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An efficient preparation of *N*-acetyl enamides catalyzed by Ru(II) complexes

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ABSTRACT

Reductive acetylation of ketoximes to give the corresponding acyl enamides can be achieved by using 1–3 mol % of $[RuCl_2(p\text{-cymene})]_2$ as the catalyst in the presence of KI as the reducing agent in high yields. This procedure has been applied to synthesize *N*-[1-(1,3-benzodioxol-5-yl)-1-butenyl]acetamide (**6**), which is the intermediate for the synthesis of DMP 777, an inhibitor of leukocyte elastase.

1. Introduction

N-Acetyl enamides are key structural motifs for synthesis of various classes of natural products as well as valuable synthetic intermediates for pharmaceutical drug candidates such as inhibitor of leukocyte elastase, GABA-B antagonist, acetylcholinesterase inhibitor, G-protein coupled receptor, β-adrenergic receptor agonist, and anti-arrhythmia agent (Fig. 1).[1] In addition, *N*-acetyl enamides are important precursors for the enantioselective hydrogenation to synthesize various chiral amine building blocks in long standing strategy.[1] In recent reports, these substrates are also utilized as precursors in catalytic asymmetric C–C and C–N bond forming reactions.[2,3] In spite of the extensive applications of *N*-acetyl enamides, preparations of this class of compounds still remain as a challenging work.

There are number of methods that have been employed for the synthesis of *N*-acetyl enamides, including addition of Grignard reagent or methyl lithium to nitriles followed by quench of an imine with acetic anhydride,[4] transition metal catalyzed cross coupling of vinyl triflates or tosylates with amides[5] and Heck reaction of aryl triflates or halides with *N*-vinylacetamides,[6] direct condensation of amides with ketones.[7] However, these methods show certain drawbacks such as less functional group tolerance, longer reaction time, higher catalyst loading, some of the reactions required low temperature and additional ligand for a better conversion.

Direct titanium-mediated conversion of ketones into enamides with NH_3 and acetic anhydride reported by Reeves and co-workers is the most efficient way.[8] Reductive acylation of ketoximes to *N*-acetyl enamides offers an alternative way and ought to be an atom-economy method. A number of reducing agents such as iron powder,[9] $Cr(OAc)_2$,[10] $Ti(OAc)_3$,[10] $Fe(OAc)_2$,[11] triethylphospine,[12] and molecular hydrogen[13] have been utilized in this transformation. Nevertheless, these procedures show some disadvantages for the preparation such as highly exothermic reaction conditions, pyrophoric reagents, and less substrate scope. Very recently, Guan and co-workers have reported a Cu(I) catalyzed reductive acylation of

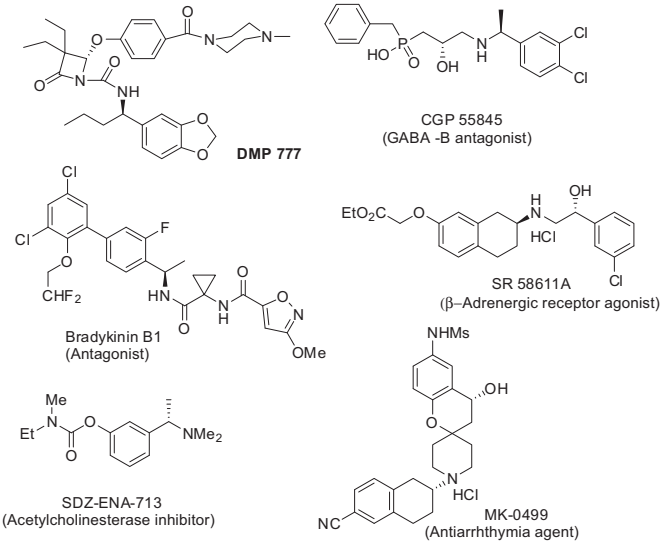

Fig. 1. Some drug molecules synthesized from enamides.

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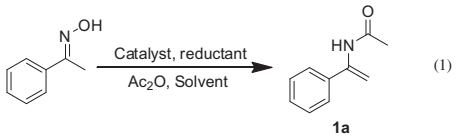
ketoxime to enamides with the use of sodium bisulfite as the reducing agent.[14] This process demonstrates a practical manner and provides a broad scope of enamides in high yields. In this work, we would like to report another efficient catalytic system by using Ru(II) for reductive acylation of various cyclic and acyclic ketoximes to *N*-acetyl enamides in the presence of KI or $NaHSO_3$ as reducing agents.

2. Results and discussion

Rhodium and ruthenium complexes are known as promising catalysts in many organic transformations.[15] Thus, we took the opportunity to utilize some common Rh(I) and Ru(II) complexes in our course of research. At the outset, acetophenone oxime was chosen as a model substrate for initial screening (Eq. 1). In a typical experiment, a mixture of acetophenone oxime (1.0 equiv), acetic anhydride (2.0 equiv), $NaHSO_3$ (2.0 equiv), and a metal complex in an organic solvent was heated to reflux for a certain period. No desired product was observed with the use of $Rh_2(OAc)_4$ as the catalyst (Table 1, entry 1). Then various rhodium complexes were screened for this purpose under similar reaction conditions. However, $RhCl(PPh_3)$, $Rh(CO)_2(acac)$, and Rh(acac)(COD) (Table 1, entries 3–5) gave unsatisfying results, only $[Rh(COD)Cl]_2$ provided the desired product **1a** in moderate yield 42% (Table 1, entry 2).



(1)

Table 1
Optimization of the *N*-acetyl enamide synthesis[a]

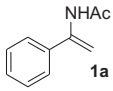
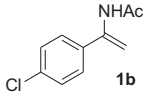
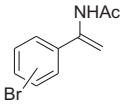
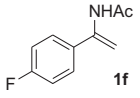
Entry	Catalyst (loading)	Reductant	Solvent	*t*, h	Yield,[b] (%)
1	$Rh_2(OAc)_2$ (10 mol %)	$NaHSO_3$	Toluene	12	0
2	$[Rh(COD)Cl]_2$ (10 mol %)	$NaHSO_3$	Toluene	12	42
3	$RhCl(PPh_3)_3$ (10 mol %)	$NaHSO_3$	Toluene	12	0
4	$Rh(CO)_2(acac)$ (10 mol %)	$NaHSO_3$	Toluene	20	5
5	Rh(acac)(COD) (10 mol %)	$NaHSO_3$	Toluene	20	10
6	$Ru(dppe)_2Cl_2$ (10 mol %)	$NaHSO_3$	Toluene	20	0
7	$Ru(CO)_3Cl_2(THF)$ (5 mol %)	$NaHSO_3$	Toluene	20	60
8	$Ru(DMSO)_4Cl_2$ (5 mol %)	$NaHSO_3$	Toluene	20	50
9	$[RuCl_2(p\text{-cymene})]_2$ (5 mol %)	$NaHSO_3$	Toluene	5	70
10	$[RuCl_2(p\text{-cymene})]_2$ (5 mol %)	$NaHSO_3$	DCE[e]	7	87
11	$[RuCl_2(p\text{-cymene})]_2$ (3 mol %)	$NaHSO_3$	DCE	12	85
12	$[RuCl_2(p\text{-cymene})]_2$ (1 mol %)	$NaHSO_3$	DCE	15	85
13	$[RuCl_2(p\text{-cymene})]_2$ (1 mol %)	$NaHSO_3$	CH_3CN	24	0
14	$[RuCl_2(p\text{-cymene})]_2$ (1 mol %)	$NaHSO_3$	DME[e]	24	60
15	$[RuCl_2(p\text{-cymene})]_2$ (1 mol %)	KI	DCE	3	90
16	$[RuCl_2(p\text{-cymene})]_2$ (1 mol %)	KI[c]	DCE	3	89
17	$[RuCl_2(p\text{-cymene})]_2$ (1 mol %)	H_2[d]	DCE	24	50
18	$[RuCl_2(p\text{-cymene})]_2$ (1 mol %)	$FeSO_4$	DCE	24	0

[a] Reaction conditions: acetophenone oxime (1.0 equiv), reductant (2.0 equiv), Ac_2O (2.0 equiv), solvent at reflux.
[b] Isolated yields.
[c] KI used 1.0 equiv.
[d] 1.0 atm.
[e] DCE=1,2-dichloroethane, DME=dimethoxyethane.

With these disappointing results on Rh(I) catalysts, we switched over to utilize Ru(II) complexes for this transformation. Under similar reaction conditions, $Ru(dppe)_2Cl_2$ (10 mol %) exhibited to be an ineffective catalyst (Table 1, entry 6), but $Ru(CO)_3Cl_2(THF)$ and $Ru(DMSO)_4Cl_2$ even 5 mol % afforded the desired enamide products in 60% and 50% yields, respectively (Table 1, entries 7 and 8). Attempts to improve the conversion with these complexes by keeping longer reaction time or reaction temperature failed. To our pleasure, $[RuCl_2(p\text{-cymene})]_2$ proved to be an effective catalyst for this transformation. At 5 mol % catalyst loading of $[RuCl_2(p\text{-cymene})]_2$ in toluene over 5 h, reaction afforded 70% yield of enamide **1a** (Table 1, entry 9). Therefore, this catalyst was further studied by variation of reaction conditions to improve the production of **1a**. In place of toluene with DCE as the solvent, a complete conversion of starting material was observed, providing **1a** in 87% yield (Table 1, entry 10). Further solvent screening, acetonitrile appeared unsuitable for the catalysis, but DME was compatible with this reaction albeit in low yield (Table 1, entries 13 and 14). Lowering the catalyst loading down to 1 mol %, the product conversion remained similar, but the reaction time took little longer (Table 1, entries 11 and 12). In addition several reductants such as KI, molecular H_2, and $FeSO_4$ were investigated, revealing that KI is also effective even with the use of 1.0 equiv of the reagent (Table 1, entries 15 and 16).

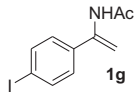
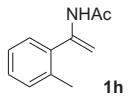
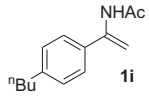
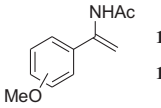
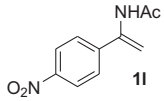
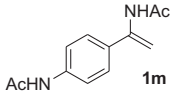
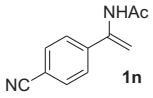
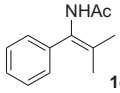
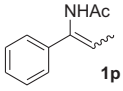
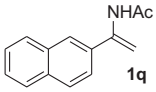
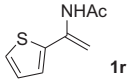
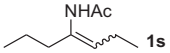
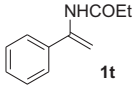
With the optimized reaction condition in hand, the scope of the reductive acylation with various acyclic ketoximes was investigated (Table 2). The reactions with chloro and bromo substituted aromatic ketoximes proceeded smoothly to give the desired enamides **1b**–**1e** in good yields at a shorter reaction time. For the substitution effect, we observed that *ortho* and *para* substituted bromo ketoximes had similar reactivity, but in the case of the *meta* substituted one showed little less reactivity. When fluoro and iodo substituted aromatic ketoximes were examined under the optimized condition, the reaction took place very rapidly and some of the undesired product formed with the use of KI as a reducing agent, to avoid that we changed to $NaHSO_3$ then reaction proceeded smoothly and yielded desired enamides **1f**–**1g** in good yields. Electron donating groups such as alkyl and methoxy substituted aromatic ketoximes exhibited high reactivity to afford corresponding enamides in slightly higher yields than electron withdrawing nitro group substituted aromatic ketoximes (Table 2, entries 6–9). Notably, the reaction with 1-(4-aminophenyl)ethanone oxime gave the amine protected enamide in high yield (**1m**). The nitrile functionality is tolerable in this condition and the corresponding enamide obtained in moderate yield. The reaction was tolerant with α-mono and disubstituted acyclic ketoxime (entries 12 and 13), in the case of propiophenone oxime gave the corresponding enamide as mixture of *E*/*Z* (1:2) isomers (**1p**). The reductive acylation reaction was compatible with bicyclic, heteroaromatic, and aliphatic acyclic ketoximes to afford the corresponding enamides in good to moderate yields (**1q**–**1s**). In

Table 2
Scope of enamide formation with acyclic ketoxime[a]

Entry	Enamide	Method	*t*, h	Yield,[b] %
1	 **1a**	A	3	89
2	 **1b**	A	5	70
3	 **1c** *o*-	A	3	88
	1d *m*-	A	3	72
	1e *p*-	A	3	89
4	 **1f**	B	15	83

(*continued on next page*)

Table 2 (*continued*)

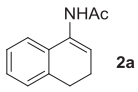
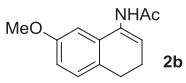
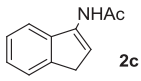
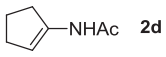
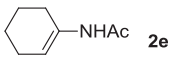
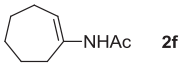
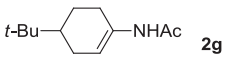
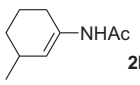
Entry	Enamide	Method	*t*, h	Yield,[b] %
5	 **1g**	B	20	82
6	 **1h**	A	1	85
7	 **1i**	A	4	73
8	 **1j** *p*- **1k** *m*-	A A	3 3	85 82
9	 **1l**	B	20	75
10	 **1m**	A	2	81
11[c]	 **1n**	B	12	60
12	 **1o**	B	4	75
13	 **1p**	B	8	75 *E*/*Z*=2:1
14	 **1q**	B	24	70
15[d]	 **1r**	B	12	66
16	 **1s**	B	6	60 *E*/*Z*=1:1.5
17[e]	 **1t**	A	4	77

[a] Conditions: method A: oxime (1.0 equiv), KI (1.0 equiv), Ac_2O (2.0 equiv), DCE at reflux. Method B: oxime (1.0 equiv), $NaHSO_3$ (2.0 equiv), Ac_2O (2.0 equiv), DCE at reflux temperature.
[b] Isolated yields.
[c] Catalyst 5 mol %.
[d] Catalyst 3 mol %.
[e] Instead of acetic anhydride, propionic anhydride was used.

addition to acetic anhydride, the reaction occurred equally well with propionic anhydride (Table 2, entry 17).

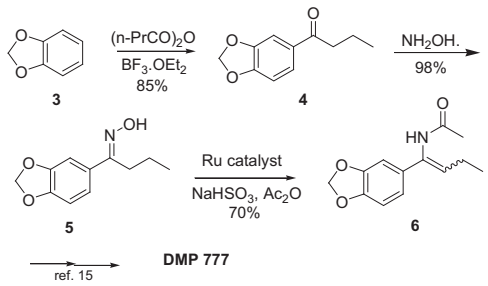
The general applicability of the ruthenium catalyzed reductive acylation of cyclic ketoximes leading to *N*-acetyl enamides is demonstrated. Under the optimized condition, α-tetralone and α-indanone oxime derivatives showed high yields (Table 3, entries 1–3). For the substrate of α-tetralone oxime, the reaction appeared to be fairly slow with 1 mol % of $[RuCl_2(p\text{-cymene})]_2$. However, the reaction reached the complete conversion within 12 h by increasing the catalyst loading up to 3–5 mol %. The efficiency of the reductive acylation of non-benzylic cyclic ketoximes was compatible with benzylic cyclic ketoximes. Five-, six-, and seven-membered cyclic ketoximes afforded the corresponding enamides in good yields at shorter reaction times. Thus, cyclopentanone, cyclohexanone, and cycloheptanone oximes were reductively acetylated to give the corresponding *N*-acetyl enamides **2d**, **2e**, and **2f**, respectively (Table 3, entries 4–6). Furthermore, the substituted cyclic ketoximes substrates also well tolerated under this developed condition to yield the corresponding enamides in good to moderate yields (Table 3, entries 7 and 8).

Table 3
Scope of enamide formation with cyclic ketoxime[a]

Entry	Enamide	*t*, h	Yield,[b] %
1[c]	 **2a**	12	81
2[d]	 **2b**	12	84
3	 **2c**	12	78
4	 **2d**	2	71
5	 **2e**	5	60
6	 **2f**	3	72
7	 **2g**	4	77
8	 **2h**	4	65[e]

[a] Reaction conditions: oxime (1.0 equiv), $NaHSO_3$ (2.0 equiv), Ac_2O (2.0 equiv) and Ru catalyst (1 mol %) in DCE under refluxing.
[b] Isolated yields.
[c] Catalyst 5 mol %.
[d] Catalyst 3 mol %.
[e] The ratio of regio-isomers is ca. 2:1.

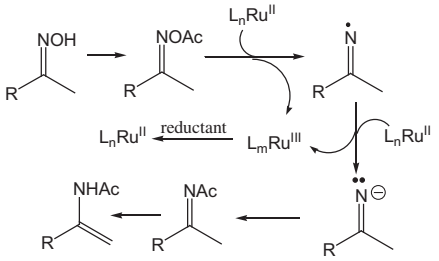
The significance of this ruthenium catalyzed reductive acylation reaction is further exploited by the synthesis of enamide intermediate **6**, which is used to prepare leukocyte elastase inhibitor DMP 777.[16] As shown in Scheme 1, the enamide **6** was synthesized starting from 1,2-methylendioxybenzene **3**. Electrophilic aromatic acylation of **3** with butyric anhydride in the presence of BF_3 gave the butanone compound **4** in 85% yield. Subsequently, compound **4** was converted into the corresponding oxime by treatment of hydroxylamine in the presence of sodium acetate. Under the optimized reductive acylation conditions developed in this work, compound **5** was transformed into the desired *N*-acetyl enamide **6** in good yield.



Scheme 1. Synthetic approach to DMP 777.

A plausible mechanism for the Ru(II)-catalyzed reductive acylation of ketoximes is shown in Scheme 2, which is similar to that Cu(I)-catalyzed reaction.[14] Acylation of ketoxime provides the corresponding *O*-acetyloxime, which is subsequently reduced by Ru(II) to yield the iminium anion. Acylation of the iminium anion followed by tautomerization provides the desired product.

In summary, we have demonstrated the efficiency of ruthenium catalysts on the reductive acylation of various cyclic and acyclic ketoximes. This method provides a practical protocol for the preparation of *N*-acyl enamides with less catalyst loading and reaction time. By adopting this method, we have successfully prepared *N*-(1-(benzo[*d*][1,3]dioxol-5-yl)but-1-enyl)-acetamide **6**, a key intermediate leading to DMP 777. Current research is focused on extending the usage of enamide in the preparation of heterocyclic compounds.



Scheme 2. Reaction pathway for the reductive acylation of ketoximes.

3. Experimental

3.1. General information

All reactions were carried out in a 10 mL reaction tube. Chemicals were purchased from Aldrich and Acros and unless otherwise noted were used without further purification. Enamides were purified by chromatography. All new compounds were characterized by ^{1}H, ^{13}C NMR and HRMS and their spectra are deposited in Supplementary data.

3.2. General procedure for the ruthenium(II) catalyzed reductive acylation of ketoxime to enamides

A reaction tube was charged with acetophenone oxime (100 mg, 0.739 mmol), KI (122 mg, 0.739 mmol), and $[RuCl_2(p\text{-cymene})]_2$ (4.5 mg, 0.0074 mmol). To that DCE (2 mL) and acetic anhydride (151 mg, 1.47 mmol) were added by syringe. The reaction mixture was stirred at reflux under N_2 as indicated time in the Tables 1–3. The reaction mixture was cooled down to rt, diluted with 10 mL of ethyl acetate, and washed with 10% NaOH solution. The organic layer dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel with hexane/ethyl acetate as eluent to yielded the desired enamide **1a** (109 mg, 0.676 mmol) in 89% yield. Products obtained in this work were characterized by spectral methods particularly with ^{1}H and ^{13}C NMR, and the data were consistent with those reported. Selected spectral data for enamides are presented below and other spectral data are collected in Supplementary data.

*3.2.1. N-(1-Phenylvinyl)acetamide (**1a**).*[11] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.29 (m, 5H), 7.07 (br s, 1H), 5.78 (s, 1H), 5.04 (s, 1H), 2.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.21, 140.5, 138.3, 128.6, 126.0, 102.6, 24.4; HRMS-ESI-MS (*m*/*z*) $[M+H]^+$: calcd for $C_{10}H_{12}NO$: 162.0919; found 162.0916.

*3.2.2. N-(1-(4-Chlorophenyl)vinyl)acetamide (**1b**).*[17] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (s, 4H), 6.86 (br s, 1H), 5.75 (s, 1H), 5.06 (s, 1H), 2.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 139.5, 136.7, 134.6, 128.8, 127.3, 103.5, 24.4; HRMS-ESI-MS (*m*/*z*) $[M+H]^+$: calcd for $C_{10}H_{11}ClNO$: 196.0529; found 196.0527.

*3.2.3. N-(1-(2-Bromophenyl)vinyl)acetamide (**1c**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J*=7.9 Hz, 1H), 7.34–7.27 (m, 2H), 7.20–7.16 (m, 1H), 6.83 (br s, 1H), 5.94 (s, 1H), 4.76 (s, 1H), 2.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 140.2, 139.4, 133.1, 131.4, 130.0, 127.6, 121.8, 104.3, 24.4; HRMS-ESI-MS (*m*/*z*) $[M+H]^+$: calcd for $C_{10}H_{11}BrNO$: 240.0024; found 240.0027.

*3.2.4. N-(1-o-Tolylvinyl)acetamide (**1h**).*[8] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.14 (m, 4H), 6.68 (br s, 1H), 6.01 (s, 1H), 4.66 (s, 1H), 2.32 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 140.2, 138.5, 135.7, 130.4, 129.1, 128.5, 125.9, 102.3, 24.4, 19.4; HRMS-ESI-MS (*m*/*z*) $[M+H]^+$: calcd for $C_{10}H_{14}NO$: 176.0075; found 176.0074.

*3.2.5. N-(1-(4-Butylphenyl)vinyl)acetamide (**1i**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J*=7.8 Hz, 2H), 7.15 (d, *J*=8.1 Hz, 2H), 6.86 (br s, 1H), 5.81 (s, 1H), 5.03 (s, 1H), 2.59 (t, J=7.6 Hz, 2H), 2.09 (s, 3H), 1.61–1.53 (m, 2H), 1.36–1.23 (m, 2H), 0.9 (t, *J*=7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 143.6, 140.3, 135.7, 128.7, 125.8, 101.7, 35.2, 33.5, 24.6, 22.3, 13.9; HRMS-ESI-MS (*m*/*z*) $[M+H]^+$: calcd for $C_{14}H_{20}NO$: 218.1545; found 218.1547.

*3.2.6. N-(2-Methyl-1-phenylprop-1-enyl)acetamide (**1o**).*[11] ^{1}H NMR (400 MHz, DMSO) δ 9.01 (s, 1H), 7.31–7.20 (m, 5H), 1.89 (s, 3H), 1.71 (s, 3H), 1.70 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ 167.9, 139.5, 129.2, 128.4, 128.1, 127.8, 127.1, 23.1, 21.1, 21.0; HRMS-ESI-MS (*m*/*z*) $[M+H]^+$: calcd for $C_{12}H_{16}NO$: 182.1154; found 182.1153.

*3.2.7. (E/Z) N-(1-Phenylvinyl)propionamide (**1p**).*[11] ^{1}H NMR (400 MHz, $CDCl_3$) (~2:1 mixture of geometric isomers) δ 7.41–7.20 (m, 5H), 6.86/6.70 (br s, 1H), 6.04/5.92 (q, *J*=7.0 Hz, 1H), 2.12 (s, 3H), 1.82/1.72 (d, *J*=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 168.3, 138.0, 135.6, 133.9, 128.6, 128.3, 128.1, 127.6, 125.3, 125.2, 122.1, 121.2, 23.2, 20.4, 13.9, 13.5; HRMS-ESI-MS (*m*/*z*) $[M+H]^+$: calcd for $C_{11}H_{14}NO$: 176.1075; found 176.1073.

*3.2.8. N-(1-(Thiophen-2-yl)vinyl)acetamide (**1r**).*[18] ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.19 (d, *J*=4.4 Hz, 1H), 7.06 (d, *J*=4.2 Hz, 1H), 6.96 (t, *J*=4.5 Hz, 1H+1H for NH), 5.73 (s, 1H), 5.20 (s, 1H), 2.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 141.6, 134.1, 127.4, 125.2, 123.6, 102.8, 24.5; HRMS-ESI-MS (*m*/*z*) $[M+H]^+$: calcd for $C_8H_{10}NOS$: 168.0483; found 168.0478.

*3.2.9. (E/Z) N-(Hept-3-en-4-yl)acetamide (**1s**).* ^{1}H NMR (400 MHz, $CDCl_3$) (~1:1.5 mixture of geometric isomers) δ 6.51 (br s, 1H), 5.73/5.00 (t, *J*=6.9 Hz, 1H), 2.22–2.14 (m, 2H), 2.04–1.89 (m, 5H),

1.43–1.35 (2H), 0.95–0.89 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 168.2, 133.6, 128.9, 123.6, 120.4, 36.9, 31.5, 24.3, 23.6, 21.1, 20.6, 20.3, 14.5, 13.7, 13.6, 13.5; HRMS-ESI-MS (m/z) $[M+H]^+$: calcd for $C_9H_{18}NO$: 156.1388; found 156.1382.

*3.2.10. N-(3,4-Dihydronaphthalen-1-yl)acetamide (**2a**).*[11] ^{1}H NMR (400 MHz, DMSO) δ 9.10 (s, 1H), 7.19–7.16 (m, 4H), 6.16 (s, 1H), 2.68 (t, J=7.8 Hz, 2H), 2.26–2.66 (m, 2H), 2.02 (s, 3H); ^{13}C NMR (100 MHz) δ 174.0, 141.2, 137.6, 136.9, 132.6, 132.3, 131.2, 127.3, 124.2, 32.3, 28.5.

*3.2.11. N-Cyclohexenylacetamide (**2e**).*[14] ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.44 (br s, 1H), 6.01 (s, 1H), 2.09–2.08 (m, 4H), 1.97 (s, 3H), 1.66–1.63 (m, 2H), 1.56–1.51 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 132.5, 113.2, 28.0, 24.4, 23.9, 22.5, 21.9; HRMS-ESI-MS (m/z) $[M+H]^+$: calcd for $C_8H_{14}NO$: 140.1075; found 140.1076.

*3.2.12. N-Cycloheptenylacetamide (**2f**).* ^{1}H NMR (400 MHz, $CDCl_3$), δ 6.67 (br s, 1H), 6.07 (t, J=6.7 Hz, 1H), 2.26 (t, J=5.2 Hz, 2H), 2.06–2.08 (m, 2H), 1.96 (s, 3H), 1.67–1.68 (m, 2H), 1.47–1.56 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 139.2, 118.7, 33.6, 31.9, 26.9, 26.6, 25.9, 24.2; HRMS-ESI-MS (m/z) $[M+H]^+$: calcd for $C_9H_{16}NO$: 154.1232; found 154.1233.

*3.2.13. N-(4-tert-Butylcyclohex-1-enyl)acetamide (**2g**).*[11] ^{1}H NMR (400 MHz, $CDCl_3$), δ 6.57 (br s, 1H), 6.00 (t, J=2.6 Hz, 1H), 2.18–2.09 (m, 3H), 1.97 (s, 3H), 1.84–1.77 (m, 2H), 1.23–1.20 (m, 2H), 0.82 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 132.5, 113.2, 43.6, 32.1, 29.4, 27.2, 25.4, 24.3, 23.8; HRMS-ESI-MS (m/z) $[M+H]^+$: calcd for $C_{12}H_{22}NO$: 196.1701; found 196.1698.

*3.2.14. N-(3-Methylcyclohex-1-enyl)acetamide (**2h**).* ^{1}H NMR (400 MHz, $CDCl_3$) (~2:1 mixture of regio-isomers) δ 8.69 (br s, 1H), 5.97/5.90 (s, 1H), 2.19–2.08 (m, 3H), 1.74 (s, 3H), 1.71–1.43 (m, 3H), 1.09–1.06 (m, 1H), 0.92 (t, J=3.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 168.3, 133.6, 133.5, 116.2, 109.5, 36.0, 31.0, 30.4, 29.3, 28.5, 27.6, 24.3, 24.2, 23.8, 22.8, 22.0, 21.3; HRMS-ESI-MS (m/z) $[M+H]^+$: calcd for $C_9H_{16}NO$: 154.1232; found 154.1234.

3.3. 1-(Benzo[*d*][1,3]dioxol-5-yl)butan-1-one (4)[16]

A pre-dried two-neck round bottom flask was charged with 1,2-methylenedioxy benzene (2.0 g, 16.37 mmol), 1,2-dichloroethane (7 mL) and *n*-butyric anhydride (3.2 mL, 19.6 mmol). The resulting mixture was cooled to −10 °C, to that $BF_3{\cdot}Et_2O$ (6.78 g, 1.38 mmol) was added by slow addition over 15 min, while maintaining the temperature −5 °C to 0 °C. After the addition, the reaction mixture was stirred at −5 °C for 3 h. The reaction was then quenched with sodium acetate solution, the organic layer was separated and washed with 5% NaOH (7 mL) followed by water. The organic layers were concentrated and the crude product was purified by column chromatography using on silica gel with hexane/ethyl acetate (10%) as eluent to yielded the desired compound **4** (1.34 g, 85%). ^{1}H NMR (400 MHz, $CDCl_3$), 7.52 (dd, J=8.1, 1.6 Hz, 1H), 7.40 (d, J=8.1 Hz, 1H), 6.80 (d, J=8.1 Hz, 1H), 5.99 (s, 1H), 2.82 (t, J=7.3 Hz, 2H), 1.70 (h, J=7.4 Hz, 2H), 0.95 (t, J=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 198.4, 151.5, 148.1, 132.0, 124.1, 107.8, 107.7, 101.7, 40.2, 18.0, 13.8; HRMS-ESI-MS (m/z) $[M+H]^+$: calcd for $C_{11}H_{13}O_3$: 193.0865; found 193.0867.

3.4. 1-(Benzo[*d*][1,3]dioxol-5-yl)butan-1-onoxime (5)[16]

To a solution of ketone **4** (1.0 g, 5.2 mmol) in methanol (2 mL) was added sodium acetate (640 mg, 7.8 mmol) followed by $NH_2OH{\cdot}HCl$ (433 mg, 6.2 mmol). The reaction mixtures were stirred at reflux for 2 h. After the completion of reaction (monitored by the TLC), the reaction mixture was cooled to rt and then water was added. The mixture was extracted with EtOAc (2×10 mL) and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The desired product **5** was obtained as white solid (1.05 g, 98%). The crude product is pure enough to carry out next stage without purification. ^{1}H NMR (400 MHz, $CDCl_3$), 7.08–7.03 (m, 12H), 6.79 (d, J=8.1 Hz, 1H), 5.96 (s, 1H), 2.72 (t, J=7.8 Hz, 2H), 1.60–1.54 (m, 2H), 0.95 (t, J=7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 159.3, 148.5, 147.9, 129.8, 120.5, 108.2, 106.5, 101.3, 28.3, 19.8, 14.2; HRMS-ESI-MS (m/z) $[M+H]^+$: calcd for $C_{11}H_{14}O_3$: 208.0974; found 208.0973.

3.5. *N*-(1-(Benzo[*d*][1,3]dioxol-5-yl)but-1-enyl)acetamide (6)[16]

A reaction tube was charged with 1-(benzo[*d*][1,3]dioxol-5-yl) butan-1-one oxime **5** (100 mg, 0.482 mmol), $NaHSO_3$ (100 mg, 0.965 mmol), and $[RuCl_2(p\text{-cymene})]_2$ (2.9 mg, 0.0048 mmol). To that, DCE (2 mL) and acetic anhydride (98 mg, 0.965 mmol) were added by syringe. The reaction mixture was stirred at reflux under N_2 for 12 h. The reaction mixture was cooled down to rt, diluted with 10 mL of ethyl acetate, and washed with 10% NaOH solution. The organic layer dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel with hexane/ethyl acetate as eluent to yielded the desired enamide **6** (39.0 mg, 70%). ^{1}H NMR (400 MHz, DMSO), 9.01 (s, 1H), 6.92 (s, 1H), 6.84 (s, 2H), 5.99 (s, 2H), 5.70 (t, J=7.1 Hz, 1H), 2.08–2.00 (m, 2H), 1.98 (s, 3H), 0.98 (t, J=7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 168.4, 147.8, 146.9, 133.3, 133.2, 125.8, 119.2, 108.3, 106.0, 101.4, 23.1, 21.5, 13.9; HRMS-ESI-MS (m/z) $[M+H]^+$: calcd for $C_{13}H_{16}NO_3$: 234.1130; found 234.1129.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2012.10.027.

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