A Green Approach for the Intramolecular Friedel-Crafts Acylation

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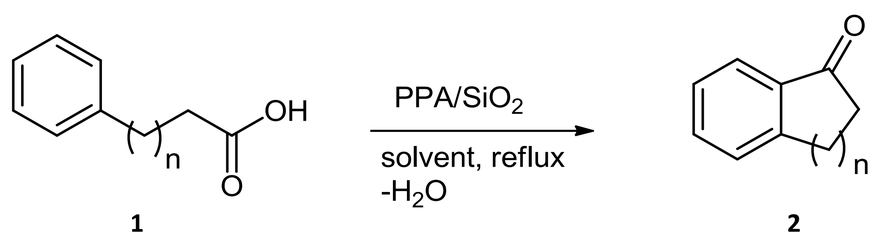
The Friedel-Crafts acylation is one of the most utilised methods for C-C bond formation in aromatic chemistry.[1] The development of an environmentally-benign and economically-feasible pathway of the Friedel-Crafts reaction is of great value and highly desired, particularly in the pharmaceutical industry wherein the acylation reaction is extensively employed.[2] In this study, the intramolecular Friedel-Crafts acylations of different aryl substituted carboxylic acids (**1**) were investigated under environmentally-friendly heterogeneous solid catalysis[3] in order to obtain the corresponding cyclic aromatic ketones (**2**), which are widely recognized as useful synthetic intermediates in various industrial fields, particularly drugs. (Scheme 1).



1 **2**

n=1, 2, 3 (**a**, **b**, **c**)

Scheme 1. Intramolecular Friedel-Crafts acylations under PPA/SiO_2

Silica-adsorbed polyphosphoric acid (PPA/SiO_2), instead of typical Lewis acid catalysts, was successfully employed as heterogeneous acidic catalyst to mediate the reactions under greener conditions because it does not produce harmful by-products and can be reused further.[4] Additionally, arylcarboxylic acids were used as substrates rather than their acid halide derivatives so as to avoid halogenated waste since they only generate water as the waste product instead of hydrogen halides. Mostly of the reactions were performed in refluxing halogenated solvents, although the use of greener ones like *m*-xylene and toluene was also attempted.

In a preliminary study the cyclization reaction of phenylpropionic, phenylbutyric and phenylvaleric acid (**1a**, **b** and **c**) mediated by PPA/SiO_2 catalyst was investigated (Table 1). The catalyst was prepared following a simple reported procedure[4a]. The general cyclization procedure involved the placing of the substrate, catalyst (200% by weight of substrate) and solvent in a round-bottomed flask and reflux at a temperature dependent on the solvent. Reaction progress was monitored by TLC, and purification was carried out by gravity column chromatography.

Table 1. Acylations under PPA/SiO_2 (200% by weight of substrate) and reflux

3-Phenylpropionic acid (**1a**) n=1			
Entry	Solvent	Reaction Time (h)	Product Yield **2a** (%) *
1	*m*-Dichlorobenzene	5	24
2	*m*-Dichlorobenzene	16	65
3	*m*-Xylene	20	15
4	Toluene	12	No reaction

4-Phenylbutyric acid (**1b**) n=2			
Entry	Solvent	Reaction Time (h)	Product Yield **2b** (%) *
5	*m*-Dichlorobenzene	3	81
6	*m*-Xylene	6	55
7	Toluene	11	27

5-Phenylvaleric acid (**1c**) n=3			
Entry	Solvent	Reaction Time (h)	Product Yield **2c** (%) *
8	*m*-Dichlorobenzene	10	27
9 **	*m*-Dichlorobenzene	30	49
10	*m*-Dichlorobenzene	30	50
11	*m*-Xylene	20	13
12	Toluene	9	No reaction

* Pure isolated product.
** Trial involved 300% w/w catalyst.

m-Dichlorobenzene was the most effective solvent because of its high boiling point, allowing for the sustaining of a higher reaction temperature and, consequently, faster reaction rate. Furthermore, since it is deactivated by the two halogen atoms, it does not take part in any side-reactions. However due to its toxicity towards the environment and cost, *m*-dichlorobenzene should be replaced by greener alternatives.

Whereas the use of *m*-xylene afforded lower yields, the major drawback was the intermolecular side-reaction that occurred with each trial. With toluene the reaction temperature was not sufficiently able to permit the reaction and, consequently, product was formed in low yield or not at all.

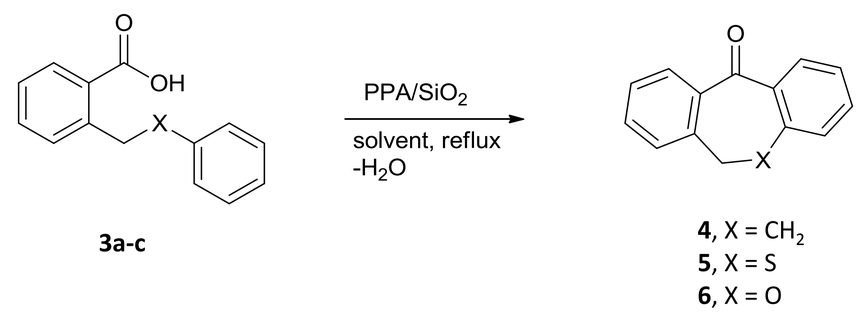
The heterogeneous catalyst can be easily obtained from the reaction mixture by simple filtration and reused further. The reusability of PPA/SiO2 was investigated by carrying out the acylation of 4-phenylbutyric acid (**1b**) in *m*-dichlorobenzene three further times (Table 2).

Table 2. Recycling of the catalyst with substrate **1b**

Entry	Solvent	Reaction Time (h)	Product Yield **2b** (%) *
1	*m*-Dichlorobenzene	3	79
2	*m*-Dichlorobenzene	3.5	76
3	*m*-Dichlorobenzene	8	78

* Pure isolated product.

The method was then applied to the synthesis of some molecules of interest to the pharmaceutical industry like 5-dibenzosuberone (DBS) (4), 6,11-dihydrodibenzo[b,e]thiepin-11-one (5) and 6,11-dihydrodibenzo[b,e]oxepin-11-one (6), starting from their respective benzoic acids precursors (**3**) (Scheme 2). DBS is a precursor to some of the tricyclic antidepressant drugs marketed, as well as first generation antihistamines/anticholinergics,[5] while compounds **5** and **6** are key intermediates in the syntheses of several pharmaceutical products[6].



3a-c

4, X = CH_2
5, X = S
6, X = O

Scheme 2. Synthesis of drug precursors **4**, **5**, and **6** using PPA/SiO_2 as catalyst

Table 3. Acylations of **3** under PPA/SiO_2 (200% w/w) in *m*-dichlorobenzene

Substrate	X	Reaction Time (h)	Product Yield (%) *
3a	CH_2	3	87 (**4**)
3b	S	10.5	63 (**5**)
3c	O	7	91 (**6**)

* Pure isolated product.

Conclusions

The PPA/SiO_2-mediated dehydrative cyclisation of arylcarboxylic acids was demonstrated to be both satisfactory and environmentally-benign. Compared to neat PPA that is tedious to handle and mix due to its very high viscosity, not practical to reuse and generating environmentally problematic waste (acidic & phosphorus salts), the silica adsorbed PPA is cheap and easily prepared via a simple method and, like many other heterogeneous catalysts, it is practical to transfer and can be reused for further trials. The ease of cyclisation is primarily dependent on the length of the aliphatic chain and for best results the reaction requires a high boiling point solvent of a deactivated nature. The method allowed the successful synthesis of three interesting pharmaceutical intermediates. More substituted arylcarboxylic acids are under investigation.

References

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