FLUORIDE-CATALYZED ALDOL-TYPE REACTIONS OF α-ISOCYANO ESTERS PRODUCING 2-OXAZOLINE DERIVATIVES[1]

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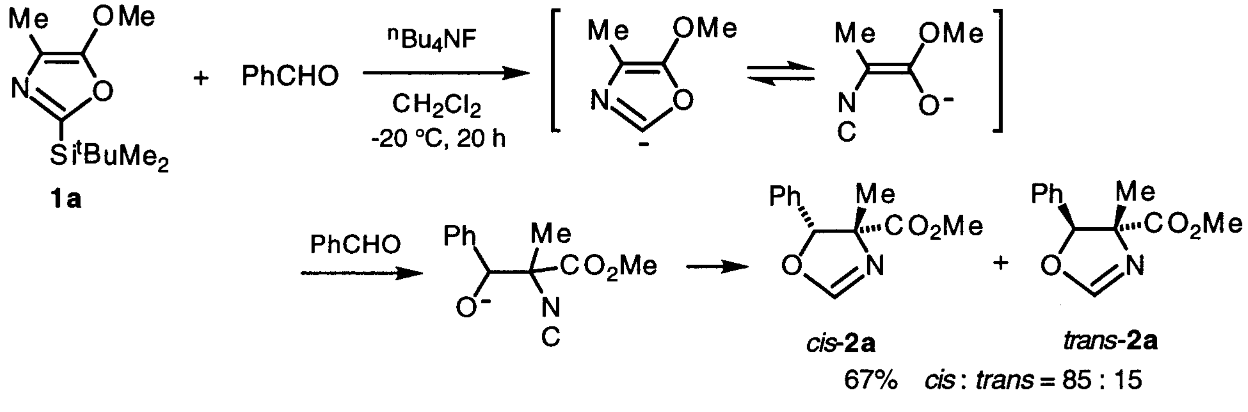
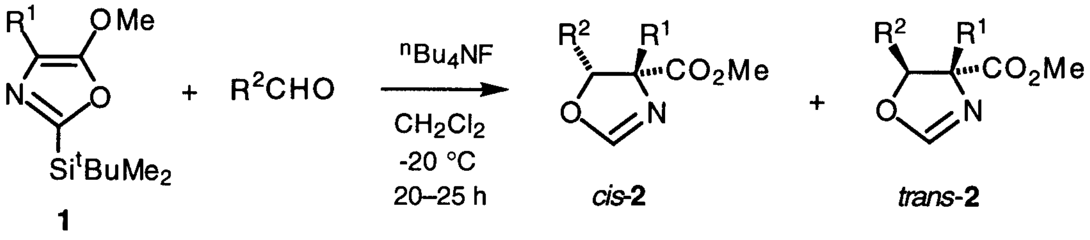
Abstract — An α-isocyano ester underwent the fluoride-catalyzed aldol-type reaction with an aldehyde to afford a 2-oxazoline derivative.

α-Isocyano esters are convenient precursors for the synthesis of a variety of amino acid derivatives.[2] The α-position can be easily rendered nucleophilic by means of a base or a transition metal, and subsequently forms a carbon–carbon bond with an electrophile. We have reported that lithiation of an α-isocyano ester with LDA followed by silylation with chlorosilane affords 5-alkoxy-2-silyloxazole.[3] The oxazole undergoes a zinc(II)-catalyzed aldol-type reaction with an aldehyde to furnish 4-alkoxycarbonyl-2-silyl-2-oxazoline,[3] which is a useful synthetic intermediate for the synthesis of a β-hydroxy-α-amino acids and their derivatives. We describe herein a new aldol-type reaction of α-isocyano esters catalyzed by a fluoride anion.[4]

Carbon–silicon bonds are susceptible to cleavage by a fluoride anion. It was expected that 5-methoxy-2-silyloxazole could also be activated by fluoride and the resulting carbanion used in an aldol-type reaction.[5,6] Thus, 5-methoxy-2-silyloxazole (**1a**), prepared by the reported procedure from methyl 2-isocyanopropanoate,[3] was treated with benzaldehyde in the presence of a stoichiometric amount of ^{n}Bu$_4$NF (1.5 equiv) in CH$_2$Cl$_2$ at -20 °C for 20 h. Quenching the reaction with Et$_3$N–MeOH and subsequent Kugelrohr distillation afforded 4-methoxycarbonyloxazoline (**2a**) in 67% yield (*cis*:*trans* = 85:15). It is likely that cleavage of the carbon–silicon bond by fluoride initially gives an oxazole carbanion, which is in equilibrium with a ring-opened enolate anion. Addition of the enolate anion to benzaldehyde is followed by cyclization forming the oxazoline skeleton.

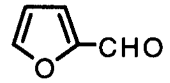
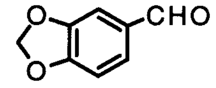


Other examples of the fluoride-induced aldol-type reactions of 5-methoxy-2-silyloxazoles are listed in Table 1. Aromatic aldehydes gave 4-methoxycarbonyloxazolines (**2**) in good yield with *cis*-isomers predominating (entries 1, 2, and 4). On the other hand, propanal gave no oxazoline derivative (**2**) (entry 3). The use of a stoichiometric amount of $^nBu_4NF$, being required for cleavage of the carbon–silicon bond of **1**, probably caused the self-aldol condensation of propanal preferentially.



1 *cis*-**2** *trans*-**2**

Table 1. Fluoride-induced Aldol-type Reactions of Oxazoles (**1**).

entry	R^1	R^2CHO	yield (%) of **2**	*cis* : *trans*
1	Me		80	75 : 25
2	Me		79	88 : 12
3	Me	Et-CHO	no reaction	—
4	^{i}Pr	Ph-CHO	77	*cis* only

In an alternative route to oxazoline derivatives (**2**), methyl 2-isocyanopropanoate (**3a**) was directly subjected to the fluoride-mediated aldol-type reaction with benzaldehyde. A stoichiometric amount of $^nBu_4NF$ caused an aldol-type reaction analogous to that of **1a** at room temperature, affording oxazoline (**2a**) (Table 2, entry 1). The diastereoselectivity was moderate, as is the case with **1a**. In this reaction, fluoride acted as a base to abstract an α-proton of **3a**, giving rise to an enolate anion. In contrast to the case of 5-methoxy-2-silyloxazole (**1a**), even a catalytic amount of $^nBu_4NF$ (5 mol%) efficiently promoted the reaction to afford **2a** in good yield (entry 2). Other examples of the direct aldol-type reaction of α-isocyano esters are shown in Table 2. Noteworthy was that acetaldehyde having α-hydrogen atoms also gave the corresponding oxazoline (**2**) in good yield by the use of a catalytic amount of $^nBu_4NF$ (entry 3). A *cis*-isomer was exclusively produced from methyl 2-isocyano-3-methylbutanoate (entries 4 and 5). In contrast, high *trans* selectivities were observed for disubstituted oxazoline (**2**, R^1 = H), probably due to steric considerations (entries 6 and 7).

In summary, it was demonstrated that aldol-type reactions of α-isocyano esters are efficiently catalyzed by fluoride.

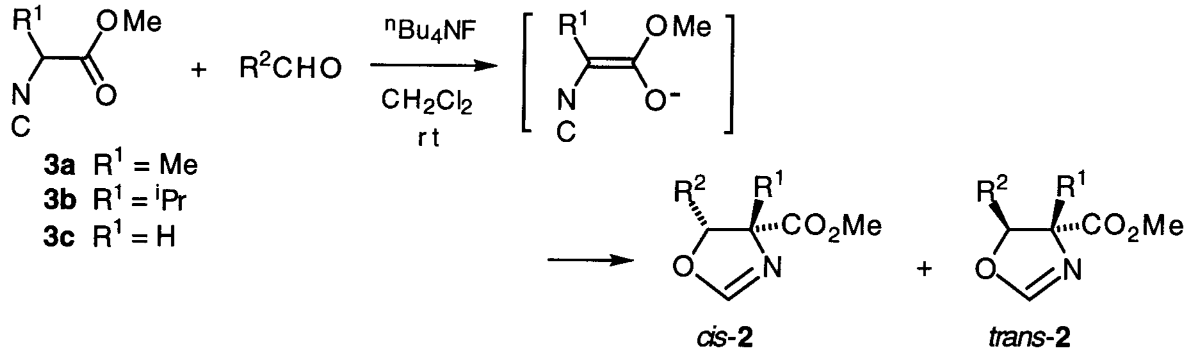


Table 2. Fluoride-mediated Aldol-type Reactions of α-Isocyano Esters (**3**).

entry	R^1	R^2CHO	amount of $^nBu_4NF$	time (h)	yield (%) of **2**	*cis* : *trans*
1	Me	Ph-CHO	1.5 equiv	1	82	87 : 13
2	Me	Ph-CHO	0.05 equiv	4	87	72 : 28
3	Me	Me-CHO	0.05 equiv	50	81	62 : 38
4	^iPr	Ph-CHO	1.5 equiv	1	93	*cis* only
5	^iPr	Ph-CHO	0.05 equiv	24	83	*cis* only
6	H	Ph-CHO	1.5 equiv	1	51	4 : >96
7	H	Ph-CHO	0.05 equiv	40	61	4 : 96

Procedure for the fluoride-catalyzed aldol-type reaction of methyl 2-isocyanoacetate with benzaldehyde: To a solution of methyl 2-isocyanoacetate (**3c**, 47.5 mg, 0.48 mmol) and benzaldehyde (64 mg, 0.60 mmol) in CH_2Cl_2 (1.5 mL) under a nitrogen atmosphere at rt was added $^nBu_4NF$ (1.0 M in THF, 23 μL, 23 μmol). The reaction mixture was stirred for 40 h. Methanol (3 μL, 0.07 mmol) and Et_3N (7 μL, 0.05 mmol) were added to the mixture, which was passed through a short Florisil column. Kugelrohr distillation of the filtrate (130 °C/2 mmHg) afforded 4-methoxycarbonyl-5-phenyl-2-oxazoline (60 mg, 61%, *trans* : *cis* = 96 : 4) as an oil.

REFERENCES AND NOTES

1. This paper is dedicated to Professor Teruaki Mukaiyama for leading us by example in his uncompromising approach to organic synthesis.
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