EXTENSION OF DECKER OXIDATION

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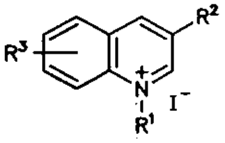
Abstract - Ferricyanide oxidation of 1-substituted 2,4,6-triaryl-, 2,3,4,6-tetraaryl- and 2,3,4,5,6-pentaarylpyridinium salts has been found to be a general approach to the synthesis of substituted pyrroles and/or imidazoheteroaromatics. The regio- and stereoselectivities of the oxidative transformations as well as their possible mechanisms are discussed.

Introduction

More than ten decades have passed after the *Decker's* pioneer discoverings[1a-c] of the ferricyanide oxidation of quaternary heteroaromatic salts like (**1**) (R^1= Me,Et; R^2= H,Br; R^3= Br,Me,NO_2) and **2** (R = Me,Et) leading to corresponding 2-quinolones (**3**) and 2-pyridones (**4**), respectively. This oxidative transformation was further applied to other pyridine-like heterocyclic quaternary salts as reviewed in a number of monographs.[2a-e] It has been recognized that the *Decker* procedure was limited for oxidation of the starting salts in which at least one of the N-neighbouring position is unsubstituted because of the preferred formation of unstable 2-methylene-1,2-dihydropyridines from corresponding methyl derivatives.[2a]



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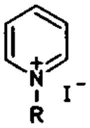

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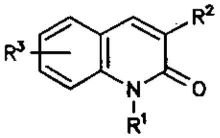

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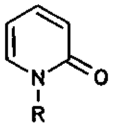

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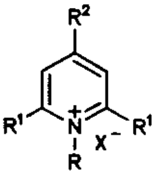
Attempts to oxidize readily accessible 1-substituted 2,4,6-triarylpyridinium salts (5) ($R^1 = R^2 =$ Ph) have appeared in the literature independently from two laboratories. *Katritzky* and coworkers reported 5 to be *unselectively* decomposed to β-amino- and β-aroylaminochalcones or to mixtures of tetraarylpyrroles (6) and 3-oxidopyridinium betaines (7) when H_2O_2-KOH oxidants were used.[3] On the other hand, in our laboratory the ferricyanide oxidation of 5 was found[4] to be useful for the *selective* preparation of pyrrole derivatives (8). Thus, our findings could be considered as a promising and interesting extension of the *Decker* oxidation. Our results[5a-j] in concern with these findings will be discussed in this review.



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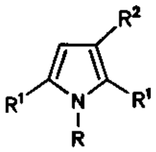

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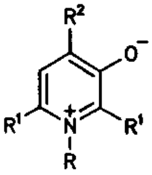

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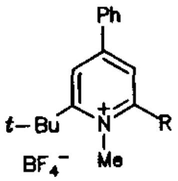
Ring-Contraction to Pyrroles

Ferricyanide oxidation of 1-substituted 2,4,6-triphenylpyridinium salts (5) (R^1= R^2= Ph, X = mainly I) in the presence of potasium hydroxide was generally accompanied by contraction of the pyridinium ring to form 1,2,3,5-tetrasubstituted pyrroles (8) [5a,b,d,g,h] as summarized in Table 1. The oxidation of substrates (5) containing alkyl groups requires a longer reaction time. Similar results were obtained when the 4-phenyl group was replaced by a *t*-butyl group (R^1= Ph, R^2= *t*-Bu).[5b] However, when one *t*-butyl group is attached at 2- or 6-position , this substituent is oxidatively eliminated as *t*-butyl alcohol and salts (9) (R = *t*-Bu, Ph) are transformed to the corresponding 2-pyridones (10).[5b]



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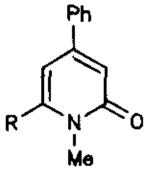

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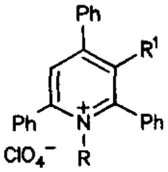

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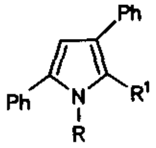

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Lower selectivity and slower oxidation rates have been observed when additional substituent is attached at the 3-position of the pyridine ring Thus, 1,2,3,4,6-pentasubstituted pyridinium salts (11) were converted into two typical pyrrole derivatives (8) (R^1= R^2= Ph) and (12) (Table 2).

In some cases the arising pyrroles were found to be sensitive to further oxidation.[5h] The ferricyanide oxidation of 1-substituted 2,3,4,5,6-pentaphenylpyridinium bromides (13) was observed to be much more slower and of higher selectivity affording exclusively the corresponding pentasubsubstituted pyrroles (14)[5f] as given in Table 3.

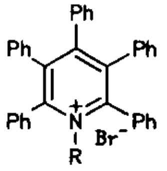
Table 1

Ferricyanide Oxidation of Salts (5)

Starting Salt (5)				Product (8)	Reference
R	R^1	R^2	X	Yield,%	
Me	Ph	Ph	I	71	5a
Et	Ph	Ph	I	80	5a
$HOCH_2CH_2$	Ph	Ph	I	65	5a
Pr	Ph	Ph	I	71	5a
$PhCH_2$	Ph	Ph	I	73	5a
Ph	Ph	Ph	I	75	5a
$4-MeC_6H_4$	Ph	Ph	I	97	5a
$4-FC_6H_4$	Ph	Ph	I	91	5a
$2,4,6-MeC_6H_4$	Ph	Ph	I	72	5a
$4-HOC_6H_4$	Ph	Ph	I	36[a]	5a
Me	Ph	t-Bu	ClO_4	18	5b
2-pyridyl	Ph	Ph	ClO_4	1.2[b]	5g
3-pyridyl	Ph	Ph	BF_4	98	5d
4-pyridyl	Ph	Ph	BF_4	87	5d
3-quinolyl	Ph	Ph	BF_4	77	5d
2-pyrimidyl	Ph	Ph	ClO_4	17[b]	5g
2-thiazolyl	Ph	Ph	ClO_4	11	5h
2-benzthiazolyl	Ph	Ph	ClO_4	52	5h

a) probably as by-product of the corresponding betaine.[3]

b) minor reaction product (see Table 4).



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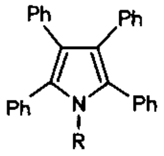

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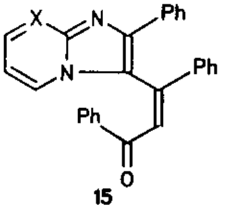

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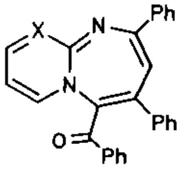

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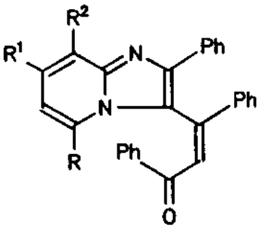
Ring-Transformation to Imidazo[1,2-x]heteroaromatics

2,4,6-Triphenylpyridinium salts (**5**) (R^1= R^2= Ph) possessing some 2-pyridyl-like substituents *R* were found to undergo the ferricyanide oxidation in several minutes giving typical yellow products (**15**) (X = CH,N),[5g] originally considered as **16** (X = CH,N).[5d] The oxidative ring transformation has been extended to prepare other similar derivatives (**17**)-(**19**) as shown in Table 4. Low yield (11%) of the product (**19**) (R = R^1= R^2= Ph) was obtained by the ferricyanide oxidation of the analogous 2,3,4,6-tetraphenylpyridinium salt (**11**) (R = 2-pyridyl, R^1= Ph).[5h] An attempt to obtain a similar product from 2,3,4,5,6-pentaphenylpyridinium salt (**13**) (R = 2-pyridyl) completely failed.[5f]



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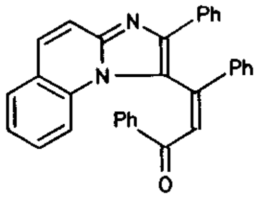

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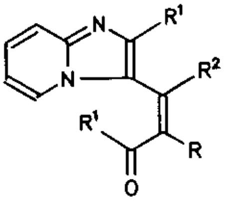

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Mechanistic Aspects

The original *Decker* oxidation has generally been accepted to proceed *via* pseudo-base anions in agreement with kinetic investigations.[6a-c] Analogous initial reaction steps can be also assumed although no similar studies have yet been performed with the discussed oxidative ring-recyclizations. The originally postulated[5b,e] intermediates like **20** (X = $Fe(CN)_6^{3-}$) may be

Table 2[a]

Ferricyanide Oxidation of Salts (11)

Starting Salt (11)		Product (8)	Product (12)	Reference
R	R^1	Yield, %	Yield, %	
Me	Me	23	59	5e
Me	Et	33	30	5e
Me	Ph	40	21	5e
Ph	Me	6	53	5e
Ph	Et	35	63	5e
Ph	Ph	-	60[b]	5e
2-pyridyl	Ph	29[c]	-	5h
2-pyridyl	Ph	-	5[d]	5h

a) reaction times 5-6 h.

b) reaction time 2 h.

c) in addition to (Z)-1,2,4-triphenylbut-2-ene-1,4-dione (10%) and ketone (19) ($R = R^1 = R^2 =$ Ph) (11%).

d) reaction time 5 min.

Table 3[5f]

Ferricyanide Oxidation of Salts (13)

Bromide (13)		Product (14)	Bromide (13)		Product (14)
R	t[a]	Yield, %	R	t[a]	Yield, %
Me	20	69	Ph	30	76
Et	20	70	$4\text{-MeC}_6\text{H}_4$	30	75
Pr	20	68	$4\text{-MeOC}_6\text{H}_4$	30	69
Bu	20	68	$4\text{-EtOC}_6\text{H}_4$	30	73
PhCH_2	20	71	2-pyridyl	30	71

a) reaction time in h.

Table 4

Oxidation of Salts (5) Possessing 2-Pyridyl-like R-Groups

Starting salt (5)				Product		Ref.
R	R^1	R^2	X	Formula	Yield,%	
2-pyridyl	Ph	Ph	ClO_4	**15**(X=CH)	73	5g
2-pyridyl	Ph	Ph	BF_4	**15**(X=CH)	71	5d,g
2-pyridyl	Ph	$4\text{-}Me_2NC_6H_4$	ClO_4	**19**[a]	53	5i
3-methyl-2-pyridyl	Ph	Ph	BF_4	**17**[b]	70	5d
3-methyl-2-pyridyl	Ph	Ph	ClO_4	**17**[b]	77	5j
4-methyl-2-pyridyl	Ph	Ph	ClO_4	**17**[c]	72	5i
6-methyl-2-pyridyl	Ph	Ph	ClO_4	**17**[d]	76	5i
2-quinolyl	Ph	Ph	BF_4	**18**	75	5d,g
2-pyrimidyl	Ph	Ph	ClO_4	**15** (X=N)	41	5g

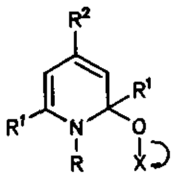
a) $R = R^1 = H,\ R^2 = 4\text{-}Me_2NC_6H_4$.

b) $R = R^1 = H,\ R^2 = Me$.

c) $R = R^2 = H,\ R^1 = Me$.

d) $R = Me,\ R^1 = R^2 = H$

involved in the reaction course to pyrrole systems (**8**), (**12**) and (**14**). In addition, the formation of imidazoheteroaromatics (**15**) and (**17**)-(**19**) requires at least one electrocyclic ring-opening step.[5h] Probable key intermediates (**21**) and (**22**) (X = H or $Fe(CN)_6^{3-}$) take into account as accelerating species.



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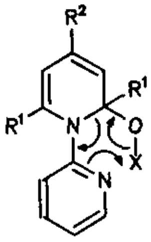

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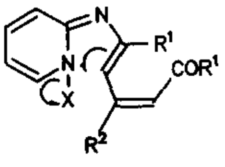

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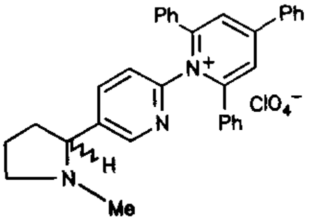
Stereochemical Aspects

Surprising stereochemical consequences of the mentioned ferricyanide oxidations could be attributed to the findings that resulting α,β-unsaturated ketones of type (**19**) are chiral. Thus, crystals of **15** (X = N) are composed of pairs of enanthiomeric molecules[5g] and solutions of **15** (X =CH,N) and **18** in deuteriochloroform contain racemic mixtures of the compounds as proved by optical active nmr shift reagents.[5j] It may be noted that the racemization barriere of ketone (**15**) (X = CH) calculated by the MMX method is rather high (15 kcal.mol^{-1}).[5i] Two diastereoisomers may be formed if another element of chirality is introduced into the skeleton of **19**. In fact, perchlorate (**23**) gave a 1:1 mixture of diastereoisomers (**24**).[5i] Analogously, the borohydride reduction of ketone (**15**) (X = CH) led to a mixture of corresponding diastereoisomeric secondary alcohols.[5j]



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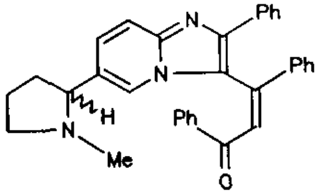

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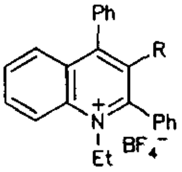
Limitations and Possible Developments

As demonstrated above, our extension of the *Decker* oxidation can be widely applied to various 1-substituted 2,4,6-triaryl- and 2,3,4,5,6-pentaaryl salts (**5**) and (**13**). Thus, the oxidative six-membered ring-contraction to typical products (**8**), (**14**) and (**19**) are of general validity. However, there are two limitations to be considered. The first one comes into account if the 1-substituent *R* is capable of ionization in alkaline medium. The formation of corresponding betaines can be then the competed reaction leading to lower yields[5a,h] or to a complete failure[5h] of the oxidation. The second limitation follows from our attempts[5c] to oxidize quinolinium salts (25) (R = H,Me,Et) which afforded 81-87% of appropriate 2-quinolones (26). Thus, it is not sure whether our approach could be extended to other annelated substrates as used in the original *Decker* oxidation.[1a-c,2a-d]



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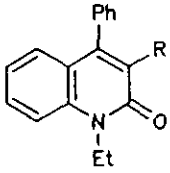

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Possible developments of the ferricyanide oxidation may be expected in further structure variations of the starting quaternary salts (especially to obtain stereochemically, optically or pharmacologically interesting products) and in investigations of modified oxidizing agents and/or reaction conditions. Kinetic and theoretical studies are essential to support the mechanistic considerations.

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