Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2016, 8(11): 75-82

Research Article

ISSN : 0975-7384

CODEN(USA) : JCPRC5

Heterogeneous Catalyst BaO-KF: Dry Synthesis of Thioaurones as Cytotoxics Agents under focused Microwaves Irradiation

Benferraha N[1], Hammadia M[2], Villeminc D[3]

[1]*URMPE Research Unit for Materials, Processes and Environment, University M'hamed Bougara Boumerdes, Faculty of Engineering Sciences, Boumerdes, 35000 Algeria.*

[2] *Center for Scientific and Technical Research in the Physical Chemical Analysis (CRAPC), Boumerdes, 35000 Algeria; e-mail: benferrahnassima@gmail.com.*

[3]*Ensicaen, LCMT—UMR 6507 CNRS, University of Caen, Caen 14050, France*

ABSTRACT

Benzo[b]thiophen-3(2H)-one and naphto[2,1-b]thiophen-3(2H)-one was condensed in the presence of barium oxide on potassium fluoride with aromatic aldehydes to give 2-arylméthylidène-1-benzothiophèn-3-ones (1) (thioaurones) without solvent under focused microwave irradiation. It is a efficient catalyst basic in knoevenagel condensation reaction.

Keywords: Solid basic; Microwave irradiation; Dry reaction; Thioaurones, 2-arylthioacetic, without solvent

---

INTRODUCTION

One of the main problems in the chemical industry is the search for tolerable procedures for chemical production. There is a growing demand in development of selective, efficient and environmentally appropriate synthetic methods. Molecules containing heterocyclic structures often have interesting biological properties [1]. These molecules are still important targets for chemical synthesis. Among the flavonoids [2] which are compounds well known to have physiological activities in various fields, Aurones or 2-arylmethylenes-3 (2H) -benzofuranones are very strong yellow colored natural pigments and constitute a particular subgroup, where the usual carbon cycle is replaced by a five-membered heterocyclic ring.

By analogy to aurones thioaurones have a long history as dyes (hemithioindigos). These are potential cytotoxic [3] agents and components for the cosmetic industry. The term thioaurones was introduced by O'Sullivan [4] as a trivial name for the sulfur analogues of aurones, and referred to 2-benzylidenebenzo [b] thiophen-3 (2H) -one derivatives. However, their chemical behavior is less well studied (Figure 1).

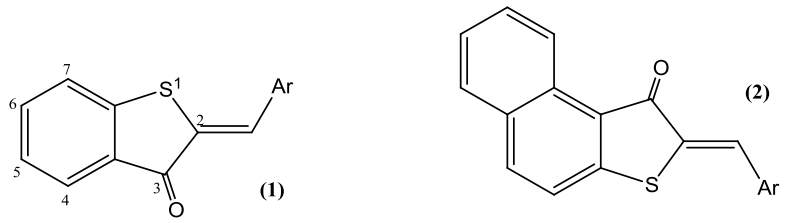


Figure 1: Thioaurones.

The synthesis of thioaurones was carried out almost a century ago by Levai [5]. Despite the growing interest in aurones as potential medicinal agents [6], The chemists have borne a similar interest to thio analogues. In addition, these compounds can be used as aqueous jet-printing ink and as a packaging aid for the thermometer.

In the literature, several methods of synthesis of thioaurones have been reported: a two-step process requiring the preparation and isolation of 1-benzothiophen-3-one, and its condensation with aromatic aldehydes [7,8]. Other multi-step processes start from epoxy [9] compounds, or 2-mercaptobenzoate [10], or from α, β-esters of acetylene [11].

The oldest method [12,13] of synthesis of thioaurones is the condensation of aromatic aldehydes with 1-benzothiophen-3-one. The reaction is carried out under reflux in ethanol in the presence of concentrated hydrochloric acid. Cabiddu et al [14]. Has described an elegant method in which thioaurones are generated in situ by lithiation at 0 ° C of methyl 2- (methylthio) benzoate in the presence of aldehydes. Sukanta Kamila [15] synthesized thioaurones by treating N, N-diethyl-2-methylsulfanyl arylamides with aromatic aldehydes in the presence of lithium diisopropylamide (LDA) in THF at 0 ° C under argon.

we have already reported [16] that five-membered ring compounds with a carbonyl groupe, like tetronic acid , pyrazolone, or rhodanine exhibit a high carbon acidity due to the pseudo-planar structure. These compounds consequently can be condensed easily with aldehydes in the presence of a solid catalyst (montmorionite-KSF, Al_2O_3, BaO-KF) without solvent (dry condensation).

The current study is devoted to the synthesis to the synthesis of 2-arylméthylidène-1-benzothiophèn-3-ones **(1) (**thioaurones) by condensation of aromatic aldehyde with Benzo*[b]*thiophen-3(2H)-one and with naphto[2,1-*b*]thiophen-3*(2H)*-one catalyzed by BaO-KF without solvent under focused microwave irradiation (MWI) (Scheme.3).

EXPERIMENTAL SECTION

Melting points (m.p) were determined with a Kofler hot apparatus and are uncorrected. Proton NMR spectra (PMR) were determined on Brucker AC 250 (250 MHz, CDCl3, Me4Si. The IR spectra were recorded as KBr pellets on JASCO FT/IR-4100. Microwave irradiation were carried out with a commercial microwave oven

(Whirlpool WMC10007AW) at 2450 MHz. and with resonance cavity TEo13, joined to a generator MES 73-800 of microwaves. MES 73-800 of microwaves.

Procedure for preparation of arylthioacetic acid

Into a 100 ml flask are placed chloroacetic acid (100 mmol, 9.45 g) and thiophenol (100 mmol, 11 g) in the presence of sodium hydroxide NaOH (8 g dissolved in 20 ml of water).The reaction mixture is placed under magnetic stirring for 20 min.Then activated under microwave (open container) at a power of 420 W for 5 min. The irradiated product is taken up with 2 ml of water,

Then acidified by hydrochloric acid addiction to pH = 2. The resulting precipitate is separated by simple filtration on a sintered glass. The solid obtained is dried in an oven for 2 hours. It is then identified by spectroscopic methods (infrared, Proton nuclear magnetic resonance and mass spectrum).

2-phenythioacetic acid (1)

Withe solid, $C_8H_8O_2S$, MM; 168.21 g. mol^{-1}, yield; 85 %, Mp; 63-64 °C, IR (KBr, ν cm^{-1}); 3200 (ν OH), 2510, 1718 (ν C=O), 1584 (ν C=C), 1492, 1436, 1398, 1321, 1199 (ν CH_2-S-Ar), 1102, 1083, 1034, 911, 747, 695 (ν CHarom), 672, 481; NMR ^1H ($CDCl_3$, δ ppm); 3.84 (s, 2H, CH_2), 7.25-7.45 (m, 5H, H_{arom}), 11.2 (s, 1H).

2-(Naphtalen-2-ylthio) acetic acid (2)

Prepared from 2-naphtalenethiol (100 mmol, 16 g); yelllow solid, $C_{12}H_{10}O_2S$, MM; 218.1 g.mol^{-1}, yield; 75 %, Mp; 175 °C; IR (KBr) ν cm^{-1}; 3300 (ν OH-libre), 1711, 1672 (ν C=O), 1666 (ν C=C), 1432, 1256, 1190 (ν S-Ar), 1182, 1029, 900, 842(ν CHsubs), 748. NMR ^1H ($CDCl_3$, δ ppm) : 4.85 (s, 2H, CH_2), 7.20-7.95 (m, 7H, H_{arom}).

Procedure for preparation of Benzo*[b]*thiophen-3(2H)-one

2-Phenanthioacetic acid (80 mmol, 13.45 g) is placed in a 250 ml round bottom flask and then heated under reflux for one hour in the presence of thionyl chloride (excess) and 2 drops of dimethylformamide (DMF). After cooling the thionyl cholide is separated by simple distillation to obtain the corresponding chloride. The chloride formed is added gently (dropwise) in a solution of AlCl 3 aluminum trichloride (10 g dissolved in 40 ml of dichloromethane), The reaction mixture is brought to reflux for half an hour, Then treated with ice water. The solution obtained is extracted with ether (4 × 100 ml). The organic phase is dried over magnesium sulphates $MgSO_4$ and then filtered. After evaporation of solvent using a rotary evaporator, A beige solid is obtained.

Benzo*[b]*thiophen-3(2H)-one (3)

Solid beige, C_8H_6OS, MM; 150.19 g. mol^{-1}, yield; 70 %, Mp; 70°C; IR (KBr, ν cm^{-1}); 1690 (ν C=O), 1608 (ν C=C); NMR ^1H ($CDCl_3$, δ ppm); 4.10 (s, 2H, CH_2), 7.35 (t, 1H, Harom), 7.53 (d, 1H, Harom), 7.57(t, 1H, Harom), 7.88 (d, 1H, Harom).

Naphto[2,1-*b*]thiophen-3*(2H)*-one (4)

Prepared from 2-(Naphtalen-2-ylthio)acetic acid (80 mmol, 17,44 g); yellow solid; $C_{12}H_8OS$; MM; 200.3 g. mol^{-1}, yield;75 %, Mp;180°C, IR (KBr, ν cm^{-1}); 1695 (ν C=O), 1611 (ν C=C), 1211 (ν S-Aryl); NMR ^1H ($CDCl_3$, δ ppm); 4,78 (s, 2H, CH_2); 7.28-8.71 (m,7H, Harom).

General procedure for preparation of 2-(Arylmethylidene)-1-benzothiophen-3-ones (thioaurones)

Into a 50 ml Erlenmeyer flask are placed benzo*[b]*thiophen-3(2H)-one (10 mmol, 1.5 g) and the corresponding aromatic aldehyde. The reaction mixture assembly is activated under microwave irradiation at a power of 480 W for 5 min in the presence of basic catalyst BaO-KF (3 g).

2-(Benzylidene)benzo[*b*]thiophen-3-one (5a)

Prepared from benzaldehyde (10 mmol; 1,06 g), Red solid , $C_{15}H_{10}OS$, MM; 238.16 g.mol^{-1}, yield; 78 %, Mp; 132 °C, IR (KBr, ν cm^{-1});1695 (ν C=O), 1202(ν S-Aryl); NMR ^1H ($CDCl_3$, δ ppm); 7.32 (t, 1 H), 7.41 (t, 1 H), 7.49 (t, 2 H); 7.51 (d, 1 H); 7.60 (t, 1 H); 7.70 (d, 2 H, H); 7.95 (d, 1 H); 8.10 (s, 1 H, C=CH); NMR ^{13}C ($CDCl_3$, δ ppm): 123,8 (CH=), 125, 125.7, 129.5, 129.7, 131.1, 131.3, 132.9, 133.6; 133.7, 139.1, 141.3, 192.5(C=O).

2-(4-ChloroBenzylidene)benzo[*b*]thiophen-3-one (5b)

Prepared from 4-chlorobenzaldehyde (10 mmol, 1.4 g), yellow solid, $C_{15}H_9ClOS$, MM; 272.75 g. mol^{-1}, yield; 79 % , Mp; 160-162°C, IR (KBr, ν cm^{-1}): 1681 (ν C=O), 1585(ν C=C), 1215 (ν S-Aryl), 770 (ν C-Cl); NMR ^1H ($CDCl_3$, δ ppm): 7.35 (d, 1H), 7.53-7.45 (m, 3H), 7.59-7.67 (m, 3H), 7.88 (d, 1H), 7.99 (s, 1H)

2-(3-Phenylallylidene)benzo[*b*]thiophen-3-one (5c)

Prepared from cinnamaldehyde (10 mmol, 1,32 g), red solid, $C_{17}H_{12}OS$, MM; 264.34 g. mol^{-1}, yield; 75 %, Mp;135-140°C, IR (KBr, ν cm^{-1}): 1666(ν C=O), 1585(ν C=C), 1564, 1199 (ν S-Aryl); RMN ^1H ($CDCl_3$, δ ppm): 7.15-6.85 (m, 2H), 7.65-7.30 (m, 8H), 7.64 (d, 1H), 8.14 (d, 1H).

2-Benzylidene naphtho[2,1-b]thiophen-1-one (6a):

Prepared from benzaldehyde (10 mmol, 1,06 g) and Naphto[2,3-*b*]thiophen-3*(2H)*-one (10 mmol ; 2 g), yellow solid, $C_{19}H_{12}OS$, MM; 288.14 g. mol^{-1}, yield; 80 % , Mp;185-186°C, IR (KBr, ν cm^{-1}): 1676 (ν C=O), 1562 (ν C=C), 1209 (ν S-Aryl); NMR ^1H ($CDCl_3$, δ ppm): 7.38-7.58 (m, 5H, Harom), 7.70-8.10 (m, 3H, Harom), 8.13 (s, 1H, CH=C), 8.15 (d, 1H, Harom).

2-(4-Chlorobenzylidene)naphtho[2,1-b]thiophen-1-one (6b).

Prepared from 4-chlorobenzaldehyde (10 mmol, 1,4 g) and Naphto[2,3-*b*]thiophen-3*(2H)*-one (10 mmol ; 2 g), yellow solid, $C_{19}H_{11}ClOS$, MM; 322.59 g. mol^{-1}, yield; 91 %, m.p.215-217°C, IR (KBr, ν cm^{-1}): 1682 (ν C=O), 1613 (ν C=C), 1213 (ν S-Aryl); NMR ^1H ($CDCl_3$, δ ppm); 7.42-7.62 (m, 4H, Harom), 7.95 (s, 1H, CH=C), 8.03 (d, 1H, Harom), 8.90 (d, 1H, Harom).

2-(3-Phenyallylidene) naphtho[2,1-b]thiophen-1-one (6c).

Prepared from cinnamaldehyde (10 mmol, 1,32 g) and Naphto[2,3-*b*]thiophen-3*(2H)*-one (10 mmol ; 2 g), red solid, $C_{17}H_{10}OS_2$, MM; 294.48 g. mol^{-1}, yield; 90 %, Mp; 181°C, IR (KBr, ν cm^{-1}); 1680 (ν C=O), 1608 (ν C=C), 1205 (ν S-Aryl); NMR ^1H ($CDCl_3$, δ ppm); 7.07-7.10 (m, 1H), 7.40-7.46 (m, 3H), 7.52-7.61(m, 2H), 7.75 (d, 1H), 8.16 (d, 1H, CH=C), 8.92 (d, 1H), 9.25 (d, 1H).

2-(4-Methoxybenzylidene)naphtho[2,1-b]thiophen-1-one (6d)

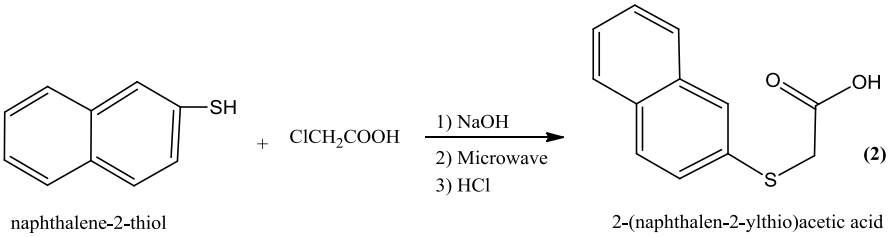
Prepared from p-anisaldehyde (10 mmol, 1,36 g) and Naphto[2,3-*b*]thiophen-3*(2H)*-one (10 mmol ; 2 g), green solid, yield 74%, Mp; 202°C, $C_{18}H_{14}O_2S$, MM; 294.15 g.mol^{-1}, IR (KBr, ν cm^{-1}); 1690 (ν C=O), 1610 (ν C=C) 1211 (ν S-Aryl); NMR ^1H ($CDCl_3$, δ ppm); 4.02 (s, 3H, CH_3O), 7.35 (d, 2H, H arom), 7.50-7.65 (d, 2H, H arom), 7.84 (t, 1H, H arom), 7.9 -8.23 (d, 3H, H arom), 8.11 (s, 1H, CH=C), 8.35 (d, 1H, H arom), 9.16 (d, 1H, H arom);

RESULTS AND DISCUSSION

Organic solvents are not only expensive, but are often flammable, toxic and environmentally hazardous. Generally the use of solvent is considered to be necessary in organic reactions. The use of phase transfer catalysts [17], dry reactions [18] and reactions between solids [19] were recently proposed as partial alternatives to reactions in solvent. In all these processes organic solvents were used for the extraction of final organic products. In the special case of poorly acid compounds, the use of organic solvent was not necessary. We report herein an example of such desirable process where only water is used.

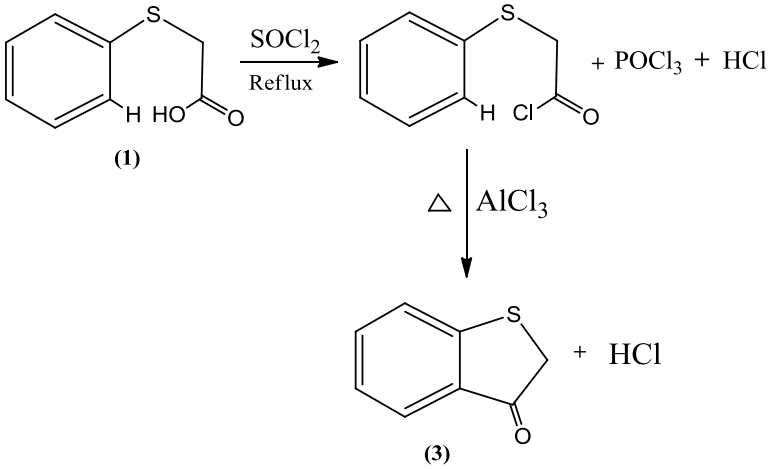
We have previously reported [20] that condensation catalysed by sodium hydroxide is efficient under microwave irradiation in the presence of a small amount of water which allows the diffusion of reactive species and also gave a large dielectric loss with microwaves.

We have obtained good yields of **(1)** and **(2)** after reaction of sodium phenolate with sodium chloracetate in the minimum of water under microwave irradiation, dissolution of product in water, and then an acidification according to the Scheme.1.



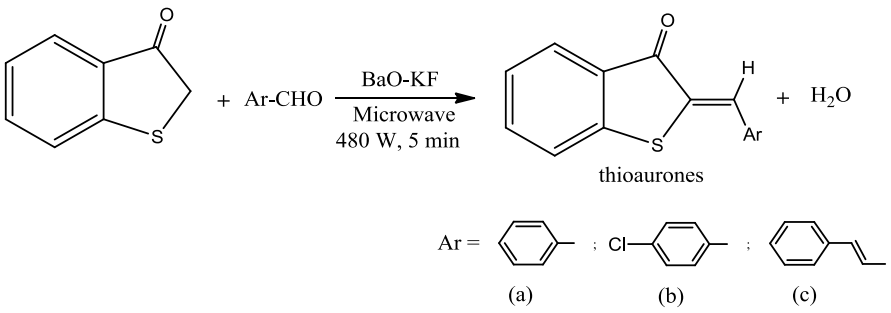
Scheme1

The previously prepared 2-phenylthioacetic acid **(1)** is brought to reflux with thionyl chloride to give the corresponding acid chloride. Its cyclization by intramolecular reaction according to Friedel-Crafts made it possible to obtain benzo [b] thiophen-3 (2H)-one (3) in a yield of 70% (Scheme.2).



Scheme 2

The cyclized product Benzo*[b]*thiophen-3 (2H)-one **(3)** and naphtho [2,1-b] thiophen-3 (2H) Comprising the methylene active (CH_2) undergoes condensation with the aromatic aldehydes according to the reaction of Knoevenagel in the presence of the basic catalyst BaO-KF by activation under microwave irradiation (P: 480 W) for 5 min. thioaurones are obtained in good yields (Scheme 3).



Scheme 3

Table. 1: The physical and analytical data of thioaurones.

Ar	Product	color	^{1}HNMR δ: ppm C=CH-	IR ν: cm^{-1} Ar-S-	Yield (%)
C_6H_5-	**5a**	Red	8.10	1202	78
4-Cl- C_6H_4-	**5b**	Yellow	7.99	1215	79
C_6H_4-CH=CH-	**5c**	Red	8.14	1199	75
C_6H_5-	**6a**	Yellow	8.13	1209	80
4-Cl- C_6H_4-	**6b**	Yellow	7.95	1213	91
C_6H_4-CH=CH-	**6c**	Red	8.16	1205	90
4-CH_3O-C_6H_4-	**6d**	Green	8.11	1211	74

CONCLUSION

Benzo*[b]*thiophen-3(2H)-one **(3)** and Naphto[2,1-*b*]thiophen-3*(2H)*-one **(4)** were condensed efficiently and rapidly in the presence of BaO-KF with aromatic aldehydes into 2-(Arylmethylidene)-1-benzothiophen-3-ones **(5)** and 2-(Arylmethylidene)-naphtho[2,1-b] thiophen-1-one **(6)** without solvent under focused microwave irradiation. The method is very simple, safe and convenient.

REFERENCES

[1] A Katritzky, CW Rees, EF Scriven. Comprehensive Heterocyclic Chemistry. Elsevier Science. Oxford, U.K., 1996
[2] JB Harbone, TJ Mabry, H Mabry. Chapman and Hall. London, 1975.
[3] (a) MT Konieczny, W Konieczny, S Okabe, H Tsujimoto, Y Suda, K Wierzba, Chem. Pharm. Bull. 2006, 54, 350; (b) T Kataoka, S Watanabe, E Mori, R Kadomoto, S Tanimura, M Kohno. Bioorg. Med. Chem., 2004, 12, 2397
[4] SS Liam,WI O'Sullivan, J. Chem. Soc., Perkin Trans., 1977, 1, 1009.
[5] A Lévai. Arkivoc., 2004 (vii), 15-13.
[6] A Boumendjel. Curr. Med. Chem., 2003, 10, 2621.
[7] K Auwers, F Arndt. Chem. Ber., 1909, 42, 537.
[8] S Rajappa. Comprehensive Heterocyclic Chemistry. ed. A. R. Katritzky and C. W. Rees, Pergamon. Oxford. 1984, 4 (14), 822.
[9] H Hofmann, H Westernacher, H Haberstrah. J. Chem. Ber., 1973, 106, 349
[10] AW Taylor, DK Dean. Tetrahedron Lett., 1988, 29, 1845
[11] DH Wadsworth, MR Detty. J. Org. Chem., 1980, 45, 4611
[12] k Auwers, F Arndt. Ber., 1909, 42, 537.
[13] P Friedlaender. Monatsh. Chem., 1909, 30, 347.
[14] MG Cabiddu, S Cabiddu, E Cadoni, S De Montis, C Fattuoni, S Melis, M. Usai. Synthesis, 2002, 875.
[15] K Sukanta, M Chandrani, P Tarun Kanti, D Asish, Arkivoc, 2006 (ii), 45-60
[16] D Villemin, B Labiad. Synth. Commun., 1990, 20, 3207; b) D. Villemin , B. Labiad. Synth. Commun., 1990, 20, 3213 ; c) D. Villemin, M. Ricard. Synth. Commun., 1987, 17 , 283; d) D. Villemin, A. Ben Alloum, B. Labiad. J. Chem. Soc. Chem. Commun., 1989, 386
[17] A Loupy, G. Bram, J Sansoulet. New J. Chem., 16,233 (1992).
[18] G Bram, A Loupy A, DVillemin. in "Solid supports and catalysts in organic synthesis", Chap. 12, 302, Ellis Horwood and Prentice Hall., 1992.

[19 F Toda, K Tanaka, S Iwata, J. Org. Chem., 1984, 54, 3007, F Toda, K Tanaka K Hamai, J. Chem. Soc. Perkin 1., 1990, 3207; F Toda, K Tanaka,Y Kagowa, Y Sakaino, Chem. Lett., 1990, 373; Z Rongshun, P Hong, S Dai, Synth. Commun., 1994, 24, 2417.
[20] D Villemin, B Martin, M Puciova, S Toma, J. Organomet. Chem., 1994, 484, 27; D Villemin, F Sauvaget, Synlett., 1994, 435.