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Unexpected Product from the Dakin-West Reaction of N-Acylprolines using Trifluoroacetic Anhydride: A Novel Access to 5-Trifluoromethyloxazoles

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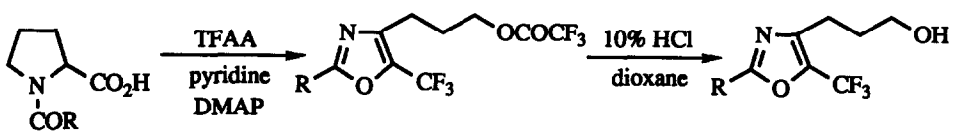
Key Words: N-acylproline; oxazole; trifluoromethyl; trifluoroacetic anhydride; rearrangement

Abstract: The base-catalyzed reaction of N-acylprolines with trifluoroacetic anhydride proceeds through mesoionic 1,3-oxazolium-5-olates followed by the pyrrolidine ring cleavage to afford the 5-trifluoromethyloxazoles in good yields.

We have recently described the reaction of N-acyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acids with trifluoroacetic anhydride (TFAA) to give the 2-trifluoromethyltetrahydro-3-benzazepine derivatives which were formed through mesoionic 1,3-oxazolium-5-olates followed by ring expansion under the Dakin-West reaction conditions.[1] This unexpected transformation prompted an examination of some related α-amino acids under comparable conditions. We report herein on a novel molecular rearrangement of a series of N-acylprolines. They have been found to undergo the pyrrolidine ring cleavage and the oxazole formation, introducing a trifluoromethyl group at position 5.



1a-e **2a-e** **3a-e**

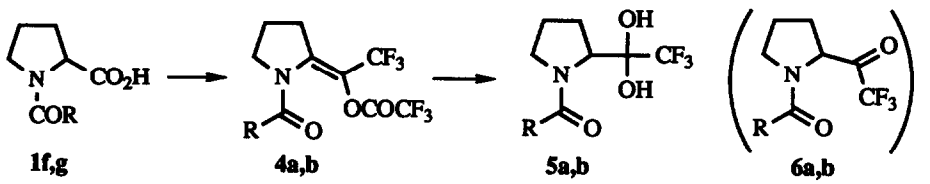
Thus, the reaction of N-acylprolines **1** with TFAA in the presence of a base results in the formation of the oxazoles **3** in good yields, after the acid hydrolysis of the resulting trifluoroacetates **2**.[2] The structure of **3** was determined from spectral[3] and analytical data and was subsequently secured by single-crystal X-ray diffraction analysis (Figure 1a).[4a]

Reaction variables and several N-acyl derivatives were briefly examined. A base was essential to this reaction and no reaction takes place in the absence of a base. A combined use of pyridine and a catalytic amount of 4-dimethylaminopyridine (DMAP) gave a high yield of **3a**. A high temperature (80 °C) was

Table 1. Reactions of N-Acylprolines with TFAA

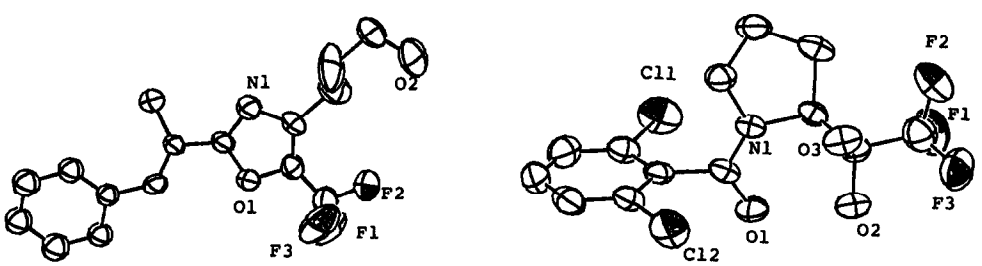
Entry	Starting material	R	Product (yield, %)[a]	M.p. or b.p. / °C (p/mmHg)[b]
1	**1a**	Bu^t	**3a** (87)	110 (1)
2	**1a**	Bu^t	**3a** (67)[c]	110 (1)
3	**1b**	Ph	**3b** (61)	51-52
4	**1c**	4-$MeOC_6H_4$	**3c** (81)	65-66
5	**1d**	4-ClC_6H_4	**3d** (46)	78-79
6	**1e**	PhCH=CMe	**3e** (65)	53-54
7	**1f**	2,6-$Cl_2C_6H_3$	**5a** (93)	89-91
8	**1g**	2,4,6-$Me_3C_6H_2$	**5b** (72)	121-124

a) Isolated yields of pure products. b) B.p. refers to the bath temperature in a 'Kugelrohr' apparatus. c) In the absence of DMAP.



1f,g **4a,b** **5a,b** **6a,b**

needed to obtain a high yield of **3a**, the lower temperature (50 °C) reducing the yield (25%). The nature of N-substituents influenced the reaction. N-Acyl derivatives **1a-e**, containing pivaloyl, benzoyl, or cinnamoyl groups, were easily transformed to the oxazoles **3a-e** in good yields (Table 1). On the other hand, N-formyl-, N-acetyl-, and N-isobutyrylprolines, bearing α-hydrogens, afforded no oxazole derivative. From the reactions of **1f** and **1g** we did not obtain the oxazole derivatives but enol trifluoroacetates **4a** and **4b**, respectively, which were isolated as a single isomer. Hydrolyses of **4** gave the trifluoromethyl ketone hydrates **5** and the structure of **5a** was determined by the X-ray crystallography (Figure 1b).[4b] The ^1H NMR

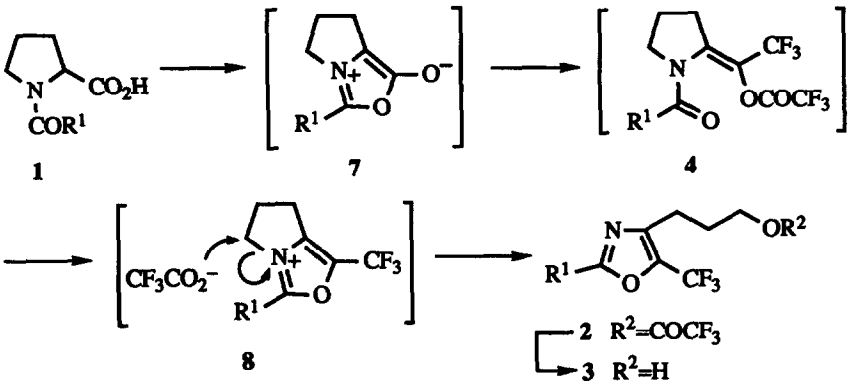


(a) (b)

Figure 1. (a) X-ray structure drawing of **3e**; (b) X-ray structure drawing of **5a**.

spectrum in $CDCl_3$ showed it to be a mixture of the hydrate **5a** and the trifluoromethyl ketone **6a** in about 3 : 1 ratio.[5] The X-ray analysis indicates that **5a** is stabilized by the intramolecular hydrogen bonding between the hydroxy group and the amide oxygen.

Scheme 1 presents a rationale for the formation of the oxazoles **3**. This reaction involves a mesoionic



Scheme 1. Possible mechanism

1,3-oxazolium-5-olates **7** formed through the cyclodehydration of **1** by TFAA. Intermediate **7** undergoes trifluoroacetylation followed by decarboxylation to give the enol trifluoroacetate **4**, which is isolated in the reactions of **1f** and **1g**: a similar mechanism has been postulated in the Dakin-West reaction.[6,7] In theory, intermediate **4** can exist in four different isomeric forms. The calculation indicates that **4** is the thermodynamically most favorable of the possible enol forms.[8] Thus, the orientation of the amide carbonyl group and the enol double bond in **4** is suited for the further cyclization to the oxazolium salt **8**. The cleavage of pyrrolidine ring in **8** by the nucleophilic attack of trifluoroacetate anion would result in the formation of oxazole derivatives **2**. Finally, the hydrolysis of **2** leads to the oxazoles **3**.

The work described herein represents a novel rearrangement of N-acylprolines in which a pyrrolidine ring is cleaved, concomitant with the formation of a oxazole ring. In addition, this reaction is a new facile synthetic procedure to the oxazole derivatives with a trifluoromethyl group at position 5, making them attractive in the synthesis of other heterocycles.[9] This class of compounds is especially important because trifluoromethylated heterocycles are compounds of current interest due to their potential biological applications.[10]

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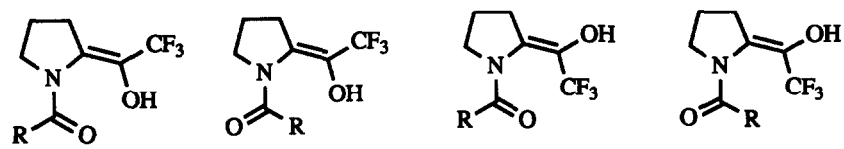
References and Notes

1. Kawase, M. *J. Chem. Soc., Chem. Commun.* **1992**, 1076.
2. In a typical experiment, TFAA (0.64 ml, 4.5 mmol) was added to a stirred solution of **1a** (298.5 mg, 1.5 mmol), pyridine (0.73 ml, 9 mmol), and DMAP (28 mg, 0.23 mmol) in dry benzene (5 ml) at 0 °C under an Ar atmosphere and the mixture was stirred at 25 °C for 3 h, then refluxed for 5 h. The mixture was evaporated in vacuo and the crude trifluoroacetate **2a** was taken up in 10% HCl-dioxane (3 : 2, 5 ml) and

the solution was stirred at 60 °C for 3 h. After the usual workup, the crude product was purified by column chromatography on silica gel eluting with EtOAc-hexane (1:4) to give **3a** (328.4 mg, 87%).

3. For **3a**: ^{1}H NMR ($CDCl_3$): δ 1.39 (s, 9H), 1.85-1.95 (m, 2H), 2.76 (tq, J=5.9, 1.5 Hz, 2H), 3.21 (s, 1H, D_2O changeable), 3.69 (t, J=5.9 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 22.76 (t), 28.37 (q), 31.24 (t), 34.05 (s), 61.87 (t), 119.81 (q, J_{C-F}=267.2 Hz), 133.85 (q, $^2J_{C-F}$=42.4 Hz), 141.57 (q, $^3J_{C-F}$=2.5 Hz), 172.19 (s); IR (oil): 3375 , 1640 cm^{-1}.
4. (a) Crystal data for **3e** ($C_{16}H_{16}F_3NO_2$), monoclinic $P2_1$. a=5.0101 (8), b=8.8904 (9), c=17.361 (2) Å, V=770.9 (6) $Å^3$, ß=94.55 (1) °, μ (Cu Kα)=9.388 cm^{-1} by Enraf-Nonius CAD-4R diffractmeter. Final R value was 0.0899 for 2963 reflections; (b) Crystal data for **5a** ($C_{13}H_{12}Cl_2F_3NO_3$), triclinic $P\bar{1}$. a=12.492 (15), b=8.046 (8), c=7.811 (6) Å, V=749.7 (13) $Å^3$, α=104.66 (6), ß=99.22 (8), γ=87.67 (10) °, μ (Mo Kα)=4.74 cm^{-1} by Rigaku AFC-5 diffractmeter. Final R value was 0.0904 for 2437 reflections. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.
5. Trifluoro ketones are known to give the corresponding hydrates readily. For a recent review on trifluoro ketones, see Begue, J. P.; Bonnet-Delpon, D. *Tetrahedron* **1991**, 47, 3207.
6. Buchanan, G. L. *Chem. Soc. Rev.* **1988**, 17, 91.
7. It is known that proline does not undergo the Dakin-West reaction using acetic anhydride; see Israili, Z. H.; Smissman, E. E. *J. Chem. Eng. Data* **1977**, 22, 357; Allinger, N. L.; Wang, G. L.; Dewhurst, B. B. *J. Org. Chem.* **1974**, 39, 1730.
8. The geometries for the enols (**9-12**) were estimated by the full geometry optimization in the MNDO method (J. J. P. Stewart, MOPAC QCPE #549) in order to determine the most stable form. Their heats of formation are shown in Figure 2.



9	**10**	**11**	**12**
a; -226.01231	**a**; -225.96751	**a**; -224.54722	**a**; -220.63954
b; -192.82779	**b**; -192.06900	**b**; -191.12368	**b**; -187.14364

a; R=Me, **b**; R=Ph

Figure 2. Possible geometries showing heats of formation (kcal mol^{-1})

9. For reviews on oxazole chemistry, see Boyd, G. V. *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R.; Rees, C. W. Eds.; Pergamon Press: Oxford, 1984; vol. 6, Part 4B, ch. 18; Turchi, I. J. *Chemistry of Heterocyclic Compounds*; Wiley: New York, 1986; vol. 45; Boger, D. L.; Weinreb, S. M. *Hetero Diels-Alder Methodology in Organic Synthesis*; Wasserman, H. H. Ed.; Academic Press: California, 1987; vol. 47, pp. 300-310; for a recent paper, see Aken, K. V.; Hoornaet, G. *J. Chem. Soc., Chem. Commun.* **1992**, 895.
10. Silvester, M. J. *Aldrichimica Acta* **1991**, 24, 31; McClinton, M. A.; McClinton, D. A. *Tetrahedron* **1992**, 48, 6555.

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