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Trifluoroacetylation and Subsequent Pyrolysis of 2-Amino-2-oxazolines

Chiaki Tanaka,* Keiko Nasu, Noriko Yamamoto, and Megumi Shibata

Osaka College of Pharmacy, 2-10-65, Kawai, Matsubara, Osaka 580, Japan

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Treatment of 2-amino-5-phenyl-2-oxazoline (I) with trifluoroacetic anhydride gave 1,3-bis(2,2,2-trifluoroacetyl)-1-[2-(2,2,2-trifluoroacetyloxy)-2-phenylethyl]urea (II). Compound II was pyrolyzed at 120°C to give 2,2,2-trifluoroacetyl isocyanate (III) and 2,2,2-trifluoro-*N*-[2-(2,2,2-trifluoroacetyloxy)-2-phenylethyl]acetamide (IV). Compound II was readily hydrolyzed to give 1-(2,2,2-trifluoroacetyl)-3-[2-(2,2,2-trifluoroacetyloxy)-2-phenylethyl]urea (VI). Compound VI was pyrolyzed at 230°C to give 2,2,2-trifluoroacetamide (VII) and 2,2,2-trifluoro-*N*-(*E*)-styrylacetamide (VIII). It was considered that the formation of VIII proceeded through the intermediate 2-(2,2,2-trifluoroacetyloxy)-2-phenylethyl isocyanate (XI) or 1-(2,2,2-trifluoroacetyl)-3-(*E*)-styrylurea (XII), as shown in Chart 1.

Keywords——2-amino-2-oxazoline; trifluoroacetylation; pyrolysis; 1,3-bis(2,2,2-trifluoroacetyl)-1-alkylurea; *O*,*N*-bis(2,2,2-trifluoroacetyl)aminoethanol; 1-(2,2,2-trifluoroacetyl)-3-alkylurea; 1-(2,2,2-trifluoroacetyl)-3-alkenylurea

Previously we reported that 2-amino-5-phenyl-2-oxazoline (I) could be analyzed by gas chromatography (GC) after conversion into the trifluoroacetyl derivative,[1] and the treatment of I with acetic anhydride gave 3-acetyl-2-acetylimino-5-phenyloxazolidine.[2] Alkylureas are known to decompose thermally to give amines and isocyanates.[3] In this paper, we have examined the trifluoroacetylation and subsequent pyrolysis of I in order to identify the structure of the trifluoroacetyl derivative used for GC analysis.

Treatment of I with trifluoroacetic anhydride (TFAA) at 50°C gave 1,3-bis(2,2,2-trifluoroacetyl)-1-[2-(2,2,2-trifluoroacetyloxy)-2-phenylethyl]urea (II), whose infrared spectrum showed characteristic bands due to NH and CO groups (3440, 1805, 1780, 1735 and 1700 cm^{-1}). The proton nuclear magnetic resonance (PMR) spectrum exhibited a methylene signal at δ 3.75 (2H, m), a methine signal at 6.15 (1H, d of d, J=4.5 and 7.5 Hz) and an imine proton signal at 9.85 (1H, br s). Heating of II at 120°C gave 2,2,2-trifluoroacetyl isocyanate (III) and 2,2,2-trifluoro-*N*-[2-(2,2,2-trifluoroacetyloxy)-2-phenylethyl]acetamide (IV) (72% from I). On the other hand, when a mixture of I and TFAA was heated at 120°C, IV (72%) and 2,2,2,2′,2′,2′-hexafluorodiacetamide (V) (59%) were obtained. Compound IV was identical with an authentic sample prepared by the reaction of 2-hydroxy-2-phenylethylamine with TFAA.

Compound II was readily decomposed to yield 1-(2,2,2-trifluoroacetyl)-3-[2-(2,2,2-trifluoroacetyloxy)-2-phenylethyl]urea (VI) (85% from I) by moisture or ethanol. Compound VI was identical with an authentic sample prepared by the reaction of 2-hydroxy-2-phenylethylurea[4] with TFAA. Heating of VI at 230°C gave 2,2,2-trifluoroacetamide (VII) (65%) and 2,2,2-trifluoro-*N*-(*E*)-styrylacetamide (VIII) (19%) . Compound VIII was identical with the sample obtained by the reaction of (*E*)-styryl isocyanate (IX) with trifluoroacetic acid (TFAOH). In order to identify the route of formation of VIII, 3-(2,2,2-trifluoroacetyloxy)-3-phenylpropionic acid (X) was prepared by the reaction of 3-hydroxy-3-phenylpropionic acid with TFAA, and then converted to 2-(2,2,2-trifluoroacetyloxy)-2-phenylethyl isocyanate (XI) *via* the corresponding azide. Heating of XI at 230°C gave VIII (28%). Further, heating of 1-(2,2,2-trifluoroacetyl)-3-(*E*)-styrylurea (XII) at 230°C gave VII (68%) and polymeric products of IX. When a mixture of XII and TFAOH was heated at 230°C, VII (69%) and VIII (22%) were obtained.

Thus, it was considered that the trifluoroacetylation and subsequent pyrolysis of I and the pyrolysis of VI proceeded as shown in Chart 1.

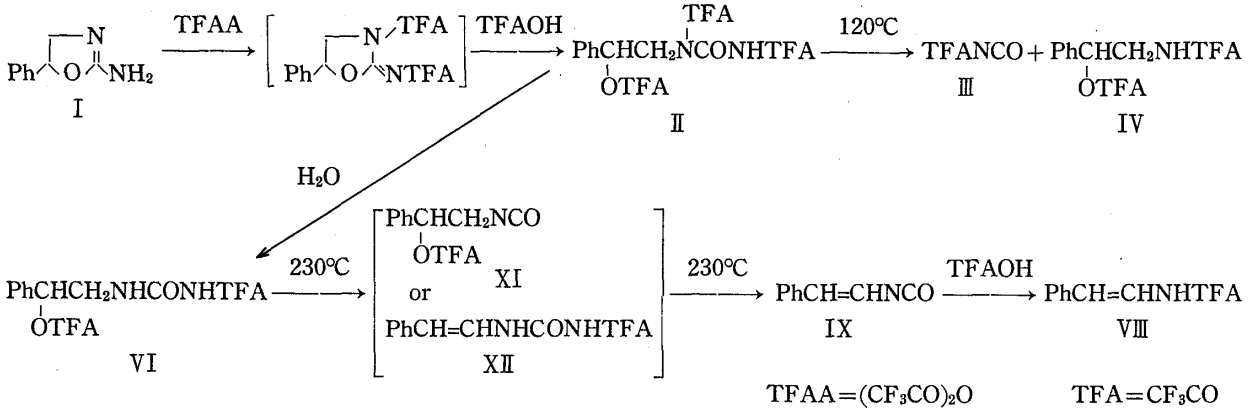

Chart 1

Experimental

All melting points are uncorrected. Infrared (IR) spectra were taken with a JASCO IRA-1 spectrophotometer. PMR spectra were taken with a Hitachi-Perkin Elmer R-40 spectrometer using tetramethylsilane as an internal standard. Mass spectra (MS) were taken with a Hitachi RMU-7L mass spectrometer.

Reaction of 2-Amino-5-phenyl-2-oxazoline (I) with TFAA at 50°C——A mixture of I (0.2 g) and TFAA (0.8 g) was heated at 50°C for 2 h. The excess TFAA was evaporated off *in vacuo* to give 1,3-bis(2,2,2-trifluoroacetyl)-1-[2-(2,2,2-trifluoroacetyloxy)-2-phenylethyl]urea (II) as a viscous oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3440 (NH), 1805, 1780, 1735, 1700 (CO). PMR (DMSO-d_6) δ: 3.75 (2H, m, CH_2), 6.15 (1H, dd, J=4.5, 7.5 Hz, CH), 7.45 (5H, s, Ar–H), 9.85 (1H, br s, NH).

Pyrolysis of II——Compound II obtained from I (0.2 g) was heated at 120°C for 30 min, and the evolved gaseous product was absorbed in $CHCl_3$ to give 2,2,2-trifluoroacetyl isocyanate (III). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2320 (NCO), 1780 (CO). The residue was recrystallized from $CHCl_3$–hexane to give 2,2,2-trifluoro-*N*-[2-(2,2,2-trifluoroacetyloxy)-2-phenylethyl]acetamide (IV) (0.31 g, 72% from I) as colorless prisms, mp 82—83°C. This product was identical with the sample derived by the reaction of 2-hydroxy-2-phenylethylamine with TFAA on the basis of mixed melting point determination and comparison of IR spectral data. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3440 (NH), 1780, 1720 (CO). PMR (DMSO-d_6) δ: 3.75 (2H, m, CH_2), 6.13 (1H, dd, J=5, 8 Hz, CH), 7.45 (5H, s, Ar–H), 9.75 (1H, br, NH). MS *m/z*: 329 (M^+). *Anal.* Calcd for $C_{12}H_9F_6NO_3$: C, 43.78; H, 2.75; F, 34.63; N, 4.26. Found: C, 43.91; H, 2.91; F, 35.38; N, 4.42.

Reaction of I with TFAA at 120°C——A mixture of I and TFAA was heated at 120°C for 2 h. The reaction mixture was distilled under reduced pressure to give 2,2,2,2′,2′,2′-hexafluorodiacetamide (V) (59%) of bp 120°C (1 mm), mp 71—77°C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3420 (NH), 1810, 1740 (CO). The residue was recrystallized to give IV (72%).

1-(2,2,2-Trifluoroacetyl)-3-[2-(2,2,2-trifluoroacetyloxy)-2-phenylethyl]urea (VI)——Compound II obtained from I (1 g) was allowed to stand overnight to leave a solid, and the solid was recrystallized from EtOH to give VI (1.8 g, 85% from I) as colorless needles, mp 177—178°C. This product was identical with the sample derived by the reaction of 2-hydroxy-2-phenylethylurea with TFAA on the basis of IR spectral comparison. IR ν_{max}^{KBr} cm^{-1}: 3360, 3260 (NH), 1780, 1730, 1700 (CO). PMR (DMSO-d_6) δ: 3.76 (2H, m, CH_2), 6.15 (1H, dd, J=4.5, 7 Hz, CH), 7.43 (5H, s, Ar–H), 8.13 (1H, t, J=6 Hz, N<u>H</u>CH_2), 12.06 (1H, br, CON<u>H</u>CO). MS *m/z*: 372 (M^+). *Anal.* Calcd for $C_{13}H_{10}F_6N_2O_4$: C, 41.95; H, 2.71; N, 7.53. Found: C, 41.87; H, 2.80; N, 7.35.

Pyrolysis of VI——Compound VI (0.5 g) was heated at 230°C for 30 min. The reaction mixture was subjected to vacuum distillation. The first fraction (bp 120°C (1 mm)) gave 2,2,2-trifluoroacetamide (VII) (0.1 g, 69%) of mp 62—65°C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3510, 3400 (NH), 1740 (CO). The second fraction (bp 140—180°C (1 mm)) solidified, and the solid was recrystallized from $CHCl_3$ to give 2,2,2-trifluoro-*N*-(*E*)-styrylacetamide (VIII) (0.05 g, 19%) as colorless leaflets, mp 141—143°C. This product was identical with the sample derived by the reaction of (*E*)-styryl isocyanate (IX) with TFAOH on the basis of IR spectral comparison. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3410 (NH), 1710 (CO), 1650 (C=C). PMR (DMSO-d_6) δ: 6.60 (1H, d, J=15 Hz, =C<u>H</u>Ph), 7.32 (1H, d, J=15 Hz, =C<u>H</u>NH), 7.15—7.5 (5H, m, Ar–H), 11.75 (1H, br, NH). *Anal.* Calcd for $C_{10}H_8F_3NO$: C, 55.82; H, 3.75; N, 6.51. Found: C, 55.83; H, 3.79; N, 6.91.

2,2,2-Trifluoro-*N*-(*E*)-styrylacetamide (VIII)——A solution of IX (1.2 g) and TFAOH (1.5 g) in $CHCl_3$ (7.5 ml) was refluxed for 13 h. The solution was concentrated *in vacuo*, and the residue was recrystallized

to give VIII (0.9 g, 60%).

3-(2,2,2-Trifluoroacetyloxy)-3-phenylpropionic Acid (X)——A solution of 3-hydroxy-3-phenylpropionic acid (1.2 g) and TFAA (1.8 g) in $CHCl_3$ (4 ml) was allowed to stand at room temperature for 4 h. The reaction mixture was washed with water, and dried. After removal of the solvent by evaporation, the residue was recrystallized from hexane to give X (1.5 g, 82%) as colorless leaflets, mp 64—66°C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3000 (OH), 1780, 1710 (CO). PMR ($CDCl_3$) δ: 3.06 (2H, m, CH_2), 6.29 (1H, dd, $J=5$, 9 Hz, CH), 7.37 (5H, s, Ar–H), 8.56 (1H, s, OH). *Anal.* Calcd for $C_{11}H_9F_3O_4$: C, 50.39; H, 3.46. Found: C, 50.64; H, 3.67.

2-(2,2,2-Trifluoroacetyloxy)-2-phenylethyl Isocyanate (XI)——A mixture of X (3.1 g) and thionyl chloride (1.7 g) was heated at 60°C for 2 h. The excess reagent was evaporated off *in vacuo* to give the corresponding chloride. A solution of the chloride in benzene was slowly added to a stirred solution of sodium azide (0.86 g) in water (3 ml) and acetone (3 ml) with ice cooling. Stirring was continued for 2 h. The reaction mixture was diluted with water, extracted with benzene, and dried. The solution was concentrated to *ca.* 5 ml, and then refluxed for 1.5 h. The product was subjected to vacuum distillation to give XI (1.4 g, 46%) of bp 80—83°C (1 mm). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2260 (NCO), 1780 (CO). PMR ($CDCl_3$) δ: 3.73 (1H, m, CH_2), 5.95 (2H, dd, $J=6$, 8 Hz, CH), 7.37 (5H, s, Ar–H). *Anal.* Calcd for $C_{11}H_8F_3NO_3$: C, 50.97; H, 3.11; N, 5.40. Found: C, 51.08; H, 3.09; N, 5.53.

Pyrolysis of XI——Compound XI (0.27 g) was heated at 230°C for 30 min, and then distilled under reduced pressure to give VIII (0.06 g, 28%).

1-(2,2,2-Trifluoroacetyl)-3-(*E*)-styrylurea (XII)——A suspension of (*E*)-styrylurea (0.5 g) and TFAA (0.8 g) in $CHCl_3$ (3 ml) was allowed to stand for 5 min with ice cooling. The solution was concentrated *in vacuo*, and the residue was recrystallized from $CHCl_3$–hexane to give XII (0.46 g, 58%) as colorless needles, mp 169—171°C. IR ν_{max}^{KBr} cm^{-1}: 3360, 3310 (NH), 1730, 1710 (CO), 1650 (C=C). PMR ($CDCl_3$) δ: 6.33 (1H, d, $J=14$ Hz, =CHPh), 7.36 (1H, dd, $J=10$, 14 Hz, =CHNH), 7.33 (5H, m, Ar–H), 9.75 (1H, d, $J=10$ Hz, CHNH), 10.36 (1H, br, CONHCO). MS *m/z*: 258 (M^+). *Anal.* Calcd for $C_{11}H_9F_3N_2O_2$: C, 51.17; H, 3.51; F, 22.07; N, 10.85. Found: C, 51.35; H, 3.54; F, 22.37; N, 11.10.

Pyrolysis of XII——a) Compound XII (0.2 g) was heated at 230°C for 20 min. The reaction mixture was subjected to vacuum distillation to give VII (0.06 g, 68%) and polymeric products of IX.

b) A mixture of XII (0.165 g) and TFAOH (0.15 g) was heated for 20 min to give VII (0.05 g, 69%) and VIII (0.03 g, 22%).

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