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SYNTHESIS OF NOVEL 5-ACETOACETYL-3-ACETYL-2-PYRIDONE DERIVATIVES BY THE RING-TRANSFORMATION OF 6-METHYL-1,3-OXAZIN-4-ONES

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Abstract – The synthesis of novel poly-functionalized 5-acetoacetyl-3-acetyl-2-pyridone derivatives was achieved *via* the ring-transformation of 6-methyl-4*H*-1,3-oxazin-4-ones with 3-methylisoxazole derivatives, followed by reductive cleavage of the isoxazole ring and hydrolysis.

Functionalized pyridine ring systems can be found in a vast array of pharmacologically active compounds.[1] A variety of methods for their preparation are currently available. Our interest in this field has been directed to the use of 4*H*-1,3-oxazin-4-ones as precursors and building blocks for the synthesis of poly-functionalized nitrogen-containing heterocyclic compounds based on their ring-transformation.[2] Our previous work described the ring-transformation of 6-methyl-4*H*-1,3-oxazin-4-ones with diethyl 1,3-acetonedicarboxylate to yield 6,8-dihydroxy-4-ethoxycarbonyl-1-isoquinolone derivatives.[3] It is noteworthy in this respect that the isoxazole ring system is very versatile building block in organic synthesis. The reason for this is that isoxazoles contain a weak N-O bond which, under certain reaction conditions, particularly in reducing or basic condition, is a potential site of ring cleavage. Thus, isoxazoles are very useful intermediates since the stability of the ring system allows the substituents to be manipulated to give functionally complex derivatives, yet it is easily cleaved when necessary. The ring opening leads to the production of

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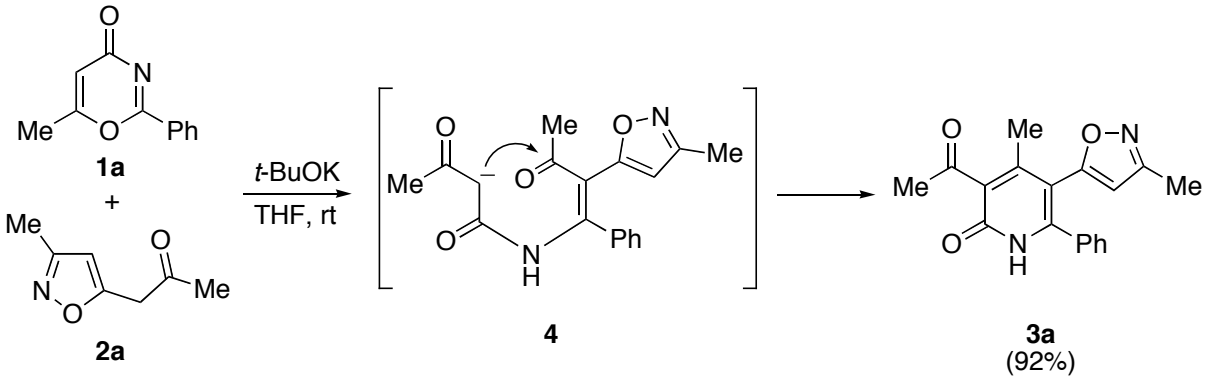
This paper is dedicated to the memory of the late Professor Kenji Koga.

difunctionalized compounds, 1,3-dicarbonyls, enamino ketones, γ-amino alcohols, α,β-unsaturated oximes, β-hydroxy nitriles or β-hydroxy ketones, so that isoxazoles can be considered to be masked forms of these synthetic units. Consequently, isoxazoles have become an important class of compounds from the synthetic point of view.[4] This paper describes the novel synthesis of poly-functionalized 5-acetoacetyl-3-acetyl-2-pyridone derivatives based on the ring-transformation of the 4*H*-1,3-oxazin-4-ones (**1**) with α-(3-methyl-5-isoxazolyl)-substituted carbonyl compounds (**2**) followed by ring cleavage of isoxazoles to give β-dicarbonyls.

The reaction of 6-methyl-2-phenyl-4*H*-1,3-oxazin-4-one (**1a**) with (3-methyl-5-isoxazolyl)acetone (**2a**) in THF in the presence of potassium *t*-butoxide at room temperature gave 3-acetyl-4-methyl-5-(3-methyl-5-isoxazolyl)-6-phenyl-2-pyridone (**3a**) in 92% yield. The formation of the 2-pyridone (**3a**) presumably proceeds *via* the nucleophilic addition of the methylene carbon of **2a** to the C-2 carbon of **1a** followed by ring opening to give the acetoacetyl intermediate (**4**), which was transformed into **3a** by an intramolecular aldol condensation, as shown in Scheme 1.[5]

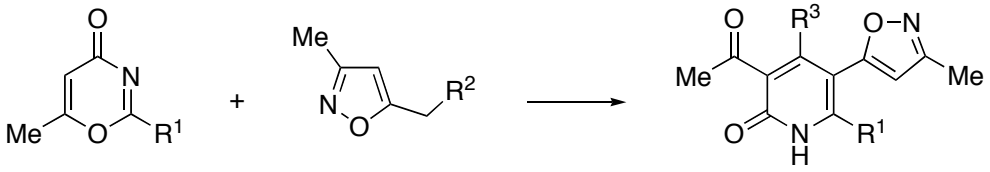


Scheme 1

Analogously, the treatment of (3-methyl-5-isoxazolyl)acetophenone (**2b**) and ethyl (3-methyl-5-isoxazolyl)acetate (**2c**) with **1a** gave 3-acetyl-4-(3-methyl-5-isoxazolyl)-6-phenyl-2-pyridone derivatives (**3b**, **c**) in good yields. When 6-methyl-2-isopropyl-4*H*-1,3-oxazin-4-one (**1b**) was employed as a substrate instead of **1a**, reactions with **2a**,**b** proceeded in a similar manner to provide 3-acetyl-6-isopropyl-5-(3-methyl-5-isoxazolyl)-2-pyridone derivatives (**3e**, **f**) in good yields. On the other hand, the reaction of **1b** with **2c** in THF in the presence of potassium *t*-butoxide at room temperature gave 4-isopropyl-5-(3-methyl-5-isoxazolyl)-2-(2-oxopropylidene)-2*H*-1,3-oxazin-6-one (**5**) as a major product, accompanied by a small amount of 2-pyridone derivative (**3g**) (Scheme 2). The yield of **3g** could be increased to 50% by refluxing of **1b** and **2c** in ethanol and the use of sodium ethoxide as a base.[6] The unexpected formation of **5** can be explained by the intramolecular nucleophilic attack of an oxide anion on the ester carbonyl group of acetacetamide intermediate (**4B**) as shown in Scheme 2. In a similar reaction of **1a**,**b** with (3-methyl-5-isoxazolyl)acetonitrile (**2d**) using *t*-BuOK (method A), however, the

expected 2-pyridone was not obtained, and the corresponding ring-opened acetoacetamide derivatives (**6a**,**b**) were isolated as the sole products (Scheme 3). Compounds (**6a**,**b**) can be regarded as intermediates in the ring-transformation. This reaction can be attributed to the lower electrophilicity of the nitrile carbon compared to a carbonyl carbon.

Table 1. Preparation of 3-Acetyl-5-(3-methyl-5-isoxazolyl)-2-pyridones (**3a**-**g**)



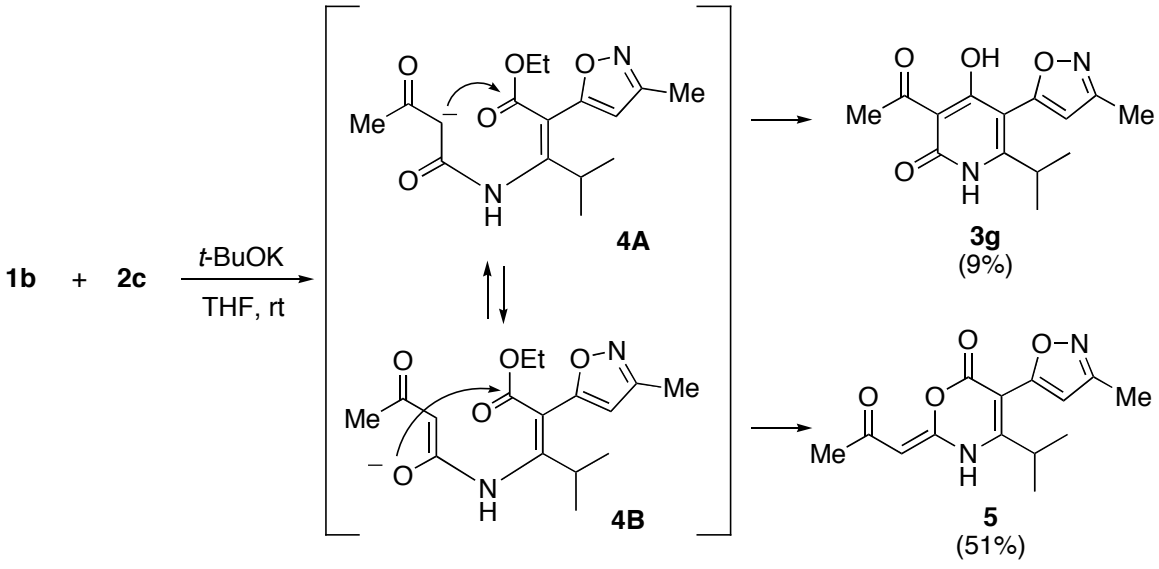
1a: R^1= Ph
1b: R^1= *i*-Pr

2a: R^2= COMe
2b: R^2= COPh
2c: R^2= CO_2Et
2d: R^2= CN

3a-g

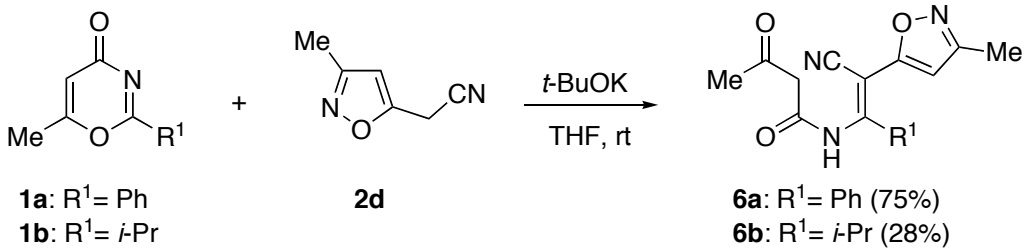
Entry	R^1	R^2	Condition	Product	R^3	Yield (%)[a]
1	Ph	COMe	A[b]	**3a**	Me	92
2	Ph	COPh	A	**3b**	Ph	86
3	Ph	CO_2Et	A	**3c**	OH	77
4	Ph	CN	B[c]	**3d**	NH_2	75
5	*i*-Pr	COMe	A	**3e**	Me	95
6	*i*-Pr	COPh	A	**3f**	Ph	76
7	*i*-Pr	CO_2Et	B	**3g**	OH	50

[a] Isolated yields. [b]Method A: *t*-BuOK, THF, at room temperature.
[c]Method B: EtONa, EtOH, reflux.



Scheme 2

The reaction of **1a** with **2d** to give 3-acetyl-4-amino-5-(3-methyl-5-isoxazolyl)-6-phenyl-2-pyridone (**3d**) was carried out as follows: mixture of **1a** and **2d** was refluxed in ethanol in the presence of sodium ethoxide to afford **3d** in 75% yield. The results obtained are summarized in Table 1.



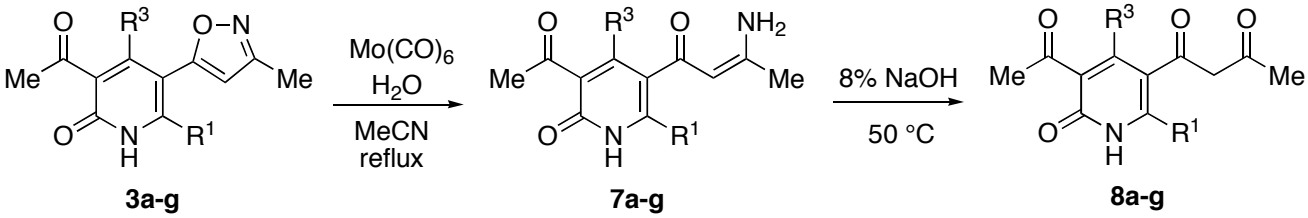
1a: R^1= Ph
1b: R^1= *i*-Pr

2d

6a: R^1= Ph (75%)
6b: R^1= *i*-Pr (28%)

Scheme 3

Table 2. Preparation of 5-Acetoacetyl-3-acetyl-2-pyridones (**8a**-**g**)



3a-g **7a-g** **8a-g**

Entry	Substituents		Hydrogenolysis			Hydrolysis		
	R^1	R^3	Product	Time(h)	Yield(%)[a]	Product	Time(h)	Yield(%)[a]
1	Ph	Me	**7a**	4	65	**8a**	3	89
2	Ph	Ph	**7b**	7	71	**8b**	7	39
3	Ph	OH	**7c**	6	–[b]	**8c**	3	29[c]
4	Ph	NH_2	**7d**	7	–[b]	**8d**	7	51[c]
5	*i*-Pr	Me	**7e**	6	87	**8e**	3	94
6	*i*-Pr	Ph	**7f**	6	77	**8f**	10	91
7	*i*-Pr	OH	**7g**	7	–[b]	**8g**	2	26[c]

[a]Isolated yields. [b]No isolation. [c]Yield for the two steps.

The reductive cleavage of isoxazole ring on **3a**-**g** was then performed using *Nitta's* hydrogenolysis conditions.[7] Treatment of **3a** with molybdenumhexacarbonyl in moist acetonitrile at reflux afforded enamino ketone (**7a**) in 65% yield. In a similar manner, enamino ketones (**7b**-**g**) were prepared from **3b**-**g**. The isolation of enamino ketones (**7c**,**d**,**g**) was difficult, and they were used without further purification.

In contrast, hydrogenolysis with Raney nickel[8] or palladium black[9] as the catalyst required a longer reaction time and resulted in a decreased yield. Finally, the hydrolysis of enamino ketones (**7a**-**g**) with 8% NaOH[10] gave the desired 5-acetoacethyl-3-acethyl-2-pyridone derivatives (**8a**-**g**). Unfortunately, an attempt under acidic condition using *conc*-HCl[11] resulted in the recovery of the starting material or the elimination of 3-amino-2-butenoyl group at the 5-position of **7**. These results are summarized in Table 2.

In summary, the ring-transformation of **1a**,**b** with **2a**-**d** is described, which provides novel poly-functionalized isoxazole-containing pyridones (**3a**-**g**), that can be further transformed into 5-acetoacetyl-3-acetyl-2-pyridones (**8a-g**) by reductive ring cleavage of the isoxazole and hydrolysis.

EXPERIMENTAL

Melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer 1600 series FT-IR spectrophotometer. MS spectra were recorded on a JEOL JMN-DX 303/JMA-DA 5000 spectrometer. ^{1}H-NMR spectra were recorded on a JEOL JNM-PMX 60si or JNM-PMX 60FT spectrometer, using tetramethylsilane as an internal standard. Elemental analyses were performed on a Perkin-Elmer 2400 CHN Elemental Analyzer. Column chromatography was carried out on Merck Silica Gel 60 (230-400 mesh for flash chromatography).

6-Methyl-2-phenyl-4*H*-1,3-oxazin-4-one (**1a**),[12] 6-methyl-2-isopropyl-4*H*-1,3-oxazin-4-one (**1b**),[13] (3-methyl-5-isoxazolyl)acetone (**2a**),[14] (3-methyl-5-isoxazolyl)acetophenone (**2b**),[14] ethyl (3-methyl-5-isoxazolyl)acetate (**2c**),[14] (3-methyl-5-isoxazolyl)acetonitrile (**2d**)[15] were prepared according to the cited methods.

General Procedure for the Ring-transformation of 4*H*-1,3-Oxazin-4-ones (1)

Under Ar atmosphere, a solution of isoxazole (**2**) (5 mmol) in THF (20 mL) was added dropwise to a stirred suspension of potassium *t*-butoxide (0.62 g, 5.5 mmol) in THF (10 mL), for 0.5 h at rt. The mixture was cooled to 0 °C, and a solution of oxazine (**1**) (5 mmol) in dry THF (10 mL) was added dropwise to the mixture. After stirring overnight at rt, the reaction mixture was quenched with 10% HCl. The mixture was basified with saturated Na_2CO_3 and concentrated under reduced pressure, followed by extraction with $CHCl_3$ (20 mL x 3). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by recrystallization or flash column chromatography on silica gel.

3-Acetyl-4-methyl-5-(3-methyl-5-isoxazolyl)-6-phenyl-2-pyridone (3a)

The crude product was purified by recrystallization from ethanol to give 1.90 g (92%) of **3a**, mp 252–254 °C. IR (KBr) cm^{-1}: 1701, 1629. ^{1}H-NMR ($CDCl_3$) δ: 2.06 (3H, s), 2.18 (3H, s), 2.34 (3H, s), 5.72 (1H, s), 7.35 (5H, s), 12.67-13.50 (1H, br s). MS (*m*/*z*): 308 (M^+). *Anal.* Calcd for $C_{18}H_{16}N_2O_3$: C, 70.12; H, 5.23; N, 9.09. Found: C, 69.96; H, 5.33; N, 8.99.

3-Acetyl-5-(3-methyl-5-isoxazolyl)-4,6-diphenyl-2-pyridone (3b)

The crude product was purified by recrystallization from ethanol to give 1.59 g (86%) of **3b**, mp 284–287 °C. IR (KBr) cm^{-1}: 1634. ^{1}H-NMR ($CDCl_3$) δ: 1.97 (3H, s), 2.23 (3H, s), 5.47 (1H, s), 6.93-7.77 (10H, m), 11.27-12.77 (1H, br s). MS (*m*/*z*): 370 (M^+). *Anal*. Calcd for $C_{23}H_{18}N_2O_3$: C, 74.58; H, 4.90; N, 7.56. Found: C, 74.28; H, 4.97; N, 7.36.

3-Acetyl-4-hydroxy-5-(3-methyl-5-isoxazolyl)-6-phenyl-2-pyridone (3c)

The crude product was purified by recrystallization from ethanol to give 1.20 g (77%) of **3c**, mp 275–277 °C. IR (KBr) cm^{-1}: 1644, 1622. ^{1}H-NMR ($CDCl_3$) δ: 2.27 (3H, s), 2.53 (3H, s), 6.17 (1H, s), 7.43 (5H, s), 11.77-12.63 (1H, br s), 16.60 (1H, s). MS (*m*/*z*): 310 (M^+). *Anal*. Calcd for $C_{17}H_{14}N_2O_4$: C, 65.80; H, 4.55; N, 9.03. Found: C, 65.67; H, 4.69; N, 9.00.

3-Acetyl-6-isopropyl-4-methyl-5-(3-methyl-5-isoxazolyl)-2-pyridone (3e)

The crude product was purified by recrystallization from ethanol to give 1.30 g (95%) of **3e**, mp 257–259 °C. IR (KBr) cm^{-1}: 1688, 1635. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (6H, d, *J* = 7.2 Hz), 2.00 (3H, s), 2.20-3.17 (1H, m), 2.37 (3H, s), 2.57 (3H, s), 6.13 (1H, s), 12.83-13.57 (1H, br s). MS (*m*/*z*): 274 (M^+). *Anal*. Calcd for $C_{15}H_{18}N_2O_3$: C, 65.68; H, 6.61; N, 10.21. Found: C, 65.48; H, 6.85; N, 10.21.

3-Acetyl-6-isopropyl-5-(3-methyl-5-isoxazolyl)-4-phenyl-2-pyridone (3f)

The crude product was purified by recrystallization from ethanol to give 1.28 g (76%) of **3f**, mp 279–280 °C. IR (KBr) cm^{-1}: 1712, 1642. ^{1}H-NMR ($CDCl_3$) δ: 1.37 (6H, d, *J* = 7.2 Hz), 2.23 (3H, s), 2.30 (3H, s), 2.40-3.10 (1H, m), 5.58 (1H, s), 6.83-7.42 (5H, m), 12.70-13.40 (1H, br s). MS (*m*/*z*): 336 (M^+). *Anal*. Calcd for $C_{20}H_{20}N_2O_3$: C, 71.41; H, 5.99; N, 8.33. Found: C, 71.42; H, 6.07; N, 8.19.

3-Acetyl-4-hydroxy-6-isopropyl-5-(3-methyl-5-isoxazolyl)-2-pyridone (3g) and 4-Isopropyl-5-(3-methyl- 5-isoxazolyl)-2-(2-oxopropylidene)-2*H*-1,3-oxazin-6(3*H*)-one (5)

The crude product was purified by flash column chromatography on silica gel (*n*-hexane : ethanol, 1 : 1) to give 0.31 g (22%) of **3g** and 0.71 g (51%) of **5**.

3g: mp 254–261 °C (decomp) (ethanol). IR (KBr) cm^{-1}: 1651. ^{1}H-NMR ($CDCl_3$) δ: 1.38 (6H, d, *J* = 7.2 Hz), 2.37 (3H, s), 2.77 (3H, s), 2.87-3.57 (1H, m), 6.30 (1H, s), 11.53-12.07 (1H, br s), 16.53 (1H, s). MS (*m*/*z*): 276 (M^+). *Anal*. Calcd for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 61.08; H, 6.04; N, 9.95.

5: mp 153–155 °C (ethyl acetate). IR (KBr) cm^{-1}: 1759, 1640, 1579. ^{1}H-NMR ($CDCl_3$) δ: 1.34 (6H, d, *J* = 7.2 Hz), 2.20 (3H, s), 2.35 (3H, s), 3.23-4.00 (1H, m), 5.38 (1H, s), 6.61 (1H, s), 13.70-14.30 (1H, br s). MS (*m*/*z*) : 276 (M^+). *Anal*. Calcd for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 60.87; H, 6.01; N, 9.97.

***N*-(2-Cyano-2-(3-methyl-5-isoxazolyl)-1-phenylvinyl)acetoacetamide (6a)**

The crude product was purified by flash column chromatography on silica gel (*n*-hexane : ethanol, 1 : 1)

to give 1.16 g (75%) of **6a**, mp 115–116 °C (ethanol). IR (KBr) cm^{-1}: 3259, 2221, 1723, 1678, 1605. ^{1}H-NMR ($CDCl_3$) δ: 1.96 (1.5H, s), 2.26 (1.5H, s), 2.49 (3H, s), 3.53 (1H, s), 5.13 (0.5H, s), 6.29 (1H, s), 7.47 (5H, s), 10.50-10.78 (0.5H, br s), 10.78-11.13 (0.5H, br s), 12.60-13.00 (0.5H, br s). MS (*m/z*): 309 (M^+). *Anal.* Calcd for $C_{17}H_{15}N_3O_3$: C, 66.01; H, 4.89; N, 13.58. Found: C, 65.88; H, 5.08; N, 13.48.

***N*-(1-Cyano-3-methyl-1-(3-methyl-5-isoxazolyl)-1-buten-2-yl)acetoacetamide (6b)**

The crude product was purified by recrystallization from *n*-hexane to give 0.39 g (28%) of **6b**, mp 90–94 °C (*n*-hexane). IR (KBr) cm^{-1}: 2210, 1718, 1709. ^{1}H-NMR ($CDCl_3$) δ: 1.47 (6H, d, J = 7.2 Hz), 1.90 (1H, s), 2.23 (2H, s), 2.77 (3H, s), 3.50 (1H, s), 3.57-4.17 (1H, m), 5.07 (0.5H, s), 6.17 (1H, s), 10.27-10.83 (1H, br s), 13.00 (0.5H, s). MS (*m/z*): 275 (M^+). *Anal.* Calcd for $C_{14}H_{17}N_3O_3$: C, 61.08; H, 6.22; N, 15.26. Found: C, 60.76; H, 6.24; N, 15.11.

3-Acetyl-4-amino-5-(3-methyl-5-isoxazolyl)-6-phenyl-2-pyridone (3d)

Under Ar atmosphere, sodium metal (1.15 g, 50 mmol) was dissolved in dry ethanol (40 mL), then a solution of isoxazole (**2d**) (0.85 g, 5 mmol) in dry ethanol (20 mL) was added dropwise. To the resulting solution, a solution of oxazine (**1a**) (0.94 g, 5 mmol) in dry ethanol (20 mL) was added dropwise. After heating under reflux for 24 h, the reaction mixture was cooled to rt and quenched with 10% HCl. The mixture was basified with saturated Na_2CO_3 and concentrated under reduced pressure. $CHCl_3$ (100 mL) was added to the residue and the mixture was washed with water (50 mL x 3). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residual crude product was recrystallized from ethyl acetate to give 1.16 g (75%) of **3d**, mp 306–307 °C (decomp). IR (KBr) cm^{-1}: 3449, 1640. ^{1}H-NMR ($CDCl_3$) δ: 2.21 (3H, s), 2.55 (3H, s), 5.70 (1H, s), 7.22-7.73 (6H, m), 10.00-11.19 (2H, br s). MS (*m/z*): 309 (M^+). *Anal.* Calcd for $C_{17}H_{15}N_3O_3$: C, 66.01; H, 4.89; N, 13.58. Found: C, 65.88; H, 4.96; N, 13.41.

Synthesis of 3-Acetyl-4-hydroxy-6-isopropyl-5-(3-methyl-5-isoxazolyl)-2-pyridone (3g)

Under Ar atmosphere, sodium metal (0.13 g, 5.5 mmol) was dissolved in absolute ethanol (10 mL), then a solution of isoxazole (**2c**) (0.85 g, 5 mmol) in dry ethanol (20 mL) was added dropwise. To the resulting solution, a solution of oxazine (**1b**) (0.77 g, 5 mmol) in dry ethanol (20 mL) was added dropwise. After heating under reflux for 24 h, the reaction mixture was cooled to rt and quenched with 10% HCl. The mixture was basified with saturated Na_2CO_3 and concentrated under reduced pressure, followed by extraction with $CHCl_3$ (30 mL x 3). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residual crude product was recrystallized from ethanol to give 0.69 g (50%) of **3g**.

General Procedures for the Synthesis of 3-Acetyl-5-(3-amino-2-butenoyl)-2-pyridone Derivatives (7) for the Hydrogenation of 5-Isoxazolyl-2-pyridones (3)

A suspension of **3** (1 mmol), molybdenum hexacarbonyl (1 mmol), and water (18 mg) in MeCN (21 mL)

was heated under reflux for the reaction time shown in Table. After cooling to rt, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel. Yield of **6** was depicted in Table 2.

3-Acetyl-5-(3-amino-2-butenoyl)-4-methyl-6-phenyl-2-pyridone (7a)

Flash column chromatography (ethyl acetate) gave **7a**, mp 245–248 °C (decomp) (ethyl acetate). IR (KBr) cm^{-1}: 3272, 1738, 1695. ^{1}H-NMR ($CDCl_3$) δ: 1.73 (3H, s), 2.17 (3H, s), 2.40 (3H, s), 4.73 (1H, s), 6.17-6.63 (1H, br s), 7.09-7.70 (5H, m), 9.53-10.13 (1H, br s), 11.40-12.33 (1H, br s). MS (*m/z*): 310 (M^+). *Anal*. Calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.32; H, 5.76; N, 8.89.

3-Acetyl-5-(3-amino-2-butenoyl)-4,6-diphenyl-2-pyridone (7b)

Flash column chromatography (*n*-hexane : ethyl acetate, 1 : 3) gave **7b**, mp 252–254 °C (decomp) (ethyl acetate). IR (KBr) cm^{-1}: 3368, 1706. ^{1}H-NMR ($CDCl_3$) δ: 1.57 (3H, s), 2.17 (3H, s), 4.57 (1H, s), 6.27-7.03 (1H, br s), 7.07-7.37 (10H, m), 9.00-9.60 (1H, br s), 11.43-12.47 (1H, br s). MS (*m/z*): 372 (M^+). *Anal*. Calcd for $C_{23}H_{20}N_2O_3$: C, 74.18; H, 5.41; N, 7.52. Found: C, 73.91; H, 5.25; N, 7.39.

3-Acetyl-5-(3-amino-2-butenoyl)-6-isopropyl-4-methyl-2-pyridone (7e)

Flash column chromatography (*n*-hexane : ethyl acetate, 1 : 2) gave **7e**, mp 245–248 °C (decomp) (ethyl acetate). IR (KBr) cm^{-1}: 3278, 1688. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (6H, d, J = 7.2 Hz), 1.97 (3H, s), 2.10 (3H, s), 2.53 (3H, s), 2.63-3.43 (1H, m), 5.03 (1H, s), 6.53-6.93 (1H, br s), 9.70-10.33 (1H, br s), 11.40-12.17 (1H, br s). MS (*m/z*): 276 (M^+). *Anal*. Calcd for $C_{15}H_{20}N_2O_3$: C, 65.20; H, 7.30; N, 10.14. Found: C, 64.86; H, 7.26; N, 10.10.

3-Acetyl-5-(3-amino-2-butenoyl)-6-isopropyl-4-phenyl-2-pyridone (7f)

Flash column chromatography (*n*-hexane : ethyl acetate, 1 : 2) gave **7f**, mp 261–262 °C (decomp) (ethyl acetate). IR (KBr) cm^{-1}: 3290, 1734, 1708. ^{1}H-NMR ($CDCl_3$) δ: 1.37 (6H, d, J = 7.2 Hz), 1.73 (3H, s), 2.27 (3H, s), 2.90-3.53 (1H, m), 4.73 (1H, s), 4.80-5.20 (1H, m), 7.27 (5H, s), 9.33-10.03 (1H, br s), 12.00-12.60 (1H, br s). MS (*m/z*): 338 (M^+). *Anal*. Calcd for $C_{20}H_{22}N_2O_3$: C, 70.99; H, 6.55; N, 8.28. Found: C, 70.72; H, 6.42; N, 8.16.

General Procedure for the Synthesis of 5-Acetoacethyl-3-acetyl-2-pyridone Derivatives (8) by Hydrolysis of 7

A suspension of enamine (**7**) (2 mmol) in 8% NaOH (100 mL) was heated at 50 °C and stirred for the reaction time shown in Table 2. The reaction mixture was cooled to rt and adjusted to pH 1 by addition of *conc*. HCl. The precipitated crystalline product was separated from the mixture by filtration. The filtrate was extracted with $CHCl_3$ (100 mL x 3). The crystalline product was dissolved in combined $CHCl_3$ extracts, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by recrystallization or flash column chromatography on silica gel. Yield of **8** was depicted in Table 2.

5-Acetoacetyl-3-acetyl-4-methyl-6-phenyl-2-pyridone (8a)

The crude product was purified by recrystallization from ethyl acetate to give **8a**, mp 191–193 °C. IR (KBr) cm^{-1}: 1706, 1634. ^{1}H-NMR ($CDCl_3$) δ: 1.87 (3H, s), 2.20 (3H, s), 2.37 (3H, s), 5.20 (1H, s), 7.43 (5H, s), 12.23-13.33 (1H, br s), 14.40-15.93 (1H, br s). MS (*m*/*z*): 311 (M^+). *Anal*. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.71; H, 5.49; N, 4.41.

5-Acetoacetyl-3-acetyl-4,6-diphenyl-2-pyridone (8b)

The crude product was purified by flash column chromatography on silica gel (*n*-hexane : ethyl acetate, 1 : 2) to give **8b**, mp 253–254 °C (decomp) (ethyl acetate). IR (KBr) cm^{-1}: 1704, 1627. ^{1}H-NMR ($CDCl_3$) δ: 1.73 (3H, s), 2.20 (3H, s), 5.13 (1H, s), 7.07-7.63 (10H, m), 7.87 (1H, s), 15.43-16.13 (1H, br s). MS (*m*/*z*): 373 (M^+). *Anal*. Calcd for $C_{23}H_{19}NO_4$: C, 73.98; H, 5.13; N, 3.75. Found: C, 73.88; H, 5.15; N, 3.68.

5-Acetoacetyl-3-acetyl-4-hydroxy-6-phenyl-2-pyridone (8c)

The crude product was purified by flash column chromatography on silica gel (*n*-hexane : ethyl acetate, 1 : 2) to give **8c**, mp 229–232 °C (ether). IR (KBr) cm^{-1}: 1700, 1670. ^{1}H-NMR ($CDCl_3$) δ: 2.27 (3H, s), 2.60 (3H, s), 6.13 (1H, s), 7.30-7.70 (5H, m), 10.90-11.63 (1H, br s), 12.63-13.40 (1H, br s), 16.73 (1H, s). MS (*m*/*z*): 313 (M^+). *Anal*. Calcd for $C_{17}H_{15}NO_5$: C, 65.17; H, 4.83; N, 4.47. Found: C, 64.89; H, 4.91; N, 4.39.

5-Acetoacetyl-3-acetyl-4-amino-6-phenyl-2-pyridone (8d)

The crude product was purified by recrystallization from ethanol to give **8d**, mp 335–338 °C (decomp). IR (KBr) cm^{-1}: 3062, 1672, 1642. ^{1}H-NMR ($CDCl_3$) δ: 2.29 (3H, s), 2.49 (3H, s), 5.83 (1H, s), 7.48 (5H, s), 10.02-11.27 (2H, br s), 11.38-12.16 (1H, br s), 13.64 (1H, br s). MS (*m*/*z*): 312 (M^+). *Anal*. Calcd for $C_{17}H_{16}N_2O_4$: C, 65.38; H, 5.16; N, 8.97. Found: C, 65.12; H, 5.27; N, 8.86.

5-Acetoacetyl-3-acetyl-6-isopropyl-4-methyl-2-pyridone (8e)

The crude product was purified by recrystallization from ethyl acetate to give **8e**, mp 239–240 °C (decomp). IR (KBr) cm^{-1}: 1702, 1640. ^{1}H-NMR ($CDCl_3$) δ: 1.33 (6H, d, J = 7.2 Hz), 2.20 (6H, s), 2.57 (3H, s), 2.77-3.40 (1H, m), 5.63 (1H, s), 12.00-13.63 (1H, br s), 14.67-16.27 (1H, br s). MS (*m*/*z*): 277 (M^+). *Anal*. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 64.67; H, 6.95; N, 5.03.

5-Acetoacetyl-3-acetyl-6-isopropyl-4-phenyl-2-pyridone (8f)

The crude product was purified by recrystallization from ethyl acetate to give **8f**, mp 248–249 °C (decomp). IR (KBr) cm^{-1}: 1708, 1645. ^{1}H-NMR ($CDCl_3$) δ: 1.40 (6H, d, J = 7.2 Hz), 1.90 (3H, s), 2.29 (3H, s), 2.80-3.57 (1H, m), 5.19 (1H, s), 7.30 (5H, s), 12.12-13.09 (1H, br s), 14.48-15.62 (1H, br s). MS (*m*/*z*): 339 (M^+). *Anal*. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.67; H, 6.25; N, 4.08.

5-Acetoacetyl-3-acetyl-4-hydroxy-6-isopropyl-2-pyridone (8g)

The crude product was purified by recrystallization from ether to give **8g**, mp 207–210 °C. IR (KBr) cm^{-1}:

3064, 1670. ^{1}H-NMR ($CDCl_3$) δ: 1.33 (6H, d, J = 7.2 Hz), 2.13 (3H, s), 2.73 (3H, s), 2.87-3.60 (1H, m), 5.77 (1H, s), 10.93-11.50 (1H, br s), 15.20-16.00 (1H, br s), 16.53 (1H, s). MS (*m/z*): 279 (M^+). *Anal.* Calcd for $C_{14}H_{17}NO_5$: C, 60.21; H, 6.14; N, 5.02. Found: C, 60.11; H, 6.05; N, 4.86.

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