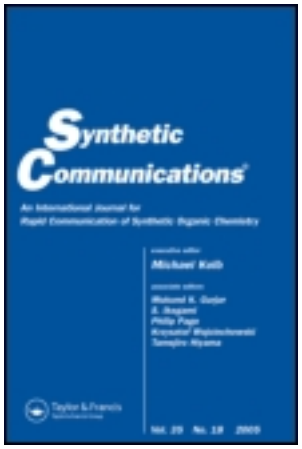

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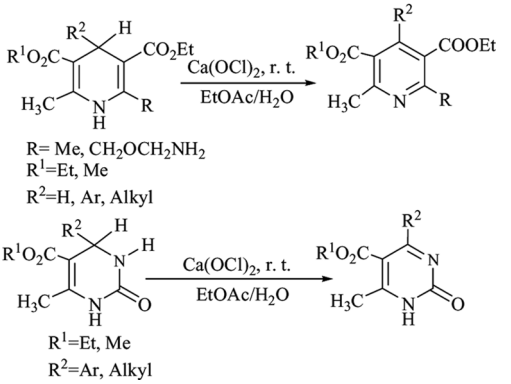
GRAPHICAL ABSTRACT



Abstract *1,4-Dihydropyridines and 3,4-dihydropyrimidin-2(1H)-ones obtained from the Hantzsch and Biginelli reactions undergo readily oxidative dehydrogenation by using calcium hypochlorite in very short times. These calcium stimulator drugs were oxidized under reaction conditions next to the in vivo transformations at room temperature.*

Keywords Biginelli reaction; $Ca(OCl)_2$; 1,4-dihydropyridines; dihydropyrimidinones; Hantzsch; oxidative dehydrogenation

INTRODUCTION

Over the past few decades, chemists have applied chemical principles and knowledge to understanding biological and medical problems. One of these problems was how hydrogen-transferase enzymes work. Hydrogen-transferase enzymes are the main subclass of oxido-reductase enzymes. The discovery and confirmation of 1,4-dihydropyridine nucleus in the structure of hydrogenase coenzymes (NADH

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Dedicated to Professor Habib Firouzabadi.
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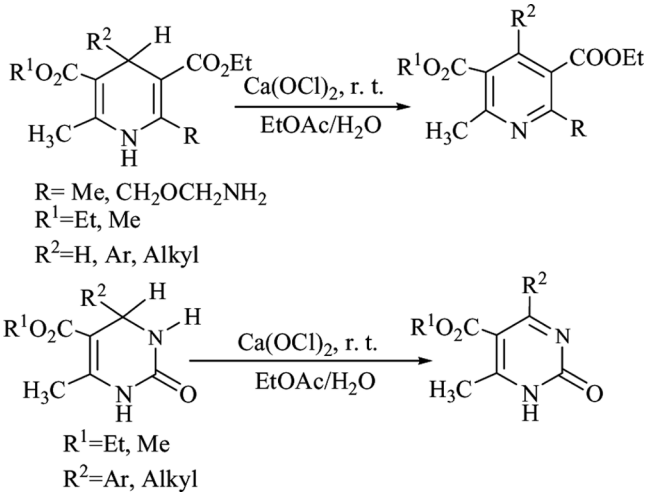
and NADPH) has offered a critical response to this problem, which highlighted the chemistry of 1,4-dihydropyridine (1,4-DHP) and pyridine derivatives.[1–4] The Hantzsch reaction,[5] as the oldest synthetic method of 1,4-DHPs and biomimetic tools for understanding the mechanistic details of NADH and NADPH, has attracted considerable attention from organic chemists in recent years. Moreover, there is much attention to the Hantzsch reaction because of the pharmacology of 1,4-dihydropyridines. Nifedipine, amlodipine (Norvasc), felodipine, and nitrendipine are among the best-known 1,4-DHP drugs used clinically in the treatment of hypertension, cardiovascular diseases, and microbial infections.[6] Similarly, 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs) obtained from the Biginelli reaction are known as calcium blockers and stimulator drugs, antihypertensive agents, and neuropeptide Y antagonists.[7] The most accepted metabolic pathway of these calcium stimulator drugs is their in vivo oxidative dehydrogenation, which is catalyzed by cytochrome P-450 in the liver.[8]

Despite the pharmacological applications of both 1,4-DHP and DHPM drugs, few reports are available about the oxidation of the latter compounds.[9] This fact may be attributed to the lesser tendency of Biginelli DHPMs to oxidize than Hasntzsch esters.[9] Because of the unique oxidation behaviors of the 1,4-DHP nucleus in coenzymes and oxidative dehydrogenation of DHP or DHPM drugs in their metabolism, synthetic chemists have created numerous oxidative methods for the in vitro oxidation of the Hantzsch and Biginelli drugs.[9–14] DHPMs remain stable toward a variety of oxidants, whereas the oxidative aromatization of 1,4-DHPs is achieved using conventional heating, ultrasound, and microwave irradiation. Oxidation of DHPMs is restricted by the sensitivity of methyl group at C-6 to oxidizing agents. However, most of the reported procedures for the oxidative aromatization of DHPM or DHP drugs are far from the in vivo physiological conditions and consume or produce a large amount of toxic and environmentally hazardous wastes. The lack of an investigation on the dehydrogenation of these drugs during their calcium-blocking activities and metabolism prompted us to study their oxidation with a calcium-containing oxidant. In continuation of our research,[15] we report herein an environmentally benign oxidation of 1,4-DHPs using calcium hypochlorite [$Ca(OCl)_2$] in H_2O at room temperature (Scheme 1).

In our initial experiments, a variety of oxidation procedures (almost close to the in vivo conditions) were applied to the oxidation of nifedipine as a model compound (Table 1). In spite of the high oxidation potential of these oxidants, stoichiometric amounts of commercially available $Ca(OCl)_2$ demonstrated significant superiority in the oxidation of nifedipine in H_2O/EtOAc at room temperature in less than 15 min (Table 1). A comparative experiment of model reaction with 2 equivalents of NaOCl proceeded slower, and reaction was not completed even after 8 h.

Calcium hypochlorite is an inexpensive hypochlorite salt, more stable and easier to handle than sodium hypochlorite,[16] and is used in the oxidation of various functional groups.[16–18] From a mechanistic point of view, it is proposed that the affinity of nifedipine to Ca^{2+}(calcium ion as a calcium blocker drug) causes to appearing a kind of symphoria effect that leads to the rapid oxidation of nifedipine with electrophilic Cl^+ in ClO^-. Thus, the highly electrophilic Cl^+ of $Ca(OCl)_2$ is captured by a nitrogen of the DHP ring to form 1,4-dihydropyridinium chloride, which under basic conditions of the reaction loses the H^+ to form an *N*-chloro derivative of

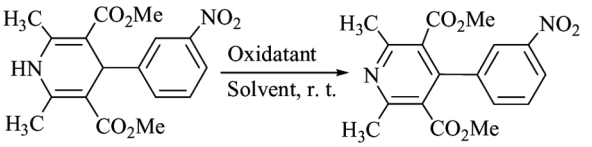


Scheme 1. Oxidations of 1,4-DHPs and 3,4-DHPMs using $Ca(OCl)_2$ in water.

DHP (Scheme 2). Further mechanistic steps are proposed that are conceptually similar to a previously reported mechanism for hypohalites. More studies of the mechanistic details of this reaction are in progress.

The generality and scope of this method are exhibited by oxidation of amlodipine and other substituted 1,4-DHPs with calcium hypochlorite in H_2O/EtOAc at room temperature (Scheme 3). Thus, a range of 4-alkyl or aryl substituted 1,4-DHPs

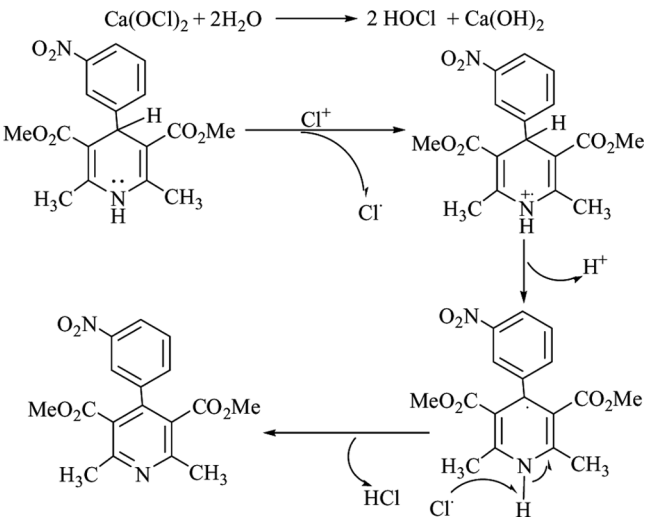
Table 1. Oxidations of nifedipine as a model reaction



Nifedipine

Entry	Oxidant (solvent)	Time (min)	Yield (%)[a]
1	$KMnO_4/CaMg(CO_3)_2$ (CH_2Cl_2)	60	90[b]
2	NaOCl (1 equiv.) (CH_2Cl_2)	120	75
3	NaOCl (2 equiv.) (CH_2Cl_2)	120	85
4	NaOCl (1 equiv.) (EtOAc)	120	90
5	NaOCl (1 equiv.) (EtOAc/H_2O)	120	87
6	$NaOCl/CaCl_2$ (EtOAc/H_2O)	60	92
7	$Ca(OCl)_2$ (1 equiv.) (EtOAc/H_2O)	10	98
8	$Ca(OCl)_2$ (1 equiv.) (CH_2Cl_2)	30	95
9	$Ca(OCl)_2$ (2 equiv.) (EtOAc/H_2O)	20	91[b]
10	$Ca(NO_3)_2 \cdot 6H_2O$ (1 equiv.) (EtOH)	180	60[b]

[a]Isolated yield.
[b]Mixture of products.

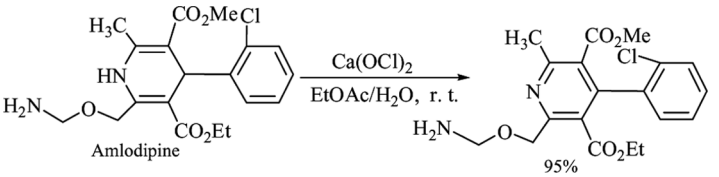


Scheme 2. Postulated mechanism for the oxidation of nifedipine in the presence of $Ca(OCl)_2$.

was converted into the corresponding pyridines in good to excellent yields under these conditions. The results illustrated in Table 2 indicate the high efficacy of this new green procedure and ready oxidation of the 1,4-DHPs to the corresponding pyridines in short times. The oxidative aromatization of 4-heteroaryl substituted DHPs such as 4-substituted 2-furyl, 3-, and 4-pyridyl DHPs produced the expected pyridines in excellent yields (entries 9–11). The physical and spectral data of the isolated products showed that dealkylation at the 4-position did not occur except for the 4-*iso*-propylsubstituted 1,4-dihydropyridine (entry 14).

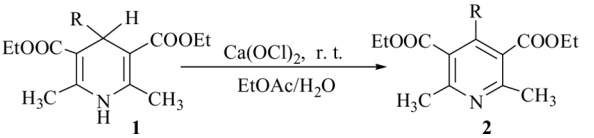
After the successful $Ca(OCl)_2$-mediated 1,4-dihydropyridines oxidation, we decided to apply this new oxidation procedure to the oxidative dehydrogenation of 3,4-DHPMs obtained from the Biginelli reaction. While these compounds are more resistant than 1,4-DHPs toward oxidation, various 4-substituted DHPMs were oxidized rapidly into the corresponding pyrimidin-2-ones in good yields at room temperature. 4-Aryl and alkyl-substituted DHPMs undertook oxidative dehydrogenation without formation of any side product (Table 3). The dehydrogenation mechanism may be the same as the postulated mechanism for nifedipine oxidation in Scheme 2.

In conclusion, $Ca(OCl)_2$ is reported as an environmentally benign, efficient, calcium-containing oxidant for the oxidative aromatization of DHP and DHPM



Scheme 3. Oxidative aromatization of amlodipine to the corresponding pyridine using $Ca(OCl)_2$.

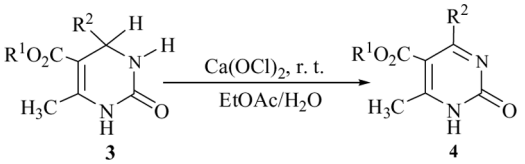
Table 2. Oxidation of 1,4-dihydropyridines using $Ca(OCl)_2$



Entry	R	Time (min)	Product	Yield (%)[a,b]
1	C_6H_5	15	**2a**	94
2	4-OMe-C_6H_4	15	**2b**	95
3	4-Cl-C_6H_4	25	**2c**	91
4	3-OMe-C_6H_4	15	**2d**	97
5	4-OH-C_6H_4	25	**2e**	85
6	3-OH-C_6H_4	20	**2f**	92
7	4-NO_2-C_6H_4	25	**2g**	88
8	2-NO_2-C_6H_4	20	**2h**	94
9	2-Furyl	15	**2i**	94
10	3-Pyridyl	20	**2j**	95
11	4-Pyridyl	20	**2k**	87
12	Cinnamyl	15	**2l**	90
13	*n* -Propyl	25	**2m**	91
14	*iso*-Propyl	20	**2n**[c]	95

[a]Isolated yield.
[b]All products were known.
[c]Only the pyridine product which in R=H was isolated.

Table 3. Oxidation of 3,4-dihydropyrimidin-(1*H*)-2-ones by $Ca(OCl)_2$



Entry	R	Time (min)	Product	Yield (%)[a,b]
1	C_6H_5	15	**3a**	91
2	4-OMe-C_6H_4	20	**3b**	96
3	4-Cl-C_6H_4	15	**3c**	94
4	3-OMe-C_6H_4	25	**3d**	87
5	4-OH-C_6H_4	25	**3e**	90
6	3-OH-C_6H_4	15	**3f**	88
7	4-NO_2-C_6H_4	25	**3g**	85
8	2-NO_2-C_6H_4	35	**3h**	75
9	*n*-Propyl	30	**3i**	82
10	*iso*-Propyl	30	**3j**	75

[a]Isolated yield.
[b]All products were known.

drugs. The oxidation reaction proceeds quantitatively in water at mild conditions, and products could be isolated by an easy workup. The proposed mechanism includes the formation of N-chloro substituted DHP or DHPM, which upon further stages give the corresponding pyridine or pyrimidin-2-one, respectively.

EXPERIMENTAL

General Procedure for the Oxidative Dehydrogenation of 1,4-DHPs and 3,4-Dihydropyrimidine-2(1H)-ones with Calcium Hypochlorite

H_2O (5 mL) and fresh $Ca(OCl)_2$ (2 mmol) were added to a solution of substrate (2 mmol) in EtOAc. The reaction mixture was stirred at room temperature, immediately heat evolved, and the oxidation completed. After completion of the reaction [thin-layer chromatography (TLC) monitoring], water (10 ml) and EtOAc (10 ml) were added and the organic layer was separated. After drying the combined organic layer over Na_2SO_4 and removing EtOAc at reduced pressure, the product was isolated. In the cases of reactions with poor yields, the crude product was purified by column chromatography on SiO_2 using EtOAc–hexane (1:8).

Representive Spectral Data

Compound 2g (2,6-dimethyl-4-(4-nitro-phenyl)-pyridine-3,5-diethyldicarboxylate). White solid, mp 115–116 °C (lit.[12] mp 114–116 °C), FT-IR: ν_{max} (KBr): 1728 (C=O), 1598 (asym. stretching N=O), 1348 (sym. stretching N=O) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): $\delta = 0.92$ (t, $J = 7.21$ Hz, 6H, $2 \times CH_3$-CH_2), 2.57 (s, 6H, $2 \times CH_3$), 3.97 (q, $J = 7.23$ Hz, 4H, O-$CH_2$$CH_3$), 7.38 (d, $J = 8.75$ Hz, $2H_{arom}$), 8.18 (d, $J = 8.75$ Hz, $2H_{arom}$) ppm.

Compound 2n (2,6-dimethyl-pyridine-3,5-diethyldicarboxylate). White solid, mp 69–72 °C (lit.[12] mp 70–71 °C), FT-IR: ν_{max} (neat): 1725 (C=O) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) $\delta = 1.35$ (t, $J = 7.00$ Hz, 6H, $2 \times CH_3$-CH_2), 2.60 (s, 6H, $2 \times CH_3$), 4.05 (q, $J = 7.00$ Hz, 4H, O-$CH_2$$CH_3$), 8.25 (s, $1H_{arom}$) ppm.

Compound 3c (ethyl 4-(4-chlorophenyl)-1,2-dihydro-6-methyl-2-oxopyrimidine-5-carboxylate). Colorless solid, mp 180–183 °C (lit.[9] mp 181–183 °C), FT-IR: ν_{max} (KBr): 1645 (C=O) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) $\delta = 1.08$ (t, $J = 7.10$ Hz, 3H, CH_3-CH_2), 2.70 (s, 3H, CH_3), 4.03 (q, $J = 7.10$ Hz, 2H, O-$CH_2$$CH_3$), 7.40 (d, 2H, $J = 8.65$ Hz, $2H_{arom}$), 7.55 (d, 2H, $J = 8.65$ Hz, $2H_{arom}$), 13.60 (br s, 1H) ppm.

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