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# One-step synthesis of thiazolo[3,2-*a*]pyridines by a multicomponent reaction of β-enaminonitriles, α,β-unsaturated aldehydes, and 2-aminothiol hydrochlorides

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ABSTRACT

A wide library of 3,7,8,8a-tetrahydro-2*H*-thiazolo[3,2-*a*]pyridines has been prepared by simple heating in acetonitrile of β-enaminonitriles, α,β-unsaturated aldehydes and 2-aminothiol hydrochlorides. Chemical yields depend on the nature, hindrance, and position of the substituents. The scope, limitations, and stereocontrol associated to this three-component reaction have been studied in detail. In general, the diastereoinduction observed in the three new stereogenic centers generated in the pro-chiral α,β-unsaturated aldehyde is low.



## 1. Introduction

The poly-functionality of β-enaminones and related compounds (β-enaminoesters and β-enaminonitriles) makes these synthons useful intermediates for heterocyclic synthesis.[1–3] From all the reported reactions, only a few of them were described as multicomponent reactions. The preparation of dihydropyridines[4] by different modified Hantzsch reactions is probably the most largely mentioned procedure. Although in less extension, it has also been described the preparation of pyridones[5] and tetrahydropyrimidines.[6] In all these cases, only the enamino group becomes part of the heterocycle, remaining the accompanying withdrawing group (ketone, ester, nitrile) untransformed. The presence of an isonitrile group provides an exceptional reactivity, giving complex reactions (Three-Component Reactions (3CR) and Four-Component Reactions (4CR)), which lead to isoxazoles[7] and dihydropyridines[4g,8] with a wide variety of substitutions.

In a recent study on tetrahydro[1,4]thiazepines[9] we found that the reaction of β-enaminocrotonitrile, acrolein, and cysteamine afforded 3,7,8,8a-tetrahydro-5-methyl-2*H*-thiazolo[3,2-*a*]pyridine-6-carbonitrile in good yield. Multicomponent reactions for the synthesis of thiazolo[3,2-*a*]pyridines have precedent in the preparation of polycyclic *N*/*O*, *N*/*S*, and *N*/*N* aminals.[10] Closely related is the reaction of β-ketoesters, α,β-unsaturated oxo-compounds and cysteamine, in which the involvement of enaminoester intermediates has been claimed to account for the stereogenic control of three chiral centers.[11]

In an effort to find new alternatives for multicomponent domino reactions and take advantage of the three chiral center stereocontrol shown by the reaction, we now describe a detailed and extensive study on the preparation of 3,7,8,8a-thiazolo[3,2-*a*]pyridines from β-enaminonitriles, α,β-unsaturated aldehydes, and 1,2-aminothiols. Different substitution patterns and sizes were chosen in order to determine the influence on yields and diastereoselectivity. The results are accompanied by a brief study regarding the optimization of the reaction conditions carried out with simple commercial substrates. A range of alkyl or aryl substituents has also been tested and we have attempted to determine the scope and limitations derived from their nature and position.

## 2. Results and discussion

### 2.1. Optimization of the reaction conditions

For simplicity, optimization of the reaction conditions was carried out using β-aminocrotonitrile **2**, acrolein **8**, and cysteamine **14** (Scheme 1), which do not lead to diastereomeric mixtures. It was observed that the rate of reagents, solvent, pH media, temperature, and reaction time influences the final outcome. Due to the large

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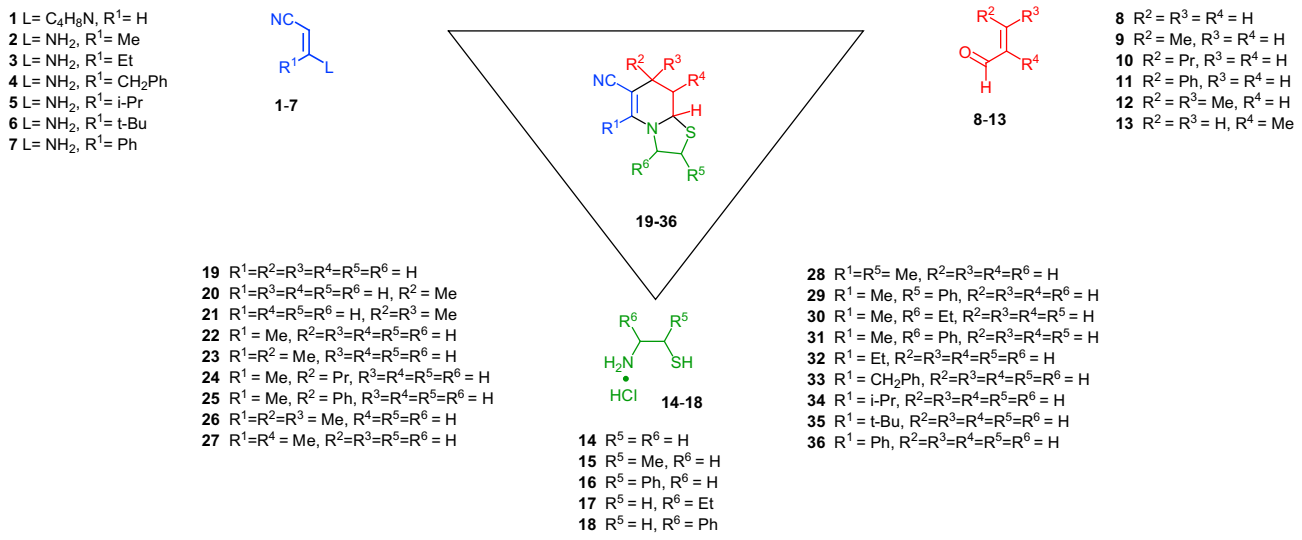



**Scheme 1.** Numeration of the starting materials and the final products.

number of side reactions that can take place, the use of an appropriate rate of reagents is an important factor that has to be considered for good results. Among the proportions tested, the rate 1:2:2 (β-enaminonitrile/aldehyde/1,2-aminothiol) led to the best yield of 3,7,8,8a-tetrahydro-5-methyl-2*H*-thiazolo[3,2-*a*]pyridine-6-carbonitrile **22** (75%) (Table 1,entry 4). Other solvents different from acetonitrile, such as water, toluene, and ethanol, do not improve former results.

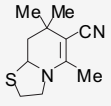
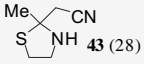
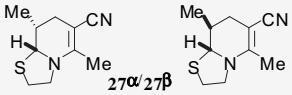
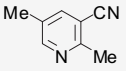
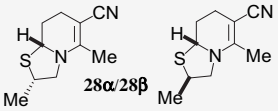
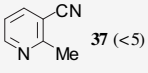
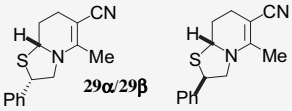
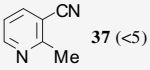
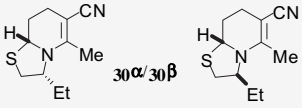
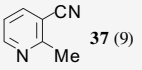
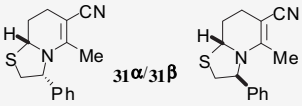
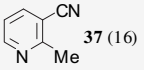
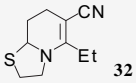
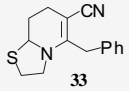
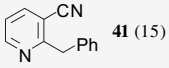
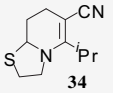
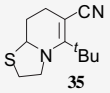
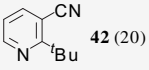
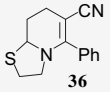
The best yield (75%) is obtained when an excess of cysteamine hydrochloride is used. This slightly acidic medium stabilizes the β-enaminonitrile, catalyzes the formation of *N*/*S* aminals while slowing down cysteamine oxidative self-coupling. Use of free-acid cysteamine led to complex mixtures.

Following the reaction by $^1$H NMR ($CD_3CN$), at 77 °C, a rapid formation of **22** was observed after 1 h; however, prolongation of time (up to 3 h) diminishes yields due to final product degradation.

**Table 1**
Preparation of 3,7,8,8a-tetrahydro-2*H*-tiazolo[3,2-*a*]pyridines **19**–**36**

| Entry | Starting material | Time (h) | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | $R^6$ | Tetrahydro-2*H*-thiazolo[3,2-*a*]pyridines | Yield[a] (%) | Ratio α/β[b] | Other[c] (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 1+8+14 | 2 | H | H | H | H | H | H | **19** | 48 | | |
| 2 | 1+9+14 | 2 | H | Me | H | H | H | H | **20**α/**20**β | 29 | 1:1 | |
| 3 | 1+12+14 | 2 | H | Me | Me | H | H | H | **21** | 17 | | |
| 4 | 2+8+14 | 2 | Me | H | H | H | H | H | **22** | 75 | | **37** (12) |
| 5 | 2+9+14 | 2 | Me | Me | H | H | H | H | **23**α/**23**β | 41 | 1:1 | **38** (10) |
| 6 | 2+10+14 | 3 | Me | Pr | H | H | H | H | **24**α/**24**β | 32 | 1:1 | **39** (10); **43** (15) |
| 7 | 2+11+14 | 3 | Me | Ph | H | H | H | H | **25**α/**25**β | 56 | 2:3 | **40**(6); **43** (30) |

**Table 1** (*continued*)

| Entry | Starting material | Time (h) | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | $R^6$ | Tetrahydro-2*H*-thiazolo[3,2-*a*]pyridines | Yield[a] (%) | Ratio α/β[b] | Other[c] (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 8 | 2+12+14 | 2 | Me | Me | Me | H | H | H |  **26** | 30 | |  **43** (28) |
| 9 | 2+13+14 | 2 | Me | H | H | Me | H | H |  **27α/27β** | 61 | 3:2 |  |
| 10 | 2+8+15 | 2 | Me | H | H | H | Me | H |  **28α/28β** | 68 | 1:1 |  **37** (<5) |
| 11 | 2+8+16 | 4 | Me | H | H | H | Ph | H |  **29α/29β** | 50 | 2:3 |  **37** (<5) |
| 12 | 2+8+17 | 3 | Me | H | H | H | H | Et |  **30α/30β** | 60 | 1:1 |  **37** (9) |
| 13 | 2+8+18 | 3 | Me | H | H | H | H | Ph |  **31α/31β** | 15 | 2:3 |  **37** (16) |
| 14 | 3+8+14 | 2 | Et | H | H | H | H | H |  **32** | 45[d] | |  |
| 15 | 4+8+14 | 2.5 | $CH_2Ph$ | H | H | H | H | H |  **33** | 31 | |  **41** (15) |
| 16 | 5+8+14 | 2 | *i*-Pr | H | H | H | H | H |  **34** | 20[d] | |  |
| 17 | 6+8+14 | 3 | *t*-Bu | H | H | H | H | H |  **35** | 0 | |  **42** (20) |
| 18 | 7+8+14 | 2 | Ph | H | H | H | H | H |  **36** | 47 | |  |

[a] Isolated yield.
[b] Ratio determined by $^1$H NMR of the crude mixture.
[c] Confirmed its presence by $^1$H NMR in the reaction mixture. Only some representative pyridines were isolated for their description.
[d] Yields were determined from the $^1$H NMR spectrum of the crude reaction mixture.

Care should be taken for not prolonging heating times unnecessarily. Surprisingly, reactions carried out at room temperature gave a complex mixture that considerably simplifies after 6 h. After 12 h of reaction at rt, results are comparable to that obtained after 45 min at 77 °C.

According to former observations we decided to use as general procedure a rate of 1:2:2 (β-enaminonitrile: α,β-unsaturated aldehyde: 2-aminothiol hydrochloride) in refluxing acetonitrile for 2 h.

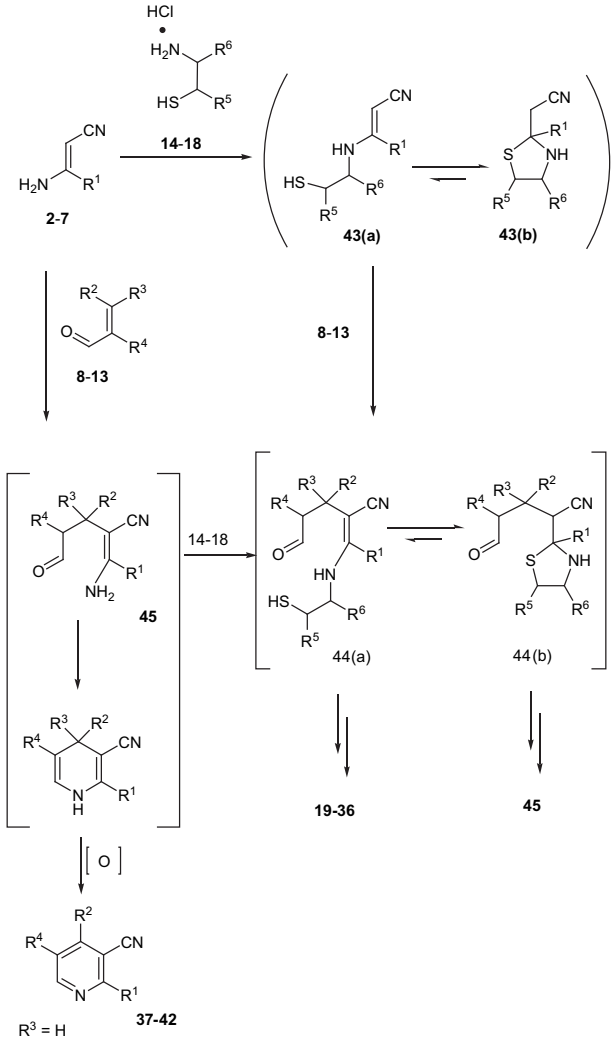
## 2.2. Scope and limitations

In order to study the scope and limitations of this reaction, we have designed different experiments (Table 1). We focused on the

hindrance of the substituents. The hindrance of $R^1$ clearly diminishes the yield of 3,7,8,8a-tetrahydro-2*H*-thiazolo[3,2-*a*]pyridines. Effectively, the 75% yield obtained for **22** ($R^1$=Me) drops to 20% in the case of **34** ($R^1$=*i*-Pr) and is almost null for **35** ($R^1$=*t*-Bu) (Table 1, entries 4, 16, and 17).

The steric effect is even higher for substituent $R^6$. A less bulky substituent as the ethyl group (**30**) shows a steric effect high enough to lower the yield up to 60%, whereas a phenyl group (**31**, $R^6$=Ph) gives only 15% (Table 1, entries 12 and 13).

On the one hand, the increase of the hindrance of $R^1$ and $R^6$ does not involve an appreciable lowering of the enaminonitrile conversion, but it produces a remarkable increase of the rate of pyridine-3-carbonitriles **37**–**42** (Table 1, see entries 4, 13, 17), which are formed in all the reactions as a side-product. On the other hand, raising the number and size of substituents $R^2$ and $R^3$ a noticeable decrease of the yield of thiazolo[3,2-*a*]pyridines **23**–**26** (Table 1, entries 5–8), and pyridine-3-carbonitriles **37**–**40** is observed (Table 1, entries 4–8). Moreover, formation of intermediate **43** resulting from β-crotonitrile **2** nitrogen-exchange occurs to a high extent (Scheme 2).




**Scheme 2.** Different theoretical routes for the formation of thiazolo[3,2-*a*]pyridines **19**–**36**.

When $R^4$ or $R^5$ is a Me group, there is no decrease in yields (Table 1, entries 9 and 10) although the overall reaction proceeds slower. This effect is enhanced if $R^5$ is a Ph group, where up to 4 h are necessary to get a 50% yield (Table 1, entry 11).

Finally, the lower reactivity and yield observed when enaminonitrile **1** ($R^1$=H) is used (Table 1, entries 1–3) is not due to the nature of $R^1$ but to the efficiency of the amino moiety (pirrolidine or ammonia) to behave as a leaving group.

### 2.3. Mechanistic insights

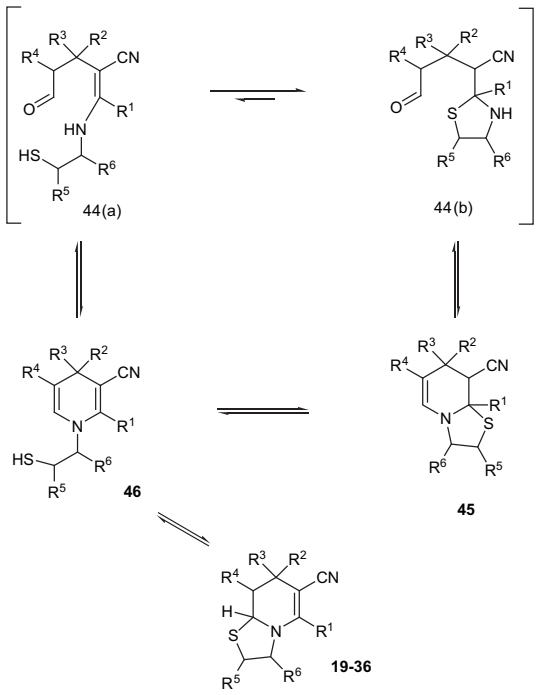
The fact that experimental results were equally reproducible whether the synthesis of the final thiazolo[3,2-*a*]pyridine is achieved in the one step multicomponent way or indistinctly from **43**(**a**, **b**) (previously prepared[12]), suggests that the reaction proceeds by nitrogen exchange between β-enaminonitrile **1**–**7** and aminothiol **14**–**18** (Scheme 2). When the steric hindrance of $R^1$ and $R^4$ hinders this step, formation of pyridine-3-carbonitrile (Hantzsch reaction) is observed in some extension (Table 1, entries 4–18).

From intermediate **43**(**a**, **b**) several alternatives can be devised (developed) for the formation of aminals **19**–**36** (Scheme 2). Although we have not been able to isolate reaction intermediates, which support the proposed pathway, San Feliciano's mechanistic proposal[11,13] for the multi-step synthesis of 3,7,8,8a-tetrahydro-2*H*-oxa(and thia)zolo[3,2-*a*]pyridines is probably closely related to our reaction.

Michael addition of enamine **43a** to unsaturated aldehydes **8**–**13** affords intermediate **44**(**a**, **b**) (Scheme 2). As the size and number of substituents attached to C-β increases, conjugate addition leading to **44** or **45** is hindered, and therefore reaction tends to stop upon formation of **43** (Table 1, entries 4–8).

Formation of intermediate **44**(**a**, **b**) could be also explained if the reaction followed an opposite sequence (first conjugate addition and then nitrogen exchange). However, compounds analogous to **45**, prepared by other alternative procedures,[14] undergo cyclization so quick that nitrogen exchange could hardly take place (Scheme 2).

Finally, formation of aminals **19**–**36** might occur by cyclization of intermediate **44a** (via **46**, Scheme 3), or through the mayor tautomer **44b** followed by cyclization to **45**, equilibration to **46** and formation of the final aminal. Although some authors succeeded to isolate compounds of type **45** (when $R^4$ is an ester[11]), we were not able to detect compound **45**, probably due to the low stability of our enamine **45** ($R^4$=Alkyl, H). Intermediate **46** should explain the observed stereochemistry.




**Scheme 3.** Formation of aminals **19**–**36** by cyclization of intermediates **44**(**a**,**b**).

### 2.4. Stereochemistry: scope and limitations

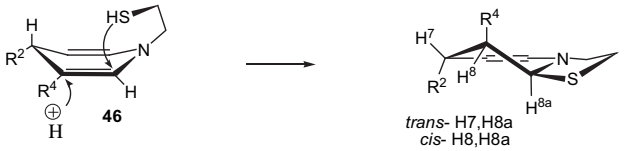
The experiments shown in Table 1 were selected with the idea of determining the individual effect caused by each substituent on the reaction. Only one of the substituents $R^2$ to $R^6$ is not constituted by a proton, which results in formation of a maximum of two chiral carbons in the final bicycle. In general, the diastereomers formed could be well separated by flash chromatography and their relative stereochemistry assigned by NOESY experiments and from the $^1$H NMR coupling constants.

The diastereoselective induction observed in the addition to aldehydes **8**–**13** is rather low compared with that observed for the preparation of other similar 3,7,8,8a-tetrahydro-2*H*-oxazolo[3,2-*a*]pyridines[15,16] and 3,7,8,8a-tetrahydro-2*H*-thiazolo[3,2-*a*]pyridines.[11] Results depend on the nature and position of the substituent.

Substituents with reduced size, such as Me, do not induce selectivity at all in any position, except in C-8 (**27**, $R^4$=Me, entry 9) where a small selectivity 60:40 (**27α**/**27β**) was shown at rt and 40:60 (**27α**/**27β**) upon heating. Some selectivity (around 40:60, Table 1, entries 7, 11, 13) is also achieved when increasing the size of $R^2$, $R^5$, or $R^6$, but not high enough to be synthetically useful. Epimerization in little extent of **25**, $R^2$=Ph was observed after 1 h of heating (Table 1, entry 7).

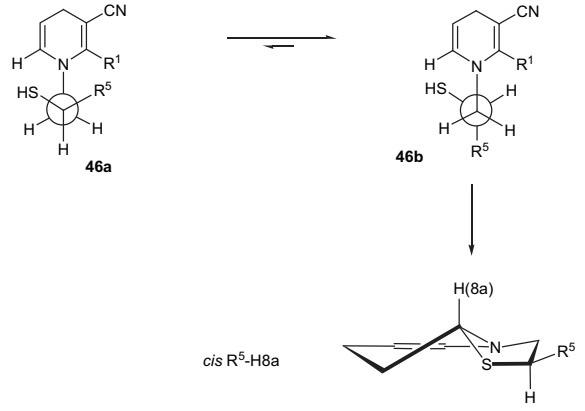
### 2.5. Stereochemistry: interpretation

During cyclization, the thiol group should approach preferably from the side opposite to $R^2$, according to the *trans*-addition pathway described for the iodolactonization of 1,4-dihydropyridines and tetrahydrooxazolopyridines.[17] Consequently, the configuration of the final bicycle should be majorly *trans*-H7,H8a/*cis*-H8,H8a (Scheme 4). Since this is not the most stable diastereomer, equilibration with epimerization of C8a takes place as the temperature increases and heating is prolonged. This has been observed in the conversion of **27α**(*cis*-H8-H8a) to **27β**(*trans*-H8-H8a).




**Scheme 4.** Cyclization of SH group through a *trans*-addition pathway.

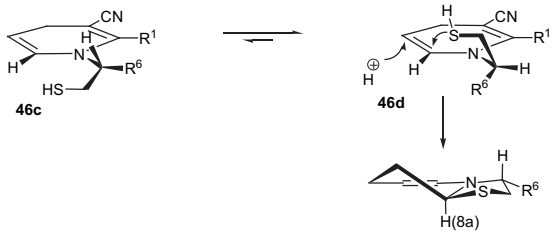
The influence of substituent $R^4$ is similar to that reported for the diastereoselective formation of perhydrothiazolopyridines[18,19] (Scheme 5). The thiol group should attack preferably through the less sterically hindered conformation **46b** leading to a *cis*-$R^5$/H8a




**Scheme 5.** Attack of SH group through the less sterically hindered conformation **46b** leading to a *cis*-$R^5$/H8a thiazolopyridine.

thiazolopyridine (Scheme 5). In this case, this is the most stable diastereomer and therefore, epimerization is not observed at all even when heating.

Regarding substituent $R^6$, sterical repulsions from the nearest substituent $R^1$ make conformation **46d** the most stable one, leading the reaction to the selective formation of *cis*-$R^6$/H8a diastereomers (Scheme 6). Analogous stereochemistry was also found in the synthesis of 3-phenyl substituted tetrahydrooxazolopyridines from *N*-substituted dihydropyridines.[17]




**Scheme 6.** Sterical repulsions between $R^6$ and $R^1$ leading the reaction to *cis*-$R^6$/H8a diastereomers.

## 3. Experimental

### 3.1. Instrumentation

Melting points were measured on a Reichert-Jung Thermo Galen and are uncorrected. IR spectra were obtained on a Perkin–Elmer 1720 X spectrometer. NMR spectra were recorded on a Bruker AC300 spectrometer, and chemical shifts are given downfield from $SiMe_4$ as an internal standard. $^{13}$C NMR spectra were carried out with complete $^1$H decoupling and the assignments were made by additional DEPT experiments.

### 3.2. Materials

The starting β-enaminonitriles were purchased from the usual suppliers (**2**) or prepared by literature procedures (**1**[20], **3**–**6**[21], **7**[22]). The corresponding 2-aminothiol hydrochlorides were purchased from the usual suppliers (**14**) or prepared by literature procedures (**15**–**18**[23]). All the α,β-unsaturated aldehydes were purchased from the usual suppliers.

### 3.3. General procedure

*3.3.1. Synthesis of tetrahydrothiazolo[3,2-a]pyridines (**19**–**36**).* A solution of β-enaminonitrile (4.4 mmol), α,β-unsaturated aldehyde (8.8 mmol) and 2-aminothiol hydrochlorides (8.8 mmol) in 25 cm$^3$ of dry acetonitrile was refluxed for the time specified in Table 1. At the end of the reaction the solvent was removed and the residue was poured in 50 cm$^3$ of water and extracted with dichloromethane (3×50 cm$^3$). The organic layer was dried over $Na_2SO_4$ and removed in vacuo. The product was chromatographed on silica gel (0.040–0.063 mm) using dichloromethane (**19**, **20**, **22**–**31**, **33**), hexane/ethyl acetate (4:1) (**36**) or hexane/ethyl acetate (3:1) (**21**) as eluent.

### 3.4. Characterization of products

*3.4.1. 2,3,8,8a-Tetrahydro-7H-thiazolo[3,2-a]pyridine-6-carbonitrile (**19**).* Yellow oil; $R_f$=0.35 ($CH_2Cl_2$); IR (film): 3436, 2931, 2871, 2853, 2184, 1729, 1615, 1463, 1382, 1325, 1306, 1235, 1178, 1153, 1137, 1055, 919, 863 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): δ=1.61–1.78 (m, 1H, C*H*H–CH–S), 2.21–2.39 (m, 3H, CH*H*–CH–S and C*H*$_2$–C═), 2.94–2.98 (m, 2H, $CH_2$–S), 3.51–3.59 (m, 1H, C*H*H–N), 3.62–3.70 (m, 1H, CH*H*–N), 4.49 (dd, *J*=3.0 and 9.8 Hz, 1H, S–C*H*–N), 6.84 (s, 1H, HC═); $^{13}$C

NMR (75.4 MHz, $CDCl_3$): $\delta$=21.8 (*C*$H_2$–C=), 26.7 (*C*$H_2$–CH–S), 29.8 ($CH_2$–S), 54.5 ($CH_2$–N), 60.0 (S–CH–N), 76.5 (=*C*–CN), 122.0 (CN), 143.8 (=CH); GC–MS (EI): *m*/*z*=166 ($M^+$, 100), 168 ([M+2]$^+$, 4); Anal. Calcd for $C_8H_{10}N_2S$: C, 57.80; H, 6.06; N, 16.85. Found: C, 58.92; H, 5.94; N, 16.56.

*3.4.2. (7R,8aS)-7-Methyl-2,3,8,8a-tetrahydro-7H-thiazolo[3,2-a]pyridine-6-carbonitrile (**20α**).* Yellow oil; $R_f$=0.27 ($CH_2Cl_2$); IR (film): 3362, 2958, 2925, 2869, 2180, 1612, 1438, 1410, 1359, 1216, 1175, 923 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$=1.24 (d, *J*=7.0 Hz, 3H, $CH_3$), 1.40 (ddd, *J*=10.9, 11.4 and 12.9 Hz, 1H, C*H*H–CH–S), 2.27 (ddd, *J*=3.6, 4.7, and 12.9 Hz, 1H, CH*H*–CH–S), 2.45–2.58 (m, 1H, C*H*–$CH_3$), 3.01 (t, *J*=6.1 Hz, 2H, S–$CH_2$), 3.65–3.70 (m, 2H, N–$CH_2$), 4.57 (dd, *J*=3.6 and 10.9 Hz, 1H, S–CH–N), 6.91 (d, *J*=1.7 Hz, 1H, HC=); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta$=19.0 ($CH_3$), 27.6 (*C*H–$CH_3$), 29.7 ($CH_2$–S), 37.0 ($CH_2$–CH–S), 54.4 ($CH_2$–N), 60.2 (S–CH–N), 81.7 (=*C*–CN), 121.6 (CN), 142.9 (=CH); GC–MS (EI): *m*/*z*=180 ($M^+$, 100), 182 ([M+2]$^+$, 5); Anal. Calcd for $C_9H_{12}N_2S$: C, 59.96; H, 6.71; N, 15.54. Found: C, 60.55; H, 6.76; N, 15.08.

*3.4.3. (7R,8aR)-7-Methyl-2,3,8,8a-tetrahydro-7H-thiazolo[3,2-a]pyridine-6-carbonitrile (**20β**).* Yellow oil; $R_f$=0.29 ($CH_2Cl_2$); IR (film): 2959, 2927, 2870, 2187, 1617, 1440, 1397, 1325, 1250, 1172, 1089, 911, 851, 692 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$=1.15 (d, *J*=7.0 Hz, 3H, $CH_3$), 1.81 (ddd, *J*=5.1, 9.1, and 13.4 Hz, 1H, C*H*H–CH–S), 2.03 (ddd, *J*=3.7, 4.0, and 13.4 Hz, 1H, CH*H*–CH–S), 2.55–2.66 (m, 1H, C*H*–$CH_3$), 2.97–3.02 (m, 2H, S–$CH_2$), 3.51–3.60 (m, 1H, N–C*H*H), 3.66–3.74 (m, 1H, N–CH*H*), 4.56 (dd, *J*=3.7 and 9.1 Hz, 1H, S–C*H*–N), 6.80 (s, 1H, HC=); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta$=20.8 ($CH_3$), 26.7 (*C*H–$CH_3$), 30.0 ($CH_2$–S), 33.7 (*C*$H_2$–CH–S), 54.7 ($CH_2$–N), 57.9 (S–CH–N), 83.9 (=*C*–CN), 121.6 (CN), 143.1 (=CH); GC–MS (EI): *m*/*z*=180 ($M^+$, 100), 182 ([M+2]$^+$, 5); Anal. Calcd for $C_9H_{12}N_2S$: C, 59.96; H, 6.71; N, 15.54. Found: C, 60.55; H, 6.76; N, 15.08.

*3.4.4. 7,7-Dimethyl-2,3,8,8a-tetrahydro-7H-thiazolo[3,2-a]pyridine-6-carbonitrile (**21**).* Yellow oil; $R_f$=0.34 (hexane/ethyl acetate (3:1)); IR (film): 3071, 2972, 2868, 2190, 1622, 1459, 1405, 1310, 1277, 1149, 955, 871, 712 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$=1.13 (s, 3H, $CH_3$), 1.24 (s, 3H, $CH_3$), 1.53 (dd, *J*=11.4 and 13.0 Hz, 1H, C*H*H–CH–S), 1.99 (dd, *J*=3.8 and 13.0 Hz, 1H, CH*H*–CH–S), 3.02 (t, *J*=6.2 Hz, 2H, S–$CH_2$), 3.62–3.75 (m, 2H, N–$CH_2$), 4.59 (dd, *J*=3.8 and 11.4 Hz, 1H, S–CH–N), 6.85 (s, 1H, HC=); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta$=28.3 ($CH_3$), 28.6 ($CH_3$), 29.8 ($CH_2$–S), 31.6 (*C*($CH_3$)$_2$), 42.5 (*C*$H_2$–CH–S), 54.6 ($CH_2$–N), 58.1 (S–CH–N), 86.1 (=*C*–CN), 121.0 (CN), 141.7 (=CH); GC–MS (EI): *m*/*z*=179 (100), 194 ($M^+$, 59), 196 ([M+2]$^+$, 3); Anal. Calcd for $C_{10}H_{14}N_2S$: C, 61.82; H, 7.26; N, 14.42. Found: C, 62.11; H, 7.19; N, 14.17.

*3.4.5. 5-Methyl-2,3,8,8a-tetrahydro-7H-thiazolo[3,2-a]pyridine-6-carbonitrile (**22**).* Yellow oil; $R_f$=0.37 ($CH_2Cl_2$); IR (film): 2930, 2854, 2179, 1690, 1630, 1590, 1422, 1326, 1247, 1174, 1103, 1050, 864, 702 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$=1.62–1.75 (m, 1H, C*H*H–$CH_2$–C=), 2.19 (s, 3H, $CH_3$), 2.21–2.28 (m, 1H, CH*H*–$CH_2$–C=), 2.32–2.37 (m, 2H, $CH_2$–C=), 2.96–3.05 (m, 2H, S–$CH_2$), 3.59–3.66 (m, 1H, N–C*H*H), 3.75–3.84 (m, 1H, N–CH*H*), 4.50 (dd, *J*=3.0 and 10.6 Hz, 1H, S–CH–N); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta$=19.4 ($CH_3$), 23.8 (*C*$H_2$–C=), 26.8 (*C*$H_2$–$CH_2$–C=), 28.9 (S–$CH_2$), 51.0 (N–$CH_2$), 61.8 (S–CH–N), 73.7 (=*C*–CN), 123.2 (CN), 151.9 (=*C*–$CH_3$); GC–MS (EI): *m*/*z*=180 ($M^+$, 100), 182 ([M+2]$^+$, 5); Anal. Calcd for $C_9H_{12}N_2S$: C, 59.96; H, 6.71; N, 15.54. Found: C, 61.47; H, 6.63; N, 15.13.

*3.4.6. (7R,8aS)-5,7-Dimethyl-2,3,8,8a-tetrahydro-7H-thiazolo[3,2-a]pyridine-6-carbonitrile (**23α**).* Yellow oil; $R_f$=0.27 ($CH_2Cl_2$); IR (film): 3517, 2956, 2927, 2849, 2174, 1589, 1424, 1374, 1306, 1259, 1190, 1118, 1056 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$=1.23 (d, *J*=6.9 Hz, 3H, $CH_3$–CH), 1.33–1.42 (m, 1H, CHH–CH–S), 2.20 (d, *J*=1.6 Hz, 3H, $CH_3$–C=), 2.22–2.29 (m, 1H, CHH–CH–S), 2.48–2.56 (m, 1H, CH–$CH_3$), 3.00–3.05 (m, 2H, S–$CH_2$), 3.63–3.80 (m, 2H, N–$CH_2$), 4.55 (dd, *J*=3.0 and 11.2 Hz, 1H, S–CH–N); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta$=19.8 ($CH_3$–C=), 19.9 ($CH_3$–CH), 28.6 ($CH_3$–CH), 28.9 ($CH_2$–S), 36.6 ($CH_2$–CH–S), 50.9 ($CH_2$–N), 61.6 (S–CH–N), 81.1 (=C–CN), 122.5 (CN), 150.4 (=C–$CH_3$); Anal. Calcd for $C_{10}H_{14}N_2S$: C, 61.82; H, 7.26; N, 14.42. Found: C, 62.49; H, 7.32; N, 14.08.

*3.4.7. (7R,8aR)-5,7-Dimethyl-2,3,8,8a-tetrahydro-7H-thiazolo[3,2-a]pyridine-6-carbonitrile (**23β**).* Yellow oil; $R_f$=0.34 ($CH_2Cl_2$); IR (film): 3517, 2956, 2927, 2849, 2174, 1589, 1424, 1374, 1307, 1259, 1190, 1119, 1056 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$=1.12 (d, *J*=7.0 Hz, 3H, $CH_3$–CH), 1.74 (m, 1H, CHH–CH–S), 1.97 (ddd, *J*=2.8, 2.9, and 12.9 Hz, 1H, CHH–CH–S), 2.18 (s, 3H, $CH_3$–C=), 2.55–2.60 (m, 1H, CH–$CH_3$), 2.94–3.08 (m, 2H, $CH_2$–S), 3.59–3.66 (m, 1H, CHH–N), 3.77–3.85 (m, 1H, CHH–N), 4.52 (dd, *J*=3.2 and 10.7 Hz, 1H, S–CH–N); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta$=19.6 ($CH_3$–C=), 21.7 ($CH_3$–CH), 28.5 ($CH_3$–CH), 29.0 ($CH_2$–S), 33.6 ($CH_2$–CH–S), 51.1 ($CH_2$–N), 58.4 (S–CH–N), 81.0 (=C–CN), 122.8 (CN), 150.8 (=C–$CH_3$); Anal. Calcd for $C_{10}H_{14}N_2S$: C, 61.82; H, 7.26; N, 14.42. Found: C, 62.49; H, 7.32; N, 14.08.

*3.4.8. 5-Methyl-7-propyl-2,3,8,8a-tetrahydro-7H-thiazolo[3,2-a]pyridine-6-carbonitrile (**24α+β**).* Yellow oil; $R_f$=0.35 ($CH_2Cl_2$); IR (film): 3369, 2956, 2928, 2870, 2180, 1692, 1585, 1422, 1378, 1342, 1306, 1263, 1168, 1120, 1057, 866, 745 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$=0.86–0.92 (m, 3H, $CH_2$–C*H*$_3$), 1.15–1.47 (m, 4H, CH–C*H*$_2$C*H*$_2$CH$_3$), 1.48–1.68 (m, 1H, S–CH–C*H*H), 2.02–2.10 (m, 1H, S–CH–CH*H*), 2.18 (s, 3H, $CH_3$–C=), 2.25–2.39 (m, 1H, =C–CH), 2.96–3.02 (m, 2H, S–$CH_2$), 3.61–3.80 (m, 2H, N–$CH_2$), 4.45–4.49 (m, 1H, S–CH–N); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta$=13.9 ($CH_2CH_3$), 14.0 ($CH_2CH_3$), 19.4 (*C*$H_2$CH$_3$), 19.5 (=C–*C*H$_3$), 19.8 (*C*$H_2$CH$_3$), 19.8 (=C–*C*H$_3$), 28.9 (S–$CH_2$), 28.9 (S–$CH_2$), 30.7 (*C*$H_2$CH$_2$CH$_3$), 33.1 (*C*$H_2$CH$_2$CH$_3$), 33.5 (=C–*C*H), 33.6 (=C–*C*H), 36.1 (S–*C*HCH$_2$), 38.3 (S–*C*HCH$_2$), 50.9 (N–$CH_2$), 51.1 (N–$CH_2$), 58.6 (S–CH–N), 61.7 (S–CH–N), 79.3 (=*C*–CN), 79.9 (=*C*–CN), 122.3 (CN), 123.4 (CN), 150.9 (=*C*–$CH_3$), 151.8 (=*C*–$CH_3$); GC–MS (EI): *m*/*z*=179 (100), 222 ($M^+$, 21), 224 ([M+2]$^+$, 3).

*3.4.9. (7S,8aS)-5-Methyl-7-phenyl-2,3,8,8a-tetrahydro-7H-thiazolo[3,2-a]pyridine-6-carbonitrile (**25α**).* Yellow oil; $R_f$=0.27 ($CH_2Cl_2$); IR (film): 3026, 2925, 2864, 2181, 1686, 1577, 1493, 1425, 1342, 1299, 1265, 1232, 1058, 912, 860, 759, 730, 702 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$=1.82 (ddd, *J*=11.2, 11.7, and 12.9 Hz, 1H, C*H*H–CH–S), 2.28 (s, 3H, $CH_3$–C=), 2.40–2.47 (ddd, *J*=2.9, 5.3, and 12.9 Hz, 1H, CH*H*–CH–S), 3.06 (dd, *J*=5.5 and 7.0 Hz, 2H, S–C*H*$_2$), 3.66–3.85 (m, 3H, N–C*H*$_2$ and C*H*–Ph), 4.68 (dd, *J*=2.9 and 11.2 Hz, 1H, S–CH–N), 7.17–7.37 (m, 5H, Ph); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta$=19.9 ($CH_3$), 28.9 (S–$CH_2$), 37.8 (S–*C*H$CH_2$), 41.3 (*C*H–Ph), 51.1 (N–$CH_2$), 61.6 (S–CH–N), 79.6 (=*C*–CN), 122.0 (CN), 127.1 (CH, Ph), 127.4 (2CH, Ph), 128.6 (2CH, Ph), 141.9 (C, Ph), 152.6 (=*C*–$CH_3$); GC–MS (EI): *m*/*z*=256 ($M^+$, 100), 258 ([M+2]$^+$, 6); Anal. Calcd for $C_{15}H_{16}N_2S$: C, 70.27; H, 6.29; N, 10.93. Found: C, 70.85; H, 6.23; N, 10.75.

*3.4.10. (7S,8aR)-5-Methyl-7-phenyl-2,3,8,8a-tetrahydro-7H-thiazolo[3,2-a]pyridine-6-carbonitrile (**25β**).* Yellow oil; $R_f$=0.38 ($CH_2Cl_2$); IR (film): 3370, 3059, 3025, 2928, 2870, 2181, 1588, 1494, 1426, 1343, 1314, 1265, 1180, 1104, 1052, 949, 912, 864, 756, 731, 702, 648 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$=1.91–2.00 (m, 1H, C*H*H–CH–S), 2.24 (ddd, *J*=2.6, 2.7, and 12.8 Hz, 1H, CH*H*–CH–S), 2.35 (s, 3H, C*H*$_3$–C=), 2.96–3.01 (m, 2H, S–C*H*$_2$), 3.72–3.83 (m, 3H, N–C*H*$_2$ and C*H*–Ph), 4.27 (dd, *J*=3.1 and 11.4 Hz, 1H, N–CH–S), 7.32–7.17 (m, 5H, Ph); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta$=19.7 ($CH_3$), 28.8 (S–$CH_2$), 34.9 (S–CH–*C*H$_2$), 39.9 (CH–Ph), 51.4 (N–$CH_2$), 57.9 (S–CH–N), 75.4 (=*C*–CN), 122.8 (CN), 126.7 (CH, Ph), 127.7 (2CH, Ph), 128.4 (2CH, Ph), 143.2 (C, Ph), 152.7 (=C–N);

GC–MS (EI): $m/z$=256 ($M^+$, 100), 258 ([M+2]$^+$, 6); Anal. Calcd for $C_{15}H_{16}N_2S$: C, 70.27; H, 6.29; N, 10.93. Found: C, 70.85; H, 6.23; N, 10.75.

*3.4.11. 2,3,8,8a-Tetrahydro-5,7,7-trimethyl-7H-thiazolo[3,2-a]pyridine-6-carbonitrile (**26**).* Yellow oil; $R_f$=0.41 ($CH_2Cl_2$); IR (film): 3314, 2960, 2866, 2177, 1692, 1583, 1420, 1344, 1303, 1265, 1191, 1058, 868, 635 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$=1.12 (s, 3H, $CH_3$), 1.24 (s, 3H, $CH_3$), 1.55 (dd, $J$=11.7 and 12.8 Hz, 1H, C*H*H–CH–S), 1.98 (dd, $J$=3.2 and 12.8 Hz, 1H, CH*H*–CH–S), 2.18 (s, 3H, $CH_3$–C=), 3.02–3.06 (m, 2H, S–C$H_2$), 3.64–3.71 (m, 1H, N–C$H_2$), 3.75–3.83 (m, 1H, N–C$H_2$), 4.56 (dd, $J$=3.2 and 11.7 Hz, 1H, S–C*H*–N); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta$=19.9 (*C*H$_3$–C=), 28.9 ($CH_2$–S), 29.1 ($CH_3$), 29.2 ($CH_3$), 32.0 (*C*(CH$_3$)$_2$), 42.0 (*C*H$_2$–CH–S), 51.1 ($CH_2$–N), 59.2 (S–CH–N), 85.2 (=C–CN), 121.8 (CN), 150.1 (=*C*–CH$_3$); GC–MS (EI): $m/z$=193 (100), 208 ($M^+$, 28), 210 ([M+2]$^+$, 1); Anal. Calcd for $C_{11}H_{16}N_2S$: C, 63.42; H, 7.74; N, 13.45. Found: C, 63.97; H, 7.70; N, 13.21.

*3.4.12. (8R,8aR)-5,8-Dimethyl-2,3,8,8a-tetrahydro-7H-thiazolo[3,2-a]pyridine-6-carbonitrile (**27α**).* Yellow oil; $R_f$=0.35 ($CH_2Cl_2$); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$=1.08 (d, $J$=6.5 Hz, 3H, CHC*H*$_3$), 1.66–1.79 (m, 1H, CH$_3$C*H*–CH$_2$–S), 2.02–2.07 (m, 1H, C*H*H–C=), 2.19 (s, 3H, =C–CH$_3$), 2.32 (dd, $J$=4.6 and 15.8 Hz, 1H, CH*H*–C=), 2.97–3.02 (m, 2H, N–CH$_2$), 3.64–3.72 (m, 1H, S–C*H*H), 3.78–3.86 (m, 1H, S–CH*H*), 4.15 (d, $J$=9.8 Hz, 1H, S–CH–N); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta$=19.3 (CH*C*H$_3$), 19.5 (=C–*C*H$_3$), 28.6 (=C–*C*H$_2$), 32.2 (S–CH$_2$), 32.8 (*C*HCH$_3$), 51.5 (N–CH$_2$), 68.7 (S–CH–N), 74.2 (=*C*–CN), 123.0 (CN), 151.6 (=*C*–CH$_3$); Anal. Calcd for $C_{10}H_{14}N_2S$: C, 61.82; H, 7.26; N, 14.42. Found: C, 62.17; H, 7.22; N, 14.30.

*3.4.13. (8S,8aR)-5,8-Dimetil-2,3,8,8a-tetrahidro-7H-tiazolo[3,2-a]piridina-6-carbonitrilo (**27β**).* Yellow oil; $R_f$=0.35 ($CH_2Cl_2$); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$=0.98 (d, $J$=6.7 Hz, 3H, CHC*H*$_3$), 2.15 (s, 3H, =C–CH$_3$), 2.19–2.43 (m, 3H, CH$_3$C*H*–C*H*$_2$–C=), 2.81–2.99 (m, 2H, N–CH$_2$), 3.41–3.49 (m, 1H, S–C*H*H), 3.86–3.93 (m, 1H, S–CH*H*), 4.69 (d, $J$=2.8 Hz, 1H, S–CH–N); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta$=14.7 (CH*C*H$_3$), 19.1 (=C–*C*H$_3$), 28.2 (*C*HCH$_3$), 29.0 (=C–*C*H$_2$), 30.1 (S–CH$_2$), 51.4 (N–CH$_2$), 67.4 (S–CH–N), 75.7 (=*C*–CN), 122.8 (CN), 151.6 (=*C*–CH$_3$); Anal. Calcd for $C_{10}H_{14}N_2S$: C, 61.82; H, 7.26; N, 14.42. Found: C, 62.17; H, 7.22; N, 14.30.

*3.4.14. 2,5-Dimethyl-2,3,8,8a-tetrahydro-7H-thiazolo[3,2-a]pyridine-6-carbonitrile (**28α+β**).* Yellow oil; $R_f$=0.40 ($CH_2Cl_2$); IR (film): 3450, 2963, 2927, 2855, 2181, 1694, 1630, 1592, 1422, 1393, 1326, 1246, 1189, 1132, 1035, 848, 698 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$=1.36 (d, $J$=8.0 Hz, 3H, C*H*$_3$–CH–S (β)), 1.38 (d, $J$=6.5 Hz, 3H, C*H*$_3$–CH–S (α)), 1.63–1.76 (m, 2H, C*H*H–CH–S (α+β)), 2.15 (s, 3H, CH$_3$–C= (α)), 2.16 (s, 3H, CH$_3$–C= (β)), 2.18–2.25 (m, 2H, CH*H*–CH–S (α+β)), 2.31–2.35 (m, 4H, C*H*$_2$–C= (α+β)), 3.19 (dd, $J$=6.4 and 10.7 Hz, 1H, N–C*H*H (α)), 3.35 (dd, $J$=7.2 and 10.1 Hz, 1H, N–C*H*H (β)), 3.46–3.60 (m, 2H, CH$_3$–C*H*–S (α+β)), 3.71 (dd, $J$=5.1 and 10.2 Hz, 1H, N–CH*H* (β)), 3.94 (dd, $J$=5.8 and 10.7 Hz, 1H, N–CH*H* (α)), 4.59 (dd, $J$=3.1 and 10.7 Hz, 1H, S–C*H*–N (β)), 4.64 (dd, $J$=3.2 and 10.3 Hz, 1H, S–C*H*–N (α)); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta$=18.3 (=C–*C*H$_3$ (β)), 18.8 (=C–*C*H$_3$ (α)), 19.5 (S–C–*C*H$_3$ (α)), 20.1 (S–C–*C*H$_3$ (β)), 23.6 (=C–*C*H$_2$ (α)), 23.9 (=C–*C*H$_2$ (β)), 27.2 (=C–CH$_2$–*C*H$_2$ (β)), 27.6 (=C–CH$_2$–*C*H$_2$ (α)), 39.8 (S–CH (β)), 39.9 (S–CH (α)), 58.2 (N–CH$_2$ (β)), 58.3 (N–CH$_2$ (α)), 61.4 (S–CH–N (α)), 63.0 (S–CH–N (β)), 73.6 (=*C*–CN (β)), 74.8 (=*C*–CN (α)), 123.0 (CN (α)), 123.2 (CN (β)), 151.8 (=*C*–CH$_3$ (α)), 151.9 (=*C*–CH$_3$ (β)); GC–MS (EI): $m/z$=135 (100), 194 ($M^+$, 28).

*3.4.15. (2S,8aR)-5-Methyl-2-phenyl-2,3,8,8a-tetrahydro-7H-thiazolo[3,2-a]pyridine-6-carbonitrile (**29α**).* Yellow oil; $R_f$=0.36 ($CH_2Cl_2$); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$=1.81–1.92 (m, 1H, C*H*H–CH$_2$–C–CN), 2.11 (s, 3H, $CH_3$), 2.25–2.41 (m, 3H, CH*H*–C*H*$_2$–C–CN), 3.75 (dd, $J$=7.4 and 10.7 Hz, 1H, N–C*H*H), 3.93 (dd, $J$=6.3 and 10.7 Hz, 1H, N–CH*H*), 4.54–4.62 (m, 1H, S–CH–Ph), 4.74 (dd, $J$=3.1 and 10.6 Hz, 1H, S–CH–N), 7.28–7.41 (m, 5H, Ph); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta$=19.5 ($CH_3$), 23.8 ($CH_2$–C=), 26.7 ($CH_2$–$CH_2$–C=), 49.0 (S–CH–Ph), 58.6 ($CH_2$–N), 63.3 (S–CH–N), 77.1 (=*C*–CN), 122.9 (CN), 127.5 (2CH, Ph), 128.1 (CH, Ph), 128.8 (2CH, Ph), 138.2 (C, Ph), 151.6 (N–C=); GC–MS (EI): $m/z$=179 (100), 252 ($M^+$, 24), 254 ([M+2]$^+$, 1); Anal. Calcd for $C_{15}H_{16}N_2S$: C, 70.27; H, 6.29; N, 10.93. Found: C, 70.75; H, 6.23; N, 10.83.

*3.4.16. (2R,8aR)-5-Methyl-2-phenyl-2,3,8,8a-tetrahydro-7H-thiazolo[3,2-a]pyridine-6-carbonitrile (**29β**).* Yellow oil; $R_f$=0.36 ($CH_2Cl_2$); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$=1.80–1.89 (m, 1H, C*H*H–CH$_2$–C–CN), 2.20 (s, 3H, $CH_3$), 2.20–2.26 (m, 1H, CH*H*–CH$_2$–C–CN), 2.30–2.41 (m, 2H, CH$_2$–C–CN), 3.61 (dd, $J$=7.3 and 11.2 Hz, 1H, N–C*H*H), 4.17 (dd, $J$=6.0 and 11.2 Hz, 1H, N–CH*H*), 4.57 (dd, $J$=6.0 and 7.3 Hz, 1H, S–CH–Ph), 4.83 (dd, $J$=3.2 and 9.6 Hz, 1H, S–CH–N), 7.28–7.41 (m, 5H, Ph); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta$=19.5 ($CH_3$), 23.3 ($CH_2$–C=), 27.4 ($CH_2$–$CH_2$–C=), 49.2 (S–CH–Ph), 58.5 ($CH_2$–N), 62.4 (S–CH–N), 77.2 (=*C*–CN), 122.6 (CN), 127.4 (2CH, Ph), 127.9 (CH, Ph), 128.8 (2CH, Ph), 139.0 (C, Ph), 151.5 (N–C=); Anal. Calcd for $C_{15}H_{16}N_2S$: C, 70.27; H, 6.29; N, 10.93. Found: C, 70.75; H, 6.23; N, 10.83.

*3.4.17. (3S,8aS)-3-Ethyl-5-methyl-2,3,8,8a-tetrahydro-7H-thiazolo[3,2-a]pyridine-6-carbonitrile (**30α**).* Yellow oil; $R_f$=0.40 ($CH_2Cl_2$); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$=0.95 (t, $J$=7.5 Hz, 3H, CH$_2$C*H*$_3$), 1.53–1.64 (m, 1H, C*H*H–CH$_2$–C=), 1.66–1.82 (m, 2H, C*H*$_2$CH$_3$), 2.19 (s, 3H, =C–CH$_3$), 2.21–2.26 (m, 1H, CH*H*–CH$_2$–C=), 2.29–2.35 (m, 2H, CH$_2$–C=), 2.77 (dd, $J$=1.0 and 10.6 Hz, 1H, S–C*H*H–CH-Et), 3.06 (dd, $J$=6.1 and 10.6 Hz, 1H, S–CH*H*–CH–Et), 4.15–4.22 (m, 1H, CH–Et), 4.52 (dd, $J$=3.5 and 10.0 Hz, 1H, S–CH–N); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta$=10.8 (CH$_2$*C*H$_3$), 19.3 (=C–*C*H$_3$), 23.3 (*C*H$_2$CH$_3$), 25.9 (*C*H$_2$–C=), 28.3 (CH$_2$–S), 32.1 (*C*H$_2$CH$_2$–C=), 59.0 (CH–Et), 63.2 (S–CH–N), 74.8 (=*C*–CN), 123.1 (CN), 151.2 (=*C*–CH$_3$); Anal. Calcd for $C_{11}H_{16}N_2S$: C, 63.42; H, 7.74; N, 13.45. Found: C, 63.81; H, 7.68; N, 13.38.

*3.4.18. (3S,8aR)-3-Ethyl-5-methyl-2,3,8,8a-tetrahydro-7H-thiazolo[3,2-a]pyridine-6-carbonitrile (**30β**).* Yellow oil; $R_f$=0.40 ($CH_2Cl_2$); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$=0.91 (t, $J$=7.5 Hz, 3H, CH$_2$C*H*$_3$), 1.39–1.58 (m, 2H, C*H*$_2$CH$_2$–C=), 1.64–1.80 (m, 2H, C*H*$_2$CH$_3$), 2.22 (s, 3H, =C–CH$_3$), 2.28–2.36 (m, 2H, CH$_2$–C=), 2.76 (d, $J$=11.7 Hz, 1H, S–C*H*H–CH–Et), 3.11 (ddd, $J$=1.8, 5.7, and 11.7 Hz, 1H, S–CH*H*–CH–Et), 3.88–3.94 (m, 1H, CH–Et), 4.41 (dd, $J$=2.1 and 11.1 Hz, 1H, S–CH–N); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta$=11.3 (CH$_2$*C*H$_3$), 19.3 (=C–*C*H$_3$), 25.0 (*C*H$_2$CH$_3$), 27.6 (*C*H$_2$–C=), 28.2 (CH$_2$–S), 32.6 (CH$_2$CH$_2$–C=), 62.2 (CH–Et), 63.9 (CH–S), 76.3 (=*C*–CN), 123.1 (CN), 151.4 (=*C*–CH$_3$); Anal. Calcd for $C_{11}H_{16}N_2S$: C, 63.42; H, 7.74; N, 13.45. Found: C, 63.81; H, 7.68; N, 13.38.

*3.4.19. 5-Methyl-3-phenyl-2,3,8,8a-tetrahydro-7H-thiazolo[3,2-a]pyridine-6-carbonitrile (**31α+β**).* Yellow oil; $R_f$=0.37 ($CH_2Cl_2$); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$=1.73–1.87 (m, 2H, C*H*H–CH$_2$–C–CN (α+β)), 1.93 (s, 3H, CH$_3$ (β)), 2.02 (s, 3H, CH$_3$ (α)), 2.23–2.47 (m, 6H, CH*H*–C*H*$_2$–C–CN (α+β)), 2.81 (d, $J$=11.8 Hz, 1H, S–C*H*H (β)), 3.01 (dd, $J$=5.6 and 11.6 Hz, 1H, S–C*H*H (α)), 3.47 (dd, $J$=6.8 and 11.6 Hz, 1H, S–CH*H* (α)), 3.55 (dd, $J$=6.8 and 11.8 Hz, 1H, S–CH*H* (β)), 4.66 (dd, $J$=2.1 and 11.1 Hz, 1H, S–CH–N (β)), 4.79 (dd, $J$=3.4 and 10.8 Hz, 1H, S–CH–N (α)), 5.18 (d, $J$=6.8 Hz, 1H, CH–Ph (β)), 5.28 (dd, $J$=5.6 and 6.8 Hz, 1H, CH–Ph (α)), 7.19–7.53 (m, 10H, 2Ph); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta$=19.4 (CH$_3$ (α)), 19.7 (CH$_3$ (β)), 24.0 (=C–CH$_2$–*C*H$_2$ (α)), 24.6 (=C–CH$_2$–*C*H$_2$ (β)), 26.1 (=C–*C*H$_2$ (β)), 28.2 (=C–*C*H$_2$ (α)), 37.5 (S–*C*H$_2$–CH–Ph (α)), 38.5 (S–*C*H$_2$–CH–Ph (β)), 63.1 (S–CH–N (α)), 63.6 (S–CH–N (β)), 65.3 (CH–Ph (β)), 66.0 (CH–Ph (α)), 74.4 (=*C*–CN (β)), 74.9 (=*C*–CN (α)), 122.9 (CN (α)), 123.0 (CN (β)), 125.2 (2CH, Ph), 125.9 (2CH, Ph), 127.8 (CH, Ph), 127.8 (CH, Ph), 128.5 (2CH, Ph),

129.0 (2CH, Ph), 141.5 (C, Ph (α)), 142.5 (C, Ph (β)), 152.0 (N–C═ (β)), 152.2 (N–C═ (α)).

*3.4.20. 5-Benzyl-2,3,8,8a-tetrahydro-7H-thiazolo[3,2-a]pyridine-6-carbonitrile (**33**).* Yellow oil; $R_f$=0.31 (hexane/ethyl acetate (4:1)); $^1$H NMR (300 MHz, $CDCl_3$): δ=1.66–1.76 (m, 1H, ═C–$CH_2$–C*H*H), 2.18–2.29 (m, 1H, ═C–$CH_2$–CH*H*), 2.34–2.39 (m, 2H, ═C–$CH_2$), 2.72–2.98 (m, 6H, S–$CH_2$ and ═C–$CH_2CH_2$–Ph), 3.46–3.54 (m, 1H, C*H*H–N), 3.67–3.75 (m, 1H, C*H*H–N), 4.48 (dd, *J*=3.1 and 10.4 Hz, 1H, S–CH–N), 7.21–7.25 (m, 5H, Ph); $^{13}$C NMR (75.4 MHz, $CDCl_3$): δ=23.8 (*C*$H_2$–C═), 27.1 (*C*$H_2$–CH–S), 29.0 ($CH_2$–S), 34.9 (*C*$H_2$*C*$H_2$–Ph), 50.8 ($CH_2$–N), 61.9 (S–CH–N), 76.2 (═*C*–CN), 122.5 (CN), 126.5 (CH, Ph), 128.4 (2CH, Ph), 128.5 (2CH, Ph), 139.8 (C, Ph), 155.2 (═C–N); Anal. Calcd for $C_{15}H_{16}N_2S$: C, 70.27; H, 6.29; N, 10.93. Found: C, 70.63; H, 6.31; N, 10.75.

*3.4.21. 5-Phenyl-2,3,8,8a-tetrahydro-7H-thiazolo[3,2-a]pyridine-6-carbonitrile (**36**).* Yellow oil; $R_f$=0.29 (hexane/ethyl acetate (4:1)); IR (film): 3366, 3058, 2929, 2851, 2189, 1965, 1817, 1693, 1586, 1494, 1325, 1248, 1146, 1034, 931, 764 $cm^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): δ=1.88–2.05 (m, 1H, ═C–$CH_2$–CHH), 2.30–2.46 (m, 2H, ═C–CHH–CHH), 2.58–2.68 (m, 1H, ═C–CHH), 2.75–2.92 (m, 2H, S–$CH_2$), 3.23–3.31 (m, 1H, CHH–N), 3.36–3.44 (m, 1H, CHH–N), 4.76 (dd, *J*=3.3 and 7.8 Hz, 1H, S–CH–N), 7.42 (m, 5H, Ph); $^{13}$C NMR (75.4 MHz, $CDCl_3$): δ=23.2 ($CH_2$–C═), 26.7 ($CH_2$–CH–C═), 29.6 ($CH_2$–S), 53.5 ($CH_2$–N), 62.1 (S–CH–N), 80.7 (═C–CN), 122.0 (CN), 128.5 (2CH, Ph), 128.6 (2CH, Ph), 129.7 (CH, Ph), 135.0 (C, Ph), 156.1 (═C–Ph); GC–MS (EI): *m*/*z*=242 ($M^+$, 100), 244 ($[M+2]^+$, 6); Anal. Calcd for $C_{14}H_{14}N_2S$: C, 69.39; H, 5.82; N, 11.56. Found: C, 69.62; H, 5.79; N, 11.39.

## 4. Conclusions

Although the synthetic interest of the multicomponent reaction for the preparation of thiazolopyridines is evident and their usefulness for the construction of libraries of compounds has been proven, the stereochemical control is rather low and has some limitations. The mechanistic proposal however seems to be in good agreement with the observed stereocontrol.

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## References and notes

1. Greenhill, J. V. *Chem. Soc. Rev.* **1977**, *6*, 277.
2. Kuckländer, U. "The Chemistry of Enaminones", Part 1 In *The Chemistry of Funcional Groups*; Rappoport, Z., Ed.; John Wiley: New York, NY, 1994.
3. (a) Lue, P.; Greenhill, J. V. "Enaminones in Heterocyclic Synthesis" In. *Advances in Heterocyclic Chemistry*; Katritzky, A., Ed.; Academic: New York, NY, 1977; Vol. 67, p 207; (b) Abdel-Zaher, A. E.; El-Khair, A. A. *Tetrahedron* **2003**, *59*, 8463; (c) Negri, G.; Kascheres, C.; Kascheres, A. J. *J. Heterocycl. Chem.* **2004**, *41*, 461.
4. (a) Dondoni, A.; Massi, A.; Minghini, E.; Bertolasi, V. *Tetrahedron* **2004**, *60*, 2311; (b) Orru, R. V. A.; de Greef, M. *Synthesis* **2003**, 1471; (c) Wan, J.-P.; Gan, S.-F.; Sun, G.-L.; Pan, Y.-J. *J. Org. Chem.* **2009**, *74*, 2862; (d) Bartoli, G.; Bosco, M.; Galzerano, P.; Giri, R.; Mazzanti, A.; Melchiorre, P.; Sambri, L. *Eur. J. Org. Chem.* **2008**, 3970; (e) Li, M.; Zuo, Z.; Wen, L.; Wang, S. *J. Comb. Chem.* **2008**, *10*, 436; (f) Sridharan, V.; Perumal, P. T.; Avendaño, C.; Menéndez, J. C. *Tetrahedron* **2007**, *63*, 4407; (g) Evdokimov, N. M.; Kireev, A. S.; Yakovenko, A. A.; Antipin, M. Y.; Magedov, I. V.; Kornienko, A. *J. Org. Chem.* **2007**, *72*, 3443; (h) Evdokimov, N. M.; Magedov, I. V.; Kireev, A. S.; Kornienko, A. *Org. Lett.* **2006**, *8*, 899.
5. (a) Nemes, P.; Balázs, B.; Tóth, G. *Synlett* **2000**, 1327; (b) Paravidino, M.; Bon, R. S.; Scheffelaar, R.; Vugts, D. J.; Znabet, A.; Schmitz, R. F.; Kanter, F. J. J.; Lutz, M.; Spek, A. L.; Groen, M. B.; Orru, R. V. A. *Org. Lett.* **2006**, *8*, 5369; (c) Gorobets, N. Y.; Yousefi, B. H.; Belaj, F.; Kappe, C. O. *Tetrahedron* **2004**, *60*, 8633.
6. (a) Lu, W.; Song, W.; Hong, D.; Lu, P.; Wang, Y. *Adv. Synth. Catal.* **2009**, *351*, 1768; (b) Muravyova, E. A.; Desenko, S. M.; Musatov, V. I.; Knyazeva, I. V.; Shishkina, S. V.; Shishkin, O. V.; Chebanov, V. A. *J. Comb. Chem.* **2007**, *9*, 797; (c) Zhang, M.; Jiang, H.-F. *Eur. J. Org. Chem.* **2008**, 3519.
7. (a) Dömling, A. *Chem. Rev.* **2006**, *106*, 17; (b) Thompson, M. J.; Chen, B. *Tetrahedron Lett.* **2008**, *49*, 5324; (c) Shestopalov, A. M.; Shestopalov, A. A.; Rodinovskayo, L. A. *Synthesis* **2008**, 1.
8. (a) Simon, C.; Constantieux, T.; Rodriguez, J. *Eur. J. Org. Chem.* **2004**, 4957; (b) Li, M.; Zuo, Z.; Wen, L.; Wang, S. *J. Comb. Chem.* **2008**, *10*, 436.
9. Calvo, L. A.; González-Ortega, A.; Marcos, R.; Pérez, M.; Sañudo, M. C. *Tetrahedron* **2008**, *64*, 3691.
10. Simon, C.; Peyronel, J.-F.; Rodriguez, J. *Org. Lett.* **2001**, *3*, 2145.
11. Caballero, E.; Puebla, P.; Medarde, M.; Honores, Z.; Sastre, P.; López, J. L.; San Feliciano, A. *Tetrahedron Lett.* **1998**, *39*, 455.
12. Compound **43** and analogous thiazolidines can be prepared in high yield (%>85) by reaction of β-enaminonitrile with cysteamine hydrochloride (1:1.2 ratio) in acetonitrile at rt NMR spectra show that equilibrium is largely shifted to cyclic tautomer **43b** where the AB coupling system corresponding to cyanomethylene ($CH_2CN$) is easily recognizable in the crude.
13. Caballero, E.; Puebla, P.; Medarde, M.; San Feliciano, A. *Tetrahedron* **1993**, *49*, 10079.
14. Catalytic hydrogenation (Ni-Raney in ethanol at rt) of 3,5-dimethyl-4-(3-oxobutyl)isoxazole gives 3-(1-aminoethylidene)heptane2,6-dione, which spontaneously cyclizes to 3-acetyl-2,6-dimethylpyridine.
15. Caballero, E.; Puebla, P.; Sánchez, M.; Medarde, M.; Morán del Prado, L.; San Feliciano, A. *Tetrahedron: Asymmetry* **1996**, *7*, 1985.
16. Caballero, E.; Puebla, P.; Medarde, M.; Sanchez, M.; Salvado, M. A.; Garcia-Granda, S.; San Feliciano, A. *J. Org. Chem.* **1996**, *61*, 1890.
17. Rodolfo, L.; Oscar, C.; Marta, N.; Bilal, A. S.; Javier, T.; Joan, B. *Eur. J. Org. Chem.* **1999**, 2997.
18. Potekhin, A. A.; Sokolov, V. V.; Ogloblin, K. A.; Esakov, S. M. *Chem. Heterocycl. Compd.* **1983**, 622.
19. Kaafarani, M.; Crozet, M. P.; Surzur, J. M. *Bull. Soc. Chim. Fr.* **1989**, *1*, 114.
20. Lue, P.; Greenhill, J. In *Adv. Heterocyclic. Chem.*; Katritzky, A. R., Ed.; Academic: New York, NY, 1997; Vol. 67, p 207.
21. Hackler, R. E.; Burow, K. W.; Kaster, S. V.; Wickiser, D. I. *J. Heterocycl. Chem.* **1989**, *26*, 1575.
22. Ridge, D. N.; Hanifin, J. W.; Harten, L. A.; Johnson, B. D.; Menschik, J.; Nicolau, G.; Sloboda, A. E.; Watts, D. E. *J. Med. Chem.* **1979**, *22*, 1385.
23. Larice, J. L.; Roggero, J.; Metzger, J. *Bull. Soc. Chim.* **1967**, 3637.