Tetrahedron Vol. 38, No. 9, pp. 1293 to 1297, 1982
Printed in Great Britain.

0040-4020/82/091293-05$03.00/0
Pergamon Press Ltd.

REDUCTIVE REACTIONS OF SUBSTITUTED PYRIDINES BY AQUEOUS TITANIUM TRICHLORIDE

ANGELO CLERICI and OMBRETTA PORTA
Istituto di Chimica del Politecnico, Pza L. de Vinci 32, 20133 Milano, Italy

(*Received in the UK* 21 *April* 1981)

Abstract—Aqueous titanium trichloride reductively removes cyano and halo groups from the correspondingly substituted pyridines by a two electron-transfer process and promotes reduction of pyridyl-ketones and aldehydes to glycols by one electron-transfer process under very simple experimental conditions.

We have recently reported[1] that 4-cyano- and 2-cyano-pyridine are quantitatively and partially reduced to pyridine respectively on treatment with aqueous titanium trichloride. In connection with the increasing interest aroused in these last years on the reducing power of low-valent titanium species,[2] such as Ti(O) or Ti(II), we have extended our research to the reducing properties of Ti(III) with regard to heteroaromatic compounds.

The use of titanium trichloride is attractive since it is commercially available and can be used under simple experimental conditions. Recently, inter- and intramolecular coupling of aldehydes and ketones has been accomplished by using low-valent titanium reagents generated from titanium trichloride with either lithium-aluminumhydride[3] or reactive metals[4] such as K, Na, Li, or Zn/Cu couple. However all these species lead not to pinacols but rather to the corresponding olefins (Scheme 1).

Only the use of well defined Ti(II)-complexes allowed Corey *et al*[5] to succeed in coupling aliphatic and aromatic carbonyl compounds to glycols. It has also been reported[6] that low-valent titanium species reductively remove halogen atoms from both sp^2 and sp^3 hybridized organic halides. Titanium trichloride, certainly a milder reducing agent, promotes the same reductive reaction of electron-poor substrates such as heteroaromatic bases, namely it can be used to advantage for both the reductive decyanation or dehalogenation of cyano- and halo-pyridines, and the pinacolic reduction of pyridinealdehydes and ketones.

RESULTS AND DISCUSSION

Decyanation and dehalogenation

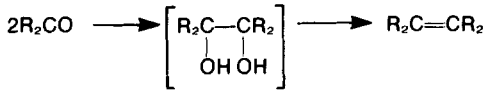
The facile and quantitative reduction of heterocyclic N-oxides by aqueous titanium trichloride has been adapted as a titrimetric method for the determination of these substances,[7] but several compounds require the presence of complex forming agents during the reaction to bring about complete reduction of the N-oxide groups. The reducing power of Ti(III) is reported[8] to be greater in acetate (pH 5.5) than in citrate (pH 5.9) medium. Accordingly we have found[1] that 4-cyano-pyridine is quantitatively reduced to pyridine only when acetic acid is present in hydrochloric acid medium while in the presence of citrate, yields range between 78 and 93% and never exceed 52% in the absence of complex-forming agents.

The best experimental conditions found[1] for 4-cyano-pyridine have been used to accomplish the reduction of all the other substrates investigated. Pyridine is the only reaction product according to Scheme 2.

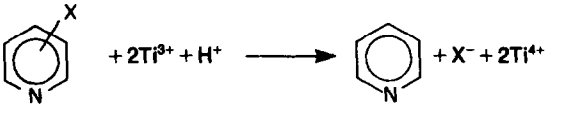
Yields are highly dependent on both X-group position in the ring and its nature. The results obtained are summarized in Table 1.

Both the reactivity orders observed (X-group position: $4 > 2 \gg 3$, and X-group nature: 4-CN > 4-Br > 4-Cl) are consistent with a mechanism (Scheme 3) involving formation of the intermediate radical **1** by a first electron-transfer to the substrate by Ti(III). In fact, the ease of formation and the stability of **1**, depending on whether the X-group position in the ring or its electron-withdrawing nature,[9] is in accordance with the observed reactivity trends.

The further reduction of radical **1** to the anion **2** by a second electron-transfer is in relation with (a) the elec-

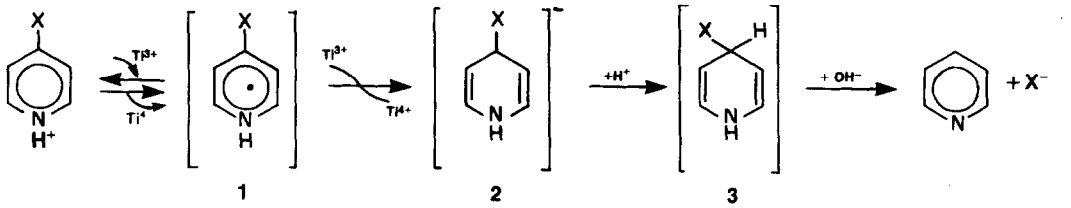


Scheme 1



X = CN, Cl, Br

Scheme 2



Scheme 3

Table 1. Reductive decyanation and dehalogenation of substituted cyano- and halo-pyridines by titanium trichloride in acetic acid

Substituent X	Molar ratio X-Py / Ti(III)	Yields[a] % Pyridine	Yields[b] % based on $TiCl_3$
4-CN	1:1	50	quantitative
4-CN	1:2	quantitative	quantitative
2-CN	1:2	70	70
3-CN	1:2	0	0
2,4-diCN	1:2	100 (2-CN-Py)	quantitative
2,4-diCN	1:4	56 (2-CN-Py) 44 (Py)	77
4-Br	1:2	70	70
2-Br	1:2	12	12
3-Br	1:2	0	0
4-Cl	1:2	43	43

[a]Yields based on starting X-Pyridine determined by GLC analysis with the internal standard method for comparison with authentic sample.

[b]Considering two-electron transfer per mole of X-Pyridine.

tron affinity of **1**, and (b) the redox potential of Ti^{3+}/Ti^{4+} system, which are both closely pH dependent. (a) The second half-wave potentials ($E_{1/2}$) of the corresponding N-ethylpyridinium iodides can be taken as a measure of the electron affinity of **1**. The electrochemical reduction of the N-ethyl-4-cyanopyridinium salt, investigated by Kosower *et al.*[10] shows two polarographic waves in basic solution; a reversible one electron reduction at -0.87 V (SCE) and a pH dependent second wave at -1.16 V (pH = 8.5). The rate of the base catalyzed elimination of the cyano group is markedly increased[11] at a pH more basic than 8.5. (b) The reducing power of Ti(III) is also strongly pH dependent according to the equation:[12]

$$E_0 = 0.029 - 0.236\,pH - 0.0591\,\lg Ti^{3+}$$

for the reaction:

$$Ti^{3+} + 2H_2O \rightarrow TiO_2 + 4H^+ + e^-$$

in which Ti(IV) is present as insoluble hydrated bioxide.

The increase in the reducing power of Ti^{3+}/Ti^{4+} system by increasing the pH may be required to make the reduction of the substrate, and especially of the radical **1**, thermodynamically possible. In fact, experimental evidence that oxidation of Ti(III) to Ti(IV) does not occur in the starting solution (0.01 mole of 4-cyanopyridine and 0.02 mole of aqueous titanium trichloride in acetic acid at pH = 0.2–0.3) is given by spectrophotometric titration of Ti^{3+} in the mixture. Such oxidation takes place only by dropwise addition of diluted NaOH solution into the starting mixture, and it has been verified that, monitoring the reaction by means of a pH-meter, no or very little decyanation occurs at pH ≤ 7.

This evidence allows us to consider that either the electron-transfer to **1** takes place at pH > 7 and the dihydrointermediate **3** gives pyridine afterwards via base catalyzed 1,4-elimination of HCN, or that **3** once formed at pH ≤ 7 undergoes 1,4-elimination only at higher pH.

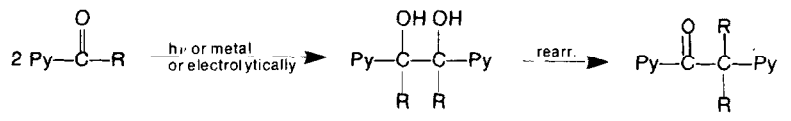
The conversion of **1** directly to **3** by hydrogen abstraction from the solvent is rather unlikely because of the lack of hydrogen–atom donor ability of the reaction medium.

Reductive pinacolic coupling

The reductive dimerization of pyridineketones to the corresponding pinacols have been widely investigated with respect to their pinacol-pinacolone type rearrangements[13] which give, as major product, the pyridyl analogs of Amphenone B (Scheme 4).

Since several compounds in this series possess valuable and specific adrenal cortical inhibitory activity, photochemical, electrochemical, and metal reduction have been alternatively employed to prepare these diols.[13,14] We now show that aqueous titanium trichloride is an excellent synthetic alternative to the above methods for the reductive pinacolization of carbonyl heteroaromatic compounds such as 2- and 4-pyridinealdehydes, and 2- and 4-pyridineketones.

The reaction takes place under very simple experi-



Scheme 4

mental conditions by dropwise addition of aqueous 15% titanium trichloride solution to the solution of the heteroaromatic substrate in acetic acid at room temperature under nitrogen. The diols are either directly recovered from the reaction mixture as insoluble hydrochlorides, or separated with adequate procedure owing to their limited solubility in most solvents (see experimental section). The pinacols are formed as a mixture of meso and dl forms. Yields and dl/meso ratios are reported in Table 2. It should be underlined that among the methylpyridylketones and pyridylaldehydes investigated, the 3-isomers do not undergo bimolecular reduction under the experimental conditions for which the 2- and 4-isomers give the corresponding diols in very good yields. A comparable effect has been observed[13] in the considerably lower rate of photochemical bimolecular reduction of 3-acetylpyridine with regard to that of 2- and 4-acetylpyridine.

A mechanism consistent with the observed reactivity order (4-R-CO- > 2-R-CO- ≫ 3-R-CO-; R = H, CH_3) is shown in Scheme 5. The radical anion **4**, formed by the uptake of one electron from Ti^{3+}, is converted into the radical **5** by proton abstraction from the solvent. This intermediate **5** is a long-lived captodative radical[15] which enjoys particular stabilization being simultaneously substituated by a donor (-OH) and acceptor ($Py-H^+$) group and dimerizes to the corresponding pinacol owing to its high concentration even in a protic solvent such as the reaction medium. Dimerization of **4** to the corresponding dianion would be unimportant in acidic media.[16] The ease of formation and the life time of **4**, and subsequently of **5**, are responsible for the observed reactivity trends. The 4-, 2-, and 3-pyridyl residues differently influence the redox potential of the carbonyl group, and hence the formation and stability of **5**. In fact the half-wave potentials ($E_{1/2}$ V vs SCE) of the corresponding 4-, 2-, and 3-acetyl-N-methylpyridine iodides (−0.70, −0.76 and −0.89 V respectively[5]), which can be taken as a measure of the redox potential of the keto group, clearly indicate that 3-acetylpyridine is the least reducible isomer. The lower captodative character of **5** in the case of the 3-pyridyl derivatives may also justify the reactivity trends.

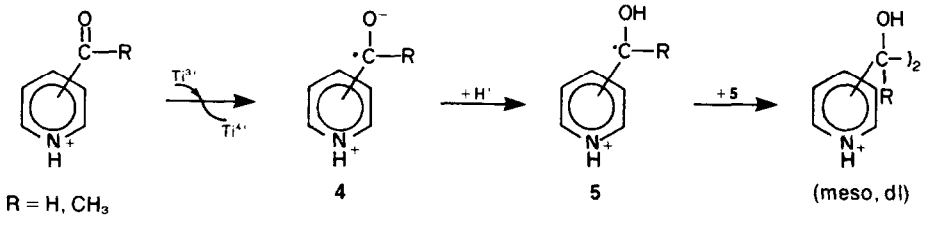
EXPERIMENTAL

Reagents. All chemicals employed (except for 2,4-dicyanopyridine) were either reagent grade or the best research grade obtainable, and were further purified by conventional techniques when necessary. 2-,4-Dicyanopyridine was prepared according to the procedure of Feely *et al.*,[17] but in contrast with this report, 2-cyano-4-amidopyridine was predominantly obtained. Only subsequent dehydration over phosphorus pentachloride afforded the desired product (*ca* 30% yield).

Analysis. All melting points are uncorrected and were determined by Kofler melting block. IR spectra were recorded on a Perkin–Elmer 177 spectrometer. Mass spectra were taken on a Hitachi–Perkin–Elmer RMU-6D spectrometer at 70 eV. ^{1}HNMR spectra were recorded on a Varian A-90 instrument with Me_4Si as internal standard (δ is 0 ppm). GLC analyses were performed on a Hewlett–Packard 5750-G instrument with a flow rate of 30 ml min^{-1} N_2. For preparative chromatography (TLC) 2 mm Merck Kieselgel GF-254 plates were used, eluting with hexame-ethyl acetate, 7 : 3.

Decyanation and dehalogenation. General procedure

To a well-stirred solution of the substituted pyridine (10 mmol), acetic acid (10 ml), water (10 ml) and 15% aqueous titanium trichloride solution (*ca* 18.5 ml, 20 mmol) a sodium hydroxide solution was added dropwise at 0°C under nitrogen until a sharp colour change form dark blue to white occurred indicating that basic pH (10–11) was reached. The resulting suspension was extensively washed with chloroform. The combined extracts were washed with water, dried over anhydrous sodium sulphate, concentrated *in vacuo* and analyzed by GLC (5 ft × 1/8-in column packed with 10% Carbowax 20M). Pyridine was the only reaction



Scheme 5

Table 2. Reductive pinacolization of carbonyl heteroaromatic substrates by titanium trichloride in acetic acid

Substrate	4-CHO-Py	2-CHO-Py	4-CH_3CO-Py	2-CH_3CO-Py
Yield[a] %	82	78	86	72
dl/meso ratio	0.5[b]	0.7[c]	1.1[d]	1.7[c]

[a] % of isolated product based on starting heteroaromatic substrate.

[b] The ratio is approximate because of the different solubility of the two stereoisomers into the same solvent, and besides the meso isomer is converted to the dl form during recrystallization[18].

[c] Determined by NMR spectroscopy[19].

[d] Meso and dl identities assigned on the basis of m.p. and crystalline forms[16].

product. Yields were determined with the internal standard method by comparison with authentic sample. When yields based on titanium trichloride were not quantitative (see Table 1) the dark blue colour remained persistent even at basic pH and disappeared only on standing of basic solution to air.

Pinacolic reduction. General procedure

To a well-stirred solution of the substrate (20 mmol) in glacial acetic acid (10 ml) at room temperature under nitrogen a 15% solution of aqueous titanium trichloride (*ca* 18.5 ml, 20 mmol) was added dropwise during 10 min. The first 8–10 ml of titanium trichloride solution were immediately discharged while the remaining were much slower decoloured. The reaction mixture was allowed to react for 7 h at room temperature under nitrogen, during which the titanium trichloride colour was still barely maintained in the reaction flask. Because of the different solubility of the pinacolic products in the reaction medium and in most common organic solvents, the respective procedures for their isolation are given.

2,3-*Di*(4-*pyridyl*)-2,3-*butanediol.* By adding 200 ml of acetone to the reaction mixture, a thick oil separated at the bottom of the flask which, on standing, slowly turned to a yellow crystalline solid. The solution was decanted and the solid was triturated with cold ethanol. Upon filtration, 1.3 g of 2,3-di(4-pyridyl)-2,3-butanediol dihydrochloride was obtained as light yellow crystalline product, m.p.200–5°C decomp (fraction A). The combined solutions of acetone and ethanol were reduced to a small volume (*ca* 30 ml) under vacuum and added with 20 ml 30% di-ammonium citrate solution. The pH of the resulting mixture was adjusted to 7–8 by adding a 10% sodium hydroxide solution. A very fine white powder precipitated which, upon filtration and washing with water/acetone, weighed 1.1 g (fraction B). The ammonium citrate solution was added to prevent the hydrolytic precipitation of Ti(IV)–bioxide hydrate. Fraction A: when the dihydrochloride was dissolved in water and the solution basified with saturated aqueous sodium carbonate, the free base precipitated from the solution in quantitative yield (1 g, 41%) as chunky colourless crystals. This compound had m.p. 210–2°C, Lit[13] 209–11°C, ^{1}H NMR (DMSO) δ 1.25 (s, 6H, $2CH_3$), 5.32 (s, 2H, 2OH, exchanged with D_2O), 7.50 (dd, 4H, Py–$H_{(\beta)}$), 8.50 (dd, 4H, Py–$H_{(\alpha)}$). Fraction B: upon recrystallization from aqueous ethanol, a lower melting form of 2,3-di(4-pyridyl)-2,3-butanediol was obtained in 45% yield. This compound had m.p. 190–5°C, Lit[13] 182–9°C, ^{1}H NMR(DMSO) δ 1.62 (s, 6H, $2CH_3$), 5.50 (s, 2H, 2OH, exchanged with D_2O), 7.10 (m, 4H, Py-$H_{(\beta)}$), 8.27 (m, 4H, Py-$H_{(\alpha)}$). Overall yield of the higher and lower melting forms of the pinacols was 86% based on the starting 4-acetylpyridine which is recovered after chloroform extraction of the basic solution along with methyl(4-pyridyl)carbinol (less than 2%). The diastereoisomer having the higher melting point is costumarily designated the meso form: for eight different diastereomeric pairs of pinacols, the dl-form has consisted of fine, silky needles while the meso form was composed of either fat needles or chunky crystals.[16]

2,3-*Di*(2-*pyridyl*)-2,3-*butanediol.* The reaction mixture was poured onto ice and made slightly alkaline with a 20% aqueous sodium hydroxide solution, then extracted three times with chloroform. The combined extracts were washed with water, dried over anhydrous sodium sulphate and evaporated to dryness under reduced pressure. The residual solid (2.1 g) was chromatographated (TLC, eluting with hexane/ethyl acetate, 7 : 3) to give the unreacted starting material and two fractions. Fraction A afforded the meso-isomer of 2,3-di(2-pyridyl)-2,3-butanediol as chunky white crystals after recrystallization from hot heptane. This compound had m.p. 142–3°C, Lit[16] 140–2°C, ^{1}H NMR($CDCl_3$) δ 1.27 (s, 6H, $2CH_3$), 7.25 (s, 2H, 2OH, exchanged with D_2O), 7.05–8.60 (m, 8H, Py-H). Fraction B afforded the dl-isomer of 2,3-di(2-pyridyl)-2,3-butanediol as fine needles after recrystallization from pentane. This compound had m.p. 140–2°C, Lit[16] 140–2°C, ^{1}H NMR($CDCl_3$) δ 1.68 (s, 6H, $2CH_3$), 6.98 (s, 2H, 2OH, exchanged with D_2O), 6.75–8.25 (m, 8H, Py-H). The dl/meso ratio[18] (1.7) and yields (82%) were directly determined on the crude material by a comparison of a peak heights of the methyl groups of the two diastereoisomers and the methyl group of the unreacted 2-acetylpyridine respectively. Yield based on the starting 2-acetylpyridine was 72%.

1,2-*Di*(4-*pyridyl*)-1,2-*ethanediol.* A first crop of 1,2-di(4-pyridyl)-1,2-ethanediol dihydrochloride precipitated directly from the reaction mixture as an insoluble white powder. The crude material was collected, washed with acetone and dried (fraction A, 1.5 g). Addition of 100 ml of acetone to the filtrate of fraction A afforded a second crop of the dihydrochloride as a thick oil, which solidified on standing at the bottom of the flask. The solid was filtered off, washed with cold ethanol and acetone (fraction B, 0.8 g). Fraction A was dissolved in water, neutralized with aqueous sodium carbonate and the free base precipitated in quantitative yield (1.1 g) as white powder. Upon recrystallization from aqueous ethanol, colourless octahedrons were obtained. The m.p. 211–3°C is in agreement with that of the meso-form of 1,2-di(4-pyridyl)-1,2-ethanediol (Lit[20] 214°C). This compound had ^{1}H NMR(D_2O) δ 5.32 (s, 2H, 2CH), 8.00 (dd, 4H, Py-$H_{(\beta)}$), 8.80 (dd, 4H, Py-$H_{(\alpha)}$); IR(nujol) λ_{max} 3230 cm^{1-} (OH). Fraction B was dissolved in water and neutralized with saturated sodium carbonate solution. On standing, very fine silky needles crystallized from the solution (0.6 g). The m.p. 178–80°C was in agreement with the dl-form of 1,2-di(4-pyridyl)-1,2-ethanediol (Lit[20] 178–80°C). This compound had ^{1}H NMR(DMSO) δ 4.70 (d, 2H, 2CH), 5.60 (d, 2H, 2OH, exchanged with D_2O), 7.14 (dd, 4H, Py-$H_{(\beta)}$), 8.35 (dd, 4H, Py-$H_{(\alpha)}$). Overall yield based on starting 4-pyridinealdheyde was 82%.

1,2-*Di*(2-*pyridyl*)-1,2-*ethanediol.* The reaction mixture was made alkaline with 20% sodium hydroxide solution and extracted three times with 250 ml portions of ethyl acetate. The ethyl acetate solution was dried over anhydrous sodium sulphate and concentrated *in vacuo.* The ^{1}H NMR spectrum of the crude extract afforded the meso diol in 45%, and the dl isomer in 33% yield, along with 22% of 2-hydroxymethylpyridine. No starting material was detected by ^{1}H NMR. The meso isomer was directly recovered from the ethyl acetate solution upon concentration as yellow powder (0.8 g), which, after recrystallization from acetone, melted at 156–7°C (Lit.[21] 156°C). This compound had ^{1}*H NMR*($CDCl_3$) δ 4.96 (s, 2H), 5.4 (s, 2H, 2OH, exchanged with D_2O), 7.1–8.7 (m, 8H, Py-H). The dl isomer was separated by TLC (eluting with hexane/ethyl acetate, 1 : 1). After recrystallization from 50% aqueous ethanol, this compound melted at 92–3°C (Lit.[22] 92–3°C) and had ^{1}H NMR($CDCl_3$) δ 5.2 (s, 2H), 5.4 (s, 2H, 2OH, exchanged with D_2O), 7.1–8.7 (m, 8H, Py-H). Overall yield based on starting 2-pyridinealdehyde was 78%.

Acknowledgements—The Italian C.N.R. is gratefully acknowledged for financial support of this research. The authors also thank Mrs A. Bellini for NMR measurements.

REFERENCES

[1]A. Clerici and O. Porta, *Tetrahedron Lett.* **21**, 1675 (1980).
[2]J. E. McMurry, *Acc. Chem. Res.* **7**, 281 (1974); Tse-Lok Ho, *Synthesis* 1 (1979).
[3]J. E. McMurry and M. P. Fleming, *J. Am. Chem. Soc.* **96**, 4708 (1974); J. E. McMurry and M. P. Fleming, *J. Org. Chem.* **40**, 2555 (1975); J. E. McMurry and M. P. Fleming, *Ibid.* **41**, 896 (1976); R. F. Longler and T. T. Tidwell, *Tetrahedron Lett.* 777 (1975); D. S. Bomse and T. H. Morton, *Ibid.* 781 (1975); H. Wynberg, K. Lammertsma and L. A. Hurshof, *Ibid.* 3749 (1975); G. A. Olah, G. K. S. Prakash and G. Liang, *Synthesis* 318 (1976); G. Newkome and J. M. Roper, *J. Org. Chem.* **44**, 502 (1979).
[4]J. E. McMurry and L. R. Krepski, *J. Org. Chem.* **41**, 3929 (1976); J. E. McMurry and K. I. Kees, *Ibid.* **42**, 2655 (1977); S. Nishida and F. Kotoaka, *Ibid.* **43**, 1612 (1978); T. Mukaiyama, *Angew. Chem. Int. Ed.* **16**, 817 (1977).
[5]E. J. Corey, R. L. Danheiser and S. Chandrasekaran, *J. Org. Chem.* **41**, 260 (1976).
[6]T. Mukaiyama, M. Hayashi and K. Nazasaka, *Chem. Lett*, 291 (1973); S. Tyrlik and I. Wolochowicz, *J. C. S. Chem. Commun.* 781 (1975); T. R. Nelson and J. J. Tufariello, *J. Org. Chem.* **40**, 3159 (1975).
[7]R. T. Brooks and P. D. Sternglanz, *Anal. Chem.* **31**, 561 (1959).

[8]I. M. Kolthoff, *Rec. Trav. Chim.* **43**, 772 (1924).
[9]R. A. Mackay, J. R. Landolph and E. J. Poziomek, *J. Am. Chem. Soc.* **93**, 5026 (1971).
[10]W. M. Schwarz, E. M. Kosower and I. Shain, *Ibid.* **83**, 3164 (1961).
[11]J. W. Patton, Ph.D. Thesis, University of Wisconsin (1961).
[12]M. Pourbaix, "Atlas d'equilibrès electrochimiquès", Gouthier-Villars Ed. Paris, p. 213 (1963).
[13]W. L. Bencze, C. A. Burckhardt and W. L. Yost, *J. Org. Chem.* **27**, 2865 (1962); W. L. Bencze and M. J. Allen, *J. Am. Chem. Soc.* **81**, 4015 (1959); E. V. Brown and M. B. Shambu, *J. Heterocycl. Chem.* **8**, 967 (1971); M. R. Kegelman and E. V. Brown, *J. Am. Chem. Soc.* **75**, 4649 (1953).
[14]W. Mathes and W. Saurmilch, *Chem. Ber.* **84**, 452 (1951); M. J. Allen, *J. Org. Chem.* **15**, 435 (1950); M. J. Allen, *Can. J. Chem.* **37**, 257 (1959); M. J. Allen and H. Cohen, *J. Am. Electrochem. Soc.* **106**, 451 (1953); F. F. Ebetino and E. D. Amstutz, *J. Am. Chem. Soc.* **28**,3249 (1963).
[15]H. G. Viehe, R. Merenyi, L. Stella and Z. Jananseck, *Angew. Chem. Int. Ed.* **18**, 917 (1979).
[16]J. H. Stocker and R. M. Jenevien, *J. Org. Chem.* **34**, 2807 (1969).
[17]W. E. Feely and E. M. Beavers, *J. Am. Chem. Soc.* **81**, 4004 (1959).
[18]M. Tissier and C. Tissier, *Bull. Soc. Chim. France* 1251 (1968).
[19]J. N. Brown, R. M. Jenevien, J. H. Stocker and L. M. Trefonas, *J. Org. Chem.* **37**, 3712 (1972).
[20]D. Jerchel and J. Heider, *Angew. Chem. Int. Ed.* **70**, 189 (1958); A. Luttringhaus and D. Berrer, *Ibid.* **70**, 439 (1958).
[21]W. Saurmilch, *Chem. Ber.* **91**, 833 (1957).
[22]M. Imuta and H. Ziffer, *J. Org. Chem.* **43**, 3530 (1978).