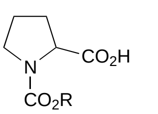
An anomalous Dakin–West reaction of *N*-carbamate substituted prolines and trifluoroacetic anhydride

Masami Kawase,*[a] Michitaka Hirabayashi,[a] Hiromi Koiwai,[a] Katsumi Yamamoto[a] and Hiroshi Miyamae[b]

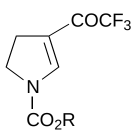
[a] *Faculty of Pharmaceutical Sciences, Josai University, 1-1 Keyakidai, Sakado, Saitama 350-0290, Japan*
[b] *Faculty of Science, Josai University, 1-1 Keyakidai, Sakado, Saitama 350-0290, Japan*

A novel transformation of *N*-alkoxycarbonylprolines 1 to 4-trifluoroacetyl-2,3-dihydropyrroles 2 was efficiently realized by utilizing trifluoroacetic anhydride, in which probable intermediates were mesoionic 1,3-oxazolium-5-olates B.

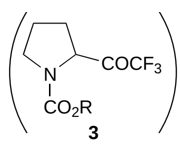
The Dakin–West (D–W) reaction of α-amino acids usually produces α-amino ketones.[1] However, treatment of *N*-acyl-*N*-alkyl-α-amino acids or *N*-acylprolines with trifluoroacetic anhydride (TFAA) under the D–W reaction conditions can lead to trifluoromethylated oxazoles,[2] acyloins[3] or morpholines,[4] depending on the nature of the *N*-substituents of the amino acids and/or reaction conditions. In the course of our studies on the reactivities of mesoionic 1,3-oxazolium-5-olates,[5] we have now found that *N*-alkoxycarbonylprolines **1** led unexpectedly, by way of a novel decarboxylative dehydration followed by trifluoroacetylation, to 4-trifluoroacetyl-2,3-dihydropyrroles **2** under the D–W reaction conditions.



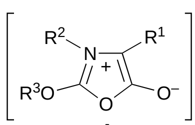
1a R = Me
b R = Et
c R = Bu
d R = Ph
e R = fluoren-9-yl
f R = Allyl
g R = Bn



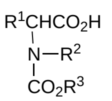
2a R = Me
b R = Et
c R = Bu
d R = Ph
e R = fluoren-9-yl
f R = Allyl



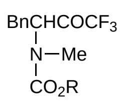
3



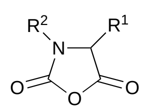
A



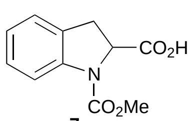
4a R^1 = Bn, R^2 = Me, R^3 = Me
b R^1 = Bn, R^2 = Me, R^3 = Bn
c R^1 = H, R^2 = Ph, R^3 = Et



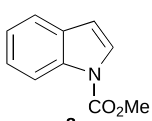
5a R = Me
b R = Bn



6a R^1 = Bn, R^2 = Me
b R^1 = H, R^2 = Ph



7



8

RNHAc
9a R = CH$_2$=CHCH$_2$
b R = Bn

Thus, treatment of **1a** (1 mmol) with TFAA (3 mmol) in MeCN (5 ml) at 80 °C for 5 h gave rise to *N*-methoxycarbonyl-4-trifluoroacetyl-2,3-dihydropyrrole **2a** in 66% yield. In the reaction, the D–W reaction product, *N*-methoxycarbonyl-2-trifluoroacetylpyrrolidine **3** (R = Me), was not isolated.

Reaction variables were briefly examined. Addition of pyridine (3 equiv.) to the reaction reduced the yield (**2c**; 22%). High temperatures (80 °C) were needed to obtain a high yield of **2c**, lower temperatures (60 °C) reducing the yield (**2c**; 46%). Various solvents such as MeCN, DMF, $ClCH_2CH_2Cl$, benzene, $MeNO_2$ and acetone are usable, and among them MeCN and DMF are the solvents of choice for this reaction, while little or no reaction takes place in THF, DME or dioxane. Several

Table 1 Reactions of *N*-alkoxycarbonylprolines with TFAA[a]

Entry	Starting material	Solvent	Product (% yield)[b]
1	**1a**	MeCN	**2a** (66)
2	**1a**	DMF	**2a** (67)
3	**1b**	MeCN	**2b** (61)
4	**1b**	DMF	**2b** (53)
5	**1c**	MeCN	**2c** (58)
6	**1c**	DMF	**2c** (68)
7	**1d**	MeCN	**2d** (32)
8	**1d**	DMF	**2d** (27)
9	**1e**	MeCN	**2e** (34)
10	**1f**	MeCN	**2f** (30) + **9a** (54)
11	**1g**	MeCN	**9b** (94)[c]
12	**7**	MeCN	**8** (86)

[a] The reactions were carried out according to the general procedure described in the text. [b] Isolated yields of pure products. All new compounds gave satisfactory spectroscopic data (IR, MS, ^{1}H and ^{13}C NMR) and analytical (combustion and/or high resolution mass) data. [c] Plus 54% of proline.

urethane-protected prolines **1a–f** were reacted in this way and the results are presented in Table 1. Among the *N*-alkoxycarbonyl groups examined, Me, Et and Bu proved to give a good yield of the product **2**. The low yields of **2d–f** could be attributable to the ease of cleavage of the alkoxy group in the mesoionic oxazole intermediate **B**. In the reaction of **1f**, *N*-allylacetamide **9a** was isolated in 58% yield as a side product.

The structure of **2** was determined from analytical and spectral data† and was subsequently secured by single-crystal X-ray diffraction analysis of **2d** (Fig. 1).‡

A plausible mechanism for the formation of **2** is suggested in Scheme 1. The existence of the mesoionic oxazole **B** is supported by the following facts. (i) The reaction of Z-proline

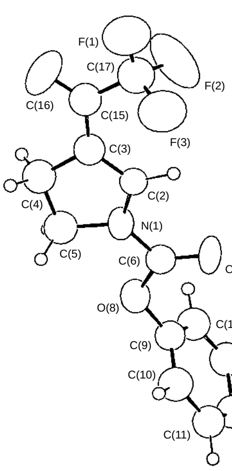
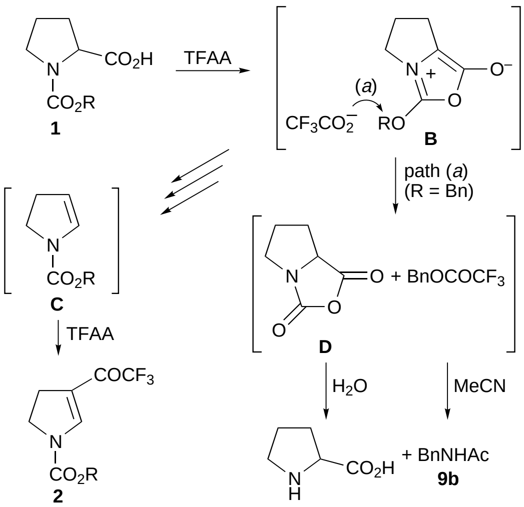


Fig. 1 X-Ray Crystal structure of **2d** (the probability level of the ellipsoids is 50%)



Scheme 1

1g with TFAA afforded proline (45%) and *N*-benzylacetamide **9b** (94%). Formation of proline is presumably due to hydrolysis of anhydride **D**,[6] which was produced by the attack of trifluoroacetate ion on the mesoionic oxazole intermediate **B** *via* path (*a*). *N*-Benzylacetamide **9a** was formed by the Ritter reaction of intermediary benzyl trifluoroacetate and the solvent MeCN. (ii) Treatment of *N*-methoxycarbonyl-*N*-methylphenylalanine **4a** with TFAA in the presence of pyridine gave the D–W reaction product, trifluoroacetyl derivative **5a**, in 93% yield.[7] In the case of *N*-benzyloxycarbonyl-*N*-methylphenylalanine **4b**, trifluoroacetyl derivative **5b** and the anhydride[8] of **6a** *N*-carboxyphenylalanine were obtained in 39 and 43% yields, respectively. (iii) In attempts to form the mesoionic oxazole **A** by treatment of *N*-ethoxycarbonyl-*N*-phenylglycine **4c** with $SOCl_2$, Potts *et al.* isolated the anhydride **6b** of *N*-carboxyglycine and ethyl chloride.[9] This suggests that ring closure to the mesoionic oxazole **A** actually occurred and that it underwent rapid deethylation. However, it is difficult to obtain a definitive explanation for the transformation of **B** to **2**. The existence of intermediary **C** is supported by the reaction of *N*-methoxycarbonyl-2,3-dihydroindole-1-carboxylic acid **7** with TFAA. Thus, the reaction yielded *N*-methoxycarbonylindole **8** in 86% yield and disclosed the probable intermediacy of **C**. Indeed, *N*-methoxycarbonylindole **8** cannot undergo trifluoroacetylation, whereas *N*-methoxycarbonyl-2-pyrroline **C** (R = Me)[10] prepared independently gave the trifluoroacetyl derivative **2a** in 65% yield under the same reaction conditions as described for **1a**. Finally, trifluoroacetylation of **C** leads to the product **2**.

In summary, this work describes the reaction of *N*-alkoxycarbonylprolines and TFAA, which has great practical potential because of the ready availability of the starting materials and reagents and the ease of manipulation. Our method makes novel compounds **2** readily accessible for further study as building blocks for the synthesis of fluorine-containing compounds, in view of the versatility of aminoenones (N–C=C–C=O) in synthetic as well as heterocyclic chemistry.[11] Detailed mechanistic studies and synthetic utilization of **2** as trifluoromethyl building blocks are now in progress.

Notes and References

† *Selected data* for **2d**: mp 99–101 °C (hexane); *m/z* 285 (M^+, 100%); ν_{max}/cm^{-1} 1670, 1740; δ_H(500 MHz; $CDCl_3$; Me_4Si) 3.04 (br s, 2 H), 4.12 (br s, 2 H), 7.17 (d, 2 H, *J* 7.9), 7.25–7.30 (m, 1 H), 7.40–7.43 (m, 2 H), 7.93 (s, 1 H); δ_C(125 MHz; $CDCl_3$; Me_4Si) 26.15 (CH_2), 46.77 (CH_2), 116.92 (C), 116.54 (CF_3, $^1J_{CF}$ 290.0), 121.16 (CH), 126.42 (CH), 129.61 (CH), 144.46 (CH), 145.85 (C), 150.15 (C), 176.49 (C, $^2J_{CF}$ 35.5).

‡ *Crystal data* for **2d**: ($C_{13}H_{10}NO_3F_3$), FW = 285.2, orthorhombic, $P2_12_12_1$, a = 8.409(7), b = 22.604(6), c = 6.774(6) Å, V = 1288(2) Å^3, Z = 4, μ(Mo-Kα) = 1.26 cm^{-1} by Rigaku AFC-5 diffractometer. Final R value was 0.074 for 1331 reflections (R_w = 0.044, S = 2.770). CCDC 182/754.

1 G. L. Buchanan, *Chem. Soc. Rev.*, 1988, **17**, 91.
2 M. Kawase, H. Miyamae, M. Narita and T. Kurihara, *Tetrahedron Lett.*, 1993, **34**, 859; M. Kawase, *Heterocycles*, 1993, **36**, 2441.
3 M. Kawase, *Tetrahedron Lett.*, 1994, **35**, 149.
4 M. Kawase, S. Saito, H. Kikuchi and H. Miyamae, *Heterocycles*, 1997, **45**, 2185.
5 M. Kawase, *Chem. Pharm. Bull.*, 1997, **45**, 1248.
6 T. S. Kaufman, V. L. Ponzo and J. Zinczuk, *Org. Prep. Proced. Int.*, 1996, **28**, 487 and references cited therein.
7 Full details of the D–W reaction of *N*-alkoxycarbonyl-*N*-alkyl-α-amino acids will be reported elsewhere.
8 R. Wilder and S. Mobashery, *J. Org. Chem.*, 1992, **57**, 2755; H. Collet, C. Bied, L. Mion, J. Tailades and A. Commeyras, *Tetrahedron Lett.*, 1996, **37**, 9043 and references cited therein.
9 K. T. Potts, D. Bhattacharjee and S. Kanemasa, *J. Org. Chem.*, 1980, **45**, 4985.
10 G. A. Kraus and K. Neuenschwander, *J. Org. Chem.*, 1981, **46**, 4791; Y. Nomura, K. Ogawa, Y. Takeuchi and S. Tomoda, *Chem. Lett.*, 1977, 693.
11 T. Nishio, C. Kashima and Y. Omote, *J. Synth. Org. Chem. Jpn.*, 1976, **34**, 526; J. V. Greenhill, *Chem. Soc. Rev.*, 1977, **6**, 277.

Received in Cambridge, UK, 18th November 1997; 7/08294K