Carbanion Stabilization in C,N-Dimethylnitroimidazoles

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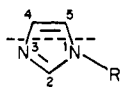
Kinetics of base-catalyzed exchange of C-methyl protons have been investigated for the six position isomers of C,N-dimethylnitroimidazoles (at 60 °C in D_2O–CD_3OD, 1:1). Rates of exchange were based on the decrease in ^1H NMR signals relative to those for the nonexchanging N-methyl groups. Values of k_{OD} covered a range of 5×10^4; in 0.01 N NaOD, values of $t_{1/2}$ range from 2.8 s to 38 h. The greatest kinetic acidity was found in 1,5-dimethyl-4-nitroimidazole and the least in 1,2-dimethyl-4-nitro- and 1,4-dimethyl-2-nitroimidazole. In the latter two compounds, the methyl and nitro groups have a "meta" relationship; their resistance to exchange indicates weak resonance stabilization of the respective carbanions. The value of k_{OD} for 1,5-dimethyl-4-nitroimidazole (1485 M^{-1} min^{-1}) is 4.8×10^6 as great as that for o-nitrotoluene but only 27-fold less than that for nitromethane. The result suggests that there may be significant localization in the 4,5 double bond of N-substituted imidazoles. The order of kinetic acidities for the C-methyl groups is consistent with the order of reactivities of the same compounds in aldol condensations.

In the course of our studies in imidazole chemistry, spanning a number of years, certain results have appeared which seem inconsistent with the general view of imidazole as a simple heteroaromatic system: for example (1) the high degree of lability of 4-aminoimidazoles vs. the stability of the 2-amino series,[2] (2) the differences in chemical behavior of 2- and 4-haloimidazoles,[3,4] (3) the facile loss of 4-substituents under hydrogenation conditions,[5] (4) the apparent difference in magnitude of electronic transmission from C-4 to C-2 and from C-5 to C-2,[6] and (5) the difference in electronic transmission from C-5 to C-2 and from C-2 to C-5.[6] These properties suggest that the imidazole ring sometimes behaves more like the fusion of an olefin with an amidine (1) than like a truly aromatic system and, further, that canonical form **1a** may not make an important contribution to amidine stabilization,[7] at least when R ≠ H.



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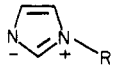
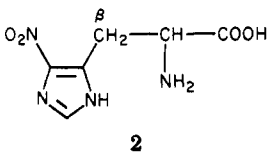


1a



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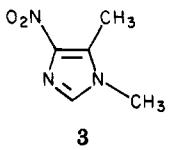
In connection with a study of the enzymatic deamination of 4-nitrohistidine (**2**),[8] we found the β-methylene group to undergo total exchange in 1 N NaOD at 60 °C in 1–2 days. This exchange is somewhat faster than that reported for o- or p-nitrotoluene[9] (after extrapolation to the same temperature), and the specific rate constant for **2** would be much larger than k_{obsd} after correcting for the fact that, in the strongly basic medium, the nitroimidazole exists overwhelmingly as its kinetically inactive imidazolate anion. We were led, therefore, to investigate the basis for this remarkably facile exchange by examining the rates of C-methyl deuteration in the simpler C,N-dimethylnitroimidazoles **3**–**8**. We also hoped that the results might



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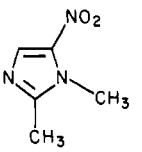

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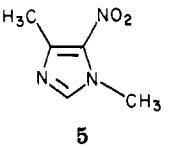

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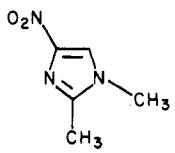

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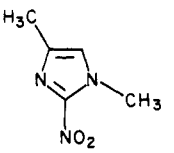

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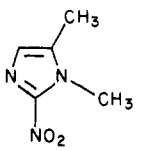

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advance our understanding of imidazole properties in general, or at least prove to be consistent with the earlier observations. In this study, we have determined the specific rate constants (k_{OD}) for C-methyl proton exchange for compounds **3**–**8**, in alkaline D_2O–CD_3OD (1:1) at 60 °C. The complexities arising from NH ionization and tautomerism were avoided by use of the 1-methyl derivatives throughout the series.

Experimental Section[10]

Materials. Compound **4** was a commercial sample which was recrystallized from hot water, mp 138–139 °C (lit.[11] mp 138–139 °C). Compounds **6**[11] and **5**[12] were prepared by literature methods. Compound **7** was obtained by methylation of the silver salt[13] of 4-methyl-2-nitroimidazole[14] with methyl iodide, mp 119–120 °C from ether (lit.[13,15] mp 119–121 °C).

1,5-Dimethyl-4-nitroimidazole (3). To 100 mL of acetone were added 4.0 g (31.5 mmol) of 4-methyl-5-nitroimidazole, 3 mL of methyl iodide, and 4 g of anhydrous potassium carbonate.[16]

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(10) Mass spectra were provided by the Microanalytical Services and Instrumentation Section of this Laboratory, under the direction of Dr. D. F. Johnson. Homogeneities and identities of all compounds were checked by TLC (silica gel GF), ^1H NMR, and chemical-ionization mass spectroscopy. Melting points are uncorrected.
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(14) This compound was obtained by a new synthetic model: Davis, D. P.; Kirk, K. L.; Cohen, L. A., manuscript submitted for publication.
(15) Apparently the melting points of **7** and **8** were reversed in ref 13.
(16) This method is based on a procedure for methylation of 4-nitroimidazole: Cox, J. S. G.; Fitzmaurice, C.; Katritzky, A. R.; Tiddy, G. J. T. *J. Chem. Soc. B* **1967**, 1251.

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Table I. Kinetic and Spectral Data for Dimethylnitroimidazoles

compd	k_{OD},[a] M^{-1} min^{-1}	k_{dec},[b] M^{-1} min^{-1}	δ (D_2O-CD_3OD, 1:1)[c] C-methyl	δ (D_2O-CD_3OD, 1:1)[c] N-methyl	δ (D_2O-CD_3OD, 1:1)[c] ring-H	δ ($CDCl_3$)[c] C-methyl	δ ($CDCl_3$)[c] N-methyl	δ ($CDCl_3$)[c] ring-H	λ_{max} (log ε),[d] nm
3	1485	e	2.63	3.72	7.65[f]	2.62	3.66	7.32[f]	312 (3.83)
4	352	24	2.50	3.92	8.00	2.48	3.94	7.92	318 (3.88)
5	137	22	2.60	4.00	7.82	2.59	3.97	7.44	314 (3.86)
6	0.03	e	2.43	3.75	8.08	2.43	3.68	7.65	313 (3.80)
7	0.035	00.005	2.27	4.00	7.22	2.26	3.99	6.79	349 (3.96)[g]
8	0.60	e	2.35	3.95	6.98	2.34	3.96	6.94	349 (3.99)[g]
o-nitrotoluene	3.1×10^{-3}		2.58						
p-nitrotoluene	3.6×10^{-3}		2.49						

[a] In D_2O-CD_3OD (1:1) at 60 °C. [b] In H_2O-CH_3OH (1:1) at 60 °C. [c] All NMR signals are sharp singlets. [d] In H_2O at pH 7. [e] No loss of absorption was observed in 0.27 N NaOH over 24 h. [f] Solvent shifts for the ring protons are consistent with the rules previously developed (ref 6) and support the assigned structures. [g] Reference 13.

The mixture was refluxed overnight, cooled, and filtered. The solvent was evaporated and the residual material was crystallized from water to give 0.5 g (11%) of yellowish needles, mp 159–160 °C (lit.[12] mp 160 °C).

1,5-Dimethyl-2-nitroimidazole (8). To 10 mL of acetone were added 0.16 g (1.26 mmol) of 4-methyl-2-nitroimidazole,[14] 0.2 mL of methyl iodide, and 0.2 g of anhydrous potassium carbonate. The mixture was refluxed for 2 h, cooled and filtered. The solvent was evaporated, and the residual material was dissolved in ether and filtered. The filtrate was evaporated to give a yellow powder which consisted of a mixture of 7 and 8 (in roughly equal amount). The isomers were separated by preparative TLC (development with ether) to give 50 mg (28%) of 8, mp 105–106 °C (lit.[13,17] mp 107–108 °C).

Kinetic Measurements. A stock solution of NaOD was prepared by careful addition of sodium metal to D_2O (99.5%). This solution was serially diluted with D_2O, final concentrations being determined by titration with standard hydrochloric acid. Compounds were dissolved in CD_3OD and the solutions were diluted with equal volumes of NaOD solutions; the final concentrations of compounds were 0.1–0.2 M. The lower pD values (7–11) could not be maintained during exchange runs in the absence of buffer; accordingly, 0.1 M buffers were prepared in D_2O by using NaD_2PO_4, $NaDCO_3$, and K_2CO_3. The deuterated salts were prepared by solution of the commercial salts in D_2O and evaporation to dryness; the process was repeated, and the solids were finally dried at 120 °C. Values of pD were determined before and after each run; variation in pD did not exceed ±0.2 unit.

Sealed NMR tubes were maintained in a thermostated water bath at 60 ± 0.2 °C. The tubes were removed at various time intervals and chilled in ice water, and the spectra were recorded. The areas of the *N*-methyl and *C*-methyl signals were integrated 3 times, and the results were averaged, variation not exceeding 3% up to 70% loss of signal. Values of k_{obsd} were calculated from plots of ln (*C*-methyl area)/(*N*-methyl area) vs. *t*, with variations not exceeding 5%. Specific rate constants, k_{OD}, were obtained as the intercepts of plots of log k_{obsd} vs. log [OD^-], several examples being shown in Figure 1. For the strongly alkaline solutions [OD^-] was taken as the final base concentration (after dilution with CD_3OD). The activity of OD^- in these solutions should be significantly less than the titer, but a constant ratio was assumed for the calculation of k_{OD}. For the less alkaline media, apparent pD values were measured with a glass electrode (at 25 °C) before and after dilution with CD_3OD; true pD values were obtained by addition of 0.40 unit to each value.[18] A plot of pD_{D_2O} vs. $pD_{D_2O-CD_3OD}$ was linear over the range 7–11.5 and provided eq 1.

$$pD_{D_2O-CD_3OD} = pD_{D_2O}(1.014) + 0.826 \quad (1)$$

Extrapolation of $pK_{D_2O} = 14.86$[19] gave 15.89 as p*K* for the 1:1 mixture of D_2O and CD_3OD. Although kinetic measurements were performed at 60 °C and pD measurements at 25 °C, the effects of temperature on pD and on pK_{D_2O} were ignored.

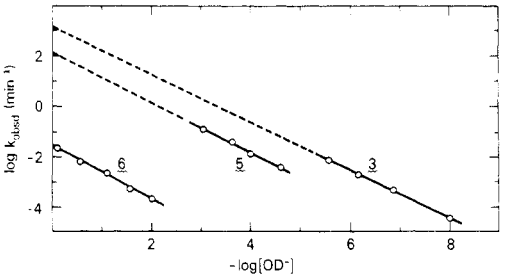

Figure 1. Representative plots of log k_{obsd} (min^{-1}) vs. log [OD^-] for exchange of dimethylnitroimidazoles at 60 °C in D_2O–CD_3OD (1:1).

The same techniques were used to measure rates of exchange in *o*- and *p*-nitrotoluene, except that concentrations were reduced to 0.05 M to maintain solubility and an equivalent concentration of 1-methylimidazole was added to provide an internal standard for peak integration.

Samples of representative runs for each compound were analyzed by chemical-ionization mass spectroscopy to verify the occurrence of total exchange (including ring hydrogens). For compounds 3 and 4, which contain the most acidic methyl groups, parital back exchange was observed when methane or ammonia was used as carrier gas. The completeness of exchange was verified for these compounds by use of electron-impact mass spectroscopy.

Decomposition of Substrates. The rates of destruction of 3–8 at 60 °C were determined by measuring the loss of intensity of the nitro chromophore at λ_{max} (Table I). Test solutions were identical in composition with those used for exchange studies except that H_2O and CH_3OH were substituted for the deuterated solvents. Rates of decomposition were followed at the three highest pD values or alkalinities used for exchange studies for each compound. The dependence of k_{obsd} on OH^- was roughly linear.

Results

Kinetics of exchange at 60 °C were followed by the rate of decrease in the ^1H NMR *C*-methyl signal (relative to the *N*-methyl signal) in deuterated alkaline media containing 50% (by volume) CD_3OD. Runs were continued to 90–100% loss of signal and followed the first-order rate law (eq 2). For the more reactive compounds, buffered

$$k_{obsd} = k_{OD}[OD^-] + k_{D_2O} \quad (2)$$

media were used below pD 12. Representative buffer dilution runs showed that the contribution to k_{obsd} due to buffer catalysis was small enough to be neglected. Similarly, the contributions of k_{D_2O} could be ignored and specific rate constants (k_{OD}, Table I) were obtained as the intercepts of plots of log k_{obsd} vs. log [OD^-] (Figure 1). Several of the nitroimidazoles underwent slow decomposition in the strongly alkaline media, as seen by the ap-

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Table II. Half-lives for Base-Catalyzed Exchange in 0.01 N NaOD in D_2O-CD_3OD (1:1) at 60 °C[a]

compd	$t_{1/2}$	compd	$t_{1/2}$
nitromethane	0.1 s[b]	7	33 h
3	2.8 s	6	38 h
4	11.8 s	o-nitrotoluene	15.5 days
5	30.4 s	p-nitrotoluene	13.4 days
8	116 min		

[a] Calculated from values of k_{OD} in Table I. [b] Extrapolated from measurements in D_2O at 25 °C (ref 20 and 22).

pearance of new NMR signals and by a decrease in UV intensity measured under the same conditions. Fortunately, rate constants for decomposition (k_{dec}, Table I) were sufficiently smaller than k_{OD} to permit reliable peak integration and rate calculation up to 70–80% exchange. Mass spectral analysis revealed only low molecular weight fragments resulting from decomposition.

Qualitative estimates showed that exchange of the ring proton occurred very rapidly in **6**, much more slowly in **3**, **5**, and **7**, and not at all in **4** or **8**. This order is wholly consistent with earlier data for exchange in 1-methyl-x-nitroimidazoles and with the operation of an adjacent lone pair (ALP) effect at C-4.[6]

Discussion

The overall range of k_{OD} values, 5×10^4, reveals a high degree of dependence on the relationship of the nitro to the C-methyl group. These groups have an "ortho" relationship in **3** and **5**, "para" in **4** and **8**, and "meta" in **6** and **7**. The rapid exchange previously observed for 4-nitrohistidine[8] is qualitatively consistent with the data for **3** and **5**. In the CD_3OD–D_2O medium, o-nitrotoluene exchanges ca. 7 times, and the para isomer ca. 18 times, as fast as in NaOD–EtOD.[9,20] According to the data in Table I, k_{OD} for **3** is 4.8×10^6 greater than for o-nitrotoluene and for **4**, 9.8×10^5 greater than for p-nitrotoluene, in the same solvent system. On the other hand, base-catalyzed exchange of nitromethane in water is only 27-fold that for **3**.[22,23] The large range of reactivities becomes particularly impressive in a comparison of half-lives for exchange at a specific base concentration (Table II). Even with qualitative consideration of some enhancement due to the inductive effect of the imidazole ring nitrogens, it is clear that k_{OD} for exchange in **3** is far closer to that for nitromethane than for o-nitrotoluene. Thus, it seems appropriate to treat **3** as a vinylogue of nitromethane whenever the ease of formation of its conjugate carbanion is of consequence.

It is not immediately apparent why **3** exchanges 10 times as fast as **5**. Ultraviolet spectra (Table I) fail to reveal any steric inhibition of resonance in the nitro group of **5**, while NMR spectra do not suggest any significant distortion of the C-methyl group. Development of the carbanion in **5** may be retarded partially by the lone pair at N-3, which phenomenon may be termed a second-order ALP effect.[6] A difference in the inductive effects of the ring nitrogens might also be considered. The δ value (in $CDCl_3$) for H-4 in 1-methyl-, 1,2-dimethyl-, and 1,5-dimethylimidazole is found at lower field that that of H-5 in the first two compounds and in 1,4-dimethylimidazole, but the orders are reversed in polar solvents.[24] In the same compounds, H-5 is subject to isotope exchange via a vinyl carbanion while H-4 does not exchange.[24] This difference is due to the operation of the ALP effect at H-4 and cannot be used as a measure of relative electron density at these positions. On the other hand, δ values for the C-methyl groups in **3**–**8** show a negligible solvent effect (Table I) and may be more reliable measures of electron density. Comparisons of NMR data for the C-methyl protons of **3** and **5**, as well as for **7** and **8**, suggest N-1 to be more electronegative than N-3. In contrast, ^{13}C NMR data for both the ring and the methyl carbons in 1,x-dimethylimidazoles[25] suggest N-3 to be more electronegative than N-1. It would seem rather difficult, therefore, to reach a decision on the basis of available data.

For **4** and **8**, carbanion stabilization is achieved via dienoid coupling of the C-methyl and nitro groups. Exchange in **4** is fourfold slower than in **3**. Although resonance stabilization is the primary basis for C-H acidity in alkyl groups, electronegative substituents can enhance the acidity by inductive effects. Thus, the ortho/para ratio in the **3**/**4** series may be due to the decrease in inductive effect with distance.[26] Resonance and distance effects are identical for **4** and **8**, but the ratio of k_{OD} values is almost 600 in favor of **4**. The same order of reactivities was observed for vinyl carbanion formation at C-2 and C-5 in nitro- and fluoroimidazoles.[6] Presumably, this difference is due to the inductive influence of two ring nitrogens at C-2 vs. one at C-5. The greater deshielding of the C-2 methyl group (in **4**) over that of the C-5 methyl group (in **8**) is consistent with this view as is the ^{13}C NMR data.[25b]

Compounds **6** and **7** exchange very slowly, since the C-methyl and nitro groups are not vinylogously coupled and resonance stabilization is not available for the corresponding carbanions. These results suggest that the methyl and nitro groups of **6** and **7** are only weakly coupled via **1a**.

Kinetic data for base-catalyzed exchange in EtOD (25 °C) has been reported for **4** and **6**.[21] Extrapolation of the k_{OD} values to 60 °C provides values of 1.8 M^{-1} min^{-1} for *both* compounds. This value of k_{OD} is considerably smaller than ours for **4** and considerably larger for **6**. A decrease in k_{OD} with decreasing solvent polarity is to be expected[27] and the 200-fold decrease for **4** may not be unreasonable; however, the larger value of k_{OD} for **6** is surprising and the equivalence of values for **4** and **6** is quite inconsistent with electronic considerations.

It is pertinent to note that nitro activation has been used as a basis for aldol condensation (especially with benzaldehyde) of certain methylimidazoles, providing an entry into functionalization of the methyl group. Such reactions have been described for **3**,[12] **4**,[28,29] **5**,[12] and **8**,[30] while **6** failed to undergo condensation.[11] In the case of 1,2,5-trimethyl-4-nitroimidazole or of 1,2,4-trimethyl-5-nitroimidazole, condensation occurs selectively at the methyl group ortho to nitro.[31] Furthermore, the C-methyl group

(20) The exchange was studied at 110 °C; we have extrapolated the data to 60 °C using E_a = 18.6 kcal/mol.[21]

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of 4 is oxidized by selenium dioxide[28] and is iodinated at elevated temperature,[29] while that of 8 is unreactive.[30] All of these results are consistent with the pattern of kinetic acidities observed in our exchange studies.

Conclusions

Two key findings have emerged from these studies: the value of k_{OD} for exchange in 1,5-dimethyl-4-nitroimidazole is much closer to that for nitromethane than for *o*-nitrotoluene; k_{OD} is greatly depressed in **6** and **7**, the two members of the series which lack vinylogous coupling between the methyl and nitro groups. We conclude that there may be significant localization in the 4,5 double bond of N-substituted imidazoles and that canonical form **1a** may not make an important contribution to amidine stabilization in such ring systems.

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Registry No. **3**, 7464-68-8; **4**, 551-92-8; **5**, 57658-79-4; **6**, 13230-04-1; **7**, 5297-92-7; **8**, 5213-48-9; 4-methyl-5-nitroimidazole, 14003-66-8; 4-methyl-2-nitroimidazole, 5213-35-4.

Stability and Reactivity of Thiirenium Ions. Dependence on Alkyl or Aryl Substitution at Ring Carbons

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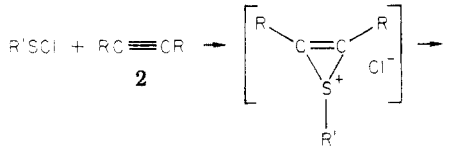
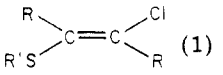
1-Methyl-2-phenyl-3-isopropylthiirenium (**1a**) hexachloroantimonate was observed at −60 °C and 1-methyl-2-phenyl-3-*tert*-butylthiirenium (**1b**) hexachloroantimonate and tetrafluoroborate were isolated as salts which were stable at room temperature. The addition of chloride ion to **1b** gives only the stereospecific anti and regiospecific Markovnikov adduct. The order of stability of ions **1a** and **1b** and the observed orientation are explained in terms of inductive and resonance properties of ring substituents.

Thiirenium ions **1** were suggested as intermediates in the addition of sulfenyl chlorides to alkynes **2** (eq 1).[1]

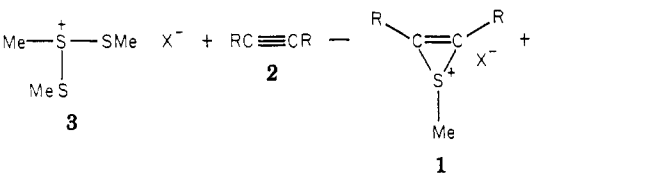


2 **1**



(1)

Recently we have reported the spectroscopic observation[2,3] and, in some cases,[4] the isolation of relatively stable 2,3-dialkylthiirenium ions formed by reaction of methylbis(methylthio)sulfonium (**3**) hexachloroantimonate[5] or tetrafluoroborate[6] with dialkylacetylenes **2** (eq 2).

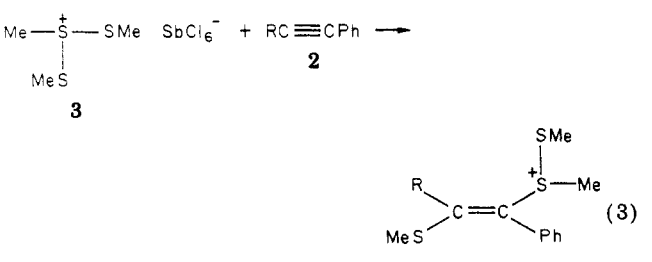


3 **2** **1**

MeSSMe (2)

R = alkyl; X = $SbCl_6$, BF_4

The stability of ions **1** depends so much on the nature of substituents on the ring carbons that we have been able to detect dialkyl-substituted species only. Attempts to detect thiirenium ions from the reaction of sulfonium ion **3** with 1-phenylpropyne or 1-phenyl-1-butyne failed as only the addition products **4** could be observed (eq 3).[6]



3 **2** **4**

(3)

R = Me,Et

We report two cases where the nature of the alkyl residue in phenylacetylenes makes 2-phenyl-substituted

(1) For pertinent reviews see: (a) Kharasch, N. In "Organic Sulfur Compounds"; Kharasch, N., Ed.; Pergamon Press: New York, 1961; Vol. 1, p 375. (b) Modena, G.; Scorrano, G. *Mech. React. Sulfur Compd.* **1968**, *3*, 115. (c) Schmid, G. H. *Top. Sulfur Chem.* **1977**, *3*, 101.
(2) Capozzi, G.; De Lucchi, O.; Lucchini, V.; Modena, G. *J. Chem. Soc., Chem. Commun.* **1975**, 248.
(3) Capozzi, G.; Lucchini, V.; Modena, G. *Rev. Chem. Intermed.* **1979**, *2*, 347.
(4) Capozzi, G.; Lucchini, V.; Modena, G.; Scrimin, P. *Tetrahedron Lett.* **1977**, 911.
(5) Capozzi, G.; Lucchini, V.; Modena, G.; Rivetti, F. *J. Chem. Soc., Perkin Trans. 2* **1975**, 900.
(6) Capozzi, G.; Da Col. L.; Lucchini, V.; Modena, G.; Valle, G. *J. Chem. Soc., Perkin Trans. 2* **1980**, 68.

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