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Application of Friedel-Crafts acylation of 2(3*H*)-benzoxazolone and 2(3*H*)-benzothiazolone using AlCl₃ supported on silica gel under solvent-free conditions

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Informations	Abstract
Keywords : silica gel-AlCl ₃ 2(3 <i>H</i>)-benzothiazolone 2(3 <i>H</i>)-benzoxazolone Friedel-Crafts reaction solvent free conditions	Catalytic Friedel-Crafts acylation of 2(3 <i>H</i>)-benzoxazolone and 2(3 <i>H</i>)-benzothiazolone has been achieved using aluminum chloride (AlCl ₃) supported on silica gel as catalyst under solvent free conditions. The obtained Ketones were characterized and confirmed by physical and spectroscopic data. The catalyst is recyclable and stable at room temperature, and the reaction protocol is simple, cost-effective, and gives good isolated yield with high purity.
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1. Introduction

The 6-acyl-2(3*H*)-benzoxazolones and 6-acyl-2(3*H*)-benzothiazolones derivatives in particular which exhibit analgesic and anti-inflammatory properties, are an important intermediates and building block in organic synthesis, and they constitute the basis of pharmacological development in the design of new pharmacophores [1-4]. Due to their wide range of applications, the syntheses of these derivatives by Friedel-Crafts acylation (FC) reaction, have received a great deal of attention [5-10].

A lot of most straight forward protocols, such as polyphosphoric acid (PPA), and Lewis acids such as AlCl₃, ZnCl₂ and FeCl₃ which are used in *N,N*-dimethylformamide as solvent using the mostly acylating agents, organic acids, acid anhydrides or acid chlorides have been reported [11-17]. However, they have intrinsic limitations such as, the use of a large excess of the catalysts, the reactivity substrate requirement and the fact that recovery and recycling of the catalyst is seldom possible after aqueous work-up, and a large amount of toxic waste which is generated [17].

In recent years, the use of heterogeneous catalysts has received considerable attention in different areas of organic synthesis because of their

easiness of handling, enhanced reaction rates, greater selectivity, simple workup, and recoverability of catalysts [18-24]. On the other hand, acylation of 2(3*H*)-benzoxazolone and 2(3*H*)-benzothiazolone in such conditions has not been reported till now.

In order to determine the scope of heterogeneous catalysts for the synthesis of 6-acyl derivatives, we decided to explore the Friedel-Crafts reaction of 2(3*H*)-benzoxazolone and 2(3*H*)-benzothiazolone with acid chlorides using aluminum chloride supported on silica gel as a catalyst SiO₂-AlCl₃ (Fig.1) [25, 26].

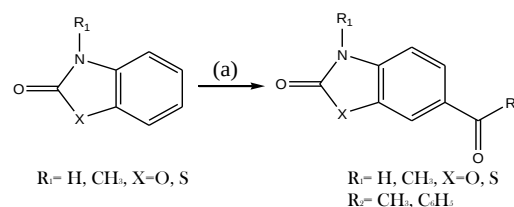


Fig.1: regioselectivity in the FC acylation of 2(3*H*)-benzoxazolone, 2(3*H*)-benzothiazolone, SiO₂-AlCl₃, 85°C.

2. Materials and methodes

2.1 Measurements

Melting points were determined in open capillary tubes using an Electro thermal melting point apparatus. IR spectra were recorded on a Perkin-Elmer 457 spectrometer using KBr pellets. Wave numbers are expressed in cm^{-1} . ^1H - and ^{13}C -NMR spectra were recorded at ambient temperature on a Bruker 400 spectrometer. Compounds were dissolved in $\text{DMSO}-d_6$. Chemical shifts are expressed in the δ scale with TMS as internal standard. Thin layer chromatography analyses were performed on Merk TLC plates (silica gel, 60 F254, E. Merk, Darmstadt, ref. 5735).

$\text{SiO}_2\text{-AlCl}_3$ catalyst was prepared as reported in a previous publications by reacting silica gel with aluminium trichloride in refluxing carbon tetrachloride [25-26].

Anhydrous AlCl_3 (5g) was added to silica gel (Merck, grade 60, F254, E. Merk, washed with 1 M HCl and dried under vacuum at 80°C for 72h, 10g) in carbon tetrachloride (30 mL). The mixture was stirred using a magnetic stirrer under reflux conditions for 2 days and filtered and washed with 50 mL of dry CCl_4 , and then dried under vacuum at 60°C . The determined loading of AlCl_3 was 1.3 mmol/g [27]

2.2. General Procedure for the F.C acylation of 2(3H)-benzoxazolone and 2(3H)-benzothiazolone using $\text{SiO}_2\text{-AlCl}_3$ catalyst.

(0.03 mol) of $\text{SiO}_2\text{-AlCl}_3$ catalyst were placed in a round bottom flask (250 mL). The flask was then equipped with a mechanical stirrer. The acylating agent (0.03 mol) was then added dropwise over 10 min. The flask was then placed in an oil bath thermostated at 45°C . The 2(3H)-benzoxazolone or 2(3H)-benzothiazolone (0.02 mol) was slowly added to ensure the formation of an homogeneous paste. The temperature was subsequently raised to 85°C . The reaction time is reported in Table-1. The products were isolated by addition of CH_2Cl_2 , stirred for 1h and filtered. The filtrate was washed with an aqueous solution of sodium bicarbonate and water, concentrated, dried, and recrystallized from ethanol to give the corresponding ketone. The yields are reported in Table-2. The physical properties (Mp, IR, ^1H -NMR and ^{13}C -NMR) are in accordance with published data [13, 14].

6-Acetyl-2(3H)-benzoxazolone(1). Yield: 61%; m.p. $226\text{-}228^\circ\text{C}$; IR (KBr, cm^{-1}) v: 3159 (NH), 1783 (CO), 1660 (CO), 1613 (C=C). ^1H -NMR ($\text{DMSO}-d_6$) δ : 2.54 (s, 3H, CH_3), 7.19 (d, 1H, $J=8.03$ Hz, Ar), 7.76 (s,

1H, Ar), 7.84 (d, 1H, $J=7.90$ Hz, Ar), 12.10 (s, 1H, NH); ^{13}C -NMR ($\text{DMSO}-d_6$, 400 MHz): 26.37, 111.67, 123.41, 123.86, 127.60, 131.53, 140.18 (aromatic carbons), 170.36 (CO), 196.08 (CO).

6-Acetyl-3-methyl-2(3H)-benzoxazolone(2).

Yield: 63%; m.p. $165\text{-}167^\circ\text{C}$; IR (KBr, cm^{-1}) v: 2935 (CH_3), 1765 (CO), 1674 (CO), 1600 (C=C). ^1H -NMR ($\text{DMSO}-d_6$) δ : 2.57 (s, 3H, CH_3), 3.38 (s, 3H, CH_3), 7.37 (d, 1H, $J=7.90$ Hz, Ar), 7.86 (s, 1H, Ar), 7.91 (d, 1H, $J=7.89$ Hz, Ar); ^{13}C -NMR ($\text{DMSO}-d_6$, 400 MHz): 26.54, 28.30, 108.63, 108.89, 125.38, 131.42, 135.99, 141.88 (aromatic carbons), 154.13 (CO), 196.33 (CO).

6-Benzoyl-2(3H)-benzoxazolone (3). Yield: 68%; m.p. $169\text{-}170^\circ\text{C}$; IR (KBr, cm^{-1}) v: 3140 (NH), 1780 (CO), 1640 (CO); 1610 (C=C). ^1H NMR ($\text{DMSO}-d_6$) δ : 7.22 (d, 1H, $J=7.99$ Hz, Ar), 7.54-7.72 (m, 7H, Ar), 12.07 (s, 1H, NH); ^{13}C NMR ($\text{DMSO}-d_6$): 107.75, 108.81, 125.74, 126.95, 127.84, 129.31, 130.76, 133.22, 135.89, 141.67 (aromatic carbons), 152.82 (CO), 192.82 (CO).

6-Benzoyl-3-methyl-2(3H)-benzoxazolone(4).

Yield: 71%; m.p. $147\text{-}148^\circ\text{C}$; IR (KBr, cm^{-1}) v: 2938 (CH_3), 1760 (CO), 1645 (CO), 1600 (C=C). ^1H -NMR ($\text{DMSO}-d_6$) δ : 3.35 (s, 3H, CH_3), 7.28 (d, 1H, $J=7.98$ Hz, Ar), 7.40-7.73 (m, 7H, Ar); ^{13}C NMR ($\text{DMSO}-d_6$, 400 MHz): 28.28, 108.50, 110.25, 127.17, 128.45, 129.35, 131.01, 132.31, 135.80, 137.28, 141.68 (aromatic carbons), 153.99 (CO), 194.26 (CO).

6-Acetyl-2(3H)-benzothiazolone(5). Yield: 64%; m.p. $189\text{-}191^\circ\text{C}$; IR (KBr, cm^{-1}) v: 3198 (NH), 1662 (CO), 1648 (CO), 1618 (C=C). ^1H -NMR ($\text{DMSO}-d_6$) δ : 2.52 (s, 3H, CH_3), 7.17 (d, 1H, $J=7.78$ Hz, Ar), 7.87 (s, 1H, Ar), 8.18 (d, 1H, $J=7.89$ Hz, Ar), 12.12 (s, 1H, NH); ^{13}C NMR ($\text{DMSO}-d_6$, 400 MHz): 26.37, 111.67, 123.41, 123.86, 127.60, 131.53, 140.18 (aromatic carbons), 170.36 (CO), 196.08 (CO).

6-Acetyl-3-methyl-2(3H)-benzothiazolone(6).

Yield: 66%; m.p. $145\text{-}146^\circ\text{C}$; IR (KBr, cm^{-1}) v: 2934 (CH_3), 1668 (CO), 1643 (CO), 1595 (C=C). ^1H -NMR ($\text{DMSO}-d_6$) δ : 2.53 (s, 3H, CH_3), 3.46 (s, 3H, CH_3), 7.36 (d, 1H, $J=7.78$ Hz, Ar), 7.94 (s, 1H, Ar), 8.01 (d, 1H, $J=7.86$ Hz, Ar); ^{13}C -NMR ($\text{DMSO}-d_6$, 400 MHz): 26.39, 29.12, 110.88, 121.53, 123.17, 127.84, 131.89, 141.12 (aromatic carbons), 169.17 (CO), 196.12 (CO).

6-Benzoyl-2(3H)-benzothiazolone(7).Yield: 72%; m.p. $216\text{-}217^\circ\text{C}$; IR (KBr, cm^{-1}) v: 3240 (NH), 1667 (CO), 1638 (CO), 1618 (C=C). ^1H -NMR ($\text{DMSO}-$

d_6) δ : 7.24 (d, 1H, J = 7.88 Hz, Ar), 7.70-7.95 (m, 7H, Ar), 12.19 (s, 1H, NH); ^{13}C NMR (DMSO- d_6 , 400 MHz): 111.35, 123.61, 124.84, 128.61, 128.96, 129.41, 131.38, 132.32, 137.37, 140.22 (aromatic carbons), 170.34 (CO), 198.71 (CO).

6-Benzoyl-3-methyl-2(3H)-benzothiazolone(8).

Yield: 75%; m.p. 147-148°C; IR (KBr, cm^{-1}) ν : 2927 (CH_3), 1677 (CO), 1650 (CO), 1610 ($\text{C}=\text{C}$). ^1H -NMR (DMSO- d_6) δ : 3.50 (s, 3H, CH_3), 7.53 (d, 1H, J = 7.99 Hz, Ar), 7.70-7.85 (m, 7H, Ar); ^{13}C NMR (DMSO- d_6 , 400 MHz): 29.27, 111.90, 121.79, 124.74, 128.93, 129.46, 131.81, 132.44, 137.28, 141.16, 141.72 (aromatic carbons), 169.39 (CO), 194.46 (CO).

3. Résultats et discussion

In order to get the best experimental condition; we initiated our studies with the $\text{SiO}_2\text{-AlCl}_3$ catalyst promoted reaction between benzoyl chloride, 2(3H)-benzoxazolone and (3H)-benzothiazolone with stirring at 85°C as a standard model reactions. In the course of systematic study and to verify the efficiency of catalyst loading, we have investigated the effect of the amount of $\text{SiO}_2\text{-AlCl}_3$ on the reaction. The ratio acid chloride/substrate was kept constant at 3/2, which is the optimal value found empirically and documented in previous publications [13-17].

Table.1: the effect of $\text{SiO}_2\text{-AlCl}_3$ on the synthesis of (6-benzoyl derivatives under solvent free conditions.

Entry	X	Catalyst (mol)	benzoyl chloride	Reaction time (h)	Yields (%)
1	O	0,01	0,03	3,5h	45
2	O	0,02	0,03	3,5h	62
3	O	0,03	0,03	3,5h	68
4	S	0,01	0,03	3h	52
5	S	0,02	0,03	3h	69
6	S	0,03	0,03	3h	75

From the results given in the table-1, the present procedure afforded 6-benzoyl-2(3H)-benzoxazolone (**3**) and 6-benzoyl-2(3H)-benzothiazolone (**6**) in good yields, when the amount of $\text{SiO}_2\text{-AlCl}_3$ was 0.03 mol as the optimum catalyst concentration in the benzoylation reaction for two equivalents of 2(3H)-benzothiazolone and 2(3H)-benzoxazolone and three equivalents of benzoyl chloride.

It is important to note that, the influence of reaction temperature was investigated. It has been shown that the reaction temperature has a significant effect on the yield of 6-benzoyl derivatives (**3**, **6**). The yield diminished sharply when the reaction temperature increased from 90 °C to 120°C due probably to sublimation of substrates [16].

Encouraged by these preliminary results, a number of 6-acyl-2(3H)-benzoxazolones and 6-acyl 2(3H)-benzothiazolones (**1-8**) were synthesized in excellent yields catalyzed by $\text{SiO}_2\text{-AlCl}_3$ using 2(3H)-benzoxazolone and 2(3H)-benzothiazolone and their *N*-methyl derivatives with acetyl and benzoyl chlorides (Table 2).

Table. 2: 6-acyl derivatives under optimized conditions.

Entry	R ₁	R ₂	X	Yields (%)
1	H	CH ₃	O	61
2	CH ₃	CH ₃	O	63
3	H	C ₆ H ₅	O	68
4	CH ₃	C ₆ H ₅	O	71
5	H	CH ₃	S	64
6	CH ₃	CH ₃	S	66
7	H	C ₆ H ₅	S	72
8	CH ₃	C ₆ H ₅	S	75

The reusability of $\text{SiO}_2\text{-AlCl}_3$ catalyst on the F.C reaction was also studied on the case of 2(3H)-benzoxazolone and 2(3H)-benzothiazolone with benzoyl chloride. At the end of the reaction, the catalyst was separated by filtration, thoroughly washed with ethyl acetate and reused under similar conditions. As shown by the formation of 6-benzoyl derivatives (**3**, **7**), there was an appreciable loss in the activity under the reuse of this catalyst (81% on the second run for 4h and 58% on the third run for 5h. This is expected mostly because the active catalyst component in the entire treatment process was diminished [25].

4. Conclusion

In conclusion, we have developed a convenient method in heterogeneous catalysis using AlCl_3 supported on silica gel for the acylation of 2(3H)-

benzoxazolone and 2(3*H*)-benzothiazolone. The advantages of this methodology are easy separation by a simple filtration process, high yields and low costs of catalyst deserve to be reported. Finally, the catalyst recovered after reaction can be washed with a solvent and reused after filtration without change in its efficiency.

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