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Remarkably fast and selective aromatization of Hantzsch esters with $MoOCl_4$ and $MoCl_5$: A chemical model for possible biologically relevant properties of molybdenum-containing enzymes

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ABSTRACT

Mo(VI) and Mo(V) salts both react selectively with Hantzsch esters to produce substitute pyridines in good-to-excellent yield (75–99%). The remarkable reactivity and selectivity of $MoOCl_4$ under reflux of acetonitrile and $MoCl_5$ in dichloromethane at room temperature encouraged us to propose that molybdenum-containing enzymes (such as xanthine or aldehyde oxidase) also participate to some degree in the metabolism of 1,4-dihydropyridine drugs in the liver analogous to NADH in the respiratory chain.

As one of the most important transition elements, molybdenum (and in some cases tungsten) is an essential microelement for plants, animals and microorganisms.[1,2] However, the use of molybdenum by biological systems was not recognized until the 1930s when Bortels first reported that molybdenum (and vanadium) acted as a catalyst in the fixation of nitrogen by *Arthrobacter chroococcum*.[3] Almost 60 years ago,[4] molybdenum was identified as the 'xanthine oxidase factor' and today it has been discovered in a variety of enzymes.[2a] Each enzyme contains a mononuclear Mo site with one or two unusual pterin-ene-dithiolate ligands and, usually, one or more oxo groups in the molybdenum co-ordination sphere.[5] The molybdenum center in these enzymes, coordinated by the variety of structurally similar ligands,[1,6] is designated as Moco (molybdenum-containing cofactor) in Figure 1.

In humans, only four families[7] of molybdenum-containing enzymes are known and they are classified by the type of biochemical transformations they execute. Aldehyde oxidase (EC 1.2.3.1), xanthine oxidase (EC 1.2.3.1), xanthine dehydrogenase (EC 1.2.1.37) and sulphite oxidase (EC 1.8.3.1) are some of the most important enzymes in organisms with molybdenum-enzyme defficient biological systems.[8] Of all enzymes, those from xanthine oxidase-dehydrogenase families are particularly important because they act as drug-metabolizing enzymes[9] and are key enzymes in biotransformations of xenobiotics.[10]

The typical substrates for xanthine as well as aldehyde oxidases are organic compounds with electron-deficient sp^2-hybridized carbon atoms mostly present in heterocycles such as purines, pyrimidines, imines, etc.[11] This is in sharp contrast to cyctochrome P450 (iron-containing heme cofactor, Fig. 1) whose substrates are mainly compounds with electron rich carbon atoms such as alkanes, amines, esters, ethers etc.[12] Therefore, it is believed that good substrates for molybdenum-containing enzymes tend to be poor substrates for cytochrome P450 and vice versa.[13] The organic compounds derived from the six membered nitrogen-containing heterocycles, 1,4-dihydropyridines (1,4-DHPs), have been recognized as valuable drugs for the treatment of hypertension and other coronary diseases.[14] On the molecular level, 1,4-DHPs cause vasorelaxation by blocking voltage-operated calcium channels in smooth muscle cells and also by increasing NO release from intact endothelial cells.[15] Newer generations of substituted 1,4-DHPs possess other pharmacological activities such as: antitumor,[16] bronchodilating,[17] antidiabetic,[18] neurotropic[19] and antianginal,[20] amongst others.[21] The oxidation (aromatization) of 1,4-DHPs into the corresponding pyridines is one of the main metabolic pathways of these drugs. This process is catalyzed by the cytochrome P450 (CYP) 3A4 isoform.[22] Moreover, during the storage of drugs containing 1,4-DHPs, slow oxidation takes place by the action of air oxygen or UV irradiation[23] to furnish the same product—substituted pyridine.

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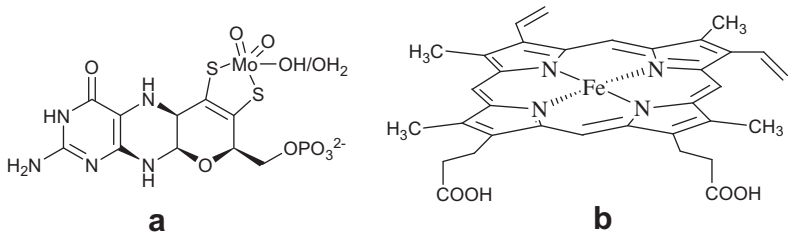


Figure 1. Molybdenum-containing cofactor (Moco) in xanthine oxidase (**a**) and iron-containing cofactor (Heme **b**) in cytochrome enzymes.

In order to better understand the mechanism of the aromatization of 1,4-DHPs, a plethora of chemical oxidants have been studied such as metallic salts,[24] non-metallic reagents[25] and catalytic methods[26] amongst others.[27] Some methods have been designed to mimic the natural biological processes[26f,28] while others have been developed mainly for the preparation of substituted pyridines used as the reference standard to study the metabolism of new drug candidates or as the standard to determine the purity of commercial 1,4-DHP drugs.[24e–g]

In continuation of our ongoing research program directed toward the development of milder and more selective models for the aromatization of 1,4-DHPs,[24e–g,26e,26f] we decided to study transition metals in higher oxidation states selected from groups 3–12 of the periodic table of elements. This was due to the fact that metal ions such as iron, molybdenum, tungsten, vanadium, etc., are usually found in the active site of many enzymes.

Herein, we wish to report a comprehensive study of the reaction performed with some representatives of group 6 (Mo(VI), W(VI)) and 7 (Mn(VII), Re(VII)) elements of the periodic table and the discovery of new, rapid and selective aromatization of 1,4-DHPs. Although chromium(VI) salts such as CrO_3 and a variety of chromates[29] produced good results in the aromatization of 1,4-DHPs, the fact that most of the Cr(VI) salts are highly carcinogenic makes these methods rather unattractive and therefore, Cr(VI) salts (eq CrO_2Cl_2) were not included in our study. To our knowledge, the salts of the other two members of group 6 (Mo and W) have not been used so far for the aromatization of 1,4-DHPs whilst use of Mo and W salts in other types of transformations in organic synthesis is well described in literature.[30] This is particularly the case with $MoCl_5$ whose synthetic potential was recognized by Waldvogel and coworkers in the oxidative dimerization of arenes to substituted biaryls and thiaanthracenes.[31]

We began our study with $MoOCl_4$, MoO_3, $MoCl_5$, WCl_6, $KMnO_4$ and Re_2O_7 on a simple model reaction (Scheme 1) and the obtained results are outlined in Table 1.

Unexpectedly, the reaction with Re_2O_7 did not furnish traces of expected product even after prolonged heating under reflux of acetic acid (Table 1, entry 13). This observation shows a sharp contrast to the reaction with $KMnO_4$, which resulted in 100% conversion after only 15 min at room temperature (Table 1, entry 12). This difference in reactivity can be attributed to the structure of these salts. Rhenium oxide (Re_2O_7), unlike $KMnO_4$, exists in polymeric structure (infinite array of alternating tetrahedral ReO_4 and ReO_6 octahedra)[32] thus preventing the contact of the metal cation with

Table 1
Aromatization of 1,4-DHP **1** by stoichiometric amount of different metallic oxidants in various solvents

Entry	Oxidant	Solvent	Time (h)	Conv.[a] (%)
1	$MoOCl_4$	CH_2Cl_2	24	92
2	$MoOCl_4$	Toluene	24	—[b]
3	$MoOCl_4$	CH_3COOH	24	—[b,c]
4	$MoOCl_4$	CH_3CN	24	93
5	$MoCl_5$	CH_3CN	48	100
6	$MoCl_5$	CH_2Cl_2	96	100
7	$MoCl_5$	CH_3COOH	168	—[b]
8	MoO_3	CH_3COOH	240	0 (90)[c]
9	WCl_6	CH_2Cl_2	72	0
10	WCl_6	CH_3CN	96	—[d]
11	WCl_6	CH_3COOH	22	97
12	$KMnO_4$	CH_3COOH	0.25	98
13	Re_2O_7	CH_3COOH	24	0 (0)[c]

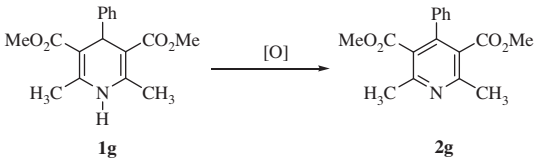
[a] Determined by TLC analysis.
[b] Low selectivity.
[c] The reaction was carried out at reflux temperature during 96 h.
[d] Traces of the product.

a 1,4-DHP molecule. Similar behavior in chemical reactions of other metal oxides such as V_2O_5, MoO_3, CeO_2, HfO_2 and GeO_2 have recently been described.[24g]

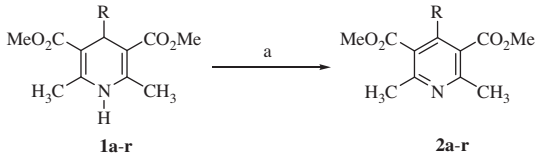
The reaction with 2 equiv of $MoOCl_4$ or $MoCl_5$ smoothly furnished product **2g** at room temperature with acetonitrile or dichloromethane as solvents (Table 1, entries 1, 4–6) whereas, in toluene and acetic acid, the reaction was sluggish and non-selective. Interestingly, tungsten hexachloride (WCl_6) proved to be much a weaker oxidant than Mo(VI) and Mo(V), with reaction only taking place under reflux of acetic acid (Table 1, entry 11). A similar result was obtained with MoO_3 which slowly furnished **2g** in 90% yield after 96 h (Table 1, entry 8) and this was predominantly due to its polymeric structure similar to Re_2O_7 as well as other metallic oxides.

The obtained results encouraged us to further explore $MoOCl_4$ and $MoCl_5$ as oxidants for the efficient aromatization of 1,4-DHPs, Scheme 2. To increase the conversion rate of reactants, a slight excess of oxidants were used (2.1 equiv compared to 2 equiv in preliminary work).[33]

The reaction of **1g** with $MoOCl_4$ was significantly accelerated under reflux of acetonitrile and was completed within a few minutes (Table 2, entry 7) compared to 24 h at rt (Table 1, entry 4). The other representatives of the substituted 1,4-DHPs, bearing a variety of substituents on positions 4 in the 1,4-DHP ring (**1a–r**), were



Scheme 1. The aromatization of 1,4-DHP **1** by variety of oxidants in different solvents.



Scheme 2. Reagents and conditions: a $MoOCl_4/CH_3CN$/reflux or $MoCl_5/CH_2Cl_2$/st.

Table 2
Aromatization of 1,4-DHPs by $MoOCl_4$ (2.1 equiv) at reflux in acetonitrile

Entry	1,4-DHP	*R*	*t*[a] (min)	Yield[b] (%)
1	**1a**	H	1	90
2	**1b**	Me	15	76[c]
3	**1c**	Et	1	75[c]
4	**1d**	*i*-Pr	15	83[c]
5	**1e**	*n*-Pr	10	83[c]
6	**1f**	CH_2Ph	15	86[d]
7	**1g**	Ph	3	93
8	**1h**	*p*-$NO_2C_6H_4$	5	99
9	**1i**	*m*-$NO_2C_6H_4$	1	98
10	**1j**	*o*-$MeOC_6H_4$	15	92
11	**1k**	*m*-$MeOC_6H_4$	5	83
12	**1l**	*p*-ClC_6H_4	10	92
13	**1m**	*o*-ClC_6H_4	15	75
14	**1n**	*p*-MeC_6H_4	10	77
15	**1o**	*m*-MeC_6H_4	1	83
16	**1p**	2-Thienyl	1	86
17	**1q**	2-Furyl	1	90
18	**1r**	2-(5-Br-thienyl)	20	89

[a] Determined by TLC analysis.
[b] Isolated yield.
[c] Isolated as a mixture with dealkylated product **2a**.
[d] Isolated as a sole dealkylated product **2a**.

also efficiently oxidized to give substituted pyridines (**2a**–**r**). The results outlined in Table 2 indicate that the reaction with $MoOCl_4$ is generally very fast (1–20 min) for all 1,4-DHPs and to our knowledge, is one of the fastest for this type of reaction performed under conventional heating.

The yields of crude products of high purity obtained after simple extractive work-up ranged between 72–99%.[34,35] Both electron-withdrawing (Table 2, entries 8–9, 12–13) and electron-donating substituents (Table 2, entries 10–11, 14–15) on the aromatic ring were well tolerated and had no significant effect on the reaction rate.

Unlike $MoOCl_4$, the reaction employing $MoCl_5$ was largely dependent on the electronic nature of substituents on the 1,4-DHP ring (Table 3). Although, performed at room temperature, the reaction is less selective and only of practical importance for acid-insensitive compounds (Table 3, entries 5, 6 and 9). Interestingly, the presence of electron-withdrawing bromine on the thiophene ring deactivated the 1,4-DHP **1r** to allow selective reaction and isolation **2b** in good yield (Table 3, entry 9). The main reason for poor selectivity of the reaction with $MoCl_5$ is probably its action as an oxidant in the oxidative coupling of electron-rich aromatic compounds to the corresponding biaryls.[31h] Although we have not been able to isolate any such side-products in reaction, we believe that this is one of the main pathways leading to the decomposition of 1,4-DHP **1f** and **1p** (Table 3, entries 4 and 7). As expected, the aromatization of 1,4-DHP **1d** bearing isopropyl substituent afforded a dealkylated product **1a** whereas **1e** furnished a mixture of dealkylated and non-dealkylated products (Table 3, entries 2 and 3).

Table 3
Aromatization of 1,4-DHPs by $MoCl_5$ (2.1 equiv) in CH_2Cl_2 at rt[36]

Entry	1,4-DHP	*R*	*t* (min)	Yield (%)
1	**1a**	H	1	75
2	**1d**	*i*-Pr	5	90
3	**1e**	*n*-Pr	1080	—[a]
4	**1f**	CH_2Ph	10	—[b]
5	**1g**	Ph	1440	97[c]
6	**1m**	*o*-Cl-C_6H_4	1440	92
7	**1p**	2-Thienyl	60	—[b]
8	**1q**	2-Furyl	20	—[c]
9	**1r**	2-(5-Br-thienyl)	240	80

[a] Isolated as a mixture with **2a** (8:2).
[b] Decomposition.
[c] Reaction not selective.

An interesting result was obtained during the aromatization of a variety of 4-alkyl-1,4-DHPs with $MoOCl_4$ as an oxidant (Table 4). Only **1f** (*R* = CH_2Ph) afforded exclusively **2a** as a result of complete dealkylation whereas **1d** (*R* = *i*-Pr) furnished a trace of non-dealkylated product **2d** (Table 4, entry 3). In case of 4-*n*-propyl-1,4-DHP **1d,** an expected mixture of products **2a** and **2d** was isolated similar to other literature metallic salts applied in the same reaction.[24g] Surprisingly, the predominant removal of the ethyl group was also obtained (Table 4, entry 2), which was not the case for most of the literature methods.[24] An even more interesting result was obtained with 4-methyl-1,4-DHP **1b,** which in reaction with $MoOCl_4$, afforded a mixture of dealkylated and non-dealkylated products containing 16% of **2a**. To our best knowledge, this is the first example of a partial dealkylation of the 1,4-DHP carrying methyl group at position 4 of 1,4-DHP ring.

As a result of the experimental behavior of 1,4-DHP bearing alkyl groups, a plausible free-radical mechanism is being proposed similar to other metallic salts as oxidants[24e–g] in Scheme 3.

In the first step, the precomplexation of 1,4-DHP **1g** with $MoOCl_4$ gives molybdenum(VI) complex **3**, which in turn rapidly decomposes by intramolecular single electron transfer (SET) to molybdenum(V) complex of nitrogen radical cation **4**. The spontaneous rearrangement of **4** to more stable benzylic radical **5** is characteristic only for 1,4-DHPs bearing alkyl groups whereas alkyl substituents dependant upon the stability of alkyl radicals follow the mechanism recently described for $VOCl_3$ as well as for some other oxidants.[24f] In the next step, if a second equivalent of oxidant ($MoOCl_4$) is present, a rapid transfer of a second electron to the oxidant furnishes product **2g** as a molybdenum(V) complex. If only 1 equiv of $MoOCl_4$ is used in reaction, the complete conversion of **1g** was obtained only after 24 h under reflux of acetonitrile. This was probably due to a slow electron transfer within deactivated (delocalization of oxygen electrons to free orbitals of molybdenum) hydroxy-molybdenum(V) complex **5**. According to the results obtained with $MoCl_5$ (Table 3), one can propose that Mo(V) is even more reactive than Mo(VI) due to the fact that reaction is easily obtained at room temperature. This difference in reactivity can be attributed to the structures of molybdenum salts. Whereas $MoCl_5$ exists in dimeric structure (Mo_2Cl_{10})[32a], $MoOCl_4$ forms infinite chains of tetragonal pyramids $(MoOCl_4)_n$.[32a] Thus by the action of the solvent under reflux of acetonitrile, polymeric $MoOCl_4$ is activated to form reactive species of oxidants (solvated monomers) by which the reaction is almost instantly completed with excellent selectivity (Table 2).

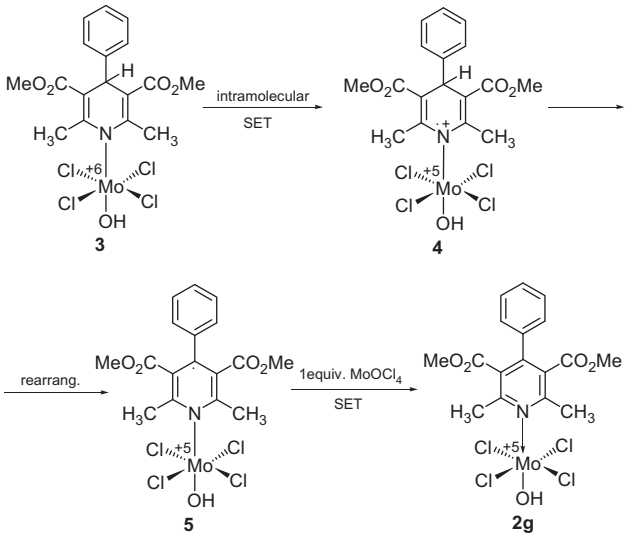
However, the observed non-typical and new dealkylation of methyl and ethyl groups in case of the 1,4-DHPs **1b** and **1c** cannot be explained by the mechanism outlined in Scheme 3 due to the fact that methyl and ethyl radicals are not stabilized by delocalization as benzyl or isopropyl radicals. Therefore, one of the possibilities is intramolecular nucleophilic attack of chloride anion within the complex of 1,4-DHP (**1b** or **1c**) and $MoOCl_4$ (Scheme 4) or the action of anhydrous hydrogen chloride released in reaction. The acetonitrile acts as a mild base as well as a dipolar aprotic solvent thus activating HCl to be more susceptible for nucleophilic attack to nonbulky methyl or ethyl groups (Scheme 4). Literature supports this claim as it is known that Cl^- anion acts as a strong but very selective nucleophile in the reaction of Krapcho dealkoxycarbonylation of malonic esters but only in dipolar aprotic solvents at elevated temperatures.[37]

The greater selectivity of Mo(VI) compared to Mo(V) encouraged us to propose the participation of molybdenum-containing enzymes, especially oxydoreductases, in the metabolism of 1,4-DHP drugs. Although it is commonly agreed that cytochrome

Table 4
The ratio of dealkylated versus non-dealkylated pyridines obtained during aromatization of 1,4-DHPs by $MoOCl_4$ at reflux in acetonitrile

Entry	1,4-DHP	*R*	Dealkylated product **2a**[a] (%)	Non-dealkylated product[a] (%)
1	**1b**	Me	16	84
2	**1c**	Et	93	7
3	**1d**	*i*-Pr	99.8	0.2
4	**1e**	*n*-Pr	87	13
5	**1f**	CH_2Ph	100	0

[a] Determined by HPLC analysis.

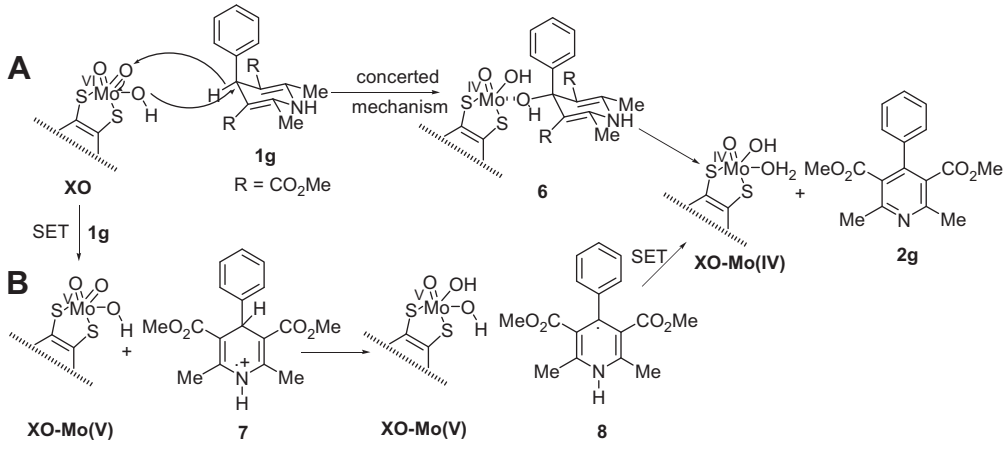


Scheme 3. The proposed mechanism of the aromatization of 1,4-DHP **1g** by $MoOCl_4$.

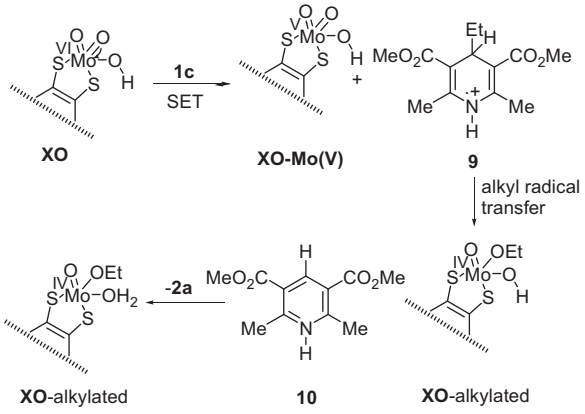
P450 is the only enzyme performing this biochemical transformation, the results obtained with 1,4-DHPs bearing alkyl substituents might also be explained by the action of molybdenum-containing enzymes. Molybdenum-containing enzymes have a broad specificity for the oxidation of a variety of substrates such as aldehydes, substituted pyridines, pyrimidines, pyrines, pteridines and in what is most important, the oxidation of NADH to NAD^+, thus acting as key enzymes in the respiratory chain.[38] It should be taken into account that a key structural fragment of NADH is the 1,4-DHP ring, which is oxidized by the interaction of enzymes with molybdenum in its active site, contrary to Hantzsch esters for which it is believed that metabolism takes place only by the action of cytochromes p450. Therefore, we are proposing that analogous to coenzyme NADH, Hantzsch esters are dependant upon their structure in being metabolized to some degree by the action of molybdenum-containing oxidoreductase. This prediction is supported by the results obtained with simple chemical models employing $MoOCl_4$ and $MoCl_5$ as oxidants.

The metabolism of 1,4-DHP **1c** is characterized by the complete dealkylation leading to an inactivation of cytochrome[39] as a result of ethylation of the enzyme porphyrine moiety with ethyl radical formed during the reaction.[40] However, according to literature results obtained by the chemical models of cytochrome,[26f,28a–c,41] dealkylation of **1c** does not take place suggesting that some other enzymes might also participate in the metabolism of this type of substrate. The results obtained employing $MoOCl_4$ (almost complete dealkylation of **1c**, Table 4) indicate that 1,4-DHPs could also be the substrates for some of the molybdenum-containing enzyme families. Thus, the two plausible mechanisms presented in Scheme 4 are proposed to explain the involvement of the xanthine oxidase (XO) family in the aromatization of model 1,4-DHP **1g**. The direct analogy to the mechanism of the XO in biological systems includes the insertion of an oxygen atom from the Moco to the benzylic group of the 1,4-DHP ring affording **6** via concerted mechanism[42] (Pathway A, Scheme 4). In the next step, via intramolecular rearrangement of an unstable reduced enzyme and substituted benzyl alcohol complex, product **2g** is released to form fully reduced XO-Mo(IV).

The second mechanism (Pathway B, Scheme 4) is characterized by the first SET from 1,4-DHP **1g** to Moco to give radical cation **7,** which upon rearrangement is converted to more stable benzylic radical **8** and in the next step, by second SET and deprotonation to product **2g**. The observed dealkylation of 1,4-DHPs bearing alkyl substituents is better explained by the latter mechanism, as is the case of 4-ethyl-1,4-DHP **1c**, which is presented in greater detail in Scheme 5.



Scheme 4. The plausible mechanism (A-concerted mechanism; B-two step electron transfer mechanism) for the action of xanthine oxidase (XO) in the aromatization of 1,4-DHP **1g**.



Scheme 5. The plausible mechanism for the action of XO in the metabolism of 4-ethyl-1,4-DHP **1c**.

The first step of the mechanism is similar to aromatization of **1g** and includes SET from **1c** to Moco to form radical cation **9** and partially reduced XO-Mo(V), whereas rearrangement of radical cation **9** is different and includes the elimination of the ethyl radical to produce a dealkylated product in the protonated form **10** and alkylated enzyme (XO-alkylated). In the last step, deprotonation of **10** by the enzyme releases product **2a** and an ethylated enzyme in a fully reduced form. The mechanisms presented in Schemes 4 and 5 are in accordance with the general behavior of molybdenum-containing enzymes and includes the formation of Mo(V) species that are well described and proved as intermediates in a mechanistic cycle of this type of enzyme.[43]

We believe that results obtained with molybdenum salts are good chemical models for the possible chemical behavior of molybdenum-containing enzymes. Results obtained employing tungsten hexachloride (WCl_6), albeit in more vigorous conditions, also showed great selectivity on the model 1,4-DHP (Table 1, entry 11). Although much less abundant in nature, this might explain why tungsten (VI) and not molybdenum is predominantly present in enzymes isolated from hyperthermophilic archaea.[44] Due to their higher chemical reactivity and under these conditions, the moybdenum-containing enzymes (VI) would probably not be selective enough to perform the same reactions as enzymes involved in the metabolism of organsims living in such a harsh environment. This prediction is based on results obtained by $MoOCl_4$ and $MoCl_5$ (Table 1, entries 3 and 7) that resulted in very poor chemical selectivity, which is in sharp contrast to tungsten(VI) chloride during which a clean reaction was observed (reflux of acetic acid).

Further research is in progress in order to clarify the role of pure isolated molybdenum-containing enzymes employed in the aromatization of 1,4-DHPs in vitro as well as their real action in living organisms.

In summary, this paper describes a remarkably fast and selective method for the aromatization of substituted Hantzsch-1,4-DHPs employing $MoOCl_4$ as an oxidant under reflux in acetonitrile as a solvent. The products, substituted pyridines, were isolated in high purity and excellent yield. The 1,4-DHPs bearing alkyl groups afforded unusual product distribution as a result of the dealkylation process. According to the obtained results, it is proposed that molybdenum-containing enzymes participate in the metabolism of 1,4-DHP drugs to some degree.

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33. IR spectra were recorded on a Perkin–Elmer Spectrum One spectrometer. ^{1}H NMR and ^{13}C NMR were recorded on a Bruker 600 for $CDCl_3$ solutions, shifts are given in ppm downfield from TMS as an internal standard. HPLC analyses for determination of the amount of dealkylation product **2a** 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. The 1,4-DHPs were prepared by modified Hantzsch procedures[45] and fully characterised (mp, IR, ^{1}H, ^{13}C, NMR, spectras, and elemental analysis) in our recent papers.[24f,24g,26e] The literature known aromatization products were characterized by a comparison with authentic samples (melting point) and their NMR (^{1}H, ^{13}C) and IR spectra.[24e,25g,26e,29b,29d,46]
34. *General procedure for the aromatization of 1,4-DHPs by $MoOCl_4$*: To a solution of corresponding 1,4-DHP (1.0 mmol) in CH_3CN (10 mL), $MoOCl_4$ (0.53 g, 2.1 mmol) was added and the reaction mixture was stirred for the time indicated in Table 2. After cooling to room temperature to the reaction mixture were added water (20 mL), dichloromethane (20 mL) and solid $NaHCO_3$ (2 g) in a few portions. After stirring for 15 min. Organic extract was separated and water layer was additionally extracted with dichloromethane (2×10 mL). Combined organic extracts were dried over anhydrous Na_2SO_4, filtered and evaporated. The crude product was purified by column chromatography on silica gel (CH_2Cl_2/EtOAc, 9:1) to yield the product of purity >98%. The identities of products were confirmed by mp, IR, ^{1}H and ^{13}C NMR spectral data and compared to the authentic samples of literature products.
35. *Analytical dana for selected product (**2r**)*: Pale yellow needles; mp: 110.0–112.0 °C; R_f (CH_2Cl_2/EtOAc, 9:1) = 0.42; IR (KBr): ν_{max}: 2953, 1732, 1559, 1530, 1433, 1400, 1374, 1337, 1238, 1208, 1125, 1102, 1037 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.57 (s, 6H, Me), 3.73 (s, 6H, OCH_3), 6.81–6.82 (d, 2H, J = 3.8 Hz), 7.01 (d, 2H, J = 3.8 Hz); ^{13}C NMR (600 MHz, $CDCl_3$): δ 22.8, 52.5, 114.6, 126.9, 128.8, 130.0, 137.2, 137.5, 155.6, 167.9; Anal. Calcd for $C_{15}H_{14}BrNO_4S$: C 46.89, H 3.67, N 3.65. Found: C 46.7, H 3.5, N 3.6.
36. *General procedure for the aromatization of 1,4-DHPs by $MoCl_5$*: To a solution of 1,4-DHP (1.0 mmol) in dichloromethane (10 mL), $MoCl_5$ (0.57 g, 2.1 mmol) was added and the reaction mixture was stired at room temperature for the time indicated in Table 3. After that to the reaction mixture were added water (20 mL), dichloromethane (10 mL) and solid $NaHCO_3$ (2 g) in a few portions. After stirring for 15 min. organic extract was separated and water layer was additionally extracted with dichloromethane (2×10 mL). Combined organic extracts were dried over anhydrous Na_2SO_4, filtered and evaporated. The crude product was purified by column chromatography on silica gel (CH_2Cl_2/EtOAc, 9:1) to yield the product of purity >98%. The identities of products were confirmed by mp, IR, ^{1}H and ^{13}C NMR spectral data and compared to the authentic samples of literature products.
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