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Synthesis and ^{1}H-NMR configurational study of Δ^3-Thiazolines from 2-Aza-1,3-dienes[1]

José Barluenga*, Raquel Pérez Carlón, Elvira Peláez, Jesús Joglar and Fernando López Ortiz

Departamento de Química Organometálica, Facultad de Química, Universidad de Oviedo, 33012 Oviedo, Spain

Santos Fustero*

Departamento de Química Orgánica, Facultad de Farmacia, Universidad de Valencia, 46010 Valencia, Spain

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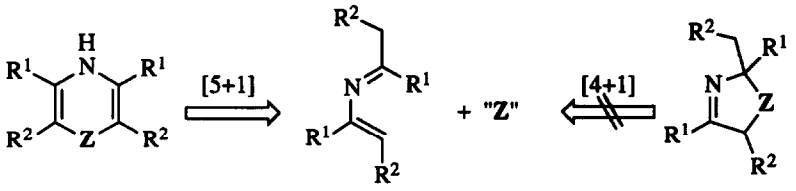
Abstract: A [4+1] heterocyclization process involving 2-aza-1,3-dienes and elemental sulphur leading to the synthesis of Δ^3-thiazolines with excellent yields is described. A 1D TOCSY and 1D NOESY study of these systems was made in order to establish the configuration of the diastereoisomeric mixture.

In previous reports[2] the reactivity and versatility of neutral 2-aza-1,3-dienes **1** in several heterocyclization processes was described. It was shown that compounds **1** are able to participate both in [4+2] cycloadditions with several dienophiles and in [5+1] heterocyclization reactions. In connection with these studies, we have recently developed new and simple methods for the synthesis of azaphosphinine and pyridine derivatives **2** (Z="P" and "C")[3] by reaction of **1** with phosphorus and carbon derivatives, respectively. It should be pointed out that in no case were the [4+1] cycloadducts **3** detected (Scheme 1).



2 **1** **3**

Scheme 1

In order to find a general entry to heterocycles of type **2**, we tried to extend this study to systems **2** containing sulphur (Z="S"). We first tested the reactivity of **1** with sulphur dichloride and thionyl chloride in a broad range of reaction conditions and found that in no case was the reaction successful because an intractable mixture of products was obtained.

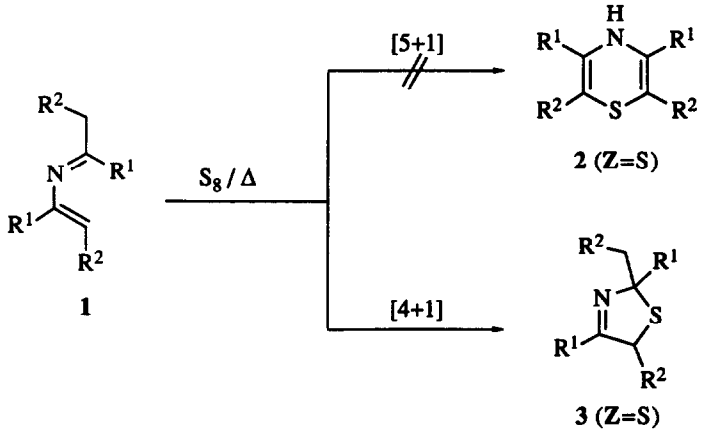
Δ^3-Thiazolines have found application as flavoring compounds and are important building blocks for synthesis of many natural products like *d*-biotin[5] and penicillins.[6] The most general method used for the preparation of these systems, described by Asinger *et al.* involves the reaction of carbonyl compounds with sulphur and ammonia.[7] The method is strongly dependent on the temperature and on the nature of the carbonyl compound, giving mostly complex mixtures. Therefore, alternative and improved methods were developed and one of them implies the reaction of 2-aza-1,3-dienes as starting material.[7] However, full experimental details

were not given and the process appears to be limited to 2-aza-1,3-dienes derived from secondary aliphatic aldehydes.

On the other hand, it was known years ago that diarylamines react in a simple way with sulphur in the presence of catalytic amounts of iodine to give the pharmacologically important phenothiazine derivatives.[7]

Taking into account that compounds **1** may react as divinylamine derivatives,[3,9] and encouraged by the above findings,[7,8] we decided to explore the behaviour of **1** towards elemental sulphur. The purpose of this paper is to disclose the results of this study, which afford a very simple and general entry to Δ^3-thiazolines **3** instead of the expected thiazine derivative **2** (Z="S") (Scheme 2).

Thereby, the treatment of 2-aza-1,3-dienes **1** with elemental sulphur without solvent, at 170°C for 30 min., led to the corresponding Δ^3-thiazolines **3** as a mixture of diastereoisomers in more than 90% yield (see Table). Compounds **3** were isolated as amber oils and purified by flash chromatography; however, all attempts to separate the isomers mixtures were unsuccessful.



Scheme 2

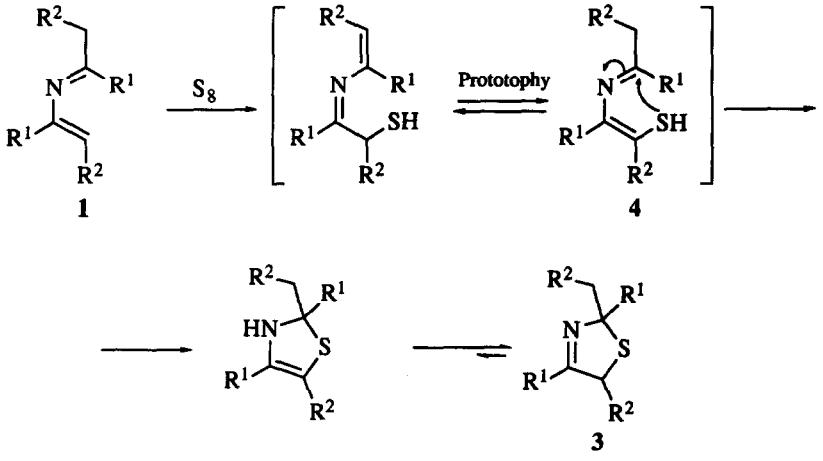
Table : Δ^3-Thiazolines **3** obtained from **1**.

Entry	Compound	R^1	R^2	Yield (%)	Conditions Solvent / Temp.(°C) / Base / Time	Isomers ratio[a]
1	**3a**	Ph	Me	99	neat / 170 / - / 30 m	1:1
2	**3a**	Ph	Me	95	neat / 120 /- /6 h	1:1
3	**3a**	Ph	Me	86	toluene / 80 / - /48 h	1:3
4	**3a**	Ph	Me	95	THF / 25 / LDA / 60 m	1:3
5	**3a**	Ph	Me	81[b]	MeOH / 60 / DBU / 16 h	1:1
6	**3b**	Ph	Et	95	neat / 170 / - / 30 m	1:2
7	**3c**	Ph	Pr	91	neat / 170 / - / 30 m	1:1
8	**3d**	*p*-Tolyl	Me	93	neat / 170 / - / 30 m	1:1.4
9	**3e**	*c*-C_6H_{11}	Me	90	neat / 170 / - / 30 m	1:1

[a] Determined by ^{1}H-NMR (400 MHz) of the crude mixture. [b] Asinger's conditions (see ref. 7)

The isomers ratio was improved using toluene as solvent at a lower temperature (80°C). The use of these conditions led, for example in the case of compound **3a**, to a best ratio of 1 : 3 (entry 3, Table). Another experiment was the treatment of **3a** with a base (LDA, entry 4, Table), and we found the same results as in the above reaction using toluene as solvent. Finally, when the reaction was carried out under the conditions reported by Asinger[7] (entry 5, Table), a 1:1 mixture of isomers was obtained in a somewhat lower yield.

For the mechanism of this reaction we propose an intramolecular version of the one described by Asinger for the formation of Δ^3-thiazolines from ketones, elemental sulphur and ammonia. This mechanism (see Scheme 3) involves the oxidation of the α-position of the imine followed by a proton [1,5] shift giving the intermediate **4**. An intramolecular attack of the thiol function in **4** to the C=N bond affords Δ^3-thiazoline, isolated as the tautomeric form **3**.



Scheme 3

The configuration of compounds **3** was ascertained by spectroscopical analysis (IR, ^{1}H-, and ^{13}C-NMR) and mass spectrometry. In order to establish the configuration of each diasteroisomer **3** a prior assignation of the prominent signals in their ^{1}H-NMR spectra were needed. The problem of assignation was tackled through a series of 1D TOCSY experiments. This pulse sequence allows the unraveling of highly overlaped multiplets based on the selective excitation of a partner well resolved and scalarly coupled with one of them, followed by a period of isotropic mixing [10,11]. The required selectivity in the excitation was achieved by Gaussian-shaped pulses [12]. Thus 1D TOCSY spectra of **3a** with the carrier set at the frequency of the methyl group at 0.93 ppm or 1.00 ppm revealed their coupling with the multiplets centered at 2.29 and 2.23/2.36 ppm respectively.

Thiazoline **3b** presents a much more complex proton spectrum. Nevertheless, 1D TOCSY experiments allowed to extract the connectivity along the side chain bonded to carbon C_5 for each diasteroisomer. The selective excitation of the triplet at 0.74 ppm showed its methylenic counterpart appearing centered at 1.40 and 1.80 ppm. These are further coupled with the proton at 4.95 ppm. Moving the carrier to the triplet at 1.05 ppm its coupling with the protons at 2.06 and 1.61 ppm was observed (See experimental section).

To stablish the stereochemistry of the thiazolines **3** a NOE study was carried out. Due to the small chemical shift differences in some of the key signals of the ^{1}H-NMR spectra of compounds **3**, we decided to apply the 1D version of the NOESY pulse sequence.[11,14] In this experiment only a multiplet is selectively excited, so that its dipolar correlationships can be exclusively obtained in about fifteen minutes. When the 1D NOESY pulse sequence with a mixing time of 1 s was applied to the doublet at 1.36 ppm in the proton spectrum of **3a**, a

positive NOE enhancement was observed for the proton at carbon C_5 as well as for the ortho protons of both phenyl substituents located on carbons 2 and 4.

This clearly identifies the isomer (*2S/2R, 5R/5S*) as the major component of **3a**. The assignement was further confirmed when the selective excitation [10] was achieved over the doublet at 1.68 ppm. For a mixing time of 1.8 s a small positive NOE can be detected with the methylenic protons at C_2 (Figure 1).

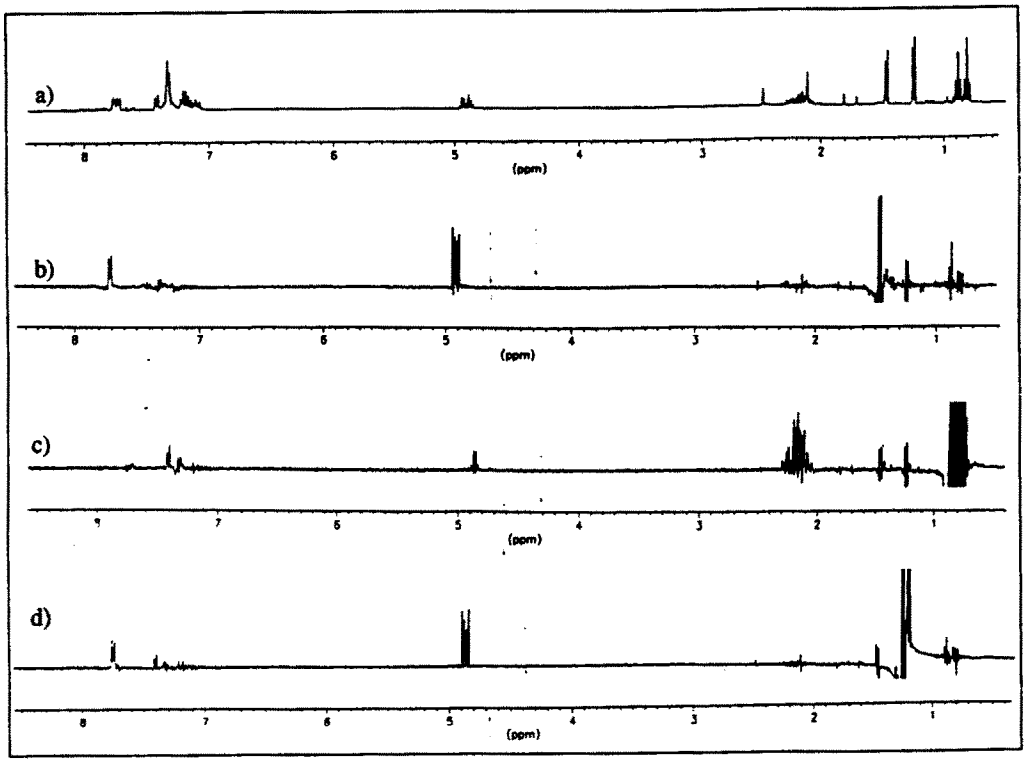
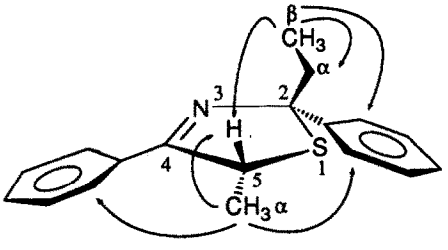
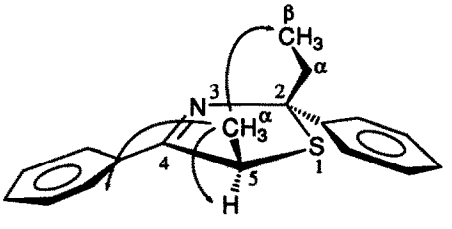


Figure 1. ^{1}H-NMR spectra of **3a**. a) normal spectrum; b-d) 1D NOESY spectra on irradiation at: b) 1.63 ppm, mixing time 1.8 s; c) 0.93 ppm, mixing time 1.5 s; and d) 1.36 ppm, mixing time 1.0 s. Selected NOEs observed are displayed on the structural formulas by arrows:



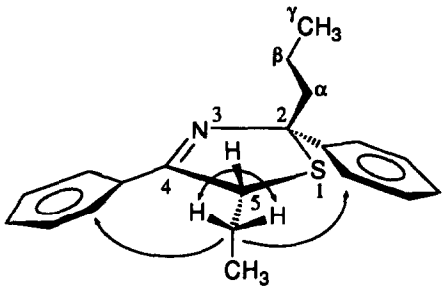
Compound **3a** major isomer (M) (*2S/R, 5R/S*)



Compound **3a** minor isomer (m) (*2S/R, 5S/R*)

For **3b** the choice of the appropiate multiplets to be excited by the 1D NOESY pulse sequence were based on the previous assignements obtained in the 1D TOCSY study. Setting the carrier frequency on the multiplet at 1.80 ppm its dipolar correlations with the ortho protons of both phenyl rings in the molecule were established. Therefore, a (*2S/2R, 5R/5S*) configuration can be again assigned to the major isomer of **3b** (Figure 2).

Thiazolines **3c** and **3e** were obtained as a 1:1 mixture of diasteroisomers. Their stereochemistry was assigned following the same procedure outlined above (see experimental section).



Compound **3b** major isomer (M) (*2S/R, 5R/S*)

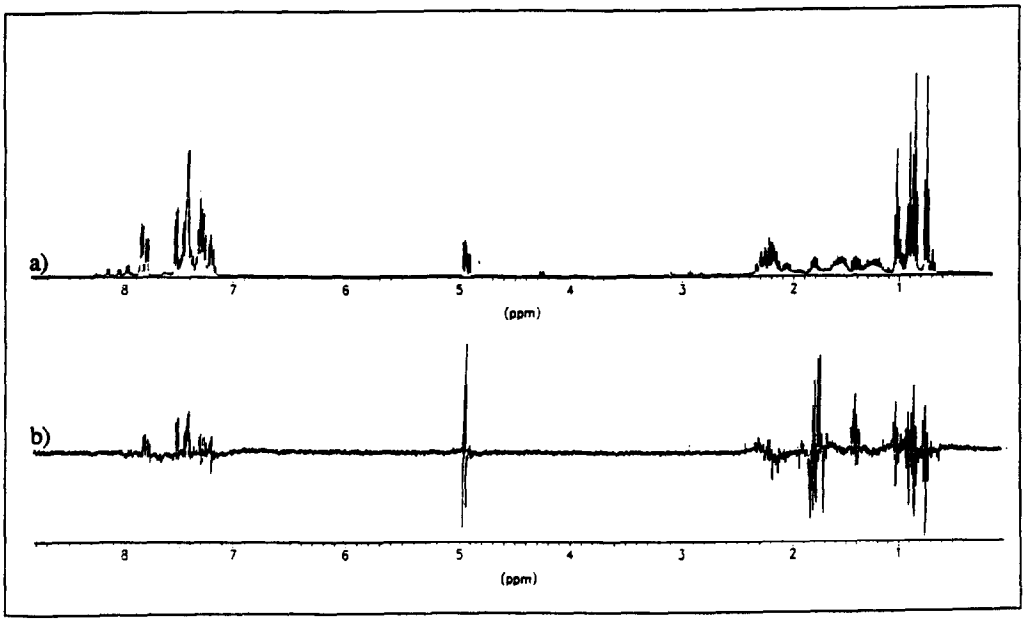


Figure 2. ^{1}H-NMR spectra of **3b**. a) normal spectrum; b) 1D NOESY spectrum on irradiation at 1.80 ppm, mixing time 1.8 s. Arrows on the structural formula refer to the NOE enhancements detected.

In summary, we have described a formal [4+1] heterocyclization of 2-aza-1,3-dienes with elemental sulphur, process that allows to obtain Δ^3-thiazolines with excellents yields, and carried out a ^{1}H-NMR configurational study which allowed us to establish the configuration of the isomeric mixture obtained.

EXPERIMENTAL

Materials and General Methods.

All organic chemicals were reagent grade and were used without further purification. The solvents used were destilled and/or dried prior to use following the standard procedures[15]. Microanalyses were performed on a Perkin-Elmer 240 B instrument. Infrared spectra were recorded on a Phillips PU 9716 and/or Perkin-Elmer 1720 X instrument. Mass spectra were obtained on a Hewlett-Packard 5987 A.

^{1}H-NMR spectra were recorded on a Brucker AMX-400 spectrometer equipped with a selective excitation unit (SEU) suitable for creating Gaussian-shaped low power pulses and on a Brucker AC-300 using the standard Bruker software. ^{13}C-NMR spectra were adquired on a Brucker AC-300. $CDCl_3$ was used as solvent and the chemical shifts are referred to that of internal TMS. All samples were degasified by several freeze-thaw cycles.

The proton spectral width was 8000 Hz. Attenuation by 3 dB of the transmitter high power output was used in the proton channel, giving a 90° hard pulse of 9.6 μs. The 90° Gaussian pulse was calibrated by setting the carrier frequency exactly on resonance on the desired multiplet and finding the maximum intensity response for the preselected excitation power and duration.

The same frequency source was used for the low and high power pulse channel. For a given multiplet the phase difference derived from the excitation by the hard and soft pulses was measured and added to the normal phase cycle of the respective pulse sequence.

1D TOCSY. The TOCSY sequence by Bax *et al.*[10] has been used with a semiselective 90° Gaussian pulse replacing the first pulse and evolution time of the original sequence[11]. Typical parameters were as follows: Relaxation delay 1 s, duration of the Gaussian pulse varied among 35 ms and 200 ms according to the desired selectivity and width of the excited multiplet. The transmitter low power level ranged between 45 dB and 55 dB. an additional external attenuation of 30 dB was needed. The MLEV-17 scheme flancked by two 2.5 ms trim pulses was used to afford a spin-lock duration of about 30 ms and a total of 256 scans were accumulated.

1D NOESY. The basic NOESY sequence of Ernst[14] modified to achieve selective excitation was applied[11]. This excitation was performed in the same manner outlined for the 1D TOCSY experiment described above. Other relevant parameters were: Relaxation delay 1 s, trials of mixing times ranging between 1 s and 1.8 s (see Figure 3) were adquired with a random variation of ± 5% to avoid responses derived from zero-quantum coherences. A total of 320 scans were accumulated.

Preparation of Δ^3-Thiazolines **3**.

A mixture of 2-aza-1,3-diene **1** (5 mmol) and elemental sulphur, S_8, (10 mmol) is heated without any solvent for 30 minutes at 170 °C. In this way, Δ^3-thiazolines **3**, are isolated as amber oils after column chromatography purification with a 20:1 *n*-hexane/ether mixture as the eluent. Several runs were performed by dissolving the 2-aza-1,3-diene **1** (5mmol) and elemental sulphur, S_8,(10 mmol) in the appropiate solvent (toluene, THF or methanol) and heated at 80 °C for 48 hours (in the case toluene) or treated with LDA (6 mmol) at room temperature for 1 hour (THF) or with DBU (5 mmol) at 60 °C for 16 hours (MeOH) and followed by the appropiate workup, leading in each case to the yields and isomer ratios reflected in the Table.

Experimental data.

In the following, the spectral assignements for each isomer (whenever it was possible to do) are described followed by an "*M*" for the major isomer and an "*m*" for the minor isomer; in the case of compound **3c** (which was obtained as a 1:1 mixture of diasteroisomers) the assignements are followed by a letter "*a*" or "*b*" to distinguish between both isomers; all other signals belong to any of both isomers.

2-Ethyl-5-methyl-2,4-diphenyl-Δ^3-thiazoline **3a**. IR (neat) ν 1635 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.93 (t,3H,C_2-$CH_3\beta$, *M*), 1.00 (t,3H, C_2-$CH_3\beta$, *m*), 1.36 (d,3H, C_5-$CH_3\alpha$, *M*), 1.63 (d,3H, C_5-$CH_3\alpha$, *m*), 2.13 (m, 1H, C_2-$CH_2\alpha$, *m*), 2.29 (m, 2H, C_2-$CH_2\alpha$, *M*), 2.36 (m, 1H, C_2-$CH_2\alpha$, *m*), 4.91 (q, 1H,C_5-H, *M*), 4.95 (q,1H,C_5-H, *m*), 7.19-7.88 (m, 20H) ppm. ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 170.5 (C,*M*), 170.2 (C, *m*), 147.8 (C, *M*), 147.3 (C, *m*), 133.0 (C, *M*), 132.8 (C, *m*), 130.6 (CH), 130.5 (CH), 128.7 (CH), 128.6 (CH), 128.5 (CH), 128.0 (CH), 126.8 (CH), 125.8 (CH), 125.6 (CH), 95.9 (C, *m*), 95.4 (C, *M*), 53.6 (CH, *m*), 53.5 (CH, *M*), 40.0 (CH_2, *m*), 39.3 (CH_2, *M*), 23.3 (CH_3, *m*), 23.1 (CH_3, *M*), 10.1 (CH_3, *m*), 9.7 (CH_3, *M*) ppm. MS (EI) m/e 281 (M^+), 252 (100%). Anal. Calcd. for $C_{18}H_{19}NS$: C, 76.86; H, 6.76; N, 4.98. Found: C, 76.85; H, 6.80; N, 5.00. R_f (*n*-hexane/ether, 20:1): 0.38.

5-Ethyl-2,4-diphenyl-2-propyl-Δ^3-thiazoline **3b**. IR (neat) ν 1636 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.74 (t, 3H, C_5-$CH_3\beta$, *M*), 0.85 (t, 3H, C_2-$CH_3\gamma$, *M*), 0.90 (t, 3H, C_2-$CH_3\gamma$, *m*), 1.05 (t,3H, C_5-$CH_3\beta$, *m*), 1.24 (m, 1H), 1.40 (m, 1H, C_5-$CH_2\alpha$, *M*), 1.52 (m, 1H), 1.61 (m, 1H, C_5-$CH_2\alpha$, *m*), 1.78 (m, 1H), 1.80 (m, 1H, C_5-$CH_2\alpha$, *M*), 2.06 (m, 1H, C_5-$CH_2\alpha$, *m*), 2.22 (m, 5H), 4.91 (q,1H,C_5-H, *m*), 4.95 (q,1H,C_5-H, *M*), 7.13- 7.90 (m, 20H) ppm. ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 169.1 (C, *M*), 168.9 (C, *m*), 147.9 (C,.*M*), 147.8 (C, *m*), 133.4 (C, *m*), 133.2 (C, *M*), 130.3 (CH, *M*), 130.2 (CH, *m*), 128.4 (CH), 128.3 (CH), 127.8 (CH), 127.7 (CH), 126.5 (CH), 126.4 (CH), 125.6 (CH), 125.4 (CH), 94.8 (C, *m*), 94.6 (C, *M*), 61.7 (CH, *m*), 61.2 (CH, *M*), 49.7 (CH_2, *m*), 49.3 (CH_2, *M*), 29.3 (CH_2, *m*), 28.4 (CH_2, *M*), 18.9 (CH_2, *m*), 18.5 (CH_2, *M*), 14.1 (CH_3, *m*), 13.8 (CH_3, *M*), 12.9 (CH_3, *m*), 11.6 (CH_3, *M*) ppm. MS (EI) m/e 309 (M^+), 266 (100%). Anal. Calcd. for $C_{20}H_{23}NS$: C, 77.67; H, 7.44; N, 4.53. Found: C, 77.65; H, 7.40; N, 4.55. R_f (*n* hexane/ether, 20:1): 0.41.

2-Butyl-2,4-diphenyl-5-propyl-Δ^3-thiazoline **3c**. IR (neat) ν 1636 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.77 (t, 3H, C_5-$CH_3\gamma$, *a*), 0.83 (t, 3H, C_2-$CH_3\delta$, *a*), 0.88 (t, 3H, C_2-$CH_3\delta$, *b*), 0.93 (t, 3H, C_5-$CH_3\gamma$, *b*), 1.29 (m, 6H), 1.31 (m, 1H, C_5-$CH_2\beta$, *a*), 1.48 (m, 5H), 1.56 (m, 1H, C_5-$CH_2\beta$, *b*), 1.78 (m, 1H, C_5-$CH_2\beta$, *a*), 2.02 (m, 1H, C_5-$CH_2\beta$, *b*), 2.23 (m, 5H), 4.95 (m, 2H), 7.15-7.94 (m, 20H) ppm. ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 169.3 (C), 169.2 (C), 147.9 (C), 147.3 (C), 133.2 (C), 133.1 (C), 130.3 (CH), 130.2 (CH), 128.4 (CH), 127.9 (CH), 127.8 (CH), 126.6 (CH), 126.5 (CH), 125.6 (CH), 125.4 (CH), 94.9 (C), 94.5 (C), 59.8 (CH), 59.6 (CH), 47.3 (CH_2), 46.7 (CH_2), 38.6 (CH_2), 37.8 (CH_2), 27.7 (CH_2), 27.3 (CH_2), 22.6 (CH_2), 22.5 (CH_2), 22.2 (CH_2), 21.2 (CH_2), 13.9 (CH_3), 13.5 (CH_3) 13.4 (CH_3) ppm. MS (EI) m/e 337 (M^+). Anal. Calcd. for $C_{22}H_{27}NS$: C, 78.34; H, 8.01; N, 4.15. Found: C, 78.30; H, 7.95; N, 4.20. R_f (*n*-hexane/ether, 20:1): 0.41.

2-Ethyl-5-methyl-2,4-di-*p*-tolyl-Δ^3-thiazoline **3d**. IR (neat) ν 1633 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.9 (t, 3H, *M*), 1.0 (t, 3H, *m*), 1.4 (d, 3H, *M*), 1.6 (d, 3H, *m*), 2.2 (m, 4H), 2.2(s, 3H, *m*), 2.3 (s, 3H, *M*),4.9 (q, 1H, *M*), 5.0 (q, 1H, *m*), 7.0-7.9 (m, 16H) ppm. ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 169.8 (C, *M*), 169.6 (C, *m*), 144.8 (C, *M*), 144.3 (C, *m*), 140.5 (C), 135.9 (C), 130.0 (CH, *m*), 129.8 (CH, *M*), 129.0 (CH), 128.9 (CH), 128.5 (CH), 125.4 (CH), 125.2 (CH), 95.5 (C, *m*), 95.0 (C, *M*), 53.2 (CH, *m*), 53.1 (CH, *M*), 39.8 (CH_2, *m*), 39.0 (CH_2, *M*), 23.2 (CH_3), 23.0 (CH_3), 21.1 (CH_3), 20.7 (CH_3), 10.0 (CH_3, *m*), 9.6 (CH_3, *M*) ppm. MS (EI) m/e 309 (M^+), 266 (100%). Anal. Calcd. for $C_{20}H_{23}NS$: C, 77.67; H, 7.44; N, 4.53. Found: C, 77.70; H, 7.45; N, 4.50. R_f (*n*-hexane/ether, 20:1): 0.37.

2,4-Dicyclohexyl-2-ethyl-5-methyl-Δ^3-thiazoline **3e**. IR (neat) ν 1690 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.79 (t, 3H, C_2-$CH_3\beta$, *M*), 0.85 (t, 3H, C_2-$CH_3\beta$, *m*), 1.23 (m, 12H), 1.40 (d, 3H, C_5-$CH_3\alpha$, *M*), 1.48 (d, 3H, C_5-$CH_3\alpha$, *m*), 1.78 (m, 30H), 1.82 (m, 1H, C_2-$CH_2\alpha$, *m*), 1.86 (m, 2H, C_2-$CH_2\alpha$, *M*), 1.92 (m, 1H, C_2-$CH_2\alpha$, *m*), 2.26 (m, 2H), 4.17 (q,1H,C_5-H, *m*), 4.24 (q,1H,C_5-H, *M*) ppm. ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 176.1 (C), 176.0 (C), 99.1 (C), 99.0 (C), 54.4 (CH), 54.1 (CH), 48.3 (CH), 47.8 (CH), 39.7 (CH), 33.7 (CH_2), 33.1 (CH_2), 32.0 (CH_2), 31.8 (CH_2), 31.4 (CH_2), 31.3 (CH_2), 28.6 (CH_2), 28.3 (CH_2), 27.8 (CH_2), 27.1 (CH_2), 26.5 (CH_2), 26.4 (CH_2), 26.1 (CH_2), 26.0 (CH_2), 25.9 (CH_2), 21.2 (CH_3), 8.9 (CH_3), 8.3 (CH_3) ppm. MS (EI) m/e 293 (M^+). Anal. Calcd. for $C_{18}H_{31}NS$: C, 73.72; H, 10.85; N, 4.78. Found: C, 73.70; H, 10.60; N, 4.70. R_f (*n*-hexane/ether, 20:1): 0.38.

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