Tetrahedron Vol. 41, No. 7, pp. 1373 to 1384, 1985
Printed in Great Britain.

0040-4020/85 $3.00 + .00
Pergamon Press Ltd.

THE REACTIONS OF SOME HALOGENATED PYRIDINES WITH METHOXIDE AND METHANETHIOLATE IONS IN DIMETHYLFORMAMIDE.

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(*Received in UK 7 February* 1985)

Abstract. The reactions of 2,6- and 2,5-dibromopyridines and of 2,3- and 3,5-dichloropyridines with sodium isopropanethiolate and methanethiolate afforded the products of mono- or of bis-substitution depending on the experimental conditions. The same pyridines reacted with sodium methoxide to give good yields of the mono-substituted products; bis-substitution occurred easily only in the case of the 2,6-dibromo- and of the 3,5-dichloropyridine. The syntheses of some methoxy thiomethoxypyridine, starting from the halogeno methoxypyridines or from the halogeno thiomethoxypyridines are also described. The bis-(alkylthio)pyridines can be fragmented by sodium in HMPA to give the bis(mercapto)pyridines.

In a series of papers we have recently reported very convenient syntheses of alkylthiobenzenes,[1,2] alkoxybenzenes,[3] and alkoxyaryl alkyl sulphides[4] by means of nucleophilic aromatic substitutions carried out on the unactivated halobenzenes or on the scarcely activated polyhalobenzenes and haloaryl alkyl sulphides. Several methods to effect the selective dealkylation of these compounds to give thiophenols, phenols, or polymercaptobenzenes by means of sodium alkanethiolates, sodium alkoxides or sodium[3,5-9] have also been described. These reactions were carried out in hexamethylphosphoric triamide but more recently we have shown that similar good results can be obtained using dimethylformamide or dimethylacetamide as solvents.[10]

We now report the results of a related investigation carried out on some dihalogenated pyridines in order to find the experimental conditions to synthetize halogeno alkylthiopyridines, bis(alkylthio)pyridines, halogeno methoxypyridines, bis(methoxy)pyridines and methoxy methylthiopyridines. In most of the cases the substitution reactions (equations 1 - 3), carried out in dimethylformamide, occurred easily and in high yields. The procedure now reported therefore represents the most convenient way to synthetize the above mentioned compounds which otherwise require a tedious multistep reaction sequence with considerably lower overall reaction yields.

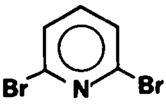
$$C_5H_3NX_2 \xrightarrow{RSNa} C_5H_3N(SR)X \xrightarrow{RSNa} C_5H_3N(SR)_2 \qquad 1)$$

$$C_5H_3NX_2 \xrightarrow{MeONa} C_5H_3N(OMe)X \xrightarrow{MeONa} C_5H_3N(OMe)_2 \qquad 2)$$

$$C_5H_3N(SMe)X \xrightarrow{MeONa} C_5H_3N(SMe)OMe \xleftarrow{MeSNa} C_5H_3N(OMe)X \qquad 3)$$

Moreover the results reported in this paper also contribute to a better understanding of the nucleophilic aromatic substitution reactions in the pyridine series.

The compounds selected for the present investigations were the 2,6-dibromopyridine (1), 2,5-dibromopyridine (2), 2,3-dichloropyridine (3) and the 3,5-dichloropyridine (4); some experiments were also carried out on the pentafluoropyridine.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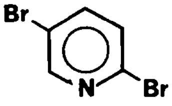
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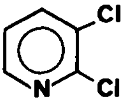
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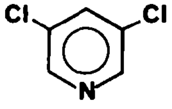
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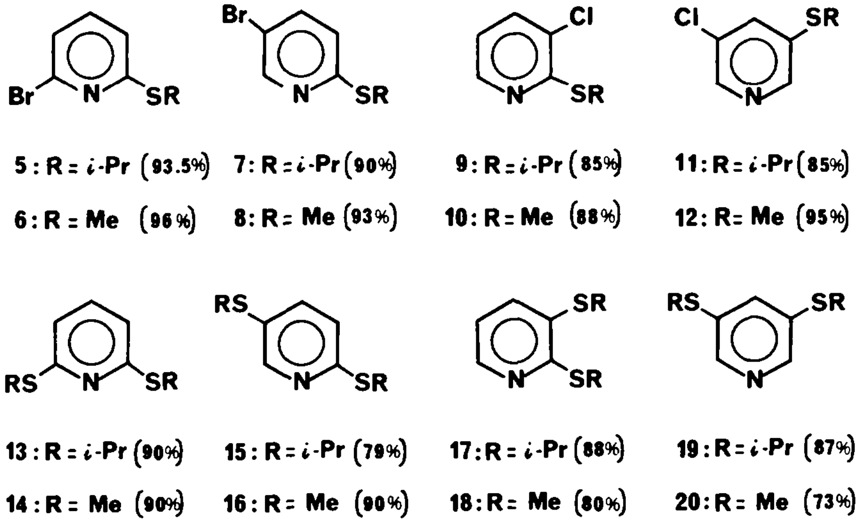
Results and Discussion

The reactions of compounds (1) - (4) with an equimolecular amounts of sodium isopropanethiolate or methanethiolate in DMF occurred easily at room temperature to give the products of monosubstitution. With MeSNa the reactions were complete in few minutes. With Me_2CHSNa the reaction time was of the order of one or two hours; the substitution was slower in the case of (4) in which a ß-halogen atom is involved (at 80°C, however, the reaction took place in 15 minutes). The compounds obtained are indicated in Scheme 1, where the reaction yields are reported in parentheses. As expected in the case of compounds (2) and (3) the substitution occurred selectively at the α-position.

If the same reactions are carried out at higher temperature (80°C) and using an excess (4 equivalents) of Me_2CHSNa or of MeSNa, both the halogen atoms are substituted to afford the bis(alkylthio)pyridines (13) - (20) in high yields. The products obtained and the reaction yields are also reported in the Scheme 1.

SCHEME 1


5 : R = *i*-Pr (93.5%)
6 : R = Me (96%)
7 : R = *i*-Pr (90%)
8 : R = Me (93%)
9 : R = *i*-Pr (85%)
10 : R = Me (88%)
11 : R = *i*-Pr (85%)
12 : R = Me (95%)
13 : R = *i*-Pr (90%)
14 : R = Me (90%)
15 : R = *i*-Pr (79%)
16 : R = Me (90%)
17 : R = *i*-Pr (88%)
18 : R = Me (80%)
19 : R = *i*-Pr (87%)
20 : R = Me (73%)

Similarily, pentafluoropyridine reacted with excess sodium isopropanethiolate and methanethiolate to afford the pentakis(isopropylthio)- and the pentakis(methylthio)pyridine in 95 and 96% yields, respectively. These results clearly indicate that the present procedure represents an extremely convenient way to synthetize both the mono- and the bis(alkylthio)pyridines as well as the penta(alkylthio)pyridine. Very likely this method can also be applied to other halogenated pyridines with similar good results.

Very recently the syntheses of the 2,5-, 2,3- and 3,5-bis(methylthio)pyridine have been reported.[11] These syntheses, which present several advantages over other previously described methods,[11] consist in the displacement of the two halogen atoms by sodium methanethiolate from the corresponding bis(halogeno)pyridines holding, as activating group, a carboxy, an ester or a cyano group in an α-position. After the substitution step, the activating groups were removed by hydrolysis followed by decarboxylation. The results described in the present paper demonstrate that the same compounds can be obtained in one step starting from the dihalogenated pyridines, directly. The synthesis of the pentakis(methylthio)pyridine from pentachloropyridine and lithium methanethiolate prepared in situ, has also been described in the literature;[12] the reaction yields however were only of 10%. In the present case the same compound could be obtained in almost quantitative yields. It has been recently shown that pentafluoropyridine also reacts with PhSNa in DMEU, at room temperature for six days, to afford the product of complete halogen substitution, pentakis(phenylthio)pyridine.[13]

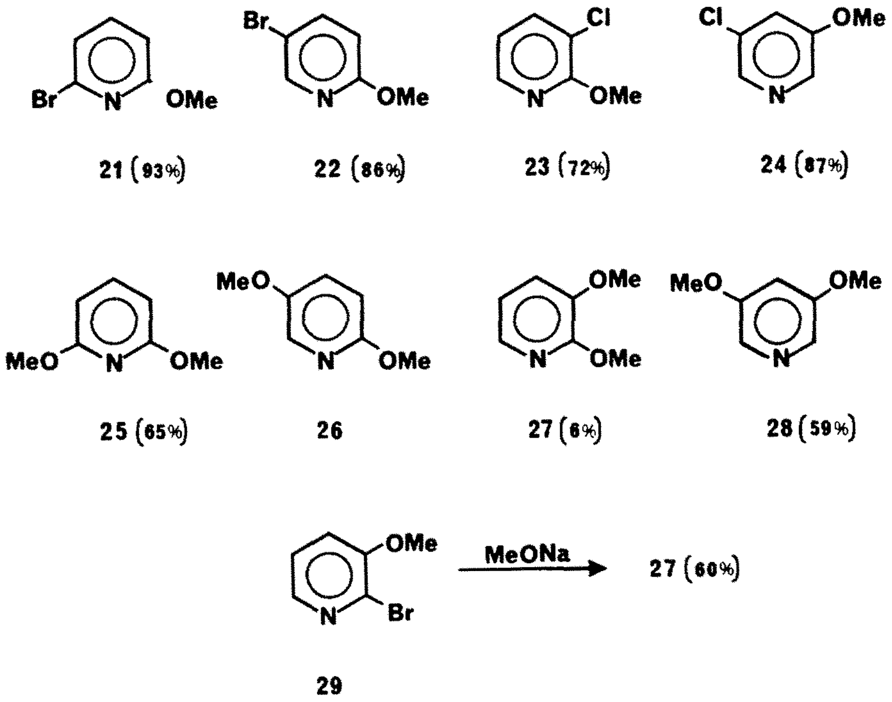
The reactions of the compounds (1) - (4) with both Me_2CHSNa and MeSNa afforded cleanly the bis-substituted compounds (13), (15), (17), (19) and (14), (16), (18), (20), respectively. In the benzene series, on the contrary, different results were obtained with the two nucleophilic reagents. The reactions of the dichlorobenzenes with Me_2CHSNa cleanly afforded the bis(isopropylthio)benzenes,[1] whereas the reactions with MeSNa gave the chlorothiophenols as the major reaction products.[2] This was due to the fact that in the initially formed chlorophenyl methyl sulphide the nucleophilic attack of MeSNa at the carbon atom of the methylthio group to give the demethylation product (equation 4) was largely preferred over the nucleophilic attack at the aromatic carbon atom to give the bis-substituted products:

$$C_6H_4Cl_2 \xrightarrow{MeSNa} C_6H_4(SMe)Cl \xrightarrow{MeSNa} C_6H_4(SH)Cl \qquad 4)$$

In the pyridine series, on the contrary, the aromatic substitution is largely preferred and compounds (6), (8), (10) and (12) react with excess MeSNa to give the bis(methylthio)pyridines (14), (16), (18) and (20); no traces of the halogeno mercaptopyridines were observed.

A different reactivity pattern emerged from the reactions of the same dihalogenated pyridines (1) - (4) with sodium methoxide. The monosubstitution process occurred easily but required higher temperatures than in the cases of the sulphur nucleophiles; moreover the reactions of bis-substitutions were much more difficult and in some cases did not occur. The reaction of (1) - (4) with MeONa in DMF were run at 80°C and using 4 equivalents of sodium methoxide; after 2 hours the starting products were completely consumed and the halogeno methoxypyridines (21) - (24) were formed in the yields indicated in parentheses in Scheme 2:

SCHEME 2



In order to obtain the bis(methoxy)pyridines (25) - (28) the reactions were carried out at 80°C and with 8 equivalents of MeONa. Discrete yields (see Scheme 2) were obtained only in the case of (25) and (28) after a reaction time of 2.5 and 38 hours, respectively. On the contrary (27) was formed in only 6% yields and (26) was not formed at all after 90 hours at 80°C; the products of these reactions were the 2-methoxy,5-bromopyridine (22) and the 2-methoxy,3-chloropyridine (23).

These results are not completely unexpected if one considers that, once the first methoxy group has been introduced, the further substitution in (21) - (24) is governed by the electronic effects of both the heterocyclic nitrogen and the methoxy group. In the reactions of polychlorobenzenes with sodium methoxide it was observed that monosubstitution occurred easily and that the substitution of the second chlorine atom was mainly governed by the electronic effect of the first introduced OMe group; these reactions involved selectively the chlorine atoms which were meta to the OMe substituent, i.e. those nuclear positions which were made more positive by the electron-attracting inductive effect of the OMe group.[3] Thus compound (21) reacts easily because the bromine atom occupies an α-position and its substitution is therefore activated by the heterocyclic nitrogen. A similar activation has a considerably lower importance in all the other cases in which the halogen atoms occupy a β-position; as a matter of fact the reaction occurs only with compound (24) in which the chlorine atom and the methoxy group are in a *meta*-like position.

The results obtained from (3) indicate that the reaction of (23) with sodium methoxide is very difficult, compound (27) being obtained only in 6% under drastic experimental conditions. The same 2,3-dimethoxypyridine (27) can be obtained easily (in 60% yields) starting from the 2-bromo,3-methoxypyridine (29) (with 4 equivalent of MeONa at 80°C in DMF for 1.5 hours); in this case in fact the halogen atom to be substituted occupies an α-position.

The products of monosubstitutions, i.e. the halogeno methylthiopyridines (6), (8), (10), (12) and the halogeno methoxypyridines (21) - (24) were then used as the starting products for the syntheses of the methoxy methylthiopyridines according to the reactions indicated in equation 3.

Previous works have shown that the reactions of the chloro methoxybenzenes with MeSNa gave exclusively the dealkylation products, i.e. the chlorophenols, as a result of a nucleophilic aliphatic substitution (equation 5),[3] whereas the reactions of the chloro thiomethoxybenzenes with MeONa afforded the methoxy thiomethoxybenzenes as a result of an aromatic nucleophilic substitution (equation 6)[5]

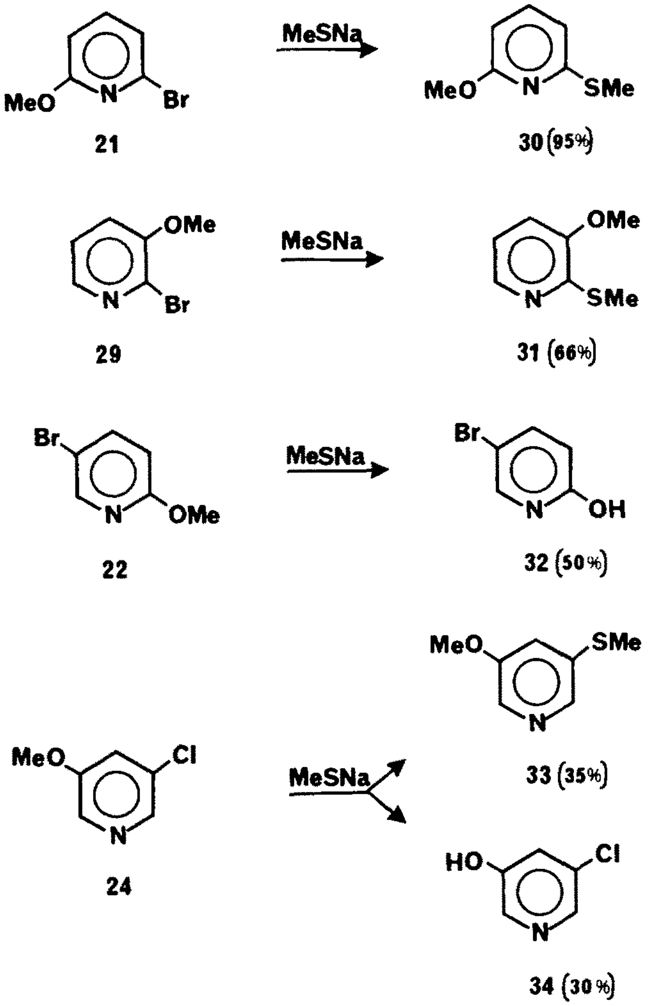
$$C_6H_4ClOMe + MeSNa \longrightarrow C_6H_4ClONa + Me_2S \qquad 5)$$

$$C_6H_4ClSMe + MeONa \longrightarrow C_6H_4(OMe)SMe + NaCl \qquad 6)$$

In the pyridine series the nucleophilic aromatic substitutions take place more readily than in simple benzenes and it was therefore expected that the two reactions could take a course different from that observed with the benzene derivatives.

The reactions of the halogeno methoxypyridines with sodium methanethiolate presented a behaviour similar to that observed with sodium methoxide. Also in this case the substitution of the halogen atom occurred easily only from the α-position. Thus, the 6-methoxy,2-bromopyridine (21) and the 3-methoxy,2-bromopyridine (29) reacted with MeSNa (2 equivalents in DMF, at 60°C, for 2 - 4 hours) to give the 6-methoxy,2-methylthiopyridine (30) and the 3-methoxy,2-methylthiopyridine (31) in 95 and 66% yields, respectively (Scheme 3). On the contrary, the same reaction carried out on the 2-methoxy,5-bromopyridine (22) did not give any substitution product, the only product obtained in 50% yields being the 2-hydroxy,5-bromopyridine (32), deriving from the nucleophilic aliphatic substitution at the methoxy group. In the case of the reactions with sodium methoxide we observed that in the 3-methoxy,5-chloropyridine (24) the chlorine atom can be displaced. Indeed in the reaction of (24) with sodium methanethiolate the aliphatic substitution at the methoxy group and the aromatic substitution of the chlorine were in competition and a mixture of the 3-methoxy,5-methylthiopyridine (33) and of the 3-hydroxy,5-chloropyridine (34) was obtained with the yields indicated in Scheme 3. The reaction of MeSNa with the 2-methoxy,3-chloropyridine (23) afforded a very complex reaction mixture which could not be analyzed.

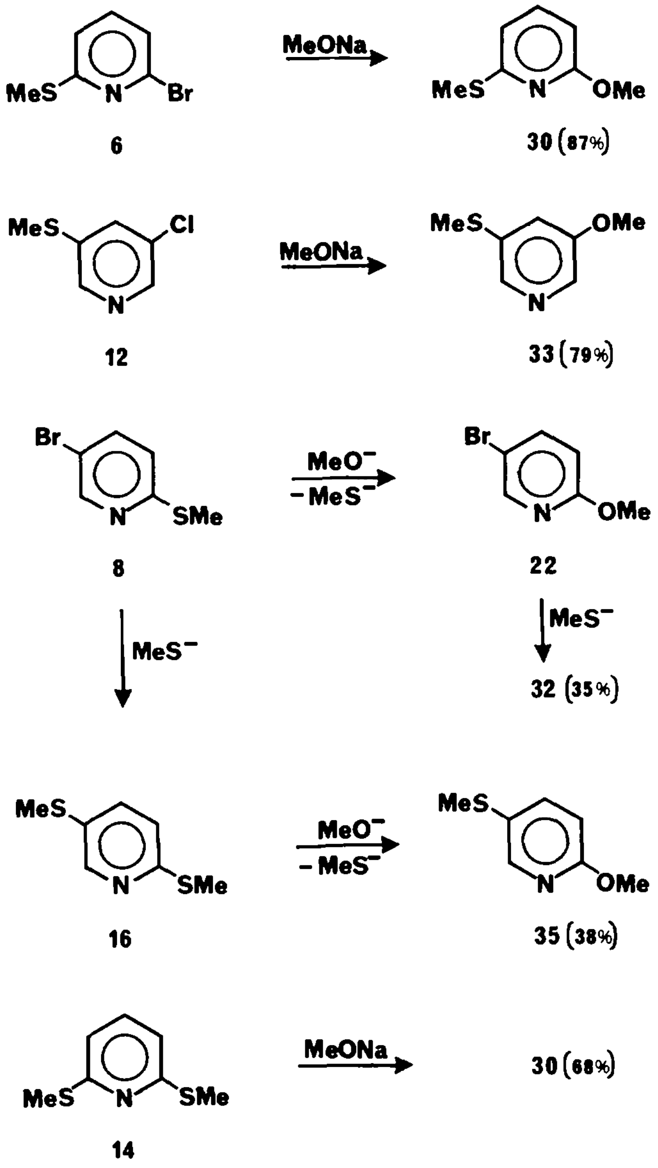
SCHEME 3



The reactions of the halogeno methylthiopyridines with sodium methoxide (4 equivalents, at 80°C in DMF for 2 - 4 hours) gave some interesting results. These are collected in Scheme 4. The 2-bromo,6-methylthiopyridine (6) and the 3-chloro,5-methylthiopyridine (12) smoothly reacted with MeONa to afford the corresponding substitution products (30) and (33) in 87 and 79% yields respectively. The 2-methylthio,3-chloropyridine (10) gave rise to a complex mixture of products.

The reaction of the 2-methylthio,5-bromopyridine (8) with MeONa gave some unexpected results; from this reaction in fact two products were isolated (with the yields reported in Scheme 4) which

SCHEME 4



were identified as the 2-hydroxy,5-bromopyridine (32) and the 2-methoxy,5-methylthiopyridine (35). Also present, in minute amounts, was the 2,5-bis(methylthio)pyridine (16). The formation of (32) clearly indicates that the first reaction occurring between (8) and MeONa is the nucleophilic displacement of the methylthio group by the methoxide anion to give (22) which is then easily dealkylated to the corresponding phenol (32). It is remarkable that the methylthio group acts as a leaving group and that this substitution is preferrred in respect to the displacement of the bromine atom from the β-position. The formation of (35) further confirms the easiness of the substitution of the methylthio group from the α-position of the pyridine ring by the methoxide ion. To explain the formation of (35) in fact one has to assume (Scheme 4) that (8) reacts with the methanethiolate anion (liberated from the reaction with MeONa) to give the 2,5-bis(methylthio)pyridine (16) and that this suffers the substitution by the methoxide anion. This process was independently confirmed by reacting (16) with MeONa under the same experimental conditions; from this reaction the substitution product (35) was obtained in 60% yield. Similarily, from the reaction of the 2,6-bis(methylthio)pyridine (14) with sodium methoxide the 2-methoxy,6-methylthiopyridine (30) was isolated in 68% yields. Thus, this substitution process seems to occur very easily and very likely other nucleophilic reagents can effect the displacement of the methylthio group from the α- or γ-positions of the pyridine ring.

The bis(alkylthio)pyridine, easily prepared as described above, can be used as the starting products for a very simple synthesis of the bis(mercapto)pyridines. The procedure is similar to that described by us for the synthesis of polymercaptobenzenes[9] and consists in the treatment with sodium of a solution of the alkylthiopyridine in HMPA. It is assumed that under these conditions radical anions are formed which fragment at the sulphur alkyl bond to give an alkyl radical and an arenethiolate anion. It is remarkable that this fragmentation process involves all the alkylthio groups present in the molecule. Thus from the bis(alkylthio)pyridines a solution of the sodium salts of the bis(mercapto)pyridines was obtained (equation 7):

$$C_5H_3N(SR)_2 \xrightarrow[Na]{HMPA} \left[C_5H_3N(SR)_2\right]^{\cdot-} \longrightarrow\longrightarrow C_5H_3N(SNa)_2 \xrightarrow[R_1X]{} C_5H_3N(SR_1)_2 \qquad 7)$$

These solutions can be used directly for further uses. In the present case, in order to make the separation and the identification of the reaction products easier, an alkylating agent was added. Thus, starting from the bis(isopropylthio)pyridines, the final reaction mixtures were treated with methyl iodide and the reaction products were therefore isolated as the bis(methylthio)pyridines. In this way compounds (13), (15), (17) and (19) were converted into compounds (14), (16), (18) and (20) in 63, 74, 80 and 68% yields, respectively. Interestingly, even the pentakis(isopropylthio)pyridine suffered the complete fragmentation of all the isopropylthio groups present in the molecule and afforded the pentakis(methylthio)pyridine in 78% yields.

EXPERIMENTAL

Commercial 2,6- and 2,5-dibromopyridines, 2,3- and 3,5-dichloropyridines, 2,6-dimethoxypyridine and 3-hydroxy,5-chloropyridine were used without further purification. 2-Bromo,3-methoxypyridine (29) was prepared as described in the literature.[14] Sodium methanethiolate, isopropanethiolate and methoxide were prepared as described in previous works.[2,4,9] Reaction products were identified by comparison of their physical and spectral properties with those reported in the literature and by proton nmr spectra. Unless otherwise specified, nmr spectra were recorded in $CDCl_3$ solution on a 90 MHz Varian EM390 instrument. Glc analyses were performed on a Hewlett-Packard 5830A chromatograph with a 20 in., 10% UCW 982 column. Elemental analyses were carried out on a Carlo Erba Model 1106 Elemental Analyzer. Sulphones were prepared by oxidation with m-chloroperbenzoic acid in $CHCl_3$ solutions.

A) Reactions of Halogenopyridines with Sodium Alkanethiolates.

To a stirred solution of the halogenopyridine (1) - (4) (0.01 mol) in DMF (40 ml), kept under N_2 at room temperature, MeSNa or Me_2CHSNa (1.1 equivs for each halogen atom present in the molecule) was added. The progress of the reaction was monitored by glc or tlc on silica gel using mixtures of light petroleum and ethyl ether as eluant. The reaction times are indicated in the Results and Discussion. The reaction mixtures were poured on water and extracted with ether; the organic layers were washed with water, dried over Na_2SO_4 and evaporated. The residue was chromatographed through a silica gel column using mixtures of light petroleum and ethyl ether as eluant.

In the case of the synthesis of the poly(alkylthio)pyridines the reactions were run at 80°C using 2 equivs of MeSNa or Me_2CHSNa for each halogen atom present in the molecule. The reactions times were of 2 hours for compound (1) and of 5 - 15 hours for the other halogenated pyridines.

The reaction yields are reported in parentheses in Scheme 1. The physical and nmr data of the obtained products are reported below.

2-Isopropylthio,6-bromopyridine (5), Oil. δ 7.4 - 6.9 (m, 3H), 3.95 (spt, 1H, J = 7.5 Hz), 1.4 (d, 6H, J = 7.5 Hz). Anal. Calcd for $C_8H_{10}BrNS$: C, 41.39; H, 4.35; N, 6.03. Found: C, 40.95; H, 4.45; N, 6.05.
Sulphone, m.p. = 96 - 97°. δ 8.15 - 7.6 (m, 3H), 3.8 (spt, 1H, J = 7.5 Hz), 1.4 (d, 6H, J = 7.5 Hz). Anal. Calcd for $C_8H_{10}BrNO_2S$: C, 36.37; H, 3.82; N, 5.30. Found: C, 36.45; H, 4.00; N, 5.50.

2-Methylthio,6-bromopyridine (6), Oil.[15] δ 7.4 - 6.9 (m, 3H), 2.5 (s, 3H).
Sulphone, m.p. = 135 - 6°. δ 8.1 - 7.6 (m, 3H), 3.25 (s, 3H). Anal. Calcd for $C_6H_6BrNO_2S$: C, 30.52; H, 2.57; N, 5.93. Found: C, 30.65; H, 2.55; N, 5.95.

2-Isopropylthio,5-bromopyridine (7), Oil. δ 8.45 (dd, 1H, J = 2.4 and 0.6 Hz), 7.5 (dd, 1H, J = 8.4 and 2.4 Hz), 7.0 (dd, 1H, J = 8.4 and 0.6 Hz), 3.95 (spt, 1H, J = 7.5 Hz), 1.4 (d, 6H, J = 7.5 Hz). Anal. Calcd for $C_8H_{10}BrNS$: C, 41.39; H, 4.35; N, 6.03. Found: C, 41.15; H, 4.60; N, 5.95.
Sulphone, m.p.= 111 - 3°. δ 8.8 (dd, 1H, J = 2.4 and 0.6 Hz), 8.1 (dd, 1H, J = 8.4 and 2.4 Hz), 7.95 (dd, 1H, J = 8.4 and 0.6 Hz), 3.75 (spt, 1H, J = 7.5 Hz), 1.35 (d, 6H, J = 7.5 Hz). Anal. Calcd for $C_8H_{10}BrNO_2S$: C, 36.37; H, 3.82; N, 5.30. Found: C, 36.15; H, 3.95; N, 5.35.

2-Methylthio,5-bromopyridine (8), m.p. = 38 - 9° (Lit.[16] 40 - 41°). δ 8.45 (dd, 1H, J = 2.4 and 0.6 Hz), 7.45 (dd, 1H, J = 8.4 and 2.4 Hz), 7.0 (dd, 1H, J = 8.4 and 0.6 Hz), 2.5 (s, 3H).
Sulphone, m.p. = 95 - 6°. δ 8.75 (dd, 1H, J = 2.4 and 0.6 Hz), 8.1 (dd, 1H, J = 8.4 and 2.4 Hz), 7.95 (dd, 1H, J = 8.4 and 0.6 Hz), 3.25 (s, 3H). Anal. Calcd for $C_6H_6BrNO_2S$: C, 30.52; H, 2.57; N, 5.93. Found: C, 30.75; H, 2.40; N, 5.75.

2-Isopropylthio,3-chloropyridine (9), Oil. δ 8.3 (dd, 1H, J = 4.5 and 1.5 Hz), 7.5 (dd, 1H, J = 7.8 and 1.5 Hz), 6.85 (dd, 1H, J = 7.8 and 4.5 Hz), 4.05 (spt, 1H, J = 7.5 Hz), 1.4 (d, 6H, J = 7.5 Hz). Anal. Calcd for $C_8H_{10}ClNS$: C, 51.19; H, 5.38; N, 7.46. Found: C, 51.35; H, 5.18; N, 7.60.

2-Methylthio,3-chloropyridine (10), Oil. δ 8.3 (dd, 1H, J = 4.5 and 1.5 Hz), 7.45 (dd, 1H, J = 7.8 and 1.5 Hz), 6.85 (dd, 1H, J = 7.8 and 4.5 Hz), 2.55 (s, 3H). Anal. Calcd for C_6H_6ClNS: C, 45.14; H, 3.80; N, 8.78. Found: C, 45.35; H, 3.65; N, 8.70.
Sulphone, m.p. = 98 - 9°. δ 8.5 (dd, 1H, J = 4.5 and 1.5 Hz), 7.9 (dd, 1H, J = 7.8 and 1.5 Hz), 7.5 (dd, 1H, J = 7.8 and 4.5 Hz), 3.4 (s, 3H). Anal. Calcd for $C_6H_6ClNO_2S$: C, 37.60; H, 3.16; N, 7.31. Found: C, 37.85; H, 3.15; N, 7.10.

3-Isopropylthio,5-chloropyridine (11), Oil. δ 8.45 (d, 1H, J = 2.0 Hz), 8.4 (d, 1H, J = 2.0 Hz), 7.65 (t, 1H, J = 2.0 Hz), 3.4 (spt, 1H, J = 7.5 Hz), 1.3 (d, 6H, J = 7.5 Hz). Anal. Calcd for $C_8H_{10}ClNS$: C, 51.19; H, 5.38; N, 7.46. Found: C, 51.38; H, 5.50; N, 7.20.
Sulphone, m.p. = 91 - 3°. δ 8.95 (d, 1H, J = 2.0 Hz), 8.85 (d, 1H, J = 2.0 Hz), 8.15 (t, 1H, J = 2.0 Hz), 3.3 (spt, 1H, J = 7.5 Hz), 1.35 (d, 6H, J = 7.5 Hz). Anal. Calcd for $C_8H_{10}ClNO_2S$: C, 43.73; H, 4.60; N, 6.38. Found: C, 43.90; H, 4.45; N, 6.55.

3-Methylthio,5-chloropyridine (12), Oil. δ 8.35 (d, 1H, J = 2.0 Hz), 8.3 (d, 1H, J = 2.0 Hz), 7.5 (t, 1H, J = 2.0 Hz), 2.5 (s, 3H). Anal. Calcd for C_6H_6ClNS: C, 45.14; H, 3.80; N, 8.78. Found: C, 45.05; H, 3.95; N, 8.85.
Sulphone, m.p. = 123 - 4°. δ 9.0 (d, 1H, J = 2.0 Hz), 8.8 (d, 1H, J = 2.0 Hz), 8.2 (d, 1H, J = 2.0 Hz), 3.15 (s, 3H). Anal. Calcd for $C_6H_6ClNO_2S$: C, 37.60; H, 3.16; N, 7.31. Found: C, 37.45; H, 3.25; N, 7.35.

2,6-Bis(isopropylthio)pyridine (13), Oil. δ 7.35 - 7.05 (m, 1H), 6.9 6.65 (m, 2H), 4.05 (spt, 2H, J = 7.5 Hz), 1.45 (d, 12H, J = 7.5 Hz). Anal. Calcd for $C_{11}H_{17}NS_2$: C, 58.09; H, 7.55; N, 6.16. Found: C, 57.90; H, 7.50; N, 6.10.
Disulphone, m.p. = 144 - 6°. δ 8.3 (s, 3H), 3.8 (spt, 2H, J = 7.5 Hz), 1.35 (d, 12H, J = 7.5 Hz); in C_6D_6 7.7 (d, 2H, J = 7.5 Hz), 6.9 (t, 1H, J = 7.5 Hz), 3.45 (spt, 2H, J = 7.5 Hz), 1.0 (d, 12H, J = 7.5 Hz). Anal. Calcd for $C_{11}H_{17}NO_4S_2$: C, 45.33; H, 5.89; N, 4.81. Found: C, 45.10; H, 6.00; N, 4.95.

2,6-Bis(methylthio)pyridine (14), Oil.[11,15] δ 7.35 - 7.05 (m, 1H), 6.9 - 6.7 (m, 2H), 2.55 (s, 6H).
Disulphone, m.p. = 197 - 8° (Lit.[11] 193 - 5°). δ 8.4 (s, 3H), 3.35 (s, 6H).

2,5-Bis(isopropylthio)pyridine (15), Oil. δ 8.45 (dd, 1H, J = 2.0 and 1.0 Hz), 7.5 (dd, 1H, J = 8.0 and 2.0 Hz), 7.05 (dd, 1H, J = 8.0 and 1.0 Hz), 4.0 (spt, 1H, J = 7.5 Hz), 3.2 (spt, 1H, J = 7.5 Hz), 1.4 (d, 6H, J = 7.5 Hz), 1.25 (d, 6H, J = 7.5 Hz). Anal. Calcd for $C_{11}H_{17}NS_2$: C, 58.09; H, 7.55; N, 6.16. Found: C, 58.15; H, 7.40; N, 6.00.
Disulphone, m.p. = 182 - 4° (Lit.[11] 181°). δ 9.15 (dd, 1H, J = 2.0 and 1.0 Hz), 8.45 (dd, 1H, J = 8.0 and 2.0 Hz), 8.3 (dd, 1H, J = 8.0 and 1.0 Hz), 3.85 (spt, 1H, J = 7.5 Hz), 3.3 (spt, 1H, J = 7.5 Hz), 1.35 (d, 12H, J = 7.5 Hz).

2,5-Bis(methylthio)pyridine (16), Oil (Lit.[11] 90°/0.1 mm). δ 8.35 (dd, 1H, J = 2.0 and 1.0 Hz), 7.4 (dd, 1H, J = 8.0 and 2.0 Hz), 7.05 (dd, 1H, J = 8.0 and 1.0 Hz), 2.55 (s, 3H), 2.45 (s, 3H).
Disulphone, m.p. = 207 - 8° (Lit.[11] 205 - 7°). In DMSO-d_6, δ 9.3 (dd, 1H, J = 2.0 and 1.0 Hz), 8.7 (dd, 1H, J = 8.0 and 2.0 Hz), 8.3 (dd, 1H, J = 8.0 and 1.0 Hz), 3.45 (s, 3H), 3.4 (s, 3H).

2,3-Bis(isopropylthio)pyridine (17), Oil. δ 8.3 (dd, 1H, J = 1.8 and 4.8 Hz), 7.5 (dd, 1H, J = 1.8 and 7.8 Hz), 6.85 (dd, 1H, J = 4.8 and 7.8 Hz), 4.05 (spt, 1H, J = 7.5 Hz), 3.45 (spt, 1H, J = 7.5 Hz), 1.45 (d, 6H, J = 7.5 Hz), 1.3 (d, 6H, J = 7.5 Hz). Anal. Calcd for $C_{11}H_{17}NS_2$: C, 58.09; H, 7.55; N, 6.16. Found: C, 57.95; H, 7.80; N, 6.30.
Disulphone, m.p. = 76 - 7°. δ 8.95 (dd, 1H, J = 1.8 and 4.8 Hz), 8.6 (dd, 1H, J = 1.8 and 7.8 Hz), 7.8 (dd, 1H, J = 4.8 and 7.8 Hz), 4.45 (spt, 1H, J = 7.5 Hz), 4.3 (spt, 1H, J = 7.5 Hz), 1.4 (d, 6H, J = 7.5 Hz), 1.35 (d, 6H, J = 7.5 Hz). Anal. Calcd for $C_{11}H_{17}NO_4S_2$: C, 45.33; H, 5.89; N, 4.81. Found: C, 45.50; H, 5.90; N, 4.65.

2,3-bis(methylthio)pyridine (18), Oil (Lit.[11] 85°/0.3 mm). δ 8.2 (dd, 1H, J = 1.8 and 4.8 Hz), 7.35 (dd, 1H, J = 1.8 and 7.8 Hz), 6.9 (dd, 1H, J = 4.8 and 7.8 Hz), 2.6 (s, 3H), 2.45 (s, 3H).
Disulphone, m.p. = 176 - 7° (Lit.[11] 175 - 6°). In DMSO-d_6, δ 9.0 (dd, 1H, J = 1.8 and 4.8 Hz), 8.6 (dd, 1H, J = 1.8 and 7.8 Hz), 8.0 (dd, 1H, J = 4.8 and 7.8 Hz), 3.55 (s, 3H), 3.45 (s, 3H).

3,5-Bis(isopropylthio)pyridine (19), Oil. δ 8.45 (d, 2H, J = 2.0 Hz), 7.7 (t, 1H, J = 2.0 Hz), 3.4 (spt, 2H, J = 7.5 Hz), 1.3 (d, 12H, J = 7.5 Hz). Anal. Calcd for $C_{11}H_{17}NS_2$: C, 58.09; H, 7.55; N, 6.16. Found: C, 58.25; H, 7.65; N, 6.25.
Disulphone, m.p. = 151 - 2°. δ 9.3 (d, 2H, J = 2.0 Hz), 8.6 (t, 1H, J = 2.0 Hz), 3.3 (spt, 2H, J = 7.5 Hz), 1.35 (d, 12H, J = 7.5 Hz). Anal. Calcd for $C_{11}H_{17}NO_4S_2$: C, 45.33; H, 5.89; N, 4.81. Found: C, 45.45; H, 5.70; N, 4.80.

3,5-Bis(methylthio)pyridine (20), Oil (Lit.[11] 90°/0.05 mm). δ 8.25 (d, 2H, J = 2.0 Hz), 7.4 (t, 1H, J = 2.0 Hz), 2.5 (s, 6H). Disulphone, m.p. = 239 - 41° (Lit.[11] 229 - 31°). δ 9.4 (d, 2H, J = 2.0 Hz), 8.75 (t, 1H, J = 2.0 Hz), 3.45 (s, 6H).

Pentakis(isopropylthio)pyridine, m.p. = 72 - 4°. δ 4.0 (spt, 1H, J = 7.5 Hz), 3.95 (spt, 2H, J = 7.5 Hz), 3.55 (spt, 2H, J = 7.5 Hz), 1.45 (d, 12H, J = 7.5 Hz), 1.3 (d, 12H, J = 7.5 Hz), 1.25 (d, 6H, J = 7.5 Hz). Anal. Calcd for $C_{20}H_{35}N$: C, 53.39; H, 7.86; N, 3.11. Found: C, 53.55; H, 7.85; N, 2.95.

Pentakis(methylthio)pyridine, m.p. = 77 - 9° (Lit.[12] 78 - 80°). δ 2.65 (s, 1H), 2.55 (s, 2H), 2.4 (s, 2H).

B) Reactions of Halogenopyridines with Sodium Methoxide

To a stirred solution of the halogenopyridine (1) - (4) (0.01 mol) in DMF (40 ml), kept under N_2 at 80°C, sodium methoxide (4 mol in the case of the monosubstitution and 8 mol in the case of the bissubstitution process) was added. The reactions were followed and worked up as described in A. These experimental conditions were also employed for the reactions of the 2-bromo,3-methoxypyridine (29). Reaction times are indicated in the Results and Discussion. The reaction yields are reported in parentheses in Scheme 2. The physical and nmr data of the obtained products are reported below.

2-Methoxy,6-bromopyridine (21), Oil.[17] δ 7.4 (t, 1H, J = 7.5 Hz), 7.0 (dd, 1H, J = 7.5 and 1.0 Hz), 6.65 (dd, 1H, J = 7.5 and 1.0 Hz), 3.95 (s, 3H).

2-Methoxy,5-bromopyridine (22), Oil.[18] δ 8.15 (dd, 1H, J = 4.0 and 1.0 Hz), 7.55 (dd, 1H, J = 4.0 and 8.7 Hz), 6.6 (dd, 1H, J = 8.7 and 1.0 Hz), 3.9 (s, 3H).

2-Methoxy,3-chloropyridine (23), Oil (Lit.[18] 107 - 9°/52 mm). δ 8.0 (dd, 1H, J = 1.8 and 4.8 Hz), 7.55 (dd, 1H, J = 1.8 and 7.5 Hz), 6.75 (dd, 1H, J = 4.8 e 7.5 Hz), 4.0 (s, 3H).

3-Methoxy,5-chloropyridine (24), m.p. = 40 - 1°. δ 8.2 (d, 2H, J = 2.0 Hz), 7.2 (t, 1H, J = 2.0 Hz), 3.9 (s, 3H). Anal. Calcd for C_6H_6ClNO: C, 50.19; H, 4.22; N, 9.76. Found: C, 50.05; H, 4.10; N, 9.95.

2,6-Dimethoxypyridine (25), Oil. δ 7.45 (t, 1H, J = 7.5 Hz), 6.25 (d, 2H, J = 7.5 Hz), 3.95 (s, 6H).

2,3-Dimethoxypyridine (27), Oil (Lit.[19] 100°/17 mm). δ 7.7 (dd, 1H, J = 1.8 and 4.8 Hz), 7.0 (dd, 1H, J = 1.8 and 7.8 Hz), 6.8 (dd, 1H, J = 4.8 and 7.8 Hz), 4.0 (s, 3H), 3.85 (s, 3H).

3,5-Dimethoxypyridine (28), Oil (Lit.[20] 112°/0.22 mm). δ 7.9 (d, 2H, J = 2.4 Hz), 6.7 (t, 1H, J = 2.4 Hz), 3.8 (s, 6H).

C) Reactions of Halogeno methoxypyridines with Sodium Methanethiolate

To a stirred solution of the halogeno methoxypyridine ((21), (22), (23), (24) or (29)) (0.01 mol) in DMF (40 ml), kept under N_2 at 60°C, sodium methanethiolate (2 mol) was added. The reactions were followed and worked up as described in A. Reaction times are indicated in the Results and Discussion. The reaction yields are reported in parentheses in Scheme 3. The physical and nmr data of the obtained products are reported below.

6-Methoxy,2-methylthiopyridine (30), Oil.[15] δ 7.3 (t, 1H, J = 7.8 Hz), 6.7 (dd, 1H, J = 7.8 and 1.0 Hz), 6.35 (dd, 1H, J = 7.8 and 1.0 Hz), 3.95 (s, 3H), 2.55 (s, 3H).
Sulphone, oil. δ 7.8 (t, 1H, J = 7.8 Hz), 7.65 (dd, 1H, J = 7.8 and 1.0 Hz), 7.0 (dd, 1H, J = 7.8 and 1.0 Hz), 4.0 (s, 3H), 3.2 (s, 3H). Anal. Calcd for $C_7H_9NO_3S$: C, 44.90; H, 4.85; N, 7.48. Found: C, 44.95; H, 4.80; N, 7.55.

3-Methoxy,2-methylthiopyridine (31), Oil. δ 8.15 - 7.95 (m, 1H), 7.2 6.8 (m, 2H), 3.85 (s, 3H), 2.55 (s, 3H). Anal. Calcd for C_7H_9NOS: C, 54.16; H, 5.86; N, 9.03. Found: C, 53.95; H, 5.95; N, 9.05.
Sulphone, m.p. = 85 - 7°. δ 8.35 - 8.1 (m, 1H), 7.6 - 7.4 (m, 2H), 4.0 (s, 3H), 3.3 (s, 3H). Anal. Calcd for $C_7H_9NO_3S$: C, 44.90; H, 4.85; N, 7.48. Found: C, 44.70; H, 4.95; N, 7.35.

2-Hydroxy,5-bromopyridine (32), m.p. = 180 - 82° (Lit.[21] 172.5 - 76°). δ 12.1br (s, 1H), 7.5 (dd, 1H, J = 10.5 and 2.4 Hz), 7.5 (d, 1H, J = 2.4 Hz), 6.5 (d, 1H, J = 10.5 Hz). Anal. Calcd for C_5H_4BrNO: C, 34.51; H, 2.32; N, 8.05. Found: C, 34.55; H, 2.20; N, 8.20.

5-Methoxy,3-methylthiopyridine (33), Oil. δ 8.2 - 7.9 (m, 2H), 7.15 6.9 (m, 1H), 3.8 (s, 3H), 2.5 (s, 3H). Anal. Calcd for C_7H_9NOS: C, 54.16; H, 5.86; N, 9.03. Found: C, 54.10; H, 5.70; N, 9.25.
Sulphone, m.p. = 184 - 6°. δ 8.4 - 8.2 (m, 2H), 7.5 - 7.35 (m, 1H), 3.9 (s, 3H), 3.4 (s, 3H). Anal. Calcd for $C_7H_9NO_3S$: C, 44.90; H, 4.85; N, 7.48. Found: C, 45.05; H, 4.65; N, 7.50.

3-Hydroxy,5-chloropyridine (34). In acetone-d_6, δ 9.35br (s, 1H), 8.15 (d, 1H, J = 2.0 Hz), 8.05 (d, 1H, J = 2.0 Hz), 7.25 (t, 1H, J = 2.0 Hz).

D) The Reactions of Halogeno methylthiopyridines and Bis(methylthio)pyridines with Sodium Methoxide.

To a stirred solution of the pyridine derivative (6), (8), (10), (12), (14) or (16) (0.01 mol) in DMF (40 ml), kept under N_2 at 80°C, sodium methoxide (4 mol) was added. The reactions were followed and worked up as described in A. Reaction times are indicated in the Results and Discussion. The products obtained are reported in Scheme 4, where the reaction yields are indicated in parentheses. The physical and nmr data of compound (30) (obtained from (6) or from (14)), compound (33) (obtained from (12)) and compound (32) (obtained from (8)) have been already described in C. The only remaining product is (35) whose properties are reported below.

2-Methoxy,5-methylthiopyridine (35), Oil. δ 8.15 (dd, 1H, J = 4.0 and 1.0 Hz), 7.55 (dd, 1H, J = 4.0 and 8.5 Hz), 6.65 (dd, 1H, J = 8.5 and 1.0 Hz), 3.9 (s, 3H), 2.4 (s, 3H). Anal. Calcd for C_7H_9NOS: C, 54.16; H, 5.86; N, 9.03. Found: C, 54.30; H, 5.80; N, 8.85.
Sulphone, m.p. = 90 - 2°. δ 8.7 (dd, 1H, J = 4.0 and 1.0 Hz), 8.0 (dd, 1H, J = 8.7 and 4.0 Hz), 6.85 (dd, 1H, J = 8.7 and 1.0 Hz), 4.0 (s, 3H), 3.05 (s, 3H). Anal. Calcd for $C_7H_9NO_3S$: C, 44.90; H, 4.85; N, 7.48. Found: C, 45.00; H, 4.70; N, 7.60.

The Reactions of Poly(alkylthio)pyridine with Sodium in HMPA.

To a stirred solution of the bis(isopropylthio)pyridines (**13**), (**15**), (**17**) or (**19**) or of the pentakis(isopropylthio)pyridine (0.01 mol) in HMPA (30 ml), kept under N_2 at 120°C, small pieces of sodium (1.3 atoms for each $SCHMe_2$ group present in the molecule) were added. The progress of the reactions was monitored by tlc. After 2 - 4 hrs the starting products were completely consumed and the mixtures were cooled at room temperature. Excess methyl iodide was added and the mixture stirred for half an hour. After the usual work up and column chromatography the methylthio-derivatives (**14**), (**16**), (**18**) and (**20**) were isolated in 63, 74, 80 and 68% yields, respectively. Pentakis(methylthio)-pyridine was obtained in 78% yields.

Acknowledgments. This work was supported by a grant from the CNR program "Chimica Fine e Secondaria".

References

1) P. Cogolli, F. Maiolo, L. Testaferri, M. Tingoli, M. Tiecco, J. Org.Chem., **44**, 2642 (1979).
2) L. Testaferri, M. Tingoli, M. Tiecco, J. Org. Chem., **45**, 4376 (1980).
3) L. Testaferri, M. Tiecco, M. Tingoli, D. Chianelli, M. Montanucci, Tetrahedron, **39**, 193 (1983).
4) D. Chianelli, L. Testaferri, M. Tiecco, M. Tingoli, Synthesis, 475 (1982).
5) L. Testaferri, M. Tingoli, M. Tiecco, Tetrahedron Lett., **21**, 3099 (1980).
6) M. Tiecco, M. Tingoli, L. Testaferri, D. Chianelli, F. Maiolo, Synthesis, 478 (1982).
7) L. Testaferri, M. Tiecco, M. Tingoli, D. Chianelli, F. Maiolo, Tetrahedron, **38**, 2721 (1982).
8) L. Testaferri, M. Tiecco, M. Tingoli, D. Chianelli, M. Montanucci, Tetrahedron, **38**, 3687 (1982).
9) F. Maiolo, L. Testaferri, M. Tiecco, M. Tingoli, J. Org. Chem., **46**, 3070 (1980).
10) L. Testaferri, M. Tiecco, M. Tingoli, D. Chianelli, M. Montanucci, Synthesis, 751 (1983).
11) S. G. Woods, B. T. Matyas, A. P. Vinogradoff, Y. C. Tong, J. Heterocyclic Chem., **21**, 97 (1984).
12) J. R. Beck and J. A. Yahner, J. Org. Chem., **43**, 2048 (1978).
13) C. J. Gilmore, D. D. MacNicol, A. Murphy, M. A. Russell, Tetrahedron Lett., **25**, 4303 (1984).
14) P. Nedenskov, N. Clauson-Kaas, J. Lei, H. Heide, G. Olsen, G. Jansen, Acta Chem. Scand., **23**, 1791 (1969).
15) N. Furukawa, S. Ogawa, T. Kawai, S. Oae, Tetrahedron Lett., **24**, 3243 (1983).
16) R.A. Abramovitch and A. J. Newman, J. Org. Chem., **39**, 2690 (1974).
17) D. S. Noyce and J. A. Virgilio, J. Org. Chem., **38**, 2660 (1973).
18) E. Spinner and J. C. B. White, J. Chem. Soc. (B), 991 (1966).
19) E. L. Stogryn, J. Heterocyclic Chem., **11**, 251 (1974).
20) C. D. Johnson, A. R. Katritzky, M. Viney, J. Chem. Soc. (B), 1211 (1967).
21) H. J. Den Hertog, J. P. Wibaut, F. R. Schepman, A. A. Van der Wal, Recueil, **69**, 700 (1950).