Some Oxidative Transformations of the Carbonyl Compounds and their Azomethine Derivatives*

J. MŁOCHOWSKI

Institute of Organic Chemistry, Biochemistry, and Biotechnology, Technical University of Wrocław, PL-50370 Wrocław

Received 21 July 1997

Oxidative transformations of the aldehydes, ketones, and their azomethine derivatives such as hydrazones, Schiff bases, azines, and oximes are presented and discussed. The oxidants used have been hydrogen peroxide in the presence of selenium compounds as catalysts, peroxycarboxylic acids, and ceric ammonium nitrate. Some of reported reactions have practical value in the synthesis of phenols, esters, carboxylic acids, nitriles, nitrones, oxaziridines, and oxadiazoles.

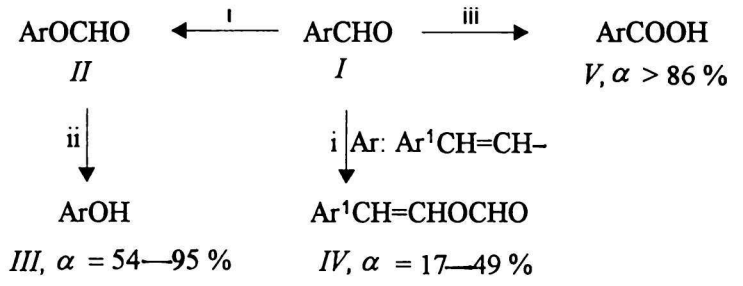
The carbonyl group C=O and azomethine group C=N occur in many organic molecules of fundamental importance, such as aldehydes, ketones, hydrazones, Schiff bases, azines, and oximes [1—4]. Both these groups have two electrons in the π orbital of the double bond. Moreover, the nitrogen or oxygen atoms have a lone pair of electrons being a nucleophilic centre. Other nucleophilic centres, such as *e.g.* oxygen atom in oximes or amine nitrogen atom in hydrazones, can also be present in the molecule and the problem is more complex when carbon and/or nitrogen atom have a substituent interacting with the C=O or C=N group. On the other hand, the carbon atom of carbonyl group has electrophilic character. Depending on the electrophilic or nucleophilic character of the oxygen donor, these centres can be attacked by the oxidant molecule [5]. As a consequence, the results of the reaction should greatly vary depending on the structure of substrate and oxidant used. Although our investigations have been generally directed to the reactions useful in synthesis, some unexpected results have been obtained which required mechanistic interpretation.

It has been known that aldehydes and ketones, oxidized with peroxy acids, such as *e.g.* *m*-chloroperoxybenzoic acid (MCPBA), produce corresponding esters *via* Baeyer—Villiger rearrangement. *Grieco* and coworkers reported that hydrogen peroxide in the presence of small amounts of benzeneseleninic acid could also be used as an oxidant [6]. In our laboratory, several selenium compounds were tested as the catalysts for hydrogen peroxide oxidation of the aromatic aldehydes *I* and aryl methyl ketones to the phenol formates *II* or acetates. The carbonyl compounds having electron-donating substituents in the aromatic ring or having polycondensed aromatic ring system were efficiently oxidized to the phenol esters, particularly when 2-nitrobenzene- or 2,4-dinitrobenzeneseleninic acids or diselenides related to them were used as the catalysts. The formates *II* or acetates were hydrolyzed in one-pot procedure and corresponding phenols *III* were obtained as the final products. As a result, a convenient and cheap method for transformation of aromatic aldehydes having electron-donating substituent or polycondensed ring system into phenols was elaborated [7]. More recently similar results were reported by *Guzman et al.* when selenium dioxide was used as the catalyst [8].

Hydrogen peroxide oxidation of α,β-unsaturated aldehydes, catalyzed by the same organoselenium compounds led to vinyl formates *IV* accompanied by the other compounds being the result of their subsequent reactions [9] (Scheme 1).

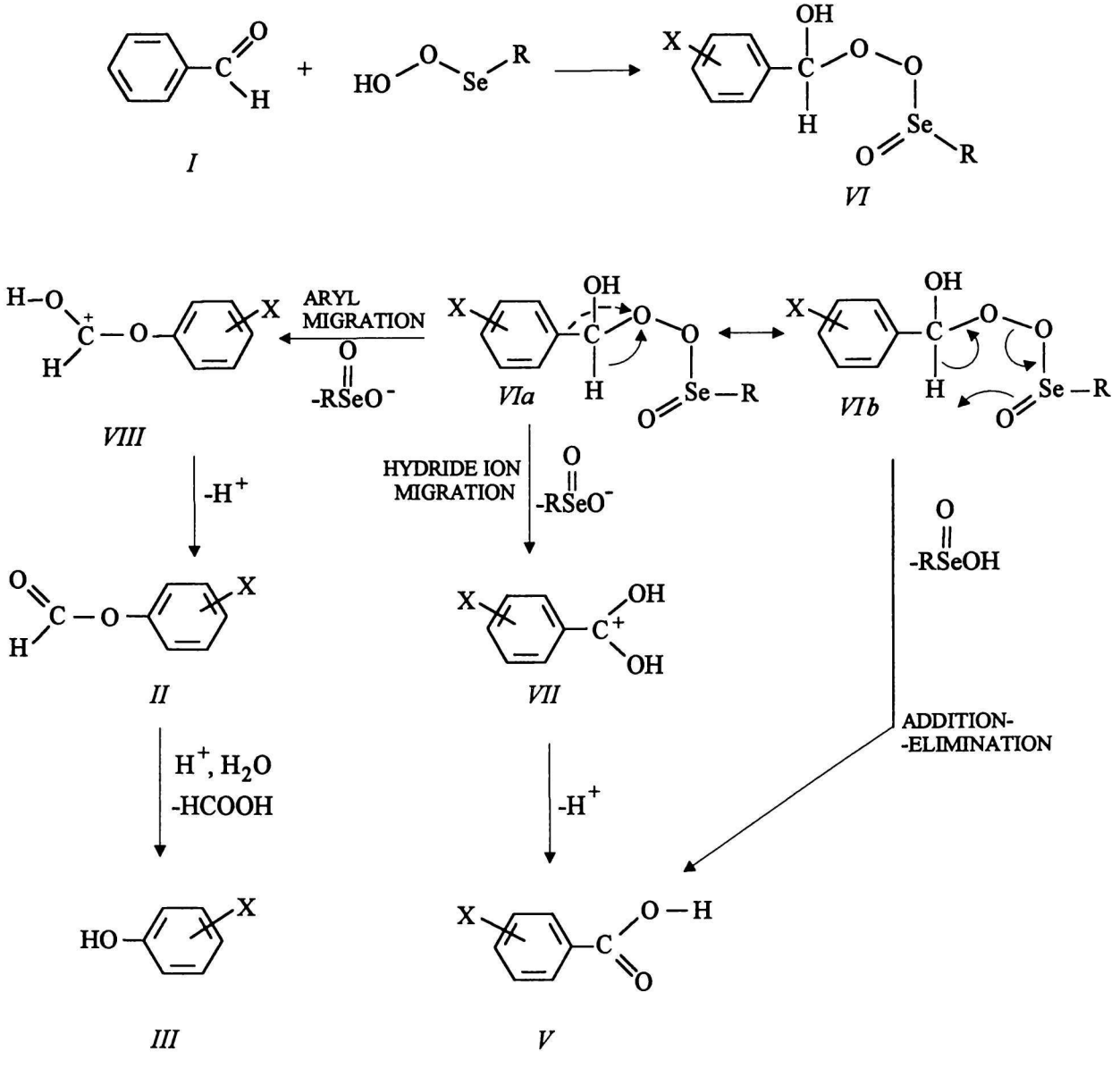
It has been a question what was the role of the selenium catalyst. One could suppose that although stoichiometric oxidant was hydrogen peroxide, the active oxygen donor was peroxyseleninic acid formed *in situ*. Since peroxyseleninic acids were unknown compounds, we synthesized benzeneperoxyseleninic acid and 2,4-dinitrobenzeneperoxyseleninic acid by oxidation of corresponding diselenides with hydrogen peroxide. When we used 2,4-benzeneperoxyseleninic acid as stoichiometric oxidant for oxidation of aromatic aldehydes and ketones as well as for α,β-unsaturated aldehydes, the results were identical as when its precursor 2,4-benzeneseleninic acid was used as the catalyst. It made the evidence that hydrogen peroxide oxidation of the organic substrate in the presence of areneseleninic acid or aryl diselenide proceeded *via* areneperoxyseleninic acid being active oxygen donor.

*Presented at the XXIInd Conference of Organic Chemists at Častá – Papiernička, June 11—13, 1997.



i H_2O_2, $(2\text{-}O_2NC_6H_4Se)_2$ or $2\text{-}O_2NC_6H_4Se(O)OH$; ii KOH, CH_3OH, 25 °C or HCl, CH_3COCH_3, reflux; iii H_2O_2, SeO_2 (cat.)

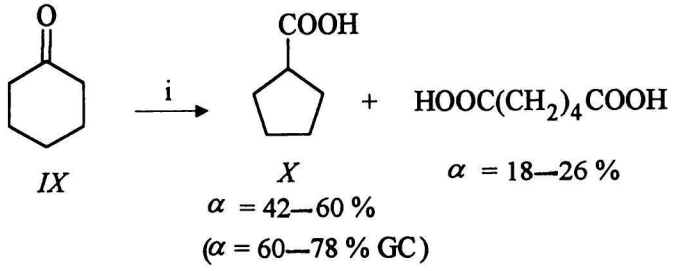
Scheme 1



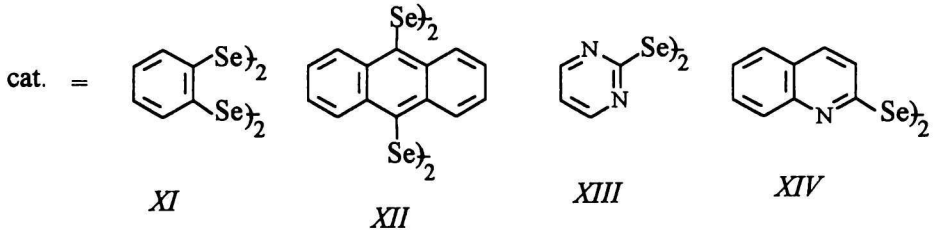
Scheme 2

Thus, organoselenium catalysts play a role of oxygen-transfer agents [10].

Nine years ago *Choi et al.* reported a method for hydrogen peroxide oxidation of the aromatic and



i cat., *t* – BuOH, 45 °C, 15 h



Scheme 3

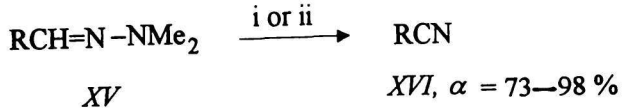
aliphatic aldehydes *I* to carboxylic acid *V*, the catalyst was benzeneseleninic acid [11]. We reinvestigated this reaction using various selenium compounds as catalysts. It was found that the most efficient catalyst was easily available and cheap selenium dioxide. The aromatic aldehydes such as benzaldehyde, 4-methylbenzaldehyde, and those having electron-withdrawing substituents produced arenecarboxylic acids which were isolated in the yields above 86 % [12]. Even when 2- or 4-methoxybenzaldehyde were oxidized, substantial amounts (44—46 %) of acids were obtained, contrary to earlier works [7, 8] where phenols were formed exclusively.

The reaction may be explained according to the mechanism presented in Scheme 2. Its initial step is addition of peroxyseleninic acid to carbonyl carbon atom of the aldehyde. From the adduct *VI* seleninic acid is eliminated and the process is of addition-elimination character. The alternative pathway involves hydride ion migration in the adduct *VI* molecule and then elimination of seleninic anion. The last step is deprotonation of the intermediate carbocation *VII*. When aromatic ring is substituted with electron-donating group, aryl migration to the electrophilic oxygen atom takes place instead of hydride ion migration. From the formed carbocation *VIII* proton is abstracted and formate *II* is produced, and then hydrolyzed to phenol *III*.

It has also been known that cycloalkanones oxidized with hydrogen peroxide in the presence of selenium dioxide underwent Favorski-type rearrangement involving ring contraction and cycloalkanecarboxylic acids have been formed [13, 14]. Although yields of the acids were low and did not exceed 37 %, the method was applied for the synthesis of some natural products [15]. We reinvestigated this reaction using different selenium compounds as the potential catalysts. Among them bisaryl diselenides *XI, XII* and bisazaaryl diselenides *XIII, XIV* were found as the most effective ones. For example, cyclohexanone *IX* oxidized in the presence of bis(2-quinolyl) diselenide was converted into cyclopentanecarboxylic acid *X* in 78 % yield (GC analysis) and isolated in 60 % yield [16] (Scheme 3).

Oxidation of azomethine compounds fascinated us even more than oxidation of carbonyl compounds because it is more complex and some unexpected results have been found. *Smith et al.* [17] oxidized aromatic *N,N*-dimethylhydrazones *XV* using hydrogen peroxide without catalyst. The products were nitriles accompanied by substantial amounts of parent aldehydes and aldazines. Moreover, the reaction was limited to benzaldehyde *N,N*-dimethylhydrazone and to *N,N*-dimethylhydrazones having electron-donating substituent in the aromatic ring. The electron-deficient substrates having NO_2 group or chlorine atom produced complex mixtures where corresponding nitriles could not be identified.

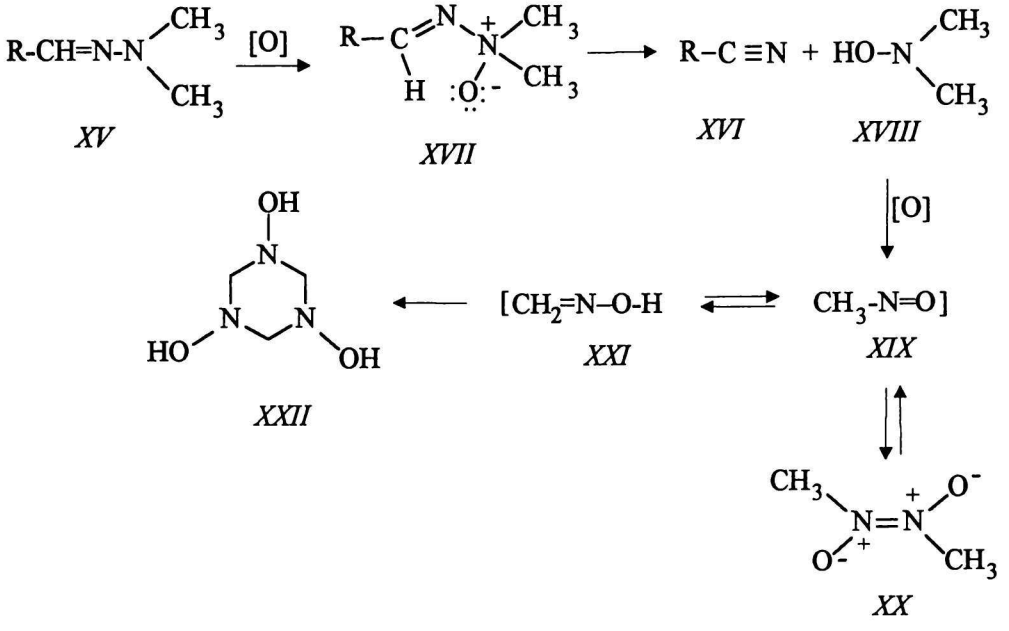
We found that the reaction proceeded with high chemoselectivity giving aromatic nitriles *XVI* in fair yields when selenium dioxide or better 2-nitrobenzeneseleninic acid is used as the catalyst [18]. Most recently excellent results were obtained when catalyst was 2-phenyl-1,2-benzisoselenazol-3(2*H*)-one (ebselen) [19]. Nevertheless, the most versatile oxidant was *m*-chloroperoxybenzoic acid. This reagent was also used for synthesis of aliphatic nitriles, while



R = alkyl, aryl, heteroaryl

i H_2O_2, 2-$NO_2C_6H_4Se(O)OH$ (cat.), MeOH, 20 °C, ii MCPBA, CH_2Cl_2, -10 °C

Scheme 4



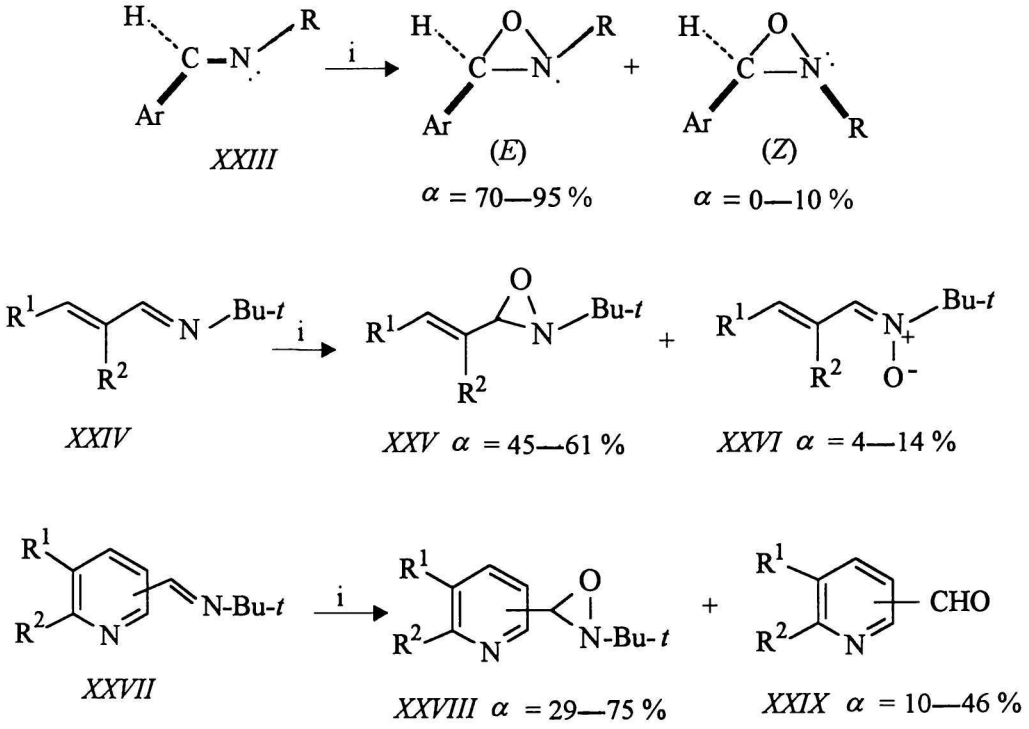
Scheme 5

activated hydrogen peroxide gave worse results, as well as for synthesis of heteroaromatic nitriles having electron-excess or electron-deficient aromatic rings [20, 21] (Scheme 4).

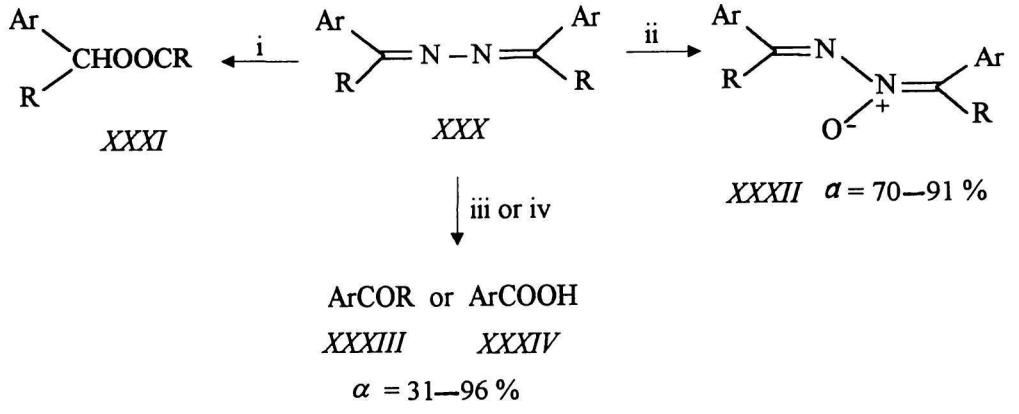
We also made the evidence that conversion of dimethylhydrazones *XV* involved their *N*-oxidation and Cope reaction of *N*-oxide *XVII* to nitrile *XVI*. Although dimethylhydroxylamine *XVIII* itself never was identified as a product of this reaction, we found products of its oxidation nitrozomethane (*XIX*) and its dimer *XX*, as well as its trimer, 1,3,5-trihydroxyhexahydro-1,3,5-triazine (*XXII*) being a product of formaldoxime (*XXI*) trimerization. The elaborated method was also successfully used for conversion of formyl into cyano group in kojic acid derivatives and analogues. These nitriles, being potential substrates for further syntheses, remained generally unknown because they have not been available by classical methods, such as dehydration of oximes since other competitive reactions take place [22] (Scheme 5).

Oxidation of aromatic aldimines *XXIII* with *m*-chloroperoxybenzoic acid led to oxaziridines accompanied by parent aldehydes being the minor products. Although epoxidation of aldimines being a two-step process is not stereospecific, diastereoselectivity was observed when aromatic aldimine had bulky substituent on the nitrogen atom. Aldimines of *E*-configuration having *t*-butyl substituent on the nitrogen atom gave only *E*-oxaziridines because two bulky groups made *Z*-form unfavourable. Aldimines having propyl substituent gave both *E*- and *Z*-oxaziridines although *E*-isomers predominated [23].

High chemoselectivity of the aldimine oxidation was observed when aldimines *XXIV* derived from α,β-unsaturated aldehydes were treated with MCPBA. Oxaziridines *XXV* being the major products were accompanied by small amounts of nitrones *XXVI*. No products of carbon—carbon double bond oxidation such as epoxides or vicinal diols were identified. This demonstrates that in conjugated azadienes the carbonyl—nitrogen double bond or the azomethine nitrogen atom are more reactive toward oxygen donor than the carbon—carbon double bond [24]. When pyridine-derived aldimines *XXVII* were oxidized, oxaziridines *XXVIII* and corresponding aldehydes *XXIX* were produced and formation of corresponding pyri-



Scheme 6

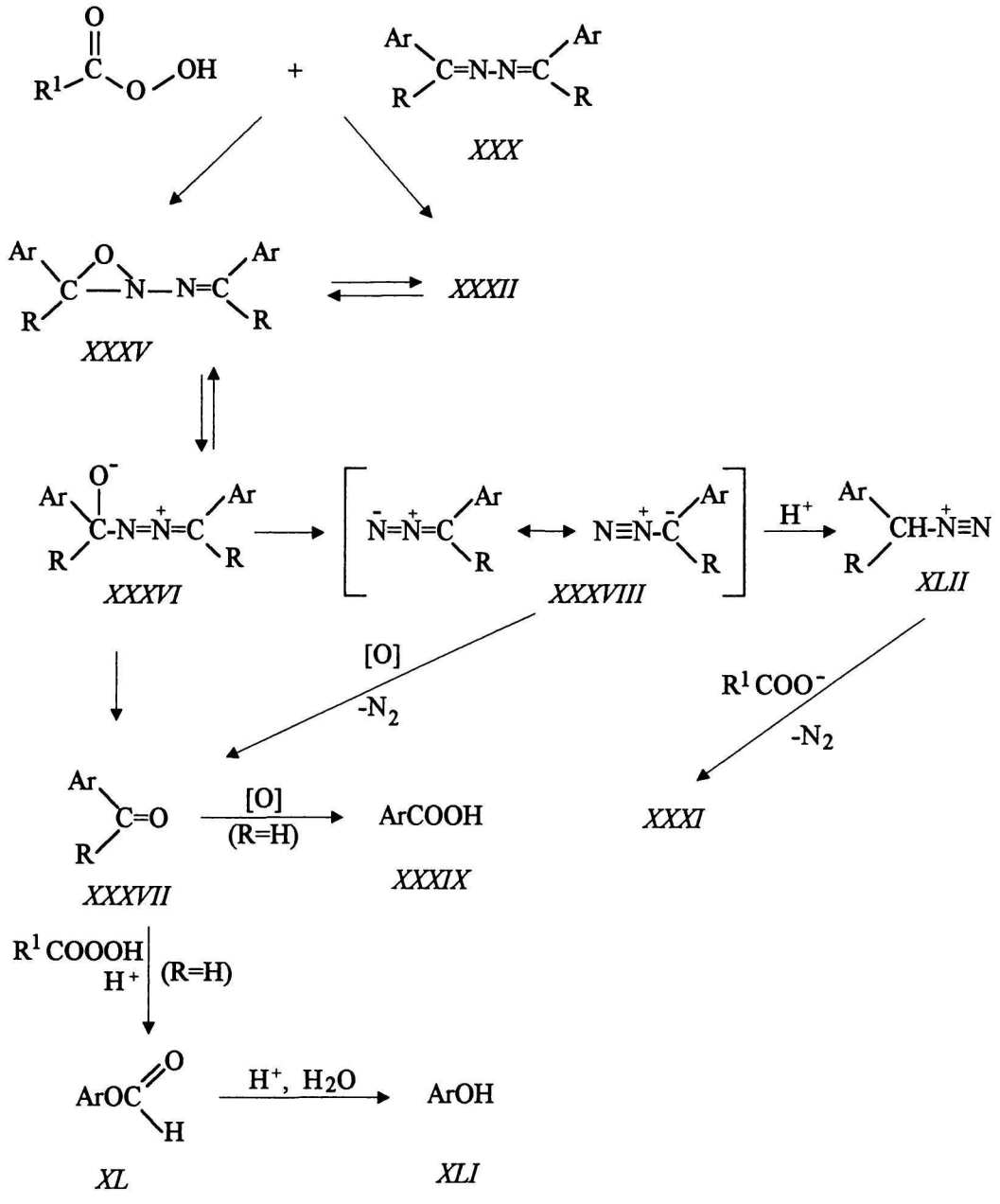


Scheme 7

dine *N*-oxides was not observed [25, 26] (Scheme 6).

Aldazines and ketazines *XXX* are specific group of azomethine compounds where both azomethine groups are linked by the nitrogen—nitrogen bond. Results of their oxidation strongly depended on the oxidant used (Scheme 7). Alkaneperoxy acids oxidize them mainly to carboxy esters *XXXI* accompanied by other products while MCPBA oxidation of aldazines in alkaline medium gives mononitrones *XXXII* [26, 27]. Oxidation of azines with activated hydrogen peroxide or ceric ammonium nitrate (CAN) leads to parent ketones or aldehydes *XXXIII* subsequently oxidized to carboxylic acids *XXXIV* [16, 19].

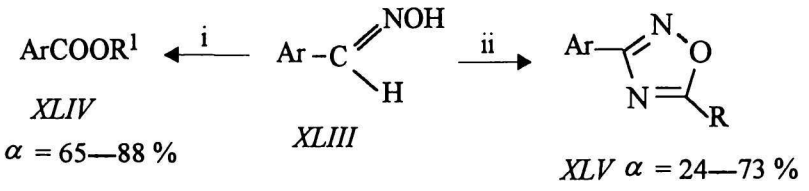
The mechanism of azine oxidative conversion into



Scheme 8

ester *XXXI* was studied in detail and it is presented in Scheme 8. Peroxy acid being an electrophilic oxygen donor oxidizes azine *XXX* to mononitrone *XXXII* which can exist in equilibrium with unstable intermediates *XXXV* and *XXXVI*. Fragmentation of the intermediate *XXXVI* leads to aldehyde or ketone *XXXVII* and diazo compound *XXXVIII*. Aldehyde *XXXVII* can be oxidized to carboxylic acid *XXXIX* or undergoes the Baeyer—Villiger rearrangement giving phenol formate *XL* hydrolyzing to phenol *XLI*. Diazo compound *XXXVIII* is oxidized to carbonyl compound *XXXVII* or it is protonated to cation *XLII* which with carboxylate anion gives ester *XXXI*. Both these reactions compete and the ratio of carbonyl compound *XXXVII* to ester *XXXI* depends on carboxylic acid present in the reaction mixture. When carboxylic acid is weak, such as MCPBA, the carbonyl compound *XXXVII* is a major product.

Aromatic and aliphatic aldoximes *XLIII* or their *O*-methyl ethers can be efficiently converted into the corresponding carboxylic acid esters *XLIV* by treatment of their alcoholic solutions with 30 % hydrogen peroxide in the presence of catalytic amount of 2-nitrobenzeneseleninic acid [28]. CAN oxidation of the aromatic aldoximes in the nitriles used as solvents leads to 5-alkyl-3-aryl-1,2,4-oxadiazoles *XLV*. Most probably, the reaction proceeds *via* 1,3-cycloaddition of the aliphatic nitrile to aromatic nitrile oxide, formed



XLIV
α = 65—88 %

XLIII

XLV α = 24—73 %

i H_2O_2, 2-$O_2NC_6H_4Se(O)OH$ (cat.), R^1OH, reflux,
ii CAN, RCN, 70—75 °C

Scheme 9

in situ, and the possible reaction mechanism has been discussed in Ref. [29] (Scheme 9).

Acknowledgements. This work was partially supported by the Polish State Committee for Scientific Research (Grant No. 3 TO9A 065 08).

REFERENCES

1. Tennant, G., in *Comprehensive Organic Chemistry,* Vol. 2. (Barton, D. H. R. and Ollis, W. D., Editors.) P. 385. Pergamon Press, Oxford, 1979.
2. Henry, P M. and Lange, G. L., in *The Chemistry of Double-Bounded Functional Groups,* Suppl. A, Part 2 (Patai, S., Editor), p. 1067. Interscience, New York, 1978.
3. Pawlenko, S., in *Houben-Weyl Methoden der Organischen Chemie,* Vol. E14b/1, p. 222. Thieme Verlag, Stuttgart, 1990; Unterhalt, B., *ibid.*, p. 289; Dumic, M., Koruncevic, K., Polak, L., and Kolbach, D., *ibid.*, p. 437, 640.
4. Młochowski, J. and Said, S. B., *Pol. J. Chem. 66,* 1901 (1992).
5. Młochowski, J. and Said, S. B., *Pol. J. Chem. 71,* 149 (1997).
6. Grieco, P. A., Yokoyama, Y., Gilman, S., and Ohfune, Y., *J. Chem. Soc., Chem. Commun. 1997,* 870.
7. Syper, L., *Synthesis 1989,* 167.
8. Guzman, J. A., Mendoza, V. Garcia, E., Garibay, C. F., Olivarez, L. Z., and Maldonado, L. A., *Synth. Commun. 25,* 2121 (1995).
9. Syper, L., *Tetrahedron 43,* 2853 (1987).
10. Syper, L. and Młochowski, J. *Tetrahedron 43,* 207 (1987).
11. Choi, J.-K., Chang, Y.-K., and Hong, S. Y. *Tetrahedron Lett. 29,* 1967 (1988).
12. Młochowski, J., Kloc, K., Brząszcz, M., and Maposah, M., unpublished results.
13. Payne, G. B. and Smith, C. W. *J. Org. Chem. 22,* 1680 (1957).
14. Somoda, N. and Tsutsumi, S., *Bull. Chem. Soc. Jpn. 32,* 505 (1959).
15. Bird, C. W. and Cooper, R., *Org. Prep. Proced. Int. 25,* 273 (1993).
16. Giurg, M. and Młochowski, J., unpublished results.
17. Smith, R. F., Albright, J. A., and Waring, A. M., *J. Org. Chem. 31,* 4100 (1966).
18. Said, S. B., Skarżewski, J. and Młochowski, J. *Synthesis 1989,* 223.
19. Młochowski, J., Giurg, M., Kubicz, E., and Said, S. B., *Synth. Commun. 26,* 291 (1996).
20. Młochowski, J., Kloc, K., and Kubicz, E., *J. Prakt. Chem. 336,* 467 (1994).
21. Uher, M., Koreňová, A., Végh, D., Giurg, M., and Młochowski, J., *Khim. Geterotsikl. Soedin. 1995,* 1356.
22. Młochowski, J., Giurg, M., Uher, M., Koreňová, A., and Végh, D., *J. Prakt. Chem. 388,* 65 (1996).
23. Kloc, K., Kubicz, E., Młochowski, J., and Syper, L., *Synthesis 1987,* 1084.
24. Said, S. B., Młochowski, J., and Skarżewski, J., *Liebigs Ann. Chem. 1990,* 461.
25. Młochowski, J., Kubicz, E., Kloc, K., Mordarski, M., Peczyńska, W. and Syper, L., *Liebigs Ann. Chem. 1988,* 455.
26. Młochowski, J., Abdel-Latif, F. F., Kubicz, E., and Said, S. B., *Pol. J. Chem. 67,* 711 (1993).
27. Giurg, M. and Młochowski, J., *Pol. J. Chem. 68,* 2333 (1994).
28. Said, S. B., Skarżewski, J., and Młochowski, J., *Synth. Commun. 22,* 1851 (1992).
29. Giurg, M. and Młochowski, J., *Pol. J. Chem. 71,* 1093 (1997).