Stereoselective Synthesis of β-Amino Ketones Possessing β-[(2*H*-Pyran-2-one)-3-Yl]-β-chlorovinyl Moiety *via* Three-Component Direct Mannich-Type Reaction, Catalyzed with $ZrOCl_2 \cdot 8H_2O$

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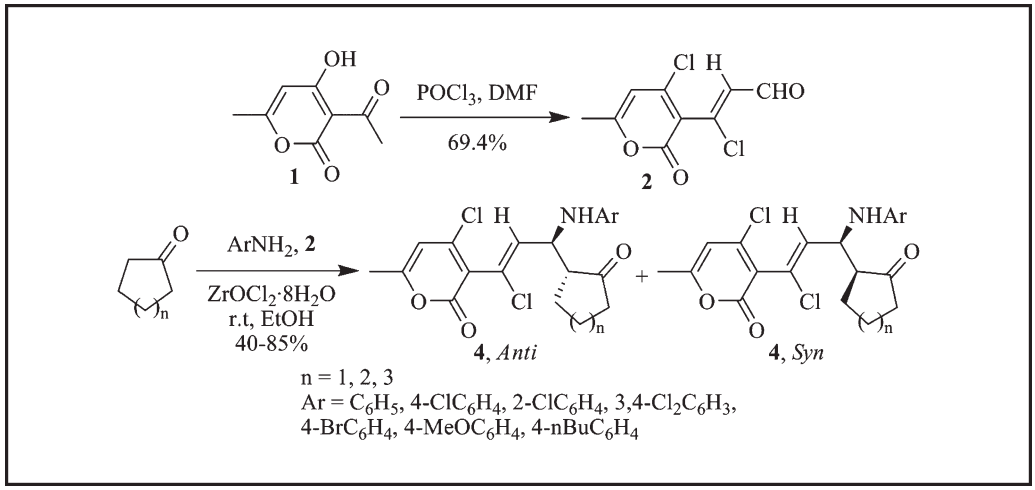

New *Z*-3-chloro-3-(4-chloro-6-methyl-2-oxo-2*H*-pyran-3-yl)acrolein was synthesized starting from dehydroacetic acid using Vilsmeier–Haack reaction and efficiently used in three component direct Mannich-type reaction with different anilines, cyclic and acyclic ketones catalyzed with zirconium oxychloride ($ZrOCl_2 \cdot 8H_2O$) in ethanol at room temperature. Also, comenic aldehyde was used in direct Mannich-type reaction at the same conditions. The reaction proceeds rapidly and affords the corresponding β-amino ketones in good to high yields with moderate to high stereoselectivity.

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INTRODUCTION

The Vilsmeier–Haack reaction is a widely used method for the formylation of activated aromatic and heteroaromatic compounds [1]. The reactions of aliphatic substrates [2], particularly carbonyl compounds [3] with chloromethylene iminium salts are highly versatile. One aspect of its importance is its reaction with a keto methylene group to produce β-chloroacroleins [4].

β-Amino carbonyl compounds are also attractive targets for chemical synthesis because of their wide utility as biologically active molecules [5]. The Mannich reaction is a classical method for preparation of the β-amino carbonyl compounds [5,6] and has been one of the most important basic reactions in organic chemistry for its use in natural product and pharmaceutical synthesis [7]. However, because of the drastic reaction conditions and long reaction times, the classical Mannich reaction is plagued by a number of serious disadvantages [6]. Therefore, catalytic Mannich reactions have been reported by several groups as an efficient method to prepare β-amino carbonyl compounds [8,9d].

Because of their easy availability [10] and low toxicity [11], Zr(IV) salts have recently attracted much attention as a catalyst for organic transformations [9]. To our knowledge, there have been only a few reports on the metal oxysalt-based organic reactions [12].

As part of our research on synthesis of pyrone derivatives[13], herein we report a simple and environmentally benign stereoselective synthesis of new β-amino ketones possessing β-[(2*H*-pyran-2-one)-3-yl]-β-chlorovinyl or 4-oxo-4*H*-pyran-2-yl moiety *via* direct Mannich-type reaction between *Z*-3-chloro-3-(4-chloro-6-methyl-2-oxo-2*H*-pyran-3-yl)acrolein **2** or *O*-protected comenic aldehyde **10**, anilines and ketones at room temperature using $ZrOCl_2 \cdot 8H_2O$ as catalyst.

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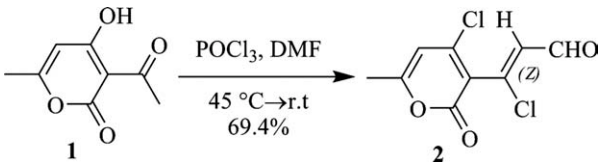
Scheme 1. Synthesis of *Z*-3-chloro-3-(4-chloro-6-methyl-2-oxo-2*H*-pyran-3-yl)acrolein **2**.



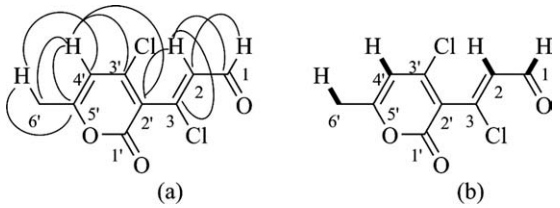


Figure 1. (a) HMBC correlations and (b) HMQC correlations for **2**.

RESULTS AND DISCUSSION

A new β-chloroacrolein with 2*H*-pyran-2-one moiety **2** was synthesized from commercially available dehydroacetic acid **1** in 69.4% yield using Vilsmeier–Haack reaction as outlined in Scheme 1.

The structure of compound **2** was established from IR, ^{1}H NMR, ^{13}C NMR, 2D-NMRs (HMQC and HMBC), and mass spectral data and elemental analyses. The values of coupling constant ^3J of the proton signals of —ClC=C**H**—CO—**H** in the ^{1}H NMR spectra equal to 6.8 Hz indicate that these atoms are located in the *s-cis* position [4h,i]. It was shown by the study of isomer composition of β-aryl-β-chloroacroleins, arising from aryl ketones [4j,k,o] and heteroaryl ketones [4o] in the reaction with Vilsmeier-Haack reagent, α-unsubstituted acroleins are obtained exclusively as a *Z* isomer. Therefore, **2** has *s-cis-Z*-configuration at the side chain. The HMBC spectral data of **2** [Fig. 1(a)] revealed long range correlations between the H_1 (δ 10.18) with C_2 (at δ 132.3); H_2 with C_1, C_3, and $C_{2'}$ (at δ 190.6, 142.8, and 120.1, respectively); $H_{4'}$ (δ 6.26) with $C_{2'}$, $C_{3'}$, $C_{5'}$, and $C_{6'}$ (at δ 120.1, 150.8, 164.1, and 20.4, respectively); $H_{6'}$ (δ 2.35) with $C_{4'}$ and $C_{5'}$ (at δ 107.1 and 164.1, respectively). There are no correlations between $C_{1'}$ (carbonyl group of α-pyrone ring) and protons. Also HMQC spectral data of **2** was shown in Figure 1(b) that revealed one bond correlation between H_1 (δ 10.18) with C_1 (δ 190.6); H_2 (δ 6.32) with C_2 (δ 132.3); $H_{4'}$ (δ 6.26) with $C_{4'}$ (δ 107.1); $H_{6'}$ (δ 2.35) with $C_{6'}$ (δ 20.4).

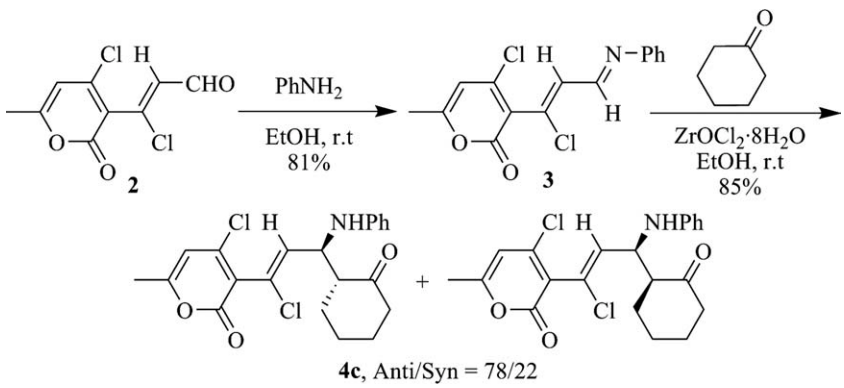
The $ZrOCl_2{\cdot}8H_2O$ catalyzed Mannich reaction was first studied with preformed imine **3**. As shown in Scheme 2, imine **3**, which was synthesized by reaction of **2** and aniline in EtOH at room temperature, was treated with cyclohexanone in the presence of catalytic amount of $ZrOCl_2{\cdot}8H_2O$ and Mannich adduct **4c** was isolated in 85% yield, with 78% anti selectivity.

Subsequently, a one-pot direct Mannich-type reaction of **2** with anilines and cyclic ketones were investigated (Scheme 3).

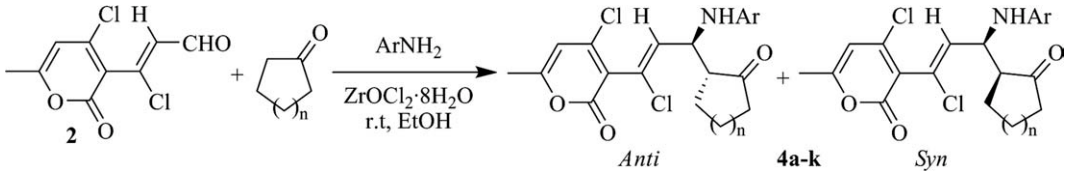
To examine the optimal conditions, Mannich reaction of **2** (1 mmol), aniline (1 equiv.), and cyclohexanone (2 equiv.), using $ZrOCl_2{\cdot}8H_2O$ as catalyst was carried out in different solvents such as acetonitrile, dichloromethane, ethanol, water, and solvent-free conditions. Ethanol was determined as a powerful solvent for high yield and anti selectivity of reaction and environmental acceptability. In dichloromethane, acetonitrile and under solvent-free conditions, in addition to Mannich adducts, side product **5** (Fig. 2), was obtained. In water, imine **3** was isolated as a sole product. Also 0.07 equiv. (7 mol %) of $ZrOCl_2{\cdot}8H_2O$ was determined as optimum amount of catalyst.

Eleven examples of the direct Mannich-type reaction of 2, anilines and cyclic ketones in ethanol are listed in Table 1. The reactions were performed by adding cyclic ketones (2 equiv.) to a mixture of the 2 (1 mmol) and anilines (1 equiv.) in ethanol in the presence of 0.07 equiv. of $ZrOCl_2{\cdot}8H_2O$ at room temperature to give the corresponding β-amino ketones 4a–k in 40–85% yields with moderate to high anti selectivity (Scheme 3).

Scheme 2. Synthesis of imine **3** and its Mannich reaction with cyclohexanone.



Scheme 3. One-pot Mannich-type reaction of **2**, anilines and cyclic ketones.



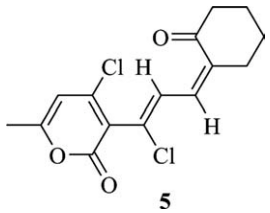


Figure 2. Structure of side product **5**.

According to the literature [8a,9d] anti/syn ratio was determined using ^{1}H NMR spectra.

Exceptionally, in the case of cyclopentanone ($n = 1$), in addition to Mannich adducts **4a**,**b** the side product **6** was obtained. With increasing reaction time (over 2 h) the Mannich adducts **4a**,**b** were completely converted to **6** (Scheme 4). In the cases of cyclohexanone, product **4c** even after 24 h was not converted to adduct **5**. This can be attributed to more acidity of cyclopentanone protons in comparison with cyclohexanone ones. In the ^{1}H NMR spectra of **5** and **6**, the values of coupling constant ^3J of the proton signals of —ClC=C**H**—C**H**= equal to 11.3 and 11.2 Hz, respectively, indicate that these atoms are located in the *s-trans* position.

Unexpectedly, from reaction of aliphatic amine such as *n*-butyl amine with **2** and cyclohexanone in the presence of $ZrOCl_2 \cdot 8H_2O$ in ethanol at room temperature, **5** was obtained as a sole product (Scheme 5). In fact, *n*-butyl amine acts as a base and aldol condensation was occurred instead of Mannich reaction.

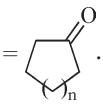
Also, direct Mannich-type reaction of **2** and anilines with acyclic ketones such as acetone and acetophenone catalyzed with $ZrOCl_2 \cdot 8H_2O$ was investigated at room temperature and corresponding β-amino ketones **7a–d** were obtained in good to high yields in short reaction time. The overall reaction is best formulated in Scheme 6.

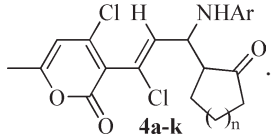
Methyl and Ethyl acetoacetate were also treated in the direct Mannich-type reaction with **2** and aniline, catalyzed with $ZrOCl_2 \cdot 8H_2O$ in ethanol at room temperature in 25 min, and interestingly corresponding dihydropyridines **8a**,**b** were isolated as sole products instead of Mannich adduct **9** (Scheme 7).

Table 1

Yields and selectivity of direct mannich-type reaction of β-[(2*H*-pyran-2-one)-3-yl]-β-chloroacrolein **2**, anilines, and cyclic ketones in the presence of $ZrOCl_2 \cdot 8H_2O$.

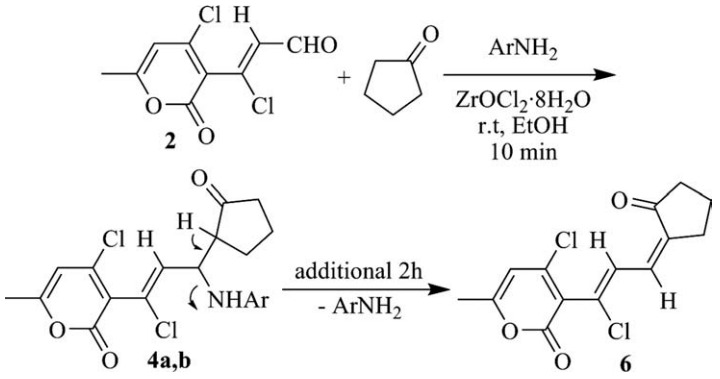
Ketone[a]	$ArNH_2$	Product[b]	Time (min)	Yield (%)[c]	Anti/Syn
$n = 1$	$C_6H_5NH_2$	**4a**	10	40	63:37
$n = 1$	4-$ClC_6H_4NH_2$	**4b**	10	55	70:30
$n = 2$	$C_6H_5NH_2$	**4c**	25	80	74:26
$n = 2$	4-$ClC_6H_4NH_2$	**4d**	30	76	58:42
$n = 2$	2-$ClC_6H_4NH_2$	**4e**	30	75	58:42
$n = 2$	3,4-$Cl_2C_6H_3NH_2$	**4f**	30	85	33:67
$n = 2$	4-$BrC_6H_4NH_2$	**4g**	30	80	70:30
$n = 2$	4-$MeOC_6H_4NH_2$	**4h**	15	85	75:25
$n = 2$	4-*n*$BuC_6H_4NH_2$	**4i**	20	78	80:20
$n = 3$	$C_6H_5NH_2$	**4j**	40	76	70:30
$n = 3$	4-$ClC_6H_4NH_2$	**4k**	45	75	62:38

[a] Ketone =  .

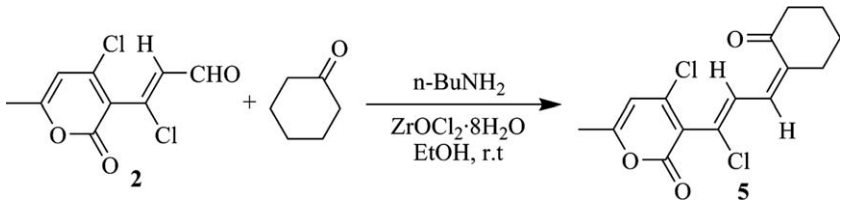
[b] Product = 

[c] Isolated yields.

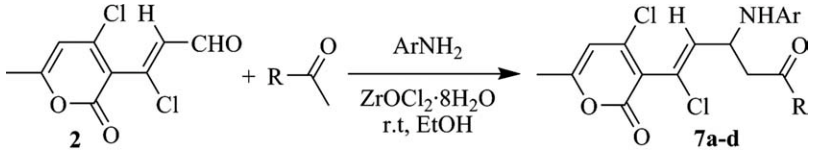
Scheme 4. Conversion of Mannich adducts **4a**,**b** to adduct **6**.



Scheme 5. Aldol reaction of **2** with cyclohexanone in the presence of *n*-$BuNH_2$/$ZrOCl_2 \cdot 8H_2O$.

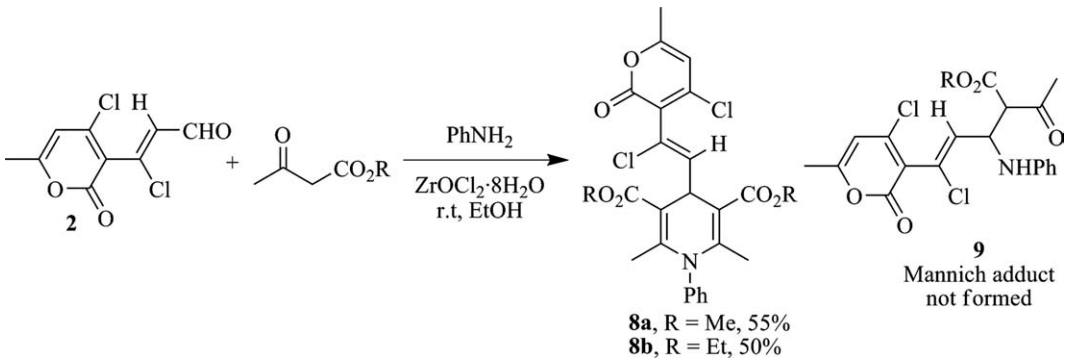


Scheme 6. Mannich reaction of **2**, anilines and acyclic ketones.



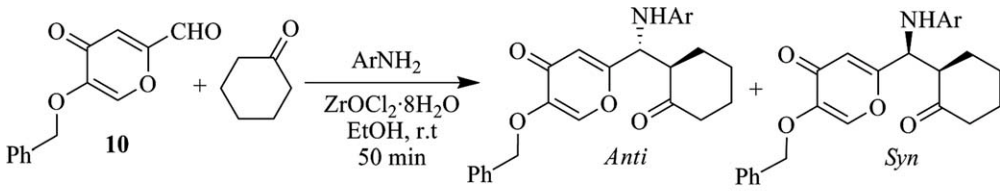
7a R = Me, Ar = C_6H_5, 10 min, 80%
7b R = Me, Ar = 4-ClC_6H_4, 10 min, 75%
7c R = Ph, Ar = C_6H_5, 90 min, 67%
7d R = Ph, Ar = 4-ClC_6H_4, 90 min, 65%

Scheme 7. Synthesis of new *N*-aryl dihydropyridines possessing β-[(2*H*-pyran-2-one)-3-yl]-β-chlorovinyl at C_4-position.



8a, R = Me, 55%
8b, R = Et, 50%

Scheme 8. Mannich-type reaction of comenic aldehyde **10**, anilines, and cyclohexanone.



11a Ar = C_6H_5, 88%, *Anti*/*Syn* = 40/60
11b Ar = 4-ClC_6H_4, 85%, *Anti*/*Syn* = 55/45
11c Ar = 3,4-$Cl_2C_6H_3$, 90% *Anti*/*Syn* = 75/25

Also, 5-(benzyloxy)-4-oxo-4*H*-pyran-2-carbaldehyde (*O*-protected comenic aldehyde) **10** was synthesized according to literature [14] and used in three component direct Mannich-type reaction with three different anilines and cyclohexanone. As shown in Scheme 8, $ZrOCl_2 \cdot 8H_2O$ efficiently catalyzed this reaction at room temperature and Mannich adducts **11a–c** were obtained in high yields with moderate stereoselectivity.

CONCLUSIONS

In summary, new β-[(2*H*-pyran-2-one)-3-yl]-β-chloroacrolein was synthesized in good yield and was subjected to the three-component Mannich-type reaction with different anilines, cyclic and acyclic ketones, catalyzed with $ZrOCl_2 \cdot 8H_2O$ in ethanol. Moderate to good anti selectivity was observed in very short reaction times at room temperature. Similarly, Mannich-type reaction with protected comenic aldehyde was also investigated, and corresponding β-amino ketones were obtained in high yields with moderate to high stereoselectivity. Ethyl and methyl acetoacetate were also treated with aniline and β-[(2*H*-pyran-2-one)-3-yl]-β-chloroacrolein and interestingly corresponding dihydropyridines were synthesized instead of Mannich adduct.

EXPERIMENTAL

General. All chemicals were purchased and used without any further purification. Melting points were determined on a Electrothermal MEL-TEMP apparatus (model 1202D) and are uncorrected. FTIR spectra were obtained with a Bruker Tensor 27 spectrometer. NMR spectra were recorded at 400 and 500 MHz for proton and at 100 and 125 MHz for carbon nuclei in $CDCl_3$. Elemental analyses were done by a Vario EL III, Elementar. The products were purified by PLC on silica gel by using hexane/acetone mixture as eluent. All compounds were characterized by their spectroscopic data and elemental analysis.

Synthesis of Z-3-chloro-3-(4-chloro-6-methyl-2-oxo-2H-pyran-3-yl)acrolein (2). $POCl_3$ (14.8 g, 96.4 mmol) was added dropwise to dimethylformamide (DMF) (24 mL) with stirring at 30–35°C. The mixture was stirred at 50°C for 1 h. Then a solution of dehydroacetic acid **1** (4 g, 19.4 mmol) in least amount of DMF was added dropwise with stirring to the reaction mixture. After that the mixture was stirred at 45–55°C for 2 h, kept over night at room temperature and poured into the water (200 mL). The obtained solution was left at room temperature. Yellowish brown crystals were filtered off and dried in air. β-[(2*H*-Pyran-2-one)-3-yl]-β-chloroacrolein **2** was obtained in 69.4% yield. Mp. 90–92°C; FTIR (KBr): 3081, 3030, 2968, 2927 (CH), 2864, 2746 ($CH_{Aldehyde}$), 1718, 1679, 1616, 1545, 1304, 1248, 1121, 837, 768 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 10.18 (d, ^3J = 6.8 Hz, 1H, CHO), 6.32 (d, ^3J = 6.8 Hz, 1H, CH_{Vinyl}), 6.26 (s, 1H, $CH_{\alpha\text{-Pyrone}}$), 2.35 (s, 3H, CH_3) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 190.6 ($C{=}O_{Aldehyde}$), 164.1, 158.5, 150.8, 142.8, 132.3, 120.1, 107.1, 20.4 (CH_3) ppm; Ms: m/z = 233 ($[M+H]^+$, 4%; $[M+H+2]^+$, 2.8%; $[M+H+4]^+$, 1.3%), 205 (25%), 189 (36%), 169 (30%), 43 (100%); Anal. Calcd. for $C_9H_6Cl_2O_3$: C, 46.38; H, 2.60. Found: C, 46.56; H, 2.65.

Synthesis of 4-chloro-3-[(1Z)-1-chloro-3-(phenylimino)-prop-1-enyl]-6-methyl-2H-pyran-2-one (3). β-[(2*H*-Pyran-2-one)-3-yl]-β-chloroacrolein **2** (1 mmol) was treated with Aniline (1 mmol) in ethanol (3 mL) at room temperature for 2 min. After completion of the reaction, mixture was poured into the water (20 mL). The resulting yellow solids were separated by filtration and dried in air. Imine **3** was obtained in 80.8% yield, Mp. 124–126°C; FTIR (KBr): 3100, 3020, 2967, 2922, 1717, 1684, 1625, 1542, 1266, 1154, 821, 764, 694 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$): δ 8.62 (d, ^3J = 8.5 Hz, 1H, CH=N), 7.39–7.43 (m, 2H, CH_{Ar}), 7.22–7.30 (m, 3H, CH_{Ar}) 6.77 (d, ^3J = 8.5 Hz, 1H, CH_{Vinyl}), 6.24 (s, 1H, $CH_{\alpha\text{-Pyrone}}$), 2.33 (s, 3H, CH_3) ppm; ^{13}C NMR(100 MHz, $CDCl_3$): δ 161.9, 157.7, 155.7, 149.8, 149.3, 132.7, 131.6, 128.2, 126.0, 119.9, 119.3, 105.7, 18.8 (CH_3) ppm; Anal. Calcd. for $C_{15}H_{11}Cl_2NO_2$: C, 58.46; H, 3.60; N, 4.55. Found: C, 58.28; H, 3.91; N, 4.77.

General procedure for Mannich-type reaction. To a solution of β-[(2*H*-Pyran-2-one)-3-yl]-β-chloroacrolein **2** (1 mmol) in ethanol (5 mL) were added aniline (1 mmol), cyclohexanone (2 eq), and $ZrOCl_2 \cdot 8H_2O$ (0.022 g), successively at room temperature (20–25°C) and stirred for 25 min. After completion of the reaction, ethanol was evaporated under reduced pressure. The crude solid was dissolved in CH_2Cl_2 (10 mL) and catalyst was removed by filtration. Filtrate was washed with a 5% aqueous $NaHCO_3$ solution and brine, dried over anhydrous Na_2SO_4, and concentrated to dryness. The crude mixture was purified by PLC on silica gel using hexane/acetone (20:3) to afford the final product. Specific detail was given for each compound.

(Z)-4-Chloro-3-[1-chloro-3-(2-oxocyclopentyl)-3-(phenylamino)prop-1-enyl]-6-methyl-2H-pyran-2-one (4a). Anti/Syn: 63/37; Yellow solid; FTIR (KBr): 3381 (NH), 3055, 3020,

2939, 2865, 1734, 1722, 1626, 1546, 1505, 1305, 1260, 840, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.13–7.18 (m, 2H, CH_{Ar}), 6.67–6.75 (m, 3H, CH_{Ar}), 6.10 (d, ^4J = 0.8 Hz, 0.63H, $CH_{\alpha\text{-Pyrone}}$, anti), 6.05 (d, ^4J = 0.7 Hz, 0.37H, $CH_{\alpha\text{-Pyrone}}$, syn), 5.93 (d, ^3J = 8.7 Hz, 0.63H, CH_{Vinyl}, anti), 5.62 (d, ^3J = 9.3 Hz, 0.37H, CH_{Vinyl}, syn), 4.70 (dd, ^3J = 3.9 Hz, ^3J = 9.3 Hz, 0.37H, CH—N, syn), 4.53 (dd, ^3J = 7.1 Hz, ^3J = 8.6 Hz, 0.63H, CH—N, anti), 2.28 (s, 3H, CH_3, (anti and syn)), 2.06–2.35 (m, 7H, CH and $CH_{2\ Cyclopentanone}$, anti and syn); ^{13}C NMR (100 MHz, $CDCl_3$): δ 220.7, 218.7 ($C{=}O_{Cyclopentanone}$), 161.1, 161.0, 158.3, 149.1, 148.9, 145.5, 136.1, 133.4, 128.1, 128.0, 123.2, 122.9, 119.8, 117.5, 117.0, 113.4, 113.1, 105.5, 105.4, 52.7, 52.2, 51.4, 50.8, 38.5, 37.9, 25.9, 25.3, 19.9, 19.7, 18.9, 18.7 ppm; Anal. Calcd. for $C_{20}H_{19}Cl_2NO_3$: C, 61.24; H, 4.88; N, 3.57. Found: C, 60.93; H, 5.01; N, 3.68.

(Z)-4-Chloro-3-[1-chloro-3-(4-chlorophenylamino)-3-(2-oxocyclopentyl)prop-1-enyl]-6-methyl-2H-pyran-2-one (4b). Anti/Syn: 70/30; Yellow solid; FTIR (KBr): 3378 (NH), 3070, 3061, 2940, 2860, 1733, 1724, 1630, 1545, 1508, 1306, 1263, 857, 761 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.08–7.12 (m, 2H, CH_{Ar}, anti and syn), 6.62–6.66 (m, 1.4H, CH_{Ar}, anti), 6.59–6.61 (m, 0.6H, CH_{Ar}, syn), 6.11 (d, ^4J = 0.7 Hz, 0.7H, $CH_{\alpha\text{-Pyrone}}$, anti), 6.07 (d, ^4J = 0.8 Hz, 0.3H, $CH_{\alpha\text{-Pyrone}}$, syn), 5.87 (d, ^3J = 8.7 Hz, 0.7H, CH_{Vinyl}, anti), 5.58 (d, ^3J = 9.4 Hz, 0.3H, CH_{Vinyl}, syn), 4.75–5.32 (s, br, 1H, NH, anti and syn), 4.63 (dd, ^3J = 3.3 Hz, ^3J = 8.9 Hz, 0.3H, CH—N, syn), 4.45 (dd, ^3J = 7.5 Hz, ^3J = 8.5 Hz, 0.7H, CH—N, anti), 1.85–2.46 (m, 7H, CH and $CH_{2\ Cyclopentanone}$, anti and syn), 2.25 (d, ^4J = 0.4 Hz, 2.1H, CH_3, anti), 2.23 (d, ^4J = 0.6 Hz, 0.9H, CH_3, syn). ^{13}C NMR (100 MHz, $CDCl_3$): δ 220.1, 219.3 ($C{=}O_{Cyclopentanone}$), 161.2, 161.0, 158.2, 158.1, 151.3, 150.1, 145.8, 136.6, 134.0, 128.8, 128.1, 124.1, 124.0, 119.6, 118.3, 118.1, 114.0, 113.8, 105.2, 52.4, 52.1, 51.1, 50.9, 38.6, 37.9, 26.1, 25.6, 20.3, 19.7, 18.3, 18.1 ppm; Anal. Calcd. for $C_{20}H_{18}Cl_3NO_3$: C, 56.29; H, 4.25; N, 3.28. Found: C, 56.01; H, 4.23; N, 3.59.

(Z)-4-Chloro-3-[1-chloro-3-(2-oxocyclohexyl)-3-(phenylamino)prop-1-enyl]-6-methyl-2H-pyran-2-one (4c). Anti/Syn: 74/26; Pale yellow solid, FTIR (KBr): 3386 (NH), 3085, 3030, 2938, 2862, 1731, 1699, 1625, 1603, 1546, 1505, 1438, 1384, 1301, 1257, 1212, 795, 752, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.14–7.18 (m, 2H, CH_{Ar}), 6.68–6.73 (m, 3H, CH_{Ar}), 6.07 (d, ^3J = 9.3 Hz, 0.26H, CH_{Vinyl}, syn), 6.06 (d, ^4J = 0.8 Hz, 0.74H, $CH_{\alpha\text{-Pyrone}}$, anti), 6.05 (d, ^4J = 0.7 Hz, 0.26H, $CH_{\alpha\text{-Pyrone}}$, syn), 6.03 (d, ^3J = 8.4 Hz, 0.74H, CH_{Vinyl}, anti), 4.53 (dd, ^3J = 3.7 Hz, ^3J = 9.3 Hz, 0.26H, CH—N, syn), 4.48 (dd, ^3J = 4.8 Hz, ^3J = 8.4 Hz, 0.74H, CH—N, anti), 2.94 (dt, ^3J = 4.4 Hz, ^3J = 12.9 Hz, 0.26H, —COCH<, syn), 2.83–2.89 (m, 0.74H, —COCH<, anti), 2.23 (s, 3H, CH_3), 1.66–2.41 (m, 8H, $CH_{2\ Cyclohexanone}$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 211.8 ($C{=}O_{Cyclohexanone}$), 160.9, 160.8, 158.2, 148.9, 146.1, 145.7, 136.8, 133.4, 128.0, 124.0, 122.6, 120.0, 119.6, 117.0, 116.9, 113.2, 112.8, 105.4, 105.3, 53.7, 53.6, 52.6, 52.5, 41.5, 41.3, 30.6, 29.6, 26.7, 25.9, 23.8, 23.4, 18.6 ppm; Anal. Calcd. for $C_{21}H_{21}Cl_2NO_3$: C, 62.08; H, 5.21; N, 3.45. Found: C, 62.07; H, 5.26; N, 3.69.

(Z)-4-Chloro-3-[1-chloro-3-(4-chlorophenylamino)-3-(2-oxocyclohexyl)prop-1-enyl]-6-methyl-2H-pyran-2-one (4d). Anti/Syn: 58/42; Pale yellow solid, FTIR (KBr): 3393 (NH), 3095, 3042, 2935, 2864, 1729, 1697, 1623, 1548, 1498, 1439, 1238, 822 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.07–7.12 (m, 2H, CH_{Ar}), 6.57–6.62 (m, 2H, CH_{Ar}), 6.07 (d, ^4J = 0.7 Hz, 0.58H, $CH_{\alpha\text{-Pyrone}}$, anti), 6.06 (d, ^4J = 0.8 Hz, 0.42H, $CH_{\alpha\text{-Pyrone}}$, syn), 6.03 (d, ^3J = 9.3 Hz, 0.42H, CH_{Vinyl}, syn), 5.98 (d, ^3J = 8.4 Hz, 0.58H, CH_{Vinyl}, anti), 4.77 (s, br, 1H, NH), 4.45 (dd, ^3J = 3.7 Hz, ^3J = 9.3 Hz, 0.42H, CH—N, syn), 4.39 (dd, ^3J = 4.6 Hz, ^3J = 8.4 Hz, 0.58H, CH—N, anti), 2.91 (dt, ^3J = 4.5 Hz, ^3J = 12.8 Hz, 0.42H, —COCH<, syn), 2.80–2.85 (m, 0.58H, —COCH<, anti), 2.23 (s, 3H, CH_3), 1.65–2.42 (m, 8H, $CH_{2\ Cyclohexanone}$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 212.0, 211.9 ($C{=}O_{Cyclohexanone}$), 161.3, 160.9, 158.2, 149.1, 148.7, 144.3, 140.4, 138.4, 137.8, 132.9, 128.1, 127.0, 126.9, 126.7, 124.4, 121.5, 120.1, 117.1, 114.3, 105.7, 105.3, 53.5, 52.7, 41.5, 40.9, 30.4, 29.5, 26.5, 25.9, 23.8, 23.7, 18.8, 18.7 ppm; Anal. Calcd. for $C_{21}H_{20}Cl_3NO_3$: C, 57.23; H, 4.57; N, 3.18. Found: C, 57.12; H, 4.62; N, 3.43.

(Z)-4-Chloro-3-[1-chloro-3-(2-chlorophenylamino)-3-(2-oxocyclohexyl)prop-1-enyl]-6-methyl-2H-pyran-2-one (4e). Anti/Syn: 58/42; Pale yellow solid, FTIR (KBr): 3384 (NH), 3092, 2937, 2865, 1733, 1703, 1625, 1595, 1550, 1504, 1438, 1244, 848, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.20–7.23 [2 × d, 7.22 (d, $^3J_{ortho}$ = 7.9 Hz, 0.42H, CH_{Ar}, syn), 7.21 (d, $^3J_{ortho}$ = 7.9 Hz, 0.58H, CH_{Ar}, anti)], 7.10–7.16 (m, 1H, CH_{Ar}), 6.82 (dd, $^4J_{meta}$ = 1.2 Hz, $^3J_{ortho}$ = 8.3 Hz, 0.42H, CH_{Ar}, syn), 6.77 (dd, $^4J_{meta}$ = 1.2 Hz, $^3J_{ortho}$ = 8.2 Hz, 0.58H, CH_{Ar}, anti), 6.60–6.65 (m, 1H, CH_{Ar}), 6.07 (d, ^4J = 0.9 Hz, 0.58H, $CH_{\alpha\text{-Pyrone}}$, anti), 6.06 (d, ^4J = 0.9 Hz, 0.42H, $CH_{\alpha\text{-Pyrone}}$, syn), 6.05 (d, ^3J = 9.4 Hz, 0.42H, CH_{Vinyl}, syn), 6.02 (d, ^3J = 8.4 Hz, 0.58H, CH_{Vinyl}, anti), 5.49 (s, br, 1H, NH), 4.57 (dd, ^3J = 3.5 Hz, ^3J = 9.3 Hz, 0.42H, CH—N, syn), 4.50 (dd, ^3J = 4.5 Hz, ^3J = 8.4 Hz, 0.58H, CH—N, anti), 2.94–3.00 (m, 0.42H, —COCH<, syn), 2.86–2.92 (m, 0.58H, —COCH<, anti), 2.23 (d, ^4J = 0.8 Hz, 3H, CH_3), 1.67–2.43 (m, 8H, $CH_{2\ Cyclohexanone}$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 211.5, 211.4 ($C{=}O_{Cyclohexanone}$), 161.0, 160.9, 158.2, 149.0, 148.8, 142.2, 141.9, 136.2, 133.0, 128.0, 126.7, 124.4, 122.9, 119.6, 119.1, 117.0, 116.9, 112.2, 111.8, 105.5, 105.4, 53.6, 52.7, 52.3, 41.54, 41.52, 30.8, 29.5, 26.8, 25.9, 23.8, 23.6, 18.7 ppm; Anal. Calcd. for $C_{21}H_{20}Cl_3NO_3$: C, 57.23; H, 4.57; N, 3.18. Found: C, 57.40; H, 4.69; N, 3.50.

(Z)-4-Chloro-3-[1-chloro-3-(3,4-dichlorophenylamino)-3-(2-oxocyclohexyl)prop-1-enyl]-6-methyl-2H-pyran-2-one (4f). Anti/Syn: 33/67; Pale yellow solid, FTIR (KBr): 3395 (NH), 3048, 2934, 2863, 1730, 1702, 1621, 1546, 1488, 1439, 1249, 844, 796, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.16–7.20 [2 × d: 7.19 (d, $^3J_{ortho}$ = 8.7 Hz, 0.33H, CH_{Ar}, anti), 7.18 (d, $^3J_{ortho}$ = 8.7 Hz, 0.67H, CH_{Ar}, syn)], 6.80 (d, $^4J_{meta}$ = 2.4 Hz, 0.33H, CH_{Ar}, anti), 6.78 (d, $^4J_{meta}$ = 2.6 Hz, 0.67H, CH_{Ar}, syn), 6.50–6.56 (m, 1H, CH_{Ar}), 6.09 (s, 0.33H, $CH_{\alpha\text{-Pyrone}}$, anti), 6.08 (s, 0.67H, $CH_{\alpha\text{-Pyrone}}$, syn), 5.97–6.01 [2 × d: 5.99 (d, ^3J = 9.4 Hz, 0.67H, CH_{Vinyl}, syn), 5.98 (d, ^3J = 8.4 Hz, 0.33H, CH_{Vinyl}, anti)], 5.12 (s, br, 1H, NH), 4.41 (dd, ^3J = 3.7 Hz, ^3J = 9.3 Hz, 0.67H, CH—N, syn), 4.37 (dd, ^3J = 4.8 Hz, ^3J = 8.5 Hz, 0.33H, CH—N, anti), 2.84–2.93 (m, 1H, —COCH<,anti+syn), 2.24 (s, 3H, CH_3), 1.62–2.43 (m, 8H, $CH_{2\ Cyclohexanone}$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 212.1, 212.0 ($C{=}O_{Cyclohexanone}$), 161.2, 161.1, 158.3, 158.2, 149.2, 148.9, 145.2, 132.3, 131.7, 131.6, 129.5, 129.4, 125.0, 119.9, 119.6, 119.5, 114.5, 112.9, 105.5, 105.4, 53.3, 53.2, 52.7, 41.5, 30.8, 29.4, 26.7, 25.8, 23.7, 23.5, 18.8 ppm; Anal. Calcd. for $C_{21}H_{19}Cl_4NO_3$: C, 53.08; H, 4.03; N, 2.95. Found: C, 53.01; H, 4.38; N, 3.21.

(Z)-3-(3-(4-Bromophenylamino)-1-chloro-3-(2-oxocyclohexyl)prop-1-enyl)-4-chloro-6-methyl-2H-pyran-2-one (4g). Anti/Syn: 70/30; Pale yellow solid, FTIR (KBr): 3390 (NH), 3093, 2935, 2864, 1729, 1698, 1627, 1592, 1549, 1493, 1300, 820 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.21–7.25 (m, 2H, CH_{Ar}), 6.51–6.57 (m, 2H, CH_{Ar}), 6.08 (d, ^4J = 0.6 Hz, 0.7H, $CH_{\alpha\text{-Pyrone}}$, anti), 6.07 (d, ^4J = 0.5 Hz, 0.3H, $CH_{\alpha\text{-Pyrone}}$, syn), 6.03 (d, ^3J = 9.3 Hz, 0.3H, CH_{Vinyl}, syn), 5.98 (d, ^3J = 8.4 Hz, 0.7H, CH_{Vinyl}, anti), 4.45 (dd, ^3J = 3.6 Hz, ^3J = 9.3 Hz, 0.3H, CH—N, syn), 4.38 (dd, ^3J = 4.5 Hz, ^3J = 8.3 Hz, 0.7H, CH—N, anti), 2.91 (dt, ^3J = 4.4 Hz, ^3J = 13.0 Hz, 0.3H, —COCH<, syn), 2.80–2.85 (m, 0.7H, —COCH<, anti), 2.24 (s, 3H, CH_3), 1.66–2.40 (m, 8H, $CH_{2\ Cyclohexanone}$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): 212.0 ($C{=}O_{Cyclohexanone}$), 161.0, 158.2, 149.0, 145.3, 144.8, 136.2, 132.9, 130.7, 124.5, 123.0, 119.6, 114.8, 114.5, 108.7, 108.6, 105.5, 105.4, 53.6, 53.5, 52.8, 52.6, 41.6, 41.5, 30.8, 30.5, 26.7, 25.9, 23.8, 23.5, 18.7 ppm; Anal. Calcd. for $C_{21}H_{20}BrCl_2NO_3$: C, 51.98; H, 4.15; N, 2.89. Found: C, 51.73; H, 4.53; N, 2.97.

(Z)-4-Chloro-3-[1-chloro-3-(4-methoxyphenylamino)-3-(2-oxocyclohexyl)prop-1-enyl]-6-methyl-2H-pyran-2-one (4h). Anti/Syn: 75/25; Pale yellow solid, FTIR (KBr): 3343 (NH), 3039, 2936, 2865, 1729, 1694, 1620, 1543, 1507, 1442, 1301, 1246, 850, 774, 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.73–6.76 (m, 2H, CH_{Ar}), 6.61–6.65 (m, 2H, CH_{Ar}), 6.04–6.07 [3 × d: 6.06 (d, ^3J = 9.2 Hz, 0.25H, CH_{Vinyl}, syn), 6.06 (d, ^4J = 0.8 Hz, 0.75H, $CH_{\alpha\text{-Pyrone}}$, anti), 6.04 (d, ^4J = 0.8 Hz, 0.25H, $CH_{\alpha\text{-Pyrone}}$, syn)], 5.99 (d, ^3J = 8.4 Hz, 0.75H, CH_{Vinyl}, anti), 4.43 (dd, ^3J = 3.7 Hz, ^3J = 9.3 Hz, 0.25H, CH—N, syn), 4.39 (dd, ^3J = 4.9 Hz, ^3J = 8.4 Hz, 0.75H, CH—N, anti), 3.71–3.72 (2 × s, 3H, —OCH_3), 2.90–2.95 (m, 0.25H, —COCH<, syn), 2.77–2.82 (m, 0.75H, —COCH<, anti), 2.22 (2 × s, 3H, CH_3), 1.65–2.40 (m, 8H, $CH_{2\ Cyclohexanone}$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 212.0, 211.9 ($C{=}O_{Cyclohexanone}$), 160.9, 160.8, 158.2, 151.6, 151.5, 148.9, 148.6, 140.2, 139.8, 133.9, 132.0, 127.0, 126.7, 124.0, 122.8, 114.9, 114.5, 113.7, 113.6, 105.4, 105.3, 54.7, 54.6, 53.7, 52.7, 41.6, 41.4, 30.6, 29.6, 26.7, 26.0, 23.9, 23.5, 18.8, 18.7 ppm; Anal. Calcd. for $C_{22}H_{23}Cl_2NO_4$: C, 60.56; H, 5.31; N, 3.21. Found: C, 60.29; H, 5.70; N, 3.38.

(Z)-3-[3-(4-Butylphenylamino)-1-chloro-3-(2-oxocyclohexyl) prop-1-enyl]-4-chloro-6-methyl-2H-pyran-2-one (4i). Anti/Syn: 80/20; Pale yellow solid, FTIR (KBr): 3381 (NH), 3094, 3019, 2930, 2861, 1733, 1684, 1623, 1550, 1517, 1299, 829, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.97 (d, $^3J_{ortho}$ = 8.3 Hz, 2H, CH_{Ar}), 6.63 (d, $^3J_{ortho}$ = 8.3 Hz, 0.4H, CH_{Ar}, syn), 6.60 (d, $^3J_{ortho}$ = 8.3 Hz, 1.6H, CH_{Ar}, anti), 6.07 (d, ^3J = 9.4 Hz, 0.2H, CH_{Vinyl}, syn) 6.06 (d, ^4J = 0.7 Hz, 0.8H, $CH_{\alpha\text{-Pyrone}}$, anti), 6.05 (d, ^4J = 0.7 Hz, 0.2H, $CH_{\alpha\text{-Pyrone}}$, syn), 6.00 (d, ^3J = 8.3 Hz, 0.8H, CH_{Vinyl}, anti), 4.50 (dd, ^3J = 3.6 Hz, ^3J = 9.3 Hz, 0.2H, CH—N, syn), 4.44 (dd, ^3J = 4.8 Hz, ^3J = 8.3 Hz, 0.8H, CH—N, anti), 2.91–2.97 (m, 0.2H, —COCH<, syn), 2.79–2.85 (m, 0.8H, —COCH<, anti), 2.47 (t, ^3J = 7.6 Hz, 2H, $CH_{2\ Butyl}$), 2.23 (s, 3H, CH_3), 1.72–2.43 (m, 8H, $CH_{2\ Cyclohexanone}$), 1.48–1.55 (m, 2H, $CH_{2\ Butyl}$), 1.26–1.34 (m, 2H, $CH_{2\ Butyl}$), 0.89 (t, ^3J = 7.4 Hz, 3H, $CH_{3\ Butyl}$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 212.0 ($C{=}O_{Cyclohexanone}$), 160.8, 158.2, 148.9, 143.9, 137.2, 131.5, 127.9, 122.6, 119.8, 113.4, 113.1, 105.4, 53.7, 53.0, 41.4, 33.6, 32.9, 30.6, 26.7, 26.0, 23.5, 21.2, 18.7, 12.9 ppm; Anal. Calcd. for $C_{25}H_{29}Cl_2NO_3$: C, 64.94; H, 6.32; N, 3.03. Found: C, 65.03; H, 6.29; N, 3.31.

(Z)-4-Chloro-3-(1-chloro-3-(2-oxocycloheptyl)-3-(phenylamino)prop-1-enyl)-6-methyl-2H-pyran-2-one (4j). Anti/Syn: 70/30; Pale yellow solid, FTIR (KBr): 3381 (NH), 3094, 3050, 2928, 2857, 1732, 1695, 1623, 1606, 1550, 1503, 1440, 1301, 861, 744 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.13–7.17 (m, 2H, CH_{Ar}), 6.65–6.70 (m, 3H, CH_{Ar}), 6.06 (s, 1H, $CH_{\alpha\text{-Pyrone}}$), 5.82 (d, ^3J = 9.4 Hz, 0.3H, CH_{Vinyl}, syn), 5.80 (d, ^3J = 8.3 Hz, 0.7H, CH_{Vinyl}, anti), 4.60 (dd, ^3J = 4.1 Hz, ^3J = 9.4 Hz, 0.3H, CH—N, syn), 4.52 (dd, ^3J = 5.9 Hz, ^3J = 8.3 Hz, 0.7H, CH—N, anti), 2.98–3.08 (m, 1H, —COCH<, anti+syn), 2.50–2.55 (m, 2H, —CH_2CO—), 2.23 (s, 3H, CH_3), 1.20–2.08 (m, 8H, $CH_{2\ Cycloheptanone}$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 215.8, 215.1 ($C{=}O_{Cycloheptanone}$), 160.9, 158.3, 148.9, 146.1, 145.4, 136.3, 133.6, 128.1, 124.3, 123.0, 119.7, 117.0, 116.8, 113.1, 112.7, 105.4, 55.3, 54.2, 54.1, 53.6, 43.3, 42.3, 28.9, 28.2, 27.9, 27.5, 27.1, 23.7, 23.1, 18.7 ppm; Anal. Calcd. for $C_{22}H_{23}Cl_2NO_3$: C, 62.86; H, 5.52; N, 3.33. Found: C, 62.82; H, 5.67; N, 3.51.

(Z)-4-Chloro-3-[1-chloro-3-(4-chlorophenylamino)-3-(2-oxocycloheptyl)prop-1-enyl]-6-methyl-2H-pyran-2-one (4k). Anti/Syn: 62/38; Pale yellow solid, FTIR (KBr): 3383 (NH), 3096, 3029, 2929, 2858, 1736, 1699, 1626, 1600, 1551, 1500, 1300, 1254, 861, 775, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.08–7.11 (m, 2H, CH_{Ar}), 6.56–6.60 (m, 2H, CH_{Ar}), 6.08 (s, 1H, $CH_{\alpha\text{-Pyrone}}$, anti+syn), 5.78 (d, ^3J = 9.9 Hz, 0.38H, CH_{Vinyl}, syn), 5.77 (d, ^3J = 8.2 Hz, 0.62H, CH_{Vinyl}, anti), 4.84 (s, br, 1H, NH), 4.53 (dd, ^3J = 4.0 Hz, ^3J = 9.5 Hz, 0.38H, CH—N, syn), 4.45 (dd, ^3J = 5.8 Hz, ^3J = 8.3 Hz, 0.62H, CH—N, anti), 3.03–3.07 (m, 0.62H, —COCH<, anti), 2.95–3.01 (m, 0.38H, —COCH<, syn), 2.49–2.51 (m, 2H, —CH_2CO—), 2.23 (s, 3H, CH_3), 1.24–2.17 (m, 8H, $CH_{2\ Cycloheptanone}$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 215.9, 215.1 ($C{=}O_{Cycloheptanone}$), 161.1, 158.2, 149.0, 148.9, 144.7, 144.1, 135.8, 133.1, 127.9, 124.7, 123.4, 121.5, 121.4, 119.6, 114.2, 113.8, 105.4, 55.2, 54.4, 54.2, 53.3, 43.3, 42.4, 28.9, 28.6, 28.3, 28.2, 27.6, 27.1, 23.7, 22.9, 18.7 ppm. Anal. Calcd. for $C_{22}H_{22}Cl_3NO_3$: C, 58.10; H, 4.88; N, 3.08. Found: C, 57.92; H, 5.06; N, 3.36.

4-Chloro-3-[(1Z)-1-chloro-3-(2-oxocyclohexylidene)prop-1-enyl]-6-methyl-2H-pyran-2-one (5). White solid; Mp. 154–156°C; FTIR (KBr): 3039, 2962, 2930, 2876, 1728, 1675, 1634, 1614, 1580, 1302, 857, 803, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.41–7.43 (m, 1H, CH_{Vinyl}), 6.60 (d, ^3J = 11.3 Hz, 1H, CH_{Vinyl}), 6.17 (s, 1H, $CH_{\alpha\text{-Pyrone}}$), 2.67 (td, ^4J = 1.9 Hz, ^3J = 7.0 Hz, 2H, $CH_{2\ Cyclohexanone}$), 2.49 (t, ^3J = 6.6 Hz, 2H, —CH_2CO—), 2.28 (s, 3H, CH_3), 1.84–1.89 (m, 2H, CH_2), 1.76–1.80 (m, 2H, CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.6 ($C{=}O_{Cyclohexanone}$), 161.3, 158.2, 149.2, 138.4, 129.0, 127.0, 126.7, 120.3, 105.7, 39.2, 26.6, 22.2, 22.0, 18.8 ppm. Anal. calcd. for $C_{15}H_{14}Cl_2O_3$: C, 57.53; H, 4.51. Found: C, 57.58; H, 4.69.

4-Chloro-3-[(1Z)-1-chloro-3-(2-oxocyclopentylidene)prop-1-enyl]-6-methyl-2H-pyran-2-one (6). White solid, Mp. 182–184°C; FTIR (KBr): 3106, 3034, 2958, 1728, 1708, 1623, 1549, 1297, 1172, 861, 805 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$):δ 7.34 (dt, ^4J = 2.8 Hz, ^3J = 11.2 Hz, 1H, CH_{Vinyl}), 6.52 (d, ^3J = 11.2 Hz, 1H, CH_{Vinyl}), 6.18 (d, ^4J = 0.7 Hz, 1H, $CH_{\alpha\text{-Pyrone}}$), 2.71 (td, ^4J = 2.8 Hz, ^3J = 7.3 Hz, 2H, $CH_{2\ Cyclopentanone}$), 2.39 (t, ^3J = 7.9 Hz, 2H, —CH_2CO—), 2.29 (d, ^4J = 0.4 Hz, 3H, CH_3), 1.95–2.03 (m, 2H, $CH_{2\ Cyclopentanone}$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.0 ($C{=}O_{Cyclopentanone}$),

161.4, 158.1, 149.2, 140.1, 129.8, 128.5, 123.7, 120.1, 105.7, 37.5, 26.6, 18.8, 18.6 ppm. Anal. Calcd. for $C_{14}H_{12}Cl_2O_3$: C, 56.21; H, 4.04. Found: C, 55.83; H, 4.06.

(Z)-4-Chloro-3-[1-chloro-5-oxo-3-(phenylamino)hex-1-enyl]-6-methyl-2H-pyran-2-one (7a). Pale yellow solid, Mp. 30–32°C; FTIR (KBr): 3384 (NH), 3095, 3052, 3024, 2959, 2924, 1734, 1669, 1626, 1602, 1550, 1503, 1302, 860, 752, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.15–7.19 (m, 2H, CH_{Ar}), 6.71–6.74 (m, 1H, CH_{Ar}), 6.66–6.68 (m, 2H, CH_{Ar}), 6.08 (d, ^4J = 0.8 Hz, 1H, $CH_{\alpha\text{-Pyrone}}$), 5.95 (d, ^3J = 7.9 Hz, 1H, CH_{Vinyl}), 4.70–4.74 (dt, ^3J = 5.2 Hz, ^3J = 7.9 Hz, 1H, CH—N), 4.54 (s, br, 1H, NH), 2.98 (d, ^3J = 5.2 Hz, 2H, CH_2), 2.24 (d, ^4J = 0.5 Hz, 3H, $CH_{3\ \alpha\text{-Pyrone}}$), 2.23 (s, 3H, CH_3CO—) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.5 ($C{=}O_{Ketone}$), 161.1, 158.2, 149.1, 145.1, 136.3, 128.2, 123.0, 119.5, 117.8, 113.4, 105.4, 48.7, 45.3, 29.5, 18.7 ppm; Anal. Calcd. for $C_{18}H_{17}Cl_2NO_3$: C, 59.03; H, 4.68; N, 3.82. Found: C, 58.91; H, 4.98; N, 4.02.

(Z)-4-Chloro-3-[1-chloro-3-(4-chlorophenylamino)-5-oxohex-1-enyl]-6-methyl-2H-pyran-2-one (7b). Pale yellow solid, Mp. 34–36°C; FTIR (KBr): 3370 (NH), 3095, 3050, 2959, 2925, 2854, 1730, 1667, 1621, 1548, 1490, 1436, 1254, 863, 821, 773, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.10–7.13 (m, 2H, CH_{Ar}), 6.61–6.65 (m, 2H, CH_{Ar}), 6.09 (d, ^4J = 0.7 Hz, 1H, $CH_{\alpha\text{-Pyrone}}$), 5.92 (d, ^3J = 8.0 Hz, 1H, CH_{Vinyl}), 4.63–4.68 (ddd, ^3J = 4.3 Hz, ^3J = 6.1 Hz, ^3J = 7.9 Hz, 1H, CH—N), 2.92–3.04 [2 × dd: 3.02 (dd, ^3J = 6.2 Hz, ^2J = 17.1 Hz, 1H, CH_2), 2.95 (dd, ^3J = 4.3 Hz, ^2J = 17.1 Hz, 1H, CH_2), $CH_{2\ Diastrotopic\ Protons}$], 2.24 (s, 3H, $CH_{3\ \alpha\text{-Pyrone}}$), 2.22 (s, 3H, CH_3CO—) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.6 ($C{=}O_{Ketone}$), 161.3, 158.2, 149.1, 143.7, 135.7, 128.0, 123.4, 122.5, 119.4, 114.6, 105.4, 48.8, 45.1, 29.6, 18.7 ppm; Anal. Calcd. for $C_{18}H_{16}Cl_3NO_3$: C, 53.96; H, 4.02; N, 3.50. Found: C, 54.07; H, 4.18; N, 3.38.

(Z)-4-Chloro-3-[1-chloro-5-oxo-5-phenyl-3-(phenylamino)-pent-1-enyl]-6-methyl-2H-pyran-2-one (7c). Pale yellow solid, Mp. 126–128°C; FTIR (KBr): 3381 (NH), 3092, 3056, 3028, 2924, 2855, 1729, 1685, 1625, 1600, 1548, 1293, 1265, 861, 751, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.98–8.00 (m, 2H, CH_{Ar}), 7.57–7.60 (m, 1H, CH_{Ar}), 7.46–7.51 (m, 2H, CH_{Ar}), 7.14–7.19 (m, 2H, CH_{Ar}), 6.69–6.74 (m, 3H, CH_{Ar}), 6.07 (s, 1H, $CH_{\alpha\text{-Pyrone}}$), 6.07 (d, ^3J = 7.8 Hz, 1H, CH_{Vinyl}), 4.89–4.93 (m, 1H, CH—N), 3.46–3.57 (m, 2H, CH_2), 2.23 (s, 3H, $CH_{3\ \alpha\text{-Pyrone}}$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.7 ($C{=}O_{Ketone}$), 161.0, 158.2, 149.1, 145.6, 137.1, 135.5, 132.6, 128.2, 127.7, 127.6, 127.3, 122.8, 117.3, 113.1, 105.4, 48.8, 40.6, 18.7 ppm; Anal. Calcd. for $C_{23}H_{19}Cl_2NO_3$: C, 64.50; H, 4.47; N, 3.27. Found: C, 64.35; H, 4.65; N, 3.55.

(Z)-4-Chloro-3-[1-chloro-3-(4-chlorophenylamino)-5-oxo-5-phenylpent-1-enyl]-6-methyl-2H-pyran-2-one (7d). Pale yellow solid, Mp. 128–130°C; FTIR (KBr): 3371 (NH), 3172, 3060, 3031, 2924, 2855, 1731, 1695, 1621, 1547, 1493, 1456, 1213, 811, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.96–7.99 (m, 2H, CH_{Ar}), 7.59–7.63 (m, 1H, CH_{Ar}), 7.47–7.53 (m, 2H, CH_{Ar}), 7.20–7.22 (m, 2H, CH_{Ar}), 6.95–6.97 (m, 2H, CH_{Ar}), 6.19 (d, ^3J = 8.4 Hz, 1H, CH_{Vinyl}), 6.08 (d, ^4J = 0.8 Hz, 1H, $CH_{\alpha\text{-Pyrone}}$), 4.90–4.95 (m, 1H, CH—N), 3.55–3.77 [2 × dd: 3.74 (dd, ^3J = 6.8 Hz, ^2J = 17.1 Hz, 1H, CH_2), 3.58 (dd, ^3J = 4.0 Hz, ^2J = 17.3 Hz, 1H, CH_2), $CH_{2\ Diastrotopic\ Protons}$], 2.25 (d, ^4J = 0.6 Hz, 3H, $CH_{3\ \alpha\text{-Pyrone}}$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.7 ($C{=}O_{Ketone}$), 162.2, 159.2, 150.1, 145.3, 137.6, 136.4, 133.7, 129.0, 128.8, 128.3, 127.4, 124.2, 122.9, 115.2, 106.5, 49.9, 41.5, 19.8 ppm; Anal. Calcd. for $C_{23}H_{18}Cl_3NO_3$: C, 59.70; H, 3.92; N, 3.03. Found: C, 59.92; H, 4.07; N, 3.36.

(Z)-Dimethyl 4-[2-chloro-2-(4-chloro-6-methyl-2-oxo-2H-pyran-3-yl)vinyl]-2,6-dimethyl-1-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (8a). yellow solid, Mp. 54–56°C; FTIR (KBr): 3096, 2948, 2926, 2852, 1734, 1694, 1629, 1586, 1551, 1290, 1208, 860, 771, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.39–7.45 (m, 3H, CH_{Ar}), 7.10–7.13 (m, 2H, CH_{Ar}), 6.10 (s, 1H, $CH_{\alpha\text{-Pyrone}}$), 5.71 (d, ^3J = 9.4 Hz, 1H, CH_{Vinyl}), 5.15 (d, ^3J = 9.4 Hz, 1H, $CH_{Dihydropyridine}$), 3.77 (s, 6H, —OCH_3), 2.29 (s, 3H, $CH_{3\ \alpha\text{-Pyrone}}$), 1.98 (s, 6H, $CH_{3\ Dihydropyridine}$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.2 ($C{=}O_{Ester}$), 160.5, 158.3, 148.5, 147.3, 139.1, 134.5, 129.3, 128.4, 127.6, 120.9, 118.6, 105.4, 101.4, 50.3, 33.5, 18.7, 17.3 ppm; Anal. Calcd. for $C_{25}H_{23}Cl_2NO_6$: C, 59.53; H, 4.60; N, 2.78. Found: C, 59.68; H, 4.63; N, 2.88.

(Z)-Diethyl 4-[2-chloro-2-(4-chloro-6-methyl-2-oxo-2H-pyran-3-yl)vinyl]-2,6-dimethyl-1-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (8b). yellow solid, Mp. 42–44°C; FTIR (KBr): 3092, 3059, 2980, 2936, 1734, 1691, 1631, 1583, 1552, 1203, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.40–7.43 (m, 3H, CH_{Ar}), 7.10–7.12 (m, 2H, CH_{Ar}), 6.10 (d, ^4J = 0.7 Hz, 1H, $CH_{\alpha\text{-Pyrone}}$), 5.71 (d, ^3J = 9.5 Hz, 1H, CH_{Vinyl}), 5.15 (d, ^3J = 9.5 Hz, 1H, $CH_{Dihydropyridine}$), 4.23 (m, 4H, $CH_{2\ Ethyl}$), 2.24 (s, 3H, $CH_{3\ \alpha\text{-Pyrone}}$), 1.99 (s, 6H, CH_3), 1.35 (t, ^3J = 7.1 Hz, 6H, $CH_{3\ Ethyl}$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7 ($C{=}O_{Ester}$), 160.4, 158.3, 148.4, 147.1, 139.1, 134.5, 129.3, 128.3, 127.6, 120.9, 118.1, 105.4, 101.7, 59.2, 33.2, 18.7, 17.3, 13.4 ppm. Anal. Calcd. for $C_{27}H_{27}Cl_2NO_6$: C, 60.91; H, 5.11; N, 2.63. Found: C, 60.93; H, 5.18; N, 2.90.

5-Benzyloxy-2-[(2-oxocyclohexyl)(phenylamino)methyl]-4H-pyran-4-one (11a). Anti/Syn: 40/60; White solid; FTIR (KBr): 3408 (NH), 3031, 2935, 2861, 1708, 1642, 1555, 1523, 1455, 1246, 1208, 992 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.50 (s, 0.4H, $CH_{Pyrone\ 6\text{-position}}$, anti), 7.49 (s, 0.6H, $CH_{Pyrone\ 6\text{-position}}$, syn), 7.28–7.37 (m, 5H, CH_{Ar}), 7.13 (m, 2H, CH_{Ar}), 6.71–6.75 (m, 1H, CH_{Ar}), 6.59 (m, 2H, CH_{Ar}), 6.50 (s, 0.6H, $CH_{Pyrone\ 3\text{-position}}$, syn), 6.49 (s, 0.4H, $CH_{Pyrone\ 3\text{-position}}$, anti), 4.99–5.00 [2 × s: 5.00 (s, 0.8H, —CH_2O—, anti), 4.99 (s, 1.2H, —CH_2O—, syn), 4.64 (d, ^3J = 5.4 Hz, 0.4H, CH—N, anti), 4.41 (d, ^3J = 4.9 Hz, 0.6H, CH—N, syn), 4.20 (s, br, 1H, NH), 2.98–3.04 (m, 0.6H, —COCH<, syn), 2.84–2.92 (m, 0.4H, —COCH<, anti), 2.25–2.41 (m, 2H, —CH_2CO—) 1.57–2.04 (m, 6H, $CH_{2\ Cyclohexanone}$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 209.7, 208.4 ($C{=}O_{Cyclohexanone}$), 173.4 ($C{=}O_{Pyrone}$), 166.1, 165.7, 146.0, 144.9, 144.7, 140.3, 139.8, 134.6, 128.3, 128.2, 127.7, 127.6, 127.4, 127.3, 126.6, 126.6, 118.0, 117.8, 113.0, 112.9, 112.8, 112.4, 70.8, 70.6, 54.6, 53.8, 52.2, 52.1, 41.1, 41.0, 28.2, 28.1, 26.4, 25.9, 23.6, 23.4 ppm; Anal. calcd. for $C_{25}H_{25}NO_4$: C, 74.42; H, 6.25; N, 3.47. Found: C, 74.08; H, 6.46; N, 3.21.

5-Benzyloxy-2-[(4-chlorophenylamino)(2-oxocyclohexyl)-methyl]-4H-pyran-4-one (11b). Anti/Syn: 55/45; White solid, FTIR (KBr): 3333 (NH), 3088, 3034, 2933, 2861, 1708, 1644, 1600, 1497, 1202, 816, 738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.50 (s, 0.55H, $CH_{Pyrone\ 6\text{-position}}$, anti), 7.49 (s, 0.45H, $CH_{Pyrone\ 6\text{-position}}$, syn), 7.30–7.35 (m, 5H, CH_{Ar}), 7.05–7.08 (m, 2H, CH_{Ar}), 6.49–6.54 (m, 2H, CH_{Ar}), 6.47 (s, 0.45H, $CH_{Pyrone\ 3\text{-position}}$, syn), 6.45 (s, 0.55H, $CH_{Pyrone\ 3\text{-position}}$, anti),

5.00 (2 × s: 2H, —CH_2O—), 4.59 (d, ^3J = 5.1 Hz, 0.55H, CH—N, anti), 4.34 (d, ^3J = 4.8 Hz, 0.45H, CH—N, syn), 2.97–3.02 (m, 0.45H, —COCH<, syn), 2.84–2.89 (m, 0.55H, —COCH<, anti), 2.29–2.45 (m, 2H, —CH_2CO—$_{Cyclohexanone}$) 1.55–2.13 (m, 6H, $CH_{2\ Cyclohexanone}$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 209.7, 208.3 (C=$O_{\ Cyclohexanone}$), 173.3 (C=O_{Pyrone}), 165.9, 165.6, 146.0, 143.7, 143.5, 139.9, 134.6, 134.5, 128.2, 128.1, 127.7, 127.6, 127.4, 127.3, 126.6, 122.5, 114.0, 113.4, 112.9, 112.7, 70.7, 54.8, 53.8, 52.3, 52.0, 41.2, 41.0, 28.0, 27.9, 26.5, 25.8, 23.7, 23.6 ppm; Anal. calcd. for $C_{25}H_{24}ClNO_4$: C, 68.57; H, 5.52; N, 3.20. Found: C, 68.21; H, 5.38; N, 3.18.

5-Benzyloxy-2-[(3,4-dichlorophenylamino)(2-oxocyclohexyl) methyl]-4H-pyran-4-one (11c). Anti/Syn: 75/25; White solid, FTIR (KBr): 3336 (NH), 3067, 3031, 2939, 2865, 1708, 1642, 1595, 1476, 1208, 812, 749, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (s, 0.75H, $CH_{Pyrone\ 6\text{-}position}$, anti), 7.49 (s, 0.25H, $CH_{Pyrone\ 6\text{-}position}$, syn), 7.29–7.37 (m, 5H, CH_{Ar}), 7.11–7.15 [2 × d: 7.14 (d, $^3J_{ortho}$ = 8.7 Hz, 0.25H, CH_{Ar}, syn), 7.12 (d, $^3J_{ortho}$ = 8.7 Hz, 0.75H, CH_{Ar}, anti)], 6.69 (d, $^4J_{meta}$ = 2.7 Hz, 0.75H, CH_{Ar}, anti), 6.63 (d, $^4J_{meta}$ = 2.7 Hz, 0.25H, CH_{Ar}, syn), 6.40–6.47 [m, 2H, (1H, CH_{Ar}) and (1H, $CH_{Pyrone\ 3\text{-}position}$)] 5.00 (s, 2H, —$CH_2O$—), 4.59 (d, ^3J = 5.1 Hz, 0.75H, CH—N, anti), 4.30 (d, ^3J = 4.6 Hz, 0.25H, CH—N, syn), 3.01–3.06 (m, 0.25H, —COCH<, syn), 2.83–2.89 (m, 0.75H, —COCH<, anti), 2.24–2.45 (m, 2H, —CH_2CO—$_{Cyclohexanone}$) 1.53–2.12 (m, 6H, $CH_{2\ Cyclohexanone}$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 209.7, 208.1 (C=$O_{\ Cyclohexanone}$), 173.3 (C=O_{Pyrone}), 165.7, 146.1, 146.0, 144.9, 144.7, 139.9, 134.6, 134.5, 131.9, 131.8, 129.7, 129.6, 127.7, 127.6, 127.4, 127.3, 126.7, 123.5, 120.2, 113.9, 113.3, 112.7, 112.5, 112.3, 111.9, 70.7, 54.6, 53.5, 52.2, 51.9, 41.3, 40.9, 28.0, 27.7, 26.6, 25.7, 23.6, 23.6 ppm; Anal. calcd. for $C_{25}H_{23}Cl_2NO_4$: C, 63.57; H, 4.91; N, 2.97. Found: C, 63.67; H, 4.89; N, 3.06.

REFERENCES AND NOTES

[1] (a) Chatterjee, A.; Biswas, K. M. J Org Chem 1973, 38, 4002; (b) Sayah, B.; Léon, N. P.; Milet, A.; Guindet, J. P.; Vallée, Y. J Org Chem 2001, 66, 2522; (c) Pundeer, R.; Ranjan, P.; Pannu, K.; Prakash, O. Synth Commun 2009, 39, 316.

[2] Jones, G.; Stanforth, S. P. Org React 2000, 56, 355.

[3] Marson, C. M. Tetrahedron 1992, 48, 3659.

[4] (a) Benson, W. R.; Pohland, A. E. J Org Chem 1965, 30, 1126; (b) Paquette, L. A.; Johnson, B. A.; Hinga, F. M. Organic Synth Cell 1973, 5, 215; (c) Karmakar, A. C.; Sharma, S.; Chattrejee, B. G.; Ray, J. K. Indian J Chem 1988, 27B, 364; (d) Ziegenbein, W.; Lang, W. Chem Ber 1960, 93, 2433; (e) Ziegenbein, W.; Franke, W. Angew Chem 1959, 71, 573; (f) Arnold, Z.; Zemilca, J. Collect Czech Chem Commun 1959, 24, 2378; (g) Gupta, S.; Kar, G. K.; Ray, J. K. Synth Commun 2000, 30, 2393; (h) Vashkevich, E. V.; Potkin, V. I.; Kozlov, N. G.; Skakovskii, E. D. Russ J Org Chem 2003, 39, 1587; (i) Gordon, A. J.; Ford, R. A. The Chemist's Companion; Wiley: New York, 1972 [Translated under the title Sputnik khimika, Moscow: Mir, 1976, p. 302]; (j) Chakraborty, A.; Ray, J. K. Synth Commun 1995, 25, 1869; (k) Prim, D.; Fuss, A.; Kirsch, G.; Silva, A. M. S. J Chem Soc Perkin Trans 2 1999, 1175; (l) Kirsch, G.; Prim, D.; Leising, F.; Mignani, G. J Heterocycl Chem 1994, 31, 1005; (m) Ziegenbein, W.; Franke, W. Ger. Pat.1.071.684 (1959); Chem Abstr 1961, 55, 16488f; (n) Brahma, S.; Ray, J. K. Tetrahedron 2008, 64, 2883; (o) Romagnoli, R.; Baraldi, P. G.; Carrion, M. D.; Cara, C. L.; Cruz-Lopez, O.; Preti, D.; Tolomeo, M.; Grimaudo, S.; Di Cristina, A.; Zonta, N.; Balzarini, J.; Brancale, A.; Sarkar, T.; Hamel, E. Bioorg Med Chem 2008, 16, 5367.

[5] Arend, M.; Westermann, B.; Risch, N. Angew Chem Int Ed 1998, 37, 1044.

[6] (a) Tramontini, M.; Angiolini, L. Mannich-Bases, Chemistry and Uses; CRC: Boca Raton, FL, 1994 and reference cited therein; (b) Volkmann, R. A. In Comprehensive Organic Synthesis; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol.1, p 355 and references cited therein.

[7] (a) Kleinmann, E. F. In Comprehensive Organic Synthesis; Trost, B. M., Flemming, I., Eds.; Pergamon Press: New York, 1991; Vol.2, Chapter 4.1; (b) Kobayashi, S.; Ishitani, H. Chem Rev 1999, 99, 1069; (c) Denmark, S.; Nicaise, O. J.-C. In Comprehensive Asymmetric Catalysis; Jacobsen, E. N., Pfaltz, A., Yamomoto, H., Eds.; Springer: Berlin, 1999; Vol.2, p 93; (d) Juaristi, E., Ed. Enantioselective Synthesis of β-Amino Acids; Wiley-VCH: New York, 1997.

[8] (a) Azizi, N.; Torkiyan, L.; Saidi, M. R. Org Lett 2006, 8, 2079; (b) Wu, Y.-S.; Cai, J.; Hu, Z.-Y.; Lin, G.-X. Tetrahedron Lett 2004, 45, 8949; (c) Chen, W. Y.; Li, X.; Lu, J. Synth Commun 2008, 38, 546; (d) Ibrahem, I.; Casas, J.; Córdova, A. Angew Chem Int Ed 2004, 43, 6528. For reviews of catalytic Mannich reactions, see: (e) Kobayashi, S.; Ueno, M. In Comprehensive Asymmetric Catalysis, Supplement; Springer: Berlin, 2004; Vol.1, p 143; (f) Xu, L.-W.; Xia, C.-G.; Li, L. J Org Chem 2004, 69, 8482; (g) Josephsohn, N. S.; Snapper, M. L.; Hoveyda, A. H. J Am Chem Soc 2004, 126, 3734; (h) Guo, Q.-X.; Liu, H.; Guo, C.; Luo, S.-W.; Gu, Y.; Gong, L.-Z. J Am Chem Soc 2007, 129, 3790; (i) Dubs, C.; Hamashima, Y.; Sasamoto, N.; Seidel, T. M.; Suzuki, S.; Hashizume, D.; Sodeoka, M. J Org Chem 2008, 73, 5859; (j) Ferlin, M. G.; Chiarelotto, G.; Castagliuolo, I. J Heterocycl Chem 2002, 39, 631; (k) Shi, H.; Shi, H.; Wang, Z. J Heterocycl Chem 2001, 38, 929.

[9] (a) Shi, M.; Cui, S. C.; Li, Q. J. Tetrahedron 2004, 60, 6679; (b) Bhanushali, M. J.; Nandurkar, N. S.; Jagtap, S. R.; Bhanage, B. M. Synth Commun 2009, 39, 845; (c) Hashemi, M. M.; Eftekhari-Sis, B.; Abdollahifar, A.; Khalili, B. Tetrahedron 2006, 62, 672; (d) Eftekhari-Sis, B.; Abdollahifar, A.; Hashemi, M. M.; Zirak, M. Eur J Org Chem 2006, 5152; (e) Smitha, S.; Reddy, C. S. Synthesis 2004, 834.

[10] Riley, J. P.; Chester, R. Introduction to Marine Chemistry; Academic Press: NY, 1971.

[11] Farnworth, F.; Jones, S. L.; McAlpine, I. Speciality Inorganic Chemicals Special publication No 40; Royal Society of Chemistry: London, 1980.

[12] (a) Anderson, A. M.; Blazek, J. M.; Garg, P.; Payne, B. J.; Mohan, R. S. Tetrahedron Lett 2000, 41, 1527; (b) Crouch, R. D.; Romany, C. A.; Kreshock, A. C.; Menconi, K. A.; Zile, J. L. Tetrahedron Lett 2004, 45, 1279; (c) Ghosh, R.; Maiti, S.; Chakraborty, A. Tetrahedron Lett 2004, 45, 6775.

[13] (a) Shahrisa, A.; Saraei, M. J Heterocycl Chem 2009, 46, 268; (b) Shahrisa, A.; Ghasemi, Z.; Saraei, M. J Heterocycl Chem 2009, 46, 273.

[14] Rudas, M.; Fejes, I.; Nyerges, M.; Szollosy, A.; Toke, L.; Groundwater, P. W. J Chem Soc Perkin Trans 1 1999, 1167.