

SYNTHESIS OF 5,6,7,8-TETRAHYDRO-2*H*-1-BENZOPYRAN-2,5-DIONES AND 1,5-DIHYDRO-2*H*-PYRROL-2-ONES

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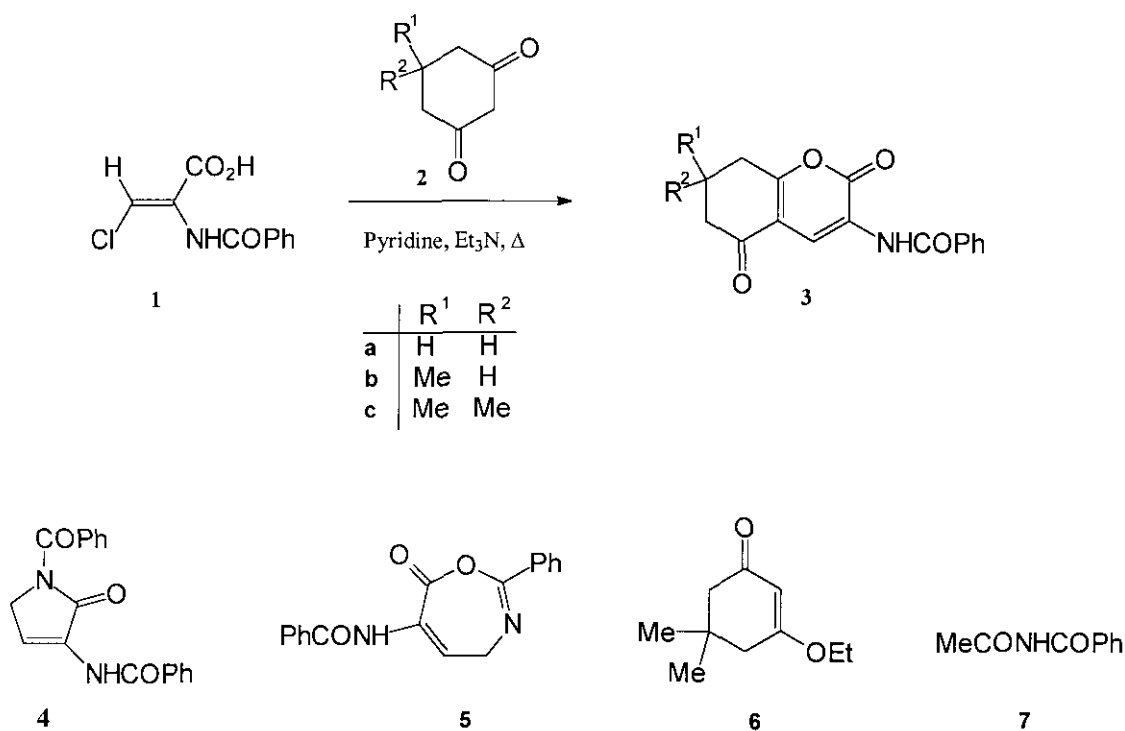
Abstract - The use of 2-benzoylamino-3-chloropropenoic acid in the synthesis of 5,6,7,8-tetrahydro-2*H*-1-benzopyran-2,5-diones and 1,5-dihydro-2*H*-pyrrol-2-ones is reported.

N-(5,6,7,8-Tetrahydro-2,5-dioxo-2*H*-1-benzopyran-3-yl)benzamides (**3**) can be prepared from 1,3-cyclohexanediones by (i) reaction with hippuric acid in acetic anhydride using one-carbon synthon (triethyl orthoformate, diethoxymethyl acetate or *N,N*-dimethylformamide dimethyl acetal),¹⁻³ (ii) treatment with 4-ethoxymethylene-2-phenyl-5(4*H*)-oxazolone,^{4,5} or (iii) reaction with methyl 2-benzoylamino-3-dimethylaminopropenoate.⁶ Recently, we reported on the use of 2-benzoylamino-3-chloropropenoic acid (**1**)⁷ in the synthesis of *N*-(heteroarylhydrazonoethyl)benzamides.⁸ Since **1** is a synthetic equivalent of the last two reagents in the above mentioned methods, we became interested in its utility in the 5,6,7,8-tetrahydro-2*H*-1-benzopyran-2,5-dione synthesis. Herein we report on the results of these investigations.

In order to test the desired synthetic utility of 2-benzoylamino-3-chloropropenoic acid (**1**) reactions with cyclohexane-1,3-dione (**2a**), 5-methylcyclohexane-1,3-dione (**2b**), and dimedone (**2c**) were performed under different reaction conditions. We found that the formation of the 5,6,7,8-tetrahydro-2*H*-1-benzopyran-2,5-dione system took place by heating in hot pyridine in the presence of triethylamine. Products (**3a**) and (**3b**) were isolated in 18 and 20% yields, respectively, whereas isolation of compound (**3c**) failed.

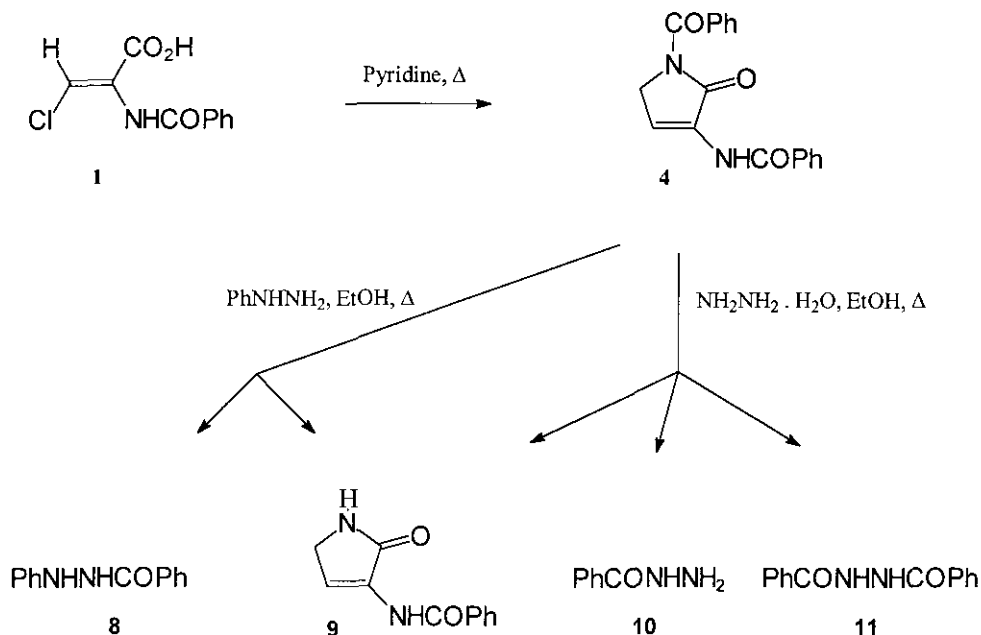
This conversion was in all three cases accompanied by the formation of a side product, isolated in the cases of **3a** and **3b** in 2% yield, with the molecular formula C₁₈H₁₄N₂O₃, determined by HRMS and confirmed by elemental analysis. The IR spectrum, showing C=O absorptions at 1725 cm⁻¹, 1680 cm⁻¹, 1660 cm⁻¹, and NH absorption at 3410 cm⁻¹, together with ¹H-NMR spectrum, showing signals for two

different phenyl groups and $-\text{CH}=\text{}$ group in the aromatic region, doublet for $-\text{CH}_2-$ group at 4.58 ppm with coupling constant of 2.5 Hz, and singlet for NH group at 9.78 ppm, suggested pyrrolinone (4) or oxazepinone (5). It was reported that the oxazepinone system could be rearranged into the pyrrolinone system.⁹ Since ^{13}C - and 2D-NMR (HMQC, HMBC) spectroscopy could not unambiguously determine the structure of this side product, its X-Ray crystal structure analysis¹⁰ was carried out confirming the structure (4). When filtrate of the reaction between 1 and dimedone (2c) was investigated in detail, compounds (6) and (7) were also isolated in 22 and 8% yields, respectively.



Taking into account that one molecule of 4 was formed from two molecules of the acid (1), we heated 1 alone in pyridine and obtained compound (4) in 46% yield. It is obvious that nucleophilic vinylic substitution of the chloro group must take place with an intermediate formed from the acid (1) which reacts on former amino acid α carbon followed by decarboxylation reaction. Our attempts to increase the yield of 4 by heating the acid (1) with equimolar amounts of possible intermediates, hippuric acid and 2-phenyl-5(4*H*)-oxazolone, were unsuccessful. It is of interest to note that the 4-hydroxy derivative of 4 was prepared from hippuric acid, 2-phenyl-5(4*H*)-oxazolone, and other α -amino acid derivatives.¹¹⁻¹³ Treatment of 4 with phenylhydrazine in ethanol afforded hydrazide (8) and 3-benzoylamino-1,5-dihydro-2*H*-pyrrol-2-one (9). Similarly, reaction with hydrazine hydrate in ethanol afforded a mixture of 9,

benzoic acid hydrazide (**10**) and *N,N'*-dibenzoylhydrazine (**11**). Although fourfold excess of hydrazine hydrate was used, no ring opening reaction was observed.



In conclusion, we found that 2-benzoylamino-3-chloropropenoic acid can be used as a new synthon for the preparation of 5,6,7,8-tetrahydro-2*H*-1-benzopyran-2,5-diones. This work also provides a novel entry to 1,5-dihydro-2*H*-pyrrol-2-ones.

EXPERIMENTAL

Melting points were determined on a Kofler micro hot stage and are uncorrected. NMR spectra were recorded on a Bruker AVANCE DPX-300 spectrometer with TMS as internal standard. Elemental analysis for C, H, N were obtained on a Perkin-Elmer CHN Analyzer 2400. IR spectra were recorded on a Perkin-Elmer 1310 or 727 B spectrometer. MS spectra were obtained on a VG-Analytical AutoSpec Q instrument. Radial chromatography was performed on Chromatotron (Harrison Research, Palo Alto). Rotor for radial chromatography was coated according to the manufacturer's instructions with Merck Silica Gel (Cat. No. 7749) in 2 mm thick layer. 2-Benzoylamino-3-chloropropenoic acid (**1**),⁷ 5-methyl-1,3-cyclohexanedione (**2b**),¹⁴ and 2-phenyl-5(4*H*)-oxazolone,¹⁵ were prepared as described in the literature. All other compounds were used without purification as obtained from commercial sources. Compounds (**6**),¹⁶ (**7**),¹⁷ and (**8**),¹⁸ were identified by comparison with authentic samples prepared by

known procedures, compounds (10) and (11) were identified by comparison with authentic samples from Aldrich.

***N*-(5,6,7,8-Tetrahydro-2,5-dioxo-2*H*-1-benzopyran-3-yl)benzamide (3a):**

A mixture of 451 mg (2 mmol) of acid 1, 231 mg (2 mmol) of cyclohexane-1,3-dione (2a), 120 mg (1.18 mmol) of triethylamine in 4 mL of pyridine was heated under reflux for 2 h. The reaction mixture was evaporated under reduced pressure and the oily residue was treated with 2 mL of ethanol. The separated solid was filtered and washed with small amount of ethanol giving 218 mg of the mixture of 3a and 4 in a ratio of 5:1, estimated on the basis of ¹H-NMR spectroscopy. Radial chromatography (petroleum ether/ethyl acetate, 5:1) of this mixture afforded 6 mg (2%) of 4 and 102 mg (18%) of 3a (mp 188-190°C, lit.,¹ 188-189°C).

***N*-(5,6,7,8-Tetrahydro-7-methyl-2,5-dioxo-2*H*-1-benzopyran-3-yl)benzamide (3b):**

A mixture of 451 mg (2 mmol) of acid (1), 252 mg (2 mmol) of cyclohexane-1,3-dione derivative (2b), 120 mg (1.18 mmol) of triethylamine in 4 mL pyridine was heated under reflux for 2 h. The reaction mixture was evaporated under reduced pressure and the oily residue was treated with 2 mL of ethanol. The separated solid was filtered and washed with small amount of ethanol giving 199 mg of the mixture of 3b and 4 in a ratio of 4.9:1, estimated on the basis of ¹H-NMR spectroscopy. Radial chromatography (petroleum ether/ethyl acetate, 5:1) of this mixture afforded 7 mg (2%) of 4 and 120 mg (20%) of 3b (mp 191-192°C, lit.,⁴ 191-192°C).

Reaction of 2-benzoylamino-3-chloropropenoic acid (1) with dimedone (2c):

A mixture of 225 mg (1 mmol) of acid (1), 140 mg (1 mmol) of dimedone (2c), 60 mg (0.59 mmol) of triethylamine in 2 mL pyridine was heated under reflux for 2 h. The reaction mixture was evaporated under reduced pressure and the oily residue was treated with 1 mL of ethanol. The separated solid was filtered and washed with small amount of ethanol giving 118 mg of the mixture of 3c⁴ and 4 in a ratio of 10:1, identified on the basis of ¹H-NMR spectroscopy. Attempts to separate this mixture with radial chromatography failed. The remaining filtrate was evaporated under reduced pressure and the oily residue was purified with radial chromatography (chloroform/methanol, 50:1) to give 67 mg of mixture which after further radial chromatography (petroleum ether/ethyl acetate, 5:1) gave 37 mg (22%) of cyclohexenone (6) (mp 42-45°C, lit.,¹⁶ 57-58°C) and 13 mg (8%) of *N*-acetylbenzamide (7) (mp 114-117°C, lit.,¹⁷ 117-118°C).

1-Benzoyl-3-benzoylamino-1,5-dihydro-2*H*-pyrrol-2-one (4):

A mixture of 113 mg (0.5 mmol) of acid (1) and 2 mL of pyridine was heated under reflux for 2 h. The reaction mixture was evaporated under reduced pressure and the solid residue was treated with 1 mL of

ethanol. The separated solid was filtered, washed with small amount of ethanol to give 35 mg (46%) of product (4); mp 212-214°C (ethanol). IR (KBr) ν_{\max} (cm⁻¹): 3410 (NH), 1725 (CO), 1680 (CO), 1660 (CO). ¹H-NMR (DMSO-d₆): δ = 4.58 (d, 2H, $J=2.5$ Hz, 5-CH₂), 7.55 (m, 9H, eight H of two Ph, 4-H), 9.30 (m, 2H, Ph), 9.78 (s, 1H, NH). ¹³C-NMR (DMSO-d₆): δ = 47.8, 124.5, 127.6, 127.8, 128.3, 128.5, 130.0, 131.4, 132.1, 133.1, 134.4, 165.0, 166.0, 168.2. MS (EI, m/z, %): 306 (M⁺, 33%). HRMS for C₁₈H₁₄N₂O₃: Calcd: 306.100442. Found: 306.099976. *Anal.* Calcd for C₁₈H₁₄N₂O₃: C, 70.58; H 4.61; N 9.15. Found: C, 70.82; H 4.81; N, 9.15.

When the reaction was performed in the presence of equimolar amounts of hippuric acid and 2-phenyl-5(4*H*)-oxazolone, product (4) was obtained in 37 and 27% yields, respectively.

3-Benzoylamino-1,5-dihydro-2*H*-pyrrol-2-one (9):

a) A mixture of 100 mg (0.33 mmol) of 4, 74 mg (0.66 mmol, 97%) of phenylhydrazine and 2 mL of ethanol was heated under reflux for 7 h. The reaction mixture was evaporated under reduced pressure, the solid residue was separated with radial chromatography (chloroform/methanol, 50:1) to give 47 mg (68%) of hydrazide (8) (mp 169-172°C, lit.,¹⁸ 168°C) and 40 mg (61%) of pyrrolinone (9); mp 193-195°C (ethanol). IR (KBr) ν_{\max} (cm⁻¹): 3310 (NH), 3230 (NH), 1700 (CO), 1670 (CO), 1650 (CO). ¹H-NMR (DMSO-d₆): δ = 3.96 (m, 2H, 5-CH₂), 7.19 (m, 1H, 4-H), 7.50 (m, 2H, Ph), 7.59 (m, 1H, Ph), 7.93 (m, 2H, Ph), 8.57 (s, 1H, NH), 9.36 (s, 1H, NH). ¹³C-NMR (DMSO-d₆): δ = 44.6, 120.9, 127.6, 128.4, 130.6, 131.9, 133.3, 165.4, 168.5. MS (FAB, m/z, %): 203 (MH⁺, 44%). *Anal.* Calcd for C₁₁H₁₀N₂O₂: C, 65.34; H 4.98; N 13.85. Found: C, 65.71; H 5.18; N, 13.99.

b) A mixture of 100 mg (0.33 mmol) of compound (4), 67 mg (1.32 mmol, 98%) of hydrazine hydrate, and 2 mL of ethanol was heated under reflux for 5 h. The reaction mixture was then evaporated under reduced pressure. Radial chromatography of the solid residue (chloroform/methanol, 50:1) afforded 7 mg (9%) of *N,N'*-dibenzoylhydrazine (11), 61 mg (92%) of compound (9), and 33 mg (74%) of hydrazide (10).

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