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Synthesis of 5-Ketothiazoles

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Abstract
Many indole derivatives are bioactive and several are useful clinically prescribed drugs, thus indole nucleus has long been recognised as a good pharmacophore. The bioactive amine tryptamine and the amino acid tryptophan contain indole nucleus. Not only natural but synthetic indole derivatives also show excellent biological activities.As part of our interest in marine alkaloids and also on aminothiazoles, we observed that the reported synthesis of dendrodoine will be useful only to prepare 3-N,N-dialkylamino derivatives alone, since mono or unsubstituted ureas would react with Cl-CO-S-Cl differently, unlike disubstituted ureas. There exists no direct cyclisation route to such acylthiadiazolylamines. Hence the preparation of dendrodoine analogs having variety of substitients is deemed to be not easy. However the substitution of a 2-aminothiazole unit in place of the amino-1,2,4-thiadiazole unit in dendrodoine appeared attractive.

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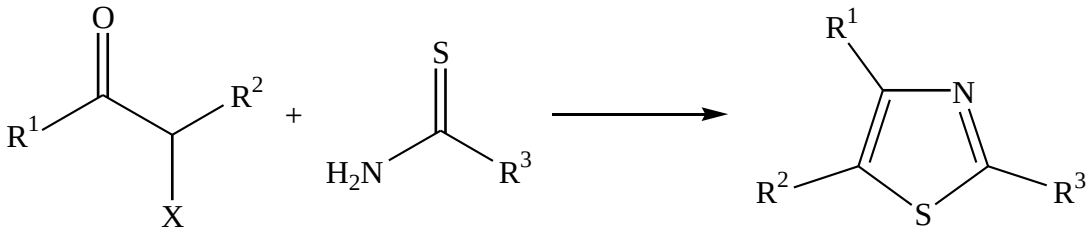
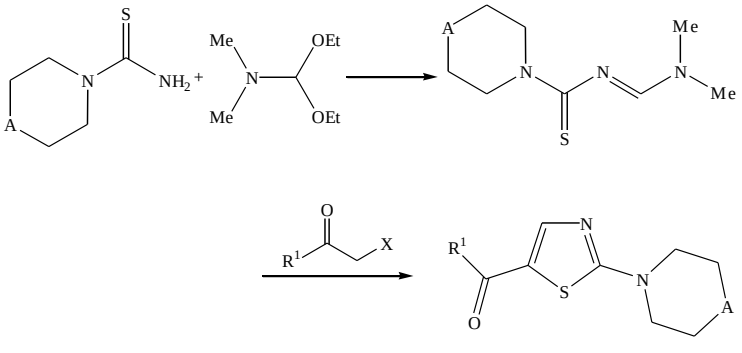
I. Introduction

Hantzsch and his coworkers deserve the credit for developing the first practical route for the formation of thiazole ring . This classical route, now known as the 'Hantzsch thiazole sunthesis' and still being actively exploited even after a century thus attesting to its generality and efficacy, involves the cyclo condensation of thioamide withα-halocarbonyl reagent . The precursor for N-C-S unit of thiazole ring is thioamide and precursor for the other two carbon atoms of the thiazole ring is the α-halocarbonyl reagent.



A wide structural variety of thioureas have been employed as the N-C-S synthon in Hantszch synthesis. Thus Meslin and Quinou prepared 5-ketothiazole by treating the thiourea derivative obtained as a condensation product of arylthioamide and dimethylformamide diethyl acetal with α-haloketone. The product 5-ketothiazole was formed through an intermediate , which eliminates one molecule of dimethylamine to produce the thiazole . Rajappa's group proved that another type of thiourea derivative, obtainable as the condensation product from 1,1-disubstituted thiourea with amide acetal **,** on treatment with aloketones and esters produces 5-ketothiazole.



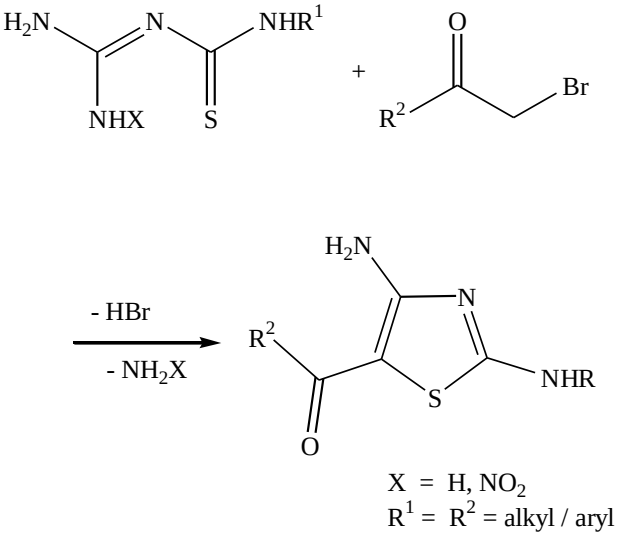
$R^1 = C_6H_5$, Me, OEt
A = O, NMe

Rajappa and coworkershave further reported that 5-chloroacetylthiazoles and were obtained by the reaction of 1,3-dichlorocecetone with thiourea derivative and respectively.

Meakins in 1983 utilized the reaction of α-bromo-β-ketoesterwith N, N-disubstituted thioureas to get a series of new 2-(N,N-dialkylamino)thiazol-5-carboxylates . By using simple thiourea, a thiazole with an unsubstituted 2-amino group can be obtained.

a. Synthetic strategy and planning

Based on our interest in the synthesis of aminothiazoles,we conceived the following retrosynthetic startegy for the access of diaminothiazoloylkindoles as novel analogs of dendrodoine. In the above scheme, the leaving group LG could be either -NH_2 or as we had found more recently,it could be a O_2NNH- group as well . We decided to examine both groups as leaving group LG in the above scheme.

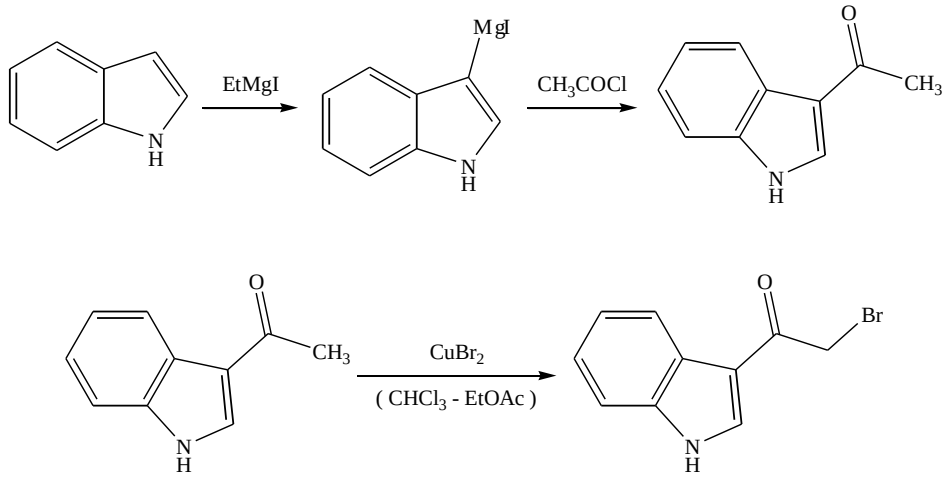


The required thiourea derivativte would be **,** which would provide the C-N-C-S atoms that go to the making of the thiazole ring. Thus out of the four N atoms in the amidino thiourea derivative**,** where X = H or NO_2, three are incorporated into the product. The remaining C_5 atom would come from an α-haloketone **22** where R^2 would be indolyl. This strategy is depicted below with the appropriate synthons chosen

Synthesis of Precursors

i. 3-(2-Bromoacetyl)indole

In 1961, Bodendorf and Walk prepared 3-(2-bromoacetyl)indole by the direct bromination of 3-acetylindole using bromine in methanol. This procedure gave only 13% yield. King and Ostrum[121] in 1964 reported an alternative method to 3-(2-bromoacetyl)indole. The bromination of 3-acetylindole by copper(II) bromide,. The required 3-acetylindole was prepared from indole by the reaction of indolyl magnesium iodide and acetyl chloride. The Grignard reagent is prepared by the reaction between indole, magnesium and ethyl iodide in dry ether. The 3-acetylindole was then treated with copper(II) bromide in chloroform-ethyl acetate (1:1) at reflux for 3 h. This method afforded 3-(2-bromoacetyl)indole in 37% yield. The overall yield of 3-(2-bromoacetyl)indole was 22% based on indole.



u et al. also used copper(II) bromide in choloform-ethyl acetate(1:1) mixture for the bromination of 3-acetylindole to get 3-(2-bromoacetyl)indole. They also found that 3-(2-bromoacetyl)indole was formed in 37% yield. The required 3-acetylindole was prepared from indole. The NH group of indole was protected with p-toluenesulphonyl chloride using a phase transfer catalyst. Friedel-Crafts acylation of N-toluenesulphonylindole with acetic anhydride and aluminium chloride in dichloromethane followed by deprotection of p-toluenesulphonyl group gave 3-acetylindole in 91% yield.

We decided to carryout a comparitive study on the above three methods as reported by King et al., Bergman et al. and Moody et al. During the early part of our work we have followed King's method to prepare 3-(2-bromoacetyl)indole. This method consisted of two steps: the conversion of indole to 3-acetylindole and and that of 3-acetylindole to 3-(2-bromoacetyl)indole. The preparation of 3-acetylindole required indole, ethyl magnesium iodide and acetyl chloride. Conversion of 3-acetylindole to 3-(2-bromoacetyl)indole needed copper(II) bromide. We found by TLC analysis that the crude product consisted of two compounds. From the crude products, 3-(2-bromoacetyl)indole could be separated by column chromatography in a final isolated yield of 37%. This method was considered to be expensive due to the use of chemicals such as ethyl iodide. In addition, this method involved a column chromatographic separation.

It was also attempted to brominate 3-acetylindole by using radical bromination. In this process 3-acetylindole was dissolved in glacial acetic acid and after the addition of azobisisobutyronitrile (AIBN) to initiate the bromination, the reaction mixture was treated with a calculated quantity of bromine in glacial acetic acid. TLC analysis showed that the product consisted of more than three compounds indicationg that the reaction was complex.

Thus, based on the above experiments and because of the operational simplicity and the better quality product obtained, we have now found that the method reported by Moody et al. is the better one for obtaining 3-(2-bromoacetyl)indole.

ii. Amidinothioureas

The discussion in the earlier section indicates that 3-(4-amino-2-arylaminothiazol-5-oyl)indoles could be synthesised either from 1-amidino-3-arylthioureas (**21;** X = H) or from 1-aryl-3-nitroamidinothioureas (**21;** X = NO_2) as the C-N-C-S synthon. We decided to find which synthon between these two classes would be a better precursor for the synthesis of 3-[(4-amino-2-arylamino)thiazol-5-oyl]indoles.

Synthesis of 3-(4-amino-2-arylaminothiazol-5-oyl)indoles
From 1-aryl-3-nitroamidinothioureas

To a solution of 1-aryl-3-(N-nitroamidino)thiourea in N,N-dimethylformamide (DMF), 3-(2-bromoacetyl)indole in was added followed by triethylamine as a base. The thin layer chromatogram of the crude product showed a fluorescent yellow spot as the only significant product. As a representative example, the reaction of 3-(2-bromoacetyl)indole with 1-(N-nitroamidino)-3-phenylthiourea is described below in detail. The reaction afforded an yellow crystalline substance. Based on elemental analysis, the molecular composition of the compound was found to be $C_{18}H_{14}N_4OS$. The IR (KBr) spectrum of the compound shows a ν_{N-H} band at 3447cm^{-1} due to NH group of indole ring.The peaks at 3233cm^{-1} and 3167cm^{-1} have been assigned to ν_{N-H} vibration. The aromatic C-H bands of phenyl group and indole ring give rise to ν_{N-H} band at 3063cm^{-1} and 2955cm^{-1}respectively. The stretching band of the highly conjugated carbonyl group occurs at 1604cm^{-1}. The $\nu_{C=C}$ band of aromatic rings appears at 1580cm^{-1} and 1546cm^{-1}. The peaks at 1517cm^{-1} and 1317cm^{-1} are

attributed to the endocyclic $\nu_{C=N}$ and ν_{C-N} bands. The phenyl substituent gives rise to peaks at 1418cm^{-1}, 1081cm^{-1}, 858cm^{-1}, 757cm^{-1}and 693cm^{-1}.

The ^{1}H NMR spectrum (400 MHz) shows three triplets at δ 7.08, 7.13 and 7.2, which can be assigned to H-6 and H-5 of the indole ring and one aryl hydrogen para to the NH of NHPh group respectively. Another two-hydrogen triplet at δ 7.38 has been attributed to two aryl hydrogens meta to NH of the NHPh. The next signal at δ 7.47 is a one- hydrogen doublet due to H-7 of the indole ring. A two-hydrogen doublet at δ 7.66 is assigned to the two aryl hydrogens ortho to the NH of the NHPh group. The H-2 of the indole ring appears as one-hydrogen doublet at δ 7.9. The broad peak at δ 7.98 arises from the amino group. A downfield one-hydrogen doublet at δ 8.19 is assignable to the H-4 of the indole ring. The two singlets, one at δ 10.72 and another at δ 11.67 are ascribed to the NH hydrogens of the NHPh group and the indole ring respectively. The FAB MS shows a strong $[M+H]^{+}$ peak at m/z 335, which confirms the molecular mass of the compound to be 334 in accordance with the elemental analysis data.The^{13}C NMR spectrum shows sixteen peaks, two of which appear to arise from two carbons each, thus accounting for all the eighteen carbon.

Based on these data the compound is formulated as 3-[(4-amino-2-phenylaminothiazol)-5-oyl]indole.

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