Acta Chemica Scandinavica B 37 (1983) 7–13

Optimum Conditions for Enamine Synthesis by an Improved Titanium Tetrachloride Procedure

ROLF CARLSON,* ÅSA NILSSON * and MATS STRÖMQVIST

Department of Organic Chemistry, University of Umeå, S-901 87 Umeå, Sweden

A modified procedure for enamine synthesis which results in shorter reaction times and increased yield has been developed. Optimum conditions for the synthesis have been obtained from a series of eight different acyclic ketones with three different amines. The optimum conditions were determined either by response surface methodology or by simplex technique. In view of the results some consideration of the mechanism is briefly discussed.

In 1967 White and Weingarten presented a new enamine synthesis.[1] In their method, titanium tetrachloride was used as a catalyst and also as a water scavenger. This made it possible to synthesize enamines from acyclic ketones, such as methyl ketones, which had previously been difficult with conventional methods.[2] An optimization of the White and Weingarten procedure has already been reported from this laboratory.[3] Though this procedure seems to be generally applicable to enamine synthesis, we found that it fails in the case of several branched acyclic ketones. As part of our studies of regiocontrol in acyclic ketones, we needed a series of enamines with increasing sterical hindrance. Some of these were not available by White and Weingarten's method. We report here a modified procedure and the optimum conditions for enamine formation from acyclic ketones. This method permits the synthesis of enamines from sterically congested ketones, for which the original procedure has failed. In this modified procedure the ketone is added to a preformed complex between the amine and titanium tetrachloride. The procedure is optimized with regard to yield and reaction time and the following experimental variables are considered: relative amount of titanium tetrachloride, relative amount of amine and reaction temperature.

It is obvious that optimum conditions may change with different substrates. Thus, it is necessary to investigate optimum conditions for each individual substrate. It is also obvious that many important conclusions about the scope and limitation of a synthetic procedure should be drawn from investigations performed under optimum conditions.

The common practice for investigating scope and limitation is to use standardized conditions and to record the variation in yield in such experiments.[4] Results from such investigations can be misleading, however, if optimum conditions are susceptible to variation when the substrate is changed. To our knowledge, the present investigation is the first where the optimum conditions have been determined for all the various substrates considered.

METHODS

Optimization. A common approach to optimization is to change one variable at a time. However, we note that this approach is bound to fail to attain a true optimum when the variables are not independent.[5] Chemical phenomena, such as yield, rarely depend on a single variable and the only reasonable way to optimize yields is to use multivariate methods for analyzing the simultaneous influence of several variables and the interaction among them. We have used the following multivariate strategies: the simplex technique[6] and response surface methodology.[5b,7] For a general discussion, see Ref. 3.

*To whom correspondence should be addressed.

0302-4369/83 $2.50

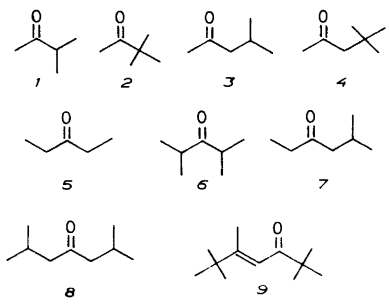

Fig. 1. Ketones *1* – *8* have been investigated. Ketone *9* is a condensation product of *2*, formed during morpholine enamine synthesis of methyl *tert*-butyl ketone.

Yield determination. Yields were determined by gas liquid chromatography (GLC) using the internal standard technique.

RESULTS

The following ketones were investigated: 3-methyl-2-butanone, *1*; 3,3-dimethyl-2-butanone, *2*; 4-methyl-2-pentanone, *3*; 4,4-dimethyl-2-pentanone, *4*; 3-pentanone, *5*; 2,4-dimethyl-3-pentanone, *6*; 5-methyl-3-hexanone, *7*; and 2,6-dimethyl-4-heptanone, *8* (Fig. 1). Optimum conditions for the synthesis of 24 enamines are shown in Tables 1 – 3. We measured the reaction times when no further increase in yield could be observed. These times are given in Tables 1 – 3. For each amine component, optimum conditions for one of the ketones *1* – *8* were determined either by response surface methodology or by the simplex technique. The remaining ketones were investigated under the established conditions. If a yield less than 90 % was found, the conditions were further investigated. The low temperature used for dimethylamine enamine

Table 1. Optimum conditions for morpholine enamine synthesis.

Ketone	Yield %	TiCl eq.	Morpholine eq.	Temp. °C	Reaction time min	Method of optimization[a]
1	93	0.9	5.7	70	15	
2	88	0.92	9.2	110	240	B
3[c]	98	0.9	5.7	70	15	B
4	89[b]	0.92	9.2	70	180	
5	98	0.9	5.7	70	15	
6	67	1.28	11	110	240	A,B
7	79[b]	0.9	6.0	110	90	
	98	1.0	8.0	70	15	A
	100	1.1	7.0	70	120	
8	94	1.33	7.8	70	120	A,B
	88[b]	1.33	7.8	70	120	

[a] A = Simplex, see Fig. 2 for an example. B = Response surface, see Fig. 3 for an example. [b] Isolated yield of distilled product. [c] Model Substrate for first optimization.

Table 2. Optimum conditions for pyrrolidine enamine synthesis.

Ketone	Yield %	$TiCl_4$ eq.	Pyrrolidine eq.	Temp. °C	Reaction time min	Method of optimization[a]
1	98	0.9	6.0	0	5	
2	96	0.9	6.0	rt[d]	15	
3[c]	100	0.9	6.0	0	5	A
4	93	1.0	7.0	rt[d]	15	
5	98	0.9	6.0	0	5	
6	93	1.2	7.5	70	240	A
7	82[b]	0.9	6.0	70	15	
8	99	0.9	7.0	70	120	

[a] A = Simplex, see Fig. 2 for an example. B = Response surface, see Fig. 3 for an example. [b] Isolated yield of distilled product. Could not be analyzed by GLC. [c] Model substrate for first optimization. [d] rt = room temperature, 20 – 25 °C.

Table 3. Optimum conditions for dimethylamine enamine synthesis.

Ketone	Yield %	$TiCl_4$ eq.	Dimethyl-amine eq.	Temp. °C	Reaction time min	Method of optimization[a]
1[c]	98	1.1	7.3	−36	60	A,B
2	79	0.9	7.7	−30	120	A
	74[b]	1.0	7.0	rt[d]	120	
3	92	0.9	7.7	−30	30	
4	97	1.0	6.0	rt[d]	5	A
5	97	0.9	7.7	−30	30	
6	64	1.0	10	35	360	A
7	92	1.1	7.0	rt[d]	15	
8	99	1.0	10	rt[d]	60	A

[a] A = Simplex, see Fig. 2. for an example. B = Response surface, see Fig. 3 for an example. [b] Isolated yield of distilled product. [c] Model substrate for first optimization. [d] rt = room temperature, 20−25 °C.

synthesis was necessary in view of the volatility of dimethylamine. However, some of the ketones showed very slow reaction rates at low temperature, and an increase in temperature was necessary to give conveniently short reaction times. The temperatures given for the pyrrolidine and morpholine enamine syntheses (0 °C, room temperature or reflux) were chosen for reasons of convenience, and optimization of the amounts of titanium tetrachloride and amine was performed subject to this practical constraint. The synthesis of the morpholine enamine from 3,3-dimethyl-2-butanone, *2*, was attended by complications owing to considerable self-condensation of *2* to give 2,2,3,6,6-pentamethyl-3-hepten-5-one, *9*, (Fig. 1). Similar conditions produced high yields of enamine from the other ketones. The enamine and *9* were difficult to separate by simple distillation, and tedious fractionation on an efficient column was necessary to obtain pure enamine. This illustrated a general problem in synthesis, namely the yield of the desired product is decreased by a parasitic reaction. To overcome these difficulties, a response surface study was undertaken, and the yields of both enamine and *9* were described as second degree polynomials in the experimental variables. A central composite experimental design[5b,8] with 18 experiments was used to establish the response surface models. Fig. 4 shows the features of these response surfaces. With the use of these response surface models we could determine the experimental conditions which give less than 5 % of *9* and which maximize the yield of enamine. These conditions are shown in Table 1. It is seen from the Tables 1 − 3 that the sterically hindered ketones, *i.e.*, those with α-branching, require more drastic reaction conditions and/or prolonged reaction time.

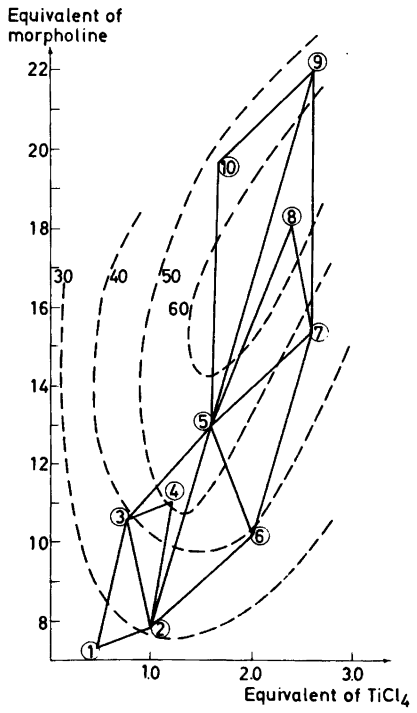

Fig. 2. Simplex optimization of the morpholine enamine synthesis of diisopropyl ketone. Encircled numbers refer to the experiments. After experiment 10, the simplex shrinks and becomes almost stationary around experiment 8.

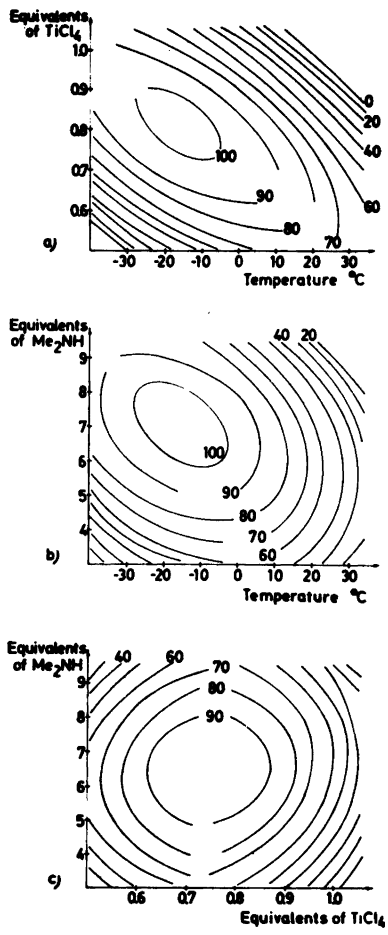

Fig. 3. Response surface obtained in optimization of the dimethylamine enamine synthesis from methyl isopropyl ketone. The numbers at the isoresponse contour lines show the yield (%). The projections are (*a*) amount of dimethylamine 6.3 equivalents, (*b*) amount of titanium tetrachloride 0.78 equivalent, (*c*) temperature −2 °C.

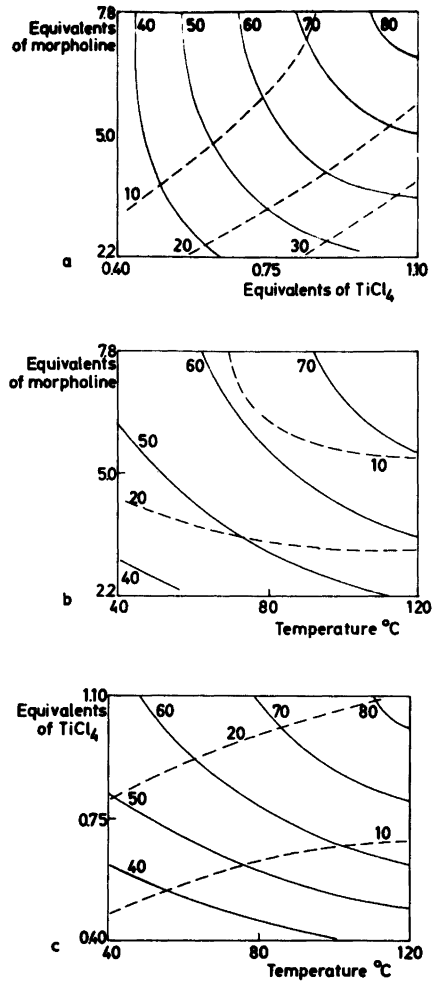

Fig. 4. Response surface obtained in optimization of the morpholine enamine from 3,3-dimethyl-2-butanone. The numbers in the figures refer to the yield (%). The solid isoresponse contour lines show the yield of enamine, the dashed isoresponse contour lines show the yield of condensation product *9*. The projections are: (*a*) temperature 80 °C, (*b*) amount of titanium tetrachloride 0.75 equivalent, (*c*) amount of morpholine 5.0 equivalents.

DISCUSSION

Our experiments were designed to ascertain the optimum conditions for enamine synthesis and not to reveal mechanistic information. However, our finding that addition of ketone to a preformed complex between amine and titanium tetrachloride gives considerably shorter reaction times as compared with the White and Weingarten procedure, suggests that the reactive species is not titanium tetrachloride *per se* but a complex between titanium tetrachloride and amine. The stoichiometry of this complex cannot be stated with any certainty but the results in Tables 1 – 3 show that at least a fivefold excess of amine over titanium tetrachloride is essential for optimum conditions. The observation that too large an excess of amine

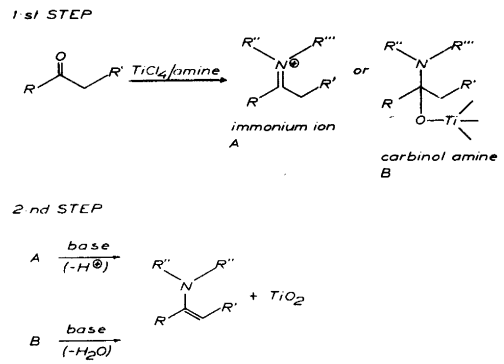

Fig. 5. The enamine formation.

leads to a decrease in yield with several ketones (see, for instance, Fig. 3) suggests that the enamine formation is at least a two-step reaction (Fig. 5). The first step is probably a reaction between a reactive amine – titanium tetrachloride complex and ketone to yield either an immonium ion or a titanium-coordinated carbinol amine. The second step involves either a deprotonation of the immonium ion or base-catalyzed elimination of the elements of water from the carbinol amine. Support for these mechanisms is furnished by some observations from the synthesis of dimethylamine enamine from diisopropyl ketone, *6*. When this ketone was treated with a dimethylamine – titanium tetrachloride complex in a 6:1 ratio, rapid consumption of the ketone was observed but no enamine was formed. A larger excess of dimethylamine resulted in enamine formation. Rapid formation of the dimethylamine enamine occurred when pyrrolidine was added to the reaction mixture (6:1 dimethylamine – titanium tetrachloride) after *ca.* 50 % of the ketone had been consumed. If a suspension in pentane of the isolated immonium trifluoroacetate from the dimethylamine enamine of *6* was treated with dimethylamine at room temperature, no deprotonation resulting in enamine could be observed (GLC). This was also found to be the case upon treatment with triethylamine, quinuclidine and *tert*-butylamine. When the isolated immonium salt was treated with pyrrolidine, rapid formation of the *pyrrolidine enamine* occurred. Previous studies on the deprotonation of immonium salts from morpholine enamines[9] have shown that the counter ion does not influence the course of the deprotonation reaction. If this also holds for dimethylamine-derived immonium salts, the observations stated above seem to rule out the involvement of a free immonium salt as an intermediate. An intermediate in the enamine-forming reaction sequence might be a titanium-coordinated immonium salt or a titanium-coordinated carbinol amine. The dependence of optimum conditions on the joint influence of the amount of amine and the amount of titanium tetrachloride can thus be rationalized; for a reactive titanium tetrachloride – amine complex of correct stoichiometry, the amine – titanium tetrachloride ratio is critical. Too high or too low a ratio shifts the complexation equilibria and reduces the overall rate of the first step. For a high rate of the base-catalyzed second step, it is essential to have a sufficiently high concentration of free amine. These results show that the mechanism of enamine formation is more complex than that suggested by White and Weingarten.[1]

EXPERIMENTAL

An ABC 80 Z-80 bit microcomputer (Scandia Metric) was used for computation and calculations for response surface modelling and for simplex optimization. The microcomputer programs were written in BASIC and are available from this laboratory.[10]

GLC analyses. PYE M 64 Gas Chromatography with FID were used with 5 % Peg 20M + 0.5 % KOH (1.5 m, 4 mm ID) and 12 % QF 1 (2.1 m, 2 mm IR) on Chromosorb W AW DMCS (100 – 120 mesh) glass columns. Phenylcyclohexane *puriss* and *t*-butylbenzene *purum* were used as internal standards. Integrated peak areas were used for quantification, and a Spectra Physics Minigrator^{R} was used to measure the peak areas.

NMR. Spectra were recorded on a JEOL C-60 HL or on a Bruker WM-250. Chemical shifts were measured at 26 °C using TMS as internal standard.

Chemicals. Ketones and amines were commercial *puriss* or *p.a.* products; titanium tetrachloride was technical grade and was used without purification.

Solvents. Pentane, hexane or ligroin (b.p. 36, 69, 110 °C) of technical grade were dried over $CaCl_2$ prior to use. *Note:* The solvents used in the enamine synthesis from pyrrolidine are preferably dried over sodium wire prior to use since these enamines are very sensitive to moisture.

A typical procedure for optimization experiments. A 250 ml three-necked flask equipped with a dropping funnel, reflux condenser and stirrer (Hershberg) was purged with dry nitrogen prior to use and protected from moisture. Using the amounts of titanium tetrachloride and amines given in Tables 1 – 3 the reactions were performed as follows: 4 g internal

standard and amine were dissolved in 100 ml of solvent. After cooling to 0 °C, the given amount of $TiCl_4$ dissolved in 10 ml of solvent was added dropwise with vigorous stirring. After addition was complete, 0.05 mol of ketone in 20 ml of solvent was added in one portion. When addition was complete, the reaction was allowed to proceed at the temperature and for the time according to Tables 1 – 3. Samples were withdrawn at regular intervals, filtered, diluted with hexane and analyzed by GLC.

Synthesis of 4-(2,6-dimethyl-3-hepten-4-yl)morpholine. To a vigorously stirred, cold (0 °C) solution of 680 g (7.8 mol) of morpholine in 1500 ml of hexane was added 146 ml (1.33 mol) of titanium tetrachloride in 300 ml of hexane. After addition was complete 142.2 g (1.0 mol) of diisobutyl ketone was added in one portion. The cooling bath was removed and the reaction allowed to proceed under reflux for two hours. After cooling, the mixture was filtered through a sintered glass filter and the solvent removed under reduced pressure, giving a yellow oil which was distilled under reduced pressure. Yield 171.4 g (87.7 %), b.p. 106 – 108 °C/10 mmHg.

Note. A similar procedure was used for the other enamines. However, pyrrolidine enamines are prone to severe foaming upon distillation, which can be somewhat relieved if, after evaporation of the solvent, the crude product is filtered a second time through a sintered glass filter of pore size 4.

Physical properties of the enamines. The ^1H NMR spectra are all in accordance with the expected spectra. For brevity, only the chemical shifts for the vinylic protons are given below.

Morpholine enamines from ketone.

1, b.p. 69 – 71 °C/7 mmHg (lit.[1] 100 °C/35 mmHg).
2, b.p. 99 – 101 °C/35 mmHg (lit.[11] 89 – 90 °C/15 mmHg).
3, b.p. 84 – 85 °C/10 mmHg (lit.[12] 76 – 77 °C/3 mmHg).
4, b.p. 99 – 101 °C/10 mmHg, NMR (benzene) δ (s) 3.97 (2 H).
5, b.p. 74 – 75 °C/10 mmHg (lit.[13] 77 – 78 °C/9 mmHg).
6, b.p. 87 °C/10 mmHg (lit.[13] 102 – 103 °C/12 mmHg).
7, b.p. 104 – 105 °C/10 mmHg, NMR($CDCl_3$) mixture of regio isomers, δ (q) 4.52, $J = 6.6$ Hz (1 H), δ (d) 4.17, $J = 9.6$ Hz (1 H).
8, b.p. 106 – 108 °C/10 mmHg, NMR($CDCl_3$) δ (d) 4.26, $J = 8.8$ Hz.

Pyrrolidine enamines from ketone.

1, b.p. 76 – 79 °C/35 mmHg, NMR (benzene) δ (s) 3.52, 3.33 (1:1 H).
2, b.p. 62 – 63 °C/10 mmHg, NMR (benzene) δ (s) 4.4, 4.05 (1:1 H).
3, b.p. 70 – 72 °C/10 mmHg, NMR (benzene) δ (s) 3.84, 3.75 (1:1 H).
4, b.p. 78 °C/12 mmHg, NMR (benzene) (s) 3.83 (1 H.
5, b.p. 62 – 63 °C/10 mmHg (lit.[13] 62 – 67 °C/8 mmHg).
6, b.p. 69 – 70 °C/9 mmHg (lit.[14] NMR data).
7, b.p. 82 – 83 °C/ – 10 mmHg, NMR (benzene) mixture of regio isomers, δ (q) 4.4, $J = 7.5$ Hz (1 H), δ (d) 4.25, $J = 9$ Hz (1 H).
8, b.p. 93 – 95 °C/10 mmHg (lit.[15] 96 – 100 °C/10 mmHg).

Dimethylamine enamine from ketone.

1, b.p. 118 – 120 °C/754 mmHg (lit.[1] 56 °C/83 mmHg).
2, b.p. 58 – 59 °C/83 mmHg (lit.[1] 57 °C/71 mmHg).
3, b.p. 76 – 78 °C/115 mmHg, NMR (benzene) δ (s) 3.95, 3.85 (1:1 H).
4, b.p. 81 – 82 °C/90 mmHg, NMR (benzene) δ (s) 3.98 (2 H).
5, b.p. 68 – 70 °C/79 mmHg (lit.[16] NMR data).
6, b.p. 73 – 75 °C/80 mmHg (lit.[1] 82 °C/82 mmHg).
7, b.p. 103 °C/48 mmHg, NMR (benzene) mixture of regio isomers, δ (q) 4.5, $J = 7.5$ Hz (1 H), δ (d) 4.18, $J = 9$ Hz (1 H).
8, b.p. 93 – 96 °C/37 mmHg, NMR (benzene) (s) 4.4, 4.23 (1:1 H).

REFERENCES

1. White, W. and Weingarten, H. *J. Org. Chem. 32* (1967) 213.
2. a. Jacquier, R., Petrus, C. and Petrus, F. *Bull. Soc. Chim. Fr.* (1966) 2845; b. Bianchetti, G., Dalla Croce, P. and Pocar, D. *Tetrahedron Lett.* (1965) 2029; c. Madsen, P. and Lawesson, S.-O. *Recl. Trav. Chim. Pays-Bas 85* (1966) 753; d. Hickmott, P. W., Hopkins, B. J. and Yoxall, C. T. *J. Chem. Soc. B* (1971) 205; e. Munk, M. E. and Kim, Y. K. *J. Am. Chem. Soc. 86* (1964) 2216.
3. Carlson, R., Phan-Tan-Luu, R., Mathieu, D., Ahouande, F. S., Babadjamian, A. and Metzger, J. *Acta Chem. Scand. B 32* (1978) 335.
4. For an example see Brown, H. C. and Krishnamurthy, S. *Tetrahedron 35* (1979) 567.
5. a. Davies, O. L. *The Design and Analysis of Industrial Experiments*, Longman, London and New York 1978; b. Box, G. E. P., Hunter, W. G. and Hunter, J. S. *Statistics for Experimenters*, Wiley, New York, Chichester, Brisbane and Toronto 1978.
6. a. Spendley, W., Hext, G. R. and Himsworth, F. R. *Technometrics 4* (1962) 441; b. Nelder, J. A. and Mead, R. *Computer J. 7* (1965) 308.
7. Myers, R. M. *Response Surface Methodology*, Allyn and Bacon Inc., Boston 1971.
8. Box, G. E. P. and Hunter, J. S. *Ann. Math. Stat. 28* (1957) 195.

9. a. Nilsson, L., Carlson, R. and Rappe, C. *Acta Chem. Scand. B 30* (1976) 271; b. Carlson, R., Nilsson, L., Rappe, C., Babadjamian, A. and Metzger, J. *Acta Chem. Scand. B 32* (1978) 85.
10. Albano, C. *Response surface program* and Nordén, B. *Simplex program* are available from the Research Group for Chemometrics, Institute of Chemistry, University of Umeå, Sweden.
11. Armarego, W. L. F. *J. Chem. Soc. C* (1969) 986.
12. Fusco, R., Bianchetti, G., Pocar, D. and Ugo, R. *Gazz. Chim. Ital. 92* (1962) 1040.
13. Stork, G., Brizzolara, A., Landesman, H., Szmuszkovicz, J. and Terrell, R. *J. Am. Chem. Soc. 85* (1963) 207.
14. Ahmed, G. and Hickmott, P. W. *J. Chem. Soc. Perkin Trans. 2* (1977) 838.
15. Nelson, P. and Pelter, A. *J. Chem. Soc.* (1965) 5142.
16. Stradi, R. and Pocar, D. *Chim. Ind. Milan 53* (1971) 265.

Received March 18, 1982.