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Research Article

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Microwave-assisted, solvent-free, acidic Al_2O_3-$ZnCl_2$ catalyzed synthesis of aromatic hydroxyketones via Fries rearrangement of aromatic esters

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ABSTRACT

A convenient synthesis of various aromatic hydroxyketones via Fries rearrangement is described by condensing a series of aromatic esters with acidic Al_2O_3-$ZnCl_2$ mixture under microwave conditions. Reactions have been carried out under solvent-free conditions with considerable reduction in reaction time and improvement in yield in comparison to classical methods. The adopted procedure provides an energy and time saving protocol.

Keywords: Fries rearrangement, Lewis acid, Al_2O_3-$ZnCl_2$complex, microwave irradiation.

INTRODUCTION

Aromatic hydroxyketones are useful organic compounds and valuable intermediates in the synthesis of pharmaceuticals [1], perfumery [2], acetophenone resin [3] etc. Products such as 4-hydroxyacetophenone, 4-hydroxybenzophenone, 4-hydroxypropiophenone and others are important drug intermediates [4] that are derived from the Fries rearrangement. Fries rearrangement of acyloxybenzenes provides useful routes to acylphenols but a longer reflux time with more than a stiochiometric amount of Lewis acids such as $AlCl_3$ [5,6], HF [6,7], BF_3 [6,8], $TiCl_4$ or $SnCl_4$ [9] is required. HF which acts both as a catalyst and solvent is highly toxic, corrosive and volatile. $AlCl_3$ and BF_3, both are corrosive and react violently with water. Furthermore, the reaction mixture, in the hydrolysis step, generates corrosive gases and contaminated salts leading to environmental problems. For these reasons, few more alternative catalysts have been reported in literature and some of them are methane sulphonic acid [10], P_2O_5 in methane sulphonic acid [11], lanthanide triflates [12], lithium diisopropyl amide [13], Zn powder [14], carboxylic acids [15]. However, the requirement for equimolar quantities of the catalyst, the corrosive and toxic conditions, violent reaction of the catalyst with water has prompted the development of newer protocols. In our continuing efforts [16] to develop and explore the newer methodologies in organic synthesis [17], we attempted the acidic Al_2O_3-$ZnCl_2$ catalyzed synthesis of aromatic hydroxyketones via Fries rearrangement of aromatic esters under microwave irradiation.

Microwave-Assisted Organic Synthesis finds application as an appealing method to achieve these goals and is an increasingly popular field of organic research since last few years, leading to enhanced reaction rates, higher yields and selectivity, easier work up coupled with several other advantages of eco-friendly approach compared to the traditional heating methods [18]. Alternative methods using microwaves have also been developed for the synthesis of aromatic hydroxyketones [19]. In this background, we report herein the microwave-assisted synthesis of aromatic hydroxyketones via Fries rearrangement using acidic Al_2O_3-$ZnCl_2$ mixed reagent, with the advantage of improved yields and shortened reaction times. This efficient eco-friendly procedure provides a green chemistry approach for the synthesis of aromatic hydroxyketones. We found that an acidic Al_2O_3-$ZnCl_2$ mixture supported on silica gel is an efficient medium for promotion of Fries rearrangement without solvent under microwave dielectric heating. It is worth noting that the reaction did not proceed on acidic Al_2O_3 or $ZnCl_2$ supported on silica gel alone. The reason as reported in the literature [20] is that, when using acidic Al_2O_3 or $ZnCl_2$, these being strong Lewis catalysts, there are circumstances where the substrate is more extensively complexed with the electrophile generating species. This applies even more to electron donating substituents possessing lone pair of electrons available for complexation. To alleviate this problem, we attempted the use of acidic Al_2O_3-$ZnCl_2$ mixed reagent where $Al_2O_3$and $ZnCl_2$ are partially complexed and consequently complex to a lesser extent with the aromatic substrate. Under these conditions, there indeed exists a dynamic equilibrium between the complexed entities of the aromatic substrate, the product formed and the electrophile generating species.

EXPERIMENTAL SECTION

General Experimental: All experiments were performed in oven dried glass apparatus. All the commercially available reagents were purchased from Aldrich and were used without further purification. The progress of the reaction was monitored by TLC (0.5-mm-thick plates using BDH silica gel G as adsorbent) and silica gel pre-coated aluminium sheets (60 F254, Merck). Visualization of spots was effected by exposure to ultraviolet light (UV) at 254nm, iodine vapours, 2% 2,4-dinitrophenylhydrazine in methanol containing few drops of H_2SO_4. All the reactions were carried out in a multimode *Sharp Carousel*^{TM} microwave oven. Melting points were taken in open capillaries using electro thermal method on a *Labotech/Perfit* instrument and are uncorrected.

Procedure for the synthesis of 2-hydroxyacetophenone (2a):
A mixture of phenyl acetate **1a**(0.32g, 2.35 mmol), acidic Al_2O_3 (1 g, 9.81 mmol) and $ZnCl_2$ (1 g, 7.34 mmol) were adsorbed on silica gel (60-120 mesh) by grinding in a mortar-pestle and irradiated under microwave oven for 5 minutes at medium power level at the intervals of 30 seconds duration to prevent uncontrolled heat generation. Progress of the reaction was monitored by TLC. Deep-violet coloration upon interaction with alcoholic Ferric chloride indicated the formation of desired product. Elution with acetone and removal of solvent afforded 2-hydroxyacetophenone in 87 % yield, b.pt. = 213 ^{o}C.

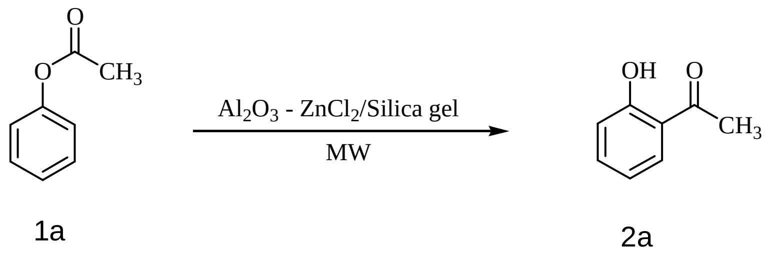
Procedure for the synthesis of 2-Acetyl-1-napthol (2b):
A mixture of 1-Napthyl acetate **1b** (0.25g, 1.34 mmol), acidic Al_2O_3 (0.5g, 4.9 mmol) and $ZnCl_2$(0.35 g, 2.57 mmol) was adsorbed on silica gel (60-120 mesh) by grinding in a mortar-pestle and irradiated under microwave oven for 6 minutes at medium power level at the intervals of 30 seconds to prevent uncontrolled heat generation. Progress of the reaction was monitored by TLC. Green coloration with alcholic ferric chloride indicated the formation of desired product. Reaction mixture was cooled and eluted with diethyl ether and the ethereal solution was washed several times with water, dried on anhydrous Na_2SO_4 and the solvent was removed. Solid obtained was recrystallized from ethanol to yield 2-Acetyl-1-napthol in 76% yield, m.pt. = 98-100 ^{o}C.

Procedure for the synthesis of 1-Acetyl-2-napthol (2c):
A mixture of 2-Napthyl acetate **1c** (0.16g, 0.86 mmol), acidic Al_2O_3 (0.5g, 4.9 mmol) and $ZnCl_2$ (0.5g, 3.67 mmol) was adsorbed on silica gel (60-120 mesh) by grinding in a mortar-pestle and irradiated under microwave oven for 6 minutes at medium power level at the intervals of 30 seconds. TLC monitoring was employed to keep track of reaction progress. Greenish colour with alcholic ferric chloride indicated the formation of desired product. Reaction mixture was eluted with diethyl ether and the ethereal solution was washed several times with water, dried on anhydrous Na_2SO_4 and solvent was finally removed. Solid obtained was recrystallized from ethanol to yield yellow coloured needles of 1-Acetyl-2-napthol in 71 % yield, m.pt. **=** 61-63 ^{o}C.

Procedure for the synthesis of 3-Acetyl-4-hydroxycoumarin (2d):
A mixture of 4-acetoxycoumarin **1d** (0.12g, 0.59 mmol), acidic Al_2O_3 (0.3g, 2.94 mmol) and $ZnCl_2$ (0.3g, 2.2 mmol) was adsorbed on silica gel (60-120 mesh) by grinding in a mortar and pestle and irradiated under microwave oven for 5 minutes at high power level at the intervals of 30 seconds to prevent uncontrolled heat generation. Progress of the reaction was monitored with TLC. Yellow coloration with alcoholic ferric chloride indicated the formation of desired product. Reaction mixture was eluted with acetone and solvent was removed. Solid obtained was recrystallized from ethanol to yield 3-Acetyl-4-hydroxycoumarin in 79 % yield, m.pt. = 134-136 ^{o}C.

RESULTS AND DISCUSSION

To begin with, an efficient synthesis of 2-hydroxyacetophenone from phenyl acetate using acidic Al_2O_3-$ZnCl_2$ adsorbed on silica gel (60-120 mesh), was carried out (**Scheme 1**). To our delight, the expected product, 2-hydroxyacetophenone **2a** was obtained in 87 % yield and was characterized by comparison of its physical and spectral data with the authentic sample [20].



Scheme 1.Acidic Al_2O_3-$ZnCl_2$ adsorbed on silica gel catalysed synthesis of 2-hydroxyacetophenone

To evaluate the versatility of the methodology employing acidic Al_2O_3-$ZnCl_2$ mixed reagent, phenolic esters like 1-napthyl acetate, 2-napthyl acetate and ester of oxygen heterocycles like 4-hydroxycoumarin were treated with acidic Al_2O_3-$ZnCl_2$ mixture, adsorbed on silica gel (60-120 mesh). The reactions were carried out under solvent-free conditions in a multimode domestic microwave oven and the results are summarized (**Table 1**). The products were obtained in good yields (71-87%) and were characterized by comparison of their physical and spectral data with the authentic samples [21, 22c]. Reactions were carried out in intervals of 30 seconds to prevent uncontrolled heat generation and optimum reaction times were precisely achieved accordingly. The problems encountered while performing the reactions using solvent were easily overcome by solvent-free technique and the yields obtained were almost quantitative. Thus, the advantage of carrying out Fries rearrangement using acidic Al_2O_3-$ZnCl_2$ under microwaves is that the reaction time has considerably shortened from hours to minutes and the yield has been improved many folds as compared to conventional procedures, reported in the literature [22] (**Table1**).

Table 1: Comparison of % yield and time (in minutes) for Fries rearrangement under microwave conditions with literature data (conventional method) [21]

Entry	Substrate 1	Product 2	Microwave		Conventional Method	
			Time (min)	Yield (%)	Time (min)	Yield (%)
a	Phenyl acetate	2-Hydroxyacetophenone	5	87	300	30
b	1-Napthyl acetate	2-Acetyl-1-napthol	6	76	60	67
c	2-Napthyl acetate	1-Acetyl-2-napthol	6	71	300	30
d	4-Acetoxycoumarin	3-Acetyl-4-hydroxycoumarin	5	79	2880	60

CONCLUSION

Microwave-assisted, solvent-free, acidic Al_2O_3-$ZnCl_2$ catalysed synthesis of aromatic hydroxyketones via Fries rearrangement of aromatic esters has been carried out with improved yields in minimum time as compared to conventional procedures reported so far in the literature. This procedure is simple, efficient and the usage of solvent-free conditions makes it eco-friendly.

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REFERENCES

[1] H Szmart, *Wiley, New York*, **1989**, 503.
[2] H Naeimi;L Moradi, *Catal.Commun.*, **2006**, 7,1067.
[3] E Heitling; F Roessner; EV Steen, *J. Mol.Catal. A: Chemical*, **2004**, 216,61.
[4] MK Bhushan; RM Virendra, *Synth. Commun.*,**1999**, 29,1195.
[5] BBRames, *Shasun Chemicals (m) Ltd., India*, **1993**, IN 171 970 .
[6] MB Hocking, *J. Chem. Technol. Biotechnol.*, **1980**, 30, 626.
[7]KG Davenport, *Celanese Corp., USA*, **1988**, EP 251 552.
[8] JL Boyer, *J. Org. Chem.*, **2000**, 65, 4712.
[9]R Martin, *Org. Prep. Proc. Int.*, **1992**, 24, 369.
[10]A Commarieu; W Hoelderich; JA Laffitte; M Dupont, *J. Mol.Catal. A: Chemical*, **2002**, 182, 137.
[11]B Kaboudin; Y Abedi, *Org. Prep. Proc. Int.*, **2009**, 41, 229.
[12](a) S Kobayashi; M Moriwaki; I Hachiya, *Bull. Chem. Soc. Jpn.*, **1997**, 70, 267.
(b) S Kobayashi; M Moriwaki; I Hachiya, *Tetrahedron Lett.*,**1996**, 37, 2053.
(c) S Kobayashi; M Moriwaki; I Hachiya, *J. Chem. Soc., Chem. Commun.*,**1995**,1527.
(d) O Mouhtady; H Gaspard-Iloughmane; N Roques; C Le Roux, *Tetrahedron Lett.*,**2003**, 44, 6379 and erratum: *Tetrahedron Lett.*,**2003**, 44, 8037.
[13]KJ Singh; DB Collum, *J. Am. Chem. Soc.*, **2006**, 128, 13753.

[14]S Paul; M Gupta, *Synthesis*, **2004**, 11, 1789.
[15]L Xu; D Du; X Yang; X Xu, *Int. J. Chem.*, **2011**, 3,123.
[16](a) R Khajuria; Y Saini; KK Kapoor, *Tetrahedron Lett.*, in press, (**2013**) DOI: 10.1016/j.tetlet.2013.08.007.
(b)S Chadha; S Paul; KK Kapoor, *J. Chem. Pharm. Res.*,2011, 3, 331.
[17](a) Rajendra; K Wanare. *J. Chem. Pharm. Res.*, **2011**, 3, 136-144.
(b)Meghasham; N Narule. *J. Chem. Pharm. Res.*, **2011**, 3, 38-47.
[18](a) L Perreux; A. Loupy, *Tetrahedron*, **2001**, 57, 9199.
(b) RS Varma, *Green Chem.*, **1999**, 1, 43.
[19](a) BM Khadilkar; VR Madyar, *Synth. Commun*., **1999**, 29, 1195.
(b) IR Tehran; JS Brar; AK Arora; GK Kad, *J. Chem. Education*, **1997**, 74, 324.
(c) FM Moghaddam; M Ghaffarzadeh; SH Abidiorkoui, *J. Chem. Research(s)*, **1999**, 574.
[20]S Yous; JH Poupaert; I Lesieur; PDepreux; D Lesieur, *J. Org. Chem.*, **1994**, 59, 1574.
[21]H Naeimi, L Moradi, *J. Mol.Catal. A: Chemical*, **2006**, 256, 242.
[22](a)Mozingo, *Org. Syntheses*, **1941**, 21, 45.
(b) EJ Chu; Z Shen; T Chien; TSTuan, *J. Chinese Chem. Soc.*, **1944**.
(c) K Fries, *Ber.*, **1921**, 54, 711.