AN EFFICIENT SYNTHESIS OF 4-TRIFLUORO-METHYLATED AND 4-PERFLUOROALKYLATED IMIDAZOLES FROM MESOIONIC 1,3-OXAZOLIUM-5-OLATES

Masami Kawase,*[a] Setsuo Saito,[a] and Teruo Kurihara[b]

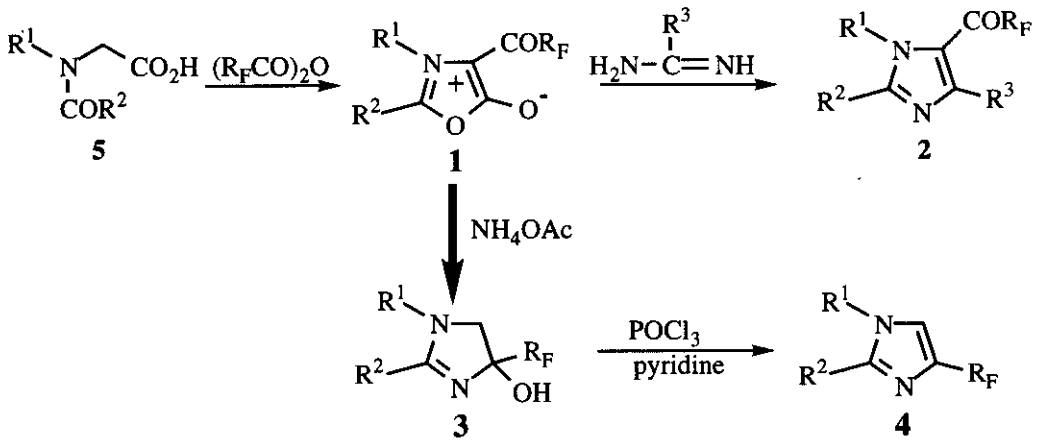
[a] Faculty of Pharmaceutical Sciences, Josai University, 1-1 Keyakidai, Sakado-shi, Saitama 350-02, Japan

[b] Faculty of Science, Josai University, 1-1 Keyakidai, Sakado-shi, Saitama 350-02, Japan

Abstract --- 4-Trifluoromethyl- and 4-perfluoroalkylimidazoles (**4**) were conveniently synthesized from mesoionic 4-trifluoroacetyl- or 4-perfluoroacyl-1,3-oxazolium-5-olate (**1**) *via* 2-imidazolines (**3**), which were formed through the regioselective attack of ammonia on the C(2) position of **1**.

The development of a convenient method for the synthesis of heterocyclic compounds bearing a trifluoromethyl or perfluoroalkyl group has received increasing interest because of their unique nature for material sciences and biological activities for medicines and agrochemicals.[1] The building block strategy for introducing a trifluoromethyl or perfluoroalkyl group is now the suject of active investigation and has often been found to be superior to a selective introduction of these groups at a late stage in synthesis.[2]

In the course of our studies on the synthetic application of mesoionic 1,3-oxazolium-5-olates,[3] we have demonstrated that mesoionic 4-trifluoroacetyl-1,3-oxazolium-5-olates (**1**) are useful synthons for the synthesis of trifluoromethyl substituted heterocycles.[3d] Thus, reactions of **1** with amidines undergo a novel ring transformation to give the 5-trifluoroacetylimidazoles (**2**) in good yields (Eq. 1). In these reactions, we noticed the formation of 2-imidazolines (**3**) as side products, which could be produced by the action of



(1)

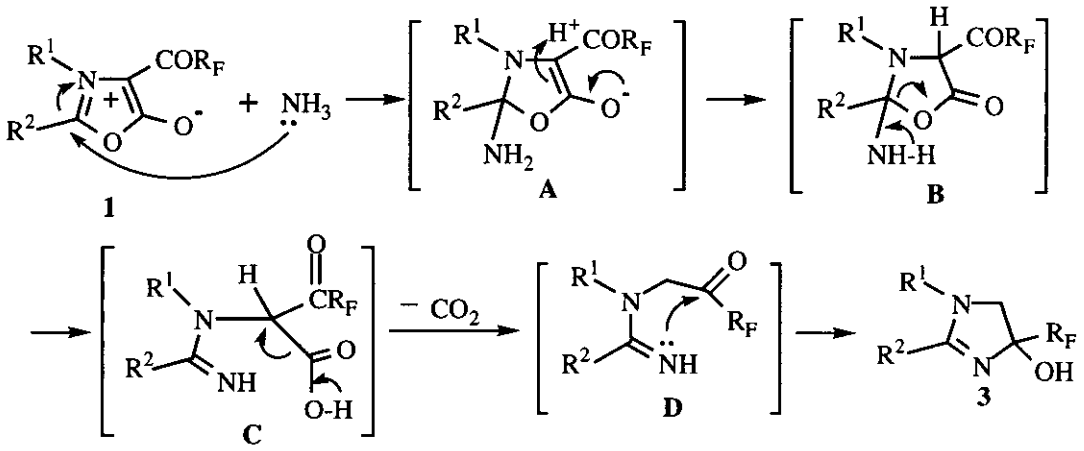
Table 1. Yields of 2-imidazolines (**3**) and 4-perfluoroalkylimidazoles (**4**).

Entry	R^1	R^2	R_F	Starting materials	Products Yield of **3** (%)	Yield of **4** (%)
1	Me	Ph	CF_3	**1a**	**3a** (92)	**4a** (88)
2	Me	Ph	CF_3	**5a**	**3a** (94)[a]	--
3	Ph	Ph	CF_3	**1b**	**3b** (84)	**4b** (93)
4	Ph	Ph	CF_3	**5b**	**3b** (91)[a]	--
5	Ph	Me	CF_3	**1c**	**3c** (91)	**4c** (96)
6	Me	Bu^t	CF_3	**1d**	**3d** (78)	**4d** (88)
7	Me	$PhCH_2$	CF_3	**5e**	**3e** (98)[a]	**4e** (91)
8	Me	Ph	C_2F_5	**5a**	**3f** (93)[a,b]	**4f** (99)
9	Me	Ph	C_3F_7	**5a**	**3g** (87)[a,c]	**4g** (93)

a) Yields refer to the one-pot procedure using **5**. b) Pentafluoropropionic anhydride was used instead of TFAA. c) Heptafluorobutyric anhydride was used instead of TFAA.

ammonia generated during the reaction. This finding prompted us to investigate the reaction of **1** with ammonia more closely and to make it more efficient method for synthesis of 2-imidazolines (**3**), which can be readily dehydrated to produce 4-perfluoroalkylimidazoles (**4**) (Eq. 1). Now we wish to communicate the results.

Treatment of **1a** (1 mmol) with ammonium acetate (1.5 mmol) in DMF (4 ml) at 70 °C for 2 h gave rise to the 2-imidazoline (**3a**) in 92% yield.[4] The first step from **1** to **3** proceeded in high yields and the purification was simply done by washing the crude **3** with hexane. The starting materials (**1**) can be readily prepared



Scheme 1

from *N*-acyl-*N*-alkylglycines (**5**) and trifluoroacetic anhydride (TFAA) and a one-pot conversion of **5** to **3** also proceeded successfully. Thus, **5a** reacted with TFAA (3 mol equiv.) in CH_2Cl_2 to give **1a** which was directly subjected to the reaction with ammonium acetate to yield **3a** in 94% yield. The one-pot procedure gave slightly higher yields. Several mesoionic compounds (**1**) and *N*-acyl-*N*-alkylglycines (**5**) reacted in this way, and the results are presented in Table 1.

Pentafluoropropionic and heptafluorobutyric anhydrides also reacted readily with *N*-benzoyl-*N*-methyglycine (**5a**) and 4-pentafluoroethyl-(**3f**) and 4-heptafluoro-*n*-propyl-2-imidazolines (**3g**) were obtained by the one-pot procedure in high yields, respectively (Table 1, Entries 8 and 9).

A plausible mechanism is described in Scheme 1. Thus, nucleophilic attack of ammonia on C(2) of **1** gives rise to an adduct (**A**). The scission of the O(1)-C(2) bond of **B** gives an open-chain intermediate (**C**), which extrudes carbon dioxide to provide the ketone (**D**). Finally, intramolecular cyclization of **D** affords **3**.

2-Imidazolines (**3**) can be readily converted into 4-perfluoroalkylimidazoles (**4**). Thus, dehydration of **3** by treatment of phosphorus oxychloride and pyridine[6] at 90 °C for 2 h gave **4** in high yields (Table 1).

In conclusion, the above results present a new method for construction of 4-trifluoromethyl- and 4-perfluoroalkylimidazoles. By this methodology, the 1- and 2-substituents can be readily varied simply by choosing the appropriate *N*-acyl-*N*-alkylglycine as the starting material. Although several synthetic methods for perfluoroalkyl substituted imidazoles have been described,[7] the method appears to be useful and convenient in terms of the ready accessibility of the starting materials, cheap reagents, operational simplicity, and high overall yields.

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; J. Elguero, A. Fruchier, N. Jagerovic, and A. Werner, *Org. Prep. Proced. Int.*, 1995, **27**, 33.
2. For reviews on fluorine-containing building blocks, see ; K. Uneyama, *J. Synth. Org. Chem. Jpn.*. 1991, **49**, 612; 1993, **51**, 232: for recent development in their preparation and application: M. Kawase and T. Kurihara, *Tetrahedron Lett.*, 1994, **35**, 8209; X. Xu, F. Jin, and W. Huang, *J. Org. Chem.*, 1994, **59**, 2638; M. Haddad, H. Molines, and C. Wakselman, *Synthesis*, 1994, 167; X. Shi, T. Ishihara, H. Yamanaka, and J. T. Gupton, *Tetrahedron Lett.*, 1995, **36**, 1527.
3. (a) M. Kawase, *Heterocycles*, 1993, **36**, 2441; (b) M. Kawase, H. Miyamae, M. Narita, and T. Kurihara, *Tetrahedron Lett.*, 1993, **34**, 859; (c) M. Kawase, *Tetrahedron Lett.*, 1994, **35**, 149; (d) M. Kawase, *J. Chem. Soc., Chem. Commun.*, 1994, 2101.
4. All new compounds exhibited ir, ^{1}H- and ^{13}C-nmr spectra, mass spectral or combustion data in agreement with the structures indicated. For **3a**: mp 196-198 °C; ^{1}H-nmr ($CDCl_3$) δ: 2.91 (s, 3H), 3.56 (d, J=11.7 Hz, 1H), 3.70 (d, J=11.7 Hz, 1H), 7.41-7.48 (m, 3H), 7.53-7.56 (m, 2H); ^{13}C-nmr ($CDCl_3$) δ: 34.60 (q), 59.73 (t), 94.01 (q, $^{2}J_{C\text{-}F}$=31.0 Hz), 124.24 (q, $J_{C\text{-}F}$=285.5 Hz), 128.44 (d), 128.52 (d), 128.59 (s), 130.81 (d), 169.71 (s). **4a**: mp 59-60 °C (lit.,[5] mp 61.5-62.5 °C).
5. J. J. Baldwin and F. C. Novello, US Pat., 4125530 (*Chem. Abstr.*, 1979, **90**, P121593n).
6. Y. Kamitori, M. Hojo, R. Masuda, M. Wada, and T. Tokahashi, *Heterocycles*, 1994, **37**, 153.
7. J. G. Lombardino, *J. Heterocyclic Chem.*, 1973, **10**, 697; J. J. Baldwin, P. A. Kasinger, F. C. Novello, and J. M. Spraque, *J. Med. Chem.*, 1975, **18**, 895; H. Kimoto, S. Fujii, L. A. Cohen, *J. Org. Chem.*, 1982, **47**, 2867; 1984, **49**, 1060; Q. Y. Chen and Z. M. Qui, *J. Chem. Soc., Chem. Commun.*, 1987, 1240; K. Burger, K. Geith, and D. Huble, *Synthesis*, 1988, 189; 194; 199; Y. Kamitori, M. Hojo, R. Masuda, S. Ohara, K. Kawasaki, Y. Kawamura, and M. Tanaka, *J. Heterocycl. Chem.*, 1990, **27**, 487; Y. Kamitori, M. Hojo, R. Masuda, Y. Kawamura, and X. Fang, *Heterocycles*, 1990, **31**, 2103; M. Medebielle, J. Pinson, and J. M. Saveant, *J. Am. Chem. Soc.*, 1991, **113**, 6872; D. J. Carini, A. T. Chiu, P. C. Wong, A. L. Johnson, R. R. Wexler, and P. B. M. W. M. Timmermans, *Bioorg. Med. Chem. Lett.*, 1993, **3**, 895.

Received, 23rd March, 1995