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Regioselective Alkylation of the Exocyclic Nitrogen of Heterocyclic Amidines via the Mitsunobu Reaction

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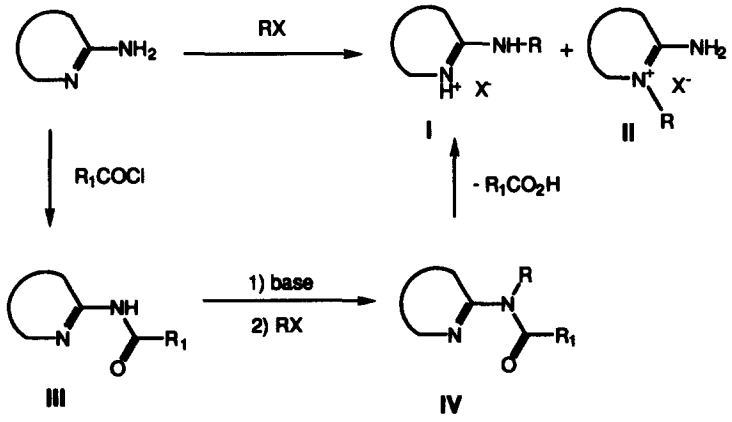
***Abstract*:**
Regioselective alkylation of heterocyclic amidines by means of Mitsunobu reaction leads to L-aminoacid derivatives.

Alkylation of heterocyclic amidines mainly occurs at the most basic endocyclic nitrogen.[1,2] However in several cases, alkylation of these 1,3-dinucleophiles affords a mixture of both the N-endosubstituted **II** and exosubstituted derivatives **I**. The composition of the mixture depends upon the basicity of the heterocycle, the solvent, and the steric hindrance at the NH_2 group, which is particularly revealed with sterically hindered electrophiles[3] (secundary or tertiary halides). In general, regioselectivity of the substitution reaction can be predicted by considering both HSAB theory and steric hindrance.[2,4,5] Thus, except with benzyl chloride[6], the heterocyclic amidines yield the solely N-endosubstituted isomer **I**, when reacted with primary halides.

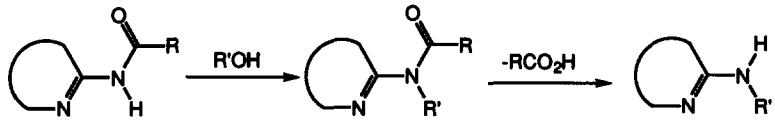
The exocyclic nitrogen of such systems may be rendered more basic by deprotonation.[7,8] However their metalation may not be quantitative, while N-acyl derivatives **III** are more easily deprotonated. N-formyl[9] and N-acetyl-2-aminopyridines[10] have been deprotonated with sodium amide and reacted with methyl iodide. After acid hydrolysis the N-methyl amino pyridine was obtained in good yield. However with other higher alkyl halides, the yields were significantly lower (below 50 %).



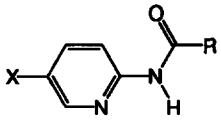
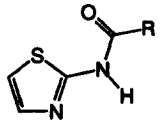
Scheme 1 : Access to regioselective alkylation on the exocyclic nitrogen of heterocyclic amidines.

Alcohols may constitute valuable electrophiles, when reacted with acids HB by means of diethyl azodicarboxylate (DEAD)-triphenyl phosphine system, as decribed by Mitsunobu.[11]

This reaction has been particularly applied to various NH amides, while few examples are dealing with substitution of the relatively less acidic NH amidine systems. However alkylation of the fairly basic 6-chloropurines[12], and imidazoles bearing an electron-widthdrawing group[13,11], has been carried out using the Mitsunobu reaction. This paper describes the regioselective N-exocyclic substitution of various primary heterocyclic N-acyl amidines with alcohols in similar conditions. N-Acyl pyridines and isosteric thiazoles have been chosen for our purposes. N-butanol and s-butanol have been used as representatives of primary and secundary alcohols respectively.



1 2 3

Entry	Heterocycle	X	R	R'	Method[1)]	Yield in 2	Yield in 3[2)]
1		H	CF_3	n-BuOH	a	0	-
2		H	Me	n-BuOH	a	0	-
3		H	OEt	n-BuOH	a	0	-
4		H	OCH_2CCl_3	n-BuOH	a	37	54
5		H	OEt	n-BuOH	b	8	65
6		H	OCH_2CCl_3	n-BuOH	b	55	54
7		H	OCH_2CCl_3	s-BuOH	b	40	52
8		NO_2	OEt	n-BuOH	a	45	82
9			CF_3	n-BuOH	a	0	-
10			Me	n-BuOH	a	35	75
11			OCH_2CCl_3	n-BuOH	a	70	85
12			OCH_2CCl_3	n-BuOH	b	77	85
13			O-t-Bu	n-BuOH	a	56	86
14			O-t-Bu	s-BuOH	a	37	80
15			O-t-Bu	t-BuOH	a	0	-
16			O-t-Bu	n-BuOH	b	66	86

1) Method a : PPh_3, DEAD, THF, RT, 24 h. Method b : TBP,ADDP, Benzene, RT, 24 h, 2) HCl, Δ, for all the compounds, except for trichloroethylcarbamates, entries 4, 6, 7, 11, 12, see ref. 18.

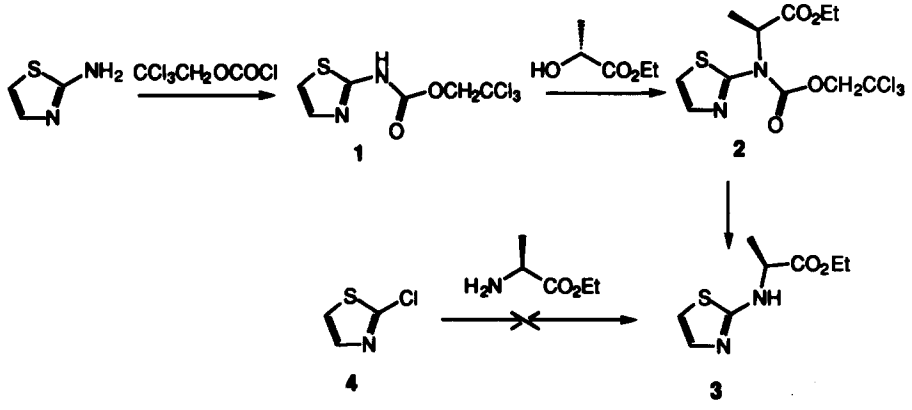
Table 1 : Alkylation of 2-aminopyridines and 2-aminothiazoles

Experimental data given in Table 1 clearly show the crucial role of the electron-widthdrawing group attached to the exocyclic nitrogen of selected heterocycles. N-acetyl derivatives did not react with n-butanol in

experimental conditions initially described by Mitsunobu[11] (PPh_3, DEAD, method a). Particularly N-trifluoroacetic derivatives failed to react in these conditions (entries **1** and **9**), even if the trifluoro acetyl group increased dramatically the acidity of the NH amidine (^{1}H-NMR signal at 10.5 ppm). Surprisingly the N-acetyl analogue was found relatively more active in the thiazole series (compare entries **9** and **10**). Moreover, in the same series, the replacement of the acetyl group by a carbamate was promising (compare entries **13** and **10**), particularly when the carbamate is bearing an electron-widthdrawing group (R = OCH_2CCl_3, compare entries **3** and **4** and **13** and **11** respectively).

A similar beneficial effect for reactivity was observed, when the acidity of the NH amidine was enhanced by the presence of an additional electron-widthdrawing group on the heterocycle (compare entries **3** and **8**). However, when n-butanol was replaced by more hindered alcohols (sec-butanol) yields were decreased (compare **13** and **14**). No reaction was observed with the highly hindered ter-butanol (entry **15**).

Recently a new redox system has been proved to be efficient in the Mitsonubu reaction. Triphenyl phosphine has been replaced by the more nucleophilic tributyl phosphine (TBP), and the use of 1,1'-(azodicarbonyl)dipiperidine (ADDP) in place of DEAD led to a more basic hydrazine derivative needed for deprotonation of NH acidic compounds.[14] Thus these new conditions were tested on our systems (TBP, ADDP, method b). A significant increase in yield was observed in all cases (compare entries **3** and **5**, **4** and **6**, **13** and **16**, respectively). Moreover a satisfactory yield was obtained with sec-butanol with method b (entry **7**).The trichloroethyloxycarbonyl group has been selected as the most suitable activating group of heterocyclic primary amidines in the Mitsunobu reaction. These stable carbamates undergo facile removal of the masking group by brief treatment with zinc dust in acetic acid.[15]



Scheme 2

This Mitsunobu reaction constitutes an efficient pathway to the preparation of analogues of chiral amino acids.[16,17] The method was successfully applied to the synthesis of the L-alanine derivative **3** starting from S-(-)-ethyl lactate.[18] It is noteworthy that other methods of preparation of the compound **3** failed, particularly the nucleophilic attack of the corresponding 2-chlorothiazole with L-alanine ethyl ester, which would need drastic unwanted experimental conditions.[19]

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18. The trichloroethyl carbamate of 2-aminothiazole 1 (0.48g, 1.76 mmol), obtained from the reaction of 2-aminothiazole with 2,2,2-trichloroethyl formate(yield 70 %, mp 133-134 °C, ^{1}H-NMR($CDCl_3$) : δ 13.55(s, D_2O exchange, 1H), 7.62(d, J = 3.6 Hz, 1H), 6.99(d, J = 3.6 Hz, 1H), 4.94(s, 2H), was reacted in benzene with S-(-)-ethyl lactate (0.21g, 1.76 mmol) and an excess of ADDP (0.67g, 2.64 mmol) and TBP (0.53g, 2.64 mmol) at 0 °C and under argon. After 10 minutes, the reaction medium was left at room temperature for 24 h. Hexane was added to the reaction mixture and dihydro ADDP was filtered off. Purification by silica gel column chromatography (AcOEt- Hex 1-2) afforded **2** as white crystals (yield 62 %, m.p. 85-86 °C). ^{1}H-NMR($CDCl_3$) : δ 7.10(d, J = 4.9 Hz, 1H), 6.69(d, J = 4.9 Hz, 1H), 5.83(q, J = 7.4 Hz, 1H), 4.88(s, 2H), 4.23(q, J = 7.1 Hz, 2H), 1.69(d, J = 7.4 Hz, 3H), 1.28(t, J = 7.1 Hz, 3H). The compound **2** was stirred overnight with 3 equivalents of zinc dust in glacial acetic acid at room temperature.[15] Another amount (2 equivalents), was added and the mixture was heated 2 h at 50 °C. After filtration and removal of the solvent the crude materiel was flash chromatographied on silica gel (AcOEt-TEA 97-3) to give **3** as a yellow oil (yield 50 %). $[\alpha]_D^{20}$ + 66 (C 1.4, $CHCl_3$), ^{1}H-NMR($CDCl_3$) : δ 6.56(d, J = 5.1 Hz, 1H), 5.80(d, J = 5.1 Hz, 1H), 5.36(q, J= 7.5 Hz, 1H), 4.20(q, J= 7.1 Hz, 2H), 1.58(d, J= 7.5 Hz, 3H), 1.25(t, J= 7.1 Hz, 3H).
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