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Synthesis of Fused Heterocycles from Heterocyclic Enaminones†

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Abstract. The reactivity of readily prepared heterocyclic enaminones with some doubly electrophilic reagents is described. Different classes of interesting fused heterocyclic systems are obtained from these enaminones in a single reaction.

The reactivity of enaminones as dinucleophiles with a wide variety of doubly electrophilic systems, to give different types of heterocyclic compounds is well known.[1] For example, the reaction of cyanoacrylates with quinones or Knoevenagel products are cited in the literature as suitable ways to synthesize pyrrolinones,[2] indoles[3] or 1,4-dihydropyridines.[4] Due to the pharmacological activities displayed by many polysubstituted polyheterocyclic compounds, it is of interest to introduce new strategies for synthesizing complex condensed heterocyclic compounds. With this aim, we have studied the reactivity of two heterocyclic enaminones prepared by us, with different α,β-unsaturated carbonyl compounds.

In previous papers we described the preparation of three different families of fused heterocycles[5] (Figure 1a), which showed long lasting antihypertensive activity.[6] The presence in the enaminone of a functionalized alkyl chain carrying a heteroatom with unshared electron pairs (X atom), promoted further cyclizations to dihydropyridines fused with other heterocyclic rings. We have now moved to the use of cyclized starting enaminones, containing the X atom incorporated into a heterocycle, as a way to prepare other types of fused heterocyclic systems (Figure 1b). In this paper we describe the synthesis of 1,4-benzothiazines, pyrido[2,1-*c*]thiazines, phenothiazines and pyrido[2,1-*c*] [1,4]benzothiazines, starting from dihydro-1,4-thiazine enaminones (Figure 1b, X=S). There are described in the literature many pharmacological activities for these type of fused compounds, such as calcium antagonism, antifungal, antipsychotic or antiprotozoal properties.[7]

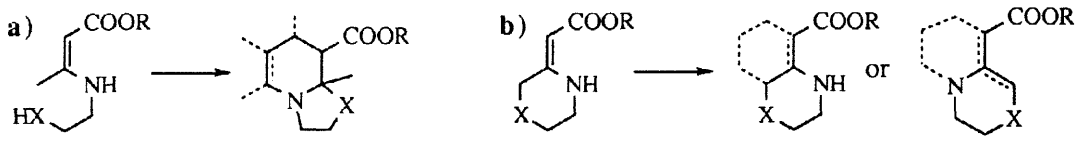

Figure 1. a) Previously prepared fused dihydropyridines from acyclic enaminones
b) Fused heterocycles from heterocyclic enaminones (X=S)

† Dedicated to the memory of Professor Joaquín de Pascual Teresa.

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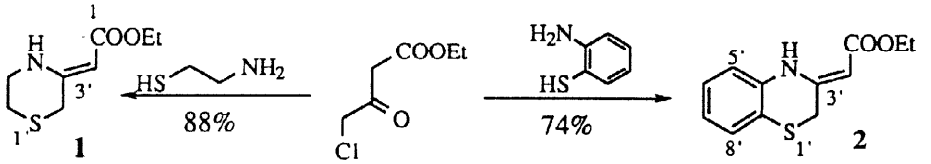
Methods and Results

The heterocyclic enaminones **1** and **2** were obtained in high yield using ethyl 4-chloroacetylacetate and 2-thioethanolamine or 2-aminothiophenol as starting materials (Scheme 1).

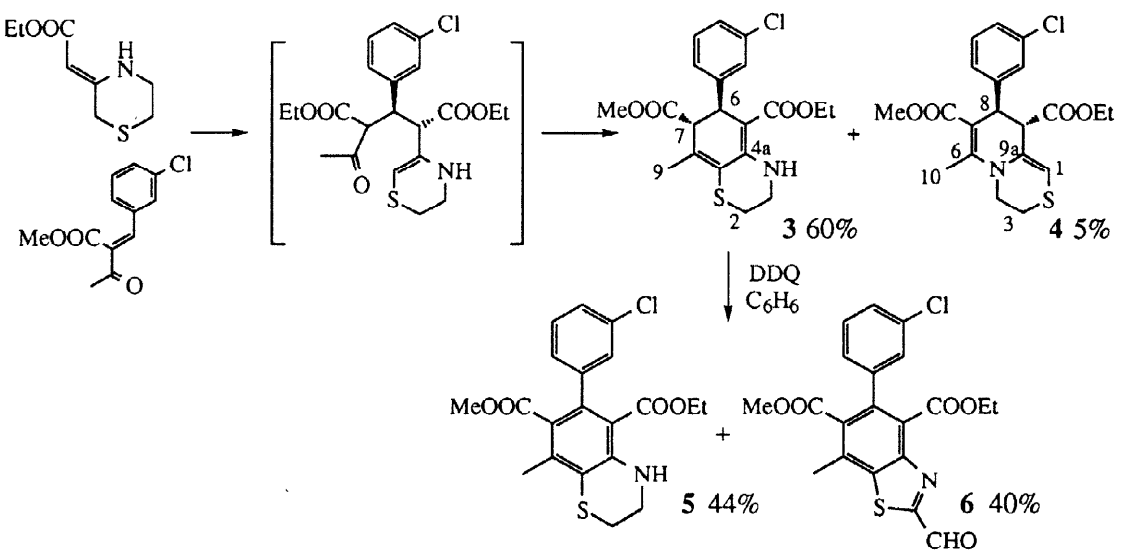


1 **2**

Scheme 1. Synthesis of starting materials **1** and **2**

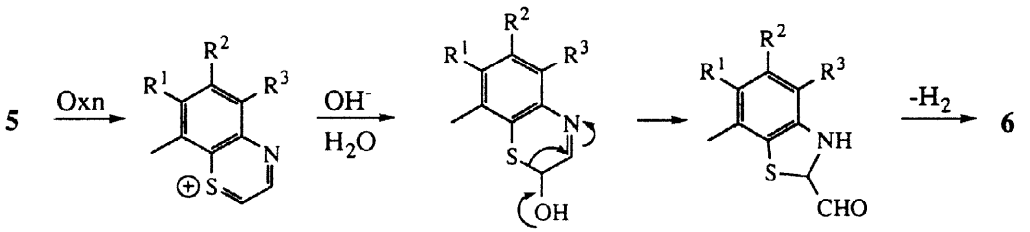
We first studied the reaction of enaminone **1** with Knoevenagel products, in order to prepare hydropyrido[2,1-*c*]thiazines related to antihypertensive thiazolo[1,2-*b*]pyridines. The reaction between **1** and methyl 2-(3-chlorobenzylidene)acetylacetate was carried out in MeOH, yielding only **3**. When the reaction was carried out in benzene, the major reaction product was the 3,4,6,7-tetrahydro-2*H*-1,4-benzothiazine **3**, isolated in 60% yield, while the expected 3,4,8,9-tetrahydropyrido[2,1-*c*]thiazine **4** was isolated in very low yield (5%). The existence of four olefinic carbons (4a, 5, 8, 8a), the lack of olefinic protons and the NH bonded to the carboxylate, allowed us to determine the structure of compound **3**, while the structure of minor product **4** was differentiated by the presence of the shielded olefinic proton H-1 at 4.90 ppm.

In both compounds the *trans* relationship between the chlorophenyl and ethoxycarbonyl substituents was deduced from the absence of coupling between the vicinal protons (H-6 and H-7 in **3**; H-8 and H-9 in **4**). The initial Michael addition of the enaminone moiety to the Knoevenagel product followed by the reaction between the keto group and the nucleophilic 2' position, could explain the formation of the major product. On the other hand, if the second reaction would take place between the keto group and the nitrogen atom compound **4** would be produced (Scheme 2). The formation of products originating from the competition between both nucleophilic sites (γ-carbon and nitrogen) in the second step of the reaction is a common feature for all these reactions.



Scheme 2

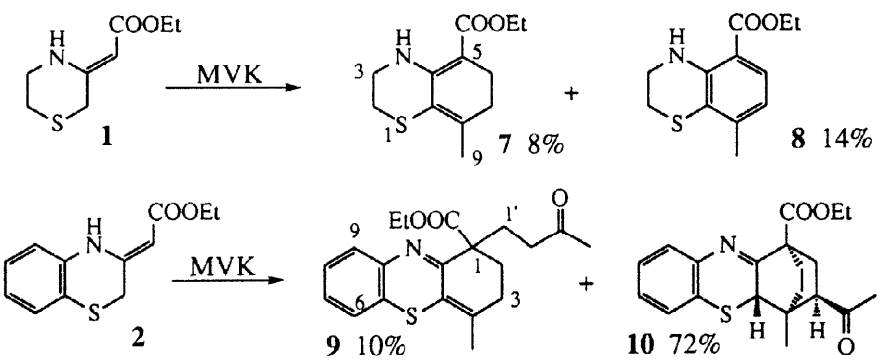
To confirm the structure of compound **3** and to check that it could be converted into benzothiazine derivatives, the dehydrogenation of **3** with DDQ was carried out. The expected benzothiazine derivative **5** and compound **6** were obtained in 45% and 40% yield, respectively. The formation of benzothiazole **6** can be explained by the oxidation to the fully aromatic benzothiazolium salt followed by rearrangement. The formation of benzothiazole derivatives by ring contraction of 1,4-benzothiazine rings upon oxidation[8] with oxygen or H_2O_2 in basic conditions or from 2*H*-3,4-dihydro-1,4-benzothiazines by irradiation with UV light has been described.[9] In our case the previous formation of a benzothiazonium cation by the DDQ, the basic treatment during the work-up and the tendence to aromatization by ligth and/or air could explain the formation of **6**, as depicted in Scheme 3.



Scheme 3. Formation of **6** from **5**

After these results we decided to study the reaction of this type of enaminones with smaller doubly electrophilic reagents, in order to gain a better understanding of their behaviour and synthetic utility for the preparation of heterocyclic systems. We examined the reaction of enaminone **1** with methyl vinyl ketone (MVK), 1:1 molar ratio, at room temperature. The yield of isolated reaction product was very low and it was only possible to identify the tetrahydro-1,4-benzothiazine **7** and its dehydrogenation product **8**. The pyridothiazine analogue of **4** corresponding to the aza-annulation, was not found among the reaction products.

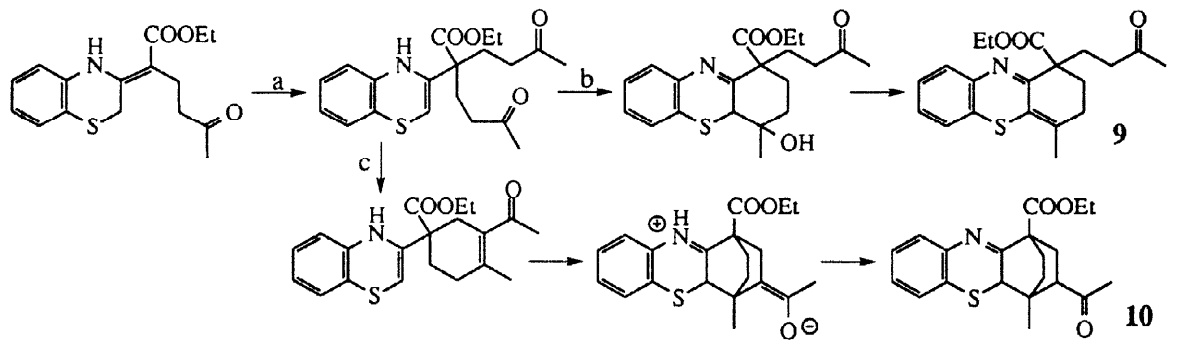
We then turned our attention to the enaminone **2**, in the first instance in the reaction with MVK. Different reaction conditions, molar ratio of reagents and temperature were assayed. When we used a 1:1 ratio between **2** and MVK, the starting material was always detected as the major component of the reaction mixture, but if we increased the MVK concentration to 1:2 ratio, at room temperature, we isolated **9** (95%) as the sole reaction product. Under MeOH reflux the reaction gave the phenothiazines **9** (10%) and **10** (72%), whose structures were established by an array of mono and bidimensional NMR experiments (HMQC, COSY, HMBC, nOe) (Scheme 4). The absence of nOe's between H-4a and other protons on the



Scheme 4

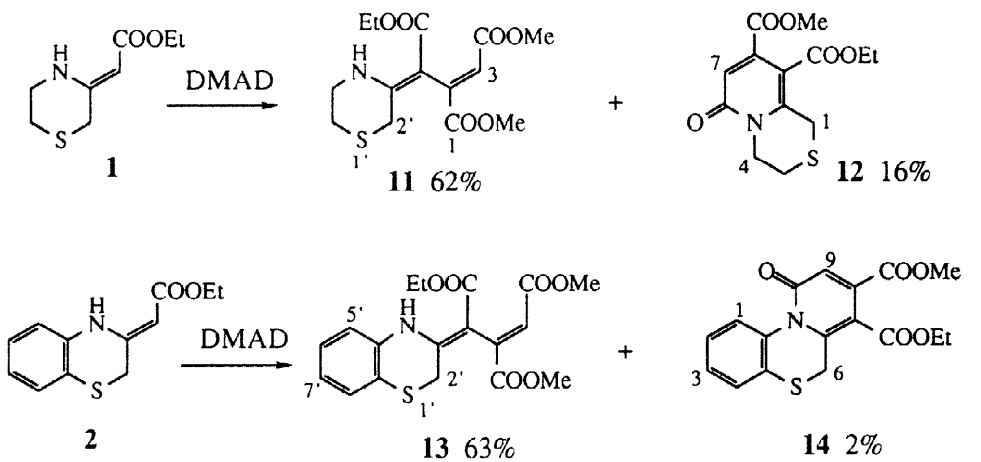
bicyclic system and the nOe's observed between H-2α, H-3 and hydrogen atoms on the ethane bridge were definitive to stablish the relative stereochemistry of compound **10**.

The double conjugate addition of the α-carbon of the enaminone system to one molecule of MVK, followed by a second addition (Scheme 5. a), accompanied by an intramolecular condensation with one of the carbonyl groups (Scheme 5. b), would account for the formation of the tricyclic structure **9**. When the reaction was carried out by heating, the aldol condensation (Scheme 5. c) became faster than reaction b, thus yielding the tetracyclic derivative **10**, through a new intramolecular conjugate addition.



Scheme 5. Formation of **9** and **10** from **2**

The condensation and aza-annulation sequence was especially attractive if heterocyclic enaminones **1** and **2** were used in the reaction with dimethyl acetylenedicarboxylate (DMAD). A mixture of the Michael addition product **11** (or **13**) and the cyclization product **12** (or **14**) were found. The simple heating of the isolated **11** (or **13**) in MeOH was enough to transform them in quantitative yield, into **12** (or **14**). The structures proposed for compounds **11** and **13** are supported by the presence of IR and ^{1}H NMR signals of hydrogen bond between the NH-group and the carbethoxy group in both cases.



Scheme 6

In summary, the Michael addition of these heterocyclic enaminones to α,β-unsaturated carbonyl compounds, followed by aza-annulation represents a simple and efficient approach to the synthesis of 1,4-benzothiazines (> 60%), phenothiazines (> 90%), 6-oxopyrido[2,1-*c*]thiazines(> 75%) or 10-oxopyrido[2,1-*c*][1,4]benzothiazines (> 65%).

EXPERIMENTAL

Melting points were determined on a Buchi 510 instrument and are uncorrected. ^1H NMR and ^{13}C NMR were recorded on a 200 (Bruker WP200SY) and 400 (Bruker SY) spectrometer, using $CDCl_3$ as solvent with TMS as internal standard. IR spectra were obtained in CH_2Cl_2 film in a Nicolet (Impact 410) spectrophotometer. GC-MS analyses were carried out with a Hewltt-Packard 5890 Serie II and Finnigan MAT95 (HRMS) instruments. Column chromathography was performed over silica gel Merck 60 (0.063-0.2 mm). For flash chromatography, an Eyela EF-10 apparatus was used, with 3-85 mL/min flow rate, over silica gel (0.040-0.063 mm). TLC was performed on precoated silica gel polyester plates (0.25 mm thickness) with fluorescent indicator UV 254 (Polychrom SI F_{254}). Microanalyses were obtained in a Perkin-Elmer 2400 CHN elemental analyzer.

Table 1.- ^{13}C NMR data for compounds **3, 5, 7** and **8.** Solvent $CDCl_3$. TMS as internal standard.

Nº C	2	3	4a	5	6	7	8	8a	9	10	11	12	13
3	26.2	41.1	150.0	87.4	39.3	53.8	132.0	120.4	21.9	171.0	170.0	52.4	14.4; 59.1
	R = Ar-3Cl : 146.2 (1'); 129.5 (2'); 133.8 (3'); 127.6 (4'); 125.3 (5'); 126.5 (6')												
5	24.4	41.7	143.2	111.5	135.2	116.6	133.4	124.1	17.5	169.0	169.4	51.6	13.1; 60.6
	R = Ar-3Cl : 142.8 (1'); 128.7 (2'); 135.9 (3'); 128.5 (4'); 126.7 (5'); 126.8 (6')												
7	26.1	41.5	151.4	86.4	31.6	20.7	140.7	117.1	21.4	170.4	14.4; 58.9	--	--
8	24.4	41.5	141.2	108.8	117.0	127.6	136.0	115.6	20.7	168.9	14.4; 60.3	--	--

Ethyl perhydrothiazin-3-ylidenacetate (1)

A solution of ethyl 4-chloroacetoacetate (2.99 g, 18.2 mmol)) and 2-aminoethanethiol (4.20 g, 54.6 mmol) in 50 mL of MeOH, was allowed to stand at room temperature for 24 hours. The solvent was evaporated *in vacuo* and by crystallization in MeOH gave *the title compound* **1** (3.0 g, 88%) as a white solid, m.p. 58-59°C; [Found: C, 51.0; H, 6.7; N, 7.6. $C_8H_{13}NO_2S$ requires C, 51.32; H, 7.00; N, 7.48 %]; υ_{max} (KBr) 3336, 1652, 1629 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 8.61 (1 H, br s, NH), 4.55 (1 H, s, H_2), 4.10 (2 H, q, *J* 7,3 Hz, -$C\underline{H_2}$-CH_3), 3.53 (2 H, m, $H_{5'}$), 3.24 (2 H, s, $H_{2'}$), 2.93 (2 H, m, $H_{6'}$), 1.26 (3 H, t, *J* 7,3 Hz, -CH_2-$C\underline{H_3}$); δ_C (200 MHz, $CDCl_3$) 170.6, 159.5, 81.6, 58.6, 40.3, 28.2, 27.9, 14.6 ; GC-MS *m/z* : 187 (M^+, 52), 141 (100).

Ethyl 3,4-dihydro-2*H*-1,4-benzothiazin-3-ylidenacetate (2)

A solution of ethyl 4-chloroacetoacetate (1.53 g, 9.3 mmol)) and 2-aminothiophenol (1.28 g, 10.3 mmol) in 50 mL of MeOH, was allowed to stand at room temperature for 24 hours. The solvent was evaporated *in vacuo* and by crystallization in MeOH gave *the title compound* **2** (1.63 g, 74%) as a pale yelow solid, m.p. 64-65°C; [Found: C, 61.2; H, 5.3; N, 5.9. $C_{12}H_{13}NO_2S$ requires C, 61.25; H, 5.56; N, 5.95 %]; υ_{max} (KBr) 3273, 1661, 1614, 1577, 975 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 10.60 (1 H, br s, NH), 6.8-7.2 (4 H, m, Ar), 4.68 (1 H, s, H_2), 4.17 (2 H, q, *J* 7.1 Hz -$C\underline{H_2}$-CH_3), 3.39 (2 H, s, $H_{2'}$), 1.29 (3 H, t, *J* 7,1 Hz, -CH_2-$C\underline{H_3}$); δ_C (200 MHz, $CDCl_3$) 170.4, 150.4, 136.4, 128.3, 127.2, 122.5, 120.4, 117.6, 85.6, 59.4, 30.0, 14.5; GC-MS *m/z* : 235 (M^+, 74), 189 (100).

Reaction of enaminone 1 with the Knoevenagel product: Preparation of 3 and 4

A mixture of enaminone **1** (250 mg, 1.33 mmol) and the Knoevenagel product (310 mg, 1.33 mmol) in 30 mL of MeOH was refluxed for 48 hours. The solvent was evaporated *in vacuo* and by crystallization in MeOH gave the *title compound* **3** as a yellow solid in quantitative yield. When the reaction was refluxed in benzene **3** (325 mg, 60%) and the *title compound* **4** (26 mg, 5%) were obtained after flash chromatography (80% hexane/EtOAc).

(±)-(6*S*,7*R*)-Ethyl 6-(3-chlorophenyl)-3,4,6,7-tetrahydro-8-methyl-7-methoxycarbonyl-2*H*-1,4-benzo thiazin-5-carboxylate (3)

m.p. 119-120°C; [Found: C, 58.6; H, 5.5; N, 3.1. $C_{20}H_{22}ClNO_4S$: requires C, 58.89; H, 5.43; N, 3.43 %]; R_f (80% hexane/EtOAc) 0.40; υ_{max} (KBr) 3355, 1733, 1640 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 9.67 (1 H, br s, NH), 7.1 (4 H, m, Ar), 4.49 (1 H, s, H_6), 4.01 (2 H, q, *J* 7.1 Hz, -$C\underline{H_2}$-CH_3), 3.71 (3 H, s, OMe), 3.14 (1 H, s, H_7), 3.03 (2 H, dd, *J* 10.6, 3.6 Hz, H_3), 2.85 (2 H, dd, *J* 10.6, 3.6 Hz, H_2), 1.83 (3 H s, H_9), 1.09 (3 H, t, *J* 7.1 Hz, -CH_2-$C\underline{H_3}$); δ_C (200 MHz, $CDCl_3$) (Table **1**). GC-MS *m/z*: 407 (M^+, 81), 361 (28), 334 (100).

(±)-(8*R*,9*S*)-Ethyl 8-(3-chlorophenyl)-6-methyl-7-methoxycarbonyl-3,4,8,9-tetrahydropyrido[2,1-*c*] thiazin-9-carboxylate (4)

R_f (80% hexane/EtOAc) 0.35; υ_{max} (liquid film) 1730, 1683 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 6.9-7.4 (4 H, m, Ar), 4.90 (1 H, s, H_1), 4.53 (1 H, s, H_8), 4.42 (2 H, dt, *J* 13.6, 3.4, Hz, H_4), 4.15 (2 H, q, *J* 6.9 Hz, -$C\underline{H_2}$-CH_3), 3.63 (2 H, m, H_3), 3.53 (3 H, s, OMe), 3.06 (1 H, s, H_9), 2.56 (3 H, s, H_{10}), 1.23 (3 H, t, *J* 6.9 -CH_2-$C\underline{H_3}$); δ_C (200 MHz, $CDCl_3$) 170.5, 168.2, 150.1, 145.7, 133.9, 129.5, 127.9, 126.4, 126.4, 125.5, 101.8, 98.8, 61.0, 52.0, 51.0, 44.2, 41.4, 26.9, 16.0, 14.2; MS *m/z*: 407 (M^+, 19), 334 (90), 296 (100). HRMS Calc. for $C_{20}H_{22}ClNO_4S$ 407.9177 found 407.9166.

Oxidation of 3 with DDQ

A solution of **3** (100 mg, 0.24 mmol) and DDQ (130 mg 0.57 mmol) in 10 mL of dry benzene was allowed to stand at room temperature for 30 minutes. The solvent was evaporated *in vacuo* and the *title compound* **5** (43 mg, 44%) and the *title compound* **6** (40 mg 40%) were isolated, as yelow oils, from the crude reaction product, by flash chromatography (85% hexane/EtOAc).

Ethyl 6-(3-chlorophenyl)-3,4-dihydro-8-methyl-7-methoxycarbonyl-2*H*-1,4-benzothiazin-5-carboxylate (5)

R_f (85% hexane/EtOAc) 0.40; υ_{max} (film) 3300, 1725, 1644, 1597, 1026 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.0-7.3 (4 H, m, Ar), 3.81 (2 H, q, *J* 7.3 Hz, -$C\underline{H_2}$-CH_3), 3.71(2 H, t, *J* 3.3 Hz, H_3), 3.43 (3 H, s, OMe), 3.03 (2 H, m, H_2), 2.22 (3 H, s, H_9), 0.68 (3 H, t, *J* 7.3 Hz, -CH_2-$C\underline{H_3}$); δ_C (200 MHz, $CDCl_3$) (Table **1**); GC-MS *m/z*: 405 (M^+, 81), 347 (10), 359 (100).

Ethyl 5-(3-chlorophenyl)-2-formyl-7-methyl-9-methoxycarbonyl-1,3-benzothiazol-4-carboxylate (6)

R_f (85% hexane/EtOAc) 0.34; υ_{max} (film) 2850, 1750, 1703 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 10.18 (1 H, s, CHO), 7.2-7.4 (4 H, m, Ar), 4.21 (2 H, q, *J* 7.1 Hz, -$C\underline{H_2}$-CH_3), 3.59 (3 H, s, OMe), 2.67 (3 H, s, H_8), 1.03 (3 H, t, *J* 7.1 Hz, -CH_2-$C\underline{H_3}$); δ_C (200 MHz, $CDCl_3$) 185.1, 167.8, 167.5, 165.9, 150.0, 138.8, 138.8, 137.6, 136.0, 134.5, 133.5, 131.8, 129.3, 129.0, 128.4, 127.2, 61.9, 52.4, 19.7, 13.6; GC-MS *m/z*: 417 (M^+, 60), 388 (6), 340 (100). HRMS Calc. for $C_{20}H_{16}ClNO_5S$ 417.8695, found 417.8699.

Reaction of enaminone 1 with methyl vinyl ketone

A solution of enaminone **1** (200 mg, 1.07 mmol) and methyl vinyl ketone (75 mg, 1.07 mmol) in 25 mL of MeOH was allowed to stand at room temperature for 3 hours. The solvent evaporated *in vacuo* and after flash chromatography (90% hexane/EtOAc) were obtained the *title compound* **7** (20 mg, 8%) and he *title compound* **8** (35 mg, 14%) as white oils.

Ethyl 3,4,6,7-tetrahydro-8-methyl-2*H*-1,4-benzothiazin-5-carboxylate (7)

R_f (90% hexane/EtOAc) 0.43; υ_{max} (film) 3346, 1731 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 9.50 (1 H, br s, NH), 4.13 (2 H, q, *J* 7.3 Hz, -$C\underline{H_2}$-CH_3), 3.50 (2 H, m, H_3), 2.88 (2 H, m, H_2), 2.37 (2 H, t, *J* 7.8 Hz, H_6), 2.14 (2 H, t, *J* 7.8 Hz, H_7), 1.94 (3 H, s, H_9), 1.25 (3 H, t, *J* 7.3 Hz, CH_2-$C\underline{H_3}$); δ_C (200 MHz, $CDCl_3$) (Table **1**); MS *m/z*: 239 (M^+, 68), 166 (100). HRMS Calc. for $C_{12}H_{17}NO_2S$ 239.3277, found 239.3270.

Ethyl 3,4-dihydro-8-methyl-2*H*-1,4-benzothiazin-5-carboxylate (8)

R_f (90% hexane/EtOAc) 0.38; υ_{max} (film) 3342, 1675, 1594, 1570, 1511, 769 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.95 (1 H, d, *J* 8.4 Hz, H_6), 6.42 (1 H, d, *J* 8.2 Hz, H_7), 4.28 (2 H q, *J* 7.1 Hz, -$C\underline{H_2}$-CH_3), 3.70 (2 H, m,

H_3), 3.00 (2 H, m, H_2), 2.22 (3 H, s, H_9), 1.36 (3 H, t, *J* 7.1 Hz, -CH_2-$C\underline{H}_3$); δ_C (200 MHz, $CDCl_3$) (Table **1**); MS *m/z*: 237 (M^+, 10), 191 (100).

Reaction between the enaminone 2 and methyl vinyl ketone: Preparation of phenothiazines 9 and 10

A mixture of enaminone **2** (200 mg, 0.85 mmol) and methyl vinyl ketone (119 mg, 1.70 mmol) in 20 mL of MeOH was refluxed for 12 hours. After flash chromatography (80% hexane/EtOAc) the *title compound* **9** (30 mg, 10%) and the *title compound* **10** (216 mg, 72%) were isolated. When the reaction is carried out at room temperature **9** was isolated in 95% yield.

Ethyl 4-methyl-1-(3-oxobutyl)-2,3-dihydro-1*H*-phenothiazin-1-carboxylate (9)

R_f (80% hexane/EtOAc) 0.40; υ_{max} (film) 1723, 1658 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.3 (4 H, m, Ar), 4.17 (2 H, q, *J* 7.1 Hz, -$C\underline{H}_2$-CH_3), 2.75 (1 H, ddd, *J* 17.2, 10.4, 5.2 Hz, $H_{2'}$), 2.60 (1 H, ddd, *J* 17.2, 10.4, 5.2 Hz, $H_{2'}$), 2.40 (1 H, m, H_2), 2.34 (2 H, m, H_3), 2.14 (3 H, s, $H_{4'}$), 2.08 and 2.27(2 H, m, $H_{1'}$), 1.84 (1 H, dd, *J* 11.2, 5.6 Hz, H_2), 1.78 (3 H, s, C_4-Me), 1.23 (3 H, t, *J* 7.1 Hz, -CH_2-$C\underline{H}_3$); δ_C (400 MHz, $CDCl_3$) 208.6, 173.4, 158.6, 139.4, 135.7, 129.7, 127.5, 126.6, 126.0, 124.9, 116.2, 61.3, 53.2, 39.4, 30.2, 30.0, 29.2, 28.0, 20.5, 14.2 ; MS *m/z*: 357 (M^+, 44), 213 (100). HRMS Calc. for $C_{20}H_{23}NO_3S$ 357.4574, found 357.4568.

Ethyl 3-acetyl-4-methyl-2,3,4,4a-tetrahydro-1*H*-1,4-ethanephenothiazin-1-carboxylate (10)

R_f (80% hexane/EtOAc) 0.36; υ_{max} (film) 1732, 1637 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.25 (1 H, m, H_8), 7.23 (1 H, m, H_7), 7.13 (1 H, m, H_9), 7.05 and 7.23 (1 H, m, H_6), 4.35 (1 H, dq, *J* 10.7, 7.1 Hz, -$C\underline{H}_2$-CH_3), 4.25 (1 H, dq, *J* 10.7, 7.1 Hz,-$C\underline{H}_2$-CH_3), 4.06 (1 H, s, H_{4a}), 2.96 (1H, dd, *J* 11.0, 8.0 Hz, H_3), 2.46 (1 H, dddd, *J* 13.5, 11.6, 2.9, 2.0 Hz, $H_{1'}$), 2.38 (1 H, ddd, *J* 13.6, 8.0, 2.9 Hz, H_2), 2.23 (1 H, ddd, *J* 13.8, 11.9, 7.4 Hz, $H_{2'}$), 2.20 (3 H, s, CO-Me), 2.16 (1 H, dd, *J* 13.6, 11.0 Hz, H_2), 1.93 (1 H, ddd, *J* 13.5, 11.3, 6.4 Hz, $H_{1'}$), 1.47 (1 H, dddd, *J* 13.5, 10.8, 2.9, 2.2 Hz, $H_{2'}$), 1.32 (3 H, t, *J* 7.1 Hz, -CH_2-$C\underline{H}_3$), 1.27 (3 H, s, C_4-Me); δ_C (400 MHz, $CDCl_3$) 210.4, 171.8, 166.1, 142.0, 127.2, 126.2, 123.3, 60.6, 51.9, 48.6, 40.5, 36.4, 32.4, 29.8, 29.8, 26.5, 22.4, 14.1; MS *m/z*: 357 (M^+, 24), 241 (100). HRMS Calc. for $C_{20}H_{23}NO_3S$ 357.4574, found 357.4581.

Reaction of enaminone 1 with dimethyl acetylenedicarboxylate

A solution of enaminone **1** (0.83 g, 4.43 mmol) and dimethyl acetylenedicarboxylate (630 mg, 4.43 mmol) in 20 mL of MeOH was allowed to stand at room temperature for 3 hours. The crude of the reaction was purified by flash chromatography (90% hexane/EtOAc) and gave the *title compound* **11** (900 mg, 62%) as a yellow solid, and the *title compound* **12** (15 mg 16%), as a yellow oil. When **11** was refluxed in MeOH, **12** was obtained in quantitative yield.

Dimethyl 2-[(ethoxycarbonyl)(perhydro-1,4-thiazin-3-yliden)methyl]fumarate (11)

m.p. 105-106°C (MeOH); [Found: C, 51.2; H, 5.7; N, 4.3. $C_{14}H_{19}NO_6S$: requires C, 51.05; H, 5.81 N, 4.25 %]; R_f (90% hexane/EtOAc) 0.45; υ_{max} (KBr) 1720, 1666 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 9.71 (1 H, br s, NH), 6.75 (1H, s, H_3), 4.16 (1H, dq, *J* 11.6, 7.3 Hz, -$C\underline{H}_2$-CH_3), 4.01 (1H, dq, *J* 11.0 , 7.3 Hz, -$C\underline{H}_2$-CH_3), 3.77 (3H, s, OMe), 3.70 (3 H, s, OMe), 3.53 (2 H, m, $H_{5'}$), 2.91 (2 H, m, $H_{6'}$), 3.15 and 3.36 (2 H, AB, *J* 14.6 Hz, $H_{2'}$), 1.15 (3 H, t, *J* 7.3 Hz, -CH_2-$C\underline{H}_3$); δ_C (200 MHz, $CDCl_3$) 168.1, 168.0, 165.0, 160.7, 141.5, 126.0, 87.6, 52.2, 58.7, 51.3, 39.5, 27.3, 24.5, 13.9.

Ethyl 8-methoxycarbonyl-6-oxo-1,3,4,6-tetrahydropyrido[2,1-*c*]thiazin-9-carboxylate (12)

R_f (90% hexane/EtOAc) 0.38; υ_{max} (film) 1739, 1715, 1683 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.06 (1 H,s, H_7), 4.02 (2 H, q, *J* 7.3 Hz, -$C\underline{H}_2$-CH_3), 3.71 (2 H, m, H_4), 3.68 (2 H, s, H_1), 3.66 (3 H, s, OMe), 3.08 (2 H, m, H_3), 1.31 (3 H, t, *J* 7.3 Hz, -CH_2-$C\underline{H}_3$); δ_C (200 MHz, $CDCl_3$) 169.8, 166.4, 162.2, 132.2, 130.8, 129.1, 112.7, 52.1, 38.6, 30.2, 25.9; MS m/z: 297 (M^+, 100).

Reaction of enaminone 2 with dimethyl acetylenedicarboxylate

A mixture of **2** (1.05 g, 4.46 mmol) and dimethyl acetylenedicarboxylate (640 mg, 4.46 mmol) in 40 mL of MeOH, was refluxed for 24 hours. The crude of the reaction was purified by flash chromatography

(80% hexane/EtOAc) and gave the *title compound* **13** (1.05 g, 63%) as a white oil, and the *title compound* **14** (15 mg, 2%), as a white solid. When **13** was refluxed in MeOH, **14** was obtained in quantitative yield.

Dimethyl 2-[(ethoxycarbonyl)(3,4-dihydro-2*H*-1,4-benzothiazin-3-yliden)methyl] fumarate (13)

R_f (80% hexane/EtOAc) 0.43; υ_{max} (film) 3270, 1724, 1662, 1606, 1571 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 11.56 (1 H, br s, NH), 6.9-7.1 (4 H, m, Ar), 6.96 (1 H,s, H_3), 4.16 (2 H, dq, *J* 10.3, 7.3 Hz, -$C\underline{H_2}$-CH_3), 3.80 (3 H, s, OMe), 3.72 (3 H, s, OMe), 3.37 (2 H, s, $H_{2'}$), 1.20 (3 H, t, *J* 7.3 Hz, -CH_2-$C\underline{H_3}$); δ_C (200 MHz, $CDCl_3$) 168.5, 167.6, 165.3, 150.0, 140.0, 136.2, 129.0, 127.9, 127.0, 123.4, 121.1, 118.0, 91.3, 60.0, 52.8, 52.0, 26.3, 14.2; MS *m/z*: 377 (M^+, 100), 331 (26). HRMS Calc. for $C_{18}H_{19}NO_6S$ 377.3856, found 377.3862.

Ethyl 10-oxo-6,10-dihydropyrido[2,1-*c*][1,4]benzothiazin-8-methoxycarbonyl-7-carboxylate (14)

m. p. 163-164 °C (MeOH); [Found: C, 59.3; H, 4.2; N, 4.1. $C_{17}H_{15}NO_5S$: requires C, 59.12; H, 4.37 N, 4.05 %]; R_f (80% hexane/EtOAc) 0.38; υ_{max} (film) 1738, 1665, 1606, 1590 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 9.19 (1 H, d, *J* 7.6 Hz, H_1), 7.52 (1 H, s, H_9), 7.1-7.2 (3 H, m, H_2, H_3 and H_4), 4.37 (2 H, q, *J* 7.3 Hz, -$C\underline{H_2}$-CH_3), 3.89 (2 H, s, H_6), 3.71 (3 H, s, OMe), 1.37 (3 H, t, *J* 7.3 Hz, -CH_2-$C\underline{H_3}$); δ_C (200 MHz, $CDCl_3$) 170.0, 165.5, 162.3, 133.2, 132.8, 129.7, 128.3, 126.3, 125.5, 124.5, 119.2, 117.1, 112.7, 61.7, 52.3, 30.7, 14.1; MS *m/z*: 345 (M^+, 100).

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