Tetrahedron Letters,Vol.23,No.45,pp 4729-4732,1982 0040-4039/82/454729-04$03.00/0
Printed in Great Britain

AN EFFICIENT SYNTHESIS OF 5-DIETHOXYMETHYLIMIDAZOLE-4-CARBOXYLATE, A POTENTIAL PRECURSOR FOR VARIOUS IMIDAZOLE DERIVATIVES

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Abstract: Anionic cycloaddition of methyl isocyanoacetate to diethoxyacetonitrile afforded efficiently methyl 5-diethoxymethylimidazole-4-carboxylate, a useful imidazole nucleus with two different functional groups.

There have been considerable advances recently in imidazole chemistry by the recognition of the importance of the imidazole nucleus in biological processes and the increasing applications of imidazoles as pharmaceuticals.[1] As a synthon of microbial origin,[2] 5-amino-1-β-D-ribofuranosylimidazole-4-carboxamide(AICAR) is of special interest due to its central role on the further elaboration of imidazole nucleosides.[3] However, there have been no synthetic report on the straightforward route to 5-substituted imidazole-4-carboxylates considered to be the potential precursors of bredinin,[4] dacarbazine,[5] or coformycin.[6] We wish to report here an efficient methodology for the synthesis of imidazole-4-carboxylates variously substituted at 5-position.

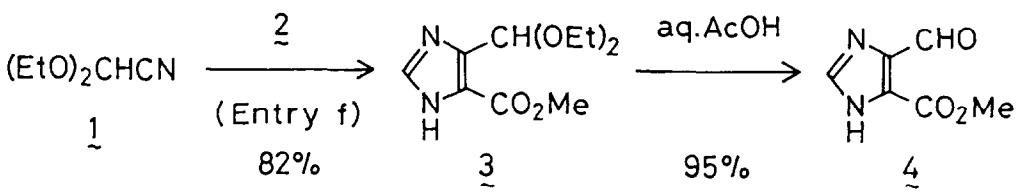
We have previously reported the synthesis of 2-formylpyrimidine derivative,[7] 3-formyltriazole nucleoside,[8] and 2-formyladenosine[9] using diethoxyacetonitrile (1) equivalent to the simplest cyanoaldehyde as a synthon. These studies revealed that the cyano carbon of diethoxyacetonitrile is electrophilic in nature and readily accepts nucleophiles,[10] and the acidic hydrogen at the α-carbon atom is not involved in any nucleophilic reaction even in the presence of basic reagents. On the other hand, isocyanoacetates(2) are known to give various heterocycles, e.g., oxazolines, pyrroles, and oxazoles through anionic cycloaddition with aldehydes, ketones, and acylating agents.[11] Therefore, we became interested in the reaction of isocyanoacetates with the nitrile function itself of 1. Thus, diethoxyacetonitrile 1 was subjected to anionic cycloaddition with methyl isocyanoacetate 2 (Scheme 1) and imidazole formation was found to be strongly dependent upon the bases and solvents employed as shown in Table 1.[12] Addition of Cu(I) catalyst showed no effect. When n-BuLi was employed as a base, no imidazole was formed, but only methyl 5-(isocyanomethyl)-

oxazole-4-carboxylate[13] was obtained in 50% yield. The best result was obtained by use of KH and diglyme, and it may be explained by the solvation of potassium cation and formation of reactive "naked anion" of 2.

A typical experimental procedure is as follows. To a stirred suspension of KH (1.38 mmol) in freshly distilled diglyme (2.0 ml), diethoxyacetonitrile[14] 1 (1.0 mmol) and methyl isocyanoacetate[15] 2 (1.0 mmol) in diglyme (1.5 ml) was added slowly with ice-cooling under argon atmosphere. The solution was heated at 70-80°C for 5h. After cooling, the reaction mixture was quenched with saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2 (10ml×3) and AcOEt (10ml×1). The combined organic layer was dried over Na_2SO_4, concentrated, and subjected to preparative TLC (developed with AcOEt) to give methyl 5-diethoxymethylimidazole-4-carboxylate 3 in 82% yield. Colorless needles, mp148-150°C (EtOH); elemental analysis, found C: 52.78, H: 7.13, N: 12.08%.[12]

The same procedure was extended to the other nitriles. (Scheme 2). The results are summarized in Table 1.[12] It has been shown that only nitriles desirably activated by inductive or/and resonance effects undergo a smooth formation of imidazoles. Trimethoxyacetonitrile (entry g) afforded the corresponding imidazole as well 1, but no imidazole was obtained from ethoxyacetonitrile. 2-Cyanopyridine and 4-cyanopyridine afforded the corresponding imidazole in excellent yields (entry i and k), but 3-cyanopyridine and benzonitrile gave in poor yields (entry h and j). 2-Cyanofuran gave in a fair yield (entry l). Aliphatic nitriles such as acetonitrile and isobutyronitrile gave no imidazole. Among 5-substituted imidazole-4-carboxylates described here, 5-diethoxymethylimidazole-4-carboxylate (3) is most important synthetically, since the two substituents are left in different oxidation states and may readily be modified separately. The aldehyde function of 3 is readily generated by treatment with aqueous acetic acid as shown in Scheme 1, and 3 and 4 are considered to be potential synthons for the synthesis of biologically active imidazole derivatives.[16]

Scheme 1



Scheme 2

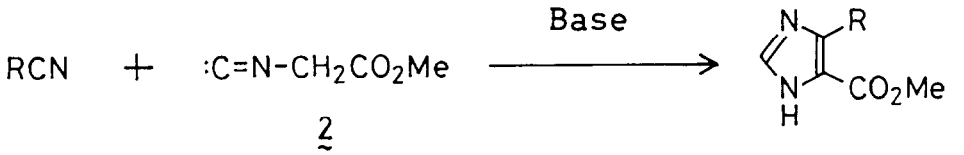


Table 1 Imidazole Formation from Nitriles and 2

Entry	R	Base	Solvent	Conditions	Yield(%)*	m.p.(°C)
a	$(EtO)_2CH$	BuLi	THF	-70°C ⟶ r.t.	0	
b	$(EtO)_2CH$	NaH	THF	80°C, 0.5h	44	148~150
c	$(EtO)_2CH$	NaH	DME	0°C ⟶ r.t., 24h	48	
d	$(EtO)_2CH$	NaH	diglyme	0°C ⟶ 70°C, 4h	72	
e	$(EtO)_2CH$	KH	THF	0°C ⟶ 70°C, 7h	35	
f	$(EtO)_2CH$	KH	diglyme	0°C ⟶ 70°C, 5h	82	
g	$(MeO)_3C$	KH	diglyme	0°C ⟶ 70°C, 5h	67	123~126
h	Ph	KH	diglyme	0°C ⟶ 70°C, 10h	13	207~209
i	2-pyridyl	KH	diglyme	0°C ⟶ 70°C, 12h	85	180~182
j	3-pyridyl	KH	diglyme	0°C ⟶ 70°C, 10h	24	190~192(dec.)
k	4-pyridyl	KH	diglyme	0°C ⟶ 70°C, 2h	81	214~218(dec.)
l	2-furyl	KH	diglyme	0°C ⟶ 50°C, 20h	40	222~224(dec.)

*Isolated yields after preparative TLC or column chromatography on silica gel. Yields were not optimized.

Spectral data of 3:
^{1}H-NMR ($CDCl_3$, δ): 1.21 (t, 7Hz, 6H) 3.69 (m, 4H) 3.92 (s, 3H) 6.15 (s, 1H) 7.75 (s, 1H). IR (KBr, cm^{-1}): 3420, 2500~3100, 1715, 1510, 1440, 1320, 1190, 1145, 1100, 1060, 1000.

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16. This work was supported in part by a Grant-in-Aid for Cancer Research of the Ministry of Education, Science and Culture of Japan.

(Received in Japan 3 August 1982)