A Novel Synthesis of 2,3-Dihydro-4*H*-1,4-oxazin-2-ones and 6-Methylene-2-morpholinones

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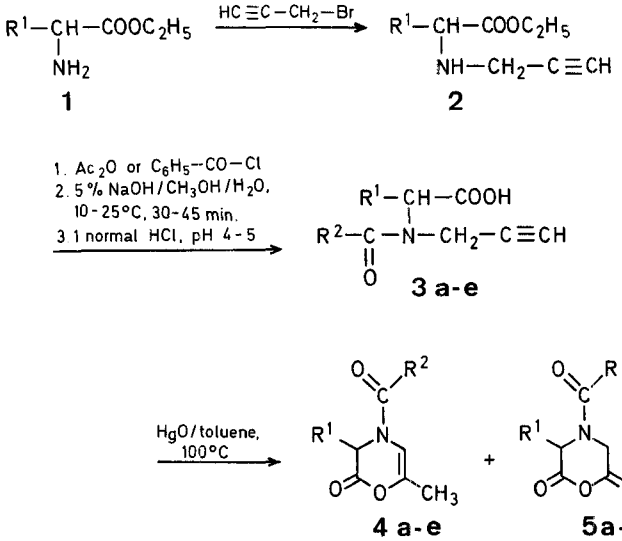
Mercury-catalyzed intramolecular cyclization reactions have appeared in the literature many times. The cyclizations were carried out between a double bond or a triple bond and hydroxy[1], carbonyl[2], and carboxy[3,4] groups in the molecule. We have now found that the mercury-catalyzed cyclization of *N*-acyl-*N*-prop-2-ynylamino acids **3** is a useful general approach to 2,3-dihydro-4*H*-1,4-oxazin-2-ones **4** and 6-methylene-2-morpholinones **5**. A general synthetic method for these heterocycles was not known till the present time.



In the presence of catalytic amount of yellow mercury(II) oxide in toluene at 100 °C, the *N*-acyl-*N*-prop-2-ynylamino acid **3** was cyclized to two heterocycles, 4-acyl-2,3-dihydro-6-methyl-4*H*-1,4-oxazin-2-one **4** and 4-acyl-6-methylene-2-morpholinone **5**. As shown in Table 2, the cyclization usually gave the two compounds and the yields were moderate.

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Table 1. *N*-Acyl-*N*-prop-2-ynylamino Acids **3a–e**

Product No.	R^1	R^2	Yield[a] [%]	m.p. [°C] (solvent)	Molecular formula[b]	M.S. *m/e* (M^+)
3a	*i*-C_3H_7—CH_2	CH_3	94–97	129–130° (benzene)	$C_{11}H_{17}NO_3$ (211.1)	211 (12%)
3b	*i*-C_3H_7—CH_2	C_6H_5	95	109–110° (*n*-hexane/benzene, 3 : 1)	$C_{16}H_{19}NO_3$ (273.1)	273 (6%)
3c	$C_6H_5CH_2$	CH_3	87	92–93° (*n*-hexane/benzene, 3 : 1)	$C_{14}H_{15}NO_3$ (245.1)	245 (13%)
3d	$C_6H_5CH_2$	C_6H_5	79	92.5–93° (*n*-hexane/benzene, 1 : 1)	$C_{19}H_{17}NO_3$ (307.1)	307 (10%)
3e	H	C_6H_5	84	oil[c]	—	217 (15%)

[a] Yield based on **2**.
[b] Satisfactory I.R., ^{1}H-N.M.R. spectra, and microanalyses obtained: C ±0.10, H ±0.17, N ±0.19 (except **3e**).
[c] Unstable oil which could not be distilled; high resolution M.S.: *m/e* = 217.0744 (M^+, $C_{12}H_{11}NO_3$ requires 217.0737).

Table 2. 2,3-Dihydro-4*H*-1,4-oxazin-2-ones **4a–e** and 6-Methylene-2-morpholinones **5a–e**

Product	Yield [%]	m.p. [°C] (solvent)	Molecular formula[a]	Selected ^{1}H-N.M.R. (CCl_4) Data δ [ppm]	M.S. *m/e* (M^+)
4a	40	oil[b]	$C_{11}H_{17}NO_3$ (211.1)	6.16 (s, 1H, 5-H); 1.98 (s, 6-H_3C)	calc. 211.1208; found 211.1223
4b	39	oil[b]	$C_{16}H_{19}NO_3$ (273.1)	5.97 (br s, 1H, 5-H); 1.90 (br s, 6-H_3C)	calc. 273.1363; found 273.1342
4c	35	96–97° (CCl_4)	$C_{14}H_{15}NO_3$ (245.1)	5.60 (s, 1H, 5-H); 1.92 (s, 6-H_3C)	—
4d	32	oil[b]	$C_{19}H_{17}NO_3$ (307.1)	5.82 (s, 1H, 5-H); 1.65 (s, 6-H_3C)	calc. 307.1208; found 307.1224
4e	27	oil[b]	$C_{12}H_{11}NO_3$ (217.1)	6.10 (s, 1H, 5-H); 1.90 (s, 6-H_3C)	calc. 217.0737; found 217.0743
5a	31	62.5–63° (*n*-hexane)	$C_{11}H_{17}NO_3$ (211.1)	3.7–4.7 (br s, 2H, 5-H); 4.56, 4.78 (2d, J = 2 Hz, 2H, =CH_2)	—
5b	35	73–74° (3 : 1 *n*-hexane/CCl_4)	$C_{16}H_{19}NO_3$ (273.1)	3.92, 4.40 (2d, J = 16 Hz, 2H, 5-H); 4.30, 4.66 (2d, J = 2 Hz, 2H, =CH_2)	—
5c	24	oil[b]	$C_{14}H_{15}NO_3$ (245.1)	3.6–4.2 (br s, 2H, 5-H); 4.53, 4.69 (2m, 2H, =CH_2)	calc. 245.1035; found 245.1050
5d	12	oil[b]	$C_{19}H_{17}NO_3$ (307.1)	4.05 (br s, 2H, 5-H); 4.12, 4.55 (m, d, 2H, J = 2 Hz, =CH_2)	calc. 307.1208; found 307.1230
5e	36	oil[b]	$C_{12}H_{11}NO_3$ (217.1)	4.28 (s, 2H, 5-H); 4.48, 4.82 (m, d, 2H, J = 2 Hz, =CH_2)	calc. 217.0737; found 217.0743

[a] Satisfactory microanalyses obtained for crystalline products: C ±0.30, H ±0.14, N ±0.12.
[b] Unstable oil which could not be distilled.

This cyclization of **3** also proceeded in dimethylformamide or hexamethylphosphoric triamide at 100 °C, or in refluxing benzene, but did not proceed in low boiling solvents, such as chloroform, acetone, or tetrahydrofuran, and in these cases starting **3** was recovered. When the cyclization of **3** was attempted without a catalyst, none of the desired heterocycles **4** and **5** were formed and compound **3** was also recovered.

Non-acylated amino acids, such as *N*-prop-2-ynylleucine and *N*-phenyl-*N*-prop-2-ynylglycine, were tried but the desired cyclized products were not obtained under similar conditions. On heating *N*-phenyl-*N*-prop-2-ynylglycine in hexamethylphosphoric triamide at 100 °C, about 5% of the cyclized product, 6-methylene-4-phenyl-2-morpholinone, was obtained[5]. In this case the starting material was not recovered.

In order to examine the stereochemistry of the products, we have chosen L- and D-leucines as starting amino acids, and L-*N*-acetyl-*N*-prop-2-ynylleucine {**3a**; $[\alpha]_D^{22}$: −19.9° (*c* 1, methanol)} and D-*N*-acetyl-*N*-prop-2-ynylleucine {**3f**; $[\alpha]_D^{22}$: +20.7° (*c* 1, methanol)} were cyclized under similar conditions. However, the obtained **4a**, **5a**, **4f**, and **5f** showed almost zero optical rotation. This suggested that the process led to the racemization.

2,3-Dihydro-4*H*-1,4-oxazin-2-ones 4 and 6-Methylene-2-morpholinones 6; General Procedure:

N-Acyl-N-prop-2-ynylamino Acids **3**: The amino acid ethyl ester **1**[6] is alkylated with prop-2-ynyl bromide and the resultant *N*-prop-2-ynylamino acid ethyl ester **2** (40–70% yield) is acylated with corresponding acid chloride or anhydride, followed by careful hydrolysis with an equimolar amount of 5% sodium hydroxide in aqueous methanol solution at 10–25 °C for 30–45 min to give **3** (Table 1).

Cyclization of **3**: A mixture of **3** (4 mmol) and 5–10% of yellow mercury(II) oxide in toluene (15 ml) is heated at 100 °C for 3–4 h under nitrogen. After cooling, the catalyst is filtered and washed with toluene. The combined filtrates are concentrated and the resulting residue is chromatographed on silica gel column with benzene/ethyl acetate as eluent to give pure **4** and **5** (Table 2).

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[5] ^{1}H-N.M.R. (CCl_4): $\delta = 3.94$ (s, 2H); 4.12 (m, 2H); 4.50 (m, 1H); 4.75 (d, 1H); 6.4–7.3 ppm (m, 5H).
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