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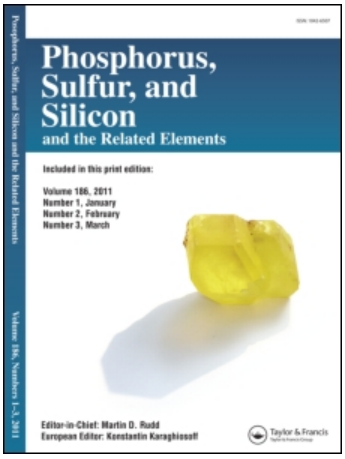

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
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SYNTHESIS OF 3-(MERCAPTOALKYL)- AND 3-(HYDROXYALKYL)-AMINO-2H-1,2,4-BENZOTHIADIAZINE 1,1 DIOXIDES

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To cite this Article Chern, Ji-Wang , Ho, Ching-Po , Wu, Ying-Hwa and Liu, Kang-Chien(1991) 'SYNTHESIS OF 3-(MERCAPTOALKYL)- AND 3-(HYDROXYALKYL)-AMINO-2H-1,2,4-BENZOTHIADIAZINE 1,1 DIOXIDES', Phosphorus, Sulfur, and Silicon and the Related Elements, 59: 1, 235 — 238
To link to this Article: DOI: 10.1080/10426509108045731
URL: http://dx.doi.org/10.1080/10426509108045731

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Phosphorus, Sulfur, and Silicon, 1991, Vol. 59, pp. 235–238
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SYNTHESIS OF 3-(MERCAPTOALKYL)- AND 3-(HYDROXYALKYL)-AMINO-2H-1,2,4-BENZOTHIADIAZINE 1,1-DIOXIDES

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Abstract The synthesis and Mitsunobu reaction of 3-(mercaptoalkyl)- and 3-(hydroxyalkyl)-amino-2H-1,2,4-benzothiadiazine 1,1-dioxides (10a,b) from 2-(chloroalkylthioureido)- and 2-(chloroalkylureido)-benzenesulfonamide (5) are discussed.

INTRODUCTION

The introduction of clonidine as a potent centrally acting antihypertensive agent[1] and the subsequent discovery of a number of other effective analogues in the imidazo[2,1-b]quinazoline series[2] prompted us to synthesize some condensed quinazoline derivatives containing a fused-in guanidine moiety as potential antihypertensive pharmacophore[3]. As a continuation of our study in this series, we extended our interests to prepare the fused 1,2,4-benzothiadizine 1,1-dioxides system for further antihypertensive evaluation.

ATTEMPTS TO SYNTHESIZE 3-(CHLOROALKYL)AMINO-2H-1,2,4-BENZOTHIADIZINE 1,1-DIOXIDES

In previous paper we described a reaction of 2-aminobenzenesulfonamide (1) with alkyl isothiocyanates leading to the formation of 3-alkylamino-2H-1,2,4-benzothiadiazine 1,1-dioxides *via* an elimination of hydrogen sulfide.[4] At the outset, we reasoned that an analogous condensed 3-(chloroalkyl)amino-2H-1,2,4-benzothiadiazine 1,1-dioxides (3) formed from 1 with the appropriate chloroalkyl isothiocyanates (2a) would undergo a second ring closure reaction to afford linear tricycles such as 4, as a result of an intramolecular nucleophilic substitution of the initially cyclized compounds.

An attempt to synthesize 4 , compound 1 was treated with 2a in isopropanol at room temperature to provide 2-(chloroalkylthioureido)-benzenesulfonamide (5a) in good yield. When 5a were treated with triethylamine in methanol at room temperature, it afforded 3-(aminoalkylthio)-2H-1,2,4-benzothiadizine 1,1-dioxides (9a) rather than the

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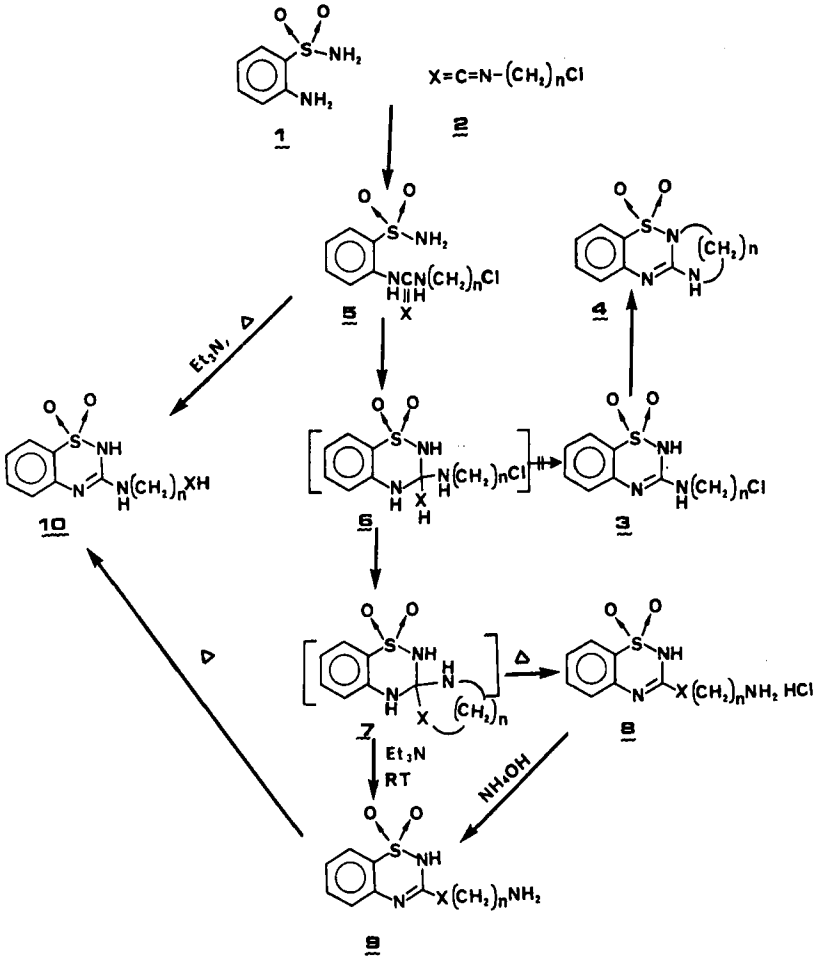
expected 4 . Howevr, when these reactions were performed at refluxing temperature, it furnished 2-(mercaptoalkyl)amino-2H-1,2,4-benzothiadiazine 1,1-dioxides (10a). It should be noted that heating 5a (n=3) to



Scheme I

reflux in methanol under neutral conditions gave 9a (n=3) but in form of the hydrochloride 8a(n=3) which was converted into the free base 9a(n=3) by treating with ammonia water.

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Repeating the above reactions using chloroalkyl isocyanates (2b) in place of 2a furnished 9b and 10b respectively. However, when 5b was refluxed in isopropanol, 9b were obtained in a form of hydrochloride (8b) in 78 to 87% yield respectively.

MECHANISM OF THE FORMATION OF 3-(MERCAPTOALKYL)- AND 3-(HYDROXYALKYL)-AMINO-2H-1,2,4-BENZOTHIADIAZINE 1,1-DIOXIDES

As shown in scheme I, the formation of 10 from 5 at elevated temperature under neutral condition probably involve the initial intramolecular nucleophilic attack of nitrogen atom of the sulfamido group to the sp^2 hybridized carbon of the thioureido or ureido moiety of 5 to form tetrahedral intermediate 6. The subsequent loss of hydrogen chloride gave spiro intermediate 7. The eliminated hydrogen chloride quarterized the ring nitrogen of 7, which might weaken the C-N bond and become a better leaving group. Thus, the ring opening of 7 by a proton transfer afforded 8. The transformation of 8 into 10 in isopropanol or methanol with triethylamine lends some support to the fact that the Smile rearrangement[5] involved in the synthesis of 10 from 5.

MITSUNOBU REACTIONS OF 3-(MERCAPTOALKYL)- AND 3-(HYDROXYALKYL)-AMINO-2H-1,2,4-BENZOTHIADIAZINE 1,1-DIOXIDES

Treatment of 3-(2'-hydroxyalkyl)amino-2H-1,2,4-benzothiadiazine 1,1-dioxides (10b) with triphenyl phosphine in the presence of DEAD[6] led to the formation of angualr tricycles- 1,2-dihydro-4H-imidazo[2,1-c][1,2,4] benzothiadiazine 5,5-dioxide (11, n=2) and 2,3-dihydro-1H, 5H-pyrimido[2,1-c][1,2,4]benzothiadiazine 6,6-dioxide (11, n=3) in 94% and 60% yield respectively (scheme II) instead of compound 4.The ^{13}C-NMR spectra obtained for 11 revealed that the chemical shift of the C-4a on the benzothiadiazine moiety is 135.05 ppm and are in agreement with values reported in the 4-substituted benzothiadiazine 1,1-dioxides.[7] However, the oxidized product of disulfide compound 12 were obtained from 3-(2'-mercaptoalkyl)amino-2H-1,2,4-benzothiadiazine 1,1-dioxides (10a) under the same condition.

CONCLUSION

1,2,4-Benzothiadiazine 1,1-dioxides draw much attention not only because of the discovery of the clinically useful diuretic chlorothiazide and

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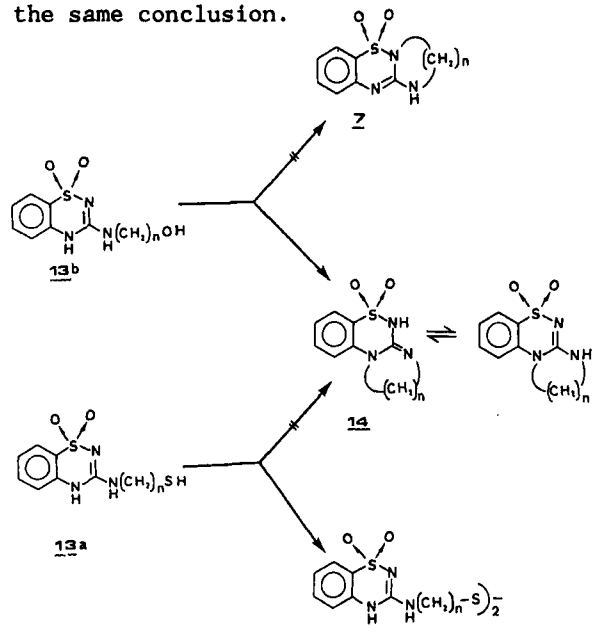
antihypertensive diazoxide[8] but also because of more than one nitrogen atom on this ring system providing extra sites for the tautomeric proton. The complicated prototropic tautomerism of this ring system has been intensively studied, it is generally agreed that the 4H-tautomer is preferred. The results obtained from this investigation demonstrate an alternative approach to the same conclusion.



Scheme II

ACKNOWLEDGEMENT

This investigation was supported by a research grant (No. NSC78-0412-B016-58) from National Science Council of the Republic of China

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