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Unsymmetrical 1,5-diaryl-3-oxo-1,4-pentadienyls and their evaluation as antiparasitic agents

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ABSTRACT

In this work the synthesis and antiparasitical activity of new 1,5-diaryl-3-oxo-1,4-pentadienyl derivatives are described. First, compounds **1a**, **1b**, **1c** and **1d** were prepared by acid-catalyzed aldol reaction between 2-butanone and benzaldehyde, anisaldehyde, *p*-*N*,*N*-dimethylaminobenzaldehyde and *p*-nitrobenzaldehyde. Reacting each of the methyl ketones **1a**, **1b**, **1c** and **1d** with the *p*-substituted benzaldehydes under basic-catalyzed aldol reaction, we further prepared compounds **2a**–**2p**. All twenty compounds were evaluated for antiproliferative activity, particularly for promastigote of *Leishmania amazonensis* and epimastigote of *Trypanosoma cruzi*. All compounds showed good activity while nitro compounds **2i** and **2k** showed inhibition activity at a few μM.

1. Introduction

The 1,5-diarylpentanoid dibenzylideneacetone (Fig. 1) is the parent of a class of compounds having an acyclic dienone attached to aryl groups in both β-positions. These structures resemble those of the curcuminoids (1,7-diarylheptanes) and the chalcones (1,3-diarylpropanes), which are very important bioactive natural compounds found in many plant species. Accompanying these structural similarities, synthetic chalcones and related compounds[1] have shown biological activities such as antitumor,[2] anticancer and antioxidant,[3] antifungal,[4,5] antimitotic,[6] chemoprotective,[7] anti-inflammatory,[8,9] antimicrobial,[10] anti-nociceptive,[11] antibacterial,[12] antimalarial.[13,14] In addition, dibenzylideneacetone potentiates TRAIL-induced apoptosis by down-regulation of cell survival proteins and up-regulation of death receptors through activation of ROS and CHOP mediated pathways.[15] The good bio-availability of some dibenzylideneacetone and their derivatives, which is required for bioactivities[16], as well as their mode of cross linking, has raised the interest of chemists in their synthesis.

Aher et al. have shown that dibenzylideneacetone have good potential to inhibit some parasites growth.[14] These findings motivated us to investigate the activity of similar compounds against *Leishmania amazonensis* and *Trypanosoma cruzi*, the etiologic agents that causes '*Leishmaniosis*' and 'Chagas disease', respectivelly. These two diseases affect, according to the World Health Organization, 12 million of people in 88 countries, and 350 million are at risk of acquiring this infection.[17] Additionally, Chagas disease is considered a serious public health problem that affects approximately 10 million people in Latin America. The incidence of this disease has been estimated to include 300,000 new cases per year, and approximately 10,000 people die from this infection annually.[18–20] In view of the lack of safe medication and the serious side effects caused by the use of available chemotherapy,[20] there is a need of new drugs for the treatment of these diseases. In the past decade, chalcones and related compounds emerged as a new class of antitrypanosomatids agents.[21–26] Thus, due to their structural similarities with chalcones and curcuminoids we attempted to synthesize some dibenzylidene derivatives. The search for fascinating pharmacologically active molecular building blocks, based on diverse structural features, easy synthetic routes and desired functionalities have attracted our attention to synthesize dibenzylideneacetones systems.

2. Synthesis plan

Dibenzylideneacetones (Fig. 1) can be formed by the direct reaction of benzaldehyde (A1) with acetone (K1) using basic or acid

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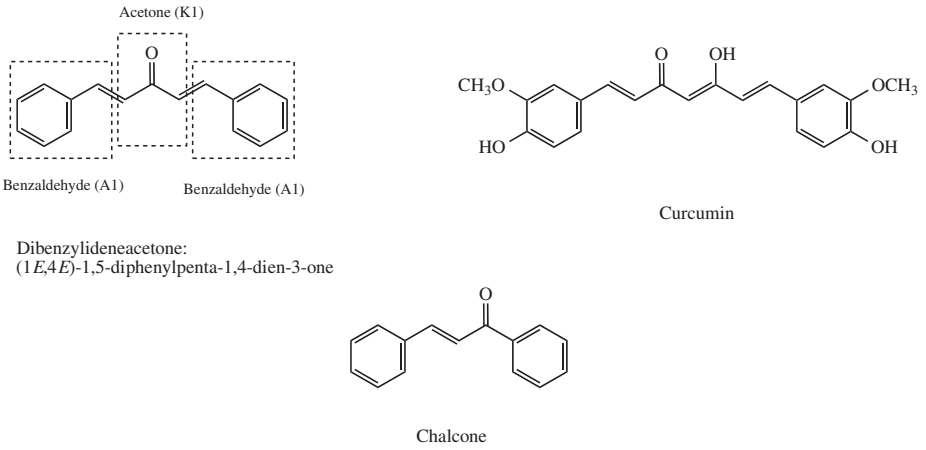


Figure 1. Basic structure of a dibenzylideneacetone and their natural congeners curcumin and chalcone.

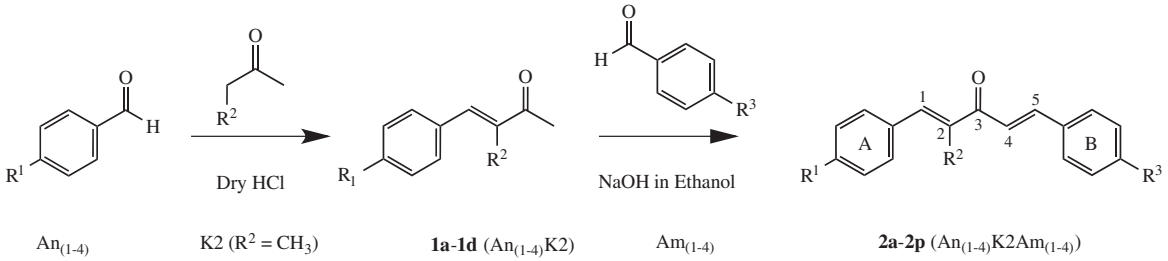
catalysis.[27] Acid catalysts used for cross–aldol condensation reaction include sulfuric, hydrochloric,[28,29] and Lewis[30–32] acids. Generally, aldol condensation can be carried at room temperature or ethanol under reflux condition.[33,34] Dibenzylideneacetones and chalcones usually are more easily synthetized in one step by aldol condensation under basic catalysis. This procedure works very well for symmetric ketones and a variety of substituted aldehydes. However, only a few studies used non-symmetric ketones and different aldehydes to be attached to the ends of the alkyl chain spacer.[16,35] These non-symmetric 1,5-diaryl-3-oxo-1,4-pentadienyls can be formed in two steps.[35] Methyl–alkyl ketones are good for aldol condensation because of the easy regiochemistry control. Therefore, these ketones react with an appropriate aldehyde in acidic medium (thermodynamic enol formation), and then the dehydrated aldol is isolated (Scheme 1). The second aldehyde is then added dropwise in cold ethanol solution, stirred, and the non-symmetric 1,5-diaryl-3-oxo-1,4-pentadienyl is formed (Scheme 1). Using this methodology[35] and combining different aldehydes with ketones, it is possible to generate a great molecular diversity, creating a library of compounds with 1,5-diarylpentane basic structures, which are still to be explored as to their bioactivities.

Thus, herein is reported a new series of dibenzylideneacetones, which have been prepared according Scheme 1, by combination of four *p*-substituted aldehydes (A1–A4) with butanone (K2) resulting in the four 4-aryl-3-methylbutenones **1a**-**1d** [R^1 = H (A1) or OCH_3 (A2) or NO_2 (A3) or $N(CH_3)_2$ (A4), respectivelly; $R^2 = CH_3$], which were individually further condensed with the same aldehydes, resulting in the sixteen compounds **2a**–**2p** ($An_{(1-4)}K2Am_{(1-4)}$). The antiproliferative activities of the twenty-synthetized compounds were evaluated, particularly in promastigotes of *L. amazonensis* and epimastigotes and trypomastigotes of *T. cruzi*.

3. Results and discussion

3.1. Chemistry

The reaction of benzaldehyde (**A1**) and three *p*-substituted benzaldehydes (**A2**–**A4**) with butanone, using gaseous HCl as catalyst as outlined in Scheme 1, produced the 4-aryl-3-methylbutenone **1a**–**1d**, which were isolated and characterized by spectroscopic data. These reactions were performed at room temperature by stirring the reaction mixture and passing dry gaseous HCl until the reaction mixture turned to red. Stirring continued until the completion of starting materials, which was monitored by TLC. The reaction was very clear giving yields of 48–61% of **1a**–**1d**, which were analyzed by NMR as follows: compound **1** showed two characteristic signals of two methyl groups in the shielded region at δ_H 2.06 and 2.47, whereas one =CHsignal was displayed at δ_H 7.39 as singlet; additionally three aromatic signals having integration for five proton were detected at δ_H 7.32, 7.41 and 7.52. ^{13}C NMR spectra of **1** showed signals for two methyl groups at δ_C 13.0 and 25.9, and six peaks from δ_C 128–139 for eight carbons, with two of these peaks having double intensity for aromatic carbons. The characteristic peak at δ_C 200.3 is due to carbonyl carbon. The ^1H NMR spectra of compounds **1a**, **1b** and **1c** are similar each other. Only compound **1b** showed an extra signal at δ_H 3.85 due to OCH_3 substitution on benzene, and a signal at δ_H 3.02 for compound **1d** due to $N(CH_3)_2$ substitution in benzene ring. By reacting each of the intermediary compounds **1a**–**1d** systematically with benzaldehyde (**A1**), anisaldehyde (**A2**), *N*,*N*-dimethylaminobenzaldehyde (**A3**) and nitrobenzaldehyde (**A4**) the respective sixteen dibenzylidene ketones **2a**–**2p** were produced in 45–93% yield after re-crystallization from ethanol. All these reactions were carried in basic medium in ethanol, and their



$An_{(1-4)}$ K2 ($R^2 = CH_3$) **1a**-**1d** ($An_{(1-4)}K2$) $Am_{(1-4)}$ **2a**-**2p** ($An_{(1-4)}K2Am_{(1-4)}$)

Scheme 1. Reaction conditions for the synthesis of the assayed compounds, using *p*-substituted aldehydes A1 (R^1,R^3 = H), A2 (R^1,R^3 = OCH_3), A3 (R^1,R^3 = NO_2) and A4 (R^1,R^3 = $N(CH_3)_2$) and butanone (K2, $R^2 = CH_3$) resulting in **1a**–**1d**, respectivelly; and further reaction of each enone **1a**–**1d** with same aldehydes to give the collection $An_{(1-4)}K2Am_{(1-4)}$ (**2a**–**2p**).