HETEROCYCLES, Vol. 53, No. 3, 2000, pp. 557 - 570, Received, 14th June, 1999

SYNTHESIS OF THE NEW TRIHETEROCYCLIC SYSTEM C_3N-C_4N-C_6N. 3-ARYL-2,5,5-TRIMETHYL-9a-METHYLSULFANYL-9-PHENOXY-4,5,6,8,9,9a-HEXAHYDRO-*3H*-AZETO[1,2-*a*]PYRROLO[3,2-*c*] AZEPIN-8-ONES

Roberto Martínez,*[†] José Gustavo Avila-Zárraga,[‡] Gema López-López,[†] and Víctor Oswaldo Nava-Salgado[†]

[†]Instituto de Química, Universidad Nacional Autónoma de México, Circuito Exterior, Ciudad Universitaria, 04510 México D.F., México
[‡]Facultad de Química, Universidad Nacional Autónoma de México, Circuito Interior, Ciudad Universitaria, 04510 México D.F., México

Abstract - The regio- and stereoselective synthesis of the *cis*-3-aryl-2,5,5-trimethyl-9a-methylsulfanyl-9-phenoxy-4,5,6,8,9,9a-hexahydro-*3H*-azeto[1,2-*a*]-pyrrolo[3,2-*c*]azepin-8-ones (**1**) was performed. A four-step sequence, which yields are good, constitutes the first synthetic way for the preparation of the first member of this new C_3N-C_4N-C_6N series.

Synthesis of tri- and tetraheterocyclic compounds are presently the focus of attention of many chemists since many of them present therapeutic properties against different illnesses like AIDS[1] and cancer.[2] Recently we described the synthesis of benzodipyrroles by use of our approach to different di- and triheterocyclic compounds from the commercially available 1,3-cyclohexanedione.[3] These benzodipyrroles can be potentially used as DNA intercalants[4] in the therapeutic treatment against cancer. On the other hand one of the most studied heterocyclic systems, because of its pharmacological activity, is the β-lactam functionality. In fact, several synthesis of a large variety of antibiotics and another biologically important β-lactams have been reported.[5] Actually, there are many synthetic methods for their preparations,[6] but the most used approaches are the reactions of imines with acid-chlorides (Staudinger reaction[7]) and the origins of its stereodivergent outcome have been recently studied.[8]

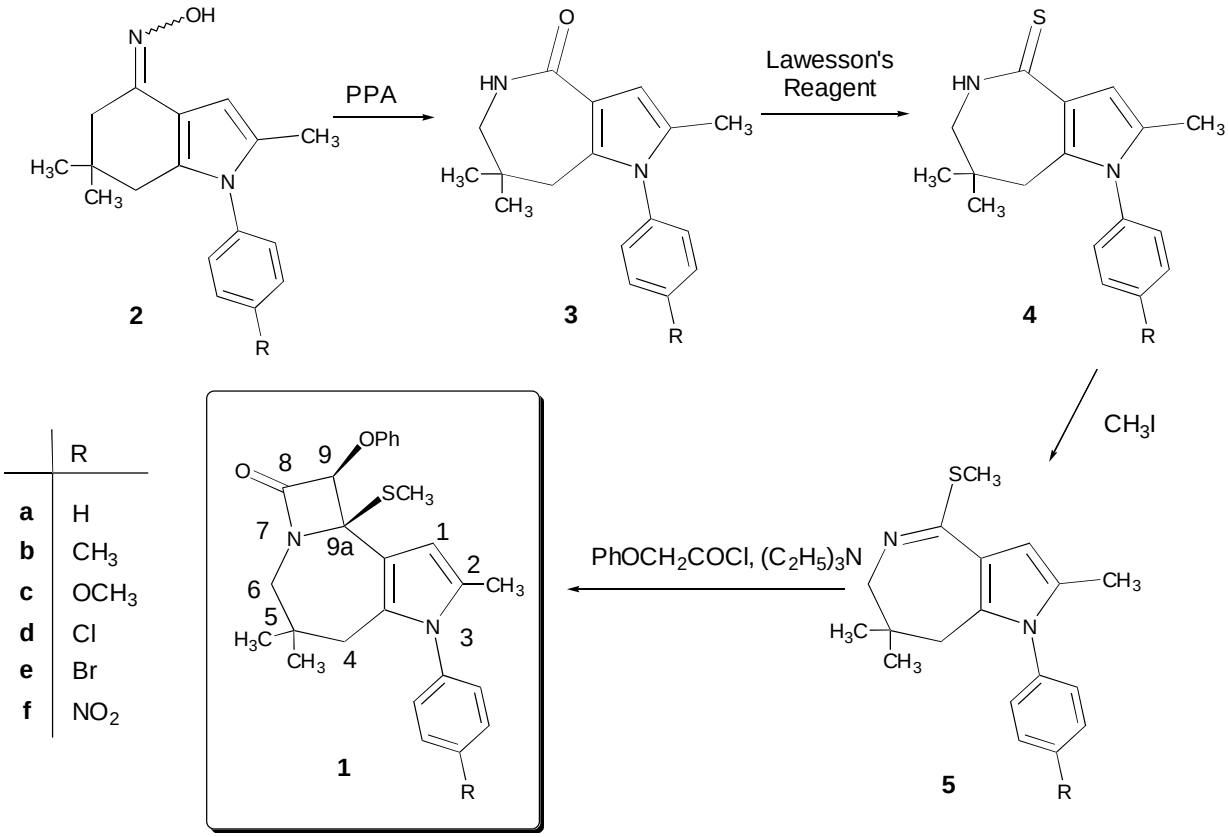
Since no general methods for the preparation of the new triheterocyclic system C_3N-C_4N-C_6N have been reported, it was of interest to extend our approach for the synthesis of benzodipyrroles to obtain the first member of the former triheterocyclic series. Therefore herein, we describe a convenient, regio- and stereo-

controlled synthesis of the hitherto unknown *cis*-3-aryl-2,5,5-trimethyl-9a-methylsulfanyl-9-phenoxy-4,5,6,8,9,9a-hexahydro-*3H*-azeto[1,2-*a*]pyrrolo[3,2-*c*]azepin-8-ones from *6H*-1-aryl-2,7,7-trimethyl-4,5,7,8-tetrahydropyrrolo[3,2-*c*]azepin-4-ones.

RESULTS AND DISCUSSION

The first simple synthesis of the triheterocyclic system C_3N-C_4N-C_6N starts with the ring expansion of the tetrahydroindolone oximes (**2**), easily prepared from dimedone,[9] to the azepinones (**3**). Thereafter a heteroatomic exchange (O□S) and methylation give the azepinthiones (**4**) and the imines (**5**)**,** respectively. Then a cycloaddition of **5** with phenoxyacetyl chloride finally leaves to the lactams (**1**) as shown in Scheme 1.

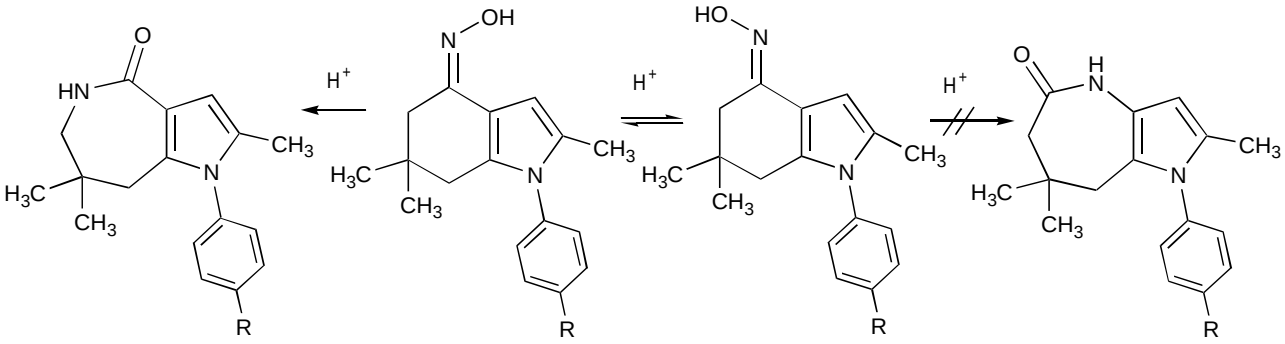
Scheme 1



The Beckmann rearrangement[10] of the *syn*- and *anti*-oximes (**2**) gave the azepinones (**3**) as only one product of the reaction. Heating of **2** in polyphosphoric acid at 100 ^{o}C carried out this reaction, and after 1 h complete conversion was observed to give the product in quantitative yields.[9] The impressive fact that only the alkyl migration occurs and no trace of the pyrrole migration product (**6**) was observed, shows that, while the *syn*-oxime is consumed during rearrangement, an equilibration of the *anti*-oxime in acid

medium occurs to give mixtures of *syn/anti*-oximes[11] instead of **6** (Scheme 2). On this way, this reaction allows to obtain in a highly regiospecific way the azepinones (**3**) from mixtures of *syn/anti*-oximes (**2**) (*ca*. 50:50) in such good yields. The use of polyphosphoric acid[12] makes to the reaction cleaner and avoids the formation of side products. For example, the use of sulfuric acid gives the sulfonation products.[13]

Scheme 2



3 *syn-* **2** *anti-* **2** **6**

In contrast to alkylation of normal amides preferentially giving rise to *N*-alkylation products,[14] the alkylation of thioamides exclusively provides the *S*-alkylated imine products.[15] For this reason, conversion of azepinones (**3**) to thioazepinones (**4**) was also carried out in quantitative yields by use of Lawesson's reagent in toluene (Table 1). The *S*-methylation of thioazepinones (**4**) with methyl iodide in CH_2Cl_2 gave the corresponding iminium salts (**7**), which precipitated in the reaction mixture and could be neutralized with $KHCO_3$ to afford exclusively the free methylsulfanylimines (**5**) in good yields (Scheme 3, Table 2).

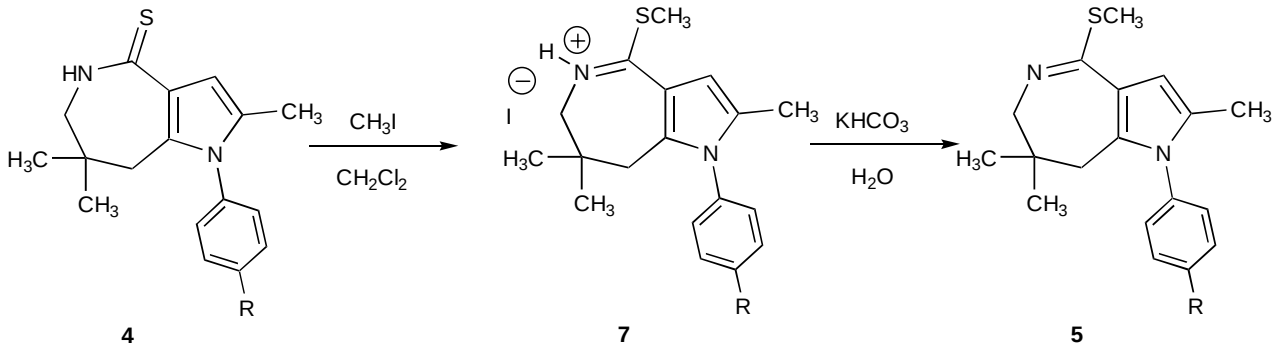
Table1. Conversion of Azepinones (**3**) to Thioazepinones (**4**) by Use of Lawesson's Reagent[a]

Product	R	Yield [b] (%)
a	H	87
b	CH_3	84
c	OCH_3	82
d	Cl	93
e	Br	93
f	NO_2	81

[a] Reaction was carried out in toluene at reflux for 1 h under nitrogen atmosphere. [b] Yield of isolated material after column chromatography, mass balance >95%.

However, in contrast to other methods which normally run under stronger reaction conditions, this *S*-methylation undergoes under quite mild reaction conditions (CH_2Cl_2 at room temperature), yielding the products with a good purity without further purification.

Scheme 3



4 **7** **5**

Table 2. Methylation of Thioazepinones (**4**) to Imines (**5**) with Methyl Iodide[a]

Product	R	Yield (%)
a	H	97
b	CH_3	91
c	OCH_3	97
d	Cl	99
e	Br	99
f	NO_2	94

[a] Reaction was carried out in CH_2Cl_2 at room temperature for 1 h. Free setting of imine was made in situ by treatment with saturated $KHCO_3$ solution at 0 ^oC.

The formation of 2-azetidinones (**1**) was carried out by use of the Staudinger's methodology for the reaction of imines with acid chlorides. So, when phenoxyacetyl chloride was added to the imines (**5**) followed by the addition of triethylamine as a base in benzene and then the mixture was heated under reflux, the new *cis*-hexahydro-*3H*-azeto[1,2-*a*]pyrrolo[3,2-*c*]azepin-8-ones (**1**) ($C_3NC_4NC_6N$) were obtained as only one product of the reaction (Scheme 1). The cycloaddition proceeded with acceptable yields (Table 3) and the conversion of the reaction was from 72 to 91 % since longer reaction times than 1 h took place decomposition of the product.

Table 3. Formation of Azetidinones (**1**) by Cycloaddition[a] of the Imines (**5**) with Phenoxy-acetyl Chloride[b] in Presence of Triethylamine

product	R	conversion [c] (%)	yield [d] (%)
a	H	72	50
b	CH_3	77	48
c	OCH_3	80	48
d	Cl	80	50
e	Br	90	50
f	NO_2	91	55

[a] Reaction was carried out in benzene at reflux for 1 h. [b] The freshly destilled phenoxy-acetyl chloride was added dropwise and then the recently destilled triethylamine. [c] Conversion obtained after 1 h reaction. Longer reaction times give to partial decomposition of the product. Unreacted starting material (imine (**5**)) was reisolated after purification (column chromatography). Mass balance >95%. [d] Yield of isolated material after column chromatography

Only the *cis* diastereoisomeric products were observed and no traces of the *trans* products could be detected. The relative *cis* stereochemistry of the β-lactam moiety was determined by NOESY experiments, where the respective effects between the α-proton of the lactam ring and the vinylic proton of the pyrrol moiety were observed (Figure 1).

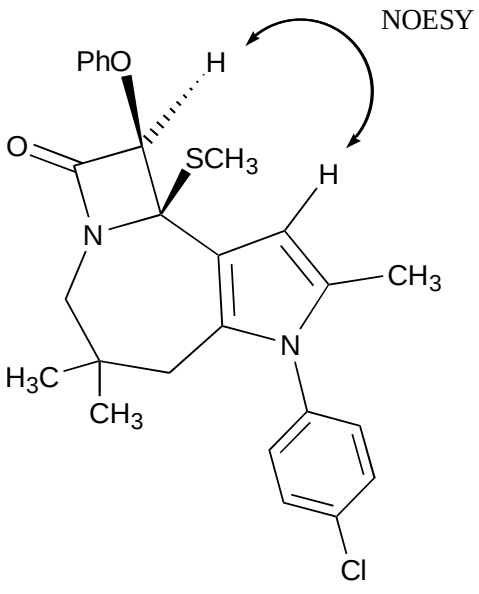
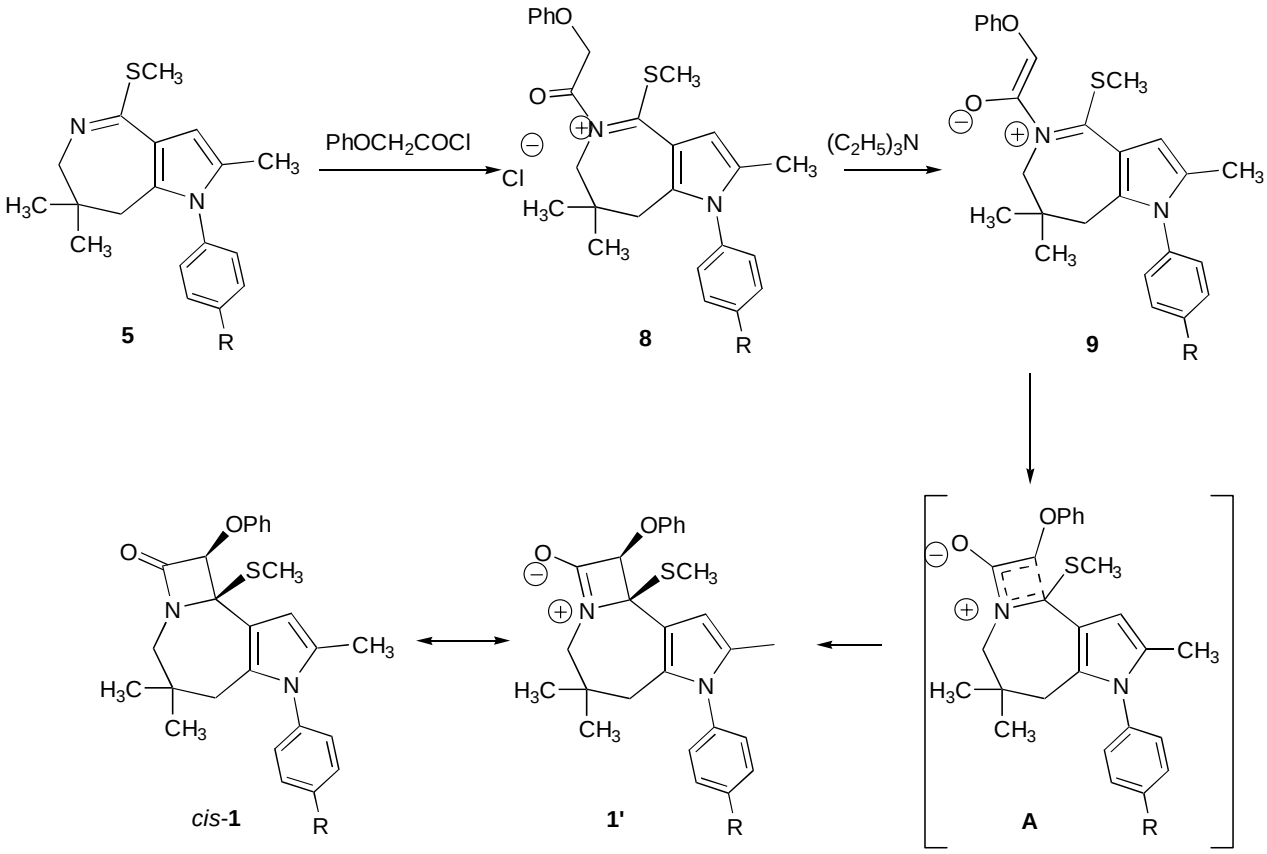


Figure 1. NOESY effects of the tricyclic compound (**1d**).

The mechanism in Scheme 4 might rationalize the exclusive formation of the *cis* diastereoisomer as function of the imine and enolate geometries. In the first step of the reaction, the direct addition of the acid chloride to the imine in absence of base generates the adduct (**8**), which in presence of triethylamine occurs in the formation of the enolate (**9**). The conrotatory ring closure step[8] proceeds with an efficient stereocontrol for the newly formed chiral centers as displayed by the transition state **A** to give the corresponding β-lactam adduct **1'1**. The practically complete diastereocontrol in the ring closure step derives from the fixed *E* geometry of the imine and the predominant *Z* geometry of the enolate.[16] Therefore in the transition state, these geometries turn in to the crucial π-facial controlling feature for guaranteeing the essential restricted conformational geometry for the high diastereoselectivity.

Scheme 4



CONCLUSIONS

The present synthetic sequence (Scheme 1) which starts from the oximes of the *N*-aryl-2,6,6-trimethyl-4,5,6,7-tetrahydroindolones, constitutes the first regio- and stereoselective synthesis of configurational defined *cis*-3-aryl-2,5,5-trimethyl-9a-methylsulfanil-9-phenoxy-4,5,6,8,9,9a-hexahydro-*3H*-azeto[1,2-*a*]-

pyrrolo[3,2-*c*]azepin-8-ones (the new System-$C_3NC_6NC_4N$). On one hand, the exclusive alkyl migration for the Beckmann rearrangement presumably due to foregoing equilibration of the oximes, results in a highly regiospecific reaction. Likewise, the addition of phenoxyacetyl chlorides prior to the triethylamine during the formation of the C_3N-ring has become the key to obtain the *cis* diastereoisomer in high diastereoselective purity (>99%). Therefore, the stereochemistry of the α,β-chiral centers of the β-lactam moiety (C_3N-ring) can be also dictated.

EXPERIMENTAL

All reactions were performed in oven-dried glassware under a positive pressure of nitrogen. Reaction mixtures and chromatography fractions were concentrated by using a rotary evaporator (*ca*. 20 ^oC/ 20 Torr). Elemental analyses were performed at Galbraith Laboratories, Inc. For column chromatography, the Merck silica gel 60 F254 was employed. Commercial grade reagents were used without further purification except when indicated. Benzene and toluene were distilled from a sodium/ benzophenone mixture immediately prior to use, and CH_2Cl_2 from P_2O_5.

6*H*-1-Aryl-2,7,7-trimethyl-4,5,7,8-tetrahydropyrrolo[3,2-*c*]azepin-4-ones (3)

The azepinones (**3a-f**) were prepared from the corresponding oximes by use of polyphosphoric acid. The spectral data were in agreement with the reported data.[9] Spectral data for the unknown azepinone (**3f**) are described below.

***6H-1-(4-Nitrophenyl)-2,7,7-trimethyl-4,5,7,8-tetrahydropyrrolo[3,2-c]azepin-4-ones* (3f)**

mp 250-255 ^oC (CH_2Cl_2/ Hexane); IR (KBr) ν_{max} (cm^{-1}) 3388, 3274, 3187, 2958, 1638, 1527, 1477, 1346, 1112, 754; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.98 (s, 6H), 2.00 (d, J = 0.9 Hz, 3H), 2.34 (s, 2H), 3.03 (d, J = 5.5 Hz, 2H), 6.22 (br t, J = 5.2 Hz, exchangeable with D_2O, 1H), 6.52 (q, J = 0.9 Hz, 1H), 7.41 and 8.40 (AB-system, J= 8.7 , 8.8 Hz, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 12.7 (q), 26.7 (q), 35.3 (s), 40.5 (t), 52.8 (t), 109.0 (d), 116.4 (s), 124.9 (d), 129.5 (d), 133.3 (s), 143.5 (s), 147.6 (d), 169.4 (s); MS (EI) m/z (relative intensity) 313 (M^+, 100), 254 (32); HRMS (EI) Calcd for $C_{17}H_{19}N_3O_3$ 313.1426, Found 313.1406.

General Procedure A for the Synthesis of 6*H*-1-Aryl-2,7,7-trimethyl-4,5,7,8-tetrahydropyrrolo-[3,2-*c*]azepin-4-thiones (4)

A 50-mL, two-necked, round-bottomed flask was equipped with a condenser and a rubber septum. It was charged with 15 mL of dry toluene and the particular azepin-4-one (**3**) (0.67 – 4.60 mmol). After the addition of Lawesson's reagent (0.40 – 2.78 mmol) the reaction mixture was warmed to reflux for 1 h and allowed to cool to rt (*ca*. 20 ^oC). The solvent was evaporated and the residue was purified by column chromatography [silica gel; hexane:CH_2Cl_2 (60:40)] to yield the corresponding azepin-4-thiones (**4**) in 81

– 95% (Table 1) as pale yellow amorphous solids. The yields and spectral data for the individual cases are described below.

6H-1-Phenyl-2,7,7-trimethyl-4,5,7,8-tetrahydropyrrolo[3,2-c]azepin-4-thione **(4a)**

According to the above general procedure A, from azepin-4-one (**3a**) (1.25 g, 4.6 mmol) and Lawesson's reagent (1.13 g, 2.79 mmol), azepin-4-thione (**4a**) (1.13 g, 87%) was obtained after column chromatography, mp 214-216 ^{o}C (CH_2Cl_2/ Hexane): IR (KBr) ν_{max} (cm^{-1}) 3180, 2957, 1596, 1514, 1497, 1454, 1408, 1315, 1178, 963, 753, 698; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.97 (s, 6H), 1.96 (d, J = 0.8 Hz, 3H), 2.29 (s, 2H), 3.10 (d, J = 5.9 Hz, 2H), 6.67 (q, J = 0.8 Hz, 1H), 7.11- 7.21 (m, 2H), 7.43-7.57 (m, 3H), 8.46 (br s, exchangeable with D_2O, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 12.3 (q), 26.4 (q), 39.0 (t), 39.6 (s), 57.3 (t), 110.7 (d), 121.9 (s), 128.0 (d), 128.6 (d), 129.2 (d), 130.4 (s), 132.5 (s), 136.9 (s), 196.4 (s); MS (EI) m/z (relative intensity) 284 (M^+, 100), 269 (56); HRMS (EI) Calcd for $C_{17}H_{20}N_2S$ 284.1347, Found 284.1352.

6H-1-(4-Methylphenyl)-2,7,7-trimethyl-4,5,7,8-tetrahydropyrrolo[3,2-c]azepin-4-thione **(4b)**

According to the above general procedure A, from methylazepin-4-one (**3b**) (510 mg, 1.80 mmol) and Lawesson's reagent (440 mg, 1.08 mmol), methylazepin-4-thione (**4b**) (460 mg, 84%) was obtained after column chromatography, mp 272-274 ^{o}C (CH_2Cl_2/ Hexane): IR (KBr) ν_{max} (cm^{-1}) 3173, 3037, 2953, 1503, 1429, 1407, 1309, 1179, 1125, 1010, 956, 807; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.96 (s, 6H), 1.94 (d, J = 0.9 Hz, 3H), 2.29 (s, 2H), 2.44 (s, 3H), 3.10 (d, J = 5.9 Hz, 2H), 6.66 (q, J = 1.0 Hz, 1H), 7.04 and 7.29 (AB-system, J= 8.6 , 8.7 Hz, 4H), 8.16 (br s, exchangeable with D_2O, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 12.6 (q), 21.2 (q), 26.7 (q), 39.3 (t), 39.9 (s), 57.7 (t), 110.9 (d), 121.9 (s), 128.0 (d), 130.1 (d), 130.8 (s), 132.8 (s), 134.6 (s), 138.9 (s), 196.9 (s); MS (EI) m/z (relative intensity) 298 (M^+, 100), 283 (61); HRMS (EI) Calcd for $C_{18}H_{22}N_2S$ 298.1504, Found 298.1508.

6H-1-(4-Methoxyphenyl)-2,7,7-trimethyl-4,5,7,8-tetrahydropyrrolo[3,2-c]azepin-4-thione **(4c)**

According to the above general procedure A, from methoxyazepin-4-one (**3c**) (1.0 g, 2.40 mmol) and Lawesson's reagent (582 mg, 1.44 mmol), methoxyazepin-4-thione (**4c**) (860 mg, 82%) was obtained after column chromatography, mp 280-282 ^{o}C (CH_2Cl_2/ Hexane): IR (KBr) ν_{max} (cm^{-1}) 3343, 2955, 1603, 1504, 1428, 1293, 1250, 1173, 1109, 1037, 964, 852, 757; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.96 (s, 6H), 1.95 (d, J = 0.7 Hz, 3H), 2.29 (s, 2H), 3.10 (d, J = 5.9 Hz, 2H), 3.88 (s, 3H), 6.65 (q, J = 0.9 Hz, 1H), 6.95 and 7.13 (AB-system, J= 8.6 , 8.7 Hz, 4H), 8.28 (br s, exchangeable with D_2O, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 12.5 (q), 26.7 (q), 39.3 (t), 39.8 (s), 55.5 (q), 57.6 (t), 110.7 (d), 114.6 (d), 121.8 (s), 129.2 (d), 129.8 (s), 131.0 (s), 133.1 (s), 159.6 (s), 196.8 (s); MS (EI) m/z (relative intensity) 314 (M^+, 100), 299 (65); HRMS (EI) Calcd for $C_{18}H_{22}N_2OS$ 314.1453, Found 314.1442.

6H-1-(4-Chlorophenyl)-2,7,7-trimethyl-4,5,7,8-tetrahydropyrrolo[3,2-c]azepin-4-thione **(4d)**

According to the above general procedure A, from chloroazepin-4-one (**3d**) (400 mg, 1.32 mmol) and Lawesson's reagent (320 mg, 0.79 mmol), chloroazepin-4-thione (**4d**) (390 mg, 93%) was obtained after column chromatography, mp 283-285 ^{o}C (CH_2Cl_2/ Hexane): IR (KBr) ν_{max} (cm^{-1}) 3174, 2955, 1544, 1511, 1492, 1405, 1309, 1179, 1090, 1009, 754; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.97 (s, 6H), 1.96 (d, *J* = 0.8 Hz, 3H), 2.28 (s, 2H), 3.11 (d, J = 5.8 Hz, 2H), 6.67 (q, J = 0.9 Hz, 1H), 7.13 and 7.49 (AB-system, J= 8.7 , 8.8 Hz, 4H), 8.45 (br t, J = 5.6 Hz, exchangeable with D_2O, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 12.6 (q), 26.7 (q), 39.4 (t), 39.8 (s), 57.5 (t), 111.4 (d), 122.2 (s), 123.0 (s), 129.9 (d), 130.5 (s), 132.6 (s), 132.8 (d), 136.3 (s), 196.3 (s); MS (EI) m/z (relative intensity) 318 (M^+, 100), 320 (M^++2, 38), 303 (65); HRMS (EI) Calcd for $C_{17}H_{19}N_2ClS$ 318.0957, Found 318.0938.

***6H-1-(4-Bromophenyl)-2,7,7-trimethyl-4,5,7,8-tetrahydropyrrolo[3,2-c]azepin-4-thione* (4e)**

According to the above general procedure A, from bromoazepin-4-one (**3e**) (340 mg, 1.07 mmol) and Lawesson's reagent (260 mg, 0.64 mmol), bromoazepin-4-thione (**4e**) (337 mg, 93%) was obtained after column chromatography, mp 267-269 ^{o}C (CH_2Cl_2/ Hexane): IR ($CHCl_3$) ν_{max} (cm^{-1}) 3397, 2961, 1570, 1514, 1490, 1409, 1318, 1173, 1007, 960, 839; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.97 (s, 6H), 1.96 (d, J = 0.9 Hz, 3H), 2.28 (s, 2H), 3.09 (d, J = 5.8 Hz, 2H), 6.67 (q, J = 1.0 Hz, 1H), 7.06 and 7.64 (AB-system, J= 8.7, 8.8 Hz, 4H), 8.30 (br s, exchangeable with D_2O, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 12.6 (q), 26.7 (q), 39.4 (t), 39.7 (s), 57.4 (t), 111.2 (d), 122.1 (s), 122.9 (s), 129.8 (d), 130.5 (s), 132.6 (s), 132.8 (d), 136.2 (s), 195.9 (s); MS (EI) m/z (relative intensity) 62 (M^+, 100), 364 (M^++2, 100), 347 (64), 349 (64); HRMS (EI) Calcd for $C_{17}H_{19}N_2BrS$ 362.0452, Found 362.0454.

***6H-1-(4-Nitrophenyl)-2,7,7-trimethyl-4,5,7,8-tetrahydropyrrolo[3,2-c]azepin-4-thione* (4f)**

According to the above general procedure A, from nitroazepin-4-one (**3f**) (210 mg, 0.67 mmol) and Lawesson's reagent (162 mg 0.40 mmol), nitroazepin-4-thione (**4f**) (179 mg, 81%) was obtained after column chromatography, mp 265-270 ^{o}C (CH_2Cl_2/ Hexane): IR (KBr) ν_{max} (cm^{-1}) 3186, 2957, 1597, 1549, 1524, 1496, 1408, 1346, 1311, 1178, 964, 757; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.97 (s, 6H), 2.00 (s, 3H), 2.30 (s, 2H), 3.08 (d, J = 3.2 Hz, 2H), 6.65 (s, 1H), 7.48 and 8.42 (AB-system, J= 8.6, 8.7 Hz, 4H), 9.47 (br s, exchangeable with D_2O, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 11.7 (q), 25.8 (q), 38.2 (s), 38.6(t), 55.8 (t), 111.1 (d), 122.0 (s), 124.0 (d), 128.6 (d), 128.8 (s), 130.7 (s), 142.0 (s), 146.6 (s), 194.4 (s); MS (EI) m/z (relative intensity) 329 (M^+, 100), 314 (75); HRMS (EI) Calcd for $C_{17}H_{19}N_3O_2S$ 329.1198, Found 329.1199.

General Procedure B for the S-Methylation of 6*H*-1-(4-R_1-Phenyl)-2,7,7-trimethyl-4,5,7,8-tetrahydropyrrolo[3,2-*c*]azepin-4-thiones

A solution of the particular azepin-4-thione (**4**) (0.27 – 3.58 mmol) in 5 mL of CH_2Cl_2 was placed in a 50-mL round-bottomed flask. After the addition of freshly distilled methyl iodide (0.33 – 5.09 mmol) the reaction mixture was stirred for 1 h at rt (*ca*. 20 ^{o}C), treated with 3 mL of saturated, aqueous $NaHCO_3$

solution, and then stirred another 5 min. The aqueous phase was separated and extracted with three 10-mL portions of dichloromethane, and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated to yield the *S*-methylazepines (**5**) in 90–99% (Table 2) as yellow amorphous solids, which were used without further purification.

***1-Phenyl-2,7,7-trimethyl-4-methylsulfanyl-4,5,7,8-tetrahydropyrrolo[3,2-c]azepine* (5a)**

According to the above general procedure B, from azepin-4-thione (**4a**) (965 mg, 3.39 mmol), and methyl iodide (723 mg, 5.09 mmol), methylsulfanylazepine (**5a**) (990 mg, 97% crude) was obtained.

***1-(4-Methylphenyl)-2,7,7-trimethyl-4-methylsulfanyl-4,5,7,8-tetrahydropyrrolo[3,2-c]azepine* (5b)**

According to the above general procedure B, from methylazepin-4-thione (**4b**) (440 mg, 1.47 mmol) and methyl iodide (270 mg, 1.90 mmol), methyl-methylsulfanyl-azepine (**5b**) (426 g, 91% crude) was obtained.

***1-(4-Methoxyphenyl)-2,7,7-trimethyl-4-methylsulfany)-4,5,7,8-tetrahydropyrrolo[3,2-c]azepine* (5c)**

According to the above general procedure B, from methoxyazepin-4-thione (**4c**) (100 mg, 0.31 mmol) and methyl iodide (58 mg, 0.40 mmol), methoxy-methylsulfanylazepine (**5c**) (101 mg, 97% crude) was obtained.

***1-(4-Chlorophenyl)-2,7,7-trimethyl-4-methylsulfany)-4,5,7,8-tetrahydropyrrolo[3,2-c]azepine* (5d)**

According to the above general procedure B, from chloroazepin-4-thione (**4d**) (300 mg, 0.94 mmol) and methyl iodide (267 mg, 1.88 mmol), chloro-methylsulfanylazepine (**5d**) (310 mg, 99% crude) was obtained.

***1-(4-Bromophenyl)-2,7,7-trimethyl-4-methylsulfanyl-4,5,7,8-tetrahydropyrrolo[3,2-c]azepine* (5e)**

According to the above general procedure B, from bromoazepin-4-thione (**4e**) (100 mg, 0.27 mmol) and methyl iodide (47 mg, 0.33 mmol), bromo-methylsulfanylazepine (**5e**) (103 mg, 99% crude) was obtained.

1-(4-Nitrophenyl)-2,7,7-trimethyl-4-methylsulfanyl-4,5,7,8-tetrahydropyrrolo[3,2-c]azepine (5f)

According to the above general procedure B, from nitroazepin-4-thione (4f) (150 mg, 0.45 mmol) and methyl iodide (83 mg, 1.30 mmol), nitro-methylsulfanylazepine (5f) (148 mg, 94% crude) was obtained

General Procedure C for the Cycloaddition of Phenoxyacetyl Chloride with 1-Aryl-2,5,5-trimethyl-4-methylsulfanyl-6,7-hexahydropyrrolo[3,2-*c*]azepines (5)

A 50-mL, two-necked, round-bottomed flask was equipped with a condenser and an addition funnel. The flask was charged with 5 mL of dry benzene and the particular methylsulfanylazepine (**5**) (0.26 – 2.40 mmol). Phenoxyacetyl chloride (88 - 816 mg, 0.52 – 4.80 mmol) and subsequently triethylamine (63 – 586 mg, 0.62 – 5.8 mmol)were added over a period of 45 min, and the reaction mixture was warmed to reflux for 1 h, allowed to cool to rt (*ca*. 20 ^{o}C) and filtered. The solvent was evaporated and the residue

was purified by column chromatography [silica gel; hexane:AcOEt (98:2)] to yield the corresponding azeto[1,2-*a*]pyrrolo[3,2-*c*]azepin-8-ones (**1**) in 47–55% (Table 3) as light pale yellow amorphous solids. The yields and spectral data for the individual cases are described below.

3-Phenyl-2,5,5-trimethyl-9a-methylsulfanyl-9-phenoxy-4,5,6,8,9,9a-hexahydro-3H-azeto[1,2-a]pyrrolo[3,2-c]azepin-8-one **(1a)**

According to the above general procedure C, from methylsulfanylazepine (**5a**) (520 mg, 1.74 mmol), phenoxyacetyl chloride (594 mg, 3.48 mmol) and triethylamine (440 mg, 4.35 mmol), azetoazepin-8-one (**1a**) (220 mg, 50%) and (**5a**) (147 mg, 72% conversion) were obtained after column chromatography, mp 160-161 ^{o}C (CH_2Cl_2/ Hexane): IR (film) ν_{max} (cm^{-1}) 3020, 2959, 1764, 1594, 1496, 1400, 1236, 756, 696; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.92 (s, 3H), 1.90 (s, 3H), 2.16 (dd, J = 2.3, 15.4 Hz, 1H), 2.19 (s, 3H), 2.65 (d, J = 15.5 Hz, 1H), 3.08 (d, J = 13.8 Hz, 1H), 3.70 (dd, J = 2.3, 13.9 Hz, 1H), 5.53 (s, 1H), 5.80 (s, 1H), 7.03 - 7.53 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 12.8 (q), 13.7 (q), 23.5 (q), 28.6 (q), 33.3 (s), 39.1 (t), 50.7 (t), 74.1 (s), 89.8 (d), 104.5 (d), 116.8 (d), 119.2 (s), 122.6 (d), 128.1 (d), 128.3 (d), 128.5 (d), 128.8 (d), 128.9 (d), 129.2 (d), 129.5 (d), 138.0 (s), 157.8 (s), 164.7 (s); MS (EI) m/z (relative intensity) 432 (M^+, 8), 385 (100). Anal. Calcd for $C_{26}H_{28}N_2O_2S$: C, 72.19; H, 6.52; N, 6.47. Found: C, 72.33; H, 6.64; N, 6.32.

3-(4-Methylphenyl)-2,5,5-trimethyl-9a-methylsulfanyl-9-phenoxy-4,5,6,8,9,9a-hexahydro-3H-azeto[1,2-a]pyrrolo[3,2-c]azepin-8-one **(1b)**

According to the above general procedure C, from methyl-methylsulfanylazepine (**5b**) (388 mg, 1.20 mmol), phenoxyacetyl chloride (424 mg, 2.40 mmol) and triethylamine (314 mg, 3.00 mmol), methyl-azetoazepin-8-one (**1b**) (140 mg, 48%) and (**5b**) (88 mg, 77% conversion) were obtained after column chromatography, mp 170-171 ^{o}C (CH_2Cl_2/ Hexane): IR (film) ν_{max} (cm^{-1}) 3015, 2958, 1763, 1594, 1515, 1493, 1398, 1234, 755, 690; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.92 (s, 3H), 1.89 (s, 3H), 2.18 (dd, J = 2.3, 15.8 Hz, 1H), 2.19 (s, 3H), 2.42 (s, 3H), 2.64 (d, J = 15.5 Hz, 1H), 3.07 (d, J = 14.1 Hz, 1H), 3.70 (dd, J = 2.2, 13.8 Hz, 1H), 5.52 (s, 1H), 5.78 (s, 1H), 6.91 - 7.42 (m, 9H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 12.9 (q), 13.7 (q), 21.1 (q), 23.5 (q), 28.6 (q), 33.3 (s), 39.0 (t), 50.7 (t), 74.1 (s), 89.7 (d), 104.3 (d), 115.3 (s), 116.8 (d), 119.0 (s), 122.6 (d), 128.2 (d), 128.6 (d), 128.8 (d), 129.3 (s), 129.5 (d), 129.8 (d), 135.3 (s), 138.2 (s), 157.8 (s), 164.7 (s); MS (EI) m/z (relative intensity) 446 (M^+, 8), 399 (100); Anal. Calcd for $C_{27}H_{30}N_2O_2S$: C, 72.61; H, 6.77; N, 6.27. Found: C, 72.30; H, 6.64; N, 6.30.

3-(4-Methoxyphenyl)-2,5,5-trimethyl-9a-methylsulfanyl-9-phenoxy-4,5,6,8,9,9a-hexahydro-3H-azeto[1,2-a]pyrrolo[3,2-c]azepin-8-one **(1c)**

According to the above general procedure C, from methoxy-methylsulfanylazepine (**5c**) (800 mg, 2.40 mmol), phenoxyacetyl chloride (848 mg, 4.80 mmol) and triethylamine (628 g, 6.00 mmol), methoxy-azetoazepin-8-one (**1c**) (432 mg, 48%) and (**5c**) (160 mg, 80% conversion) were obtained after column

chromatography, mp 181-183 ^{o}C (CH_2Cl_2/ Hexane): IR (film) ν_{max} (cm^{-1}) 3001, 2959, 1764, 1598, 1514, 1495, 1402, 1292, 1250, 1168, 1036, 755, 690; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.92 (s, 3H), 0.93 (s, 3H), 1.89 (s, 3H), 2.18 (dd, J = 2.2, 15.6 Hz, 1H), 2.19 (s, 3H), 2.64 (d, J = 15.7 Hz, 1H), 3.08 (d, J = 13.9 Hz, 1H), 3.70 (dd, J = 2.3, 13.8 Hz, 1H), 3.87 (s, 3H), 5.52 (s, 1H), 5.78 (s, 1H), 6.91 - 7.43 (m, 9H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 12.8 (q), 13.7 (q), 23.5 (q), 28.6 (q), 33.3 (s), 39.0 (t), 50.7 (t), 55.5 (q), 74.1 (s), 89.7 (d), 104.2 (d), 114.3 (d), 114.4 (d), 116.8 (d), 118.9 (s), 122.6 (d), 128.4 (s), 129.0 (s), 129.5 (d), 129.6 (d), 129.8 (d), 130.6 (s), 157.8 (s), 159.2 (s), 164.7 (s); MS (EI) m/z (relative intensity) 462 (M^+, 10), 415 (100); HRMS (EI) Calcd for $C_{27}H_{30}N_2O_3S$ 462.1977, Found 462.1956.

3-(4-Chlorophenyl)-2,5,5-trimethyl-9a-methylsulfanyl-9-phenoxy-4,5,6,8,9,9a-hexahydro-3H-azeto[1,2-a]pyrrolo[3,2-c]azepin-8-one **(1d)**

According to the above general procedure C, from chloro-methylsulfanylazepine (**5d**) (200 mg, 0.60 mmol), phenoxyacetyl chloride (247 mg, 1.44 mmol) and triethylamine (145 mg, 1.44 mmol), chloro-azetoazepin-8-one (**1d**) (110 mg, 50%) and (**5d**) (40 mg, 80% conversion) were obtained after column chromatography, mp 177-179 ^{o}C (CH_2Cl_2/ Hexane): IR (film) ν_{max} (cm^{-1}) 3004, 2962, 1765, 1493, 1402, 1091, 1014, 837; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.91 (s, 3H), 0.94 (s, 3H), 1.89 (s, 3H), 2.13 (dd, J = 2.2, 15.7 Hz, 1H), 2.19 (s, 3H), 2.65 (d, J = 15.6 Hz, 1H), 3.08 (d, J = 13.7 Hz, 1H), 3.70 (dd, J = 2.2, 13.9 Hz, 1H), 5.50 (s, 1H), 5.80 (s, 1H), 6.99 - 7.48 (m, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.8 (q), 13.6 (q), 23.5 (q), 28.6 (q), 33.4 (s), 39.1 (t), 50.6 (t), 74.0 (s), 89.8 (d), 104.9 (d), 116.8 (d), 119.6 (s), 122.6 (d), 128.0 (s), 128.7 (s), 129.5 (d), 129.8 (d), 130.2 (d), 134.4 (s), 136.5 (s), 157.8 (s), 164.6 (s); MS (EI) m/z (relative intensity) 466 (M^+, 12), 468 (M^++2, 5), 419 (100). Anal. Calcd for $C_{26}H_{27}N_2O_2ClS$: C, 66.86; H, 5.83; N, 5.60. Found: C, 66.48; H, 5.99; N, 5.96.

3-(4-Bromophenyl)-2,5,5-trimethyl-9a-methylsulfanyl-9-phenoxy-4,5,6,8,9,9a-hexahydro-3H-azeto[1,2-a]pyrrolo[3,2-c]azepin-8-one **(1e)**

According to the above general procedure C, from bromo-methylsulfanylazepine (**5e**) (90 mg, 0.52 mmol), phenoxyacetyl chloride (100 mg, 0.26 mmol) and triethylamine (67 mg, 0.65 mmol), bromoazetoazepin-8-one (**1e**) (59.7 mg, 50%) and (**5e**) (10 mg, 90% conversion) were obtained after column chromatography as yellow oil: IR (film) ν_{max} (cm^{-1}) 3020, 2959, 1762, 1594, 1491, 1400, 1235, 1009, 757; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.91 (s, 3H), 0.94 (s, 3H), 1.89 (s, 3H), 2.13 (dd, J = 2.1, 15.7 Hz, 1H), 2.19 (s, 3H), 2.64 (d, J = 15.7 Hz, 1H), 3.08 (d, J = 13.9 Hz, 1H), 3.70 (dd, J = 2.2, 13.9 Hz, 1H), 5.51 (s, 1H), 5.80 (s, 1H), 6.90 - 7.70 (m, 9H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 12.8 (q), 13.6 (q), 23.5 (q), 28.6 (q), 33.3 (s), 39.1 (t), 50.6 (t), 73.9 (s), 89.7 (d), 104.9 (d), 116.8 (d), 119.6 (s), 122.4 (s), 122.6 (d), 128.0 (s), 128.7 (s), 129.6 (d), 130.1 (d), 130.5 (d), 132.5 (d), 132.6 (s), 157.7 (s), 164.6 (s); MS (EI) m/z (relative intensity) 510 (M^+, 9), 512 (M^++2, 9), 463 (98), 465 (100); HRMS (EI) Calcd for $C_{26}H_{27}N_2O_2BrS$ 511.1055, Found 511.1035.

3-(4-Nitrophenyl)-2,5,5-trimethyl-9a-methylsulfanyl-9-phenoxy-4,5,6,8,9,9a-hexahydro-3H-azeto[1,2-a] pyrrolo[3,2-c]azepin-8-one **(1f)**

According to the above general procedure C, from nitro-methylsulfanylazepine (**5f**) (120 mg, 0.34 mmol), phenoxyacetyl chloride (118 mg, 0.69 mmol) and triethylamine (87.5 mg, 0.87 mmol), nitroazetoazepin-8-one (**1f**) (75 mg, 55%) and (**5f**) (11 mg, 91% conversion) were obtained after column chromatography, mp 136-140 ^{o}C (CH_2Cl_2/ Hexane): IR (film) ν_{max} (cm^{-1}) 3075, 2958, 1761, 1595, 1524, 1494, 1399, 1343, 1235, 756; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.93 (s, 3H), 0.95 (s, 3H), 1.93 (s, 3H), 2.11 (dd, J = 2.2, 15.6 Hz, 1H), 2.21 (s, 3H), 2.71 (d, J = 15.5 Hz, 1H), 3.10 (d, J = 13.8 Hz, 1H), 3.72 (dd, J = 2.2, 13.9 Hz, 1H), 5.51 (s, 1H), 5.85 (s, 1H), 7.04-7.43 (m, 7H), 8.33-8.40 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 12.9 (q), 13.6 (q), 23.5 (q), 28.6 (q), 33.4 (s), 39.3 (t), 50.5 (t), 73.7 (s), 89.7 (d), 106.1 (d), 116.9 (d), 120.7 (s), 122.7 (d), 124.7 (d), 127.8 (s), 128.6 (s), 129.4 (d), 129.6 (d), 129.8 (d), 143.7 (s), 138.5 (d), 147.5 (s), 157.7 (s), 164.5 (s); MS (EI) m/z (relative intensity) 477 (M^+, 11), 430 (100). Anal. Calcd for $C_{26}H_{27}N_3O_4S$: C, 65.39; H, 5.70; N, 8.80. Found: C, 65.16; H, 5.74; N, 8.73.

ACKNOWLEDGMENT

We are grateful to C. Contreras, B. Quiróz, H. Rios, W. Matus, R. Gaviño, L. Velasco and F.J. Peréz for their assistance in obtaining the IR, NMR and mass spectral data. We thank also to DGAPA, UNAM Proy. IN-206598 for financial support. G.L.L. thanks the Consejo Nacional de Ciencia y Tecnología (CONACYT) for a master fellowship. Contribution No. 1705 from Instituto de Química, UNAM.

REFERENCES

1. (a) H. Breslin, M. Kukla, D. W. Ludovici, R. Mohrbacher, W. Ho, M. Miranda, J. D. Rodgers, T. K. Hitchens, G. Leo, D. A. Gauthier, C. Y. Ho, M. Scott, E. De Clercq, R. Patwels, K. Andries, L. Moens, M. A. C. Jansse and P. Janssen, *J. Med. Chem.*, 1995, **38**, 771. (b) M. Kukla, H. Breslin, R. Pauwels, C. Fedde, M. Miranda, M. Scott, R. Sherrill, A. Raeymaekers, J. Van Gelder, K. Andries, M. A. C. Janssen and P. Janssen, *J. Med. Chem.*, 1991, **34**, 746. (c) M. Kukla, H. Breslin, C. Diamond, P. Grous, C. Y. Ho, M. Miranda, J. Rodgers, R. Sherrill, E. De Clercq, R. Patwels, K. Andries, L. Moens, M. A. C. Janssen and P. Janssen, *J. Med. Chem.*, 1991, **34**, 3187. (d) K. D. Hargrave, J. R. Proudfoot, K. D. Krozinger, E. Cullen, S. R. Kapadia, V. R. Patel, V. U. Fuchs, S. C. Mauldin, J. Vitous, M. L. Behnke, J. M. Klunder, K. Pal, J. W. Skiles, D. W. MacNeil, J. M. Rose, G. C. Chow, M. T. Skoog, J. C. Wu, G. Schmidt, W. W. Engel, W. G. Eberlen, T. D. Saboe, S. J. Campbell, A. S. Rosenthal and S. Adams, *J. Med. Chem.*, 1991, **34**, 2231.

2. (a) G. J. Finlay, E. Marshall, J. H. L. Matthews, K. D. Paull and B. C. Baguley, *Cancer Chemother.*, 1993, **31**, 401. (b) C. Rehn and U. Pindur, *Monatsh. Chem.*, 1996, **127**, 645. (c) J. Y. Kim, T. -L. Su, T. -C. Chou, B. Koehler and A. Scarborough, *J. Med. Chem.*, 1996, **39**, 2812.

3. R. Martínez, J. Sandoval Oloarte and G. Avila, *J. Heterocycl. Chem.*, 1998, **35**, 585.

4. (a) U. Pindur, M. Haber and K. Sattler, *J. Chem. Ed.*, 1993, **70**, 263. (b) U. Asseline, N.T. Thuong, and C. Hélène, *New J. Chem.*, 1997, **21**, 5. (c) Y. Fukuda, S. Seto, H. Furuta, H. Ebisu and Y. Oomori, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 2003.

5. (a) M. S. Manhas, S. G. Amin and A. K. Bose, *Heterocycles*, 1976, **5**, 699. (b) R. B. Morin and M. Gorman, 'Chemistry and Biology of β-Lactam Antibiotics', Academic Press, New York, 1982, Vols. 1-3. (c) M. S. Manhas, D. R. Wagle, J. Chiang and A. K. Bose, *Heterocycles*, 1988, **27**, 1755. (d) R. C. Thomas, 'Recent Progress in the Chemical Synthesis of Antibiotics', G. Lukacs and M. Ohno, Springer, Berlin, 1988, p. 533. (e) F. H. van der Steen and G. van Koten, *Tetrahedron*, 1991, **47**, 7503. (f) L. Ghosez and J. Marchand-Brynaert, 'Comprehensive Organic Synthesis', ed. by B. Trost and I. Fleming, Pergamon, Oxford, 1991, Vol. 5, p. 85. (g) I. Ojima, *Acc. Chem.Res.*, 1995, **28**, 383.

6. G. I. Georg and V. T. Ravikumar, 'The Chemistry of β-Lactams', VCH: New York, 1993, p. 331.

7. (a) H. Staudinger, *Ann. Chem.*, 1907, **356**, 51. (b) L. S. Hegedus, J. Montgomery, Y. Narukawa and D. C. Snustad, *J. Am. Chem. Soc.*, 1991, **113**, 5784. (c) G. I. Georg and V. T. Ravikumar, 'The Organic Chemistry of β-Lactams', VCH, New York, 1993, p. 331.

8. A. Arrieta, B. Lecea and F. P. Cossío, *J. Org. Chem.*, 1998, **63**, 5869.

9. R. Martínez, G. López and J. G. Avila, *J. Heterocycl. Chem.*, 1995, **32**, 491.

10. R. E. Gawley, *Org. React.*, 1988, **35**, 1.

11. A. P. Stoll and F. Troxler, *Helv. Chim. Acta*, 1968, **51**, 1864.

12. V. Bardakos and W. Sucrow, *Chem. Ber.*, 1978, **111**, 1780.

13. R. Martínez, G. Avila and E. Reyes, *Synth. Commun.*, 1995, **25**, 1071.

14. (a) T. Gajda and A. Zwierzak, *Synthesis*, 1981, 1005. (b) A. Koziara, S. Zawadzki and A. Zwierzak, *Synthesis*, 1979, 527. (c) T. Gajda, A. Koziara, S. Zawadzki and A. Zwierzak, *Synthesis*, 1979, 549.

15. (a) R. E. Ireland and F. R. Brown, *J. Org. Chem.*, 1980, **45**, 1868. (b) K. Shiosaki, G. Fels and H. Rapoport, *J. Org. Chem.*, 1981, **46**, 3230.

16. (a) F. Babudri, L. Di Nunno and S. Florio, *Tetrahedron Lett.*, 1983, **24**, 3883. (b) D. A. Evans, J. Bartroli and T. L. Shih, *J. Am. Chem. Soc.*, 1981, **103**, 2127. (c) H. Danda, M. M. Hansen and C. H. Heathcock, *J. Org. Chem.*, **1990**, *55*, 173.