ESCHENMOSER REACTION: AN UNEXPECTED ROUTE TO TETRAHYDROTHIENO[2,3-*b*]PYRIDIN-3-ONES AND AZEPAN-3-ONES

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Abstract - Eschenmoser condensation of various commercial secondary α-bromo esters (**2**) with six and seven membered thiolactams (**1**) surprisingly gives tetrahydrothieno[2,3-*b*]pyridin-3-ones and azepan-3-ones (**4**), while ethyl bromoacetate yields, after sulfur extrusion, the expected cyclic β-enamino esters (**3**).

The Eschenmoser condensation-extrusion reaction is an efficient method to prepare trisubstituted cyclic β-enamino esters by alkylation of pyrrolidinic or piperidinic thiolactams with α-bromoacetates.[1]

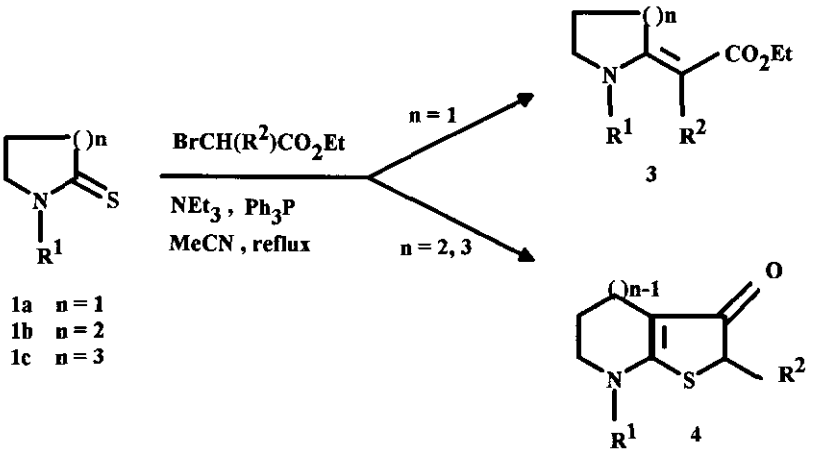
This coupling reaction has also been used to obtain tetrasubstituted cyclic enamino esters, but a secondary triflate was then required.[2] However, in this case, only pyrrolidinic thiolactams were involved in the condensation .

Recently, we reported a new convenient synthetic method of *N*-alkylated tetrasubstituted β-enamino esters (**3**) from five membered thiolactams (**1a**) and secondary α-bromo esters (**2**) using the Eschenmoser reaction.[3]

In this paper, we describe an extension of this reaction to six and seven membered thiolactams (**1b**) and

(**1c**). In contrast to pyrrolidine-2-thione (**1a**), the behaviour of piperidine- and azepane-2-thiones (**1b**) and (**1c**) towards esters (**2**) was quite different in the same reaction conditions .

In this last case, the condensation did not lead to the expected β-enamino ester (**3**) but yielded exclusively tetrahydrothieno[2,3-*b*]pyridin- and azepan-3-ones (**4**) (Scheme 1).



Scheme 1

Thus, a mixture of triethylamine and triphenylphosphine slowly added to a solution of **1b-c** and **2** in refluxed MeCN gave compound (**4**) as sole product (Table 1).[4]

The structure of tetrahydrothieno[2,3-*b*]pyridin- and azepan-3-ones (**4**) was unambigously established by ^{1}H and ^{13}C nmr. The presence of a signal beyond 190 ppm on ^{13}C spectra, assigned to the carbonyl group, excluded enamino ester structure: for compounds (**3**) previously described,[3] the carbonyl group was observed between 160 and 165 ppm.

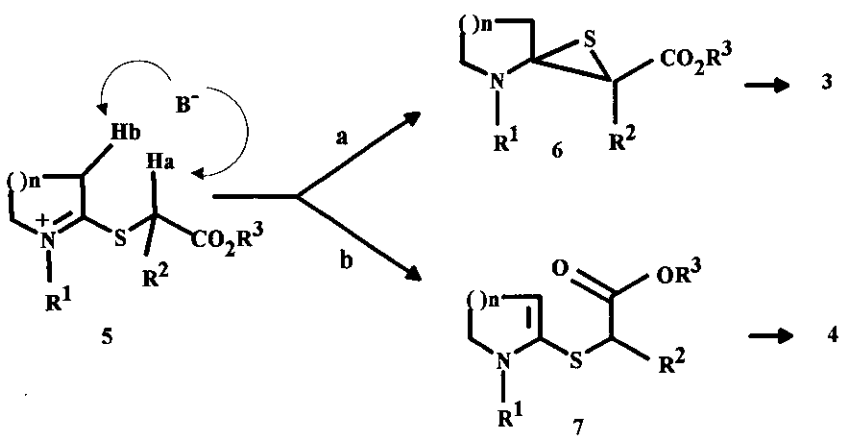
Two different pathways could be proposed to explain compounds (**3**) or (**4**) formation.

(Scheme 2).

Table 1. Condensation of Thiolactams with Secondary Bromo Esters

Product	n	R^1	R^2	Reaction time (h)	Yield [a] %
4a	2	Me	Me	2	80
4b	2	Me	Et	2	70
4c	2	Me	Pr	2.5	68
4d	2	Bn	Me	2	80
4e	2	Bn	Et	2	61
4f	2	Bn	Pr	2.5	51
4g	3	Bn	Me	2.5	68
4h	3	Bn	Et	2	90
4i	3	Bn	Pr	2	60

[a] Experiments conducted without Ph_3P



Scheme 2

In the first step of the Eschenmoser reaction, the condensation of thiolactam (**1**) and bromo ester (**2**) gives the intermediate α-thioiminium salt (**5**), in which Ha or Hb proton can be abstracted. Triethylamine attack

of Ha leads to episulfide (**6**) formation (route a), precursor of the enamino ester (**3**), whereas abstraction of Hb (route b) yields the ketene *N,S*-acetal (**7**) which affords compound (**4**). An intermediate such as (**7**) has been postulated by Rapoport in thioimidate salt proton abstraction to explain the formation of an α-alkylated thiolactam.[5] (We never observed such a transalkylation product.) Furthermore, a reversible conversion of thioiminium salt to ketene N,S-acetal was evidenced by Hart and coll. [6]

The orientation of the reaction seems to depend on two factors: first, the class of the halogeno derivative, therefore the nature of R^2. Thus, the condensation of thiolactams (**1b**) or (**1c**) and bromo acetate in the conditions mentioned above , with or without Ph_3P, yields exclusively trisubstituted enamino esters (**3**) (R^2 = H). In the absence of Ph_3P, no trace of tetrahydrothieno[2,3-*b*]pyridin-3-one was detected and enamino ester (**3a**) is then obtained in poor yield (Table 2).

Table 2. Condensation of Thiolactams with Ethyl Bromoacetate

Product	n	R^1	R^2	Ph_3P	Reaction time (h)	Yield %
3a	2	Bn	H	2 eq	1	72
3a	2	Bn	H	-	2	33
3b	3	Bn	H	2 eq	1	63
3c	2	Me	H	2 eq	1	80

In iminium salt (**5**), the presence of an alkyl substituent R^2, decreases the relative acidity of Ha compared to Hb and promotes the route to **4** in the case of secondary bromo esters condensation .

The second factor which affects the reaction pathway is the size of the thiolactam ring. In the case of five membered substrates the reaction follows the natural course of Eschenmoser reaction, both with primary and secondary bromo esters, and gives, after desulfuration, enamino esters (**3**). For six and seven membered rings, no desulfuration step occurs: tetrahydrothieno[2,3-*b*]pyridin-3-ones and azepan-3-ones are then obtained as sole products .

An analogous behaviour has been previously mentioned for the Eschenmoser condensation of α-bromo ketones which can undergo an unexpected cyclisation to give aminothiophenes.[6]

Nevertheless, our results constitute the first example of such a reaction observed with α-bromo esters.

The literature records only few examples of tetrahydrothieno[2,3-*b*]pyridin-3-ones.[7] The cyclisation we describe here represents a facile and convenient route to these compounds.

EXPERIMENTAL

α-Bromo esters (**2**) were commercialy available. Thiolactams (**1**) were prepared by thionation of the corresponding commercial lactams according to D. Brillon procedure.[8] Their analytical and spectroscopic data are in agreement with literature.[9,10] ^{1}H and ^{13}C nmr spectra were recorded on a Bruker AC 200 spectrometer in $CDCl_3$ as internal standard and coupling constants are expressed in Hz. Solvents and reagents were used as received from Aldrich.

General Procedure for Preparation of Compounds (4) A mixture of thiolactam (**1**) (3.0 mmol), NaI (0.45 g , 3.0 mmol) , α-bromo ester(**2**) (6.0 mmol) and Et_3N (0.84 ml , 6.0 mmol) was refluxed in CH_3CN (5 ml) during 2-2.5 h (Table 1). After cooling, the reaction mixture was concentrated under reduced pressure. The residue was diluted with $CHCl_3$ (20 ml) and extracted with 2M HCl (5x20 ml). The combined aqueous layers were made alkaline by addition of solid Na_2CO_3 and extracted with EtOAc . The organic phase was dried over $MgSO_4$, solvent was removed and the residue was chromatographed on a silica gel column using EtOAc or EtOAc-MeOH (8 : 2) to give the product .

2,7-Dimethyl-4,5,6,7-tetrahydrothieno[2,3-*b*]pyridin-3-one (4a) . mp 80°C; yield 80 %; ir (nujol) 1730, 1630, 1540 cm^{-1} ; ^{1}H nmr δ 3.75 (q, J = 7.3, 1H), 3.33 (t, J = 5.5, 2H), 3.10 (s , 3H), 2.32 (m, 2H), 1.89 (m, 2H), 1.55 (d, J = 7.3, 3H); ^{13}C nmr δ 194.2, 171.9, 100.3, 50.9, 49.4, 39.2, 20.5, 18.9, 18.1. Anal. Calcd for $C_9H_{13}NOS$: C, 59.00; H, 7.15; N, 7.65. Found: C, 59.08; H, 7.09; N, 7.76.

2-Ethyl-7-methyl-4,5,6,7-tetrahydrothieno[2,3-*b*]pyridin-3-one (4b). Oil; yield 70 %; ir (neat) 1730,

1630, 1540 cm^{-1} ; ^1H nmr δ 3.76 (m, 1H), 3.32 (t, J = 5.5, 2H), 3.10 (s, 3H), 2.30 (m, 2H), 1.95-1.65 (m, 2H), 1.02 (t, J = 7, 3H); ^{13}C nmr δ 194.0, 172.8, 101.9, 56.4, 51.3, 39.6, 26.1, 21.0, 19.2, 11.5. Anal. Calcd for $C_{10}H_{15}NOS$: C, 60.89; H, 7.67; N, 7.10. Found : C, 61.10; H, 7.58; N, 7.14.

2-Propyl-7-methyl-4,5,6,7-tetrahydrothieno[2,3-*b*]pyridin-3-one (4c). Oil; yield 68 %; ir (neat) 1730, 1640, 1550 cm^{-1} ; ^1H nmr δ 3.75 (m, 1H), 3.32 (t, J = 5.5 , 2H), 3.09 (s, 3H), 2.30 (m, 2H), 1.87 (m, 2H), 1.70-1.35 (m, 2H), 0.95 (t, J = 7, 3H); ^{13}C nmr δ 193.6, 172.2, 101.2, 54.3, 50.9, 39.2, 34.7, 20.6, 18.8, 13.3. Anal. Calcd for $C_{11}H_{17}NOS$: C, 62.54; H, 8.11; N, 6.63. Found : C, 62.67; H , 8.03 ; N , 6.65.

2-Methyl-7-phenylmethyl-4,5,6,7-tetrahydrothieno[2,3-*b*]pyridin-3-one (4d). Oil; yield 80 % ; ir (neat) 1750, 1650, 1550 cm^{-1} ; ^1H nmr δ 7.40-7.20 (m, 5H), 4.51 (s, 2H), 3.83 (q, J = 7, 1H), 3.26 (t, J = 5.5, 2H), 2.45 -2.25 (m, 2H), 1.90-1.75 (m, 2H), 1.59 (d, J = 7, 3H); ^{13}C nmr δ 194.2, 171.9, 134.7, 128.3, 127.5, 126.9, 100.8, 55.8, 48.3, 47.8, 20.4, 19.1, 18.0. Anal. Calcd for $C_{15}H_{17}NOS$: C, 69.48; H, 6.61; N, 5.40. Found : C, 69.72; H, 6.54; N, 5.47.

2-Ethyl-7-phenylmethyl-4,5,6,7-tetrahydrothieno[2,3-*b*]pyridin-3-one (4e). mp 77 °C; yield 61 %; ir (nujol) 1645, 1550 cm^{-1} ; ^1H nmr δ 7.60-7.10 (m, 5H), 4.45 (s, 2H), 3.73 (m, 1H), 3.16 (t, J = 5.5, 2H), 2.30-2.10 (m, 2H), 1.80-1.60 (m, 4H), 0.95 (t, J = 7, 3H); ^{13}C nmr δ 194.7, 172.1, 135.4, 128.8, 128.3, 127.4, 102.5, 56.5, 56.4, 46.8, 26.1, 21.0, 19.6, 14.1. Anal. Calcd for $C_{16}H_{19}NOS$: C, 70.33; H, 6.96; N, 5.13. Found : C, 69.97; H, 7.13; N, 5.08.

2-Propyl-7-phenylmethyl-4,5,6,7-tetrahydrothieno[2,3-*b*]pyridin-3-one (4f). mp 72 °C; yield 51 %; ir (nujol) 1630, 1535 cm^{-1} ; ^1H nmr δ 7.40-7.20 (m, 5H), 4.53 (s, 2H), 3.84 (m, 1H), 3.25 (t, J = 5.5, 2H), 2.40 -2.10 (m, 2H), 1.90 -1.70 (m, 4H), 1.60 -1.40 (m, 2H), 0.97 (t, J = 7, 3H); ^{13}C nmr δ 194.2, 171.5, 134.8, 128.3, 127.5, 127.0, 101.6, 55.8, 54.4, 48.3, 34.7, 20.5, 19.1, 13.3. Anal. Calcd for $C_{17}H_{21}NOS$: C, 71.08; H, 7.32; N, 4.88. Found : C, 71.03; H, 7.39; N, 4.91.

2-Methyl-8-phenylmethyl-5,6,7,8-tetrahydrothieno[2,3-*b*]azepan-3-one (4g). Oil; yield 68 %; ir (neat) 1740, 1630, 1530 cm^{-1} ; ^1H nmr δ 7.50-7.15 (m, 5H), 4.46 (s, 2H), 3.71 (q, J = 7, 1H), 3.42

(t, J = 5.5, 2H), 2.45 (t, J = 4.5, 2H), 1.80 -1.60 (m, 4H), 1.49 (d, J = 7, 3H); ^{13}C nmr δ 198.4, 176.5, 136.1, 128.5, 128.2, 127.4, 107.3, 58.0, 51.5, 48.0, 27.6, 24.7, 22.4, 18.6. Anal. Calcd for $C_{16}H_{19}NOS$: C, 70.33; H,6.96; N, 5.13. Found : C, 70.39; H, 6.81; N, 4.95.

2-Ethyl-8-phenylmethyl-5,6,7,8-tetrahydrothieno[2,3-*b*]azepan-3-one (4h). Oil; yield 90 %, ir (neat) 1730, 1635, 1530 cm^{-1} ; ^{1}H nmr δ 7.50 - 7.20 (m, 5H), 4.58 (s, 2H), 3.81 (m, 1H), 3.55 - 3.45 (m, 2H), 2.53 (m, 2H), 1.90 - 1.60 (m, 6H), 1.01 (t, J = 7.5, 3H); ^{13}C nmr δ 197.2, 176.8, 135.9, 128.5, 127.7, 127.2, 108.2, 57.8, 55.8, 51.3, 27.3, 25.9, 24.6, 22.0, 10.9. Anal. Calcd for $C_{17}H_{21}NOS$: C, 71.08; H, 7.32; N, 4.88. Found : C, 70.85; H, 7.54; N, 4.87.

2-Propyl-8-phenylmethyl-5,6,7,8-tetrahydrothieno[2,3-*b*]azepan-3-one (4i). Oil; yield 60 %; ir (neat) 1730, 1635, 1530 cm^{-1} ; ^{1}H nmr δ 7.40 -7.20 (m, 5H), 4.57 (s, 2H), 3.63 (m, 1H), 3.55 - 3.45 (m, 2H), 2.70 - 245 (m, 2H), 1.90 - 1.40 (m, 8H), 0.95 (t, J = 7, 3H); ^{13}C nmr δ 198.8, 176.1, 135.5, 128.0, 127.3, 126.6, 107.3, 59.8, 57.6, 50.8, 34.9, 26.9, 24.3, 21.8, 20.1, 13.2. Anal. Calcd for $C_{18}H_{23}NOS$: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.91; H, 7.62; N, 4.72.

General Procedure for Preparation of Compounds (3). A mixture of thiolactam **(1)** (3 mmol) NaI (0.45 g , 3 mmol) and ethyl bromoacetate (1.0 g , 6 mmol) was refluxed in MeCN (10 ml) . A solution of Ph_3P (1.57 g , 6 mmol) and Et_3N (0.84 ml , 6 mmol) in MeCN (20 ml) was added dropwise during 1 h . After cooling to room temperature , the reaction mixture was concentrated under reduced pressure . The residue was diluted with CH_2Cl_2 (20 ml) then extracted with 2M HCl (5 x 20 ml). Aqueous layers were combined , made alkaline by addition of solid Na_2CO_3 and extracted with EtOAc . The organic phase was dried over $MgSO_4$, solvent removed and the residue was chromatographed on a silica gel column using EtOAc - hexane (1 : 6) to give compounds **(3)**.

Ethyl *(E)* - (1-phenylmethyl-2-piperidinylidene)acetate (3 a).White solid, mp 66 °C; yield 72 % ; Spectral data are in agreement with the literature.[11]

Ethyl *(E)* - (1- phenylmethyl-2-azepanylidene)acetate (3b). White solid,[11] mp 74 °C; yield 63 % .

Ethyl *(E)* - (1-methyl-2-piperidinylidene)acetate (3c). Oil; R_f = 0.55 (EtOAc); ^{1}H nmr is in agreement with the literature.[12,13]

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