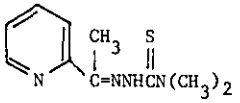
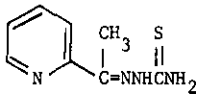
thiosemicarbazones were reported by us to have antimalarial, antibacterial, and antiviral activities. The two of the most commonly used methods for the preparation of the title compounds are via (a) direct displacement of S-methyl group of methyl 3-[1-(2-pyridyl)ethylidene]-hydrazinecarbodithioate by primary or secondary amines and (b) condensation of an isothiocyanate with the hydrazone of 2-acetylpyridine. Recently, we have found that direct amination of 4,4-dimethyl-3-thiosemicarbazone of 2-acetylpyridine (1) is a new and facile route for the preparation of mono- and disubstituted analogs. The reaction was carried out by refluxing the starting material 1 with a primary or secondary amine in acetonitrile for 6-8 hrs with resultant elimination of dimethylamine. In all cases, this method gave a product with higher yield and purity than method (a). Overall, the scope and the limitations of this reaction parallel these of method (a). Two factors, the basicity and steric hindrance of the amines, appear to influence the rate of the reactions. Thus, aliphatic amines react faster than aromatic amines and hindered amines react slower than the less hindered amines. Under identical conditions, unsubstituted (2) or mono substituted thiosemicarbazones (3) of 2-acetylpyridine do not undergo the transamination reaction even after 24 hrs.



1



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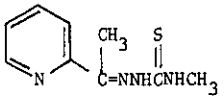

3

PYRIMIDINES FROM FURFURAL. A CONVENIENT SYNTHESIS AND SOME REACTIONS OF 5-BROMO- AND 5-CHLOROPYRIMIDINE

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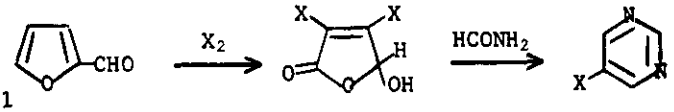
Our interest in developing a convenient synthesis of halopyrimidines[1] from readily available and inexpensive starting materials has continued primarily because 5-bromopyrimidine (3a) has proven to be a key intermediate in the elaboration of either the 5-position by lithium-halogen exchange,[2] and more recently the 4-position by reaction with lithium diisopropylamide.[3] In this report we describe a convenient two step preparation (eq.1) of both 5-bromo-(3a), and 5-chloropyrimidine (3b) from furfural (1).[4] The intermediate mucohalic acids (2a,b) were



eq.1

1 → 2a, X=Br; 2b, X=Cl → 3a, X=Br; 3b, X=Cl

readily prepared by treatment of furfural (1) with either bromine or chlorine.[5,6] Prior to this report, 5-chloropyrimidine was available only by multistep sequences in low overall yield.[7]

The mechanism of this reaction and some chemistry will be described.

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NEW APPLICATIONS OF MONONUCLEAR HETEROCYCLIC REARRANGEMENTS (MHR's) IN ORGANIC SYNTHESIS

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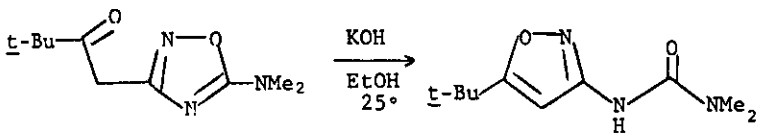
Mononuclear heterocyclic rearrangements[1] represent a class of azole/azole interconversions first systematized by Boulton and Katritzky[2]. Interest in the synthesis of LY 108887 prompted our consideration of a scarcely documented version of this rearrangement. Thus, reaction of methyl pivalate with 3-methyl-5-dimethylamino-1,2,4-oxadiazole in the presence of lithium diisopropylamide (LDA) at low temperature, followed by quench with aqueous acid at 0° gave LY 156544 in high yield. Treatment of this compound with ethanolic potassium hydroxide gave LY 108887 in quantitative yield.



LY 156544 LY 108887

Further examples of this condensation/rearrangement sequence and extensions to other heterocyclic ring systems are discussed.

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6-SUBSTITUTED NICOTINIC ACIDS FROM 2-METHYL-5-ETHYLPYRIDINE

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Work was done by Dr. Daniel Quarroz, Lonza AG, 3930 Visp, Switzerland

In our continuing exploration or the chemistry of isocinchomeronic