A Novel Ring Transformation of Mesoionic 1,3-Oxazolium-5-olates into 5-Trifluoroacetylated and 5-Perfluoroacylated Imidazoles by Reaction with Amidines

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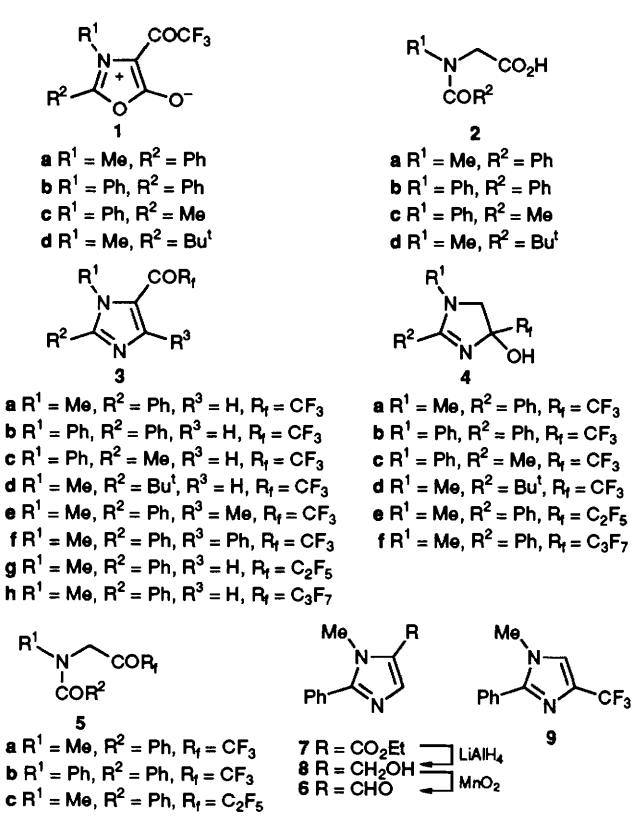
Treatment of mesoionic 1,3-oxazolium-5-olates with amidines causes a novel ring transformation affording 5-trifluoroacetyl- and 5-perfluoroacyl-imidazoles in moderate yields.

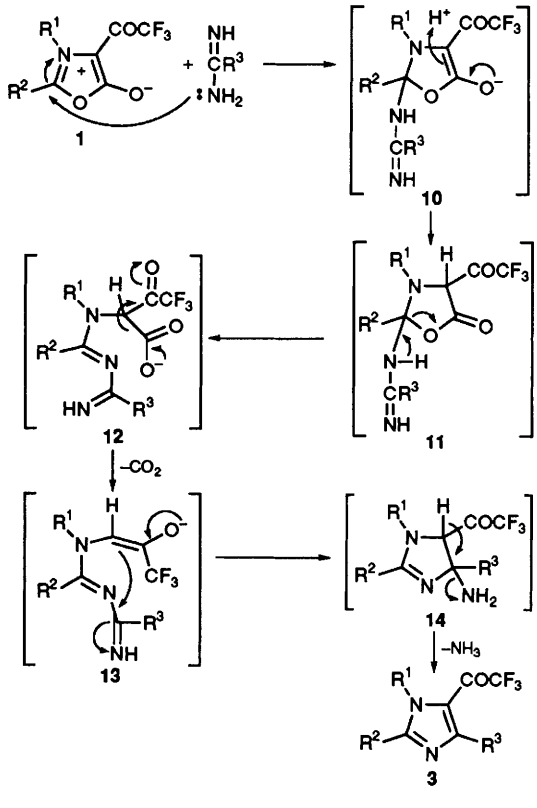
The development of new methodologies for the synthesis of various fluorine-containing compounds has received increasing interest owing to their potential biological activity.[1] For example, certain enzyme inhibitors bearing CF_3CO groups[2] and many heterocycles that incorporate perfluoroalkyl groups have been evaluated as pharmaceuticals, agricultural chemicals or high-performance materials.[3] In the course of our studies on the reactivities of mesoionic 1,3-oxazolium-5-olates,[4] we became interested in the synthesis of fluorine-containing heterocycles through the reactions of mesoionic 4-trifluoroacetyl-1,3-oxazolium-5-olates **1** with bis-nucleophiles such as amidines. It is known that compounds **1** which could easily be prepared from *N*-acyl-*N*-alkylglycines **2** with trifluoroacetic anhydride (TFAA), showed high reactivity towards nucleophilic reagents such as H_2O, EtOH and AcOH, bringing about ring-opening reactions.[5] These reactions occur *via* initial attack of a nucleophile on the C(5) position of the ring.

We report herein a novel type of ring transformation of mesoionic oxazoles **1** into imidazoles **3** *via* an initial attack of amidines on the C(2) position of the ring. This involves direct displacement of the O(1)–C(5) portion by a N–C fragment of the amidines, which corresponds with the 1,3-dipolar cycloaddition of mesoionic oxazoles with nitriles to afford imidazoles.[6] However, the cycloaddition has limited synthetic applicability, for only electron-deficient nitriles can react as dipolarophiles, and only one case using 2,4-diphenyl-1,3-oxazolium-5-olate as a dipole has been recorded.[6]

Treatment of **1a** (1 mmol) with formamidine hydrochloride (1.5 mmol) and K_2CO_3 (1.5 mmol) in dry DMF (5 ml) at 70 °C for 2 h gave rise to the imidazole **3a** (63%) and the dihydroimidazole **4a** (19%), respectively. A one-pot conversion of **2** to **3** also proceeded successfully. Thus, **2a** reacted with TFAA (3 mol. equiv.) in CH_2Cl_2 to give **1a** which was directly subjected to the ring transformation reaction to yield **3a** in 68% yield. Several mesoionic compounds **1** and *N*-acyl-*N*-alkylglycines **2** reacted in this way, and the results are presented in Table 1. The structure of **3a** was supported by spectral and microanalytical data.† The ultimate proof of the structure of compound **3a** rests upon its conversion into the known[7] 5-formyl-1-methyl-2-phenylimidazole **6** *via* ethyl 1-methyl-2-phenylimidazole-5-carboxylate **7**, in which the conversion of **3a** to **7** is effected by treatment with NaH followed by ethyl iodide.[8] On the other hand, the minor product **4a** could be dehydrated by $POCl_3$ and pyridine[9] to give the known[10] 1-methyl-2-phenyl-4-trifluoromethylimidazole **9** in 88% yield.

A plausible mechanism for this reaction is suggested in Scheme 1. Thus, initial nucleophilic attack of amidines on C(2) of **1** gives rise to an adduct **10** which is converted to **11**. Intermediate **11** gives an open-chain intermediate **12**, which is then decarboxylated to afford an enolate anion **13**. The intermediate **13** can undergo cyclization to give **14**, which loses ammonia leading to the imidazole **3**. A similar reactivity of amidines which extrudes ammonia has been postulated in





Scheme 1

Table 1 Reactions of mesoionic 1,3-oxazolium-5-olates **1** or *N*-acyl-*N*-alkylglycines **2** with amidines [HN=C(R^3)NH_2]

Entry	Starting material	R^3	Product (%)[a]
1	**1a**	H	**3a** (63), **4a** (19)
2	**1b**	H	**3b** (54), **5b** (11)
3	**1c**	H	**3c** (55), **4c** (14)
4	**1d**	H	**3d** (49), **4d** (15)
5	**1a**	Me	**3e** (46), **4a** (16)
6	**1a**	Ph	**3f** (55), **4a** (25), **5a** (4)
7[b]	**2a**	H	**3g** (60), **4e** (14), **5c** (11)
8[c]	**2a**	H	**3h** (56), **4f** (20)

[a] Isolated yields of pure products. All new compounds have satisfactory spectroscopic data (IR, MS, ^1H and ^{13}C NMR) and analytical (combustion and/or high resolution mass) data. [b] Pentafluoropropionic anhydride was used instead of TFAA in a one-pot conversion procedure. [c] Heptafluorobutyric anhydride was used instead of TFAA in a one-pot conversion procedure.

their reactions with benzoins[11] or cyanohydrins[12] to yield oxazoles. Compound **4** may be formed by the reaction of the ammonia produced and **5**, which could be produced by the hydrolysis of **1** during the reaction.

By this methodology, the 1- and 2-substituents can be readily varied simply by choosing the appropriate *N*-acyl-*N*-alkylglycines as the starting materials and the 4-substituents can also be changed by use of the appropriate substituted amidines. Therefore, the wide variety of substituents tolerated in this reaction as well as the synthetic potential of the perfluoroacyl moiety in the imidazole product adds to the utility of this procedure. In addition, the new synthesis of the imidazoles appears to be useful and convenient in terms of the ready accessibility of the starting materials and operational simplicity.[13] The application of this methodology to the synthesis of biologically active fluorine-containing imidazoles will be reported in the future.

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Footnote

† *Selected data* for **3a**: mp 107–108 °C (hexane); *m/z* 254 (M^+, 99%), 185 (100%); ν_{max}/cm^{-1} 1680; δ_H (500 MHz; $CDCl_3$; Me_4Si) 4.00 (s, 3H), 7.51–7.54 (br s, 3H), 7.61–7.66 (br s, 2H), 8.15 (s, 1H); δ_C (125 MHz; $CDCl_3$; Me_4Si) 35.23 (q), 116.59 (q, J_{CF} 290.7 Hz), 126.34 (s), 128.31 (s), 128.94 (d), 129.45 (d), 130.66 (d), 143.31 (dq, $^3J_{CF}$ 5.2 Hz), 156.16 (s), 170.79 (q, $^2J_{CF}$ 37.3 Hz).

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