# 267. Synthesis with 1,2-Oxazines. I. A Synthesis of 4,5-Dihydro-6*H*-1,2-Oxazin-6-one Derivatives

by **Bruno Hardegger** and **Shimon Shatzmiller**

Department of Chemistry, Tel-Aviv University, Tel-Aviv, Israel

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*Summary.* A synthesis of some 4,5-dihydro-6*H*-1,2-oxazin-6-one derivatives is described.

For synthetic studies, we were interested in the N-alkyl-6-oxo-4,5-dihydro-6*H*-1,2-oxazinium system **7**, (*Scheme*). This 1,2-oxazine derivative has received only little attention [1]. Since the reaction of α-chloronitrones with multiple C–C bonds gave a new pathway to the 1,2-oxazine ring, we examined the reaction of α-chloro aldonitrone [2] [3] as well as the solution of α-chloro-acetone-N-methyl-nitrone [4] with ketene under the described reaction conditions. Unfortunately, all our experiments were unsuccessful and yielded only an intractable mixture of products.

*Ohta et al.* [5] reported the synthesis of related materials **6a** and **6b** by dehydration of 4-oximino-carboxylic acids with DCC. We thought of utilizing the resulting products as a basis for further N-alkylation. However, we could not repeat the procedure described. Therefore, we were forced to look for an alternative way to the 4,5-dihydro-6*H*-1,2-oxazin-6-one ring system.

Earlier work by *Carpino* [6] and *House* [7] suggested as a possible route the intramolecular formation of six-membered cyclic oxime esters. Reaction of acid chloride derivatives with *t*-butyl-N-hydroxycarbamate in dichloromethane gave the *t*-butyl-N-acyl derivatives in high yield (Table). Efforts directed towards the isolation

Table. *Methods and yields for the formation of 1,2-oxazines from γ-ketoacids*

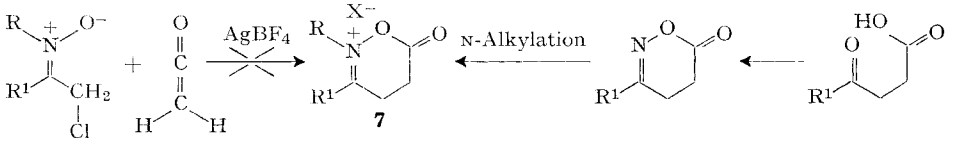
| γ-ketoacid No. | *t*-butyl-N-acyl-carbamate | | | 4,5-dihydro-6*H*-1,2-oxazine-6-one | | |
|---|---|---|---|---|---|---|
| | Compound | Yield (%) | Method | No. | Yield (%) | Method[a] |
| **2a** | **4a** | 95 | A | **6a** | 81 | C |
| **2b** | **4b** | 84 | B | **6b** | 71 | D |
| **8** | **9** | 85 | B | **10** | 62 | D |

[a] Methods of preparation: C Cyclisation with $CF_3COOH$; D Cyclisation with *p*-TsOH.

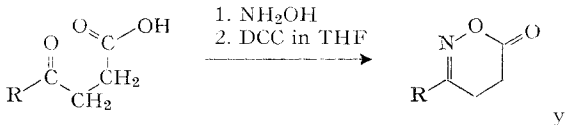
of corresponding O-acyl-hydroxylamine derivatives **5** (*Scheme*) were abortive [6]. However, cyclic oxime esters could be isolated on treatment of the corresponding *t*-butyl-N-acyl-carbamates (Table) in acidic media, as a result of the facile intramolecular cyclization of the corresponding 'unisolated' O-(γ-oxo-acyl)-hydroxylamine derivatives in yields from 62 to 81%, data of these matched those published earlier [5]. On the other hand, this work also presents a procedure for 4,5-dihydro-6*H*-1,2-oxazin-6-one compounds, which do not carry aromatic substituents.

On treatment of the above oxazine derivatives (**6a**, **6b**, and **10**) with ethanol, corresponding open chain γ-oximino esters were obtained as indicated [5]. Treatment

*Scheme*

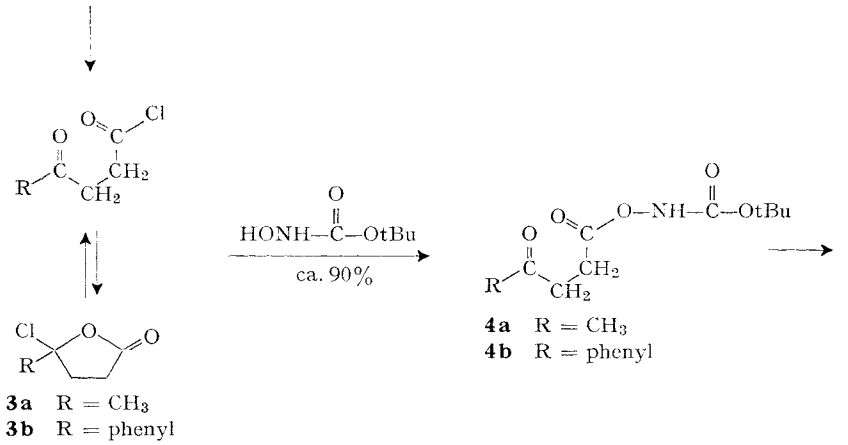



**1a′** R = cyclohexyl **7a′** R = cyclohexyl $R^1$ = H **3a** $R^1$ = $CH_3$ **2a** R = $CH_3$
**1b′** R = $R^1$ = $CH_3$ **7b′** R = $CH_3$ $R^1$ = $CH_3$ **3b** $R^1$ = phenyl **2b** R = phenyl
**7a** R = alkyl $R^1$ = $CH_3$
**7b** R = alkyl $R^1$ = phenyl



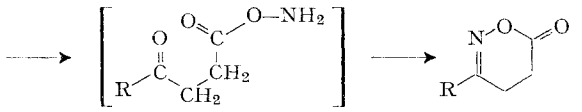

**2a** R = $CH_3$
**2b** R = phenyl

**6a** R = $CH_3$ yield: not isolated (5)
**6b** R = phenyl ca. 80% (5)



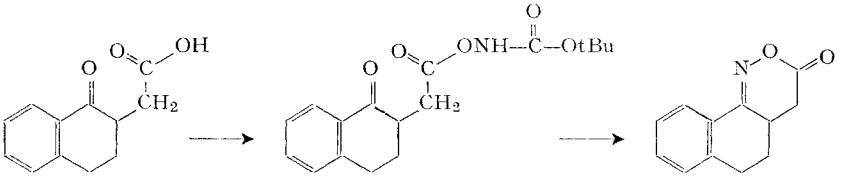

**3a** R = $CH_3$
**3b** R = phenyl

**4a** R = $CH_3$
**4b** R = phenyl



**5a** R = $CH_3$
**5b** R = phenyl

**6a** R = $CH_3$ yield: ca. 80%
**6b** R = phenyl 71%



**8** **9** **10**

of **6a** and **6b** with triethyloxoniumtetrafluoroborate or with methyl fluorosulfonate in dichloromethane, gave solutions having IR.-absorptions at 1830 $cm^{-1}$ indicating the presence of alkylated cyclic oxime esters [7]. Further work with these highly reactive intermediates is still in progress.

## Experimental Part

$^1$H-NMR. spectra were determined in $CDCl_3$ with tetramethyl silane as internal standard; chemical shifts are expressed in $\delta$ values (ppm). Unless otherwise indicated, IR. and UV. spectra were determined in chloroform and acetonitrile solutions respectively. Melting points were determined on a *Büchi* SMP-20 apparatus and are uncorrected.

Dry solvents were obtained by filtration over 100-fold amount of basic aluminium oxide (activity 1; *Merck*).

*O-t-Butyl-N-levulinoxy-carbamate* (**4a**) (*Method A*). 3.8 ml (4.33 g = 37.3 mmol) levulinic acid (**2a**, *Fluka* puriss.) was dissolved in 100 ml dry benzene together with 10 drops of pyridine. 14 ml (20.7 g = 0.163 mol) oxalylychloride were added dropwise at 0° over 15 min. The solution was stirred for another 1.5 h at RT. and the solvent was then removed under reduced pressure. The crude oily product showed a strong IR.-absorption at 1800 $cm^{-1}$ ($CHCl_3$). It was dissolved in 30 ml ether and added dropwise to a solution of 5 g (37.6 mmol) *t*-butyl-N-hydroxyurethane and 5.5 ml (4 g = 40 mmol) triethylamine in 30 ml ether at 0°. A thick, white precipitate was formed and was stirred for another hour at RT. It was diluted with ether, shaken with 2 portions of an ice-cooled 1 M aqueous solution of sodium hydrogen carbonate, and extracted 3 times with *ca.* 50 ml ether. The organic layers were combined, dried on magnesium sulfate, filtered and evaporated to dryness. The product was a yellowish oil. The NMR. showed 70 mol-% carbamate **4a** (yield about 95%), the rest being solvent. The analytical sample was obtained by distilling this oil in a ball tube at 140°/10.05 Torr. – IR.: 3360, 1783, 1750, 1722, 1374, 1162 and 1120 $cm^{-1}$. – NMR.: 1.42 (*s*, 9H); 2.13 (*s*, 3H); 2.64 (*t*, $J$ = 5 Hz, 2H); 2.76 (*t*, $J$ = 5 Hz, 2H) and 8.05 (br. *s*, 1H). – MS. (*m/e*): 157 (8), 129 (22) and 99 (100).

$C_{10}H_{17}NO_5$ (231.2) Calc. C 51.94 H 7.41 N 6.06% Found C 51.60 H 7.44 N 6.30%

*3-Methyl-4,5-dihydro-6H-1,2-oxazin-6-one* (**6a**) (*Method C*). 1.05 (~85% by weight = 4.0 mmol) of the crude carbamate **4a** was dissolved in 2 ml dichloromethane and 2 ml trifluoroacetic acid were added under stirring (gas evolved). The solution was stirred for 20 min at RT. The solvents were then removed under reduced pressure (bath temp. ≤ 40°). The resulting oil was dissolved in dichloromethane, shaken quickly with 20 ml of an ice-cooled 1 M aqueous solution of sodium hydrogen carbonate and extracted twice with dichloromethane. The organic layers were combined, dried on magnesium sulfate, filtered and evaporated. The crude product (366 mg = 81%) was a yellowish oil which was immediately distilled at 115°/0.02 Torr in a ball tube. The resulting colourless oil was dissolved in ether and quickly crystallized in liquid nitrogen to give 180 mg (1.6 mmol = 40%) white crystals of 3-methyl-4,5-dihydro-6*H*-1,2-oxazin-6-one (**6a**), which melted at RT. The IR. of the crude materials was identical with the analytical one except for a broader CO-band at 1760 $cm^{-1}$. – IR.: 1760, 1431, 1382, 1318, 1150, 922 and 903 $cm^{-1}$. – NMR.: 2.16 (*s*, 3H) and 2.64 (*s*, 4H). – MS. (*m/e*): 113 (100), 96 (18), 85 (20) and 68 (45).

$C_5H_7NO_2$ (113.1) Calc. C 53.09 H 6.24 N 12.38% Found C 52.89 H 6.54 N 12.28%

*O-t-Butyl-N-(4-oxo-4-phenyl-butyroxy)-carbamate* (**4b**) (*Method B*). Preparation as that of carbamate **9** starting from 5.55 g (31.2 mmol) 3-benzoyl-propionic acid (**2b**, m.p. 115°). The resulting product was crystallized from dichloromethane/pentane to yield 7.7 g (26.3 mmol) 84% brownish crystals of **4b** (m.p. 71°).

The analytical sample was obtained by recrystallizing 3 times from dichloromethane/pentane (m.p. 74–75°). – IR.: 3360, 1785 (sh), 1755, 1690, 1600, 1452, 1375 and 1120 $cm^{-1}$. – NMR.: 1.47 (*s*, 9H); 2.88 (*t*, $J$ = 6 Hz, 2H); 3.38 (*t*, $J$ = 6 Hz, 2H); 7.32–7.858 (*m*, 3H) and 7.88–8.18 (*m*, 2H). – UV. ($\lambda_{max}$ ($\varepsilon$)): 241 (14.300) and 277 (1.600) nm. – MS. (*m/e*): 220 (8), 161 (100), 133 (14), 115 (8), 105 (92) and 77 (60).

$C_{15}H_{19}NO_5$ (293.3) Calc. C 61.42 H 6.53 N 4.76% Found C 61.38 H 6.59 N 5.00%

*3-Phenyl-4,5-dihydro-6H-1,2-oxazin-6-one* (**6b**) (*Method D*). Preparation analogous to that of **10**, starting from 1.05 g (3.6 mmol) carbamate **4b** (m.p. 74–75°) and 244 mg (1.3 mmol) *p*-TsOH

monohydrate. Crystallization from dichloromethane/hexane yielded 484 mg (2.57 mmol) brownish crystals of **6b** (71%, m.p. 96°).

The analytical sample was obtained by recrystallizing 3 times from dichloromethane/pentane (m.p. 98–99°; lit. 99.5–100.5° [5]). – IR.: 1170, 1450, 1323, 1281, 1173, 1150 and 904 $cm^{-1}$. – NMR.: 2.73 (*t*, J = 7 Hz, 2H); 3.07 (*t*, *J* = 7 Hz, 2H); 7.37–7.57 (*m*, 3H) and 7.65–7.83 (*m*, 2H). – MS. (*m/e*): 175 (60), 158 (5), 146 (18), 130 (100), 115 (19) and 103 (76).

*O-t-Butyl-N-(α-tetralone-2-acetoxy)-carbamate* (**9**) (*Method B*). 10 g (49 mmol) of α-tetralone-2-acetic acid (**8**, m.p. 108°) was dissolved in 100 ml benzene. To this solution, 12 drops of pyridine were added. 19.2 ml (28.5 g = 0.225 mol) oxalylchloride were added dropwise with ice-cooling over 20 min. The solution was stirred for another 2 h at RT. and the solvent was then removed under reduced pressure. The resulting product was a red crystalline material (IR.: 1810 $cm^{-1}$). This was dissolved in 60 ml dry dichloromethane and added dropwise to an ice-cooled solution of 6.5 g (49 mmol) O-*t*-butyl-N-hydroxy-carbamate and 7.5 ml (5.4 g = 54 mmol) triethylamine in 40 ml dry ether. The resulting mixture was stirred for 1 h at RT. It was diluted with dichloromethane, shaken with 2 portions of an ice-cooled 1 M aqueous solution of sodium hydrogen carbonate, then with 2 portions of an ice-cooled aqueous solution of 10% ammoniumchloride and extracted 3 times with *ca.* 50 ml dichloromethane. The organic layers were combined, dried on magnesium sulfate, filtered and evaporated. Crystallization from dichloromethane and pentane resulted in 14.9 (46.7 mmol) yellow crystals 95% of **9** (m.p. 85°).

The analytical sample was obtained by recrystallizing 3 times from dichloromethane/pentane (m.p. 88°). – IR.: 3360, 1780 (sh), 1753, 1685, 1604, 1374, 1158 and 1116 $cm^{-1}$. – NMR.: 1.44 (*s*, 9H); 1.85–2.85 (*m*, 3H); 2.95–3.31 (*m*, 4H); 7.14–7.56 (*m*, 3H); 7.98 (*d*, *J* = 8 Hz, 1H) and 12.5 (br.*s*, 1H). – UV. ($\lambda_{max}$ (ε)): 246 (12.500) and 289 (2.000) nm. – MS. (*m/e*): 263 (4), 246 (6), 187 (100), 158 (6), 144 (10) and 86 (50).

$C_{17}H_{21}NO_5$ (319.4) Calc. C 63.94 H 6.63 N 4.39% Found C 63.93 H 6.67 N 4.60%

*4,4a,5,6-tetrahydro-naphth[1,2-c]-1,2-oxazin-6-one* (**10**) (*Method D*). 740 mg (2.4 mmol) carbamate **9** and 150 mg (0.8 mmol) *p*-TsOH monohydrate were dissolved in 50 ml of benzene and refluxed for 40 min. The refluxing solvent was dried on its return by a soxhlet filled with anhydr. calcium sulfate. The mixture was then heated with charcoal for about 5 min, filtered through cellite and evaporated. Crystallization from dichloromethane/hexane yielded 295 mg (1.48 mmol) brownish crystals of **10** (62%, m.p. 100°).

The analytical sample was obtained by recrystallizing 3 times from dichloromethane/pentane (m.p. 102°). – IR.: 1773, 1170, 1151, 926, 910 and 889 $cm^{-1}$. – NMR.: 1.36–1.90 (*m*, 1H); 2.06–2.48 (*m*, 2H); 2.70–3.12 (*m*, 4H); 7.10–7.50 (*m*, 3H) and 8.09 (*d*, *J* = 8 Hz, 1H). – UV. ($\lambda_{max}$ (ε)): 261 (19.500), 290 sh (4.000) and 299 sh (2.700) nm. – MS. (*m/e*): 201 (47), 182 (20), 156 (42), 149 (35), 129 (100), 116 (72) and 102 (11).

$C_{12}H_{11}NO_2$ (201.2) Calc. C 71.62 H 5.51 N 6.96% Found C 71.64 H 5.57 N 7.24%

*Alkylation of 3-methyl-4,5-dihydro-6H-1,2-oxazin-6-one* **6a** *with triethyloxoniumtetrafluoroborate.* 4.5 ml of a 1.5 M solution of triethyloxoniumtetrafluoroborate in dry dichloromethane was added to 565 mg (5 mmol) oxazinone compound **6a** in 2 ml dichloromethane. The solution was stirred at RT. during 2 h. The IR. of the resulting reaction mixture showed a strong absorption at 1830 $cm^{-1}$ ($CH_2Cl_2$). All efforts to isolate the salt were unsuccessful.

## REFERENCES

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