Tetrahedron Letters,Vol.26,No.29,pp 3423-3426,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

A GENERAL SYNTHESIS OF 4(5)-ACYLIMIDAZOLES FROM 4-ACYLAMINOISOXAZOLES.[1]

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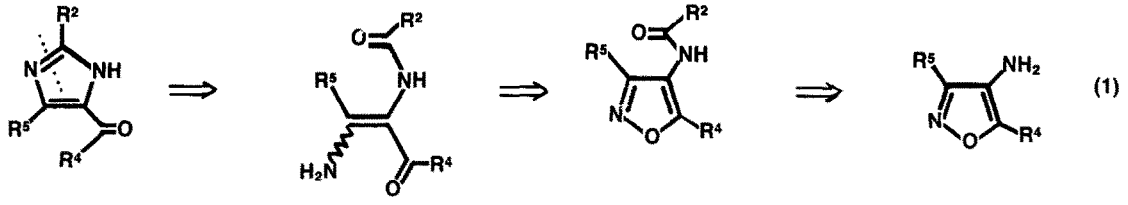
2-Substituted-4(5)-acyl, 1,2-disubstituted 4-acyl and 1,2-disubstituted-5-acylimidazoles can be specifically prepared from 4-aminoisoxazoles.

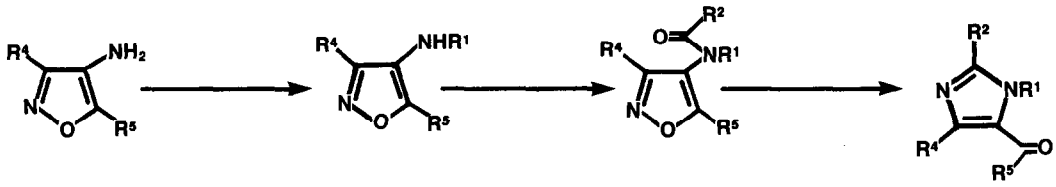
Attempted electrophilic acylation of imidazoles does not lead to 4(5)-acylimidazoles and as a result these compounds are relatively unavailable.[2] Specific methods for the preparation of 4(5)-imidazolecarboxaldehydes by oxidation of the corresponding hydroxymethyl compounds[3] and of 4(5)-acetylimidazoles by photochemical rearrangement[4] or ring synthesis[5] have been described but these are all limited in their scope. Our continuing interest in this class of compounds led us to consider retrosynthetic paths other than those already explored and one of the more attractive of these is outlined in Equation 1. We now report the application of this sequence to the synthesis of a variety of 2-substituted-4(5)-acetylimidazoles[6] and, with some slight modification, to the unambiguous synthesis of 1,2-disubstituted-4- and 5-acylimidazoles. This route is the most general synthesis of 4(5)-acylimidazoles to date.



(1)

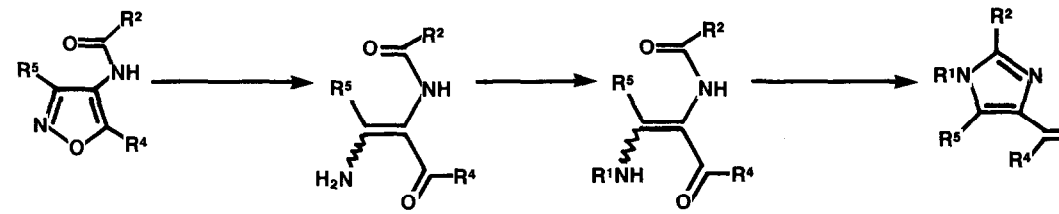
The key intermediates in this sequence are aminoisoxazoles which are prepared by reduction of the corresponding nitroisoxazoles[7] and these in turn are prepared by nitration of the isoxazoles[7a,b,8] or by various ring forming reactions.[7d,e,9] In our case, because of our interest in acetylimidazoles, we have utilized 4-amino-5-methylisoxazole (1)[8b] in our studies. This amine is readily acylated with activated acids, generally in high yield as is shown in Table 1. Subsequent catalytic reduction gives the acylaminoenaminone intermediate which is cyclized by treatment with sodium hydroxide in an alcohol. The intermediate can be isolated and purified if desired. The crude 4(5)-acetylimidazoles that are obtained are usually quite pure and can be easily further purified by flash chromatography giving good to excellent yields of the products. The 2-substituent in these imidazoles is derived from the acylating agent and our work provides examples in which this substituent is a proton, an alkyl group, a substituted alkyl group or an aryl group. Of particular note are entries 3d and 3h which contain bulky and electron withdrawing substituents, respectively. These imidazoles are unavailable by other existing methods.

The synthesis of 1,2,5-trisubstituted imidazoles is usually not a straightforward procedure. Alkylation of 2,4(5)-disubstituted imidazoles leads predominantly to the 1,2,4-trisubstituted derivatives.[10] Olofson's method of obtaining the 1,2,5-trisubstituted derivatives is limited by the availability of alkylating agents potent enough to react with an intermediate N-acylated imidazole.[11] The present method of imidazole synthesis, however, can be readily adapted to the synthesis of 1,2,5-trisubstituted compounds by alkylating the 4-aminoisoxazole prior to acylation as is shown in Equation 2. Through such substitution, a wide variety of 1,2-disubstituted-5-acylimidazoles is potentially available. The synthesis of compounds 4a and 4b in 49% and 50% yields respectively from 1 exemplifies the method.[12]



(2)

The synthesis of 1,2,4-trisubstituted imidazoles, as noted above, is generally readily achieved by alkylation of the 2,4(5)-disubstituted compound.[10] Selective formation of the 1,2,4-isomer is presumably due to the steric effect of the 4(5)-substituent. However, in cases where the 4(5)-substituent is small or where both 4 and 5 positions are substituted by groups of similar size, alkylation may again lead to mixtures of isomers. The present method provides a solution to this problem as well. If after hydrogenation, the acylaminoenaminone is treated with a primary amine rather than sodium hydroxide, exchange of the amine for ammonia occurs rather than cyclization. Subsequent treatment with sodium hydroxide then gives the 1,2-disubstituted-4-acylimidazole, Equation 3. This was exemplified by the synthesis in good yield of the N-methyl and N-benzylimidazoles, 5a and 5b.[13]

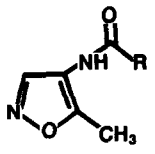


(3)

In conclusion, we have demonstrated that the "rearrangement" of 4-acylaminoisoxazoles to 4(5)-acylimidazoles can be exploited for the synthesis of a wide variety of 2,4-disubstituted, and 1,2,5- and 1,2,4-trisubstituted imidazoles. The potential of this method to produce acylimidazoles with a broad range of substituents coupled with the utility of the acyl group as a "handle" for further synthetic elaboration makes this route one of most general imidazole syntheses available.

General procedure for conversion of 4-acylamino-5-methylisoxazoles to 4-acetyl-2-substituted imidazoles: The isoxazole is hydrogenated at 40 p.s.i. at room temperature over 10% palladium on carbon (25% to 50% by weight) in ethanol. After 1 hour the reaction is usually complete as determined by TLC (10% methanol in chloroform) and the catalyst is filtered and washed with ethanol. The filtrate containing the acylaminoenaminone is treated with sodium hydroxide (pellets, 1.1 equivalents) at reflux for 1 hour. Solid ammonium chloride (1.2 equivalents) is then added and after 30 min the reaction allowed to cool to room temperature and the ethanol removed *in vacuo*. The residue is slurried in acetone and the salts filtered. Concentration of the filtrate gives the crude product generally as a solid which can be flash chromatographed to give pure imidazole.

TABLE 1



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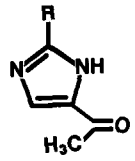
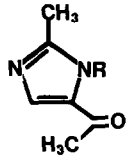


3

	R	Yield[a] (mp)	Yield (mp)
a	H	98% (77-78°)	98% (169-170°)
b	CH_3	98% (94-96°)	78% (128-130°)
c	CH_2CH_3	98% (58-60°)	93% (117-119°)
d	$C(CH_3)_3$	94% (113-115°)	98% (198-199°)
e	Ph	71% (148-149°)	80% (155-156°)
f	CH_2OCH_3	89% (53-55°)	70% (90-92°)
g	$CH_2N(CH_3)_2$	36% (oil)	52% (219-225° HCl salt)
h	CF_3	97% (59-61°)	97% (187-188°)

[a] Amides prepared from the HCl salt of 1 with: entry a) formic acid in ethyl formate, entries b and c) RCO_2O and RCO_2Na in RCO_2H, entries d and e) RCOCl and pyridine in $CHCl_3$, entry f) RCO-imidazolide in THF, entry g) RCO_2CO_2Et and pyridine in $CHCl_3$, entry h) neat TFAA.



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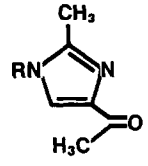

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a: R = CH_3
b: = CH_2Ph

References and Notes

1. All compounds displayed satisfactory ^{1}H-NMR and mass spectra. All new compounds had combustion analyses (CHN) within ±0.4% of the theoretical except the oils 3g and 5b which displayed exact masses consistent with the desired structures (3g: obs. 183.0998, calcd for $C_8H_{13}N_3O_2$ 183.1007; 5b: obs. 214.1098, calcd $C_{13}H_{14}N_2O$ 214.1105).

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12. The formamide 2a was reduced with borane-dimethyl sulfide complex in THF [90%, mp 125-127° (HCl salt)] and the resulting methylamine acetylated (100%, mp 45-47°). Reduction and cyclization gave 4a (mp 79-82°). This material was identical to a sample of 4a prepared from 3b by Olofson's method. Reductive alkylation of 1 with benzaldehyde and sodium cyanoborohydride (83%, mp dec 145-70° (HCl salt), followed by acetylation (98%, mp 84-86°), reduction and cyclization gave 4b (mp 43-45°).

13. Acetamide 2b was hydrogenated, the catalytst filtered and the resulting enaminone (100%, mp 184-185°) treated with a 10-fold excess of methylamine at room temperature. The resulting adduct was not isolated but cyclized to 5a by treatment with sodium hydroxide (72%, mp 89-91°). Alternatively, treatment of the enaminone with a 10% excess of benzylamine at reflux in ethanol gives a stable and isolable benzylamino adduct (80%, mp 160-162°) which was cyclized to 5b by treatment with sodium hydroxide (75%, oil). Alkylation of 3b with sodium hydride and methyl iodide or benzyl chloride in THF gave, as expected, the 1,2,4-trisubstituted compounds 5a (90%) and 5b (71%). The regioisomers 4 and 5 were readily distinguished from each other by ^{1}H-NMR.

(Received in USA 17 April 1985)