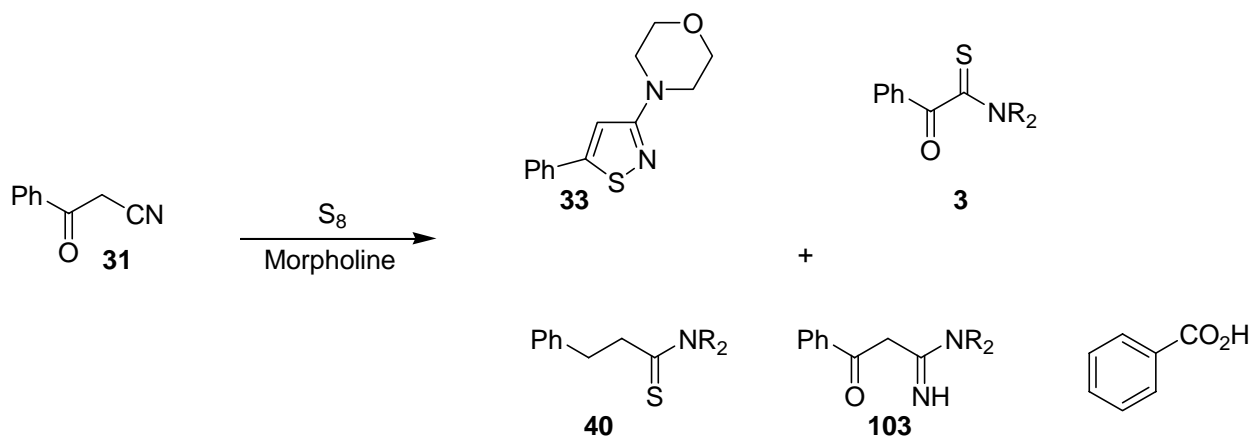
Less frequently, the reaction of an organic compound with sulfur and amines leads to isomeric 1,3-dithiole derivatives (Scheme 6). Their structure does not consent a “conventional” synthesis. Indeed, the 3-benzyliden-5-phenyl-1,3-dithiole (**56**) is formed by the reaction of styrylmorpholine (**55**) with sulfur in benzene or pyridine at 80 °C (Scheme 6). The experimental results show that the yield of the dithiole derivative is higher in the presence of excess sulfur. The “canonical” products of the thiophene synthesis, compounds (**29** and **57**), are also obtained. Concerning the chemism of the process, the most substantial hypothesis considers compound (**100**) as the first intermediate, which then undergoes rearrangement to give phenylthioacetamide (**2**) and phenylthioacetene (**101**) (Scheme 28). The 1,3-dithiole derivative **56** is obtained from ketene dimerization (Scheme 28). In a similar manner, the products of the thiophene syntheses, compounds (**29** and **57**), are also obtained.²⁶



Scheme 28

4.3. ISOTHIAZOLE DERIVATIVES

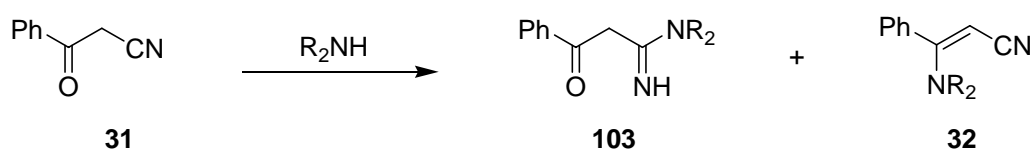
When cyanoacetophenone (**31**) reacts with sulfur and a secondary amine, the formation of several compounds can occur, among which is the amidine (**103**) and isothiazole (**33**) (Scheme 29).¹⁷



Scheme 29

The amidine (**103**) does not seem to be an intermediate in the formation of compound (**33**). This reaction with sulfur and amine gives the corresponding isothiazole only, in conditions more strained than those used for reactions with cyanoacetophenones. In non-acid environments, the amidine forms a hydrogen bond that inactivates the compounds towards reactions with sulfur and amine.

In the formation of isothiazole compounds, it is possible that they can be derived from the reaction of cyanostyrylamine (**32**) with sulfur and amine (Scheme 30).



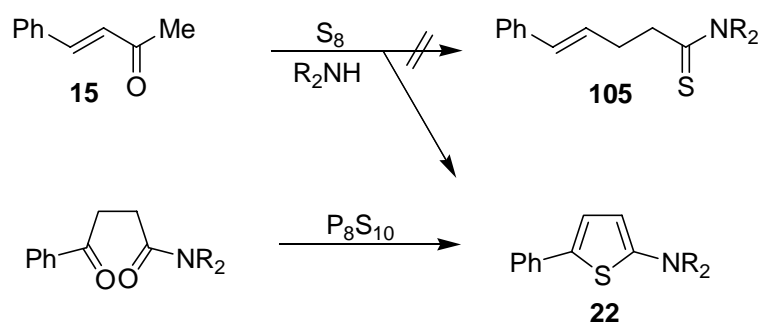
Scheme 30

The intermediate (**32**) is in accord with the behavior of ω -cyanostyryl- α,N -morpholine (**32a**), from which the isothiazole (**33a**) is obtained in an excellent yield.

4.4. THIOPHENE DERIVATIVES

The hypothesis that α,β -unsaturated ketones are among the first intermediates formed in the

Willgerodt–Kindler reaction (Scheme 11) has led to the observation that the unsaturated activated groups react vigorously when treated with sulfur and a secondary amine. Accordingly, we reported⁵ that the reaction of benzylideneacetone (**15**) with sulfur and morpholine leads to the formation of 2-*N*-morpholine-5-phenylthiophene (**22**)⁵ (see below), and not to styrylacetomorpholide, as is reported in Reference 37.



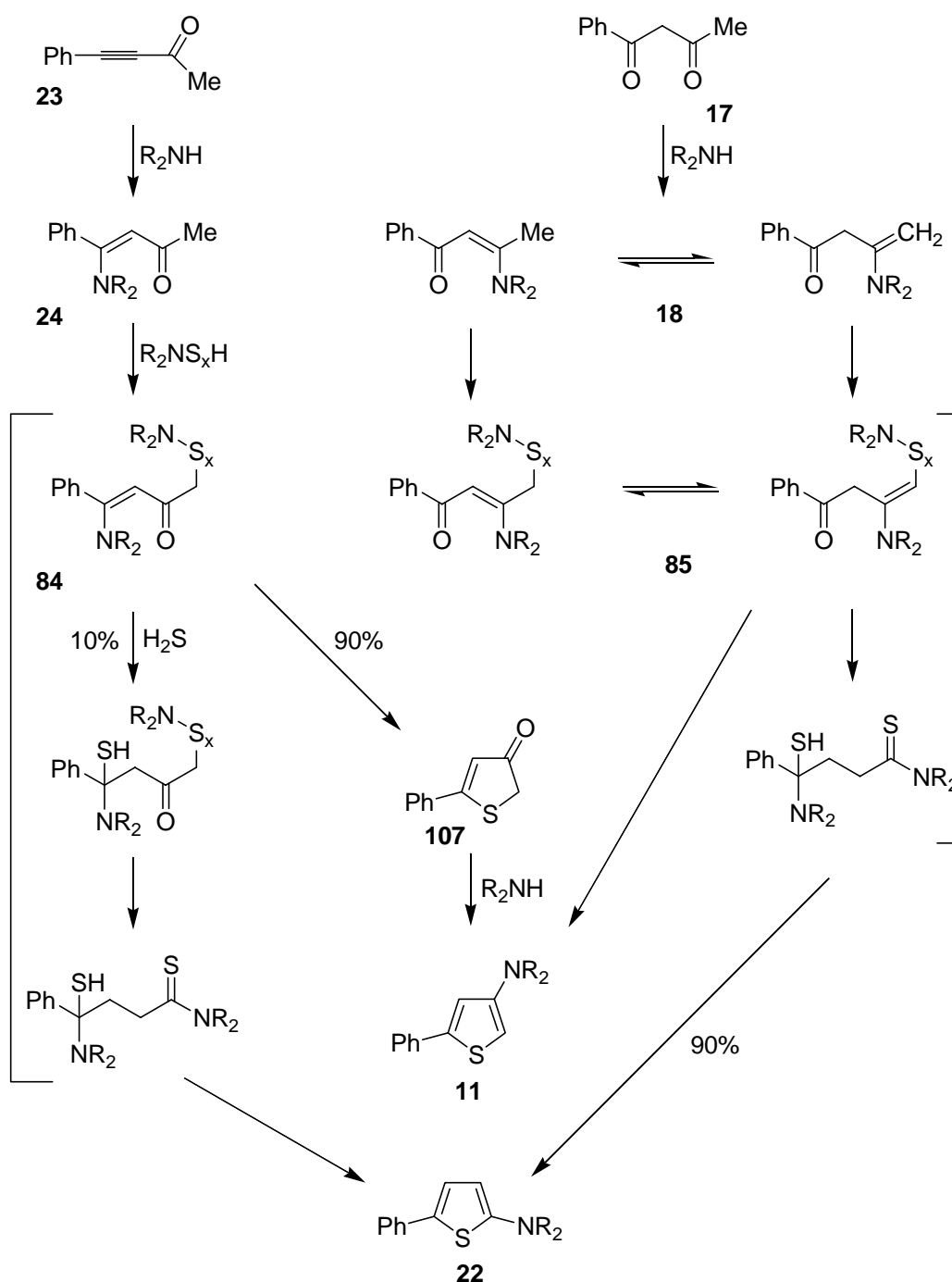
Compound (**22**) is formed as the main product starting with compounds (**15–21**). In contrast, the isomer phenyl-4-*N*-morpholinothiophene (**11**) is the main product from the reaction of compounds (**23** and **24**) with sulfur and morpholine. The different course of the reaction of the two isomeric compounds (**18** and **24**) may be due to the high stability of the enamino ketone system to electrophilic attack, which can occur on behalf of the sulfur species. Therefore, an attack on the terminal carbon atom is favored. This determines, in the case of compound (**24**), the formation of an intermediate (**84**), that can easily cycle into the thiophene derivative (**79**), from which compound (**11**) results, due to the action of the amine. In the case of the intermediate isomer (**85**), deriving from the enamino ketone (**18**), the higher resistance of the carbonyl group to nucleophilic attack slows the process. Thus, the process forming the thiophene derivative (**22**) is favored, which leads to the already verified reaction of the enamine system to afford a thioamide.

In accordance with the above hypothesis, it was found that, if compound (**24**) reacts with sulfur and an amine in the presence of hydrogen sulfide, the yield of 2-*N*-morpholine-5-phenylthiophene (**22**) increases markedly¹⁰ (Scheme 31).

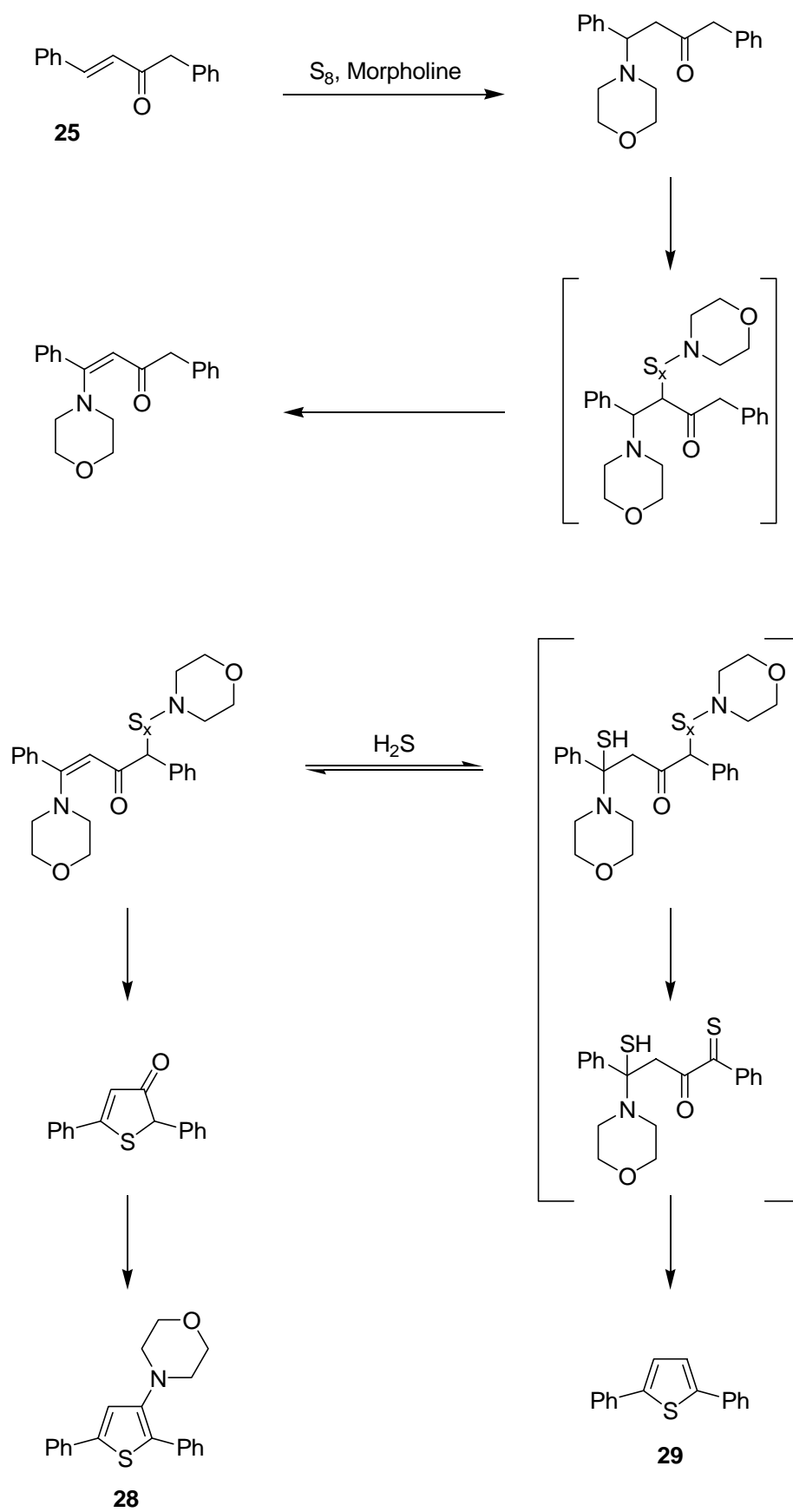
The general validity of the formation of thiophene compounds due to the reaction of butanone derivatives with sulfur and secondary amines has been verified by tests using the benzylstyryl ketone (**25**). The formation of compounds (**28** and **29**) is analogous to obtaining the two thiophene derivatives (**11** and **22**) starting from the butanone monoaryl-substitutes.¹⁰

As stated, thiophene compounds have also been obtained from the reactions of cinnamylidene acetophenone (**26**) and dibenzylideneacetone (**10**) (Scheme 32). The formation of

1-benzoyl-5-phenylthiophene (**30**) starting from compound (**26**) is proof of the lower reactivity of the carbonyl group compared with the aliphatic chain, whether saturated or unsaturated. In contrast, 2-phenyl-4-*N*-morpholinethiophene (**11**) is formed starting from compound (**10**) *via* a fragmentation process.



Scheme 31



Scheme 32

CONCLUSIONS

The reaction of compounds containing CH-acids, generally activated by a carbonyl group, with sulfur and a secondary amine (Willgerodt–Kindler reaction) consists of alternative electrophilic and nucleophilic processes (due to the sulfurized species formed by the sulfur and amine, and by the amine and nucleophilic sulfur species, respectively). Starting from propanone derivatives, the sequence includes the formation of intermediate unsaturated ketones, β -amino ketones, and β -enamino ketones. Afterwards, the formation of ketothiamides and/or thioamides takes place. The carbonyl group is much less reactive by far in the Willgerodt–Kindler reaction conditions than acid protons, which react at room temperature.

According to the experimental conditions adopted, it is possible to determine some reaction intermediates that are formed through a series of reactions that includes the thiation of acid protons formed by the electrophilic sulfur species, the expulsion of sulfur species with the resulting formation of an unsaturated carbonyl compound, and nucleophilic addition to an unsaturated carbonyl compound. The reiteration of this sequence leads to the final products. These can be thioamides and ketothiamides or, if the length of the chain allows intra-molecular cyclization, derivatives of thiophene, isothiazole, 1,2-dithiole, and 1,3-dithiole. Dithiole derivatives play a major role in the reduction of carbonyl group and in isomerization; this last process is particularly observed in the case of α,ω -bisaryl compounds. Still, it is not clear if the transformation of the monothio diketone (**73**) into the saturated ketone (**4**) or into the β -amino ketone (**12**) has the chalcone (**5**) as the intermediate (Scheme 11) under the experimental conditions adopted, or if these are formed by a different mechanism.

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2. In the original formulation of Willgerodt,³ the reagent was a polysulfide in aqueous ammonia, and the product of the reaction was an amide; *e.g.*, in the case of **1**, Ar-CH₂CONH₂, **4**, the reagent actually used was proposed by Kindler.⁴

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