

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

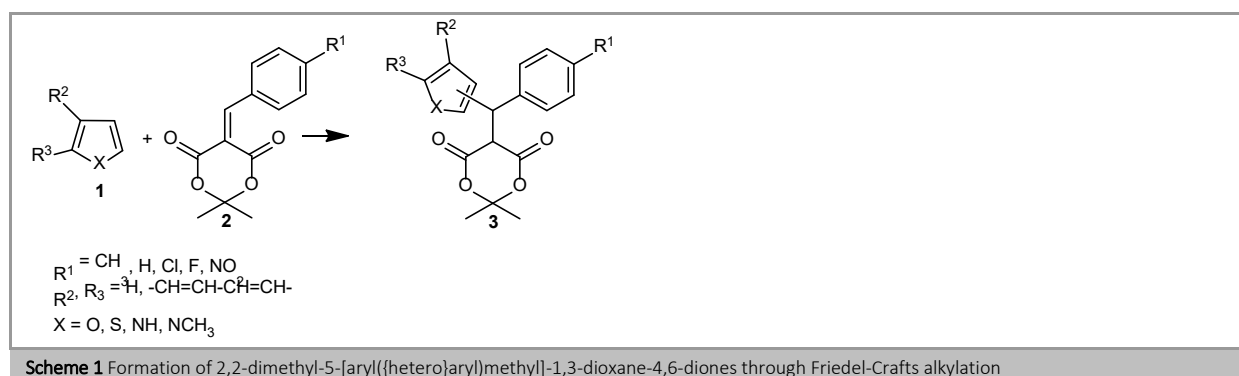
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Abstract: An efficient practical synthetic procedure has been developed for the synthesis of 2,2-dimethyl-5-[aryl((hetero)aryl)methyl]-1,3-dioxane-4,6-diones through Friedel-Crafts alkylation. The scope and limitation of the reaction of 2,2-dimethyl-5-arylidene-1,3-dioxane-4,6-diones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

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 What is more important, acyl derivative in a moderately mild thermolysis condition are converted to 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 acetylcholinesterase inhibitors,⁷ oxindole alkaloids⁸ or Uhle ketones.⁹

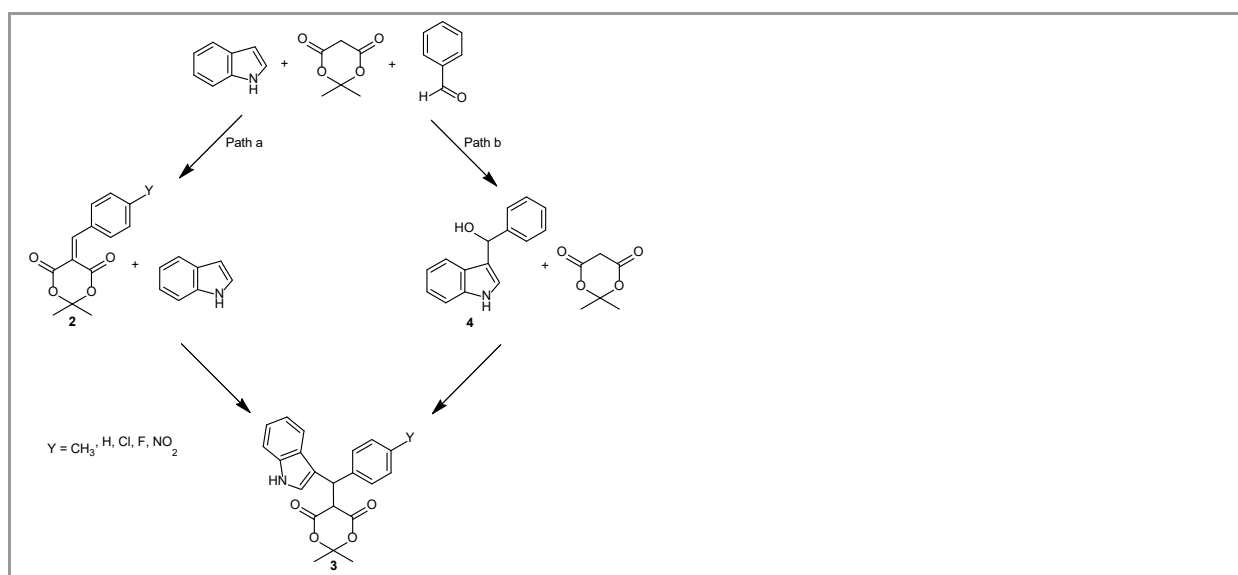
The simplest strategy for the preparation of 2,2-dimethyl-5-[aryl((hetero)aryl)methyl]-1,3-dioxane-4,6-diones (**3**) is based on the addition of nucleophilic aromatic species to electron deficient 2,2-dimethyl-5-arylidene-1,3-dioxane-4,6-diones (**2**). (Scheme 1).



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-heteroarylidene-1,3-dioxane-4,6-diones.¹⁰ Such an approach is also used for the formation of 2,2-dimethyl-5-[homo-diarylmethyl]-1,3-dioxane-4,6-diones with a Cu(I) a catalyst¹¹ or without catalyst.¹² In the case of a heteroaromatic highly π -excess donors would be expected 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 a narrow specialized methods could be found: as reaction of indoles in three

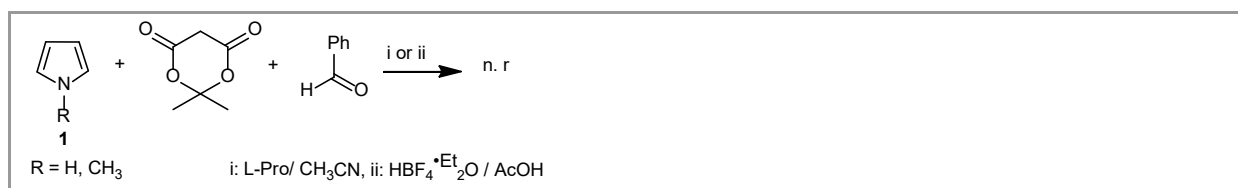
components process in the presence of L-proline described by Laronze and co-workers,¹³ enantioselective addition of 2-furfurylketones to 2,2-dimethyl-5-arylidene-1,3-dioxane-4,6-diones (**2**),¹⁴ or organoboron compounds addition¹⁵

In this article, we describe a general method for the preparation of **3**, which allows for the obtainment of the target compound independently of the type of heteroaromatic reagent used. As was mentioned earlier, Laronze has described an effective method for the preparation of **3** with indole as a heteroatomic moiety; however, when we tried to apply this method for the slightly less π -excess aromatic donors such as pyrrole or furan, we did not obtain the desired **3**. Therefore, we were forced to find a more universal methodology for the effective preparation of **3** which would exploit the widest possible range of aromatic substrates and electrophilic 2,2-dimethyl-5-arylidene-1,3-dioxane-4,6-diones. Next, the mechanism of the reaction between a benzaldehyde derivative, Meldrum's acid and π -nucleophile in the presence of a catalyst was investigated. From the theoretical point of view, there are two possible routes: First, the previous formation of the Knoevenagel product and then the Friedel-Crafts alkylation to yield **3** (Path a, Scheme 2); and second,



Scheme 2 Possible ways for formation of 2,2-dimethyl-5-[aryl((hetero)aryl)methyl]-1,3-dioxane-4,6-diones in the three component reaction.

initial hydroxyalkylation of aromatic ring by aldehyde in condition of an acid or base catalyst. The first initial steps for both types of reactions are possible and known processes^{16, 17} in the two-component reactions. To distinguish which is a plausible reaction mechanism we planned and performed a series of experiments. At the beginning, we performed a reaction between benzaldehyde, Meldrum's acid and pyrrole or N-methylpyrrole in acetonitrile in the presence of L-proline. As a result, we did not obtain the desired product **3** (Scheme 3), even if we applied more acidic conditions such tetrafluoroboric acid in acetic acid.



Scheme 3 Attempts for preparation of 2,2-dimethyl-5-[aryl(1H-pyrrol-2-yl)methyl]-1,3-dioxane-4,6-diones in three component process.



However, in the reaction of benzaldehyde, Meldrum's acid and N-methylpyrrole in acetonitrile in the presence of L-proline, we observed the formation of **2**), but the subsequent addition to the aromatic ring of N-methylpyrrole was not effective in these conditions and the reaction resulted in the formation of a complex mixture of products. However, when we used previously prepared **2**) and indole in the presence of L-proline, the product **3** was formed with a similar yield as was reported by Laronge^{13d} for a three-component reaction. Also, the use of **2a**, N-methylpyrrole and L-proline in acetonitrile resulted in the formation of the desired product (Table 1, Entries 18, 19, 20). The above facts strongly suggests (Path a, Scheme 2) as a plausible mechanism for the investigated process. Additionally, we checked whether indole can be hydroxylated with an aldehyde in the presence of L-proline. In the reaction of indole and benzaldehyde, we did not observe the formation of **4**, in fact, for the effective hydroxyalkylation of indole, tetramethylguanidine is required.¹⁷ Moreover, independently formed 3-(1-hydroxybenzyl)-1H-indole or 3-(1-hydroxybenzyl)-pyrrole did not react with Meldrum's acid in the presence of L-proline. On the basis of these experiments, we conclude that the first step of the reaction is the formation of **2**, which, in the in the further course of the reaction, plays the role of electrophile in the reaction with the aromatic ring. To reduce the number of variables during the search for the optimal conditions for the preparation of **1**, we decided to use the previously prepared **2** as substrates. It should also be added that use of the mixture of Meldrum's acid and aldehyde for in-situ formation of **2** is the source of problems associated with dimer formation.¹⁸ At the beginning, we tried to find the most effective catalyst for the reaction between **1** and **2**. As the first, we tested tetrafluoroboric acid etherate in DCM at RT in the reaction of 1 eq of **2a** and 5 eq of N-methylpyrrole, resulting in a moderate yield of **3ba** (Table 1, Entry 15), probably due to the decomposition of previously formed product in acidic media. In another combination of reagents HBF₄•Et₂O proved to be ineffective. The next catalyst under investigation was ZrCl₄. In the reaction of **2a** with N-methylindole, we obtained a complex mixture of products that were difficult to separate. Furthermore, we tried to use SnCl₄ in the reaction of **2a** and pyrrole, but this approach was also unsuccessful, as was an approach with TMSCl (Table 1, Entry16). Finally, we took anhydrous ZnCl₂ under consideration as a moderately strong Lewis acid. We carried out an experiment where 1 eq of **2a** and 10eq of N-methylpyrrole was treated with ZnCl₂ in DCE at 40°C for 0.5 h. From the reaction mixture we isolated product **3ba** with a 50% yield (Table 1, Entry12). The obtained yield was similar to the reaction with L-proline as a catalyst, but the reaction time was shorter (Table 1, Entry19). Therefore, we tried to optimize this reaction; however, increasing the temperature of the process to the boiling point of DCE resulted in the formation of a complex mixture of products, while decreasing the temperature led to a drop in yield (Table 1, Entry8). In most cases with ZnCl₂ as a catalyst, the use of a large excess of volatile heteroaromatic compound furnished good yields (Table 1, Entries4, 5, 7, 10, 21, 22, 23). Nevertheless, we had to pay attention to the fact that two different catalysts such as ZnCl₂ in DCM and L-proline in acetonitrile led to similar results (Table 1, Entries 12 and 19). We performed control experiments with DCM as solvent between: pyrrole and **2a** (Table 1, Entry 2); N-methylpyrrole and **2a, b, e** (Table 1, Entries9, 11, 13, 14, 25);, indole and **2a-e** (Table 1, Entries28, 30, 32, 34, 36); N,N-dimethylaniline and **2a, c, e** (Table 1, Entries38, 41, 44); without any additional catalyst. These experiments led to surprising results: in the case of the combination nitrogen heteroaromatic substrates and acceptors **2a-d**, the best results were obtained without a catalyst in the reaction mixture, whereas in the case of the reaction of N-methylpyrrole with **2d**, furan with **2e** and N,N-dimethylaniline with **2a-d** the addition of ZnCl₂ caused higher yields of **3**. It must be noted that prepared **3** are not a very stable compounds and particularly in a solution containing protic acids^{12a}, they undergoes slow decomposition, which was proven by ¹H NMR monitoring of the solution of **3aa** after the addition of a catalytic amount of TFA. Therefore, purification on silica gel must be done as quickly as possible, otherwise a significant drop in yield occurs.

In conclusion, extensive studies to develop effective methods for the preparation of 2,2-dimethyl-5-[aryl({hetero}aryl)methyl]-1,3-dioxane-4,6-diones (**3**) were carried out with a wide range of variables such as type of substrates, process temperature, solvents, and catalyst. We proved the undeniable superiority of the use of 2,2-dimethyl-5-arylidene-1,3-dioxane-4,6-diones (**2**) that has been previously prepared and purified, rather than the in-situ formation of **2** in a three-component reaction. From the tested catalysts, ZnCl₂ proved to be most universal for all types of reagent combinations; however, for highly π -excess aromatic reagents, better results were acquired without the addition of a catalyst.

Commercially available reagents were purchased from Sigma-Aldrich. 5-Arylidene-1,3-dioxane-4,6-diones were prepared according to literature procedure **2a-c, e, g**^{16b} **2f**. DCM, DCE were distilled from P₄O₁₀ under argon and stored over molecular sieves A4. Acetonitrile and nitromethane were distilled from molecular sieves A4 and stored over them. Analytical TLC was performed on aluminum sheets of silica gel UV-254 Merck and visualized with UV lamp at 254 nm. Flash chromatography was performed using 40-63 microns of Zeochem silica gel. The ¹H, ¹³C were recorded at Varian Gemini 200 and Varian Unity Plus 500, chemical shifts (δ) are expressed in ppm. Melting points are uncorrected.

2,2-dimethyl-5-(4-fluorophenyl)methyl-1,3-dioxane-4,6-dione (**2d**).

Prepared according to literature procedure^{16b}. 4-fluorobenzaldehyde (0.62g, 5mmol, 1 equiv) was added to a stirred solution of Meldrum's acid (0.79g, 5.5mmol, 1.1 equiv) in dry benzene 25 ml. To this was added acetic acid (28 μ l, 0.5mmol, 10 mol %) and pyrrolidine (30 μ l, 0.5mmol, 10 mol %). The resulted mixture was stirred for 16 h. After diluting with EtOAc 50 ml the reaction mixture was washed with saturated NaHCO₃, and dried over MgSO₄. Solvent was removed under reduced pressure and residue was crystalized from EtOH to give **2d**; yellow crystals, yield: 0.25g (20 %); mp 138–140 °C

¹H NMR (CDCl₃, 500 MHz): δ = 8.39 (s, 1 H), 8.16-8.19 (m, 2 H), 7.15-7.19 (m, 2 H), 1.80 (s, 6 H).

¹³C NMR (CDCl₃, 125 MHz): δ = 166.0 (d, J = 259.0 Hz), 163.5, 160.1, 156.9, 137.0 (d, J = 9.6 Hz), 128.3, 116.4 (d, J = 21.5 Hz), 114.3, 104.9, 27.9.

HRMS (ESI+): m/z [M + H]⁺ calcd for C₁₃H₁₂FO₄: 251.0720; found: 251.0701.

2,2-dimethyl-5-[(hetero)aryl(aryl)methyl]-1,3-dioxane-4,6-diones; General Procedure (3aa-ee)

A solution of 5-arylidene-1,3-dioxane-4,6-dione **2a-e** (0.5 mmol), aromatic compound **1a-e** (amount specified in Table 1) and catalyst 10% mol in anhydrous solvent (5 ml) was stirred under argon. Catalyst, solvent, reaction time and temperature was specified in the Table 1. After completion of the reaction the solvent was removed under vacuum, and the residue was purified as follows:

2,2-dimethyl-5-(phenyl(1H-pyrrol-2-yl)methyl)-1,3-dioxane-4,6-dione (**3aa**)

Entry 2; Purification by flash column chromatography, (EtOAc/Hex, 1:2), brown oil; yield: 44 mg (30 %).

¹H NMR (CD₂Cl₂, 500 MHz): δ = 9.13 (s, 1 H), 7.30-7.22 (m, 3 H), 7.14-7.13 (m, 2 H), 6.78 6.77 (m, 1 H), 6.18-6.17 (m, 1 H), 6.14 (q, J = 2.9 Hz 1 H), 5.44 (d, J = 1.4 Hz, 1H), 4.26 (d, J = 1.4 Hz, 1 H), 1.79 (s, 3H), 1.67 (s, 3H)

¹³C NMR (CD₂Cl₂, 125 MHz): δ = 166.0, 165.6, 140.0, 130.1, 128.9, 128.3, 127.5, 118.7, 109.1, 108.3, 106.0, 52.4, 42.3, 28.5, 27.5.

HRMS (ESI+): m/z [M + H]⁺ calcd for C₁₇H₁₈NO₄: 300.1236; found: 300.1258

2,2-dimethyl-5-(4-chlorophenyl(1H-pyrrol-2-yl)methyl)-1,3-dioxane-4,6-dione (**3ac**)

Entry 4, Purification by flash column chromatography, (EtOAc/Hex, 1:1), brown oil; yield 96 mg (58 %).

¹H NMR (CDCl₃, 400 MHz): δ = 9.22 (s, 1 H), 7.25(d, J = 8.8 Hz, 2H), 7.09 (d, J = 8.8 Hz, 2H) 6.80-6.71 (m, 1H), 6.26- 6.18 (m, 2H), 5.47 (d, J = 2.1 Hz, 1H), 4.16 (d, J = 2.1 Hz, 1H), 1.80 (s, 3H), 1.70 (s, 3H).

¹³C NMR (CDCl₃, 125 MHz): δ = 165.6, 165.2, 137.9, 133.2, 129.5, 128.9, 128.9, 118.9, 109.1, 108.3, 105.8, 52.1, 41.4, 28.4, 27.4.

HRMS (ESI+): m/z [M + H]⁺ calcd for C₁₇H₁₇ClNO₄: 334.0845; found: 334.0848.

2,2-dimethyl-5-(4-fluorophenyl(1H-pyrrol-2-yl)methyl)-1,3-dioxane-4,6-dione (3ad)

Entry 5, Purification by flash column chromatography, (EtOAc/Hex, 1:1), yellow oil; yield 71 mg (45 %).

^1H NMR (CD_2Cl_2 , 500 MHz): δ = 9.14 (s, 1 H), 7.18-7.14 (m, 2 H), 7.00-6.97 (m, 2 H), 6.79-6.78 (m, 1 H), 6.17-6.15 (m, 1 H), 6.15-6.13 (m, 1 H), 5.43 (s, 1 H), 4.24 (d, J = 2.4 Hz, 1 H), 1.78 (s, 3 H), 1.68 (s, 3 H).

^{13}C NMR (CD_2Cl_2 , 125 MHz): δ = 165.9, 165.4, 162.2 (d, J = 245.0 Hz), 135.8, 130.3 (d, J = 7.9 Hz), 129.9, 118.8, 115.3 (d, J = 21.5 Hz), 109.1, 108.4, 106.1, 52.5, 41.6, 28.5, 27.5.

HRMS (ESI+): m/z [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{17}\text{H}_{16}\text{FNO}_4\text{Na}$: 340.0960; found: 340.0961

2,2-dimethyl-5-(4-nitrophenyl(1H-pyrrol-2-yl)methyl)-1,3-dioxane-4,6-dione (3ae)

Entry 7, Purification by flash column chromatography, (EtOAc/Hex, 4:1), yellow oil; yield 144 mg (84 %).

^1H NMR (CDCl_3 , 200 MHz): δ = 9.15 (s, 1H), 8.11 (d, J = 8.8 Hz, 2H), 7.28 (d, J = 8.8 Hz, 2H), 6.83-6.81 (q, J = 2.9 Hz, 1H), 6.24-6.20 (m, 1H), 6.18-6.19 (m, 1H), 5.53 (d, J = 2.0 Hz, 1H), 4.25 (d, J = 2.0 Hz, 1H), 1.81 (s, 3H), 1.73 (s, 3H).

^{13}C NMR (CDCl_3 , 125 MHz): δ = 165.4, 165.0, 147.0, 146.9, 129.0, 128.3, 123.8, 119.4, 109.8, 108.5, 106.1, 52.1, 41.5, 28.4, 27.3.

HRMS (ESI+): m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{17}\text{H}_{17}\text{N}_2\text{O}_6$: 345.1087; found: 345.1080.

2,2-dimethyl-5-(phenyl(1-methyl-1H-pyrrol-2-yl)methyl)-1,3-dioxane-4,6-dione (3ba)

Entry 13, Purification by flash column chromatography, (EtOAc/Hex, 1:2), white solid; yield 123 mg (79 %).

^1H NMR (CDCl_3 , 400 MHz): δ = 7.32-7.24 (m, 5 H), 6.60-6.59 (m, 1 H), 6.29-6.27 (m, 1 H), 6.14-6.11 (m, 1 H), 5.34 (d, J = 2.5 Hz, 1 H), 4.24 (d, J = 2.5 Hz, 1 H), 3.36 (s, 3 H), 1.77 (s, 3 H), 1.64 (s, 3 H).

^{13}C NMR (CDCl_3 , 125 MHz): δ = 165.0, 164.2, 139.0, 130.5, 129.3, 128.6, 127.5, 122.6, 108.6, 107.0, 105.3, 52.3, 41.5, 34.3, 28.5, 27.8.

HRMS (ESI+): m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{18}\text{H}_{20}\text{NO}_4$: 314.1391 found: 314.1388.

2,2-dimethyl-5-(*p*-tolyl(1-methyl-1H-pyrrol-2-yl)methyl)-1,3-dioxane-4,6-dione (3bb)

Entry 21, Purification by flash column chromatography, (EtOAc/Hex, 1:3), yellow solid; yield 96 mg (59 %).

^1H NMR (CDCl_3 , 200 MHz): δ = 7.16-7.02 (m, 4 H), 6.57 (s, 1 H), 6.25-6.23 (m, 1 H), 6.13-6.10 (m, 1 H), 5.29 (s, 1 H), 4.22 (d, J = 2.5 Hz, 1 H), 3.34 (s, 3 H), 2.30 (s, 3 H), 1.77 (s, 3 H), 1.62 (s, 3 H).

^{13}C NMR (CDCl_3 , 125 MHz): δ = 165.1, 164.2, 137.1, 135.9, 130.7, 129.3, 129.2, 122.5, 108.4, 106.9, 105.2, 52.3, 41.2, 34.2, 28.4, 27.7, 21.3.

HRMS (ESI+): m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{19}\text{H}_{22}\text{NO}_4$: 328.1548; found: 348.1572.

2,2-dimethyl-5-(4-chlorophenyl(1-methyl-1H-pyrrol-2-yl)methyl)-1,3-dioxane-4,6-dione (3bc)

Entry 22, Purification by flash column chromatography, (EtOAc/Hex, 1:1), yellow oil; yield 159 mg (92 %).

^1H NMR (CDCl_3 , 200 MHz): δ = 7.26-7.17 (m, 4 H), 6.57-6.54 (m, 1 H), 6.246.22 (m, 1 H), 6.13-6.10 (m, 1 H), 5.30 (d, J = 2.5 Hz, 1 H), 4.22 (d, J = 2.5 Hz, 1 H), 3.33 (s, 3 H), 1.77 (s, 3 H), 1.63 (s, 3 H).

^{13}C NMR (CDCl_3 , 125 MHz): δ = 164.9, 163.8, 137.4, 133.4, 130.9, 130.0, 128.7, 122.8, 108.6, 107.1, 105.3, 52.2, 40.6, 34.2, 28.4, 27.6.

HRMS (ESI+): m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{18}\text{H}_{19}\text{ClNO}_4$: 348.1003; found: 348.0999.

2,2-dimethyl-5-(4-fluorophenyl(1-methyl-1H-pyrrol-2-yl)methyl)-1,3-dioxane-4,6-dione (3bd)

Entry 23, Purification by flash column chromatography, (EtOAc/Hex, 1:3), white solid; yield 105 mg (64 %).

^1H NMR (CDCl_3 , 200 MHz): δ = 7.26-7.22 (m, 2 H), 6.97-6.94 (m, 2 H), 6.58-6.57 (m, 1 H), 6.25-6.24 (m, 1 H), 6.12-6.11 (m, 1 H), 5.31 (d, J = 2.0 Hz, 1 H), 4.22 (d, J = 2.0 Hz, 1 H), 3.33 (s, 3 H), 1.77 (s, 3 H), 1.66 (s, 3 H).

¹³C NMR (CDCl₃, 125 MHz): δ = 165.0, 163.9, 162.2 (d, *J* = 245.9 Hz), 134.5, 131.1 (d, *J* = 7.9 Hz), 130.5, 122.7, 115.4 (d, *J* = 21.5 Hz), 108.6, 107.0, 105.3, 52.3, 40.6, 34.2, 28.4, 27.7.

HRMS (ESI⁺): *m/z* [M + H]⁺ calcd for C₁₈H₁₉FNO₄: 332.1297; found: 332.12942, **2-dimethyl-5-(4-nitrophenyl(1-methyl-1H-pyrrol-2-yl)methyl)-1,3-dioxane-4,6-dione (3be)**

Entry 24, Purification by flash column chromatography, (EtOAc/Hex, 4:1), yellow oil; yield 107 mg (60 %).

¹H NMR (CDCl₃, 400 MHz): δ = 8.13 (d, *J* = 9.1 Hz, 2 H), 7.45 (d, *J* = 9.1 Hz, 2 H), 6.63-6.61 (m, 1 H), 6.26-6.23 (m, 1 H), 6.16-6.13 (m, 1 H), 5.42 (d, *J* = 2.5 Hz, 1 H), 4.29 (d, *J* = 2.5 Hz, 1 H), 3.38 (s, 3 H), 1.82 (s, 3 H), 1.73 (s, 3 H).

¹³C NMR (CDCl₃, 125 MHz): δ = 164.6, 163.6, 147.3, 146.7, 130.4, 128.9, 123.7, 123.2, 108.9, 107.5, 105.6, 52.2, 40.5, 34.2, 28.4, 27.6.

HRMS (ESI⁺): *m/z* [M + H]⁺ calcd for C₁₈H₁₉N₂O₆: 359.1242; found: 359.1240.

2,2-dimethyl-5-(4-nitrophenyl(furan-2-yl)methyl)-1,3-dioxane-4,6-dione (3ce)

Entry 26, Purification by flash column chromatography, (EtOAc/Hex, 4:1), oil; yield 40 mg (23 %).

¹H NMR (CDCl₃, 500 MHz): δ = 8.17 (d, *J* = 8.8 Hz, 2 H), 7.65 (d, *J* = 8.8 Hz, 2 H), 7.38 (s, 1 H), 6.37 (t, *J* = 4.4 Hz, 1 H), 6.09 (d, *J* = 2.9 Hz, 1 H), 5.41 (d, *J* = 2.4 Hz, 1 H), 4.29 (d, *J* = 2.4 Hz, 1 H), 1.80 (s, 3 H), 1.68 (s, 3 H).

¹³C NMR (CDCl₃, 125 MHz): δ = 163.9, 163.8, 151.7, 145.2, 142.2, 131.1, 129.9, 123.9, 111.1, 108.8, 105.7, 50.4, 43.2, 28.4, 27.6.

HRMS (ESI⁺): [M + H]⁺ calcd for C₁₇H₁₆NO₇: 346.0927; found: 346.0925.

2,2-dimethyl-5-(phenyl(1H-indol-3-yl)methyl)-1,3-dioxane-4,6-dione (3da)¹⁹

Entry 28, Purification by flash column chromatography, (EtOAc/Hex, 1:2), yellow oil; yield 124 mg (71 %).

¹H NMR (CDCl₃, 500 MHz): δ = 8.18 (s, 1 H), 7.44-7.35 (m, 5 H), 7.30-7.17 (m, 4 H), 7.08-7.05 (m, 1 H), 5.65 (d, *J* = 2.0 Hz, 1 H), 4.31 (d, *J* = 2.4 Hz, 1 H), 1.71 (s, 3 H), 1.42 (s, 3 H).

¹³C NMR (CDCl₃, 125 MHz): δ = 165.8, 164.9, 140.0, 136.0, 129.3, 128.6, 127.4, 127.2, 124.4, 122.5, 119.9, 119.3, 115.2, 111.4, 105.4, 52.1, 41.9, 28.3, 28.2.

2,2-dimethyl-5-(p-tolyl(1H-indol-3-yl)methyl)-1,3-dioxane-4,6-dione (3db)

Entry 30, Purification by flash column chromatography, (EtOAc/Hex, 1:2), yellow oil; yield 118 mg (65 %).

¹H NMR (CDCl₃, 500 MHz): δ = 8.18 (s, 1 H), 7.44 (d, *J* = 7.8 Hz, 1 H), 7.37-7.34 (m, 2 H), 7.30-7.25 (m, 2 H), 7.21-7.14 (m, 2 H), 7.09-7.05 (m, 2 H), 5.61 (d, *J* = 1.9 Hz, 1 H), 4.29 (d, *J* = 2.5 Hz, 1 H), 2.30 (s, 3 H), 1.71 (s, 3 H), 1.43 (s, 3 H).

¹³C NMR (CDCl₃, 125 MHz): δ = 165.8, 164.9, 137.0, 136.9, 136.0, 129.5, 129.3, 129.1, 124.3, 122.5, 119.9, 119.3, 115.4, 111.4, 105.4, 52.1, 41.6, 28.4, 28.2, 27.8.

HRMS (ESI⁺): *m/z* [M + H]⁺ calcd for C₂₂H₂₂NO₄: 364.1549; found: 364.1572

2,2-dimethyl-5-(4-chlorophenyl(1H-indol-3-yl)methyl)-1,3-dioxane-4,6-dione (3dc)

Entry 32, Purification by flash column chromatography, (EtOAc/Hex, 1:3), yellow oil; yield 162 mg (85 %).

¹H NMR (CDCl₃, 500 MHz): δ = 8.20 (s, 1 H), 7.40-7.34 (m, 5 H), 7.26-7.18 (m, 3 H), 7.07 (t, *J* = 7.3 Hz, 1 H), 5.64 (d, *J* = 2.4 Hz, 1 H), 4.28 (d, *J* = 2.4 Hz, 1 H), 1.73 (s, 3 H), 1.52 (s, 3 H).

¹³C NMR (CDCl₃, 125 MHz): δ = 165.5, 164.7, 138.6, 136.0, 133.2, 130.8, 128.7, 127.0, 124.2, 122.7, 120.1, 119.1, 114.8, 111.4, 105.4, 52.0, 40.7, 28.4, 27.9.

HRMS (ESI⁺): *m/z* [M + H]⁺ calcd for C₂₁H₁₉ClNO₄: 384.1002; found: 384.09882, **2-dimethyl-5-(4-fluorophenyl(1H-indol-3-yl)methyl)-1,3-dioxane-4,6-dione (3dd)**

Entry 34, Purification by flash column chromatography, (EtOAc/Hex, 1:2), yellow oil; yield 152 mg (83 %).

¹H NMR (CDCl₃, 500 MHz): δ = 8.17 (s, 1 H), 7.40-7.36 (m, 5 H), 7.19 (t, *J* = 7.3 Hz, 1 H), 7.06 (t, *J* = 7.8 Hz, 1 H), 6.97-6.94 (m, 1 H), 5.64 (d, *J* = 2.4 Hz, 1 H), 4.28 (d, *J* = 2.4 Hz, 1 H), 1.73 (s, 3 H), 1.49 (s, 3 H).

¹³C NMR (CDCl₃, 125 MHz): δ = 165.7, 164.8, 162.1 (d, *J* = 245.9 Hz), 136.1, 135.7 (d, *J* = 3.0 Hz), 131.1 (d, *J* = 7.9 Hz), 127.0, 124.2, 122.6, 120.0, 119.2, 115.3 (d, *J* = 21.5 Hz), 115.0, 111.5, 105.5, 52.2, 40.9, 28.4, 27.9.

HRMS (ESI+): *m/z* [M + H]⁺ calcd for C₂₁H₁₉FNO₄: 367.1297 found: 368.1287.

2,2-dimethyl-5-(4-nitrophenyl(1*H*-indol-3-yl)methyl)-1,3-dioxane-4,6-dione (3de)

Entry 36, Purification by flash column chromatography, (EtOAc/Hex, 4:1), yellow oil; yield 87 mg (44 %).

¹H NMR (CDCl₃, 500 MHz): δ = 8.33 (s, 1 H), 8.10 (d, *J* = 8.7 Hz, 2 H), 7.58 (d, *J* = 8.7 Hz, 2 H), 7.38-7.35 (m, 3 H), 7.22-7.19 (m, 1 H), 7.08 (t, *J* = 7.8 Hz, 1 H), 5.76 (d, *J* = 2.4 Hz, 1 H), 4.35 (d, *J* = 2.4 Hz, 1 H), 1.78 (s, 3 H), 1.60 (s, 3 H).

¹³C NMR (CDCl₃, 125 MHz): δ = 165.1, 164.3, 147.8, 147.1, 135.9, 130.7, 130.3, 124.3, 123.6, 122.9, 120.3, 118.9, 113.8, 111.6, 105.6, 52.1, 40.4, 28.4, 27.7.

HRMS (ESI+): *m/z* [M + H]⁺ calcd for C₂₁H₁₉N₂O₆: 395.1243; found: 395.1268

2,2-dimethyl-5-(phenyl(4-(dimethylamino)phenyl)methyl)-1,3-dioxane-4,6-dione (3ea)

Entry 37, Purification by flash column chromatography, (EtOAc/Hex, 1:1), oil; yield 37 mg (21 %).

¹H NMR (acetone-*d*₆, 400 MHz): δ = 7.34-7.26 (m, 4 H), 7.23 - 7.13 (m, 1 H), 7.14 (d, *J* = 8.8 Hz, 2 H), 6.68 (d, *J* = 8.8 Hz, 2 H), 5.23 - 5.21 (m, 1 H), 4.90 (d, *J* = 3.2 Hz, 1 H), 2.93 (s, 6 H), 1.87 (s, 3 H), 1.58 (s, 3 H).

¹³C NMR (CDCl₃, 125 MHz): δ = 165.2, 165.0, 140.8, 130.6, 129.2, 128.6, 127.1, 113.7, 105.3, 51.5, 48.8, 41.4, 28.5, 27.9.

HRMS (ESI+): *m/z* [M + H]⁺ calcd for C₂₁H₂₄NO₄: 354.1705; found: 354.1756

2,2-dimethyl-5-((*p*-tolyl)(4-(dimethylamino)phenyl)methyl)-1,3-dioxane-4,6-dione (3eb)

Entry 39, Purification by flash column chromatography, (EtOAc/Hex, 1:1), oil; yield 85 mg (46 %).

¹H NMR (acetone-*d*₆, 400 MHz): δ = 7.20-7.18 (m, 2 H), 7.17 - 7.08 (m, 4 H), 6.68 (d, *J* = 8.8 Hz, 2 H), 5.18 - 17 (m, 1 H), 4.86 (d, *J* = 3.2 Hz, 1 H), 2.92 (s, 6 H), 2.29 (s, 3 H), 1.86 (s, 3 H), 1.57 (s, 3 H).

¹³C NMR (CDCl₃, 125 MHz): δ = 165.3, 165.1, 137.8, 136.7, 130.5, 129.3, 129.1, 113.8, 105.3, 51.6, 48.6, 41.4, 28.5, 27.9, 21.3.

HRMS (ESI+): *m/z* [M+H]⁺ calcd for C₂₂H₂₆NO₄: 368.1862; found: 368.1856.

2,2-dimethyl-5-((4-chlorophenyl)(4-(dimethylamino)phenyl)methyl)-1,3-dioxane-4,6-dione (3ec)

Entry 40, Purification by flash column chromatography, (EtOAc/Hex, 1:1), oil; yield 42 mg (22 %).

¹H NMR (CDCl₃, 500 MHz): δ = 7.27 (s, 4H), 7.17(d, *J*=8.8 Hz, 2 H), 6.68 (d, *J* = 8.8 Hz 2 H), 5.29 (d, *J* = 2.4 Hz, 1 H), 4.26 (d, *J* = 2.4 Hz, 1 H), 2.98 (s, 6 H), 1.76 (s, 3 H), 1.58 (s, 3 H).

¹³C NMR (CDCl₃, 125 MHz): δ = 165.0, 139.6, 135.3, 132.9, 130.7, 130.4, 129.4, 128.6, 113.3, 105.4, 51.5, 48.0, 41.2, 28.5, 27.8.

HRMS (ESI+): *m/z* [M + H]⁺ calcd for C₂₁H₂₃ClNO₄: 388.1316; found: 388.1309.

2,2-dimethyl-5-((4-fluorophenyl)(4-(dimethylamino)phenyl)methyl)-1,3-dioxane-4,6-dione (3ed)

Entry 42, Purification by flash column chromatography, (EtOAc/Hex, 1:1), oil; yield 28 mg (15 %).

¹H NMR (CDCl₃, 500 MHz): δ = 7.30-7.26 (m, 2 H), 7.16 (d, *J* = 8.8 Hz, 2 H), 6.95-6.99 (m, 2 H), 6.67 (d, *J* = 8.8 Hz, 2 H), 5.28 (s, 1 H), 4.25 (d, *J* = 2.4 Hz, 1 H), 2.93 (s, 6H), 1.74 (s, 3 H), 1.53 (s, 3 H).

¹³C NMR (CDCl₃, 125 MHz): δ = 164.9, 161.9 (d, *J* = 245.9 Hz), 131.0, 130.9, 130.4, 115.1 (d, *J* = 21.5 Hz), 105.4, 51.6, 47.9, 41.7, 28.5, 27.8.

HRMS (ESI+): *m/z* [M + H]⁺ calcd for C₂₁H₂₃FNO₄: 372.1610; found: 372.1607.

2,2-dimethyl-5-((4-nitrophenyl)(4-(dimethylamino)phenyl)methyl)-1,3-dioxane-4,6-dione (3ee)

Entry 44, Purification by flash column chromatography, (EtOAc/Hex, 1:1), yellow oil; yield 38 mg (19 %).

^1H NMR (CDCl_3 , 400 MHz): δ = 8.14 (d, J = 7.8 Hz, 2 H), 7.47 (d, J = 8.7 Hz, 2 H), 7.17 (d, J = 8.7 Hz, 2 H), 6.72 (d, J = 7.8 Hz, 2 H), 5.38 (d, J = 2.4 Hz, 1 H), 4.32 (d, J = 2.4 Hz, 1 H), 2.96 (s, 6 H), 1.80 (s, 3 H), 1.60 (s, 3 H).

^{13}C NMR (CDCl_3 , 125 MHz): δ = 164.7, 164.6, 148.8, 146.9, 130.7, 130.1, 123.6, 113.5, 105.7, 51.4, 48.1, 41.2, 28.5, 27.7.

HRMS (ESI+): m/z [$M + \text{H}$] $^+$ calcd for $\text{C}_{21}\text{H}_{23}\text{N}_2\text{O}_6$: 399.1555; found: 399.1550.

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