Cyclizations of Dianions from 2-Imino-1,2-diphenylethanone to Oxazolines, Oxazocines, and Oxazonines

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The reaction of 2-imino-1,2-diphenylethanone with sodium in ether and subsequent addition of carbon disulfide or ethyl chloroformate resulted in the formation of 3,4,5-trisubstituted 4-oxazoline-2-thiones and 2-ones, respectively. 1,4-Oxazonines and 1,4-oxazocines were also synthesised from the reaction of 2-imino-1,2-diphenylethanone with sodium in THF followed by addition of dihaloalkanes.

The reported cyclization reactions of anils and dianils leading to the imidazolidine,[1,2] imidazoline,[3] diazocine and diazonine[4] derivatives prompted us to investigate the reactions of dianions from α-imino ketones. This study has led to new, convenient and general synthetic routes to oxazolines, oxazocines and oxazonines. These five-, eight-, and nine-membered heterocycles each containing one oxygen and one nitrogen atoms draw a special attention as potential biologically active compounds.

Results and Discussion

The reaction of (±)-2-(α-phenylethylimino)-1,2-diphenylethanone (**1a**) with sodium in dry ether followed by addition of carbon disulfide gave (±)-3-(α-phenylethyl)-4,5-diphenyl-4-oxazoline-2-thione (**2a**, 49%). The structural assignment of **2a** was made on the basis of its analytical and spectral data. In the above reaction replacing carbon disulfide by ethyl chloroformate gave (±)-3-(α-phenylethyl)-4,5-diphenyl-4-oxazolin-2-one (**3a**, 35%) identified by its analytical and spectral data. Similar treatment of the dianions from 2-imino-1,2-diphenylethanone **1b—f** with carbon disulfide and ethyl chloroformate gave 3-substituted 4,5-diphenyl-4-oxazoline-2-thiones **2b—f** and -2-ones **3b—f**, respectively. The products have been characterized on the basis of their analytical and spectral data.

Treatment of 2-imino-1,2-diphenylethanone **1d—e** with sodium in dry THF and subsequent addition of 1,4-dichlorobutane gave 2,3,4-triaryl-5,6,7,8-tetrahydro-4*H*-1,4-oxazocines **4d—e** which were crystallized from hexane.

Similar treatment of the dianions from imino ketones **1d—e** with 1,5-dichloropentane gave 2,3,4-triaryl-4,5,6,7,8,9-hexahydro-1,4-oxazonines **5d—e** which were recrystallized from hexane. The structural assignments of the products **4d—e** and **5d—e** were made on the basis of their analytical and spectral data.

When the dianions from imino ketones **1d—e** were similarly treated with 1,3-dibromopropane the expected cyclization products 1,4-oxazepines were not obtained and 2-anilino-1,2-diphenyl-4-penten-1-ones (**6d—e**) were formed. The products **6d—e** have been identified by their analytical and spectral data. One of the three vinyl protons (H_A) appeared downfield as compared to others. An inspection of the models of compounds **6d—e** reveals that this proton would be deshielded by the carbonyl group and the nitrogen lone pair. The formation of diazepine derivatives from the reactions of the dianion from benzil dianils with 1,3-dibromopropane and 1,3-diiodopropane,[5] in low yields have been observed due to the steric factors. It has been reported earlier that in the reaction of benzil dianil with sodium in ether followed by addition of 1,3-dichloropropane no diazepine derivative was obtained.[6]

The formation of products **2a—f**, **3a—f**, **4d—e**, **5d—e**, **6d—e** from 2-imino-1,2-diphenylethanone **1a—f** is depicted in the following scheme:

The above reactions involve the initial formation of dianions, by the electron transfer from sodium to 2-imino-1,2-diphenylethanone, which attack carbon disulfide, ethyl chloroformate, 1,3-, 1,4-, and 1,5-dihaloalkanes with elimination of sulfide ions (detected by the formation of lead(II) sulfide with aq lead(II) acetate) or halide ions (detected by the formation of silver halide with aq silver nitrate) or/and ethoxide ions to give rise to the observed products. These reactions provide new, convenient one-pot syntheses of heterocycles which would be difficult to prepare otherwise.

Experimental

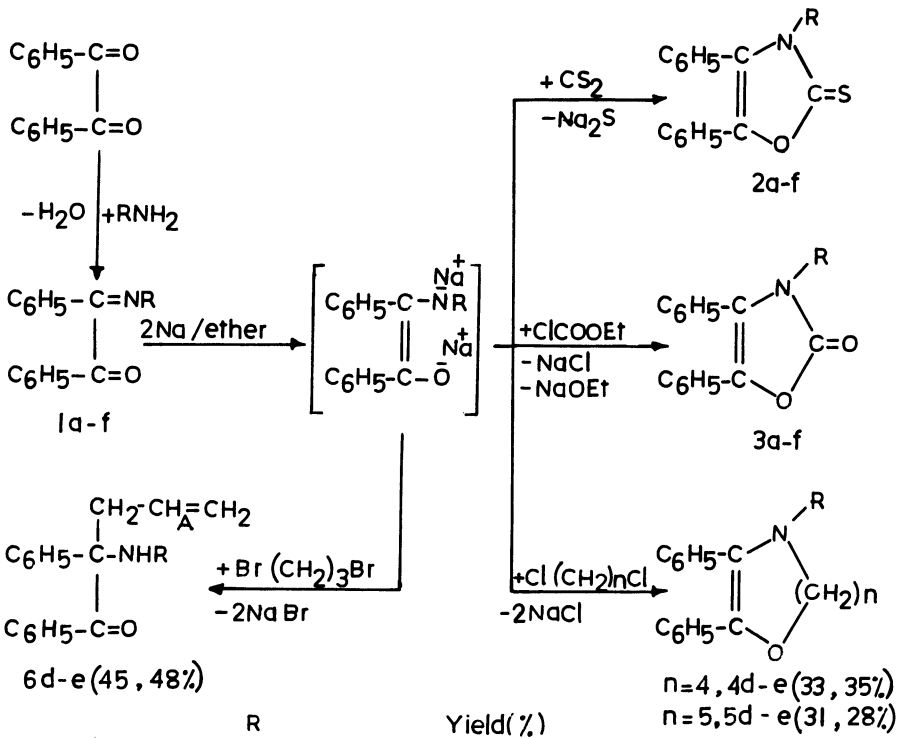
Instrumentation. Melting points have been determined in capillaries on Büchi melting point apparatus and are uncorrected. The NMR spectra in $CDCl_3$ were recorded on Varian A-60D and VN 1009 (S-60T) spectrometers with TMS as an internal standard. The IR spectra were measured on a Perkin Elmer 720 spectrophotometer and UV spectra on a Beckman DB-G spectrophotometer.

Materials The 1,2-diketones, amines and dihaloalkanes were obtained from Ega, Chemie, West Germany.

Preparation of 2-Imino-1,2-diphenylethanone 1a—f.
General Procedure From Alkylamines: The starting α-imino ketones **1a—c** and **1f** were obtained by keeping an equimolar mixture of benzil and alkylamine in 95% ethanol at room temperature for a week, following the reported method[7] and purified by fractional crystallization from ethanol (78—88%).

From Arylamines. The starting 2-imino-1,2-diphenylethanones **1d—e** were obtained by heating an equimolar mixture of benzil and aromatic amine at 150°C for 2—3 h following the reported method[8] and purified by fractional crystallization from ethanol (75—78%).

Preparation of 3-Substituted 4,5-Diphenyl-4-oxazoline-2-thiones 2a—f. *General Procedure*: Sodium pieces (**1g**) were slowly added to dry ether (60 ml) in a three-necked round-



	R	Yield(%) 2	3
a	-CH(CH3)C6H5	49	35
b	-CH2CH2CH3	35	33
c	-CH2CH2CH2CH3	36	35
d	-C6H5	48	45
e	-C6H4CH3(p-)	50	55
f	-CH(CH3)CH3	32	35

Scheme

bottomed flask, fitted with a condenser, a mercury trap and a pressure-equalizing addition funnel, with stirring under a nitrogen atmosphere. A solution of imino ketone (**2g**) in dry ether (10 ml) was added dropwise. Stirring at reflux temperature was continued for 4 h and the contents were allowed to cool. Unreacted sodium pieces were removed by filtration. Dry carbon disulfide (2 ml) was slowly added and the mixture was heated under reflux for 1 h. The ethereal suspension was washed 2—3 times with water and dried over sodium sulfate. The solvent was removed on a rotary evaporator and the residual material was purified by column (neutral alumina, hexane/benzene: 90/10).

*3-(α-Phenylethyl)-4,5-diphenyl-4-oxazoline-2-thione (**2a**).* A yield of 49% was obtained, mp 135—137 °C. UV (Ethanol): 310 (ε 21100) and 223 (22600) nm; IR (Nujol, cm^{-1}): 1165 (ν C=S); NMR ($CDCl_3$, δ): 7.20 (m, 15H, aromatic protons); 6.40 (m, 1H, CH) and 1.70 (bd, 3H, CH_3, J=7 Hz). Found: C, 77.35; H, 5.38; N, 4.21%. Calcd for $C_{23}H_{19}NOS$: C, 77.31; H, 5.32; N, 3.92%.

*4,5-Diphenyl-3-propyl-4-oxazoline-2-thione (**2b**).* A yield of 35% was obtained, mp 128—129 °C. UV (Ethanol): 310 (ε 9740) and 275 (19800) nm; IR (Nujol, cm^{-1}): 1160 (ν C=S); NMR ($CDCl_3$, δ): 7.42 (m, 10H, aromatic protons); 3.80 (t, 2H, N-CH_2, J=7 Hz): 1.60 (m, 2H, C-CH_2); 0.82 (t, 3H, methyl, J=7 Hz). Found: C, 73.55; H, 5.61; N, 4.61%. Calcd for $C_{18}H_{17}NOS$: C, 73.22; H, 5.76; N, 4.74%.

*3-Butyl-4,5-diphenyl-4-oxazoline-2-thione (**2c**).* A yield of 36% was obtained, mp 133—134 °C. UV (Ethanol): 310 nm; IR (Nujol, cm^{-1}): 1180 (ν C=S); NMR ($CDCl_3$, δ): 7.40 (m, 10H, aromatic protons); 3.80 (t, 2H, N-CH_2, J=7 Hz); 1.50 (m, 4H, C-CH_2); 0.80 (t, 3H, methyl, J=7 Hz). Found: C, 73.71; H, 6.10; N, 4.32%. Calcd for $C_{19}H_{19}NOS$: C, 73.78; H, 6.14; N, 4.53%.

*3,4,5-Triphenyl-4-oxazoline-2-thione (**2d**).* A yield of 48% was obtained, mp 228—229 °C (lit,[9] 229 °C). UV (Ethanol): 308 (ε 15700) and 226 (17500) (lit,[10] 308, 225) nm; IR (Nujol, cm^{-1}): 1162 (lit,[11] 1161) (ν C=S); NMR ($CDCl_3$, δ): 7.40 (m, aromatic protons). Found: C, 76.40; H, 4.73; N, 4.51%. Calcd for $C_{21}H_{15}NOS$: C, 76.59; H, 4.55; N, 4.25%.

*4,5-Diphenyl-3-(p-tolyl)-4-oxazoline-2-thione (**2e**).* A yield of 50% was obtained, mp 235—237 °C. UV (Ethanol): 310 (ε 16000) and 225 (22500) nm; IR (Nujol, cm^{-1}): 1162 (ν C=S); NMR ($CDCl_3$, δ): 7.30 (m, 14H, aromatic protons); 2.30 (s, 3H, methyl). Found: C, 76.64; H, 4.65; N, 4.31%. Calcd for $C_{22}H_{17}NOS$: C, 76.96; H, 4.95; N, 4.08%.

*4,5-Diphenyl-3-isopropyl-4-oxazoline-2-thione (**2f**).* A yield

of 32% was obtained, mp 172—173 °C. UV (Ethanol): 310 (ε 18000) and 225 (14300) nm; IR (Nujol, cm^{-1}): 1161 (ν C=S); NMR ($CDCl_3$, δ): 7.51 (m, 10H, aromatic protons); 4.80 (sept, 1H, methine, J=7 Hz); 1.40 (d, 6H, methyl, J=7 Hz). Found: C, 73.60; H, 6.00; N, 5.01%. Calcd for $C_{18}H_{17}NOS$; C, 73.22; H, 5.76; N, 4.74%.

Preparation of 3-Substituted 4,5-Diphenyl-4-oxazolin-2-ones ***3a—f.*** *General Procedure*: In place of carbon disulfide in the above method dry ethyl chloroformate (2 ml) was slowly added and the product was purified by column chromatography as mentioned above.

*3-(α-Phenylethyl)-4,5-diphenyl-4-oxazolin-2-one (**3a**).* A yield of 35% was obtained, mp 155—157 °C. IR (Nujol, cm^{-1}): 1600 (ν C=C), 1750 (ν C=O); NMR ($CDCl_3$, δ): 7.30 (m, 15H, aromatic protons); 4.30 (m, 1H, CH) and 1.40 (bd, 3H, methyl, J=7 Hz). Found: C, 80.65; H, 5.62; N, 4.30%. Calcd for $C_{23}H_{19}NO_2$: C, 80.92; H, 5.61; N, 4.01%.

*4,5-Diphenyl-3-propyl-4-oxazolin-2-one (**3b**).* A yield of 33% was obtained, mp 92—93 °C. UV (Ethanol): 282 (ε 22100) and 221 (29100) nm; IR (Nujol, cm^{-1}): 1610 (ν C=C) and 1745 (ν C=O); NMR ($CDCl_3$, δ): 7.60 (m, 10H, aromatic protons); 3.50 (t, 2H, N-CH_2, J=7 Hz); 1.60 (m, 2H, C-CH_2); 0.80 (t, 3H, methyl, J=7 Hz). Found: C, 77.45; H, 6.20; N, 5.25%. Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01%.

*3-Butyl-4,5-diphenyl-4-oxazolin-2-one (**3c**).* A yield of 35% was obtained, mp 73—75 °C. UV (Ethanol): 286 (ε 17700) and 217 (4350) nm; IR (Nujol, cm^{-1}): 1610 (ν C=C) and 1740 (ν C=O); NMR ($CDCl_3$, δ): 7.50 (m, 10H, aromatic protons); 3.50 (t, 2H, N-CH_2, J=7 Hz); 1.40 (m, 4H, C-CH_2); 0.84 (t, 3H, methyl, J=7 Hz). Found: C, 77.90; H, 6.50; N, 4.63%. Calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77%.

*3,4,5-Triphenyl-4-oxazolin-2-one (**3d**).* A yield of 45% was obtained, mp 215—217 °C (lit,[12] 211 °C). UV (Ethanol): 293 (ε 18900) and 226 (14700) (lit,[10] 225, 291.5) nm; IR (Nujol, cm^{-1}); 1600 (ν C=C) and 1750 (lit, [11] 1750) (ν C=O); NMR ($CDCl_3$, δ): 7.40 (m, aromatic protons). Found: C, 80.50; H, 4.62; N, 4.35%. Calcd for $C_{21}H_{15}NO_2$: C, 80.49; H, 4.82; N, 4.47%.

*4,5-Diphenyl-3-(p-tolyl)-4-oxazolin-2-one (**3e**).* A yield of 55% was obtained, mp 224—226 °C. UV (Ethanol): 294 (ε 18900) nm; IR (Nujol, cm^{-1}): 1600 (ν C=C) and 1750 (ν C=O); NMR ($CDCl_3$, δ): 7.42 (m, 14H, aromatic protons); 2.33 (s, 3H, methyl). Mass (m/z): 327. Found: C, 80.75; H, 5.40; N, 4.32%. Calcd for $C_{22}H_{17}NO_2$: C, 80.71; H, 5.23; N, 4.28%.

*3-Isopropyl-4,5-diphenyl-4-oxazolin-2-one (**3f**).* A yield of 35% was obtained, mp 120—124 °C. UV (Ethanol): 286 (ε 15100) and 220 (15400) nm; IR (Nujol, cm^{-1}): 1600 (ν C=C) and 1750 (ν C=O); NMR ($CDCl_3$, δ): 7.50 (m, 10H, aromatic protons); 4.80 (sept, 1H, methine, J=7 Hz); 1.40 (d, 6H, methyl, J=7 Hz). Found: C, 77.80; H, 6.00; N, 5.20%. Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01%.

Preparation of 2,3,4-Trisubstituted-5,6,7,8-tetrahydro-4H-1,4-oxazocines ***4d—e.*** *General Procedure*: A solution containing 2 g of imino ketone (**1d—e**) in dry THF (30 ml) was added dropwise to 2 g of sodium pieces in 30 ml of dry THF under a nitrogen atmosphere and the mixture was stirred for 5—6 h at refluxing temperature. The reaction mixture was allowed to stand at room temperature for 1/2 h. Sodium pieces were removed by filtration. Dry 1,4-dichlorobutane (2 ml) was slowly added and the mixture was heated to reflux for 10—12 h. The excess of THF was removed under reduced pressure and the residual matter was extracted with ether. The ethereal layer was washed 2—3 times with water, dried over sodium sulfate. The solvent was removed on a rotary evaporator and the residual material was purified by column (neutral alumina, hexane) chromatography.

*2,3,4-Triphenyl-5,6,7,8-tetrahydro-4H-1,4-oxazocine (**4d**).* A yield of 33% was obtained, mp 125—126 °C. UV (Ethanol): 352 (ε 10500) and 273 (11500) nm; IR (Nujol, cm^{-1}): 1605 (ν C=C); NMR ($CDCl_3$, δ): 6.90 (m, 15H, aromatic protons); 4.10 (m, 4H, N-CH_2 and O-CH_2); 1.90 (m, 4H, C-CH_2). Mass (m/z): 341. Found: C, 84.10; H, 6.85; N, 3.95%. Calcd for $C_{24}H_{23}NO$: C, 84.42; H, 6.79; N, 4.10%.

*2,3-Diphenyl-4-(p-tolyl)-5,6,7,8-tetrahydro-4H-1,4-oxazocine (**4e**).* A yield of 35% was obtained, mp 128—129 °C. UV (Ethanol): 356 (ε 12000) and 273 (12200) nm; IR (Nujol, cm^{-1}): 1605 (ν C=C); NMR ($CDCl_3$, δ): 7.00 (m, 14H, aromatic protons); 4.00 (m, 4H, N-CH_2 and O-CH_2); 2.20 (s, 3H, methyl); 1.90 (m, 4H, C-CH_2). Mass (m/z): 355. Found: C, 84.20; H, 6.91; N, 4.10%. Calcd for $C_{25}H_{25}NO$: C, 84.47; H, 7.09; N, 3.94%.

Preparation of 2,3,4-Trisubstituted-4,5,6,7,8,9-hexahydro-1,4-oxazonines ***5d—e.*** *General Procedure*: In place of 1,4-dichlorobutane in the above procedure dry 1,5-dichloropentane was slowly added and the product was purified by column chromatography as mentioned above.

*2,3,4-Triphenyl-4,5,6,7,8,9-hexahydro-1,4-oxazonine (**5d**).* A yield of 31% was obtained, mp 141—143 °C. UV (Ethanol): 350 (ε 2370) and 265 (3760) nm; IR (Nujol, cm^{-1}): 1605 (ν C=C); NMR ($CDCl_3$, δ): 6.90 (m, 15H, aromatic protons); 4.00 (m, 4H, N-CH_2 and O-CH_2); 1.80 (m, 6H, C-CH_2). Mass (m/z): 355. Found: C, 84.15; H, 6.95; N, 3.64%. Calcd for $C_{25}H_{25}NO$: C, 84.47; H, 7.09; N, 3.94%.

*2,3-Diphenyl-4-(p-tolyl)-4,5,6,7,8,9-hexahydro-1,4-oxazonine (**5e**).* A yield of 28% was obtained, mp 142—144 °C. UV (Ethanol): 265 and 350 nm; IR (Nujol, cm^{-1}): 1615 (ν C=C); NMR ($CDCl_3$, δ): 7.00 (m, 14H, aromatic protons); 4.00 (m, 4H, N-CH_2 and O-CH_2); 2.20 (s, 3H, methyl); 1.80 (m, 6H, C-CH_2). Found: C, 84.24; H, 7.26; N, 3.90%. Calcd for $C_{26}H_{27}NO$: C, 84.55; H, 7.31; N, 3.79%.

Preparation of 2-Arylamino-1,2-diphenyl-4-penten-1-ones ***6d—e.*** *General Procedure*: In place of 1,4-dichlorobutane, 1,3-dibromopropane was slowly added and the same procedure for purification was followed as described above.

*2-Anilino-1,2-diphenyl-4-penten-1-one (**6d**).* A yield of 45% was obtained, mp 102—104 °C. UV (Ethanol): 250 (ε 25200) nm; IR (Nujol, cm^{-1}): 3370 (N-H) and 1660 (C=O); NMR ($CDCl_3$, δ): 7.00 (m, 16H, aromatic and CH); 5.70 (bs, 1H, NH, D_2O exchangeable); 4.80 (m, 2H, =CH_2); 3.30 (m, 2H, -CH_2). Mass (m/z): 327. Found: C, 84.60; H, 6.41; N, 3.95%. Calcd for $C_{23}H_{21}NO$: C, 84.37; H, 6.46; N, 4.28%.

*1,2-Diphenyl-2-(p-toluidino)-4-penten-1-one (**6e**).* A yield of 48% was obtained, mp 109—110 °C. UV (Ethanol): 250 (ε 23000) nm; IR (Nujol, cm^{-1}): 3355 (NH) and 1660 (ν C=O); NMR ($CDCl_3$, δ): 7.00 (m, 15H, aromatic and CH); 5.50 (bs, 1H, NH, D_2O exchangeable); 4.80 (m, 2H, =CH_2); 3.30 (m, 2H, -CH_2); 2.25 (s, 3H, CH_3). Found: C, 84.10; H, 6.65; N, 3.90%. Calcd for $C_{24}H_{23}NO$: C, 84.42; H, 6.79; N, 4.10%.

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