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Development of a Sustainable and Solventless Friedel-Crafts Acylation Reaction of an Aromatic Natural Product "Ar-Himachalene" over Nanostructured ZnO as a New Catalyst

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Abstract

We describe the development of a sustainable and solventless acylation reaction of the naturally occurring product, namely 2,5,9,9-tetramethyl-6,7,8,9-tetrahydro-5H-benzocycloheptene [ar-himachalene], with acid chlorides over a new type of flower-shaped ZnO nanosructure as a hetrogenous catalyst at room temperature. The ZnO nanoflowers can efficiently and selectively catalyze the acylation of the aromatic group of ar-himachalene and be reused up to three times by simple filtration and washing without significant loss in their catalytic activity.

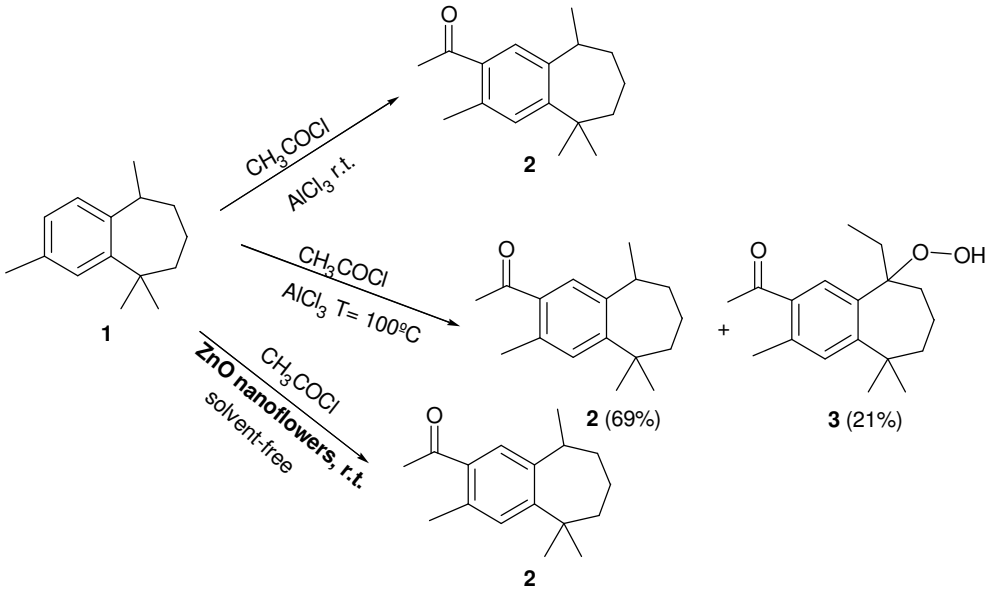
Keywords: Acylation, Natural product, Solventless, Zin Oxide nanostructure, Heterogenous Catalysis, Sustainability.

1. Introduction

The Friedel-Crafts acylation of aromatic compounds is one of the most fundamental and important reactions in organic synthesis, with potential application in pharmaceutical and biological settings [1]. In fact, it represents the most popular method for the synthesis of arylketones units present in many natural products and pharmacologically important molecules [2]. Typically, in a Friedel-Crafts acylation, an aromatic compound undergoes electrophilic substitution reaction with an acylating reagent in the presence of Lewis acid catalyst such as anhydrous $ZrCl_4$ [3] or Bronsted acid like super-acidic systems [4]. Other solid acids such as HZSM zeolite have been employed as catalysts for the liquid-phase acylation of anisole with carboxylic acids [5]. Recently, zinc powder was found to catalyze the acylation of activated and unactivated aromatics under microwave irradiation [6]. Though these reactions were friendly and easier to perform and to work-up, they present limitations in term of efficiency and generality. Consequently, reliable approaches for the acylation reaction are keenly sought. Interestingly, among these innovative approaches is to perform catalytic reactions on the surface of solids due to their specific properties that are not duplicated in the solution or gas phase [7]. In this regard, zinc oxide powder (ZnO) has been recently found to promote conveniently the acylation of ferrocene with acid chloride in dichloromethane as well as in solvent-free conditions in higher yields [8]. Such methodology offers greater reaction efficiency and minimizes environmental impact.

In order to extend the scope of surface synthetic organic chemistry methodology to natural product acylation and explore the effect and efficiency of new type of ZnO nanostructure in Friedel-Crafts acylation reaction, we reasoned there was scope to address both the green credentials and scalability of the acylation process of natural products. In this paper, and as part of our ongoing interests in the functionalization of the naturally occurring essential oil, namely ar-himachalene (1) [9,10] a minor component of cedarwood oil, highly valued in perfumery, and in the advancement of efficient and environmentally benign synthetic methods for organic process [11], we report our efforts to develop a significantly more sustainable Fridel-Crafts acylation reaction of ar-himachalene with a variety of carboxylic acids chloride using catalytic amount of cheap and readily accessible ZnO nanflowers, a new type of flower-like ZnO nanostructure [12] and demonstrate its applicability to the synthesis

of a range of ar-himachalene –like products with potential fragrances and pharmaceutical applications (Scheme 1).



Scheme 1: Synthetic approaches to the Friedel-Crafts acylation of ar-himachalene

2. Result and discussion

In order to identify a suitable catalyst and sustainable conditions such as solvent and temperature for the acylation reaction of ar-himachalene, we performed a step of experiments investigating the catalytic potential of a variety of metal oxides and solvents. The results are summarized in table 1. Using ZnO nanoflowers as catalyst in dichloromethane as solvent lead to the completion of the Friedel-Crafts acylation of ar-himachalene with acid acetyl in less than 1h at room temperature, as evidenced by TLC technique and 1H NMR spectroscopy (entry 9, Table 1). Most of the other protocols listed either take a longer time for completion under high temperature, or require toxic solvent such as benzene (entry 10, Table 1). It is noteworthy to mention that ZnO powder was found to be less efficient for catalyzing ar-himachalene that the type of flower-shaped ZnO nanostructure under the same conditions reaction. (entry 4, Table 1).

To confirm the role of the catalyst, ar-himachalene and acetyl chloride were mixed in dichloromethane in absence of ZnO nanoflowers. No reaction takes place even after vigorous stirring for 10h, which clearly points to the role of ZnO nanoflowers in promoting the acylation reaction. The influence of the reaction medium on the acylation of ar-himachalene was also addressed. In fact, the yield of the acetylated ar-himachalene product (2) dropped in the order of CH_2Cl_2, $CHCl_3$, and dichloroethane (entries 9, 11-12, Table 1). Interestingly, the best yield of acylation of ar-himachalene was obtained in solvent-free conditions, using 1 equiv of the acetyl chloride, for 1h at room temperature.

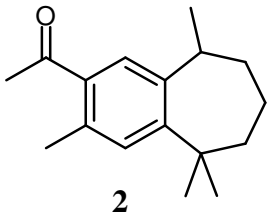
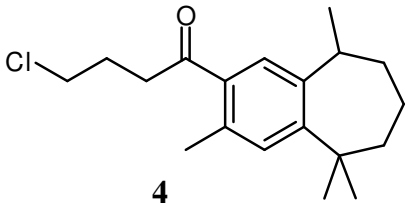
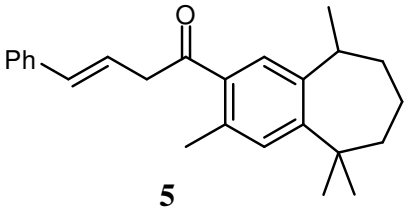
Table 1. Screening of alternative metal-oxides and reaction conditions for the acylation of ar-himachalene with acetyl chloride

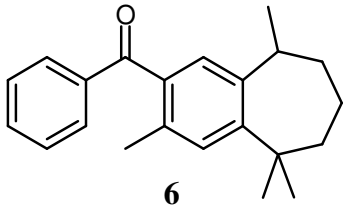
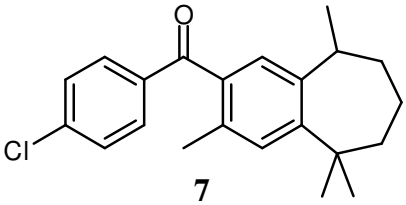
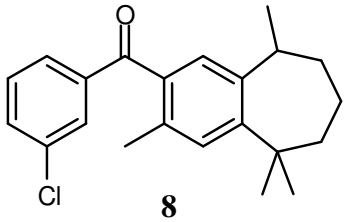
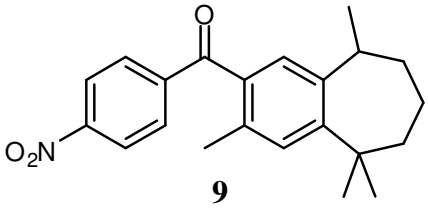
Entry	Catalyst	Solvent	Temperature (ºC)	Time (h)	Yield [a] %
1	None	CH_2Cl_2	80°	10	n.r.d
2	SiO_2	CH_2Cl_2	r.t. / Δ	1/ 3	n.r.
3	Al_2O_3	CH_2Cl_2	r.t. / Δ	1, 3	n.r.
4	ZnO[b]	CH_2Cl_2	r.t. / Δ	5 / 5	10 / 34
5	CuO	CH_2Cl_2	r.t. / Δ	5 / 5	15 / 55
6	Fe_2O_3	CH_2Cl_2	r.t. / Δ	5 / 5	n.r. / Trace
7	$AlPO_4$	CH_2Cl_2	r.t. / Δ	5 / 5	Trace / 56
8	TiO_2	CH_2Cl_2	r.t. / Δ	5 /5	0 / 24
9	ZnO[c]	CH_2Cl_2	r.t.	1	80
10	ZnO[c]	Benzene	Δ	1	67
11	ZnO[c]	$CHCl_3$	r.t.	1	71
12	ZnO[c]	$ClCH_2CH_2Cl$	r.t.	1	59
13	ZnO[c]	none	r.t.	1	95

Reaction conditions: catalyst (0.01 mmol), 5mL of solvent, 1equiv. CH_3COCl, 1 equiv. ar-himachalene.
[a] isolated yield, [b] ZnO powder, [c] ZnO nanoflowers. n.r.: no reaction.

The scope and generality of the present acylation protocol were addressed by using a variety of carboxylic acids chloride under the above optimized conditions. The results of such study are collected in table 2. Almost all acylation reactions afford good to excellent yields of the corresponding acetylated product (entries 1–5, Table 2). In particular, aliphatic acid chlorides such as 4-chloro-butyryl chloride and acetyl chloride gave excellent yields of (entries 1-2, Table 2). Acylation of ar-himachalene with benzoyl chloride and 4-chloro-benzoyl chloride lead to excellent yields too (entries 4-5, Table 2). Whereas in the presence of electron-withdrawing group (NO_2) a high decrease in the yield was obtained (entry 7, Table 2). Interestingly, the acylation reactions with aliphatic chlorides proceeds quite rapidly compared to the one with aromatic acid chlorides, which can be attributed to the steric effect.

Table 2. Friedel-Crafts acylation of ar-himachalene with different acid chlorides-catalyzed by ZnO nanoflowersa

Entry	Products	Time (h)	Yield[a] %
1	 **2**	1	95
2	 **4**	5	82
3	 **5**	14	75

4	 **6**	6	95
5	 **7**	7	98
6	 **8**	8	45
7	 **9**	12	13

Acylating agent (1 equiv), ar-himachalene (1 equiv), ZnO-nano-flowers (0.01 mmol),

[a] Isolated yield.

No attempt has been made to study the mechanism of the reaction. However, it was reported that the $ZnCl_2$ could be the true catalyst generated in situ by the reaction of ZnO with acid chloride. In fact, in the absence of a chlorinating agent, for example, using an acid anhydride as the reagent and ZnO, acylation does not take place.

A key issue of heterogeneous catalysis is the recovery and reusability of the employed catalyst which makes such catalysis more economical and then accomplishes one of the criterions of sustainable chemical processes. In line with that, we studied the recyclability of ZnO nanoflowers in the acylation of ar-himachalene with acid chloride. The results of recovery and reuse of ZnO nanoflowers are shown in table 3. During each time, the catalyst was separated by simple filtration, washed with distilled water and methanol and then used for the next catalytic run. The catalyst showed a remarkable activity (95-88% yield) being reused for up to three consecutive times without any significant loss in catalytic activity (Table 3).

Table 3. Recyclability of ZnO nanoflowers.

Number of runs	Recovery of ZnO nanoflowers	Yielda %
1	98	95
2	95	90
3	90	88

Acetylchloride (1 equiv), ar-himachalene (1 equiv),

ZnO nanoflowers (0.01 mmol),a isolated yield.

3. Conclusion

In conclusion, the inexpensive and easily available new type of flower-like ZnO nanostructure is an efficient catalyst for the Firidel-Crfats acylation of the aromatic unit of a natural product, ar-himachalene. The procedure is convenient for the preparation of aryl ketones units in good yields using a variety of carboxylic acids chloride under solventless conditions and at room temperature. This methodology verifies all the sustainable credentials and scalability because of it is operational simplicity, generality, selectivity and low economical cost. Furthermore, ZnO nanoflowers are inexpensive and environmentally benign nanomaterilas with superior catalytic activity over the commercially available ZnO, which is may be due to their large uniform hexagonal-structured nano- spheres. This issue is now under investigation by us.

Experimental Section

NMR studies were performed on a Bruker Avance 300 spectrometer in $CDCl_3$, chemicals shifts are given in ppm relative to external TMS and coupling constant (J) in Hz. Mass spectra were recorded on a GC–MS Thermofinnigan Polaris-Q mass spectrometer. Liquid chromatography was performed on silica gel (Merk 60, 220-440 mesh; eluent: hexane/ethylacetate). All reagents and solvents used in the experiments were purchased from commercial sources and used as received without further purification (Aldrich, Fluka, Acros). ZnO nanoflowers were prepared as reported elsewhere.19

Typical procedure for acylation of Ar-himachalene: A reaction mixture of ZnO nanoflowers (0.1 mmol), acetyl chlorides (1.0 mmol) and ar-himachalene (1.0 mmol), was stirred at room temperature for appropriate time. The progress of the reaction was monitored by TLC. After completion of the reaction, the resulting mixture was extracted with AcOEt (2× 10 mL) and filtered to remove ZnO nanoflowers. The organic layer was dried over Na2SO4, and concentrated in vacuum. Pure acetyl-ar-himachalene was obtained by purification in column chromatography over silica gel using hexane/ethyl acetate mixture as eluent.

1-(3,5,5,9-Tetramethyl-6,7,8,9-tetrahydro-5H-benzocyclohepten-2-yl)-ethanone (2). NMR 1H (CDCl3), δppm: 1.24 (3H, s, CH3), 1.32 (3H, d, J= 6.9, CH3), 1.36 (3H, s, CH3), 1.54-1.57 (2H, m, CHCH2), 1.67-1.74 (4H, m, CH2), 2.44 (3H, s, CH3CO), 2.48 (3H, s, ArCH3), 3.20 (1H, m, CHCH3), 7.14 (1H, s, ArH), 7.49 (1H, s, ArH); NMR 13C (CDCl3): 19.82, 20.61, 22.73, 27.95, 28.54, 32.67, 33.21, 35.24, 38.61, 39.74, 125.97, 129.57, 133.70, 134.98, 140.03, 150.42, 198.79; HRMS, Calcd: 244.1830, Found: 244.1903.

1-(4-tert-Butyl-5-isopropyl-2-methyl-phenyl)-4-chloro-butan-1-one (4). NMR 1H (CDCl3), δppm: 1.40 (3H, s, CH3), 1.45 (3H, d, J= 6.9, CHCH3), 1.45 (3H, s, CH3), 1.45- 1.59 (2H, m, CHCH2), 1.61-1.67 (2H, m, CH2), 1.67-1.76 (4H, m, CH2), 2.02-2.11 (2H, m, CH2), 2.43 (3H, s, ArCH3), 2.45 (2H, m, CH2CO), 3.24 (1H, m, CHCH3), 7.15 (1H, s, ArH), 7.45 (1H, s, ArH); NMR 13C (CDCl3): 20.97, 21.50, 23.84, 27.64, 29.66, 33.81, 34.41, 36.34, 37.06, 39.77, 40.82, 63.89, 126.12, 130.73,134.77, 135.87, 141.33, 151.59, 172.11; HRMS, Calcd: 306.1750, Found: 306.1783.

4-Phenyl-1-(3,5,5,9-tetramethyl-6,7,8,9-tetrahydro-5H-benzocyclohepten-2-yl)-but-3-en-1-one (5). NMR 1H (CDCl3), δppm: 1.17 (3H, s, CH3), 1.24 (3H, d, J= 6.9, CHCH3), 1.41 (3H, s, CH3), 1.55- 1.77 (6H, m, CHCH2), 2.44 (3H, s, ArCH3), 3.19 (1H, m, CHCH3), 7. 11 (1H, s, ArH), 7.16 (1H, s, ArH), 7.18 (1H, m, ArH), 7.26 (2H, dd, J= 1.5, 8, ArH), 7.33 (2H, dd, J= 1.5, 8, ArH); NMR 13C (CDCl3): 18.93, 19.86, 22.91, 28.51, 32.83, 33.35, 35.25, 38,62, 39.85, 125.36, 127.11, 128.12, 129.08, 131.46, 133.14, 134.78, 137.16, 139.85, 149.11, 197.05; HRMS, Calcd: 346.2297, Found: 346.2313.

Phenyl-(3,5,5,9-tetramethyl-6,7,8,9-tetrahydro-5H-benzocyclohepten-2-yl)-methanone (6). NMR 1H (CDCl3), δppm: 1.19 (3H, s, CH3), 1.23 (3H, d, J= 6.9, CHCH3), 1.39 (3H, s, CH3), 1.46- 1.77 (6H, m, CHCH2), 2.42 (3H, s, ArCH3), 3.19 (1H, m, CHCH3), 7. 08 (1H, s, ArH), 7.16 (1H, s, ArH), 7.38 (2H, dd, J= 1.5, 8, ArH), 7.46 (1H, dd, J= 1.5, 8, ArH), 7.73 (2H, dd, J= 1.5, 8, ArH); NMR 13C (CDCl3): 18.90, 19.76, 23.96, 28.51, 32.83, 34.35, 35.25, 38,99, 39.15, 42.65, 121.83, 125.36, 127.61, 128.16, 128.14, 129.28, 131.49, 133.17, 134.18, 137.06, 139.75, 149.01, 198.11; HRMS, Calcd: 306.1973, Found: 306.2002.

(4-Chloro-phenyl)-(3,5,5,9-tetramethyl-6,7,8,9-tetrahydro-5H-benzocyclohepten-2-yl)-methanone (7). NMR 1H (CDCl3), δppm: 1.17 (3H, s, CH3), 1.24 (3H, d, J= 6.9, CHCH3), 1.39 (3H, s, CH3), 1.47-1.58 (2H, m, CHCH2), 1.62–1.78 (4H, m, CH2), 2.38 (3H, s, ArCH3), 3.20 (1H, m, CHCH3), 7.06 (1H, s, ArH), 7.17 (1H, s, ArH), 7.34 (2H, d, J= 8, ArH), 7.68 (2H, d, J= 8, ArH); NMR 13C (CDCl3):18.91, 19.86, 22.90, 28.49, 32.80, 33.38, 35.24, 38,70, 39.83, 125.34, 127.54, 128.67, 130.43,133.27, 134.15, 135.55, 138.12, 149.65,151.00, 196.03; HRMS, Calcd: 340.1593, Found: 340.1621.

(3-Chloro-phenyl)-(3,5,5,9-tetramethyl-6,7,8,9-tetrahydro-5H-benzocyclohepten-2-yl)-methanone (8). NMR 1H (CDCl3), δppm: 1.16 (3H, s, CH3), 1.21 (3H, d, J= 6.8, CHCH3),1.2(3H, s, CH3), 1.37-1.45 (2H, m, CHCH2), 1.49-1.53 (2H, m, CH2), 1.62-1.69 (2H, m, CH2), 2.15 (3H, s, ArCH3), 3.11-3.15 (1H, m, CHCH3), 6.99 (1H, d, J= 1.5 ArH), 7.08 (1H, s, ArH), 7.25 (1H, dd, J= 1.5, 8, ArH), 7.35 (1H, s, ArH), 7.47 (1H, d, J=8, ArH), 7.65 (1H, s, ArH); NMR 13C (CDCl3): 19.82, 20.25, 24.11, 29.69, 34.00, 34.58, 36.44, 39.931, 41.02, 120.69, 123.18, 126.44, 126.85, 128.44, 129.85, 132.64, 133.09, 134.77, 140.16, 141.35, 151.00, 197.00; HRMS, Calcd: 340.1593, Found: 340.1621.

(4-Nitro-phenyl)-(3,5,5,9-tetramethyl-6,7,8,9-tetrahydro-5H-benzocyclohepten-2-yl)-methanone (9). NMR 1H (CDCl3), δppm: 1.19 (3H, s, CH3), 1.27 (3H, d, J= 6.9, CHCH3), 1.41 (3H, s, CH3), 1.49-1.60 (2H, m, CHCH2), 1.62-1.79 (4H, m, CH2), 2.26 (3H, s, ArCH3), 3.31 (1H, m, CHCH3), 7.14 (1H, s, ArH), 7.20 (1H, s, ArH), 7.37 (2H, d, J= 8, ArH), 7.80 (2H, d, J= 8, ArH); NMR 13C (CDCl3): 18.80, 19.81, 21.90, 28.45, 32.94, 33.81, 35.22, 38.64, 39.80, 125.31, 127.88, 128.91, 131.48, 134.31, 134.99, 136.59, 139.17, 149.69, 151.46, 198.07; HRMS, Calcd: 351.1811, Found: 351.1833.

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