TERT-BUTYL 2-{1-[2-ARYL-4-OXOTHIAZOL-5(4*H*)-YLIDENE]ETHYL}DIAZENE-1-CARBOXYLATES: A NEW CLASS OF 1,2-DIAZA-1,3-BUTADIENES

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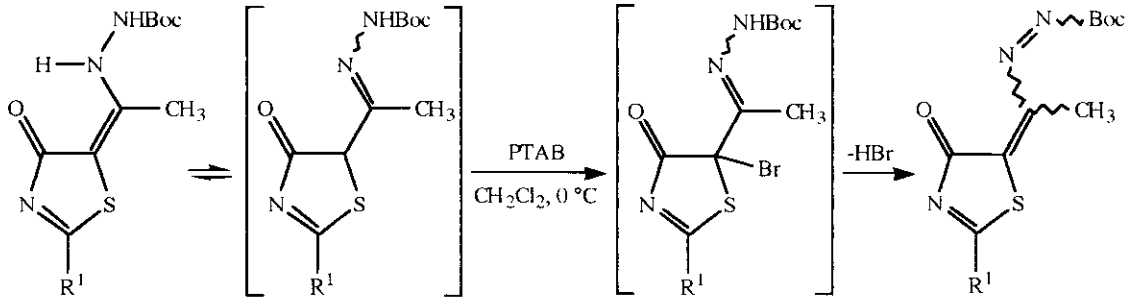
Abstract - The synthesis and reactions of *tert*-butyl 2-{1-[2-aryl-4-oxothiazol-5(4*H*)-ylidene]ethyl}diazene-1-carboxylates: a new class of 1,2-diaza-1,3-butadienes is reported.

Many syntheses of five-membered heterocycles containing sulfur and nitrogen have been reported because of their various interesting biological activities.[1,2] In particular, the thiazole ring has been identified as a central feature of a number of biologically active natural products.[3]

In previous papers we reported the results of the reaction between some 1,2-diaza-1,3-butadienes and thioureas or thioamides that produced hydrazino-hydrazono derivatives of 2-thiazolin-4-one.[4,5] The hydrolitic cleavage of the *NH*-Boc (*NH*-*tert*-butoxycarbonyl) protecting hydrazono moiety of 2-thiazolin-4-ones afforded a new convenient entry to 5-acetyl-4-hydroxythiazole derivatives,[5] that showed useful intermediates in organic synthesis.[6] Our ongoing interest in synthetic uselfulness of conjugated heterodiene systems encouraged us in exploring the use of hydrazino-hydrazono-2-thiazolin-4-one derivatives as precursors of a new class of conjugated azoalkenes including the thiazole ring. We planned to exploit the tautomeric equilibrium between hydrazino and hydrazono forms frequently manifested by these 2-thiazolin-4-one derivatives[4] with the aim to introduce a good leaving group at the carbon in position 5. For this purpose we chose phenyltrimethylammonium tribromide (PTAB) as mild and extremely efficient α-brominating reagent (Scheme 1).[7] Hydrazino-hydrazono*NH*-Boc protected 2-thiazolin-4-ones (**1a-e**) prepared as previously reported[4,5] were dissolved in CH_2Cl_2 at 0°C and PTAB was added portionwise until the complete disappearance of the starting materials. The isolation and characterization of α-bromohydrazone derivative (**3**) was hindered because of its rapid conversion into *tert*-butyl 2-{1-[2-aryl-4-oxothiazol-5(4*H*)-ylidene]ethyl}diazene-1-carboxylate[8] derivatives (**4a-e**).

However, the 1,4-dehydrobromination of **3** was completed by a base treatment (Na_2CO_3) and compounds (**4a-e**) were obtained in excellent yields (70-92%) as orange, red or dark red powders (Table 1). This route to 2-{1-[2-aryl-4-oxothiazol-5(4*H*)-ylidene]ethyl}diazene-1-carboxylate derivatives (**4a-e**) is remarkable for good yields and simplicity. The starting materials hydrazino-hydrazono-2-thiazolin-4-one derivatives and PTAB are easily accessible. The reactions are performed under mild conditions and

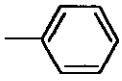
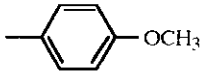
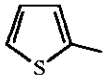
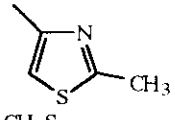
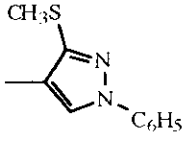
generally are free from by-products which might interfere with a smooth isolation of this new class of highly conjugated 1,2-diaza-1,3-butadienes.



1a-e **2** **3** **4a-e**

Scheme 1

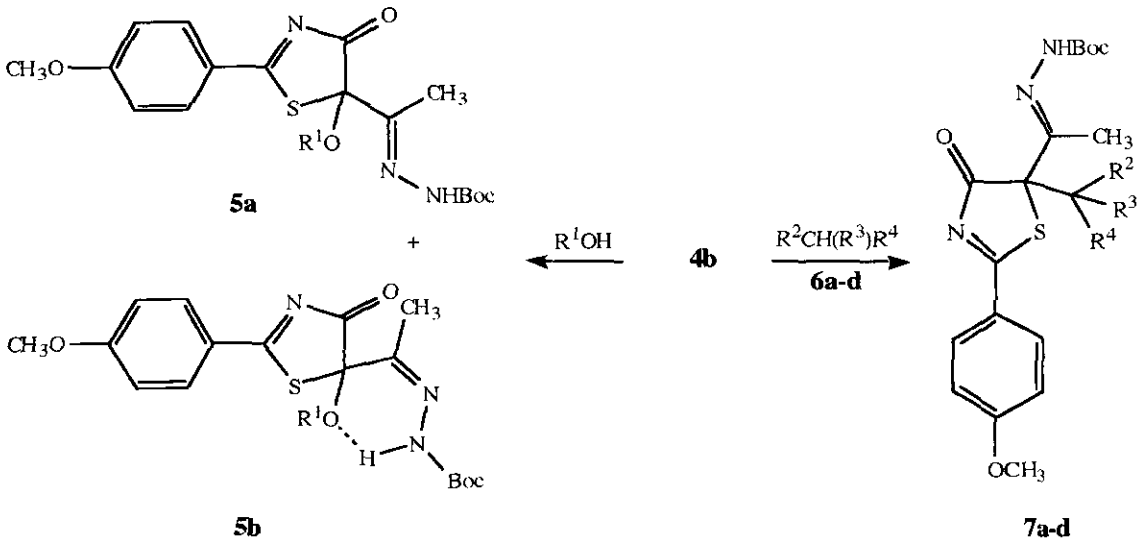
Table 1

1	4	R^1	Yields of **4** (%)
a	**a**		84
b	**b**		92
c	**c**		90
d	**d**		70
e	**e**		80

The electronic situation of the title compounds determines their great affinity towards nucleophilic attacks by carbon- and hetero-nucleophiles concluding in 1,4-conjugate additions that are very important both in carbon-carbon and carbon-heteroatom bond formation. In fact, 2-{1-[2-(4-methoxyphenyl)-4-oxothiazol-5(4*H*)-ylidene]ethyl}diazene-1-carboxylate (**4b**) readily reacted with methanol affording two hydrazone isomers (**5a**) and (**5b**) (Scheme 2 and Table 2). Their configuration was established by NOE experiments. In compound (**5a**) irradiation of CH_3 caused 5% enhancement of NH, moreover irradiation of NH resulted in 15% enhancement of CH_3. On the contrary, similar experiments for compound (**5b**) did not reveal any NOE enhancement. According to these studies, **5a** was identified as *E*-isomer whereas **5b** as

Z-isomer.

The base-catalysed addition to **4b** of carbon nucleophiles as acetylphenylacetonitrile (**6a**), ethyl phenylcyanoacetate (**6b**), dimethyl malonate (**6c**) or ethyl acetacetate (**6d**) was also studied. These reactions afforded the corresponding hydrazone derivatives (**7a-d**) in *E*-configuration as established by NOE experiments on derivative (**7b**) and as resulted by ^{1}H- and ^{13}C-NMR data comparison (Scheme 2 and Table 2). All new compounds showed satisfactory elemental analysis (C ±0.35, H ±0.30, N ±0.30).



Scheme 2

Table 2

5	R^1	Yield of 5 (%)	6	7	R^2	R^3	R^4	Yields of 7 (%)
a	CH_3	51	**a**	**a**	C_6H_5	CN	$COCH_3$	68
b	CH_3	32	**b**	**b**	C_6H_5	CN	$COOCH_2CH_3$	75
			c	**c**	$COOCH_3$	H	$COOCH_3$	67
			d	**d**	$COCH_3$	H	$COOCH_2CH_3$	72

The hydrazones obtained by conjugate addition of nucleophiles to heterodiene systems of the title compounds are both interesting products and useful intermediates for the preparation of many other compounds important in organic and/or medicinal chemistry.[9,10] In fact, the adducts permit the functionalization of the position 5 of the thiazole ring by various nucleophilic reagents.[1,2] Moreover, the Boc-hydrazine group can be considered as protecting group of carbonyl function that can be easily regenerated by cleavage of C=N bond.[5,11] In this way, functionalized thiazole rings useful as products

and intermediates in organic synthesis are available.[1,2] Indeed, *tert*-butoxycarbonylhydrazones are valuable building blocks in the synthesis of HIV-1 protease inhibitors.[12] Furthermore, the title derivatives are suitable for hetero Diels-Alder-type cycloadditions thank to the conjugated double bond system.[13]

EXPERIMENTAL

Hydrazino-hydrazono-2-thiazolin-4-one derivatives (**1a-e**) were prepared according to our methods.[4,5] PTAB, acetylphenylacetonitrile (**6a**), ethyl phenylcyanoacetate (**6b**), dimethyl malonate (**6c**), and ethyl acetacetate (**6d**) were commercial materials and were used without further purification. Melting points were determined in open capillary tubes with a Gallenkamp apparatus and are uncorrected. FT-IR spectra were obtained as Nujol mull in KBr with a Nicolet Impact 400 spectrophotometer. ^{1}H-NMR spectra were recorded at 200 MHz, while ^{13}C-NMR at 50.32 MHz (Bruker AC-200) using $CDCl_3$ or DMSO-d_6. Chemical shifts (δ) are reported relative to TMS as internal standard and the *J* values in Hz. The multiplicities in ^{13}C-NMR spectra were obtained by using 135 and 90° DEPT experiments. All the NH exchanged with D_2O. NOE enhancement factors were determined on degassed DMSO 0.01 M solutions at 300 K, using NOEDIFF pulse program of Bruker. Generally, irradiation time was 2 sec, with a power level of 30 low. Macherey-Nagel precoated silica gel SIL G-25UV$_{254}$ plates (0.25 mm) were employed for analytical thin layer chromatography (TLC) and silica gel Amicon LC 60 Å (35-70 mμ) for column chromatography.

Synthesis of *tert*-butyl 2-{1-[2-aryl-4-oxothiazol-5(4*H*)-ylidene]ethyl}diazene-1-carboxylate[8] derivatives (4a-e): typical procedure.

To a magnetically stirred ice-cooled solution of hydrazino-hydrazono-2-thiazolin-4-one derivatives (**1a-e**) (1 mmol) in CH_2Cl_2 (40 mL) PTAB (1.5 mmol) was added portionwise until the total disappearance of the starting material (1-2 h). The reaction mixture was poured into a separatory funnel, washed with water and then shaken vigorously with a Na_2CO_3 saturated solution (4x10 mL). The organic layer previously neutralized was dried over Na_2SO_4 and then evaporated under reduced pressure at room temperature affording **4a-e** as orange, red or dark red powder in satisfactory purity. Further purification may be obtained by crystallization from the appropriate solvent.

4a: red powder; mp 111-114 °C (decomp) (pentane); IR (KBr) 1757, 1695, 1600 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 1.65 (9H, s, Bu^t), 2.53 (3H, s, CH_3), 7.53 (2H, t, *J*=7 Hz, Ar), 7.65 (1H, t, *J*=7 Hz, Ar), 8.17 (2H, d, *J*=7 Hz, Ar) ppm; ^{13}C-NMR ($CDCl_3$) δ: 10.67 (q), 27.79 (q), 86.04 (s), 128.86 (d), 129.18 (d), 131.26 (s), 135.42 (d), 141.77 (s), 156.10 (s), 160.60 (s), 182.20 (s), 187.40 (s) ppm. Anal. Calcd for $C_{16}H_{17}N_3O_3S$: C, 57.99; H, 5.17; N, 12.68. Found: C, 58.02; H, 5.14; N, 12.70.

4b: orange powder; mp 142-146 °C (decomp) (ethyl acetate/pentane); IR (KBr) 1757, 1693, 1598 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 1.63 (9H, s, Bu^t), 2.50 (3H, s, CH_3), 3.89 (3H, s, OCH_3), 7.00 (2H, d, *J*=9 Hz, Ar), 8.14 (2H, d, *J*=9 Hz, Ar) ppm; ^{13}C-NMR ($CDCl_3$) δ: 10.67 (q), 27.88 (q), 55.78 (q), 85.94 (s), 114.77 (d), 123.90 (s), 131.47 (d), 142.64 (s), 155.33 (s), 160.74 (s), 166.12 (s), 182.37 (s), 187.99 (s) ppm. Anal.

Calcd for $C_{17}H_{19}N_3O_4S$: C, 56.50; H, 5.30; N, 11.63. Found: C, 56.53; H, 5.32; N, 11.60.

4c: orange powder; mp 141-144 °C (decomp) (pentane); IR (KBr) 3106, 3083, 1761, 1746, 1696, 1602 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 1.64 (9H, s, Bu^t), 2.51 (3H, s, CH_3), 7.24-7.26 (1H, m, Ar), 7.88 (1H, d, *J*=4 Hz, Ar), 7.99 (1H, d, *J*=4 Hz, Ar) ppm; ^{13}C-NMR ($CDCl_3$) δ: 10.72 (q), 27.88 (q), 86.07 (s), 129.33 (d), 134.35 (d), 135.91 (s), 137.24 (d), 142.18 (s), 155.58 (s), 160.63 (s), 179.23 (s), 181.62 (s) ppm. Anal. Calcd for $C_{14}H_{15}N_3O_3S_2$: C, 49.84; H, 4.48; N, 12.45. Found: C, 49.81; H, 4.51; N, 12.48.

4d: red powder; mp 144-148 °C (decomp) (ethyl acetate/ether); IR (KBr) 3071,1754, 1690, 1603 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 1.65 (9H, s, Bu^t), 2.54 (3H, s, CH_3), 2.82 (3H, s, CH_3), 8.48 (1H, s, CH) ppm; ^{13}C-NMR ($CDCl_3$) δ: 10.61 (q), 19.27 (q), 27.85 (q), 86.04 (s), 127.42 (d), 142.20 (s), 147.66 (s), 156.79 (s), 160.86 (s), 167.96 (s), 181.51 (s), 182.46 (s) ppm. Anal. Calcd for $C_{14}H_{16}N_4O_3S_2$: C, 47.71; H, 4.58; N, 15.90. Found: C, 47.68; H, 4.60; N, 15.91.

4e: dark red powder; mp 136-139 °C (decomp) (ether/pentane); IR (KBr) 3128, 1752, 1694, 1602 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 1.67 (9H, s, Bu^t), 2.50 (3H, s, CH_3), 2.71 (3H, s, SCH_3), 7.38 (1H, t, *J*=7 Hz, Ar), 7.50 (2H, t, *J*=8 Hz, Ar), 7.73 (2H, d, *J*=8 Hz, Ar), 8.73 (1H, s, CH) ppm; ^{13}C-NMR ($CDCl_3$) δ: 10.55 (q), 14.83 (q), 27.88 (q), 85.92 (s), 116.45 (s), 119.19 (d), 128.11 (d), 129.73 (d), 131.35 (d), 138.51 (s), 142.09 (s), 152.83 (s), 155.37 (s), 160.74 (s), 178.01 (s), 181.71 (s) ppm. Anal. Calcd for $C_{20}H_{21}N_5O_3S_2$: C, 54.16; H, 4.77; N, 15.79. Found: C, 54.19; H, 4.74; N, 15.76.

Synthesis of compound (5a-b): typical procedure.
Conjugated azoalkene (**4b**) (0.361 g, 1 mmol) was suspended in MeOH (56 mL) under magnetic stirring and allowed to stand at room temperature until its complete disappearance (monitored by *TLC*, 3 h). After the evaporation of MeOH under reduced pressure, compound (**5a-b**) was purified by chromatography of the crude on a silica gel column (cyclohexane/ethyl acetate, 70/30 v/v) and further purificated by crystallization.

5a: *E*-isomer; white powder; mp 156-158 °C (decomp) (ethyl acetate/cyclohexane); IR (KBr) 3226, 3151, 3110, 1727, 1696, 1601, 1580 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ: 1.40 (9H, s, Bu^t), 2.01 (3H, s, CH_3), 3.28 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 7.19 (2H, d, *J*=9 Hz, Ar), 8.11 (2H, d, *J*=9 Hz, Ar), 9.90 (1H exchangeable, s, NH) ppm; ^{13}C-NMR (DMSO-d_6) δ: 13.28 (q), 28.09 (q), 53.88 (q), 56.16 (q), 80.10 (s), 104.65 (s), 115.19 (d), 124.37 (s), 131.44 (d), 149.55 (s), 152.58 (s), 165.95 (s), 186.34 (s), 191.63 (s). Anal. Calcd for $C_{18}H_{23}N_3O_5S$: C, 54.95 H, 5.89; N, 10.68. Found: C, 54.99; H, 5.92; N, 10.65.
NOE enhancement factors: NH{CH_3} 5%; CH_3{NH} 15%.

5b: *Z*-isomer; white powder; mp 152-155 °C (decomp) (ether); IR (KBr) 3150 (br), 1710, 1701, 1606, 1594, 1575 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ: 1.47 (9H, s, Bu^t), 2.03 (3H, s, CH_3), 3.43 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 7.11 (2H, d, *J*=9 Hz, Ar), 7.80 (2H, d, *J*=9 Hz, Ar), 8.27 (1H exchangeable, br s, NH) ppm; ^{13}C-NMR (DMSO-d_6) δ: 13.30 (q), 28.00 (q), 52.52 q), 55.56 (q), 80.40 (s), 107.26 (s), 114.49 (d),

120.39 (s), 124.13 (s), 129.99 (d), 149.91 (s), 150.25 (s), 162.76 (s), 164.11 (s). Anal. Calcd for $C_{18}H_{23}N_3O_5S$: C, 54.95 H, 5.89; N, 10.68. Found: C, 54.97; H, 5.93; N, 10.62.
NOE enhancement factors: NH{CH_3} 0%; CH_3{NH} 0%.

Synthesis of compounds (7a-d): typical procedure.
To a stirred solution of compound (**6a-d**) (1 mmol) in THF (10 mL) at rt was added a catalytic amount of NaH. After 15 min, small portions of conjugated azoalkene (**4b**) were added every 5-10 min and the progress of the reaction was monitored by TLC. After the complete addition of **4b**, the reaction mixture was further stirred for 30 min. The reaction between **4b** and **6b** directly afforded **7b** as solid precipitate. In all other cases, THF was removed under reduced pressure and crystallization from appropriate solvents afford **7a**,**c**-**d** in satisfactory purity.

7a: *E*-isomer; white powder; mp 175-177 °C (decomp) (chloroform/ether); IR (KBr) 3219, 3113, 2237, 1720, 1700, 1645, 1600, 1575 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ: 1.49 (9H, s, Bu^t), 1.70 (3H, s, CH_3), 2.63 (3H, s, $COCH_3$), 3.84 (3H, s, OCH_3), 7.04 (2H, d, *J*=9 Hz, Ar), 7.32 (5H, s, Ar), 7.89 (2H, d, *J*=9 Hz, Ar), 10.23 (1H exchangeable, s, NH) ppm; ^{13}C-NMR (DMSO-d_6) δ: 13.74 (q), 28.04 (q), 28.18 (q), 55.90 (q), 61.27 (s), 76.12 (s), 80.22 (s), 114.93 (d), 117.87 (s), 122.98 (s), 127.58 (s), 128.53 (d), 128.93 (d), 129.74 (d), 131.10 (d), 142.30 (s), 152.61 (s), 165.72 (s), 187.81 (s), 195.76 (s), 197.11 (s) ppm. Anal. Calcd for $C_{27}H_{28}N_4O_5S$: C, 62.29; H, 5.42; N, 10.76. Found: C, 62.31; H, 5.45; N, 10.79.

7b: *E*-isomer; white powder; mp 179-181 °C (decomp) (THF); IR (KBr) 3220, 3115, 2240, 1732, 1700, 1649, 1600, 1579 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ: 1.24 (3H, t, *J*=7 Hz, $OCH_2\underline{CH_3}$), 1.49 (9H, s, Bu^t), 1.71 (3H, s, CH_3), 3.86 (3H, s, OCH_3), 4.34 (2H, q, *J*=7 Hz, $OC\underline{H_2}CH_3$), 7.06 (2H, d, *J*=9 Hz, Ar), 7.28-7.34 (5H, m, Ar), 7.88 (2H, d, *J*=9 Hz, Ar), 10.18 (1H exchangeable, s, NH) ppm; ^{13}C-NMR (DMSO-d_6) δ: 13.36 (q), 13.94 (q), 28.01 (q), 55.96 (q), 56.88 (s), 63.70 (t), 76.43 (s), 79.87 (s), 114.98 (d), 115.91 (s), 122.90 (s), 128.27 (d), 128.41 (d), 129.54 (d), 129.70 (s), 131.10 (d), 142.27 (s), 152.32 (s), 165.40 (s), 165.78 (s), 186.98 (s), 195.38 (s) ppm. Anal. Calcd for $C_{28}H_{30}N_4O_6S$: C, 61.08; H, 5.49; N, 10.18. Found: C, 61.11; H, 5.46; N, 10.15.
NOE enhancement factors: NH{CH_3} 3%; CH_3{NH} 11%.

7c: *E*-isomer; white powder; mp 139-141 °C (decomp) (dichloromethane/pentane); IR (KBr) 3338, 1761, 1727, 1714, 1605, 1575 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ: 1.46 (9H, s, Bu^t), 1.63 (3H, s, CH_3), 3.54 (3H, s, $COOCH_3$), 3.73 (3H, s, $COOCH_3$), 3.91 (3H, s, OCH_3), 4.55 (1H, s, CH), 7.18 (2H, d, *J*=9 Hz, Ar), 8.16 (2H, d, *J*=9 Hz, Ar), 9.90 (1H exchangeable, s, NH) ppm; ^{13}C-NMR (DMSO-d_6) δ: 12.57 (q), 28.10 (q), 52.78 (q), 53.20 (q), 56.13 (q and d), 70.98 (s), 80.01 (s), 115.21 (d), 123.84 (s), 131.50 (d), 144.35 (s), 152.53 (s), 165.83 (s), 166.68 (s), 167.95 (s), 189.49 (s), 195.59 (s) ppm. Anal. Calcd for $C_{22}H_{27}N_3O_8S$: C, 53.54; H, 5.51; N, 8.51. Found: C, 53.58; H, 5.49; N, 8.52.

7d: *E*-isomer; yellow powder; mp 116-119 °C (decomp) (ethyl acetate/pentane); IR (KBr) 3309, 1751, 1739, 1710, 1604, 1577 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ: 1.00 (3H, t, *J*=7 Hz, $OCH_2\underline{CH_3}$), 1.46 (9H, s,

Bu^t), 1.59 (3H, s, CH_3), 2.60 (3H, s, $COCH_3$), 3.91-4.22 (5H, m, OCH_3 and $OC\underline{H_2}CH_3$), 4.95 (1H, s, CH), 7.18 (2H, d, *J*=9 Hz, Ar), 8.16 (2H, d, *J*=9 Hz, Ar), 9.94 (1H exchangeable, s, NH) ppm; ^{13}C-NMR (DMSO-d_6) δ: 12.18 (q), 13.39 (q), 27.98 (q), 31.64 (q), 55.90 (q), 59.94 (d), 61.54 (t), 70.72 (s), 80.02 (s), 114.93 (d), 123.85 (s), 131.13 (d), 144.90 (s), 152.76 (s), 165.40 (s), 166.39 (s), 190.24 (s), 195.90 (s), 201.79 (s) ppm. Anal. Calcd for $C_{23}H_{29}N_3O_7S$: C, 56.20; H, 5.95; N, 8.55. Found: C, 56.24; H, 5.92; N, 8.52.

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