Tetrahedron Vol 46, No 7, pp 2525–2538, 1990
Printed in Great Britain

0040-4020/90 $3 00+ 00

HOMOLYTIC ALKYLATION OF HETEROAROMATIC BASES : THE PROBLEM OF MONOALKYLATION .

F.Fontana , F.Minisci* , M.C.Nogueira Barbosa and E.Vismara*
Dipartimento di Chimica del Politecnico - piazza Leonardo da Vinci , 32
20133 Milano (Italy)

(*Received in UK* 14 *December* 1989)

Abstract - The silver-catalyzed decarboxylation of carboxylic acids by persulphate leads to alkyl radicals , which have been utilized for the selective alkylation of heteroaromatic bases . The method is particularly efficient in a water-chlorobenzene two-phase system for two reasons : it considerably increases the selectivity in monoalkylation when more positions of high nucleophilic reactivity (i.e. α and γ) are available in the heterocyclic ring (i.e. quinoline , 4-cyano- and 4-ethylpyridine , pyrazine , quinoxaline etc.) and it determines a much higher efficiency for the radical sources when the silver salt catalysis is deactivated by complexation of the salt with the heterocyclic compound . The high selectivity in monoalkylation has been obtained by the combination of polar effects and the increased lipophilicity of the alkylated product , which makes its extraction from the aqueous solution by the organic solvent easier .

The substitution of protonated heteroaromatic bases by nucleophilic alkyl and carbonyl radicals reflects most of the aspects of the Friedel-Crafts aromatic substitution , but with opposite reactivity and selectivity[1] . Both reactions can be divided , in a generalized sense , into alkylations and acylations , which include reactions of considerable diversity . Also the synthetic advantages and disadvantages are , therefore , opposite . Thus , in the electrophilic process , acylation is much more selective than alkylation , for two reasons : i) the acylating electrophiles are characterized by an intrinsically higher regio- and chemoselectivity compared with the alkylating species ; ii) the introduction of an acyl

group strongly deactivates the aromatic ring towards further acylation so that selective monoacylation is easy to obtain at high conversions of the aromatic substrate , whereas the introduction of an alkyl group activates the substrate towards further alkylation , thus favouring polysubstitution .

In the substitution of protonated heteroaromatic bases by nucleophilic carbon-centered radicals the behaviour is opposite , due to the opposite character of the reacting species : carbonyl groups activate (i.e. the 2-position of 4-cyanoquinoline is about 130 times more reactive than the corresponding position in 4-methylquinoline towards the benzoyl radical) and alkyl groups deactivate the heterocyclic ring , so that polysubstitution by carbonyl radicals easily occurs when more than one position of high nucleophilic reactivity is available in the heterocyclic ring (i.e. α and γ) , whereas it is difficult to stop the reaction to monosubstitution[1]. On the other hand , the polar character of the alkyl groups is relatively poor as compared to that of the carbonyl groups (i.e. , the σ_m , σ_p , and σ_+ Hammett constants for the ethyl group are respectively - 0.07 , - 0.15 and - 0.30 , whereas the σ_m , σ_p and σ_+ for the acetyl group are + 0.38 , + 0.50 and + 0.87) and the degree of deactivation is not sufficient to arrest the alkylation to monosubstitution at high conversions of the substrate , when more reactive positions (α and γ) are available . The problem of polysubstitution is , therefore , important also for homolytic alkylation .

These limitations are much less severe as compared with electrophilic alkylation , because in any case only the α and γ positions of protonated heterocyclic rings are attacked by alkyl and acyl radicals and , when only one of these positions is free , only monosubstitution takes place in high yields at complete conversions ; that is , a carbonyl group is much less activating than the protonated heterocyclic nitrogen and that is not surprising , because , treating the heterocyclic nitrogen atom of pyridine as a substituent in the benzene ring , the exceptionally high value of 4 was estimated[2] for the σ -Hammett constant of the para position in protonated pyridine , 0.5 being the corresponding value for the acetyl group .

We have already shown how it is possible to overcome the difficulty for the selectivity in monoacylation by using α-ketoacids as source of acyl radicals and by taking advantage of the decreased basicity and increased lipophilicity of the monoacylated products in a two-phase system[3] similar to the modification introduced by G.Heinisch[4] to our[5] method of alkoxy carbonylation by alkoxycarbonyl radicals , ·COOR , in aqueous solution . Now we report the synthetic advantages obtained by a two-phase system in the homolytic alkylation of protonated heteroaromatic bases for what concerns the selectivity of monoalkylation and the efficiency of the procedure .

Results and discussion

Among the numerous sources of alkyl radicals , developed by us for the alkylation of heteroaromatic bases[1] , the silver-catalyzed oxidative decarboxylation of carboxylic acids by persulphate[1,6] revealed to be particularly suitable for a two-phase procedure . The generation of the alkyl radical takes place according to eqs. 1-3 and has a general character for carboxylic acids .

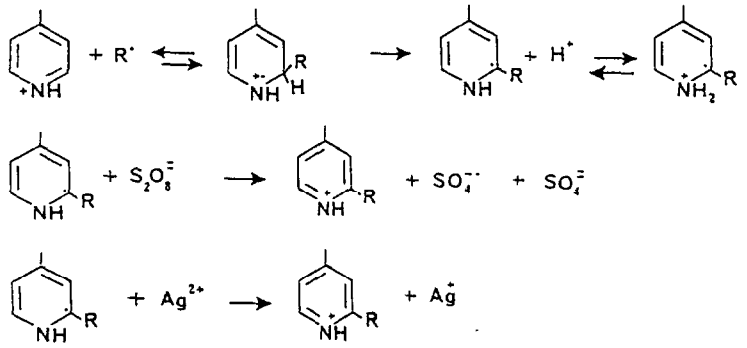
$$Ag^{+} + S_2O_8^{=} \longrightarrow Ag^{2+} + SO_4^{-\cdot} + SO_4^{=} \qquad (1)$$

$$Ag^{+} + SO_4^{-\cdot} \longrightarrow Ag^{2+} + SO_4^{=} \qquad (2)$$

$$R\text{-}COOH + Ag^{2+} \longrightarrow R^{\cdot} + CO_2 + H^{+} + Ag^{+} \qquad (3)$$

The reaction 3 takes place in aqueous solution and it is particularly selective : a small concentration of the carboxylic acid in aqueous solution is sufficient for the reaction to proceed effectively ; this makes the use of a two-phase system possible , even when the carboxylic acid is much more soluble in organic solvents than in water .

The alkylation takes place according to a chain process (eqs. 4-6) , whose features are general for substitutions of protonated heteroaromatic bases by nucleophilic radicals[1] .



(4)

(5)

(6)

Reaction 6 should be very fast ; however , reaction 3 keeps the stationary concentration of the Ag(II) salt very low and the chain process is maintained more by reaction 5 than by reaction 6 .

The results on Table 1 indicate that an alkyl group always deactivates heterocyclic rings towards further alkylation and that the degree of deactivation increases with the nucleophilic character of the attacking radical (methyl < primary < secondary < tertiary alkyl) . The data of Table 1 were determined by the competitive method in aqueous solution ; they only have a qualitative meaning and do not reflect the actual relative rates the addition of alkyl radicals to the heterocyclic ring being reversible , expecially with secondary and tertiary alkyl radicals , as shown by the isotopic effect[7] . However , these data clearly show that , at high conversions of the heterocyclic compound , polysubstitution becomes a significant process .

Table 1 - Relative rates in homolytic alkylation of heteroaromatic bases .

Radical	4-Me-pyridine : Pyridine	Lepidine : Quinoline	2-c-hex-4-CN-Pyridine : 4-Cyanopyridine
Me	0.53	-	-
n-Bu	0.32	0.70	0.33
i-Bu	0.28	0.60	0.20
t-Bu	0.15	0.16	< 0.10
c-Hex	0.23	0.48	-

We have , therefore , utilized a two-phase procedure : one phase was formed by the aqueous solution and the other by chlorobenzene . The results with quinoline , 4-cyanopyridine , 4-ethylpyridine , pyrazine and quinoxaline , as heteroaromatic bases bearing more than one free reactive position , and valeric , isovaleric , pivalic and cyclohexancarboxylic acids as sources of primary , secondary and tertiary alkyl radicals are reported in Tables 2-6 .

These results show that the two-phase system offers a twofold advantage : it allows a considerable increase in selectivity for monosubstitution and , at the same time , it significantly increases the synthetic potentiality of this radical source . This is due to the fact that , in acidic aqueous medium , the decarboxylation of carboxylic acids by persulphate does not occur in the absence of silver salt , because oxidation takes place according to eq. 3 . Besides , the silver catalysis is deactivated in aqueous solution by heterocyclic derivatives bearing two heteroatoms in the ring , such as diazines , which complex the silver salt , thus reducing its catalytic activity . The degree of deactivation is strictly connected with the rate of decarboxylation , which is related to the stability of the generated carbon-centered radical . Thus , deactivation is moderate with tertiary carboxylic acids , while it is substantial with secondary , and almost complete with primary , carboxylic acids .

Some years ago , we[8] tried to overcome this difficulty by using an aqueous solution of carboxylic acid and sodium carboxylate ; decarboxylation occurs , in this case , also in the absence of silver salt , according to eqs. 7 and 8 .

$$S_2O_8^{=} \longrightarrow 2\ SO_4^{-\cdot} \qquad (7)$$

$$RCOO^- + SO_4^{-\cdot} \longrightarrow R^{\cdot} + CO_2 + SO_4^{=} \qquad (8)$$

This method , however , is less useful than the silver-catalyzed process , mainly for two reasons : reaction 8 is much less selective than reaction 3 , so that the presence of relatively high concentrations of carboxylate

is necessary in order to obtain good results , whereas with silver catalysis low concentrations of carboxylic acids in acidic aqueous solution give excellent results . Moreover , the low acidity in the absence of silver salt reduces protonation , reactivity and selectivity of weak bases , such as diazines .

Now , the two-phase system allows to overcome all these problems and makes the silver-catalyzed decarboxylation of carboxylic acids very effective also in the presence of heterocyclic derivatives bearing more than one heteroatom , as the results of Tables 5 and 6 show : under the same conditions and utilizing an excess of persulphate , the conversions of quinoxaline are in all cases complete with a two-phase system , but they are less than 10 % with primary and 65 % with secondary carboxylic acids in aqueous solution . The higher efficiency of the two-phase system is noteworthy also with the less reactive heteroaromatic bases , such as 4-ethylpyridine , as shown by the results in Table 3 . With the same amount of persulphate and the same acidity , the conversions are always higher in the two-phase system than in aqueous solution ; the phenomenon becomes more marked with tertiary than with primary alkyl radicals : with t-butyl radical no attack occurs in aqueous solution , whereas a 33 % conversion is obtained by the two-phase procedure . This is related to the facts that the addition of alkyl radicals to the heterocyclic ring is reversible , that the reversibility increases from primary to tertiary alkyl radicals[7] and that it becomes particularly important with the less reactive substrates . Considering that pivalic acid is faster oxidized than primary and secondary carboxylic acids , the two-phase system appears to provide higher efficiency for the alkyl radical source (eq.3) , but also for the rearomatization of the heteroaromatic radical adduct (eqs. 5 and 6) .

The fact that the rate of decarboxylation increases with the stability of the generated alkyl radical suggests an inner-sphere electron-transfer mechanism , in which either the breaking of the O-Ag^{+} bond is simultaneous to the breaking of the R-CO bond , or a contribution of the bond breaking occurs in the transition state of electron transfer (eqs. 9 and 10)

Table 2 - Alkylation of quinoline by RCOOH and $S_2O_8^{=}$.

R	Acid (mol)[a]	Persulphate (mol)[a]	Solvent	Conversion (%)	Monoalkyl (%)	Dialkyl (%)
n-Bu	H_2SO_4 (2)	1	H_2O	38	100 2(46);4(54)	-
n-Bu	H_2SO_4 (2)	2	H_2O	87	67 2(41);4(59)	33
n-Bu	CF_3COOH(1)	1	PhCl/H_2O	31	100 2(43);4(57)	-
n-Bu	CF_3COOH(1)	2	PhCl/H_2O	63	100 2(38);4(62)	-
i-Bu	H_2SO_4 (2)	1	H_2O	64	86 2(39);4(61)	14
i-Bu	H_2SO_4	2	H_2O	100	43 2(30);4(70)	57
i-Bu	CF_3COOH(1)	1	H_2O	68	90 2(40);4(60)	10
i-Bu	CF_3COOH(1)	1	PhCl/H_2O	56	100 2(37);4(63)	-
i-Bu	CF_3COOH(1)	2	PhCl/H_2O	100	82 2(34);4(66)	18
t-Bu	H_2SO_4 (2)	2	H_2O	96	100 2(100);4(0)	-
t-Bu	CF_3COOH(1)	2	PhCl/H_2O	88	100 2(100);4(0)	-
c-Hex	H_2SO_4 (2)	1	H_2O	67	88 2(42);4(58)	12
c-Hex	H_2SO_4 (2)	2	H_2O	100	40 2(34);4(66)	60
c-Hex	CF_3COOH(1)	2	H_2O	100	56 2(33);4(67)	44
c-Hex	CF_3COOH(1)	1	PhCl/H_2O	63	100 2(39);4(61)	-
c-Hex	CF_3COOH(1)	2	PhCl/H_2O	100	83 2(32);4(68)	17

a) moles per mole of heteroaromatic base

Table 3 - Alkylation of 4-cyanopyridine by RCOOH and $S_2O_8^{=}$.

R	Acid (mol)[a]	Persulphate (mol)[a]	Solvent	Conversion (%)	Monoalkyl (%)	Dialkyl (%)
n-Bu	H_2SO_4 (1)	2	H_2O	97	30	70
n-Bu	CF_3COOH(1)	2	PhCl/H_2O	93	65	35
n-Bu[b]	CF_3COOH(1)	2	PhCl/H_2O	18	100	-
i-Bu	H_2SO_4(1)	2	H_2O	83	67	33
i-Bu	CF_3COOH(1)	2	PhCl/H_2O	90	87	13
t-Bu	H_2SO_4(1)	2	H_2O	100	23	77
t-Bu	CF_3COOH(1)	2	PhCl/H_2O	100	77	23
t-Bu[b]	CF_3COOH(1)	2	PhCl/H_2O	100	85	15
t-Bu[B]	-	2	PhCl/H_2O	35	75	25
c-Hex	H_2SO_4(1)	2	H_2O	98	52	48
c-Hex[b]	CF_3COOH(1)	2	PhCl/H_2O	100	92	8
c-Hex[b]	CF_3COOH(1)	1.1	H_2O	73	84	16
c-Hex[b]	H_2SO_4(1)	2	H_2O	100	38	62
c-Hex[b]	H_2SO_4(0.5)	3	H_2O	100	-	100
c-Hex[b]	CF_3COOH(1)	3	PhCl/H_2O	100	70	30
c-Hex[b]	CF_3COOH(1)	2	PhCl/H_2O	71	97	3
c-Hex[b]	-	4	PhCl/H_2O	100	49	51

a) mol for mol of heterocyclic compound ; b) at 50°C

Table 4 - Alkylation of 4-ethylpyridine by RCOOH and $S_2O_8^{=}$ (3 mol per mol of base) .

R	Solvent	Acid (mol)[a]	Conversion (%)	Monoalkyl (%)	Dialkyl (%)
n-Bu	H_2O	H_2SO_4(2)	65	62	38
n-Bu	PhCl/H_2O	CF_3COOH(1)	76	75	25
i-Bu	H_2O	H_2SO_4(2)	54	75	25
i-Bu	PhCl/H_2O	CF_3COOH(1)	90	96	4
t-Bu	H_2O	H_2SO_4(2)	0	-	-
t-Bu	PhCl/H_2O	CF_3COOH(1)	3	100	-
c-Hex	H_2O	H_2SO_4(2)	58	73	27
c-Hex	PhCl/H_2O	CF_3COOH(1)	94	97	3

a) mol for mol of heteroaromatic compound .

Table 5 - Alkylation of pyrazine with RCOOH and $S_2O_8^{=}$.

R	Acid (mol)[a]	Conversion (%)	Solvent	Monoalkyl (%)	Dialkyl (%)
n-Bu	H_2SO_4(2)	45	H_2O	62	38
n-Bu	CF_3COOH(1)	65	PhCl/H_2O	100	-
i-Bu	H_2SO_4(2)	65	H_2O	51	49
i-Bu	CF_3COOH(1)	100	PhCl/H_2O	86	14
t-Bu	H_2SO_4(2)	90	H_2O	40	60
t-Bu	CF_3COOH(1)	100	PhCl/H_2O	90	10

a) mol per mol of pyrazine

Table 6 - Alkylation of quinoxaline by RCOOH and $S_2O_8^{=}$.

R	Acid (mol)[a]	Persulphate (mol)[a]	Solvent	Conversion (%)	Monoalkyl (%)	Dialkyl (%)
n-Bu	CF_3COOH(1)	2	H_2O	4	100	-
n-Bu	H_2SO_4(1)	2	H_2O	8	100	-
n-Bu	CF_3COOH(1)	2	$PhCl/H_2O$	100	84	16
n-Bu	CF_3COOH(1)	1.3	$PhCl/H_2O$	67	93	7
i-Bu	H_2SO_4(1)	2	H_2O	65	85	15
i-Bu	CF_3COOH(1)	2	$PhCl/H_2O$	100	52	48
i-Bu	CF_3COOH(1)	1.3	$PhCl/H_2O$	87	92	8
t-Bu	H_2SO_4(1)	2	H_2O	90	100	-
t-Bu	CF_3COOH(1)	2	$PhCl/H_2O$	100	100	-
c-Hex	H_2SO_4(1)	2	H_2O	58	84	16
c-Hex	CF_3COOH(1)	2	$PhCl/H_2O$	100	78	22
c-Hex	CF_3COOH(1)	1.3	$PhCl/H_2O$	75	91	9
c-Hex	CF_3COOH(1)	2	$PhCl/H_2O$	56	100	-

a) mol for mol of quinoxaline ; b) at 50°C

$$RCOOH + Ag^{2+} \rightleftharpoons RCOOAg^{+} + H^{+} \qquad (9)$$

$$R\dot{C}OO\dot{A}g^{+} \longrightarrow R^{\cdot} + CO_2 + Ag^{+} \qquad (10)$$

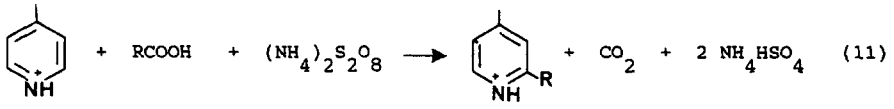
As the energy of the C-O bond decreases , the electron transfer reaction becomes faster .

The results of Tables 2-6 indicate that in all cases , under the same conditions , the selectivity of monoalkylation is higher by the two-phase procedure than in aqueous solution . The conversion of the heterocyclic compound obviously influences the ratio between mono- and polyalkylation ; the higher the conversions , the lower these ratios will be , all the other conditions being equal . The comparison between the two procedures is therefore significant only at similar conversions . When the conversions in the reactions of Tables 2-6 are quantitative , which can be achieved by using an excess of persulphate , the ratios between mono- and dialkylation are affected by the fact that we do not know the excess of reagent after complete conversions in the two different procedures , which have different efficiency for what concerns silver salt catalysis , and the comparison is less significant .

Another important factor , which affects selectivity in monoalkylation , is the lipophilicity of heteroaromatic bases and of their alkylderivatives , which determines the ease of extraction of the reaction products from the aqueous solution by the organic solvent : thus , selectivity is higher with quinoxaline than with pyrazine . On the other hand , the introduction of an alkyl group does not significantly affect the basicity of the heteroaromatic substrate , while it considerably increases its lipophilicity , thus favouring the extraction of the product by the organic layer .

On the purpose of making the extraction of the unprotonated alkylation product by the organic solvent easier , thus favouring monosubstitution , the medium acidity should be the lowest consistent with the need for protonation , at least partial , of the starting heteroaromatic base . We have , in most cases , utilized equimolar amounts of CF_3COOH , but heteroaromatic bases in Tables 2-6 have quite different strenghts ; thus , for instance , quinoxaline (pK_a 0.56) being much less basic than quinoline

(pK_a 4.94) , it is less protonated under the same reaction conditions , so that it shows higher selectivity in monoalkylation . It should be also considered that the acidity of the medium varies during the reaction , according to the alkylation stoichiometry (eq. 11)



(11)

The steric effect can as well be important in the selectivity of monoalkylation for quinoxaline , in which positions 2 and 3 are particularly reactive towards nucleophilic alkyl radicals . The introduction of an alkyl group in position 2 reduces reactivity for position 3 not only for polar , but also for steric reasons ; the effect increases with the bulk of the alkyl group . Steric effects are also important with quinoline : t-butyl radical only attacks position 2 , the steric hindrance of hydrogen in position 5 preventing it from attacking position 4 , so that a highly selective monoalkylation takes place in any case ; with pyridine this steric effect is not present , and position 4 is as reactive as position 2 towards t-butyl radical .

Compared with alkoxycarbonylation and acylation[3] , in which the selectivity of monosubstitution is mainly due to the decreased basicity and increased lipophilicity of the acylated product , with elimination or minimization of the effects of polar activation , selectivity in monoalkylation is favoured in a two-phase system by the combination of polar deactivation and increased lipophilicity of the alkylated product .

The two-phase system , combined with a suitable acidity of the medium , is therefore a considerable general improvement for substitution of hetero-aromatic bases by nucleophilic carbon-centered radicals , not only for the increased selectivities , but also for the higher efficiency , and it contributes to make this reaction , even more , one of the most important ones for this class of aromatic compounds .

Experimental section

The heteroaromatic bases and the carboxylic acids are commercial products. All the reaction products were identified by comparison (g.l.c. , IR , NMR and MS) with authentic samples , previously[6] prepared by the same procedure in aqueous solution .

General procedure of alkylation - A mixture of heteroaromatic base (2.5 mmol) , carboxylic acid (7 mmol) , $AgNO_3$ (0.2 mmol) , ammonium persulphate and CF_3COOH or H_2SO_4 in the amounts reported in Tables 2-6 in 25 ml of water and 25 ml of chlorobenzene was refluxed for 2h . The aqueous solution was made basic with NaOH , the organic solvent was separated and the aqueous solution further extracted with CH_2Cl_2 . The extract was analyzed by g.l.c. with the same procedures previously[6] utilized ; the reaction products were isolated by flash chromatography on silica gel (6:1 hexane/ethyl acetate) . Some exeriments were carried out at 50°C . The results are reported in Tables 2-6 .

The relative rates were determined by the same procedure , using 2 mmol of pairs of heterocyclic derivatives , 2 mmol of H_2SO_4 and only 0.2 mmol of persulphate , in order to keep conversions low (3-8 %) as necessary for the competitive method to be valid . The results are reported in Table 1 .

References

1 - Reviews in the subject : (a) Minisci , F. Top.Curr.Chem. 1968 , 62 , 1 ; (b) Minisci , F. "Substituent Effects in Radical Chemistry" , H.G.Viehe ed. , Reidel Publ.Co. , Dordrecht , 1986 391-433 ; (c) Minisci , F.; Vismara , E. "Organic Synthesis : Modern Trends" , O.Chizhov ed. , Blackwell Sci.Publ. , 1987 ,229 ; (d) Minisci , F.;Vismara , E.; Fontana , F. Heterocycles 1989, 28 , 489 .

2 - Jaffè , H.H J.Am.Chem.Soc. 1955 , 77 , 4445 .

3 - (a) Minisci , F. ; Vismara , E. ; Fontana , F. J.Heter.Chem. , in press ; (b) Minisci , F. ; Vismara , E. ; Fontana , F. J.Org.Chem , submitted for publ.

4 - Heinisch , G. "Free Radicals in Synthesis and Biology" , F.Minisci ed. , Kluwer Acad.Publ. , Dordrecht ,1989 ,71 and references therein

5 - Bernardi , R. ; Caronna , T. ; Galli , R. ; Minisci , F. ; Perchinunno , M. Tetrahedron Lett. 1973 , 645 .

6 - (a) Minisci , F. ; Bernardi , R. ; Bertini ,F. ; Galli, R. ; Perchinunno , M. Tetrahedron 1971, 27 , 35 ; (b) Bertini , F. ; Galli, R. ; Minisci , F ; Porta , O. Chim.Ind. (Milan) 1972 , 54 , 223 ; (c) Minisci , F. ; Mondelli , R. ; Gardini , G.P. ; Porta , O. Tetrahedron 1972, 28 , 2403 ; (d) Caronna , T. ; Fronza , G. ; Minisci , F. ; Porta , O. ; Gardini , G.P. J.Chem Soc.Perkin II , 1972 , 1477

7 - Minisci , F. ; Vismara , E. ; Fontana , F. ; Morini , G. ; Serravalle, M. ; Giordano , C. J.Org.Chem. 1986 , 51 , 4411.

8 - Bertini , F. ; Caronna , T. ; Galli , R. ; Minisci , F. ; Porta , O. Chim.Ind. (Milan) 1972 , 54 , 425 .