N-[5,5-Dimethyl-2(5*H*)-thiophenyliden]amines and *N*-(1-thiaspiro[4.5]dec-3-en-2-yliden)amines: Synthesis and isomerism

Nina A. Nedolya[a]*, Lambert Brandsma[b], Nataly I. Schlyakhtina[a], Igor M. Lazarev[a], Alexander I. Albanov[a], Sergei V. Zinchenko[a], Lyudmila V. Klyba[a]

[a] *A.E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch of the Russian Academy of Sciences, RU-664033 Irkutsk, Russia*
[b] *Julianalaan 273, 3722 GN Bilthoven, The Netherlands*
E-mail: nina@irioch.irk.ru
E-mail: l.brandsma@wxs.nl

Dedicated to Academician Michael G. Voronkov on the occasion of his 80th birthday
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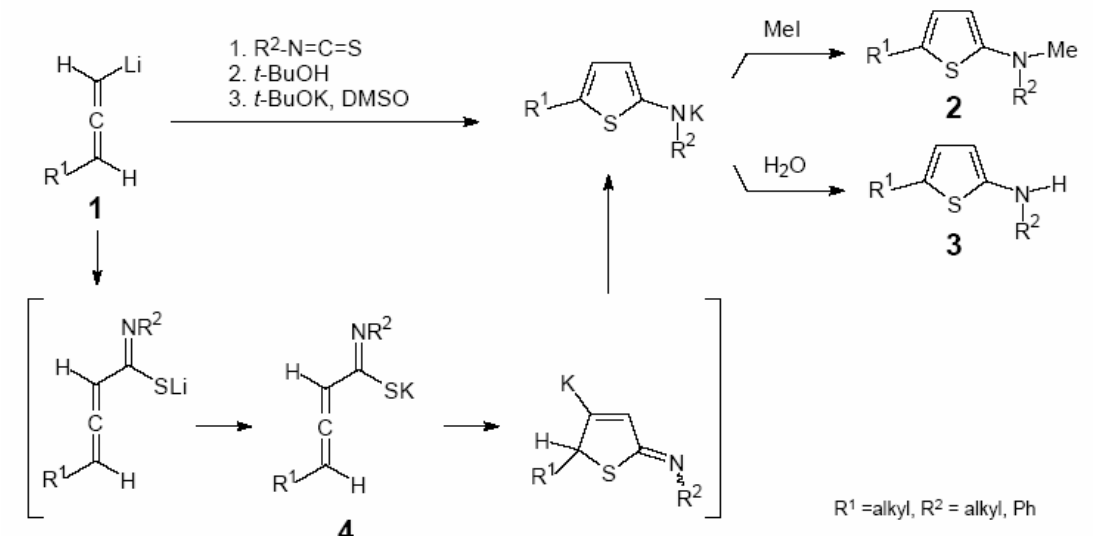
Abstract
A number of *N*-[5,5-dimethyl-2(5*H*)-thiophenyliden]amines and *N*-(1-thiaspiro[4.5]dec-3-en-2-yliden)amines, existing exclusively in one isomeric form, have been obtained in good to excellent yields by reaction of lithiated 1,1-disubstituted 1,2-dienes with isothiocyanates followed by treatment with *t*-BuOH and *t*-BuOK in DMSO. Investigation of the isomeric structures using 1H, 13C, 15N, 2D NOESY NMR spectroscopy and quantum-chemical calculation (*ab initio* HF/6-31G*) of the total energies of the fully optimized geometries indicated that for both *N*-[5,5-dimethyl-2(5*H*)-thiophenyliden]methanamine and *N*-(1-thiaspiro[4.5]dec-3-en-2-yliden)methanamine the *Z*-isomers are more stable, the energy differences with respect to *E*-isomers being 3.37-3.87 kcal/mol. It was established that the chair conformer with axial orientation of sulfur of (*Z*)-*N*-(1-thiaspiro[4.5]dec-3-en-2-yliden)methanamine the has the lowest energy of all possible conformers.

Keywords: 3-Methyl-1,2-butadiene, ethenylidenecyclohexane, isothiocyanates, lithiation, base-catalyzed cyclization, *E-/Z*-isomerism, optimization, quantum-chemical calculations

Introduction

In a series of papers we have shown that carbanionic species derived from unsaturated compounds readily add to isothiocyanates.[1] This reaction provides ready access to a variety of heterocyclic systems with R = alkyl, Ar, HetAr, C=C, C≡C; OR, SR, NHR, NR_2 substituents.[2,3] Part of our investigations is dealing with base-catalyzed cyclizations.[4-6] For example, reaction of

lithiated allene **1** (R^1 = *t*-Bu) with isothiocyanates $R^2N{=}C{=}S$, followed by successive addition of *t*-BuOH and *t*-BuOK in DMSO and final methylation or reaction with water gave 5-(*tert*-butyl)-substituted 2-aminothiophenes **2** or **3**, respectively, in good yields (Scheme 1).[5]
Intermediates **4** could also be generated by treatment of the adducts from lithiated acetylenes $R^1CH_2C{\equiv}CLi$ and $R^2N{=}C{=}S$ with *t*-BuOH, *t*-BuOK and DMSO.[5,6]



Scheme 1

Results and Discussion

If the addition to isothiocyanates was carried out with the geminally disubstituted lithiated allene **5** (Scheme 2), the potassium *tert*-butoxide-catalyzed cyclizations resulted in the anionic species **6**, and eventually, in the protonation products, the thiophenylidenamines **7**.

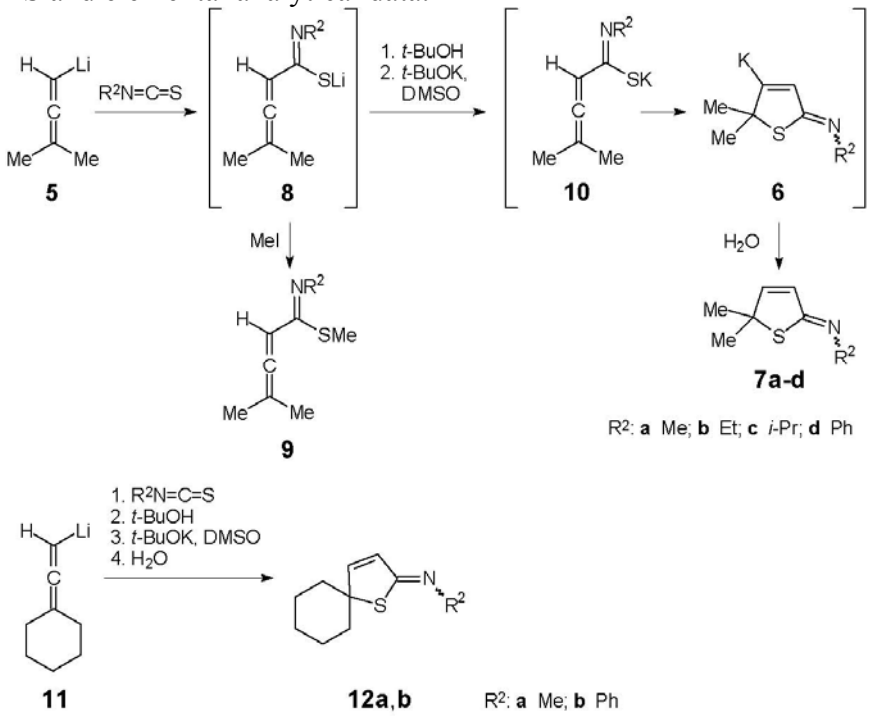
For generating the lithiated intermediate **5**, 1,1-dimethylallene was allowed to react with BuLi in THF and hexane at temperatures between −50 and −10 °C.[7] At temperatures at about −90 °C all isothiocyanates reacted extremely fast. The progress of the formation of adducts **8** was determined by taking small samples from the reaction mixtures, quenching with methyl iodide and determining the resulting azatrienes **9** by GLC.

In order to affect cyclization by intramolecular nucleophilic attack of the thioimidates **8**, at least one equivalent amount of *tert*-butyl alcohol and a solution of an equivalent amount of potassium *tert*-butoxide in DMSO were successively added at temperatures between −40 and −10 °C; thereafter, the reaction mixtures were gradually warmed. The progress of the conversion of the thioimidates**10** into cyclic intermediates **6** was followed by withdrawing samples from the reaction mixtures and quenching them at first with methyl iodide, then with water. The cyclization was considered complete, when the GLC peak ascribed to the azatriene **9** had vanished and was replaced by peaks of thiophenylidenamine **7**.

Products **12** were obtained from lithiated ethenylidenecyclohexane (**11**) and were isolated in

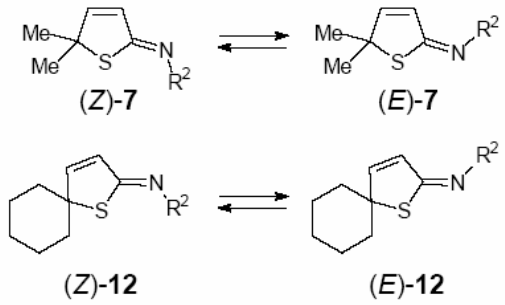
good to excellent yields (Scheme 2).

The structure assignments of *N*-[5,5-dimethyl-2(5*H*)-thiophenyliden]amines **7a-d** and *N*-(1-thiaspiro[4.5]dec-3-en-2-yliden)amines **12a** and **12b** are based on IR, ^{1}H, ^{13}C and ^{15}N NMR spectroscopy, MS and elemental analytical data.



Scheme 2

The thiophenylidenamines **7** and **12** may exist as *Z*- and *E*-forms (Scheme 3). Furthermore, compounds **12** may consist of a mixture of a few possible conformers derived from different configurations of the spirocyclic (cyclohexane) moiety with different substituent orientation. However, in the NMR spectra of the thiophenylidenamines **7** and **12** only one geometrical isomer was observed in all cases.



Scheme 3

Recording the NMR spectra at elevated temperature (150 °C) or replacement of CCl_4 by more polar solvents ($CDCl_3$, DMSO-d_6) did not result in a change of the isomer equilibrium. For this reason a stereochemical (isomeric and conformational) analysis of the **7a** and **12a** by

quantum chemical calculations was carried out.

The total energies and their differences for the fully optimized geometries of **7a** and **12a** were computed with the *ab initio* HF/6-31G* basis set and are listed in Table 1. As judged from the quantum-chemical calculation data, (*Z*)-**7a** is the most stable isomer, the energy difference to (*E*)-**7a** is 3.87 kcal/mol (Table 1). The calculation revealed (*Z*)-**12a** in the chair conformation with axial sulfur as the most stable isomer (Table 1).

Table 1. Total Energies and their Differences for Isomers of **7a** and **12a**

Structure	Total Energies [a.u.]		Energy Differences [kcal/mol]		
	Z-	*E*-	*Z*-	*E*-	ΔE
7a	–723.4174061	–723.4112374	0.00	3.87	3.87
12a, chair (*a*)	–839.3614380	–839.3560676	0.00	3.37	3.37
12a, chair (*e*)	–839.3600616	–839.3544742	0.86	4.37	3.51
12a, boat (*b*)	–839.3495185	–839.3441064	7.48	10.88	3.40
12a, boat (*f*)	–839.3482709	–839.3427212	8.26	11.74	3.48

The *Z*-configuration of structures **7a** and **12a** was derived from the 2D NOESY spectra (^{1}H NMR chemical shift assignment). For the *E*-isomers, the interaction of 3-H with the *N*-methyl group is expected to be observable in the 2D NOESY spectra. We consider the absence of the corresponding cross-peaks as evidence for the absence of the *E*-isomers.

Experimental Section

General Procedures. All reactions were conducted under a dry nitrogen atmosphere. Solvents were dried over machine-powdered potassium hydroxide and distilled under nitrogen from sodium benzophenone. The preparation of 3-methyl-1,2-butadiene and ethenylidenecyclohexane has been described.[8] Isopropyl isothiocyanate was synthesized from isopropylamine, carbon disulfide, acetic anhydride and triethylamine in chloroform.[2] Methyl, ethyl and phenyl isothiocyanates and other reagents are commercially available. BuLi was purchased from Chemetall (Germany) as a 1.6 M solution in hexane. Liquid nitrogen was used as coolant of the reactions. NMR spectra were recorded on Varian EM-390 (^{1}H: 90 MHz) and Bruker DPX-400 (^{1}H: 400, ^{13}C: 100 and ^{15}N: 40.56 MHz) spectrometers at room temperature and at 150 °C. Chemical shifts are given in ppm (δ) relative to TMS or HMDS (for ^{1}H and ^{13}C) and to $MeNO_2$ (for ^{15}N); CCl_4, $CDCl_3$ and DMSO-d_6 were used as solvents. IR spectra were recorded on a Specord IR-75 spectrophotometer. GLC analyses were carried out on a Varian 3400 gas chromatograph (15 m capillary column coated with a 1.5 μ DB-5, internal diameter 0.53 mm). Mass-spectra were recorded on an LKB-2091 GC-MS spectrometer using the system of chromatographic introduction of the sample into the ion source (length of the glass capillary column 38 m, with an SE-54 phase, temperature of the evaporator 250 °C, velocity of the

temperature rise from 70 to 250 °C 10 deg·min^{-1}).

Lithiation of 3-methyl-1,2-butadiene and ethenylidenecyclohexane. To a solution of BuLi (3.84 g, 60 mmol) in hexane (37 mL) and THF (80 mL) 3-methyl-1,2-butadiene (4.8 g, 70 mmol) or ethenylidenecyclohexane (7.6 g) was added in one portion at –50 °C. After the temperature has risen to –15 °C or –10 °C, respectively, the solution was stirred at this temperature for an additional 15 min. The clear solutions of the lithiated allenes **5** and **11** were then cooled to –100 °C and used for the reaction with isothiocyanates.

***N*-[5,5-Dimethyl-2(5*H*)-thiophenyliden]methanamine (7a). Typical procedure.** A solution of **5**, prepared as described above, was cooled to –100 °C, and a solution of methyl isothiocyanate (3.78 g, 51.8 mmol) in THF (15 mL) was added in one portion with vigorous stirring. After the reaction mixture had been stirred for 15 min at approx. −60 °C, a mixture of *t*-BuOH (9.2 g, 124.3 mmol) and diethyl ether (10 mL) was added at –55 °C; after 2 min at –35 °C, a solution of *t*-BuOK (6.7 g, 59.8 mmol) in DMSO (35 g) was added. The temperature was then allowed to rise to approx. 0 °C; subsequently, the mixture was heated at 40 to 45 °C for 30 min. Addition of water (100 mL) was followed by extraction with ether. The combined organic solutions were washed five times with water (in order to remove DMSO and *t*-BuOH) and were then dried over potassium carbonate. After removal of the solvents under reduced pressure, the remaining liquid was distilled to give a very mobile, almost colorless liquid **7a** (5.1 g, 70%; the yield of the undistilled product was almost quantitative, the purity was practically 100% according to GLC); bp approx. 45 °C (0.7 mm Hg); n = 1.5240. IR (film): [cm^{-1}] 600, 690, 790, 860, 940, 1005, 1060, 1100, 1150, 1160, 1360, 1390, 1440, 1450, 1600, 1640, 2850, 2890, 2920, 2950, 2960, 2970, 3040; ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.84 (1H, d, J = 6.0 Hz, 3-CH=), 6.17 (1H, d, J = 6.0 Hz, 4-CH=), 3.07 (3H, s, NMe), 1.55 (6H, s, CMe_2); ^{1}H NMR (400 MHz, DMSO-d_6, 150 °C): δ 6.68 (1H, d, J = 6.4 Hz, 3-CH=), 6.09 (1H, d, J = 6.0 Hz, 4-CH=), 3.08 (3H, s, NMe), 1.55 (6H, s, CMe_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.52 (2-C), 153.43 (4-C), 129.42 (3-C), 60.09 (5-C), 43.96 (NMe), 29.92 (CMe_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.58 (2-C), 154.57 (4-C), 128.64 (3-C), 60.26 (5-C), 43.75 (NMe), 29.61 (CMe_2); ^{13}C NMR (100 MHz, DMSO-d_6, 150 °C): δ 168.89 (2-C), 152.86 (4-C), 128.01 (3-C), 58.95 (5-C), 42.49 (NMe), 28.81 (CMe_2); ^{15}N NMR (40.56 MHz, $CDCl_3$): δ −91.52; EI-MS (60 eV): *m/z* (%), 141 ($M^{+\cdot}$, 85). Anal. Calcd for $C_7H_{11}NS$ (141.24): C, 59.53; H, 7.85; N, 9.92; S, 22.70. Found: C, 59.71; H, 7.93; N, 9.80; S, 22.56.

***N*-[5,5-Dimethyl-2(5*H*)-thiophenyliden]ethanamine (7b).** After the addition of ethyl isothiocyanate (4.6 g, 52.8 mmol) in THF (10 mL) at –100 °C the experiment was carried out as described in the typical procedure affording a mobile, transparent light-yellow liquid **7b** (4.86 g, 59.4%; the yield of the crude product was approx. 100%, purity 94.5%); bp approx. 60 °C (1 mm Hg); n = 1.5133. (IR (film): [cm^{-1}] 570, 610, 680, 690, 785, 860, 900, 945, 1045, 1090, 1110, 1140, 1220, 1340, 1355, 1365, 1430, 1445, 1455, 1600, 1620, 1630, 2830, 2860, 2930, 2965, 3030; ^{1}H NMR (90 MHz, CCl_4): δ 6.54 (1H, d, J = 6.3 Hz, CH=), 6.14 (1H, d, J = 6.3 Hz, CH=), 3.20 (2H, q, J = 7.5 Hz, NCH_2), 1.63 (6H, s, CMe_2), 1.26 (3H, t, J = 7.5 Hz, Me); ^{1}H NMR (400

MHz, $CDCl_3$): δ 6.57 (1H, d, *J* = 6.1 Hz, CH=), 6.18 (1H, d, *J* = 6.1 Hz, CH=), 3.26 (2H, q, *J* = 7.3 Hz, NCH_2), 1.58 (6H, s, CMe_2), 1.30 (3H, t, *J* = 7.3 Hz, Me); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.71 (2-C), 153.60 (4-C), 129.57 (3-C), 60.21 (5-C), 52.08 (NCH_2), 30.01 (CMe_2), 15.51 (Me); ^{15}N NMR (40.56 MHz, $CDCl_3$): δ −75.02; EI-MS (60 eV): *m/z* (%) 155 (M+**.**, 67). Anal. Calcd for $C_8H_{13}NS$ (155.27): C, 61.89; H, 8.44; N, 9.02; S, 20.65. Found: C, 61.72; H, 8.40; N, 9.11; S, 20.77.

***N*-[5,5-Dimethyl-2(5*H*)-thiophenyliden]-2-propanamine (7c).** Light-yellow liquid **7c** (5.85 g, 67.5%; yield of undistilled product 100%, purity 96.1%); bp approx. 55 °C (1 mm Hg); *n* = 1.5065. IR (film): [cm^{-1}] 570, 600, 640, 670, 760, 840, 865, 900, 935, 995, 1005, 1030, 1060, 1140, 1165, 1190, 1225, 1270, 1360, 1390, 1420, 1430, 1495, 1505, 1640, 1660, 1670, 1680, 2890, 2900, 2930, 2950, 3035; ^1H NMR (90 MHz, CCl_4): δ 6.50 (1H, d, *J* = 6.3 Hz, CH=), 6.10 (1H, d, *J* = 6.3 Hz, CH=), 3.10 (1H, m, NCH), 1.60 (6H, s, CMe_2), 1.20 (6H, d, *J* = 7.1 Hz, $CHMe_2$); 1H NMR (400 MHz, $CDCl_3$): δ 6.56 (1H, d, *J* = 6.1 Hz, CH=), 6.17 (1H, d, *J* = 6.1 Hz, CH=), 3.25 (1H, m, NCH), 1.57 (6H, s, CMe_2), 1.20 (6H, d, *J* = 6.2 Hz, $CHMe_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.53 (2-C), 153.41 (4-C), 129.67 (3-C), 59.79 (5-C), 58.63 (NCH), 30.05 (CMe_2), 22.92 ($CHMe_2$); ^{15}N NMR (40.56 MHz, $CDCl_3$): δ −62.05; EI-MS (60 eV): *m/z* (%) 169 (M+**.**, 34). Anal. Calcd for $C_9H_{15}NS$ (169.30): C, 63.85; H, 8.93; N, 8.27; S, 18.94. Found: C, 63.91; H, 8.98; N, 8.20; S, 18.91.

***N*-[5,5-Dimethyl-2(5*H*)-thiophenyliden]aniline (7d).** After the usual operations **7d** (10.5 g) was obtained as a red oil in almost quantitative yield (purity 99.1%); bp approx. 120 °C (0.5 mm Hg); the product solidified after distillation. ^1H NMR (90 MHz, CCl_4): δ 7.40−6.93 (5H, m, Ph), 6.65 (1H, d, *J* = 6.3 Hz, CH=), 6.35 (1H, d, *J* = 6.3 Hz, CH=), 1.60 (6H, s, CMe_2). Anal. Calcd for $C_{12}H_{13}NS$ (203.31): C, 70.89; H, 6.45; N, 6.89; S, 15.77. Found: C, 70.95; H, 6.40; N, 6.80; S, 15.85.

***N*-(1-Thiaspiro[4.5]dec-3-en-2-yliden)methanamine (12a).** The yellowish liquid remaining after the usual work-up and evaporation of the solvent *in vacuo* consisted of almost pure (NMR; purity 97.8% by GLC) **12a** (9.1 g, 100%), isolated yield 6 g (66.3%, purity 99.5% by GLC); bp approx. 100 °C (approx. 1 mm Hg); *n* = 1.5543. IR (film): [cm^{-1}] 550, 570, 610, 680, 700, 780, 790, 820, 840, 900, 940, 955, 1010, 1080, 1100, 1120, 1155, 1190, 1250, 1265, 1340, 1400, 1450, 1610, 1640, 2860, 2900, 2940, 3040; ^1H NMR (90 MHz, CCl_4): δ 6.56 (1H, d, *J* = 6.3 Hz, CH=), 6.15 (1H, d, *J* = 6.3 Hz, CH=), 3.14 (3H, s, NMe), 1.76 [10H, m, $(CH_2)_5$]; ^1H NMR (400 MHz, $CDCl_3$): δ 6.61 (1H, d, *J* = 6.2 Hz, CH=), 6.20 (1H, d, *J* = 6.2 Hz, CH=), 3.18 (3H, s, NMe), 1.77 [7H, m, $(CH_2)_5$], 1.51 [2H, m, $(CH_2)_5$], 1.30 [1H, m, $(CH_2)_5$]; ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.92 (2-C), 152.25 (4-C), 129.52 (3-C), 66.96 (5-C), 43.50 (NMe), 38.43 (α-CH_2), 24.84 (γ-CH_2), 24.41 (β-CH_2); ^{15}N NMR (40.56 MHz, $CDCl_3$): δ −93.02; EI-MS (60 eV): *m/z* (%) 181 (M+**.**, 100). Anal. Calcd for $C_{10}H_{15}NS$ (181.31): C, 66.25; H, 8.34; N, 7.73; S, 17.69. Found: C, 66.38; H, 8.54; N, 7.69; S, 17.39.

***N*-(1-Thiaspiro[4.5]dec-3-en-2-yliden)aniline (12b).** The crude product **12b** (13.8 g) was obtained in almost quantitative yield (purity 96.1% by GLC); the product solidified at room temperature. A small sample was crystallized from ethanol: mp 108 °C. IR (KBr): ~ [cm^{-1}] 580,

630, 675, 690, 755, 770, 800, 820, 890, 900, 940, 965, 980, 1005, 1050, 1060, 1075, 1120, 1150, 1200, 1240, 1260, 1420, 1430, 1465, 1565, 1585, 1600, 2845, 2920; ^{1}H NMR (90 MHz, CCl_4): δ 7.37−6.90 (5H, m, Ph), 6.68 (1H, d, *J* = 7.2 Hz, CH=), 6.35 (1H, d, *J* = 7.2 Hz, CH=), 1.75 [10H, m, $(CH_2)_5$]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (2H, m, Ph), 7.10 (1H, m, Ph), 7.04 (2H, m, Ph), 6.76 (1H, d, *J* = 6.2 Hz, CH=), 6.40 (1H, d, *J* = 6.2 Hz, CH=), 1.77 [5H, m, $(CH_2)_5$], 1.64 [2H, m, $(CH_2)_5$], 1.44 [2H, m, $(CH_2)_5$], 1.25 [1H, m, $(CH_2)_5$]; ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.28 (2-C), 154.54 (4-C), 151.89 (1-C_{Ph}), 130.61 (3-C), 129.13 (*m*-CH_{Ph}), 124.58 (*p*-CH_{Ph}), 120.47 (*o*-CH_{Ph}), 67.68 (5-C), 38.45 (α-CH_2), 25.00 (γ-CH_2), 24.65 (β-CH_2); ^{15}N NMR (40.56 MHz, $CDCl_3$): δ −77.21; EI-MS (60 eV): *m/z* (%) 243 (M+**.**, 100). Anal. Calcd for $C_{15}H_{17}NS$ (243.38): C, 74.03; H, 7.04; N, 5.76; S, 13.18. Found: C, 74.17; H, 7.28; N, 5.56; S, 12.99.

Acknowledgements

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