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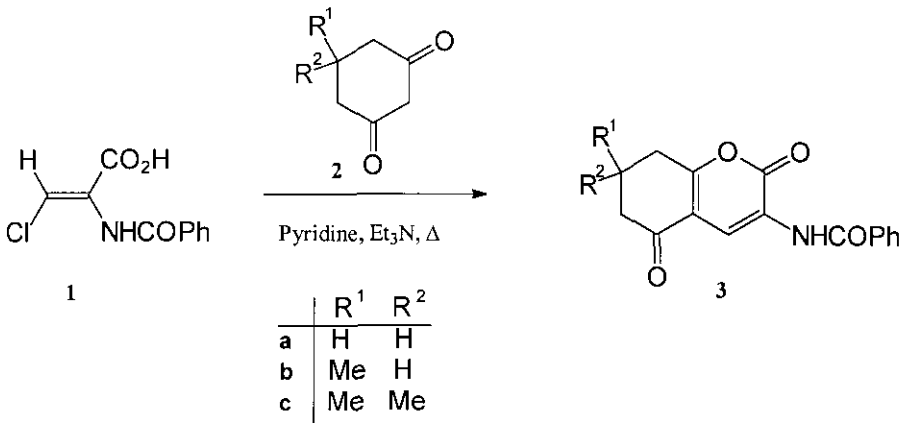
Abstract - The use of 2-benzoylamino-3-chloropropenoic acid in the synthesis of 5,6,7,8-tetrahydro-2*H*-1-benzopyran-2,5-diones and 1,5-dihydro-2*H*-pyrrol-2-ones is reported.

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.

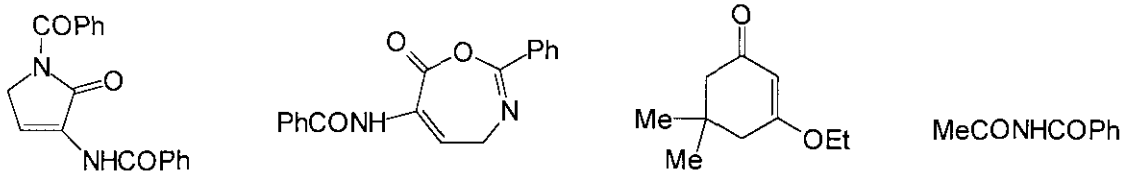
In order to test the desired synthetic utility of 2-benzoylamino-3-chloropropenoic acid (**1**) reactions with cyclohexane-1,3-dione (**2a**), 5-methylcyclohexane-1,3-dione (**2b**), and dimedone (**2c**) were performed under different reaction conditions. We found that the formation of the 5,6,7,8-tetrahydro-2*H*-1-benzopyran-2,5-dione 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 $C_{18}H_{14}N_2O_3$, 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 ^{1}H-NMR spectrum, showing signals for two

different phenyl groups and -CH= group in the aromatic region, doublet for -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 determined the structure of this side product, its X-Ray crystal structure analysis[10] 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.

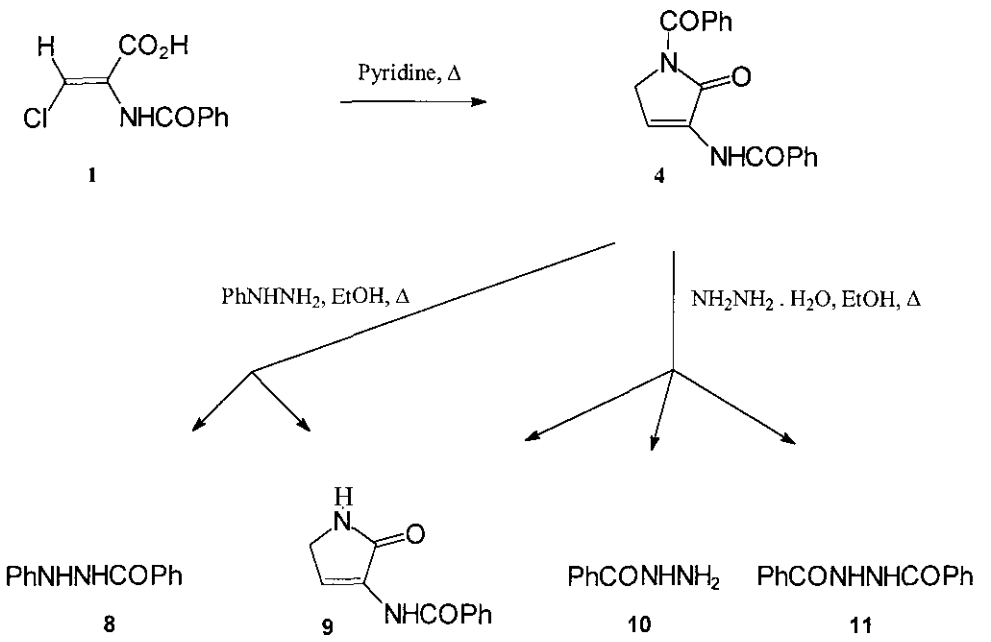


	R^1	R^2
a	H	H
b	Me	H
c	Me	Me



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 ^{1}H-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 ^{1}H-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 **3c**[4] and **4** in a ratio of 10:1, identified on the basis of ^{1}H-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). ^{1}H-NMR (DMSO-d_6): δ = 4.58 (d, 2H, *J*=2.5 Hz, 5-CH_2), 7.55 (m, 9H, eight H of two Ph, 4-H), 9.30 (m, 2H, Ph), 9.78 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6): 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 $C_{18}H_{14}N_2O_3$: Calcd: 306.100442. Found: 306.099976. *Anal.* Calcd for $C_{18}H_{14}N_2O_3$: 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). ^{1}H-NMR (DMSO-d_6): δ = 3.96 (m, 2H, 5-CH_2), 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). ^{13}C-NMR (DMSO-d_6): 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 $C_{11}H_{10}N_2O_2$: 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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REFERENCES

1. M. Kočevar, S. Polanc, M. Tišler, and B. Verček, *Synth. Commun.*, 1989, **19**, 1713.
2. V. Kepe, M. Kočevar, S. Polanc, B. Verček, and M. Tišler, *Tetrahedron*, 1990, **46**, 2081.

3. M. Kočevar, S. Polanc, B. Verček, and M. Tišler, *Liebigs Ann. Chem.*, 1990, 501.
4. H. Behringer and K. Falkenberg, *Chem. Ber.*, 1963, **96**, 1428.
5. V. Kepe, M. Kočevar, A. Petrič, S. Polanc, and B. Verček, *Heterocycles*, 1992, **33**, 843.
6. B. Ornik, Z. Čadež, B. Stanovnik, and M. Tišler, *J. Heterocycl. Chem.*, 1990, **27**, 1021.
7. I. T. Strukov, *Zh. Obshch. Khim.*, 1957, **27**, 432.
8. K. Čuček, I. Mušič, and B. Verček, *Synth. Commun.*, 1996, **26**, 1135.
9. M. J. Haddadin and A. Hassner, *J. Org. Chem.*, 1973, **38**, 3466.
10. Detailed data of X-Ray crystal structure analysis will be reported elsewhere.
11. O. Igglessi-Markopoulou and C. Sandris, *J. Heterocycl. Chemistry*, 1982, **19**, 883.
12. S. Hamilakis, D. Kontonassios, and C. Sandris, *J. Heterocycl. Chemistry*, 1994, **31**, 1145.
13. R. A. F. Bullerwell and A. Lawson, *J. Chem. Soc.*, 1952, 1350.
14. J. P. Blanchard and H. L. Goering, *J. Amer. Chem. Soc.*, 1951, **73**, 5863.
15. J. W. Cornforth, 'The Chemistry of Penicillin,' ed. by H. T. Clarke, J. R. Johnson, and R. Robinson, Princeton University Press, Princeton, 1949, p. 778.
16. R. L. Frank and H. K. Hall, *J. Amer. Chem. Soc.*, 1950, **72**, 1645.
17. C. D. Hurd and A. G. Prapas, *J. Org. Chem.*, 1959, **24**, 388.
18. F. Just, *Ber.*, 1886, **19**, 1203.

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