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Double catalytic effect of $(PhNH_3)_2CuCl_4$ in a novel, highly efficient synthesis of 2-oxo- and thioxo-1,2,3,4-tetrahydropyrimidines

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Abstract: An innovative route for the construction of 2-oxo- and thioxo-1,2,3,4--tetrahydropyrimidines was delineated through a multicomponent reaction under Biginelli conditions, starting from different aromatic aldehydes, *β*-keto esters and urea or thiourea. The proper choice of the copper complex $(PhNH_3)_2CuCl_4$, as a novel homogeneous catalyst, enabled a facile, efficient, and inexpensive reaction under mild experimental conditions. Moreover, the first application of this complex salts in organic synthesis ever is presented. The obtained products were of high purity, and could be easily isolated from the reaction mixture in good to excellent yields. Moreover, compared to the classical Biginelli reaction conditions, the present method has the advantages of higher yields and experimental and work-up simplicity. To illustrate the joint catalytic action of the Cu^{2+} and phenylammonium ions, two key steps of Biginelli reaction were examined using the M06 functional.

Keywords: aldehydes; multicomponent reactions; heterocycles; homogeneous catalysis; density functional calculations.

INTRODUCTION

The 2-oxo- and thioxo-1,2,3,4-tetrahydropyrimidines (3,4-dihydropyrimidine-2(1*H*)-thi(ones)) are a class of compounds that have attracted the enormous interest of the medicinal chemistry community in recent years. Dihydropyrimidinones are very attractive compounds because of the wide range of their biological activities, such as: antihypertensive,[1–4] anti-HIV,[5] antitumor,[6–10] antiepileptic,[11] antimalarial,[12] anti-inflammatory,[13] antitubercular,[14] antioxidative[15] and anti-HBV (hepatitis B virus).[16] In addition, they act as potassium channel blockers[17,18] and α_{1A} adrenergic receptor antagonists.[19] Therefore, the pre-

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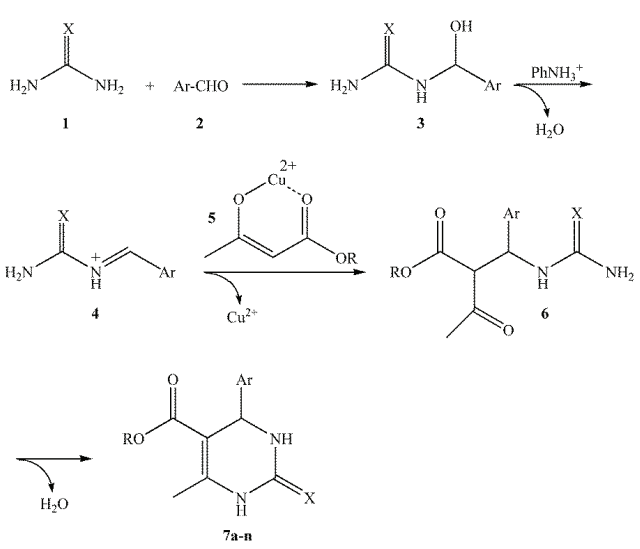
paration of this heterocyclic nucleus has gained great importance in organic synthesis. A simple method for the preparation of the dihydropyrimidinones was first reported by Biginelli in 1893 (Fig. 1).[20] His original reaction is the acid-supported cyclocondensation of an aldehyde, β-ketoester and urea. However, this method suffers from low product yields (20–50 %), strong acidic condition and difficult isolation of the products.



	Ar	R	X
7a	C_6H_4, 3-NO_2	Et-	O
7b	C_6H_5	Et-	O
7c	C_6H_3, 4-OH, 3-OCH_3	Et-	O
7d	C_6H_5CH=CH	Et-	O
7e	C_6H_5	Et-	S
7f	C_6H_3, 4-OH, 3-OCH_3	Et-	S
7g	2-Furyl	Et-	O
7h	C_6H_5	Me-	O
7i	C_6H_3, 4-OH, 3-OCH_3	Me-	O
7j	C_6H_5CH=CH	Me-	O
7k	C_6H_4, 3-NO_2	Me-	O
7l	2-Furyl	Me-	O
7m	C_6H_3, 4-OH, 3-OCH_3	Me-	S
7n	C_6H_5	Me-	S

Fig. 1. General outline of the Biginelli Reaction.

In the last decades, numerous improved procedures with new catalysts for Biginelli reaction have been reported[21,22]. Many Lewis acids, such as copper salts, proved to be very good catalysts for the preparation of dihydropyrimidinones. This field of investigation is still very vigorous. Namely, some copper-based catalysts, such as: $Cu(OTf)_2$,[23] copper methanesulfonate (CMS),[24] $CuCl_2$,[25] $Cu(NO_3)_2 \cdot 3H_2O$,[26] Cu sulfamate,[27] $Cu(NTf)_2$,[28] [[Gmim]Cl–Cu(II)],[29] Cu nanoparticles,[30] $Cu(acac)_2$[bmim]BF_4,[31] $CuCl_2 \cdot 2H_2O$,[32] $Cu(ClO_4)_2 \cdot 6H_2O$,[33] $Cu(BF_4)_2$,[34] poly(4-vinylpyridine-co-divinylbenzene)–Cu(II) complex,[35] and CuI[36] have recently been successfully employed. However, some inorganic and organic ammonium salts, such as ammonium carbonate,[37] alkylammonium salts,[38] and benzyltriethylammonium chloride,[39] were used as catalysts in the Biginelli reaction.

The catalytic behavior of Cu(II) and ammonium compounds in the Biginelli reaction motivated us to focus our attention on the application of a compound with Cu(II) and the phenylammonium ion in same molecule, that is bis(phenylammonium) tetrachloridocuprate(2–), $(PhNH_3)_2CuCl_4$. This complex salt was

synthesized by modification of earlier described procedures[40] and successfully applied as a catalyst for the synthesis of dihydropyrimidinones. To elucidate the catalytic role of the complex, a mechanistic insight into the crucial reaction steps is provided.

It is generally accepted that the catalytic action of the Cu^{2+} conforms to the mechanism depicted in Fig. 1. The first phase of the reaction is a spontaneous proton transfer from urea (**1**) to the oxygen of an aromatic aldehyde (**2**), whereby N-substituted (thio)urea (**3**) is built. In the further course of the reaction, a Brønsted acid removes HO^- from **3**, thus yielding the imminium ion (**4**). In the next reaction step, a new C–C bond between the benzylidene carbon of **4** and the α-C atom of an active methylene compound (**5**) is formed. This phase of the Biginelli reaction is catalyzed by Cu^{2+}, and yields the condensation product (**6**). This intermediate undergoes intramolecular nucleophilic addition, followed by the formation of a new C–N bond and dehydration. In this way, the final product of the reaction, dihydropyrimidinone (**7**) is formed.

EXPERIMENTAL

General

The ^{1}H- and ^{13}C-NMR spectra were recorded in DMSO-d_6 on a Varian Gemini 200 MHz NMR spectrometer. The IR spectra were obtained with a Perkin-Elmer Model 137B and Nicolet 7000 FT spectrophotometers. Microanalyses for C, H and N were obtained on a Dornis & Kolbe instrument. Melting points (m.p.) were determined on a System Kofler type WME apparatus and are uncorrected. Thin layer chromatography (TLC) was performed on 0.25 mm Merck precoated silica gel plates (60F-254) using an ethyl acetate–methanol (8:2) mixture as the mobile phase and UV light for visualization. All aromatic aldehydes, β-keto-esters, urea and thiourea were used as supplied by Aldrich. Aniline (reagent grade) from Merck was distilled prior to use. Copies of the ^{1}H- and ^{13}C-NMR spectra of all compounds (**7a**–**n**, Figs. S-1–S-26), as well as analytical and spectral data are given in the Supplementary material to this paper.

Preparation of the catalyst $(PhNH_3)_2CuCl_4$

Hydrochloric acid (6 M, 20 mL) was taken in a 100-mL round-bottom flask and $CuSO_4 \cdot 5H_2O$ (2.49 g, 10 mmol) was added slowly with stirring and constant cooling. To the resulting dark green solution, freshly distilled aniline (1.86 g, 0.02 mmol) was added very slowly. The precipitated yellow powder was filtered and washed with ethanol (5 mL, 95 %) and dichloromethane (5 mL). The copper complex powder was dried at 100 °C to constant weight.

General experimental procedures for the synthesis of 2-oxo- and thioxo-1,2,3,4-tetrahydro-pyrimidines

In a 50-mL round-bottom flask, urea or thiourea (15 mmol) was dissolved in ethanol (20 mL, 95 %). Then an aromatic aldehyde (10 mmol), β-keto ester (12 mmol) and catalyst (10 mol % with respect to aldehyde) were added. The solution was magnetically stirred at room temperature. The reaction was followed by TLC to verify its completion. The formed white solid was filtered, washed with small portions of cold ethanol and DCM, and then dried under vacuum to afford the desired product with a good purity grade.

Computational details

All calculations were performed with the Gaussian 09 program package[41] using the M06 functional. This hybrid meta functional was developed by Zhao and Truhlar as "a functional with good accuracy "across-the-board" for transition metals, main group thermochemistry, medium-range correlation energy, and barrier heights".[42] This method was recommended "for application in organometallic and inorganometallic chemistry and for noncovalent interactions".[43] The 6-311+G(d,p) basis set was applied for C, H, N, and O, whereas the Def2-TZVPD basis set[44] was used for Cu. These triple split valence basis sets add the polarization functions to all atoms and diffuse functions to heavy atoms. The structures of all investigated species in ethanol were optimized, and frequency calculations performed. The influence of the solvent (dielectric constant = 24.852) was taken into account by applying the CPCM solvation model (polarizable conductor calculation model).[45] An unrestricted scheme was applied for the open shell structures containing a Cu^{2+}. The obtained stationary points were verified to be equilibrium geometries (no imaginary frequencies), or transition states (one imaginary frequency) on the potential energy surface. The activation free energies were calculated at 298.15 K. Natural bond orbital (NBO) analysis[46-48] was realized for all calculated structures.

The ^{13}C-NMR chemical shifts for all carbon atoms of **7h** in DMSO relative to TMS were calculated using the gauge independent atomic orbital (GIAO) method, as implemented in Gaussian 09. For this purpose, the geometries of **7h** and TMS in DMSO were optimized using the M06/6-311+G(d,p) and CPCM models (dielectric constant of DMSO = 46.826). The nuclear magnetic shielding tensors were calculated for TMS and **7h**. The values for all carbon atoms in **7h** were subtracted from the value for the carbon in TMS (178.4833). Compound **7h** belongs to the C_1 point group and, thus, the *ortho* and *meta* carbons show two different chemical shifts. In this case, the corresponding mean values were taken to represent the chemical shifts of the *ortho* and *meta* carbons. As the so-obtained chemical shifts were systematically overestimated, their values were scaled by a factor of 0.94.

RESULTS AND DISCUSSION

In this paper, a simple but effective and convenient method for the synthesis of 2-oxo- and thioxo-1,2,3,4-tetrahydropyrimidines from urea or thiourea (**1**), some aromatic aldehydes (**2**) and *β*-keto ester (**5**) in the presence of copper complex $(PhNH_3)_2CuCl_4$ as a catalyst is reported. The results of the investigation are given in Tables I–III.

TABLE I. Optimization of the solvent for synthesis of the product **7h** at room temperature for 24 h (ε - dielectric constant, *DN* - donor number, *AN* - acceptor number, *HBD* - hydrogen bond donor, *HBA*- hydrogen bond acceptor)

Entry	Solvent	ε[49]	*DN*[50]	*AN*[50]	*HBD* / α[51]	HBA / β[52]	Catalyst, mol %	Yield[a], %
1	DCM	8.9	–	20.4	–	–	1	8
2	Toluene	2.4	–	–	–	–	1	11
3	MeOH	32.7	20.0	41.5	0.99	0.70	1	32
4	EtOH	24.6	19.0	37.1	0.85	0.77	1	41
5	THF	7.6	20.0	8.0	–	0.52	1	28
6	MeCN	36.6	14.1	18.9	0.29	–	1	24

[a]Isolated yields

For the purpose of the investigations, the reaction of benzaldehyde, methyl acetoacetate and urea was selected as a model reaction. The first task was to optimize the conditions of the Biginelli reaction. To investigate the effects of different solvents on the catalytic process, the reaction was performed in the presence of 1 mol % of the catalyst at room temperature, in solvents of different polarity. The results of optimization of the solvent for synthesis of **7h** are presented In Table I. Based on the isolated yields, the best results were achieved with ethanol as the solvent (Entry 4). In the Biginelli reaction, the solvent polarity plays a very important role. In light of this, the polar solvents (MeOH, EtOH, THF, MeCN) were found to be very suited for the reaction conditions. The solvent polarity had effects on the reaction yield, but it was not of crucial importance. For example, the solvents MeCN and MeOH, in spite of having higher values of ε (36.6 and 32.7) than EtOH (24.6) afforded 24 and 32 % of **7h**, respectively. Moreover, the donor number (*DN*) did not exert the main effect on the yield, because MeOH and THF have identical values (*DN* = 20.0), but the yields were different. The key for better yields in EtOH than in all other applied solvents is the value of hydrogen bond acceptor (*HBA*). The oxygen atom in EtOH is a very strong hydrogen bond acceptor. This solvent probably coordinates with the hydrogen atoms on the α-C atom of the active methylene compound, and thus promotes the generation of the carbanion. The best results were obtained by performing the reaction with 1:1.2:1.5 mol ratios of aldehyde, β-keto ester and urea or thiourea.

After the solvent had been optimized, the effects of different amounts (1, 5 and 10 mol %) of the catalyst on the yields were investigated (Table II). All used amounts of the catalyst gave different results, implying that the amount of the added catalyst is of significant importance for the reaction yields.

TABLE II. Optimization of the amount of catalyst for the synthesis of **7h** at room temperature in EtOH

Entry	Time, h	Catalyst, mol %	Yield[a], %
1	1	1	4
2	3	1	5
3	5	1	5
4	7	1	7
5	9	1	8
6	24	1	41
7	24	5	71
8	24	10	89

[a]Isolated yields

First, the reaction with 1 mol % catalyst was performed with increasing reaction time. The maximum yield of **7h** was obtained after 24 h with 1 mol % of the catalyst (see Entry 6). Then, two parallel reactions were performed with 5 and

10 mol % of the catalyst. The dose of 10 mol % catalyst gave a yield of 89 % after 24 h. However, the best yield of the product **7h** was achieved after 28 h (91 %). Equimolar amounts of the catalyst were also used, but no increases in the product yields were registered. The reaction conditions optimized in this way were further applied to a series of reactions of various aldehydes, *β*-keto esters and urea or thiourea. The results for the copper complex-promoted reactions are presented in Table III. All the obtained products were characterized by their m.p., and IR, ^{1}H- and ^{13}C-NMR spectra. Very good yields were achieved in all cases.

TABLE III. Yields for the Cu(II) complex-catalyzed syntheses of 2-oxo- and thioxo-1,2,3,4--tetrahydropyrimidines at room temperature

Product	Ar	R	X	Reaction time, h	Yield[a], %
7a	C_6H_4, 3-NO_2	CH_3CH_2–	O	19	96
7b	C_6H_5	CH_3CH_2–	O	24	90
7c	C_6H_3, 4-OH, 3-OCH_3	CH_3CH_2–	O	29	94
7d	C_6H_5CH=CH	CH_3CH_2–	O	28	93
7e	C_6H_5	CH_3CH_2–	S	19	95
7f	C_6H_3, 4-OH, 3-OCH_3	CH_3CH_2–	S	25	92
7g	2-Furyl	CH_3CH_2–	O	30	96
7h	C_6H_5	CH_3–	O	28	91
7i	C_6H_3, 4-OH, 3-OCH_3	CH_3–	O	27	88
7j	C_6H_5CH=CH	CH_3–	O	28	97
7k	C_6H_4, 3-NO_2	CH_3–	O	40	90
7l	2-Furyl	CH_3–	O	24	93
7m	C_6H_3, 4-OH, 3-OCH_3	CH_3–	S	27	82
7n	C_6H_5	CH_3–	S	34	95

[a]Isolated yields

It could be concluded, based on the presented results, that this improved procedure is very suitable for the preparation of 2-oxo- and thioxo-1,2,3,4-tetrahydropyrimidines and related systems. It is characterized with high yields and purity of the obtained products, the mildness of the reaction conditions and simplicity of the experimental process.

In spite of the fact that different copper and ammonium compounds as catalysts of Biginelli reaction were the subject of numerous investigations,[23–39] their catalytic role was not elucidated at the molecular level.

To gain insight into the synergic action of the Cu^{2+} and phenylammonium ions, two crucial steps of the model reaction were examined: the formation of the imminium ion and the new C–C bond (Fig. 2). The phenylammonium ion is involved in the formation of **4**. This reaction step occurs *via* the transition state TS1 (Fig. 2), which requires an activation energy of 64.2 kJ mol^{-1}. In TS1, the simultaneous cleavage of the C–O and N–H bonds, and the formation of O–H bonds occur, whereby the C–N bond becomes double. In this way, a water molecule is liberated, and the formed intermediate **4** further reacts with **5** yielding the

reactant complex RC2. It could be supposed that the α-C atom will perform a nucleophilic attack at the benzylidene carbon. This assumption was supported with the NBO charges on these atoms (–0.497 and 0.308), and confirmed by revealing the transition state TS2. This transition state, in which a new C–C bond is being formed, requires an activation energy of 60.3 kJ mol^{-1}. In RC2, TS2 and PC2, copper is chelated with the oxygens of methyl acetoacetate. The NBO analysis of all three structures showed that the unpaired electron is delocalized over Cu and the proximate oxygens. Further liberation of the Cu^{2+} and intramolecular cyclization of intermediate **6** led to the formation of the final product **7**.

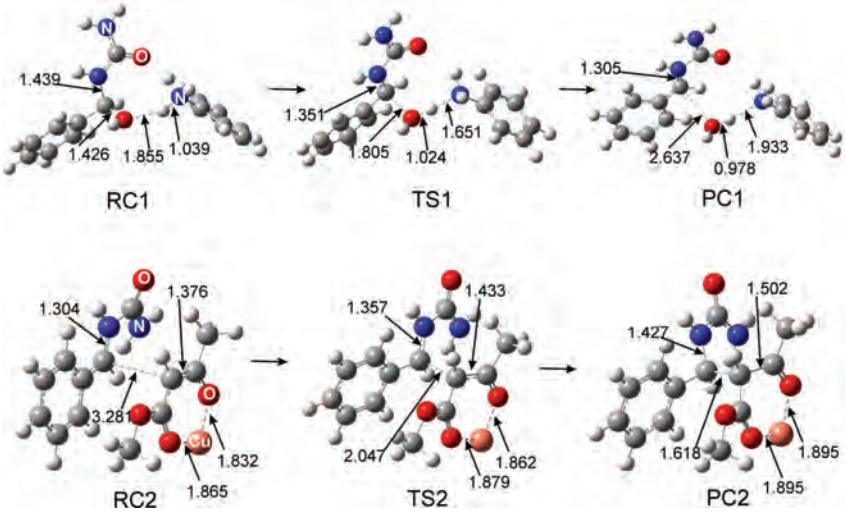


Fig. 2. Optimized geometries of the reactant complexes (RCs), transition states (TSs), and product complexes (PCs) for two crucial catalytic steps, with bond distances (Å) indicated.

To the best of our knowledge, the crystal structure of methyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**7h**), the product of the model reaction, is not available in the literature. For this reason, the ^{13}C-NMR spectrum of **7h** in DMSO was simulated. The calculated chemical shifts are given (in brackets) with the corresponding experimental values in the Supplementary material for **7h**, whereas a plot of the calculated *versus* the experimental chemical shifts is depicted in Fig. S-27 of the Supplementary material. The average absolute error is notably small (2.0 ppm), and the correlation coefficient is high (0.9990). The very good agreement between the experimental and simulated ^{13}C-NMR spectra confirmed the predicted arrangement of atoms in the carbon skeleton of **7h** (Fig. 3; the Cartesian coordinates for **7h** are provided in Table S-I of the Supplementary material). The carbonyl group of the ester moiety and double bond of the heterocycle adopt the *s-trans* position. The dihedral angle C5–C4–C1′–C2′ of 41.6° determines the mutual position of the two rings.

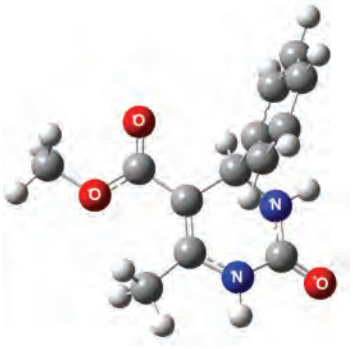


Fig. 3. Optimized structure of **7h** in ethanol.

CONCLUSIONS

Bis(phenylammonium) tetrachloridocuprate(2–), a non-hygroscopic, very stable, and easy to synthesize complex, proved to be an efficient and inexpensive catalyst for the Biginelli reaction. This is the first use of the said complex salt in organic synthesis. The catalytic behavior of the complex is realized through the synergic action of the Cu^{2+} and phenylammonium ions. As for the yields and purity of the reaction products, the procedure described herein achieves excellent results. Bearing in mind the other merits, such as the mildness of the reaction conditions and simplicity of the experimental work, this procedure could be considered very attractive for the one-pot conversion of different aromatic aldehydes, *β*-keto esters and urea or thiourea into 2-oxo- and thioxo-1,2,3,4-tetrahydropyrimidines.

SUPPLEMENTARY MATERIAL

Analytical and spectral data, copies of the ^{1}H- and ^{13}C-NMR spectra (Figs. S-1–S-26) of all compounds, a plot of the calculated *versus* experimental chemical shifts (Fig. S-27) and the Cartesian coordinates for **7h** (Table S-I) are available electronically from http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

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ИЗВОД

ДВОСТРУКИ КАТАЛИТИЧКИ ЕФЕКТ $(PhNH_3)_2CuCl_4$ У НОВОЈ, ВИСОКО ЕФИКАСНОЈ СИНТЕЗИ 2-ОКСО- И ТИОКСО-1,2,3,4-ТЕТРАХИДРОПИРИМИДИНА

НЕНАД ЈАНКОВИЋ, ЗОРИЦА БУГАРЧИЋ И СВЕТЛАНА МАРКОВИЋ

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Представљен је иновативни пут за синтезу 2-оксо- и тиоксо-1,2,3,4-тетрахидропиримидина преко мултикомпонентне Бињинелијеве реакције полазећи од различитих ароматичних алдехида, *β*-кето-естара и урее или тиоурее. Избор $(PhNH_3)_2CuCl_4$ као новог, хомогеног катализатора омогућава лаку, ефикасну и јефтину реакцију при благим експерименталним условима. Штавише, овде је представљена прва примена ове

комплексне соли у органској синтези икада. Добијени производи су високе чистоће, и могу се лако изоловати из реакционе смеше у добрим или чак одличним приносима. Такође, у односу на класичне Бињинелијеве реакционе услове, ова метода има предности јер се постижу виши приноси и експериментална једноставност. Да би се илустровао заједнички каталитички ефект Cu^{2+} и $PhNH_3^+$, два кључна корака Бињинелијеве реакције су испитана на молекулском нивоу помоћу M06 функционала.

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