A Convenient Procedure for Synthesis of Derivatives of 2-Oxazolin-5-one

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Substituted derivatives of 2-oxazolin-5-one have been used as key intermediates in the synthesis of α-amino acids[2], peptides[3], and related compounds[4,5,6]. These heterocycles, also referred to as azlactones, are commonly, prepared by dehy-

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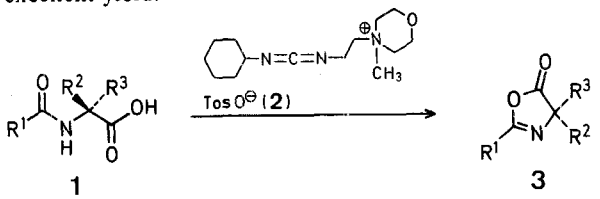
dration/cyclization of *N*-acyl-α-amino acids under acidic reaction conditions[7,8,9]. An alternative method for synthesis which avoids acidic reactants or byproducts utilizes *N,N'*-dicyclohexylcarbodiimide as the dehydration agent[3,10]. These methods of synthesis are satisfactory only if the product azlactone is carried into additional reaction without isolation of the heterocycle. An excellent example of this application is the synthesis of the rugulovasines[11].

If the oxazolin-5-one derivative is to be isolated, these methods of synthesis are not satisfactory. In particular, use of acetic anhydride as the dehydration agent yields 2-phenyl-2-oxazolin-5-one in 66–68% yield from hippuric acid[8]. Use of *N,N'*-dicyclohexylcarbodiimide (DCC) in the synthesis of the same azlactone yields product in 56% yield[12]. These moderate yields result from the difficulty of separating the desired product from undesired reaction byproduct while avoiding decomposition of the reactive azlactone. This decomposition is particularly evident when azlactone products are purified by recrystallization, the described procedure when *N,N'*-dicyclohexylcarbodiimide is employed as the dehydration agent. Problems in the purification of products from DCC-mediated reactions are documented for compounds of lesser reactivity than azlactones[13]. We report in this communication a general procedure for synthesis of derivatives of 2-oxazolin-5-one under neutral reaction conditions allowing the isolation of pure products in excellent yield.



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The procedure is highly efficient but it does not provide optically pure products. With the exception of *N*-benzoyl-L-phenylalanine **(1g)**, reaction of *N*-acyl derivatives of L-amino acids according to the described procedure routinely generated optically inactive azlactones. The exception, **1g**, provided a white crystalline azlactone which in three separate reactions displayed spectral data in accord with **3g**, but with three different, narrow range melting points. The sample of lowest melting point (70–71 °C) was optically inactive[16]. The higher melting samples were optically active and displayed significantly different optical rotations, but we have not determined the level of racemate present in either sample. The sample of intermediate melting point (84–85 °C; $[\alpha]_D^{29}$: −25.2°, *c* 1.0, CH_2Cl_2) is comparable to that reported[17]. The sample with the highest melting point displayed the largest optical rotation (91–93 °C; $[\alpha]_D^{29}$: −32.4°, *c* 1.1, CH_2Cl_2). Although stable when stored under an inert atmosphere, the higher melting samples could be converted to the lower melting, optically inactive sample by maintaining the liquid melt at 95 °C for a period of 1 h, by silica gel chromatography, or by dissolution in a solvent such as acetone followed by evaporative removal of solvent.

2-Phenyl-2-oxazolin-5-one (3a); Typical Procedure:

A solution of *N*-cyclohexyl-*N'*-2-(*N*-methylmorpholinio)-ethylcarbodiimide *p*-toluenesulfonate (**2**[14]; 270.0 mg, 0.64 mmol) in anhydrous dichloromethane (10 ml) is added to a stirred solution of hippuric acid (**1a**; 112.5 mg, 0.63 mmol) in anhydrous dichloromethane (5 ml). The reaction mixture is vigorously stirred and heated to reflux using an oil bath maintained at 55 °C. After 1 h, the reaction mixture is cooled to room temperature. Suspended white solid is removed by filtration and then washed with dichloromethane (10 ml). The combined organic solution is extracted with distilled water (15 ml). The organic layer is dried with anhydrous sodium sulfate and then evaporated under reduced pressure to give **3a** as a white solid; yield: 91.2 mg (90%); m.p. 89–90 °C (Lit.[8], m.p. 89–92 °C).

$C_9H_7NO_2$	calc.	C 67.07	H 4.38	N 8.69	
(161.2)	found	67.07	4.40	8.68	

I.R. (CH_2Cl_2): ν = 1825; 1655; 1450; 1325; 1270; 1250; 1135; 1120; 885; 855 cm^{-1}.

^{1}H-N.M.R. (CD_3COCD_3): δ = 4.49 (s, 2H); 7.5 (m, 3H); 7.95 ppm (m, 2H).

Table. 2-Oxazolin-5-one Derivatives **3a–h**

Product No.	R^1	R^2	R^3	Yield [%][a]	m.p. [°C]	Lit. m.p. [°C]	Molecular formula[b]	
3a	C_6H_5	H	H	90	89–90°	89–92°[8]	$C_9H_7NO_2$	(161.2)
3b	C_6H_5	CH_3	H	96	39–40°	39°[18]	$C_{10}H_9NO_2$	(175.2)
3c	C_6H_5	CH_3	CH_3	82	oil	—	$C_{11}H_{11}NO_2$	(189.2)
3d	C_6H_5	*i*-C_3H_7	H	88	41–45°	48–50°[19]	$C_{12}H_{13}NO_2$	(203.2)
3e	C_6H_5	*i*-$C_3H_7CH_2$	H	95	52–54°	54.5–55°[20]	$C_{13}H_{15}NO_2$	(217.3)
3f	*t*-C_4H_9	H	H	84	oil	—	$C_7H_{11}NO_2$	(141.2)
3g[c]	C_6H_5	$C_6H_5CH_2$	H	88	70–71°	70.5–71°[16]	$C_{16}H_{13}NO_2$	(251.3)
				88	84–85°	86–87°[17]		
				80	91–93°	—		
3h	$C_6H_5CH_2OCONHCH_2$	$C_6H_5CH_2$	H	86	68–70°	70.5–72°[16]	$C_{19}H_{18}N_2O_4$	(338.4)

[a] Yield of isolated product.
[b] Satisfactory microanalyses obtained: C ±0.25, H ±0.14, N ±0.35.
[c] See text.

Treatment of an *N*-acyl-α-amino acid **(1)** with *N*-cyclohexyl-*N'*-2-(*N*-methylmorpholinio)-ethylcarbodiimide *p*-toluenesulfonate **(2)**[14] followed by aqueous extraction workup yielded azlactone **(3)**. Reaction temperatures higher than that of refluxing dichloromethane led to a lower yield of product and contamination by uncharacterized byproducts. Temperature control was a less serious problem with simple derivatives of **3** but was an essential feature for synthesis of more sensitive compounds such as **3h**[15]. All azlactone products were fully characterized. Recrystallization or Kugelrohr distillation of the isolated products was not a necessary step in order to obtain pure material.

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