Tetrahedron Letters, Vol. 35, No. 1, pp. 149-152, 1994
Printed in Great Britain

0040-4039/94 $6.00 + .00
Pergamon Press Ltd

Unusual Reactions of *Secondary* Amino Acids with Trifluoroacetic Anhydride: A Novel Access to α-Trifluoromethylated Acyloins

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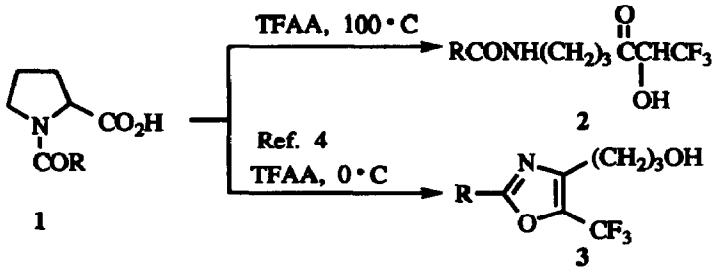
Abstract: A new fragmentation reaction of secondary α-amino acids with trifluoroacetic anhydride under Dakin-West reaction conditions proceeds through oxazolium salt intermediates followed by ring cleavage to form α-trifluoromethylated acyloins in good yields.

The reaction of α-amino acids with acetic anhydride in the presence of a base to give α-acetaminoalkyl ketones is known as the Dakin-West (D-W) reaction and has received much attention.[1] *Secondary* amino acids are likewise known to undergo the D-W reaction employing acetic anhydride at slightly higher temperatures and its mechanism has been studied in detail.[1] Recently, the D-W reaction employing trifluoroacetic anhydride (TFAA) has gained renewed interest in the preparation of trifluoromethyl ketones,[2] an important class of inhibitors of a variety of hydrolytic enzymes.[3] However, our recent discovery[4] of the unusual formation of 5-trifluoromethyloxazoles (3) from *N*-acylprolines (1) or *N*-acyl-*N*-benzyl-α-amino



a: R=Ph, b: R=4-MeOC$_6$H$_4$, c: R=4-ClC$_6$H$_4$, d: R=Bu^t

Scheme 1

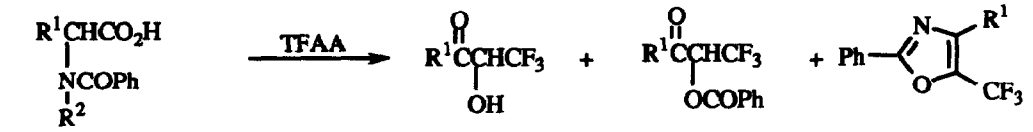
acids and TFAA under the D-W reaction conditions prompted us to investigate in detail the D-W reaction of *secondary* α-amino acids with TFAA, which has not been previously reported in the literature.[5] We now found that the reaction of *secondary* amino acids with TFAA is more complex, yielding instead of 3

trifluoromethylated acyloins (2 and 5) as main products. These compounds possess a unique structural feature and are of great synthetic interest[6] as novel trifluoromethylated building blocks[7] which are subject of active investigation.

Table 1. Reactions of *Secondary* Amino Acids and TFAA

Run	Amino acid	Method[a]	Product (yield, %)[b]
1	**1a**	A	**2a** (88)
2	**1b**	A	**2b** (85)
3	**1c**	A	**2c** (81)
4	**1d**	A	**2d** (62), **3d** (12)
5	**4a**	A	**5a** (54), **6a** (11), **7a** (5)
6	**4a**	B	**5a** (50), **6a** (14), **7a** (13)
7	**4b**	A	**5a** (27), **6a** (23), **7a** (1)
8	**4b**	B	**5a** (17), **6a** (43), **7a** (16)
9	**4c**	A	**5a** (41), **6a** (10), **7a** (33)
10	**4d**	A	**5b** (68), **6b** (8), **7b** (12)
11	**4e**	A	**6c** (43), **7c** (2)[c]

a) Method A: The addition of TFAA was done at 100 °C, according to general procedure described in the text. Method B: The addition of TFAA was done at 0 °C, according to the procedure described in ref. 4. b) Satisfactory spectral and analytical (combustion and/or high resolution mass) data were obtained for all new compounds. c) No isolation of **5c** is probably due to the loss during extraction because the product may be water-soluble.



4a: R^1=$PhCH_2$, R^2=Me
4b: R^1=$PhCH_2$, R^2=Et
4c: R^1=R^2=$PhCH_2$
4d: R^1=Ph, R^2=Me
4e: R^1=R^2=Me

5a: R^1=$PhCH_2$
5b: R^1=Ph
5c: R^1=Me

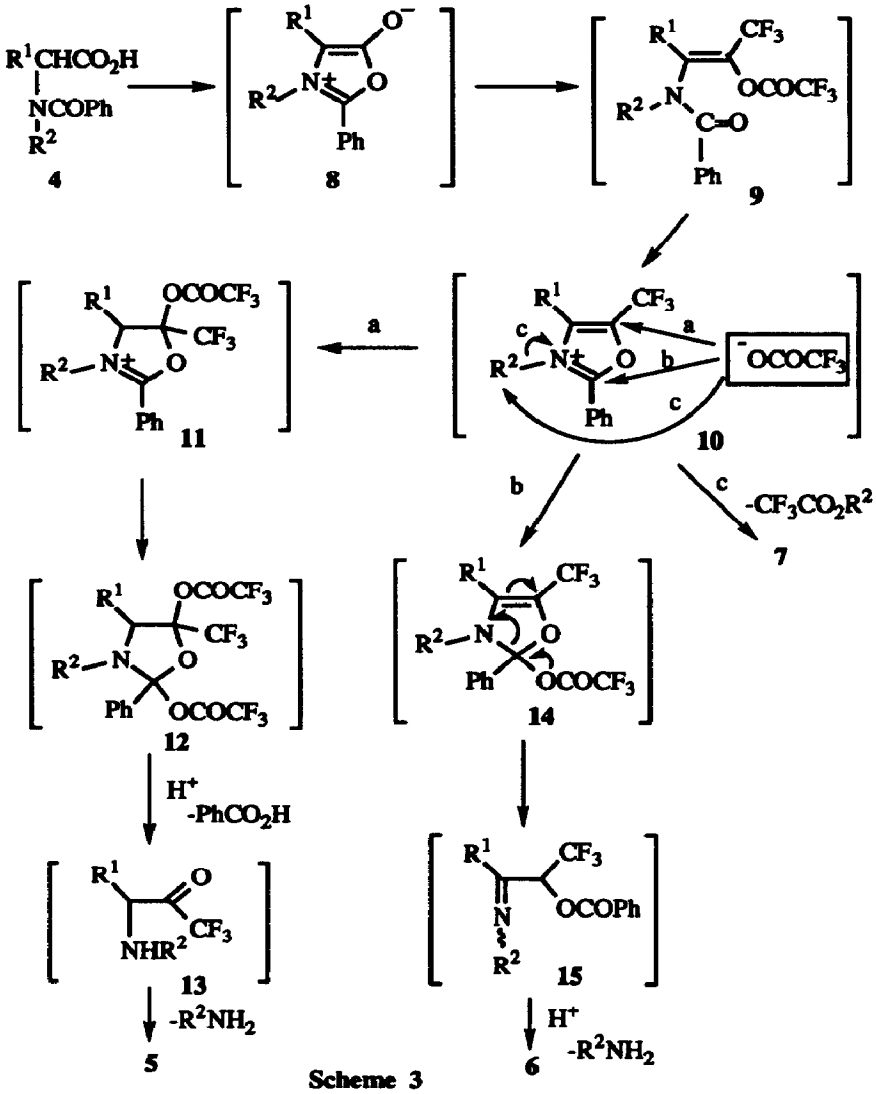
6a: R^1=$PhCH_2$
6b: R^1=Ph
6c: R^1=Me

7a: R^1=$PhCH_2$
7b: R^1=Ph
7c: R^1=Me

Scheme 2

According to a previous report,[4] the reaction was initially carried out by the addition of TFAA at 0 °C to a solution of *N*-acylproline (**1**) and pyridine in benzene and gave 5-trifluoromethyloxazole (**3**) in good yield (Scheme 1). In contrast, when addition of TFAA was done at 100 °C, the results were quite different. Thus, TFAA (0.64 ml, 4.5 mmol) was added to a refluxing solution of **1a** (313.5 mg, 1.5 mmol) and pyridine (0.73 ml, 9 mmol) in dry benzene (6 ml) and the mixture was further refluxed for 1 h. The mixture was evaporated

in vacuo and the residue was taken up in 10% HCl-dioxane (1:1, 6 ml); the solution was stirred at 60 °C for 2 h. After workup, the product was purified by column chromatography on silica gel eluting with EtOAc-hexane (1:1) to give **2a** (383.1 mg, 88%).[8] The reason why the reaction affords a completely different product depending on the temperature of the reaction mixture is still unclear. This reaction is generally applicable to not only *N*-acylprolines (**1**) but also other *N*-acyl-*N*-alkyl-α-amino acids (**4**), as shown in Scheme 2 and Table 1. In the case of **4a**, the temperature at addition of TFAA does not have a profound effect on product distributions (Table 1, run 5 and 6).



Scheme 3

Although precise mechanistic details need yet to be established, the reaction appears to proceed *via* a similar mechanism to that described in the reaction of *N*-acylprolines.[4] Several observations help to

delineate the gross mechanistic details of the way how **4** is converted to **5**, **6**, and **7**, respectively. First, in the reaction of **4c** (Table 1, run 9), benzoic acid (40%), benzylamine (35%, isolated as *N*-acetyl derivative) and benzyl alcohol (13%) were isolated as the acidic and basic fractions after extraction of the products. Second, it was proved that **5** and **6** were not the direct reaction products, but they were formed after acid hydrolysis of the reaction mixture. On the other hand, oxazoles (**7**) were formed before the acid hydrolysis. Third, we proved that **5** was not derived from the hydrolysis of **6**, because **6a** was recovered unchanged under the same reaction conditions as **4a**. In Scheme 3, key intermediate oxazolium ion **10**, the postulated common intermediate for the formation of oxazoles,[4] could have three sites which could be attacked by trifluoroacetate anion. Further addition of trifluoroacetate anion to intermediate **11** could lead to **12** and acid hydrolysis of **12** *via* α-amino trifluoromethyl ketones (**13**)[9] may account for the formation of **5**.

In summary, this work describes the unusual fragmentation reaction of *secondary* amino acids, which provides an access to synthetically useful trifluoromethylated acyloins. Studies are in progress to elucidate the precise mechanism of this reaction and to fully explore the synthetic potential of these products.

References and Notes

1. Buchanan, G. L. *Chem. Soc. Rev.* **1988**, 17, 91.
2. The D-W reaction of amino acids with TFAA yields the corresponding α-amide trifluoromethyl ketones. See: (a) Kolb, M.; Neises, B.; Gerhart, F. *Liebig Ann. Chem.* **1990**, 1; (b) Peet, N. P.; Burkhart, J. P.; Angelastro, M. R.; Giroux, E. L.; Mehdi, S.; Bey, P.; Kolb, M.; Neises, B.; Schirlin, D. *J. Med. Chem.* **1990**, 33, 394 and references cited therein.
3. (a) Begue, J. P.; Bonnet-Delpon, D. *Tetrahedron* **1991**, 47, 3207; (b) Boivin, J.; Kaim, L. El.; Zard, S. Z. *Tetrahedron Lett.* **1992**, 33, 1285; (c) Edwards, P. D. *Tetrahedron Lett.* **1992**, 33, 4279.
4. (a) Kawase, M.; Miyamac, H.; Narita, M.; Kurihara, T. *Tetrahedron Lett.* **1993**, 34, 859; (b) Kawase, M. *Heterocycles* **1993**, 36, 2441.
5. It is reported that *N*-acyl-*N*-phenylglycines are treated with TFAA at room temperature to afford anhydro-4-trifluoroacetyl-5-hydroxy-1,3-oxazolonium hydroxides. This is the case hitherto reported, to our knowledge, concerning reaction of *secondary* amino acids and TFAA in the absence of a base. See: (a) Singh, G.; Singh, S. *Tetrahedron Lett.* **1964**, 3789; (b) Greco, C. V.; Gray, R. P.; Grosso, V. G. J. *J. Org. Chem.* **1967**, 32, 4101.
6. The usefulness of acyloins in synthetic organic chemistry has been well recognized. See: Moriarty, R. M.; Berglund, B. A.; Penmasta, R. *Tetrahedron Lett.* **1992**, 33, 6065 and references cited therein.
7. (a) Fuchikami, T. *J. Synth. Org. Chem. Jpn.* **1984**, 42, 775; (b) Tanaka, K. *J. Synth. Org. Chem. Jpn.* **1990**, 48, 16.
8. The acyloins (**2** and **5**) were isolated as a single isomer. For **2a**: bp_2 235 °C (bath temp.); ^{1}H NMR ($CDCl_3$): δ 1.84-2.01 (m, 2H), 2.64-2.85 (m, 2H), 3.31-3.47 (m, 2H), 4.51 (q, J=7.9 Hz, 1H), 5.00 (d, J=6.4 Hz, 1H, D_2O changeable), 6.96-7.00 (br, 1H, D_2O changeable), 7.33-7.49 (m, 3H), 7.70-7.73 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 23.21 (t), 36.65 (t), 39.15 (t), 75.11 (q, $^2J_{C-F}$=31.1 Hz), 122.70 (q, J_{C-F}=284.0 Hz), 126.94 (d), 128.64 (d), 131.74 (d), 134.13 (s), 168.62 (s), 203.82 (s); IR (oil): 3325, 1730, 1640 cm^{-1}.
9. It is suggested that α-amino trifluoromethyl ketones are easily hydrolyzed to α-hydroxy ketones *via* the enolic form of the ketones. See: Begue, J. P.; Bonnet-Delpon, D.; Sdassi, H. *Tetrahedron Lett.* **1992**, 33, 1879.

(*Received in Japan* 13 *September* 1993; *accepted* 27 *October* 1993)