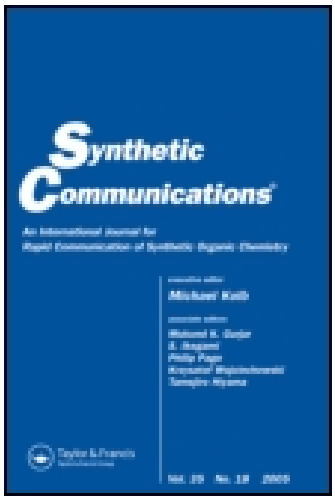

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

# THE SYNTHESIS OF A SERIES OF 3,5-DISUBSTITUTED TETRAHYDRO- 1H-IMIDAZOLE-2,4-DIONES UTILIZING LITHIUM ALUMINUM HYDRIDE

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Published online: 21 Aug 2006.

To cite this article: M. Lee Sanders & I. O. Donkor (2002) THE SYNTHESIS OF A SERIES OF 3,5-DISUBSTITUTED TETRAHYDRO-1H-IMIDAZOLE-2,4-DIONES UTILIZING LITHIUM ALUMINUM HYDRIDE, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 32:7, 1015-1021, DOI: 10.1081/SCC-120003149

To link to this article: http://dx.doi.org/10.1081/SCC-120003149

SYNTHETIC COMMUNICATIONS, 32(7), 1015–1021 (2002)

# THE SYNTHESIS OF A SERIES OF 3,5-DISUBSTITUTED TETRAHYDRO-1*H*-IMIDAZOLE-2,4-DIONES UTILIZING LITHIUM ALUMINUM HYDRIDE

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## ABSTRACT

A series of 3,5-disubstituted tetrahydro-1*H*-imidazole-2,4-diones were synthesized from the corresponding urea methyl ester precursors utilizing lithium aluminum hydride as the cyclization agent.

Lithium aluminum hydride (LAH) is a versatile reagent utilized in a variety of synthetic reactions. The most predominant role of LAH in the organic laboratory is its use in the reduction of various functional groups. LAH has long been identified as a reagent for the transformation of alkyl esters to the corresponding alcohols.[1] It has also been demonstrated that the urea functional group is quite stable in the presence of LAH.[2] Therefore, as a part of a program aimed at synthesizing urea-based peptidomimetic calpain inhibitors, LAH was employed as the reducing agent in an attempt

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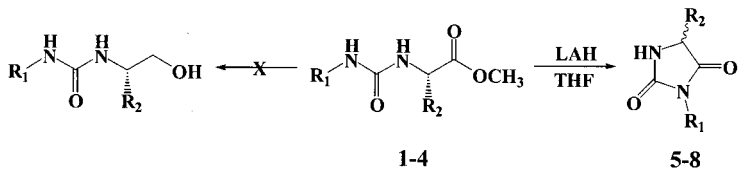
to transform urea methyl esters **1–4** to the corresponding alcohols. However, upon reacting LAH with compounds **1–4** it was observed that cyclization to the corresponding tetrahydro-1*H*-imidazole-2,4-diones (hydantoins) occurred rather than reduction of the methyl ester group to the alcohol (Scheme 1). 3,5-Disubstituted tetrahydro-1*H*-imidazole-2,4-diones have previously been synthesized from urea methyl ester precursors utilizing a variety of reagents.[3–17] However, to our knowledge this is the first report describing the use of LAH as a cyclization agent in the transformation of urea methyl esters to the corresponding tetrahydro-1*H*-imidazole-2,4-diones. In this report we describe the synthesis of four 3,5-disubstituted tetrahydro-1*H*-imidazole-2,4-diones (**5–8**) using LAH as the cyclization agent to further demonstrate the versatility of this reagent in organic synthesis.




***Scheme 1.*** $R_1$ = i-Pro, $CH_2Ph$, $(CH_2)_2Ph$ $R_2$ = i-Pro, $CH_2Ph$.

## EXPERIMENTAL

All reagents and solvents were purchased from either Aldrich Chemical Company or Advanced ChemTech Inc. and used without further purification. Melting points were obtained utilizing a Thomas Hoover capillary melting point apparatus and were uncorrected. $^1$H NMR spectra were determined at 300 MHz and $^{13}$C NMR spectra at 75 MHz (Bruker ARX 300 instrument). Elemental analyses were obtained from Atlantic Microlab, Inc. (Norcross, GA).

### General Procedure 1. Reaction of L-Amino Acids with Alkyl Isocyanates

The reactions were conducted utilizing a modified procedure of Hill and DePree.[18] To a solution of L-amino acid methyl ester hydrochloride (1 equivalent) and toluene (3 equivalents) at 50°C was slowly added triethylamine (1.5 equivalents). After 15 min, isocyanate (1.1 equivalents) was added portion wise over a 30 min interval. The mixture was stirred at 50°C for 16 h. After the reaction mixture was cooled to room temperature,

water (5 ml) was added followed by dichloromethane (10 ml). The organic layer was successively treated with saturated sodium bicarbonate (5 ml), water (5 ml), 1N hydrochloric acid (5 ml), water (5 ml), and brine (5 ml). The organic layer was dried over magnesium sulfate, filtered, and concentrated in vacuo to obtain a white solid. The compounds were purified by recrystalization from ethyl acetate/hexane to obtain the product in 53–71% yield. Compounds **1–4** were synthesized utilizing this procedure.



### Methyl-(2*S*)-2{[(benzylamino)carbonyl]amino}-3-phenylpropanoate (1)

Compound **1** was synthesized from a solution of 0.57 g (2.66 mmoles) of L-phenylalanine methyl ester hydrochloride, 0.85 ml of toluene, 0.56 ml triethylamine (3.99 mmoles), and 0.36 ml benzyl isocyanate (2.92 mmoles). Recrystalization gave **1** as a white solid, 0.92 g (71%), m.p. 94–96°C. $^1$H NMR ($CDCl_3$): δ 3.01–3.06 ppm (m, 2H, $PhCH_2CH$), 3.66 (s, 3H, $OCH_3$), 4.28 (dd, 2H, $PhCH_2NHCO$), 4.77 (t, 1H, $PhCH_2CHCOOCH_3$), 7.10–7.29 ppm (m, 10H, phenyl protons). Anal. calcd for $C_{18}H_{20}N_2O_3$: C, 69.21; H, 6.45; N, 8.97. Found: C, 69.05; H, 6.49, N, 9.05.

### Methyl-(2*S*)-2{[(phenethylamino)carbonyl]amino}-3-phenylpropanoate (2)

Compound **2** was synthesized from a solution of 0.51 g (2.37 mmoles) of L-phenylalanine methyl ester hydrochloride, 0.76 ml of toluene, 0.50 ml triethylamine (3.56 mmoles) and 0.36 ml phenethyl isocyanate (2.61 mmoles). Recrystalization gave **2** as a white solid, 0.68 g (68%), m.p. 110–111°C. $^1$H NMR ($CDCl_3$): δ 2.79 (dd, 2H, $PhCH_2CH$), 3.01–3.14 ppm (m, 2H, $PhCH_2CH_2NH$), 3.32–3.50 ppm (m, 2H, $PhCH_2CH_2NH$), 3.70 (s, 3H, $OCH_3$), 4.34–4.38 ppm (t, 1H, $PhCH_2CHCOOCH_3$), 4.69 ppm (d, 1H, NH), 4.74–4.79 ppm (m, 1H, NH), 7.10–7.30 ppm (m, 10H, phenyl protons). Anal. calcd for $C_{19}H_{22}N_2O_3$: C, 69.92; H, 6.79; N, 8.58. Found: C, 69.87; H, 6.81; N, 8.54.

### Methyl-(2*S*)-2{[(isopropylamino)carbonyl]amino}-3-phenylpropanoate (3)

Compound **3** was synthesized from a solution of 0.62 g (2.89 mmoles) of L-phenylalanine methyl ester hydrochloride, 0.92 ml of toluene, 0.61 ml

triethylamine (4.34 mmoles), and 0.31 ml of isopropyl isocyanate (3.18 mmoles). Recrystalization gave **3** as a white solid, 0.69 g (58%), m.p. 115°C. $^1$H NMR ($CDCl_3$): δ 0.97–1.01 (dd, 6H, $CH_3CHCH_3$), 2.72–2.98 (m, 2H, $PhCH_2CH$), 3.54–3.66 (m, 1H, $CH_3CHCH_3$), 3.59 (s, 3H, $OCH_3$), 4.35–4.43 (m, 1H, $PhCH_2CHCOOCH_3$), 5.94 (d, 1H, NH), 6.00 (d, 1H, NH), 7.14–7.31 ppm (m, 5H, phenyl protons). Anal. calcd for $C_{14}H_{20}N_2O_3$: C, 63.62; H, 7.63; N, 10.60. Found: C, 63.65; H, 7.58; N, 10.74.

### Methyl-(2*S*)-2{[(benzylamino)carbonyl]amino}-3-methylbutanoate (4)

Compound **4** was synthesized from a solution of 0.50 g (2.99 mmoles) of L-valine methyl ester hydrochloride, 0.96 ml of toluene, 0.63 ml triethylamine (4.49 mmoles), and 0.41 ml benzyl isocyanate (3.29 mmoles). Recrystalization gave **4** as a white solid, 0.42 g (53%), m.p. 82–84°C. $^1$H NMR ($CDCl_3$): δ 0.84 (d, 3H, $CH_3CHCH_3$), 0.93 (d, 3H, $CH_3CHCH_3$), 2.03–2.15 ppm (m, 1H, $CH_3CHCH_3$), 3.69 (s, 3H, $OCH_3$), 4.36 (d, 2H, $PhCH_2NHCO$), 4.43 (d, 1H, $CH_3OCOCHNHCO$), 7.23–7.35 ppm (m, 5H, phenyl protons). Anal. calcd for $C_{14}H_{20}N_2O_3$: C, 63.62; H, 7.63; N, 10.60. Found: C, 63.78; H, 7.62; N, 10.51.

### General Procedure 2. Preparation of 3,5-Disubstituted Tetrahydro-1*H*-imidazole-2,4-diones

To a stirring solution of the urea methyl ester compounds (**1–4**) (0.326 mmoles) in excess anhydrous tetrahydrofuran was added lithium aluminum hydride (0.652 mmoles) under nitrogen at room temperature. After 30 min, water was slowly added to the mixture followed by product extraction with dichloromethane. The organic layer was washed with water (3 × 10 ml), dried over magnesium sulfate, and evaporated to obtain the crude product. Flash chromatography (2 : 1 ethyl acetate : hexanes) on silica gel was utilized to obtain the product in purified form. Compounds **5–8** were synthesized utilizing this procedure.

### 3,5-Dibenzyltetrahydro-1*H*-imidazole-2,4-dione (5)

Compound **5** was synthesized as a white solid from 0.10 g (0.326 mmoles) of **1** in 34% yield, 0.03 g, m.p. 146°C. $^1$H NMR ($CDCl_3$): δ 2.79 (dd, 1H, $PhCH_2CH$), 3.14 (dd, 1H, $PhCH_2CH$), 4.15 (ddd, 1H,

$PhCH_2CH$), 4.49 (dd, 2H, $PhCH_2NCO$), 5.38 (s, 1H, NH), 6.98–7.26 ppm (m, 10H, phenyl protons). $^{13}C$ NMR ($CDCl_3$); δ 37.66 ($CH_2$), 42.07 ($NCH_2$), 58.31 (CH), 127.34, 127.74, 128.21, 128.59, 128.81, 129.27, 134.94, 135.71 (Ar), 156.90 (N(CO)N), 172.76 (CO). Anal. calcd for $C_{17}H_{16}N_2O_2$ 0.03 $H_2O$: C, 72.70; H, 5.76; N, 9.97. Found: C, 72.30; H; 6.09, N, 9.84.

### 5-Benzyl-3-phenethyltetrahydro-1*H*-imidazole-2,4-dione (6)

Compound **6** was synthesized as a white solid from 0.11 g (0.326 mmoles) of **2** in 41% yield, 0.04 g, m.p. 130–132°C. $^1H$ NMR ($CDCl_3$): δ 2.67 (dd, 1H, $PhCH_2CH$), 2.84 (t, 2H, $PhCH_2CH_2NCO$), 3.22 (dd, 1H, $PhCH_2CH$), 3.62–3.78 ppm (m, 2H, $PhCH_2CH_2NCO$), 4.15 (ddd, 1H, $PhCH_2CH$), 5.31 (s, 1H, NH), 7.17–7.30 ppm (m, 10H, phenyl protons). $^{13}C$ NMR ($CDCl_3$); δ 34.0 ($NCH_2CH_2Ph$), 37.6 ($CHCH_2Ph$), 45.3 ($NCH_2CH_2Ph$), 60.1 ($CHCH_2Ph$), 125.7, 127.9, 128.4, 140.2 (Ar), 159.0 (N(CO)N), 173.4 (CO). Anal. calcd for $C_{18}H_{18}N_2O_2$ 0.04 $H_2O$: C, 73.27; H, 6.18; N, 9.49. Found: C, 72.90; H, 6.22; N, 9.20.

### 3-Benzyl-5-isopropyltetrahydro-1*H*-imidazole-2,4-dione (7)

Compound **7** was synthesized as a white solid from 0.09 g (0.326 mmoles) of **3** in 60% yield, 0.05 g, m.p. 109–111°C. $^1H$ NMR ($CDCl_3$): δ 0.80 (d, 3H, $CH_3CHCH_3$), 1.00 (d, 3H, $CH_3CHCH_3$), 2.17–2.23 ppm (m, 1H, $CH_3CHCH_3$), 3.92 (d, 1H, HNCHCO), 4.63 (d, 2H, $PhCH_2NCO$), 6.81 (s, 1H, NH), 7.26–7.38 ppm (m, 5H, phenyl protons). $^{13}C$ NMR ($CDCl_3$): δ 16.2 ($CH_3CHCH_3$), 28.0 ($CH_3CHCH_3$), 48.7 ($NCH_2Ph$), 64.6 (CH), 126.5, 127.1, 128.3, 142.4 (Ar), 160.0 (N(CO)N), 173.0 (CO). Anal. calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.28; H, 6.97; N, 11.89.

### 5-Benzyl-3-isopropyltetrahydro-1*H*-imidazole-2,4-dione (8)

Compound **8** was synthesized as a colorless oil from 0.09 g (0.326 mmoles) of **4** in 25% yield, 0.02 g. $^1H$ NMR ($CDCl_3$): δ 1.25 (d, 6H, $NCH(CH_3)_2$), 2.95 (dd, 1H, $PhCH_2CH$), 3.16 (dd, 1H, $PhCH_2CH$), 4.08–4.19 ppm (m, 2H, $PhCH_2CH$ and $NCH(CH_3)_2$), 5.89 (s, 1H, NH), 7.12–7.27 ppm (m, 5H, phenyl protons). $^{13}C$ NMR ($CDCl_3$): δ 19.33 ($CH_3CHCH_3$), 19.42 ($CH_3CHCH_3$), 37.79 ($CHCH_2Ph$), 43.50 ($CH_3CHCH_3$), 57.48

($CHCH_2Ph$), 127.33, 128.70, 129.42, 134.93 (Ar), 157.18 (N(CO)N), 173.05 (CO). Anal. calcd for $C_{13}H_{16}N_2O_2$ 0.1 $H_2O$: C, 66.70; H, 6.98; N, 11.97. Found: C, 66.35; H, 7.06; N, 11.65.

## ACKNOWLEDGMENT

The work was supported by grant 5 K14 HL03536 from the U.S. Public Health Service to I.O.D.



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Received in the USA March 29, 2001