Indian Journal of Chemistry
Vol. 47B, December 2008, pp. 1903-1905

Note

Synthesis of *N*-(substituted benzyl)-2-(3′,5′-dimethyl-4′-hydroxyphenyl) acetamides

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Received 31 August 2007; accepted (revised) 28 August 2008

4-Benzyloxy-3,5-dimethylphenylacetate **1** reacts with substituted benzyl amines **2a-e** affords *N*-substituted benzyl-2-(4′-benzyloxy-3′,5′-dimethylphenyl) acetamides **3a-e**, which on debenzylation give *N*-substituted benzyl-2-(3′,5′-dimethyl-4′-hydroxy phenyl) acetamides **4a-e** in very good yields which are important intermediates for the synthesis of 1,2,3,4-tetrahydroisoquinolines.

Keywords: Acetamides, 4-benzyloxy-3,5-dimethylphenylacetate, substituted benzyl amines, tetrahydroisoquinolines

N-Substituted acetamides are important synthetic organic compounds for the synthesis of pyridines[1], quinolines[2] and isoquinolines[3]. In continuation of our ongoing work on biologically active molecules[4] and pesticide compounds[5], a simple and convenient syntheses of a series of new *N*-substituted benzyl-2-(3′,5′-dimethyl-4′-hydroxyphenyl) acetamides **4a-e** in very good yields is reported and are found to be important intermediates for the synthesis of natural product such as cherylline, an alkaloid of 1,2,3,4-tetrahydroisoquinoline[6] (**Scheme I**).

4-Benzyloxy-3,5-dimethylphenylacetate **1** obtained from 2,5-dimethyl phenol according to our earlier procedure[6], reacted with 3,4-dimethoxybenzyl amine **2a** at 150°C for 6-8 hr without using any solvent and catalyst gave *N*-1-(3,4-dimethoxybenzyl)-2-(4′-benzyloxy-3′,5′-dimethylphenyl) acetamide **3a**. The acetamide obtained was subjected to catalytic hydrogenation with 5% palladium on charcoal under hydrogen atmosphere in ethyl acetate afforded *N*-1-(3,4-dimethoxybenzyl)-2-(3′,5′-dimethyl-4′-hydroxyphenyl) acetamide **4a**. The structure of the compound was established on the basis of spectral data. Similarly the compounds **4b-e** were prepared and all the new products were well characterized by ^{1}H NMR, IR and mass spectra.

Experimental Section

The ^{1}H NMR spectra were recorded on Gemini 200 MHz spectrometer in $CDCl_3$ with TMS as an internal standard. IR spectra were recorded on a Nicolet 740 FT IR spectrophotometer and mass spectra on VG Micro mass 7070 H. Melting points were obtained on a Toshniwal melting point apparatus and are uncorrected.

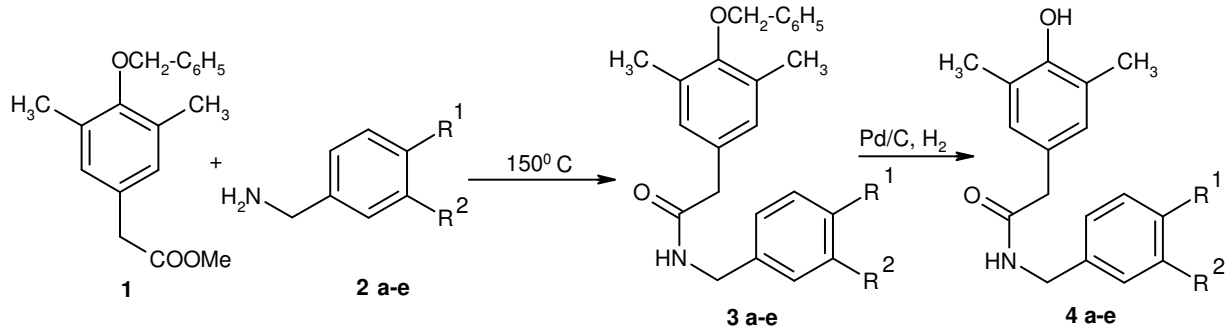
General procedure for the preparation of 3a-e: 4-Benzyloxy-3,5-dimethylphenylacetate (**1**, 0.6 g, 0.002 moles) and 3,4-dimethoxy benzyl amine (**2a**, 0.35 g, 0.002 moles) were heated under stirring at 150°C for 8 hr. The reaction mixture was cooled and diluted with chloroform (20 mL). The organic layer was washed with dilute hydrochloric acid to remove unreacted amine followed by water. It was dried over sodium sulfate and the solvent was removed under reduced pressure. The crude product was subjected to column chromatography to afford *N*-1-(3,4-dimethoxybenzyl)-2-(4′-benzyloxy-3′,5′-dimethy lphenyl) acetamide (**3a**) in 86% yield.

General procedure for the preparation of 4a-e: To *N*-1-(3,4-dimethoxybenzyl)-2-(4′-benzyloxy-3′,5′-dimethylphenyl) acetamide (0.350 g, 0.0008 moles) dissolved in ethyl acetate (5 mL), 5% palladium charcoal (0.035 g, 0.00008 moles) was added and stirred under hydrogen atmosphere (balloon) at room temperature for 4 hr. The contents were filtered using celite as filter aid and the solvent was evaporated under reduced pressure. Purification of the crude compound by flash chromatography gave *N*-1-(3,4-dimethoxybenzyl)-2-(3′,5′-dimethyl-4′-hydroxyphenyl) acetamide **4a** as solid in 96% yield.

Spectral Data

***N*-1-(3,4-Dimethoxybenzyl)-2-(4′-benzyloxy-3′,5′-dimethylphenyl) acetamide 3a**. 86% yield, Solid, m.p. 145°C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.18 (s, 6H, 2 × CH_3), 3.40 (s, 2H, CH_2CO), 3.74 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 4.25 (d, 2H, NCH_2), 4.70 (s, 2H, OCH_2), 5.68 (t, 1H, NH), 6.59-6.72 (m, 3H, aromatic), 6.82 (s, 2H, aromatic), 7.22-7.4 (m, 5H, aromatic); IR (KBr): 3420, 1638, 1460 and 1025 cm^{-1}. Mass: *m/z* 419 (M^+); Anal. Calcd for $C_{26}H_{29}NO_4$: C, 74.46; H, 6.92; N, 3.34. Found: C, 74.44; H, 6.97; N, 3.38.

***N*-1-(3,4-Dimethoxybenzyl)-2-(3′,5′-dimethyl-4′-hydroxyphenyl) acetamide 4a**. 96% yield, solid, m.p: 163.7°C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.23 (s,



4a R^1, R^2 = OMe, OMe
4b R^1 = OMe, R^2 = H
4c R^1 = H, R^2 = OMe
4d R^1= CH_3, R^2 = H
4e R^1= Cl, R^2 = H

Scheme I

6H, 2 × CH_3), 3.50 (s, 2H, CH_2CO), 3.84 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 4.38 (d, 2H, NCH_2), 4.65 (s, 1H, OH, D_2O exchangeable), 5.68 (t, 1H, NH), 6.68-6.78 (m, 3H, aromatic), 6.86 (s, 2H, aromatic). IR (KBr): 3300, 1615, 1510 and 1255 cm^{-1}. Mass: *m/z* 329 (M^+); Anal. Calcd for $C_{19}H_{23}NO_4$: C, 69.30; H, 6.99; N, 4.25. Found: C, 69.33; H, 6.95; N, 4.28.

***N*-1-(4-Methoxybenzyl)-2-(4′-benzyloxy-3′,5′-dimethylphenyl) acetamide 3b**. 82% yield, solid, m.p. 146°C, ^1H NMR (200 MHz, $CDCl_3$): δ 2.25 (s, 6H, 2 × CH_3), 3.44 (s, 2H CH_2CO), 3.76 (s, 3H, OCH_3), 4.30 (d, 2H, NCH_2), 4.78 (s, 2H, OCH_2), 5.68 (bt, 1H, NH), 6.78 (d, 2H, aromatic), 6.86 (s, 2H, aromatic), 7.18 (s, 2H, aromatic), 7.28-7.46 (m, 5H, aromatic). IR (KBr): 3430, 1628, 1455 and 1015 cm^{-1}. Mass: *m/z* 389 (M^+); Anal. Calcd for $C_{25}H_{27}NO_3$: C, 77.12; H, 6.94; N, 3.59. Found: C, 77.15; H, 6.93; N, 3.53.

***N*-1-(4-Methoxybenzyl)-2-(3′,5′-dimethyl-4′-hydroxyphenyl) acetamide 4b**. 91% yield, solid, m.p. 159°C. ^1H NMR (200 MHz, $CDCl_3$): δ 2.28 (s, 6H, 2 × CH_3), 3.52 (s, 2H, CH_2CO), 3.86 (s, 3H, OCH_3), 4.42 (d, 2H, NCH_2), 5.74 (bt, 1H, NH), 6.83 (d, 2H, aromatic), 6.94 (s, 2H, aromatic), 7.26 (s, 2H, aromatic). IR (KBr): 3360, 1618, 1515 and 1245 cm^{-1}. Mass: *m/z* 299 (M^+); Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.24; H, 7.02; N, 4.68. Found: C, 72.23; H, 7.08; N, 4.64.

***N*-1-(3-Methoxybenzyl)-2-(4′-benzyloxy-3′,5′-dimethylphenyl) acetamide 3c**. 78% yield, thick viscous liquid, ^1H NMR (200 MHz, $CDCl_3$): δ 2.24 (s, 6H, 2 × CH_3), 3.46 (s, 2H CH_2CO), 3.74 (s, 3H, OCH_3), 4.38 (d, 2H, NCH_2), 4.76 (s, 2H, OCH_2), 5.66 (bt, 1H, NH), 6.62-6.78 (m, 3H, aromatic), 6.86 (s, 2H, aromatic), 7.18 (s, 1H, aromatic), 7.24-7.46 (m, 5H, aromatic). IR (KBr): 3415, 1635, 1455 and 1015 cm^{-1}. Mass: *m/z* 389 (M^+); Anal. Calcd for $C_{25}H_{27}NO_3$: C, 77.12; H, 6.94; N, 3.59. Found: C, 77.17; H, 6.95; N, 3.57.

***N*-1-(3-Methoxybenzyl)-2-(3′,5′-dimethyl-4′-hydroxyphenyl) acetamide 4c**. 94% yield, solid, m.p. 151°C. ^1H NMR (200 MHz, $CDCl_3$): δ 2.26 (s, 6H, 2 × CH_3), 3.54 (s, 2H, CH_2CO), 3.84, (s, 3H, OCH_3), 4.46 (d, 2H, NCH_2), 5.76 (bt, 1H, NH), 6.64-6.88 (m, 3H, aromatic), 6.96 (s, 2H, aromatic), 7.28 (s, 1H, aromatic). IR (KBr): 3365, 1625, 1525 & 1215 cm^{-1}. Mass: *m/z* 299 (M^+); Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.24; H, 7.02; N, 4.68. Found: C, 72.26; H, 7.05; N, 4.63.

***N*-1-(4-Methylbenzyl)-2-(4′-benzyloxy-3′,5′-dimethylphenyl) acetamide 3d**. 75% yield, viscous liquid, ^1H NMR (200 MHz, $CDCl_3$): δ 2.24 (s, 6H, 2 × CH_3), 2.38 (s, 3H, CH_3), 3.48 (s, 2H, CH_2CO), 4.38 (d, 2H, NCH_2), 4.80 (s, 2H, OCH_2), 5.64 (bt, 1H, NH), 6.86 (s, 2H, aromatic), 7.16-7.22 (m, 4H, aromatic), 7.36-7.54 (m, 5H, aromatic). IR (KBr): 3426, 1638, 1465 and 1010 cm^{-1}. Mass: *m/z* 373 (M^+); Anal. Calcd for $C_{25}H_{27}NO_2$: C, 80.42; H, 7.23; N, 3.75. Found: C, 80.47; H, 7.25; N, 3.77.

***N*-1-(4-Methylbenzyl)-2-(3′,5′-dimethyl-4′-hydroxyphenyl) acetamide 4d**. 90% yield, viscous liquid, ^1H NMR (200 MHz, $CDCl_3$): δ 2.28 (s, 6H, 2 × CH_3), 2.42 (s, 3H, CH_3), 3.54 (s, 2H, CH_2CO), 4.42 (d, 2H, NCH_2), 5.64 (bt, 1H, NH), 6.86 (s, 2H,

aromatic), 7.28-7.37 (m, 4H, aromatic). IR (KBr): 3446, 1638, 1565 and 1210 cm^{-1}. Mass: *m/z* 283 (M^+); Anal. Calcd for $C_{25}H_{27}NO_2$: C, 76.32; H, 7.42; N, 4.94. Found: C, 76.37; H, 7.45; N, 4.97.

***N*-1-(4-Chlorobenzyl)-2-(4′-benzyloxy-3′,5′-dimethylphenyl) acetamide 3e**. 77% yield, liquid, ^1H NMR (200 MHz, $CDCl_3$): δ 2.24 (s, 6H, 2 × CH_3), 3.44 (s, 2H, CH_2CO), 4.36 (d, 2H, NCH_2), 4.78 (s, 2H, OCH_2), 5.66 (bt, 1H, NH), 6.86 (s, 2H, aromatic), 7.12 (d, 2H, aromatic); 7.22 (d, 2H, aromatic), 7.28-744 (m, 5H, aromatic). IR (KBr): 3435, 1640, 1450 & 1025 cm^{-1}. Mass: *m/z* 393 (M^+); Anal. Calcd for $C_{24}H_{24}ClNO_2$: C, 73.28; H, 6.10; N, 3.56. Found: C, 73.27; H, 6.13; N, 3.57.

***N*-1-(4-Chlorobenzyl)-2-(3′,5′-dimethyl-4′-hydroxyphenyl) acetamide 4e**. 92% yield, solid, m.p. 177°C. ^1H NMR (200 MHz, $CDCl_3$): δ 2.28 (s, 6H, 2 × CH_3), 3.49 (s, 2H, CH_2CO), 4.42 (d, 2H, NCH_2), 5.74 (bt, 1H, NH), 6.92 (s, 2H, aromatic), 7.24 (d, 2H, aromatic), 7.32 (d, 2H, aromatic); IR (KBr): 3445, 1640, 1555 and 1215 cm^{-1}. Mass: *m/z* 303 (M^+). Anal. Calcd for $C_{17}H_{18}ClNO_2$: C, 67.32; H, 5.94; N, 4.62. Found: C, 67.37; H, 5.93; N, 4.66.

Acknowledgement

The Author is thankful to the Director, IICT and Head, Organic Chemistry Division for constant encouragement.

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