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$Cs_{2.5}H_{0.5}PW_{12}O_{40}$ catalyzed diastereoselective synthesis of β-amino ketones via three component Mannich-type reaction in water

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ABSTRACT

A series of insoluble salts of Keggin heteropoly compounds were prepared and used as catalysts for the Mannich-type reaction of benzaldehyde, aniline, and cyclohexanone in water. Among them, $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ showed excellent catalytic activity. Effects of surfactant, catalyst loading and temperature were studied to introduce the best reaction condition. The optimized reaction conditions were extended to Mannich reaction of various aldehydes, ketones, and amines in water. This rapid procedure afforded structurally divers β-amino ketones with major *anti* diastereoselectivity. Additionally, four new compounds were reported. The catalyst was recovered and reused for subsequent runs.

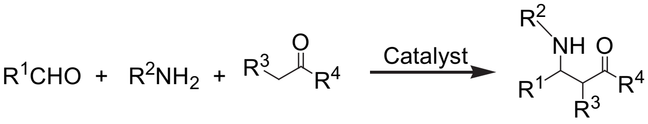
1. Introduction

One of the important goals in organic chemistry is the development of new methodologies for the synthesis of functionalized biologically active compounds with structural diversity from simple and readily available precursor molecules.

β-Amino carbonyl compounds are important intermediates for various pharmaceutical and natural product syntheses including β-amino alcohols, β-amino acids, and lactams.[1–3] Among the various methods for the synthesis of these compounds, Mannich-type reaction constitutes a method of choice in many cases due to its versatility.[4]

Numerous versions of the Mannich reaction have been developed to overcome drawbacks associated with the classical Mannich reaction. One of the efficient routes is to conduct a one-pot three-component reaction of an aldehyde, an amine and a ketone (Scheme 1) with the assistance of ultrasound irradiation[5] or using Lewis acids,[6–8] Lewis base,[9] Brönsted acids,[10–14] organocatalyst[15] or praline[16] to catalyze the reaction.

Despite the merits of these methodologies, problems recycling and reusing of the catalysts, harsh reaction conditions, toxicity or difficulty in product separation remain concerns. Therefore, the search for new readily available green catalysts is still being actively pursued. In this context, we focused on the development of reusable heteropoly acid (HPA) catalyst to perform this transformation under milder reaction conditions and to enhance the generality of the reaction.



Scheme 1. Three-component Mannich reaction.

2. Results and discussion

The pK_a of HPAs is lower than that of the conventional solid acid catalysts.[17] Therefore, they are generally active catalysts, which allow efficient operation under mild conditions. Owing to inherent advantages of HPAs, heterogeneous acid catalysis by these compounds has the potential of a great economic reward and green benefits. In order to achieve this goal, one way is to exchange their protons with large alkali metal cations such as K^+, Cs^+, or $[(n\text{-Bu})_4N]^+$ to form insoluble salts.[18]

Taking the above into account, a series of HPA-salts with varied cations and different catalytic mechanisms were prepared and their catalytic activities were evaluated in the Mannich reaction of benzaldehyde (1.0 mmol), aniline (1.0 mmol), and cyclohexanone (1.0 mmol). Without addition of catalyst, the reaction proceeds via imine formation

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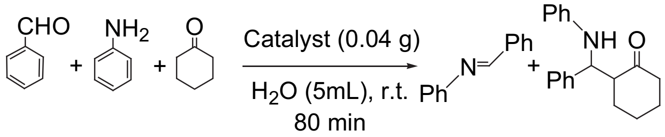
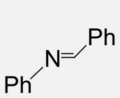
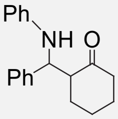
through the condensation of benzaldehyde and aniline, and no products from the aldol reaction and Mannich-type reaction were observed (Table 1, entry 1). The formation of imine was confirmed by using ^1H NMR and performing the condensation between benzaldehyde and aniline as a control reaction. This result indicates that the catalyst is necessary to produce a Mannich product.

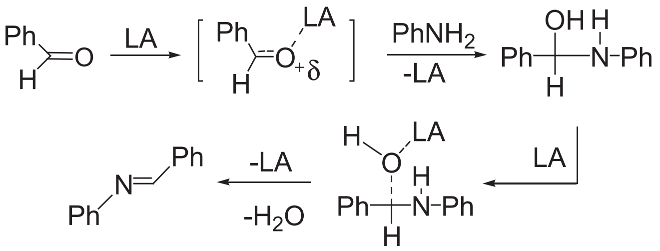
Table 1
Mannich-type reaction of benzaldehyde, aniline, and cyclohexanone in the presence of various catalysts



Entry	Catalyst	Yield[a] (%)	
			
1	—	38	0
2	$K_5CoW_{12}O_{40}$	49	38
3	$[(n\text{-Bu})_4N]_5PMo_2W_9O_{39}$ ($Sn^{2+}\cdot H_2O$)	75	19
4	$[(n\text{-Bu})_4N]_3PMo_2W_9O_{39}$ ($Sn^{4+}\cdot H_2O$)	74	17
5	$[(n\text{-Bu})_4N]_3PMo_2W_9O_{39}$ ($Ti^{4+}\cdot H_2O$)	81	11
6	$[(n\text{-Bu})_4N]_5PMo_2W_9O_{39}$ ($Zn^{2+}\cdot H_2O$)	72	10
7	$[(t\text{-Bu})_4N]_4PW_{11}CoO_{39}$	60	26
8	$Cs_2H_1PW_{12}O_{40}$	44	50
9	$Cs_1H_2PW_{12}O_{40}$	31	64
10	$Cs_{2.5}H_{0.5}PW_{12}O_{40}$	7	86
11	$Cs_{2.5}H_{0.5}PMo_{12}O_{40}$	56	15

[a] Isolated yield.

$K_5CoW_{12}O_{40}$ is the most important example of an HPA, based on a d-transition-metal heteroatom, that is, used as electron-transfer catalyst in some organic transformations.[19] The poor catalytic performance of $K_5CoW_{12}O_{40}$ indicated that this conversion is not proceed via electron-transfer mechanism (Table 1, entry 2). Metal substituted HPAs afforded the desired product only in low yields while the imine product was obtained in good yield (Table 1, entries 3–7). Presumably, they act as Lewis acids (LA) to catalyze nucleophilic attack on the carbonyl group of benzaldehyde by aniline, as well as serving as dehydrating agents to facilitate the removal of water and formation of the corresponding imine (Scheme 2). In the next step, the carbonyl group of ketone should be activated by the coordination of oxygen atom with the LA sites of the catalyst to form an enolate, which then reacts with the imine leading to the formation of the Mannich product. It seems that metal substituted HPAs catalyze the imine formation preferentially over the Mannich reaction due to their low ability to coordinate ketone.

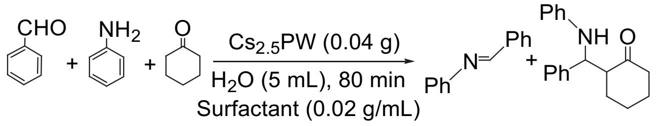


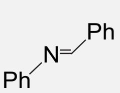
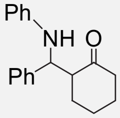
Scheme 2. Metal substituted HPAs catalyzed imine formation.

In general, the neutral salts of HPA gave poor yields in comparison with acidic salts, indicating that a Brönsted acid is clearly involved in the process (Table 1, entries 2–11). Obviously, tungsten containing heteropoly compounds exhibited higher reactivity in comparison with the molybdenum analogs. $Cs_xH_{3-x}PW_{12}O_{40}$ catalysts showed better results in comparison with others and the highest activity was achieved upon partially substitution of HPA protons with Cs stoichiometry equal to 2.5 (Table 1, entries 8–10). Thus, $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ ($Cs_{2.5}PW$) was selected as the best catalyst for further investigation.

Since the reactants were insoluble in water, we decided to examine the use of a surfactant to solubilize the hydrophobic substrates. In the presence of cationic surfactants, CPB and CTAB, the product yield was decreased (Table 2, entries 1 and 2). It may be due to the positively charged micellar interface, which provided an unfavorable electrostatic interaction with protonated imine present in water solution, thus decreasing the yield compared to the same reaction carried out in the absence of surfactant (Table 1, entry 10). Triton X-100 also did not afford the desired product (Table 2, entry 3) this neutral surfactant formed two immiscible layers, so was not effective in this reaction. Anionic surfactants afforded the desired product in a modest yield (Table 2, entries 4–6). They formed a white muddy reaction mixture and this colloidal dispersion in the presence of the substrates leads to efficient catalysis. However, addition of these surfactants only slightly improved the yield (in comparison with entry 10, Table 1). Additionally, these surfactants produce colloidal dispersion by emulsion formation as a result of which, phase separation was difficult. Hence, further studies were performed in the presence of $Cs_{2.5}PW$ without the addition of surfactant.

Table 2
Effect of surfactants in Mannich-type reaction of benzaldehyde, aniline, and cyclohexanone

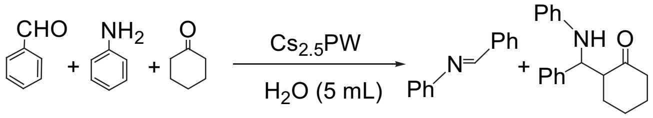


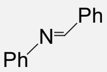
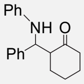
Entry	Surfactant	Yield[a] (%)	
			
1	Cetylpyridium bromide (CPB)	71	26
2	Cetyltrimethylammonium bromide (CTAB)	65	31
3	Poly(ethylene glycol) mono [4-(1,1,3, 3-tetramethylbutylphenyl) ether (Triton X-100)	69	0
4	Sodium octyl sulfate (SOS)	Trace	82
5	Sodium decyl sulfate (SDeS)	11	85
6	Sodium dodecyl sulfate (SDS)	Trace	84

[a] Isolated yield.

Increasing the quantity of $Cs_{2.5}PW$ from 0.04 to 0.12 g did not improve the result to a greater extent while with a lesser amount (0.02 g), the reaction remained incomplete (Table 3, entries 1–3). Thus, 0.04 g of $Cs_{2.5}PW$ is the suitable choice for catalyst loading. The effect of temperature was also studied. Faster reactions occurred on increasing the temperature but the product yield decreased at high temperatures possibly because the Mannich base is unstable at elevated temperatures (Table 3, entries 5 and 6). As can be seen, by using of 2 equiv of cyclohexanone, the desired product

Table 3
Optimization of reaction conditions in the presence of $Cs_{2.5}PW$



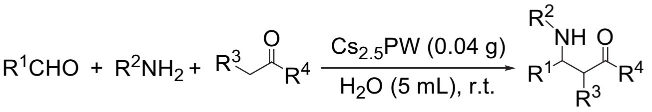
Entry	$Cs_{2.5}PW$ (g)	Ketone (equiv)	Temp (°C)	Time (min)	Yield[a] (%)	
						
1	0.02	1	25	80	25	72
2	0.04	1	25	80	7	86
3	0.08	1	25	80	12	88
4	0.12	1	25	80	9	88
5	0.04	1	50	40	73	10
6	0.04	1	80	40	75	Trace
7	0.04	2	25	30	Trace	94
8	0.04	3	25	30	Trace	95

[a] Isolated yield.

was obtained in excellent yield within short reaction time while more than 2 equiv had no effect on product yield (Table 3, entries 2, 7, and 8).

The results in entry 7 of Table 3 became particularly interesting. From ^1H NMR spectra, the ratio of Mannich-product/imine was 94:6 after 30 min of mixing. Thus, these optimized conditions were extended to a series of aldehydes, ketones and amines to explore the generality of this catalytic system (Table 4).

Table 4
Synthesis of various β-amino ketones via three component Mannich reaction



1a-14n

Entry	R^1	R^2	R^3	R^4	Ketone (equiv)	Product	Time (min)	Yield (%)[a]	*anti*/*syn* ratio[b]	Ref.
1	Ph	Ph	$-(CH_2)_4-$		2	**1**	30	94	66:34	20
2	Ph	$4-Cl-C_6H_4$	$-(CH_2)_4-$		2	**2**	170	76	64:36	20
3	$4-MeO-C_6H_4$	$4-Cl-C_6H_4$	$-(CH_2)_4-$		2	**3**	120	71	67:33	20
4	$4-NO_2-C_6H_4$	$4-Cl-C_6H_4$	$-(CH_2)_4-$		2	**4**	90	45	—	21
5	$4-NO_2-C_6H_4$	$4-Cl-C_6H_4$	$-(CH_2)_4-$		5	**4**	200	96	62:38	21
6	$3-NO_2-C_6H_4$	Ph	$-(CH_2)_4-$		2	**5**	165	45	—	21
7	$3-NO_2-C_6H_4$	Ph	$-(CH_2)_4-$		5	**5**	210	81	58:42	21
8	2-Furyl	Ph	$-(CH_2)_4-$		2	**6**	60	55	—	20
9	2-Furyl	Ph	$-(CH_2)_4-$		5	**6**	120	84	54:46	20
10	$4-MeO-C_6H_4$	Ph	H	Ph	2	**7**	40	92	—	20
11	$4-MeO-C_6H_4$	$4-Cl-C_6H_4$	H	Ph	2	**8**	50	89	—	21
12	$4-Cl-C_6H_4$	$4-Cl-C_6H_4$	H	Ph	2	**9**	50	91	—	21
13	$4-NO_2-C_6H_4$	Ph	H	Ph	2	**10**	50	82	—	20
14	$4-Cl-C_6H_4$	Ph	H	Ph	2	**11**	30	93	—	20
15	$4-Me-C_6H_4$	Ph	H	Ph	2	**12**	20	81	—	20
16	Ph	Ph	H	$4-Me-C_6H_4$	2	**13**	50	80	—	20
17	Ph	Ph	H	$4-Cl-C_6H_4$	2	**14**	40	89	—	20
18	$n-C_3H_7$	Ph	H	Ph	2	**15**	200	66	—	14
19	Ph	$n-C_4H_9$	H	Ph	2	**16**	130	64	—	14

[a] Isolated yield.
[b] *anti*/*syn*-ratio measured by ^1H NMR spectroscopy analysis of the crude reaction mixture.

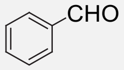
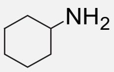
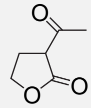
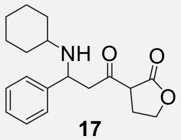
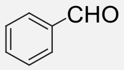
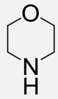
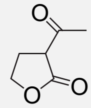
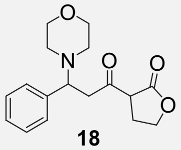
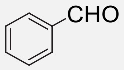
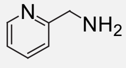
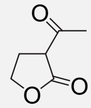
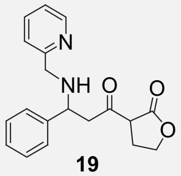
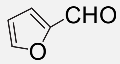
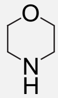
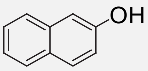
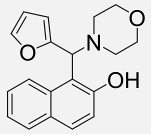
In the cases of β-amino-cyclohexanones, stereoselectivity was determined by ^1H NMR spectroscopy and by comparison with known compounds. The selectivity for *anti*-isomer was favored in all cases (Table 4, entries 1–9). It was found that while reaction worked well with 2 equiv of aromatic ketones, the use of 5 equiv was required in the case of cyclohexanone for reaction completion (Table 4, entries 5, 7, and 9). It may be due to the low activity of α-hydrogen of cyclohexanone. To our surprise, aliphatic aldehyde and amines as substrates afforded the corresponding products in good yield (Table 4, entries 18 and 19), as previous approaches gave negative results, or very poor yields, for similar reactions.[14,20,21]

Many unique structures can be attained when three or more reactants were combined in a single step to afford new compounds possessing the combined features of the building blocks. Encouraged by the above excellent results, we decided to investigate the reaction of structurally diverse substrates in order to obtain the new compounds **17**–**20** (Table 5). These compounds containing reactive functionalities for further elaboration of new molecular system and they will most likely to be useful for the synthesis of biologically active molecules.

A possible mechanism of the Mannich-type reaction in the presence of $Cs_{2.5}PW$ as a Brönsted acid catalyst is proposed (Scheme 3). The reaction proceeded typically through the imine formation of the aldehyde and amine, protonation of the imine, and the attack of the enol derived from the ketone to the protonated imine, leading to the formation of Mannich product.

To exam the reusability of the catalyst, 0.4 g of $Cs_{2.5}PW$ was added to a mixture of benzaldehyde (10 mmol), aniline (10 mmol), and cyclohexanone (20 mmol) in water. Then the mixture was stirred. After 30 min, water was removed from the mixture to leave residue. Then, the residue was dissolved in 30 mL diethyl ether to isolate the catalyst via centrifugation. The isolated catalyst was washed with diethyl ether and used for catalyzing the next reaction cycle. In a test of five cycles, the change of product yield is minimal, indicating that $Cs_{2.5}PW$ is stable and reusable (Fig. 1). Only trace amounts of imine were observed in all runs.

Table 5
Synthesis of new Mannich products

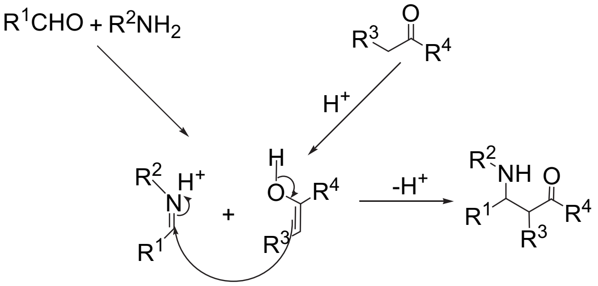
Entry	Aldehyde	Amine	Ketone or alcohol	Product	Time (min)/yield (%)[a]
1[b]				 **17**	180/85
2[b]				 **18**	220/70
3[b,c]				 **19**	70/60
4[d]				 **20**	85/90

[a] Isolated yield.

[b] Reaction conditions: aldehyde (1 mmol), ketone (2 mmol), amine (1 mmol), catalyst (0.04 g), H_2O (5 mL), room temperature.

[c] Catalyst (0.12 g) was used in this reaction.

[d] Reaction conditions: aldehyde (1.3 mmol), β-naphthol (1 mmol), amine (1 mmol), catalyst (0.04 g), H_2O (5 mL), room temperature.



Scheme 3. Proposed mechanism.

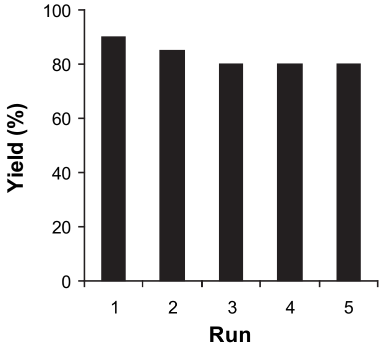


Figure 1. Reusability of $Cs_{2.5}PW$ catalyst (after 30 min).

3. Conclusion

$Cs_{2.5}PW$ as heterogeneous catalyst showed effective catalytic activity in the synthesis of β-amino ketones via three component Mannich reaction in water. The good yields, mild conditions, low catalyst loading and convenient operations as well as no formation of by-products, such as aldol or deamination products made it believable that this protocol would play important role in the synthesis of natural products.

4. Experimental section

4.1. General

$H_3PMo_{12}O_{40}$, $[(n\text{-}C_4H_9)_4N]Br$, $[(t\text{-}C_4H_9)_4N]Br$, Cs_2CO_3, $TiCl_4$, $SnCl_4$, KCl, HOAc, H_3PO_4, sodium molybdate and sodium tungstate were obtained from Merck and $SnCl_2$ from Fluka were used as supplied. $H_3PW_{12}O_{40}$, $Co(OAc)_2\cdot 4H_2O$ and potassium persulfate purchased from Aldrich. CPB, CTAB, Triton X-100, SOS, SDeS, and SDS were obtained from Aldrich and used as received without further purification. The organic materials were commercially available and purchased from Fluka, Merck, and Aldrich chemical companies.

^1H NMR spectra were recorded on a Bruker Avance 200 MHz NMR spectrometer with $CDCl_3$ as solvent and TMS as internal standard. IR spectra were recorded with KBr pellets or Nujol using a Shimadzu 470 spectrophotometer. Melting points were determined using a digital Gallenkamp apparatus.

4.2. Synthesis of catalysts

The synthesis of $[(n\text{-}Bu)_4N]_5PMo_2W_9O_{39}$ $(Sn^{2+}\cdot H_2O)$, $[(n\text{-}Bu)_4N]_3PMo_2W_9O_{39}$ $(Sn^{4+}\cdot H_2O)$, $[(n\text{-}Bu)_4N]_3PMo_2W_9O_{39}$ $(Ti^{4+}\cdot H_2O)$, and $[(Bu)_4N]_5PMo_2W_9O_{39}$ ($Zn^{2+}\cdot H_2O$) were started with the preparation of α-$K_7PMo_2W_9O_{39}\cdot 19H_2O$ from β-$Na_8HPW_9O_{34}\cdot 24H_2O$ and sodium molybdate, according to the procedure described previously.[22] $[(t\text{-}Bu)_4N]_4$ $PW_{11}CoO_{39}$ and $Cs_xH_{3\text{-}x}PW_{12}O_{40}$ catalysts were prepared according to our previously published paper.[22] $K_5CoW_{12}O_{40}$ catalyst were prepared and purified by literature procedures.[23]

4.3. Typical procedure for Mannich reaction

Typically, to a mixture of aldehyde (1 mmol), amine (1 mmol) and ketone (2 or 5 mmol), and H_2O (5 mL), catalyst (0.04 g) was added. The reaction mixture was vigorously stirred for the period of time listed in the Tables. Progress of the reaction was monitored by TLC. The resulting solid substance was filtered off and diethyl ether was added to dissolve of the target product. After filtration, the filtrate was concentrated at room temperature to generate the crude product. The crude products were purified either by crystallization from ethanol or by column chromatography on silica-gel using ethyl acetate/hexane as eluent. Known products (**1**–**16**) were identified by comparing of their spectral data with those of the authentic samples.[20,21]

4.4. Characterization of compounds 1–20

*4.4.1. Compound **1***. Yield (0.26 g, 94%), a white solid, mp 136–138 °C; R_f (25% ethyl acetate/hexane) 0.49; ν_{max} (KBr) 3386, 2939, 1689, 1500 cm^{-1}; δ_H (200 MHz, $CDCl_3$ major/minor=68:32) 7.43–7.31 (5H, m, aromatic), 7.21–6.43 (5H, m, aromatic), 4.84 (0.34H, d, *J* 4.0 Hz, NHC*H*), 4.76 (0.66H, d, *J* 7.2 Hz, NHC*H*), 2.93–2.84 (1H, m, C(O)C*H*), 2.44–2.22 (2H, m, C(O)CH_2), 1.86–1.53 (6H, m, CH_2).

*4.4.2. Compound **2***. Yield (0.24 g, 76%), a pale yellow solid, mp 137–138 °C; R_f (25% ethyl acetate/hexane) 0.45; ν_{max} (KBr) 3378, 2951, 1676, 1510 cm^{-1}; δ_H (200 MHz, $CDCl_3$ major/minor=64:36) 7.55–7.21 (5H, m, aromatic), 6.60–6.51 (4H, m, aromatic), 4.67 (0.36H, d, *J* 4.0 Hz, NHC*H*), 4.57 (0.64H, d, *J* 7.2 Hz, NHC*H*), 2.72–2.65 (1H , m, C(O)C*H*), 2.32–2.29 (2H, m, C(O)CH_2), 1.92–1.60 (6H, m, CH_2).

*4.4.3. Compound **3***. Yield (0.25 g, 71%), a pale yellow solid, mp 132–134 °C; R_f (25% ethyl acetate/hexane) 0.48; ν_{max} (KBr) 3362, 2964, 1703, 1512 cm^{-1}; δ_H (200 MHz, $CDCl_3$ major/minor=67:33) 7.27–6.99 (4H, m, aromatic), 6.85–6.43 (4H, m, aromatic), 4.75 (0.33H, d, *J* 4.8 Hz, NHC*H*), 4.59 (0.67H, d, *J* 6.4 Hz, NHC*H*), 3.78 (3H, s, OCH_3), 2.69 (1H, m, C(O)C*H*), 2.43–2.32 (m, 2H, C(O)CH_2), 1.93–1.81 (4H, m, CH_2), 1.68–1.63 (2H, m, CH_2).

*4.4.4. Compound **4***. Yield (0.35 g, 96%), a white solid, mp 169–171 °C; R_f (25% ethyl acetate/hexane) 0.43; ν_{max} (KBr) 3386, 3021, 1673, 1527, 1348 cm^{-1}; δ_H (200 MHz, $CDCl_3$ major/minor=62:38) 8.18–7.57 (4H, m, aromatic), 7.05–6.41 (4H, m, aromatic), 4.80 (0.38H, d, *J* 5.8 Hz, NHC*H*), 4.64 (0.62H, d, *J* 7.2 Hz, NHC*H*), 2.86–2.83 (1H, m, C(O)C*H*), 2.48–2.30 (2H, m, C(O)CH_2), 2.10–2.01 (2H, m, CH_2), 1.95–1.58 (4H, m, CH_2).

*4.4.5. Compound **5***. Yield (0.26 g, 81%), a white solid, mp 163–165 °C; R_f (25% ethyl acetate/hexane) 0.24; ν_{max}(KBr) 3386, 3021, 1673, 1527, 1348 cm^{-1}; δ_H (200 MHz, $CDCl_3$ major/minor=58:42) 8.26–8.24 (1H, m, aromatic), 8.09–8.07 (1H, m, aromatic), 7.80–7.12 (4H, m, aromatic), 6.70–6.52 (3H, m, aromatic), 4.86 (0.42H, d, *J* 4.0 Hz, NHC*H*), 4.84 (0.58H, d, *J* 5.2 Hz, NHC*H*), 2.89–2.86 (1H, m, C(O)C*H*), 2.42–2.34 (2H, m, C(O)CH_2), 2.08–1.95 (3H, m, CH_2), 1.79–1.58 (3H, m, CH_2).

*4.4.6. Compound **6***. Yield (0.23 g, 84%), a white solid, mp 120–121 °C; R_f (25% ethyl acetate/hexane) 0.46; ν_{max} (KBr) 3362, 2938, 1673, 1597, 1500 cm^{-1}; δ_H (200 MHz, $CDCl_3$ major/minor=54:46) 7.29–7.10 (3H, m, furyl), 6.71–6.61 (3H, m, aromatic), 6.26–6.17 (2H, m, aromatic), 4.88 (0.46H, d, *J* 4.8 Hz, NHC*H*), 4.82 (0.54H, d, *J* 5.4 Hz, NHC*H*), 4.5 (1H, br s, N*H*), 2.99–2.89 (1H, m, C(O)C*H*), 2.40–1.60 (8H, m, CH_2).

*4.4.7. Compound **7***. Yield (0.30 g, 92%), a white solid, mp 150–152 °C; R_f (25% ethyl acetate/hexane) 0.53; ν_{max} (KBr) 3387, 3021, 1668 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.93–7.55 (3H, m, aromatic), 7.46–7.35 (4H, m, aromatic), 7.11–6.86 (4H, m, aromatic), 6.70–6.54 (3H, m, aromatic), 4.96 (1H, t, *J* 6.4 Hz, NHC*H*), 3.77 (3H, s, OCH_3), 3.54 (1H, d, *J* 6.4 Hz, C(O)CH_2), 3.34 (1H, d, *J* 6.4 Hz, C(O)CH_2).

*4.4.8. Compound **8***. Yield (0.33 g, 89%), a pale yellow solid, mp 149–151 °C; R_f (25% ethyl acetate/hexane) 0.55; ν_{max} (KBr) 3381, 3020, 1669 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.90–7.42 (5H, m, aromatic), 7.33–7.01 (4H, m, aromatic), 6.87–6.45 (4H, m, aromatic), 4.90 (1H, t, *J* 7.4 Hz, NHC*H*), 4.57 (1H, br s, N*H*), 3.77 (3H, s, OCH_3), 3.50–3.35 (2H, m, C(O)CH_2).

*4.4.9. Compound **9***. Yield (0.34 g, 91%), a yellow solid, mp 155–157 °C; R_f (25% ethyl acetate/hexane) 0.50; ν_{max} (KBr) 3378, 3020, 1668 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.93–7.94 (d, 2H, *J* 4.6 Hz), 7.59–7.44 (5H, m, aromatic), 7.31–7.05 (4H, m, aromatic), 6.50 (2H, d, *J* 8.2 Hz, aromatic), 4.95 (1H, t, *J* 4.6 Hz, NHC*H*), 3.47–3.36 (2H, m, C(O)CH_2).

*4.4.10. Compound **10***. Yield (0.28 g, 82%), a white solid, mp 107–110 °C; R_f (25% ethyl acetate/hexane) 0.49; ν_{max} (KBr) 3410, 3020, 1663, 1349 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 8.14–7.82 (4H, m, aromatic), 7.65–7.49 (4H, m, aromatic), 6.73–6.70 (4H, m, aromatic), 7.13 (2H, m, aromatic), 5.12 (1H, t, *J* 6.1 Hz, NHC*H*), 3.52 (2H, d, *J* 6.1 Hz, C(O)CH_2).

*4.4.11. Compound **11***. Yield (0.31 g, 93%), a white solid, mp 116–117 °C; R_f (25% ethyl acetate/hexane) 0.51; ν_{max}(KBr) 3376, 3020, 1667 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.89–7.66 (2H, m, aromatic), 7.35–7.05 (7H, m, aromatic), 6.89–6.71 (3H, m, aromatic), 6.48–6.31 (2H, m, aromatic), 4.99 (1H, t, *J* 5.6 Hz, NHC*H*), 4.57 (1H, br s, N*H*), 3.49–3.38 (2H, m, C(O)CH_2).

*4.4.12. Compound **12***. Yield (0.26 g, 81%), a white solid, mp 131–132 °C; R_f (25% ethyl acetate/hexane) 0.56; ν_{max}(KBr) 3400, 3020, 1678 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.90 (2H, m, aromatic), 7.56–7.39 (5H, m, aromatic), 7.09–6.85 (4H, m, aromatic), 6.65–6.51 (3H, m, aromatic), 5.76 (1H, t, *J* 6.8 Hz, NHC*H*), 3.71 (3H, s, OCH_3), 3.58–3.46 (2H, m, C(O)CH_2).

*4.4.13. Compound **13***. Yield (0.25 g, 80%), a white solid, mp 138–139 °C; R_f (25% ethyl acetate/hexane) 0.47; ν_{max}(KBr) 3380, 3020, 1665 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.76 (2H, m, aromatic), 7.40–7.14 (8H, m, aromatic), 6.80–6.41 (4H, m, aromatic), 4.91 (1H, m, NHC*H*), 3.49–3.41 (2H, m, C(O)CH_2), 2.40 (3H, s, CH_3).

*4.4.14. Compound **14***. Yield (0.30 g, 89%), a pale yellow solid, mp 119–120 °C; R_f (25% ethyl acetate/hexane) 0.49; ν_{max}(KBr) 3380, 3020, 1685 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.85–7.66 (3H, m, aromatic), 7.48–7.35 (4H, m, aromatic), 7.29–7.08 (5H, m, aromatic), 6.48 (2H, m, aromatic), 4.90 (1H, t, *J* 6.3 Hz, NHC*H*), 3.48 (2H, m, C(O)CH_2).

*4.4.15. Compound **15***. Yield (0.21 g, 66%), a white solid, mp 93–95 °C; R_f (25% ethyl acetate/hexane) 0.38; ν_{max}(KBr) 3385, 3020, 1685, 1495, 1378 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.88–7.38 (5H, m, aromatic), 7.10–6.55 (5H, m, aromatic), 4.65 (1H, m, NHC*H*), 3.51–3.44 (2H, m, C(O)CH_2), 1.48 (2H, m, CH_2CH_2CH), 1.33 (2H, m, CH_3C$H_2$$CH_2$), 0.96 (3H, t, *J* 6.8 Hz, C$H_3$$CH_2$).

4.4.16. Compound ***16****.* Yield (0.20 g, 64%), a white solid, mp 98–101 °C; R_f (25% ethyl acetate/hexane) 0.41; ν_{max}(KBr) 3382, 3020, 1668, 1489, 1383 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.89–7.34 (5H, m, aromatic), 7.21–7.08 (5H, m, aromatic), 4.89 (1H, m, NHC*H*), 3.50–3.43 (2H, m, C(O)CH_2), 2.89 (1H, br s, N*H*), 2.55 (2H, m, CH_2CH_2NH), 1.41 (2H, m, $CH_2CH_2CH_2$), 1.35 (2H, m, $CH_3CH_2CH_2$), 1.03 (3H, t, *J* 6.8 Hz, CH_3CH_2).

4.4.17. Compound ***17****.* Yield (0.27 g, 85%), a white solid, mp 135–138 °C; [found: C, 72.47; H, 7.90; N, 4.52. $C_{19}H_{25}NO_3$ requires C, 72.35; H, 7.99; N, 4.44%]; R_f (25% ethyl acetate/hexane) 0.18; ν_{max}(KBr) 3374, 3021, 1744, 1683 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.34–7.11 (5H, m, aromatic), 4.85 (1H, m, NHC*H*), 4.42–4.31 (2H, t, *J* 8.3 Hz, OCH_2), 3.66 (1H, m, C*H*C(O)), 3.59–3.42 (2H, m, C(O)CH_2), 3.29–3.34 (1H, m, NHC*H*), 2.89–2.75 (2H, m, CH_2), 1.92–1.31 (10H, m, cyclohexyl).

4.4.18. Compound ***18****.* Yield (0.21 g, 70%), a white solid, mp 122–125 °C; [found: C, 67.40; H, 6.95; N, 4.70. $C_{17}H_{21}NO_4$ requires C, 67.31; H, 6.98; N, 4.62%]; R_f (25% ethyl acetate/hexane) 0.21; ν_{max}(KBr) 3019, 1752, 1685, 1272, 1238, 1085 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.09–7.30 (5H, m, aromatic), 4.87 (1H, m, NHC*H*), 4.42–4.28 (2H, t, *J* 8.3 Hz, OCH_2), 3.64 (1H, m, C*H*C(O)), 3.79 (4H, m, CH_2OCH_2), 3.57–3.38 (2H, m, C(O)CH_2), 2.91–2.73 (6H, m, CH_2).

4.4.19. Compound ***19****.* Yield (0.19 g, 60%), a colorless oil; [found: C, 70.42; H, 6.18; N, 4.60. $C_{19}H_{20}N_2O_3$ requires C, 70.35; H, 6.21; N, 8.64%]; R_f (43% ethyl acetate/hexane) 0.23; ν_{max} (Nujol) 3381, 3021, 1748, 1679 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 8.46–7.35 (4H, m, aromatic), 7.25–7.11 (5H, m, aromatic), 4.83 (1H, m, NHC*H*), 4.45–4.29 (4H, m, CH_2), 3.66 (1H, m, C*H*C(O)), 3.59–3.42 (2H, m, C(O)CH_2), 2.89–2.75 (2H, m, CH_2).

4.4.20. Compound ***20****.* Yield (0.28 g, 90%), an orange solid, mp 184–188 °C; [found: C, 73.62; H, 6.17; N, 4.61. $C_{19}H_{19}NO_3$ requires C, 73.77; H, 6.19; N, 4.53%]; R_f (43% ethyl acetate/hexane) 0.15; ν_{max} (KBr) 3264, 1595, 1271, 1236, 1080 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 13.98 (1H, s, O*H*), 7.98–6.11 (9H, m, aromatic), 5.35 (1H, s, C*H*N), 3.68–2.55 (8H, m, CH_2).

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.06.052.

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