A Study of the Mechanism of the Oxidative Cyclization of Benzaldehyde Semicarbazones Induced by Cupric Perchlorate in Acetonitrile

Renato Noto,* Michelangelo Gruttadauria, Paolo Lo Meo, Vincenzo Frenna and Giuseppe Werber

Dipartimento di Chimica Organica, Università di Palermo, Via Archirafi 20, 90123 Palermo, Italy
Received December 30, 1994

Treatment of benzaldehyde semicarbazones **1a-i** with cupric perchlorate in acetonitrile at 40° provided selectively the corresponding 1,2,4-triazolin-5-ones **2a-i**. The relative rate constants for **2a-i** formation were determined by the competitive method. The results obtained showed that electron-donating substituents (methyl and methoxy) increase the reaction rate, while the reverse was found for electron-withdrawing substituents (chloro and nitro group). The reactivity data are discussed on the grounds of two possible mechanisms.

Introduction.

The oxidative cyclization of aldehyde semicarbazones, methyl substituted on the N(2) nitrogen atom **1** induced by metallic salts leads to 1,2,4-triazolin-5-one derivatives **2** (Scheme 1) [1].

Scheme 1
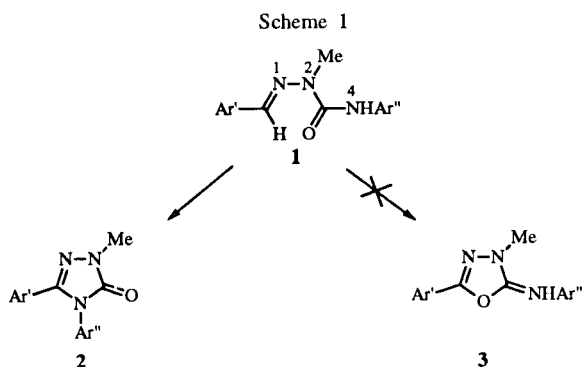
The nature of the metallic salt as well as the structure of the semicarbazone affects rate and yield of cyclization while they do not show any influence on the regiochemistry of the reaction. Indeed formation of 1,3,4-oxadiazol-2-imino derivatives **3** was never detected [1] under experimental conditions adopted. This can be somewhat surprising especially if one considers that when the semicarbazide chain is unsubstituted at the N(2) nitrogen atom, oxidative cyclization of aldehyde semicarbazones leads to the 1,3,4-oxadiazole ring [2] or to 1,2,4-triazole ring [3] or to both [4] depending on the experimental conditions.

We have recently proposed [1] a mechanism (electrophilic cyclization) for the oxidation induced by metallic salts of aldehyde semicarbazones **1** into the corresponding 1,2,4-triazolin-5-ones **2**.

The electrophilic cyclization consists of the following steps (Scheme 2): (a) reversible electrophilic attack of the metal atom on the N(4) nitrogen atom; (b) reversible deprotonation of the salt **A**; (c) heterolytic rupture of the M-N(4) metal-nitrogen bond of the species **B** with forma-

tion of a nitrogen electrophilic cation **C**; (d) cyclization due to an electrophilic attack of the nitrogen cation **C** on the carbon-nitrogen double bond.

Scheme 2
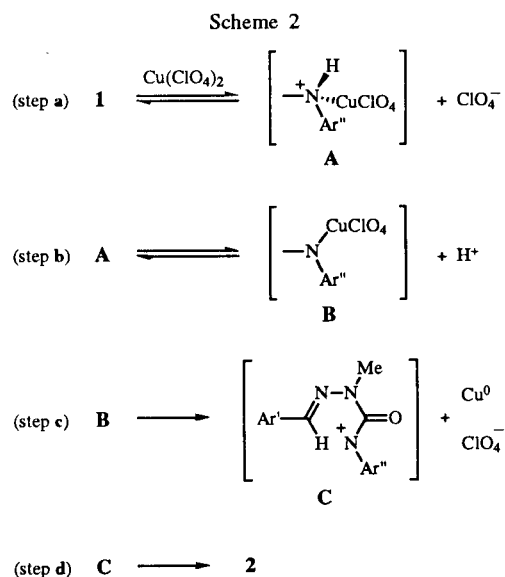
The formation of intermediate **C** is open to criticism as this species, containing a nitrogen atom with six electrons can seem to be unlikely. However, the formation of an amino cation ArN+ has been suggested in the oxidation of thiosemicarbazone [5], of 2,4,6-tris(1,1-dimethylethyl)aniline [6] and also in the solvolysis of substituted N-chloroanilines [7].

A different mechanism (nucleophilic cyclization) has been suggested to us, consisting (Scheme 3) of a reversible electrophilic attack of the metal atom on the N(2) nitrogen atom followed by rate determining nucleophilic attack of the N(4) nitrogen atom on the carbon nitrogen double bond with oxidative rupture of the M-N(2) bond.

In order to decide which of the two above mechanisms is more reliable, we studied the cyclization of benzaldehyde semicarbazones **1a-i** into the corresponding

Scheme 3
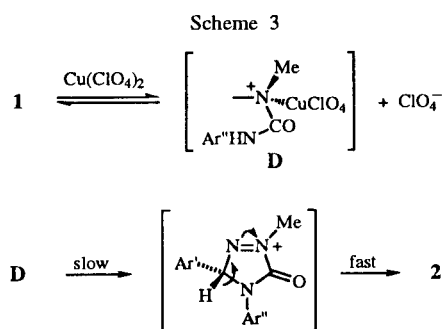
1,2,4-triazolin-5-one derivatives **2a-i** induced by cupric perchlorate at 40° by determining the relative reactivities of the different substrates.

Scheme 4
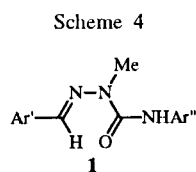
	Ar'	Ar''
a:	C_6H_5	C_6H_5
b:	4-MeO-C_6H_4	C_6H_5
c:	4-Me-C_6H_4	C_6H_5
d:	4-Cl-C_6H_4	C_6H_5
e:	4-NO$_2$-C_6H_4	C_6H_5
f:	C_6H_5	4-MeO-C_6H_4
g:	C_6H_5	4-Me-C_6H_4
h:	C_6H_5	4-Cl-C_6H_4
i:	C_6H_5	4-NO$_2$-C_6H_4

The semicarbazones **1a-i** were chosen in such a way as to have a change of electronic density on both the carbon-nitrogen double bond and the N(4) nitrogen atom.

Cupric perchlorate in acetonitrile [8] was chosen as the cyclising agent because it gave faster and cleaner reactions than other oxidizing systems [1]. The involvement of Cu^{II} in redox processes of organic compounds is well known [9]. Moreover, Cu^{II} can act towards a hydrazone or a hydrazone-like group as a complexing agent [10].

The relative constants of formation of 1,2,4-triazolin-5-ones, **2a-i**, with respect to **2a** were determined by the competitive method. Equimolecular quantities of any given semicarbazone and the unsubstituted derivative **1a**, were reacted with 25% of the stoichiometric amounts of oxidizing salt. Each experiment was quenched after a few percent of starting compounds had reacted. The concentration ratios of **2a-i** were determined by ^{1}H nmr spectroscopy by measuring the ratio of the peak areas of the methyl groups [11] on the N(1) nitrogen atom of 1,2,4-triazolin-5-ones **2** obtained from oxidation reactions. The reaction mixture was purified by flash chromatography to remove unreacted semicarbazones before carrying out nmr measurements.

In spite of considerable overlapping of the absorption bands of the starting semicarbazone **1** and the triazolone **2** produced, it would be possible to follow spectroscopically the disappearance of the former compound. However the occurrence of a side reaction (hydrolysis of **1**) [12] generally prevented accurate determination of the rates of formation of the corresponding triazolones **2**. Only in the case of **1a**, whose hydrolysis turned out to be negligible, were we able to measure the absolute kinetic constant of formation of **2a** by following the disappearance of **1a** spectroscopically in the presence of an excess of cupric perchlorate.

Results and Discussion.

The kinetic data of the oxidative cyclization of semicarbazone **1a** are summarized in Table I.

Table I

Kinetic Data for the Oxidative Cyclization of **1a** with $[Cu(ClO_4)_2] \cdot 6H_2O$ in Acetonitrile at 40°C

[1a] x 10^5 (M)	[ox] x 10^3 (M)	k_{obs} [a] x 10^4 (s^{-1})	k_a [b] ($M^{-1}s^{-1}$)
1.67	0.653	1.81	0.277
2.78	0.653	1.94	0.297
2.78	1.09	2.62	0.240
2.78	1.63	3.56	0.218
2.78	2.18	4.30	0.197
2.78	2.72	5.25	0.193
4.17	1.63	3.55	0.218
5.56	2.18	4.47	0.205

[a] The rate constants are accurate to ±3%. [b] Calculated from $k_{obs} = k_a$ [ox].

The values of the concentration ratios of 1,2,4-triazolin-5-ones, **2a-i** with reference to **1a** are reported in Table II.

Table II

The Concentrations Ratios for the Oxidative Cyclization of Semicarbazones **1a-i** with Reference to the Unsubstituted Semicarbazone **1a**

semicarbazone	[2a-i] / [2a]
1a	1.000
1b	2.723
1c	1.340
1d	0.390
1e	0.028
1f	1.750
1g	1.390
1h	0.511
1i	0.055

The apparent second-order kinetic constant of **1a**, determined by keeping constant either the substrate-oxidizing

agent concentration ratio or the substrate concentration, decreases as the cupric perchlorate concentration is increased (see data in Table I and the Figure). This behavior could be linked to the formation of at least one unreactive species between the semicarbazone **1a** and the metallic salt.
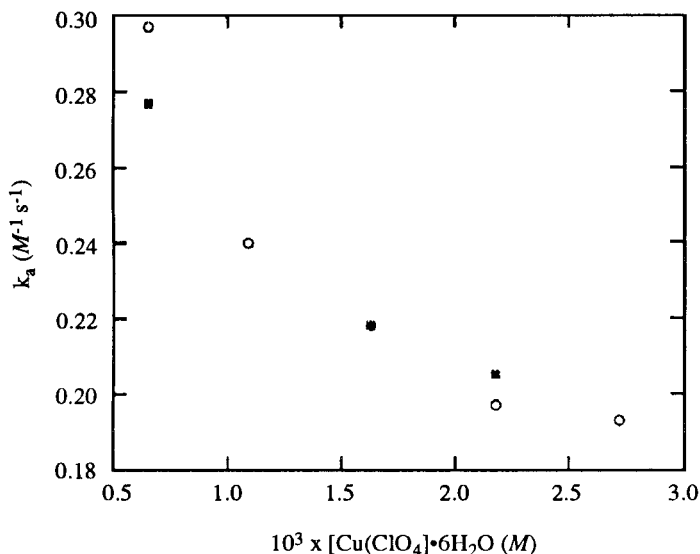

Figure. Plot of apparent second order kinetic constants (k_a) for the oxidative cyclization of **1a** with cupric perchlorate at 40°C in acetonitrile *versus* cupric perchlorate concentration: (round symbols) substrate concentration constant; (square symbols) substrate-cupric perchlorate concentration ratio constant.

The formation of an unreactive species explains the observed curvilinear trend of the apparent second order kinetic constant provided that the association constants of the unreactive species is higher than that of the reactive one. It can be noted that species **A** is reactive for the electrophilic mechanism and unreactive for the nucleophilic one, which is the opposite for the species **D**. Due to the fact that the N(2) nitrogen atom should be a stronger basic site than the N(4) nitrogen atom, the association constant relative to M-N(2) bond formation should be higher than that relative to M-N(4) bond formation. Therefore **D** could be an unreactive species for the electrophilic mechanism and this is responsible for the curvilinear trend of the apparent second order kinetic constant, whereas **A** cannot be accounted for by the nucleophilic mechanism. It is also possible that an unreactive complex is formed between semicarbazone **1a** and cupric perchlorate such as the complex of the Cu^{II} ion with semicarbazide [14]. We have evidence of unreactive complex formation when a semicarbazone is able to act as a three coordinate ligand, for example when the 2-methyl-4-phenylsemicarbazone of pyridine-2-carboxaldehyde was treated with cupric perchlorate no

oxidation derivatives were detected and a 1:1 complex between semicarbazone and metallic salt could only be isolated [15]. Moreover, it is interesting to note that benzaldehyde 4-phenylsemicarbazone treated with cupric perchlorate in acetonitrile was recovered largely (80%) unchanged and partially (20%) hydrolysed after one day [16]. The formation of a very stable complex as **4** could explain the failure of the oxidation reaction.

Scheme 5

4
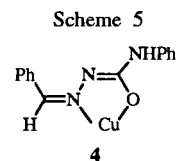
The semicarbazone **1a** can behave as a bidentate ligand through the lone pairs on the N(2) and N(4) atoms or more probably through the lone pairs on N(1) and N(4) or N(1) and the oxygen atom. The complex between semicarbazone **1a** and the metal atom cannot be directly in equilibrium with the reactive species as this is contrary to the observed curvilinear trend of the apparent second order kinetic constant. Therefore among the aforesaid complexes those bearing the metal bonded to N(4) or to N(2) do not seem suitable to describe the observed inhibitory effect for electrophilic and nucleophilic mechanisms respectively. So, if the observed curvilinear trend was due to the formation of a complex, such a complex should be formed through metal bonding at both N(1) and oxygen atoms of the semicarbazone [17]. This is in accord with the fact that in metal semicarbazone complexes the organic moiety coordinates to the metal ion as a bidentate ligand through the N(1) and oxygen atoms.

As it can be seen from the data reported in Table II, electron-donating substituents (methyl and methoxy groups) cause an increase in the reaction rate. The opposite behavior is observed for electron-withdrawing substituents (nitro group and chloro). It is interesting to note that the substituent effect is qualitatively the same independently of which of the two phenyl rings bears the substituents.

In order to quantify the above substituent effects we have attempted to correlate the data reported in Table II with σ substituent constants [18] in terms of Hammett's equation [19] obtaining the following good correlations:

$$\log k_x/k_a = -0.06(0.03) - 1.81\,(0.07)\sigma \quad r = 0.998 \quad n = 5 \quad (1)$$

for substitution on the phenyl group bonded to C=N double bond and

$$\log k_x/k_a = -0.06(0.04) - 1.42(0.10)\sigma \quad r = 0.993 \quad n = 5 \quad (2)$$

for substitution on the phenyl ring bonded to the N(4) nitrogen atom. According to the above mentioned sub-

stituent effects in both correlations the value the of susceptibility constant ρ is negative. It is interesting to note that the oxidative cyclization is more sensitive to substitution on the phenyl ring bonded to the carbon-nitrogen double bond than to substitution on the other phenyl ring as shown by the corresponding susceptibility values -1.81 and -1.42.

The increase in reactivity due to introduction of a methyl or methoxy group on the phenyl ring bonded to the carbon atom of the C=N double bond can be explained as a consequence of a decrease of carbon-nitrogen bond order [20].

The decrease in bond order should allow the nucleophilic and electrophilic centres to reach a better arrangement for a more favourable reactive interaction. The same effect of substituents was observed in the similar cyclization of substituted N-benzohydroxamoyl-N-methylhydrazones to 3-aryl-1 -methyl-5-phenyl-1,2,4-triazoles [21].

The effect of substituents bonded to the phenyl on the N(4) nitrogen atom can be easily explained by the nucleophilic mechanism. The methyl and methoxy groups increase the nucleophilicity of the N(4) nitrogen atom and consequently increase the rate of reaction, and the opposite explains the chloro and nitro group.

It is more difficult to explain the above effect for the electrophilic mechanism. On the grounds of the mechanism reported in the Scheme 2, when the phenyl group on the N(4) nitrogen atom bears an electron-donating substituent, the electron density on N(4) increases, consequently the attack of the metallic salt on nitrogen (step **a**) should be easier, but at the same time the proton departure from species **A** (step **b**) should be more difficult. In other words a substituent on N(4) should have opposite effects on the above two steps of the reaction. The substituent effects on the other two steps of reaction: heterolytic rupture of metal-nitrogen bond (step **c**) and cyclization (step **d**); again should be opposite, *i.e.* an electron-donating substituent, which stabilizes the nitrogen-cation **C**, favours step **c** (formation of **C**) and disfavours step **d** (intramolecular electrophilic attack to the C=N double bond). However, remembering that methyl and methoxy groups favour, and that nitro group and chloro disfavour the reaction, it may be concluded that the substituents on N(4) phenyl ring affect steps **a** and **c** more than steps **b** and **d**.

An important result obtained by the correlations is that the data relative to semicarbazones **1a,f-i**, bearing a substituent on the phenyl ring bonded to the N(4) nitrogen atom, give a better correlation with σ rather than σ+ substituent constants. This fact seems to exclude the formation of a nitrogen cation **C**, which should require the use of σ+ substituent constant, but if the heterolytic rupture of M-N(4) bond and the electrophilic attack on C=N double bond occur in one concerted non syncronous [22] way, rather than in two subsequent steps, a positive charge due to an electronic gap

does not develop on the nitrogen atom, consequently σ substituent constants are adapted to describe the substituent electronic effect. Also for the nucleophilic mechanism it is necessary, in order to explain the dependence of reactivity data on σ substituent constants, that rupture and formation of bonds takes place in a concerted manner leading to a transition state as that reported.

<div style="text-align:center">Scheme 6</div>
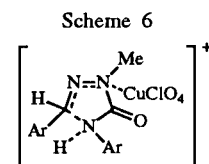
The occurrence of an heterolytic rupture of the M-N bond in a rate determining step is consistent with the fact that the semicarbazone reactivity depends on the particular metal salt used as an oxidizing agent [1]. As far as the rupture of the M-N bond is concerned, it should be noted that Cu^0, obtained by the above heterolytic rupture, is quickly oxidized by Cu^{II} to Cu^I [23]. However we cannot discard the possibility that rupture of M-N bond and metal-metal electron transfer are concerted.

In conclusion we think that the data collected can be explained with both mechanisms reported, the nucleophilic mechanism seems preferable on the grounds of the fact that usually the imino moiety gives nucleophilic reactions.

EXPERIMENTAL

The melting points are uncorrected. Infrared (ir) spectra were obtained with a Perkin-Elmer 1310 infrared spectrophotometer. The ^1H nmr spectra were recorded on a Bruker AC-E Series 250 MHz spectrometer in deuteriochloroform solutions. Chemical shifts are reported as δ values (ppm) relative to TMS as an internal standard. Product mixtures were separated by flash chromatography on Merck silica gel (0.040-0.063 mm). The columns were eluted with cyclohexane/ethyl acetate mixture of differing volume ratios. The uv absorption spectra were monitored on a Beckman DU-6 spectrometer.

Acetonitrile 99.5% (Aldrich) was used without further purification. Cupric perchlorate hexahydrate (Aldrich) was kept in a dessiccator over phosphorus pentoxide. The semicarbazones **1a-c,e-g,i** and 1,2,4-triazolones **2a-c,e-g,i** were prepared by the methods described in the literature [1].

2-Methyl-4-phenylsemicarbazone of *p*-Chlorobenzaldehyde (1d).

This compound had mp 162°, (86% yield); ir (nujol mull): 3370, 1690 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.42 (s, 3H), 7.27,7.50 (2 m, J = 8.95 Hz), 7.30-7.43 (m, 3H), 7.59 (s, 1H), 7.60-7.70 (m, 2H), 8.77 (s, 1H).

Anal. Calcd. for $C_{15}H_{14}N_3OCl$: C, 62.61; H, 4.90; N, 14.60. Found: C, 62.34; H, 5.02; N, 14.74.

2-Methyl-4-(*p*-chlorophenyl)semicarbazone of Benzaldehyde (**1h**).

This compound had mp 154°, (91% yield); ir (nujol mull): 3350, 1670 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 3.44 (s, 3H), 7.05-7.12 (m, 1H), 7.30-7.38 (m, 2H), 7.41,7.61 (2 m, J = 8.49 Hz), 7.52-7.59 (m, 3H overlapped with CH), 8.71 (s, 1H).

Anal. Calcd. for $C_{15}H_{14}N_3OCl$: C, 62.61; H, 4.90; N, 14.60. Found: C, 62.40; H, 5.00; N, 14.70.

1-Methyl-3-(*p*-chlorophenyl)-4-phenyl-1,2,4-triazolin-5-one (**2d**).

This compound had mp 200°, (90% yield); ir (nujol mull): 1705 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 3.61 (s, 3H), 7.19-7.30 (m, 6H), 7.40-7.48 (m, 3H).

Anal. Calcd. for $C_{15}H_{12}N_3OCl$: C, 63.05; H, 4.23; N, 14.71. Found: C, 62.74; H, 4.34; N, 14.80.

1-Methyl-3-phenyl-4-(*p*-chlorophenyl)-1,2,4-triazolin-5-one (**2h**).

This compound had mp 139-140°, (79% yield); ir (nujol mull): 1700 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 3.61 (s, 3H), 7.17,7.39 (2 m, J = 6.66 Hz), 7.28-7.34 (m, 5H).

Anal. Calcd. for $C_{15}H_{12}N_3OCl$: C, 63.05; H, 4.23; N, 14.71. Found: C, 63.21; H, 4.17; N, 14.60.

General Method for the Determination of Relative Rate Constants.

Semicarbazone 1 (4·10^{-4} mole), whose relative reactivity had to be determined, and 4·10^{-4} mole of the unsubstituted semicarbazone **1a**, taken as a reference, were dissolved in 6 ml of acetonitrile. A solution (6 ml) of cupric perchlorate hexahydrate (4·10^{-4} mole) in acetonitrile was added. The reactions were carried out at 40±0.1°. After 0.5 hour the solvent was removed under reduced pressure. Water was added to the residue and this extracted with chloroform and then chromatographed to separate the triazolones 2 from unreacted semicarbazones 1. The relative quantities of **2a-i** were determined by ^{1}H nmr spectra, measuring the ratio of peak areas of the methyl groups on the N(1) nitrogen atom of 1,2,4-triazolin-5-one, for compounds **2e** and **2i** peak areas of the hydrogen atoms ortho to the nitro groups were monitored. The relative rate constants were determined by the equation:

$$k_x/k_a = [2x]/[2a] \quad (3)$$

where a and x refer to **2a**, taken as a reference, and to a generic 1,2,4-triazolin-5-one **2a-i** respectively. The above equation arises by a more strict one:

$$k_x/k_a = \log [1x]/([1x]-[2x])/\log[1a]/([1a]-[2a]) \quad (4)$$

after a series development of the two logarithmic terms. In the equations (3) and (4) [1x] and [1a] are the concentrations of semicarbazones **1x** and **1a** before starting the reaction, [2x] and [2a] are the concentrations of 1,2,4-triazolin-5-ones after 0.5 hour.

Kinetic Procedures.

The kinetics were followed spectroscopically in acetonitrile at 40±0.1°, in a heated compartment, by measuring the disappearance of **1a** at the wavelength (300 nm) of its absorption maxi-

mum, where the absorptions of cupric perchlorate hexahydrate and triazolone **2a** are very low.

The concentrations employed and the observed first order kinetic constants are shown in Table I.

REFERENCES AND NOTES

[1]   M. Gruttadauria, F. Buccheri, G. Cusmano, P. Lo Meo, R. Noto, and G. Werber, J. *Heterocyclic Chem.*, **30**, 765 (1993).
[2]   G. Valenti F. and Maggio, *Ann. Chim. (Rome)*, **42**, 18 (1952); H. Gehelen K. and Moekel, *Liebigs Ann. Chem.*, **133**, 651 (1962); T. M. Lambe, R. N. Butler, and F. L. Scott, *Chem. Ind.* (London), 966 (1971); T. H. Nguyen, R. Milcent, and G. Barbier, J. *Heterocyclic Chem.*, **22**, 1383 (1985).
[3]   E. Hoggarth, J. *Chem. Soc.*, 1918 (1949); R. Noto and M. Gruttadauria, unpublished results.
[4]   F. L. Scott, T. M. Lambe, and R. N. Butler, J. *Chem. Soc., Perkin Trans. 1*, 1918 (1972); O. Hammerich and V. D. Parker, J. *Chem. Soc., Perkin Trans. 1*, 1718 (1972).
[5]   R. Noto, F. Buccheri, G. Cusmano, M. Gruttadauria, and G. Werber, J. *Heterocyclic Chem.*, **28**, 1421 (1991).
[6]   R. Okazaki, T. Hosogai, M. Hashimoto, and N. Inamoto, *Bull. Chem. Soc. Japan*, **42**, 3559 (1969).
[7]   P. G. Gassman, G. A. Campbell, and R. C. Frederick, J. *Am. Chem. Soc.*, **94**, 3884 (1972).
[8]   Methanol did not permit the oxidation reaction. In fact, the semicarbazones **1a-i** were recovered unreacted when were treated with methanolic cupric perchlorate solutions.
[9]   F. Minisci, R. Galli, and M. Cecere, *Gazz. Chim. Ital.*, **95**, 751 (1965); J. Tsuji, H. Takahashi, and T. Kajimoto, *Tetrahedron Letters*, 147 (1976); J. Tsuji, H. Kezuka, Y. Toshida, H. Takayanagi, and K. Yamamoto, *Tetrahedron*, **39**, 3279 (1983); P. Bisiacchi, A. Corsica Coda, G. Desimoni, P. Righetti, and G. Tacconi, *Gazz. Chim. Ital.*, **115**, 119 (1985); A. Corsica Coda, G. Desimoni, H. L. Monaco, P. Quadrelli, and P. Righetti, *Gazz. Chim. Ital.*, **119**, 13 (1989).
[10]   S. Buscemi, V. Frenna, N. Vivona, and D. Spinelli, J. *Chem Soc., Perkin Trans 1*, 2491 (1993); S. Padnyé and G. B. Kauffman, *Coord. Chem. Rev.*, **63**, 127 (1985).
[11]   For compounds **2e** and **2i** peak areas of the hydrogen atoms ortho to the nitro group were monitored.
[12]   The hydrolysis of some semicarbazones induced by cupric sulphate pentahydrate gave the corresponding carbonyl derivatives [13].
[13]   O. Attanasi and S. Gasperoni, *Gazz. Chim. Ital.*, **108**, 137 (1978).
[14]   S. O. Ajayi and D. R. Goddard, J. *Chem. Soc. (A)*, 2673 (1971).
[15]   G. Gulì and M. Gruttadauria, unpublished results.
[16]   R. Noto and M. Gruttadauria, unpublished results.
[17]   A complex formed through metal bonding at both N(1) and N(4) atoms could explain the inhibitory effect if nucleophilic mechanism is operative for semicarbazone oxidation.
[18]   O. Exner, in Correlation Analysis in Chemistry, Recent Advances, N. B. Chapman and J. Shorter, eds, Plenum Press, New York, 1978.
[19]   L. P. Hammett, Physical Organic Chemistry, 2nd Ed, McGraw-Hill, New York 1970, Chapter 11.
[20]   J. Pacansky, A. D. McLean, and M. D. Miller, J. *Phys. Chem.*, **94**, 90 (1990).

[21]   F. Risitano, G. Grassi, F. Foti, G. Bruno, and F. Nicolò, *Tetrahedron*, **49**, 10427 (1993).

[22]   The rupture of the M-N(4) bond should be more advanced than the nitrogen attack, in order that a partial positive charge on N(4) can account for the substituent effect. In fact, the observed ρ value (-1.42) is the combination of the ρ values of two acid-base equilibria (steps **a** and **b**) and the rate determining step. Tentatively, we can suppose that activating and deactivating substituents affect the two acid-base equilibria and approximately cancel the substituent effect on the phenyl ring bonded to the N(4) nitrogen atom. These do not influence the first part (steps **a** and **b**) of the reaction.

[23]   A. G.Massey, in Comprehensive Inorganic Chemistry, Vol. 3, J. C. Bailar, H. J. Emeléus, R. Nyholm, and A. F. Trotman-Dickenson, eds, Pergamon Press, Oxford, 1973.