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Rapid, efficient, room temperature aromatization of Hantzsch-1,4-dihydropyridines with vanadium(V) salts: superiority of classical technique versus microwave promoted reaction

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ABSTRACT

The aromatization of 1,4-dihydropyridines (1,4-DHPs) employing group 4 (Zr and Hf) and 5 (V, Nb, Ta) elements of periodic system has been studied. The reaction with $VOCl_3$ in dichloromethane at room temperature afforded products, substituted pyridines, in high-to-excellent yield. For the first time, the formation of charge-transfer complexes (CTCs) has been evidenced in preorganization step between 1,4-DHP and oxidant before electron transfer. The CTC has been formed only in neutral solvents such as dichloromethane and is characterized by intensive coloration. The aromatization of 1,4-DHP with V_2O_5 in refluxing acetic acid has found to be superior over microwave promoted reaction in solventless media. The only reasonable explanation was found in polymeric structure of V_2O_5, which slowly transfer energy of microwaves needed for the activation of the reactants. The solvent polarity dependent oxidative dealkylation of 4-*n*-propyl-1,4-DHP has been discovered. Unexpectedly, the reaction in acetic acid afforded only 33% of dealkylated product compared to 91% obtained in dichloromethane under the same reaction conditions.

1. Introduction

Described more than one century ago by Arthur Hantzsch,[1] 1,4-dihydropyridines (1,4-DHPs) have now been recognized as valuable drugs for the treatment of hypertension and other coronary deseases.[2] On the molecular level 1,4-DHP compounds cause vasorelaxation by blocking voltage-operated calcium channel in smooth muscle cells and also by increasing NO release from intact endothelium.[3] Newly synthesized generation of substituted 1,4-DHPs posses other pharmacological activities such as antitumor,[4] bronchodilating,[5] antidiabetic,[6] neurotropic,[7] antianginal[8] amongst others.[9] Some of the representatives such as nifedipine,[10] nicardipine,[11] felodipine (**1**),[12] and amlodipine (**2**)[13] are today some of the best selling drugs used for treatment of hypertension, Figure 1. In recent years Böcker and co-workers have studied the metabolism of Hantzsch-1,4-DHPs and shown that first metabolic step includes aromatization to corresponding pyridine derivatives,[14] which have found its application for the treatment of atherosclerosis and other coronary deseases.[15] The main representative of such type of compounds is cerivastatin (**3**).[15] The metabolism of 1,4-DHPs is catalyzed by the cytochrome P450 (CYP) 3A4 isoform.[14,16] Additionally, during the storage of drugs containing 1,4-DHPs slow oxidation takes pace by the action of air oxygen or UV irradiatiaon.[17] In order to understand this processes the aromatization of 1,4-DHPs has attracted considerable attention from synthetic chemists.

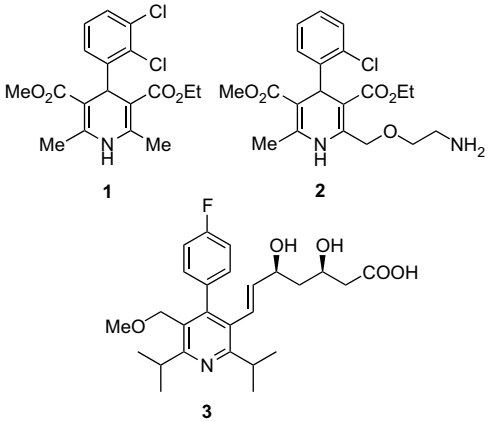

Figure 1.

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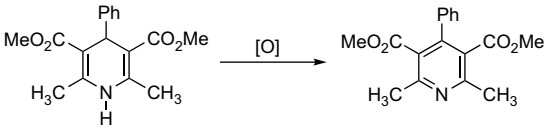
Numerous methods for the aromatization of 1,4-DHPs have been developed for that purpose including the use of metallic salts,[18] non-metallic reagents,[19] catalytic methods[20] among others.[21] Recently, microwave irradiation has been used to accelerate the reaction in solventless media.[22] However, despite a plethora of reagents used for the aromatization of 1,4-DHPs most of them suffer from low selectivity, the use of harsh reaction condition, a lack of selectivity, production of toxic water waste, cumbersome work-up, etc. Moreover, a detailed study of 1,4-DHP aromatization employing high-valent salts of transition metals lack in the literature.

In continuation of our program toward development of milder and more selective methods for the aromatization of 1,4-DHPs,[18t,u] we wish to report a comprehensive study with group 4 (Ti(IV), Zr(IV), Hf(IV)) and 5 (V(V), Nb(V) and Ta(V)) elements of the periodic table.

2. Results and discussion

We began our research with several higher valent metallic salts of groups 4 and 5 elements of the periodic system. In the literature only $Zr(NO_3)_4$ has been used[23] for the aromatization of 1,4-DHPs but from the results it was not clear whether the aromatization took place by the action of Zr(IV) or an equilibrium amount of nitric acid formed by hydrolysis of the salt. Thus, we have decided to test salts with non-oxidizing anions such as $ZrCl_4$, $TiCl_4$, and $HfCl_4$ from the same group of the elements as well as vanadium(V) oxytrichloride ($VOCl_3$), $NbCl_5$, and $TaCl_5$ from group 5 of the periodic table. The 1,4-DHP **4** was used as a model compound in reactions. The preliminary results outlined in Table 1 showed that reaction with stoichiometric amount of $ZrCl_4$ in chloroform as a solvent (entry 2) proceeded selectively at room temperature affording substituted pyridine **5** in almost quantitative yield. In other solvents (entries 3–5) the reaction was also selective suggesting that Zr(IV) is the real oxidant in method employing $Zr(NO_3)_4$ as reagent.[23] As expected the reaction with $TiCl_4$ did not give a trace of the product even at the higher temperatures (reflux). Similar to zirconium(IV), $HfCl_4$ selectively afforded product **5**. However, due to its higher molecular weight the reaction with $ZrCl_4$ has greater preparative value. The stoichiometry of the reactions with $ZrCl_4$ and $HfCl_4$ show that the metals are reduced from oxidation states +4 to +2, which is in agreement with the chemistry of these two metals.[24]

Table 1
Aromatization of 1,4-DHP **5** by different metallic oxidants in various solvents at rt

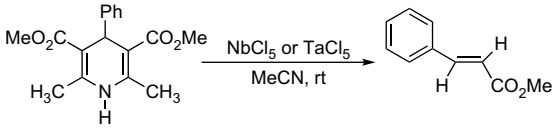


4 **5**

Entry	Oxidant	Solvent	Time (h)	Conv. (%)
1	$TiCl_4$	$CHCl_3$	24[a]	0
2	$ZrCl_4$	$CHCl_3$	72	100 (96)[b]
3	$ZrCl_4$	CH_3CN	24	98
4	$ZrCl_4$	EtOH	192	100 (94)[b]
5	$ZrCl_4$	CH_3COOH	24	95
6	$HfCl_4$	$CHCl_3$	168	100 (91)[b]
7	$HfCl_4$	CH_3CN	216	93
8	$HfCl_4$	CH_3COOH	24	88
9	HfO_2	CH_3COOH	72	90
10	$VOCl_3$	$CHCl_3$	29[c]	100 (99)[b]
11	$VOCl_3$	$CHCl_3$	24[a,d]	98 (90)[b]
12	VOF_3	$CHCl_3$	29	100 (97)[b]
13	V_2O_5	CH_3CN	960	40
14	V_2O_5	CH_3COOH	168	84
15	V_2O_5	CH_3COOH	24[a]	100 (95)[b]
16	NH_4VO_3	EtOH	24	0
17	NH_4VO_3	CH_3COOH	24	100 (96)[b]
18	$NbCl_5$	$CHCl_3$	960	—[e]
19	$NbCl_5$	CH_3CN	504	—[f]
20	$NbCl_5$	CH_3COOH	72	83
21	$TaCl_5$	$CHCl_3$	48	0
22	$TaCl_5$	CH_3CN	312	—[f]
23	$TaCl_5$	CH_3COOH	96	87

[a] The reaction was carried out at reflux temperature.
[b] Isolated yield.
[c] Two equivalents of oxidant were used.
[d] One equivalent of oxidant was used.
[e] The reaction was not selective.
[f] Methyl-*trans*-cinnamate **6** was formed.

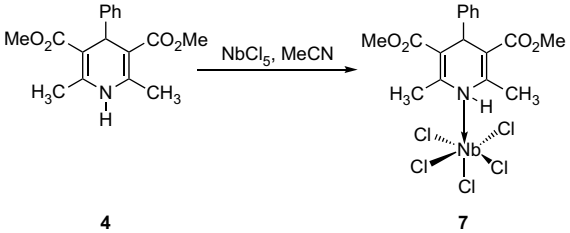
From the fifth group of elements Vanadium(V) salts such as VOF_3 and $VOCl_3$ efficiently and selectively oxidized 1,4-DHP **4** at room temperature in chloroform as solvent. The product was isolated in almost quantitative yield (entries 10–12). Unlike their oxohalides V_2O_5 and NH_4VO_3 as less corrosive V(V) salts were less effective in neutral solvents. However, in acetic acid NH_4VO_3 selectively aromatized 1,4-DHP **4** to give product in excellent yield. The complete conversion of starting material at room temperature employing V(V) salts as oxidants was obtained with 2 equiv suggesting reduction of oxidant to +4 oxidation state. Interestingly, if the reaction was carried out at reflux temperature (chloroform) only 1 equiv was required to reach complete conversion of 1,4-DHP **4**. These findings indicate that V^{4+} is strong enough oxidant at elevated temperature. In comparison to V(V) salts, $NbCl_5$ and $TaCl_5$ showed much lower reactivity and reaction slowly proceeded only in acetic acid as solvent. The conversions of 83 and 87% were obtained in 72 and 96 h, respectively (entries 20 and 23). In acetonitrile both salts afforded less polar side-product isolated after extractive work-up in 5% yield. The structure according to NMR spectra (^1H and ^{13}C NMR, COSY, NOESY, HETCOR, APT) was proved to be methyl-*trans*-cinnamate **6**, Scheme 1.



4 **6**

Scheme 1.

To our knowledge, this type of hydrolysis of 1,4-DHPs has not been described in the literature so far. The formation of **6** probably takes place in coordination sphere of metals, which was concluded from the observation that brown precipitate was formed on treatment of acetonitrile solutions of 1,4-DHP with $NbCl_5$ and $TaCl_5$, Scheme 2. The evolution of hydrogen chloride was observed upon stirring the reaction mixture for several hours. The formation of exclusively methyl-*trans*-cinnamate **6**, without a trace of corresponding cis-isomer probably takes place within the complex **7**



4 **7**

Scheme 2.

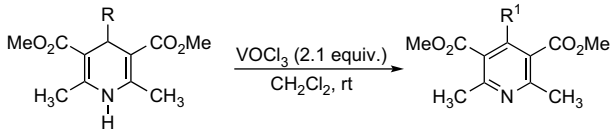
with equatorial position of phenyl ring. Usually, due to the lower energy of the 1,4-DHP **4** the phenyl ring predominantly occupy axial position which is not a favorable position when sterically demanded metal halogenides are present such as in complex **7**.

Of all the salts tested from the groups 4 and 5 periodic system, due to its low molecular weight and high reactivity, $VOCl_3$ was chosen for further investigation on series of substituted 1,4-DHPs. The preliminary results on the model 1,4-DHP **4** showed that reaction with 2 equiv of $VOCl_3$ is, at the beginning of the reaction, very fast and 90% conversion was reached within 1 h. However, the complete conversion was obtained after only 29 h. If the same reaction was carried out with 2.1 equiv of oxidant in dichloromethane as solvent at room temperature 100% conversion was reached within 60 min and the product was isolated in excellent yield. The results outlined in Table 2 indicate that reaction is generally very fast (1–115 min) for all substituted 1,4-DHPs. The yields of crude products of high purity obtained after simple extractive work-up ranged between 88 and 99%. Interestingly, the method is not sensitive to electronic nature and sterical hindrances of substituents present on aromatic ring. Moreover, the compound **19** (entry 13) was almost instantly oxidized to yield product in 94% yield. The derivatives having thienyl, bromothienyl, and furyl substituents, usually poorly reactive 1,4-DHPs and acid sensitive compounds were effectively aromatized to yield products in good yields (entries 19–21). As expected the aromatization of 4-alkyl-1,4-DHPs **9** and **11** having ethyl and isopropyl substituents afforded dealkylation product **29** in almost quantitative yield. Unexpectedly, 4-benzyl-1,4-DHP **10** afforded product of dealkylation contaminated with 2.5% of nondealkylated pyridine **30**. Recently, we have described this phenomena employing $SbCl_5$ as oxidant.[18u] However, the two electron transfer proposed to explain this observation could not be applied in this case due to the fact that V(V) is reduced to V(IV) by one electron transfer. Moreover, the aromatization of 4-*n*-propyl-1,4-DHP **12** (entry 5) afforded 9% of nondealkylated and 91% dealkylated product. If the reaction was performed in acetic acid as solvent instead of dichloromethane a mixture of 67% of **31** and 31% of **29** was obtained. These findings indicate that generally accepted theory of complete dealkylation of 4-alkyl-1,4-DHP employing strong metallic oxidants is no longer acceptable. Our results have was clearly shown that even a polarity of solvent determine the ratio of dealkylation and nondealkylation. In order to explain the obtained results further investigation is required including reexamination of published methods employing metallic oxidants. A detailed and comprehensive study of this work is beyond the scope of this article and will be published in due course.

Although the method employing $VOCl_3$ as oxidant is valuable addition to published methods for the aromatization of 1,4-DHPs due to the fact that substituted pyridines were prepared in mild condition and excellent yield, we have decided to explore V_2O_5 as less corrosive vanadium(V) salt. Moreover, the regeneration of V_2O_5 is much easier to accomplish in comparison to $VOCl_3$. The preliminary results showed that reaction in refluxing acetic acid as solvent gave a product in almost quantitative yield. Therefore, we expected similar results in much shorter reaction times employing microwave irradiation in solventless media.

From the literature, microwave irradiation has intensively studied as effective promoter for the aromatization of 1,4-DHPs[22] as well as many other organic transformations.[25] The reactions were usually completed within a few minutes compared to the several hours needed when conventional heating is employed.[22] Beside V_2O_5 as oxidant other metallic oxides were tested such as MoO_3, GeO_2, HfO_2, and CeO_2, which respective halides or nitrates are capable of reacting with 1,4-DHPs to furnish aromatization products in high yields.[18d,26] The initial experiments on model 1,4-DHP **4** were carried out at 100 °C and power of 150 W under conditions employed for the microwave promoted aromatization of 1,4-DHPs by MnO_2.[18m] Interestingly, even a trace of the product **5** was not obtained with any of oxidants whilst reaction with MnO_2 afforded product in quantitative yield. Under very harsh reaction conditions (180 °C and power of 1000 W) the oxidation with V_2O_5 reached 90% conversion within 30 min (Table 3, entry 3). Under the same reaction conditions MoO_3 gave only 10% of the product (entry 5), whilst GeO_2, CeO_2, and HfO_2 did not react (entries 7–9). Prolonged irradiation caused formation of decomposition products without improvement in the yield. These results clearly indicate that microwave promoted aromatization of 1,4-DHPs compared to conventional heating has no practical value due to lower selectivity and very harsh reaction condition employed to initiate the reaction. The low reactivity of CeO_2, GeO_2, and HfO_2 is probably caused by their polymeric structures.[24] The layered structures of MoO_3 and V_2O_5 allow limited contact between 1,4-DHP molecule and metal cation needed for oxidation process. Contrary to metallic oxides, a high

Table 2
Aromatization of substituted 1,4-DHPs with $VOCl_3$ (2.1 equiv) in CH_2Cl_2 at rt



4, **8-28** **5**, **29-47**

Entry	1,4-DHP	R	Product	R^1	Time (min)	Yield (%)
1	**8**	H	**29**	H	1	98
2	**9**	*i*-Pr	**29**	H	1	96
3	**10**	CH_2Ph	**29**/**30**	H/CH_2Ph[a]	60	99
4	**11**	Et	**29**	H	52	97
5	**12**	*n*-Pr	**29**/**31**	H/*n*-Pr[b,c]	32	95
6	**4**	Ph	**5**	Ph	60	97
7	**13**	*o*-ClC_6H_4	**32**	*o*-ClC_6H_4	80	95
8	**14**	*m*-ClC_6H_4	**33**	*m*-ClC_6H_4	80	90
9	**15**	*p*-ClC_6H_4	**34**	*p*-ClC_6H_4	60	92
10	**16**	*o*-$NO_2C_6H_4$	**35**	*o*-$NO_2C_6H_4$	10	0[d]
11	**17**	*m*-$NO_2C_6H_4$	**36**	*m*-$NO_2C_6H_4$	70	89
12	**18**	*p*-$NO_2C_6H_4$	**37**	*p*-$NO_2C_6H_4$	85	91
13	**19**	*o*-$CH_3C_6H_4$	**38**	*o*-$CH_3C_6H_4$	1	94
14	**20**	*m*-$CH_3C_6H_4$	**39**	*m*-$CH_3C_6H_4$	85	94
15	**21**	*p*-$CH_3C_6H_4$	**40**	*p*-$CH_3C_6H_4$	90	90
16	**22**	2,4-$(CH_3)_2C_6H_3$	**41**	2,4-$(CH_3)_2C_6H_3$	50	95
17	**23**	*m*-$CH_3OC_6H_4$	**42**	*m*-$CH_3OC_6H_4$	75	91
18	**24**	*p*-$CH_3OC_6H_4$	**43**	*p*-$CH_3OC_6H_4$	60	89
19	**25**	2-Thienyl	**44**	2-Thienyl	60	88
20	**26**	2-(5-Br-thienyl)	**45**	2-(5-Br-thienyl)	115	92
21	**27**	2-Furyl	**46**	2-Furyl	60	89
22	**28**	*p*-Ph–C_6H_4	**47**	*p*-Ph–C_6H_4	85	92

[a] According to HPLC a mixture of dealkylated and nondealkylated pyridines was obtained (98.5:2.5).
[b] According to HPLC a mixture of dealkylated and nondealkylated pyridines was obtained (91.0:9.0).
[c] The reaction in acetic acid afforded a mixture of **29** and **31** in ratio of 33.0:67.0.
[d] Decomposition of starting material observed.

Table 3
The aromatization of 1,4-DHP **4** by different metallic oxides under microwave irradiation[a]

Entry	Metallic oxidant	Time (min)	Conv. (%)
1	V_2O_5	10	10
2	V_2O_5	20	40
3	V_2O_5	30	90
4	MoO_3	10	0
5	MoO_3	20	5
6	MoO_3	30	10
7	GeO_2	30	0
8	CeO_2	30	0
9	HfO_2	30	0

[a] At 180 °C and power of 1000 W.

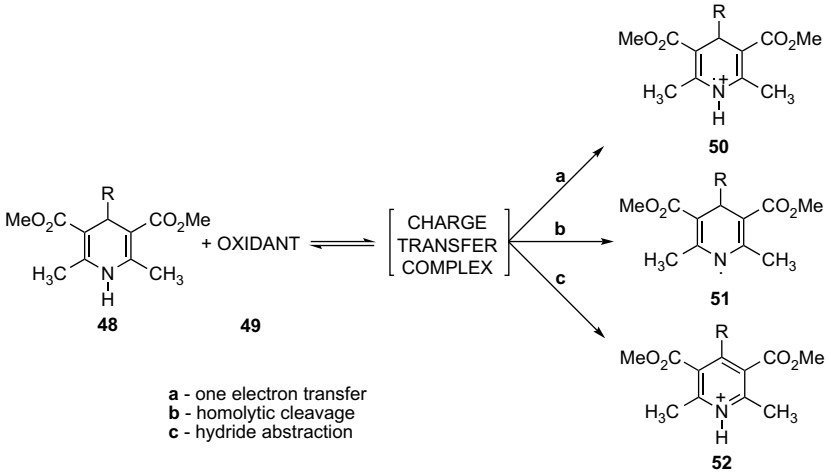
Figure 2. (A) The solution of 1,4-DHP **8** in dichloromethane; (B) charge transfer complex formed upon treatment of solution A with solid $TaCl_5$ under ultrasound; (C) suspension of $TaCl_5$ in dichloromethane.

reactivity of $VOCl_3$ is determined by its monomeric structure, which easily complexes a 1,4-DHP molecule.

Our results have shown that oxidation reactions under microwave irradiation employing metallic oxides as oxidants is not always an alternative to classical technique although the redox potential of metal cations are high enough to initiate the reaction. The structure of oxidant must always be taken into consideration before the reaction is performed in practice.

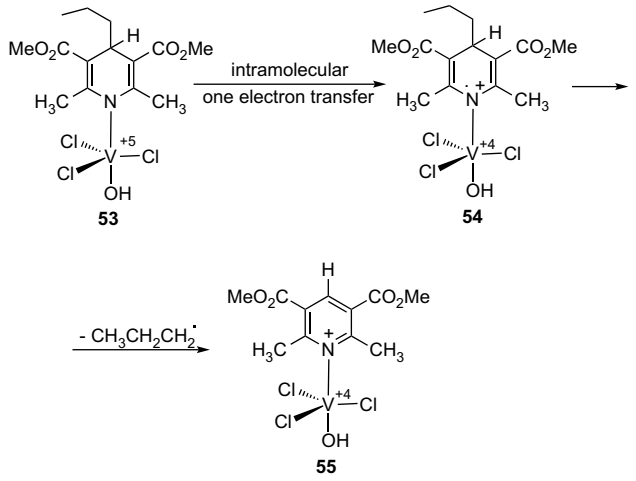
During the preliminary studies of the 1,4-DHP aromatization employing metallic halides as oxidants the color changes have been observed at the beginning and during the reaction. This was explained by the formation of colored complexes characteristic for the salts of the transition metals and organic ligands. However, the treatment of the dichloromethane solution of 1,4-DHP **4** with solid $TaCl_5$ afforded an orange-to-red coloration after several minutes. Interestingly, the formation of color was not observed if chloroform, acetonitrile, and acetic acid were used as solvent. The solvent polarity dependent coloration is not characteristic of metallic complexes with organic ligands. The only reasonable explanation is formation of charge-transfer complex (CTC) between 1,4-DHP and $TaCl_5$. This type of species is well described if electron rich and electron poor organic compounds are mixed in nonpolar solvents such as, for example, 1,2,3,4,5,6-hexamethylbenzene and 1,1,2,2-tetracyanoethylene in dichloromethane solution.[27] Recently, this type of precomplex has been evidenced in the preorganization step of reactants to form products in well-known reactions such as electrophilic aromatic substitution (halogenation, nitration, etc.).[28] Taking into account the stability of CTC and prediction that it was formed between $TaCl_5$ and 1,4-DHP ring rather than phenyl substituents as in **4** we have performed further testings with non-substituted 1,4-DHP **8** in freshly prepared dry dichloromethane. The intensive orange coloration appeared within a few minutes upon addition of solid $TaCl_5$ to solution of **8** in dichloromethane. The ultrasound irradiation accelerates formation of the complex and the intensive red color was obtained almost instantly, Figure 2.

Interestingly, the color immediately disappeared upon treatment of solution **B** (Fig. 2) with a drop of polar solvents such as ethanol or acetic acid. This finding explains why coloration was not observed in chloroform as a solvent although its polarity is similar to dichloromethane. The commercial chloroform contains up to 1% of ethanol as stabilizer and thus formation of charge-transfer complex has been prevented. In order to characterize the complex by UV–vis spectrophotometry incremental concentrations of complex have been prepared according to the literature method.[27] Unfortunately, all attempts to record the spectra failed due to the fact that precipitation of red solid occurred upon standing the 'solution' of complex at room temperature. These findings indicate that in diluted media very small particles of CTC was formed rather than a real solution. In concentrated media the colored precipitate was released from the solvent within a few seconds. Thus formed, the red solid was filtered and its IR spectra were recorded. Unfortunately, fast decomposition of the complex was observed and therefore no significant difference in absorption frequencies was noticed. Despite the inability to spectroscopically characterize the CTC it is undoubtly formed by mixing the solution of 1,4-DHP in dichloromethane and solid $TaCl_5$. Similarly to $TaCl_5$, under the same condition $NbCl_5$ afforded a yellow-to-green dichloromethane solution with the same characteristics as complex with $TaCl_5$. Owing to their slower reactivity (Table 1, entries 18 and 21) the formation of complexes with $TaCl_5$ and $NbCl_5$ were easily noticed. More reactive oxidants such as $VOCl_3$, $ZrCl_4$, and $HfCl_4$ afforded immediate colorations that disappeared within a second or changed to colors characteristic of complex salts. Moreover, even non-metallic oxidants such as molecular iodine and 1,1,2,2-tetracyanoethylene gave characteristic colors due to formation of a CTC with 1,4-DHPs. All of these findings encouraged us to conclude that the first step of the mechanism of aromatization of 1,4-DHP is not, as according to articles dealing with mechanism of 1,4-DHP oxidation, an electron transfer to oxidant but preequilibrium formation of metastable CTC according to Scheme 3. Thus, the CTC is decomposed via three possible paths to give corresponding intermediates, which are in the next steps subsequently transformed to the substituted pyridine product. According to path **a** one electron transfer (OET) from 1,4-DHP **48** to oxidant **49** takes place to give radical cation **50**. This type of the mechanism is characteristic for metallic salts such as CAN,[18d] $Mn(OAc)_3$,[18q] $FeCl_3$,[18r,s] etc. According to path **b** aminyl radical **51** is formed by homolytic cleavage of *N*-nitroso[21a] or *N*-iodo[20g] intermediates. And finally, path **c** includes direct hydride abstraction from 1,4-DHP ring to give substituted pyridine in

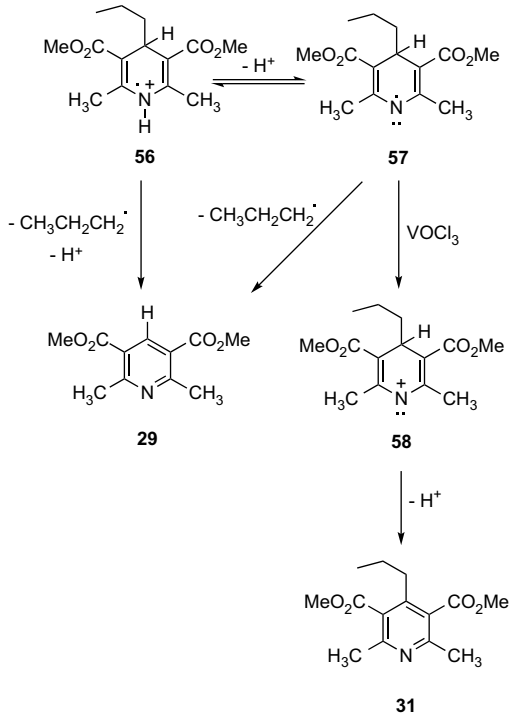


Scheme 3.

protonated form **52**. This is actually two electron transfer to oxidant **49** and is characteristic for electron deficient organic compounds as oxidants such as DDQ[21b] and chloranil. As one could predict the mechanism of $VOCl_3$ promoted aromatization of 1,4-DHPs takes place exclusively according to path **a**, via OET as other metallic salts. However, the results obtained with 4-*n*-propyl-1,4-DHP **12** are not easily explained by this mechanism especially the solvent polarity dependent dealkylation/nondealkylation ratio. In order to explain



Scheme 4.



Scheme 5.

the results obtained in dichloromethane as solvent formation of vanadium complex **53** (Scheme 4) is proposed. This type of vanadium complex with nitrogen ligands is well known in the chemistry of its oxohalides.[24] By intramolecular OET **53** is transformed to radical cation **54** and further rearranged to pyridinium salt **55** with subsequent loss of *n*-propyl radical. In case of 4-aryl-substituted 1,4-DHPs a more stable benzylic radical is produced upon rearrangement and deprotonation of corresponding nitrogen radical cation similar to $Mn(OAc)_3$[18q] and $Pb(OAc)_4$[18t] promoted aromatization of 1,4-DHPs. However, the presented mechanism is characteristic only for the reaction in aprotic solvents (Scheme 4) and is not applicable for the aromatization of 1,4-DHP **12** in acetic acid mostly that explains formation of exclusively dealkylation product, which is not in agreement with experimental results (Table 2, entry 5).

The rapid complexation of $VOCl_3$ by acetic acid rather than 1,4-DHP **12** is the main reason why complex **53** is not formed in that solvent. Thus, more likely radical cation **56** but not **54** is formed by bimolecular contact via OET from 1,4-DHP **12** to oxidant. Furthermore, equilibrium deprotonation of **56** to give radical **57** followed by its rapid quenching with a second equivalent of oxidant yields unstable nitrogen cation **58**, which after deprotonation gives exclusively nondealkylated pyridine **31**, Scheme 5. The dealkylation process takes place either by direct homolytic rearrangement of radical cation **56** or aminyl radical **57** according to the literature.[21a] However, our recent results employing urea hydrogen peroxide adduct as oxidant catalyzed by molecular iodine have shown that corresponding aminyl radical is selectively oxidized to product without the loss of *n*-propyl group.[20g] Therefore, the rearrangement of **56** is the main pathway to dealkylation product **29**.

The aminyl radical as reactive intermediate has not been proposed so far in the literature for the aromatization of 1,4-DHP by metallic salts probably due to the fact that radical cation obtained in the first step is rapidly decomposed to more stable benzylic radical prior to its deprotonation. In case of strong oxidants such as $VOCl_3$ the equilibrium amount of **57** produced by deprotonation is instantly oxidized to give nitrogen cation **58**, which upon second deprotonation produces nondealkylated product **31**.

3. Conclusions

Vanadium oxytrichloride acts as an efficient and selective oxidant for room temperature aromatization of substituted 1,4-DHPs. The products of high purity were isolated in high-to-excellent yield. For the first time it was shown that aromatization of 1,4-DHPs with V_2O_5 in refluxing acetic acid is more efficient method versus microwave promoted reaction in solventless media. The red coloration obtained upon addition of solid $TaCl_5$ to dichloromethane solution of 1,4-DHP **8** have been explained by charge-transfer complex (CTC) formed in preorganization step prior to electron transfer to oxidant. Beside $TaCl_5$ the formation of CTCs have also been noticed employing other metallic salts such as $NbCl_5$, $HfCl_4$, $ZrCl_4$, etc. The influence of solvent polarity on dealkylation/nondealkylation of 4-*n*-propyl-1,4-DHP **12** has been described. The possible explanation of the results has been provided by study of reaction mechanism and includes rapid oxidation of aminyl radical **57** formed by equilibrium deprotonation of radical cation **56** prior to its rearrangement and loss of alkyl substituents.

4. Experimental section

4.1. General

All IR spectra were recorded on a Perkin–Elmer Spectrum One spectrometer. ^1H NMR and ^{13}C NMR were recorded on a Bruker 600 for $CDCl_3$ solutions, and shifts are given in parts per million downfield from TMS as an internal standard. HPLC analyses were performed with a Thermo Separation Products (San Jose, USA) instrument equipped with vacuum degasser SCM 1000, quaternary gradient pump P 4000, autosampler AS 3000, scanning UV/VIS detector UV 3000 HR, and ChromQuest 251 software. TLC analyses were performed on Merck's (Darmstadt, Germany) DC-alufolien

with Kieselgel 60_{254}. Melting points were determined using a Büchi B540 instrument. Elemental analyses were performed at the Central Analytical Service (CAS) at Ruđer Bošković Institute. Microwave irradiation promoted reactions were carried out in Milestone MLS-1200 pyro oven. All chemicals and solvents were purchased from Aldrich and Merck-Darmstadt. The 1,4-DHPs have been prepared according to modified Hantzsch methods.[20g,18t,29–31] All products of aromatization are known in the literature and were fully characterized by a comparison with authentic samples (melting point) and their NMR (^{1}H, ^{13}C) and IR spectra.[20g]

4.2. Reaction of 2,6-dimethyl-3,5-dimethoxy-carbonyl-1,4-dihydropyridine (4) with $NbCl_5$ in acetonitrile at room temperature

To a solution of 1,4-DHP (**12**, 6 mmol; 1,86 g) in acetonitrile (30 mL) at room temperature, $NbCl_5$ (6 mmol, 1.62 g) was added at once. The resulting suspension was stirred at room temperature for 18 days. After that to the reaction mixture were added water (30 mL) and dichloromethane (30 mL). The phases were separated and the aqueous phase was additionally extracted with dichloromethane (3×20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated to dryness. The residue was triturated with diisopropylether (50 mL), stirred at room temperature for 24 h, and filtered. The brown crystals were washed with two portions of diisopropylether (2×5 mL). The mother liquor was evaporated to dryness and the residue was suspended in *n*-hexane (50 mL) and stirred at room temperature for 12 h. The inorganic crystals were filtered and washed with *n*-hexane (2×5 mL). The organic extracts were gathered and evaporated to dryness. The oily residue was purified by PTLC on silica gel plates using dichloromethane as eluent. The fraction with R_f=0.55 was extracted with dichloromethane (50 mL) and evaporated to dryness to give **6**; 50 mg (5.2%) as yellow oil. IR (KBr): ν=3028, 2991, 2947, 1698, 1679, 1496, 1451, 1440, 1332, 1283, 1260, 1185, 1074, 1039, 1029, 1016 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ=3.81 (t, 3H, OC*H*$_3$), 6.45 (d, 1H, C*H*, *J*=16.0 Hz), 7.38–7.39 (m, 3H, arom.), 7.51–7.53 (m, 2H, arom.), 7.70 (d, 1H, C*H*, *J*=16.0 Hz); ^{13}C NMR ($CDCl_3$): δ=51.6, 117.8, 128.0, 128.8, 130.2, 134.3, 144.8, 167.3. Anal. Calcd for $C_{10}H_{10}O_2$: C, 74.06; H, 6.21. Found: C, 74.2; H, 6.4.

4.3. General procedure for the aromatization of 1,4-DHPs by $VOCl_3$ in dichloromethane at room temperature

To a solution of 1,4-DHP derivatives (**4**, **8**–**28**, 1 mmol) in dichloromethane (10 mL) $VOCl_3$ was added at once (2.1 mL, 2.1 mmol, 1 M solution in dichloromethane). The reaction mixture was stirred at room temperature for the time indicated in Table 2. After that to the reaction mixture was added water (15 mL) and the pH of water layer was adjusted to 7 with solid $NaHCO_3$. The phases were separated and the aqueous phase was additionally extracted with dichloromethane (2×10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated to dryness. The crude products were chromatographed on silica gel column eluting with dichloromethane/ethyl acetate (9:1) to give products of purity >99%.

4.4. General procedure for the aromatization of 1,4-DHPs with metallic oxides under microwave irradiation

To a solution of 1,4-DHP **4** (1.50 g, 5 mmol) in dichloromethane (20 mL) was added the corresponding metallic oxide (10 mmol, V_2O_5; 5 mmol, MoO_3; 10 mmol, CeO_2; 5 mmol, HfO_2; 5 mmol, GeO_2). After stirring at room temperature for 15 min, the suspension was evaporated to dryness and dried in vacuum to constant weight. Thus obtained adsorbed 1,4-DHP was irradiated in microwave oven (180 °C and power of 1000 W) for the times indicated in Table 3. The product was extracted with dichloromethane (3×20 mL) and analyzed by HPLC to determine the conversion of the reaction.

4.5. Charge-transfer probes

To a solution of corresponding 1,4-DHPs in dry dichloromethane[27,28] metallic halide was added ($TaCl_5$, $NbCl_5$, $HfCl_4$, $ZrCl_4$) at once. The suspension was stirred at room temperature to furnish characteristic coloration. The same test was performed under ultrasound sonification to yield more intensive colors in shorter time (Fig. 2).

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