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# Microwave synthesis of some substituted pyridazinones and their effect on the extraction efficiency of Pb(II) and Cd(II)

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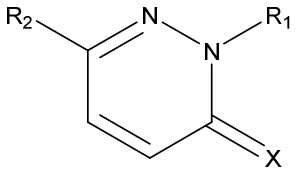
## Abstract
In this work, we study the extraction efficiency of Lead (II) and Cadmium (II) from an aqueous solution using some N-substituted pyridazines compounds synthesized by the solid-liquid Phase Transfer Catalysis conditions without any solvent using a Maxidigest MX 350 Prolabo microwave monomode reactor fitted with a rotational system. The extraction of heavy metals ions was carried out by liquid-liquid extraction from an aqueous solution ($7.10^{-5}$ M) by an organic solution of pyridazinic compounds in dichloromethane ($7.10^{-5}$ M). The percentage of extraction was measured by atomic absorption spectrometry using air-acetylene flame atomization. Our results show a significant affinity to Pb (II) against Cd (II).

*Keywords:* Pyridazine, Phase Transfer Catalysis reaction, Heavy Metal Ions, Ligand-Metal complexes, Liquid-Liquid extraction, Microwave irradiation.

## Introduction
The environmental contamination by heavy metal ions is a major world concern and an alarming global issue. Several researches were devoted to the development of various chemical compounds used especially as extracting agents from aqueous milieu [1-6]**.** Pyridazin-3 (2H)-ones are known for their important biological role in the therapeutic domain: Antihypertensive, cardiac and analgesic [7-8]. Different studies have shown that the substitution of pyridazinones at the pyridazinic nucleus leads to some interesting biological and physicochemical properties [9-11]. The substitution techniques of pyridazinones are well-documented [12-13]. For example, Taoufiq and al. synthesized the methyl-pyridazinone and the N-phenyl-pyridazinone by the action of the methyl hydrazine on 3-acetyl-4-butanolides [14]. Furthermore, Yamada and al. [15] used a Phase Transfer Catalysis alkylation (PTC) for N-alkylation of the pyridazin-3 (2H)-ones using benzene as solvent in the presence of tetrabutylammonium bromide and N-hydroxide potassium. However, we should notice that the most of the reported methods require expensive reagents, hazardous organic solvents, longer reaction time and tedious workup. In this study, the technique of microwave-assisted synthesis was used essentially for its ecological convenience. Thus, we have prepared five substituted pyridazinones (Figure 1) using a microwave irradiation technique in a nearly similar conditions of previous studies [16-18].

## 2. Material and methods
All solvents and other chemicals were purchased from commercial sources. No further purification is performed as they were of analytical grade quality. Melting points (MP) were measured using a Buchi-Tottoli apparatus and are uncorrected. Atomic absorption measurements were performed using a double beam Varian AA 20 Spectrophotometer. $^{1}$H NMR and $^{13}$C NMR spectra were recorded in $CDCl_3$ or DMSO using a Bruker AC 300 MHz ($^{1}$H) or 75 MHz ($^{13}$C) spectrometer and chemical shifts are reported as parts per million (ppm) using Tetramethylsilane (TMS) as an internal standard. The Infrared (IR) spectra were recorded on a Perkin-Elmer Fourier Transformer FT Pargamon 1000 PC Spectrophotometer using potassium bromide disks (KBr).




1: $R_1$= H; $R_2$= Ph; X= O [19]
2: $R_1$=$CH_2CH_2OH$; $R_2$= Ph, X=O [20]
3: $R_1$= CH2COOEt; $R_2$= Ph; X=O [21]
4: $R_1$= CH2COOEt; $R_2$= Ph; X=S [21]
5: $R_1$= CH2COOEt; $R_{2=}$ CH3; X=O [22]

**Figure 1:** Chemical structure of the studied pyridazinones

*2.1. Chemistry*

*2.1.1. Synthesis of 6-phenylpyridazin-3 (2H)-one (1).*

15g (0,086 mol) of 6-phenyl-4,5-dihydropyridazin-3(2H)-one were dissolved in 41 mL of acetic acid and heated to 50 °C, then 12,7 mL (0,246 mol) of $Br_2$ was added dropwise into the solution without cooling. The reaction is exothermic with an abundant release of hydrogen bromide gas. The mixture was allowed to stand for four hours before adding 55 mL of glacial acetic acid and 18 g (0,225 mol) of sodium acetate. This milieu was refluxed for 20 min. Acetic acid was then evaporated under reduced pressure and 103 mL of water was added to the residue and heated to boiling for 10 minutes. A solid: 6-phenylpyridazin-3 (2H)-one was obtained after cooling and recrystallizing in ethanol with the following physicochemical properties:

MP: 120 °C; Yield = 95 %.

IR ($cm^{-1}$): 3208,6 (NH); 3092,2 (C=C); 2857,9 (C-H); 1648 (C=N).

$^1$H NMR (ppm): 7,09 (d, CH-CO); 7,12 (d, CH-C Ar-N); 7,26 (s, NH); 7,49 (dd, 3H de Ar); 7,786 (d, 2H de Ar).

*2.1.2. Synthesis of (6-phenyl-3oxopyridazin-2-yl) ethanol (2)*

In a Pyrex tube we put 1 g (6 mmol) of Pyridazine (1), 2,75 g (20 mmol) of potassium carbonate, 0,3 g (1 mmol) of TBAB and 0,73 g (6 mmol) of 2-bromoethanol. The Pyrex tube was then introduced into a Maxidigest MX 350 Prolabo microwave monomode reactor fitted with a rotational system. At the end of the irradiation time (10 min on 90 W as irradiation power), the mixture was cooled to ambient temperature. After elution with ethyl acetate (30 mL) and subsequent filtration on florisil, the organic product was purified by chromatography on silica gel using dichloromethane as eluent.

MP= 98 °C; Yield = 92 %

IR($cm^{-1}$): 3337,9 (O-H), 3090,6-3058,9 (Csp2-H of C=C-H: ASY, SY), 2996,6-2950,8-2876,2 (Csp3-H), 1652,3 (CON), 1589,3 (C=C), 1070,2 (C-O).

$^1$H NMR (ppm): 3,04 (s, OH); 4,07 (t, $CH_2$-N); 4,46 (td, $CH_2$-OH); 7,06 (d, CH-C Ar-N); 7,44 (d, CH-CO); 7,46 (dd, 3H of Ar); 7,7 (d, 2H of Ar).

$^{13}$C NMR: 55,4 ($CH_2$-N); 61,7($CH_2$-OH); 125,9 (CH-CO); 129,05 (m, 2CH of Ar); 129,71 (o, 2CH of Ar); 130,09 (p, CH); 134,42 (C de Ar); 145,3 (CH-C Ar-N); 161,03 (CO).

*2.1.3. Synthesis of ethyl 2-(6-oxo-3-phenylpyridazin-1(6H)-yl) acetate (3).*

To 1 g of pyridazine (1) (6 mmol) we added 2,75 g ( 20 mmol) of potassium carbonate, 0,3 g (1 mmol) of TBAB and 1 g (6 mmol) of ethyl 2-bromoacetate. The mixture was treated as described above in *2.1.2*. The mixture was filtered and concentrated under vacuum then the precipitated crystals was washed with petroleum ether and dried in an oven at 60 °C. The ethyl 2-(6-oxo-3-phenylpyridazin-1(6H)-yl) acetate was obtained.

MP= 90°C; Yield = 92,1 %.

IR($cm^{-1}$): 3059,4 (Csp2-H of =C-H), 2984,3 (Csp3-H of CH2), 1750 (C=O of the ester group), 1674,4 (CON), 1595,9 (C=C), 1209,9 (C-N), 1027,3, 1208 (C-O-C sym and asym).

$^1$H NMR (ppm): 1,29 (t, $CH_3$); 3,78 (s, $CH_2$-CO); 4,25 (q, O-$CH_2$); 4,97 (d, CH-C Ar-N); 7,05 (d, CH-CO); 7,42 (dd, 3H de Ar); 7,71 (d, 2Hde Ar).

$^{13}$C NMR: 14,1 (CH3); 53,7 ($CH_2$-CO); 61,5 ($CH_2$-O); 126,05 (CH-CO); 128,9 (m, 2CH of Ar); 129,6 (o, 2CH of Ar); 130,1 (p, CH of Ar); 134,4 (C of Ar); 145,02 (CH-C Ar-N); 159,7 (C=O); 167,3 (COOEt).

*2.1.4. Synthesis of ethyl 2-(3-phenyl-6-thioxopyridazin-1(6H)-yl) acetate (4).*
To 1 g of pyridazine (3) 1 g (4 mmol) we added 1,32 g (3 mmol) of phosphorus pentasulfide. The mixture was treated as in *2.1.3*. The mixture was cooled to ambient temperature then 10 mL of boiling water was added and the mixture allowed cooling, the formed precipitate was filtered and recrystallized using ethyl acetate. The obtained compound was ethyl 2-(3-phenyl-6-thioxopyridazin-1(6H)-yl) acetate.
MP= 96°C; Yield = 90,65 %.
IR($cm^{-1}$): 3486,6 (trace of water), 3059 (Csp2-H of C=C-H), 2984 (Csp3-H of $CH_2$), 1749,2 (C=O of ester group), 1674,3 (C=S), 1595 (C=C) 1027, 1208 (C-O-C sym, asym).
$^1$H NMR (ppm): 1,29 (t, $CH_3$); 3,8 (s, $CH_2$); 4,25 (q, $CH_2$); 4,9 (d, CH-C Ar-N); 7,05 (d, CH-CS); 7,43 (dd, 3H of Ar); 7,71 (d, 2H of Ar).
$^{13}$C NMR: 14,1 ($CH_3$); 53,7 ($CH_2$-N); 61,7 ($CH_2$-O); 126,05 (m, 2CH Ar); 128,95 (o, 2CH); 129,6 (p, CH); 130,6 (CH=CS); 131 (CH=C Ar-N); 134,4 (C Ar); 145 (C); 159,6 (COO); 167,3 (C=S).

*2.1.5. Synthesis of ethyl (6-methyl-3-oxopyridazin-2-yl) acetate (5).*
The product (5) was prepared by the solid-liquid PTC conditions without solvent from 6-methylpyridazin-3(2H)-one. In a Pyrex tube we put 1 g (9 mmol) of 6-methylpyridazin-3 (2H)-one, 1,24 g (9 mmol) of potassium carbonate, 0,3 g (1 mmol) of TBAB and 0,73 g (4 mmol) of ethyl 2-bromoacetate. The tube was irradiated as explained above and the obtained mixture was filtered and concentrated under vacuum then the precipitated crystals was washed with petroleum ether and dried at 60 °C. The ethyl 2-(6-oxo-3-methylpyridazin-1(6H)-yl) acetate was obtained.
MP= 76°C; Yield = 84,3 %
IR($cm^{-1}$): 3053(Csp2-H of C=C-H), 2987,9-2961,3(Csp3-H of CH3 Asym, Sym), 2875,2 (Csp3-H of $CH_2$), 1752,5(C=O ester), 1673,7 (CONH), 1599,5(C=C), 1033, 1208 (C-O-C Asym, Sym)
$^1$H NMR (ppm): 1,00(s, $CH_3$); 1,27(t, $CH_3$); 2,309(s, $CH_2$); 4,220(q, $CH_2$); 6,88(d, CH); 7,110(d, CH)
$^{13}$C NMR: 14,09($CH_3$); 20,68($CH_3$ de OEt); 52,9($CH_2$); 61,5($CH_2$ de OEt); 129,92(CH-CO); 133,96(CH-$CCH_3$); 144,14(C-$CH_3$); 159,66(C=O); 167,58(COOEt).

***2.2. Liquid-Liquid Extraction***
*2.2.1 Preparation of the organic solution $7.10^{-5}$ M*
The organic solution was prepared by dissolving, in 150 mL of dichloromethane, an amount $m_i$ of the pyridazinic compounds. The table 1 shows the used amounts for the preparation of the organic solution $7.10^{-5}$ M.

**Table 1:** Required masses for the preparation of organic solutions $7.10^{-5}$

| Compound | m(mg) | M($g.mol^{-1}$) | $VCH_2Cl_2$(mL) |
|---|---|---|---|
| 1 | 1,81 | 172,18 | 150 |
| 2 | 2,27 | 216,24 | 150 |
| 3 | 2,71 | 258,27 | 150 |
| 4 | 2,88 | 274,34 | 150 |
| 5 | 2,06 | 196,2 | 150 |

**Table 2:** Liquid-Liquid Extraction of Lead (II) and Cadmium (II)

| Compound | %E Pb(II) | %E Cd(II) |
|---|---|---|
| 1 | 36,8 | 0 |
| 3 | 38,2 | 2,9 |
| 2 | 37,0 | 0 |
| 4 | 36,2 | 3,0 |
| 5 | 36,2 | 0 |

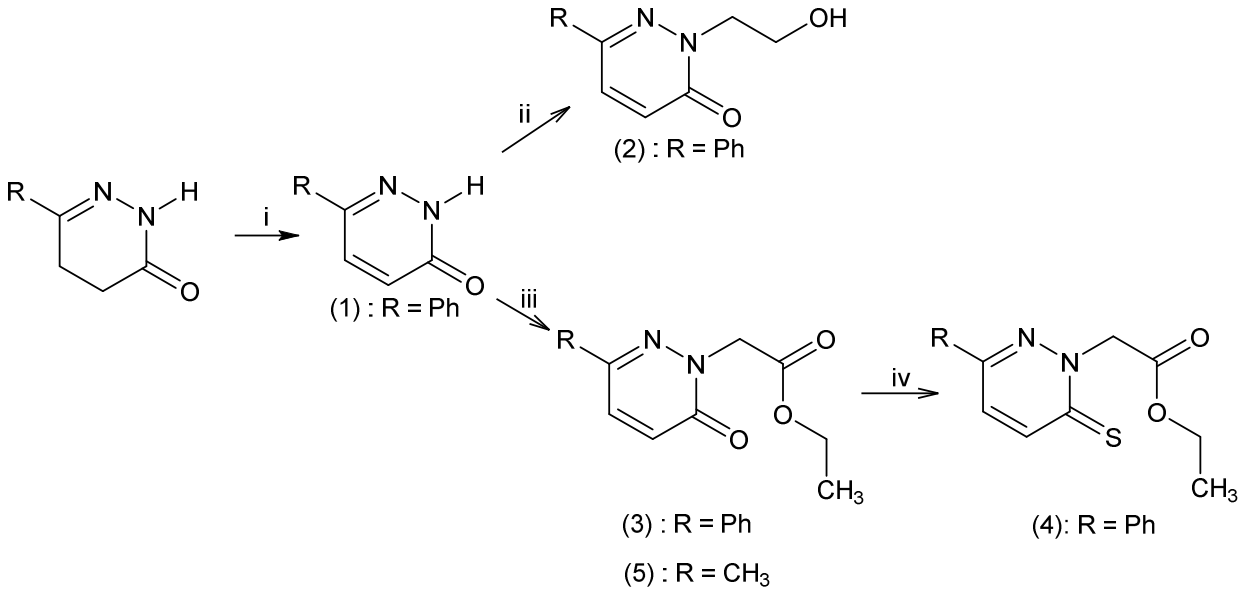
*2.2.3 Implementation of the liquid-liquid extraction*
The organic solution is brought into contact, in a beaker, with aqueous solution containing the heavy metal ions at a concentration of $7.10^{-5}$M. Magnetic stirring for 2 hours ensures the contact between the two immiscible

phases. This time is considered largely sufficient to reach the equilibrium during which the pH of the mixture is maintained neutral and the temperature at room temperature 25 °C [23-26]. Once the equilibrium is achieved, the two phases are separated by decantation and the aqueous phase is collected and analyzed using atomic absorption spectrophotometer Varian A20. The results of the liquid-liquid extraction percentage are listed in Table 2.

## 3. Results and discussion

*3.1 Chemistry*

The synthesis of pyridazinones was initiated by a dehydrogenation step of 6-phenyl-4,5-dihydropyridazin-3(2H)-one in presence of bromine. This step lead to the formation of 6-phenylpyridazin-3 (2H)-one (**1**), the latter, under microwave conditions lead to the formation of (6-phenyl-3oxopyridazin-2-yl) ethanol (**2**) by action of 2-bromoethanol and to the formation of ethyl 2-(6-oxo-3-phenylpyridazin-1(6H)-yl) acetate (**3**) by action of 2-bromoacetate. The action of Phosphorus Pentasulfide on pyridazinone (**3**), under microwave conditions, lead to the formation of ethyl 2-(3-phenyl-6-thioxopyridazin-1(6H)-yl) acetate (4). The ethyl (6-methyl-3-oxopyridazin-2-yl) acetate (**5**) is synthesized from 6-methylpyridazin-3 (2H)-one and 2-bromoacetate in presence of TBAB.




**Scheme 1:** Synthesis process of pyridazinones. Reagent and conditions: i) acetic acid, 50°C, $Br_2$, glacial acetic acid, sodium acetate, 20 min. ii) Potassium carbonate, TBAB, 2-Bromoethanol, microwave 10 min 90w. iii) Potassium carbonate, TBAB, 2-bromoacetate, microwave 10 min 90w. iv) $P_2S_5$, microwave 10 min 90w.

*3.2 Liquid-Liquid Extraction*

Our results show that the five ligands present a remarkable affinity for Pb(II) ions compared to Cd(II). The extraction efficiency reaches 38 % for Pb(II) while it doesn't exceed 2% in the case of Cd(II). On the other hand, taking into account the structural differences between the studied pyridazinones, several remarks can be deduced:

- The pyridazinones 1, 2 and 3 show a structural difference in the substituent attached to the nitrogen N1 of the Pyridazinic ring. This substitution seems to be ineffective regarding the extraction efficiency of the two metal ions under consideration.
- Similarly, the comparison of the extraction percentage of ligand 2 with the ligand 4 shows clearly that sulfurization of the pyridazinic ring does not improve the extraction as the difference does not exceed 2%.
- Finally, the substitution of phenyl by a methyl does not hugely improve the extraction level, as it remains comparable for the two ligands 2 and 5.

## Conclusion

In conclusion, we tested the effect of substitution of a series of pyridazinones on the extraction efficiency of Lead (II) and Cadmium (II) metal ions. In these conditions, our results show a significant affinity for Lead (II) and very poor performance for Cadmium (II). Some other substituted pyridazines must be synthesized in order to improve the extraction efficiency through introducing various electron-donating substituents, which may enhance coordination bonds occurrence with these two metals.

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