Synthesis E. Najda et al. Paper

Practical Method for the Preparation of 2,2-Dimethyl-5-{aryl[(hetero)aryl]methyl}-1,3-dioxane-4,6-diones: Synthesis and Mechanistic Study

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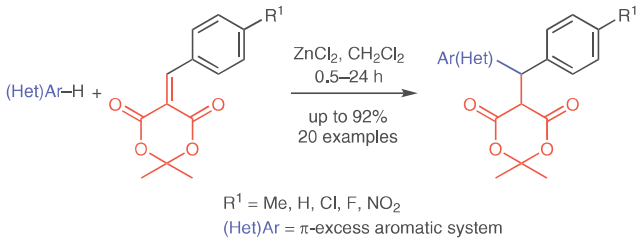

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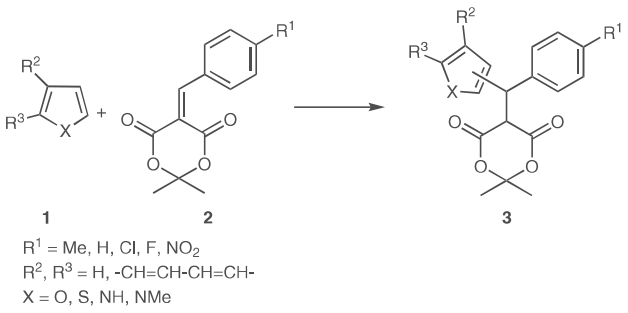
Abstract An efficient practical synthetic procedure has been developed for the synthesis of 2,2-dimethyl-5-{aryl[(hetero)aryl]methyl}-1,3-dioxane-4,6-diones through Friedel–Crafts alkylation. The scope and limitation of the reaction of 2,2-dimethyl-5-arylidene-1,3-dioxane-4,6-diones with π-excess aromatic systems have been delineated.

Key words heterocycles, indoles, pyrroles, electrophilic aromatic substitution, Lewis acids

Functionalized derivatives of Meldrum's acid have gained an established position in organic synthesis. Most practical applications are related to the use of various acyl derivatives of 1,3-dioxane-4,6-diones, which are easily formed by the acylation of Meldrum's acid with activated acyl compounds or isocyanates.[1] These acyl derivatives are important in that under moderately mild thermolysis conditions they are converted into β-oxoketenes – a broadly exploited chemical species. In comparison, alkyl or arylmethyl derivatives of Meldrum's acid belong to a less explored class of compounds; however, these reagents could also be a starting point for various syntheses, particularly those leading to bioactive species.[2]

Recently, we focused our research efforts on the synthesis and application of 2,2-dimethyl-5-{aryl[(hetero)aryl]methyl}-1,3-dioxane-4,6-diones, which could be considered as the starting molecules for a broad scope of bioactive compounds possessing a heteroaromatic ring fused with cyclic ketones, for example, strigolactone analogues,[3] antitumor agents,[4] aurora kinase inhibitors,[5] necroptosis inhibitors,[6] acetylcholinestrase inhibitors,[7] oxindole alkaloids,[8] or Uhle ketones.[9]

The simplest strategy for the preparation of 2,2-dimethyl-5-{aryl[(hetero)aryl]methyl}-1,3-dioxane-4,6-diones **3** is based on the addition of nucleophilic aromatic species to electron-deficient 2,2-dimethyl-5-arylidene-1,3-dioxane-4,6-diones **2** (Scheme 1).



Scheme 1 Formation of 2,2-dimethyl-5-{aryl[(hetero)aryl]methyl}-1,3-dioxane-4,6-diones through Friedel–Crafts alkylation

Since the α,β-unsaturated system of vinyl derivatives of Meldrum's acid are rather moderate electrophiles, the method of choice for the preparation of **3** is usually the addition of organometallic reagent to 2,2-dimethyl-5-heteroarylideno-1,3-dioxane-4,6-diones.[10] Such an approach is also used for the formation of 2,2-dimethyl-5-(homodiarylmethyl)-1,3-dioxane-4,6-diones with Cu(I) as catalyst[11] or without catalyst.[12] In the case of heteroaromatic highly π-excess donors, one would expect to obtain **3** in a Friedel–Crafts type of reaction with α,β-unsaturated electrophiles. However, in the chemical literature there is a lack of general and simple procedures for the preparation of such compounds. Only narrow specialized methods could be found: as reaction of indoles in three-component process in the presence of L-proline described by Laronze and co-work-