Kinetics and Mechanism of the Reaction of Thionyl Chloride with Substituted Acetophenone Semicarbazones. The Synthesis of 1,2,3-Thiadiazoles

By **Richard N. Butler** * and **Denis A. O'Donoghue,** Chemistry Department, University College, Galway, Ireland

The reaction of thionyl chloride with a series of *para*-substituted acetophenone semicarbazones, which gives 1,2,3-thiadiazoles, involved an electrophilic attack. The rates correlated with the substituent σ^+ constants and gave a Hammett ρ value of -0.55. The reaction had a low activation energy and a high negative entropy in the solvents thionyl chloride and carbon tetrachloride ($\Delta E^{\ddagger}$ 9.46 kcal mol^{-1}; $\Delta H^{\ddagger}$, 8.8 kcal mol^{-1}; $\Delta S^{\ddagger}$ -43.3 cal K^{-1} mol^{-1} for *p*-methylacetophenone semicarbazone in SOCl$_2$). The rates of reaction of the semicarbazones were the same as the rates of appearance of the cyclised products, and there were no long-lived intermediates. The stoicheiometry of the reaction involved equimolar proportions of SOCl$_2$ and of semicarbazone and the reaction was first-order in both reagents. Along with 4-aryl-1,2,3-thiadiazoles the final products were carbon dioxide, ammonium chloride, and hydrogen chloride. The mechanism proposed involves an ordered transition state with an approach of the electrophile above the plane of the hydrazone *E*-isomer *via* complexation with the conjugated π–n electron system. Tautomeric non-hydrazone forms of the semicarbazone are not involved in the rate-determining step.

TREATMENT of semicarbazones (1) or *N*-amidohydrazones (2) containing a methylene group in the methine carbon with thionyl chloride provides an interesting direct one-flask route to the 1,2,3-thiadiazole system (3).[1] Although the reaction has been widely used [2-7] in synthesis, no kinetic or detailed mechanistic study has been reported but speculation on possible intermediates † has been made in some synthetic papers. Our interest in the oxidations of semicarbazones [8] prompted us to carry out a kinetic investigation of the mechanism of this interesting reaction.

RESULTS AND DISCUSSION

The reaction occurs readily under mild conditions at 0 °C but it requires a period of stirring since it does not.

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† In the reaction of deoxybenzoin benzenesulphonylhydrazone with thionyl chloride a compound (m.p. 154—155 °C) assigned structure (6a), was isolated [1] in 12% yield (as well as 63% of 4,5-diphenyl-1,2,3-thiadiazole the main product) and claimed [1] as an intermediate since, on being separately heated in nucleophilic solvents (methanol, ethanol, pyridine, or aniline), it gave

Ph—N
Ph—⟨ ⟩N·SO$_2$Ar
      S
      ‖
      O

(6) a; Ar = Ph
    b; Ar = *p*-tolyl

Ph—N
Ph—⟨ ⟩N.HO·SO$_2$Ar
      S
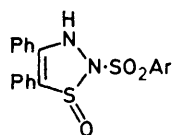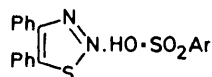
(7)

high yields of the thiadiazole. It was unaffected by heating in non-nucleophilic solvents such as carbon tetrachloride. In view of the kinetic results herein, and since the arylsulphonyl moiety is a better leaving group than the semicarbazone carboxamido-moiety,[8] a high-melting stable intermediate of type (6) seemed most unlikely. We have repeated this work [1] and confirmed the formation of the compound assigned (6a) and also prepared its *p*-tolyl analogue (6b) to provide a second example. Neither compound was an intermediate but, rather, each was a stoicheiometric complex of the products 4,5-diphenyl-1,2,3-thiadiazole and the arylsulphonic acid, *i.e.* structure (7). They can be readily obtained in comparable low yields by stirring 4,5-diphenyl-1,2,3-thiadiazole separately with the arenesulphonic acid in thionyl chloride.

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occur instantly. The synthetic results for a series of *p*-substituted acetophenone semicarbazones are in Table 1. In general, good yields of 1,2,3-thiadiazoles (3) were obtained after evaporation of the thionyl chloride solvent and chromatographic separation of the residue on a

(1) X = CO·NH$_2$
(2) X = COR; SO$_2$Ar

(3)
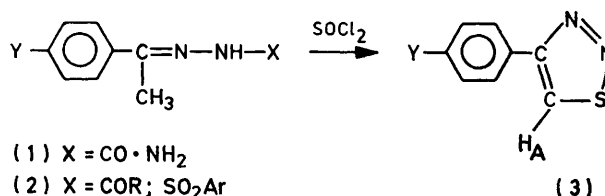
column of silica gel. The reaction was not entirely clean, however, and the product balance (Table 1) was made up by a waxy polymer. Substituent effects in the synthetic reactions were evident in the lower yields and recovered substrate encountered with *p*-electron-withdrawing substituents, compounds (1d—e) (Table 1). While most synthetic work on the reaction has involved an excess of thionyl chloride, which is used as solvent, the reaction proceeded equally well with an equimolar proportion of thionyl chloride in carbon tetrachloride as solvent; thus, compound (3a) was isolated in 81% yield on treatment of acetophenone semicarbazone with 1 mol equiv. of SOCl$_2$ for 1 h at 45 °C in carbon tetrachloride.

The kinetics of the reaction were studied at 28 °C with thionyl chloride as solvent under pseudo-first-order conditions, and also in carbon tetrachloride at 46 °C under second-order conditions. The rates were measured by following the disappearance of the methine CH$_3$ n.m.r. signal of compounds (1) and also by measuring the concomitant appearance of the H$_A$ signal of the products (3). Both sets of data for substrate consumption and product appearance gave identical rates within experimental error (Table 1). Therefore there are no long-lived intermediates † or slow steps after the attack on the semicarbazone. Linear first-order plots were obtained in thionyl chloride as solvent and the rate constants

paralleled the synthetic substituent effects and gave a linear correlation ($r = 0.983$) with the substituent Hammett σ^+ constants.[9] This corresponded to a Hammett ρ value of -0.55 for the methine phenyl ring. The order of the reaction was established by the half-life method in carbon tetrachloride using equimolar ratios of

Part of this high negative entropy could be due to stoicheiometric solvent involvement [10] where the solvent is the reagent. To estimate the contribution from such solvent factors Arrhenius data were also measured under second-order conditions in carbon tetrachloride as solvent (Table 3). A similar low activation energy and high

TABLE 1

Substrate (1)		Product (3) [a]		Kinetics [d]		
				$10^4 k/\text{s}^{-1}$		
No.	Y	Yield (%)	M.p. (°C)			σ^+ Value [g]
(1a)	H	80	77—78	4.28 [e]	4.26 [f]	0
(1b)	p-Me	60	63—64	7.61	7.58	-0.311
(1c)	p-MeO	65	88—89	10.61	10.75	-0.778
(1d)	p-Cl	35 [b]	132—133	3.75	3.68	0.114
(1e)	p-NO$_2$	16 [c]	183	1.72	1.70	0.79
(1f)	p-Br			3.37	3.48	0.150
(1g)	p-CN			2.45	2.55	0.66
(1h)	H;PhCH$_2$ for Me			4.73		

[a] Synthetic reactions were carried out at 0—5 °C for 0.5—4 h. [b] Semicarbazone recovered 25%. [c] Reaction time 48 h. Substrate recovered, 73%. [d] Measured at 28 °C. [e] Disappearance of substrate. [f] Appearance of product (3). [g] From ref. 9.

reactants (Table 2). A plot of log a vs. log $t_{\frac{1}{2}}$ was linear (r, 0.989) with slope -0.99 corresponding to a second-order reaction (expected slope -1). Since the reaction is first-order in semicarbazone it is therefore first-order also

TABLE 2

Order [a] of reaction in CCl$_4$ at 46 °C for compound (1a)

Initial conc. (aM)	$10^3 k/\text{l mol}^{-1}\text{ s}^{-1}$	$t_{\frac{1}{2}}/\text{s}$
0.1	2.9	3 449
0.2	2.5	2 000
0.3	2.66	1 250
0.4	3.4	736
1.0	2.66	378

[a] A plot of log a vs. log $t_{\frac{1}{2}}$ was linear ($r = 0.989$) with slope -0.99.

in thionyl chloride. An Arrhenius study (Table 3) showed a low activation energy, which is in agreement with the synthetic ease of the reaction at low temperatures. The reaction, however, had a high negative entropy (Table 3) which suggests a highly ordered transition state compatible with a cyclisation process.

negative entropy was observed. It is unlikely that similar extents of solvent organisation would arise in solvents as different as $SOCl_2$ and CCl_4 and these data confirm an ordered transition state compatible with a cyclisation process. We have found no evidence for radicals in this reaction. No CIDNP was observed in careful monitoring of ^1H n.m.r. signals within seconds of mixing the reactants and no e.s.r. signals were detected from the solutions.
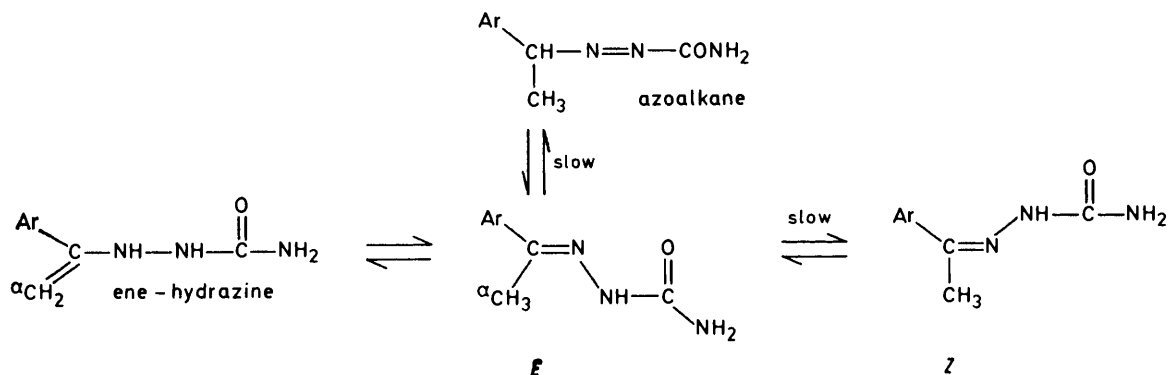
DISCUSSION

The reaction is clearly electrophilic in character with a transition state of the type $Hy^{\delta+} \cdots \overset{\delta+}{SOCl} \cdots Cl^-$ (where HY = substrate). The Hammett σ^+ correlation and the ρ value of -0.55 indicate through-bond resonance to the methine $para$-substituents. The ρ value for the methine phenyl ring is similar in magnitude to those observed for attacks by other electrophiles on the adjacent hydrazone moiety. These include bromine,[11] lead tetra-acetate,[12] and diazonium ion [13] where the

TABLE 3

Arrhenius data

Substrate	T/K	$10^4 k/\text{s}^{-1}$	$\Delta E^{\ddagger}$ kcal mol^{-1}	$\Delta H^{\ddagger}$ kcal mol^{-1}	$\Delta S^{\ddagger}$ cal K^{-1} mol^{-1}
Solvent: SOCl$_2$					
(1b)	301	7.61	9.46 [a]	8.86	-43.4
(1b)	311	11.48	9.46	8.84	-43.65
(1b)	321	22.30	9.46	8.82	-43.35
(1b)	331	31.32	9.46	8.80	-43.6
(1d)	301	3.75	10.59 [b]	9.99	-41.21
(1d)	311	6.17	10.59	9.97	-41.23
(1d)	321	11.42	10.59	9.95	-41.24
(1d)	331	18.40	10.59	9.93	-41.24
(1h)	301	4.73	10.89	10.29	-39.58
(1h)	311	10.58	10.89	10.27	-39.34
(1h)	321	16.01	10.89	10.25	-39.54
(1h)	331	25.50	10.89	10.23	-39.68
Solvent: CCl$_4$		$10^3 k/\text{l mol}^{-1}\text{ s}^{-1}$			
(1d)	308	1.9	11.25 [a]	10.66	-36.43
(1d)	318	3.45	11.27	10.645	-36.46
(1d)	328	7.45	11.28	10.625	-36.25

[a] Correlation coefficient for Arrhenius plot, $r = 0.999$. [b] Correlation coefficient $r = 0.998$.

attack occurred on the hydrazone π-system and the
ρ values for methine phenyl substituents were —0.62,
—0.60, and —0.38 respectively. The attack could
possibly occur on either of the E, Z, azoalkane or ene-
hydrazine forms of the semicarbazones (Scheme 1).

resonance to the methine aryl ring and also stabilises the
overall electrophilic species. This approach renders the
electrophile adjacent to, and almost co-planar with, the
axial proton of the methine α-sp³ carbon, an orientation
which is especially favourable for loss of a second HCl

Scheme 1

Only one form, which we assign as the expected E-form,
was observed in the n.m.r. spectra and it was the dis-
appearance of this which was measured kinetically and
found to be identical with the rate of appearance of
product. Previously we have found [14] that the attack of
bromine on aldehyde semicarbazones occurred on the
minor Z-isomer. In this case the reaction was zero-order
in bromine and the rate-determining step was the slow
$E \rightarrow Z$ isomerization. For aldehyde semicarbazones [14]
this geometric isomerization was an order of magnitude
slower than the rates observed herein and the possible
azoalkane tautomerism is orders of magnitude slower
still.[15] The rate of the ene-hydrazine tautomerism in a
non-polar medium such as carbon tetrachloride should
also be particularly slow. If the attack were occurring
on a minor tautomeric form the reaction would then be
expected to be zero-order in thionyl chloride and first-
order in semicarbazone, the measured rate being that of
the isomerization. This was not the case. Further-
more if the ene-hydrazine form was involved in the rate-
determining step then replacement of a H atom on the
α-carbon by a Ph substituent should cause a substantial
increase in the rate. No such effect was observed and
the rates found for the semicarbazone of methyl phenyl
ketone and benzyl phenyl ketone (Table 1 Nos. 1a, 1h)
differed by only ca. 10%. Similar Arrhenius para-
meters (Table 3) were also obtained for compound (1h) as
for the other reactions and the introduction of a phenyl
substituent on the α-carbon had little or no effect on the
rate-determining step. A mechanism involving attack
on a minor tautomeric form of the semicarbazone is not
compatible with these data.

The data are consistent with an ordered electrophilic
transition state (4a) involving the E-isomer of the semi-
carbazone (Scheme 2, path a). The incoming electro-
phile is above the C–N–N plane and is complexed to the
orthogonally oriented amino-n-electrons and imino π-
electrons; the latter accommodates the σ⁺ through-bond

molecule and for bonding of the sulphur atom to the
α-carbon as well as to the amino-nitrogen. Alter-
natively, the electrophilic attack need not involve an
ordered conformation of the methine α-carbon. The
electrophilic attack on the hydrazone π-p system could
give an intermediate (4b) in which a fast ene-hydrazine
tautomerism occurred prior to cyclisation (Scheme 2,
path b) and this would not influence the rates. An
unstable intermediate (5) may, therefore, be formed by
either path a or path b and this gives rise to products in
subsequent rapid steps.

Data cannot be obtained directly for these last stages
of the reaction and indeed the final fragments of the
cyclisation have not been identified previously for semi-
carbazones. In this present work these fragments have
now been identified by carrying out the reaction in an
evacuated sealed system connected to an i.r. gas cell
using carefully dried solvent (CCl_4; 10 ml), thionyl
chloride (1 mmol), and acetophenone semicarbazone (1
mmol) dried at 100 °C for 4 h. The reaction flask was
held at 44—48 °C and the gases over the carbon tetra-
chloride solvent were monitored by continual i.r. scan-
ning. Within 10 min i.r. absorptions due to CO_2 appeared
at 2 340, 2 360, and 668 cm⁻¹ and continued to grow as
the reaction progressed over ca. 90 min. The only
other absorptions encountered were due to HCl and
CCl_4. When the reaction was complete the carbon
tetrachloride solution was extracted with water and the
aqueous extract on evaporation gave ammonium chloride
(49 mg, 92%). Hence the products of the reaction are
CO_2, NH_3, HCl, and the compounds (3).

The conversion of the intermediates (5) into these
products is probably a thermal aromatization. Since no
more than 1 mol equiv. of thionyl chloride is necessary
and this is destroyed in the early steps no further mole-
cules of $SOCl_2$ could be involved (except of course in
$SOCl_2$ solvent). It is possible that HCl or H⁺ could be
involved but the ease of the reaction in CCl_4 from which
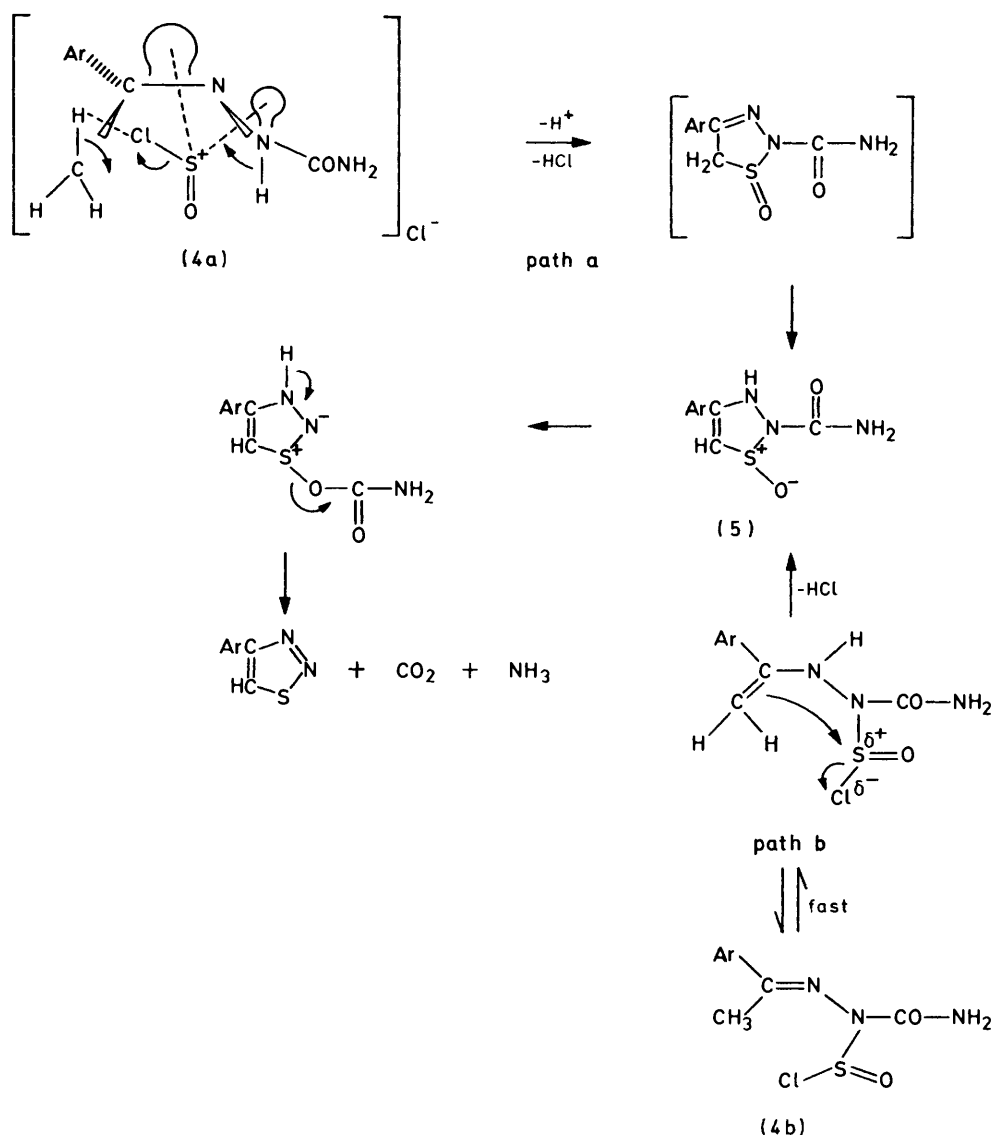
Scheme 2

HCl vapours (not held as NH_4Cl) are rapidly expelled, favours a thermal rather than a medium-induced fragmentation in this solvent. A series of 1,3 H-migrations concomitant with a 1,3 N→O carboxamido-migration (Scheme 2) could readily lead to the observed products. Comparable aromatisations have been postulated previously in the synthesis of isothiazoles from the reaction of thionyl chloride with α-aminoketones.[16]

EXPERIMENTAL

M.p.s were measured with an Electrothermal apparatus. [1]H N.m.r. spectra were measured with a JEOL JNM-MH-100 spectrometer. The semicarbazone substrates were prepared by standard procedures.[8] All of the compounds herein gave satisfactory C, H, N, elemental analyses and the expected [1]H n.m.r. spectra. The semicarbazone methine CH_3 signal appeared at 2.20—2.37 $\delta[(CD_3)_2SO]$.

The general procedure for the synthetic reactions of thionyl chloride with the semicarbazones was as follows:

A quantity (2 mmol) of semicarbazone was added to thionyl chloride (2 ml) at 0—5 °C and stirred for periods of 0.5—4 h. The thionyl chloride solvent was removed under reduced pressure and the residue was distributed between chloroform and 5% sodium hydrogen carbonate solution. The chloroform extract was dried ($MgSO_4$), evaporated, and the residue separated on a column of silica gel made up in light petroleum (b.p. 40—60 °C) [chloroform eluted compounds (3) and ethanol eluted unchanged substrate] giving the products shown (Table 1). The thiadiazoles (3) showed the expected [1]H n.m.r. spectra in which the proton H_A appeared as a sharp singlet at $\delta(CDCl_3)$ 8.62—8.83. A similar work-up procedure was used with carbon tetrachloride as solvent using equimolar quantities of reactants for 1 h at 46 °C.

Kinetics.—The kinetics were measured on solutions of semicarbazone (0.166 mmol) in thionyl chloride 1 ml (13.8 mmol) at 28 °C. The rates of disappearance of semicarbazone (Table 1) were obtained from plots log $(I_t - I_\infty)$ for the methine methyl signal (intensity I) versus t. These plots were linear with slope $-k/2.303$ as expected for a

pseudo-first-order reaction arising from the 83-fold excess of thionyl chloride used. The rates of appearance of the products (3) were similarly obtained from linear plots of log $(I_\infty - I_t)$ for the growing thiadiazole H_A proton signal (intensity I) vs. t which were linear with slope $-k/2.303$. Arrhenius data were obtained using a JNM-VT-3B variable-temperature control. Temperatures were calibrated before and after each rate measurement using the standard methanol chemical shift and are accurate to ± 0.2 °C. The rate constants are mean values of three measurements and are accurate to $\pm 2\%$. Similar procedures were followed for rate measurements in carbon tetrachloride.

The thionyl chloride solvent used was purified by the recommended literature procedure [17a] of successive fraction-ations from quinoline in glass apparatus fitted with an anhydrous calcium chloride drying tube. The purified fraction was then refractionated from boiled linseed oil. The pure liquid obtained had b.p. 76—77 °C. The carbon tetrachloride solvent was purified [17b] by repeated distil-lations to b.p. 76 °C.

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