Indium(III) Bromide: A Novel and Efficient Reagent for the Rapid Synthesis of 1,5-Benzodiazepines under Solvent-Free Conditions

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Abstract: *o*-Phenylenediamines (OPDA) undergo rapid condensation with ketones having hydrogens at the α-position in the presence of 10 mol% indium(III) bromide under extremely mild reaction conditions to afford the corresponding 1,5-benzodiazepines in excellent yields with high selectivity. The remarkable features of this new procedure are high conversions, short reaction times, cleaner reaction profiles, high regioselectivity in the case of unsymmetrical ketones, solvent-free conditions, and simple experimental and work-up procedures. This method works well for both electron-rich as well as electron-deficient *o*-phenylenediamines.

Keywords: indium, ketones, heterocycles, benzodiazepines, solvent-free reaction, drugs

Benzodiazepines are a very important class of compound in the field of drugs and pharmaceuticals.[1] Many members of diazepine family are nowadays widely used as anticonvulsant, antianxiety, analgesic, sedative, antidepressive, and hypnotic agents.[2] Benzodiazepine derivatives also find commercial use as dyes for acrylic fibers[3] and as anti-inflammatory agents.[4] In addition, 1,5-benzodiazepines are key intermediates for the synthesis of various fused ring compounds such as triazolo-, oxadiazolo-, oxazino-, or furano-benzodiazepines.[5] Thus, the preparation of this heterocyclic nucleus is of much current importance. Consequently, numerous methods have been reported for the preparation of benzodiazepines.[6] Of these methods, the acid catalyzed condensation of *o*-phenylenediamines with ketones is one of the most simple and straightforward approaches for the synthesis of benzodiazepines.[7] A variety of reagents such as $BF_3{\cdot}OEt_2$, $NaBH_4$, polyphosphoric acid–SiO_2, MgO–$POCl_3$, Yb(OTf)$_3$, Al_2O_3–P_2O_5, HOAc–microwave, SO_4^{2-}–ZrO_2, and 1-butyl-3-methylimidazolium bromide ([bmim]Br) have been employed to accomplish this transformation.[7,8] However, many of these methods involve the use of strong acids, high temperature conditions and extended reaction times, and also entail several side reactions resulting in low yields of products. Due to their wide range of biological, industrial, and synthetic applications, the synthesis of benzodiazepines has recently received renewed interest of researchers for the discovery of improved protocols and still awaits further developments towards milder and high-yielding approaches.

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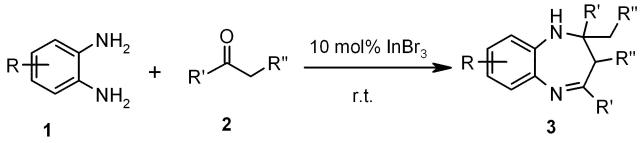
In recent years, indium halides have emerged as mild and water-tolerant Lewis acids imparting high regio-, chemo- and stereoselectivity in various functional group transformations.[9] Compared to conventional Lewis acids, particularly, indium tribromide has advantages of low catalyst loading, moisture stability and catalyst recycling. Recently, indium tribromide has been shown to be the most efficient catalyst over conventional Lewis acids in promoting various transformations including glycosidation, thioacetalization, cyanation of ketones and conjugate addition reactions.[10] However, there are no examples of the use of indium tribromide as a catalyst for the preparation of benzodiazepines.

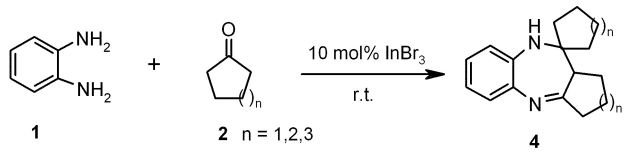
In view of the recent surge in the activity of indium reagents as mild and water-tolerant Lewis acids,[11] we wish to disclose a novel protocol for the rapid synthesis of a variety of biologically significant 1,5-benzodiazepines using a catalytic amount of indium(III) bromide under extremely mild conditions (Scheme 1).



Scheme 1

For instance, treatment of *o*-phenylenediamine with acetone in the presence of 10 mol% indium(III) bromide for 1.5 h afforded 2,3-dihydro-2,2,4-trimethyl-1*H*-1,5-benzo[*b*][1,4]diazepine in 95% yield. Similarly, various ketones such as acetophenone, 2-butanone, isobutyl methylketone, and 3-pentanone reacted smoothly with *o*-phenylenediamines under similar reaction conditions to give the corresponding 1,5-benzodiazepines in 79–96% yields. Several pharmacologically relevant 1,5-benzodiazepines were prepared by using this procedure (Table 1). This method is even effective for the preparation of benzodiazepines from electron-deficient *o*-phenylenediamines (entries k and l, Table 1). Interestingly, cyclic ketones such as cyclopentanone, cyclohexanone and cycloheptanone also worked well with similar success to afford fused ring 1,5-benzodiazepines in high yields (entries h, m, n, o Table 1, Scheme 2).

In all cases, the reactions are clean and are completed within 1.5–3.5 h. The reactions proceeded well at room temperature under solvent-free conditions. The crude



Scheme 2

products were purified by recrystallization from diethyl ether–hexane or by silica gel column chromatography. All the products were characterized by ^{1}H, ^{13}C NMR, IR, and mass spectral analysis and also by comparison with authentic samples.[7,8] The efficacy of various Lewis acids such as $InBr_3$, $CeCl_3 \cdot 7\ H_2O$, $BiCl_3$, $In(OTf)_3$, $Cu(OTf)_2$, $Sc(OTf)_3$ and $Bi(OTf)_3$ was studied for this conversion. Among these Lewis acids, $InBr_3$ was found to be superior in terms of conversion and reaction rates (Table 2). Although the reactions also proceeded with $InCl_3$, high catalyst loading (20 mol%) and longer reaction times (5–8 h) are typical to achieve comparable yields to those obtained with 10% of $InBr_3$. The scope and generality of this process is illustrated with respect to various *o*-phenylenediamines and a wide range of ketones and the results are presented in the Table 1. This method offers several advantages such as high conversions, short reaction times, cleaner reaction profiles, high regioselectivity in the case of unsymmetrical ketones, solvent-free conditions, simple experimental and work-up procedures.

In summary, we describe a novel and efficient protocol for the synthesis of 2,3-dihydro-1*H*-1,5-benzodiazepines from *o*-phenylenediamines and ketones having hydrogens at the α-position using air and water-tolerant indium(III) bromide as a catalyst in solvent-free conditions. This method is very useful to prepare a wide variety of biologically potent 1,5-benzodiazepines under extremely mild conditions.

Mps are uncorrected. TLC was performed using precoated silica gel 60 F_{254} (0.25 mm) glass plates. Chromatography was performed using silica gel (100–200 mesh). IR spectra were recorded neat on refractive spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 200 MHz. Chemical shifts are given in ppm with respect to internal TMS, and *J* values are quoted in Hz. Mass spectra were recorded at 70 eV.

2,3-Dihydro-1,5-benzodiazepines; General Procedure

A mixture of *o*-phenylenediamine (1 mmol), ketone (2.5 mmol), and $InBr_3$ (0.1 mmol) or $InCl_3$ (0.2 mmol) was stirred at r.t. for the appropriate time (Table 1). After completion of the reaction, as indicated by TLC, the reaction mixture was diluted with H_2O and extracted with EtOAc (2 × 10 mL). The combined organic layers were dried (Na_2SO_4), concentrated in vacuo and the resulting product was directly charged on small silica gel column (EtOAc–*n*-hexane) to afford pure diazepine. The products thus obtained were characterized by comparison of their NMR, IR, mass, TLC, mixed TLC analysis and physical data with authentic samples. The spectral data of all the products were identical with those of authentic samples.[6–8] The reactions have also been carried out in both CH_2Cl_2 and MeCN, and the latter was found to give the best results.

2,2,4-Trimethyl-2,3-dihydro-1*H*-1,5-benzodiazepine (3a)

Light yellow crystals; mp 136–138 °C.

IR (KBr): 3340, 1650, 1600 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.35 (s, 6 H), 2.20 (s, 2 H), 2.35 (s, 3 H), 2.95 (br s, 1 H, NH), 6.65–7.3 (m, 4 H).

^{13}C NMR (proton decoupled, 50 MHz, $CDCl_3$): 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* (% relative intensity) = 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 °C.

IR (KBr): 3325, 1635, 1598 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.80 (s, 3 H), 2.95 (d, 1 H, *J* = 12.8 Hz), 3.15 (d, 1 H, *J* = 12.8 Hz) 3.45 (br s, NH), 6.55–7.0 (m, 3 H), 7.15–7.35 (m, 7 H), 7.55–7.65 (m, 4 H).

^{13}C NMR (proton decoupled, $CDCl_3$): δ = 29.7, 42.9, 73.3, 121.2, 121.4, 125.2, 126.1, 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)

Yellow solid, mp 137–139 °C.

IR (KBr): 3329, 1637, 1605 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.99 (t, 3 H, *J* = 6.9 Hz), 1.25 (t, 3 H, *J* = 7.0 Hz), 1.70 (q, 2 H, *J* = 6.9 Hz), 2.15 (m, 2 H), 2.35 (s, 3 H), 2.69 (q, 2 H, *J* = 7.0 Hz), 3.25 (br s, 1 H, NH), 6.78–7.35 (m, 4 H).

^{13}C NMR (proton decoupled, 50 MHz, $CDCl_3$): δ = 8.7, 10.8, 26.9, 35.5, 35.7, 42.1, 70.5, 121.8, 125.4, 126.2, 127.0, 137.9, 140.8, 175.6.

EIMS: *m*/*z* = 216 (M^+, 15), 141(5), 108 (100), 80 (38), 40 (75).

2,2,4-Triethyl-3-methyl-2,3-dihydro-1*H*-1,5-benzodiazepine (3d)

Colorless solid; mp 143–144 °C.

IR (KBr): 3320, 1638, 1596 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 0.75–1.05 (m, 10 H), 1.20–1.38 (m, 4 H), 1.50–1.65 (m, 2 H), 2.40–2.60 (m, 2 H), 2.87 (q, 1 H, *J* = 6.9 Hz), 3.75 (br s, 1 H, NH), 6.57 (d, 1 H, *J* = 8.0 Hz), 6.65 (t, 1 H, *J* = 8.0 Hz), 6.90 (t, 1 H, *J* = 8.0 Hz), 7.38 (d, 1 H, *J* = 8.0 Hz).

^{13}C NMR (proton decoupled, 50 MHz, $CDCl_3$): 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 (25), 215 (100).

2-Methyl-2,4-diisobutyl-2,3-dihydro-1*H*-1,5-benzodiazepine (3e)

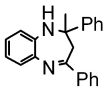
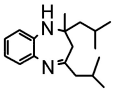
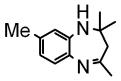
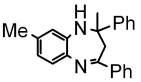
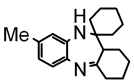
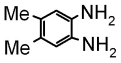
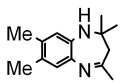
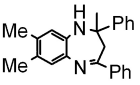
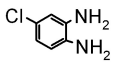
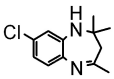
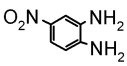
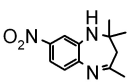
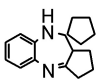
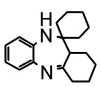
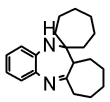
Light yellow solid; mp 118–120 °C.

IR (KBr): 3320, 1650, 1599 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.95–1.05 (m, 12 H), 1.32 (s, 3 H), 1.49–1.52 (m, 2 H), 1.65–1.75 (m, 1 H), 2.05–2.25 (m, 3 H), 2.24 (d, 2 H, *J* = 12.7 Hz), 6.60–6.65 (m, 1 H), 6.85–6.95 (m, 2 H), 7.05–7.15 (m, 1 H).

^{13}C NMR (proton decoupled, 50 MHz, $CDCl_3$): 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.

Table 1 Indium(III) Halide-Promoted Synthesis of 1,5-Benzodiazepines

Entry	Diamine	Ketone	Product[a]	Conversion[b]	$InBr_3$ (10%)		$InCl_3$ (20%)	
					Time (h)	Yield (%)[c]	Time (h)	Yield (%)[c]
a				100	1.5	95	5.0	91
b	"			96	2.5	89	6.5	85
c	"			100	1.5	91[d]	6.0	87[d]
d	"			100	2.0	94	5.5	90
e	"			97	2.5	87[d]	6.5	75[d]
f				100	1.5	96	4.0	92
g	"			98	2.0	90	6.0	82
h	"			99	2.5	86	5.0	80
i				100	1.5	97	5.0	92
j	"			98	2.5	88	6.5	83
k				100	2.0	93	5.0	89
l				99	3.0	85	6.0	76
m				96	2.5	83	6.5	72
n	"			99	3.0	85	6.0	79
o	"			97	3.5	79	8.0	70

[a] All products were reported previously in literature.[6–8,]
[b] Conversions were determined by GC analysis.
[c] Yield refers to the isolated pure products after column chromatography.
[d] The other regioisomer (5–7%) was observed by NMR.

Table 2 Comparison of Indium(III) Bromide with Various Lewis Acids

Entry	Diamine	Ketone	Catalyst	Product[a]	Time (h)	Yield (%)[b]
1			10% $InBr_3$		1.5	95
2	"		20% $InCl_3$		5.0	91
3	"		20%$CeCl_3 \cdot 7H_2O$		24	60
4	"		20% $BiCl_3$		3.0	75
5	"		10% $In(OTf)_3$		6.0	82
6	"		10% $Cu(OTf)_2$		8.0	75
7	"		10% $Sc(OTf)_3$		6.0	86
8	"		10% $Bi(OTf)_3$		5.0	89

[a] All products were characterised by ^1H NMR
[b] Yield refers to pure products after column chromatography.

EIMS: *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)
Solid; mp 127–129 °C.

IR (KBr): 3325, 1665, 1600 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.30 (s, 6 H), 2.19 (s, 2 H), 2.23 (s, 3 H), 2.80 (s, 3 H), 6.65–6.75 (s, 1 H), 6.70–6.80 (1 H), 7.05–7.10 (m, 1 H).

^{13}C NMR (proton decoupled, 75 MHz, $CDCl_3$): 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, 174.3.

EIMS: *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 °C.

IR (KBr): 3315, 1657, 1600 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.80 (s, 3 H), 2.41 (s, 3 H), 2.98 (d, 1 H, *J* = 12.7 Hz), 3.15 (d, 1 H, *J* = 12.7 Hz), 3.50 (br s, 1 H, NH), 6.70–7.69 (m, 13 H).

^{13}C NMR (proton decoupled, 50 MHz, $CDCl_3$): δ = 20.6, 28.5, 45.8, 51.2, 113.5, 125.5, 126.4, 127.3, 128.1, 128.3, 128.6, 128.8, 129.1, 130.9, 131.2, 134.0, 136.8, 164.8.

EIMS: *m*/*z* = 326 (M^+, 10), 261 (100), 246 (90), 206 (40), 145 (50), 102 (35), 76 (30).

11-Spirocyclohexane-2,3,4,10,11,11a-hexahydro-8-methyl-1*H*-dibenzo[*b*,*e*][1,4] diazepine (4h)
Pale yellow liquid.

IR (KBr): 3305, 1660, 1597 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.20–1.80 (m, 16 H), 2.25 (s, 3 H), 2.30–2.70 (m, 3 H), 4.50 (br s, 1 H, NH), 6.40 (s, 1 H), 6.70 (d, 1 H, *J* = 8.1 Hz), 7.20 (d, 1 H, *J* = 8.1 Hz).

^{13}C NMR (proton decoupled, 50 MHz, $CDCl_3$): 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: *m*/*z* = 281 (M^+, 15), 199 (30), 142 (20), 98 (10), 71 (35), 43 (100).

2,2,4-Trimethyl-2,3-dihydro-7,8-dimethyl-1*H*-1,5-benzodiazepine (3i)
Yellow solid; mp 112–114 °C.

IR (KBr): 3290, 1635, 1597 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.35 (s, 6 H), 2.19 (s, 3 H), 2.20 (s, 3 H) 2.22 (s, 2 H), 2.34 (s, 3 H), 2.80 (br s, NH, 1 H), 6.52 (s, 1 H), 6.39 (s, 1 H).

^{13}C NMR (proton decoupled, 75 MHz, $CDCl_3$): 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 (3j)
Solid, mp 115–116 °C.

IR (KBr): 3285, 1635, 1609 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.70 (s, 3 H), 2.25 (s, 6 H), 2.90 (d, 1 H, *J* = 12.8 Hz), 3.10 (d, 1 H, *J* = 12.8 Hz), 3.45 (br s, NH), 6.60 (s, 1 H), 7.15 (s, 1 H), 7.30–7.18 (m, 6 H), 7.50–7.60 (m, 4 H).

^{13}C NMR (proton decoupled, $CDCl_3$): δ = 18.6, 19.3 29.7, 43.2, 73.0, 122.3, 125.4, 126.8, 126.9, 127.8, 128.2, 129.3, 129.4, 129.6, 134.8, 135.7, 137.6, 139.7, 147.8, 166.8.

EIMS: *m*/*z* = 340 (M^+), 195, 103, 77, 65.

2,2,4-Trimethyl-2,3-dihydro-8-chloro-1*H*-1,5-benzodiazepine (3k)
Pale yellow solid; mp 90–92 °C.

IR (KBr): 3283, 1649, 1597 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27 (s, 6 H), 2.23 (s, 2 H), 2.26 (s, 3 H), 5.58–6.60 (s, 1 H), 6.86–6.90 (s, 1 H), 6.98–7.05 (s, 1 H).

^{13}C NMR (proton decoupled, 75 MHz, $CDCl_3$): 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: *m*/*z* = 222 (M^+ 10), 207 (24), 167 (38), 142 (100), 114 (20), 80 (25), 41 (30).

2,2,4-Trimethyl-2,3-dihydro-8-nitro-1*H*-1,5-benzodiazepine (3l)
Pale yellow solid; mp 113–114 °C.

IR (KBr): 3280, 1645, 1600 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.90 (s, 6 H), 2.95 (s, 3 H), 3.20 (s, 2 H), 7.15–7.20 (s, 1 H), 8.0–8.15 (m, 1 H), 8.75–8.80 (m, 1 H).

^{13}C NMR (proton decoupled, 75 MHz, $CDCl_3$): δ = 29.9, 30.0, 30.2, 45.6, 60.8, 118.3, 121.2, 126.2, 132.4, 137.9, 145.2, 170.7.

EIMS: *m*/*z* = 233 (M^+ 30), 218 (100), 177 (48), 172 (48), 131 (30), 90 (40), 63 (45).

10-Spirocyclopentane-1,2,3,9,10,10a-hexahydrobenzo[*b*]cyclopenta[*e*][1,4]diazepine (4m)
Yellow solid; mp 137–138 °C.

IR (KBr): 3338, 1659, 1600 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.30–1.90 (m, 12 H), 2.30–2.60 (m, 3 H), 4.50 (br s, NH, 1 H), 6.70–7.39 (m, 4 H).

^{13}C NMR (proton decoupled, 50 MHz, $CDCl_3$): 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: *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-2,3,4,10,11,11a-hexahydro-1*H*-dibenzo[*b*,*e*][1,4]diazepine (4n)
Pale yellow solid; mp 136–137 °C.

IR (KBr): 3290, 1640, 1600 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.23–1.85 (m, 16 H), 2.30–2.70 (m, 3 H), 4.45 (br s, 1 H, NH), 6.65–7.35 (m, 4 H).

^{13}C NMR (proton decoupled, 50 MHz, $CDCl_3$): 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: *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-Spirocycloheptan-6,7,8,9,10,10a,11,12-octahydrobenzo[*b*]cyclohepta[*e*] [1,4]diazepine (4o)
Pale yellow solid; mp 135–136 °C.

IR (KBr): 3320, 3275, 1630, 1600 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.90–1.95 (m, 20 H), 2.25–2.95 (m, 3 H), 3.60 (br s, NH, 1 H), 6.60–7.38 (m, 4 H).

^{13}C NMR (proton decoupled, 50 MHz, $CDCl_3$): 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: *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, 81.29; H, 9.73; N, 9.91.

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