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Article

p-Nitrobenzoic Acid Promoted Synthesis of 1,5-Benzodiazepine Derivatives

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Entre vários ácidos carboxílicos testados, o ácido *p*-nitrobenzóico mostrou ser o mais versátil para a preparação de derivados de 1,5-benzodiazepinas a partir de uma série de o-fenilenodiaminas substituídas e cetonas. Os produtos foram obtidos em bons rendimentos (62-92%) sob condições brandas, usando acetonitrila como solvente, a temperatura ambiente. Adicionalmente, o reagente pode ser facilmente recuperado e re-utilizado.

p-Nitrobenzoic acid was found to be the versatile Bronsted organic acid promoter among the carboxylic acids tested for the preparation of 1,5-benzodiazepine derivatives from a wide range of substituted o-phenylenediamines and ketones. The corresponding products were obtained in good isolated yields (62-92%) under mild conditions using acetonitrile as solvent at ambient temperature. Further, the reagent could be easily recovered and reused.

Keywords: 1,5-benzodiazepines, bronsted acid, *o*-phenylenediamines and ketones, *p*-nitrobenzoic acid

Introduction

1,5-benzodiazepine derivatives have received significant attention and the core is indeed a "privileged scaffold" found in compounds active against a variety of target types including peptide hormones (such as CCK), interleukin converting enzymes (ICE) and potassium blockers (I_k).[1] More recently, the area of biological interest of 1,5-benzodiazepines has been extended to various diseases such as cancer, viral infection (non-nucleoside inhibitors of HIV-1 reverse transcriptase), cardiovascular disorders.[2] In addition, 1,5-benzodiazepines show antidepressive, antifungal, antibacterial, antifeedant, antiinflammatory, analgesic and anticonvulsant activities.[3] Besides these derivatives are also used as dyes for acrylic fibre in photography.[4] Moreover, 1,5-benzodiazepines are valuable synthons used for the preparation of other fused ring compounds such as triazolo-, oxadiazolo-, oxazino-, or furano-benzodiazepines.[5]

Despite their importance from a pharmacological, industrial and synthetic point of view, comparatively few methods for their preparation are reported in the literature, a great number of which have appeared only very recently employing BF_3-etherate, $NaBH_4$, polyphosphoric acid or SiO_2, $MgO/POCl_3$, $Yb(OTf)_3$, and $InBr_3$ as catalysts or as stoichiometric reagents.[6] However, many of these methods have some drawbacks such as low yields of the products, high temperatures, drastic reaction conditions, long reaction times, and relatively expensive reagents. From the viewpoints above, the development of environmentally benign, less expensive and easily handled promoters for the preparation of 1,5-benzodiazepines (hereafter 1,5-BDPs) is still highly desirable.

Very recently, we have reported synthesis of 1,5-BDPs using CAN as catalyst in methanol.[7] In recent years, lot of attention has been paid to organocatalysts owing to their eco-friendliness and can proceed under aerobic atmosphere, other notable advantages are: usually less expensive and commercially available.[8] Intrigued by the results achieved by Zhao *et al.*[9] in allylation of aldehydes using carboxylic acids as Bronsted organocatalysts and Gopal's report[9] which was limited only for the reaction between acetone and *o*-phenelynediamine (*o*-PD) involving supramolecular chemistry, we have undertook advantage of both the reports and tried to explore the utility of several organo acids in the preparation of various structurally and electronically divergent 1,5-BDPs.

Results and Discussion

In continuation of our efforts to develop novel synthetic routes for carbon-carbon and carbon-heteroatom bond formations and heterocycles,[10] we have studied the efficacy

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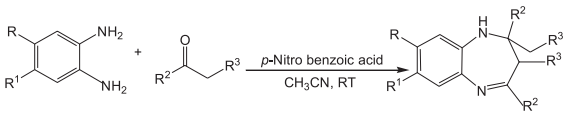
of chosen organoacids (1 equiv. as standard) for the model reaction using *o*-PD (1 mmol) and acetophenone (2.2 mmol) in acetonitrile at ambient temperature to afford the corresponding 1,5-benzodiazepine (Table 1).



R,R^1=H ; R=CH_3, R^1=H;
R=Cl, R^1=H;R=NO_2, R^1=H;
R=CH_3, R^1=CH_3; R=Cl, R^1=Cl
R=COPh, R^1=H

Scheme 1.

Among the acids screened, *p*-nitrobenzoic acid (*p*-NBA) was found to be the best promoter in terms of reaction times and yields (entry 2, Table 1). To the best of our knowledge, there are no earlier reports on the preparation of 1,5-benzodiazepines using *p*-nitrobenzoic acid (Scheme 1). The optimum yields of the product were obtained when a ratio of *o*-PD to ketone 1:2.2 is used. The reaction is found to be sluggish when carried out using even 0.5 equiv. of catalyst amounts. In all cases, the reactions are clean and are completed within 3.5-15 h. The benzodiazepines were the only products obtained and the rest of the material was essentially starting material.

Table 1. Reaction of *o*-PD with acetophenone promoted by organoacids in 1,5-benzodiazepines synthesis

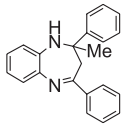
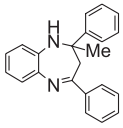
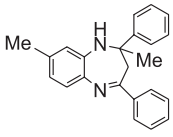
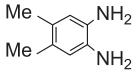
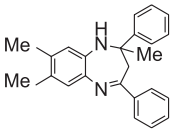
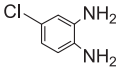
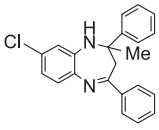
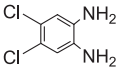
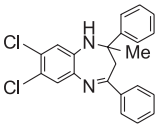
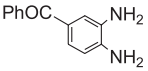
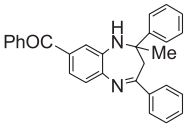
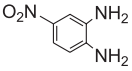
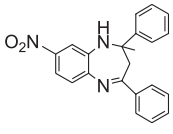
Entry	Organo acid	time/h	Yield/(%)[a]
1	benzoic acid	24	80
2	*p*-nitrobenzoic acid	07	90
3	*m*-bromobezoic acid	24	60
4	phenylacetic acid	24	80
5	mandelic acid	24	32
6	*p*-tolunesulphonic acid	72	N.R
7	cinnamic acid	24	N.R
8	anthranilic acid	24	83
9	*o*-picolinic acid	24	79
10	isonicotinic acid	24	83
11	malonic acid	24	35
12	adipic acid	12	78
13	valaric acid	24	40
14	citric acid	12	88
15	imino diacetic acid	24	N.R
16	*p*-anisic acid	24	85

[a] G.C Yield %; N.R = No Reaction.

The crude product was filtered and washed with DCM to recover the *p*-nitrobenzoic acid, the filtrate was extracted with DCM and after usual workup and further purification by silica gel column chromatography yielded the desired pure product. Furthermore, *p*-NBA could be recovered and repeated minimum three times with slight decrease in the yield (88%, 80%, 77%) due to the loss of *p*-NBA in recovery.

Encouraged by these results, at first, we studied the condensation of acetophenone with divergent *o*-PD's for the synthesis of corresponding 1,5-benzodiazepine derivatives under standardized conditions and the results were quite satisfactory (Table 2). The scope and generality of the present procedure was then extended to electronically divergent acetophenones towards *o*-PD and the results are presented in Table 3. It is interesting to note that under our optimized conditions, *exclusively one regioisomer* is favoured para position in relation to the imine moiety as confirmed by ^{1}H NMR spectroscopic data. (entries 2, 4, 6 and 7, Table 2).

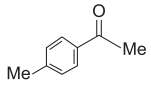
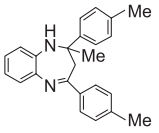
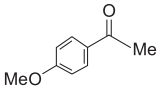
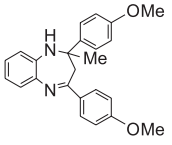
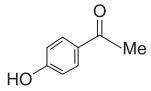
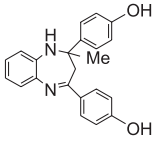
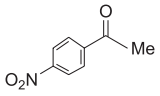
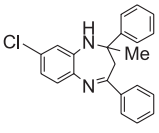
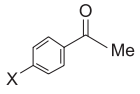
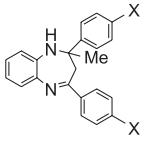
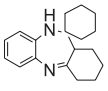
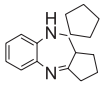
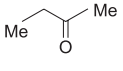
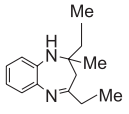
Table 2. *p*-NBA mediated synthesis of 1,5-benzodiazepines from acetophenone

Entry	Diamine	Benzodiazepine	time/h	Yields/(%)[a]
1			7	90
2			4.5	76
3			15	70
4			12	75
5			4.5	88
6			6	85
7			12	83

[a] Yields refer to the isolated pure products.

In a similar fashion, cyclic ketones such as cyclopentanone and cyclohexanone also reacted well with *o*-PD to furnish the corresponding 1,5-BDPs in good yields (entries 6-7, Table 3). In case of unsymmetrical ketones such as 2-butanone (entry 8, Table 3), the ring closure occurred selectively giving a single product.

Table 3. *p*-NBA mediated synthesis of 1,5-benzodiazepines from *o*-PD

Entry	Ketone	Benzodiazepine	time/h	Yields/(%)[a]
1			6.0	85
2			6.5	72
3			6.0	83
4			12	62
5		X=F, 5a X=Cl, 5b X=Br, 5c X=I, 5d 	5.0 4.5 5.0 4.5	86 80 72 88
6			4.5	88
7			4.0	92
8			3.5	85

[a]Yields refer to isolated pure products.

Conclusions

In conclusion, we have developed a practical and novel procedure for the synthesis of 2,3-dihydro-1H-1,5-benzodiazepine derivatives using *p*-NBA in acetonitrile. The present protocol has several advantages: mild reaction conditions (at room temperature), operational and experimental simplicity, readily availability, study of wide range of electronically divergent ketones and *o*-PDs, easily recoverable and reusable organo promoter for applicability in large scale synthesis. We believe that this *p*-NBA promoted methodology will be a valuable contribution to the existing processes in the field of synthesis of 1,5-benzodiazepines.

Experimental

General

Melting points were measured using a Buchi R-535 apparatus. IR spectra were taken on a Bruker Vector-22 spectrometer in KBr pellets and reported in cm^{-1}. ^1H NMR spectra were recorded at 300 MHz on a Bruker Avance-300 spectrometer in $CDCl_3$ with chemical shifts (δ) given relative to TMS as an internal standard. ^{13}C NMR spectra were recorded on a Bruker Avance-300 (75.5 MHz) spectrometer with complete proton decoupling; chemical shifts are reported in ppm relative to the solvent resonance as the internal standard ($CDCl_3$, δ 77.16 ppm. CHN analyses were recorded on a Vario EL analyzer.

Representative procedure

To a suspension of *p*-nitrobenzoic acid (1 mmol) in acetonitrile (3 mL) were added successively *o*-phenylenediamine (1 mmol) and acetophenone (2.2 mmol) at room temperature for the time specified in Table 2. After the reaction was over, the reaction mixture was filtered and washed with DCM to recover *p*-nitrobenzoic acid. The filtrate was extracted with DCM (20 mL) and the combined organic layer was dried over Na_2SO_4, concentrated under reduced pressure to furnish the crude product, which was purified by silica gel chromatography using EtOAc/Hexane (1:5), to afford corresponding pure product. All compounds gave satisfactory spectroscopic data in accordance to their proposed structures.

Spectral data for compounds

Entry 1, Table 2

Yellow solid. mp 150–152 °C. IR (KBr) ν_{max}/cm^{-1}: 3320, 1631, 1597. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.80 (s, 3H), 2.95 (d, 1H, *J* 12.8 Hz), 3.15 (d, 1H, *J* 12.8 Hz) 3.45 (br s, NH), 6.55–7.01 (m, 3H), 7.15–7.35 (m, 7H), 7.55–7.65 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) 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. MS (EI), *m/z* [M$^+$] = 312. Anal. Calc. for $C_{22}H_{20}N_2$: C, 84.58; H, 6.45; N, 8.97: Found: C, 84.55; H, 6.51; N, 8.94.

Entry 2, Table 2

Yellow solid. mp 92-94 °C. IR (KBr) ν_{max}/cm^{-1}: 3275, 1659, 1614. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.80 (s, 3H), 2.41 (s, 3H), 3.01 (d, *J* 13.2 Hz, 1H), 3.15 (d, *J* 13.2 Hz, 1H), 3.51 (br s, 1H, NH), 6.70–7.69 (m, 13H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.9, 28.7, 45.9, 51.0, 113.5, 123.5, 125.7, 126.3, 127.4, 128.2, 128.3, 128.5, 128.6, 129.0, 130.8, 131.2, 134.0, 136.9, 164.6. MS (EI), *m/z* [M$^+$] = 326. Anal. Calc. for $C_{23}H_{22}N_2$: C, 84.63; H, 6.79; N, 8.58: Found: C, 84.53; H, 6.85; N, 8.62.

Entry 3, Table 2

Yellow solid. mp 115-116 °C. IR (KBr) ν_{max}/cm^{-1}: 3285, 1635, 1609. ^{1}H NMR (300 MHz, $CDCl_3$) 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), 6.60 (s, 1H), 7.15 (s, 1H), 7.18-7.30 (m, 6H), 7.50–7.60 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) 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. MS (EI), *m/z* [M$^+$] = 340. Anal. Calc. for $C_{24}H_{24}N_2$: C, 84.66; H, 7.10; N, 8.22: Found: C, 84.78; H, 7.25; N, 8.35.

Entry 4, Table 2

Yellow solid. mp 121–123 °C. IR (KBr) ν_{max}/cm^{-1}: 3290, 1647, 1598, 854. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.76 (s, 3H), 2.96 (d, *J* 12.8 Hz, 1H), 3.15 (d, *J* 12.8 Hz, 1 H), 3.35 (br s, NH), 6.78-6.81 (m, 1H), 6.95-6.98 (m, 1H), 7.15-7.27 (m, 6H), 7.42-7.58 (m, 3H), 7.91-7.96 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 29.6, 44.7, 71.2, 120.9, 122.9, 124.1, 128.9, 139.9, 130.5, 132.0, 137.6, 138.2, 146.0, 169.1. MS (EI), *m/z* [M$^+$] = 346. Anal. Calc. for $C_{22}H_{19}ClN_2$: C, 76.18; H, 5.52; N, 8.08: Found: C, 76.07; H, 5.49; N, 8.12.

Entry 5, Table 2

Yellow crystalline solid. mp 158–160 °C. IR (KBr) ν_{max}/cm^{-1}: 3304, 1638, 1603, 761. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.75 (s, 3 H), 2.93 (d, *J* 12.8 Hz, 1 H), 3.12 (d, *J* 12.8 Hz, 1 H), 3.49 (br s, NH), 6.88 (s, 1 H), 7.13-7.30 (m, 5 H), 7.36 (s, 1H), 7.50-7.53 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 29.9, 43.2, 72.9, 121.9, 124.1, 125.3 127.3, 128.4, 128.7, 130.1, 137.8, 139.3, 146.8, 168.8. MS (EI), *m/z* [M$^+$] = 381. Anal. Calc. For $C_{22}H_{18}Cl_2N_2$: C, 69.30; H, 4.76; N, 7.35: Found: C, 69.28; H, 4.81; N, 7.32.

Entry 6, Table 2

Yellow solid. mp 114-116 °C. IR (KBr) ν_{max}/cm^{-1}: 3327, 1681, 1649, 1601, 1249, 1178, 981, 820. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.78 (s, 3H), 2.96 (d, 1H, *J* 12.8 Hz), 3.31 (d, 1H, *J* 12.8 Hz), 3.51 (br s, 1H, NH), 7.12-7.26 (m, 5H), 7.34-7.61 (m, 7H), 7.72-7.78 (m, 2H), 7.81-7.85 (m, 1H), 7.88-7.92 (m, 2H), 7.98-8.01 (m, 1H); MS (FAB), *m/z* [M$^+$+H] = 417. Anal. Calc. for $C_{29}H_{24}N_2O$: C, 83.63; H, 5.81; N, 6.73; Found: C, 83.49; H, 5.94; N, 6.69.

Entry 7, Table 2

Yellow solid. mp 136-138 °C. IR (KBr) ν_{max}/cm^{-1}: 3318, 1638, 1554, 1356. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.79 (s, 3H), 3.06 (d, 1H, *J* 13.4 Hz), 3.32 (d, 1H, *J* 13.4 Hz), 4.41 (br s, 1H, NH), 6.92-6.94 (d, 1H, *J* 8.7 Hz), 7.17-7.55 (m, 10H), 7.92-7.96 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 29.1, 45.8, 65.8, 111.8, 116.9, 124.2, 125.8, 127.6, 128.8, 129.2, 132.2, 132.5, 133.4, 135.6, 137.8, 139.6, 143.1, 166.8. MS (EI), *m/z* [M$^+$] =357. Anal. Calc. for $C_{22}H_{19}N_3O_2$: C, 73.93; H, 5.36; N, 11.76; Found: C, 73.87; H, 5.41; N, 11.67.

Entry 1, Table 3

Pale yellow crystalline solid. mp 98-99 °C. IR (KBr) ν_{max}/cm^{-1}: 3318, 1630, 1598. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.72 (s, 3H), 2.26 (s, 3H), 2.32 (s, 3H), 2.98 (d, 1H, *J* 13.4 Hz), 3.05 (d, 1H, *J* 13.4 Hz), 3.43 (br s, 1H, NH), 6.74-6.76 (m, 1H), 6.98-7.02 (m, 6H), 7.21-7.23 (m, 1H), 7.47-7.50 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.7, 21.2, 29.8, 42.9, 73.1, 121.3, 121.4, 125.2, 126.0, 127.1, 128.5, 128.6, 128.9, 129.2, 136.4, 137.0, 138.2, 139.7, 140.3, 145.0, 166.8. MS (EI), *m/z* [M$^+$] = 340. Anal. Calc. for $C_{24}H_{24}N_2$: C, 84.70; H, 7.05; N, 8.23: Found: C, 84.68; H, 7.13; N, 8.18.

Entry 2, Table 3

Yellowish solid. mp 114-116 °C. IR (neat) ν_{max}/cm^{-1}: 3325, 1135, 1640, 1594, 1190. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.71 (s, 3H), 2.85 (d, 1H, *J* 12.8 Hz), 2.98 (d, 1H, *J* 12.8 Hz), 3.73 (s, 3H), 3.77 (s, 3H), 6.65-6.78 (m, 4H), 6.95-7.02 (m, 2H), 7.18-7.25 (m, 2H), 7.42-7.55 (m, 4H); MS (EI), *m/z* [M$^+$] = 372. Anal. Calc. for $C_{24}H_{24}N_2O_2$: C, 77.37; H, 6.52; N, 7.50: Found: C, 77.18; H, 6.64; N, 7.52.

Entry 3, Table 3

Yellow crystalline solid. mp 219-220 °C. IR (KBr) ν_{max}/cm^{-1}: 3339, 1636, 1599. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.65 (s, 3H), 2.77 (d, 1H, *J* 12.6 Hz), 2.89 (d, 1H, *J* 12.6 Hz), 4.18 (br s, NH), 6.57-6.64 (m, 4H), 6.81-7.00

(m, 1H), 7.10-7.18 (m, 1H), 7.28-7.55 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 29.2, 42.0, 72.6, 114.4, 114.6, 120.5, 120.9, 124.9, 125.8, 127.0, 128.2, 130.0, 137.9, 139.5, 155.3, 158.6, 166.8. MS (EI), *m/z* [M$^+$] = 344. Anal. Calc. for $C_{22}H_{20}N_2O_2$: C, 76.74; H, 5.81; N, 8.15: Found: C, 76.76; H, 5.84; N, 8.13.

Entry 4, Table 3

Red crystalline solid. mp 156-158 °C. IR (KBr) ν_{max}/cm^{-1}: 3325, 1642, 1597. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.83 (s, 3H), 2.96 (d, 1H, *J* 13.4 Hz), 3.27 (d, 1H, *J* 13.4 Hz), 3.52 (br s, NH), 6.97-6.98 (m, 1H), 7.00-7.02 (m, 6H), 7.21-7.22 (m, 1H), 7.45-7.47 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 30.0, 42.9, 73.4, 121.3, 122.2, 123.5, 123.4, 126.8, 127.6, 127.7, 129.6, 137.2, 138.8, 144.6, 146.9, 148.4, 154.1, 163.8. MS (EI), *m/z* [M$^+$] = 402. Anal. Calc. for $C_{22}H_{18}N_4O_4$: C, 65.67; H, 4.47; N, 13.93: Found: C, 65.65; H, 4.40; N, 13.98.

Entry 5a, Table 3

Pale yellow crystalline solid. mp 104-105 °C. IR (KBr) ν_{max}/cm^{-1}: 3271, 1651, 1603, 1231. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.75 (s, 3H), 2.87 (d, 1H, *J* 13.6 Hz), 3.04 (d, 1H, *J* 13.6 Hz), 3.30 (br s, NH), 6.75-6.79 (m, 1H), 6.82-6.92 (m, 4H), 7.00-7.05 (m, 2H), 7.19-7.25 (m, 1H), 7.48-7.62 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 29.7, 42.9, 73.4, 114.7, 114.8, 115.0, 115.1, 126.2, 127.0, 128.5, 129.2, 135.5, 137.4, 140.3, 143.2, 160.2, 162.2, 165.3, 165.5, 163.5. MS (EI), *m/z* [M$^+$] = 348. Anal. Calc. for $C_{22}H_{18}F_2N_2$: C, 75.86; H, 5.17; N, 8.04: Found: C, 75.82; H, 5.20; N, 8.07.

Entry 5b, Table 3

Pale yellow crystalline solid. mp 143-145 °C. IR (KBr) ν_{max}/cm^{-1}: 3269, 1636, 1593, 765. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.70 (s, 3H), 2.79 (d, 1H, *J* 13.3 Hz), 2.97 (d, 1H, *J* 13.3 Hz), 3.25 (br s, NH), 6.68-6.75 (m, 1H), 6.92-7.02 (m, 1H), 7.12-7.20 (m, 5H), 7.38-7.52 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 29.7, 42.8, 73.4, 121.4, 121.9, 126.6, 127.0, 128.2, 128.3, 128.6, 133.0, 137.5, 137.7, 139.8, 145.8, 165.9. MS (EI), *m/z* [M$^+$] = 381. Anal. Calc. for $C_{22}H_{18}Cl_2N_2$: C, 69.29; H, 4.72; N, 7.34: Found: C, 69.30; H, 4.78; N, 7.31.

Entry 5c, Table 3

Yellow solid. mp 145-146 °C. IR (KBr) ν_{max}/cm^{-1}: 3325, 1640, 1589, 1198, 574. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.72 (s, 3H), 2.87 (d, 1H, *J* 13.6 Hz), 3.00 (d, 1H, *J* 13.6 Hz), 2.65 (br s, NH), 6.97-6.98 (m, 1H), 7.00-7.04 (m, 6H), 7.18-7.24 (m, 1H), 7.45-7.48 (m, 4H). MS (FAB), *m/z* [M$^+$+H] = 471. Anal. Calc. for $C_{22}H_{18}Br_2N_2$: C, 56.17; H, 3.82; N, 5.95: Found: C, 56.19; H, 3.78; N, 5.89.

Entry 5d, Table 3

Pale yellow crystalline solid. mp 143-144 °C. IR (KBr) ν_{max}/cm^{-1}: 3259, 1636, 1579, 462. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.71 (s, 3H), 2.85 (d, 1H, *J* 12.8 Hz), 2.99 (d, 1H, *J* 12.8 Hz), 3.32 (br s, NH), 6.73-6.75 (m, 1H), 6.98-7.03 (m, 2H), 7.21-7.33 (m, 5H), 7.53-7.58 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 30.3, 43.4, 74.1, 93.4, 97.4, 122.1, 122.6, 127.3, 128.2, 129.2, 129.3, 137.8, 138.0, 139.4, 140.4, 147.6, 166.8. MS (FAB), *m/z* [M$^+$+H] = 565. Anal. Calc. for $C_{22}H_{18}I_2N_2$: C, 46.97; H, 3.20; N, 4.98: Found: C, 46.92; H, 3.22; N, 5.01.

Entry 6, Table 3

Yellow solid. mp 137-138 °C. IR (KBr) ν_{max}/cm^{-1}: 3290, 1640, 1600. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.23-1.85 (m, 16H), 2.30-2.70 (m, 3H), 4.49 (br s, 1H), 6.65-7.35 (m, 4H); ^{13}C NMR (75 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. MS (EI), *m/z* [M$^+$] = 268. Anal. Calc. for $C_{18}H_{24}N_2$: C, 80.55; H, 9.01; N, 10.44: Found: C, 80.26; H, 9.54; N, 10.31.

Entry 7, Table 3

Yellow solid. mp 138-140 °C. IR (KBr) ν_{max}/cm^{-1}: 3338, 1659, 1600. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.30-1.90 (m, 12H), 2.30-2.61 (m, 3H), 4.50 (br s, 1H), 6.70-7.39 (m, 4H); ^{13}C NMR (75 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. MS (EI), *m/z* [M$^+$] = 240. Anal. Calc. for $C_{16}H_{20}N_2$: C, 79.96; H, 8.39; N, 11.66: Found: C, 79.64; H, 8.22; N, 11.45.

Entry 8, Table 3

Yellow solid. mp 137-139 °C. IR (KBr) ν_{max}/cm^{-1}: 3329, 1637, 16057. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.99 (t, *J* 6.9 Hz, 3H), 1.25 (t, *J* 6.9 Hz, 3H), 1.70 (q, *J* 6.9 Hz, 2H), 2.15 (m, 2H), 2.35 (s, 3H), 2.69 (q, *J* 6.9 Hz, 2H), 3.27 (br s, 1H, NH), 6.78-7.35 (m, 4H); ^{13}C NMR (75 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. MS (FAB), *m/z* [M$^+$+H] = 216. Anal. Calc. for $C_{14}H_{20}N_2$: C, 77.73; H, 9.32; N, 12.95: Found: C, 77.71; H, 9.36; N, 12.93.

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