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## Inorganica chimica acta

**Elementary and efficient Catalyst process for the Knoevenagel** 

Condensation of analdehydes with anylmethylidene malononitrile

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#### **Graphical abstract**



#### Synopsis

The preparation of a new complex has been accomplished. The single-XRD shows that it adopts a polymeric structure. The title compound is found to be a good catalyst for the Knoevenagel condensation reaction.

### **Highlights:**

- A new Cd(II) complex derived from arylhydrazone has been elaborated.
- The single X-ray diffraction showed polymer crystal structure.
- The Cd(II) complex was found to be a good catalyst for the Knoevenagel condensation reaction.

#### Abstract

A comparative study of the Knoevenagel condensation of an aromatic aldehyde with an active methylene compound (e.g., malononitrile or ethyl cyanoacetate), using solvent free grindstone conditions and microwave irradiation is reported. Our solvent free approaches led these reactions to proceed faster, more cleanly and in higher yields. Moreover, they also allowed the use of nitrobenzaldehydes, which failed to yield the desired products under traditional and water based approaches. Thus, an efficient procedure for the Knoevenagel condensation of heteroaromatic aldehydes malononitrile. aryl and with using the complex  $[CdNa_2(\mu-L^2)]_n 6.34H_2O$  or commercial CdO as catalyst under solvent-free and very mild conditions has been developed.

**Key words:** Knoevenagel condensation, grindstone technique, microwave, malononitrile; solvent-free reaction.

#### Introduction

The Knoevenagel condensation is one of known C-C coupling reactions in Chemistry. In the last couple of years its application ranged from pharmaceutical industry [1], to polymers [1] and even the application of alternative solvents, such as ionic liquids [2], have been reported. However, most of these methods have drawbacks like harsh reaction conditions, low yield, long reaction time and the use of organic solvents which causes environmental waste and pollution. Thus, the development of an alternative method, more particularly with the application of novel, simple, efficient, cost-effective, high-yielding, and green methodologies is highly desirable.

Grinding solvent-free reactions, as well as microwave-assisted reactions, offer the above advantages, and the reactions are complete within minutes [1]. Moreover, the work-up is very simple and does not require complicated purification procedure or the use of volatile organic

solvents [3-6]. This useful novel reaction tool relies on the power of the microwaves to reduce the times of reaction and the energy consumption increasing the yields and selectivities of the investigated reactions in many cases [7, 8].

#### Experimental

#### Equipment and materials

Grinding solvent-free reactions were performed in open vessels at room temperature using a pestle and a mortar. Also, these reactions were without any mechanical stirring.

Furthermore, the reactions were monitored by thin layer chromatography (TLC) and all the products were characterized by comparison with authentic samples on TLC.

The solvent-free microwave assisted reactions were performed in a focused Anton Paar Monowave 300 reactor, using a 10-mL capacity reaction tube with a 13-mm internal diameter and equipped with a rotational system and an IR temperature detector.<sup>1</sup>H (300 MHz) NMR spectra were obtained at room temperature (RT) on a Bruker Advance II + 300 (UltraShield<sup>TM</sup>Magnet) spectrometer using tetramethylsilane [Si(CH<sub>3</sub>)<sub>4</sub>] as an internal reference.

#### Preparation of $[CdNa_2(\mu-L^2)]_n 6.34H_2O$

#### Synthesis of Na<sub>2</sub>HL

Na<sub>2</sub>HL<sup>1</sup> is synthesized by aqueous diazotization of 2-aminoterephthalic acid (99%, Aldrich) with subsequent coupling with 5,5-dimethylcyclohexane-1,3-dione (95%, Aldrich), respectively [9].

*Diazotization:* A 20 mmol portion of 2-aminoterephthalic acid was dissolved in 50 mL of water upon addition of 1.6 g (40 mmol) of crystalline NaOH (97%, Aldrich). The solution was cooled in an ice bath to 0 °C and 20 mmol of NaNO<sub>2</sub> (98%, Aldrich), were added with

subsequent addition of 4 mL HCl (33%, Aldrich), in portions of 0.4 mL for 1 h, under vigorous stirring. During the reaction, the temperature of the mixture must not exceed  $+5^{\circ}$ C. The obtained diazonium salt was used for the next stage.

*Azocoupling:* 20 mmol of NaOH were added to a mixture of 20 mmol of 5,5dimethylcyclohexane-1,3-dione in 50 mL ethanol with 50 mL of water. The solution was cooled in an ice bath, and a suspension of the diazonium salt was added in two equal portions under rigorous stirring for 1 h. The formed yellow precipitate of 2-(2-(4,4-dimethyl-2,6dioxocyclohexylidene)hydrazinyl)terephthalate (Na<sub>2</sub>HL<sup>1</sup>)) was filtered off, recrystallized frommethanol and dried in air.

#### Coordination reaction

2 mmol of Na<sub>2</sub>HL<sup>1</sup> were dissolved in 50 mL of a DMF (99.8%, Aldrich) mixture (1:1, v/v), and then 2 mmol of Cd(CH<sub>3</sub>COO)<sub>2</sub>·H<sub>2</sub>O (98%, Aldrich), were added, and the system was stirred for 5 min. After 2 days at room temperature, yellow crystals precipitated, by the slow evaporation method, which were then filtered off and dried in air.

#### X-ray single crystal diffraction and structure determination

Crystallographic data for the studied crystal were collected at 100 K and processed with the CrysAlis PRO program [10]. The crystal structure was solved by Patterson method using the *SHELXS-97* and refined by full-matrix least-squares on  $F^2$  using *SHELXL-2013* program [11]. An analytical absorption corrections were introduced [10]. For preparation pictures a graphical program DIAMOND [12] was used. In the structure H atoms of aromatic rings were treated as riding atoms in geometrically idealized positions, with C—H = 0.95 and  $U_{iso}(H) = 1.2U_{eq}(C)$  as well as H atoms of methyl and methylene groups were introduced in positions calculated from geometry, with C—H = 0.98 Å and  $U_{iso}(H) = 1.5U_{eq}(C)$ , and C—H = 0.99 Å and  $U_{iso}(H) = 1.2U_{eq}(C)$  respectively. The main crystallographic data are listed in Table 1.

formula	$[CdNa_2(\mu-L^2)]_n = 6.34H_2O$
Formula weight (g/mol)	933.18
Crystal system	Trigonal
Space group	P3 <sub>2</sub> 21
a (Å)	19.865 (6)
b (Å)	19.865 (6)
c (Å)	13.110 (3)
γ (°)	120
V (Å <sup>3</sup> )	4480 (3)
Z	3
Color	Yellow
calculated density	1.038
$\lambda$ (MoK $\alpha$ ) (Å)	0.71073
calculated density	Analytical
Measured reflections	12825
Independent reflections	8180
Reflections $[I > 2\sigma (I)]$	6345
Domain of $\theta$ (°)	2,8-30.8
T <sub>min</sub> and T <sub>max</sub>	0.916 - 0.984
Index ranges	$-9 \leq h \leq 28$
	$-17 \le k \le 18$
	$-18 \le 1 \le 9$
Number of parameters	307
$\mathbf{R}_1$	7.1%
wR <sub>2</sub>	17.3%
GooF	1.14

Table 1:	Crystallogra	phic data for	$[CdNa_2(\mu - L^2)]$	$[]_{n}6.34H_{2}O$
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After the refinement of the positions of all atoms in the structure, on the difference Fourier map additional maxima were observed close to the sodium atom, and were introduced as oxygen atoms derived from disordered water molecules. The disorder was modelled over several positions of O atoms, which were refined isotropically with partial occupation factors. As a result of low s.o.f factors of particular components of H<sub>2</sub>O molecules the maxima from H atoms were not observed on the difference Fourier map. Bond distances and angles

calculated from the final atomic coordinates, as well as probable hydrogen bonds, are listed in

Tables 2 and 3 respectively.

dista	nces (Å)	angles (°	)
~	Dodece	ahedron $CdO_8$	
Cd—O1	2.356 (5)	O1_Cd_O1	144.1 (10)
Cd—O1 <sup>m</sup>	2.356 (5)	$O1^{m}$ —Cd— $O4^{n}$	132.704 (5)
Cd—O2	2.357 (5)	O2—Cd—O4 <sup>n</sup>	84.217 (5)
Cd—O2 <sup>m</sup>	2.357 (5)	$O2^{m}$ —Cd— $O3^{n}$	135.113(5)
Cd—O3 <sup>1</sup>	2.371 (5)	O3 <sup>1</sup> —Cd—O1	80.173(8)
Cd—O3 <sup>ii</sup>	2.371 (5)	$O3^{ii}$ —Cd— $O3^{i}$	101.481(8)
Cd—O4 <sup>i</sup>	2.565 (5)	O4 <sup>i</sup> —Cd—O3 <sup>ii</sup>	74.917(6)
Cd—O4 <sup>ii</sup>	2.565 (5)	O4 <sup>ii</sup> —Cd—O2 <sup>iii</sup>	170.138(5)
		O2—Cd—O2 <sup>iii</sup>	99.546(6)
		O2—Cd—O3 <sup>ii</sup>	96.252(6)
	Octal	hedron $NaO_6$	
Na-O1	2.393 (6)	O3 <sup>n</sup> —Na—O1W	95.0 (3)
Na-O3 <sup>i</sup>	2.342 (6)	O5 <sup>iii</sup> —Na—O1W	79.8 (3)
Na-O4 <sup>ii</sup>	2.437 (6)	O3 <sup>ii</sup> —Na—O5 <sup>iii</sup>	151.5 (2)
Na-O5 <sup>ii</sup>	2.347 (6)	$O3^{ii}$ —Na—O1	80.01 (19)
Na-O1W	2.378(11)	$05^{iii}$ —Na—O1	97 4 (2)
Na-O2W	2.575(11) 2 425 (15)	$0.1W - N_2 - 0.1$	164.3(3)
144-0210	2.425 (15)	$O_{3ii}^{ii}$ Na $O_{2W}^{ii}$	108.8(4)
		$O_{5}$ $M_{a}$ $O_{2}W$	080(4)
		0.5 - Na - 0.2W	20.2 ( <del>4</del> ) 112 0 (5)
		01 w $-1$ Na $-02$ W	112.9(3)
			82.7 (4)
		03 - Na - 04	77.95 (19)
		05 <sup></sup> —Na—O4 <sup></sup>	73.8 (2)
		O1W—Na—O4 <sup>m</sup>	87.5 (3)
		01—Na—O4 <sup>m</sup>	77.0(2)
		O2W—Na—O4 <sup>m</sup>	157.2 (4)
01 01	<u>li</u>	gand HL	122.0 (7)
	1.270 (8)	02-01-01	123.0(7)
02	1.247 (8)	03-08-05	118.1 (6)
O3—C8	1.248 (8)	Na <sup>w</sup> —O3—Cd <sup>v</sup>	89.62 (19)
O4—C8	1.258 (8)	C8—O3—Cd <sup>v</sup>	97.2 (4)
O6—C16	1.245 (10)	O3—C8—O4	122.3 (6)
N1—N2	1.306 (8)	C8—O4—Na <sup>v</sup>	155.8 (5)
N2—C11	1.338 (9)	C8—O4—Cd <sup>v</sup>	87.8 (4)
C1—C2	1.514 (10)	C12—O5—Na <sup>v</sup>	135.0 (5)
C2—C7	1.383 (11)	O6-C16-C11	121.7 (7)
$C_2 - C_3$	1.405 (10)	N1—N2—C11	119.3 (6)
$C_{3}$ $C_{4}$	1400(10)	N2-C11-C12	1249(7)
$C_4 - C_5$	1409(10)	$C_{3}$ $C_{2}$ $C_{1}$	12.1.9(7) 118.1(7)
$C_{4}$ N1	1,409 (10)	$C_{5} - C_{2} - C_{1}$	110.1(7) 120 4 (6)
$C_{1}$	1.413 (0)	$C_{4} C_{3} C_{2}$	120.4(0) 119.7(7)
$C_{J}$	1.370 (9)	$C_{4}$ $C_{5}$ $C_{2}$ $C_{4}$ $C_{5}$	110.7 (7)
	1.3/2(10)	$C_3 - C_4 - C_5$	120.8 (6)
	1.499 (10)	$C_{0}$	118.3 (6)
C11-C16	1.453 (11)	C3-C4-N1	119.5 (6)
C11—C12	1.475 (10)	C6—C5—C8	118.9 (6)
C12—O5	1.221 (9)	C7—C6—C5	121.2 (6)
C12—C13	1.500 (9)	C4—C5—C8	122.8 (6)
C13—C14	1.520 (10)	C11-C16-C15	119.4 (7)
C15—C14	1.529 (11)	C11—C12—C13	118.1 (6)
C15—C16	1.511 (10)	O5-C12-C11	121.1 (6)
C17—C14	1.549 (10)	C12-C13-C14	115.3 (6)
C18 - C14	1.572(10) 1 524(12)	C13 - C14 - C18	109.4(7)
	1.524 (12)	C13 C14 C10	102.4 (7)
		$C_{13} - C_{14} - C_{13}$	110.0 (0)
		00-010-015	118.8 (/)
			109.1(6)

Table 2: Selected bond distances (Å) and angles (°)

D−H <sup>…</sup> A	D–H	HA	D <sup>…</sup> A	D−H <sup>…</sup> A
N1-H1O4	0.88	1.95	2.606(8)	131
N1-H1O5	0.88	1.93	2.610(8)	133
C17–H17B <sup>…</sup> O2 <sup>vi</sup>	0.98	2.58	3.507(10)	158
<i>Symmetry code:</i> (vi) = -y+1, x-y+1, z+2/3				

	-			
Tahla 3+	Geometry	of hydrogen	hondel	$(\Delta \circ)$
Lanc J.	Ocometry y	of flyulogen	UUIIus (	( <b>n</b> , )

#### **Results and discussion**

#### Description of the crystal

The studied crystal has a three-dimensional polymeric structure that comprises of  $Cd^{2+}$  ions (L), namely 2-(2-(4,4-dimethyl-2,6connected to ligands dioxocyclohexylidene)hydrazinyl)terephthalate [13], (Fig. 1). In the structure each cadmium cation (lying in special position on the two-fold axis) is coordinated via carboxylate groups {from terephthalate fragments} of four ligands in a bidentate way (Table. 2) resulting in the formation of the eight-coordination sphere of Cd<sup>2+</sup> that may be described as a distorted dodecahedron DD-8 [14]. In the structure of ligand the six-membered ring of 4,4-dimethyl-2,6-dioxocyclohexylidene fragment adopts approximately a half-chair conformation where C11, C12, C13, C15 and C16 atoms are located in the same plane whereas C14 atom is deviated of 0.65 (1) Å from the plane. Similarly, in the analogous fragments of the copper polymeric structure [13] carbon atoms bonded to methyl groups are deviated of about 0.32 and 0.61 Å.



**Figure 1:** Cadmium polymeric structure. Symmetry codes: <sup>i</sup> 1+x-y, 1-y, 1/3-z, <sup>ii</sup> 1-y, 1+x-y, -1/3+z, <sup>iii</sup> y, x, -z, <sup>iv</sup> x-y, 1-y, 1/3-z, <sup>v</sup> -x+y, 1-x, 1/3+z

In the studied crystal the intramolecular bifurcated hydrogen bond N1–H1…O4, N1–H1…O5 is observed forming two six-membered cyclic entities: O4/C8/C5/C4/N1/H1 and O5/C12/C11/N2/N1/H1 (Fig. 1).

The polymeric structure is stabilized by the C–H···O intermolecular hydrogen bonds (Table. 3) as well as by the interactions of ligands with sodium cations *via* carbonyl O5 atom, and in a monodentate manner *via* carboxylate O atoms: O1, O3 and O4, which also act as bridging atoms between  $Cd^{2+}$  and Na<sup>+</sup> ions. Additionally, sodium cations are involved in the interactions with water molecules which form networks of O–H···O hydrogen bonds (not discussed because of the complicated disorder of water molecules).

In the crystal the ribbons made up from ligands coordinated to cadmium and interacting with sodium cations, (viewed down the c axis) stretch along [100], [010] and [110] directions (Fig. 2).



Figure 2: Packing diagram viewed down c axis

# Grinding general procedure for the Knoevenagel condensation between aldehydes and malononitrile

To understand which technique presents better results, we tested first the commercial salt and the  $[CdNa_2(\mu-L^2)]_n$ :6.34H<sub>2</sub>O in solvent free conditions, using a mortar and a pestle.



Scheme 1: Synthesis of aldehydes with malonitrile and ethyl cyanoacetate uisng grindstone

#### method

Benzaldehyde was chosen for the initial assessment of the catalytic activity of the salt and complex, and also the role that the additive will have in the reaction yield.

Without catalyst the yield, after 20 min, is only 5%, while the addition of the acid promotes the reaction more intensively, producing 17% of product after 20 min. In the case of the commercial salt, the highest value of yield produced without acid is 36%, while the addition of the acid for the same amount of catalyst increases until 66%. In the case of CdHL the behavior is similar, showing that the addition of acid is beneficial to the promotion of the reaction (Table. 4).

**Table 4:** The effect of the amount of catalyst and of the nitric acid for the Knoevenagel condensation, using benzaldehyde with malonitrile using the grindstone method. <sup>a</sup>

_	Nº	Catalyst	Catalyst amount (mmol)	Nitric acid amount (mmol)	Yield (%)
	1	-	2	-	5
	2	CdO	0.05	-	30
	3	CdO	0.135	-	36
	4	$[CdNa_2(\mu-L^2)]_n$ 6,34H <sub>2</sub> O	0.04	-	31
	5	[CdNa <sub>2</sub> (µ-L <sup>2</sup> )] <sub>n</sub> 6.34H <sub>2</sub> O	0.15	-	50
6	0				
	6	CdO + $[CdNa_2(\mu-L^2)]_n^{-6.34H_2O}$	0.15+0.01	-	88



<sup>a</sup> Reaction conditions: All the reactions are carried out using benzaldehyde (1 mmol), malononitrile (1 mmol) using a pestle and a mortar, room temperature, 20 min.

To improve further the yield, we tested a mixture made in situ and observed that the yield increase to 88% without the additive and with the nitric acid reached 95%. This approach in situ has been tested previous using ball milling for oxidation reactions. In the case of Knoevenagel no report for the mixing in situ of 2 compounds that formed a very active specie. To assess if for the same total molar amount, we can have different yields due to different molar ratios of 2 metal from different sources, we tested 2 ratios and observed that increasing the ratio of CdHL increased the yield. We tested the best catalyst, with the ratio (0.15/0.01), in 2 substituted aldehydes (Table. 5). The 4-hydroxybenzaldehyde and the 2hydroxybenzaldehyde were used. For the reaction without the additive and with 4hydroxybenzaldehyde reach 86% yield while the reaction with 2-hydroxybenzaldehyde obtained 82%. Where we performed the same reactions using  $HNO_3$  as additive, all the yields increase almost 10%. It is important to mention that we observed a trend, regarding the presence of a substitute. As we can observe in the graph, the reaction with non-substituted aldehyde always obtains higher yield that the ones with substituted groups. Between the position para and orto, we observe a decrease in yield from the position 4 to 2, probably due

to steric hindrance where the OH group probably interacts with the aldehyde group, deactivating partially the reactivity.

**Table 5:** The effect of the amount of catalyst and of the nitric acid for the Knoevenagel condensation, using benzaldehyde and aldehydes derivatives with malonitrile using the grindstone method.<sup>a</sup>



<sup>a</sup> Reaction conditions: All the reactions are carried out using aldehyde (1 mmol), malononitrile (1 mmol) using a pestle and a mortar, room temperature, 20 min.

#### Knoevenagel condensation under microwave irradiation conditions

One of the green chemistry principles is the necessity of minimize the use of energy, in order to reduce the economic and environment impact of a chemical process. One step towards energy efficiency is represented by alternative energy sources, such as microwave sources. Although these technologies are not new, they are just recently emerging in process industry. In this study we use microwave irradiation to promote a faster reaction with improved yields. We tried two irradiation powers and used benzaldehyde as the test for our different catalysts. The results are in table 6. We can observe that the increase in reactional time promotes an increase in yields for all the reactions with different catalysts. In comparison with the solvent free experiments, there is a slight decrease in the yield, most likely due to the effect of the dispersion of the radiation (dipolar polarization), since the irradiation power applied is quite small (7 W).

Table 6: Effect of irradiation power on Knoe	evenagel condensations yields(%) for several
catalysts vs. reaction time.	

Entry	Catalyst	Time (min)			
		5	10	15	20
		70W			
1	CdO	14 %	20 %	29 %	37 %
2	$[CdNa_2(\mu-L^2)]_n 6.34H_2O$	38 %	43 %	47 %	59 %
3	CdO+[CdNa <sub>2</sub> ( $\mu$ -L <sup>2</sup> )] <sub>n</sub> ·6.34H <sub>2</sub> O	73 %	73 %	80 %	82%
		150 W			
4	CdO	52 %	53 %	63 %	66 %
5	$[CdNa_2(\mu-L^2)]_n 6.34H_2O$	58 %	61 %	64 %	70 %
6	$CdO+[CdNa_2(\mu-L^2)]_n 6.34H_2O$	77 %	79 %	85 %	90%

The stirring in comparison with grinding leads to decrease in the yield. More studies have to be performed to understand the role of the irradiation in the mechanism of the reaction.

In an alternative to improve the yield we tried to increase temperature, by increasing irradiation applied to the medium. We observe that when 150 W of power was applied, the temperature increased until 100°C. We can observe an increase in the yield, but in comparison with the solvent free procedure these values of yield are still smaller.

#### Conclusion

To sum up, we have synthesized the AHBD chelating ligand bearing  $\beta$ -diketone fragments as well as carboxyl groups to obtain the polymeric Cd<sup>II</sup> complex.

Regarding Knoevenagel condensation, it was found that a simple solvent-free method using a mortar and a pestle, at room temperature, achieves higher yields than the microwave technique. Therefore, the use of a solvent-free approach in fields such as synthesis in industry or medicinal and pharmaceutical in order to generate molecules of biological interest using Knoevenagel chemistry is a possibility to be explored.

Furthermore, the combination of both sources of metal to promote an increase in yield was tested for the first time and an increment in the yield due to the mixture is also an issue worth to be explored.

#### Supplementary data

CCDC 1542120 contains the supplementary crystallographic data for the title compound. These data can be obtained free of charge from the Cambridge Crystallographic data centre, 12 Union Road, Cambridge CB2 1EZ, UK. E-mail: deposit@ccdc.cam.uc.uk.

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#### **Conflicts of interest**

The authors declare no competing financial interest.

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[14] IUPAC Recommendation.

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