Synthesis of Novel Diaminithiazoloylsydnones

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Abstract

Sydnone derivatives have recently been screened for a wide spectrum of bioactivity that includes antitumor and antianginal in addition to the known antimicrobial, anti-inflammatory, analgesic and antipyretic activities. We have recently found excellent cancer cell cytotoxicity in hetaryl thiazolyl ketone and concequently have developed a solid phase combinatorial approach to such compounds. As part of these studies, we have now synthesized novel diaminothiazoloylsydnones by ring assembly of the thiazole moiety in a [4+1] ring construction strategy developed earlier in our Laboratory. Thus, 1-amidino-3-arylthioureas serving as a [C-N-C-S] synthon, and bromoacetylsydnones, as the source of the remaining C atom in the [4+1] heterocyclization, were reacted to afford hitherto unreported diaminothiazoloylsydnones. The synthetic route also will be presented.

Keywords

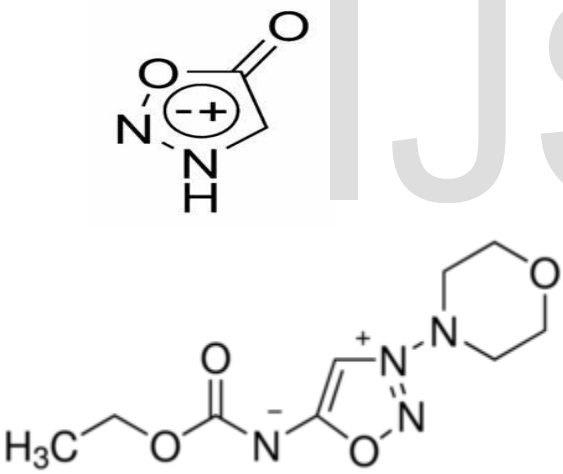
Amidinothiourea, Bromoacetylsydnones, Molsidomine, Sydnone, Thiazole

Introduction

Among heterocycles, mesoionic heterocycles are of special interest due to their unusual structures and large dipole moments which lead to interesting bioactivity profiles. Sydnones are mesoionic 1,2,3-oxadiazole system. Molsidomine is a clinically prescribed cororary drug incorporating a sydnone ring and is used in ischaemic heart disease, chronic heart failure and pulminory hypertension. Molsidomine is metabolized in liver into linsidomine which being unstable in the bioenvironment, releases the potent vascodialotor nitric oxide NO. Its advantage is that NO release from linsidomine does not require any endogenous enzymes or thiols in the body. In addition to Molsidomine, other sydnones are being screened for their potential therapeutic use.

Sydnone- a 1,2,3-Oxadiazole system

Molsidomine- A cardiac drug

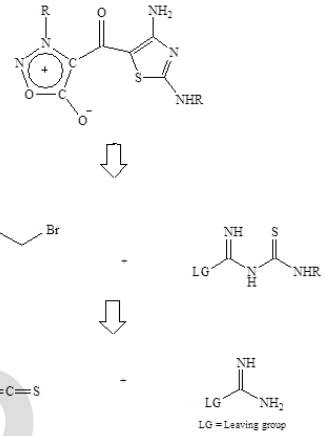


Background

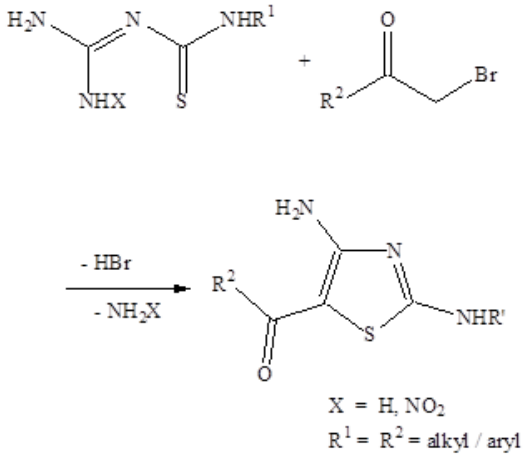
Sydnone derivatives have recently been screened for a wide spectrum of bioactivity that includes antitumor, antimicrobial, antianginal, antioxidant and analgesic activities. We have recently found excellent cancer cell cytotoxicity in hetaryl/aryl thiazolyl ketones which are analogs modeled on the marine 1,2,4-thiadiazole alkaloid dendrodoine. This interest led us to develop a synthetic route to sydnonyl thiazolyl ketones that would be later amenable to combinatorial synthesis adaptation.

Synthetic strategy and planning

Based on our long-standing interest in the synthesis of 2-aminothiazoles, we 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 (Binu, 1996), 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 would provide the [C^4-N^3-C^2-S^1] atoms that go into the making of the thiazole ring. The remaining C^5 atom would originate from an α-haloketone where R^2 would be sydnonoyl. Thus, out of the four N atoms in the amidinothiourea derivative , where X = H or NO_2, three are incorporated into the product.

Synthesis of Precursors

1. **Synthesis of 4-bromoacetyl-3-arylsydnones** *[Baker W, Ollis W. D. & Poole V. D. J. Chem. Soc; (1949) 307; Upadhyaya K.G, Badami B. V, Puranik G S & Biradar V N; Arch. Pharm, 313(1980)684]*

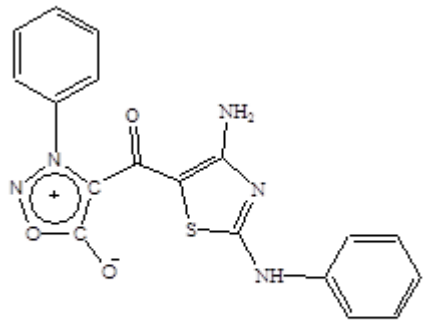
2. Preparation of 1-(N-nitoamidino)-3-substituted thioureas *[R. Binu, K K Thomas, G C Jenardanan and K N Rajasekharan, Org. Prep. Procedures Intl; 1998,30.93-96]*

Reaction Protocol

To a solution of 0.5mmol 1-nitroamidino-3-(substituted)thioureas in DMF, 3-aryl-4-(bromoacetyl)sydnone aws added, it was warmed and Et_3N (2.2 Eq.) was added in one lot. The rection mixture was then heated on a waterbath at 75-85^{0}C for 30 min. It was then cooled and poured into water, filtered, dried and the crude product was crystallised from EtOH-H_2O.

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 ^{1}H 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 **1A**.



1A

Table 1.0. Synthesized 4-amino-2-arylamino-5-(3-arylsydnon-4-oyl)thiazoles 1a-p

1	Ar	Ar^1
A	Phenyl	Phenyl
B		4-methylphenyl
C		4-methoxyphenyl
D		4-chlorophenyl
E		Phenyl
F	4-methylphenyl	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

Conclusions

We have synthesized 16 novel diaminothiazoloylsydnones by a thiazole ring assembly in a [4+1] ring construction strategy developed earlier in our laboratory. Thus, 1-nitroamidino-3-substituted thioureas serving as a [C4-N3-C2-S1] synthon and bromoacetylsydnone as the source of the remaining [C5] atom in the [4+1] heterocyclization were reacted to afford hitherto unreported diaminothiazololoylsydnones. 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. We have also studied the antibacterial, anticancer and antifungal activities and found a few compounds are promisingly active.

References:

1. *Dunkley & Thoman, Bioorg. Med. Chem. Lett. 2003,13,2899.*
2. *Moustafa et al. Archiv Pharm. 2004, 337,164*
3. *Anto et al. j. Clin. Biochem. And Nutr. 1994, 17, 73.*
4. *Shih & Ke, Bioorg. Med. Chem. 2004, 12, 4633.*
5. *Kalluraya eta al, Arch. Pharm 2001, 334,263.*
6. *Binu, R., Ph.D. Dissertation, University of Kerala, 1996.*
7. *Devi, S. K. C., Ph.D. Dissertation, University of Kerala, 1999.*
8. *Devi, S. K. C., Rajasekharan, K. N., Padmakumar, K., Tanaka, J. and Higa , T., Biological activity and chemistry of the compound ascidian Eusynstyela tincta. in "The Biology of Ascidians" ed. Sawada, H., Yokosawa, H., and Lambert, C .C., Springer-Verlag Tokyo, 2001, 341.*