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ortho-Amidoalkylation of Phenols via Tandem One-Pot Approach Involving Oxazine Intermediate

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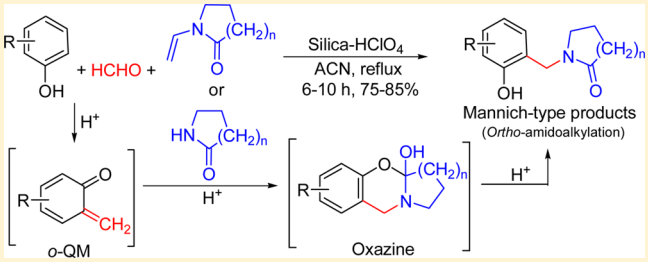
Supporting Information

ABSTRACT: A new and efficient method for *ortho*-amidoalkylation of phenols via Mannich-type condensation with formaldehyde and lactams using recyclable solid acid catalyst is described. This is the first report for *ortho*-amidoalkylation of phenols by lactams via Mannich-type condensation. LC-ESI-MS/MS based mechanistic study revealed that reaction proceeds through *o*-quinone methide (*o*-QM) and an oxazine intermediate via tandem Knoevenagel condensation, formal [4 + 2]-Diels–Alder cycloaddition and acid catalyzed oxazine ring-opening.



Mannich reaction is one-pot multicomponent approach for aminoalkylation of enolizable CH-acidic substrates. It is one of the most widely used reactions in synthetic and medicinal chemistry,[1−4] and its utility in asymmetric synthesis of α- and β-amino acids[2] and complex natural products[5] has been reported. Further, Mannich bases and derivatives are versatile synthetic intermediates and are employed in diverse types of organic transformations.[6] The reaction tolerates diversity of reactants such as ammonia, primary or secondary aliphatic as well as aromatic amines and active hydrogen components such as ketones, esters, α-alkyl pyridines as well as electron-rich aromatics.[4] Although several variations of this reaction are published,[3,7] its utility for cyclic *ortho*-amidoalkylation of phenols has never been reported. In the present paper, we discovered new simple and efficient protocol for *ortho*-amidoalkylation of phenols using modified Mannich reaction.

Amidoalkylation is a useful variation of classical Mannich reaction, wherein amine precursor is replaced with amide.[8,9] The reaction has great utility for synthesis of versatile synthons in total synthesis of alkaloids,[9] for example, pyrrolidinone/piperidinone class of alkaloids, that widely occur in nature.[10] Primarily two types of amidoalkylation protocols are known viz. acid-catalyzed and metal catalyzed electrophilic substitution reactions. Acid catalyzed protocols involve the use of various amidomethyl electrophiles[11] in the presence of acidic catalysts such as H_2SO_4, HCl, TFA, methanesulfonic acid or Lewis acid. Metal-catalyzed protocols include dinuclear Zn-catalyzed sulfonamidoalkylation,[12] $Ru(bpy)_3Cl_2$ catalyzed amidoalkylation of electron-rich aromatics,[13] bismuth(III) triflate catalyzed amidoalkylation of α-acetoxy lactams using allyltrimethylsilane nucleophile[14] and SmI_3 catalyzed amidoalkylation of 1,3-dicarbonyl compounds.[8] Poor substrate scope and harsh reaction conditions of available amidoalkylation protocols necessitates development of an efficient, widely applicable, diversity oriented protocol.

In continuation to our recent methodology[15] for one-pot multicomponent synthesis of flavans directly from phenolic precursors, we observed formation of Mannich-type product $\mathbf{1a_2}$ when 2,4-diformyl phloroglucinol (**2a**) was treated with *N*-vinyl caprolactam (**3a**) and formaldehyde (**4**) in presence of silica–$HClO_4$ (50 mol %) in acetonitrile as depicted in Figure 1. On the basis of our flavan protocol, we expected formation of 2-caprolactam linked benzopyran product $\mathbf{1a_1}$; however, Mannich-type product $\mathbf{1a_2}$ was obtained.

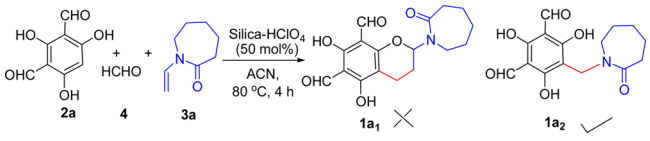


Figure 1. Reaction of 2,4-diformyl phloroglucinol (**2a**) with formaldehyde (**4**) and *N*-vinyl caprolactam (**3a**).

Formation of Mannich-type of product $\mathbf{1a_2}$ indicated that the reaction sequence must be involving devinylation of *N*-vinyl-caprolactam (**3a**) followed by Mannich-type of condensation. Thus, first we sought to investigate reaction conditions essential for devinylation for which control experiments shown in Table 1 were performed. It was interesting to observe that no thermal degradation occurred in presence of only acetonitrile (entry 1)

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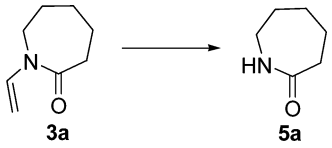
Table 1. Investigation of Reaction Conditions for Devinylation



3a 5a

entry	reaction conditions	time (h)	% yield of 9a[a]
1	ACN, 80 °C	4	0[b]
2	ACN, HCHO, 80 °C	4	0[b]
3	ACN, Silica–$HClO_4$, 80 °C	2	70
4	ACN, Silica–$HClO_4$, rt	6	0[b]

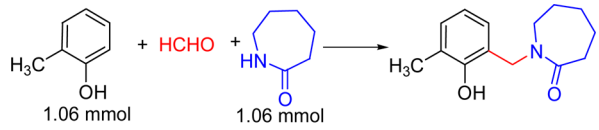
[a]GC–MS yield. [b]Unreacted starting material **3a** was recovered.

or with formaldehyde and acetonitrile (entry 2). However, when *N*-vinyl caprolactam (**3a**) was heated in presence of silica–$HClO_4$ in acetonitrile at 80 °C, caprolactam (**5a**) was formed in 70% yield. These results indicated that devinylation occurs only under acidic conditions. Further optimization revealed that presence of silica–$HClO_4$ catalyst as well as heating condition is required for devinylation.

After investigating devinylation of *N*-vinyl lactam, we then looked at the substrate scope of *tandem* three-component devinylation followed by Mannich-type condensation reaction by varying vinyl caprolactam as well as phenolic precursors (Figure 2). Like *N*-vinyl caprolactam (**3a**), *N*-vinyl pyrrolidinone (**3b**) also participated well in this reaction (products **1f** and **1i**). Diacyl phloroglucinols **2b–2e** produced corresponding Mannich-type products **1b–1f** in good yields. Next, we studied this reaction for phenol and *ortho*-substituted phenols, which produced the corresponding Mannich products $\mathbf{1g_1}$, **1h** and **1i** in good yields. *o*-Cresol showed better reactivity compared to phenol. Earlier, Bieräugel et al.[16] prepared compound $\mathbf{1g_1}$ in 7-steps starting from salicylaldehyde, as key precursor to synthesize corresponding lactam.

Further, we investigated whether the reaction proceeds simply with the use of caprolactam (**5a**) instead of *N*-vinyl caprolactam (**3a**). Reaction of *ortho*-cresol (**2g**) with caprolactam (**5a**) and formaldehyde (**4**) in presence of silica–$HClO_4$ in acetonitrile produced Mannich-type product **1h** in 85% yield (Table 2, entry 1). This result further

Table 2. Optimization of Reaction Conditions for Mannich-Type Reaction



1.06 mmol 2g 4 1.06 mmol 5a 1h

entry	solvent	catalyst	temp (°C)	time (h)	yield (%)[a]
1	MeCN	Silica–$HClO_4$	80	6	85
2	DMSO	none	100	6	0
3	MeOH	none	80	6	0
4	MeOH:H_2O (1:1)	none	80	6	0
5	MeCN	none	80	6	0
6	MeOH:H_2O (1:1)	Silica–$HClO_4$	90	6	0
7	MeCN:H_2O (1:1)	Silica–$HClO_4$	90	6	<5
8	Acetic acid	Acetic acid/ CH_3COONa	80	10	<10

[a]Isolated yields after silica gel (#100–200) column chromatography.

supported our assumption that devinylation occurs before Mannich-type condensation. Solvents commonly employed in classical Mannich reaction were not found suitable for amidoalkylation (entries 2–5). When the reaction was performed in the presence of acetic acid/sodium acetate (entry 8), the desired Mannich-type product was formed,

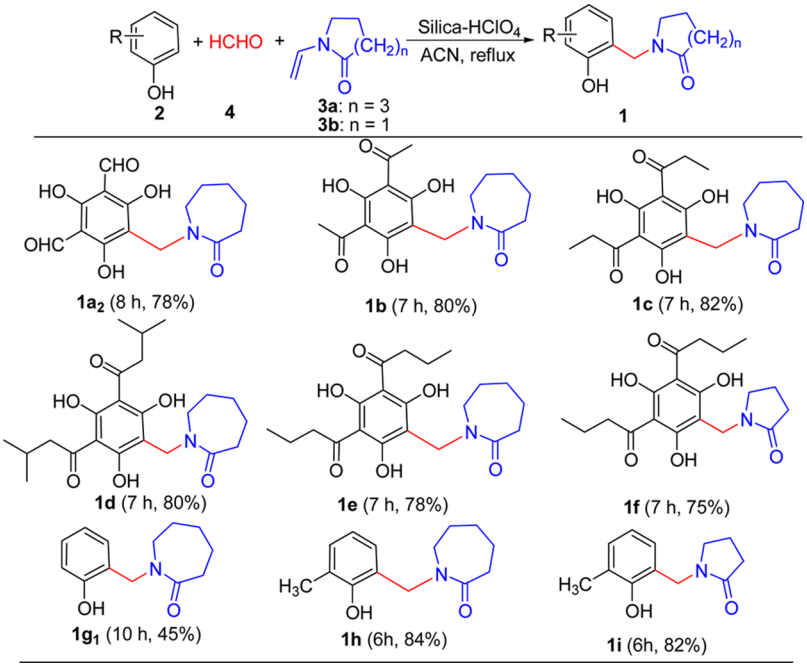


Figure 2. Scope of the reaction for *tandem* devinylation followed by Mannich-type condensation. Reaction time and isolated yields are shown in the parentheses. For entry $\mathbf{1g_1}$, a dicaprolactam linked product $\mathbf{1g_2}$ was also formed (~35% yield); however, it was difficult to isolate.

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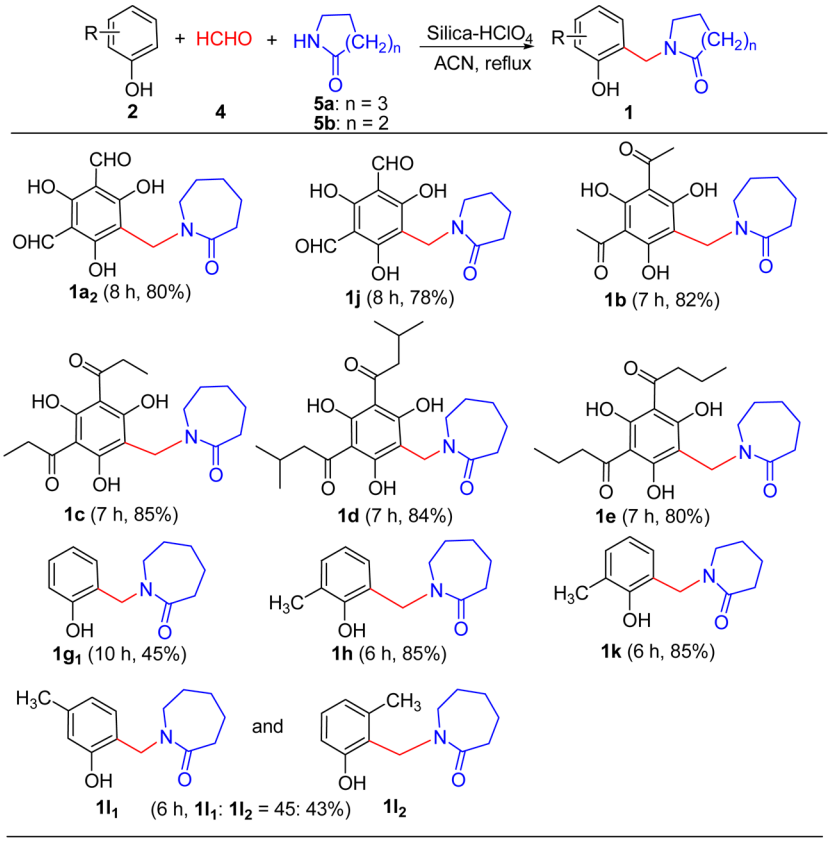

Figure 3. Mannich-type condensation of phenols with lactams. Reaction time and isolated yields are shown in the parentheses. For entry $\mathbf{1g_1}$, a dicaprolactam linked product $\mathbf{1g_2}$ was also formed (~32%); however, it was difficult to isolate.

however only in <10% yield. Thus, silica–$HClO_4$ (50 mol %) in acetonitrile at 80 °C for 6 h was found be optimal condition for preparation of Mannich-type products. These optimization results clearly indicate that presence of acidic catalyst is necessary for the reaction to occur. Furthermore, the reaction works well with acetonitrile but not with protic solvents such as methanol or water. This is probably due to leveling of acidity of the catalyst ("buffer effect") through partial protonation/exchange with the protic solvent. The catalyst needs to be acidic enough for the reaction to proceed. Next, we studied reactivity difference between *N*-vinyl lactam and parent *NH*-lactam, for which a model reaction between *o*-cresol (**2g**), **4** and *N*-vinyl lactam **3a** or *NH*-lactam **5a** was chosen. During initial 1 h, the rate of reaction for formation of Mannich product **1h** was higher in the case of *NH*-lactam **5a** as compared to *N*-vinyl lactam **3a**; however, both reactions required similar time for completion (6 h) with similar yields of Mannich product **1h** (>85%). To check formation of side products (dimers) in absence of one of the coupling partners, a series of experiments were carried out. When the model reaction between **2g**, **4** and **5a** was performed under optimized reaction conditions in the absence of either **2g** or **5a**, we could not see formation of expected dimers viz. *o*-cresol-CH_2-*o*-cresol or caprolactam-CH_2-caprolactam. However, when 2,4-diacetyl phloroglucinol (**2b**) was treated with formaldehyde under similar conditions, dimer **6** (dimer of **2b** linked with methylene unit; structure shown in the Experimental Section) was formed in 55% yield.

Under optimized reaction conditions, the scope was explored for different lactams and phenolic precursors (Figure 3). Reaction of 2,4-diformyl phloroglucinol (**2a**) with formaldehyde (**4**) and caprolactam (**5a**) or piperidin-2-one (**5b**) in acetonitrile in presence of silica–$HClO_4$ (50 mol %) led to formation of Mannich type products $\mathbf{1a_2}$ and **1j** in 80 and 78% yield, respectively. Similarly 2,4-diacyl phloroglucinols produced Mannich products **1b–1e** in good yields. Phenol also participated well in this reaction, which on reaction with caprolactam (**5a**) produced mono- and disubstituted Mannich products $\mathbf{1g_1}$ and $\mathbf{1g_2}$. Cresols showed better reactivity in this reaction producing excellent yields of Mannich products **1h**, **1k** and $\mathbf{1l_1}$-$\mathbf{1l_2}$.

The method applicability was also investigated for amidoalkylation of natural product butin (**7**).[17] Reaction of 0.152 mmol of **7** with formaldehyde (**4**) and caprolactam (**5a**) under optimized reaction conditions produced corresponding Mannich-type products **8a** and **8b** in 42 and 34% yield, respectively, as depicted in Figure 4. It is noteworthy to mention that apart from high yields of the reaction, silica–$HClO_4$ catalyst showed recyclability, thus making the process eco-friendly and economical.

For synthesis of Mannich products **1** (or **8a**,**b**), three mechanisms are considered: first via classical Mannich reaction involving a Schiff base intermediate, second via formation of *o*-quinone methide (*o*-QM) followed by formal [4 + 2]-Diels–Alder cycloaddition to form oxazine intermediate, and last via formation of *o*-QM followed by Michael addition.[18] In the case of lactams, the nitrogen electrons get delocalized into the carbonyl and exist as a resonance mixture of $\mathbf{5a_1}$ and $\mathbf{5a_2}$. Thus unlike amines, amides are less reactive toward nucleophilic addition to carbonyl group of aldehyde to generate electrophilic Schiff base, which is a key reactive intermediate in classical Mannich reaction. To unravel the mechanism for formation of Mannich-type product **1**, model reaction between *o*-cresol (**2g**),

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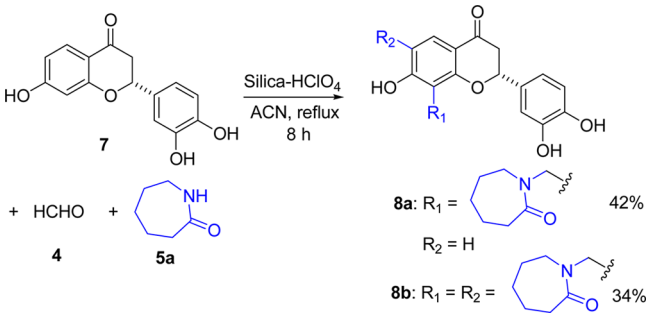

Figure 4. Mannich-type condensation of butin (**7**) with caprolactam (**5a**).

formaldehyde (**4**) and caprolactam (**5a**) was chosen. Since we always observed solely *ortho*-selectivity, we presumed that the product **1h** gets formed via second mechanism involving formation of *o*-QM **II** and oxazine intermediate **III** (Figure 5).

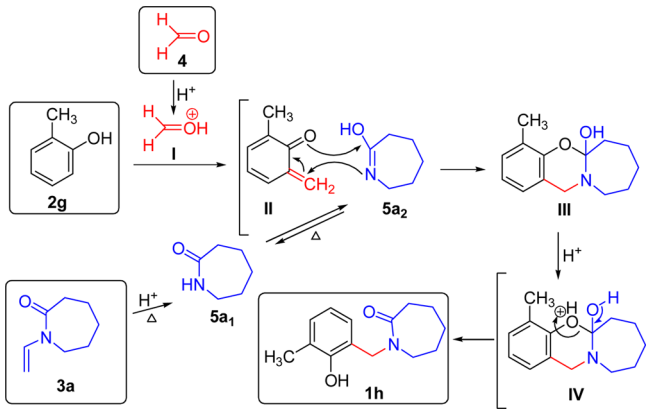

Figure 5. Proposed mechanism for formation of Mannich product **1h**.

To confirm our proposed mechanism, we performed a stepwise experiment in which *o*-cresol (**2g**), formaldehyde (**4**) and silica−$HClO_4$ in acetonitrile were refluxed for 2 h. The reaction was monitored for formation of *o*-QM by TLC (indication for disappearance of **2g** in TLC) and MS studies. MS analysis indicated formation of *o*-quinone methide species **II** at m/z 121 $[M + 1]^+$ (see Section S-1 of the Supporting Information). Further addition of **5a** to the reaction led to formation of desired product **1h**, indicative of the reaction proceeding via *o*-quinone methide **II** intermediate. Next, in order to prove the formation of oxazine intermediate **III**, reaction of **2g**, HCHO (**4**) and **5a** in presence of Silica−$HClO_4$ in acetonitrile after 2 h reflux was analyzed by LC-ESI-MS/MS. LC spectrum showed two peaks with same mass m/z 234 $[M + 1]^+$ at t_R 3.8 and 8.2 min (Figure 6a,c,d). Mannich product **1h** and oxazine intermediate **III**, both having same molecular weight (mol. wt. 233.14) appeared as separate peaks in LC−MS, which evidenced formation of **III** during the course of reaction. Next, we assigned these peaks as t_R 3.8 min for **III** and t_R 8.2 min for **1h** by analyzing pure isolated product **1h** (Figure 6b). As observed in optimization studies (Table 2), catalyst needs to be acidic enough for the reaction to proceed, probably because the high acidity of perchloric acid causes the *O*-protonation of the amide $\mathbf{5a_1}$ allowing a fast lactam $\mathbf{5a_1}$−lactim $\mathbf{5a_2}$ equilibrium to occur. Because the lactim form $\mathbf{5a_2}$ is a key intermediate for the [4 + 2]-Diels−Alder cycloaddition, formation of the final product heavily depends on this step. Thus, our proposed mechanism involves formation of *o*-quinone methide **II** from **2g** and **4**. The transient *o*-quinone methide **II** further undergoes formal [4 + 2]-Diels−Alder cycloaddition with enol form of caprolactam to produce oxazine intermediate **III**. This intermediate, on protonation, undergoes ring-opening to produce product **1h**.

In conclusion, we have reported new method for *ortho*-amidoalkylation of phenols and a proposed mechanism via Mannich-type condensation involving oxazine intermediate.

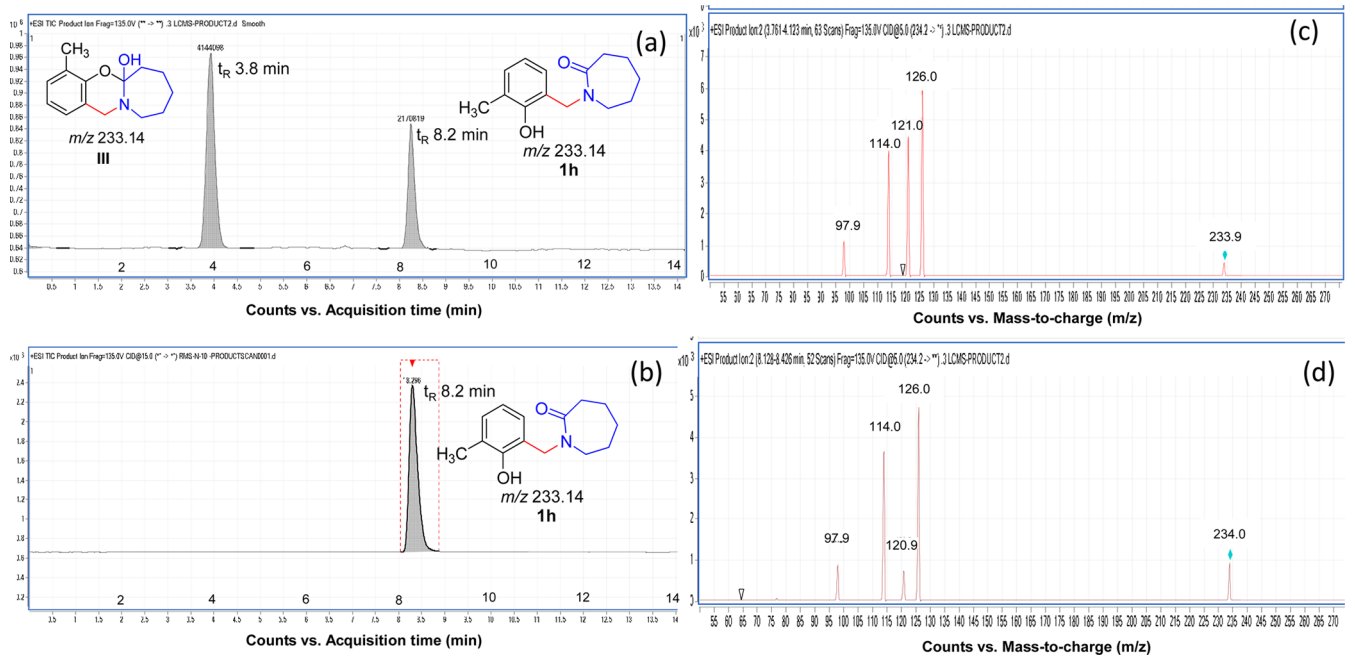

Figure 6. LC-ESI-MS/MS analysis to investigate mechanism for formation of **1h**. (a) LC spectra for product scan of reaction mixture after 2 h; (b) LC spectra of pure product **1h**; (c) MS spectra for peak at t_R 3.8 min; (d) MS spectra for peak at t_R 8.2 min.

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Method is regioselective for *ortho*-substitution. The developed protocol can be utilized for short and efficient synthesis of a diverse range of natural and synthetic alkaloids.

EXPERIMENTAL SECTION

General Information. All chemicals were obtained from Sigma-Aldrich Company and used as received. ^{1}H, ^{13}C and DEPT NMR spectra were recorded on Bruker-Avance DPX FT-NMR 500 and 400 MHz instruments. Chemical data for protons are reported in parts per million (ppm) downfield from tetramethylsilane and are referenced to the residual proton in the NMR solvent ($CDCl_3$, 7.26 ppm). Carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded at 125 or 100 MHz; chemical data for carbons are reported in parts per million (ppm, δ scale) downfield from tetramethylsilane and are referenced to the carbon resonance of the solvent ($CDCl_3$, 77 ppm). ESI-MS and HRMS spectra were recorded on Agilent 1100 LC-Q-TOF and HRMS-6540-UHD machines. IR spectra were recorded on Perkin-Elmer IR spectrophotometer. Melting points were recorded on digital melting point apparatus. LC-ESI-MS/MS analysis was carried out on Agilent Triple-Quad LC−MS/MS system (model 6410).

Procedure for Preparation of 2,4-Diformyl Phloroglucinol (2a). Phosphoryl chloride (1.6 mL, 16.7 mmol) was added dropwise to DMF (1.3 mL, 16.7 mmol) with strong stirring, at room temperature under a nitrogen atmosphere. Stirring was continued for 30 min. This Vilsmeier reagent was then slowly added to a stirred solution of anhydrous phloroglucinol (1 g, 7.9 mmol) in dioxane (5 mL) at room temperature, under a nitrogen atmosphere. This solution was then stirred at room temperature for 12 h, whereupon it turned into a yellow amorphous solid. This solid mixture was cooled to 0 °C before being added to ice−water slurry (~40 mL). The solution was allowed to slowly warm to room temperature, and stirring was continued for a further 4 h, during which time a salmon colored precipitate formed. This precipitate was then filtered off and washed with more water, to get 2,4-diformyl phloroglucinol **2a** (1.22 g): Yield 85%; cream colored solid; mp 218−220 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.09 (s, 2H), 5.83 (s, 1H); ESI-MS m/z 183 $[M + 1]^+$.[15]

General Procedure for Preparation of Diacylphloroglucinols 2b−2e. A solution of phloroglucinol (10 g, 79.36 mmol) and acetic acid or propionic acid/isovaleric acid/butyric acid (3 equiv) in BF_3−etherate (100 mL) was refluxed at 100 °C for 2.5 h. Reaction mixture was cooled to room temperature, poured into crushed ice and extracted with ethyl acetate (100 mL × 3). Combined organic layers were evaporated on rotary evaporator. Crude product was purified by silica gel (#100−200) column chromatography to get diacyl phloroglucinols. 1,3-Diacetyl-2,4,6-trihydroxy benzene (**2b**): Yield 70%; cream colored solid; mp 172−174 °C; ^{1}H NMR (CD_3OD, 400 MHz) δ 5.84 (s, 1H), 2.65 (s, 6H); ESI-MS m/z 211 $[M + 1]^+$. 1,3-Dipropanoyl-2,4,6-trihydroxy benzene (**2c**): Cream colored solid; mp 158−160 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 16.21 (s, 1H), 5.81 (s, 1H), 3.15 (q, J = 6.8, 13.8 Hz, 4H), 1.27 (d, J = 7.0 Hz, 6H); ESI-MS m/z 239.0 $[M + 1]^+$. 1,3-Di-(3-methyl-butanoyl)-2,4,6-trihydroxy benzene (**2d**): Yield 75%; yellow solid; mp 114−116 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.85 (s, 1H), 2.99 (d, J = 6.7 Hz, 4H), 2.26 (m, 2H), 0.99 (d, J = 6.7 Hz, 12H); ESI-MS m/z 295 $[M + 1]^+$. 1,3-Dibutanoyl-2,4,6-trihydroxy benzene (**2e**): Cream colored solid; mp 130−132 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 16.27 (s, 1H), 5.81 (s, 1H), 3.10 (t, J = 7.2 Hz, 4H), 1.75 (m, 4H), 1.01 (t, J = 7.3 Hz, 6H); ESI-MS m/z 267.0 $[M + 1]^+$.[15]

General Procedure for *ortho*-Amidoalkylation: Synthesis of Mannich-Type Products 1a−1l and 8a,b. To a solution of phenolic precursor (**2** or **7**, 300 mg, 1 equiv) in acetonitrile was added formaldehyde (**4**, 3 equiv), *N*-vinyl lactam (**3**, 1.5 equiv) or *NH*-lactam (**5**, 1.5 equiv) and silica−$HClO_4$ (50% w/w). Reaction mixture was then refluxed at 80 °C for 6−10 h. Completion of the reaction was monitored by TLC. Reaction mixture was cooled to room temperature and filtered through Whatman filter paper. Filtrate was concentrated on vacuo rotavapor to get crude product. Crude products were purified by silica gel (#100−200) column chromatography to get Mannich-type products **1a−1l** and **8a,b** in 75−85% yield.

*1-(2,4,6-Trihydroxy-3,5-diformyl-benzyl)azepan-2-one (**1a$_1$**).* Light yellow solid: mp 167−169 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 13.62 (s, 1H, OH), 13.56 (s, 1H, OH), 12.88 (s, 1H, OH), 10.14 (s, 2H, 2 x CHO), 4.40−4.01 (brs, 2H), 3.82−3.54 (brs, 2H), 2.59 (t, J = 5.6 Hz, 2H), 1.75−1.67 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 193.4, 191.6, 179.4, 169.6, 169.5, 169.0, 104.8, 103.4, 103.1, 51.3, 41.5, 36.1, 29.7, 27.7, 22.7; IR ($CHCl_3$) ν_{max} 3368, 2854, 2925, 1503, 1445, 1304, 1176, 1194, 1019 cm^{-1}; ESI-MS m/z 308.0 $[M + 1]^+$; HRMS m/z 306.0985 calcd for $C_{15}H_{17}NO_6 - H^+$ (306.0978).

*1-(2,4,6-Trihydroxy-3,5-diacetyl-benzyl)azepan-2-one (**1b**).* Light yellow solid: mp 149−151 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 16.36 (s, 1H, OH), 15.48 (s,1H, OH), 12.85 (s, 1H, OH), 4.49−4.28 (brs, 2H), 3.71−3.49 (brs, 2H), 2.77 (s, 6H), 2.63 (t, J = 7.6 Hz, 2H), 1.73−1.59 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 205.0, 204.5, 179.2, 171.8, 170.0, 167.3, 104.6, 103.8, 103.3, 51.3, 42.4, 36.2, 33.1, 33.0, 29.8, 27.7, 23.0; IR ($CHCl_3$) ν_{max} 3400, 2925, 2853, 1620, 1503, 1425, 1366, 1277, 1152, 1116, 1021 cm^{-1}; ESI-MS m/z 336 $[M + 1]^+$; HRMS m/z 336.1419 calcd for $C_{17}H_{21}O_6 + H^+$(336.1442).

*1-(2,4,6-Trihydroxy-3,5-dipropanoyl-benzyl)azepan-2-one (**1c**).* White solid: mp 114−116 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 16.45 (s, 1H), 15.55 (s, 1H), 12.77 (s, 1H), 4.60−4.2 (m, 2H), 3.71 (brs, 2H), 3.21 (m, 4H), 2.58 (d, J = 10.4 Hz, 2H), 1.71−1.66 (m, 6H), 1.18 (d, J = 2.4 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 208.3, 207.8, 179.2, 171.6, 169.8, 166.9, 104.2, 103.6, 103.4, 51.3, 42.5, 37.6, 36.2, 29.9, 27.8, 23.0, 8.7, 8.6; IR ($CHCl_3$) ν_{max} 2934, 2853, 1620, 1592, 1503, 1422, 1365, 1202, 1034 cm^{-1}; ESI-MS m/z 362.1 $[M-1]^+$; HRMS m/z 362.1619 calcd for $C_{19}H_{25}NO_6 - H^+$ (362.1604).

*1-(2,4,6-Trihydroxy-3,5-diisovaleryl-benzyl)azepan-2-one (**1d**).* Light yellow solid: mp 87−88 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 12.7 (s, 1H), 4.42−4.23 (m, 2H), 3.65−3.52 (brs, 2H), 2.94 (d, J = 6.8 Hz, 4H), 2.51 (d, J = 9.6 Hz, 2H), 2.23−2.12 (m, 2H), 1.66−1.60 (m, 6H), 0.99 (d, J = 6.4 Hz, 12H); ^{13}C NMR ($CDCl_3$,100 MHz) δ 207.3, 206.9, 179.1, 171.8, 170.1, 166.9, 104.5, 103.9, 103.4, 52.9, 51.3, 42.5, 36.2, 29.8, 27.8, 25.2, 25.1, 23.0, 22.8; IR($CHCl_3$) ν_{max} 2956, 2869, 2503, 1620, 1503, 1463, 1421, 1367, 1300, 1262, 1201, 1124, 1072, 1049 cm^{-1}; ESI-MS m/z 420.2 $[M + 1]^+$; HRMS m/z 418.2248 calcd for $C_{23}H_{33}NO_6 - H^+$ (418.2230).

*1-(2,4,6-Trihydroxy-3,5-dibutanoyl-benzyl)azepan-2-one (**1e**).* Yellow solid: mp 122−123 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 16.50 (s, 1H), 15.59 (s, 1H), 12.75 (s, 1H), 4.43−4.13 (brs, 2H), 3.73 (brs, 2H), 3.13 (m, 4H), 2.58 (d, J = 10.4 Hz, 2H), 1.74−1.62 (m, 10H), 0.99 (d, J = 3.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 207.6, 207.2, 179.2, 171.7, 170.0, 166.9, 104.3, 103.7, 103.4, 51.3, 46.2, 42.5, 36.2, 29.9, 27.8, 23.0, 18.1, 18.0, 14.0, 13.9; IR ($CHCl_3$) ν_{max} 3745, 3400, 2957, 2929, 2875, 1619, 1503, 1460, 1421, 1376, 1199, 1043 cm^{-1}; ESI-MS m/z 392.0 $[M + 1]^+$; HRMS m/z 390.1927 calcd for $C_{21}H_{29}NO_6 - H^+$(390.1917).

*1-(2,4,6-Trihydroxy-3,5-dibutanoyl-benzyl) pyrrolidin-2-one (**1f**).* White solid: mp 128−130 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 16.48 (s, 1H), 16.47 (s, 1H), 15.42 (s, 1H), 12.07 (s, 1H), 4.34 (s, 2H), 3.69 (t, J = 7.2 Hz, 2H), 3.14 (m, 4H), 2.48 (t, J = 8.0 Hz, 2H), 2.07 (m, 2H), 1.72 (m, 4H), 1.01 (t, J = 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 207.6, 207.2, 178.1, 171.6, 169.8, 166.3, 104.5, 103.9, 103.1, 49.3, 46.2, 35.9, 30.3, 18.1, 18.0, 13.9; IR ($CHCl_3$) ν_{max} 3369, 2930, 2873, 1621, 1588, 1507, 1475, 1421, 1377, 1201, 1179, 1021 cm^{-1}; ESI-MS m/z 364.1 $[M + 1]^+$; HRMS m/z 364.1763 calcd for $C_{19}H_{25}NO_6$+H^+ (364.1755).

*1-(2-Hydroxybenzyl)azepan-2-one (**1g$_1$**).* White solid: mp 110−112 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.58 (s, 1H), 7.21 (t, J = 7.6 Hz, 1H), 7.19 (d, J = 7.6 Hz, 1H), 6.92 (d, J = 7.6 Hz, 1H), 6.80 (t, J = 7.6 Hz, 1H), 4.41 (s, 2H), 3.46 (t, J = 5.6 Hz, 2H), 2.56 (t, J = 6.0 Hz, 2H), 1.73−1.62 (m, 4H), 1.59−1.52 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 178.01, 156.1, 130.7, 130.1, 122.3, 119.1, 117.4, 49.8, 49.4, 36.3, 29.6, 27.4, 22.9; IR ($CHCl_3$) ν_{max} 3744, 2928, 2854, 1731, 1607, 1494, 1445, 1353, 1245, 1185, 1141, 1104, 1083, 1032 cm^{-1}; ESI-MS m/z 220.1 $[M + 1]^+$; HRMS m/z 220.1332 calcd for $C_{13}H_{17}NO_2$+H^+ (220.1332).

*1-(2-Hydroxy-3-methyl benzyl)azepan-2-one (**1h**).* White solid: mp 141−143 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.63 (s, 1H), 7.10 (d, J = 7.6 Hz, 1H), 6.96 (d, J = 6.4 Hz, 1H), 6.71 (t, J = 7.6 Hz, 1H),

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4.42 (s, 2H), 3.44 (t, J = 4.8 Hz, 2H), 2.57 (d, J = 6.0 Hz, 2H), 2.28 (s, 3H), 1.74−1.71 (m, 4H), 1.69−1.63 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 178.1, 154.5, 131.4, 128.6, 126.5, 121.9, 118.8, 50.0, 49.7, 36.6, 29.9, 27.6, 23.2, 16.6; IR ($CHCl_3$) ν_{max} 3089, 2929, 2855, 1609, 1590, 1496, 1445, 1354, 1261, 1229, 1197, 1174, 1085, 1019 cm^{-1}; ESI-MS m/z 234.1 [M + 1]$^+$; HRMS m/z 234.1495 calcd for $C_{14}H_{19}NO_2$+H$^+$ (234.1489).

*1-(2-Hydroxy-3-methyl benzyl)pyrrolidin-2-one (**1i**).* White solid: mp 105−107 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.26 (s, 1H), 7.30 (d, J = 7.2 Hz, 1H), 6.99 (d, J = 7.2 Hz, 1H) 6.78 (t, J = 7.6 Hz, 1H), 4.36 (s, 1H), 3.56 (t, J = 4.0 Hz, 2H), 2.49 (t, J = 4.0 Hz, 2H), 2.30 (s, 3H), 2.11 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 176.7, 153.8, 131.1, 128.3, 126.7, 121.2, 118.9, 47.6, 43.8, 30.2, 17.4, 16.3; IR ($CHCl_3$):ν_{max} 3233, 2926, 2728, 1651, 1594, 1498, 1470, 1438, 1380, 1350, 1314, 1257, 1228, 1161, 1117, 1090, 1020 cm^{-1}; ESI-MS m/z 206.1 [M + 1]$^+$; HRMS m/z 204.1027 calcd for $C_{12}H_{15}NO$ − H$^+$(204.1025).

*1-(2,4,6-Trihydroxy-3,5-diformyl-benzyl)piperidin-2-one (**1j**).* Light yellow solid: mp 150−152 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 13.60 (s, 1H), 13.59 (s, 1H), 13.12 (s, 1H), 10.14 (s, 1H), 10.10 (s, 1H), 4.66−4.24 (brs, 2H), 3.57−3.40 (brs, 2H), 2.45 (brs, 2H), 1.83 (brs, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 193.4, 191.6, 173.3, 169.7, 169.2, 104.8, 103.4, 102.6, 49.5, 40.1, 31.4, 22.7, 20.4; IR ($CDCl_3$) ν_{max} 2951, 2635, 1742, 1633, 1510, 1469, 1429, 1383, 1353, 1334, 1196, 1176, 1142, 1015 cm^{-1}; ESI-MS m/z 292.1 [M-1]$^+$; HRMS m/z 294.0976 calcd for $C_{14}H_{15}NO_6$+H$^+$ (294.0972).

*1-(2-Hydroxy-3-methyl benzyl)piperidin-2-one (**1k**).* Light yellow solid: mp 68−70 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.92 (s, 1H), 7.11 (d, J = 7.2 Hz, 1H), 6.96 (d, J = 7.6 Hz, 1H), 6.70 (t, J = 7.2 Hz, 1H), 4.42 (s, 2H), 3.41 (t, J = 4.0 Hz, 2H), 2.43 (t, J = 6.4 Hz, 2H) 2.25 (s, 3H), 1.81 (m, 4H); ^{13}C NMR ($CDCl_3$,125 MHz) δ 171.9, 154.4, 131.3, 128.9, 126.6, 121.2, 118.5, 48.7, 47.7, 31.6, 22.6, 20.6, 16.5; IR ($CDCl_3$) ν_{max} 3368, 2945, 2872, 1607, 1588, 1504, 1470, 1444, 1417, 1354, 1258, 1231, 1151, 1078, 1020 cm^{-1}; ESI-MS m/z 220.1 [M + 1]$^+$; HRMS m/z 218.1184 calcd for $C_{13}H_{17}NO_2$ − H$^+$ (218.1186).

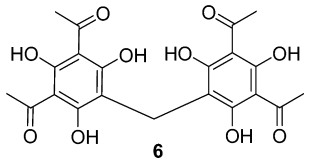
*1-(2-Hydroxy-4-methyl benzyl)azepan-2-one (**1l$_1$**).* Light yellow solid: mp 75−76 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.47 (s, 1H), 6.99 (d, J = 7.6 Hz, 1H), 6.74 (s, 1H), 6.61 (d, J = 7.6 Hz, 1H), 4.39 (s, 2H), 3.47 (t, J = 5.2 Hz, 2H), 2.56 (t, J = 4.8 Hz, 2H), 2.31 (s, 3H), 1.70−1.60 (m, 4H), 1.58−1.52 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 178.0, 156.0, 140.3, 130.6, 120.0, 119.6, 118.1, 49.9, 49.3, 36.4, 29.7, 27.6, 23.0, 21.1; IR ($CHCl_3$) ν_{max} 3203, 2928, 2856, 1609, 1508, 1493, 1445, 1367, 1287, 1262, 1190, 1142, 1113, 1020 cm^{-1}; ESI-MS m/z 234.1 [M + 1]$^+$; HRMS m/z 234.1494 calcd for $C_{14}H_{19}NO_2$+H$^+$ (234.1489).

*1-(2-Hydroxy-6-methyl benzyl)azepan-2-one (**1l$_2$**).* Light yellow solid: mp 155−157 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.57 (s, 1H), 7.11 (t, J = 7.6 Hz, 1H), 6.82 (d, J = 8.0 Hz, 1H), 6.70 (d, J = 7.6 Hz, 1H), 4.60 (s, 2H), 3.50 (t, J = 8.0 Hz, 2H), 2.60 (t, J = 6.4 Hz, 2H), 2.44 (s, 3H), 1.72−1.58 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 178.5, 157.0, 137.1, 129.1, 121.6, 121.1, 115.3, 50.0, 44.5, 36.3, 29.6, 27.5, 23.0, 20.6; IR ($CHCl_3$):ν_{max} 3369, 2927, 2855, 1726, 1606, 1579, 1465, 1364, 1285, 1196, 1020 cm^{-1}; ESI-MS m/z 234.1 [M + 1]$^+$, 256.1 [M + Na]$^+$; HRMS m/z 232.1341 calcd for $C_{14}H_{19}NO_2$ − H$^+$ (232.1338).

*1-((3,4-Dihydro-7-hydroxy-2-(3,4-dihydroxyphenyl)-4-oxo-2H-chromen-8-yl)methyl) azepan-2-one (**8a**).* Light yellow solid: mp 250−252 °C; ^{1}H NMR (CD_3OD, 500 MHz) δ 7.79 (d, J = 8.8 Hz, 1H), 6.98 (d, J = 2.0 Hz, 1H), 6.68 (m, 2H), 6.60 (d, J = 8.8 Hz, 1H), 5.42 (d, J = 10.2 Hz, 1H), 4.58 (d, J = 14.5 Hz, 1H), 4.53 (d, J = 14.5 Hz, 1H), 3.59 (m, 2H), 3.10 (dd, J = 13.7, 16.9 Hz, 1H), 2.76 (dd, J = 3.0, 16.9 Hz, 1H), 2.55 (m, 2H), 1.72 (m, 2H), 1.69 (m, 2H), 1.62 (m, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 190.2, 177.3, 163.3, 161.3, 145.6, 145.2, 129.8, 127.7, 117.6, 115.3; 114.0, 113.4, 111.4, 111.1, 79.4, 49.1, 43.0, 40.8, 35.5, 29.8, 27.2, 22.6; IR ($CHCl_3$) ν_{max} 3369, 2923, 2852, 1742, 1609, 1446, 1266, 1080, 1020 cm^{-1}; ESI-MS m/z 396 [M-1]$^+$; HRMS m/z 396.1471 calcd for $C_{22}H_{23}NO_6$ − H$^+$ (396.1452).

*1-((3,4-Dihydro-7-hydroxy-2-(3,4-dihydroxyphenyl)-6-(2-oxoazepan-1-yl-methyl)-4-oxo-2H-chromen-8-yl)methyl)azepan-2-one (**8b**).* Light yellow solid: mp 240−242 °C; ^{1}H NMR (CD_3OD, 500 MHz) δ 7.72 (s, 1H), 6.97 (s, 1H), 6.85 (m, 2H), 5.42 (d, J = 12.6 Hz, 1H), 4.53 (m, 4H), 3.62 (brs, 2H), 3.49 (brs, 2H), 3.06 (m, 1H), 2.76 (m, 1H), 2.72−2.56 (m, 4H), 1.75−1.50 (m, 12H); ^{13}C NMR (CD_3OD, 100 MHz) δ 193.2, 180.5 (2 x CO-N), 175.2, 163.5, 162.7, 147.2, 146.7, 131.6, 129.1, 120.9, 119.4, 116.4, 114.8, 114.7, 113.1, 81.9, 51.8, 50.9, 47.9, 44.8, 43.1, 37.5, 36.8, 30.8, 30.6, 30.1, 24.3, 24.1, 24.0; IR ($CHCl_3$) ν_{max} 3401, 2923, 2852, 1610, 1402, 1384, 1155, 1021 cm^{-1}; ESI-MS m/z 521 [M-1]$^+$; HRMS m/z 521.2318 calcd for $C_{29}H_{34}N_2O_7$ − H$^+$ (521.2293).

Dimerization of 2,4-Diacetyl Phloroglucinol. To check formation of any side product(s) in the absence of one of coupling partner, this experiment was carried out. To a solution of 2,4-diacetyl phloroglucinol (**2b**, 1 equiv) in acetonitrile was added formaldehyde (**4**, 3 equiv) and silica−$HClO_4$ (50% w/w). Reaction mixture was then refluxed at 80 °C for 6 h. Reaction mixture was cooled to room temperature and filtered through Whatman filter paper. Filtrate was concentrated on vacuo rotavapor to get crude product. Crude product was purified by silica gel (#100−200) column chromatography to get methylene-*bis*-(3,5-diacetyl-2,4,6-trihydroxybenzene) (**6**) in 55% yield.



6

Cream colored solid: mp 279−281 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 17.37 (s, 2H), 16.20 (s, 2H), 10.22 (s, 2H), 3.74 (s, 2H), 2.76 (s, 6H), 2.73 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 205.7, 171.4, 169.1, 166.5, 106.6, 105.8, 104.9, 34.1, 33.1, 15.6; ESI-MS m/z 433.1 [M + 1]$^+$; IR (KBr) ν_{max} 3204, 1617, 1586, 1470, 1366, 1268, 1180, 1010 cm^{-1}.[19]

Silica−$HClO_4$ Catalyst: Preparation, Recyclability Studies and Determination of Acidity. Perchloric acid (1.25 g, as a 70% aqueous solution) was added to the suspension of silica gel (23.75 g, #230−400) in Et_2O. The mixture was concentrated and the residue heated at 100 °C for 72 h under a vacuum to afford $HClO_4$−SiO_2 as a free-flowing powder.[20]

Recyclability of the catalyst was checked to prove the heterogeneous nature and its repeated use. To a solution of *ortho*-cresol (**2g**, 300 mg, 1 equiv) in acetonitrile (10 mL) were added formaldehyde (**4**, 3 equiv), caprolactam (**5a**, 3.57 mmol) and silica−$HClO_4$ (250 mg, 50% w/w). Mixture was then refluxed at 80 °C for 6 h. After completion of reaction, catalyst was recovered by filtration followed by washing with acetonitrile. Recovered catalyst was dried in oven and reused in next cycle. Product **1h** was obtained in 80, 62, 54% yield over three cycles, respectively. In order to understand the reason for decreased catalytic activity of Silica−$HClO_4$ catalyst after its use, total acidity of fresh and used catalyst (after first use) was determined by ammonia-TPD experiment using CHEMBET-3000 TPD/TPR/TPO instrument, containing a quartz reactor and TCD detector. Prior to TPD studies, samples were pretreated at 250 °C for 2 h with continuous flow of pure nitrogen (99.9%) and then cooled to room temperature. After pretreatment, samples were saturated with NH_3 gas until saturated adsorption. Temperature was increased to 80 °C and kept there for 2 h, while a helium flow of 20 cm^3/min removed the physisorbed ammonia. Finally the system was heated from 80 to 1000 °C at the rate of 10 °C/min and desorbed gas monitored with TCD detector. All the flow rates were maintained at normal temperature and pressure.

Total acidity of the fresh catalyst was found to be 10.95 mmol NH_3/g; however it was decreased to 7.8 mmol NH_3/g after first use. This decreased acidity is a clear indication of the catalyst leaching after its use, which justifies the reason for a decrease in the product yield from 80% (fresh catalyst) to 62% (first recycle). However, the catalyst could be recycled up to three times, producing >50% yield of desired Mannich product.

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■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, NMR spectra scans. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.
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