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Regioselective Friedel-Crafts Hydroxyalkylation Using Friendly Conditions: Application to the Synthesis of Unsymmetrical Triarylmethanes

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Abstract: Friedel-Crafts alkylation is one of the most important methods used in organic chemistry to create carbon-carbon bonds. The traditional conditions using alkyl halides activated by a Lewis or Brønsted acid have been widely described in the literature. Nevertheless, the Friedel-Crafts reaction using aldehydes or ketones as substrates, known as hydroxyalkylation, has been poorly described. The development of regioselective Friedel-Crafts conditions is a challenge in organic synthesis. The growing interest in developing “metal and solvent free" reactions justifies the particular attention that the Brønsted acids have received as an alternative to toxic and precious metals. During the last years, triarylmethanes attract considerable attention due to their applications in fine, medicinal and industrial chemistry. They have been used as protecting groups, dyes or photochromic agents. They also exhibit interesting biological properties including anti-tumor and antioxidant activities. Different methods of preparation of symmetrical triarylmethanes have been described in the literature, nonetheless the synthesis of unsymmetrical ones has been very little explored. In this work we describe an efficient regioselective method to prepare unsymmetrical triarylmethanes from enriched aromatic compounds, *via* a Friedel-Crafts hydroxyalkylation catalyzed by Brønsted acids using pyridylarylcarbinols as alkylating agents. The method described here is consistent with the principles of green chemistry and has significant advantages, such as the use of an inexpensive catalyst and mild conditions. This regioselective method offers good yields, shorter reaction times and a possible extension to various substrates.

Keywords: regioselective hydroxyalkylation; triarylmethanes, Friedel-Crafts reaction

1. Introduction

In recent years triarylmethanes (TAMs) have received considerable attention from scientific community due to their numerous applications. In chemical industry they have been used as leuco dyes, photochromic agents, protective groups in organic synthesis or building blocks for generating dendrimers .They have been used in food industry, in textile industry, as well as antifungal agents and parasiticides in the fish farm industry. [1-4] Recent studies have shown a widespread application of TAMs in therapeutics due to their several biological activities such as antiviral, antitumor, antitubercular, antifungal, anticancer and anti-inflammatory agents [5-7].

The synthesis of unsymmetric TAMs is less described in the literature because it generally leads to low yields and to the formation of byproducts principally due to lack of regioselectivity. As a result, the development of new approaches to synthesize unsymmetrical TAMs in simpler, efficient, regioselective and environmentally friendly ways is a real challenge.

The most common method for preparing unsymmetrical TAMs is a Friedel-Crafts hydroxyalkylation from the corresponding carbinols. Unsymmetrical TAMs bearing electrowithdrawing groups have been also prepared *via* the formation of alkylbenzotriazoles. [8-11]. Finally, coupling reactions using metal catalysts (Pd, Cu…), or Friedel-Crafts reactions using sulfone or α-amidosulfones have been also reported [12-14].

In this work we described the regioselective synthesis of unsymmetrical triaylmethanes *via* a Friedel-Crafts hydroxyalkyalation from the corresponding functionalized carbinols and activated aromatic compounds using a Brønsted acid as catalytic system. The scope of this method is also noted herein.

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2. Results and Discussion

As part of our studies involving the synthesis of bioactive compounds structurally related with a triarylmethane skeleton, we have recently focused our attention on the synthesis of unsymmetrical TAMs with interesting anti-inflammatory properties. We were particularly interested in the synthesis of the *p-p* regioisomers derived from pyridinophenylcarbinols and phenol. In our preliminary studies we noticed that a major regioisomer could be obtained according to the amounts of catalyst used. These results encouraged us to develop an efficient and regioselective method to prepare unsymmetrical TAMs via a Friedel-Crafts hydroxyalkylation. To carry out this study we selected the (4-*tert*-butyl-phenyl) pyridine-2-yl-methanol **1** as a model. Each assay was carried out on a scale of 0.4 mmol with 1.2 equivalents of phenol using sulfuric acid as catalyst. The reactions were monitored by thin layer chromatography (TLC). Finally, the influence of solvent, temperature and the amount of catalyst was studied in details.

2.1 *Screening of solvents*

We decided to use either benzene, toluene, 1,2-dichloroethane or nitrobenzene as solvent. The first experiments were carried out at 80 °C with 4 to 20 equivalents of sulfuric acid. In benzene and toluene with 4 equivalents of sulfuric acid the *p-p* TAM is obtained as a major regioisomer, with a yield not exceeding 45%. In addition, these aromatic solvents may compete with phenol, thereby favoring the formation of byproducts.

In 1,2-dichloroethane, the same trend was observed, i.e. the formation of a major *o-p* regioisomer using 20 equivalents of sulfuric acid and the formation of a major *p-p* regioisomer using 4 equivalents of sulfuric acid. Nonetheless *o-p* and *p-p* regioisomers were obtained with modest yields of 46% and 35% respectively.

The best results were obtained when nitrobenzene was used. It allowed short reaction times, homogeneous reaction medium and it did not react with the corresponding carbinol thus limiting the formation of by-products. Moreover a very good regioselectivity was observed, with total conversion and good yields (98% *o-p* regioisomer with 20 equivalents of sulfuric acid and 72% *p-p* regioisomer with 4 equivalents of sulfuric acid). However it can be noticed that the high boiling point of nitrobenzene (bp = 210 ° C) prevents its removal by distillation and flash chromatography must be used in the purification step. Taking into account these arguments the nitrobenzene has been selected for further studies.

2.2 Screening of temperature

The temperature screening was carried out in nitrobenzene, with 4 or 20 sulfuric acid equivalents. We studied the reaction at 80 ° C, 20 ° C and 0 ° C (Table 1). At 80 °C with 20 equivalents of sulfuric acid only the *o-p* regioisomer is obtained with 98% yield after purification by flash chromatography on silica gel. On the other hand at 80 °C and using 4 equivalents of sulfuric acid the *p-p* regioisomer is principally obtained with 72% yield.

The same conditions were evaluated at 20 °C. In such conditions when 20 equivalents of catalyst were used the *p-p* regioisomer was obtained as the major compound in 5 min with 71% yield. On the other hand the use of 4 equivalents of acid at 20°C reduces the reaction time. After 48 h, *p-p* regioisomer and the *o-p* regioisomer were obtained with yields of 66% and 3% respectively.

At 0 ° C, the reaction was only carried out with 20 equivalents of sulfuric acid. Under these conditions, the *p-p* regioisomer **3** is mainly obtained after 15 min with a good yield of 78%.

To summarize, the temperature plays an important role in the regioselectivity of the Friedel and Crafts hydroxyalkylation when 20 equivalents of acid are used. By eating at 80 °C the *o-p* regioisomer **4** is obtained with a yield of 98%. At room temperature or at 0 ° C the *p-p* regioisomer is isolated with respective yields of 72% and 78%.

These results suggest that *p-p* regioisomer would be the kinetic compound since it is obtained at low temperature and *o-p* regioisomer obtained at 80 °C would be the thermodynamic compound. This can be justified by assuming that hydrogen bonds may be formed between the pyridine nitrogen and the hydroxyl function of the phenol, leading to better stability of the molecule (Figure 2).

2.3 Screening of amounts of catalyst

To focus on the influence of the amount of catalyst, we studied this reaction using 0.02; 2; 4; 5 and 20 equivalents of sulfuric acid. In the literature, the synthesis of TAMs is reported using a catalytic amount of acid. [15-18]. In our study when 0.02 or 2 equivalents of acid were used, the reaction did not occur. This could be explained by the protonation of the pyridine carbinol in acidic media. Theoretically almost 2 acid equivalents of acid should be enough. However, 4 equivalents of sulfuric acid are required to completely consume the corresponding carbinol. The *p-p* regioisomer **3** is predominantly isolated using 4 equivalents of sulfuric acid however at 20 ° C the reaction is

rather slow in comparison with the reaction carried out at 80 ° C (5 min). The use of 20 equivalents of acid affords exclusively the *o-p* regioisomer with an excellent yield of 98%.

In conclusion, we outline the regioselective conditions for the Friedel-Crafts hydroxyalkylation between phenol and the carbinol **1**. The best conditions use nitrobenzene as solvent and 80 °C. The amount of sulfuric acid influences the formation of the corresponding regioisomers.

The best conditions for synthesizing the *p-p* regioisomer are: 4 equivalents of sulfuric acid in 5 min at 80 ° C. 20 equivalents of sulfuric acid at 80 °C lead to the *o-p* regioisomer in 5 min.

A study on different functionalized carbinols and activated aromatic compounds is currently underway.

Figure 1. Reaction between (4-*tert*-butyl-phenyl) -pyridin-2-yl-methanol and phenol.

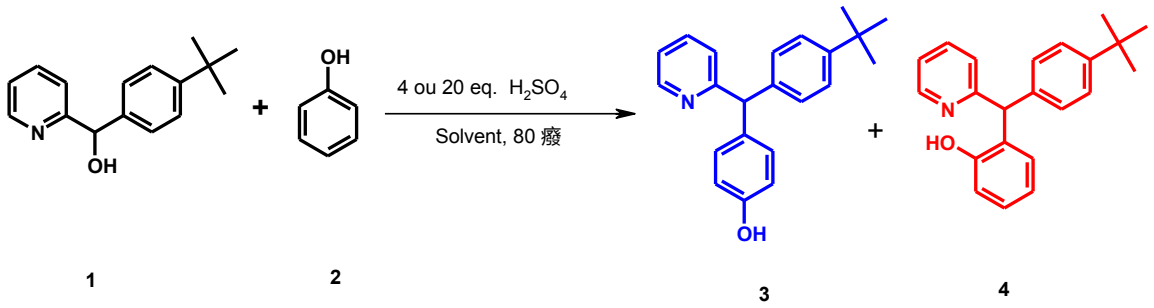
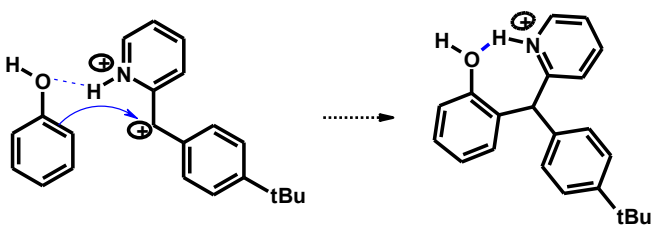


Table 1. Results obtained at different temperatures

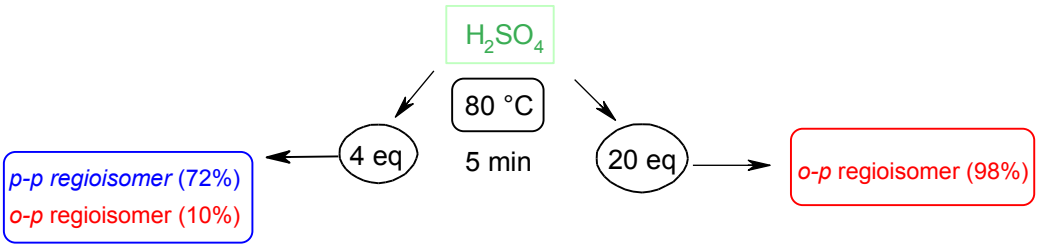
T °C	eq H_2SO_4	time	yield*% *p-p* **1**	yield* % *o-p* **2**
80	20	5 min	0	98
	4	5 min	72	10
20	20	5 min	72	3
	4	48 h	66	3
		5 h	58	3
0	20	15 min	78	2

* *After purification by silica gel chromatography*

Figure 2. Stabilization by establishing a hydrogen bond between the hydroxyl group and the nitrogen atom of pyridine



Scheme 1 : Selected conditions for the best regioselectivity



3. Materials and Methods

All reagents were obtained from commercial sources unless otherwise noted, and used as received. Heated experiments were conducted using thermostatically controlled oil baths and were performed under an atmosphere oxygen-free in oven-dried glassware. All reactions were monitored by analytical thin layer chromatography (TLC) or by Gas chromatography-Mass spectrometry (GC-MS). TLC was performed on aluminium sheets precoated silica gel plates (60 F_{254}, Merck). TLC plates were visualized using irradiation with light at 254 nm or in an iodine chamber as appropriate. Flash column chromatography was carried out when necessary using silica gel 60 (particle size 0.040-0.063 mm, Merck). All synthesized compounds were characterized by NMR, IR, MS data and by the TLC behavior.

General Procedure for the synthesis of carbinols

To a solution of 2-bromopyridine (1 eq.) in anhydrous THF at -78 ° C, was added a solution of *i*-propylmagnesium chloride 1M. After 2 h at room temperature the corresponding aldehyde (1.03 eq.) was added dropwise. After stirring for 20 hours at room temperature, the mixture was hydrolysed with distilled water and then extracted with dichloromethane. The organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated to give an oil which crystallized when cold. The precipitated product was filtered and rinsed with CyHex/EtOAc mixture and dried. If necessary product was purified by flash chromatography on silica gel.

General procedure for the synthesis of o-p regioisomers

To a solution of the corresponding carbinol (1 eq.) and phenol (1.2 eq.) in nitrobenzene (0.4 M) was added dropwise concentrated sulfuric acid (20 eq.). After 5 min at 80 ° C, the reaction medium was cooled to ambient temperature and then neutralized with a saturated solution of $NaHCO_3$ until pH 7, then extracted with EtOAc. The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography on silica gel.

General procedure for the synthesis of o-p regioisomers

To a solution of the corresponding carbinol (1 eq.) and phenol (1.2 eq.) in nitrobenzene (0.4 M) was poured dropwise concentrated sulfuric acid (4 eq.). After 5 min at 80 ° C the reaction mixture was cooled to room temperature and then neutralized by pouring slowly a saturated solution of $NaHCO_3$ until pH 7-8, then extracted with EtOAc. The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated, filtered and

concentrated. The crude product was purified by flash chromatography on silica gel.

4. Conclusions

The study of the regioselective Friedel-Crafts hydroxyalkylation between a functionalized carbinol and phenol was developed using a Brønsted acid as promoting system. The obtained results highlight an effective method to synthesize unsymmetrical triarylmethanes, regioselectively, under mild conditions with good yields.

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Author Contributions

C.R. performed experiments and analyzed data; M.S-IV designed experiment, analyzed data and wrote the paper and C. F. wrote the paper and supervised the project. All authors contributed to the drafting and revision of the article and approved the final version.

Conflicts of Interest

The authors declare no conflict of interest

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