PAPERS

The Preparation of Some *N*- and *S*-Acetals of Benzaldehyde and Terephthalaldehyde

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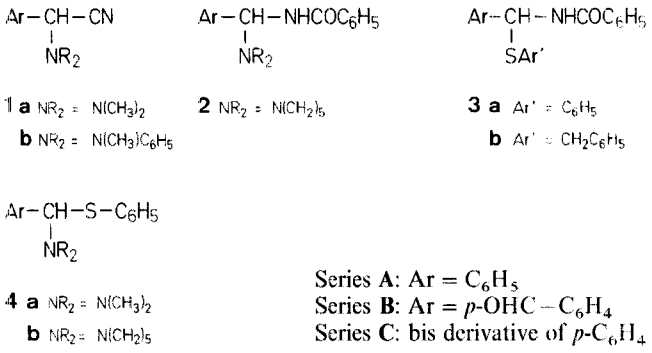
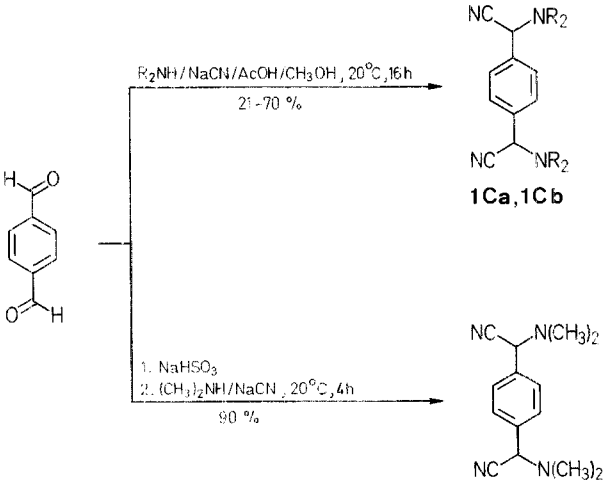
Improved preparative methods are reported for title compounds of types comprising aminonitriles, amidoamines, amidothioethers, and aminothioethers.

In connection with other work designed to apply the principles of merostabilization[1] to dyestuffs[2], our attention was drawn to *N,S*-acetals. Our investigations revealed novel routes to a variety of compounds of Types **1–4** as described in this paper, which enable their preparation considerably more efficiently than by previous methods.



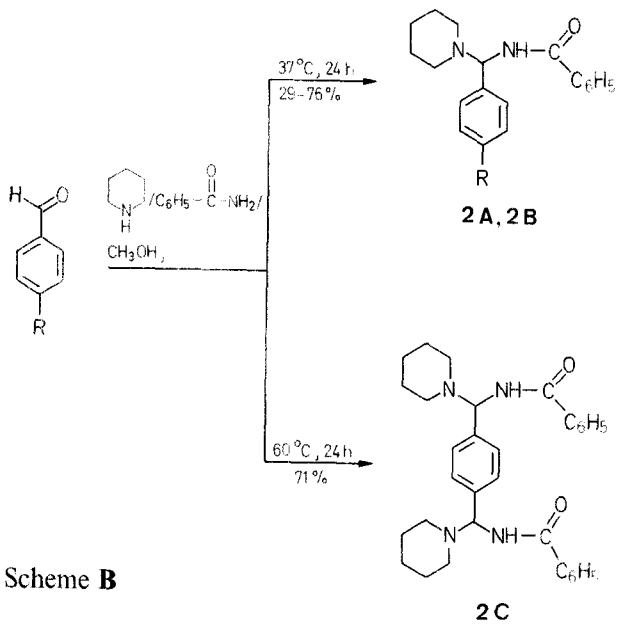
Series **A**: Ar = C_6H_5
Series **B**: Ar = *p*-OHC–C_6H_4
Series **C**: bis derivative of *p*-C_6H_4

Following the modified Strecker synthesis described[3] for the preparation of aminonitriles from α,β-unsaturated aliphatic aldehydes, we have prepared α,α′-bis(dimethylamino)-α,α′-dicyano-*p*-xylene **1Ca** (70%) and α,α′-bis(methylphenylamino)-α,α′-dicyano-*p*-xylene **1Cb** (21%) from terephthalaldehyde (Scheme **A**). Our attempts to make these compounds by other modifications[4–6] of the Strecker reaction failed, but aminonitrile **1Ca** was also prepared (in 90% yield) by reacting the terephthalaldehyde-bisulfite addition product first with 25% aqueous dimethylamine and then with sodium cyanide[7]; this procedure failed for aminonitrile **1Cb**. These methods are preferable to the only previously reported synthesis of **1Aa** by initial conversion of benzaldehyde to the *N*-(α-dialkylaminobenzyl)benzamide and then substituting the amide group by cyanide[8] in addition to being more laborious, the overall yields of the latter process are modest (about 40% at best). The aminonitriles **1Ca** and **1Cb** displayed in the ^{1}H-NMR spectra three singlets characteristic for the CH_3, CH and *p*-C_6H_4 protons. ^{13}C-NMR, showed the expected signals for both compounds, and the IR spectrum of **1Ca** exhibited moderate C=N stretching absorption at $\nu = 2200\ cm^{-1}$.



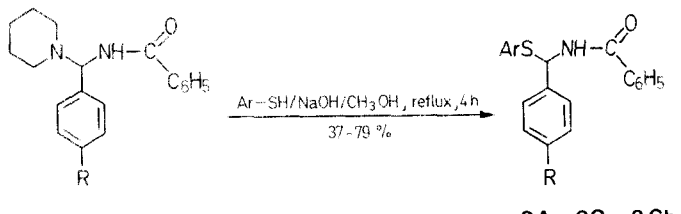
Scheme **A**

N-(α-Dialkylaminobenzyl)amides **2** are potentially useful intermediates because they undergo nucleophilic substitutions[8] in which either the amine or the amide residue is displaced. However, the reported syntheses of *N*-(α-dialkylaminobenzyl)acetamides from *N*-benzylidene-α-acetamidobenzylamine[9] and of *N*-[α-(benzylamino)benzyl] benzamides and *N*-[α-(dibenzylamino)benzyl]benzamides substituted benzylamines *via* potassium permanganate oxidations[10,11] are unsatisfactory as regards convenience and yields. Also the synthesis of **2A** from benzaldehyde through the intermediate formation of *N,N'*-benzylidenebisdimethylamine by substituting one of the amine moieties by a desired amide group[12] is also laborious, and requires the purification of the intermediate *N,N'*-benzylidenebisamine. We now report that simple reaction of benzaldehyde with piperidine and benzamide at 37 °C in methanol gives *N*-(α-piperidinobenzyl)benzamide[13] **2A** (76%), (Scheme **B**). Under similar conditions terephthalaldehyde with piperidine and benzamide at 37 °C gave te product **2B** of reaction at just one of the aldehyde groups as shown by ^{1}H-NMR and IR spectroscopy. However, on raising the temperature to 60 °C, terephthalaldehyde gave the expected product of bis-reaction **2C** (73%) as confirmed by ^{1}H-NMR spectroscopy.



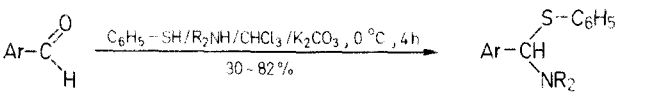
Scheme **B**

Our attempts to utilise the method of Sakai and coworkers[8] to convert *N*-(α-piperidinobenzyl)benzamide **2A** and its bis analog **2C** into the corresponding aminothioethers (type **4A** and **4C**) by reaction with thiophenol and benzyl mercaptan in alkaline methanol at 20–65 °C did not give the expected products. Instead of the amide residue, we found that the amino group was displaced under these conditions: thus *N*-(α-piperidinobenzyl) benzamide **2A** with thiophenol gave *N*-[α-(phenylthio)benzyl]benzamide **3Aa** (37%) (Scheme **C**). We also found that the reaction of **2C** with mercaptans gave best results when performed with 0.1 molar sodium hydroxide: benzyl mercaptan thus afforded 1,4-bis[(benzylthio) (benzamido)methyl]benzene **3Cb** (79%). Similarly, the reaction of **2C** with thiophenol resulted in the substitution of both amino residues but neither of the amide groups to give **3Ca** (73%) as shown by elemental analysis, IR, and ^{1}H-NMR spectroscopy.



Scheme **C**

Having failed to convert **2** → **4** by the reported literature method, we sought other routes to **4**. We have now achieved the synthesis of aminothioethers **4** in satisfactory yield by a method analogous to that previously described[14] for α-dialkylaminobenzyl butyl ethers. The reactions of benzaldehyde and thiophenol with dimethylamine and with piperidine, effected in chloroform in the presence of potassium carbonate, gave *N*-[α-(phenylthio)benzyl]dimethylamine **4Aa** and *N*-[α-(phenylthio)benzyl]piperidine **4Ab**, respectively (Scheme **D**). The spectral properties of **4Aa** agreed with those reported[8,15]. ^{1}H-NMR, ^{13}C-NMR and mass spectroscopy of **4Ab** were consistent with the assigned structure. Terephthalaldehyde and thiophenol underwent similar condensations with dimethylamine and piperidine yielding the bis-aminothioethers **4Ca** and **4Cb**. The assigned structures for both products were confirmed by ^{13}C-NMR and ^{1}H-NMR spectroscopy.



Scheme **D**

^{1}H-NMR revealed the presence of small amounts to α,α'-bis(dimethylamino)toluene and α,α'-bis(piperidino)toluene as contaminants in crude **4Aa** and **4Ab**. A similar observation was also reported[14] during the preparation of α-dialkylaminobenzyl butyl ethers. To detect whether the diamines were formed as by-products or as possible intermediates, we prepared α,α'-bis(dimethylamino)toluene[16] and the piperidine analog[14] and treated both with thiophenol. They were converted into the aminothioethers **4Aa** and **4Ab** respectively. Thus diamines could be formed as possible intermediates in the direct synthesis of aminothioethers, but whether their reactions with thiophenol are reversible or not requires further investigation.

Melting points are uncorrected and were determined on a Bristoline hot stage microscope. IR spectra were recorded on a Perkin-Elmer 283 B grating spectrophotometer. ^{1}H-NMR spectra were obtained on a Varian EM-360L (60 MHz) spectrometer using tetramethylsilane as internal standard and ^{13}C-NMR spectra were obtained on a JEOL FX-100 FT spectrometer operating at 25.00 MHz with tetramethylsilane as internal standard. Mass spectra were measured at 70 eV using A.E.I. MS-30 mass spectrometer operating with a Kratos DS-55 data system. Reactions were followed by TLC, and analytical specimens were shown to be homogeneous by TLC.

α-α'-Bis(dimethylamino)-α,α'-dicyano-*p*-xylene (1Ca):

Method A: To terephthalaldehyde (4.02 g, 30 mmol), dimethylamine (2.70 g, 60 mmol) and glacial acetic acid (3.60 g, 60 mmol) in methanol (30 ml) is added sodium cyanide (3.70 g, 76 mmol) in water (50 ml). After stirring at 20 °C for 16 h, the precipitate is filtered off and washed with ether (50 ml). The filtrate is extracted with ether (2 × 20 ml) and the combined ethereal portion is washed with water (30 ml), dried with magnesium sulfate and the solvent removed at 30 °C at 20 torr. The product is crystallized from benzene to give colourless needles: yield: 5.08 g (70%); m.p. 148–150 °C.

$C_{14}H_{18}N_4$ (242.3) calc. C 69.39 H 7.49 N 23.12 found 69.26 7.79 23.22

IR ($CHBr_3$): ν = 2220 cm^{-1} (C≡N).

^{1}H-NMR (DMSO-d_6): δ = 2.36 (s, 12 H, 4 × CH_3); 4.93 (s, 2 H, 2 × CH); 7.70 ppm (s, 4 H_{arom}).

^{13}C-NMR (DMSO-d_6): δ = 41.70 (CH_3); 62.70 (methine-C); 114.80 (cyano-C); 128.20 (C-2 of *p*-C_6H_4); 134.60 ppm (C-1 of *p*-C_6H_4).

Method B: To a solution obtained by stirring sodium hydrogensulfite (6.24 g, 60 mmol) with water (15 ml) at 20 °C, is added terephthalaldehyde (4.02 g, 30 mmol) and the mixture stirred at 20 °C for 20 min to form the dialdehyde-bisulfite addition product. 25% Aqueous dimethylamine (3.60 g, 80 mmol) is run in with continuous stirring and most of the bisulfite addition product dissolves. Sodium cyanide (2.94 g, 60 mmol) is added at 0–4 °C over 25 min, and the mixture is stirred at 20 °C for 4 h. The solid product crystallizes from benzene as colourless needles; yield: 6.53 g (90%); m.p. 148–150 °C.

α,α′-Bis(methylphenylamino)-α,α′-dicyano-p-xylene (1Cb):
Sodium cyanide 3.66 g, 75 mmol) in water (50 ml) is added to terephthalaldehyde (5.00 g, 37 mmol), *N*-methylaniline (8.03 g, 75 mmol) and acetic acid (4.50 g, 75 mmol) in methanol (30 ml). The mixture is stirred at 20 °C for 16 h and then worked up as described under **1Ca**, Method A. The product crystallizes as colourless plates; yield: 2.80 g (21%); m.p. 188–190 °C (ethanol/acetone).

$C_{24}H_{22}N_4$ (366.5) calc. C 78.66 H 6.05 N 15.29 found 78.66 6.24 15.13

^{1}H-NMR (DMSO-d_6): δ = 2.73 (s, 6 H, 2 × CH_3); 6.66 (s, 2 H, 2 × CH); 7.06–7.60 (m, 10 H, C_6H_5); 7.71 ppm (s, 4 H, *p*-C_6H_4).

^{13}C-NMR (DMSO-d_6): δ = 34.50 (CH_3); 56.70 (methine-C); 115.80 (cyano-C); 116.70, 120.10, 127.70, 129.10, 134.50, 148.30 ppm (Ar—C).

***N*-(α-Piperidinobenzyl)benzamide (2A):**
Benzaldehyde (12.99 g, 0.123 mol), piperidine (10.46 g, 0.123 mol) and benzamide (15.00 g, 0.124 mol) are stirred in methanol (150 ml) at 37 °C for 24 h. Separated solid is filtered out; water (70 ml) is added to precipitate the product from the filtrate. After washing with water and ice-cold methanol the product gives colourless needles; yield: 27.50 g (76%); m.p. 147–150 °C (benzene) (Lit.[13], m.p. 148–149 °C).

IR ($CHBr_3$): ν = 3360 (NH), 1640 (C=O), 1632 cm^{-1} (NH).

^{1}H-NMR ($CDCl_3$): δ = 1.53 (m, 6 H, piperidine protons of C-3, C-4 and C-5); 2.60 (m, 4 H, piperidino protons of C-2 and C-6); 6.03 (d, 1 H, *J* = 2.5 Hz, CH); 6.93 (d, 1 H, *J* = 2.5 Hz, NH); 7.50 (m, 8 H_{arom}); 7.96 ppm (m, 2 H_{arom}).

4-[(1-Piperidino)(benzamido)methyl]benzaldehyde (2B):
Terephthalaldehyde (10.60 g, 80 mmol), piperidine (6.80 g, 80 mmol) and benzamide (9.60 g, 80 mmol) are stirred in methanol (100 ml) at 37 °C for 24 h. The reaction mixture is then worked up as previously described under **2A**. The product crystallizes in colourless needles; yield: 7.40 g (29%); m.p. 159–160 °C (benzene).

$C_{20}H_{22}N_2O_2$ (322.4) calc. C 74.50 H 6.87 N 8.69 found 74.71 7.04 8.50

IR ($CHBr_3$): ν = 3305 (NH), 1703, 1642 (C=O), 1633 cm^{-1} (NH).

^{1}H-NMR [DMSO-d_6/$CDCl_3$]: δ = 1.53 (m, 6 H, C-3, C-4 and C-5 protons of piperidino group); 2.60 (m, 4 H, C-2 and C-6 protons of piperidino group); 6.16 (d, 1 H, *J* = 2.5 Hz, CH; 7.83 (m, 9 H_{arom}); 8.90 (d, 1 H, *J* = 2.5 Hz, N—H); 10.20 ppm (s, 1 H, —CHO).

1,4-Bis[(1-piperidino)(benzamido)methyl]benzene (2C):
Terephthalaldehyde (5.30 g, 40 mmol), piperidine (6.80 g, 80 mmol) and benzamide (9.60 g, 80 mmol) in methanol (100 ml) are stirred at 60 °C for 24 h. The insoluble white product is collected, washed thoroughly with water and ice-cold methanol; yield: 14.30 g (71%); m.p. 212–214 °C.

$C_{32}H_{38}N_4O_2$ (510.7) calc. C 75.26 H 7.50 N 10.97 found 75.23 7.76 10.70

IR ($CHBr_3$): ν = 3320 (NH), 1640 (C=O), 1635 cm^{-1} (NH).

^{1}H-NMR [DMSO-d_6/CF_3COOH]: δ = 1.51 (m, 12 H, piperidino protons of C-3, C-4 and C-5); 2.65 (m, 8 H, piperidino protons of C-2 and C-6); 6.70 (d, 2 H, *J* = 2.5 Hz, 2 × CH); 7.67 (s, 4 H, *p*-C_6H_4); 7.85 (m, 10 H_{arom}) 8.92 ppm (d, 2 H, *J* = 2.5 Hz, NH).

***N*-[α-(Phenylthio)benzyl]benzamide (3Aa):**
N-(α-Piperidinobenzyl)benzamide (**2A**; 8.00 g, 27 mmol), thiophenol (3.06 g, 28 mmol) and sodium hydroxide (0.20 g, 5 mmol) are stirred in methanol (100 ml) at reflux for 4 h. On cooling, the product precipitates, it recrystallizes in colourless needles from ethanol; yield: 3.20 g (37%); m.p. 174–177 °C [Lit.[8], m.p. 170–171 °C].

IR ($CHBr_3$): 3280 (NH), 1655 (C=O), 1640 cm^{-1} (NH).

^{1}H-NMR [DMSO-d_6/$CDCl_3$]: δ = 6.90 (d, 1 H, *J* = 2.5 Hz, CH); 7.60 (m, 15 H_{arom}); 9.40 ppm (d, 1 H, *J* = 2.5 Hz, NH).

1,4-Bis-[phenylthio)(benzamido)methyl]benzene (3Ca):
1,4-Bis[(1-piperidino)(benzamido)methyl]benzene **2C**; (4.52 g, 9 mmol), thiophenol (2.00 g, 18 mmol) and sodium hydroxide (0.20 g, 5 mmol) are stirred in methanol (100 ml) at reflux for 4 h. The white solid product is filtered off, washed thoroughly with water and ice-cold methanol; yield: 3.6 g (73%); m.p. 261–263 °C.

$C_{34}H_{28}N_2O_2S_2$ (560.7) calc. C 72.82 H 5.03 N 4.99 found 73.06 5.09 4.97

IR ($CHBr_3$): 3287 (NH), 1645 (C=O), 1637 cm^{-1} (NH).

^{1}H-NMR (DMSO-d_6): δ = 6.90 (d, 2 H, *J* = 2.5 Hz, CH); 7.63 (m, 24 H_{arom}); 9.66 (d, 2 H, *J* = 2.5 Hz, NH).

1,4-Bis[(benzylthio)(benzamido)methyl]benzene (3Cb):
1,4-Bis-[(1-piperidino)(benzamido)methyl]benzene **2C**; (5.93 g, 12 mmol), benzyl mercaptan (3.00 g, 24 mmol) and sodium hydroxide (0.20 g, 5 mmol) are stirred in methanol (100 ml) for 4 h at reflux. After cooling, the solid product is washed thoroughly with water and ice-cold methanol; yield: 5.40 g (79%); m.p. 240–241 °C.

$C_{36}H_{32}N_2O_2S_2$ (588.8) calc. C 73.44 H 5.48 N 4.76 found 73.00 5.68 4.62

^{1}H-NMR (DMSO-d_6): δ = 3.80 (s, 4 H, 2 × CH_2); 6.25 (d, 2 H, *J* = 2.5 Hz, CH); 7.24–7.47 (m, 20 H_{arom}); 7.89 (m, 4 H_{arom}); 9.40 (d, 2 H, *J* = 2.5 Hz, NH).

***N*-[α-(Phenylthio)benzyl]dimethylamine (4Aa):**
Benzaldehyde (10.60 g, 0.10 mol), thiophenol (26.83 g, 0.24 mol), dimethylamine (5.50 g, 0.12 mol) and anhydrous potassium carbonate (13.80 g, 0.10 mol) are stirred in dry chloroform (50 ml) at 0 °C for 4 h. The mixture is filtered and the potassium carbonate residue washed with chloroform (2 × 20 ml) and combined with the filtrate. The filtrate is washed with 8% aqueous sodium hydrogen carbonate, (30 ml) then with water (30 ml), and dried with potassium carbonate. After evaporation of the solvent at 45 °C/40 torr the colourless oil is distilled to give the product; yield: 20 g (82%); b.p. 112–120 °C/0.01 torr [Lit.[8], b.p. 112–120 °C/0.01 torr].

^{1}H-NMR ($CDCl_3$): δ = 2.36 (s, 6 H, 2 × CH_3); 5.45 (s, 1 H, CH); 7.12–7.28 (m, 10 H_{arom}).

^{13}C-NMR ($CDCl_3$): δ = 41.23 (CH_3); 84.65 (CH); 126.32, 127.44, 127.54, 128.71, 129.59, 134.27 (aromatic C—H); 137.43 (aromatic C-1 of benzyl group); 140.02 ppm (aromatic C-1 of thiophenyl group).

***N*-[α(Phenylthio)benzyl]piperidine (4Ab):**
Benzaldehyde (1.15 g, 11 mmol), piperidine (1.03 g, 12 mmol), thiophenol (6.01 g, 55 mmol) and anhydrous potassium carbonate (1.54 g, 11 mmol) are stirred at 20 °C in dry tetrahydrofuran (10 ml) for 4 h. Work up as described under **4Aa**, gives after distillation, the product as a colourless oil; yield: 2.14 g (70%); b.p. 145–150 °C/35 torr.

^{1}H-NMR ($CDCl_3$): δ = 1.55 (s, 6 H, protons of piperidino C-3, C-4 and C-5); 2.80 (s, 4 H, protons of piperidino C-2 and C-6); 5.25 (s, 1 H, CH); 6.87–7.11 (m, 5 H_{arom}); 7.23–7.48 ppm (m, 5 H_{arom}).

^{13}C-NMR ($CDCl_3$): δ = 22.80, 23.44, 44.69 (C-3, C-2 and C-1 of piperidino group respectively); 84.60 (CH); 121.84, 126.86, 127.20, 127.93, 128.76, 132.02, 142.75 ppm (aromatic C).

1,4-Bis[phenylthio)(dimethylamino)methyl]benzene (4Ca):
Terephthalaldehyde (4.56 g, 34 mmol), dimethylamine (3.37 g, 75 mmol), thiophenol (37.45 g, 0.34 mol) and anhydrous potassium carbonate (9.40 g, 68 mmol) are stirred in dry chloroform (30 ml) at 0 °C for 4 h. Work up as described under **4Aa** gives colourless needles; yield: 4.17 g (30%); m.p. 68–70 °C [petroleum ether (40–60 °C)/chloroform].

^{1}H-NMR ($CDCl_3$): $\delta = 2.40$ (s, 12H, $4 \times CH_3$); 5.53 (s, 2H, $2 \times CH$); 7.43 (m, 10H, $2 \times C_6H_5$); 7.73 ppm (s, 4H, p-C_6H_4).

1,4-Bis[thiophenyl)(piperidino)methyl]benzene (4Cb):
Terephthalaldehyde (3.96 g, 30 mmol), piperidine (5.58 g, 66 mmol), thiophenol (32.19 g, 0.29 mol) and anhydrous potassium carbonate (8.22 g, 60 mmol) are stirred at 20 °C in dry chloroform (30 ml) for 4 h. Work up as described under **4Aa** gives colourless needles; yield: 9.70 g (67%); m.p. 119–120 °C (hexane).

$C_{30}H_{36}N_2S_2$	calc.	C 73.21	H 7.43	N 5.73
(488.7)	found	73.48	7.21	5.50

^{1}H-NMR ($CDCl_3$): $\delta = 1.48$ (s, 12H, protons of C-3, C-4 and C-5 of piperidino groups); 2.63 (s, 8H, protons of C-2 and C-6 of piperidino groups); 5.50 (s, 2H, methine protons); 7.00–7.63 (m, 10H, C_6H_5); 7.77 ppm (s, 4H, p-C_6H_4).

^{13}C-NMR ($CDCl_3$): $\delta = 24.32$, 25.93, 50.35 (C-4, C-3 and C-2 of piperidino groups respectively), 84.56 (CH); 126.23, 128.42, 128.72, 131.93 (aromatic C); 137.98 (C-1 and C-4 of p-C_6H_4); 139.29 ppm (C-1 of C_6H_5).

MS: m/e = 270 (81.7%), 227 (19.5), 213 (10.2), 187 (25.7), 110 (100), 104 (14.2), 84 (14.8), 77 (15.7), 69 (12.0), 66 (33.2) and 51 (15.4).

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