A FACILE ONE-POT SYNTHESIS OF 5-TRIFLUORO-METHYL- AND 5-PERFLUOROALKYLOXAZOLES FROM *N*-ALKYL-*N*-ACYLAMINO ACIDS

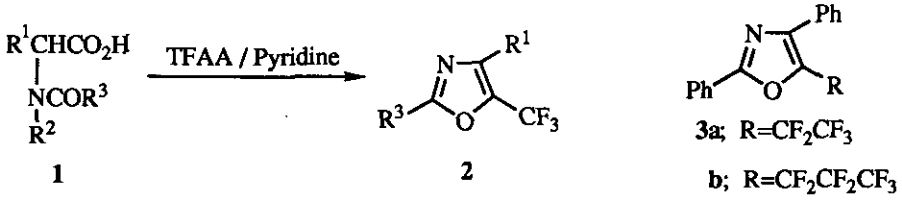
Masami Kawase

Faculty of Pharmaceutical Sciences, Josai University, 1-1 Keyakidai, Sakado-shi, Saitama 350-02, Japan

Abstract - The reaction of *N*-acyl-*N*-benzyl-α–amino acids with trifluoroacetic or perfluorocarboxylic anhydride in the presence of pyridine affords 5-trifluoromethyl- or 5-perfluoroalkyloxazoles in high yields.

The development of synthetic methodology for heterocyclic compounds bearing trifluoromethyl or perfluoroalkyl group is of current interest because of their ability to enhance biological activities and various applications to the material sciences.[1]

We have already described the unexpected formation of 5-trifluoromethyloxazoles by the reaction of *N*-acylprolines with trifluoroacetic anhydride (TFAA) under the Dakin-West reaction conditions.[2] This reaction could proceed through mesoionic 1,3-oxazolium-5-olates (**A**) [R^1-R^2=$(CH_2)_3$] followed by oxazolium salts (**C**) [R^1-R^2=$(CH_2)_3$] as shown in Scheme 1. As an extension[3] and mechanistic study of this work, we tried the reaction of *N*-benzoyl-*N*-methylphenylalanine (**1a**) with TFAA and the yield of oxazole (**2a**) isolated was poor 13%. Interestingly, the yield of **2a** was increased to 88% by the use of *N*-benzoyl-*N*-benzylphenylalanine (**1c**) as a starting material.[4] These results prompted us to develop a new versatile synthesis of 5-trifluoromethyl- and 5-perfluoroalkyloxazole derivatives from *N*-acyl-*N*-benzyl-α-amino acids (**1**) in good yields.



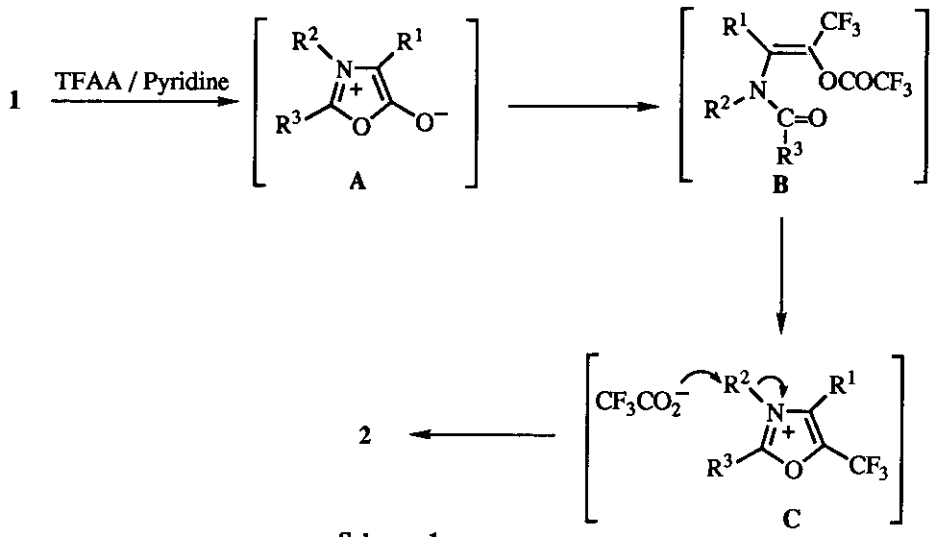
1 2

Table 1. Transformations of *N*-Alkyl-*N*-acylamino Acids (**1**) to Oxazoles (**2** or **3**)

Entry	Starting material	R^1	R^2	R^3	Product (yield, %)[a]
1	**1a**	$PhCH_2$	Me	Ph	**2a** (13)
2	**1b**	$PhCH_2$	Et	Ph	**2a** (16)
3	**1c**	$PhCH_2$	$PhCH_2$	Ph	**2a** (88)
4	**1d**	$PhCH_2$	$PhCH_2$	Bu^t	**2b** (83)
5	**1e**	$PhCH_2$	$PhCH_2$	PhCH=CMe	**2c** (61)
6	**1f**	Ph	$PhCH_2$	Ph	**2d** (92)
7	**1g**	Ph	$PhCH_2$	2-Thienyl	**2e** (93)
8	**1h**	Me	$PhCH_2$	Ph	**2f** (46)
9	**1i**	$CH_3CH_2CH(Me)$	$PhCH_2$	Ph	**2g** (51)
10[b]	**1f**	Ph	$PhCH_2$	Ph	**3a** (92)
11[c]	**1f**	Ph	$PhCH_2$	Ph	**3b** (98)

a) Satisfactory spectral and analytical (combustion and/or high resolution mass) data were obtained for all new compounds (**2** and **3**). b) Pentafluoropropionic anhydride was used. c) Heptafluorobutyric anhydride was used.

A comparative study of the suitability of several *N*-alkyl groups in the reaction was undertaken (Table 1, Entries 1-3). The *N*-benzyl group was found to afford better yield. During the previous work,[2] we observed that a substituent of *N*-acyl group plays an important role in the reaction of *N*-acylprolines. Indeed, *N*-acyl derivatives (**1c-e**), containing benzoyl, cinnamoyl, or pivaloyl group, worked well (Table 1, Entries 3-5). On the other hand, *N*-acetyl- and *N*-isobutyryl-*N*-benzylphenylalanines, bearing α-hydrogens, afforded no oxazole derivatives. These results clearly indicate that the reaction is markedly influenced by the nature of both alkyl substituent and acyl substituent on the nitrogen of amino acids. Some examples are summarized in Table 1.[5]



Scheme 1

Next, we considered extending this reaction to introduce other perfluoroalkyl groups, such as pentafluoroethyl and heptafluoro-*n*-propyl, for which the corresponding perfluorocarboxylic anhydrides are commercially available. Pentafluoropropionic and heptafluorobutyric anhydride reacted readily with *N*-benzoyl-*N*-benzylphenylglycine (**1f**) to give 5-pentafluoroethyl-(**3a**) and 5-heptafluoro-*n*-propyl-2,4-diphenyloxazole (**3b**) in high yields, respectively (Table 1, Entries 10 and 11).

The present procedure discloses a new synthetic route to 5-trifluoromethyl- and 5-perfluoroalkyloxazoles from *N*-alkyl-*N*-acylamino acids. By this methodology, the 2- and 4-substituents can be readily varied simply by choosing the appropriate *N*-acyl-*N*-benzyl-α-amino acids as a starting material. In addition, the method appears to be useful and convenient in terms of the ready accessibility of the starting materials and operational simplicity.[6] A synthesis for trifluoromethyl-substituted oxazoles has been described recently.[7] In particular, we note that this approach suggests easy access to perfluoroalkyl groups at the C-5 oxazole position.

REFERENCES AND NOTES

1. R. Filler, ' Organofluorine Chemicals and Their Industrial Applications,' ed. by R. E. Banks, Ellis Horwood, Chichester, 1979, p. 123; R. Filler and Y. Kobayashi, 'Biomedicinal Aspects of Fluorine

Chemistry,' Kodansha, Tokyo, 1982; J. T. Welch, *Tetrahedron*, 1987, **43**, 3123; K. Tanaka, *J. Synth. Org. Chem. Jpn.*, 1990, **48**, 16; M. J. Silvester, *Aldrichimica Acta.*, 1991, **24**, 31; M. A. McClinton and D. A. McClinton, *Tetrahedron*, 1992, **48**, 6555.

2. M. Kawase, H. Miyamae, M. Narita, and T. Kurihara, *Tetrahedron Lett.*, 1993, **34**, 859.
3. In the oxazoles obtained from N-acylprolines,[2] the 4-substituent is limited to the 3-hydroxypropyl group.
4. Mechanistic consideration is that , if R^2 group is easily removable in the step of intermediate (**C**), the reaction could proceed efficiently. It is noted that benzyl alcohol was also isolated in 41% yield in the reaction of **1c**. The possible mechanism has been described in ref. 2.
5. In a typical experiment, to a stirred solution of TFAA (0.64 ml, 4.5 mmol) and pyridine (0.73 ml, 9 mmol) in dry benzene (6 ml) was added **1c** (538.5 mg, 1.5 mmol) at 0 °C and the mixture was stirred at 25 °C for 3 h, then refluxed for 5 h. After the usual workup, the crude product was purified by column chromatography on silica gel eluting with EtOAc-hexane (1 :10) to give **2a** (401.0 mg, 88%): mp 75-76 °C; ^{1}H-nmr ($CDCl_3$) δ: 4.04 (2H, s), 7.20-7.35 (5H, m), 7.40-7.50 (3H, m), 8.01-8.07 (2H, m); ^{13}C-nmr ($CDCl_3$) δ: 32.27 (t), 119.93 (q, J_{C-F}=267.9 Hz), 126.13 (s), 126.77 (d), 127.07 (d), 128.64 (d), 128.72 (d), 128.85 (d), 131.49 (d), 134.15 (q, $^2J_{C-F}$=42.0 Hz), 137.35 (s), 142.30 (q, $^3J_{C-F}$=2.0 Hz), 162.18 (s).
6. For reviews on oxazole chemistry, see G. V. Boyd, '*Comprehensive Heterocyclic Chemistry*,' vol. 6, Part 4B, eds., by A. R. Katritzky and C. W. Rees, Pergamon Press, Oxford, 1984, ch. 18; I. J. Turchi, '*Chemistry of Heterocyclic Compounds*,' vol. 45, Wiley, New York, 1986; D. L. Boger and S. M. Weinreb, '*Hetero Diels-Alder Methodology in Organic Synthesis*,' vol. 47, ed., H. H. Wasserman, Academic Press, California, 1987, pp. 300-310; for recent development in oxazole synthesis methodology, see K. V. Aken and G. Hoornaet, *J. Chem. Soc., Chem. Commun.*, 1992, 895; T. Fukumoto, Y. Aso, T. Otsubo, and F. Ogura, *J. Chem. Soc., Chem. Commun.*, 1992, 1070; A. R. Gangloff, B. Akermark, and P. Helquist, *J. Org. Chem.*, 1992, **57**, 4797; R. F. Curico and C. P. Kaun, *J. Org. Chem.*, 1992, **57**, 6999; E. L. Williams, *Tetrahedron Lett.*, 1992, **33**, 1033; S. K. Yoon, *Tetrahedron Lett.*, 1992, **33**, 2159; J. Das, J. A. Reid, D. R. Kronenthal, J. Singh, P. D. Pansegrau, and R. H. Mueller, *Tetrahedron Lett.*, 1992, **33**, 7835; K. M. Short and C. B. Ziegler, Jr., *Tetrahedron Lett.*, 1993, **34**, 71.
7. K. Burger, K. Geith, and D. Hubl, *Synthesis*, 1988, 189; 194; 199; G. Shi and Y. Xu, *J. Chem. Soc., Chem. Commun.*, 1989, 607; Y. Kamitori, M. Hojo, R. Masuda, T. Takahashi, and M. Wada, *Heterocycles*, 1992, **34**, 1047.

Received, 9th July, 1993