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Derivatives of α,β-Dehydro Amino Acids: III. Reaction of 4-Arylmethylidene-4,5-dihydro-1,3-oxazol-5-ones with Hexamethyldisilazane

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Abstract—4-Arylmethylidene-4,5-dihydro-1,3-oxazol-5-ones reacted with hexamethyldisilazane in ethyl acetate, acetonitrile, or DMF at room temperature to give mainly 2-acylamino-3-arylmethylideneprop-2-enamides, whereas in boiling DMF the corresponding 4-arylmethylidene-4,5-dihydro-1*H*-imidazol-5-ones were formed. The reaction of 2-benzoylamino-3-phenylprop-2-enamide with hexamethyldisilazane also led to the formation of 4-benzylidene-2-phenyl-4,5-dihydro-1*H*-imidazol-5-one, while its reaction with chlorotrimethylsilane afforded either a 1:1 mixture of 4-benzylidene-2-phenyl-4,5-dihydro-1,3-oxazol-5-one and 4-benzylidene-2-phenyl-4,5-dihydro-1*H*-imidazol-5-one or only the latter, depending on the solvent.

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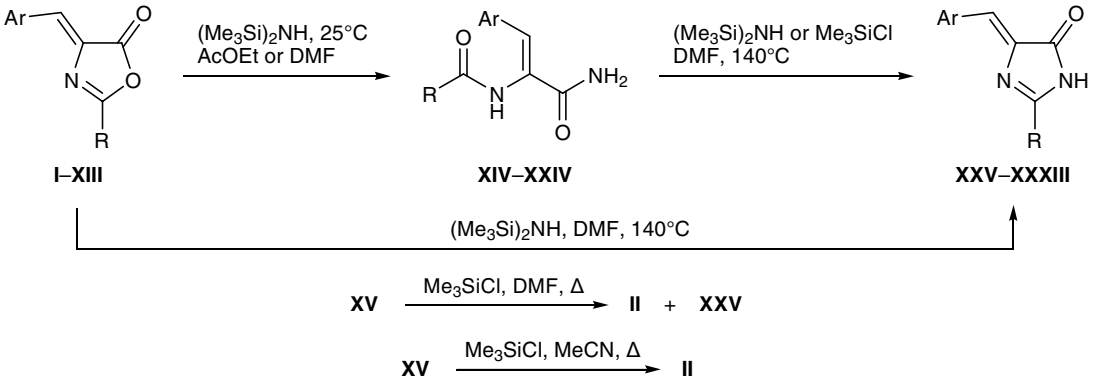
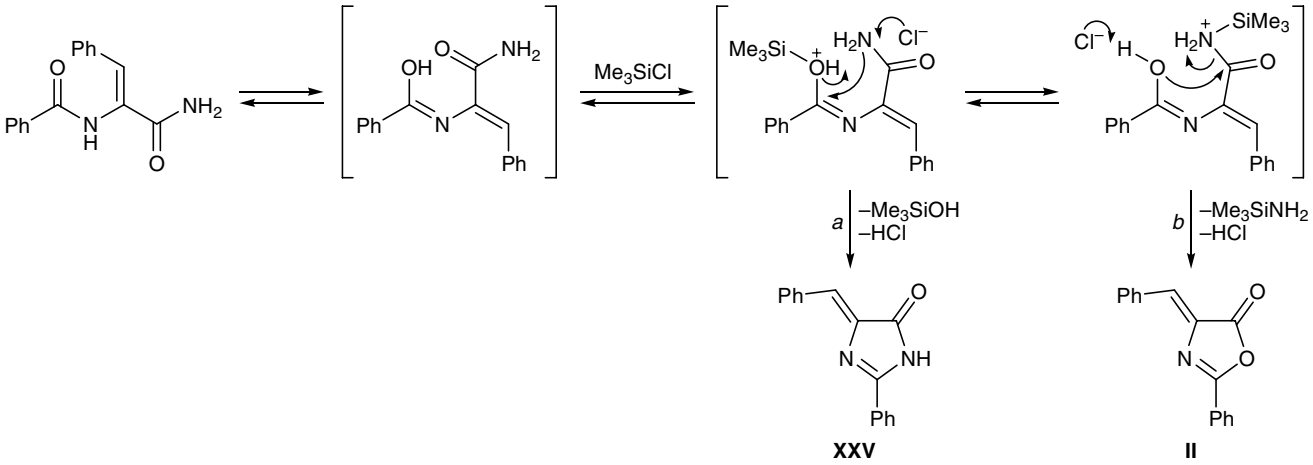
Hexamethyldisilazane (HMDS) in reactions with carboxylic acid derivatives (such as anhydrides and acid chlorides) can act as a source of ammonia to give primary amides [1, 2]. In the present work we examined reactions of 4-arylmethylidene-4,5-dihydro-1,3-oxazol-5-ones **I**–**XIII** with HMDS. Oxazolone **II** reacted with HMDS at a ratio of 1:3 in ethyl acetate, acetonitrile, or DMF at room temperature to form 2-benzoylamino-3-phenylprop-2-enamide (**XV**) (Scheme 1). The best yield of **XV** (85%, reaction time 24 h) was obtained when the reaction was carried out in ethyl acetate. Therefore, the other primary amides (compounds **XIV** and **XVI**–**XXIV**) were synthesized from the corresponding oxazolones and HMDS in ethyl acetate at room temperature. In the reaction of **II** with HMDS in DMF or acetonitrile (24 h), the yield of

Scheme 1.



I, **XIV**, Ar = Ph, R = Me; **II**, **XV**, **XXV**, Ar = R = Ph; **III**, **XVI**, **XXVI**, R = Ph, Ar = 4-$MeOC_6H_4$; **IV**, **XVII**, **XXVII**, R = Ph, Ar = 4-*i*-$PrOC_6H_4$; **V**, **XVIII**, **XXVIII**, R = Ph, Ar = 4-ClC_6H_4; **VI**, **XIX**, **XXIX**, R = 2-MeC_6H_4, Ar = 4-ClC_6H_4; **VII**, **XXX**, R = 2-MeC_6H_4, Ar = 3,4-$CH_2O_2C_6H_4$; **VIII**, **XX**, **XXXI**, R = 4-MeC_6H_4, Ar = 2-furyl; **IX**, **XXXII**, R = 4-*t*-BuC_6H_4, Ar = Ph; **X**, **XXI**, **XXXIII**, R = 2-$MeOC_6H_4$, Ar = 4-BrC_6H_4; **XI**, **XXII**, R= 4-$MeOC_6H_4$, Ar = Ph; **XII**, **XXIII**, R = 2-furyl, Ar = 3-$O_2NC_6H_4$; **XIII**, **XXIV**, R = 2-furyl, Ar = 4-(4-$MeC_6H_4SO_2$)C_6H_4.

Scheme 2.



XV was relatively poor (57 and 20%, respectively). Moreover, the reaction in DMF was accompanied by formation of 7% of imidazolone **XXV**. The yield of the latter increased to 84% when the reaction mixture was heated for 1 h under reflux. By heating oxazolones **I**–**XIII** with 3 equiv of HMDS in boiling DMF we synthesized the corresponding 2-substituted 4-arylmethylidene-4,5-dihydro-1*H*-imidazol-5-ones **XXV**–**XXXIII** (Scheme 1).

Presumably, imidazol-5-ones **XXV**–**XXXIII** are formed from oxazol-5-ones **I**–**XIII** through the corresponding primary amides. This follows from the fact that heating of amide **XV** with HMDS in boiling DMF for 1 h gave imidazolone **XXV** in 73% yield. The reaction of HMDS with amide **XV** is likely to involve silylation of the latter. To verify this assumption we examined the reaction of amide **XV** with Me_3SiCl. Chlorotrimethylsilane is known to act as condensing agent in the synthesis of carboxylic acid esters [3], acetals [4], dioxolanes, oxazolidinones [5], and 2,4-disubstituted 1-arylimidazol-5-ones [6]. By reaction of **XV** with Me_3SiCl at a ratio of 1:3 in boiling DMF we obtained a mixture of products; according to the IR and ^1H NMR data, this mixture consisted of 4-benzylidene-2-phenyl-4,5-dihydro-1*H*-imidazol-5-one (**XXV**) and 4-benzylidene-2-phenyl-4,5-dihydro-1,3-oxazol-5-one (**II**) at a ratio of 4.7:5.3. When the reaction was performed in acetonitrile, oxazolone **II** was obtained as the only product (yield 16%). The formation of compounds **XXV** and **II** in the reaction of amide **XV** with Me_3SiCl may be rationalized as shown in Scheme 2. The reaction in DMF is likely to follow both pathways *a* and *b*, while in MeCN, only pathway *b*.

We can conclude that the reaction of 4-arylmethylidene-4,5-dihydro-1,3-oxazol-5-ones with hexamethyldisilazane provides a convenient method of synthesis of both 2-acylamino-3-arylprop-2-enamides and 2-substituted 4-arylmethylidene-4,5-dihydro-1*H*-imidazol-5-ones.

The IR spectra of amides **XIV**–**XXIV** contained characteristic absorption bands in the regions 1620–1645 (C=C), 1670–1690 (C=O), and 3120–3150, 3320–3350, and 3450–3490 cm^{-1} (N–H). Imidazol-5-ones **XXV**–**XXXIII** displayed absorption bands at 1640–1650 (C=C), 1700–1710 (C=O), and 3330–3360 cm^{-1} (N–H). In the ^1H NMR spectra of amide **XV** and imidazol-5-one **XXV**, the exocyclic vinyl proton (CH=C) resonated at δ 6.96 ppm, indicating *Z* configuration of these compounds. Initial oxazolone **II** is also *Z* isomer.

EXPERIMENTAL

The IR spectra were recorded on a Specord M-80 spectrometer. The ^1H NMR spectra were measured on a Varian Mercury 300 instrument. The purity of the products was checked by TLC on Silufol UV-254 plates using toluene–hexane–ethanol (1:1:1) as eluent; spots were visualized under UV light or by treatment with iodine vapor. Initial oxazolones **I**–**XIII** were synthesized according to the procedure reported in [7].

2-Benzoylamino-3-phenylprop-2-enamide (XV). Hexamethyldisilazane, 2.53 ml (1.93 g, 12 mmol), was added to a solution of 1.0 g (4 mmol) of 4-benzylidene-2-phenyl-4,5-dihydro-1,3-oxazol-5-one in 15 ml of ethyl acetate, and the mixture was stirred for 24 h at room temperature. The precipitate was filtered off, washed with diethyl ether, dried in air, and recrystallized from ethanol. Yield 0.9 g (85%), mp 170–172°C; published data [8]: mp 168–169°C; R_f 0.58. IR spec-

trum, ν, cm^{-1}: 1700, 1630, 3175, 3265, 3390. ^1H NMR spectrum (DMSO), δ, ppm: 6.96 s (1H, CH=C), 7.22–8.06 m (10H, H_{arom}, and 2H, NH_2), 9.64 s (1H, NH). Found, %: C 72.33; H 5.02; N 10.24. $C_{16}H_{14}N_2O_2$. Calculated, %: C 72.16; H 5.30; N 10.52.

Amides **XIV** and **XVI–XXIV** were synthesized in a similar way.

When the reaction was carried out in DMF, the mixture was diluted with water, and the precipitate was filtered off, dried, and ground with diethyl ether. The undissolved material (compound **XV**) was filtered off and recrystallized from ethanol. Yield 0.6 g (57%). Evaporation of the filtrate gave compound **XXV**. Yield 0.07 g (7%), yellow crystalline substance, mp 272–275°C (from ethanol). IR spectrum, ν, cm^{-1}: 1640, 1690, 3380.

2-Acetylamino-3-phenylprop-2-enamide (XIV). Yield 61%, mp 209–211°C, R_f 0.46. IR spectrum, ν, cm^{-1}: 1690, 1625, 3135, 3305. Found, %: C 64.41; H 6.03; N 13.39. $C_{11}H_{12}N_2O_2$. Calculated, %: C 64.69; H 5.92; N 13.72.

2-Benzoylamino-3-(4-methoxyphenyl)prop-2-enamide (XVI). Yield 76%, mp 189–191°C; published data [8]: mp 190–192°C; R_f 0.44. IR spectrum, ν, cm^{-1}: 1690, 1630, 3215, 3450. Found, %: C 69.09; H 5.62; N 9.67. $C_{17}H_{16}N_2O_3$. Calculated, %: C 68.89; H 5.44; N 9.45.

2-Benzoylamino-3-(4-isopropoxyphenyl)prop-2-enamide (XVII). Yield 81%, mp 197–199°C, R_f 0.53. IR spectrum, ν, cm^{-1}: 1900, 1635, 3115, 3280, 3490. Found, %: C 70.00; H 6.54; N 8.29. $C_{19}H_{20}N_2O_3$. Calculated, %: C 70.34; H 6.20; N 8.63.

2-Benzoylamino-3-(4-chlorophenyl)prop-2-enamide (XVIII). Yield 78%, mp 172–174°C, R_f 0.57. IR spectrum, ν, cm^{-1}: 1690, 1635, 3155, 3225, 3450. Found, %: C 64.03; H 4.10; N 9.53. $C_{16}H_{13}ClN_2O_2$. Calculated, %: C 63.89; H 4.35; N 9.31.

3-(4-Chlorophenyl)-2-(2-methylbenzoylamino)-prop-2-enamide (XIX). Yield 65%, mp 205–208°C, R_f 0.65. IR spectrum, ν, cm^{-1}: 1695, 1630, 3155, 3225, 3480. Found, %: C 63.77; H 4.51; N 9.07. $C_{17}H_{15}ClN_2O_2$. Calculated, %: C 63.85; H 4.76; N 8.76.

3-(2-Furyl)-2-(4-methylbenzoylamino)prop-2-enamide (XX). Yield 80%, mp 170–172°C, R_f 0.50. IR spectrum, ν, cm^{-1}: 1680, 1630, 3190, 3390, 3440. Found, %: C 67.01; H 5.43; N 10.60. $C_{15}H_{14}N_2O_3$. Calculated, %: C 66.60; H 5.20; N 10.36.

3-(4-Bromophenyl)-2-(2-methoxybenzoylamino)-prop-2-enamide (XXI). Yield 76%, mp 174–176°C, R_f 0.63. Found, %: C 64.41; H 6.03; N 13.39. $C_{11}H_{12}N_2O_2$. Calculated, %: C 64.69; H 5.92; N 13.72.

2-(4-Methoxybenzoylamino)-3-phenylprop-2-enamide (XXII). Yield 59%, mp 227–229°C, R_f 0.69. IR spectrum, ν, cm^{-1}: 1690, 1635, 3155, 3255, 3390. Found, %: C 68.10; H 5.69; N 9.87. $C_{17}H_{16}N_2O_3$. Calculated, %: C 68.89; H 5.44; N 9.45.

2-(2-Furoylamino)-3-(3-nitrophenyl)prop-2-enamide (XXIII). Yield 80%, mp 202–205°C, R_f 0.42. IR spectrum, ν, cm^{-1}: 1695, 1635, 3165, 3270, 3450. Found, %: C 56.15; H 4.00; N 14.19. $C_{14}H_{11}N_3O_5$. Calculated, %: C 55.80; H 3.68; N 13.95.

2-(2-Furoylamino)-3-(4-tosyloxyphenyl)prop-2-enamide (XXIV). Yield 88%, mp 292–295°C, R_f 0.40. Found, %: C 59.31; H 4.56; N 6.91. $C_{21}H_{18}N_2O_6S$. Calculated, %: C 59.14; H 4.25; N 6.57.

4-[(*Z*)-Benzylidene]-2-phenyl-4,5-dihydro-1*H*-imidazol-5-one (XXV). A mixture of 1.0 g (4 mmol) of oxazolone **II** and 2.53 ml (1.94 g, 12 mmol) of HMDS in 10 ml of DMF was heated for 1 h under reflux. The mixture was cooled, diluted with 50 ml of water, acidified with hydrochloric acid to pH 6, and left to stand for 2 h at 0°C. The precipitate was filtered off and recrystallized from ethanol. Yield 0.8 g (80%), mp 273–275°C, R_f 0.71. IR spectrum, ν, cm^{-1}: 1640, 1690, 3380. ^1H NMR spectrum (DMSO), δ, ppm: 6.96 s (1H, CH=), 7.22–8.06 m (10H, H_{arom}), 11.90 s (1H, NH). Found, %: C 77.03; H 5.10; N 11.59. $C_{16}H_{12}N_2O$. Calculated, %: C 77.40; H 4.87; N 11.28.

4-[(*Z*)-4-Methoxybenzylidene]-2-phenyl-4,5-dihydro-1*H*-imidazol-5-one (XXVI). Yield 80%, mp 280–281°C, R_f 0.61. IR spectrum, ν, cm^{-1}: 1700, 1630, 3110. Found, %: C 73.51; H 5.29; N 10.52. $C_{17}H_{14}N_2O_2$. Calculated, %: C 73.36; H 5.07; N 10.06.

4-[(*Z*)-4-Isopropoxybenzylidene]-2-phenyl-4,5-dihydro-1*H*-imidazol-5-one (XXVII). Yield 64%, mp 255–258°C, R_f 0.77. IR spectrum, ν, cm^{-1}: 1700, 1625, 3120. Found, %: C 74.02; H 5.78; N 9.60. $C_{19}H_{18}N_2O_2$. Calculated, %: C 74.49; H 5.52; N 9.14.

4-[(*Z*)-4-Chlorobenzylidene]-2-phenyl-4,5-dihydro-1*H*-imidazol-5-one (XXVIII). Yield 54%, mp 224–227°C, R_f 0.78. IR spectrum, ν, cm^{-1}: 1700, 1625, 3120. Found, %: C 68.11; H 4.07; N 10.14. $C_{16}H_{11}ClN_2O$. Calculated, %: C 67.97; H 3.92; N 9.91.

4-[(*Z*)-4-Chlorobenzylidene]-2-(2-methylphenyl)-4,5-dihydro-1*H*-imidazol-5-one (XXIX). Yield 55%, mp 294–297°C, R_f 0.65. IR spectrum, ν, cm^{-1}: 1700, 1625, 3150. Found, %: C 68.45; H 4.05; N 9.91. $C_{17}H_{13}ClN_2O$. Calculated, %: C 68.81; H 4.41; N 9.44.

4-[(*Z*)-1,3-Benzodioxol-5-ylmethylidene]-2-(2-methoxyphenyl)-4,5-dihydro-1*H*-imidazol-5-one (XXX). Yield 56%, mp 341–343°C, R_f 0.72. IR spectrum, ν cm^{-1}: 1700, 1630, 3150. Found, %: C 70.29; H 4.18; N 9.50. $C_{18}H_{14}N_2O_3$. Calculated, %: C 70.58; H 4.61; N 9.34.

4-[(*Z*)-Furfurylidene]-2-(4-methylphenyl)-4,5-dihydro-1*H*-imidazol-5-one (XXXI). Yield 17%, mp 296–299°C, R_f 0.62. IR spectrum, ν, cm^{-1}: 1705, 1630, 3140. Found, %: C 71.64; H 5.00; N 11.56. $C_{15}H_{12}N_2O_2$. Calculated, %: C 71.42; H 4.79; N 11.12.

4-[(*Z*)-Benzylidene]-2-(4-*tert*-butylphenyl)-4,5-dihydro-1*H*-imidazol-5-one (XXXII). Yield 59%, mp 254–256°C, R_f 0.66. IR spectrum, ν, cm^{-1}: 1710, 1635, 3160. Found, %: C 81.13; H 6.51; N 9.62. $C_{20}H_{20}N_2O$. Calculated, %: C 81.54; H 6.62; N 9.20.

4-[(*Z*)-4-Bromobenzylidene]-2-(4-methoxyphenyl)-4,5-dihydro-1*H*-imidazol-5-one (XXXIII). Yield 66%, mp 270–272°C, R_f 0.74. IR spectrum, ν, cm^{-1}: 1705, 1630, 3240. Found, %: C 57.34; H 4.03; N 8.07. $C_{17}H_{13}BrN_2O_2$. Calculated, %: C 57.16; H 3.66; N 7.84.

Reaction of 2-benzoylamino-3-phenylprop-2-enamide (XV) with hexamethyldisilazane. A mixture of 1.0 g (3.76 mmol) of amide **XV** and 1.78 g (2.3 ml, 1.13 mmol) of HMDS in 10 ml of DMF was heated for 1 h under reflux. The mixture was diluted with 50 ml of water, and the yellow precipitate was filtered off, dried in air, and purified by recrystallization. Yield 0.69 g (74%). The product was identical to imidazolone **XXV** in physical constants and IR and ^{1}H NMR spectra.

Reaction of 2-benzoylamino-3-phenylprop-2-enamide (XV) with chlorotrimethylsilane. *a*. A mixture of 1.0 g (3.7 mmol) of amide **XV** and 1.2 g (1.4 ml, 11 mmol) of chlorotrimethylsilane in 10 ml of acetonitrile was heated for 1 h under reflux. After cooling, the precipitate was filtered off and treated with 10 ml of diethyl ether. The solution was separated by decanting from the undissolved tarry material and evaporated. The residue was a yellow crystalline substance which was identified as oxazolone **II**. Yield 0.15 g (16%), mp 165–166°C [7], R_f 0.88. IR spectrum, ν, cm^{-1}: 1650 (C=C), 1770 (C=O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 7.20 s (1H, CH=C), 7.40–8.32 m (H_{arom}). The filtrate was evaporated to obtain a white amorphous substance (0.8 g) whose physical constants coincided with those of initial amide **XV**, mp 172–175°C, R_f 0.51.

b. A mixture of 1.0 g (3.7 mmol) of amide **XV** and 1.2 g (1.4 ml, 11 mmol) of chlorotrimethylsilane in 10 ml of DMF was heated for 1 h under reflux. The mixture was then diluted with 100 ml of water and acidified with hydrochloric acid to pH 2. The light yellow precipitate was filtered off and treated with 10 ml of diethyl ether, and the solution was separated from the undissolved material, 0.2 g (22%), mp 273–276°C, R_f 0.71. IR spectrum, ν, cm^{-1}: 1645 (C=C), 1700 (C=O), 3145 (NH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 6.90 s (1H, C=CH), 7.30–8.32 m (10H, H_{arom}), 11.88 s (1H, NH). The ether solution was evaporated to obtain 0.22 g of a mixture of imidazolone **XXV** (R_f 0.71) and oxazolone **II** (R_f 0.88) at a ratio of 9:1 (according to the ^{1}H NMR data).

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