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The influence of the ring size of thiolactams in the Eschenmoser coupling reaction in presence of DBU. Formation of bicyclic thiazolidinones or thioimines ☆

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Abstract—The different behaviors of pyrrolidin-2-thione and piperidin-2-thione under a modified Eschenmoser sulfur contraction reaction protocol using DBU as base was observed. The pyrrolidin-2-thione **1b** follows the expected reaction course, leading to thioimines **5a–d**, which can be transformed subsequently into the respective by action of a thiophile, while the piperidin-2-thione leads to the formation of bicyclic thiazolidinones **4b–d** in moderate to good yields. The β-enaminocarbonyl compound **11** was hydrogenated to afford the respective five-membered analogue of methylphenidate **12**.

The *exo*-cyclic enamines, are useful building blocks for the synthesis of natural products.[1] The Eschenmoser sulfide contraction reaction[2] is an elegant way to prepare this special class of compounds and it is an important tool in organic synthesis.[3] This methodology has been successfully applied as a key pathway in many synthetic strategies addressed to the synthesis of natural products, notably in the synthesis of alkaloids.[4–8]

The Eschenmoser sulfide contraction reaction, also called the Eschenmoser coupling reaction,[9] occurs when a thiolactam condenses with an α-bromocarbonyl compound in the presence of a base and a sulfur scavenger, leading to the respective β-enaminocarbonyl derivative. The classical conditions generally employ a tertiary amine (Et_3N) as the base and a phosphine (Ph_3P-thiophile) as the sulfur scavenger, although other tertiary amines and phosphorous thiophiles[10] have been reported as being effective, as well as reactions performed in the absence of a thiophile.[11]

While N-secondary or N-tertiary trisubstituted β-enaminocarbonyl compounds are readily prepared under classical conditions, the tetrasubstituted derivatives need carefully controlled conditions.[12,13] Secondary α-triflate-esters[14,15] are required in the cases where pyrrolidine thiolactams were involved. The principal examples to prepare the N-secondary tetrasubstituted *exo*-cyclic β-enaminocarbonyl compounds from piperidine thiolactams use a α-bromocarbonyl reagent with a second electron withdrawing substituent groups (CN,[16] COR or CO_2R[17]) attached to the α-carbonyl carbon.

In connection with our interest in the synthesis of β-aminocarbonyl compounds,[18,19] we have recently applied the Eschenmoser coupling reaction to synthesize the β-enaminoester **3a** as the key intermediary in the synthesis of (±)-*erythro*-methylphenidate. The reaction of the piperidin-2-thione (**1a**) with the α-bromoester **2a**, under the Eschenmoser protocol, produced **3a** and a variable quantity of the unexpected thiazolidinone **4a**, depending on the base employed (Scheme 1). However, **3a** was obtained as a sole product when the reaction was carried using DBU (2 equiv) as base and in the absence of Ph_3P as a thiophile.[20]

In attempt to generalize this modified Eschenmoser protocol to prepare the N-secondary tetrasubstituted β-enaminocarbonyls, we would like to disclose here, our results regarding the different behaviors observed for the

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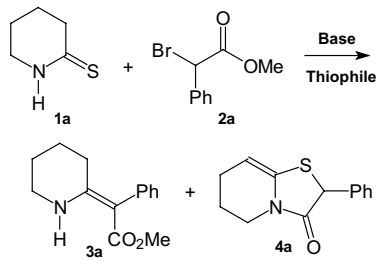


Scheme 1. Formation of β-enaminocarbonyl **3a** and the thiazolidinone **4a**.

reactions of thiolactams **1a** ($n = 2$) and **1b** ($n = 1$) with the α-bromoesters **2a–d** (Scheme 2).

As previously mentioned, the reaction of piperidine-thione **1a** ($R^1 = Ph$) with the bromoester **2a** in presence of 2 equiv of Et_3N or DBU and 2 equiv of Ph_3P (see Table 1, entries 1 and 2, respectively) or Et_3N in absence of Ph_3P (entry 3) afforded a mixture of the enamino compound **3a** and the thiazolidinone **4a**. On the other hand, when the reaction was carried out with DBU in absence of Ph_3P (entry 4), only the enaminocarbonyl compound **3a** was obtained in 60% yield.

Based on these results, we decided to investigate a possible general method for the preparation of alkylated secondary tetrasubstituted β-enaminoesters carrying out the condensations of the piperidine-thione **1a** and the α-bromoesters **2b–d** ($R^1 =$ Me, *n*-Pr, and *n*-Bu, respectively) by this modified Eschenmoser coupling reaction protocol.

To our surprise, the reactions of **1a** with the bromoesters **2b–d** ($R^1 =$ alkyl), in the presence of 2 equiv of DBU did not undergo the extrusion of the sulfur atom to give the corresponding β-enaminoesters but gave the thiazolidinones **4b–d** in good yields (entries 5–7).

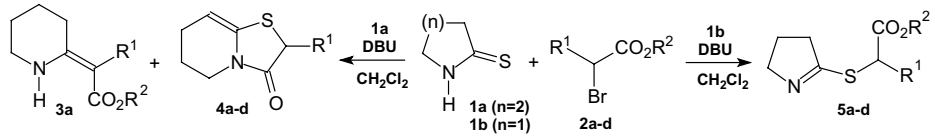
It should be noted that in all performed examples, the formation of the β-enaminocarbonyl compound was only observed when the R^1 substituent group is phenyl group and the change of DBU by Et_3N was not effective to promote the condensation and the starting materials were totally recovered.

Next, we carried out the reactions of pyrrolidine-thione **1b** ($n = 1$) with the bromoesters **2a–d** under the same reaction conditions. In all cases, we did not observe the formation of either β-enaminocarbonyls or the thiazolidinones but rather the respective thioimines **5a–d**[21] were obtained in high yields (Table 1, entries 8–11), independent of the nature of the R^1 group.

The structures of the β-enaminoester **3a**, as well as of the thiazolidinones **4a–d** and thioimines **5a–d** were in accordance with their ^1H NMR, ^{13}C NMR, and IR spectral data.[22]

The unexpected formation of thiazolidinones in the Eschenmoser coupling reaction was recently reported independently by Padwa et al.[23] and Michael et al.[24] for analogous compounds but the factors controlling their formation are not clear yet.

In an earlier report, Lhommet and co-workers,[25] trying to prepare the tetrasubstituted β-enaminocarbonyls, observed a different behavior of N-tertiary five and six-membered ring thiolactams in the Eschenmoser coupling reaction. The author's explanation for the different course of this reaction is that the potentially acidic hydrogen Hb in the initially formed thionium salt **6** is abstracted preferentially by the base when $n = 2$, giving



Scheme 2. Eschenmoser sulfide contraction reaction.

Table 1. Compounds **3a**, **4a–d**, and **5a–d** by Scheme 2

Entry	Thiolactam	Bromoester			Base	Products	Yield (%)
			R^1	R^2			
1	**1a**	**2a**	Ph	OMe	Et_3N[a]	**3a**(46):**4a**(21)	67
2	**1a**	**2a**	Ph	OMe	DBU[a]	**3a**(35):**4a**(41)	76
3	**1a**	**2a**	Ph	OMe	Et_3N	**3a**(6):**4a**(25)	31
4	**1a**	**2a**	Ph	OMe	DBU	**3a**	60
5	**1a**	**2b**	Me	OMe	DBU	**4b**	72
6	**1a**	**2c**	*n*-Pr	OEt	DBU	**4c**	85
7	**1a**	**2d**	*n*-Bu	OEt	DBU	**4d**	89
8	**1b**	**2a**	Ph	OMe	DBU	**5a**	91
9	**1b**	**2b**	Me	OMe	DBU	**5b**	87
10	**1b**	**2c**	*n*-Pr	OEt	DBU	**5c**	92
11	**1b**	**2d**	*n*-Bu	OEt	DBU	**5d**	94

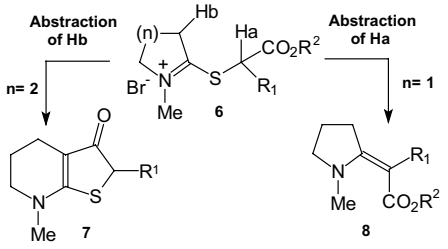
[a] Reaction performed with 2 equiv of Ph_3P.

the tetrahydrothieno[2,3-*b*]pyridin-3(2H)-one (**7**). On the other hand, when $n = 1$, the hydrogen Ha is abstracted and the expected β-enaminocarbonyl **8** is produced (Scheme 3).

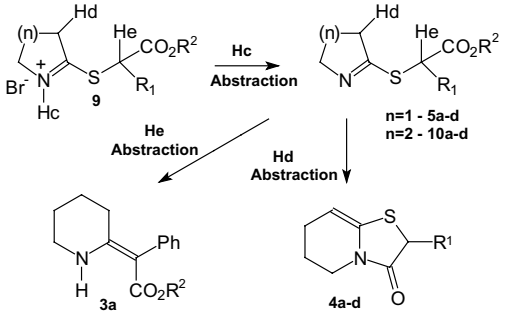
Although our examples are restricted to N-secondary thiolactams, this rationale can be extended to our studied cases. Based on the currently accepted mechanism of the Eschenmoser coupling reaction,[3] the first step is the thio-alkylation reaction that gives the thionium cation **9a** ($n = 1$) or **9b** ($n = 2$), which have three potentially acidic hydrogens: Hc, Hd, and He. In the second step, the first equivalent of DBU abstracts preferentially the more acidic Hc hydrogen and the thioimines **5a–d** ($n = 1$) and **10a–d** ($n = 2$) were formed. In this step, the thioimines **5a–d** were sufficiently stable to be isolated and characterized by ^{1}H NMR and IR, while **10a–d** were not detected. Next, the second equivalent of the base abstracts the acidic benzylic hydrogen He in **10a** ($R^1 = Ph$) giving the corresponding β-enaminocarbonyl **3a** through the usual accepted mechanism with subsequent sulfide extrusion (Scheme 4).

The allylic hydrogen Hd seems to become more acidic than He in intermediaries **10b–d**, when the R^1 substituent group is an alkyl group, and is preferentially abstracted by the base leading to the exclusive formation of thiazolidinones **4b–d** by a subsequent intramolecular cyclization (see Scheme 4).

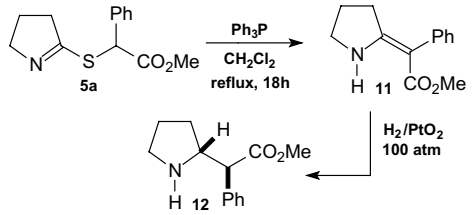
For the reactions of N-secondary five-membered ring thiolactam **1b** the DBU is not sufficiently basic to abstract the allylic hydrogen Hd in the thioimines **5a–d**. In addition, the normal course of the Eschenmoser



Scheme 3. Reaction carried out by Lhommet.



Scheme 4. Possible pathways to the formation of compounds **3a**, **4a–d**, and **5a–d**.



Scheme 5. Synthesis of methylphenidate analogue **12**.

sulfide contraction also does not occurred in absence of a thiophile. In this way, we performed the reactions of compounds **5a–d** with Ph_3P (4 equiv) in $CHCl_3$ under reflux for 18 h. In only one case, the compound **5a** furnished the respective β-enaminocarbonyl compound **11** in 86% yield as a unique *Z* stereoisomer[26] (Scheme 5).

The direct Eschenmoser coupling reaction of pyrrolidine-thione **1b** with the bromoester **2a** in presence of DBU (2 equiv) and Ph_3P (4 equiv) was also proceeded and we were able to isolate the respective β-enaminocarbonyl derivative **11** in 75% yield after purification by chromatography. Finally, due to the interest in the synthesis of analogues of methylphenidate,[27,28] the compound **11** was tentatively hydrogenated under H_2/PtO_2 at various H_2 pressures and the reaction was only completed by the utilization of 100 atm of H_2 which afforded the five-membered ring analogue of methylphenidate **12** in 95% yield (see Scheme 5) as a single isomer.[29]

In conclusion, the formation of N-secondary tetrasubstituted β-enaminocarbonyl compounds or bicyclic thiazolidinones promoted by DBU from piperidine-thiones or pyrrolidine-thiones depends on the nature of the R^1 group of the bromoester, the strength and/or the bulkiness of the employed tertiary amine, and the size of the thiolactam ring.

Supplementary material

Supplementary material includes the ^{1}H NMR and ^{13}C NMR spectra and data of compounds **3a**, **4a**, **5a**, **11**, and (±)-*erythro*-**12**. The supplementary data is available online with the paper in ScienceDirect.

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22. Spectral data for compounds **3a**: ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 9.72 (br s, 1H), 7.34–7.10 (m, 5H), 3.55 (s, 3H), 3.51–3.33 (m, 2H), 2.10 (t, $J = 6.6$ Hz, 2H), 1.79–1.68 (m, 2H), 1.63–1.54 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 170.3, 161.3, 152.9, 138.1, 132.3, 127.8, 94.4, 50.4, 41.4, 27.7, 22.3, 19.9; IR (KBr): ν 3344, 3046, 2926, 1581. Spectral data of compound **4a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.45–7.31 (m, 5H), 5.06 (s, 1H), 4.92 (t, $J = 4.3$ Hz, 1H), 3.75–3.67 (m, 2H), 2.42 (dd, $J = 15.6$, 5.9 Hz, 2H), 1.95–1.83 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 170.8, 137.5, 129.8, 128.2, 98.1, 51.1, 42.1, 22.5, 20.4; IR (neat): ν 3061, 2928, 2849, 1696, 1645, 1387. Spectral data of compound **5a**: ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.55–7.27 (m, 5H), 5.55 (s, 1H), 3.89–3.81 (m, 2H), 3.72 (s, 3H), 2.66–2.56 (m, 2H), 1.99 (qt, $J = 7.6$ Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 170.9, 170.7, 134.9, 128.8, 128.4, 128.3, 60.8, 53.9, 37.9, 23.5; IR (neat): ν 3063, 2951, 1740, 1693, 1594.
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29. Based on our previous report (see Ref. 20) we attributed the relative stereochemistry of compound **12** as being analogue to the *erythro*-methylphenidate. Spectral data of compound **12**: ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.36–7.26 (m, 5H), 6.16 (br s, 1H), 4.14 (s, 1H), 3.69 (s, 3H), 3.55–3.30 (m, 2H), 2.35–1.87 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 171.4, 133.6, 128.9, 128.8, 128.5, 62.9, 52.8, 52.3, 46.8, 28.4, 23.4; IR (neat): ν 3022, 2935, 1735, 1453, 1161.