Synthesis of Imides and Amides from Diacetyl-L-Tartaric Acid Anhydride

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Received August 12, 2008: Revised February 13, 2010: Accepted February 18, 2010

Abstract: Diacetyl-L-tartaric acid anhydride reacted with aromatic primary amines to yield imides (**3g-l**) and amides (**4a-f**). The *ortho*-substituted aromatic primary amines either with electron donating or withdrawing groups yielded amides, whereas *para*-substituted amines produced imides. However, *meta*-substituted aromatic primary amines with electron withdrawing residues afforded amides while electron donating counterparts furnished imides.

Keywords: Diacetyl-L-tartaric acid anhydride, aromatic primary amines, imides, amides.

INTRODUCTION

Imides are classically defined as cyclic secondary amides of the dicarboxylic acids with wide range of applications [1]. The interest in structural characterization of cyclic imides is most frequently attributed to the biological importance of some of their naturally abundant analogues [2]. *N*-Substituted imides exhibited a variety of biological activities such as antimicrobial [3], antiepileptic [4], anticonvulsive [5], and antifungal [6]. Maleimides are an important class of substrates for various pharmacological and chemical applications. In pharmacological applications, maleimides are used as chemical probes for protein structures [7], as immunoconjugates for cancer therapy as well as for the production of antibiotics [8]. They are also used as analogues for cyclic tetra-peptide chlamydocin [9], photoactivatable fluorescence derivatives [6] and as new herbicides and pesticides [10]. Among other uses, imides are utilized in the production of polyimides, which are necessary materials for a variety of purposes including their use in the electronics and space craft industry [6].

Amides also possess a variety of biological activities, for example, paracetamol is a potent non-steroidal anti-inflammatory (NSAID) and antipyretic drug having an amide moiety. Analgesic properties of paracetamol were discovered accidentally when a similar molecule, acetanilide, was serendipitously found to possess analgesic as well as antipyretic properties, and was quickly introduced into medical practice under the name of Antifebrin [11].

Different methods have been reported for the synthesis of imides including solid phase synthesis [12], solution phase and microwave synthesis [13]. Most of these methods involve the reaction of anhydride with primary amines. Various other methods were also reported for the synthesis of amides involving the reaction of isocyanides with acids [14], Ugi reaction [15] (from aldehydes and primary amines), Schmidt reaction [16] (from ketones and ammonia), Schotten-Baumann reaction [17] (from acyl halides and primary amines).

RESULTS AND DISCUSSION

In our continuation of studies towards the development of new routes for the synthesis of organic compounds [18], we herein report a facile synthesis of imides and amides by using diacetyl-L-tartaric acid anhydride and substituted primary aromatic amines (Scheme **1**). All the synthesized compounds were purified by column chromatography and characterized by using spectroscopic techniques like ^{1}H- and ^{13}C-NMR spectroscopy, mass and elemental analysis.

In our studies we found that the steric as well as electronic factors determine the formation of amides or imides. *Ortho*-substituted aromatic primary amines only give amides irrespective of the nature of substituent which suggests that once the amide is formed the steric hindrance offered by the *ortho*-substituent prevents the ring closure to yield the imide. On the other hand when the same substituent is at the *para*- position they exclusively gave imides as product which supports our argument given above. Surprisingly, in case of *meta*-substituted primary aromatic amines, amides and imides, both, are formed depending upon the nature of substituents. Primary aromatic amines having electron donating groups yield exclusively imides, while, amines with electron withdrawing groups afforded amides only. The difference in the nucleophilicity of amino group may be rationalized on electronic and steric factors, respectively.

Synthesis of some imides and amides was carried out by using diacetyl-L-(+)-tartaric acid anhydride with primary amines (Scheme **1**). All the synthesized compounds were

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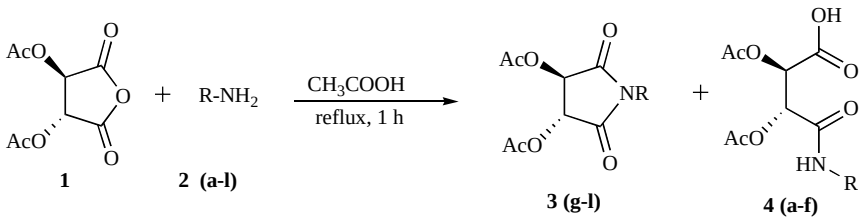

1 **2 (a-l)** **3 (g-l)** **4 (a-f)**

S. No.	R	Yield (%)	S. No.	R	Yield (%)
3g	3-$CH_3C_6H_4$-	68	**4a**	2-OHC_6H_4	68
3h	4-OHC_6H_4-	75	**4b**	2-$COOHC_6H_4$	75
3i	4-$COOHC_6H_4$	65	**4c**	2-$NO_2C_6H_4$	71
3j	4-$NO_2C_6H_4$	79	**4d**	2-$OCH_3C_6H_4$	80
3k	4-$OCH_3C_6H_4$	76	**4e**	2-$CH_3C_6H_4$	70
3l	4-$CH_3C_6H_4$	73	**4f**	3-$COOHC_6H_4$	55

Scheme 1. Synthesis of imides and amides.

purified by column chromatography and characterized by using spectroscopic techniques like ^{1}H- and ^{13}C NMR spectroscopy, mass and elemental analysis.

EXPERIMENTAL GENERAL

All the synthesized compounds were characterized by IR, ^{1}H-NMR, ^{13}C-NMR spectral data, mass spectrometry and elemental analysis. IR spectra (KBr) were recorded on a Schimadzu FT-IR 270 spectrophotometer. ^{1}H-NMR spectra were recorded at 300 MHz (Bruker Avance 300 MHz). ^{13}C NMR spectra were recorded at 75 MHz. Tetramethylsilane (TMS) was used as internal reference. Electron impact mass spectra were performed on VG: 70 SE mass spectrometer.

General Procedure for the Synthesis of Imides (3g-l) and Amides (4a-f)

Imides and amides were synthesized by using 0.005 mole (1.08 g) of diacetyl-L-tartaric acid anhydride (2,5-dioxotetrahydrofuran-3,4-diyldiacetate), respective amine (0.005 mole) and 10 mL of glacial acetic acid. The resulting mixture was refluxed for one hour under nitrogen. Glacial acetic acid was removed by extracting the reaction mixture with ethyl acetate or chloroform and water. Products were purified by column chromatography.

3-(3,4-Diacetoxy-2,5-dioxopyrrolidine-1-yl)toluene (3g)

Yield: 68%, solid, M.p. = 106-108 °C; IR (KBr): 2958 (C-H stretching), 1740 (CO imide), 1737 (CO ester), 1559 (aromatic) cm^{-1}; ^{1}H-NMR (300 MHz, CD_3OD): δ 7.41-7.13 (m, 4H), 5.88 (s, 2H), 2.20 (s, 6H), 2.39 (s,3H); ^{13}C-NMR (75 MHz, CD_3OD): δ 169.3 (-*CO*OR), 170.3 (-*CO*N), 139.1-123.3 (*C_6H_4*), 72.8 (-*CH*), 19.8 (*CH_3*-CO), 19.4 (CH_3-Ar); EIMS *m/z* (rel. abund. *%*): 305 (M^+, 5), 202 (100), 187 (2), 91 (16).

4-(3, 4-Diacetoxy-2,5-dioxopyrrolidine-1-yl)phenol (3h)

Yield: 75%, solid, M.p. = 73-75 °C; FTIR (KBr): 3250-2615(O-H), 2961 (C-H stretching), 1745 (CO imide), 1735 (CO ester) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.68-7.38 (m, 4H), 6.39 (s, 2H), 2.63 (s, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 178.9 (-*CO*OR), 170.1 (-*CO*N), 156.3-116.6 (*C_6H_4*), 72.8 (-*CH*-), 20.4 (*CH_3*-CO); Anal. Calcd. for $C_{14}H_{13}O_7N$: C, 54.32; H, 4.26; N, 4.55. Found: C, 53.95; H, 4.51; N, 4.46.

4-(3,4-Diacetoxy-2,5-dioxopyrrolidine-1-yl) Benzoic Acid (3i)

Yield: 65%, solid, M.p. = 127-129 °C; IR (KBr): 3500-2677 (O-H) 2955 (C-H stretching), 1735 (CO imide),1730 (CO acid) 1703 (CO ester), 1609 (aromatic) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.20-7.48 (m, 4H), 5.69 (s, 2H), 2.26 (s, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 170.1 (-*CO*OR), 170.7 (-*CO*N), 168.1 (-*CO*OH), 135.3-126.0 (*C_6H_4*), 72.7 (-*CH*-), 20.3 (*CH_3*-CO); EIMS *m/z* (rel. abund. *%*): 335 (M^+, 8), 295 (1), 232 (100), 194 (53), 163(38), 146 (79), 59 (36).

4-(3,4-Diacetoxy-2,5-dioxopyrrolidine-1-yl) Aniline (3j)

Yield: 79%, solid, M.p. = 117-118 °C; IR (KBr): 2932 (C-H stretching), 1757 (CO imide), 1741 (CO ester), 1597 (aromatic) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ, 8.39-7.64 (m, 4H), 5.63 (s, 2H), 2.26 (s, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 168.9 (-*CO*OR), 170.1 (-*CO*N), 147.4-136.1 (*C_6H_4*), 72.7 (-*CH*), 20.3 (*CH_3*-CO); EIMS *m/z* (rel. abund. *%*): 336 (M^+, 35), 293 (4), 134 (22), 122 (11), 101 (100), 59 (8).

4-(3,4-Diacetoxy-2,5-dioxopyrrolidine-1-yl) Anisidine (3k)

Yield: 76%, solid, M.p. = 150-152 °C; IR (KBr): 2934 (C-H stretching), 1760 (CO imide), 1736 (CO ester), 1513 (aromatic) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ, 7.98-7.24 (m, 4H), 5.66 (s, 2H), 2.24 (s, 6H), 3.84 (s,3H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ, 168.7 (-*CO*OR), 170.0 (-*CO*N), 159.6-114.6 (*C_6H_4*), 72.8 (-*CH*), 20.4 (*CH_3*-CO), 55.5 (-OCH_3); EIMS *m/z* (rel. abund. *%*): 321 (M^+, 23), 219 (100), 203 (2), 148 (80).

4-(3,4-Diacetoxy-2,5-dioxopyrrolidine-1-yl) Toludine (3l)

Yield: 73%, solid, M.p. = 118-120 °C; IR (KBr): 2952 (C-H stretching), 1750 (CO imide), 1723 (CO ester), 1558 (aromatic) cm^{-1}; ^{1}H-NMR (300 MHz, Acetone *d*): δ 7.35-

7.25 (m, 4H), 5.97 (s, 2H), 2.18 (s, 6H), 2.38 (s.3H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ, 168.8 (-*CO*OR), 170.0 (-*CO*N), 138.7-126.5 (*C_6H_4*), 72.6 (-*CH*), 19.4 (*CH_3*-CO); EIMS *m/z* (rel. abund. *%*): 305 (M^+, 5), 202 (100), 187 (2), 91 (16).

2,3-Diacetoxy-4-(2-hydroxyphenyl amino)-4-oxobutanoic Acid (4a)

Yield: 68%, liquid; FTIR (NaCl): 3503 (N-H stretching), 3559-2677 (O-H), 2941 (C-H stretching), 1750 (CO ester), 1730 (CO acid), 1670 (CO amide), 1599 (aromatic) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ, 7.47 (dd, *J* = 7.8,1.5 Hz, 1H, Ar), 6.98 (d,d, *J* =8.1,1.5 Hz, 1H, Ar), 6.93 (ddd, *J* = 7.6, 1.2, 1.2 Hz, 1H, Ar), 7.14 (d,d,d *J* = 8.4, 1.5, 1.5 Hz, 1H, Ar), 5.97 (d, *J* = 2.4 Hz, 1H, -*CH*), 5.67 (d, *J* = 2.4 Hz, 1H, -*CH*), 2.14 (s, 3H, -*CH_3*), 2.27 (s, 3H, -*CH_3*),8.30 (s,N-H), 7.37 (OH phenolic); ^{13}C-NMR (75 MHz, $CDCl_3$): δ, 169.5 (-*CO*OH), 166.5(-*CO*OR), 165.0 (-*CO*OR), 168.5 (-*CO*N), 147.5-118.3 (C_6H_4), 71.3(-*CH*-), 71.2 (-*CH*-), 20.3 (-*CH_3*), 20.5 (-*CH_3*).

2-(2,3-Diacetoxy-3-carboxypropanamido)benzoic Acid (4b)

Yield: 75%, solid, M.p. = 103-105° C; IR (KBr): 3511 (N-H), 3250-2615 (O-H), 2903 (C-H stretching), 1750 (CO ester), 1730 (CO acid), 1670 (CO amide) cm^{-1}; ^{1}H-NMR (300 MHz, CD_3OD): δ 8.64 (dd, *J* = 7.0, 2.5 Hz, 1H, Ar), 8.13 (dd, *J* = 6.8, 3.0 Hz, 1H, Ar), 7.61 (ddd, *J* = 7.0, 2.0, 2.0 Hz, 1H, Ar), 7.21 (ddd, *J* = 7.2, 3.1, 3.1 Hz, 1H, Ar), 5.87 (d, *J* = 2.1 Hz, 1H,-*CH*), 5.70 (d, *J* = 2.4 Hz, 1H, -*CH*), 2.30 (s, 3H, -*CH_3*), 2.05 (s, 3H, -*CH_3*); ^{13}C-NMR (75 MHz, CD_3OD): δ 170.0 (-CH*CO*OH), 169.4 (-*CO*OR), 168.4 (-*CO*OR), 169.8 (-*CO*N), 165.4 (Ar-*CO*OH), 140.0-116.1 (C_6H_4), 72.4 (-*CH*), 71.2 (-*CH*-), 19.1 (-*CH_3*), 18.8 (-*CH_3*); Anal. Calcd. for $C_{15}H_{15}O_9N$: C, 50.99; H, 4.27; N, 3.96. Found: C, 49.67; H, 4.57; N, 3.88.

2,3-Diacetoxy-4-(2-nitrophenylamino)-4-oxobutanoic Acid (4c)

Yield: 71%, solid, M.p. = 110-111 °C; IR (KBr): 3503 (N-H stretching), 3250-2615 (O-H), 2941 (C-H stretching), 1753(CO ester), 1725 (CO acid), 1690 (CO amide), 1587&1346 (N-O stretching) cm^{-1}; ^{1}H-NMR (300 MHz, Acetone *d_6*): δ 8.57 (dd, *J* = 6.8,3.0 Hz, 1H,Ar), 8.26 (d,d, *J* = 6.5,3.0 Hz, 1H, Ar), 7.852 (ddd, *J* = 7.1, 3.2, 3.2 Hz, 1H, Ar), 7.41 (ddd, *J* = 7.0, 2.0, 2.0 Hz, 1H, Ar), 5.93 (d, *J* = 3.0 Hz, 1H, -*CH*), 5.69 (d, *J* = 3.0 Hz, 1H, -*CH*), 2.25 (s, 3H, -CH_3), 2.08 (s, 3H, -CH_3); ^{13}C-NMR (75 MHz, Acetone d_6): δ 169.2 (-CH*CO*OH), 167.7 (-*CO*OR), 167.4 (-*CO*OR), 168.7 (-*CO*N), 138.1-122.4 (C_6H_4), 72.4 (-*CH*-), 71.0 (-*CH*), 19.6 (-*CH_3*), 19.4 (-*CH_3*); Anal. Calcd. for $C_{14}H_{14}O_9N_2$: C, 47.46; H, 3.98; N, 7.90. Found: C, 46.65; H, 4.13; N, 7.77; EIMS *m/z* (rel. abund. *%*): 354 (M^+, 4), 217 (8), 189 (3), 137 (100), 91 (26), 65 (25).

2,3-Diacetoxy-4-(2-methoxyphenylamino)-4-oxobutanoic Acid (4d)

Yield: 80%, solid, M.p. = 98-100 °C; IR (KBr): 3503 (NH stretching), 3423-2846 (OH), 2941 (CH stretching), 1744 (CO ester), 1760 (CO acid), 1637 (CO amide) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ, 7.47 (dd, *J* = 7.8, 1.5 Hz, 1H, Ar), 7.17 (dd, *J* = 8.1, 1.5 Hz, 1H, Ar), 7.03 (ddd, *J* = 7.6, 1.2, 1.2 Hz, 1H, Ar), 7.28 (ddd, *J* = 8.4, 1.5, 1.5 Hz, 1H, Ar), 5.88 (d, *J* = 6.0 Hz, 1H,-*CH*), 5.74 (d, *J* = 6.0 Hz, 1H, -*CH*), 2.26 (s, 3H, -*CH_3*), 2.24 (s, 3H, -*CH_3*); ^{13}C-NMR (75 MHz, $CDCl_3$): δ, 170.0 (-CH*CO*OH), 168.2 (-*CO*OR), 168.3 (-*CO*OR), 169.7 (-*CO*N), 154.5-119.3 (C_6H_4), 72.4 (-*CH*), 73.0 (-*CH*-), 20.4 (-*CH_3*), 20.4 (-*CH_3*); EIMS *m/z* (rel. abund. *%*): 339 (M^+, 1), 308 (2), 222 (3), 204 (5), 108 (100).

4-(o-Toluidino)-2,3-diacetoxy-4-oxobutanoic Acid (4e)

Yield: 70%, solid, M.p. = 125-127 °C; IR (KBr): 3510 (N-H stretching), 3448-2677 (O-H), 2948 (C-H stretching), 1735(CO ester), 1760 (CO acid), 1670 (CO amide), 1590 (aromatic) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.40 (dd, *J* = 7.8,1.5 Hz, 1H,Ar), 7.29 (d,d, *J* = 8.1,1.5 Hz, 1H, Ar), 7.21(ddd, *J* = 7.21, 1.2, 1.2 Hz, 1H, Ar), 7.35 (ddd, *J* = 8.4,1.5, 1.5 Hz, 1H, Ar), 5.74 (d, *J* = 5.1 Hz, 1H, -*CH*), 5.53 (d, *J* = 5.4 Hz, 1H, -*CH*), 2.24 (s, 3H, -*CH_3*), 2.23 (s, 3H, -*CH_3*), 2.25 (Ar-CH_3); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 170.2 (-CH*CO*OH), 168.4 (-*CO*OR), 168.5(-*CO*OR), 170.1 (-*CO*N), 147.5-118.3 (C_6H_4), 73.6 (-*CH*), 72.6 (-*CH*), 17.5 (-*CH_3*), 17.6 (-*CH_3*); EIMS *m/z* (rel. abund. *%*): 323 (M^+, 6), 278 (2), 218 (71), 148 (100), 70(23).

3-(2,3-Diacetoxy-3-carboxypropanamido) Benzoic Acid (4f)

Yield: 55%, liquid; IR (KBr): 3500 (N-H stretching), 3498-2600 (O-H), 2943 (C-H stretching), 1740 (CO ester),1765 (CO acid), 1687 (CO amide), 1587 (aromatic) cm^{-1}; ^{1}H-NMR (300 MHz, CD_3OD): δ 8.18 (dd, *J* = 1.8,1.8 Hz, 1H, Ar), 7.81-7.78 (m, 2H, Ar), 7.43 (dd, *J* = 8.1, 7.8 Hz, 1H, Ar), 5.71 (d, *J* = 2.7 Hz, 1H, -*CH*), 5.55 (d, *J* = 2.7 Hz, 1H, -*CH*), 2.21 (s, 3H, -*CH_3*), 2.11 (s, 3H, -*CH_3*); ^{13}C-NMR (75 MHz, CD_3OD): δ 170.0 (-CH*CO*OH), 167.0 (-*CO*OR), 170.5 (-Ar*CO*OH), 167.0 (-*CO*OR), 168.6 (-*CO*N), 137.7-121.8 (C_6H_4), 73.1 (-*CH*-), 74.0 (-*CH*), 19.3 (-*CH_3*), 19.2 (-*CH_3*); Anal. Calcd. for $C_{15}H_{15}O_9N$: C, 50.99; H, 4.27; N, 3.96. Found: C, 49.67; H, 4.57; N, 3.88.

ACKNOWLEDGEMENT

This work was financially supported by the Higher Education Commission (HEC) Pakistan under "National Research Program for Universities."

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