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RESEARCH ARTICLE

Stereoselective Alkylation of Indole with 5-Arylidene-Meldrum's Acids in the Presence of Organocatalysts

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Abstract: ***Background***: Indole motif is frequently present in biologically active compounds. Enantiomerically pure or enriched 2,2-dimethyl-5-(aryl(1*H*-indol-3-yl)methyl)-1,3-dioxane-4,6-diones can be considered as a convenient starting point for the synthesis of a indole ring fused with cyclic ketones with biological activity. Preparation of chiral 2,2-dimethyl-5-(aryl(1*H*-indol-3-yl)methyl)-1,3-dioxane-4,6-diones requires the reaction of indole with 2,2-dimethyl-5-arylidene-1,3-dioxane-4,6-diones in the presence of chiral catalysts or other source of chiral induction.

Methods: Enantioselective Friedel-Crafts alkylation of indole has been performed with 2,2-dimethyl-5-arylidene-1,3-dioxane-4,6-diones in the presence of organocatalysts to give 5-((1*H*-indol-3-yl)(aryl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-diones. Broad scope of organocatalysts as well as various temperatures and solvents used for the reaction were tested.

Results: 2,2-Dimethyl-5-(aryl(1*H*-indol-3-yl)methyl)-1,3-dioxane-4,6-diones were obtained with quantitative yield and enantiomeric ratio 1:3 using thiourea organocatalyst. Also a new spectroscopic method for discrimination of 5-((1*H*-indol-3-yl)(aryl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-diones enantiomers was developed.

Conclusion: Enantioselective Friedel-Crafts alkylation of indole has been developed. In the presence of thiourea catalysts, 2,2-dimethyl-5-arylidene-1,3-dioxane-4,6-diones react with indole to give 2,2-dimethyl-5-(aryl(1*H*-indol-3-yl)methyl)-1,3-dioxane-4,6-diones with good yields and reasonable ee.

Keywords: Stereoselective 1,3-dioxane-4,6-dione, heteroaromatic, thiourea organocatalyst, alkylation, Meldrum's acid, ketone.

1. INTRODUCTION

The significant progress in enantioselective organocatalysis which has been made over the last few decades, enables the consideration of this methodology on an equal footing with well-established method of stereoselective synthesis of organic compounds means: transition-metal complexes and enzymatic catalysis [1-4]. So far, the organocatalyst approach has been used in chemical processes, *e.g.* Mannich condensation [5], Pudovik reaction [6], Michael addition [7], Strecker [8], domino [9], aldol [10] and Freidel-Crafts reaction [11]. In terms of their applicability and high degree of stereoselectivity, thiourea organocatalyst are one of the most important groups of organocatalysts. Their importance also stems from the fact that their structure can be easily tuned to the requirements of specific reactions [12]. We have focused our research efforts on stereoselctive Friedel-Crafts alkylation of indoles with 5-arylidene Meldrum's acid derivatives.

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The problem of enantioselective organocatalytic Friedel-Crafts alkylation has been studied thoroughly on many levels [11, 13]; however, to the best of our knowledge, there have been no reports of successfully stereocontrolled Friedel-Crafts alkylation of indoles with 5-arylidene-2,2-dimethyl-1,3-dioxane-4,6-diones (**1**) [14]. 2,2-Dimethyl-5-(aryl(1*H*-indol-3-yl)methyl)-1,3-dioxane-4,6-diones, (**3**) the products of Friedel-Crafts alkylation of indole, contain a thermal labile moiety, which can easily be converted to ketenes (**4**) and used for intra- and inter-molecular reaction with nucleophiles (Scheme **1**).

Fillion and co-workers demonstrated a series of examples for 2,2-dimethyl-5-benzyl-1,3-dioxane-4,6-diones transformation to useful bioactive 1-indanones through intramolecular Friedel-Crafts acylation [15]. Considering the versatility of the indole motif in biologically active compounds, we can anticipate that optically pure or enriched 2,2-dimethyl-5-(aryl(1*H*-indol-3-yl)methyl)-1,3-dioxane-4,6-diones (**3**) can be considered as a convenient starting point for the synthesis of a ring fused with cyclic ketones with biological activity (*e.g.*; strigolactone [16], aurora kinase inhibitors [17], acetyl-

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