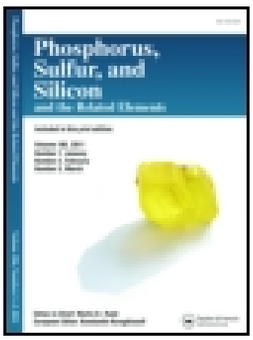

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Simple, rapid and clean condensation of sulfonamide and maleic anhydride derivatives: Synthesis of novel 1*H*- Pyrrole-2,5-diones under heterogeneous conditions

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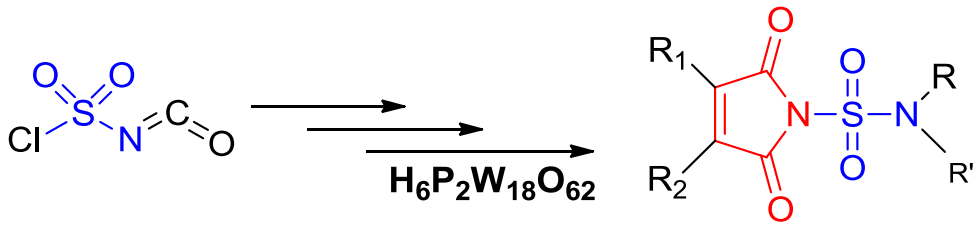
Abstract- $H_6P_2W_{18}O_{62}$ is used as an efficient catalyst for the synthesis of novel N-substituted sulfonyl maleimides (1*H*-Pyrrole-2,5-diones) via the condensation of sulfonamide and maleic anhydride derivatives. The Dawson heteropolyacid was used with a catalytic amount of 2 mmol % in acetonitrile at reflux. The reuse of $H_6P_2W_{18}O_{62}$ as heterogeneous catalyst several times without decrease their activity, short reaction times,

easy isolation of desired products with good to excellent yields shows the advantages of this novel methodology.



Keywords: Sulfonamide, maleimides (1*H*- Pyrrole-2,5-diones), Dawson heteropolyacid, heterogeneous conditions, catalyst reuse.

INTRODUCTION

Cyclic imides, such as succinimide, maleimide and phthalimide are known as one of the important nitrogen heterocyclic rings. These compounds possess structural features, which confer potential biological activity and pharmaceutical use [1-4]. Their molecules contain an imide ring and the general structure –CO–N(R)–CO–, so they are hydrophobic and neutral, and can therefore cross biological membranes [5].

Maleimide derivatives, in particular, exhibit a wide range of biological activities such as antibacterial [6], antifungal [7, 8], analgesic [9], antistress agents [10], antiprotozoal [11], antiangiogenic [12], cytotoxic, DNA binding and apoptotic inducing activity [13], and as selective inhibitors [14-18].

Also a number of natural products such as polycitrin [19], camphorataimides [20], rebeccamycine and staurosporine [21] which contain maleimide as a part in their framework have been reported. These compounds exhibit angiogenesis inhibition [21], protein kinase inhibition [22] and antiproliferative [23] activities (Fig 1, **I-III**).

The introduction of the sulfonyl group with some rings such as oxazolidinone [24], phthalimide [25] and benzothiazole [26] could be very interesting due to their high biological activity. Sulfonamide analogs posses a wide range of bioactivities including antibacterial [27-30], anti-inflammatory [31], anti-hyperglycemic [32], antihypertensive [33], antiviral and antitumor [34] activities (Fig 1, **IV** and **V**).

Recently, a series of maleimide analogs bearing benzenesulfonamide were synthesized and evaluated for anti-inflammatory activity using carrageenan induced rat paw edema model and COX-2 potency through in vitro cyclooxygenase assays[35] (Fig 1, **VI**).

In view of the high degree of bioactivity shown by maleimide and sulfonamide analogs, we have focused on the design of novel structural entities that incorporate both of these structural and functional moieties into a single molecular scaffold (Fig. 1, **3a-j** and **4a-j**)

Evaluation of the available methods for the synthesis of *N*-substituted cyclic imides indicates that generally the amines are first reacted with the desired cyclic anhydride and the resulting amic acids are then cyclized to the corresponding imides using reagents such as Ac_2O/NaOAc,[36] Et_3N/Ac_2O,[37] dimethyl sulfate/Na_2CO_3/tetrabutylammonium bromide, [38] cyanuric chloride/Et_3N, [39]

[Bmim] [40] among others. [41-46]

However, some of these procedures lack generality and scalability[37, 38], use harsh reaction conditions and hazardous[39], non-green reagents[42], involve tedious work-up and expensive reagents[40], give low yield and sometimes result in concomitant addition of HCl to the maleimide.[45]

We now report our results to overcome these shortcomings and have examined the formation of amic acids and their cyclization to the corresponding imides using an acidic solid as a catalyst in a one-pot synthesis.

In last decade, there has been considerable interest in the use of solid acids as heterogeneous catalysts in organic synthesis. Heterogeneous solid acids are more advantageous than conventional homogeneous acid catalysts because they can be easily recovered from the reaction mixture by simple filtration and reused [47].

Dawson heteropolyacid (HPA) is a common inorganic acid with mild acidity that is nonvolatile, noncorrosive, and utilized as a stable, highly efficient green catalyst in organic synthesis [48-52].

However, there are no reports of the use of Dawson heteropolyacid (HPA) as a catalyst for the synthesis of maleimides.

Based on the previous studies on the use of heteropolyacids as catalysts, and in a continuation of our endeavors for the development of simple and highly expedient methods for the synthesis of novel molecules [53, 54], we examined herein the possibility of using Dawson type heteropolyacid $H_6P_2W_{18}O_{62}$, as a catalyst for the synthesis of substituted *N* -sulfonyl-maleimide (3a–j and 4a-j) by the reaction of sulfonamides with maleic anhydride derivatives .

Results and discussion

The synthesis of *N*-substituted sulfonyl maleimide derivatives proceeded uneventfully and is shown in Scheme 1. Briefly, chlorosulfonyl isocyanate was added dropwise to *tert*-butanol kept in an ice bath and the resulting mixture was stirred with an appropriate primary or secondary amine in the presence of triethylamine [55], yielding compounds (1a–j). Removal of the Boc group transformed compounds (1a-j) into deprotected sulfonamides (2a-j) [56]. Condensation of sulfonamides with maleic anhydride derivatives gave *N*-substituted-sulfonyl-maleimides (3a–j and 4a-j).

The reaction of benzyl sulfonamide (2f) and maleic anhydride in the presence of $H_6P_2W_{18}O_{62}$ as catalyst was chosen as a model to optimize the reaction conditions (Scheme 2) and the results are listed in Tables 1, 2 and 3.

No product was detected in the absence of the catalyst. It was surprising to discover that 0.5 mmol% of $H_6P_2W_{18}O_{62}$ could accelerate the reaction, but the reaction afforded the corresponding product in a low conversion. Further study showed that the use of 2 mmol% of $H_6P_2W_{18}O_{62}$ was

sufficient to provide a satisfactory conversion in 60 min. An increase in the amount of catalyst did not produce a better result (Table 1).

The reaction was carried out in different solvents such as CH_2Cl_2, $CHCl_3$, THF, toluene and CH_3CN.

Preliminary experiments on model reaction in CH_2Cl_2, $CHCl_3$, and THF showed that the desired *N*-benzylsulfonamide maleimide (3f) was actually formed but with lower conversions; when toluene was used as solvent a good conversion was found and the best result was obtained when the reaction was carried at reflux in acetonitile as solvent (Table 2).

The efficacy of Dawson heteropolyacid $H_6P_2W_{18}O_{62}$ was compared against other catalysts such as Montmorrillonite clay K10, H_2SO_4, Keggin heteropolyacids ($H_3PW_{12}O_{40}$, $H_3PMo_{12}O_{40}$) and Dawson heteropolyacids ($H_6P_2W_{18}O_{62}$, $H_6P_2W_{12}Mo_6O_{62}$) on the reaction of benzylsulfonamide (2f) with maleic anhydride at refluxing acetonitrile (Table 3).

The results show that the reaction in the presence of $H_6P_2W_{18}O_{62}$ and $H_6P_2W_{12}Mo_6O_{62}$ (2 mmol %) furnished the expected *N*-benzylsulfonyl maleimide (3f) in good to high conversions (85–90%) in 60 min. The reactions in the presence of other catalysts required longer reaction time (60–90 min) and led to the product in lower conversions (20–50%). Notably, no product was observed when the reaction was carried out in the absence of catalyst after 2 h. Therefore, $H_6P_2W_{18}O_{62}$ was chosen for further study.

We also investigate the reusability of the catalyst. For this purpose after completion of the model reaction in refluxing acetonitrile, the solvent was evaporated and dichloromethane (5 mL) was added to the residue.

The catalyst could be separated by a simple filtration, washed with dichloromethane and dried at 45 °C. The recovered $H_6P_2W_{18}O_{62}$ catalyzed the same reaction without significant decrease in the catalytic activity even after the five runs (Table S 1 Supplemental Materials).

To show the general applicability of the method, the reaction of various sulfonamides and maleic anhydride derivatives (maleic and dichloromaleic anhydrides) in the presence of 2 mmol% of $H_6P_2W_{18}O_{62}$ at reflux in acetonitile was investigated and the results are summarized in Table 4.

All the mentioned reactions delivered good product yields and accommodated a wide range of sulfonamides bearing both primary and secondary amines derivatives.

EXPERIMENTAL

All the chemicals were commercially available and used as received.

$H_6P_2W_{18}O_{62}$ was prepared according to the literature.[57] Melting points were determined in open capillary tubes on Buchi B-540. Proton nuclear magnetic resonance was determined with a 400 MHz Bruker spectrometer using $CDCl_3$ and CD_3OD as solvent and TMS as an internal standard. Chemical shifts are reported in δ units (ppm). All coupling constants J are reported in Hertz. Multiplicity is indicated as s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet) and combination of these signals. The mass spectra were recorded on a DSQ Thermoelectron apparatus (70 eV) by chemical ionization (gaseous ammonia) by direct introduction. Elemental analysis was performed with a Perkin-Elmer 2400 C, H, N analyser and determined values were within the acceptable limits of the calculated values. The Supplemental Materials contains sample characterization data (^{1}H, ^{13}C NMR and MS) for products 3 and 4 (Figures S 1 – S 25

General procedure for the Synthesis of N-sulfonyl maleimides (3 a-j** and **4a-j):

Under nitrogen atmosphere, a mixture of sulfonamide 2a-h (1 mmol), maleic anhydride derivatives (2 mmol) and $H_6P_2W_{18}O_{62}$ catalyst (2 mmol %) in acetonitrile (2 mL), was stirred at reflux. Reaction was monitored by TLC. After achieving the reaction, dichloromethane (2 x 10 mL) was added and the catalyst was filtered; water (10 ml) was then added. The organic layers were combined and dried over anhydrous

sodium sulfate and removed under reduced pressure. The residue obtained was purified by flash chromatography (Merck silica gel 60 H, CH_2Cl_2/MeOH, 9:1) to afford the corresponding sulfonyl maleimide derivatives.

N-(propyl)-2,5-dioxopyrrole-1-sulfonamide (3a)

Yield: 81%, mp 142°C, R_f = 0.75 (CH_2Cl_2/MeOH, 9/1), ^{1}H NMR ($CDCl_3$, δ ppm): 0.99 (t, 3H, *J*=5.02Hz, C**H**$_3$),1.65 (m, 2H, C**H**$_2$), 2.67 (m, 2H, C**H**$_2$), 5.31 (t, *J*=5.4Hz, 1H, N**H**), 6.96 (s, 2H, C**H**= C**H**). ^{13}C NMR ($CDCl_3$, δ ppm): 11.2, 22.2, 42.7, 136.2, 166.4 MS(ESI$^+$70em/s): 58.12(25%), 219.13 ([M+1]$^+$, 15 %), 236([M+NH_4]$^+$,100%).

Elemental anal. (%), calculated for $C_7H_{10}N_2SO_4$: C, 38.53; H, 4.59; N, 12.84; found: C, 38.57; H, 4.62; N, 12.79.

N-(Bromo-propyl)-2,5-dioxopyrrole-1-sulfonamide (3b)

Yield: 80%, mp 142°C, R_f = 0.72 (CH_2Cl_2/MeOH, 9/1), ^{1}H NMR ($CDCl_3$, δ ppm): 2.10 (m, 2H, C**H**$_2$), 3.26 (m, 2H, C**H**$_2$), 3.38 (m, 2H, C**H**$_2$), 5.25 (t, 1H, *J*=5.4Hz, N**H**), 6.94 (s, 2H, C**H**= C**H**). ^{13}C NMR ($CDCl_3$, δ ppm): 30.7, 31.7, 38.4, 135.7, 166.4 MS(ESI$^+$70em/s): 298.17 ([M+1]$^+$, 15 %), 315.14([M+NH_4]$^+$,100%).

Elemental anal. (%), calculated for $C_7H_9N_2SO_4Br$: C, 28.28; H, 3.03; N, 9.42; found: C, 28.36; H, 3.01; N, 9.40.

N-(butyl)-2,5-dioxopyrrole-1-sulfonamide (3c)

Yield: 82%, mp 139°C, R_f = 0.76(CH_2Cl_2/MeOH, 9/1), ^{1}H NMR ($CDCl_3$, δ ppm): 0.91 (t, 3H, ***J***=5.02 Hz, C**H**$_3$), 1.37 (m, 2H, C**H**$_2$), 1.54 (m, 2H, C**H**$_2$), 3.11 (m, 2H, C**H**$_2$-N), 6.87 (s, 2H, C**H**= C**H**). ^{13}C NMR ($CDCl_3$, δ ppm): 13.5, 19.8, 30.9, 43.5, 136.6, 175.3. MS (ESI$^+$ 70 eV m/z): 72.18 (30%), 136(15%), 250.07 ([M+NH_4]$^+$, 100%). Elemental anal. (%), calculated for $C_8H_{12}N_2SO_4$: C, 41.38; H, 5.17; N, 12.06; found: C, 41.42; H, 5.14; N, 12.08.

N-(tert-butyl)-2.5-dioxopyrrole-1-sulfonamide (3d)

Yield: 85%, mp 134°C, R_f= 0.76(CH_2Cl_2/MeOH, 9/1), ^{1}H NMR($CDCl_3$, δppm): 1.42(s, 9H, 3(C**H**$_3$); 6.78(s, 2H, C**H**= C**H**). ^{13}CNMR($CDCl_3$, δppm): 29.6; 37.2, 135.9, 169.4. Ms(ESI$^+$ 70 eVm/s): 233.09 ([M+1]$^+$, 100%). Elemental anal. (%), calculated for $C_8H_{12}N_2SO_4$: C, 41.38; H, 5.17; N, 12.06; found: C, 41.35; H, 5.24; N, 12.01.

N-(phenyl)-2,5-dioxopyrrole-sulfonamide (3e):

Yield: 80%, mp 140 °C, R_f = 0.72(CH_2Cl_2/MeOH, 9/1), ^{1}H NMR ($CDCl_3$, δ ppm): 6.86(m, 3H, Ar-**H**), 6.97(s, 2H, C**H**= C**H**), 7.22(m, 2H, Ar-**H**). ^{13}C NMR ($CDCl_3$, δ ppm): 117.9; 121.1, 129.5, 136.2, 139.6, 172.8. MS (ESI$^+$ 70 eV m/z): 275.2 ([M+Na]$^+$, 87 %), 291.2 ([M+K]$^+$, 12 %), 527.3([2M+Na]$^+$, 25%).

Elemental anal. (%), calculated for $C_{10}H_8N_2SO_4$: C, 47.62; H, 3.17; N, 11.11; found: C, 47.65; H, 3.24; N, 11. 20.

N-benzyl-2.5-dioxopyrrole-1-sulfonamide (3f):

Yield: 83%, mp 138 °C, R_f = 0.75(CH_2Cl_2/MeOH, 9/1), ^{1}H NMR ($CDCl_3$, δ ppm): 4.24(d, *J*=4.02 Hz, 2H, C**H**$_2$-Ph), 5.51(t, 1H, *J*=5.6Hz, **H**-N); 6.94(d, 2H, *J*=12.2Hz, C**H**=C**H**), 7.34(m, 5H, **H**-Ar). ^{13}C NMR ($CDCl_3$, δ ppm): 39.0, 122.4, 123.2, 124.4, 133.2, 136.2, 164.8. MS (ESI^+ 70 eV m/z): 91.96 (100%), 105.99 (64%), 267.06 ($[M+1]^+$, 40%).

Elemental anal. (%), calculated for $C_{11}H_{10}N_2SO_4$: C, 49.62; H, 3.76; N, 10.53; found: C, 49.68; H, 3.70; N, 10.58.

N-(3-fluorophenyl)-2,5-dioxopyrrole-1-sulfonamide (3g):

Yield: 81%, mp 148°C, R_f = 0.73(CH_2Cl_2/MeOH, 9/1), ^{1}H NMR ($CDCl_3$, δ ppm): 6.94(m, 1H, **H**-Ar), 6.90(s, 2H, C**H**= C**H**), 7.26(m, 1H, **H**-Ar), 7.46(m, 1H, **H**-Ar), 7.66(m, 1H, **H**-Ar). ^{13}C NMR ($CDCl_3$, δ ppm): 105.6, 110.1, 114.6, 130.7, 136.2, 139.4, 167.5. MS (ESI^+ 70 eV m/z): 111.04 (10%), 190.06 (6 %), 271,19($[M+1]^+$, 15%), 288.13 ($[M+NH_4]^+$, 100%). Elemental anal. (%), calculated for $C_{10}H_7N_2SO_4F$: C, 44.44; H, 2.59; N, 10.37; found: C, 44.49; H, 2.62; N, 10.32.

1-(3,4-dihydroisoquinolin-2(1H)-yl) sulfonyl) 1H-pyrrole-2.5-dione (3h):

Yield: 84%, mp 130 °C, R_f = 0.76(CH_2Cl_2/MeOH, 9/1), ^{1}H NMR ($CDCl_3$, δ ppm): 2.97(t, 2H, *J*=5.8Hz, C**H**$_2$-ph), 3.77(t, 2H, *J*=5.7Hz, C**H**$_2$N), 4.64(s, 2H, C**H**$_2$N), 6.76 (s, 2H, C**H**= C**H**), 7.15(m, 4H, Ar-**H**). ^{13}C NMR ($CDCl_3$, δ ppm): 28.4, 44.4, 47.2, 126.3, 126.7, 127.2, 129.8, 131.4, 133.5, 136.2, 167.2. MS (ESI^+ 70 eV m/z): 315.1($[M+Na]^+$, 70%), 607.1 ($[2M+Na]^+$, 100%). Elemental anal. (%), calculated for $C_{13}H_{12}N_2SO_4$: C, 53.42; H, 4.11; N, 9.59; found: C, 53.47; H, 4.08; N, 9.57.

1-((4-phenylpiperazine-1yl)sulfonyl)1H-pyrrole-2,5-dione (3i):

Yield: 83 %, mp 143 °C, R_f = 0.71(CH_2Cl_2/MeOH, 9/1), ^{1}H NMR ($CDCl_3$, δ ppm): 3.27(t, 4H, *J*=6.3Hz, C**H**$_2$-N), 3.59(t, 4H, *J*=6.4Hz, C**H**$_2$-N), 6.83 (s, 2H, C**H**= C**H**), 6.93(m, 3H, Ar-**H**), 7.27(m, 2H, Ar-**H**). ^{13}C NMR ($CDCl_3$, δ ppm): 46.4, 49.1, 117.1, 121.1, 129.4, 135.3, 150.6, 167.8. MS (ESI^+ 70 eV m/z): 322.2($[M+H]^+$, 24%), 344.1($[M+Na]^+$, 89%), 665.1 ($[2M+Na]^+$, 33%). Elemental anal. (%), calculated for $C_{14}H_{15}N_3SO_4$: C, 52.33; H, 4.67; N, 13.08; found: C, 52.30; H, 4.74; N, 13.05.

1-tosyl- 1H-pyrrole-2,5-dione (3j)

Yield: 84%, mp 142°C, R_f = 0.74 (CH_2Cl_2/MeOH, 9/1), ^{1}H NMR (CD_3OD, δ ppm): 2.46 (s, 3H, C**H**$_3$), 6.33 (s, 2H, C**H**= C**H**), 7.41(dd, 2H, *J*=8.6Hz, Ar-**H**), 7.91(dd, 2H, *J*=8.5Hz, Ar-**H**). ^{13}C NMR (CD_3OD, δ ppm): 24.2, 127.4, 129.5, 135.9, 136.5, 141.3, 166.4 MS(ESI^+70em/s): 252.12 ($[M+1]^+$, 15 %), 269.14($[M+NH_4]^+$,100%).

Elemental anal. (%), calculated for $C_{11}H_9NSO_4$: C, 52.59; H, 3.58; N, 5.57; found: C, 52.56; H, 3.55; N, 5.61.

N-(propyl) - 3,4- dichloro -2,5-dioxopyrrole-1-sulfonamide (4a)

Yield: 83%, mp 146°C, R_f = 0.68 (CH_2Cl_2/MeOH, 9/1), ^{1}H NMR ($CDCl_3$, δ ppm): 0.98 (t, 3H, *J*=5.02Hz, C**H**$_3$),1.62 (m, 2H, C**H**$_2$), 3.06 (m, 2H, **CH**$_2$), 4.28 (t, 1H, *J*=5.4Hz, N**H**).. ^{13}C NMR ($CDCl_3$, δ ppm): 11.3, 22.1, 42.7, 136.2, 166.4 MS(ESI^+70em/s): 165.04(45%), 288.11 ($[M+1]^+$, 10 %), 305.15.($[M+NH_4]^+$, 5%). Elemental anal. (%), calculated for $C_7H_8N_2SO_4Cl_2$: C, 29.26; H, 2.78; N, 9.75; found: C, 29.97; H, 2.90; N, 9.69.

N-(Bromo-propyl) - 3,4- dichloro -2,5-dioxopyrrole-1-sulfonamide (4b)

Yield: 78%, mp 146°C, R_f = 0.68(CH_2Cl_2/MeOH, 9/1), ^{1}H NMR ($CDCl_3$, δ ppm): 2.06 (m, 2H, C**H**$_2$), 3.20 (m, 2H, C**H**$_2$), 3.44 (m, 2H, **CH**$_2$), 5.25 (t, 1H, *J*=5.4Hz, N**H**), 6.96 (s, 2H, C**H**= C**H**). ^{13}C NMR ($CDCl_3$, δ ppm): 30.9, 31.8, 38.8, 137.2, 166.5 MS(ESI$^+$70em/s): 367.13 ([M+1]$^+$, 15 %), 384.12([M+NH_4]$^+$,100%).

Elemental anal. (%), calculated for $C_7H_7N_2SO_4BrCl_2$: C, 22.95; H, 1.91; N, 7.65; found: C, 22.92; H, 1.96; N, 7.61.

N-(butyl)- 3,4- dichloro- 2,5-dioxopyrrole-1-sulfonamide (4c)

Yield: 84%, mp 147°C, R_f = 0.72(CH_2Cl_2/MeOH, 9/1), ^{1}H NMR ($CDCl_3$, δ ppm): 0.96 (t, 3H, ***J***=5.02 Hz, C**H**$_3$), 1.39(m, 2H, C**H**$_2$), 1.56 (m, 2H, C**H**$_2$), 3.11 (m, 2H, C**H**$_2$-N), 4.51(s, 1H, N**H**). ^{13}C NMR ($CDCl_3$, δ ppm): 13.7, 20.6, 31.1, 41.8, 137.5, 167.2. MS (ESI$^+$ 70 eV m/z): 72.18 (30%), 136(15%), 302.18 ([M+1]$^+$, 46%).

Elemental anal. (%), calculated for $C_8H_{10}N_2SO_4Cl_2$: C, 31.90; H, 3.32; N, 9.30; found: C, 31.82; H, 3.24; N, 9.38.

N-(tert-butyl)- 3,4- dichloro-2.5-dioxopyrrole-1-sulfonamide (4d)

Yield: 83%, mp 139C, R_f= 0.71(CH_2Cl_2/MeOH, 9/1), ^{1}H NMR($CDCl_3$, δ ppm): 1.42(s, 9H, 3(C**H**$_3$). ^{13}CNMR($CDCl_3$, δ ppm): 29.5; 37.4, 137.3, 166.5. Ms(ESI$^+$ 70 eVm/s): 302.09 ([M+1]$^+$, 100%). Elemental anal. (%), calculated for $C_8H_{10}N_2SO_4Cl_2$: C, 31.90; H, 3.32; N, 9.30; found: C, 31.95; H, 3.34; N, 9.26.

N-(phenyl)- 3,4- dichloro-2,5-dioxopyrrole-sulfonamide (4e)

Yield: 81%, mp 143 °C, R_f = 0.70(CH_2Cl_2/MeOH, 9/1), ^{1}H NMR ($CDCl_3$, δ ppm): 6.88(m, 3H, Ar-**H**), 7.25(m, 2H, Ar-**H**). ^{13}C NMR ($CDCl_3$, δ ppm): 117.8; 121.3, 129.4, 137.4, 139.4, 173.8. MS (ESI^+ 70 eV m/z): 322.2($[M+H]^+$, 24%), 344.1($[M+Na]^+$, 89%), 665.1 ($[2M+Na]^+$, 33%). Elemental anal. (%), calculated for $C_{10}H_6N_2SO_4Cl_2$: C, 37.38; H, 1.87; N, 8.72; found: C, 37.42; H, 1.90; N, 8.69.

N-benzyl-3,4- dichloro -2.5-dioxopyrrole-1-sulfonamide (4f)

Yield: 80%, mp 141 °C, R_f = 0.71(CH_2Cl_2/MeOH, 9/1), ^{1}H NMR ($CDCl_3$, δ ppm): 4.33(d, 2H, *J*=4.02 Hz, C**H**$_2$-Ph), 6.15(t, 1H, *J*=5.7Hz, **H**-N); 7.34(m, 5H, **H**-Ar). ^{13}C NMR ($CDCl_3$, δ ppm): 39.2, 122.2, 123.1, 124.5, 133.4, 137.5, 166.2. MS (ESI^+ 70 eV m/z): 105.98 (8%), 353.18 ($[M+NH_4]^+$, 100%).

Elemental anal. (%), calculated for $C_{11}H_8N_2SO_4Cl_2$: C, 39.40; H, 2.40; N, 8.36; found: C, 39.43; H, 2.38; N, 8.39.

N-(3-fluorophenyl)- 3,4- dichloro-2,5-dioxopyrrole-1-sulfonamide (4g)

Yield: 79%, mp 152°C, R_f = 0.70(CH_2Cl_2/MeOH, 9/1), ^{1}H NMR (CD_3OD, δ ppm): 6.86(m, 1H, **H**-Ar), 7.05(m, 2H, **H**-Ar), 7.36(m, 1H, **H**-Ar). ^{13}C NMR ($CDCl_3$, δ ppm): 105.7, 110.3, 114.4, 130.9, 137.7, 139.6, 169.5. MS (ESI^+ 70 eV m/z): 111.04 (10%), 340,10($[M+1]^+$, 15%), 357.12 ($[M+NH_4]^+$, 100%). Elemental anal. (%), calculated for $C_{10}H_5N_2SO_4FCl_2$: C, 35.40; H, 1.47; N, 8.26; found: C, 35.44; H, 1.50; N, 8.22.

3,4-Dichloro-1-(3,4-dihydroisoquinolin-2(1H)-yl)sulfonyl)-1H-pyrrole-2.5-dione (4h)

Yield: 85%, mp 135 °C, R_f = 0.73(CH_2Cl_2/MeOH, 9/1), ^{1}H NMR ($CDCl_3$, δ ppm): 2.99(t, 2H, *J*=5.8Hz, C**H**$_2$-ph), 3.75(t, 2H, *J*=5.7Hz, C**H**$_2$N), 4.63(s, 2H, C**H**$_2$N), 7.20(m, 4H, Ar-**H**). ^{13}C NMR ($CDCl_3$, δ ppm): 28.8, 44.5, 47.6, 126.2, 126.4, 126.9, 128.8, 131.8, 133.3, 137.6, 167.9. MS (ESI^+ 70 eV m/z): 362.10($[M+1]^+$, 70%).

Elemental anal. (%), calculated for $C_{13}H_{10}N_2SO_4Cl_2$: C, 43.21; H, 2.77; N, 7.75; found: C, 43.18; H, 2.75; N, 7.78.

3,4- Dichloro 1-((4-phenylpiperazine-1yl)sulfonyl)1H-pyrrole-2,5-dione (4i)

Yield: 81 %, mp 140 °C, R_f = 0.68 (CH_2Cl_2/MeOH, 9/1), ^{1}H NMR (CD_3OD, δ ppm): 3.17(s, 8H, C**H**$_2$-N), 6.68(t, 1H, *J*=6.4Hz, Ar-**H**), 6.92(d, 1H, *J*=6.5Hz, Ar-**H**), 7.18(t, 2H, *J*=6.5Hz, Ar-**H**). ^{13}C NMR ($CDCl_3$, δ ppm): 46.1, 49.3, 117.1, 121.1, 129.4, 136.9, 150.5, 167.7. MS (ESI^+ 70 eV m/z): 391.2($[M+H]^+$, 24%). Elemental anal. (%), calculated for $C_{14}H_{13}N_3SO_4Cl_2$: C, 43.06; H, 3.33; N, 10.77; found: C, 43.10; H, 3.34; N, 10.74.

3,4- Dichloro-1-tosyl- 1H-pyrrole-2,5-dione (4j)

Yield: 82%, mp 142°C, R_f = 0.68 (CH_2Cl_2/MeOH, 9/1), ^{1}H NMR ($CDCl_3$, δ ppm): 2.46 (s, 3H, C**H**$_3$), 7.35(dd, *J*=8.6Hz, 2H, Ar-**H**), 7.85(dd, *J*=8.7Hz, 2H, Ar-**H**). ^{13}C NMR ($CDCl_3$, δ ppm): 24.3, 127.2, 129.6, 136.4, 137.5, 141.3, 167.1 MS(ESI^+70em/s): 343.2($[M+Na]^+$, 100%), 359.1($[M+K]^+$, 38%), 663.4 ($[2M+Na]^+$, 20%). Elemental anal. (%), calculated for $C_{11}H_7NSO_4Cl_2$: C, 41.25; H, 2.18; N, 4.37; found: C, 41.30; H, 2.22; N, 4.31.

Conclusion

In summary, we describe a convenient and efficient protocol for the synthesis of *N*-sulfonyl maleimides (*N*-sulfonyl-1*H*- Pyrrole-2,5-dione) derivatives via condensation of sulfonamides with maleic anhydride derivatives using $H_6P_2W_{18}O_{62}$ as a green recyclable and heterogeneous catalyst. The simple experiment procedure combined with ease of recovery and reuses of this catalyst make this procedure quite simple, more convenient and environmentally benign.

Supporting information

Full experimental detail for the first two steps and selected supplemental data of new compounds (3a-j) and (4a-j) can be found via the ‘‘Supplemental Materials’’ section of this article’s Web page.

References

[1] Laronze, M.; Boisbrun, M.; Léonce, S.; Pfeiffer, B.; Renard, P.; Lozach, O.; Meijer, L.; Lansiaux, A.; Bailly, C.; Sapi, J.; Laronzea, J. Y. *Bioorg. Med. Chem*. **2005**, 13, 2263-2283.

[2] Amr, A. E. G. E.; Sabry, N. M.; Abdulla, M. M. *Monatsh. Chem*. **2007**, 138, 699-707.

[3] Anizon, F.; Belin, L.; Moreau, P.; Sancelme, M.; Voldoire, A.; Prudhomme, M.; Ollier, M.; Severe, D.; Riou, J. F.; Bailly, C.; Fabbro, D.; Thomas, M. *J. Med. Chem.* **1997**, 40, 3456-3465.

[4] Zentz, F.; Valla, A.; Le Guillou, R.; Labia, R.; Mathot, A. G.; Sirot, D. *Il Farmaco* **2002**, 57, 421-426.

[5] Bansode, T.N.; Shelke, J.; Dongre, V. *Eur. J. Med. Chem*. **2009**, 44, 5094-5098.

[6] Lopez, S.N.; Sortino, M.; Escalante, A.; Campos, F.; Correa, R.; Nunes, R.J.; Zacchino, S.A. Arzneim-Forsch. *Drug. Res*. **2003,** 53, 280-288.

[7] Aqueveque, P.; Anke, T.; Sterner, O.; Naturforsch, Z. *Biosci.* **2002**, 57, 257-262.

[8] Sortino, M.; Garibotto, F.; Filho, V.; Gupta, M.; Enriz, R.; Zacchina, S. *Bioorg. Med. Chem*. **2011**, 19, 2823-2834.

[9] Mahle, F.; Guimaraes, T. ; Meira, A. ; Correa, R. ; Cruz, R. ; Cechinel-Filho, V. ; Campos-Buzzi, F. *Eur. J. Med. Chem.* **2010**, 45, 4761-4768.

[10] Badru, R. ; Anand, P.; Singh, B. *Eur. J. Med. Chem.* **2012**, 48, 81-91.

[11] Durust, Y.; Karakus, H.; Kaiser, M.; Tasdemir, D. *Eur. J. Med. Chem.* **2012**, 48, 296-304.

[12] Acero, N.; Brana, M.F.; Anorbe, L.; Dominguez, G.; Munoz-Mingarro, D.; Mitjans, F. ; Piulats, J. *Eur. J. Med. Chem.* **2012**, 48, 108-113.

[13] Alaa, A.; Abdel-Aziz, M. *Eur. J. Med. Chem.* **2007**, 42, 614-626.

[14] Matuszak, N.; Muccioli, G.; Laber, G.; Lambert, D. *J. Med. Chem*. **2009**, 52, 7410-7420.

[15] Sivaprakasam, P.; Xie, A.; Doerksen, R. *Bioorg. Med. Chem*. **2006**, 14, 8210-8218.

[16] Chen, H.; Liu, Y.; Wang, L.; Shen, Q.; Li, J.; Nan, F. *Bioorg. Med. Chem*. **2010**, 20, 2876-2879.

[17] Cashman, J.R.; MacDonald, M.; Ghirmai, S.; Okolotowicz, K.J.; Sergienko, E.; Brown, B.; Garcia, X.; Zhai, D.; Dahl, R.; Reed, J.C. *Bioorg. Med. Chem.* **2010**, 20, 6560-6564.

[18] Suzuki, T.; Tanaka, R.; Hamada, S.; Nakagawa, H.; Miyata, N. *Bioorg. Med. Chem.* **2010**, 20, 1124-1127.

[19] Burtoloso, A.B.; Garcia, A.L.; Miranda, K.C.; Correia, C.D. *Synlett.* **2006**, 18, 3145-3149.

[20] Stewart, S.G.; Polomska, M.; Lim, R. *Tetrahedron Lett*. **2007**, 48, 2241-2244.

[21] Peifer, C.; Stoiber, T.; Unger, E.; Totzke, F.; Schachtele, C.; Marme, D.; Brenk, R.; Klebe, G. Dannhardt, G. *J. Med. Chem.* **2006**, 49, 1271-1281

[22] Trapp, J.; Jochum, A.; Meier, R.; Saunders, L.; Marshall, B.; Kunick, C. Verdin, E.; Goekjian, P.; Sippl, W.; Jung, M. *J. Med. Chem*. **2006**, 49, 7307-7316.

[23] Routier, S.; Merour, J.; Dias, N.; Lansiaux, A.; Bailly, C.; Lozach, O.; Meijer, L. *Med. Chem*. **2006**, 49, 789-799.

[24] Kim, S. J.; Jung, M.H.; Yoo, K. H.; Cho, J.H.; Oh. C.H. *Bioorg. Med. Chem. Lett.* **2008**, 18, 5815–5818

[25] Abdel-Aziz, A.M.; El-Azab, A. S.; Ceruso, M.; Supuran, C. T. *Bioorg. Med. Chem. Lett.* 2014, 24, 5185–5189.

[26] Ibrahim, D. A.; Lasheen, D. S.; Zaky, M.Y.; Ibrahim, A. W.; Vullo, D.; Ceruso, M.; Supuran, C. T.; Abou El Ella, D. A. *Bioorg. Med. Chem.* **2015**, 23, 4989-4999.

[27] Abraham, D.J.; (Ed.), *Burger's Medicinal Chemistry & Drug Discovery*, John Wiley and Sons, Hoboken, NJ, **2003**.

[28] Gadad, A. K.; Mahajanshetti, C. S.; Nimbalkar, S.; Raichurkar, A. *Eur. J. Med.Chem*. **2000**, 35, 853-857.

[29] Misra, V.; Saxena, V. K.; Srivastava, R. *J. Indian Chem. Soc*. **1982**, 59, 781-781.

[30] Zani, F.; Vicini, P. *Arch. Pharm*. **1998**, 331, 219-223.

[31] Li, J. J.; Anderson, D.; Burton, E. G.; Cogburn, J. N.; Collins, J. T.; Garland, D. J.; Gregory, S. A.; Huang, H. C.; Isakson, P. C.; Koboldt, C. M.; Logusch, E. W.; Norton, M. B.; Perkins, W. E.; Reinhard, E. J.; Seibert, K.; Veenhuizem, A. W.; Zang, Y.; Reitz, D. B. *J. Med. Chem*. **1995**, 38, 4570-4578.

[32] United Kingdom prospective diabetes study (UKPDS) Review. 13. *BMJ*. **1995**, 310, 83-88.

[33] Wu, C.; Decker, E.R.; Holland, G.W.; Brown, F.D.; Stavros, F.D. ; Brock, T.A. ; Dixon, R.A.C. *Drugs Today***. 2001**, 37, 441–453.

[34] Majumdar, K. C.; Mondal, S.; De, N. *Synthesis.* **2009**, 18, 3127-3135.

[35] Firke, S. D.; Bari, S. B.; *Bioorg. Med. Chem.* **2015**, 23, 5273-5281.

[36] Mehta, N. B.; Phillips, A. P.; Lui, F. F.; Brooks, R. E. *J. Org. Chem*. **1960**, 25, 1012-1015.

[37] Wang, Z. Y. *Synth. Commun*. **1990**, 20, 1607-1610.

[38] Deshpande, S. R.; Maybhate, S. P.; Likhite, A. P.; Chaudhary, P. M. *Indian J. Chem*. **2010**, 49B, 487-488.

[39] Haval, K. P.; Mhaske, S. B.; Argade, N. P. *Tetrahedron*, **2006**, 62, 937-942.

[40] Le, Z. G.; Chen, Z. C .; Hu, Y.; Zheng, Q. G. *Synthesis*, **2004**, 7, 995-998.

[41] Peterson, J. M. Eggleston, . I. J. *Synth. Commun*., **2007**, 38, 303-311.

[42] Kondo, T.; Nomura, M.; Ura, Y.; Wada, K.; Mitsudo, T. *J. Am. Chem. Soc*., **2006,** 128, 14816-14817.

[43] Shetgiri, N. P.; Nayak, B. K. *Indian J. Chem.,* **2005**, 44B, 1933-1936.

[44] Reddy, P. Y.; Kondo, S.; Ueno, Y. *J. Org. Chem.*, **1997**, 60, 2652 -2654.

[45] Braish, T. F.; Fox, D. E. *Synlett*, **1992**, 12, 979-980.

[46] Wagh, S. B.; Balasubramaniyan, P.; Balasubramaniyan, V. *Indian J. Chem*., **1982**, 21B, 1071-1074.

[47] Mizuno, N.; Misono, M. *Chem. Rev*. **1998**, 98, 199-218.

[48] Heravi, M.; Bamoharram, F. F.; Rajabzadeh, G.; Seifi, N.; Khatami, M. *J. Mol. Catal. A: Chem.* **2006**, 256, 238-241.

[49] Bamoharram, F.; Heravi, M.M.; Roshani, M. *J. Mol. Catal. A: Chem*. **2006**, 252, 90-95.

[50] Pasquale, G. ; Ruiz, D. ; Juan Autino, Baronetti, G. ; Thomas, H.; Romanelli, G. *C. R. Chimie,* **2012**, 15, 758–763.

[51] Rajguru, D.; Keshwal, B.; Shubha Jain, S. *Chin. Chem. Lett*. **2013**, 24, 1033–1036.

[52] Tayebee, R.; Rostamian, H.; Aliakbari , A. *Dalton Trans*. **2014**, 43, 1550-1563.

[53] Bougheloum, C.; Barbey, C.; Berredjem, M.; Messalhi, A.; Dupont, N. *J. Mol. Struct*. **2013**, 1041, 6-15.

[54] Bougheloum, C.; Belghiche, R.; Messalhi, A. *Phosphorus, Sulfur Silicon Relat. Elem*. **2015**, 190, 269–276.

[55] (a) Abdaoui, M.; Dewynter, G.; Aouf, N.; Favre, G.; Morère, A.; Montero, J. L. *Bioorg. Med. Chem*. **1996**, 4, 1227-1235.

(b) Abdaoui, M.; Dewynter, G.; Montero, J. L. *Tetrahedron Lett*. **1996**, 37, 5695-5698.

[56] Wang, G.; Li, C.; Li, J.; Jia, X. *Tetrahedron Lett*. **2009**, 50, 1438-1440.

[57] Kozhevnikov, I. *Catalysts for Fine Chemical Synthesis*, vol. 2, Catalysis by Polyoxometalates, Wiley ed., England, **2002**.

Table 1. Effect of catalytic amount of $H_6P_2W_{18}O_{62}$ on the synthesis of 3f (scheme 2)

Entry[a]	$H_6P_2W_{18}O_{62}$(mmol %)	Time (min)	Conversion (%) [b]
1	0	120	00
2	0.5	90	35
3	1	90	66
4	1.5	60	78
5	**2**	**60**	**90**
6	2.5	60	91
7	3	60	91
8	5	60	91

The bold values indicate the best results

[a] Reaction conditions: Benzyl sulfonamide 2f (2 mmol) and Maleic anhydride (2 mmol) at reflux in the presence of the indicated amount of catalyst and CH_3CN as solvent.

[b] The conversion was determined by ^{1}H NMR analysis of the crude product.

Table 2. Effect of solvent on the synthesis of 3f (scheme 2)

Entry	Solvent	Time (min)	Conversion (%)
1	CH_2Cl_2	120	55
2	$CHCl_3$	120	60
3	THF	90	65
4	Toluene	60	78
5	**CH_3CN**	**60**	**90**

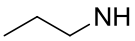
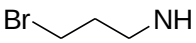
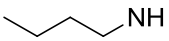
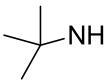
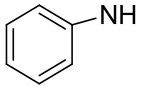
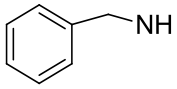
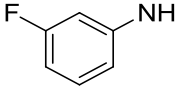
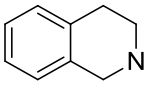
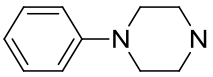
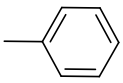
Reaction conditions: Benzyl sulfonamide 2f (2 mmol), Maleic anhydride (2 mmol), $H_6P_2W_{18}O_{62}$ (2% mmol), in CH_3CN as solvent at reflux

Table 3. Effect of different catalysts on the synthesis of 3f (scheme 2)

Entry	Catalyst (2 % mmol)	Time (min)	Conversion (%)
1	None	120	00
2	K10	90	20
3	H_2SO_4	90	30
4	$H_3PW_{12}O_{40}$	60	50
5	$H_3P\ Mo_{12}O_{40}$	60	38
6	**$H_6P_2W_{18}O_{62}$**	**60**	**90**
7	$H_6P_2W_{12}Mo_6\ O_{62}$	60	85

Reaction conditions: Benzyl sulfonamide 2f (2 mmol) and Maleic anhydride (2 mmol) in CH_3CN as solvent at reflux using various catalysts.

Table 4. $H_6P_2W_{18}O_{62}$ catalyzed synthesis of *N*-sulfonyl 1*H*-Pyrrole-2,5-dione derivatives (3a-j) and (4a-j) in acetonitrile under refluxing conditions

Entry	R	Product	Yield(%)[c]
1		3a/4a	81/83
2		3b/4b	80/78
3		3c/4c	82/84
4		3d/4d	85/83
5		3e/4e	83/80
6		3f/4f	83/80
7		3g/4g	81/79
8		3h/4h	84/85
9		3i/4i	83/81
10 [d]		3j/4j	84/82

[c] isolated Yield after 1 hour of reaction

[d] commercial substrate

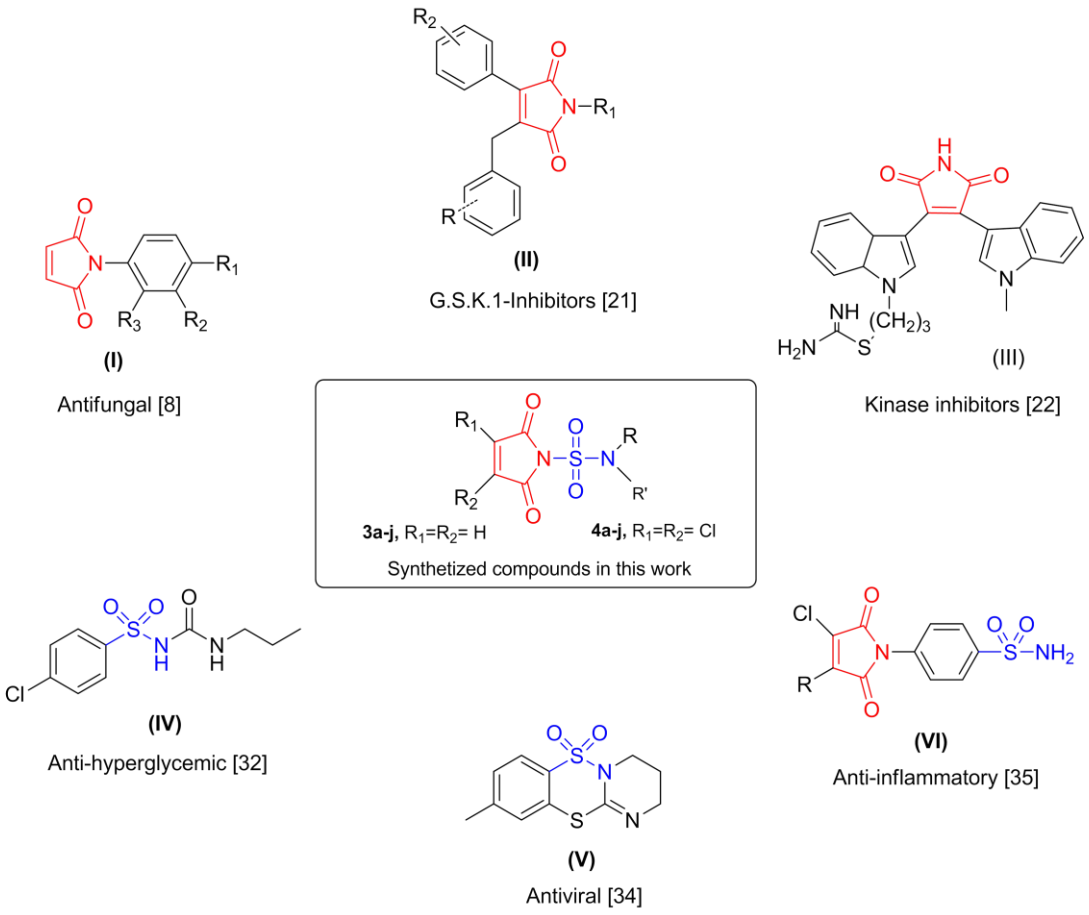
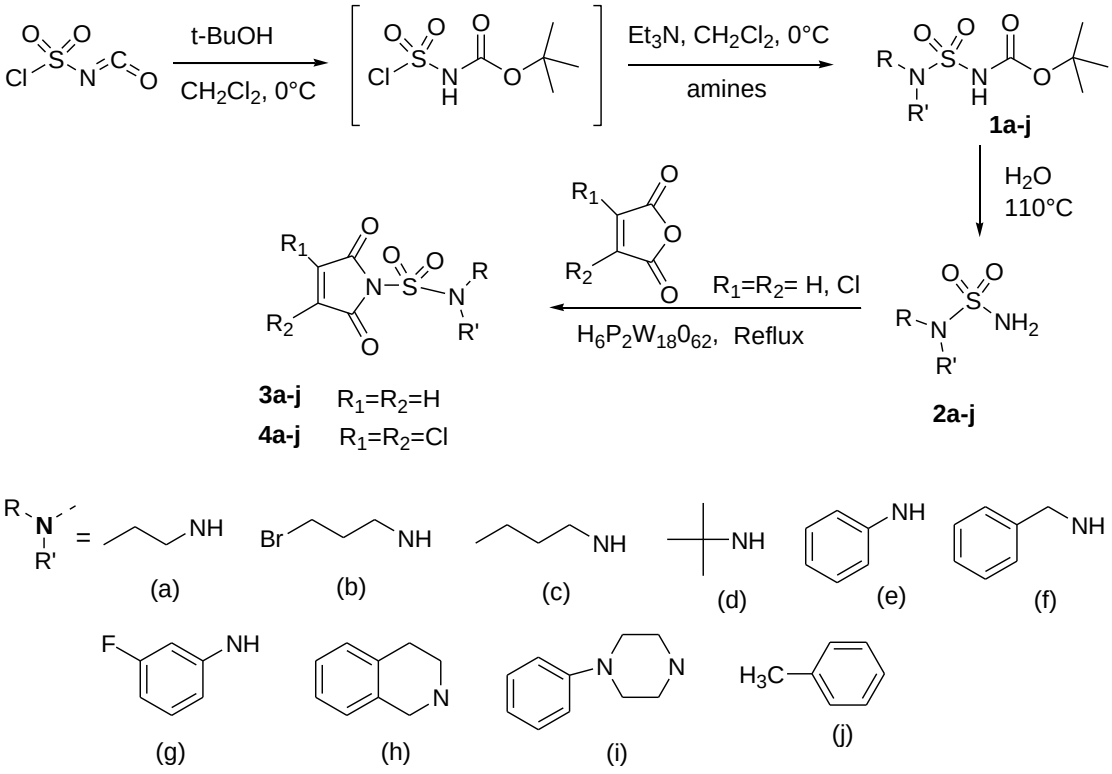
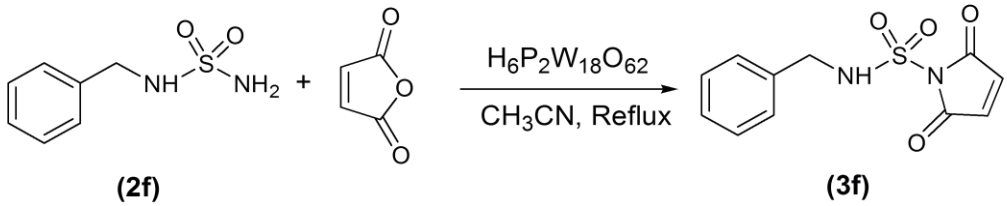


Figure 1. Biological activities of some maleimide derivatives and sulfonamide scaffold.



Scheme 1. Synthesis of *N*-sulfonyl 1-H Pyrrole-2,5-dione (3a-j and 4a-j) in the presence of $H_6P_2W_{18}O_{62}$.



(2f) (3f)

Scheme 2. Model reaction