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Samarium (III) triflate: catalyzed for the synthesis of 1,5-benzodiazepines

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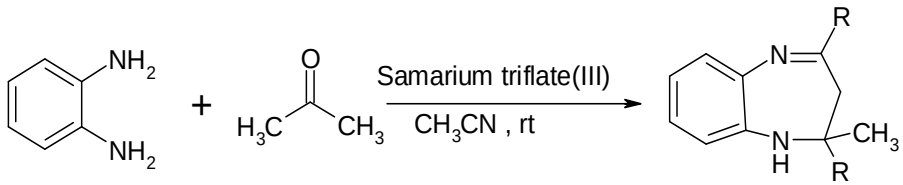
ABSTRACT

A simple and versatile method for the synthesis of 1,5-benzodiazepines is via condensation of o-phenylenediamines (OPDA) and ketones in the presence of Samarium trifled Sm(OTf)3 catalytic using acetonitrile as solvent at room temperature. In all the cases, the reactions are highly selective and are completed within 1 h. The method is applicable to both cyclic and acyclic ketones without significant differences. The reaction proceeds efficiently under ambient conditions with good-to-excellent yields

Keywords*:* Acetonitrile, Benzodiazepine, ketones, o-phenylenediamine, Samarium trifflet, solvent free.

INTRODUCTION

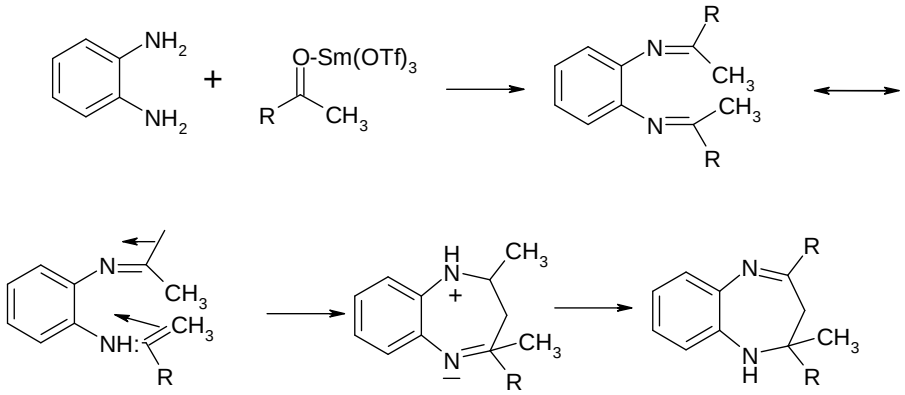
The multicomponent condensation reactions are occupying an autstading position in organic and medical chemistry for thier high degree of atom economy. Many members of this family are in fact, nowadays widely used as anti-convulsant, anti-anxiety, analgesic, sedative, anti-depressive, and hypnotic agents[2]. In addition, 1,5-benzodiazepines are used as starting materials for the preparation of fused ring compounds such as triazolo-[4], oxadiazolo-[5], axazino-[6], or furano-benzodiazepine[7]. Benzodiazepine derivatives also find commercial use as dyes for acrylic fibers and as anti-inflematory agents. Despite their wide range of pharmacological activity, industrial and synthetic applications.the synthesis of 1,5-benzodiazepines has received little attention,and few methods for their preparations are reported in the literature, a great number of which have appeared only very recently. These include condansation reaction of o-phenylenediamines with α,β-unsaturated carbonyl compounds[8]. β-haloketones[9] or ketones in the presence of BF_3-etherate[10], $NaBH_4$, Polyphosphoric acid , SiO_2 [12], MgO and $POCl_3$ [13], $Yb(OTf)_3$, Al_2O_3/P_2O_5 [14] , AcOH [16] Under microwave(MW) irradiation and ionic liquid [17]. Many of these processes suffer from one or other limitations such as drastic reaction conditions, expensive reagents and low to moderate yields, relativily long reaction times, and the occurrence of several side reactions. Almost all of them make use of an acid catalyst giving rise to tedious work-up procedures. In recent year Samarium trifflet has received considerable attention as an inexpensive and easily available catalyst for effecting various organic transformations[18]. We now report here the synthesis of 1,5-benzodiazepine derivatives by condensation of o-phenylenediamine with both cyclic and acyclic ketones using molecular Samarium trifflet in acetinitrile(CH_3CN) as an efficient catalyst under solvent-free condensation(scheme-1).



Scheme -1

The synthesis were carried out simply by mixing o-phenylenediamine(1mmol) with the ketone(2mmol) in the presence of a catalytic amount(10%)of Samarium trifflet in CH_3CN, where upon the benzodiazepine derivatives were abtained in almost quantitative yield. It is hightly rapid method as compored to literature reported.

As show table -1, OPDA undergoes rapid condensation with ketones having hydrogens at the alpha-position in the presence of 10 mol% Samerium trifflet under extremely mild reaction conditions to affort the corresponding 2,3-dihydro 1H, 1,5-benzodiazepines in excellent yields with high selectivity. interesting both cyclic and acyclic ketones reacted with OPDA to give the corresponding products in good yield, without any significant difference this method offers several advantages such as high conversions, short reaction time, clear reaction profiles, high regioselectivity in the case of unsymmetrical ketones, solvent-free condition and simlpe experimental and work-up procedures. A possible mechanism for the condensation of OPDA with ketones is show in scheme-2.



Scheme-2

The amino group of OPDA attacks the carbonyl group of the ketone, which is activated by Samerium trifflet giving the intermediate diamine A, A 1,3-shift of the hydrogen attached to the methyl group then occurs to form an isomeric enomine B, Which cyclizes to afford a seven-membered ring.

MATERIALS AND METHODS

General Procedure: A mixture of o-phenylenediamine or 4-methyl 0-phenylenediamine (1mmol), ketones(2mmol) Samerium trifflet (0.1mmol) in acetonitrile (10mL) was stirred at room temperature. Affter completion of the reaction as indicated by TLC, the solvent was removed under reduced pressure. The residue was dissolved in ethyacetate and washed with water and brine solution. The organic layer was dried over Na_2SO_2 and concentrated undur reduced pressure. The crude products were purified by column chromatography using ethylacetate – hexane(1:9 ratio). All the product were identified by their 1HNMR, IR, and MASS Spectroscopy data and compared with literature reports.

Spectroscopic data for all the products

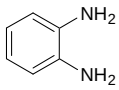
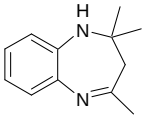
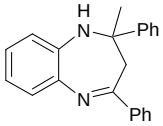
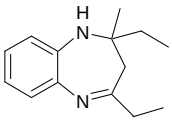
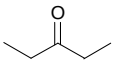
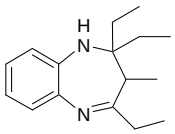
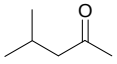
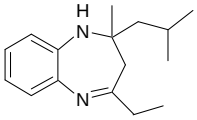
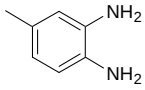
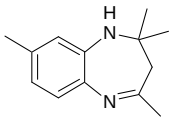
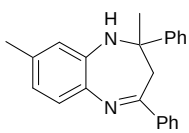
2, 2, 4-Trimethyl-2,3-dihydro-1*H*-1, 5-benzodiazepine (**3a**): Light yellow crystals: Mp. 136-138 ^oC. IR (KBr): 340, 1650, 1600 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 1.35 (s, 6H), 2.20 (s, 2H), 2.35 (s, 3H), 2.95 (brs, 1H, NH), 6.65-7.30(m, 4H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 29.7, 30.4, 45.0, 67.8, 121.6, 122.0, 125.4, 126.7, 137.8, 140.6, 171.8. EIMS *m/z* (%). 188 (m^+, 100), 173 (52), 132 (15), 104 (15), 77 (32), 65 (20).

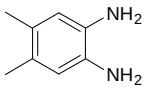
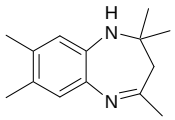
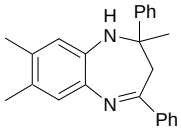
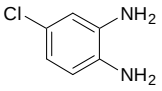
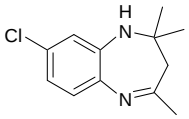
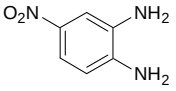
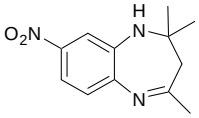
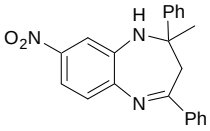
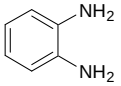
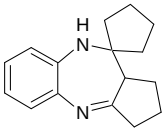
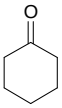
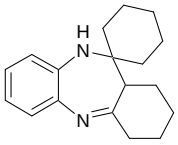
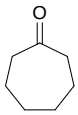
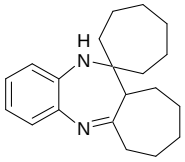
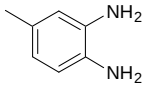
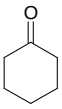
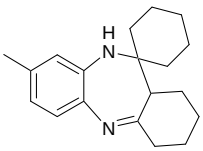
2-Methyl-2, 4-diphenyl-2, 3-dihydro-1*H*-1, 5-benzodiazepine (**3b**): Yellow crystalline solid. Mp. 150-152 ^{o}C. IR (KBr): 3325, 1635, 1598 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.80 (s, 6H), 2.95 (d, 1H, *J* = 12.8 Hz), 3.95 (d, 1H, *J* = 12.8 Hz), 3.45 (brs, NH), 6.55-7.00 (m, 3H), 7.15-7.35 (m, 7H), 7.55-7.65 (m, 4H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 29.7, 42.9, 73.3, 121.2, 121.4, 125.2, 126.12, 126.8, 126.9, 127.8, 128.1, 128.5, 129.5, 137.9, 139.5, 139.9, 147.4, 167.3. EIMS *m/z* (%). 312 (m^{+}, 10), 295 (100), 235 (25), 194 (30), 103 (20), 77 (60), 40 (80).

2-4-Diethyl-2-methyl-2, 3-dihydro-1*H*-1, 5-benzodiazepine (**3c**): Colorless solid; M.P. 118-120 ^{o}C. IR (KBr): 3320, 1650, 1599 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.95-1-05 (m, 12H), 1.32 (s, 3H), 1.49-1.52 (m, 2H), 1.65-1.75 (m, 1H), 2.05-2.25 (m, 3H), 2.24 (d, 2H, *J* = 12.7 Hz), 6.60-6.65 (m, 1H), 6.85-6.95 (m, 2H), 7.05-7.15 (m, 1H). EIMS *m/z* (%). 272 (m^{+} 10), 157 (12), 141 (25), 105 (100), 80 (50), 53 (14).

2,2,4-Trimethyl-3-methyl-2, 3-dihydro-1*H*-1, 5-benzodiazepine (**3d**): Colorless solid; Mp. 143-144 ^{o}C. IR (KBr): 3320, 1638, 1596 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.75-1-05 (m, 10H), 1.20-1.38 (m, 4H), 1.50-1.65 (m, 2H), 2.40-2.60 (m, 2H), 2.87 (q, 1H, *J* = 6.9 Hz), 3.75 (brs, 1H, NH), 6.57 (d, 1H, *J* = 8.0 Hz), 6.65 (t, 1H, *J* = 8.0 Hz), 6.90 (t, 1H, *J* = 8.0 Hz), 7.38 (d, 1H, *J* = 8.0 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 7.5, 7.9, 11.5, 12.3, 28.0, 28.4, 35.6, 46.2, 68.6, 117.5, 118.0, 126.6, 132.8, 139.0, 142.4, 173.8. EIMS *m/z* (%). 244 (m^{+}, 30), 229 (29), 215 (100).

Table 1: synthesis of 1, 5-benzodiazepines using samarium triflate(III) catalyst

Entry	Diamine	Ketone	Product	Conversion (%)	Time (h)	Yield (%)
3a				100	1.5	95
3b	"			96	2.5	89
3c	"			100	1.5	91
3d	"			100	2.0	94
3e	"			97	2.5	87
3f				100	1.5	96
3g	"			98	2.0	90

3h				100	1.5	97
3i	"			98	2.5	88
3j				100	2.0	93
3k				99	3.0	85
3l	"			61	3.5	80
5m				96	2.5	83
5n	"			99	3.0	85
5o	"			97	3.5	79
5p				99	2.5	86

2-Methyl-2,4-diisobutyl-2,3-dihydro-1*H*-1, 5-benzodiazepine (**3e**): Light yellow solid; Mp. 118-120 ^{o}C. IR (KBr): 3320, 1650, 1599 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.95-1.05 (m, 12H), 1.32 (s, 3H), 1.49-1.52 (m, 2H), 1.65-1.75 (m, 1H), 2.05-2.25 (m, 3H), 2.24 (d, 2H, *J* = 12.7 Hz), 6.60-6.65 (m, 1H), 6.85-6.95 (m, 2H), 7.05-7.15 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 22.5, 22.7, 24.2, 24.9, 25.0, 26.3, 28.1, 43.5, 51.7, 51.9, 70.8, 121.4, 121.5, 125.2, 127.2, 137.8, 140.4, 173.9. EIMS (relative intensity): *m/z* 272 (M^+, 10), 157 (12), 141 (25), 105 (100), 80 (50), 53 (14).

2,2,4-Trimethyl-2,3-dihydro-8-methyl-1*H*-1,5-benzodiazepine (3f): White crystalline solid; Mp. 127-129 ^{o}C; IR (KBr): 3325, 1665, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.30 (s, 6H), 2.19 (s, 2H), 2.23 (s, 3H), 2.80 (s, 3H), 6.65-6.75 (s, 1H), 6.70-6.80 (m, 1H), 7.05-7.10 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.9, 29.6, 30.4, 30.8, 45.8, 67.0, 122.6, 126.6, 127.0, 131.8, 136.7, 138.1, 174.; EIMS (relative intensity): *m/z* 202 (M^+, 40), 187 (100), 146 (70), 77 (15), 41 (20).

2-Methyl-2,4-diphenyl-2,3-dihydro-8-methyl-1*H*-1,5-benzodiazepine (3g): Yellow solid; Mp. 91-93 ^{o}C; IR (KBr): 3315, 1657, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.80 (s, 3H), 2.41 (s, 3H), 2.98 (d, 1H, *J* = 12.7 Hz), 3.15 (d, 1H, *J* = 12.7 Hz), 3.50 (br s, 1H, NH), 6.70-6.69 (m, 13H); ^{13}C NMR (proton decoupled**,** $CDCl_3$, 50 MHz): δ 20.6, 28.5, 45.8, 51.2, 113.5, 125.5, 126.4, 127.3, 128.1, 128.3, 128.6, 129.1, 130.9, 131.2, 134.0, 136.8, 164.8; EIMS (relative intensity): *m/z* 326 (M^+, 10), 261 (100), 246 (90), 206 (40), 145 (50), 102 (35), 76 (30).

2, 2, 4-Trimethyl-2,3-dihydro-7,8-dimethyl-1*H*-1, 5-benzodiazepine (**3h**): Yellow solid; Mp. 112-114 ^{o}C; IR (KBr): 3290, 1635, 1597 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.35 (s, 6H), 2.19 (s, 3H), 2.20 (s, 3H), 2.22 (s, 2H), 2.34 (s, 3H), 2.80 (br s, NH, 1H), 6.52 (s, 1H), 6.39 (s, 1H). ^{13}C NMR **(**proton decoupled**,** $CDCl_3$, 75 MHz): δ 18.9, 19.1, 29.8, 30.3, 30.4, 45.3, 67.7, 122.8, 127.8, 129.9, 133.6, 135.5, 138.4, 171.3. EIMS *m/z* (%). 216 (m^+, 20), 201 (60), 161 (30), 145 (15), 97 (17), 71 (50), 43 (100).

2-Methyl-2,4-diphenyl-2,3-dihydro-7,8-dimethyl-1*H*-1,5-benzodiazepine (3i): Light Colored solid; Mp. 115-116 ^{o}C; IR (KBr): 3285, 1635, 1609 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.70 (s, 3H), 2.25 (s, 6H), 2.90 (d, 1H, *J* = 12.8 Hz), 3.10 (d, 1H, *J* = 12.8 Hz), 3.45 (br s, 1H, NH), 6.60 (s, 1H), 7.15 (s, 1H), 7.30-7.18 (m, 6H), 7.50-7.60 (m, 4H); ^{13}C NMR (proton decoupled, $CDCl_3$, 50 MHz): δ 18.6, 19.3, 29.7, 43.2, 73.0, 122.3, 125.4, 126.8, 128.9, 127.8, 128.2, 129.4, 129.6, 134.8, 135.7, 137.6, 139.7, 147.8, 166.8; EIMS (relative intensity): *m/z* 340 (M^+, 10), 195 (30), 103(100), 77 (50), 65 (20).

2, 2, 4-Trimethyl-2, 3-dihydro-8-chloro-1*H*-1, 5-benzodiazepine (3j): Pale yellow solid; Mp. 90-92 ^{o}C; IR (KBr): 3283, 1649, 1597 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.27 (s, 6H), 2.23 (d, 2H, *J* = 7.2 Hz), 2.26 (s, 3H), 6.86 (d, 1H, *J* = 3.6 Hz), 6.98 (dd, 1H, *J* = 6.6 Hz), 7.05 (d, 1H, *J* = 7.1 Hz); ^{13}C NMR (proton decoupled**,** $CDCl_3$, 75 MHz): δ 29.2, 29.8, 30.0, 44.9, 67.0, 120.4, 120.8, 125.9, 127.8, 129.8, 139.1, 172.5; EIMS (relative intensity): *m/z* 222 (M^+, 10), 207 (24), 161 (38), 142 (100), 114 (20), 80 (25), 41 (30).

2, 2, 4-Trimethyl-2, 3-dihydro-8-nitro-1*H*-1, 5-benzodiazepine (3k): Pale yellow solid; Mp. 113-114 ^{o}C; IR (KBr): 3280, 1645, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.90 (s, 6H), 2.95 (s, 3H), 3.20 (s, 2H), 7.15-7.20 (s, 1H), 8.00-8.15 (m, 1H), 8.75-8.80 (m, 1H); ^{13}C NMR (proton decoupled**,** $CDCl_3$, 75 MHz): δ 29.9, 30.2, 45.6, 60.8, 118.3, 121.2, 126.2, 132.4, 137.9, 145.2, 170.7; EIMS (relative intensity): *m/z* 233 (M^+, 30), 218 (100), 177 (48), 172 (48), 131 (30), 90 (40), 63 (45).

2-Methyl-2, 4-diphenyl-2, 3-dihydro-8-nitro-1*H*-1, 5-benzodiazepine (3l): Yellow solid; Mp. 103-104 ^{o}C; IR (KBr): 3220, 1610, 1630 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.40 (s, 3H), 1.80 (s, 3H), 3.10 (d, 1H, *J* = 15.3 Hz), 3.35 (d, 1H, *J* = 15.3 Hz), 4.41 (br s, 1H, NH), 6.80 (d, 1H, *J* = 11.5 Hz), 7.20-7.45 (m, 8H), 7.63 (d, 2H, *J* = 7.6 Hz), 7.95 (d, 1H, *J* = 6.0 Hz), 8.28 (d, 1H, *J* = 1.9 Hz); EIMS (relative intensity): *m/z* 359 (M^+, 40), 345 (10), 282 (25), 241 (100), 192 (10), 130 (30), 119 (35), 78 (15), 57 (30).

10-Spirocyclopentane-1, 2, 3, 9, 10, 10a-hexahydrobenzo [*b*] cyclopenta [*e*] [1, 4] diazepine (5m): Yellow solid; Mp. 137-138 ^{o}C; IR (KBr): 3338, 1659, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$**,** 200 MHz): δ 1.30-1.90 (m, 12H), 2.30-2.60 (m, 3H), 4.50 (br s, NH, 1H), 6.70-7.39 (m, 1H); ^{13}C NMR (proton decoupled**,** $CDCl_3$, 50 MHz): δ 23.4, 24.1, 24.3, 28.7, 33.4, 38.5, 39.2, 54.4, 67.3, 118.6, 119.3, 126.9, 132.1, 139.2, 143.4, 178.0; EIMS (relative intensity): *m/z* 240 (M^+); Anal. Calcd for $C_{16}H_{20}N_2$ (240.347): C, 79.96; H, 8.39; N, 11.66. Found: C, 79.54; H, 8.21; N, 11.47.

10-Spirocyclohexane-2, 3, 4, 11, 11a-hexahydro-1*H*-dibenzo [*b, e*] [1, 4] di azepine (5n): Pale yellow solid; Mp. 136-137 ^{o}C; IR (KBr): 3290, 1640, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.23-1.85 (m, 16H), 2.30-2.70 (m, 3H), 4.45 (br s, NH, 1H), 6.65-7.35 (m, 4H); ^{13}C NMR (proton decoupled**,** $CDCl_3$, 50 MHz): δ 21.6, 21.7, 23.2, 24.5, 25.3, 33.2, 34.4, 39.3, 40.5, 52.4, 63.1, 121.3, 121.5, 126.3, 129.6, 138.1, 142.6, 178.9; EIMS (relative intensity): *m/z* 268 (M^+); Anal. Calcd for $C_{18}H_{24}N_2$ (268.401): C, 80.55; H, 9.01; N, 10.44; Found: C, 80.26; H, 9.54; N, 10.31.

10-Spirocycloheptane-6, 7, 8, 9, 10, 10a, 11, 12 octahydrobenzo [*b*] cyclo hepta [*e*] [1,4] diazepine (5o): Pale yellow solid; Mp. 135-136 ^{o}C; IR (KBr): 3320, 3275, 1630, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.90-1.95 (m, 20H), 2.25-2.95 (m, 3H), 3.60 (br s, NH, 1H), 6.60-7.38 (m, 4H); ^{13}C NMR (proton decoupled**,** $CDCl_3$, 50 MHz): δ 22.5, 23.2, 26.5, 28.4, 28.9, 29.5, 29.7, 30.1, 38.2, 38.5, 40.9, 54.3, 72.5, 121.3, 121.6, 125.5, 127.6, 137.5, 139.8, 179.1; EIMS (relative intensity): *m/z* 296 (M^+); Anal. Calcd for $C_{20}H_{28}N_2$ (296.455): C, 81.03; H, 9.52; N, 9.45; Found: C, 81.26; H, 9.73; N, 9.91.

11-Spirocyclohexane-2,3,4,10,11,11a-hexahydro-8-methyl-1*H*-dibenzo [*b, e*] [1, 4] diazepine (5p): Pale yellow liquid; IR (KBr): 3305, 1660, 1597 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.20-1.80 (m, 16H), 2.25 (s, 3H), 2.30-2.70 (m, 3H), 4.50 (br s, 1H, NH), 6.70 (d, 1H, *J* = 8.1 Hz), 7.20 (d, 1H, *J* = 8.1 Hz); ^{13}C NMR (proton decoupled**,** $CDCl_3$, 50 MHz): δ 20.2, 20.8, 23.6, 26.5, 27.5, 33.2, 34.8, 43.9, 47.6, 113.4, 123.6, 127.5, 128.6, 132.8, 134.1, 164.8; EIMS (relative intensity): *m/z* 281 (M^+, 15), 199 (30), 142 (20), 98 (10), 71 (35), 43 (100).

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