

Micellar Promoted Multi-Component Synthesis of 1,2,3-Triazoles in Water at Room Temperature

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Reagents and Materials.

General

¹H NMR were recorded at 298 K, unless otherwise stated, on a Bruker AVANCE 300 spectrometer operating at 300.15 MHz. δ values in ppm are relative to SiMe₄. GC analysis were performed on HP SERIES II 5890 equipped with a HP5 column (30 m, I.D. 0.25 mm, film 0.25 μ m) using He as gas carrier and FID. GC-MS analyses were performed on a GC Trace GC 2000 equipped with a HP5-MS column (30 m, I.D. 0.25 mm, film 0.25 μ m) using He gas carrier and coupled with a quadrupole MS Thermo Finnigan Trace MS with *Full Scan* method.

Solvents and reactants were used as received; otherwise they were purified as reported in the literature.¹ TLC analysis were performed on TLC Polygram[®] Sil G/UV254 of 0.25 mm thickness and flash-chromatography separations were performed on silica gel Merk 60, 230-400 mesh.²

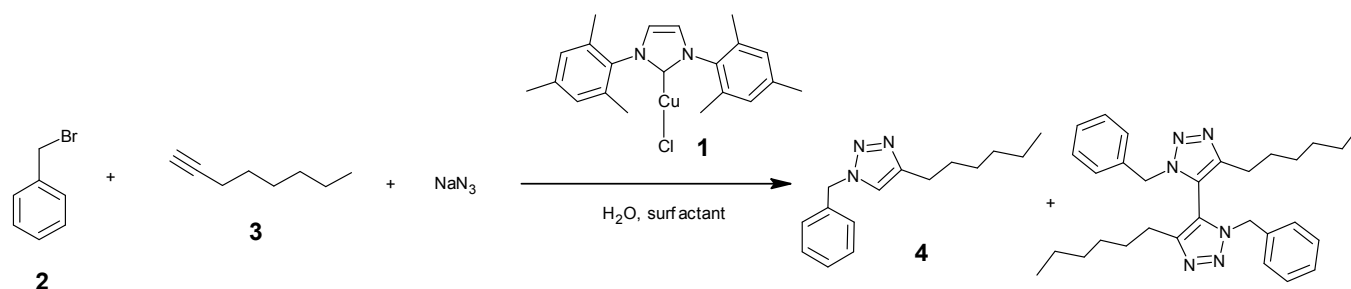
Substrates and surfactants

All the organic bromides, aliphatic and aromatic terminal alkynes, surfactants and Cu(I) catalyst [Cu(IMes)Cl] **1** (IMes 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene) are all commercially available products (Aldrich) and were used as received without any further purification. All the triazoles products were identified by GC-MS and ¹H-NMR analysis.

Catalytic Studies

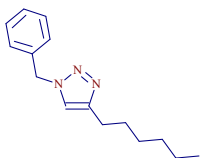
Catalytic multicomponent reaction between alkyl bromides with sodium azide and alkyne mediated by [Cu(IMes)Cl] **1**

General procedure for the multicomponent triazole synthesis in water: in a vial equipped with a screw capped septum and magnetic bar the alkyl bromide (0.25 mmol), the alkyne (0.37 mmol) and sodium azide (0.37 mmol) were dissolved in water (1 mL) with the aid of the proper amount of surfactant (180 mM). The reaction mixture was stirred at 750 rpm at room temperature for 1h. A methanol solution of the catalyst **1** (0.0025 mmol) was added to this solution and the vial was stirred at room temperature for 15, 30 minutes, 1h or 2h as a function of the substrates considered. Subsequently, 2 mL of AcOEt or Et₂O were added to the vial, the mixture was stirred for 10' and the organic phase was separated and concentrated under vacuum. ¹H NMR and GC-MS analysis were employed to determine product yield.



Scheme S1. Structure of the correct triazole product **4** and of the dimeric atropisomeric by-product 3,3'-dibenzyl-5,5'-di-*n*-hexyl-3H,3'H-4,4'-bis-1,2,3-triazole observed in the multi-component reaction when carried out with catalyst **1** present since the beginning of the reaction.

1-benzyl-4-hexyl-1,2,3-triazole

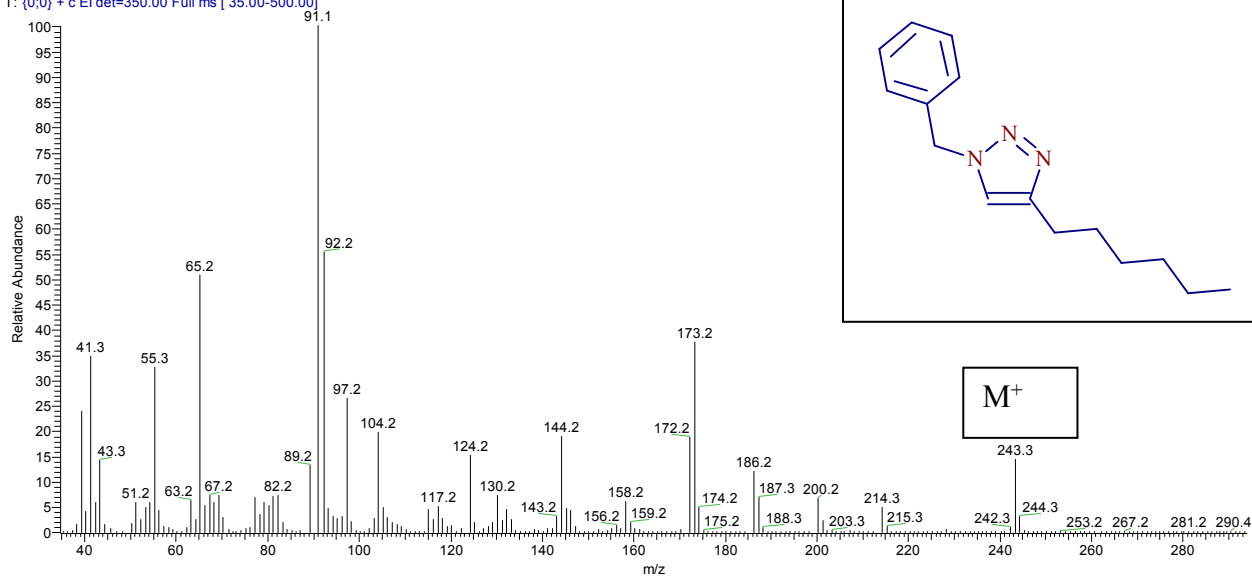


^1H NMR 300 MHz δ (ppm), 7.35 (m, 3H), 7.25 (m, 2H), 7.17 (s, 1H), 5.49 (s, 2H), 2.68 (t, J = 7.7 Hz, 2H), 1.63 (q, J = 7.4 Hz, 2H), 1.29 (m, 4H), 0.85 (t, J = 6.7 Hz, 3H).

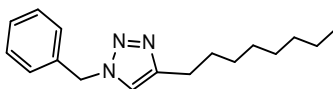
D:\1_chimi\Elena-243_300914

30/09/2014 15.02.33

Elena-243_300914 #1271 RT: 12.28 AV: 1 NL: 4.80E6
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1-benzyl-4-octil-1,2,3-triazole

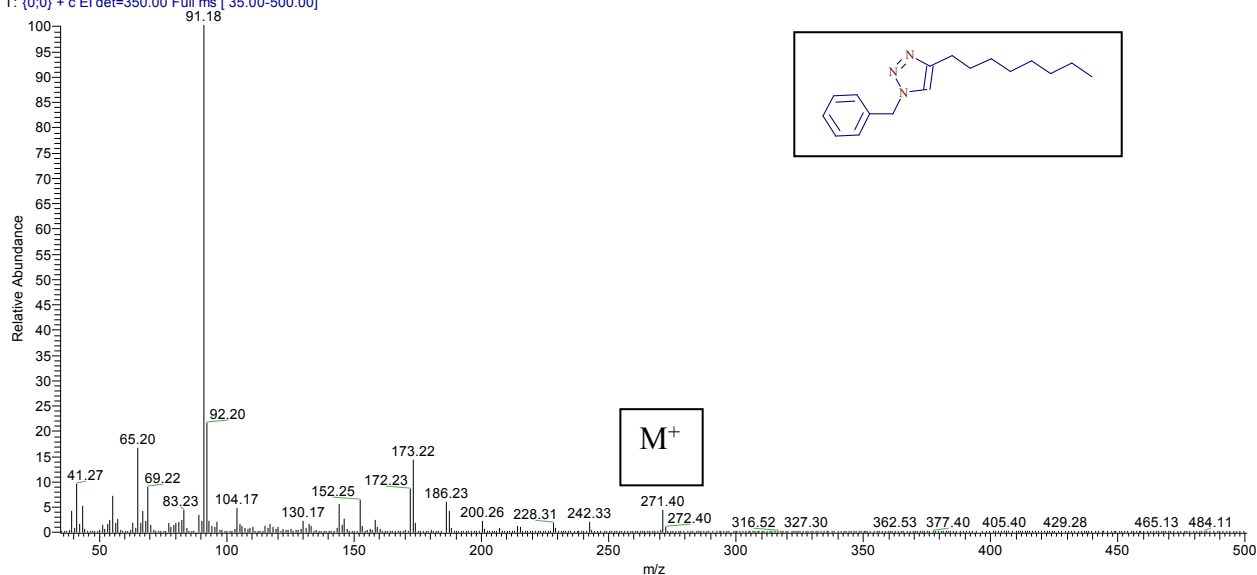


^1H NMR 300 MHz δ (ppm), 7.41-7.32 (m, 3H), 7.27-7.24 (m, 2H), 7.17 (s, 1H), 5.49 (s, 2H), 2.68 (t, J = 7.7 Hz, 2H), 1.62 (dd, J = 14.3, 7.0 Hz, 2H), 1.27 (m, 10 H), 0.87 (t, J = 6.8 Hz, 3H).

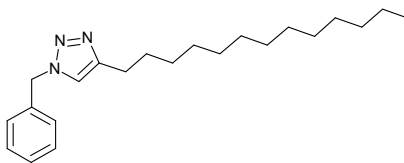
D:\1_chimi\elena-268_040914

04/09/2014 12.27.30

elena-268_040914 #1366 RT: 12.97 AV: 1 NL: 2.91E6
T: {0,0} + c EI det=350.00 Full ms [35.00-500.00]



1-benzyl-4-tridecyl-1,2,3-triazole

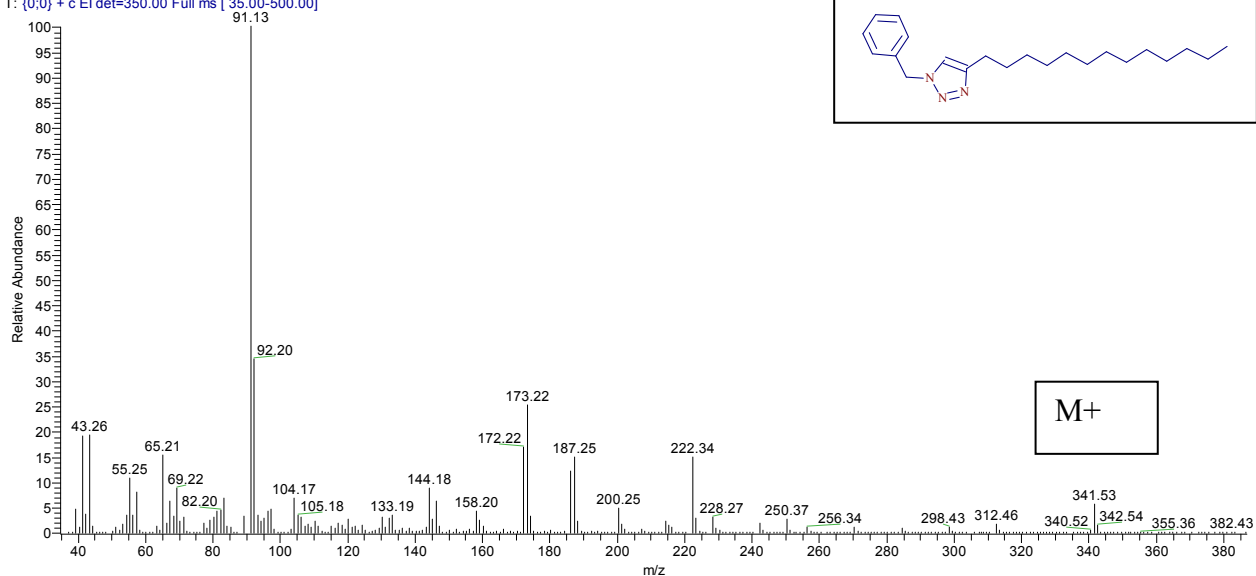


^1H NMR 300 MHz δ (ppm), 7.43 – 7.28 (m, 3H), 7.23 (m, 2H), 7.17 (s, 1H), 5.49 (s, 2H), 2.72 – 2.62 (m, 2H), 1.71 – 1.57 (m, 2H) 1.26 (m, 20 H), 0.88 (t, J = 6.6 Hz, 3H).

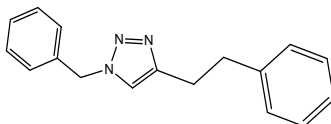
D:\1_chimii\Elena-208_020914

02/09/2014 9.54.39

Elena-208_020914 #1749 RT: 15.77 AV: 1 SB: 2 9.70, 9.78 NL: 3.64E6
T: {0,0} + c EI det=350.00 Full ms [35.00-500.00]



1-benzyl-4-phenyl-1,2,3-triazole

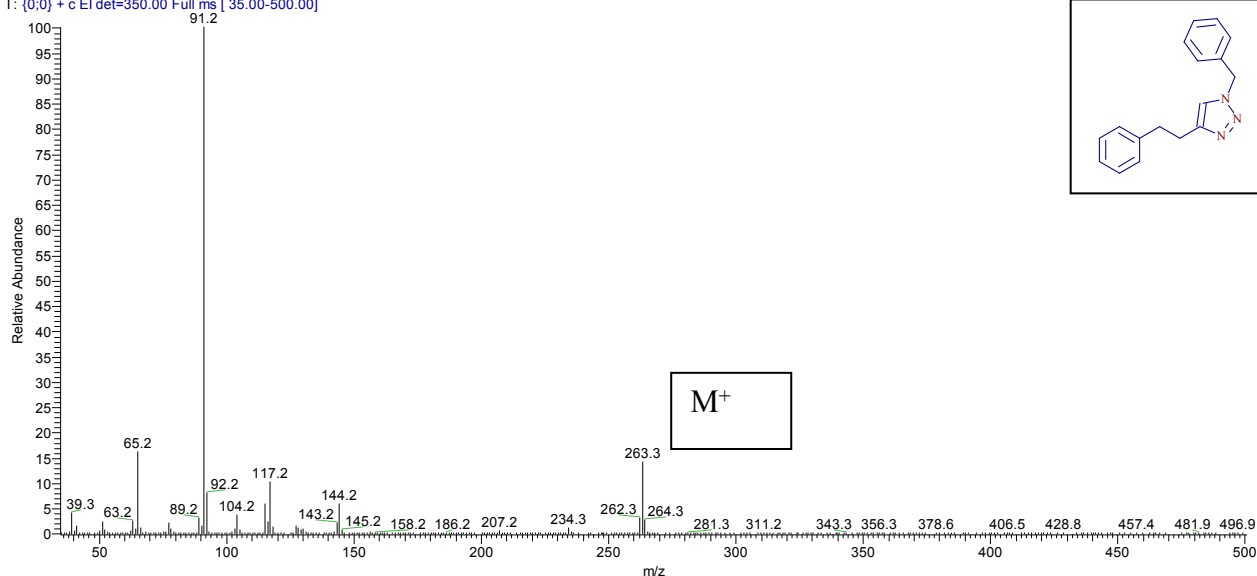


^1H NMR 300 MHz δ (ppm), 7.40–7.10 (m, 10 H), 7.02 (s, 1 H), 5.47 (s, 2H), 3.01 (m, 4 H).

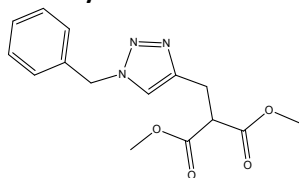
D:\1_chimii\elena-267_040914

04/09/2014 11.50.34

elena-267_040914 #1421 RT: 13.37 AV: 1 SB: 2 12.94, 13.18 NL: 1.13E6
T: {0,0} + c EI det=350.00 Full ms [35.00-500.00]



1-benzyl-1H-[1,2,3]triazolo-4-ylmethyl)-malonate dimethyl ester

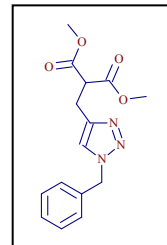
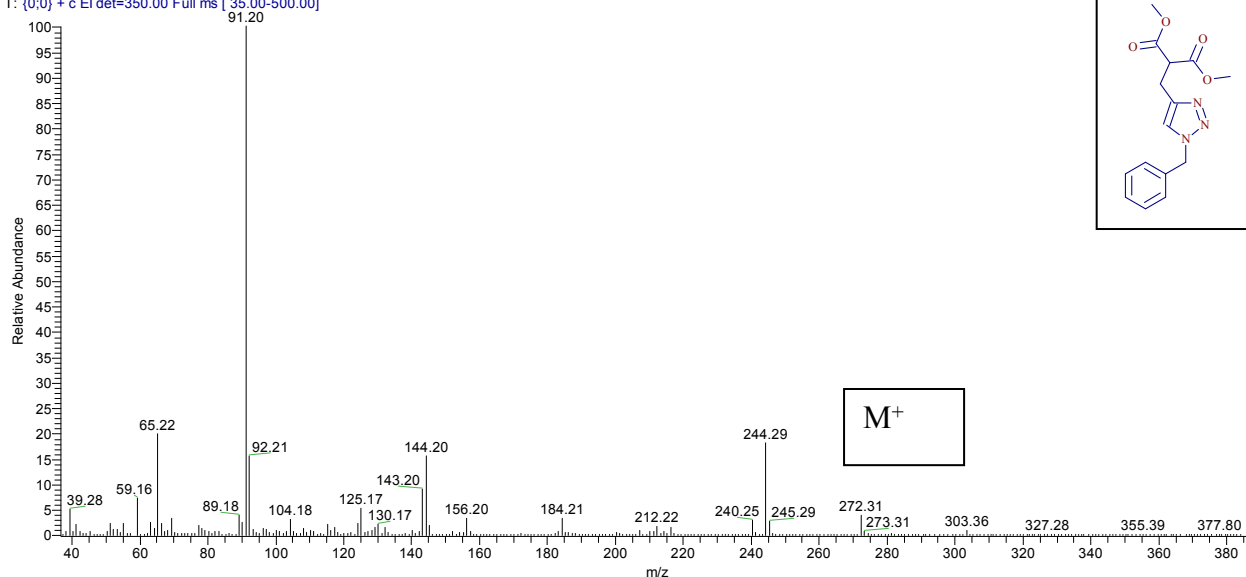


^1H NMR 300 MHz δ (ppm), 7.41 – 7.15 (m, 6H), 5.48 (s, 2H), 3.89 (t, J = 7.5 Hz, 1H), 3.69 (s, 6H), 3.29 (d, J = 7.5 Hz, 2H).

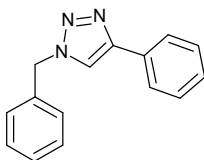
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04/09/2014 14.41.58

elena-266-3_040914 #1394 RT: 13.18 AV: 1 NL: 2.80E6
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1-benzyl-4-phenyl-1,2,3-triazole

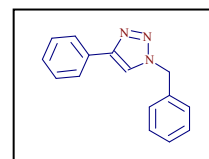
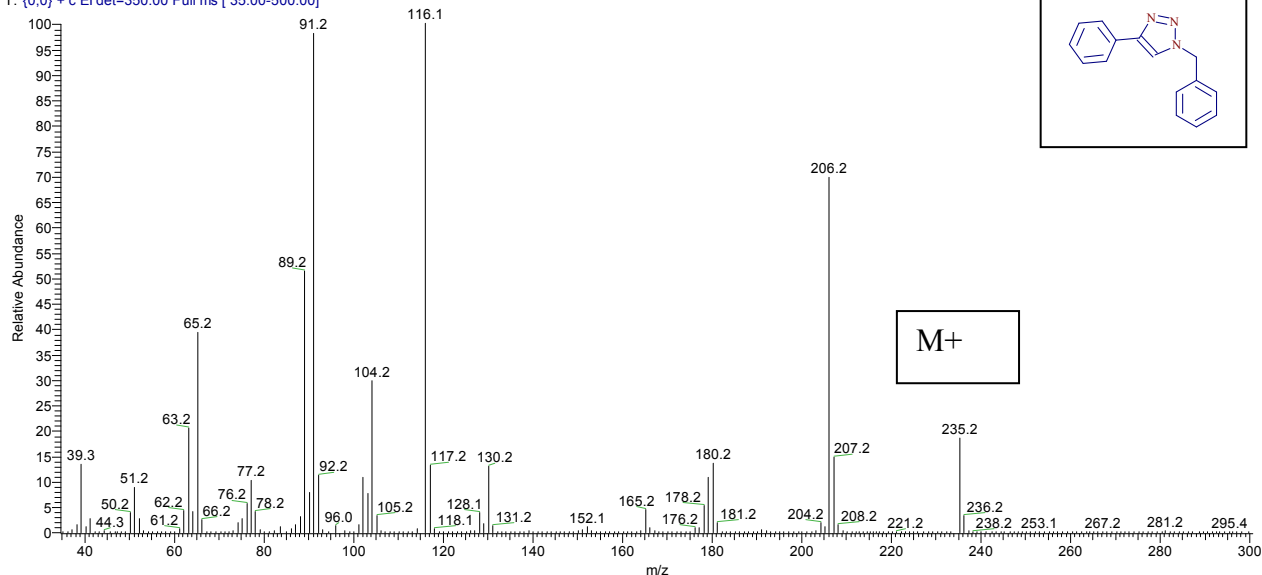


^1H NMR 300 MHz δ (ppm), 7.81-7.83 (d, 2H); 7.69 (s, 1H), 7.29-7.42 (m, 8H), 5.60 (s, 2H).

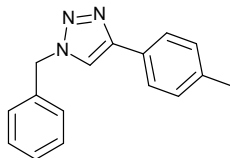
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03/09/2014 10.46.38

elena-255_030914 #1378 RT: 13.06 AV: 1 NL: 2.83E6
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1-benzyl-4-p-tolyl-1,2,3-triazole

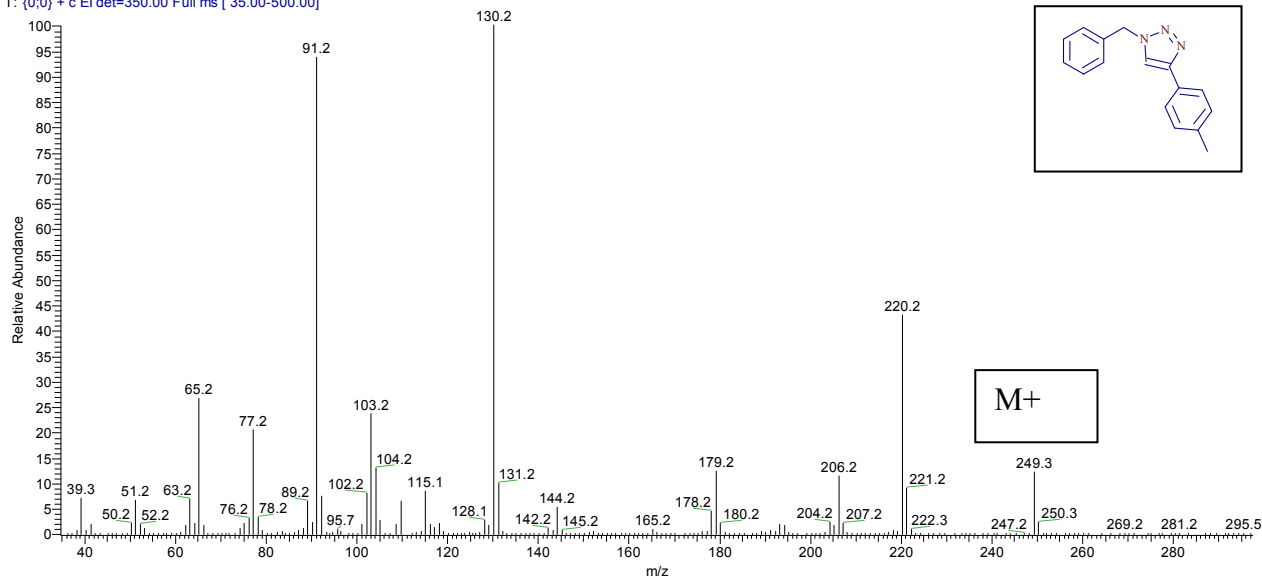


^1H NMR 300 MHz δ (ppm), 7.69 (d, J = 8.0 Hz, 2H), 7.62 (s, 1H), 7.43 – 7.28 (m, 5H), 7.21 (d, J = 8.0 Hz, 2H), 5.57 (s, 2H), 2.33 (s, 3H)

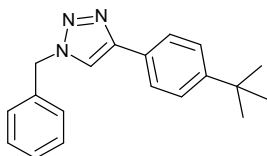
D:\1_chimi\Elena-207_020914

02/09/2014 9.29.30

Elena-207_020914 #1446 RT: 13.56 AV: 1 SB: 2 13.43, 13.71 NL: 1.16E6
T: {0,0} + c EI det=350.00 Full ms [35.00-500.00]



1-benzyl-4-(4-(tert-butyl)phenyl)-1,2,3-triazole

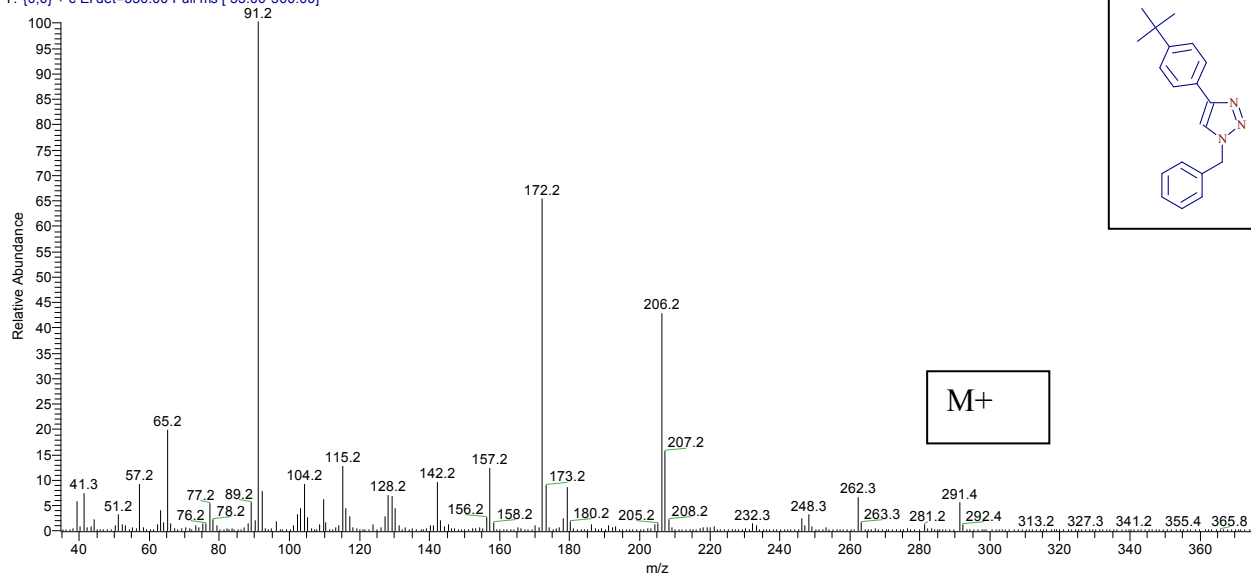


^1H NMR 300 MHz δ (ppm), 7.69 (d, J = 7.8 Hz, 2H), 7.63 (s, 1H), 7.42 – 7.20 (m, 7H), 5.51 (s, 2H), 1.32 (s, 9H).

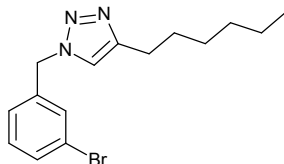
D:\1_chimi\Elena-210_020914

02/09/2014 10.26.44

Elena-210_020914 #1636 RT: 14.94 AV: 1 NL: 7.30E5
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1-(3-bromobenzyl)-4-hexyl-1,2,3-triazole



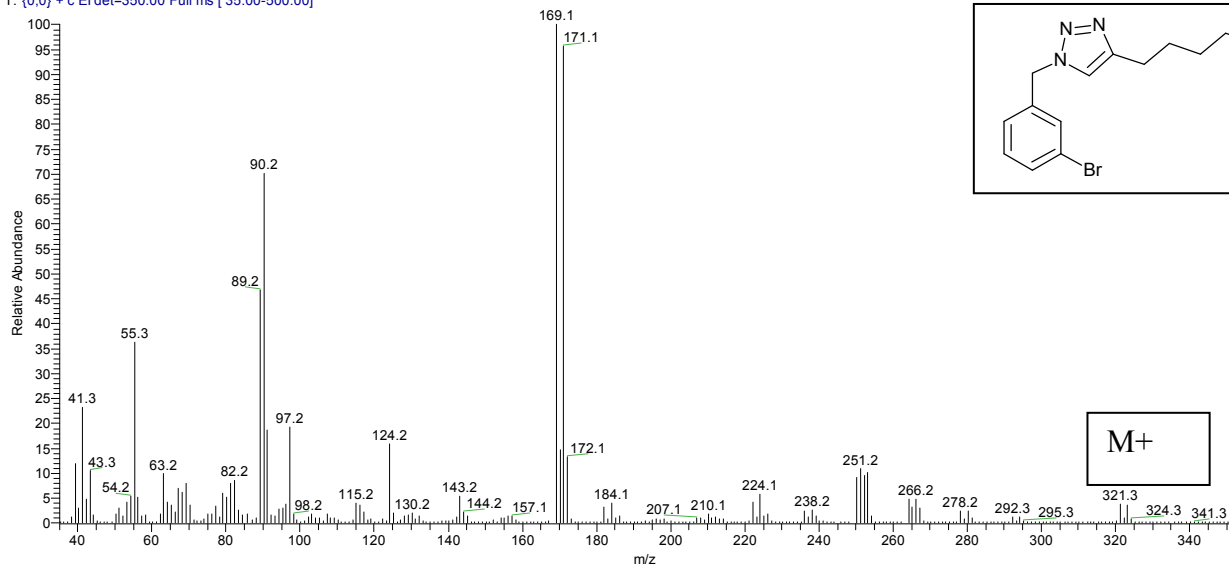
^1H NMR 300 MHz δ (ppm), 7.50 -7.15 (m, 5H), 5.46 (s, 2H), 2.69 (t, J = 7.7 Hz, 2H), 1.76 – 1.55 (m, 2H), 1.43 – 1.17 (m, 6H), 0.87 (t, J = 6.6 Hz, 3H).

D:\1_chim\Elena-227_020914

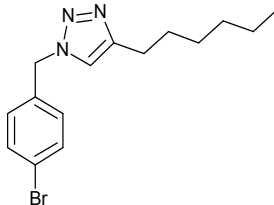
02/09/2014 12.03.02

Elena-227_020914 #1415 RT: 13.33 AV: 1 NL: 2.93E6

T: {0:0} + c El det=350.00 Full ms [35.00-500.00]



1-(4-bromobenzyl)-4-hexyl-1,2,3-triazole



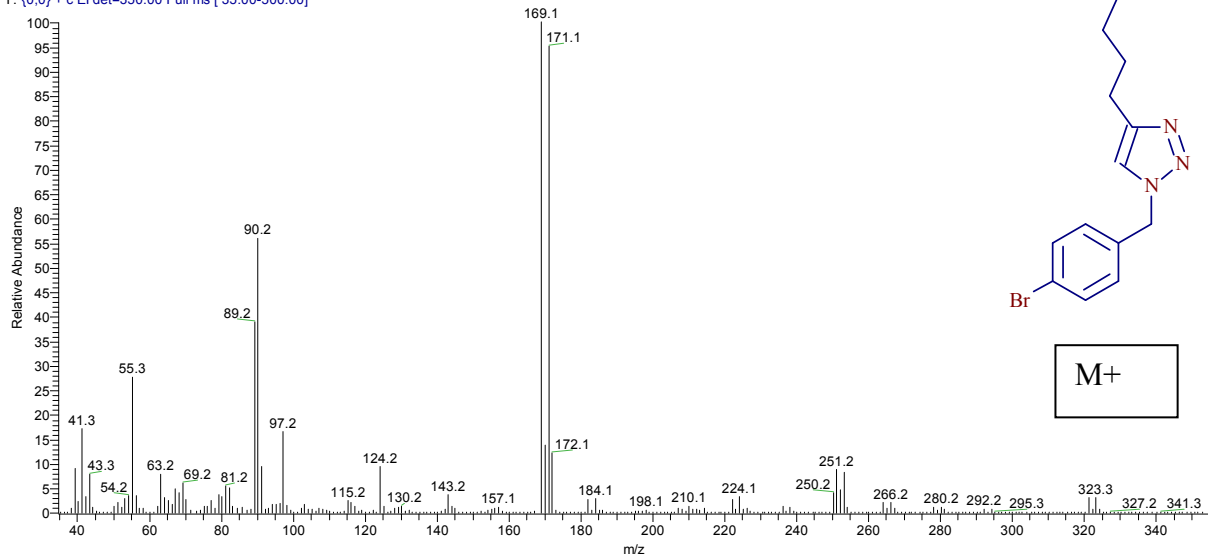
^1H NMR 300 MHz δ (ppm), 7.50 -7.15 (m, 5H), 5.44 (s, 2H), 2.68 (t, J = 7.7 Hz, 2H), 1.62 (bs, 2H), 1.29 (M 6H), 0.85 (T, J = 6.8 Hz, 3H)

D:\1_chim\Elena-226_020914

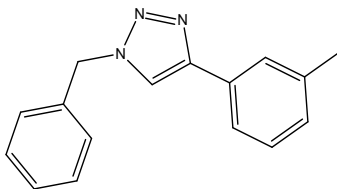
02/09/2014 11.28.38

Elena-226_020914 #1426 RT: 13.41 AV: 1 NL: 3.03E6

T: {0:0} + c El det=350.00 Full ms [35.00-500.00]



1-benzyl-4-(m-tolyl)-1H-1,2,3-triazole

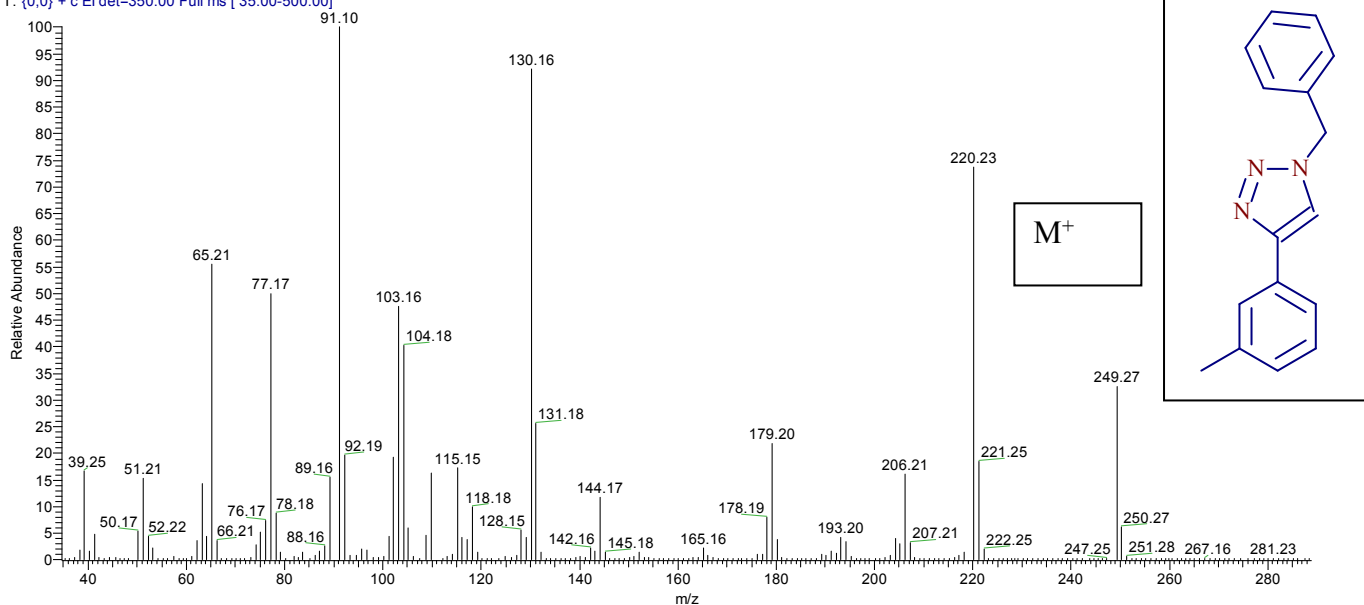


^1H NMR 300 MHz δ (ppm) 7.69 – 7.53 (m, 3H), 7.65 (s, 1H), 7.27 – 7.08 (m, 6H), 5.57 (s, 2H), 2.38 (s, 3H).

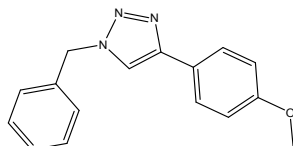
D:\1_chim\Elena-C_131014

13/10/2014 16.14.04

Elena-C_131014 #1441 RT: 13.52 AV: 1 NL: 3.61E6
T: {0:0} + c EI det=350.00 Full ms [35.00-500.00]



1-benzyl-4-(4-methoxyphenyl)-1,2,3-triazole

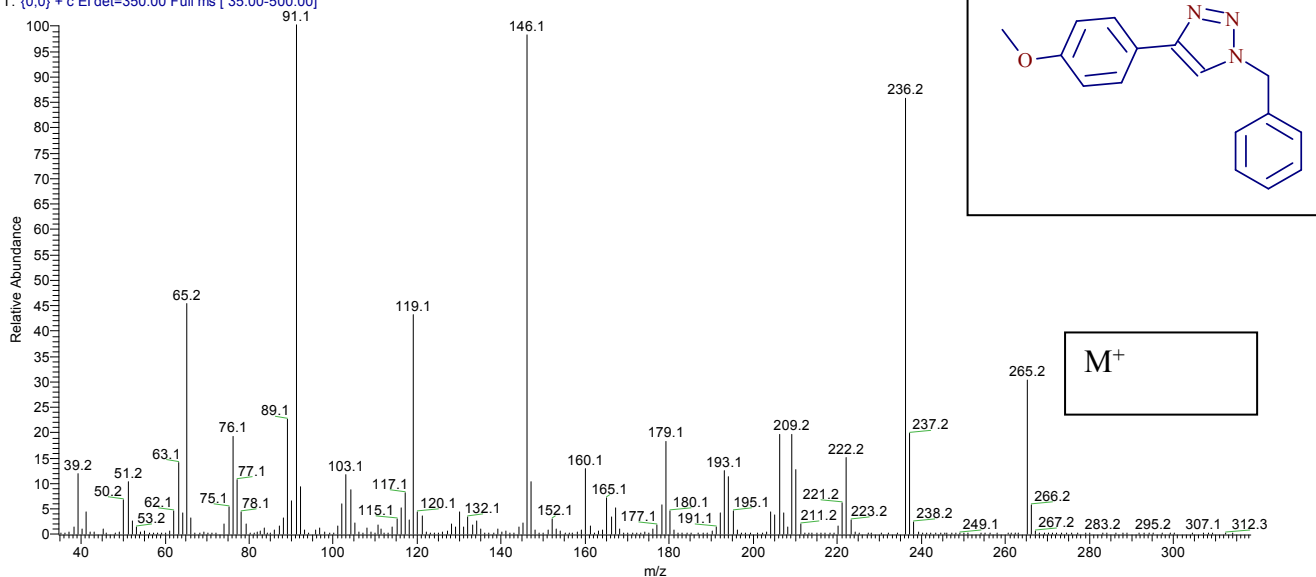


^1H NMR 300 MHz δ (ppm) 7.72 (d, J = 8.5 Hz, 2H), 7.57 (s, 1H), 7.46 – 7.27 (m, 5H), 6.93 (d, J = 8.5 Hz, 2H), 5.56 (s, 2H), 3.83 (s, 3H).

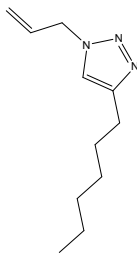
D:\1_chim\Elena-A_131014

13/10/2014 14.53.47

Elena-A_131014 #1559 RT: 14.38 AV: 1 SB: 2 14.23, 14.68 NL: 1.20E6
T: {0:0} + c EI det=350.00 Full ms [35.00-500.00]



1-allyl-4-hexyl-1,2,3-triazole

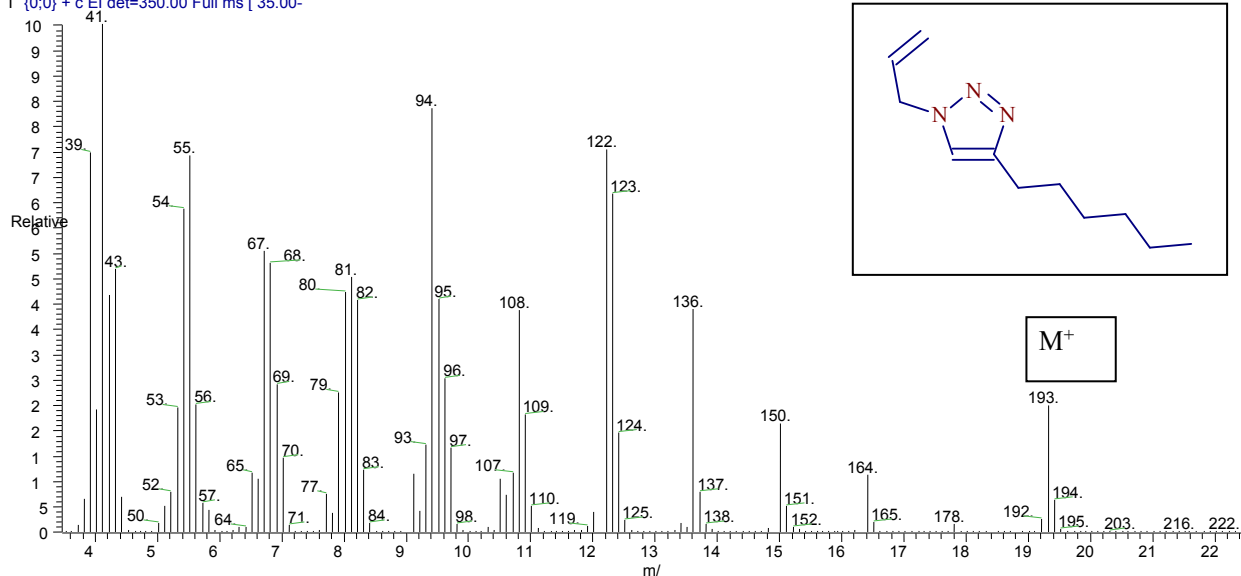


^1H NMR 300 MHz δ (ppm), 7.26 (s, 1H), 6.00 (ddt, $J = 16.3, 10.3, 6.1$ Hz, 1H), 5.30 (m, 2H), 4.93 (dd, $J = 6.1, 1.1$ Hz, 1H), 2.70 (t, $J = 7.7$ Hz, 2H), 1.65 (dt, $J = 15.2, 7.5$ Hz, 2H), 1.30 (m, 6H), 0.87 (t, $J = 6.5$ Hz, 3H)

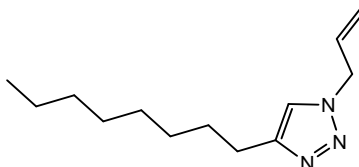
D:\1_chimi\Elena-

25/09/2014

Elena- #118 RT: 11.6 AV: 1 SB: 2 11.59, NL: 4.08E
T: {0,0} + c EI det=350.00 Full ms [35.00-



1-allyl-4-octyl-1,2,3-triazole

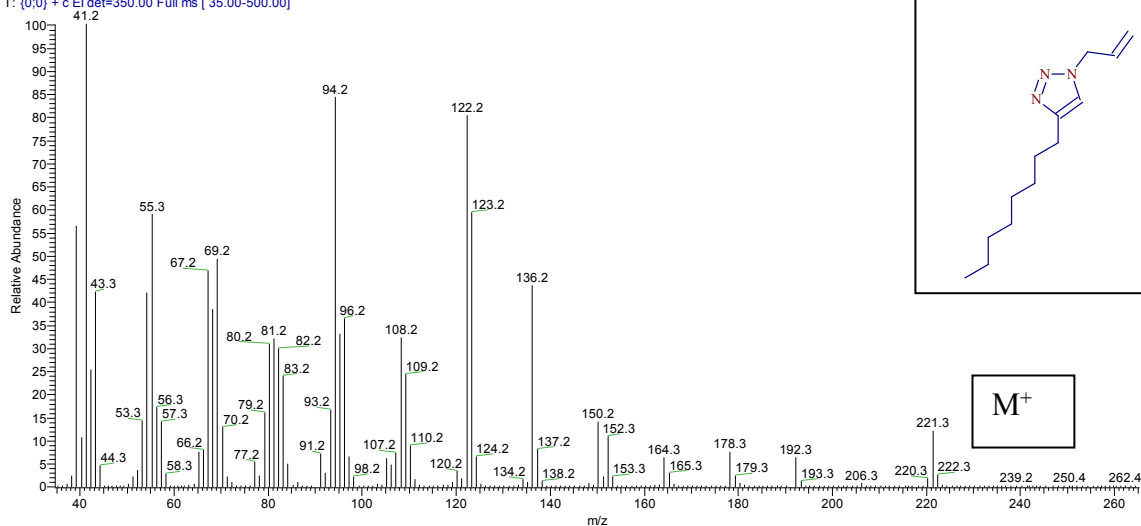


^1H NMR 300 MHz δ (ppm), 7.26 (s, 1H), 6.00 (ddt, $J = 16.7, 10.8, 6.0$ Hz, 1H), 5.29 (m, 2H), 4.93 (dd, $J = 6.1, 1.0$ Hz, 2H), 2.69 (t, $J = 7.7$ Hz, 2H), 1.63 (m, 2H), 1.23 (m, 10H), 0.86 (t, $J = 6.4$ Hz, 3H).

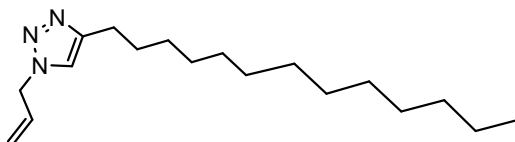
D:\1_chimi\Elena-A-221_011014

01/10/2014 15.42.39

Elena-A-221_011014 #1135 RT: 11.29 AV: 1 SB: 2 3.01, 3.01 NL: 3.27E6
T: {0,0} + c EI det=350.00 Full ms [35.00-500.00]



1-allyl-4-tridecyl-1,2,3-triazole

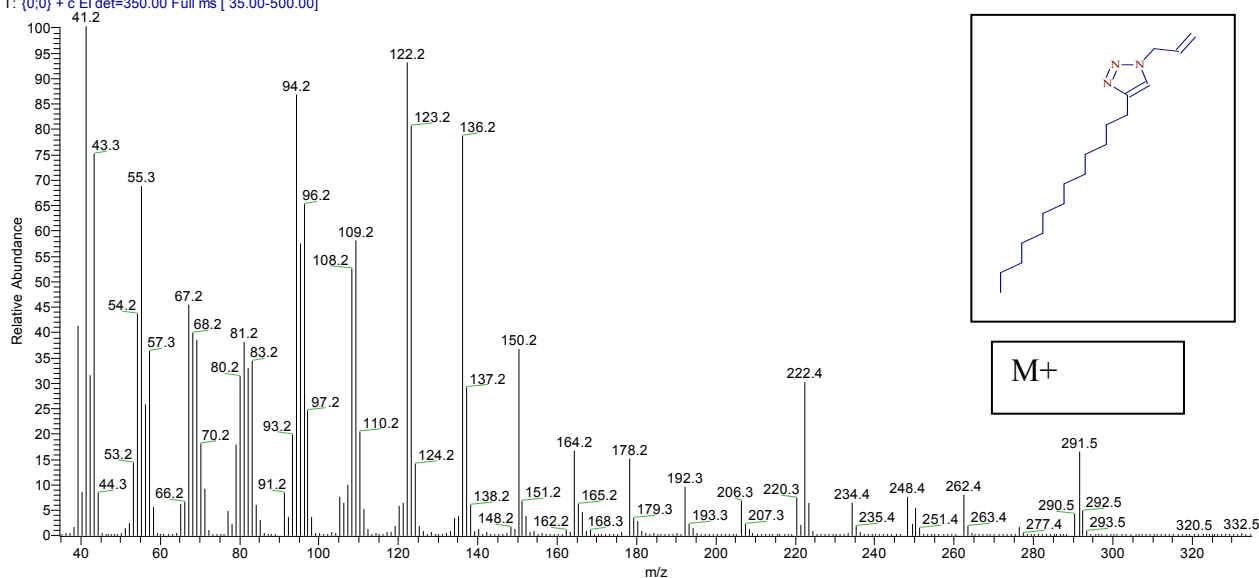


^1H NMR 300 MHz δ (ppm), 7.26 (s, 1H), 6.00 (ddt, J = 16.7, 10.8, 6.0 Hz, 1H), 5.36 – 5.20 (m, 2H), 4.92 (dd, J = 6.1, 1.0 Hz, 2H), 2.69 (t, J = 7.7 Hz, 2H), 1.63 (m, 2H), 1.24 (s, 20H), 0.86 (t, J = 6.5 Hz, 3H)

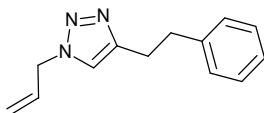
d:\1_chimi\elena-b-291_011014

01/10/2014 16.08.23

elena-b-291_011014 #1376 RT: 13.05 AV: 1 SB: 2 3.01, 3.01 NL: 3.53E6
T: {0,0} + c EI det=350.00 Full ms [35.00-500.00]



1-allyl-4-phenethyl-1,2,3-triazole

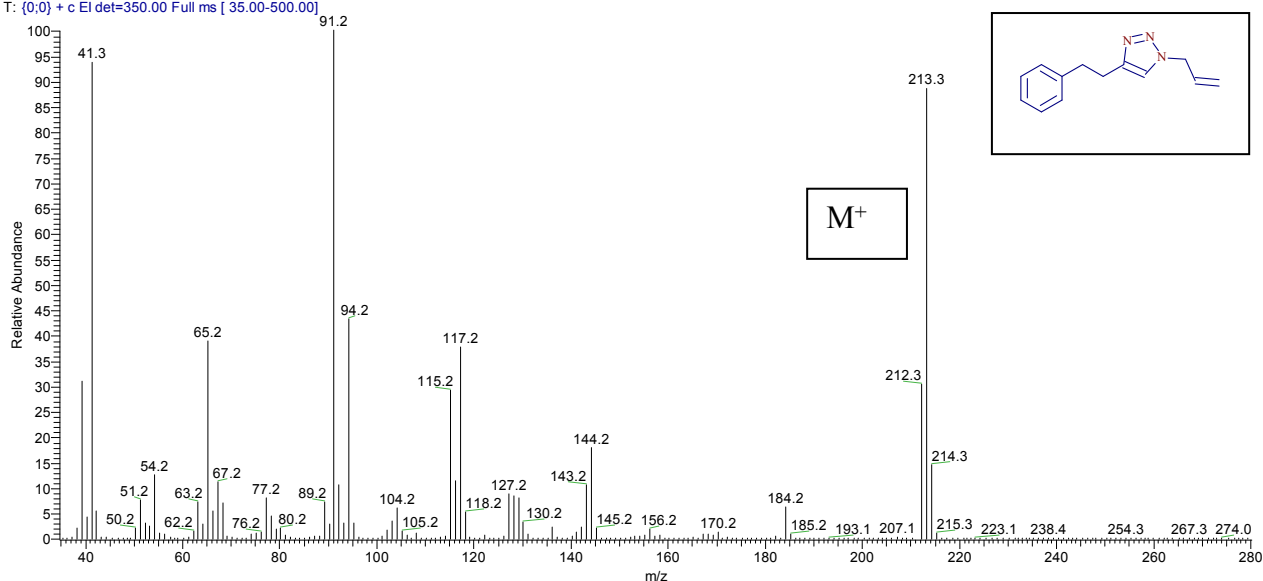


^1H NMR 300 MHz δ (ppm), 7.32 – 7.15 (m, 5H), 7.13 (s, 1H), 5.97 (ddt, J = 16.3, 10.2, 6.0 Hz, 1H), 5.26 (ddd, J = 17.9, 13.6, 1.1 Hz, 2H), 4.91 (dt, J = 6.0, 1.1 Hz, 2H), 3.09 – 2.94 (m, 4H).

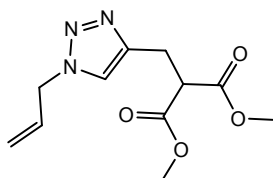
D:\1_chimi\Elena-213_011014

01/10/2014 13.37.01

Elena-213_011014 #1172 RT: 11.56 AV: 1 NL: 2.52E6
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Dimethyl-2-((1-allyl-1H-1,2,3-triazo-4-yl)methyl)malonate

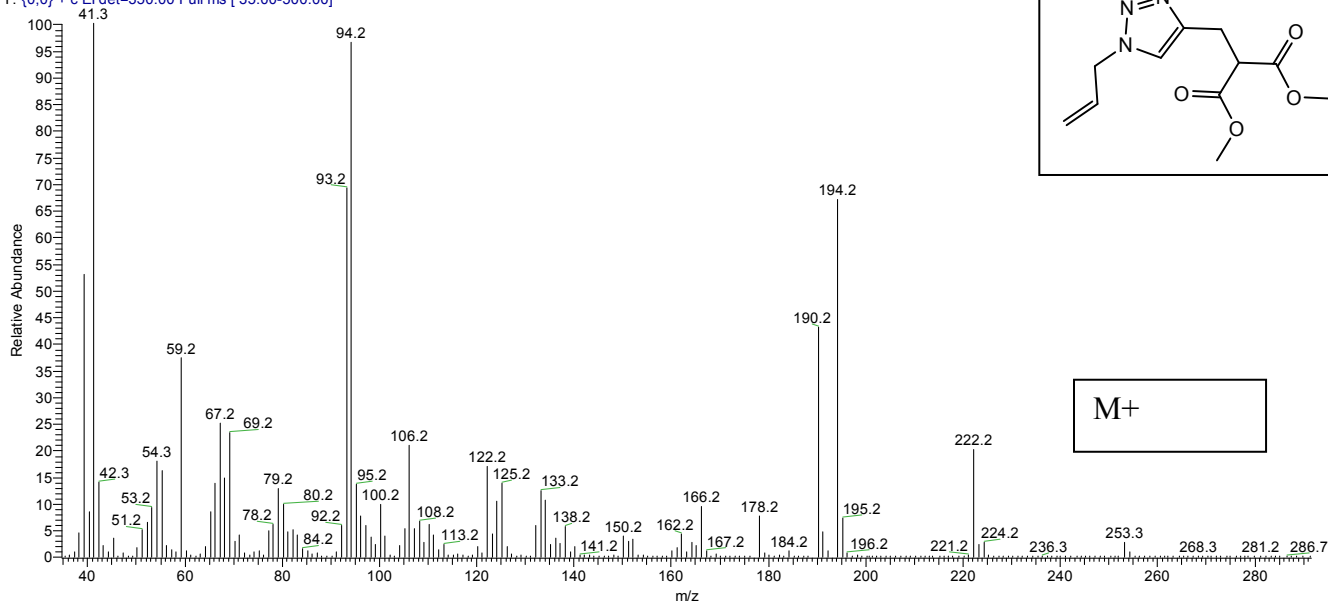


^1H NMR 300 MHz δ (ppm), 7.37 (s, 1H), 5.98 (ddt, J = 16.3, 10.3, 6.1 Hz, 1H), 5.41 – 5.19 (m, 2H), 4.91 (d, J = 6.1 Hz, 2H), 3.89 (t, J = 7.4 Hz, 1H), 3.72 (s, 6H), 3.30 (d, J = 7.4 Hz, 2H).

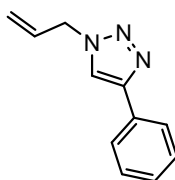
d:\1_chimi\elena-c-253_011014

01/10/2014 16.44.06

elena-c-253_011014 #1162 RT: 11.48 AV: 1 SB: 2 3.01, 3.01 NL: 2.88E6
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1-Allyl-4-phenyl-1,2,3-triazole

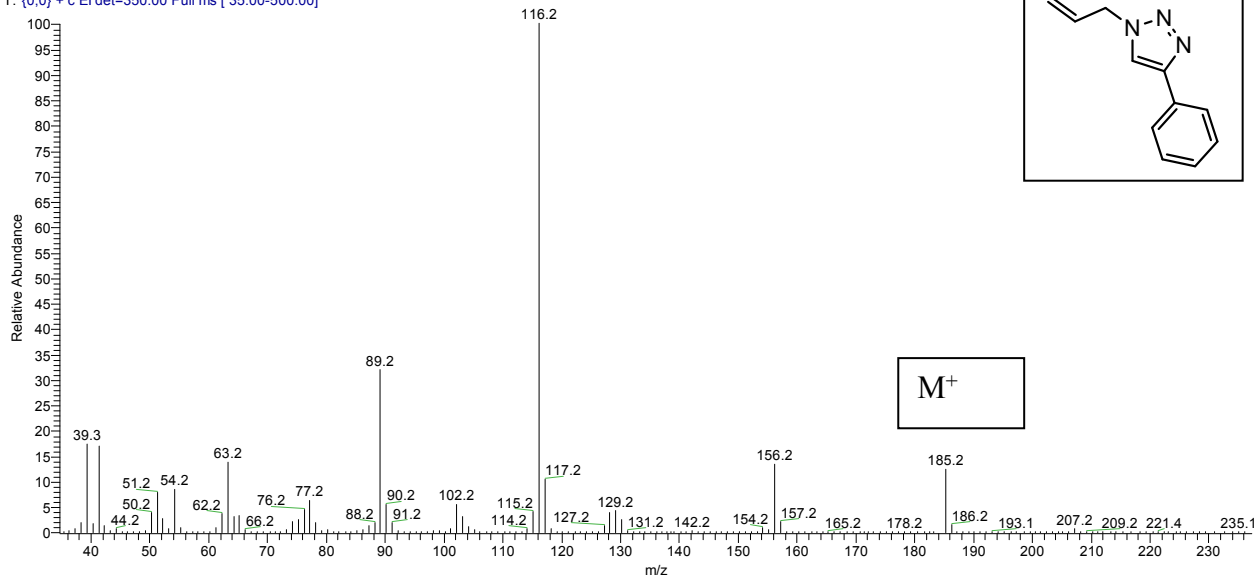


^1H NMR 300 MHz δ (ppm), 7.76 (s, 1H), 7.52 – 7.46 (m, 2H), 7.36 – 7.29 (m, 3H), 6.06 (ddd, J = 16.4, 10.4, 5.8 Hz, 1H), 5.41 – 5.30 (m, 2H), 5.03 (d, J = 6.1 Hz, 2H).

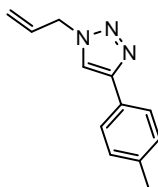
D:\1_chimi\Elena-CH_300914

30/09/2014 15.30.09

Elena-CH_300914 #1128 RT: 11.24 AV: 1 NL: 6.59E5
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4-(p-tolyl)-1-allyl-1,2,3-triazole

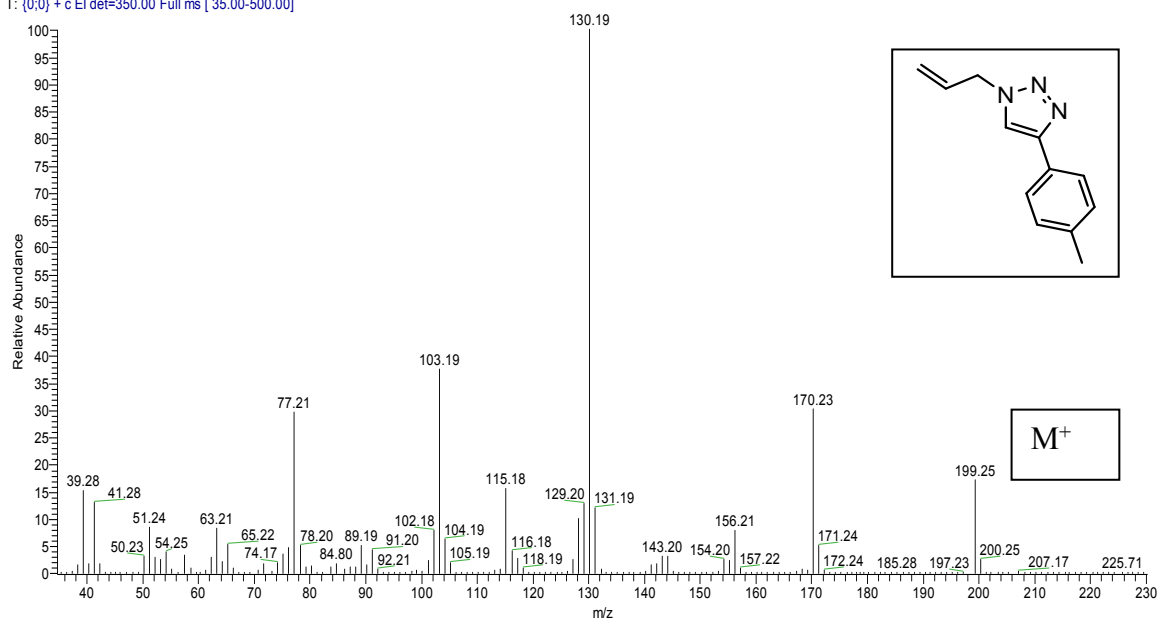


^1H NMR 300 MHz δ (ppm), 7.72 (d, J = 8.2 Hz, 2H), 7.71 (s, 1H), 7.23 (d, J = 8.2 Hz, 2H), 6.06 (ddt, J = 16.6, 10.4, 6.1 Hz, 1H), 5.41 – 5.29 (m, 2H), 5.01 (d, J = 6.1 Hz, 2H), 2.37 (d, J = 4.2 Hz, 2H).

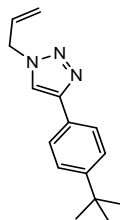
D:\1_chimi\Elena-CMe_300914

30/09/2014 15.54.04

Elena-CMe_300914 #1185 RT: 11.65 AV: 1 NL: 2.60E6
T: [0:0] + c EI det=350.00 Full ms [35.00-500.00]



4-(t-butyl-phenyl)-1-allyl-1,2,3-triazole

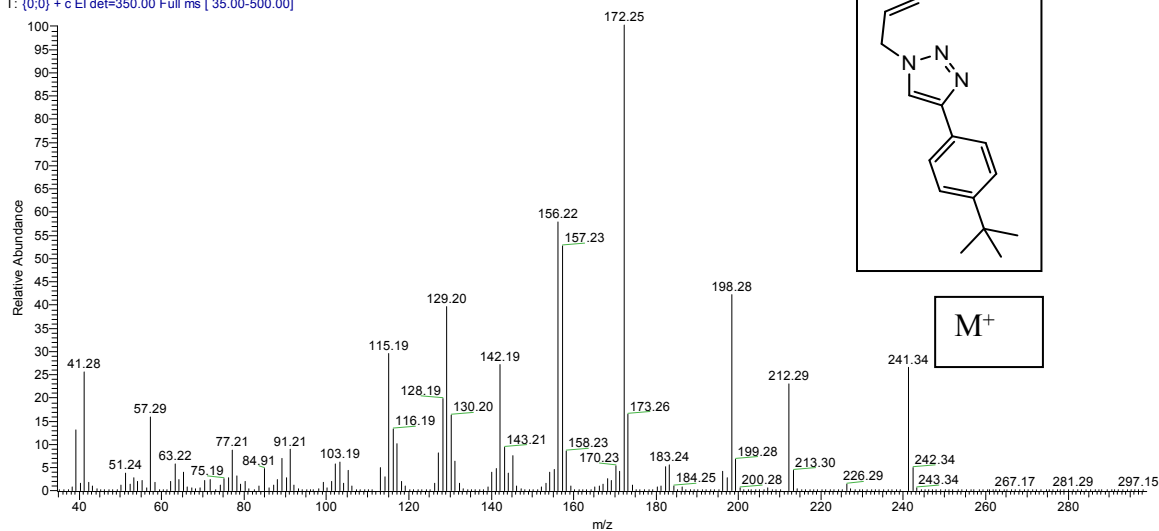


^1H NMR 300 MHz δ (ppm), 7.76 (d, J = 8.3 Hz, 2H), 7.73 (s, 1H), 7.30-7.40 (m, 2H), 6.06 (ddt, J = 16.4, 10.3, 6.1 Hz, 1H), 5.33 (m, 2H), 5.01 (d, J = 6.1 Hz, 1H), 1.35 (s, 9H).

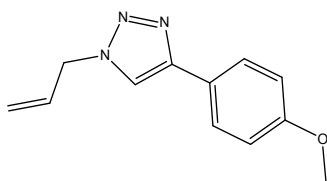
D:\1_chimi\Elena-CtBu_300914

30/09/2014 16.11.34

Elena-CtBu_300914 #1298 RT: 12.48 AV: 1 NL: 2.68E6
T: [0:0] + c EI det=350.00 Full ms [35.00-500.00]



1-allyl-4-(4-methoxyphenyl)-1,2,3-triazole

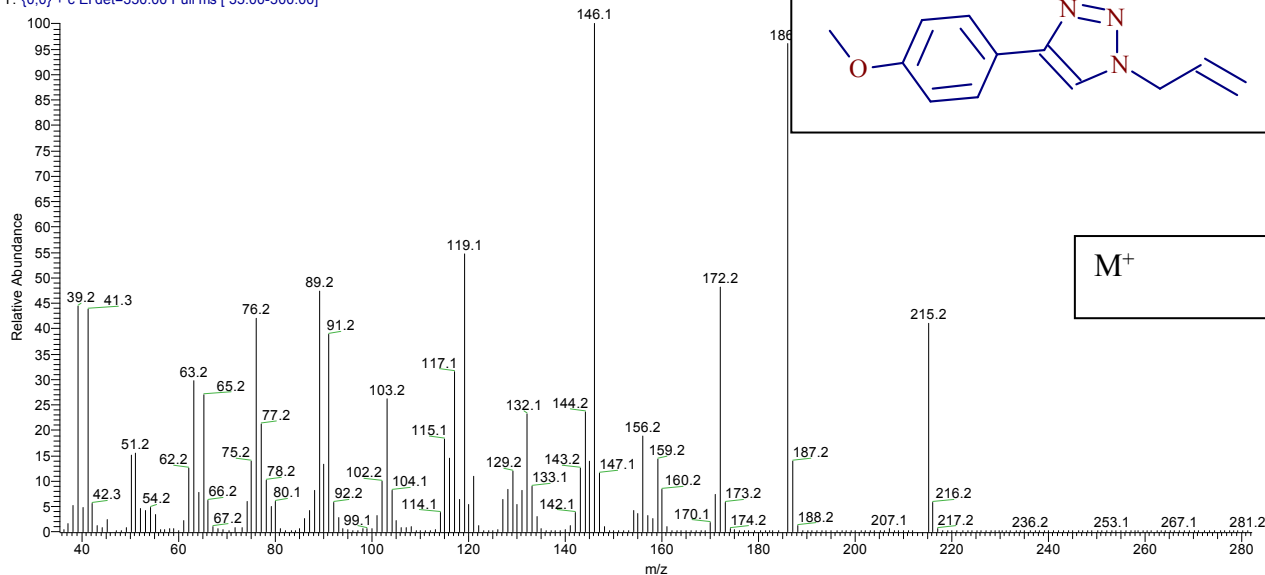


^1H NMR 300 MHz δ (ppm) 7.74 (d, J = 8.9 Hz, 2H), 7.67 (s, 1H), 6.95 (d, J = 8.9 Hz, 2H), 6.14 – 5.95 (m, 1H), 5.42 – 5.28 (m, 2H), 5.00 (dt, J = 6.1, 1.4 Hz, 1H), 3.83 (s, 3H).

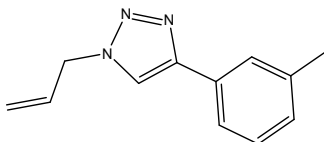
D:\1_chimi\Elena-B_131014

13/10/2014 15.23.15

Elena-B_131014 #1261 RT: 12.21 AV: 1 NL: 2.31E6
T: {0:0} + c EI det=350.00 Full ms [35.00-500.00]



1-allyl-4-(m-tolyl)-1,2,3-triazole

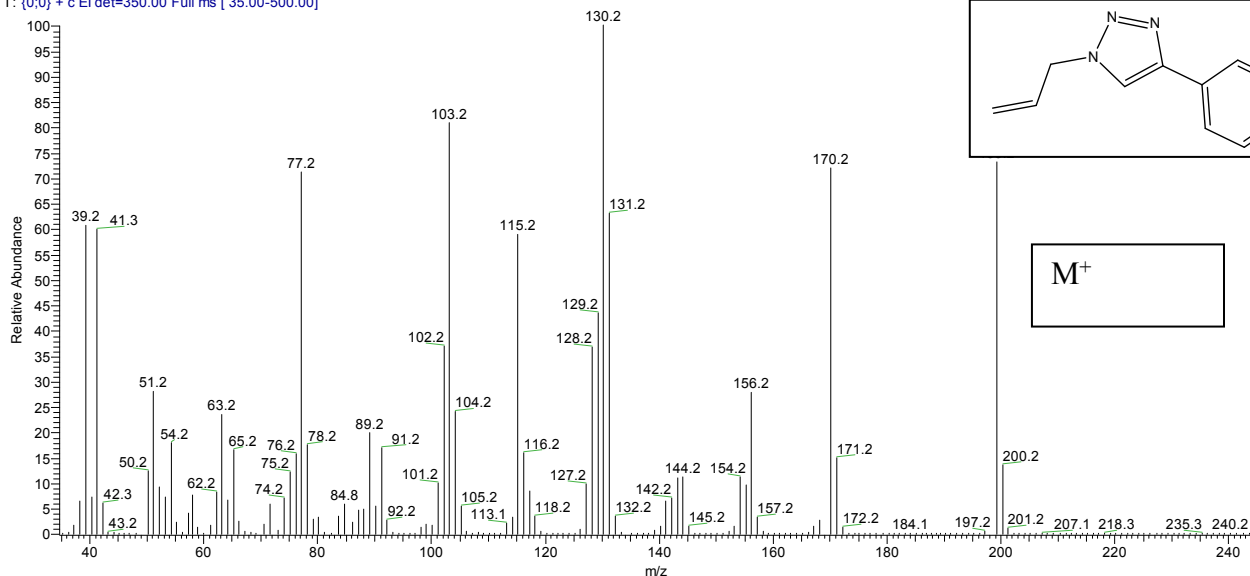


^1H NMR 300 MHz δ (ppm) 7.74 (s, 1H), 7.72 – 7.53 (m, 2H), 7.34 – 7.09 (m, 2H), 6.14 – 5.94 (m, 1H), 5.42 – 5.25 (m, 2H), 5.05 – 4.93 (m, 2H), 2.39 (s, 3H).

D:\1_chimi\Elena-D_131014

13/10/2014 15.50.16

Elena-D_131014 #1183 RT: 11.64 AV: 1 NL: 4.00E6
T: {0:0} + c EI det=350.00 Full ms [35.00-500.00]



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- 1 D.D. Perrin, W.L.F. Armarego, Purification of laboratory chemicals, 3rd edition, , Pergamon Press, 1993.
 - 2 W. C. Still, M. Khan, A. Mitra *J. Org. Chem.* **1978**, *43*, 2923.