CYCLIZATION OF C- AND O-ACYL DERIVATIVES OF p-TOLUAMIDE O-ACETOACETYLOXIME[1]

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Abstract — Reaction of p-toluamide O-acetoacetyloxime (**1**) with acyl chloride (**2**) in the presence of basic catalyst gave the corresponding O- and C-acyl derivatives (**3** and **4**). Cyclization of **3** afforded 5-(2-acyloxypropenyl)-3-(p-tolyl)-1,2,4-oxadiazole derivatives (**6**) and 5-acetonyl-3-(p-tolyl)-1,2,4-oxadiazole (**7**). Cyclization of **4** gave 5-(1-acyl-2-oxopropyl)-1,2,4-oxadiazole derivatives (**8**), 4-[1-amino-1-(p-tolyl)]methylene-3-methyl-2-isoxazolin-5-one (**9**) and 5-substituted 3-(p-tolyl)-1,2,4-oxadiazole derivatives (**10**).

Amide oxime derivatives are widely used for the synthesis of heterocyclic compounds; however, little is known regarding the synthesis of seven-membered heterocycles using amide oxime derivative. The reaction of 2,6-dichlorobenzamide oxime with 1,3-dibromopropane gave 3-(2,6-dichlorophenyl)-4,5,6,7-tetrahydro-4-oxadiazepine.[2] In anticipation of the formation of seven-membered heterocycles, a study was made of the acylation of p-toluamide O-acetoacetyloxime and cyclization of the O- and C-acyl derivatives thus obtained. Although efforts to obtain the expected product were not successful, an isoxazoline derivative was obtained as one of the cyclization products. These results are discussed in detail in the following.

The acylation of p-toluamide O-acetoacetyloxime (**1**) was carried out using an equivalent molar amount of acetyl chloride (**2a**) in the presence of triethylamine

at 0°C to give p-toluamide O-(3-acetoxy-2-butenoyl)oxime (**3a**) and p-toluamide O-(α-acetylacetoacetyl)oxime (**4a**) in 16.3 and 4.5% yields, respectively. When two equivalent molar amounts of **2a** were used, p-toluamide O-acetyloxime (**5a**) was also obtained but in low yield. On using sodium hydride as a base, total product yield slightly increased. The starting material (**1**) was recovered in 40-45% yield from these reactions.

Reactions of **1** with benzoyl chloride (**2b**), ethyl chloroformate (**2c**) and p-nitrobenzoyl chloride (**2d**) afforded the corresponding O-acyl derivatives (**3b-d**), C-acyl derivatives (**4b-d**) and p-toluamide O-acyloxime derivatives (**5b-c**). The structures of **3**, **4** and **5** were determined from analytical and spectral data. The yields and mps of the products are listed in Table I.

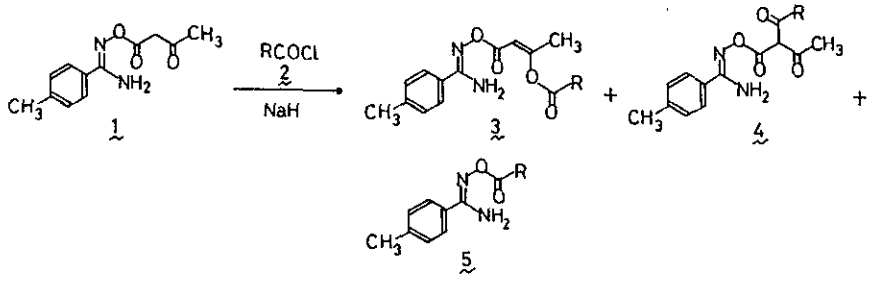

Chart 1

Table I. Acylation of p-Toluamide O-Acetoacetyloxime (**1**)

R-COCl		Base	Mp (°C) and Yield (%) of Products								
2	R		**3**	Mp	Yield	**4**	Mp	Yield	**5**	Mp	Yield
2a	CH_3	Et_3N	**3a**	169	16.3	**4a**	123	4.5	**5a**	136	---
		NaH			11.0			18.8			7.9
2b	C_6H_5	Et_3N	**3b**	166	58.9	**4b**	135	13.7	**5b**	188	---
		NaH			13.3			5.9			trace[a]
2c	OC_2H_5	Et_3N	**3c**	138	89.0	**4c**	77	10.8	**5c**	193	---
		NaH			15.0			51.9			trace
2d	p-$C_6H_4NO_2$	Et_3N	**3d**	186	70.2	**4d**	153	11.3	**5d**	---	---
		NaH			8.3			10.4			---

a) Detected by TLC.

Cyclization of p-Toluamide O-(3-Acyloxy-2-butenoyl)oxime Derivatives (3)

On heating p-toluamide O-(3-acetoxy-2-butenoyl)oxime (**3a**) in dry toluene under reflux, 5-(2-acetoxypropenyl)-3-(p-tolyl)-1,2,4-oxadiazole (**6a**) and 5-acetonyl-3-(p-tolyl)-1,2,4-oxadiazole (**7**) were obtained in 34.8 and 3.8% yields, respectively. Refluxing of the reaction mixture for more 6 h failed to result in high yield. The starting material, **3a**, was recovered in about 50% yield in both cases. Compound **6a** converted slowly to **7** on heating in toluene.

The structure of **6a** was determined by mixed melting point determination using an authentic sample. The reaction of **7** with **2a** in the presence of triethylamine afforded **6a** and 5-(1-acetyl-2-oxopropyl)-3-(p-tolyl)-1,2,4-oxadiazole (**8a**) in 54 and 45% yields, respectively.

3-Benzoxy- (**3b**), 3-ethoxycarbonyloxy- (**3c**) and 3-(p-nitrobenzoxy)- (**3d**) derivatives were refluxed in the same manner as above to afford the corresponding 5-(2-acyloxypropenyl)-3-(p-tolyl)-1,2,4-oxadiazole derivatives (**6b-d**) as the main products. The yields and mps of these products are listed in Table II.

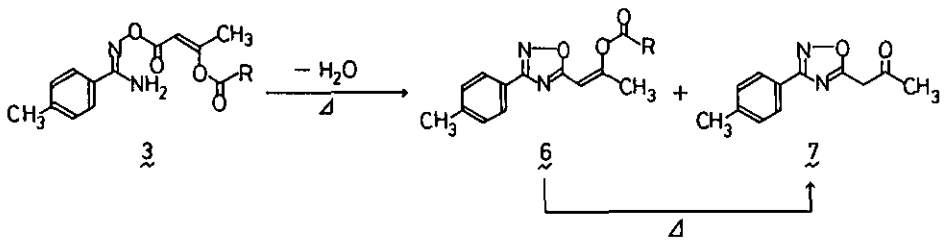

Chart 2

Table II. Cyclization of p-Toluamide O-(3-Acyloxy-2-butenoyl)oxime (3)

Material		Reaction Time	Mp (°C) and Yield (%) of Products					
3	R	(h)	**6**	Mp	Yield	**7**	Mp	Yield
3a	CH_3	6	**6a**	66	34.8	**7**	96	3.8
3b	C_6H_5	7	**6b**	102	11.4			---
		12			77.6			trace[a]
3c	OC_2H_5	11	**6c**	46	86.2			2.2
3d	p-$C_6H_4NO_2$	6	**6d**	158	41.1			trace

a) Detected by TLC.

From the above results, it is clear that O-acyl derivative **3** gives 1,2,4-oxadiazole derivatives exclusively in the same manner as the cyclization of usual amide O-acyloxime derivatives.[3]

Cyclization of p-Toluamide O-(α-Acylacetoacetyl)oxime Derivatives (4)

Cyclization of **4a** was carried out by heating it in toluene for 2 h to obtain colorless prisms of mp 237°C, $C_{12}H_{12}N_2O_2$ (**9**), 5-methyl-3-(p-toly)l-1,2,4-oxadiazole (**10a**), **5a**, **7** and **8a** in yields of 27.8, 15.7, 15.3, 3.8 and 7.9%, respectively. When the reaction mixture was refluxed for 6 h, the yields of **7**, **9** and **10a** were slightly improved to 10.9, 31.5 and 24.1%, respectively.

Compound **9** showed characteristic absorption bands at 3310 and 3120 (NH_2), 1710 (C=O), and 1670 (C=C) cm^{-1}. In the ^1H-nmr spectra of compound **9**, characteristic signals due to methyl, tolyl-methyl and two NH groups appeared at 1.63 (3H, s), 2.45 (3H, s), 6.19 (1H, br s) and 9.48 (1H, br) ppm, respectively. The typical fragment ion peak for $CH_3C_6H_4$-CNO^+ could not be detected at m/z 133 in the mass spectrum of **9**, thus confirming this compound not to have a 3-aryl-1,2,4-oxadiazole skeleton.

When **9** was allowed to react with acetic anhydride at room temperature, a monoacetyl derivative of mp 147° C, $C_{14}H_{14}N_2O_3$, (**11**) was obtained in 91% yield. Compound **11** showed characteristic absorption bands at 3300 region (NH), 1760 (C=O), 1700 (C=O) cm^{-1}. In the ^1H-nmr spectrum of **11**, characteristic signals due to NH, methyl, acetylmethyl and tolyl-methyl groups appeared at 11.5 (1H, br s), 1.50 (3H, s), 2.23 (3H, s) and 2.43 (3H, s) ppm, respectively. Reaction of **9** with chloroacetyl chloride and triethylamine in refluxing toluene also afforded the monochloroacetyl derivative $C_{14}H_{13}ClN_2O_3$ of mp 177°C, (**12**) in 28% yield.

The structure of **9** was finally determined to be Z-4-[1-amino-1-(p-tolyl)]-methylene-3-methyl-2-isoxazolin-5-one on the basis of X-ray structure analysis data for compound **12**. (Figure 1)

The above hydrogen-bonded Z-form structure reasonably explains why the methyl proton signal of compound **9** appeared in an abnormally high field region, 1.63 ppm. This may have come about as a result of the deshielding effect of the twisted aryl ring as illustrated in the above drawing. Regarding this high field shift, Maquestiau *et al.* mentioned that the methyl proton signal of Z-4-benzylidene-3-methyl-2-isoxazolin-5-one appeared in the 1.6 ppm region.[4]

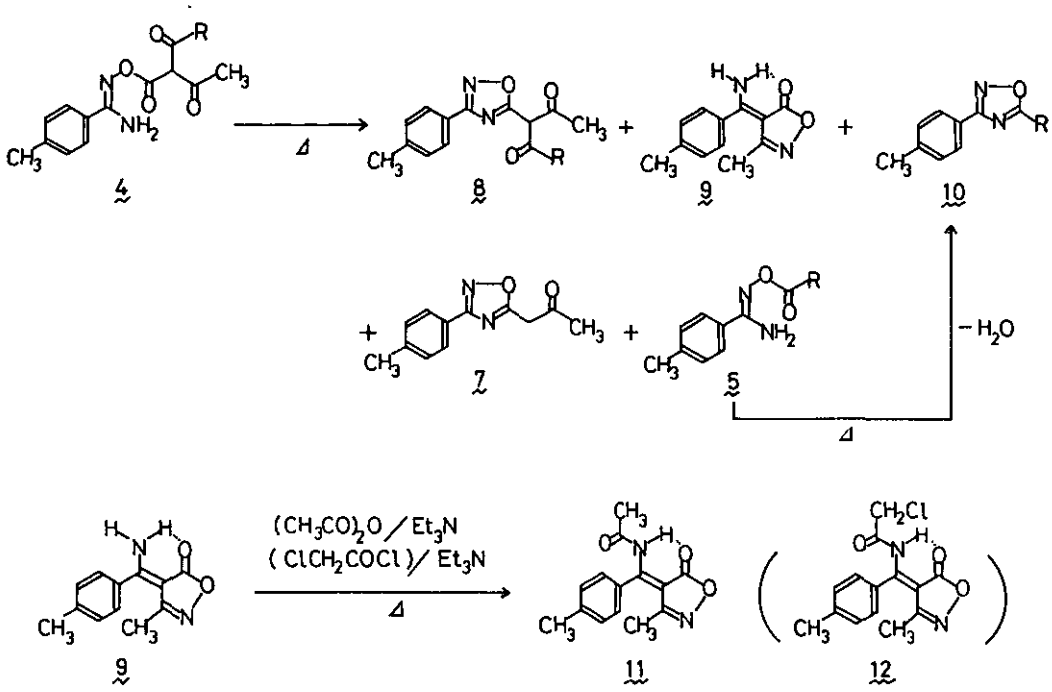

Chart 3

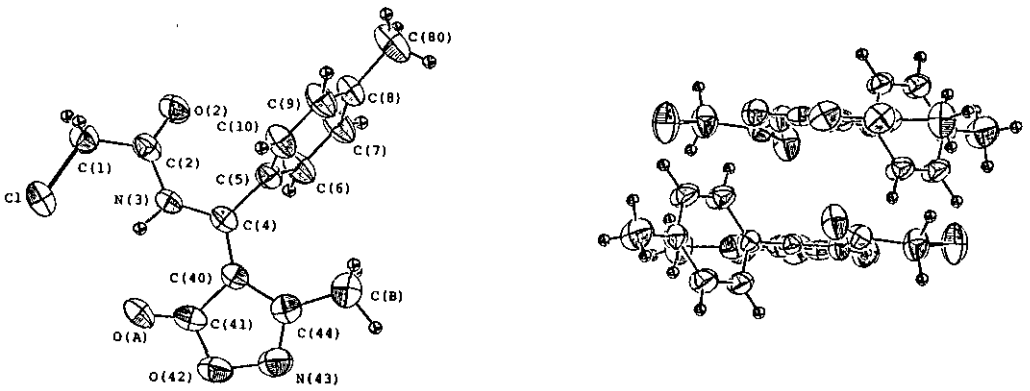

Figure 1. Perspective Views of The Chloroacetyl Derivative (12)[5]

The structures of compounds **7**, **8a** and **10a** were confirmed by a comparison of their ir spectra with those of authentic specimens.[6]

p-Toluamide O-(α-benzoylacetoacetyl)oxime (**4b**), p-toluamide O-(α-ethoxycarbonylacetoacetyl)oxime (**4c**) and p-toluamide O-[α-(p-nitrobenzoyl)acetoacetyl)oxime (**4d**) were heated in dry toluene under reflux for 6 h to give the corresponding 5-(1-acyl-2-oxopropyl)-3-(p-tolyl)-1,2,4-oxadiazole derivatives (**8**) and 5-substituted 3-(p-tolyl)-1,2,4-oxadiazole derivatives (**10**) as well as

products **7** and **9**. In the cyclization of **4c**, 4,5-dihydro-3-(p-tolyl)-1,2,4-oxadiazol-5-one (**10'**) was obtained instead of **10c**. Isoxazoline derivative **9** was not isolated in the cyclization of **4b** or **4d**. The mps and yields of these products are listed in Table III.

Table III. Cyclization of p-Toluamide O-(α-Acylacetoacetyl)oxime Derivatives (**4**)

Material		Reaction	Yields (%) of Products[a]							
4	R	Time (h)	**5**		**7**	**8**		**9**	**10**	(**10'**)
4a	CH_3	2	**5a**	15.3	3.8	**8a**	7.9	27.8	**10a**	15.7
		6		9.1	10.9		4.3	31.5		24.1
4b	C_6H_5	6		---	---	**8b**	45.5	---	**10b**	24.8
		12		---	4.9		54.2	trace[b]		30.6
4c	OC_2H_5	3	**5c**	3.3	6.1	**8c**	32.1	7.1	**10'**	---
		6		---	13.1		41.6	8.5		19.0
4d	$p\text{-}C_6H_4NO_2$	6		---	7.2	**8d**	30.8	trace	**10d**	29.5

a) Melting points of products are as follows: **5a**, 136°C; **5c**, 193°C; **7**, 96°C; **8a**, 90°C; **8b**, 96°C; **8c**, 58°C; **8d**, 157°C; **9**, 237°C; **10a**, 77°C; **10b**, 101°C; **10d**, 173°C; **10'**, 223°C.

b) Detected by TLC experiment.

Possible mechanisms for the formation of compounds **9** and **10** from **4** are shown in Chart 4. As the first step in the formation of compound **9**, intermediate **A**, a tautomer of **4**, may decompose in the retro-addition reaction (path a) to form an isoxazole intermediate (**B**) and p-tolunitrile intermediate (**C**). Intermediate **B** may transform by elimination of water into the 3-methyl-3-isoxazolin-5-one intermediate (**D**) which, on recombining with inetermediate **C**, affords intermediate **E**. Intermediate **E** thus formed can transform into product **9** through elimination of the R-COOH group by water attack. When the R group of **4** is phenyl or p-nitrophenyl, the concerted retro-addition reaction of intermediate **A** may be sterically hindered, and consequently, compound **9** is obtained only in low yield in the reactions of **4b** and **4d**.

Compound **4** can exchange an acetoacetyl group with the acyl group (R-CO) through path b to give compound **5** which, on cyclization by elimination of water, affords 5-substituted 3-(p-tolyl)-1,2,4-oxadiazole derivative (**10**). Cyclization of p-toluamide O-ethoxycarbonyloxime (**5c**) gives solely 4,5-dihydro-3-(p-tolyl)-1,2,4-oxadiazol-5-one (**10'**).

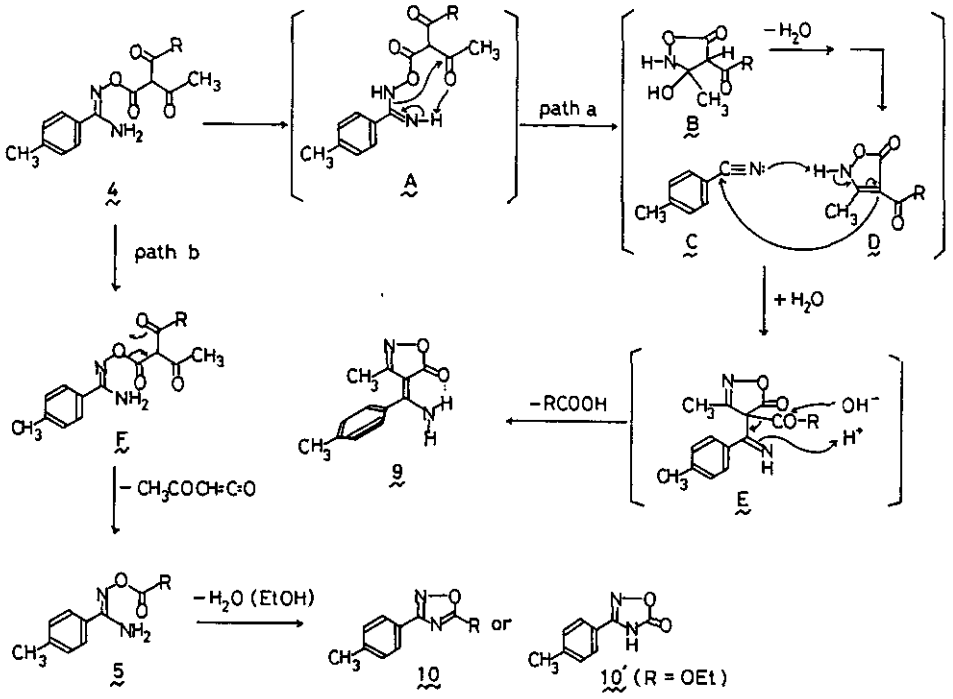

Chart 4

EXPERIMENTAL

All melting points were determined with Yanagimoto hot-stage micro melting point apparatus without correction. IR spectra were recorded on a Hitachi 215 spectrometer and the ^{1}H-nmr spectra, on Varian EM-390 and Bruker AM-400 spectrometers with TMS as the internal standard in each case. The mass spectra were recorded on a JEOL JMS-D 300 spectrometer.

Flash chromatography was carried out with Kimura Kagaku flash chromatography apparatus and Kieselgel 60, using an n-hexane:EtOAc mixture as the eluent under elution conditions described in the literature.[7] HPLC was performed with Kusano Kagaku KP-7H hplc apparatus, a CIG column (silica gel 50μ) and UVILOG 254 detector.

Acylation of p-Toluamie O-Acetoacetyloxime (1)

To a solution of **1** (234 mg, 1 mM) and triethylamine (101 mg, 1 mM) in 5 ml of dry acetonitrile was added 1 mM of acetyl chloride (**2a**), benzoyl chloride (**2b**), ethyl chloroformate (**2c**) or p-nitrobenzoyl chloride (dissolved in 2 ml of acetonitrile)(**2d**) at 0°C. After stirring for 1 h at that temperature, the reaction mixture was concentrated under reduced pressure to dryness. The residue was subjected to flash chromatography on a silica gel column using n-hexane:EtOAc (5:3 - 1:1) as the eluent to give three fractions. Each fraction was subjected to HPLC using the same eluent to afford the p-toluamide O-(3-acyloxy-2-butenoyl)oxime derivative (**3**), p-toluamide O-(α-acylacetoacetyl)oxime derivative (**4**) and unreacted starting material (**1**), in this order.

In the reaction of **1** with **2a**, p-toluamide O-acetyloxime (**5a**) was obtained from the third fraction. In the case of **2b**, p-toluamide O-benzoyloxime (**5b**) was obtained from the second fraction.

The mps and yields are listed in Table I. Physical and spectral data for compounds **3** and **4** are listed in Table IV.

Cyclization of p-Toluamide O-(3-Acyloxy-2-butenoyl)oxime Derivatives (**3a-d**)

A solution of **3** (1 mM) in 10 ml of toluene was refluxed for 6 h. After evaporation of the solvent, the residue was subjected to flash chromatography on a silica gel using n-hexane:EtOAc (4:3 - 1:1) as the eluent to give three fractions. Each of these fractions was then subjected to HPLC using n-hexane:EtOAc (10:1 - 1:1) as the eluent to give the 5-(2-acyloxypropenyl)-3-(p-tolyl)-1,2,4-oxadiazole derivative (**6a-d**), 5-acetonyl-3-(p-tolyl)-1,2,4-oxadiazole (**7**) and unreacted starting material (**3**), in this order.

The mps and yields of these products are listed in Table II and their physical and spectral data in Table IV.

Cyclization of p-Toluamide O-(α-Acylacetoacetyl)oxime Derivatives (**4a-d**)

A solution of **4** (1 mM) in 10 ml of toluene was heated under reflux for 6 h. After evaporation of the solvent, the residual solid was dissolved in a small portion of $CHCl_3$ and subjected to flash chromatography on a silica gel column using n-hexane:EtOAc (4:3 - 1:1) as the eluent to give five fractions. Each fraction was then subjected to HPLC using the same eluent as above to give the

5-substitited 3-(p-tolyl)-1,2,4-oxadiazole derivative (**10a,b,d**), 5-(1-acyl-2-oxopropyl)-3-(p-tolyl)-1,2,4-oxadiazole derivative (**8a-d**), 5-acetonyl-3-(p-tolyl)-1,2,4-oxadiazole (**7**), p-toluamide O-acyloxime derivative (**5a-d**) and 4-[1-amino-1-(p-tolyl)]methylene-3-methyl-2-isoxazolin-5-one (**9**) in this order. In the reaction of **4c**, 4,5-dihydro-3-(p-tolyl)-1,2,4-oxadiazol-5-one (**10'**) was obtained instead of **10**. The mps and yields are listed in Table III. Physical and spectral data for these products are also listed in Table IV.

Acetylation of Compound **9**

A mixture of **9** (21.6 mg, 0.1 mM), triethylamine (15.2 mg, 0.15 mM), a catalytic amount of 4-dimethylaminopyridine and acetic anhydride (21.4 mg, 0.21 mM) was stirred for 45 min at room temperature. The pale yellow reaction mixture was treated with 3 ml of water and 0.1 g of NaCl. The mixture was then extracted with EtOAc and the extract was dried over Na_2SO_4. After evaporation of the solvent, the residue was subjected to HPLC using n-hexane:EtOAc (5:3) as the eluent to give 4-[1-acetamino-1-(p-tolyl)]methylene-3-methyl-2-isoxazolin-5-one (**11**), mp 147°C [from n-hexane:EtOAc 1:1] in 91% yield (23.5 mg). IR ν cm^{-1}: 1760, 1700. ^{1}H-nmr δ ppm [$CDCl_3$]: 1.50 (3H, s, 3-CH_3), 2.23 (3H, s, acetyl-CH_3), 2.43 (3H, s, tolyl-CH_3), 7.17 and 7.30 (4H, AB_q, J = 8 Hz, aromatic H), 11.5 (1H, br, NH).

Anal. Calcd. for $C_{14}H_{14}N_2O_3$: C, 65.10; H, 5.46; N, 10.85. Found: C, 65.28; H, 5.52; N, 10.70.

Chloroacetylation of Compound **9**

A mixture of **9** (21.6 mg, 0.1 mM), chloroacetyl chloride (17 mg, 0.15 mM) triethylamine (15.2 mg, 0.15 mM) and a catalytic amount of 4-DMAP was refluxed for 12 h. The reaction mixture was treated with 5 ml of water and extracted with EtOAc by salting out and the extract was dried over Na_2SO_4. After evaporation of the solvent, the residual solid was subjected to HPLC using n-hexane:EtOAc (3:1 - 1:1) as the eluent to afford 4-[1-chloroacetamino-1-(p-tolyl)]methylene-3-methyl-2-isoxazolin-5-one (**12**), mp 177°C [from n-hexane:CH_2Cl_2 (1:5)] in 28% yield (10 mg). IR ν cm^{-1}: 1720, 1710. ^{1}H-nmr δ ppm [$CDCl_3$]:1.52 (3H, s, 3-CH_3), 2.44 (3H, s, tolyl-CH_3), 4.14 (2H, s, $ClCH_2CO$), 7.20 and 7.38 (4H, AB_q, J = 8 Hz, aromatic H), 12.16 (1H, br, NH).

Table IV. Physical and Spectral Data for Products 3, 4, 5, 6, 7, 8, 9 and 10[a)]

Compd.	Mp[b)] (°C)	MS m/z (M^+)	IR ν cm^{-1} [KBr]	^{1}H-nmr δ ppm [$CDCl_3$]
3a	169[A]	276	3500, 3350 1770, 1730	2.20 (3H, s, $COCH_3$), 2.38 (3H, s, 4-CH_3), 2.40 (3H, s, Ar-CH_3), 5.00 (2H, b, NH_2), 5.95 (1H, s, 2-CH), 7.20 and 7.60 (4H, AB_q, J = 8 Hz, Ar-H).
3b	166[A]	338	3480, 3320 1740, 1725	2.40 (3H, s, Ar-CH_3), 2.56 (3H, s, 4-CH_3), 5.07 (2H, b, NH_2), 6.07 (1H, s, 2-CH), 7.15 - 8.20 (9H, m, Ar-H).
3c	138[B]	306	3480, 3330 1765, 1720	1.36 (3H, t, J = 7 Hz, $OCH_2\underline{CH_3}$), 2.40 (3H, s, Ar-CH_3), 2.46 (3H, s, 4-CH_3), 4.30 (2H, q, J = 7 Hz, OCH_2CH_3), 5.02 (2H, b, NH_2), 6.03 (1H, s, 2-CH), 7.26 and 7.64 (4H, AB_q, J = 8 Hz, Ar-H).
3d	186[A]	383	3485, 3320 1735, 1720	2.47 (3H, s, Ar-CH_3), 2.55 (3H, s, 4-CH_3), 5.05 (2H, b, NH_2), 6.10 (1H, s, 2-CH), 7.22 and 7.61 (4H, AB_q, J = 8 Hz, Ar-H), 8.26 and 8.34 (4H, AB_q, J = 8 Hz, Ar-H).
4a	123[A]	276	3480, 3360 1760, 1725	2.10 and 2.30 (3H x 2, s x 2, $COCH_3$ x 2), 2.43 (3H, s, Ar-CH_3), 5.08 (2H, b, NH_2) 5.88 (1H, s, 2-CH), 7.28 and 7.70 (4H, AB_q, J = 8 Hz, Ar-H).
4b	135[A]	338	3510, 3400 1735, 1730	2.20 (3H, s, $COCH_3$), 2.34 (3H, s, Ar-CH_3), 4.90 (2H, b, NH_2), 5.84 (1H, s, 2-CH), 7.04 - 8.16 (9H, m, Ar-H).
4c	77[B]	306	3500, 3380 1760, 1730	1.33 (3H, t, J = 7 Hz, $OCH_2\underline{CH_3}$), 2.12 (3H, s, $COCH_3$), 2.36 (3H, s, Ar-CH_3), 4.30 (2H, q, J = 7 Hz, OCH_2CH_3), 5.18 (2H, b, NH_2), 5.80 (1H, s, 2-CH), 7.24 and 7.60 (4H, AB_q, J = 8 Hz, Ar-H).
4d	153[A]	383	3480, 3350 1765, 1730	2.26 (3H, s, $COCH_3$), 2.37 (3H, s, Ar-CH_3), 4.96 (2H, b, NH_2), 5.94 (1H, s, 2-CH), 7.28 and 7.54 (4H, AB_q, J = 8 Hz, Ar-H), 8.26 (4H, br s, Ar-H).
5a	136[A]	192	3500, 3400 1750	2.26 (3H, s, $COCH_3$), 2.38 (3H, s, Ar-CH_3), 5.00 (2H, b, NH_2), 7.24 and 7.57 (4H, AB_q, J = 8 Hz, Ar-H).

(continued)

5b	188[A]	254	3500, 3380 1720	2.40 (3H, s, Ar-CH_3), 5.15 (2H, b, NH_2), 7.24 - 8.20 (9H, m, Ar-H).
5c	193[B]	222	3500, 3350 1755	1.33 (3H, t, $\underline{J}$ = 7 Hz, $OCH_2C\underline{H}_3$), 2.35 (3H, s, Ar-CH_3), 4.27 (2H, q, $\underline{J}$ = 7 Hz, $OC\underline{H}_2CH_3$), 5.00 (2H, b, NH_2), 7.10 and 7.52 (4H, AB_q, $\underline{J}$ = 8 Hz, Ar-H).
6a	66[C]	258	1760, 1680	2.22 (3H, s, $COCH_3$), 2.40 (3H, s, Ar-CH_3), 2.56 (3H, s, 4-CH_3), 6.34 (1H, s, 2-CH), 7.32 and 7.98 (4H, AB_q, $\underline{J}$ = 8 Hz, Ar-H).
6b	102[B]	320	1735, 1680	2.40 (3H, s, Ar-CH_3), 2.68 (3H, s, 4-CH_3), 6.48 (1H, s, 2-CH), 7.18 - 8.20 (9H, m, Ar-H).
6c	46[C]	288	1765, 1660	1.40 (3H, t, $\underline{J}$ = 7 Hz, $OCH_2C\underline{H}_3$), 2.37 (3H, s, Ar-CH_3), 2.60 (3H, s, 4-CH_3), 4.26 (2H, q, $\underline{J}$ = 7 Hz, $OC\underline{H}_2CH_3$), 6.40 (1H, s, 2-CH), 7.20 and 7.80 (4H, AB_q, $\underline{J}$ = 8 Hz, Ar-H).
6d	158[B]	365	1760, 1675	2.43 (3H, s, Ar-CH_3), 2.71 (3H, s, 4-CH_3), 6.53 (1H, s, 2-CH), 7.31 and 7.99 (4H, AB_q, $\underline{J}$ = 8 Hz, Ar-H), 8.32 (4H, br s, Ar-H).
7	96[B]	216	1725, 1600	2.30 (3H, s, $COCH_3$), 2.38 (3H, s, Ar-CH_3), 4.20 (2H, s, CH_2), 7.20 and 7.85 (4H, AB_q, $\underline{J}$ = 7 Hz, Ar-H).
8a	90[C]	259[c)]	1760, 1685	2.20 and 2.36 (3H x 2, s x 2, $COCH_3$ x 2), 2.43 (3H, s, Ar-CH_3), 6.23 (1H, s, CH), 7.30 and 7.94 (4H, AB_q, $\underline{J}$ = 9 Hz, Ar-H).
8b	96[C]	320	1740, 1690	2.35 (3H, s, $COCH_3$), 2.37 (3H, s, Ar-CH_3), 6.35 (1H, s, CH), 7.15 - 8.40 (9H, m, Ar-H).
8c	58[C]	288	1750, 1690	1.40 (3H, t, $\underline{J}$ = 8 Hz, $OCH_2C\underline{H}_3$), 2.23 (3H, s, $COCH_3$), 2.40 (3H, s, Ar-CH_3), 4.30 (2H, q, $\underline{J}$ = 8 Hz, $OC\underline{H}_2CH_3$), 6.16 (1H, s, CH), 7.20 and 7.88 (4H, AB_q, $\underline{J}$ = 9 Hz, Ar-H).
8d	157[B]	365	1750, 1680	2.35 (3H, s, $COCH_3$), 2.38 (3H, s, Ar-CH_3), 6.37 (1H, s, CH), 7.09 and 7.59 (4H, AB_q, $\underline{J}$ = 8 Hz, Ar-H), 8.37 - 8.43 (4H, m, Ar-H).

(continued)

9	237[D]	216	3310, 3120 1710, 1670	1.63 (3H, s, CH_3), 2.45 (3H, s, Ar-CH_3), 6.19 (1H, s, NH), 7.33 (4H, s, Ar-H), 9.48 (1H, b, NH)
10a	77[C]	174	1615	2.41 (3H, s, Ar-CH_3), 2.64 (3H, s, 5-CH_3), 7.28 and 7.94 (4H, AB_q, $\underline{J}$ = 8 Hz, Ar-H).
10b	101[C]	236	1615	2.44 (3H, s, Ar-CH_3), 7.45 - 8.40 (9H, m, Ar-H)
10d	173[C]	281	1615	2.44 (3H, s, Ar-CH_3), 7.30 and 8.02 (4H, AB_q, $\underline{J}$ = 8 Hz, Ar-H), 8.38 (4H, s, Ar-H).
10'	223[D][d]	176	3120, 1765	2.42 (3H, s, Ar-CH_3), 7.31 and 7.78 (4H, AB_q, $\underline{J}$ = 9 Hz, Ar-H), 11.4 (1H, b, NH).

a) Analytical data [Found] are as follows:

3a ($C_{14}H_{16}N_2O_4$): C, 60.86; H, 5.84; N, 10.14 [C, 60.69; H, 5.87; N, 9.93].
3b ($C_{19}H_{18}N_2O_4$): C, 67.44; H, 5.36; N, 8.28 [C, 67.55; H, 5.33; N, 7.99].
3c ($C_{15}H_{18}N_2O_5$): C, 58.81; H, 5.92; N, 9.15 [C, 58.73; H, 5.87; N, 9.08].
3d ($C_{19}H_{17}N_3O_6$): C, 59.53; H, 4.47; N, 10.96 [C, 59.57; H, 4.41; N, 10.97].
4a ($C_{14}H_{16}N_2O_4$): C, 60.86; H, 5.84; N, 10.14 [C, 60.75; H, 5.83; N, 10.22].
4b ($C_{19}H_{18}N_2O_4$): C, 67.44; H, 5.36; N, 8.28 [C, 67.38; H, 5.44; N, 8.28].
4c ($C_{15}H_{18}N_2O_5$): C, 58.84; H, 5.84; N, 9.15 [C, 58.81; H, 5.92; N, 9.15].
4d ($C_{19}H_{17}N_3O_6$): C, 59.53; H, 4.47; N, 10.96 [C, 59.70; H, 4.43; N, 10.92].
5a ($C_{10}H_{12}N_2O_2$): C, 62.48; H, 6.29; N, 14.58 [C, 62.44; H, 6.35; N, 14.31].
5b ($C_{15}H_{14}N_2O_2$): C, 70.85; H, 5.55; N, 11.02 [C, 70.71; H, 5.51; N, 10.93].
5c ($C_{11}H_{14}N_2O_3$): C, 59.45; H, 6.35; N, 12.60 [C, 59.75; H, 6.26; N, 12.57].
6a ($C_{14}H_{15}N_2O_3$): C, 65.10; H, 5.46; N, 10.85 [C, 64.85; H, 5.46; N, 10.75].
6b ($C_{19}H_{16}N_2O_3$): C, 71.24; H, 5.03; N, 8.75 [C, 71.52; H, 5.08; N, 8.73].
6c ($C_{15}H_{16}N_2O_4$): C, 62.49; H, 5.59; N, 9.72 [C, 62.21; H, 5.40; N, 9.53].
6d ($C_{19}H_{15}N_3O_5$): C, 62.46; H, 4.14; N, 11.50 [C, 62.68; H, 4.19; N, 11.55].
7 ($C_{12}H_{12}N_2O_2$): C, 66.65; H, 5.59; N, 12.96 [C, 66.65; H, 5.58; N, 12.97].
8a ($C_{14}H_{15}N_2O_3$): C, 65.10; H, 5.46; N, 10.85 [C, 64.82; H, 5.70; N, 10.63].
8b ($C_{19}H_{16}N_2O_3$): C, 71.24; H, 5.03; N, 8.75 [C, 71.45; H, 5.07; N, 8.87].
8c ($C_{15}H_{16}N_2O_4$): C, 62.49; H, 5.59; N, 9.72 [C, 62.51; H, 5.60; N, 9.64].
8d ($C_{19}H_{15}N_3O_5$): C, 62.46; H, 4.14; N, 11.50 [C, 62.58; H, 4.11; N, 11.67].
9 ($C_{12}H_{12}N_2O_2$): C, 66.65; H, 5.59; N, 12.96 [C, 66.58; H, 5.56; N, 12.93].
10a ($C_{10}H_{10}N_2O$) : C, 68.95; H, 5.79; N, 16.08 [C, 68.77; H, 5.89; N, 16.15].
10b ($C_{15}H_{12}N_2O$) : C, 76.25; H, 5.12; N, 11.86 [C, 75.99; H, 5.07; N, 11.82].
10d ($C_{15}H_{11}N_3O_3$): C, 64.05; H, 3.94; N, 14.94 [C, 64.09; H, 3.92; N, 15.05].

b) Recrystallization solvents are abbreviated as follows:
[A] EtOAc; [B] n-Hexane:EtOAc; [C] n-Hexane; [D] EtOAc:MeOH(10:1).

c) (M^++1) peak.

d) Lit., mp 229°C [Ref. 5].

Anal. Calcd. for $C_{14}H_{13}ClN_2O_3$: C, 57.44; H, 4.48; N, 9.57. Found: C, 57.71; H, 4.52; N, 9.64.

X-Ray Analysis Data for 4-[(1-Chloroacetamino-1-(p-tolyl)]methylene-3-methyl-2-isoxazolin-5-one (12)

$C_{14}H_{13}ClN_2O_3$, Mr = 292.7, monoclinic, space group $P2_1/C$, Z = 4, a = 11.097(1), b = 11.713(1), c = 10.962(1) Å, β = 102.502(6)°, U = 1391.1(2) Å^3, D_x = 1.321, D_m = 1.196g · cm^{-3}, μ(CuKα_1, λ = 1.54173 Å) = 2.54mm^{-1}. Crystal size ca. 0.4 x 0.3 x 0.1 mm.

The cell dimensions and intensities were measured on a Rigaku AFC-5 automatic four-circle diffractometer with graphite-monochromated CuKα radiation. A total of 2632 reflections were counted up to 2θ = 130°, in which 1963 independent reflections [$|F_o| \geqq 3\sigma(|F_o|)$] were used for structure determination. The latter problem was solved by the heavy atom method, and refined by the block-diagonal least-squares method. The final R was 0.062. Atomic scattering factors were taken from International Tables for X-ray Crystallography.[8] All calculations were carried out on a FACOM M-360 computer at the computer center of Josai University, using the UNICS-III program system.[9]

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