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A rapid and direct access to symmetrical/unsymmetrical 3,4-diarylmaleimides and pyrrolin-2-ones☆

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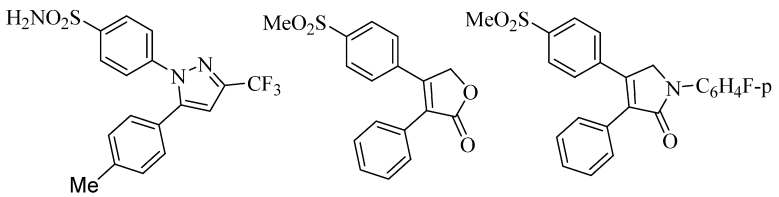
Abstract—1,8-Diazabicyclo[5.4.0]undec-7ene (DBU) facilitated the oxidative cyclization of phenacyl amide in the presence of atmospheric oxygen under environmentally friendly conditions. The reaction has been studied under various conditions and a plausible mechanism is proposed. This 'green' reaction proceeds via intramolecular ring closure of the amide followed by subsequent reaction with molecular oxygen where DBU played a crucial role. A variety of phenacyl amides were treated with DBU in acetonitrile under an oxygen atmosphere to give the symmetrical/unsymmetrical 3,4-diarylsubstituted maleimides in good yields. Corresponding pyrrolin-2-ones however, were obtained in good to excellent yields when K_2CO_3 was used in place of DBU affording a practical synthesis of these compounds of potential biological interest.

1. Introduction

The tricyclic class of compound having two aryl groups attached to the vicinal positions of the central ring is the focus of many recent reports due to their importance for the development of selective cyclooxygenase-2 (COX-2) inhibitors.[1] This is exemplified by the development of several COX-2 inhibitors (Fig. 1) such as celecoxib[2a] (Celebrex) (**1**), rofecoxib[2b] (Vioxx) (**2**) or the pyrrolin-2-one derivative[3a] (**3**). These compounds are known to be useful for the treatment of inflammation and other related diseases with reduced gastrointestinal side effects when compared to traditional NSAIDs (non-steroidal anti-inflammatory drugs).[3b] Many of these compounds possess a common structural feature i.e. a central ring having a diaryl stilbene-like moiety with a methanesulfonyl or aminosulfonyl group at the C-4 position of one of the aryl rings. These groups usually confer optimal COX-2 inhibitory potency when one of them is present at the C-4 position of an appropriate aryl ring.[3c] In connection with our studies on the synthesis of novel diaryl heterocycles as COX inhibitors[4] we decided to explore the biological as well as pharmacological properties of **II**, having a maleimide or pyrrolin-2-one moiety as the central ring (Fig. 2).



1 (Celecoxib) **2** (Rofecoxib) **3**

Figure 1. Examples of tricyclic compounds as selective COX-2 inhibitors.

☆ DRF Publication No. 339; 3,4-diarylsubstituted maleimides are commonly known as 3,4-diarylpyrrole-2,5-dione or 3,4-diaryl-2,5-dihydro-1*H*-2,5-azoledione according to the IUPAC nomenclature.

Keywords: 3,4-Diarylmaleimide and pyrrolin-2-one; Oxidative cyclization; Phenacyl amide; Oxygen.
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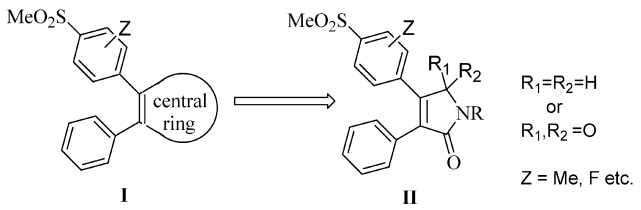
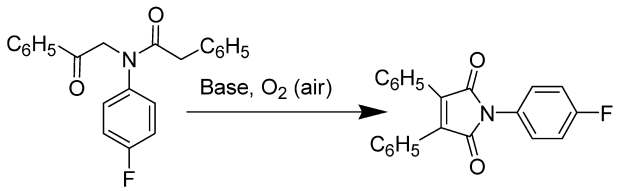


Figure 2. Design of new COX-2 inhibitor.

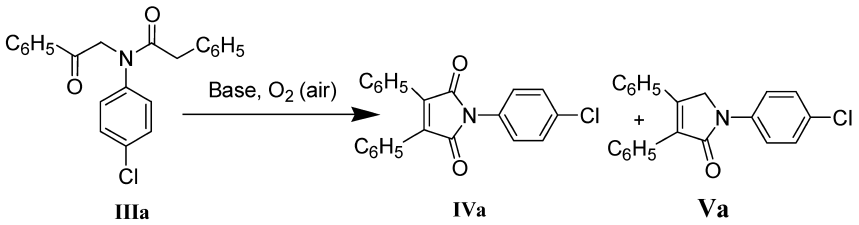
3,4-Disubstituted maleimides i.e. 3,4-disubstituted pyrrole-2,5-diones or 3,4-disubstituted-2,5-dihydro-1*H*-2,5-azole-diones are known to be useful for electrophotographic photoreceptors[5] as well as for maleimide-based fluorophores that are thiol-reactive probes for protein labeling[6a–c] or micromorphological probes[6d–e] for monitoring bulk polymerization. Maleimides, on the other hand, have been reported as rapid and time-dependent inhibitors of PGHS (prostaglandin endoperoxide synthase)[7a] and selective inhibitors of PKC (protein kinase C).[7b] They are also known to be useful as potent and selective inhibitors of glycogen synthase kinase-3 (GSK-3)[7c] as well as cyclin D1/CDK4 inhibitors.[7d]

A number of methods are available in the literature for the synthesis of symmetrical and unsymmetrical 3,4-disubstituted maleimides.[8–9] Among them, the most convenient involves the synthesis[7a,8d,10] from the corresponding maleic anhydrides (and appropriate amine in the presence of acid or base catalyst), which in turn are prepared via a number of methods[11] including the reaction of glyoxylic acids with acetic acids,[8f] or condensation of glyoxalate esters with acetamides.[9a] In both cases however, the required glyoxylic acids or esters are either not readily available or require complicated synthetic procedure. Use of diphenylfumaronitrile[9b] for the synthesis of diphenylmaleimide was also assessed recently and was found to be inappropriate due to the unsatisfactory yields of products, tedious purification procedure and difficulties in the preparation of starting materials.[12] Therefore an alternative single-step method has been developed employing arylacetonitrile and elemental iodine under strongly basic conditions.[12] While this method was found to be operative for the synthesis of symmetrical 3,4-disubstituted maleimides in low to reasonably good yields, its application in the preparation of unsymmetrical derivatives appeared to be unsuitable. Unlike maleimides, only few methods have been reported for the synthesis of 3,4-diarylpyrrolin-2-ones.[13] In our effort for the synthesis of 3,4-diaryl-substituted maleimides, we have developed a mild and environmentally friendly method for the preparation of such compounds via unusual oxidative cyclization of phenacyl amide [i.e. *N*1-(2-oxo-2-arylethyl)-*N*1,2-diaryl-acetamide][4b] (Scheme 1). However, only one example was investigated previously and the methodology was not established as a general protocol for the synthesis of these compounds. In this article we now describe this newly found single-step procedure as a general method for the synthesis of symmetrical/unsymmetrical 3,4-diaryl-substituted maleimides. We also describe a practical and general method for the synthesis of pyrrolin-2-one derivatives where generation of the corresponding maleimide as a side product was not observed.



Scheme 1. Base promoted cyclization of phenacyl amide.

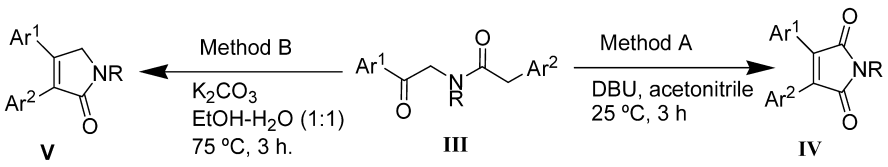
Table 1. Cyclization of *N*1-(2-oxo-2-phenylethyl)-*N*1,2-diphenylacetamide (**IIIb**) in the presence of different bases[a]



IIIa **IVa** **Va**

Entry	Base	Time (h)	Temperature (°C)	Yield (%)[b]	
				IVa	**Va**
1	DBU	3	25	67	11
2	Triethylamine	24	25	n.d.	21
3	Triethylamine	7	75	13	55
4	Diisopropylamine	7	75	11	43
5	Prolinol	7	75	10	40
6	NMP	24	75	n.d.	n.d.
7	NMM	24	75	n.d.	n.d.
8	K_2CO_3	3	75	n.d.	50
9	K_2CO_3	3	75	n.d.	87[c]

[a] Reactions were carried out by using **IIIa** (1.0 equiv.) and base (3.0 equiv.) in acetonitrile.
[b] Isolated yields.
[c] 1.5 equiv. of base was used and EtOH–H_2O (1:1) was used as a solvent. n.d.=not detected.



Scheme 2. Base promoted cyclization of phenacylamide in the presence of oxygen.

2. Results and discussion

2.1. Oxidative cyclization of phenacyl amide in the presence of various bases

Our earlier synthesis of 3,4-diaryl-substituted maleimide was carried out in acetonitrile using three equivalent of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) as a base in the presence of atmospheric oxygen. However, DBU mediated cyclization of phenacyl amide led to the formation of pyrrolin-2-ones as major products in the absence of oxygen. While exclusion or inclusion of oxygen, and equivalents of base used were established as crucial factors for determining the nature of the products formed, the effect of basicity of the base used on product distribution was not studied extensively. We therefore, examined the cyclization reaction of *N*1-(2-oxo-2-phenylethyl)-*N*1,2-diphenylacetamide (**IIIa**) in the presence of a variety of bases as well as atmospheric oxygen and results are summarized in Table 1. The conversion time of **IIIa** to **IVa** in the presence of DBU was found to be much shorter than other amine bases such as triethylamine, diisopropylamine or prolinol. After 3 h, **IVa** was isolated in 67% yield using DBU (entry 1, Table 1) when 10–13% yield was observed using other bases (entries 3–5, Table 1). *N*-Methylmorpholine (NMM) and *N*-methylpyrrolidone (NMP) gave no product after 24 h. Interestingly, the inorganic base K_2CO_3 afforded the corresponding pyrrolin-2-one **Va** in 87% yield when the reaction was carried out at 75 °C in aqueous ethanol even in the presence of atmospheric oxygen (entry 9, Table 1). These results therefore suggest that intramolecular ring closure of **IIIa** could be carried out successfully by using a variety of bases when the conversion of **Va** to **IVa** occurred effectively in the presence of DBU only.

2.2. Synthesis of symmetrical/unsymmetrical 3,4-diaryl-substituted maleimides and pyrrolin-2-one derivatives

It is evident from Table 1 that intramolecular ring closure of phenacyl amide i.e. *N*1-(2-oxo-2-arylethyl)-*N*1,2-diarylacetamide can be utilized for the synthesis of 3,4-diaryl maleimides or corresponding pyrrolin-2-ones depending on the nature of the base used. To investigate the synthetic utility of this reaction a number of phenacyl amides **III** were treated with DBU in acetonitrile (Method A) or K_2CO_3 in aqueous ethanol (Method B) in the presence of atmospheric oxygen at 25 °C (Scheme 2). Results of this study are summarized in Tables 2 and 3.

As can be seen from Table 2, the oxidative cyclization reaction (Method A) proceeds well in the presence of various R groups in the starting amide **III**. Both symmetrical and unsymmetrical 3,4-diaryl-substituted maleimides were prepared efficiently via the one step procedures in good yields. Halogens (Cl and Br) are well tolerated during the course of the reaction irrespective of their presence in Ar^1 or R (entries 1–6, Table 1). Better yields of products **4** and **11** (entries 1 and 8) were obtained using the present methodology compared to the earlier method where these compounds were prepared in low yields from appropriately substituted pyridine-2-one in the presence of *m*-chloroperbenzoic acid (32 and 14%).[9c] Moreover, Method A has advantages over reported procedures involving the successive treatment of 2,3-dibromo-*N*-methylmaleimide with the moisture sensitive organo-magnesium bromide[8e,g] or the condensation of appropriate glyoxylate chloride (which usually decomposes in the presence of moisture) with aryl acetic acids[7b] for the synthesis of unsymmetrical maleimides. To asses the merit of the present methodology synthesis of 1-(4-chlorophenyl)-3,4-diphenyl-2,5-dihydro-1*H*-2,5-azoledione (**VIa**) was carried out in a bigger scale and 10 g of **VIc** was prepared efficiently in 60% yield.

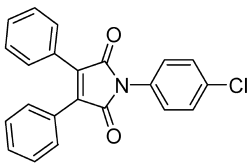
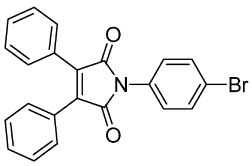
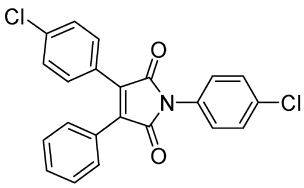
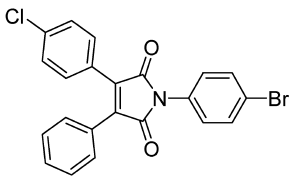
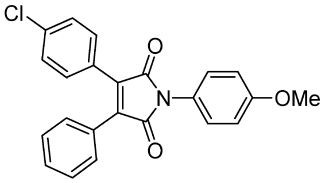
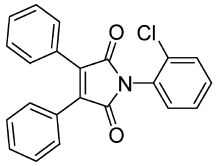
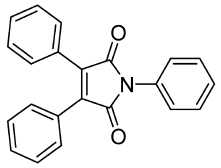
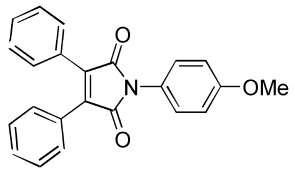
Good to excellent yields of 3,4-diaryl-substituted pyrrolin-2-ones (**V**) were also obtained when the reaction was carried out according to Method B (Table 3). The use of 1:1 ethanol–water in this method was found to be optimum as precipitation of reactants occurred in the presence of excess water whereas use of pure ethanol was found to be less effective (entry 8, Table 1). Products (**V**) isolated from the reaction mixture after dilution with water were often analytically pure. The observed high yield and purity of the isolated products as well as our continuing interest in the parallel synthesis strategy[14] prompted us to investigate the synthesis of **V** using parallel synthesis technique. Yields of products isolated after usual work-up is shown in Table 3.

We have described a direct and practical synthesis of 3,4-diarylmaleimides or pyrrolin-2-ones starting from a common amide. All phenacyl amides **III** used for the synthesis of maleimidies **IV** or pyrrolin-2-ones **V** were prepared from the appropriate *N*-phenacylaniline (**VI**) and arylacetyl chloride (**VII**) according to a similar procedure reported earlier (Scheme 3).[3a] *N*-Phenacylanilines (**VI**) were prepared from phenacyl bromide and corresponding anilines according to the known procedure.[15]

2.3. Application of the methodology

Having demonstrated the present methodology as an efficient tool for the preparation of a variety of diaryl-substituted maleimide as well as pyrrolin-2-one, synthesis of compounds of potential biological interest (Scheme 4) was undertaken. Because of our continuing interest in the development of COX-2 inhibitors for the treatment of inflammatory diseases with reduced ulcerogenic side effects we synthesized some methansulfone derivatives of **IV** as potential COX-2 inhibitors.[4a] Thus, 2-(4-fluoroanilino)-1-(3-methyl-4-methylsulfonylphenyl)-1-ethanone **4** was treated with phenylacetyl chloride to give the desired phenacyl

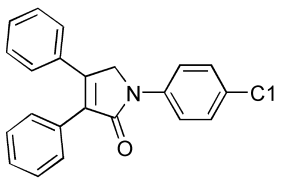
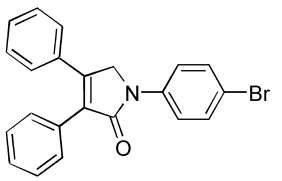
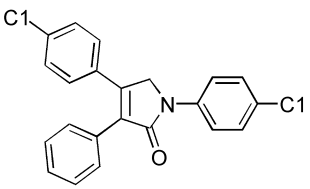
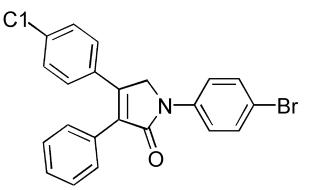
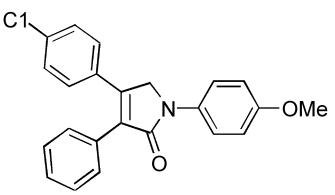
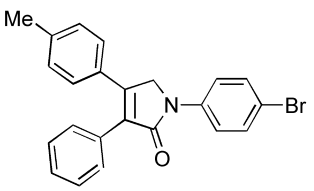
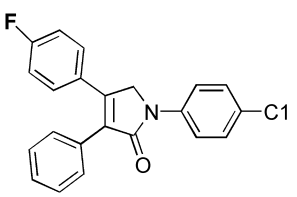
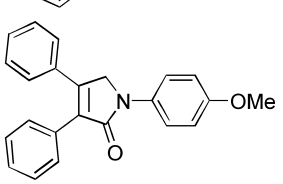
Table 2. Synthesis of 3,4-diaryl substituted maleimides[a]

Entry No.	Ar^1	Ar^2	R	Product (**IV**)[b]		Yield of **IV** (%)[c]
1	Phenyl	Phenyl	4-Chloro phenyl		**IVa**	67
2	Phenyl	Phenyl	4-Bromo phenyl		**IVb**	65
3	4-Chloro phenyl	Phenyl	4-Chloro phenyl		**IVc**	62
4	4-Chloro phenyl	Phenyl	4-Bromo phenyl		**IVd**	55
5	4-Chloro phenyl	Phenyl	4-Methoxy phenyl		**IVe**	71
6	Phenyl	Phenyl	2-Chloro phenyl		**IVf**	59
7	Phenyl	Phenyl	Phenyl		**IVg**	67
8	Phenyl	Phenyl	4-Methoxy phenyl		**IVh**	65

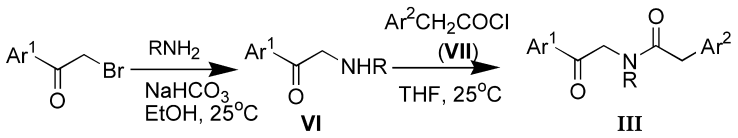
[a] Method A: reactions were carried out by using **III** (1.0 equiv.) and DBU (3 equiv.) in acetonitrile 25 °C for 3 h.
[b] Identified by ^{1}H NMR, IR, Mass.
[c] Isolated yields.

amide **5**, which on treatment with DBU in acetonitrile in the presence of atmospheric oxygen (Method A), yielded 4-methansulfonylphenyl substituted maleimide **6**. Phenacyl amide **5** on treatment with K_2CO_3 in aqueous ethanol (Method B) afforded pyrrolin-2-one **7**. Compound **7** showed 70 and 27% inhibition when tested against recombinant human COX-2 (expressed in sf9 insect cells using baculovirus) and COX-1 (Ram Seminal vesicles) enzyme in vitro[16] (% inhibition was recorded at10 μM concentration of the compound), respectively.

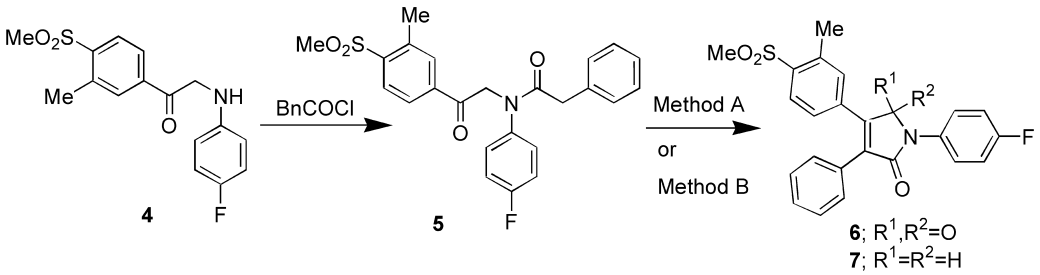
Table 3. Synthesis of 3,4-diaryl substituted pyrrolin-2-ones[a]

Entry No.	Ar^1	Ar^2	R	Product (**V**)[b]		Yield of **V** (%)[c]	
						Normal synthesis	Parallel synthesis
1	Phenyl	Phenyl	4-Chloro phenyl		**Va**	82	85
2	Phenyl	Phenyl	4-Bromo phenyl		**Vb**	87	83
3	4-Chloro phenyl	Phenyl	4-Chloro phenyl		**Vc**	85	85
4	4-Chloro phenyl	Phenyl	4-Bromo phenyl		**Vd**	85	86
5	4-Chloro phenyl	Phenyl	4-Methoxy phenyl		**Ve**	89	90
6	4-Methyl phenyl	Phenyl	4-Bromo phenyl		**Vf**	97	93
7	4-Fluoro phenyl	Phenyl	4-Chloro phenyl		**Vg**	94	93
8	Phenyl	Phenyl	4-Methoxy phenyl		**Vh**	85	87

[a] Method B: reactions were carried out by using **III** (1.0 equiv.) and K_2CO_3 (1.5 equiv.) in 1:1 ethanol–water at 75 °C for 3 h.
[b] Identified by ^1H NMR, IR, Mass.
[c] Isolated yields.



Scheme 3. Preparation of phenacyl amides **III**.[3a,15]



Scheme 4. Synthesis of COX-2 inhibitor.

3. Conclusions

To summarize, the present study demonstrates phenacyl amides as useful precursors for the synthesis of symmetrical and unsymmetrical 3,4-diarylsubstituted maleimides via an oxidative cyclization reaction. The cyclization could be carried out effectively in the presence of DBU and atmospheric oxygen. K_2CO_3 however, facilitated the cyclization of the same amide in aqueous ethanol affording the corresponding pyrrolin-2-one even in the presence of air. Since both reactions (Method A and B) were carried out in an open vessel, i.e. in the presence of atmospheric oxygen, no extra precautions (e.g. inert atmosphere, anhydrous condition) are needed for effective cyclization. They are amenable to scale-up synthesis and the methodology has been utilized for the synthesis of compounds of potential biological interest. Current efforts are now directed to the extension of this methodology to more complex molecules.

4. Experimental

4.1. General methods

Unless stated otherwise, reactions were performed in dried glassware under a nitrogen atmosphere. All the solvents used were commercially available and distilled before use. Reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F254; Merck), visualizing with ultraviolet light or iodine spray. Flash chromatography was performed on silica gel (SRL 230–400 mesh) using distilled petroleum ether, ethyl acetate, dichloromethane, chloroform and methanol. ^1H and ^{13}C NMR spectra were determined in $CDCl_3$, DMSO-d_6 or MeOH-d_4 solutions on Varian Gemini 200 MHz spectrometers. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, δ=0.00) as internal standard and expressed in ppm. Spin multiplicities are given as s (singlet), d (doublet), t (triplet) and m (multiplet) as well as b (broad). Coupling constants (J) are given in Hertz. Infrared spectra were recorded on a Perkin–Elmer 1650 FT-IR spectrometer. UV spectra were recorded on Shimadzu UV 2100S UV–vis recording spectrophotometer. Melting points were determined using a Buchi melting point B-540 apparatus and are uncorrected. Thermal analysis data was generated with the help of Shimadzu DSC-50 detector. MS spectra were obtained on a HP-5989A mass spectrometer. Purity was determined by HPLC (AGIL-AUTO) using the condition specified in each case: column, mobile phase (range used), flow rate (range used), detection wavelength, retention times. Microanalyses were performed using Perkin–Elmer 2400 C H N S/O analyzer. All the arenes/heteroarenes used are commercially available.

4.2. General procedure for the preparation of phenacyl amide [*N*1-(2-oxo-2-arylethyl)-*N*1,2-diarylacetamide; III]

Step 1. To a mixture of arylamine (10.3 mmol) and $NaHCO_3$ (10.3 mmol) in ethanol was added the appropriately substituted α-bromoacetophenone (10.3 mmol) at 25 °C under a nitrogen atmosphere. The mixture was stirred vigorously for 6 h at the same temperature and then diluted with water (10 mL). The mixture was extracted with EtOAc (3×20 mL), the organic layers were combined, washed with water (2×15 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum to give the 2-arylamino-1-arylethanone (**VI**).

Step 2. To a solution of 2-arylamino-1-arylethanone (**VI**, 4.08 mmol) in dry THF (15 mL) was added arylacetyl chloride (**VII**, 4.08 mmol) at 25 °C under a nitrogen atmosphere. The mixture was stirred for 2 h then poured into water (50 mL) and extracted with EtOAc (3×30 mL). Combined organic layers were washed with water (2×20 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum to give the desired product.

4.2.1. 2-(4-Chlorophenylamino)-1-phenylethanone (VIa). Light brown solid; yield 83%; mp 177–178 °C (lit.[17a] 177–179 °C); δ_H (200 MHz, $CDCl_3$) 8.0 (d, J=7.3 Hz, 2H), 7.67–7.48 (m, 3H), 7.16 (d, J=8.6 Hz, 2H), 6.62 (d, J=8.8 Hz, 2H), 4.95 (bs, D_2O exchangeable, 1H, N–H), 4.58 (s, 2H, CH_2).

4.2.2. *N*1-(4-Chlorophenyl)-*N*1-(2-oxo-2-phenylethyl)-2-phenylacetamide (IIIa). Light orange solid; yield 85%; mp 88–90 °C; δ_H (200 MHz, $CDCl_3$) 7.93 (d, J=7.2 Hz, 2H), 7.58–7.08 (m, 12H), 5.07 (s, 2H, CH_2), 3.59 (s, 2H, CH_2); ν_{max} (KBr) 1738 (w), 1701, 1668, 1596 cm^{-1}; m/z (CI,

i-Butane) 364 (100, MH^+); found C, 72.37; H, 5.09; N, 3.95; $C_{22}H_{18}ClNO_2$ requires C, 72.63; H, 4.99; N, 3.85%.

4.2.3. 2-(4-Bromophenylamino)-1-phenylethanone (VIb). Brown solid; yield 60%; mp 165–166 °C (lit.[17b] 162 °C); δ_H (200 MHz, $CDCl_3$) 8.0 (d, J=7.3 Hz, 2H), 7.64 (d, J=7.3 Hz, 1H), 7.56 (m, 2H), 7.28 (d, J=8.8 Hz, 2H), 6.60 (d, J=8.6 Hz, 2H), 4.99 (bs, D_2O exchangeable, 1H, N–H), 4.59 (s, 2H, CH_2).

4.2.4. *N*1-(4-Bromophenyl)-*N*1-(2-oxo-2-phenylethyl)-2-phenylacetamide (IIIb). Off white solid; yield 71%; mp 90–92 °C; δ_H (200 MHz, $CDCl_3$) 7.92 (d, J=7.3 Hz, 2H), 7.57–7.09 (m, 12H), 5.07 (s, 2H, CH_2), 3.58 (s, 2H, CH_2); ν_{max} (KBr) 1738 (w), 1701, 1668, 1597 cm^{-1}; *m/z* (CI, *i*-Butane) 410 (100, M+2), 408 (80, M^+); found C, 64.55; H, 4.19; N, 3.62; $C_{22}H_{18}NO_2Br$ requires C, 64.72; H, 4.44; N, 3.43%.

4.2.5. 1-(4-Chlorophenyl)-2-(4-chlorophenylamino)ethanone (VIc). White solid; yield 77%; mp 155–156 °C (lit.[17c] 155–157 °C); δ_H (200 MHz, $CDCl_3$) 7.96 (d, J=7.8 Hz, 2H), 7.50 (d, J=7.8 Hz, 2H), 7.16 (d, J=8.3 Hz, 2H), 6.63 (d, J=8.3 Hz, 2H), 4.91 (D_2O exchangeable, 1H, N–H), 4.55 (s, 2H, CH_2).

4.2.6. *N*1-(4-Chlorophenyl)-*N*1-[2-(4-chlorophenyl)-2-oxoethyl]-2-phenylacetamide (IIIc). Light brown solid; yield 64%; mp 105–107 °C; δ_H (200 MHz, $CDCl_3$) 7.87 (d, J=8.6 Hz, 2H), 7.45–7.08 (m, 11H), 5.03 (s, 2H, CH_2), 3.57 (s, 2H, CH_2); ν_{max} (KBr) 1696, 1663, 1590 cm^{-1}; *m/z* (CI, *i*-Butane) 398 (100, MH^+); found C, 66.20; H, 4.29; N, 3.82; $C_{22}H_{17}NO_2Cl_2$ requires C, 66.34; H, 4.30; N, 3.52%.

4.2.7. 2-(4-Bromophenylamino)-1-(4-chlorophenyl)ethanone (VId). Brown solid; yield 75%; mp 165–166 °C (lit.[17c] 165–168 °C); δ_H (200 MHz, $CDCl_3$) 7.96 (d, J=8.3 Hz, 2H), 7.50 (d, J=8.3 Hz, 2H), 7.30 (d, J=8.8 Hz, 2H), 6.58 (d, J=8.8 Hz, 2H), 4.93 (bs, D_2O exchangeable, 1H, N–H), 4.55 (s, 2H, CH_2).

4.2.8. *N*1-(4-Bromophenyl)-*N*1-[2-(4-chlorophenyl)-2-oxoethyl]-2-phenylacetamide (IIId). Yellow solid; yield 73%; mp 104–108 °C; δ_H (200 MHz, $CDCl_3$) 7.87 (d, J=8.3 Hz, 2H), 7.52–7.08 (m, 11H), 5.02 (s, 2H, CH_2), 3.57 (s, 2H, CH_2); ν_{max} (KBr) 1698, 1665, 1590 cm^{-1}; *m/z* (CI, *i*-Butane) 444 (100, M+2), 442 (80, M^+); found C, 59.49; H, 3.88; N, 3.32; $C_{22}H_{17}BrNO_2Cl$ requires C, 59.68; H, 3.87; N, 3.16%.

4.2.9. 1-(4-Chlorophenyl)-2-(4-methoxyphenylamino)-ethanone (VIe). Off white solid; yield 91%; mp 116–118 °C (lit.[17d] 118–120 °C); δ_H (200 MHz, $CDCl_3$) 7.96 (d, J=8.3 Hz, 2H), 7.50 (d, J=8.8 Hz, 2H), 6.83 (d, J=8.8 Hz, 2H), 6.67 (d, J=8.8 Hz, 2H), 4.95 (D_2O exchangeable, 1H, N–H), 4.55 (s, 2H, CH_2), 3.76 (s, 3H, OCH_3).

4.2.10. *N*1-[2-(4-Chlorophenyl)-2-oxoethyl]-*N*1-(4-methoxyphenyl)-2-phenylacetamide (IIIe). Light brown solid; yield 86%; mp 67–69 °C; δ_H (200 MHz, $CDCl_3$) 7.86 (d, J=8.3 Hz, 2H), 7.40 (d, J=8.3 Hz, 2H), 7.28–7.09 (m, 7H), 6.88 (d, J=8.6 Hz, 2H), 5.02 (s, 2H, CH_2), 3.81 (s, 3H, OCH_3), 3.56 (s, 2H, CH_2); ν_{max} (KBr) 1701, 1655, 1590 cm^{-1}; *m/z* (CI, *i*-Butane) 394 (100, MH^+); found C, 70.05; H, 5.19; N, 3.72; $C_{23}H_{20}NO_3Cl$ requires C, 70.14; H, 5.12; N, 3.56%.

4.2.11. 2-(2-Chlorophenylamino)-1-phenylethanone (VIf). White solid; yield 50%; mp 104–105 °C (lit.[17e] 105 °C); δ_H (200 MHz, $CDCl_3$) 8.0 (d, J=7.3 Hz, 2H), 7.97–7.2 (m, 5H), 6.66 (d, J=7.8 Hz, 2H), 4.95 (D_2O exchangeable, 1H, N–H), 4.65 (s, 2H, CH_2).

4.2.12. *N*1-(2-Chlorophenyl)-*N*1-(2-oxo-2-phenylethyl)-2-phenylacetamide (IIIf). Off white solid; yield 50%; mp 116–118 °C; δ_H (200 MHz, $CDCl_3$) 7.95 (d, J=7.3 Hz, 2H), 7.69–7.21 (m, 10H), 7.10 (d, J=7.6 Hz, 2H), 5.88 (d, J=17.6 Hz, 1H), 4.24 (d, J=17.6 Hz, 1H), 3.50 (s, 2H, CH_2); ν_{max} (KBr) 1742, 1691, 1662 cm^{-1}; *m/z* (CI, *i*-Butane) 364 (100, MH^+); found C, 73.02; H, 4.89; N, 3.99; $C_{22}H_{18}NO_2Cl$ requires C, 72.63; H, 4.99; N, 3.85%.

4.2.13. 1-Phenyl-2-phenylaminoethanone (VIg). Yellow solid; yield 57%; mp 110–112 °C (lit.[17c] 113–115 °C); δ_H (200 MHz, $CDCl_3$) 8.03 (d, J=7.3 Hz, 2H), 7.67–7.48 (m, 3H), 7.27–7.19 (m, 2H), 6.79–6.70 (m, 3H), 4.95 (bs, D_2O exchagable, 1H, NH), 4.63 (s, 2H, CH_2); ν_{max} (KBr) 3370, 1693, 1603, 1512 cm^{-1}; *m/z* (CI, *i*-Butane) 212 (100, MH^+).

4.2.14. *N*1-(2-Oxo-2-phenylethyl)-*N*1,2-diphenylacetamide (IIIg). Brown solid; yield 80%; mp 108–110 °C; δ_H (200 MHz, $CDCl_3$) 7.93 (d, J=7.1 Hz, 2H), 7.59–7.09 (m, 13H), 5.1 (s, 2H, CH_2), 3.58 (s, 2H, CH_2); ν_{max} (KBr) 1698, 1659, 1594 cm^{-1}; *m/z* (CI, *i*-Butane) 330 (100, MH^+); found C, 80.05; H, 5.89; N, 4.54; $C_{22}H_{19}NO_2$ requires C, 80.22; H, 5.81; N, 4.25%.

4.2.15. 2-(4-Methoxyphenylamino)-1-phenylethanone (VIh). Off white solid; yield 50%; mp 95–96 °C (lit.[17f] 94–96 °C); δ_H (200 MHz, $CDCl_3$) 8.02 (d, J=8.1 Hz, 2H), 7.62–7.49 (m, 2H), 7.44 (d, J=8.1 Hz, 2H), 6.86–6.71 (m, 3H), 4.92 (bs, D_2O exchangeable, 1H), 4.60 (s, 2H, CH_2), 3.76 (s, 3H, OCH_3); ν_{max} (KBr) 3390, 1682, 1595, 1514 cm^{-1}; *m/z* (CI, *i*-Butane) 242 (100, MH^+).

4.2.16. *N*1-(4-Methoxyphenyl)-*N*1-(2-oxo-2-phenylethyl)-2-phenylacetamide (IIIh). White solid; yield 31%; mp 68–70 °C; δ_H (200 MHz, $CDCl_3$) 8.0 (d, J=7.3 Hz, 2H), 7.60 (d, J=6.9 Hz, 1H), 7.50 (m, 5H), 7.29 (d, J=6.9 Hz, 2H), 7.17 (d, J=7.3 Hz, 2H), 6.93 (d, J=8.9 Hz, 2H), 5.14 (s, 2H, CH_2), 3.88 (s, 3H, OMe), 3.64 (s, 2H, CH_2); ν_{max} (KBr) 1701, 1659 cm^{-1}; *m/z* (CI, *i*-Butane) 360 (100, MH^+); found C, 76.65; H, 6.01; N, 3.93; $C_{23}H_{21}NO_3$ requires C, 76.86; H, 5.89; N, 3.90%.

4.3. Method A. General procedure for the preparation of IV

To a solution of phenacyl amide **III** (1.3 mmol) in acetonitrile (40 mL) was added DBU (0.61 mL, 4.1 mmol) dropwise at 0–5 °C. The mixture was stirred at 25 °C for 3 h under air. After completion of the reaction the mixture was poured into ice-cold 3 M HCl solution (100 mL) with stirring. The solid precipitate was collected by filtration and then washed with water (2×8 mL) and petroleum ether

(2×5 mL). When a solid precipitate did not form the mixture was extracted with ethyl acetate (3×20 mL) and the combined organic layers were washed with water (2×20 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude product thus obtained was purified by column chromatography using petroleum ether–EtOAc as eluant.

4.3.1. 1-(4-Chlorophenyl)-3,4-diphenyl-2,5-dihydro-1*H*-2,5-azoledione (IVa). Yellow solid; yield 67%; mp 186–188 °C; δ_H (200 MHz, $CDCl_3$) 7.52 (d, J=7.3 Hz, 2H), 7.46–7.38 (m, 12H); ν_{max} (KBr) 1760 (w), 1710, 1497 cm^{-1}; m/z (CI, i-Butane) 360 (100, MH^+); UV (MeOH, nm) 363.5, 289.0, 235.0; HPLC: 99.8%, INERTSIL ODS 3V (250×4.6 mm), 0.01 M KH_2PO_4)/CH_3CN 30/70, 1.0 mL/min, 235 nm, retention time 18.73 min; ^{13}C NMR (50 MHz, $CDCl_3$): 168.0 (C=O, 2C), 136.35 (2C), 133.37, 130.31 (2C), 130.10 (2C), 129.97 (4C), 129.22 (2C), 128.63 (4C), 128.28, 127.19 (2C); found C, 73.05; H, 4.09; N, 3.92; $C_{22}H_{14}NO_2Cl$ requires C, 73.44; H, 3.92; N, 3.89%.

4.3.2. 1-(4-Bromophenyl)-3,4-diphenyl-2,5-dihydro-1*H*-2,5-azoledione (IVb). Yellow solid; yield 65%; mp 198–200 °C; δ_H (200 MHz, $CDCl_3$) 7.63 (d, J=8.7 Hz, 2H), 7.53–7.37 (m, 12H); ν_{max} (KBr) 1766 (w), 1712, 1594 (w), 1491 cm^{-1}; m/z (CI, i-Butane) 406 (100, M+2), 404 (100, M^+); UV (MeOH, nm) 237; HPLC: 99.8%, INERTSIL ODS 3V (250×4.6 mm), 0.01 M KH_2PO_4/CH_3CN 30/70, 1.0 mL/min, 237 nm, retention time 23.46 min; ^{13}C NMR (50 MHz, $CDCl_3$): 165.0 (C=O, 2C), 131.80 (C), 126.99 (2C), 124.91 (4C), 124.77 (4C), 123.43 (4C), 123.05 (2C), 122.26 (2C), 116.0 (C); found C, 65.48; H, 3.69; N, 3.37; $C_{22}H_{14}NO_2Br$ requires C, 65.36; H, 3.49; N, 3.46%.

4.3.3. 3-(4-Chlorophenyl)-1-(4-chlorophenyl)-4-phenyl-2,5-dihydro-1*H*-2,5-azoledione (IVc). Yellow solid; yield 62%; mp 140–142 °C; δ_H (200 MHz, $CDCl_3$) 7.49–7.33 (m, 13H); ν_{max} (KBr): 1768 (w), 1710, 1594 (w), 1496 cm^{-1}; m/z (CI, i-Butane) 394 (100, MH^+); UV (MeOH, nm) 368.5, 302.5, 237.0; HPLC: 99.62%, INERTSIL ODS 3V (250×4.6 mm), 0.01 M KH_2PO_4/CH_3CN 30/70, 1.0 mL/min, 238 nm, retention time 28.89 min; ^{13}C NMR (50 MHz, $CDCl_3$): 168.94 (C=O, 2C), 136.38, 136.37, 135.03, 133.45, 131.32 (2C), 130.31, 130.16, 129.87 (2C), 129.23 (2C), 128.99 (2C), 128.76 (2C), 128.01, 127.13 (2C), 126.69; found C, 67.08; H, 3.38; N, 3.50; $C_{22}H_{13}NO_2Cl_2$ requires C, 67.02; H, 3.32; N, 3.55%.

4.3.4. 3-(4-Chlorophenyl)-1-(4-bromophenyl)-4-phenyl-2,5-dihydro-1*H*-2,5-azoledione (IVd). Pale yellow solid; yield 55%; mp 136–138 °C; δ_H (200 MHz, $CDCl_3$) 7.62 (d, J=8.6 Hz, 2H), 7.49–7.33 (m, 11H); ν_{max} (KBr): 1767, 1711, 1591 (w), 1490 cm^{-1}; m/z (CI, i-Butane) 440 (100, M+2), 438 (80, M^+); UV (MeOH, nm) 363.0, 300.5, 238.5; HPLC: 97.60%. INERTSIL ODS 3V (250×4.6 mm), 0.01 M KH_2PO_4/CH_3CN 30/70, 1.0 mL/min, 238 nm, retention time 32.38 min; ^{13}C NMR (50 MHz, $CDCl_3$): 168.91 (C=O, 2C), 136.38, 135.05, 132.20 (2C), 131.32 (2C), 131.01, 130.70, 130.33, 129.87 (2C), 129.57, 129.30, 129.00 (2C), 128.77 (2C), 127.40 (2C), 121.45; found C, 60.41; H, 2.98; N, 3.24; $C_{22}H_{13}NO_2ClBr$ requires C, 60.23; H, 2.99; N, 3.19%.

4.3.5. 3-(4-Chlorophenyl)-1-(4-methoxyphenyl)-4-phenyl-2,5-dihydro-1*H*-2,5-azoledione (IVe). Yellow solid; yield 71%; mp 146–148 °C; δ_H (200 MHz, $CDCl_3$) 7.52–7.32 (m, 11H), 7.0 (d, J=8.9 Hz, 2H), 3.84 (s, 3H, OMe); ν_{max} (KBr) 1763 (w), 1706, 1588 (w), 1511 cm^{-1}; m/z (CI, i-Butane) 390 (100, M^+); UV (MeOH, nm) 308.5, 235.0; HPLC: 99.18%, INERTSIL ODS 3V (250×4.6 mm), 0.01 M KH_2PO_4/CH_3CN 30/70, 1.0 mL/min, 235 nm, retention time 18.87 min; ^{13}C NMR (50 MHz, $CDCl_3$): 169.54 (C=O, 2C), 159.04, 136.49, 136.16, 134.87, 131.34 (2C), 130.14, 129.90 (2C), 128.93 (2C), 128.70 (2C), 128.26, 127.56 (2C), 126.95, 124.16, 114.40 (2C), 55.43; found C, 70.95; H, 4.14; N, 3.54; $C_{23}H_{16}ClNO_3$ requires C, 70.86; H, 4.14; N, 3.59%.

4.3.6. 1-(2-Chlorophenyl)-3,4-diphenyl-2,5-dihydro-1*H*-2,5-azoledione (IVf). Yellow solid; yield 59%; mp 195–197 °C; δ_H (200 MHz, $CDCl_3$) 7.56–7.39 (m, 14H); ν_{max} (KBr) 1766 (w), 1712, 1483 cm^{-1}; m/z (CI, i-Butane) 360 (100, MH^+); ^{13}C NMR (50 MHz, $CDCl_3$): 168.83 (C=O, 2C), 136.49, 133.20, 130.67, 130.46, 130.36, 130.02 (4C), 129.99 (4C), 129.63, 128.56 (4C), 128.36, 127.64; HPLC: 95%, INERTSIL ODS 3V (250×4.6 mm), 0.01 M KH_2PO_4/CH_3CN 30/70, 1.0 mL/min, 210 nm, retention time 15.24 min; found C, 73.50; H, 3.99; N, 3.81; $C_{22}H_{14}NO_2Cl$ requires C, 73.44; H, 3.92; N, 3.89%.

4.3.7. 1,3,4-Triphenyl-2,5-dihydro-1*H*-2,5-azoledione (IVg). White solid; yield 67%; mp 179–180 °C (lit.[18] 180–181 °C); δ_H (200 MHz, $CDCl_3$) 7.68–6.84 (m, 15H); m/z (CI, i-Butane) 326 (100, MH^+).

4.3.8. 1-(4-Methoxyphenyl)-3,4-diphenyl-2,5-dihydro-1*H*-2,5-azoledione (IVh). Yellow solid; yield 65%; mp 191–192 °C (lit.[9c] 193–194 °C); δ_H (200 MHz, $CDCl_3$) 7.67–6.88 (m, 14H), 3.80 (s, 3H, OCH_3); m/z (CI, i-Butane) 355 (100, MH^+).

4.3.9. Scale-up synthesis for IVc. To a solution of phenacyl amide **IIIc** (16 g, 0.04 mol) in acetonitrile (0.48 L) was added DBU (20 mL, 0.12 mol) dropwise at 0–5 °C. The mixture was stirred at 25 °C for 3 h in the open air and was then poured into cold 3 M HCl (0.84 L) with stirring. The mixture was extracted with ethyl acetate (3×0.20 L) and the combined organic layers were washed with water (2×0.20 L), dried over anhydrous Na_2SO_4 and concentrated under vacuum to afford 10.5 g of the crude product. The crude material obtained was re-crystallized from isopropanol to give 9.6 g (60%, 24.2 mmol) of the desired compound.

4.4. Method B. General procedure for the preparation of V

To a solution of phenacyl amide **III** (1.6 mmol) in 1:1 EtOH–H_2O (40 mL) was added powdered K_2CO_3 (2.4 mmol) and the mixture was stirred at 25 °C for 10 min. The mixture was then heated to 75 °C for 2.5 h. After completion of the reaction the mixture was cooled and poured into water (50 mL) with stirring. The solid precipitate was collected by filtration, washed with water (2×8 mL) and dried under vacuum to afford analytically pure product.

4.4.1. Parallel synthesis of V. Parallel synthesis was carried out using eight reaction flasks simultaneously each containing the appropriate amide **III** and powdered K_2CO_3. To a solution of phenacyl amide **III** (0.8 mmol) in 1:1 EtOH–H_2O (20 mL) was added powder K_2CO_3 (1.2 mmol) and the mixture was stirred at 25 °C for 10–15 min. The mixture was then heated to 75–80 °C for 2.5 h. After completion of the reaction each mixture was cooled and poured into water (25 mL) with stirring. In all cases products appeared as solid, and the filtered solid, after washing with cold hexane (2×5 mL), was analytically pure.

4.4.2. 1-(4-Chlorophenyl)-3,4-diphenyl-2,5-dihydro-1*H*-2-azolone (Va). Off white solid; yield 82%; DSC 178.27 °C; δ_H (200 MHz, $CDCl_3$) 7.80 (d, J=8.8 Hz, 2H), 7.40–7.35 (m, 12H), 4.74 (s, 2H, CH_2); ν_{max} (KBr) 1677, 1595 cm^{-1}; *m/z* (CI, *i*-Butane) 346 (100, MH^+); ^{13}C NMR (50 MHz, DMSO-d_6): 168.76 (C=O), 148.59, 138.14, 132.20, 131.72, 129.55, 129.36 (2C), 128.74 (2C), 128.61 (2C), 128.34 (2C), 128.10 (2C), 127.71 (2C), 127.36, 120.03 (2C), 52.25 (CH_2); HPLC: 95%, HICHROM RPB (250×4.6 mm), 0.01 M KH_2PO_4/CH_3CN 0/40, 5/40, 20/80, 30/80, 35/40, 40/40, 1.0 mL/min, 242 nm, retention time 23.91 min; found C, 76.22; H, 4.69; N, 3.87; $C_{22}H_{16}NOCl$ requires C, 76.41; H, 4.66; N, 4.05%.

4.4.3. 1-(4-Bromophenyl)-3,4-diphenyl-2,5-dihydro-1*H*-2-azolone (Vb). Light yellow solid; yield 87%; DSC 173.31 °C; δ_H (200 MHz, $CDCl_3$) 7.76 (d, J=9.1 Hz, 2H), 7.50 (d, J=9.1 Hz, 2H), 7.41–7.34 (m, 10H), 4.73 (s, 2H, CH_2); ν_{max} (KBr) 1678, 1588 cm^{-1}; *m/z* (CI, *i*-Butane) 392 (100, M+2), 390 (100, M^+); ^{13}C NMR (50 MHz, DMSO-d_6): 168.78 (C=O), 148.60, 138.56, 132.20, 131.72, 131.65, 129.56 (2C), 129.37 (2C), 128.62 (2C), 128.35 (2C), 128.11 (2C), 127.72 (2C), 120.38 (2C), 115.42, 52.20 (CH_2); HPLC: 99%, INERTSIL ODS 3V (150×4.6 mm), 0.01 M KH_2PO_4/CH_3CN 0/40, 10/40, 30/85, 40/85, 45/40, 50/40, 1.0 mL/min, 240 nm, retention time 30.06 min; found C, 67.50; H, 4.34; N, 3.71; $C_{22}H_{16}NOBr$ requires C, 67.71; H, 4.13; N, 3.59%.

4.4.4. 1,4-Di(4-chlorophenyl)-3-phenyl-2,5-dihydro-1*H*-2-azolone (Vc). Yellow solid; yield 85%; DSC 190.90 °C; δ_H (200 MHz, $CDCl_3$) 7.79 (d, J=9.0 Hz, 2H), 7.38–7.25 (m, 11H), 4.70 (s, 2H, CH_2); ν_{max} (KBr) 1668, 1594 cm^{-1}; *m/z* (CI, *i*-Butane) 380 (100, MH^+); ^{13}C NMR (50 MHz, DMSO-d_6): 168.58 (C=O), 147.37, 138.10, 134.25, 132.27, 131.43, 131.11, 129.54 (2C), 129.35 (2C), 128.78 (4C), 128.49 (2C), 128.30, 127.48, 120.09 (2C), 52.21 (CH_2); HPLC: 99%, INERTSIL ODS 3V (150×4.6 mm), 0.01 M KH_2PO_4/CH_3CN 0/70, 5/70, 15/85, 25/85, 30/70, 35/70, 1.0 mL/min, 240 nm, retention time 13.79 min; found C, 69.81; H, 3.99; N, 3.41; $C_{22}H_{15}NOCl_2$ requires C, 69.49; H, 3.98; N, 3.68%.

4.4.5. 1-(4-Bromophenyl)-4-(4-chlorophenyl)-3-phenyl-2,5-dihydro-1*H*-2-azolone (Vd). Off white solid; yield 85%; DSC 170.45 °C; δ_H (200 MHz, $CDCl_3$) 7.75 (d, J=7.3 Hz, 2H), 7.50 (d, J=7.1 Hz, 2H), 7.48–7.25 (m, 9H), 4.70 (s, 2H, CH_2); ν_{max} (KBr) 1669, 1590 cm^{-1}; *m/z* (CI, *i*-Butane) 426 (100, M+2), 424 (80, M^+); ^{13}C NMR (50 MHz, DMSO-d_6): 168.59 (C=O), 147.21, 138.49, 134.49, 134.30, 132.28, 131.66, 131.40, 131.04, 129.50 (2C), 129.36 (2C), 128.75 (2C), 128.45 (2C), 128.29, 120.32 (2C), 115.54, 52.11 (CH_2); HPLC: 99%, INERTSIL ODS 3V (150×4.6 mm), 0.01 M KH_2PO_4/CH_3CN 0/40, 10/40, 30/85, 40/85, 45/40, 50/40, 1.0 mL/min, 240 nm, retention time 32.73 min; found C, 62.47; H, 3.59; N, 3.01; $C_{22}H_{15}BrNOCl$ requires C, 62.21; H, 3.56; N, 3.30%.

4.4.6. 4-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-phenyl-2,5-dihydro-1*H*-2-azolone (Ve). White solid; yield 89%; DSC 154.86 °C; δ_H (200 MHz, $CDCl_3$) 7.70 (d, J=8.9 Hz, 2H), 7.43–7.28 (m, 9H), 6.94 (d, J=8.9 Hz, 2H), 4.69 (s, 2H, CH_2), 3.82 (s, 3H, OCH_3); ν_{max} (KBr) 1681, 1594 cm^{-1}; *m/z* (CI, *i*-Butane) 376 (100, MH^+); ^{13}C NMR (50 MHz, DMSO-d_6): 168.06 (C=O), 155.72, 146.64, 134.04, 132.43, 131.69, 131.35, 129.47 (2C), 129.37 (2C), 128.73 (2C), 128.40 (2C), 128.17 (2C), 120.53 (2C), 114.05 (2C), 55.18 (OCH_3), 52.51 (CH_2); HPLC: 98%, INERTSIL ODS 3V (250×4.6 mm), 0.01 M KH_2PO_4/CH_3CN 0/40. 10/40, 30/85, 40/85, 45/40, 50/40, 1.0 mL/min, 240 nm, retention time 28.38 min; found C, 73.54; H, 4.99; N, 3.61; $C_{23}H_{18}NO_2Cl$ requires C, 73.50; H, 4.83; N, 3.73%.

4.4.7. 1-(4-Bromophenyl)-4-(4-methylphenyl)-3-phenyl-2,5-dihydro-1*H*-2-azolone (Vf). Yellow solid; yield 97%; DSC 167.72 °C; δ_H (200 MHz, $CDCl_3$) 7.76 (d, J=8.8 Hz, 2H), 7.50 (d, J=8.8 Hz, 2H), 7.40–7.22 (m, 7H), 7.12 (d, J=7.8 Hz, 2H), 4.71 (s, 2H, CH_2), 2.35 (s, 3H, CH_3); ν_{max} (KBr) 1680, 1598 cm^{-1}; *m/z* (CI, *i*-Butane) 404 (100, MH^+), 406 (100, M+2); ^{13}C NMR (50 MHz, DMSO-d_6): 168.91 (C=O), 148.56, 139.49, 138.62, 131.93, 131.66 (2C), 131.03, 129.40 (2C), 129.26, 129.22 (2C), 128.39 (2C), 128.06, 127.64 (2C), 120.34 (2C), 115.35, 52.10 (CH_2), 20.86 (CH_3); HPLC: 99%, INERTSIL ODS 3V (150×4.6 mm), 0.01 M KH_2PO_4/CH_3CN 0/75, 10/75, 15/80, 25/80, 30/75, 35/75, 1.0 mL/min, 210 nm, retention time 13.30 min; found C, 68.54; H, 4.39; N, 3.31; $C_{23}H_{18}NOBr$ requires C, 68.33; H, 4.49; N, 3.46%.

4.4.8. 1-(4-Chlorophenyl)-4-(4-fluorophenyl)-3-phenyl-2,5-dihydro-1*H*-2-azolone (Vg). Light yellow solid; yield 94%; DSC 163.04 °C; δ_H (200 MHz, $CDCl_3$) 7.80 (d, J=9.0 Hz, 2H), 7.39–7.30 (m, 9H), 7.01 (t, J=8.5 Hz, 2H), 4.71 (s, 2H, CH_2); ν_{max} (KBr) 1668, 1603 cm^{-1}; *m/z* (CI, *i*-Butane) 364 (100, MH^+); ^{13}C NMR (50 MHz, DMSO-d_6): 168.64 (C=O), 165.01, 160.08, 147.34, 138.07, 131.62, 131.54, 130.09, 129.92, 129.34, 129.02, 128.70, 128.60, 128.39 (2C), 128.15, 127.37, 119.86 (2C), 115.88, 115.45, 52.21 (CH_2); HPLC: 99%, INERTSIL ODS 3V (250×4.6 mm), 0.01 M KH_2PO_4/CH_3CN 0/75, 10/75, 15/80, 25/80, 30/75, 35/75, 1.0 mL/min, 210 nm, retention time 9.04 min; found C, 72.84; H, 3.98; N, 3.79; $C_{22}H_{15}NOClF$ requires C, 72.63; H, 4.16; N, 3.85%.

4.4.9. 1-(4-Methoxyphenyl)-3,4-diphenyl-2,5-dihydro-1*H*-2-azolone (Vh). White solid; yield 85%; DSC 139.94 °C; δ_H (200 MHz, $CDCl_3$) 7.73 (d, J=8.9 Hz, 2H), 7.42–7.33 (m, 10H), 6.94 (d, J=8.9 Hz, 2H), 4.73 (s, 2H, CH_2), 3.82 (s, 3H, OMe); ν_{max} (KBr) 1689 cm^{-1}; *m/z* (CI, *i*-Butane) 342 (80, MH^+), 341 (100); ^{13}C NMR (50 MHz, DMSO-d_6): 168.0 (C=O), 156.28, 146.57, 132.77, 132.61, 131.63, 129.59 (2C), 129.34 (2C), 128.72 (2C), 128.38 (2C), 128.18 (2C), 127.62 (2C), 120.64 (2C), 114.28, 55.44 (OCH_3), 53.0 (CH_2); HPLC: 97%, INERTSIL ODS 3V

(250×4.6 mm), 0.01 M KH_2PO_4/CH_3CN 0/60, 5/60, 15/80, 25/80, 30/60, 35/60, 1.0 mL/min, 234 nm, retention time 16.54 min; found C, 80.81; H, 5.68; N, 4.29; $C_{23}H_{19}NO_2$ requires C, 80.92; H, 5.61; N, 4.10%.

4.4.10. Preparation of 2-(4-fluoroanilino)-1-(3-methyl-4-methylsulfonylphenyl)-1-ethanone (4). To a mixture of *p*-fluoroaniline (1.14 g, 10.3 mmol) and $NaHCO_3$ (0.87 g, 10.3 mmol) in ethanol (25 mL) was added 2′-bromo-3-methyl-4-methylsulfonyl acetophenone (3 g, 10.3 mmol) under a nitrogen atmosphere at 25 °C. The mixture was stirred vigorously for 3.5 h then diluted with water (100 mL). The solid precipitated was filtered, washed with water (2×25 mL) and petroleum ether (2×10 mL) then dried under vacuum to give the title compound (2.9 g, 88%). Brown solid; mp 156–158 °C; δ_H (200 MHz, $CDCl_3$) 8.19 (d, *J*=8.7 Hz, 1H), 7.98–7.95 (m, 2H), 6.98–6.89 (m, 2H), 6.68–6.62 (m, 2H), 4.60 (s, 2H, CH_2), 3.12 (s, 3H, SO_2CH_3), 2.81 (s, 3H, CH_3); MS (CI, *i*-Butane) *m/z* 322 (M+1, 100); ^{13}C NMR (50 MHz, DMSO-d_6): 196.57 (C═O), 156.96, 144.73, 142.73, 138.84, 138.05, 131.97, 129.02, 125.95, 115.42, 114.97, 113.40, 113.26, 50.91 (CH_2), 43.14 (CH_3SO_2), 19.67(CH_3); HPLC: 98%, INERTSIL ODS 3V (250×4.6 mm), 0.01 M KH_2PO_4/CH_3CN 0/30, 5/30, 20/80, 30/80, 35/30, 40/30, 1.0 mL/min, 244 nm, retention time 16.3 min; found C, 59.85; H, 5.00; N, 4.30; $C_{16}H_{16}FNO_3S$ requires C, 59.80; H, 5.02; N, 4.36%.

4.4.11. Preparation of N*1*-(4-fluorophenyl)-N*1*-[2-(3-methyl-4-methylsulfonylphenyl)-2-oxoethyl]-2-phenylacetamide (5). To a solution of 2-(4-fluoroanilino)-1-(3-methyl-4-methylsulfonylphenyl)-1-ethanone (1.5 g, 4.67 mmol) in anhydrous THF (15 mL) was added phenacylchloride (0.72 g, 0.62 mmol) very slowly under nitrogen atmosphere at 25 °C. The mixture was stirred for 2 h and diluted with water (25 mL). The solid separated was filtered, washed with water (2×15 mL) followed by petroleum ether (2×5 mL) and dried under vacuum to give 1.6 g of the title compound in 78% yield, Low melting yellow solid; δ_H (200 MHz, $CDCl_3$) 8.12 (d, *J*=8.7 Hz, 1H), 7.89–7.86 (m, 2H), 7.32–7.23 (m, 5H), 7.10–7.01 (m, 4H), 5.03 (s, 2H, CH_2), 3.56 (s, 2H, CH_2), 3.08 (s, 3H, SO_2CH_3), 2.75 (s, 3H, CH_3); ν_{max} (KBr) 1698, 1660 cm^{-1}; MS (CI, *i*-Butane) *m/z* 440 (M+1, 100); ^{13}C NMR (50 MHz, DMSO-d_6): 193.03 (C═O), 171.32 (C═O), 164.51, 159.56, 146.66, 142.62, 138.90, 138.52, 138.29, 134.61, 131.96, 130.41, 130.24, 129.67, 128.87, 128.30, 126.67, 125.84, 116.70, 116.25, 56.60 (CH_2), 43.38 (CH_3SO_2), 40.56 (CH_2), 20.18 (CH_3); HPLC: 98%, Hichrom RPB (250×4.6 mm), 0.01 M KH_2PO_4/CH_3CN 0/40, 5/40, 20/80, 30/80, 35/40, 40/40, 1.0 mL/min, 243 nm, retention time 17.6 min; found C, 65.50; H, 5.01; N, 3.49; $C_{24}H_{22}$ FNO_4S requires C, 65.59; H, 5.05; N, 3.19%.

4.4.12. Preparation of 1-(4-fluorophenyl)-3-(3-methyl-4-methylsulfonylphenyl)-4-phenyl-2,5-dihydro-1*H*-2,5-azoledione (6). The title compound was prepared in 63% yield from *N*1-(4-fluorophenyl)-*N*1-[2-(3-methyl-4-methylsulfonylphenyl)-2-oxoethyl]-2-phenylacetamide (0.79 g, 1.58 mmol) using DBU (0.48 g, 1.58 mmol) according to the procedure described above (Method A). Light orange solid; mp>200 °C; δ_H (200 MHz, $CDCl_3$) 7.8–7.6 (m, 3H), 7.38–7.01 (m, 9H), 3.1 (s, 3H, SO_2CH_3), 2.58 (s, 3H, CH_3); IR (KBr, cm^{-1}) 1713, 1600, 1511; MS (CI, *i*-Butane) *m/z* 436 (M^+, 100); ^{13}C NMR (50 MHz, $CDCl_3$): 168.0 (C═O, 2C), 139.75, 138.11, 133.99, 133.85, 130.82, 130.82, 130.01 (2C), 129.54, 128.90 (2C), 128.05 (2C), 127.86, 124.46, 123.96, 119.09, 116.42, 116.12, 115.96, 43.61 (CH_3SO_2), 20.68 (CH_3); found C, 66.09; H, 4.18; N, 3.39; $C_{24}H_{18}FNO_4S$ requires C, 66.19; H, 4.17; N, 3.22%.

4.4.13. Preparation of 1-(4-fluorophenyl)-4-(3-methyl-4-methylsulfonylphenyl)-3-phenyl-2,5-dihydro-1*H*-2-azolone (7). The title compound was prepared in 69% yield from *N*1-(4-fluorophenyl)-*N*1-[2-(3-methyl-4-methylsulfonylphenyl)-2-oxoethyl]-2-phenylacetamide (1 g, 2.27 mmol) using K_2CO_3 (7.72 g, 3.40 mmol) in 1:1 EtOH–H_2O according to the procedure described above (Method A). White powder; mp 207–209 °C; δ_H (200 MHz, $CDCl_3$) 7.96 (d, *J*=8.4 Hz, 1H), 7.83–7.76 (m, 2H), 7.39–7.07 (m, 9H), 4.74 (s, 2H, CH_2), 3.09 (s, 3H, SO_2CH_3), 2.63 (s, 3H, CH_3); IR (KBr, cm^{-1}) 1680; MS (CI, *i*-Butane) *m/z* 421 (M^+, 100); ^{13}C NMR (50 MHz, DMSO-d_6): 168.64 (C═O), 161.9, 157.06, 144.33, 139.26, 138.21, 137.92, 135.94, 135.10, 131.63, 129.80, 129.44 (2C), 128.96, 128.70 (2C), 125.92, 120.75, 120.59, 116.13, 115.69, 52.70 (CH_2), 43.63 (CH_3SO_2), 20.29 (CH_3); HPLC: 98%, INERTSIL ODS 3V (250×4.6 mm), 0.01 M KH_2PO_4/CH_3CN 0/50, 5/50, 20/80, 30/80, 35/50, 40/50, 1.0 mL/min, 233 nm, retention time 17.6 min; found C, 68.29; H, 4.69; N, 3.49; $C_{24}H_{20}FNO_3S$ requires C, 68.39; H, 4.78; N, 3.32%.

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