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SeO_2-Mediated Ritter reaction of aryl methyl ketones catalyzed by boron trifluoride etherate at room temperature

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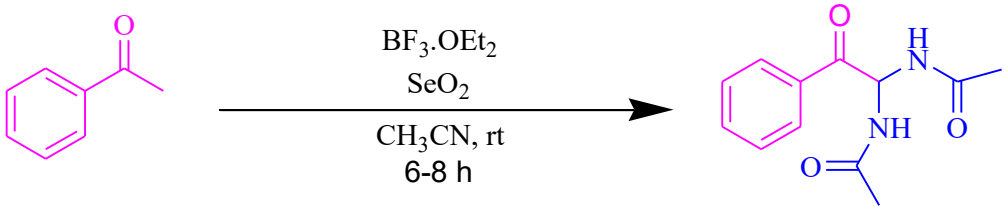
Abstract

A straightforward one-pot oxidative bis-amidation of aryl methyl ketones method has been developed. This method utilizes aryl/heteroaryl methyl ketones and SeO_2 in the presence of $BF_3.Et_2O$ in acetonitrile at room temperature. This protocol provides the desired products in moderate to good yields and tolerates a broad substrate scope. The products are isolated in a simple procedure and purified by recrystallization. No chromatography is required.



● One-pot ● 16 examples ● Mild reaction conditions ● Yield upto 80%

Keywords: Bis-amidation, Selenium dioxide, Acetonitrile, $BF_3.Et_2O$, Ritter reaction

Introduction

Ketoamides are an important class of functionality of various bioactive molecules [1,2] (anti-tumor anti-HIV, anti-bacterial), agrochemicals (FK506) and Pharmaceuticals (enzyme inhibitors, rapamycin).[3-5] Aryl ketoamide derivatives also serve as useful intermediates in drug discovery and medicinal chemistry.[6-9] Some of the representative structures include paracetamol, colchicines, antiarrhythmic agent, potential neuroleptic agents.[10-19] Based on their pharmacological relevance, a wide variety of synthetic methodologies has been been developed to access them. Among these methods first classical approach to the preparation of N-alkyl amides is the Ritter reaction resembles to the conversion of nitriles into N-alkyl amides. The preparation of N-mono substituted amides from olefins or tertiary alcohols in the presence of acids, through the electrophilic alkylation of nitriles with carbenium ions.[20-35] However, these reactions have some limitations, because of bulky group of alcohols such as benzylic alcohols and adamentyl carbinols to generate stable ions.[36-38] Versatility of this reaction gives enhanced features due to its high atom efficiency and are to synthesize the different biologically active molecules, especially those bearing bulky amides.[39-42]

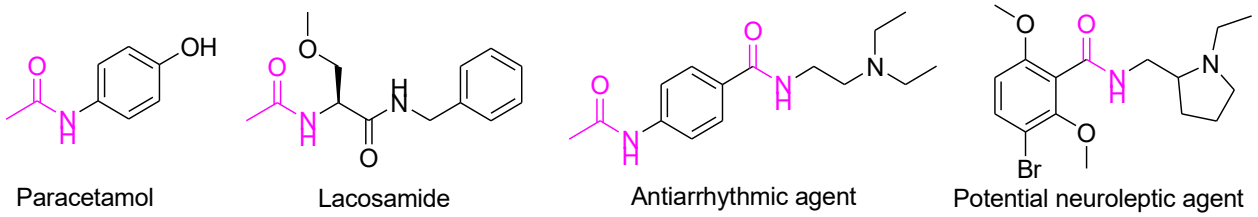
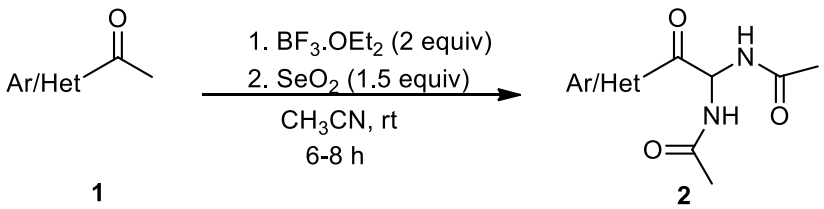


Figure 1. Examples of molecules containing an amide group.

Literature survey reveals that aldehydes can react with acetonitrile to generate the cyanomethylation products using metals/acidic conditions.[20-32,43] Nevertheless, there is no report on the reaction of different aldehydes with acetonitrile to contribute directly in the classic Ritter reaction.[20-32] Recently Khan *et al* reported mono and di Ritter products using 2-oxoaldehydes under acidic environment at room temperature was successfully developed.[44] Thus, there remains the need to develop efficient and economical methodologies for elaborating Ketoamide derivatives under mild conditions.

The use of selenium dioxide as a mediator has also been reported in the conversion of arylglyoxals to α-Ketoamides.[45] Selenium dioxide as a common oxidant has also been reported in the conversion of methyl aryl ketones to arylglyoxals.[46,47] Based on the above points, it was reasoned to explore SeO_2 for the oxidative bis-amidation of aryl methyl ketones (acetophenones) at room temperature.

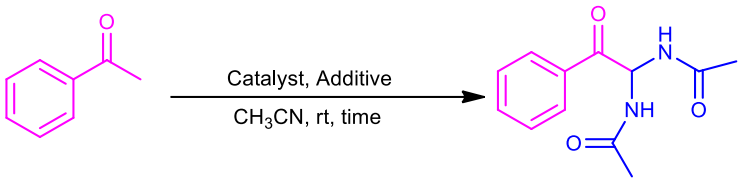


Scheme 1. Synthesis of oxidative bis-amidation of aryl methyl ketones.

Results and Discussion

To test our hypothesis, we scrutinized the model reaction of acetophenones and acetonitrile. The use of acetophenone (**1a**, 1 equiv), and SeO_2 (1 equiv) were treated with PTSA, $FeCl_3$, CuOTf in dry acetonitrile, the desired product was not observed (Table 1, entries 1-3). Whereas treated with BF_3 Et_2O (0.5 equiv) in dry acetonitrile exclusively generated the di-Ritter product **2a** in 40% yield at room temperature (Table 1, entry 4). We subsequently investigated the effect of different amounts of BF_3 Et_2O and SeO_2 on the reaction outcome, finding that 1.5 equiv of SeO_2 gave the optimum yield (Table 1, entries 4–10). Moreover, results suggested that reaction times were shortened by increasing the amount of SeO_2 (entries 8-10). There was no improvement in the results in excess amount of SeO_2 comparable isolated yields (entries 9, 10). The reaction did not proceed in without dry acetonitrile.

Table 1. Optimization of reaction parameters for the synthesis of bis-amidation of aryl methyl ketones[a]



1a **2a**

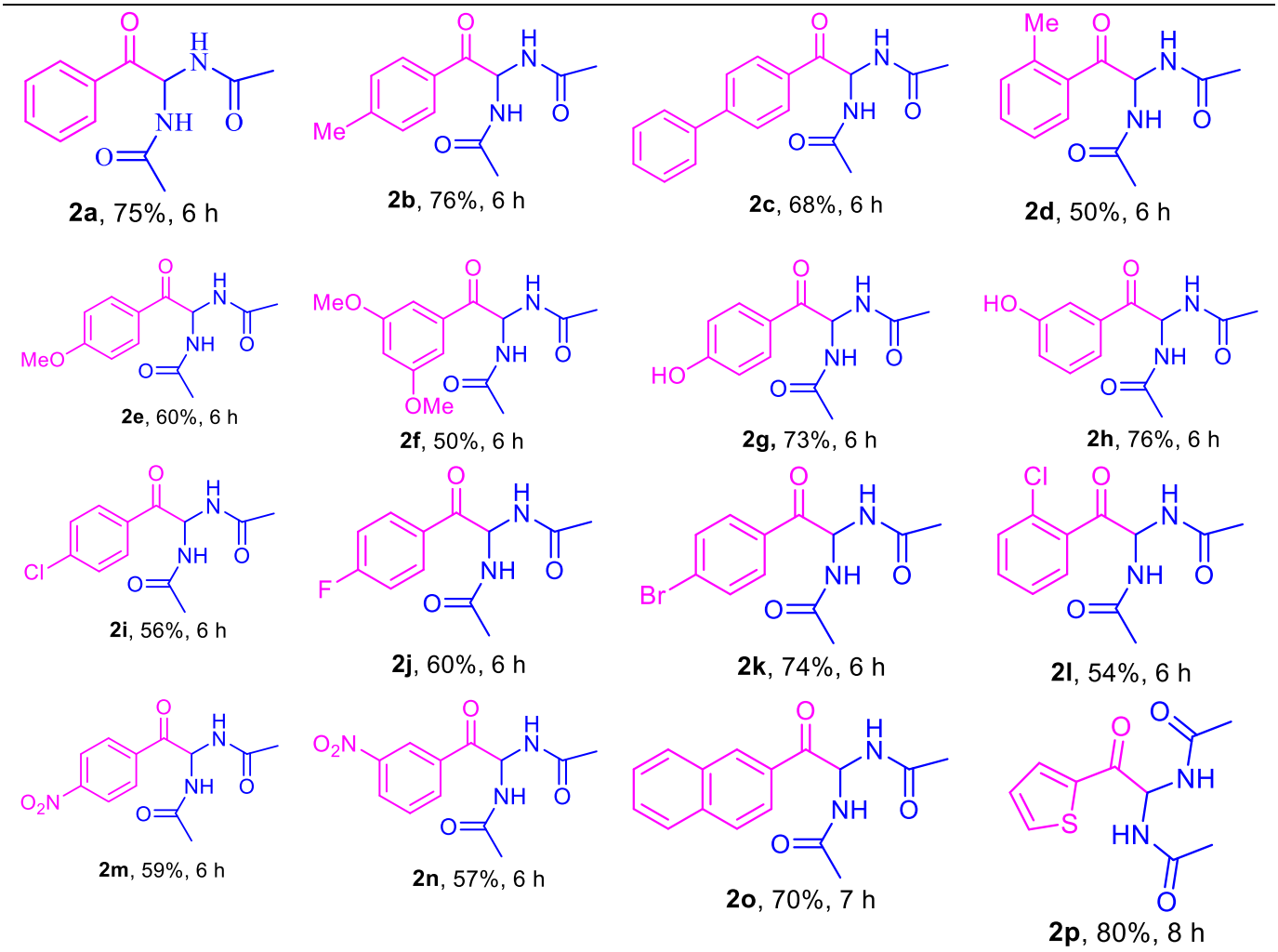
Entry	Catalyst	Additive	Time (h)	Yield (%)[b]
1.	PTSA (0.2 equiv)	SeO_2 (1 equiv)	10	-
2.	$FeCl_3$ (0.2 equiv)	SeO_2 (1 equiv)	10	-
3.	CuOTf (0.2 equiv)	SeO_2 (1 equiv)	10	-
4.	BF_3OEt_2 (0.5 equiv)	SeO_2 (1 equiv)	10	40
5.	BF_3OEt_2 (1 equiv)	SeO_2 (1 equiv)	8	58
6.	BF_3OEt_2 (2 equiv)	SeO_2 (1 equiv)	8	70
7.	BF_3OEt_2 (2 equiv)	SeO_2 (0.5 equiv)	8	60
8.	BF_3OEt_2 (2 equiv)	SeO_2 (1.5 equiv)	6	75
9.	BF_3OEt_2 (2 equiv)	SeO_2 (1.7 equiv)	6	76
10.	BF_3OEt_2 (2 equiv)	SeO_2 (2 equiv)	6	76

[a]Reaction conditions: Acetophenone (1 mmol), SeO_2 (1.5 mmol) and BF_3OEt_2 (2 mmol) in 3mL dry acetonitrile. [b]Isolated yield.

Having the optimized conditions, a wide variety of substituted aromatic/hetroaryl ketones containing both electron-donating and electron-withdrawing groups was submitted to investigate the substrate generality. As shown in Table 2, firstly aromatic ketones substituted with electron-neutral groups at para position such as *p*-CH_3 and *p*-phenyl acetophenone gave the targeted products in good yields (Table 2, **2b-c**, 68-76%). In case of ortho substituted electron neutral group such as *o*-CH_3 furnished the corresponding α-ketoamides in low yield (Table 2, **2d**, 50%). Alternatively, the acetophenones with an electron-donating group at the para-position such as *p*-methoxy and 2,5-dimethaoxy provided the corresponding *α*-ketoamides in lower yields (Table 2, **2e-f,** 50-60%). Surprisingly hydroxyl groups present at the meta, para positions gave yields of the corresponding α-ketoamides 73, 76% respectively in good yields (Table 2, **2g-h**). Whereas *α*-ketoamides with an electron-withdrawing group at the para-position such as *p*-Cl, *p*-F, and *p*-Br was achieved moderate to good yields (Table 2, **2i-k,** 56-74%). We also studied the effect of electron-withdrawing

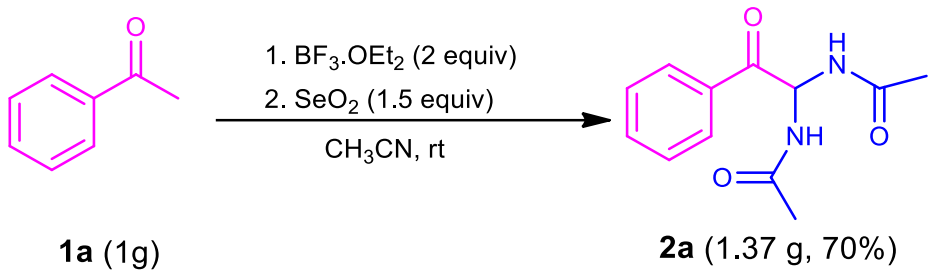
substituents at the ortho-position. Ortho electron-withdrawing substituted acetophenone gave lower yield of the desired product compared to that of unsubstituted analogue (Table 2, **2l**, 54%). Interestingly, electron poor aromatic ketones such as 4-nitro acetophenone, and 3-nitro acetophenone also furnished *α*-ketoamides in moderate yields (Table 2, **2m-n,** 57-59%). The scope of this methodology was further extended to the reaction of heteroaryl or fused aromatic methyl ketones were observed. We observed the highly noteworthy of the performance of 2-acetyl thiophene (**2p**) in this sequence, which gave good yield 80% (Table 2) while heteroaryl such as 2-acetyl napthanone (**2o**) afforded ketoamides in 70% yields (Table 2). It is worth noting that neither aromatic ketones nor heteroaryl ketones yield the corresponding ketoamide products under these standard reaction conditions.

Table 2. Substrate scope[a]



[a]Reaction conditions: **1** (1 mmol), $BF_3.OEt_2$ (2 mmol), SeO_2 (1.5 mmol), 3 mL of CH_3CN, rt. [b] Isolated yield.

In continuation, we successfully performed the reaction with acetophenone **1a** on a 1 gram scale (Scheme 2) which we observed to work well too.



Scheme 2. Gram scale synthesis.

Unambiguously, the structure of the compound **2l** was confirmed by single-crystal X-ray analysis (Fig. 2). All the compounds are stable solid compounds, and their structures were established by IR, ^{1}H NMR, ^{13}C NMR, and mass spectroscopy. The structure of N,N'-(2-(2-chlorophenyl)-2-oxoethane-1,1-diyl)diacetamide (**2l**) was unambiguously proved by X-ray single-crystal studies (Figure 2).

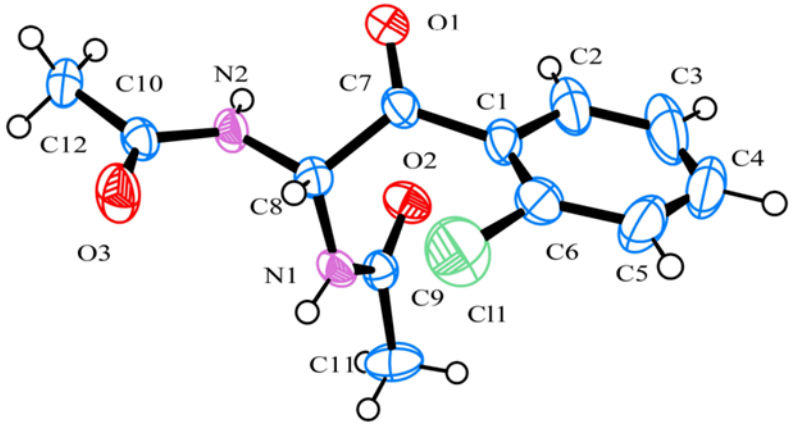
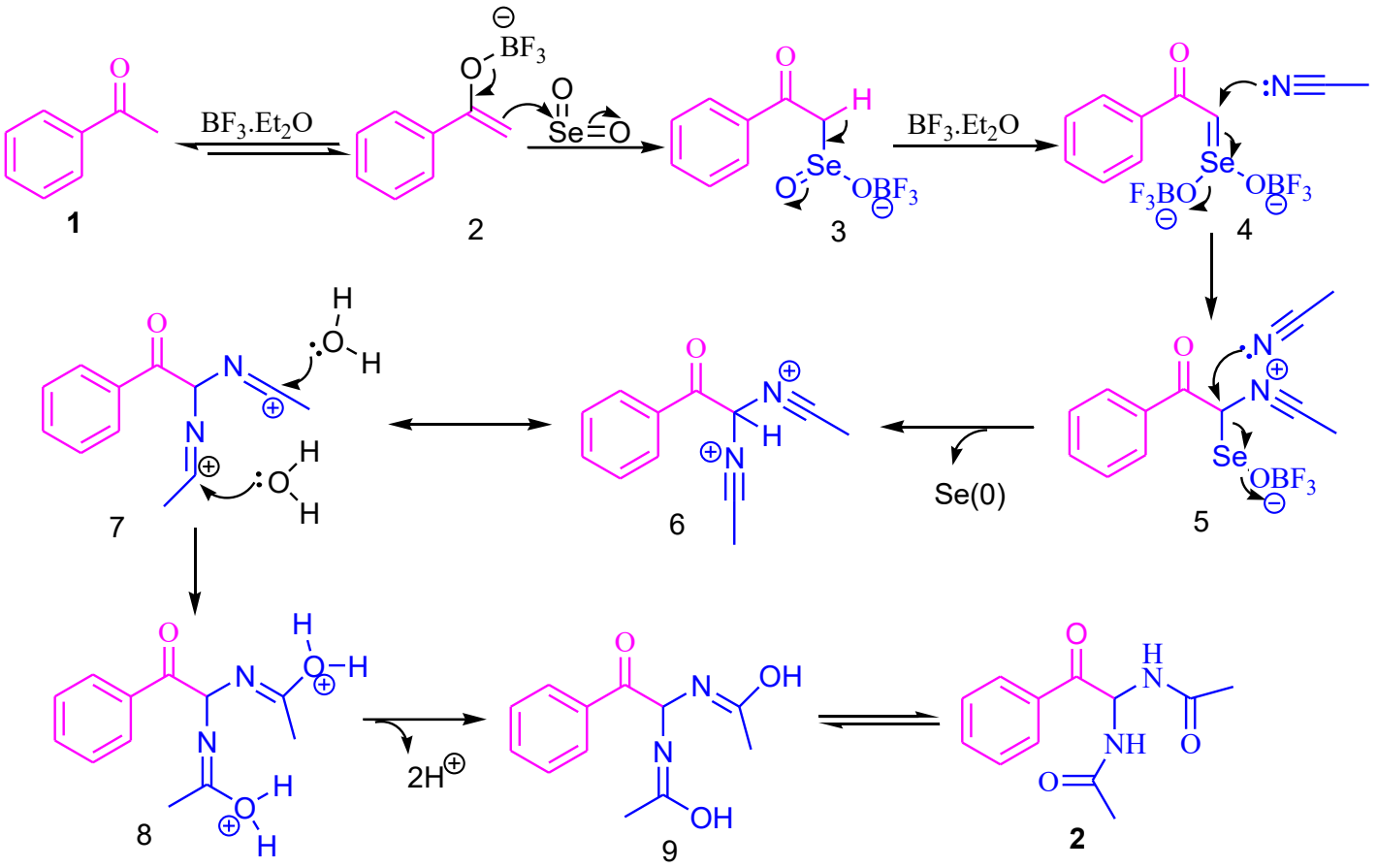


Figure 2. ORTEP image of **2l** (CCDC 2386688).

From a mechanistic point of view based on the observations and literature studies, a tentative mechanism for the formation of di-Ritter product is presented in Scheme **3**. Initially the enolization of the ketone **1** in the presence of BF_3 Et_2O followed by the reaction with SeO_2 to generate the selenium intermediate **3**. The activating effect of the keto group generates a strong electrophilic center at the α-carbon of **4**. In the presence of SeO_2 promotes the activation of acetonitrile that ultimately leads to the generation of resonance stabilized corresponding nitrilium ion. The resulting nitrilium ion is then hydrolyzed by water to get the desired di-Ritter product.



Scheme 3. A plausible reaction mechanism.

Conclusions

In summary, we have developed an efficient, atom economical, novel amidation method for the synthesis of di-Ritter product using aromatic/hetroaryl ketones via the SeO_2 mediated catalyzed by boron trifluoride etherate at ambient temperate. The reactions proceeded smoothly with a broad range of substrates, and the scale up procedure for the generation of was demonstrated. High yields, low cost and mild reaction conditions are the main advantages of this method.

Experimental Section

General. ^{1}H, ^{13}C and Nuclear Magnetic Resonance (NMR) spectra were obtained on a BRUKER AVANCE-II 400 MHz instrument using $CDCl_3$ or DMSO-d_6 as the solvent. Chemical shifts were reported as δ values in parts per million (ppm) relative to the solvent. Infrared (IR) spectra were recorded on a perkin-Elmer Spectrum one FTIR spectrometer in ATR mode and wave lengths (ν_{max}) are reported in cm^{-1}. All reactions were performed under the inert condition. Analytical thin layer chromatography (TLC) was performed on Merck aluminium-backed 60 F 254 silica plates visualized with UV light. The structures of compounds for known compounds were confirmed by associating spectroscopic data with reported literature values. HRMS analysis (for novel

compounds) was carried out using a BRUKER Impact HD mass spectrometer UHR-TOF, ESI with positive mode. Melting points were recorded using a SRSEZ-Melt automated melting point apparatus by capillary methods.

General procedure for the preparation of N,N'-(2-oxo-2-phenylethane-1,1-diyl)diacetamide. To a mixture of 1 mmol aryl (hetro) methyl ketones, in dry acetonitrile (3mL) and SeO_2 (1.5 mmol, 164 mg) were taken in 50 ml round bottom flask was stirred in an ice salt mixture (-5°C) followed by the drop wise addition of $BF_3.Et_2O$ (2 mmol, 0.5 mL), The reaction mixture was then allowed to stir for a period of the time till the completion of the reaction (monitoring by the TLC). After completion of the reaction, the reaction mixture was diluted with ethyl acetate (50 mL), and filtered through celite bed. The combined filtrate was washed with saturated aqueous sodium hydrogen carbonate solution, water (10 mL), and brine (10 mL). The combined organic layers were then dried with anhydrous sodium sulphate and concentrated under reduced pressure. Finely, the products were recrystallized from methanol to obtain pure products.

***N,N'*-(2-Oxo-2-phenylethane-1,1-diyl)diacetamide(2a).** White solid, 75% yield (165 mg), Melting point 211-212 °C (lit mp 211-214)[44]; IR ν_{max} (Neat): 3307, 3280, 1661, 1554, 1513, 1449, 1364, 1131, 1071, 831 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.99 (d, *J* = 7.8 Hz, 2H), 7.58 (t, *J* = 14.7, 7.6 Hz,1H), 7.46 (t, *J* = 15.4, 7.7 Hz, 2H), 7.36 (d, *J* = 5.3, Hz, 2H), 6.20 (t, *J* = 13, 6.5 Hz, 1H), 1.98 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 192.46, 170.36, 133.96, 133.66, 128.61, 59.42, 22.88; MS (ESI): *m/z* = 235.1 $[M+H]^+$.

***N,N'*-(2-Oxo-2-(p-tolyl)ethane-1,1-diyl)diacetamide(2b).** White solid; 76% yield (188 mg); Melting point 243-245°C(ref = 243-246)[44]; IR ν_{max}(Neat): 3310, 3277, 1662, 1508, 1367, 1125, 751cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.90 (d, *J* = 8.2, 2H), 7.26-7.25 (m, 2H), 6.21 (t, *J* = 13.2, 6.6 Hz, 2H), 4.78 (s, 2H), 2.41 (s, 3H), 1.97 (s, 6H);^{13}C NMR ($CDCl_3$, 100 MHz) δ: 192.06, 170.19, 144.60, 129.34, 128.77, 59.16, 22.91, 21.73;MS (ESI): *m/z* = 249.12 $[M+H]^+$.

***N,N'*-(2-([1,1'-Biphenyl]-4-yl)-2-oxoethane-1,1-diyl)diacetamide(2c).** White solid. 68% yield (212 mg); Melting point (ref = 258-260°C)[39]; IR ν_{max}(Neat): 3341, 3317, 3300, 1661, 1648, 1603, 1200, 1100, 732 cm^{-1};^1H NMR ($CDCl_3$, 400 MHz) δ: 8.07 (d, *J* = 7.8 Hz, 2H), 7.68 (d, *J* = 7.8 Hz, 2H), 7.64-7.61 (m, 3H), 7.49-7.46 (m, 2H), 7.43-7.39 (m, 2H), 6.22 (t, *J* = 13.1, 6.5 Hz,1H), 2.00 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ:195.00, 170.18, 146.24, 139.51, 133.88, 129.46, 128.98, 128.38, 127.34, 127.26, 34.12, 22.95; ESI-HRMS: Anal. Calcd for $C_{18}H_{18}N_2O_3$: 333.1210, Found: 333.1214 $[M+Na]^+$.

***N,N'*-(2-Oxo-2-(o-tolyl)ethane-1,1-diyl)diacetamide(2d).** White solid. 50% yield (125 mg); Melting point 230-232 °C; IR ν_{max}(Neat): 3337, 3067, 1709, 1648, 1500, 1371, 1290, 1127, 746, cm^{-1};^1H NMR ($CDCl_3$, 400 MHz) δ: 7.53 (d, *J* = 7.6Hz, 1H), 7.40-7.37 (m, 1H), 7.29-7.28 (m, 1H), 7.24-7.20 (m, 3H), 5.97 (t, *J* = 12.4, 6.2 Hz, 2H), 2.54 (s, 3H), 1.93 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ:194.60, 170.57, 140.25, 133.50, 132.23, 131.76, 127.89, 125.01, 60.53, 22.72, 20.65; ESI-HRMS: Anal. Calcd for $C_{13}H_{16}N_2O_3$: 271.1053, Found: 271.1059 $[M+Na]^+$.

***N,N'*-(2-(4-Methoxyphenyl)-2-oxoethane-1,1-diyl)diacetamide(2e).** White solid. 60% yield (159 mg); Melting point 251-254 °C (ref = 251-255)[44];IR ν_{max}(Neat): 3314, 3270, 1662, 1601,1513, 1368, 1268, 516 cm^{-1};^1H NMR ($CDCl_3$, 400 MHz) δ: 8.02 (d, *J* = 8.8 Hz, 2H), 7.13 (s, 2H), 6.94 (d, *J* = 8.8 Hz,2H), 6.29 (t, *J* = 13.4, 6.7 Hz, 1H), 3.87 (s, 1H), 1.98 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ:170.00, 164.17, 131.16, 113.97, 58.67, 56.51, 22.96; MS (ESI): *m/z* = 287.1 $[M+Na]^+$.

***N,N'*-(2-(2,*5*-Dimethoxyphenyl)-2-oxoethane-1,1-diyl)diacetamide(2f).** White solid. 50% yield (148 mg); Melting point 184-186 °C;IR ν_{max}(Neat): 3273, 2939, 1685, 1633, 1496, 1297, 1175, 1016, 722 cm^{-1};^1H NMR (DMSO-d_6, 400 MHz) δ: 8.65 (d, *J* = 7.6 Hz,2H), 7.09-7.02 (m, 2H), 6.93 (d, *J* = 2.9 Hz, 1H),6.20 (t, *J* = 15.2, 7.6 Hz, 1H), 3.78 (s, 3H), 3.71 (s, 3H), 1.77 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 196.49, 169.92, 153.14, 151.97, 127.34, 118.84, 115.42, 113.50, 62.11, 56.88, 55.99, 22.55; ESI-HRMS: Anal. Calcd for $C_{14}H_{18}N_2O_5$: 317.1108, Found: 317.1099 $[M+Na]^+$.

***N,N'*-(2-(4-Hydroxyphenyl)-2-oxoethane-1,1-diyl)diacetamide(2g).** White solid. 73% yield (182 mg); Melting point 199-201 °C(ref = 198-203)[44]**;**IR ν_{max}(Neat): 3371, 3283, 1652, 1574, 1516, 1172, 1023, 989 cm^{-1};^{1}H NMR (DMSO-d_6, 400 MHz) δ: 10.48 (s, 1H), 8.62 (d, *J* = 7.8 Hz, 2H), 7.81 (d, *J* = 7.3 Hz, 2H), 6.85 (d, *J* = 8.4 Hz, 2H), 6.59 (t, *J* = 15.6, 7.6 Hz, 3H), 1.84 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 191.86, 169.50, 162.92, 131.27, 125.94, 115.84, 57.58, 22.75;MS (ESI): *m/z* = 251.10$[M+H]^+$.

***N,N'*-(2-*(3*-Hydroxyphenyl)-2-oxoethane-1,1-diyl)diacetamide(2h).** White solid. 76% yield (190 mg); Melting point 214-216 °C**;** IR ν_{max}(Neat): 3459, 3280, 1664, 1558, 1450, 1368, 1310, 1270, 881, 678cm^{-1};^{1}H NMR (DMSO-d_6, 400 MHz) δ: 9.84 (s, 1H), 8.69 (d, *J* = 7.6 Hz, 2H), 7.30-7.32 (m, 3H),7.02(m, 1H), 6.50 (t, *J* = 15.4, 7.7 Hz,1H), 1.83 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ:193.66, 169.71, 157.97, 136.13, 130.19, 121.06, 119.38, 115.01, 58.28, 22.69; ESI-HRMS: Anal. Calcd for $C_{12}H_{14}N_2O_4$: 273.0846, Found: 273.0846 $[M+Na]^+$.

***N,N'*-(2-(4-Chlorophenyl)-2-oxoethane-1,1-diyl)diacetamide(2i).** White solid. 56% yield (150 mg); Melting point 258-260 °C(ref = 258-262)[44]**;**IR ν_{max}(Neat): 3324, 3300, 1696, 1650, 1516, 1139, 762 cm^{-1};^{1}H NMR (DMSO-d_6, 400 MHz) δ: 8.80 (d, *J* = 7.5 Hz, 2H), 7.88 (d, *J* = 8.5 Hz, 2H), 7.60 (d, *J* = 8.5 Hz, 2H), 6.45 (t, *J* = 15.1, 7.5 Hz, 1H), 1.83 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 193.44, 169.75, 138.14, 138.06, 134.31, 130.75, 130.16, 126.76, 58.57, 22.66; MS (ESI): *m/z* = 291.05$[M+Na]^+$.

***N,N'*-(2-(4-Fluorophenyl)-2-oxoethane-1,1-diyl)diacetamide(2j).** White solid. 60% yield (151 mg); Melting point 251-253 °C(ref = 249-253)[44]**;**IR ν_{max}(Neat): 3317, 3270, 1661, 1598, 1510, 1371, 1216, 859 cm^{-1};^{1}H NMR (DMSO-d_6, 400 MHz) δ: 8.78 (d, *J* = 7.6 Hz, 2H), 7.98-7.95 (m, 2H), 7.38-7.34 (m, 2H), 6.50 (t, *J* = 15.2, 7.6 Hz, 1H), 1.84 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6)δ: 192.44, 169.73, 131.54, 131.45, 116.34, 116.12, 58.48, 22.65;MS (ESI): *m/z* = 253$[M+H]^+$.

***N,N'*-(2-(4-Bromophenyl)-2-oxoethane-1,1-diyl)diacetamide(2k).** White solid. 74% yield (230 mg); Melting point 253-256 °C(ref = 253-256)[44]**;**IR ν_{max}(Neat): 3307, 1692, 1647, 1516, 1314, 1131, 1003, 800cm^{-1};^{1}H NMR ($CDCl_3$+DMSO-d_6, 400 MHz) δ: 8.36 (d, *J* = 7.3 Hz, 2H),7.81 (d, *J* = 8.5 Hz, 2H), 7.51(d, *J* = 8.5 Hz, 2H), 6.34(t, *J* = 15.1, 7.6 Hz, 1H), 1.85 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6) δ: 190.13, 167.154, 130.84, 129.23, 127.72, 125.68, 56.04, 20.17;MS (ESI): *m/z* = 334.99$[M+Na]^+$.

***N,N'*-(2-(2-Chlorophenyl)-2-oxoethane-1,1-diyl)diacetamide(2l).** White solid. 54% yield (145 mg); Melting point 192-194 °C**;**IR ν_{max}(Neat): 3341, 3239, 1716, 1634, 1504, 1371, 1302, 1137, 743 cm^{-1};^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.57-7.56 (m, 1H), 7.41-7.39 (m, 2H), 7.34-7.27 (m, 3H), 6.21(t, *J* = 12.7, 6.3 Hz, 1H), 1.93 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ:195.74, 170.80, 135.96, 132.22, 131.05, 130.59, 129.86, 126.94, 62.27, 22.63; ESI-HRMS: Anal. Calcd for $C_{12}H_{13}ClN_2O_3$: 291.0507, Found: 291.0510 $[M+Na]^+$.

***N,N'*-(2-(4-Nitrophenyl)-2-oxoethane-1,1-diyl)diacetamide(2m**). White solid. 59% yield (164 mg); Melting point (ref = 237-239 °C)[40]**;** IR ν_{max}(Neat): 3282, 3200, 1668, 1610, 1580, 1300, 1036, 786 cm^{-1};^{1}H NMR ($CDCl_3$+DMSO-d_6, 400 MHz) δ: 8.56 (d, *J* = 6.7 Hz, 2H), 8.27 (d, *J* = 8.8 Hz, 2H), 8.16 (d, *J* = 8.8 Hz, 2H), 6.36 (t, *J* = 14.6, 7.3 Hz, 1H), 1.93 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6) δ:190.03, 167.88, 147.58, 137.35, 127.07, 120.96, 56.85, 20.05; ESI-HRMS: Anal. Calcd for $C_{12}H_{13}N_3O_5$: 302.0747, Found: 302.0748 $[M+Na]^+$.

***N,N'*-(2-(3-Nitrophenyl)-2-oxoethane-1,1-diyl)diacetamide(2n).** White solid. 57% yield (158 mg); Melting point 232-234 °C**;**IR ν_{max}(Neat): 3290, 1663, 1646, 1527, 1342, 1141, 1020, 723 cm^{-1};^{1}H NMR ($CDCl_3$+DMSO-d_6, 400 MHz) δ: 8.82(s, 1H), 8.41-8.36 (m, 4H), 7.70-7.66 (m, 1H), 6.34-6.31 (m, 1H), 1.96 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6) δ:191.67, 170.59, 148.45, 135.98, 134.23, 129.79, 127.29, 123.33, 59.37, 22.60;ESI-HRMS: Anal. Calcd for $C_{12}H_{13}N_3O_5$: 302.0747, Found: 302.0748 $[M+Na]^+$.

***N,N'*-(2-(Naphthalen-2-yl)-2-oxoethane-1,1-diyl)diacetamide(2o).** White solid. 70% yield (200 mg); Melting point (ref = 186-188 °C)[39]; IR ν_{max}(Neat): 3287, 1642, 1521, 1308, 1122, 745 cm^{-1};^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.57 (s, 1H), 8.02 (dd, *J* = 10.4, 1.8 Hz,1H), 7.96 (d, *J* = 8.1Hz, 1H), 7.91-7.86 (m, 2H), 7.64-7.60 (m, 1H), 7.57-7.55 (m, 1H), 7.40 (d, *J* = 5.6 Hz, 2H), 6.38 (t, *J* = 13.4, 6.5 Hz, 1H), 1.99 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ:

192.35, 170.38, 142.26, 135.84, 133.89, 132.31, 131.82, 131.19, 130.40, 129.77, 128.85, 128.56, 127.79, 126.92, 124.16, 59.39, 22.91; ESI-HRMS: Anal. Calcd for $C_{16}H_{16}N_2O_3$: 307.1053, Found: 307.1054 $[M+Na]^+$.

***N,N'*-(2-Oxo-2-(thiophen-2-yl)ethane-1,1-diyl)diacetamide(2p).** White solid. 80% yield (191 mg); Melting point 262-264 °C(ref = 260-264)[44];IR ν_{max}(Neat): 3300, 3283, 1644, 1540, 1365, 1141, 735cm^{-1};^{1}H NMR (DMSO-d_6, 400 MHz) δ: 8.79(d, *J* = 7.7 Hz, 2H), 8.04 (d, *J* = 4.8 Hz, 1H), 7.87(d, *J* = 3.6 Hz, 1H), 7.25(t, *J* = 8.9, 4.5 Hz, 1H), 6.42 (t, *J* = 15.4, 7.7 Hz,1H), 1.86 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ:186.82, 169.79, 140.94, 135.79, 133.47, 129.23, 59.07, 22.75;MS (ESI): *m/z* = 263.05$[M+Na]^+$.

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Supplementary Material

^{1}H NMR, ^{13}C NMR and Single Crystal-XRD analysis are facilitiesd in the Supplementary Information file.

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