

An Eco-Friendly Paradigm for the Production of Potentially Anti-Parasitic Drugs

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Abstract: A cleaner production of various potentially anti-parasitic drugs based bis-(arylmethylidene)cycloalkanones have been developed using a heterogeneous catalysis technology in aqueous media without organic solvent. The higher activity and selectivity of our solid-state synthetic phosphate catalyst coupled with their ease of use and reduced environmental problems makes them attractive alternatives to homogeneous basic reagents.

Keywords: Green Synthesis, Heterogeneous Catalysis, Anti-Parasitic Drugs, Bis-(Arylmethylidene) Cycloalkanones, Synthetic Phosphate, Aqueous Media

1. Introduction

Chagas' disease and Leishmaniasis are endemic protozoan diseases recognized as epidemiological priorities by the World Health Organization (WHO). Chagas' disease is found mainly in Latin America and it is estimated to affect 12 to 14 million people. Leishmaniasis affects 12 million people in 88 countries, 72 of which are developing countries [1].

Chagas' disease [2] and Leishmaniasis [3] are caused by the trypanosomatid parasites *Trypanosoma cruzi* and *Leishmania* sp, respectively.

There are limited drugs available for the treatment of both diseases, and the currently used chemotherapeutic agents are still inadequate due to their extreme toxicity [4]. In addition, drug resistant parasite strains have become more prevalent. The search for more effective and less toxic drugs to treat both diseases have become mandatory [5].

In search for new drugs with improved antiparasitic profiles, the Brazilian authors showed that the bis-(arylmethylidene)cycloalkanones presented a activity against amastigotes forms of *Trypanosoma cruzi* and promastigotes forms of *Leishmania amazonensis* [6].

Cross-aldol condensation [7] is an important protocol for the synthesis of various bis-(arylmethylidene)cycloalkanones. This reaction is classically carried out using strong acid or base [8]. Indeed, different organometallic complexes, Lewis acid are found to be able to catalyze this reaction [9]. However, most of the above-mentioned process generated a large amount of toxic waste and involved tedious separation procedures since the reactions were homogeneous and the catalysts were destroyed or discarded on the work-up procedure [10].

Recently, because of increased environmental concerns and strong economic driver in chemical research and industry, great efforts have been made on heterogeneous catalysis, which allows the catalyst for easy isolation and recycling. Thus, solid catalysts have drawn considerable attention in organic synthesis due to their advantages such as environmental compatibility, reusability, high selectivity, simple operation, non-corrosiveness and low cost [11].

In continuation of our ongoing program to develop new environmentally process in organic synthesis, we describe in

this paper, an environmentally friendly method for the synthesis of various bis-(arylmethylidene)cycloalkanones-based potentially anti-parasitic drugs by Cross-aldol condensation catalyzed by synthetic phosphate in aqueous media.

2. Materials and Methods

2.1. Chemicals and Instrumentations

All commercial reagents and solvents were used without further purification. X-ray diffraction (XRD) patterns of the catalysts were obtained on a Philips 1710 diffractometer using Cu-K α radiation. Surface areas were determined at 77 K using a Coulter SA 31000 instrument with an automated gas volumetric method employing nitrogen as the adsorbate. NMR spectra were recorded on a Bruker ARX 300 spectrometer. Mass spectra were recorded on a VG Autospec spectrometer. FTIR spectra were recorded on an ATI Mattson-Genesis Series spectrophotometer using the KBr disc method.

2.2. Preparation and Characterization of Catalysts

The fluorapatite (FAP) have been prepared by reaction between diammonium phosphate, calcium nitrate and ammonium fluoride in presence of ammonia [12]. The FAP obtained was calcined at 900°C before use. The structure of this catalyst was confirmed by X-ray diffraction, infrared spectra and chemical analysis. The surface area of calcined FAP was determined by the BET method and found to be $S=15.4 \text{ m}^2 \text{ g}^{-1}$. The total pore volume was calculated by the BJH method ($V_T=0.058 \text{ cm}^3 \text{ g}^{-1}$).

The modified fluorapatite (Na/FAP) has been prepared by impregnation of the FAP with a solution of sodium nitrate followed by calcination at 900°C [13]. The surface area of the new catalyst Na/FAP was determined by the BET method as $5.4 \text{ m}^2 \text{ g}^{-1}$ and the total pore volume obtained by the BJH method is $0.0032 \text{ cm}^3 \text{ g}^{-1}$.

2.3. General Procedure

The general procedure for synthesis of bis-(arylmethylidene)cycloalkanones is reported in Figure 1, as follows: To a flask containing a mixture by taking 1:2 mole ratios of cyclopentanone 1 and arylaldehydes 2 in aqueous media, the Na/FAP catalyst was added and the mixture was stirred at reflux during 3 hours.

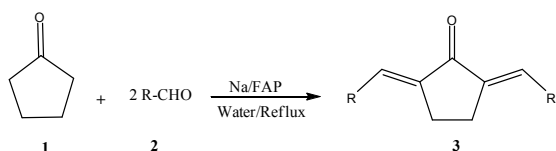


Figure 1. Synthesis of Potentially Anti-Parasitic Drugs.

Hot water (2×20 mL) was added, followed by simple filtration. After filtration and extraction with hot water, the solution was concentrated and purified by silica gel chromatography (*n* hexane/ethyl acetate: 7/3). Na/FAP was

reactivated by drying at 150 °C or, alternatively washed with acetone and calcined at 900 °C for 1 h. The crude product 3 was identified by melting point, ^1H NMR, ^{13}C NMR, and IR spectroscopies.

3. Results and Discussion

After synthesis and characterization of fluorapatite and Na/FAP, we tested these two materials as catalysts in the synthesis of bis-(arylmethylidene)cycloalkanones in aqueous media, which tends to a green synthesis strategy, going from modernization of organic synthesis toward sustainability. The cross-aldol condensation between cyclopentanone 1 and benzaldehyde 2a, were chosen as model substrates to determine suitable reaction conditions for synthesis of bis-(arylmethylidene)cycloalkanones. The optimal reaction condition for synthesis of this product was obtained by central composite design [14] and it's reported in Figure 2.

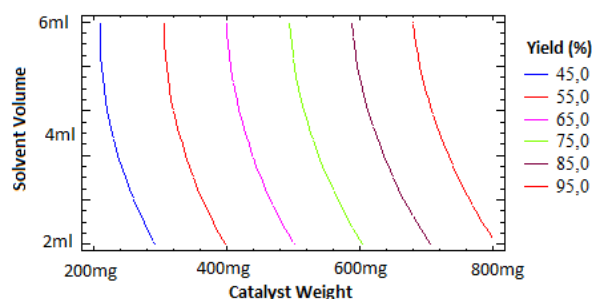


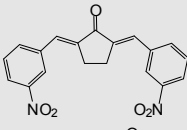
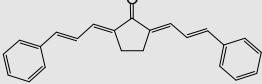
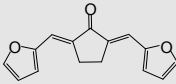
Figure 2. Optimization of reaction condition for cross-aldol condensation by central composite design.

We studied the influence of several parameters on a model cross-aldol condensation, specifically: (i) optimal catalyst preparation conditions (Na/FAP), (ii) quantity of catalyst, and (iii) kinetics of the reaction.

The investigation of central composite design showed that the optimum model reaction conditions are: catalyst weight = 700 mg, reaction time = 3 h and solvent volume = 5 mL. To determine the scope and limitation of this reaction, the optimum condensations were applied to other substrates as shown in table 1.

Table 1. Synthesis of various bis-(arylmethylidene)cycloalkanones.

Entry	R-CHO	Product (*)	Yield (%)
3a	C ₆ H ₅ CHO		92
3b	4-Cl-C ₆ H ₄ CHO		83
3c	4-MeO-C ₆ H ₄ CHO		72

Entry	R-CHO	Product (*)	Yield (%)
3d	3-NO ₂ -C ₆ H ₄ CHO		64
3e	PhC ₂ H ₂ CHO		80
3f	C ₄ H ₃ CHO		93

* The analytical data were identical to those reported in the literature.

In this regard, the preparation of potentially anti-parasitic drugs was carried out under reflux conditions by taking 1:2 mole ratios of cyclopentanones and arylaldehydes in water in the presence of modified fluorapatite Na/FAP catalyst to give the desired bis-(arylmethylidene)cycloalkanones in excellent yields. In general, the use of FAP as the heterogeneous catalyst in the crossed-aldol condensation has allowed the isolation of our products in low yields with slow reaction time. Under similar conditions in the absence of synthetic phosphate FAP or Na/FAP catalyst, only the starting material was regenerated, thus highlighting the role of this catalyst. When the reactions were examined in different solvents such as methanol, toluene, chloroform, water and THF, we found that water is the best solvent due to high yields and shorter reaction times. Moreover, using water as the reaction medium made the separation process much easier with high purity of final product than using organic solvents. However, when toluene, THF, chloroform, and methanol were used as solvents, a homogenous mixture of product and starting materials was obtained at the end of the reaction. After filtration of the final product, synthetic phosphate catalyst was recovered quantitatively by simple filtration and regenerated by calcination for each new reuse. The table show that the comparison of the results obtained by our method with some of those reported shows the efficiency of this method because of shorter reaction times, high yields, and application of an inexpensive and readily available catalyst. A simple procedure and the use of water as a solvent are expected to contribute to the development of more benign crossed-aldol reactions. The modified synthetic phosphate Na/FAP catalyst is a new, inexpensive, and attractive solid support which can contribute to the development of catalytic processes and reduced environmental problems and it is the first use of this material as the catalyst.

4. Conclusions

In conclusion, we have developed a clean and easy method for the synthesis of potentially anti-parasitic drugs based bis-(arylmethylidene)cycloalkanones using an inexpensive, reusable, easy to handle, noncorrosive, and environmentally benign catalysts, fluorapatite and especially sodium-modified fluorapatite. The use of these catalysts offers diverse

advantages including simplicity of operation due to the heterogeneous nature of reaction, easy workup, high yields, and catalyst reusability.

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