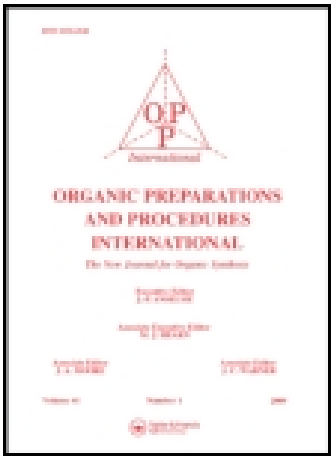

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An Efficient Synthesis of N-Alkyl-N-arylputrescines and Cadaverines

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An Efficient Synthesis of *N*-Alkyl-*N*-arylputrescines and Cadaverines

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N-Substituted 1,4-diaminobutane (*putrescine*) and 1,5-diaminopentane (*cadaverine*) derivatives are of biochemical and pharmacological interest as synthetic analogs of natural polyamines.[1] Several derivatives have been reported to act as antibiotic, anti-neoplastic, anti-parasitic agents, and NMDA or cholinergic modulators.[2–8] In addition, such compounds represent key intermediates for acyclic and heterocyclic polyamine derivatives.[9–12]

The methods usually employed for the synthesis of symmetrically *N,N′*-disubstituted 1,*n*-diamines involve functionalization of the parent diamine but cannot be applied to unsymmetrical derivatives, which require more elaborate strategies.[9,13–15] In particular, selectively *N*-substituted putrescines and cadaverines present a challenge, since the available methods for di- and trimethylenediamines are not generally suitable for their higher homologues. Several preparations of *N*-alkyl tetra and pentamethylenediamines have already been described,[16–18] but very few general methods are available for *N*-aryl derivatives.[19–21] The literature regarding *N*-alkyl-*N*-arylputrescines and cadaverines **1** is even scarcer. Recently, Ramírez *et al.* reported the synthesis of two derivatives, by a three-step strategy starting from $\omega-$haloalkanoyl chlorides,[21] in which the substituted amino group is generated from an amide, while the primary amine results from reduction of an azide.[22]

N-Alkylation is conceptually the most straightforward disconnection towards secondary and tertiary amines.[23] Although this transformation seems rather simple, the fact that the newly formed amines are also nucleophilic brings about the formation of *bis*- and/or *poly*alkylation by-products. Thus, the crude reaction mixture often contains the desired product together with the starting amine and variable amounts of collateral products, all of them with similar R_f values, a fact that complicates the chromatographic purification of the desired compounds. In this context, new methodologies combining operational simplicity, high yields, readily available starting materials and low cost reagents are desirable

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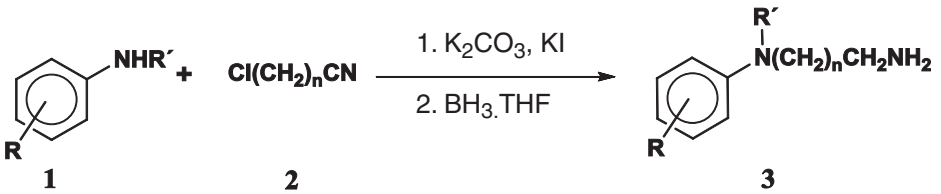
for the high throughput preparation of the target compounds. This work describes a practical method for the synthesis of tertiary *N*-alkyl-*N*-aryltetra- and pentamethylenediamines **3**, by selective monoalkylation of *N*-alkylanilines with $\omega-$haloalkylnitriles followed by reduction. The optimized reaction conditions resulted in an efficient procedure, of remarkable selectivity in the alkylation step and high overall yields of the diamines.

We first examined the synthesis of *N*-methyl-*N*-phenylputrescine (**3a**) using different reaction conditions for the *N*-alkylation step. The starting conditions were chosen on the basis of previous reports on the selective alkylation of amines[19,24–26] using equimolar amounts of the reagents, DMF as the solvent, Cs_2CO_3 as the base, and KI (2 equiv.). Under these conditions, the *N*-alkylated product **3a** was obtained in 60% yield. Reduction of the intermediate aminonitrile with BH_3.THF (81%) led to *N*-methyl-*N*-phenylputrescine (**3a**, 49% overall yield from **1a**). A significant improvement in the yield of the first step (74%) was observed employing K_2CO_3 instead of cesium carbonate as the base (60% overall yield). Furthermore, TLC analysis of the crude amination product showed the absence of any *bis*-alkylation product, thus allowing for its reduction without previous purification. This led to a further increase in the overall yield (78%), and considerable simplification of the whole procedure. In fact, the small R*f* difference between *N*-methylaniline and the aminonitrile complicates its chromatographic purification. In contrast, the crude reduction product contained only the starting arylamine and the desired compound **3a** ($\Delta Rf > 0.6$, dichloromethane), and was easily purified by short-column filtration. On changing the molar ratio arylamine:halonitrile from 1:1 to 2:1, a further improvement in the overall yield to 83% was observed. The unreacted arylamine was recovered quantitatively after BH_3.THF treatment.

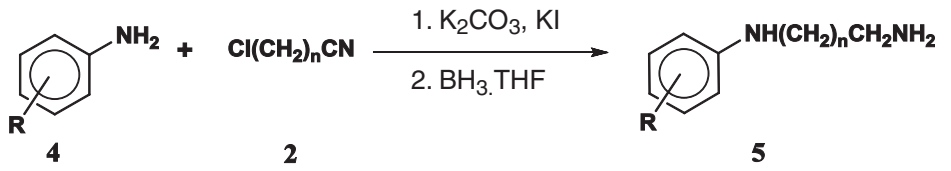
The use of the optimized experimental conditions (*Scheme 1*) allowed the preparation of a series of *N*-aryl-*N*-alkylcadaverines and putrescines **3b-m** in high overall yields, as shown in *Table 1*.



a) R = H, R′ = Me, n = 3. b) R = H, R′ = Et, n = 3. c) R = H, R′ = iPr, n = 3. d) R = 4-Cl, R′ = Et, n = 3. e) R = 4-Me, R′ = Et, n = 3. f) R = 2-Me, R′ = Et, n=3. g) R = H, R′ = Ph, n=3. h) R = H, R′ = Me, n=4. i) R = H, R′ = Et, n=4. j) R = H, R′ = iPr, n=4. k) R = 4-Cl, R′ = Et, n=4. l) R = 4-Me, R′ = Et, n=4. m) R = 2-Me, R′ = Et, n = 4.

Scheme 1

The results obtained for tertiary amines **3**, prompted us to examine the synthesis of compounds **5** (*Scheme 2*) using the improved experimental protocol (Table 2). Due to the higher reactivity of primary arylamines, a 4:1 mixture of DME:DMF was used as the solvent in the first step. Also in this case, the complete selectivity of the *N*-monoalkylation step allowed for the reduction of the crude amination products without purification.



(a) R = H, n = 3. (b) R = 2-Me, n = 3. (c) R = 4-Cl, n = 3. (d) R = 4-Br, n = 3. (e) R = 4-F, n = 3. (f) R = 4-NO_2, n = 3. (g) R = H, n = 4. (h) R = 2-Me, n = 4. (i) R = 4-Me, n = 4. (j) R = 4-Cl, n = 4. (k) R = 4-Br, n = 4. (l) R = 4-F, n = 4.

Scheme 2

Table 1
Synthesis of *N*-Alkyl-*N*-arylputrescines and Cadaverines **3**

Cmpd	Yield (%)	mp (°C)	lit. mp. (°C)	Temp. (°C)
3a	83	pale yellow oil	oil[a]	100
3b	75	pale yellow oil	—	100
3c	71	pale yellow oil	—	100
3d	64	light brown oil	—	110
3e	73	pale yellow oil	—	100
3f	70	pale yellow oil	—	110
3g	8	pale yellow oil	—	110
3h	87	pale yellow oil	oil[a]	100
3i	83	pale yellow oil	oil[b]	100
3j	77	pale yellow oil	—	100
3k	69	light brown oil	—	110
3l	75	pale yellow oil	—	100
3m	71	pale yellow oil	—	110

(a) Lit. mps. from ref. 21. (b) Lit. mp. from ref. 27.

These results (*Table 2*) constitute a remarkable improvement (about 20% average) in the yields of compounds **5** compared to those obtained under our previous conditions,[19] which involved a two-step procedure and equimolar amounts of the reagents, DMF as the solvent, Cs_2CO_3 as the base, KI (2 equivalents) for the amination reaction followed by chromatographic purification and subsequent reduction.[19] The present method is also advantageous with respect to the alternative synthetic approaches described in the literature,[20,21] leading to improved yields in a minimum number of steps.

In conclusion, we have developed an efficient protocol for the high throughput synthesis of tertiary *N*-arylputrescines and cadaverines, which are potentially bioactive as synthetic analogs of the natural polyamines. The sequence employs readily available and inexpensive starting materials, and involves two steps and one column purification. It represents an advantageous alternative to other synthetic approaches[21] regarding yields, number of steps and operational simplicity. The method was successfully adapted to the preparation of

Table 2
Synthesis of *N*-Arylputrescines and Cadaverines **5**

Cmpd	Yield[a] (%)	mp. (°C)	lit. mp. (°C)	Temp. (°C)
5a	92 (55)	light brown oil	oil[b]	100
5b	78 (59)	light brown oil	oil[b]	95
5c	69 (62)	light brown oil	—[c]	100
5d	74 (51)	pale yellow oil	oil[b]	100
5e	78 (54)	light brown oil	oil[b]	95
5f	46 (—)	101–102, orange solid	101[c]	100
5g	71 (53)	light brown oil	oil[b]	100
5h	72 (46)	light brown oil	oil[b]	95
5i	71 (58)	light brown oil	—[c]	85
5j	69 (55)	90–92, pale yellow solid	—[c]	100
5k	73 (49)	pale yellow oil	oil[b]	100
5l	71 (—)	light brown oil	oil[d]	95

(a) Yields from ref. 19 in parenthesis. (b) Lit. mps. from ref. 19. (c) Lit. mps. from ref. 20. (d) Lit. mps. from ref. 21.

N-arylputrescines and cadaverines **5**, key intermediates in the preparation of acyclic and heterocyclic 1,*n*-diamine derivatives.

Experimental Section

^{1}H NMR spectra were recorded on a 500 MHz Bruker Avance II 500 spectrometer, in $CDCl_3$. Chemical shifts are reported in δ (ppm) relative to TMS as an internal standard and coupling constants are given in Hz. Elemental analyses were determined using an Exeter CE 440 elemental analyzer. IR spectra were obtained as films on a Perkin-Elmer Spectrum One FT-IR spectrometer. Reagents, solvents and starting materials were purchased from standard sources and purified according to literature procedures.[29] Potassium iodide was dried (2 h, 120°C) prior to use.

Two-step Procedure for the Synthesis of N-methyl-N-phenyl-1,4-butanediamine (3a)

N-Methyl-N-phenyl-4-aminobutyronitrile

A solution of 4-chlorobutyronitrile (258.8 mg, 2.5 mmol) in dimethylformamide (0.5 ml) was added over 1.5 h to a mixture of *N*-methylaniline (267.9 mg, 2.5 mmol), K_2CO_3 (345.5 mg, 2.5 mmol) and KI (830 mg, 5 mmol) in dimethylformamide (3 ml). The mixture was stirred 5 h at 100°C. After completion of the reaction, as indicated by TLC, the mixture was treated with ethyl ether (50 ml) and water (10 ml). The aqueous phase was separated and extracted with ethyl ether (30 ml). The combined organic layers were dried over anhydrous sodium sulfate and filtered. The solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (silica gel, hexane:chloroform 3:7) to furnish 322 mg (74%) of *N*-methyl-*N*-phenyl-4-aminobutyronitrile as a pale yellow oil. ^{1}H NMR:

δ 7.25-7.28 (2H, m), 6.74–6.77 (3H, m), 3.47 (2H, t, $J = 7.0$), 2.96 (3H, s), 2.39 (2H, t, $J = 7.0$), 1.95 (2H, p, $J = 7.0$). ^{13}C NMR: δ 148.88, 129.26, 119.33, 117.00, 112.56, 51.17, 38.68, 23.02, 14.63. IR: 2967, 2959, 2254, 1722, 1596 cm^{-1}.

Anal. Calcd for $C_{11}H_{14}N_2$: C, 75.82; H, 8.10; N, 16.08. Found: C, 75.78; H, 8.03; N, 15.98.

Under identical experimental conditions, but using Cs_2CO_3 instead of K_2CO_3 as the base, *N*-methyl-*N*-phenyl-4-aminobutyronitrile was obtained in 60% yield.

*N-Methyl-N-phenyl-1,4-butanediamine (**3a**)*

N-Methyl-*N*-phenyl-4-aminobutyronitrile (348.5 mg, 2 mmol) was treated with 1M borane/THF (30 ml). The solution was refluxed for 2 h, cooled and treated with methanol. The solvent was then evaporated *in vacuo*. The residue was refluxed with 10% hydrochloric acid (30 ml) for 2 h, filtered and made alkaline with 10% aqueous sodium hydroxide. The alkaline mixture was extracted with ethyl acetate (4 × 20 ml). The organic phase was washed with water (5 ml), dried over sodium sulfate and filtered. The solvent was evaporated *in vacuo* and the resulting crude liquid was purified by column chromatography (silica gel, dichloromethane:methanol:isopropylamine 10:1:0.1) to provide 288 mg (81%) of *N*-methyl-*N*-phenyl-1,4-butanediamine (**3a**) as a pale yellow oil. Compound **3a** has been described and its characterization data match those previously reported in the literature.[21]

General Procedure for the Synthesis of N-Alkyl-N-arylputrescines and Cadaverines (3) and N-Arylputrescines and Cadaverines (5).

A solution of the corresponding $\omega-$halonitrile (2.5 mmol) in dimethylformamide (0.5 ml) was added over 1.5 h to a mixture of the arylamine (5 mmol), K_2CO_3 (345.5 mg, 2.5 mmol) and KI (830 mg, 5 mmol) in dimethylformamide (3 ml) for compounds **1** or dimethylformamide (0.6 ml) and dimethoxyethane (2.4 ml) for compounds **4**. The mixture was stirred at the indicated temperature for 5 h. After completion of the reaction, as indicated by TLC, the mixture was diluted with ethyl ether (50 ml) and water (10 ml). The aqueous phase was separated and additionally extracted once with ethyl ether (30 ml). The combined organic layers were washed with water, dried over anhydrous sodium sulfate and filtered. The filtrate was evaporated *in vacuo* and the resulting crude material was dissolved in tetrahydrofuran and treated with 1M borane/THF (30 ml). The solution was refluxed for 2 h, cooled and treated with methanol. The solvent was then evaporated *in vacuo*. The residue was refluxed with 10% hydrochloric acid (30 ml) for 2 h, filtered and made alkaline with 10% aqueous sodium hydroxide. The alkaline mixture was extracted with ethyl acetate (4 × 20 ml). The organic phase was washed with water (5 ml), dried over sodium sulfate and filtered. The solvent was evaporated *in vacuo* and the crude product was purified by column chromatography (silica gel, dichloromethane:methanol:isopropylamine 10:1:0.1).

Compounds **3h**,[21] **3i**,[27] **5a, 5b, 5d, 5e**, 5**h**,[19] **5c**, **5h, 5i**, **5j**,[20] **5k**,[11] **5l**,[20] **5f**[28] have been described in the literature, and their physical and spectroscopic data match those previously reported in the literature.[11,19–21,27,28] The characterization of new compounds is reported below.

*N-Ethyl-N-phenyl-1,4-diaminobutane (**3b**)*

This compound was obtained as a pale yellow oil. ^{1}H NMR: δ 7.20–7.25 (2H, m), 6.70-6.69 (2H, m), 6.65 (1H, tt, $J = 7.2$, 1.0), 3.38 (2H, q, $J = 7.0$), 3.28 (2H, t, $J = 7.7$), 2.74 (2H, t, $J = 7.1$), 2.01(2H, bs), 1.63 (2H, p, $J = 7.7$), 1.50–1.56 (2H, m), 1.35–1.43 (2H, m), 1.17 (3H, t, $J = 7.1$). ^{13}C NMR: δ 147.89, 129.18, 115.29, 111.77, 50.26, 44.88, 41.94, 33.22, 27.35, 24.43, 12.23.

Anal. Calcd for $C_{12}H_{20}N_2$: C, 74.95; H, 10.48; N, 14.57. Found: C, 74.82; H, 10.57; N, 14.49.

*N-Isopropyl-N-phenyl-1,4-diaminobutane (**3c**)*

This compound was obtained as a pale yellow oil. ^{1}H NMR: δ 7.22-7.26 (2H, m), 6.77 (2H, d, $J = 8.0$), 6.70 (1H, tt, $J = 7.2$, 0.9), 4.06 (1H, h, $J = 6.6$), 3.15 (2H, t, $J = 7.8$), 2.75 (2H,t,7.0), 1,73 (2H, bs), 1.58-1.64 (2H, m), 1.47–1.55 (2H, m), 1.2 (6H, d, $J = 6.6$). ^{13}C NMR: δ 148.75, 129.16, 116.2, 113.54, 48.79, 43.80, 42.08, 31.38, 26.70, 20.10. IR: 3345, 3058, 3021, 2968, 1597 cm^{-1}.

Anal. Calcd for $C_{13}H_{22}N_2$: C, 75.68; H, 10.75; N, 13.58. Found: C, 75.58; H, 10.89; N, 13.50.

*N-Ethyl-N-(4-chlorophenyl)-1,4-diaminobutane (**3d**)*

This compound was obtained as a light brown oil. ^{1}H NMR: δ 7.14 (2H, dd, $J = 9.2$, 3.5), 6.58 (2H, dd, $J = 9.2$, 3.4), 3.35 (2H, q, $J = 7.1$), 3.26 (2H, t, $J = 7.3$), 2.76 (2H, t, $J = 7.1$), 2.16 (2H, bs), 1.58–1.66 (2H, m), 1.48–1.55 (2H, m), 1.14 (3H, t, $J = 7.1$); ^{13}C NMR: δ 146.42, 128.93, 120.10, 112.98, 50.32, 45.13, 41.81, 30.69, 24.79, 12.10. IR: (3404, 2969, 2933, 2869, 1596, 1563, 1500 cm^{-1}.

Anal. Calcd for $C_{12}H_{19}ClN_2$: C, 63.56; H, 8.45; N, 12.35. Found: C, 63.46; H, 8.60; N, 12.27.

*N-Ethyl-N-(4-methylphenyl)-1,4-diaminobutane (**3e**)*

This compound was obtained as a pale yellow oil. ^{1}H NMR: δ 7.03 (2H, d, $J = 8.6$), 6.62 (2H, d, $J = 8.6$), 3.33 (2H, q, $J = 7.0$), 3.24 (2H, t, $J = 7.5$), 2.74 (2H, t, $J = 7.1$), 2.25 (3H, s), 2.06 (2H, bs), 1.58–1.65 (2H, m), 1.46-1.54 (2H, m), 1.13 (3H, t, $J = 7.0$); ^{13}C NMR: δ 145.81, 129.70, 124.80, 112.49, 50.39, 45.19, 41.92, 30.94, 24.89, 20.10, 12.21. IR: 3321, 2966, 2930, 2864, 1618, 1568 cm^{-1}.

Anal. Calcd. for $C_{13}H_{22}N_2$: C, 75.68; H, 10.75; N, 13.58. Found: C, 75.61; H, 10.88; N, 13.51.

*N-Ethyl-N-(2-methylphenyl)-1,4-diaminobutane (**3f**)*

This compound was obtained as a pale yellow oil. ^{1}H NMR: δ 7.18 (1H, d, $J = 7.5$), 7.12–7.16 (1H, m), 7.07 (1H, dd, $J = 7.8$, 1.1), 6.98 (1H, td, $J = 7.3$, 1.4), 2.95 (2H, t, $J = 7.0$)*, 2.96 (2H, q, $J = 7.1$)*, 2.65–2.67 (2H, m), 2.29 (3H, s), 2.08 (2H, bs), 1.41–1.47 (4H, m), 0.98 (3H, t, $J = 7.1$) *: overlapping signals; ^{13}C NMR: δ 149.84, 135.08, 130.84, 125.94, 123.16, 122.11, 52.60, 48.40, 41.85, 31.05, 24.70,18.24, 12.18. IR: 3346, 3017, 2967, 1597, 1491, cm^{-1}.

Anal. Calcd. for $C_{13}H_{22}N_2$: C, 75.68; H, 10.75; N, 13.58. Found: C, 75.59; H, 10.91; N, 13.50.

*N,N-Diphenyl-1,4-diaminobutane (**3g**)*

This compound was obtained as a pale yellow oil. ^{1}H NMR: δ 7.26–7.30 (4H, m), 7.00 (4H, d, $J = 7.8$), 6.96 (2H, t, $J = 7.3$), 3.73 (2H, t, $J = 7.6$), 3.42 (2H, bs), 2.77 (2H, t, $J =$ 7.2), 1.70–1.76 (2H, m), 1.57–1.63 (2H, m); ^{13}C NMR: δ 147.89, 129.25, 121.19, 120.88, 51.93, 41.38, 29.64, 24.83. IR: 3357, 3034, 2932, 1588 cm^{-1}.

Anal. Calcd. for $C_{16}H_{20}N_2$: C, 79.96; H, 8.39; N, 11.66. Found: C, 79.89; H, 8.42; N, 11.61.

*N-Isopropyl-N-phenyl-1,5-diaminopentane (**3j**)*

This compound was obtained as a pale yellow oil. ^{1}H NMR: δ 7.22–7.26 (2H, m), 6.76 (2H, d, $J = 8.0$), 6,69 (1H, tt, $J = 7.32$, 1.0), 4.06 (1H, h, $J = 6.6$), 3.14 (2H, t, $J = 7.9$), 2.74 (2H, t, $J = 7.0$), 1.77 (2H, bs), 1.58–1,64 (2H, m), 1.53 (2H, p, $J = 7.3$), 1.36–1.42 (2H, m), 1,20 (6H, d, $J = 6.6$). ^{13}C NMR: δ 148.71, 129.07, 115.95, 113.25, 48.55, 43.84, 42.07, 33.37, 29.11, 24.50, 20.01. IR: 3405, 2968, 2934, 2868, 1597 cm^{-1}.

Anal. Calcd. for $C_{14}H_{24}N_2$: C, 76.31; H, 10.98; N, 12.71. Found: C, 76.25; H, 11.10; N, 12.66.

*N-Ethyl-N-(4-chlorophenyl)-1,5-diaminopentane (**3k**)*

This compound was obtained as a light brown oil. ^{1}H NMR δ: 7.13 (2H, dd, $J = 9.2$, 3.5), 6.56 (2H, dd, $J = 9.2$, 3.5), 3.32 (2H, q, $J = 7.0$), 3.24 (2H, t, $J = 7.7$), 2.72 (2H, t, $J =$ 7.2), 2.26 (2H, bs), 1.55–1.62 (2H, m), 1.49–1.55 (2H, m), 1.32–1.39 (2H, m), 1.12 (3H, t, $J = 7.0$); ^{13}C NMR δ: 146.48, 128.92, 120.00, 112.91, 50.42, 45.09, 41.82, 32.93, 27.21, 24.38, 12.10. IR: 3422, 2970, 2934, 1636, 1596 cm^{-1}.

Anal. Calcd. for $C_{13}H_{21}ClN_2$: C, 64.85; H, 8.79; N, 11.63. Found: C, 64.79; H, 8.86; N, 11.61.

*N-Ethyl-N-(4-methylphenyl)-1,5-diaminopentane (**3l**)*

This compound was obtained as a pale yellow oil. ^{1}H NMR: δ 7.03 (2H, d, $J = 8.5$), 6.61 (2H, d, $J = 8.5$), 3.33 (2H, q, $J = 7.1$), 3.22 (2H, t, $J = 7.6$), 2.73 (2H, t, $J = 7.1$), 2.52 (2H, bs), 2.25 (3H, s), 1.56–1.62 (2H, m), 1.49-1.55 (2H, m), 1.34-1.40 (2H, m), 1.13 (3H, t, $J = 7.1$); ^{13}C NMR: δ 145.87, 129.68, 124.64, 112.36, 50.47, 45.10, 41.75, 32.87, 27.33, 24.43, 20.10, 12.20. IR: 3338, 2966, 2931, 2860, 1618 cm^{-1}.

Anal. Calcd. for $C_{14}H_{24}N_2$: C, 76.31; H, 10.98; N, 12.71. Found: C, 76.27; H, 11.07; N, 12.68.

*N-Ethyl-N-(2-methylphenyl)-1,5-diaminopentane (**3m**)*

This compound was obtained as a pale yellow oil. ^{1}H NMR: δ 7.18 (1H, d, $J = 7.6$), 7.12-7.16 (1H, m), 7.07 (1H, dd, $J = 7.8$, 1.0), 6.97 (1H, td, $J = 7.3$, 1.4), 2.95 (2H, q, J $= 7.1$)*, 2.92–2.95 (2H, m)*, 2.65 (2H, t, $J = 7.1$), 2.29 (3H, s), 2.00 (2H, bs), 1.39–1.45 (4H, m), 1.27-1.33 (2H, m), 0.98 (3H, t, $J = 7.1$); ^{13}C NMR: δ:149.98, 135.07, 130.81,

125.91, 123.09, 122.12, 52.81, 48.37, 41.96, 33.18, 27.16, 24.51, 18.24, 12.22. IR: 3422, 2969, 2939, 2858, 1639, 1598 cm^{-1}.

Anal. Calcd. for $C_{14}H_{24}N_2$: C, 76.31; H, 10.98; N, 12.71. Found: C, 76.28; H, 11.04; N, 12.69.

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