Pergamon

Tetrahedron Letters 39 (1998) 455–458

TETRAHEDRON LETTERS

# Synthesis of Thiazolo[3,2-*a*]pyridines from Enaminoesters by Tandem Conjugate Addition-Cyclization

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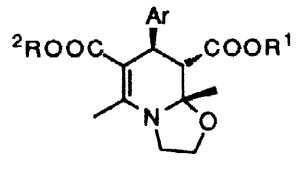
Received 5 August 1997; revised 6 November 1997; accepted 7 November 1997

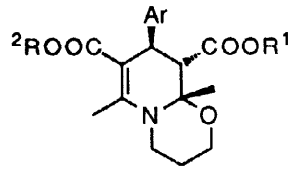
***Abstract.*** Several representative compounds with the new heterocyclic system thiazolo[3,2-*a*]pyridine have been obtained by condensation between α,β-unsaturated ketoesters and the N-mercaptoethylenamines of β-ketoesters in a tandem conjugate addition-cyclization process. The stereochemistry of these products is different from that observed for the products obtained from related N-hydroxyethylenamines.


1,4-Dihydropyridines (DHP) constitute a major class of calcium channel blockers. These compounds are very important cardiovascular drugs for the treatment of angina pectoris and hypertension[1], and are also being studied for additional therapeutic purposes[2]. During our research directed at the synthesis of new antihypertensive agents, we prepared several 2,3,8,8a-tetrahydrooxazolo[3,2-*a*]pyridines[3,4,5] and 3,4,9,9a-tetrahydropyrido[2,1-*b*]oxazines[6] showing long lasting antihypertensive activity. This was explained in terms of their biotransformation into the related 1,4-dihydropyridines[7]. These fused heterocyclic systems were synthesized by coupling of α,β-unsaturated carbonyl compounds and the β-enaminoesters of ethanolamine or propanolamine respectively. In a single conjugate addition-cyclization process, medium yields of these heterocycles were obtained, together with several cyclohexane derivatives as minor products.

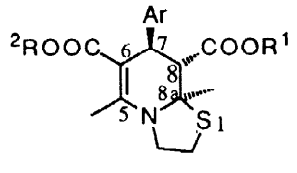
In order to extend the synthetic methodology to other heterocyclic systems, we have now used enamines of cysteamine (thioethanolamine) to prepare the analogous tetrahydrothiazolo[3,2-*a*]pyridine derivatives. In this paper we describe the synthesis of this new heterocyclic system.




Tetrahydrooxazolo[3,2-*a*] pyridines




Tetrahydropyrido[2,1-*b*] oxazines




Tetrahydrothiazolo[3,2-*a*] pyridines

The starting enaminoester of cysteamine was prepared by reaction between methyl acetylacetate and cysteamine. The resulting product was a mixture of the expected enaminoester **1** and the thiazolidine **2**. Both compounds are characterized in the mixture[8] because their separation was not possible by chromatographic

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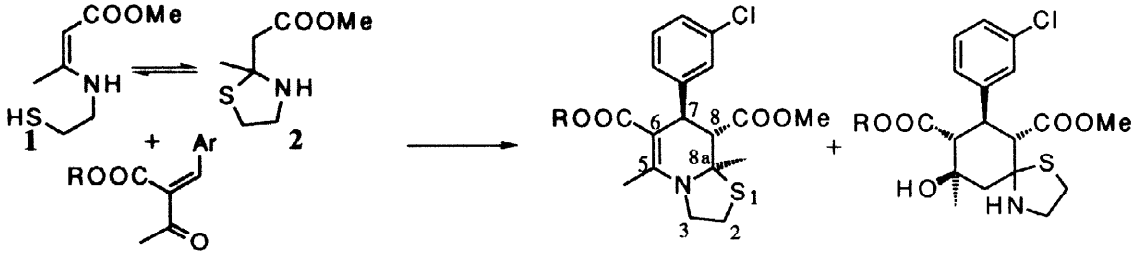
0040-4039/98/$19.00 
*PII:* S0040-4039(97)10574-3

procedures. The stronger nucleophilic character of sulfur accounted for the transformation of **1** into thiazolidine **2**, a process that was not observed for enaminoesters of ethanolamine. In consequence, the mixture of **1** and **2** was used as source of enaminoester for the reaction with α,β-unsaturated ketoesters.

The reaction between mixture **1+2** and unsatured ketoesters **3** (R=Me) or **4** (R=Et) was achieved in refluxing MeOH. The main reaction products were the thiazolopyridines **5** (R=Me) and **6** (R=Et) in 48% and 40% yield respectively, wich were isolated by crystallization from the reaction mixture. The minor product **7** was isolated in a 15% yield in the first case.



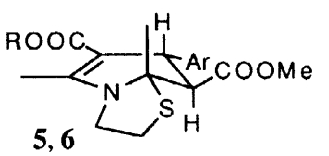

**3**: R=Me, Ar=3-Cl-Ph
**4**: R=Et, Ar=3-Cl-Ph

**5**: R=Me
**6**: R=Et

**7**: R=Me

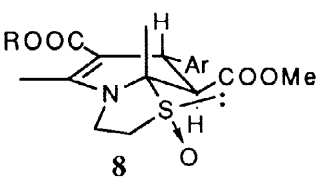
The constitution of compounds **5** and **6** was readily deduced from their spectroscopic properties[9] and comparison with those of their oxazolopyridine analogues[5], but their stereochemistry proved to be different from that of those oxygen derivatives. Although initially unexpected, this change in the stereochemical fate of the reaction was unequivocally deduced from the spectroscopic properties.

The *trans*-1,2-diaxial relationship between H7 and H8 was supported by its large coupling constant ($J$=12 Hz) and the *cis*-1,3-diaxial relationship between H7 and Me-$C_{8a}$ by nOe experiments. The geometry deduced for these new tetrahydrothiazolopyridines is depicted in Figure 1 and was also confirmed by the oxydation of **5** to sulfoxide **8**.[10,11] This reaction must take place by the less hindered α-side, thus yielding the sulfoxide with α-orientation of the oxygen. This stereochemistry of the sulfoxide is also supported by the stronger shielding of the $C_8$ signal (-10.5 ppm: γ-gauche with respect to the oxygen) in comparision with that of the other β-carbon, the methyl group $C_{8a}$-Me (-4.9 ppm: γ-anti with respect to the oxygen).[12]




**5, 6**

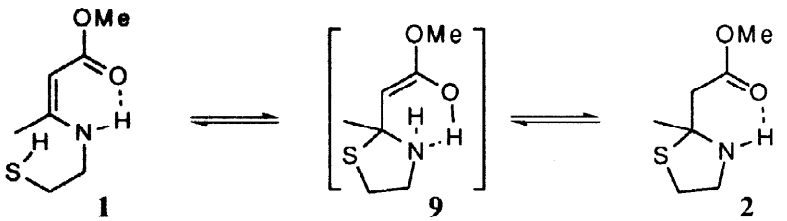
Figure 1. Stereochemistry of 2,3,8,8a-tetrahydrothiazolo[3,2-*a*] pyridines




**8**

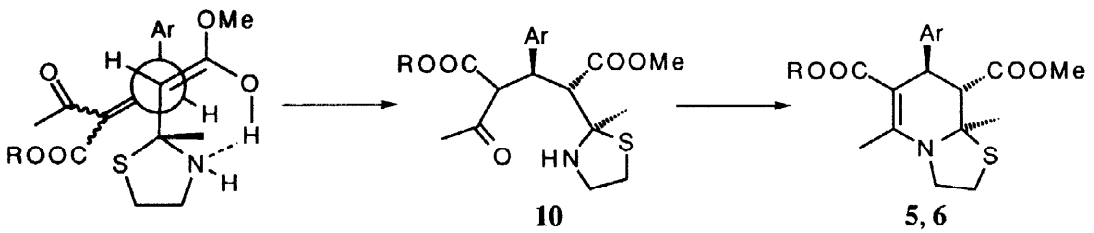
The stereochemical results can be explained by taking into account that the cyclization reaction to 2,3,8,8a-tetrahydrothiazolo[3,2-*a*]pyridines is stereospecific, since no other stereoisomers were obtained, and three stereogenic centers are produced in this process. The mechanism previously proposed for the formation of 2,3,8,8a-tetrahydrooxazolo[3,2-*a*]pyridines[5] is not appropriate to explain this even though the reagents and reaction products used are similar. Furthermore, there are not many possibilities for the approach of both reagents producing final compounds **4** and **5**. As a consequence, a different mechanism based on: 1) the 7,8-*trans*-8,8a-*cis* stereochemistry of final products, 2) the equilibrium between enaminoester **1** and thiazolidine **2** in solution, and 3) the formation of cyclohexanes as minor products must be proposed.

In view of the above, the reaction can not be explained in terms of a direct process from **1** or **2**. From enaminoester **1** the reaction would lead to 2,3,8,8a-tetrahydrothiazolo[3,2-*a*] pyridines with 7,8-*trans*-8,8a-*trans* stereochemistry, as is the case with many enaminones of ethanolamine. From thiazolidines **2** it is not possible to explain the reaction because the α-carbon to the ester group does not have the required nucleophilic character. Accordingly, a nucleophilic species derived from the mixture of **1** and **2** must be the nucleophile attacking the α,β-unsaturated ketoesters **3** or **4**. The equilibrium between **1** and **2** (Scheme 1) could take place through the attack of the sulfur atom on the conjugate system, thus producing the enol **9**. This intermediate enol could be transformed into the thiazolidine **2**, which could also reverse to **1** by opening of the thiazolidine ring, favoured by the leaving character of the sulfur.



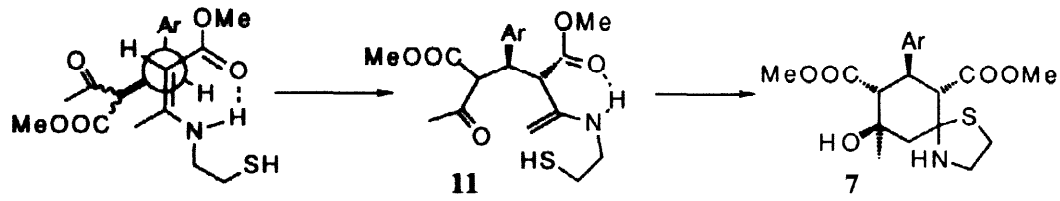

Scheme 1. Equilibrium between **1** and **2**, through intermediate **9**.

Intermediate **9** is an adequate species for the nucleophilic attack on the α,β-unsaturated ketoesters, accounting for the observed 8,8a-*cis* stereochemistry shown in Scheme 2. The relative 7,8-*trans* stereochemistry can also be explained if the approach of the reagents avoids crowding, by placing bulky groups in *anti* disposition. According to both processes, presented in schemes 1 and 2, the resulting stereochemistry of the tetrahydrothiazolopyridines and the difference observed in the formation of the related tetrahydrooxazolopyridines can be fully explained on the basis of the different nucleophilic character of sulfur, which favours the equilibrium of scheme 1. A thermodynamic equilibrium similar to the Hantzsch synthesis of DHP, with all the steps reversible except the final dehydration yielding **5** or **6**, could also explain the different results, although theoretical calculations of the relative stability of the intermediate and final products[13] predict the same stereochemistry in the formation of 2,3,8,8a-tetrahydrooxazolo- and 2,3,8,8a-tetrahydrothiazolo[3,2-*a*]pyridines.




Scheme 2. Stereochemical course of the reaction between α,β-unsaturated ketoesters **3**, **4** and the intermediate species **9**.

The formation of cyclohexane products must take place through intermediate **11**, produced directly by the attack of the enaminoester **1** to **3**, in a similar process to that described for the cyclohexane derivatives obtained from other enaminoesters.[4,14,15] The stronger nucleophilic character of sulfur terminates the reaction by producing the thiazolidine ring of **7**, while for oxygen analogues oxazolidines are not observed.




In conclusion, although related the reactions of enaminoesters of ethanolamine and thioethanolamine with α,β-unsaturated ketoesters produce different results. These can be explained in terms of the stronger nucleophilic character of sulfur, which also is responsible for the equilibrium mixture observed for the enaminoester reagent. As now presented, the previously described method for the synthesis of tetrahydrooxazolo[3,2-*a*]pyridines can readily be extended for the preparation of tetrahydrothiazolo[3,2-*a*]pyridines.

**Acknowledgements.-** Financial support came from Spanish CICYT (**SAF 95-1566**) and the Junta de Castilla y Leon (**SA 97/96**).

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8.- Reaction product is a ~1:1 mixture. $^1$H-NMR: **1**: 1.96 (3H,*s*), 2.80 (2H,*m*), 3.60 (2H,*m*), 3.61 (3H,*s*), 4.49 (1H,*s*), 8.73 (1H,*bt*,NH); **2**: 1.56 (3H,*s*), 2.8-3.5 (6H,*m*), 3.70 (3H,*s*). $^{13}$C-NMR: **1**: 19.2 (*q*), 37.5 (*t*), 41.5 (*t*), 82.7 (*d*), 160.0 (*s*), 170.9 (*s*); **2**: 30.8 (*q*), 38.4 (*t*), 45.7 (*t*), 51.1 (*t*), 76.0 (*s*), 170.6 (*s*).
9.- **5**: Mp=113°C (MeOH). $^1$H-NMR: 1.59 (3H,*s*;$C_{8a}$-Me), 2.50 (3H,*d*,J=1.4Hz;$C_5$-Me), 2.84 (1H,*d*,J=12.0Hz;$H_8$), 3.09 (2H,*m*;$H_2$), 3.25 (3H,*s*;$C_{10}$-OMe), 3.51 (3H,*s*;$C_{11}$-OMe), 3.95 (2H,*t*,J=7.3Hz;$H_3$), 4.02 (1H,d,J=12Hz;$H_7$), 7.0-7.3 (4H,*m*;Ar). $^{13}$C-NMR: 19.0 ($C_5$-Me), 22.3 ($C_{8a}$-Me), 28.2 ($C_2$), 43.5 ($C_7$), 50.1 ($C_{10}$-OMe), 51.6 ($C_{11}$-OMe), 51.6 ($C_3$), 59.7 ($C_8$), 68.9 ($C_{8a}$), 99.4 ($C_6$), 125.6 ($C_4$'), 126.2($C_2$'), 127.1 ($C_6$'), 129.2 ($C_5$'), 133.6 ($C_3$'), 146.7 ($C_1$'), 151.0 ($C_5$), 167.9 ($C_{10}$), 171.0 ($C_{11}$).
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12.- Wiseman, J.R.; Krabbenhft, H.O.; Anderson, B.R. *J. Org. Chem.* **1976**, *41*, 1518. $^{13}$C-NMR: 17.4 ($C_{8a}$-Me), 18.3 ($C_5$-Me), 41.3 ($C_7$), 45.0 ($C_2$), 47.2 ($C_3$), 49.2 ($C_8$), 50.1 ($C_{10}$-OMe), 52.1 ($C_{11}$-OMe), 81.8 ($C_{8a}$), 99.0 ($C_6$), 125.9 ($C_4$'), 126.4($C_2$'), 127.1 ($C_6$'), 129.1 ($C_5$'), 133.6 ($C_3$'), 146.2 ($C_1$'), 150.3 ($C_5$), 167.8 ($C_{10}$), 171.2 ($C_{11}$).
13.- Relatives stabilities of reaction intermediates 5-hydroxy-2,3,5,6,8,8a-hexahydrooxazolo/ thiazolo[3,2-*a*]pyridines, analogues to those of the Hantzsch reaction (Katritzky, A.R.; Ostercamp, D.L.; Yousaf, T.I. *Tetrahedron* **1986**, *42*, 5729), and final products 2,3,8,8a-tetrahydrooxazolo/ thiazolo[3,2-*a*]pyridines were calculated by MM2 force field implemented in Macromodel (Mohamadyi, F.; Richards, N.G.J.; Guida, W.C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W.C. *J.Comput.Chem.* **1990**, *11*,440). In all cases the most stable stereoisomers were the 7,8-*trans*-8,8a-*cis* products indicating that the thermodynamic control of the reaction would produce the same stereochemistry from enaminones of ethanolamine and thioethanolamine.
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