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Synthesis and Bioactivity OF 2-Amino-5-(3-Arylsydnon-4-OYL) Thiazoles

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1. Introduction

Marine natural products have garnered significant interest from biologists and chemists globally over the past five decades due to their potential for new drug discovery. This interdisciplinary fascination has led to the identification of approximately 8,500 marine natural products, many exhibiting promising biological activities. Among these, nitrogen-containing heterocyclic compounds, such as sydnone and thiazole derivatives, have shown extensive physiological activities, including antimicrobial, anti-inflammatory, and analgesic properties. This study aims to synthesize a series of novel thiazole derivatives incorporating the sydnonyl moiety to explore their biological activities. An efficient method for synthesizing these new sydnone-substituted thiazoles has been developed. The synthesized compounds were characterized using various spectral analyses and their antioxidant properties were evaluated, leading to the identification of several promising antioxidant compounds.

2. Objectives

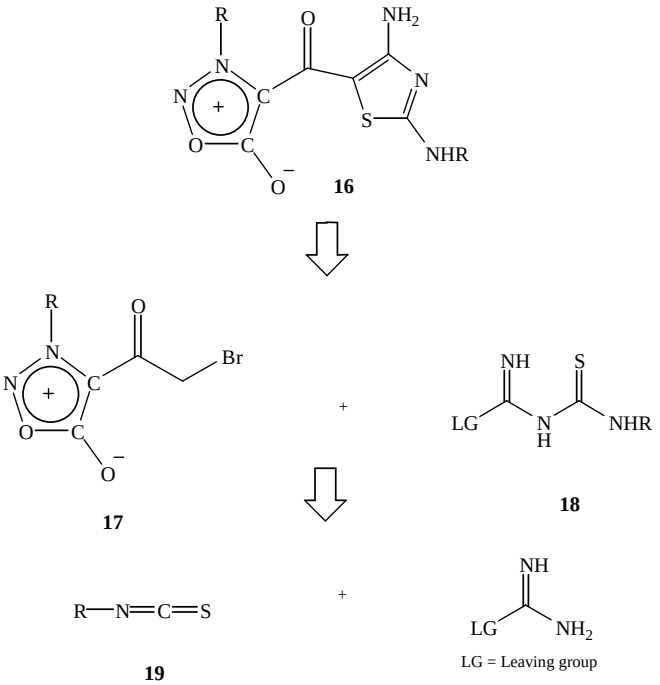
1) To Synthesis 4-amino-2-arylamino-5-(3-arylsydnon-4-oyl)thiazoles.
2) To characterize these newly synthesized thiazoles by various spectral analysis.
3) To study their anti-oxidant character

3. Results and Discussion

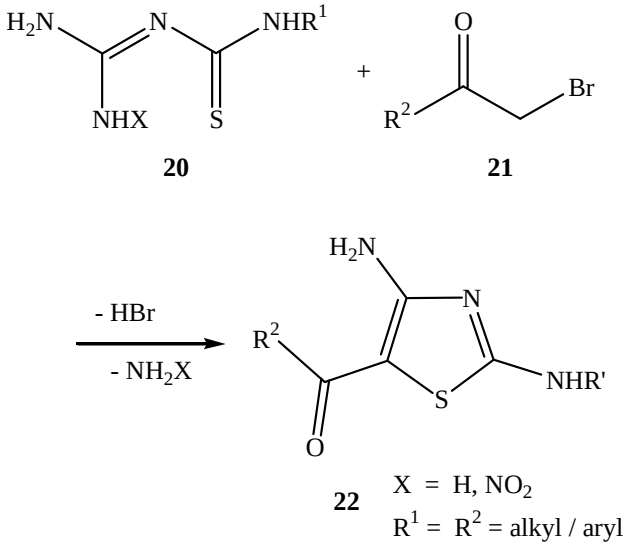
Synthesis of 4-amino-2-arylamino-5-(3-arylsydnon-4-oyl)thiazoles 16

1) Synthetic strategy and planning

Based on the long-standing interest in the synthesis of 2-aminothiazoles, I have conceived the following retro synthetic strategy for the access of diaminothiazoloylsydnones .



In the above scheme, the leaving group LG could be either -NH_2 or as we had found some time ago, it could be a O_2NNH- group as well. We decided to examine both groups as leaving group LG in the above scheme.



Accordingly, the required thiourea derivative would be **20,** which would provide the [C^4-N^3-C^2-S^1] atoms that go into

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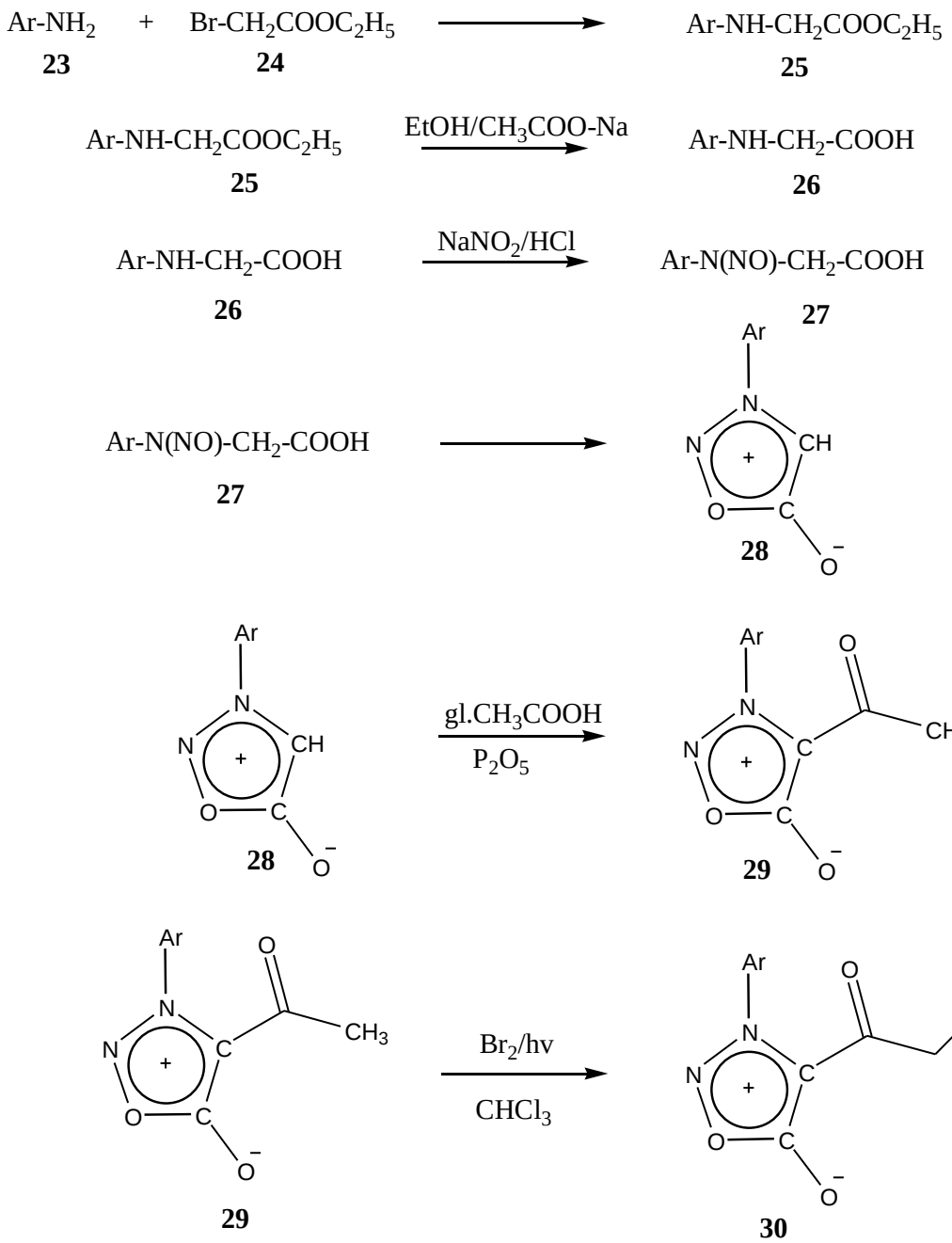
the making of the thiazole ring. The remaining C^5 atom would originate from an α-haloketone **21** where R^2 would be sydnonoyl. Thus, out of the four N atoms in the amidinothiourea derivative **20,** where X = H or NO_2, three are incorporated into the product **22**.

2) Synthesis of Precursors

a) Synthesis of 4-bromoacetyl-3-arylsydnones (30)

The synthesis of the halomethyl compound required for the present [4+1] thiazole ring assembly namely 3-aryl-4-bromoacetylsydnone **30** was synthesized in a six step process.



In brief, starting from arylamine **23** and ethyl bromoacetate **24**, the ethyl ester of N-arylglycine **25** was prepared. This on hydrolysis gave N-arylglycine **26** which upon nitrosation yielded N-nitroso-N-arylglycine **27** which was cyclised next to obtain 3-arylsydnone **28**. In the next step, acetylation of 3-arylsydnone gave 4-acetyl-3-arylsydnone **29**, subsequent bromination of which provided the required 3-aryl-4-bromoacetylsydnone **30**. Reported procedures from literature which has been suitably modified for our laboratory conditions were used in these reaction steps.

3) Synthesis of amidinothioureas

Nitroguanidine **35,** which was prepared by the isomerisation of guanidine nitrate **34** on treatment with aryl isothiocyanates in the presence of a base gave 1-aryl-3-(N-nitroamidino)thiourea **32** 1-Amidino-3-arylthioureas (31) were prepared by the reaction of aryl isothiocyanates with guanidine carbonate **33** in the presence of sodium hydroxide.

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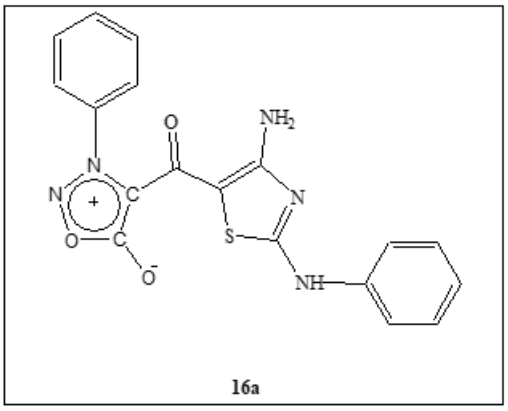
4) Synthesis of 4-amino-2-arylamino-5-sydnon-4-oylthiazoles (16)

To a solution of 1-aryl-3-(N-nitroamidino)thiourea **32** in N,N-dimethylformamide (DMF), 3-aryl-4-bromoacetylsydnone was added followed by triethylamine (Et_3N). 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 4-bromoacetyl-3-phenylsydnone **30a** with 1-(N-nitroamidino)-3-phenylthiourea **32a** is described below in detail. The reaction afforded an orange crystalline substance.

5) Elemental Analysis

Based on elemental analysis, the molecular composition of the compound was found to be $C_{18}H_{13}N_5O_3S$. The IR (KBr) spectrum of the compound shows peaks at 3362, 3277 and 3070 cm^{-1} which have been assigned to ν_{N-H} vibration of amino groups. The IR spectrum further shows a strong peak at 1741 cm^{-1}, which is attributed the C=O group in sydnone. The stretching band of the highly conjugated carbonyl group occurs at 1601 cm^{-1}. These assignments are supported by the observation of a $\nu_{C=O}$ of a sydnone carbonyl group at 1781 cm^{-1} and a $\nu_{C=O}$ band arising from a highly conjugated pentadienone carbonyl at 1644 cm^{-1} in the case of 5-phenyl-1-(3-phenylsydnon-4-yl)-penta-2,4-dien-1-one as reported recently by Sanyal and Badami. The presence of a phenyl substituent is indicated by the peaks at 754 and 688 cm^{-1} arising from the δ_{C-H} bending bands of phenyl ring hydrogens. The ^1H NMR spectrum (300 MHz) shows a broad peak at δ 9.18 ppm due to the –NH group. The aromatic region shows a set of three multiplets together accounting for ten aryl hydrogens. These multiplets are seen at δ 7.18-7.26, 7.39-7.49 and 7.56-7.65 ppm. The FAB MS shows a strong $[M+H]^+$ peak at m/z 380, which confirms the molecular mass of the compound to be 379 in accordance with the elemental analysis data. The ^{13}C NMR spectrum of the compound shows ten peaks, four of which appear to arise from two carbons each, thus accounting eighteen carbon atoms. The peak at δ 170.76 ppm is assigned to the carbonyl carbon of the sydnone moiety. This assignment is based on a similar observation in the case of 5-phenyl-1-(3-phenylsydnon-4-yl)penta-2,4-dien-1-one where the sydnonyl carbonyl carbon was seen at δ 174.55 ppm, as reported by Sanyal and Badami. (Sanyal and Badami, 2009) Based on these data the compound is formulated as 4-amino-2-phenylamino-5-(3-phenylsydnon-4-oyl)thiazole **16a**.



16a

Table 1.0: Synthesized 4-amino-2-arylamino-5-(3-arylsydnon-4-oyl)thiazoles 16a-p

16	Ar	Ar^1
A	Phenyl	Phenyl
B		4-methylphenyl
C		4-methoxyphenyl
D		4-chlorophenyl
E	4-methylphenyl	Phenyl
F		4-methylphenyl
G		4-methoxyphenyl
h		4-chlorophenyl
I	4-methoxyphenyl	Phenyl
J		4-methylphenyl
K		4-methoxyphenyl
L		4-chlorophenyl
M	4-chlorophenyl	Phenyl
N		4-methylphenyl
O		4-methoxyphenyl
P		4-chlorophenyl

4. Conclusion

1) From 1-aryl-3-(N-nitroamidino)thioureas **32a-d,** we have synthesized sixteen novel 2-amino-4-arylamino-5-(3-arylsydnon-4-oyl)thiazoles **16a-p i**n 80-85% yield.
2) We have characterized all the synthesized 2-amino-5-(3-arylsydnon-4-oyl)thiazoles by various spectral data.
3) The antioxidant activities of all the synthesized 2-amino-5-(3-arylsydnon-4-oyl)thiazoles were studied and we could identify promising antioxidant compounds among these.

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