

## SYNTHESIS OF 2-BENZAMIDOISOQUINOLIN-1(2H)-ONE FROM 2-VINYLBENZOIC ACID

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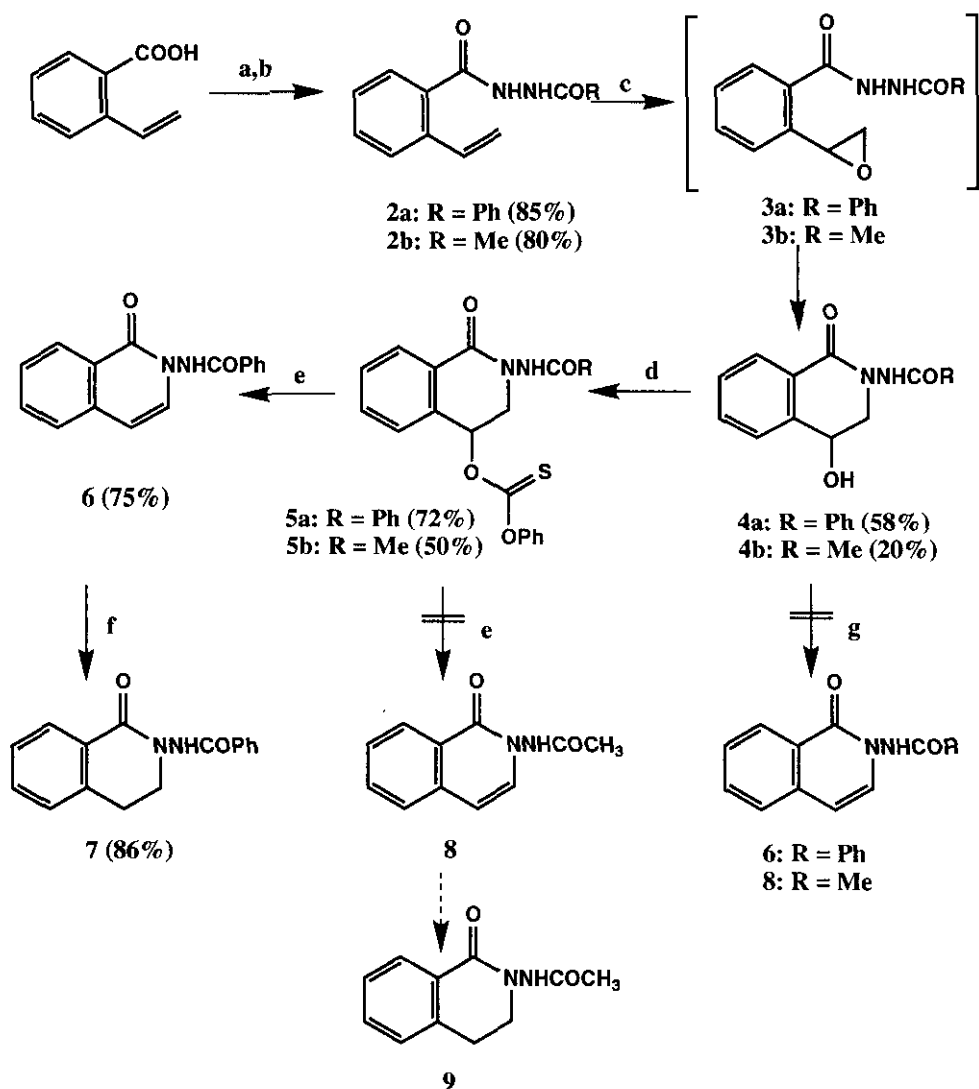
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**Abstract** -Treatment of *N*<sup>1</sup>-(2-vinylbenzoyl)-*N*<sup>2</sup>-benzoylhydrazine (**2a**) with 3-chloro-peroxybenzoic acid led to a cyclization of the intermediate epoxy derivative (**3a**) to give the alcohol (**4a**). Conversion of **4a** to the thiocarbonate (**5a**) followed by a Chugaev type reaction gave the title compound (**6**).

As part of our program aimed at the discovery of pesticidal agents we became interested in preparing 2-(acylamino)-3,4-dihydroisoquinolin-1(2H)-one derivatives. These compounds together with the corresponding unsaturated 2-(acylamino)isoquinolin-1(2H)-ones have been described in the literature as having antiinflammatory, anticonvulsant, antianalgesic, antipyretic and tranquilizer activities.<sup>2-6</sup> We were particularly interested in preparing 2-benzamido and 2-acetamido-3,4-dihydroisoquinolin-1(2H)-ones (**7**) and (**9**) respectively. The synthesis of these materials have been reported from the acylation of 2-amino-3,4-dihydroisoquinolin-1(2H)-one which was prepared from the cleavage of isochromanone with phosphorus pentachloride followed by esterification with ethanol and cyclization with hydrazine.<sup>3</sup> In this paper we present the results from our approach to these 2-(acylamino)-3,4-dihydroisoquinolin-1(2H)-ones (**7** and **9**). We envisioned that these structures could be obtained from reduction of the corresponding 2-(acylamino)isoquinolin-1(2H)-ones (**6** and **8** respectively). The synthesis of **8** has been reported from the reaction of 2-aminoisoquinolinium bromide with lead tetraacetate in acetic acid.<sup>7</sup> Surprisingly, the synthesis of 2-benzamidoisoquinolin-1(2H)-one (**6**) has not been reported in the literature.

Our synthetic sequence begins with the reaction of 2-vinylbenzoic acid<sup>8</sup> with thionyl chloride followed by treatment with benzoylhydrazine which gave the hydrazide derivative (**2a**) in 85% yield (Scheme).

## Scheme



(a)  $\text{SOCl}_2$ ,  $\Delta$ ; (b)  $\text{RCONHNH}_2$ ,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$  to  $20^\circ\text{C}$ ; (c) *mcpba*,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$  to  $20^\circ\text{C}$ ; (d)  $\text{PhOCSCl}$ , pyridine,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$  to  $20^\circ\text{C}$ ; (e) *o*-xylene,  $\Delta$ ; (f) 5% Pd/C (cat.), EtOH, 30 psi of  $\text{H}_2$ ; (g) *p*-toluenesulfonic acid (cat.), toluene,  $\Delta$

Reaction of **2a** with 3-chloroperoxybenzoic acid in methylene chloride was expected to give the epoxide (**3a**). However, work up of the reaction mixture and purification by chromatography on silica gel gave the cyclized 3,4-dihydroisoquinolinone alcohol (**4a**) as the only isolated product in 58% yield. It was anticipated that acid catalyzed dehydration of the alcohol (**4a**) would provide 2-benzamidoisoquinolin-1(2H)-one (**6**). However, treatment of **4a** with a catalytic amount of *p*-toluenesulfonic acid in refluxing toluene led to a mixture of uncharacterized products from which **6** was not isolated. Thus, **4a** was converted to the thiocarbonate (**5a**) in 72% yield *via* treatment with phenyl chlorothionoformate in methylene chloride in the presence of pyridine. Heating **5a** in refluxing *o*-xylene led to smooth conversion to the title compound (**6**) *via* a Chugaev type reaction. Finally, catalytic hydrogenation of **6** with 5% palladium on carbon at 30 psi of hydrogen gave the desired 2-benzamido-3,4-dihydroisoquinolin-1(2H)-one (**7**) in 86% yield.

The above reaction sequence using acetylhydrazine provided the corresponding thiocarbonate (**5b**). It should be noted that the reaction of **2b** with 3-chloroperoxybenzoic acid led to the isolation of **4b** in poor (20%) yield. Furthermore, heating **5b** in refluxing *o*-xylene led to decomposition materials from which the desired product (**8**) was not isolated.

In summary, we have demonstrated a new method for the preparation of 2-benzamidoisoquinolin-1(2H)-one (**6**) *via* cyclization of the epoxy-hydrazide intermediate (**3a**) to give the alcohol (**4a**) followed by derivatization to the thiocarbonate (**5a**) which yields **6** *via* a Chugaev type reaction. It appears that a similar procedure for the conversion of the 2-acetamido-4-hydroxy-3,4-dihydroisoquinolin-1(2H)-one (**4b**) to provide 2-acetamidoisoquinolin-1(2H)-one (**8**) is unsuitable.

## EXPERIMENTAL

Melting points were determined in open capillary tubes using a Thomas-Hoover apparatus and are uncorrected. The  $^1\text{H}$  (300 MHz) nmr spectra were recorded on a General Electric QE300 spectrometer. Chemical shifts are expressed in parts per million downfield from internal tetramethylsilane. Mass spectra (ms) were recorded on a Varian MAT 311A or a Kratos Concept 1HQ instrument. Column chromatography was performed on Merck silica gel 60 (240-400) mesh; silica gel plates were routinely used for tlc determinations. Elemental analyses were performed at FMC Corporation, Analytical Services Department.

***N*<sup>1</sup>-(2-Vinylbenzoyl)-*N*<sup>2</sup>-benzoylhydrazine (2a).** A mixture of 2-vinylbenzoic acid<sup>B</sup> (21.4 g, 0.144 mol) and thionyl chloride (30 ml, 0.411 mol) was heated at reflux under nitrogen for 2 h. The excess thionyl chloride was removed by evaporation under reduced pressure. The residue was dissolved in anhydrous methylene chloride (50 ml) and added dropwise to a stirred mixture of benzoylhydrazine (19.6 g, 0.144 mol), triethylamine (100 ml, 0.72 mol) and methylene chloride (100 ml) cooled to 5°C. The mixture was stirred under nitrogen at 5°C for 1 h and then allowed to warm to

20°C and stirred for a further 48 h. The reaction mixture was poured into water (400 ml) and extracted with methylene chloride (3 X 200 ml). The combined organic phase was dried over anhydrous sodium sulfate, filtered and the solvent evaporated under reduced pressure. The residue was chromatographed on silica gel eluting with 5% methanol in methylene chloride to give 32.6 g (85%) of a colorless solid. Recrystallization from ethyl acetate gave an analytical sample, mp 164-165°C.  $^1\text{H Nmr}$  ( $\text{CDCl}_3$ ):  $\delta$  5.38 (d,  $J = 9$  Hz, 1H), 5.75 (d,  $J = 14$  Hz, 1H), 7.10 (m, 1H), 7.3 (m, 1H), 7.38-7.60 (m, 6H), 7.80 (d,  $J = 8$  Hz, 2H), 9.1 (br s, 1H), 9.78 (br s, 1H); ms (EI)  $m/z$ : 266 ( $\text{M}^+$ ). Anal. Calcd for  $\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}_2$ : C, 72.17; H, 5.30; N, 10.52. Found: C, 72.45; H, 5.53; N, 10.31

**2-Benzamido-4-hydroxy-3,4-dihydroisoquinolin-1(2H)-one (4a):** To a solution of **2a** (5 g, 0.0187 mol), in methylene chloride (100 ml) was added 3-chloroperoxybenzoic acid (60%; 6.48 g, 0.0225 mol). The reaction mixture was stirred at 20 °C for 48 h and then poured into a solution of saturated sodium bicarbonate (150 ml). The organic layer was separated, washed with water, dried over anhydrous sodium sulfate and filtered. The solvent was evaporated and the residue was chromatographed on silica gel eluting with 5% methanol in methylene chloride to give a colorless solid (3 g, 58%), mp 91-93 °C.  $^1\text{H Nmr}$  ( $\text{CDCl}_3$ )  $\delta$ : 4.00 (m, 1H), 4.30 (m with overlapping br s, 2H), 5.70 (m, 1H), 7.10-7.58 (m, 7H), 7.70 (d,  $J = 8$  Hz, 2H), 9.28 (s, 1H), ms (EI)  $m/z$ : 282 ( $\text{M}^+$ ). Anal. Calcd for  $\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}_3$ : C, 68.01; H, 4.96; N, 9.92. Found: C, 67.98; H, 4.85; N, 9.72.

**Phenyl 1,2,3,4-tetrahydro-1-oxo-2-benzamido-4-isoquinolinyl thiocarbonate (5a):** To a stirred mixture of **4a** (1.0 g, 3.54 mmol), pyridine (1.45 ml, 17.7 mmol) and anhydrous methylene chloride (20 ml) was added phenyl chlorothionoformate (0.54 ml, 3.9 mmol) dropwise over 10 min. The mixture was stirred at 23°C under nitrogen for 2 h and then poured into 1M hydrochloric acid (20 ml). The organic layer was separated and the aqueous phase was extracted with methylene chloride (2 X 30 ml). The combined organic phase was dried over anhydrous sodium sulfate, filtered and the solvent was evaporated. The residue was chromatographed on silica gel eluting with 5% methanol in methylene chloride to give a colorless solid (1.06 g, 72%), mp 67-68°C.  $^1\text{H Nmr}$  ( $\text{CDCl}_3$ ):  $\delta$  4.76 (m, 1H), 5.03 (m, 1H), 6.00 (m, 1H), 7.08 (d,  $J = 8$  Hz, 2H), 7.20-7.60 (m, 9H), 7.90 (d,  $J = 8$  Hz, 2H), 8.04 (d,  $J = 8$  Hz, 1H), 9.30 (br s, 1H); ms (FAB)  $m/z$ : 419 ( $\text{M}^+ + 1$ ). Anal. Calcd for  $\text{C}_{23}\text{H}_{18}\text{N}_2\text{O}_4\text{S}$ : C, 65.95; H, 4.3; N, 6.7. Found: C, 65.73; H, 4.1; N, 6.63.

**2-Benzamidoisoquinolin-1(2H)-one (6):** A solution of **5a** (0.65 g, 1.55 mmol) in *o*-xylene (20 ml) was heated at reflux for 18 h. The solvent was removed by evaporation under reduced pressure and the residue was partitioned between methylene chloride and 5% sodium carbonate solution. The organic layer was separated, dried over anhydrous sodium sulfate, filtered and the solvent evaporated. The residue was recrystallized from ethyl acetate to give a colorless solid (0.3 g, 75%), mp 216-217°C.  $^1\text{H Nmr}$  ( $\text{CDCl}_3$ ):  $\delta$  6.58 (d,  $J = 8$  Hz, 1H), 7.06 (d,  $J = 8$  Hz, 1H), 7.27-7.70 (m, 6H), 7.93 (d,  $J = 8$  Hz, 2H), 8.40 (d,  $J = 8$  Hz, 1H), 9.70 (br s, 1H); ms (EI)  $m/z$ : 264 ( $\text{M}^+$ ). Anal. Calcd for  $\text{C}_{16}\text{H}_{12}\text{N}_2\text{O}_2$ : C, 72.64, H, 4.54; N, 10.60. Found: C, 72.38; H, 4.35, N, 10.49.

by filtration through a pad of celite and the pad washed several times with ethanol. The solvent from the filtrate was evaporated to give a colorless solid (0.59 g, 86%), mp 243-245°C (lit.,<sup>3</sup> mp 244-245°C).

***N*<sup>1</sup>-(2-Vinylbenzoyl)-*N*<sup>2</sup>-acetylhydrazine (2b):** This was prepared in 80% yield from the reaction between 2-vinylbenzoyl chloride and acetylhydrazine using a procedure similar to that described for the preparation of **2a** (mp 138-139°C). <sup>1</sup>H Nmr (CDCl<sub>3</sub>): δ 2.14 (s, 3H), 5.40 (d, J = 8 Hz, 1H), 5.74 (d, J = 14 Hz, 1H), 7.10 (m, 1H), 7.30-7.63 (m, 4H), 8.70 (br s, 1H), 9.15 (brs, 1H), ms (EI) *m/z*: 204 (M<sup>+</sup>). Anal. Calcd for C<sub>11</sub>H<sub>12</sub>N<sub>2</sub>O<sub>2</sub>: C, 64.63; H, 5.87; N, 13.71. Found: C, 64.60; H, 5.77; N, 13.56.

**2-Acetamido-4-hydroxy-3,4-dihydroisoquinolin-1(2H)-one (4b):** This was prepared in 20% yield from the reaction between **2b** and 3-chloroperoxybenzoic acid using a procedure similar to that described for the preparation of **4a** (mp 175-176°C). <sup>1</sup>H Nmr (CDCl<sub>3</sub>): δ 2.34 (s, 3H), 3.70 (m, 1H), 4.06 (m, 1H), 5.70 (m, 1H), 7.18-7.60 (m, 3H), 7.78 (d, J = 8 Hz, 1H), 10.06 (br s, 1H); ms (EI) *m/z*: 220 (M<sup>+</sup>). Anal. Calcd for C<sub>11</sub>H<sub>12</sub>N<sub>2</sub>O<sub>3</sub>: C, 60.00; H, 5.50; N, 12.73. Found: C, 60.18; H, 5.25; N, 12.54.

**Phenyl 1,2,3,4-tetrahydro-1-oxo-2-acetamido-4-isoquinolinyl thiocarbonate (5b):** This was prepared in 50% yield from the reaction between **4b** and phenyl chlorothionoformate using a procedure similar to that described for the preparation of **5a** to give a colorless oil. <sup>1</sup>H Nmr (CDCl<sub>3</sub>): δ 2.18 (s, 1H), 2.28 (s, 2H), 4.70 (m, 1H), 5.00 (m, 1H), 6.00 (m, 1H), 7.10 (d, J = 7 Hz, 2H), 7.20-7.60 (m, 7H), 8.63 and 8.78 (2 brs, 1H); hrms calcd for C<sub>18</sub>H<sub>16</sub>N<sub>2</sub>O<sub>4</sub>S: 356.08308. Found: 356.08305.

## REFERENCES AND NOTES

1. Present Address. Department of Chemistry, University of Memphis, Memphis, TN 38152, U.S.A
2. G. Nathansohn, G. Winters, and G. Glasso, *Fr Demande* 2,187,329 (*Chem. Abstr.*, 1974, **81**, 13401d).
3. G. Odasso, G. Winters, P. Schiatti, D. Selva, and G. Nathansohn, *Farmaco, Ed. Sc.*, 1977, **32**, 159 (*Chem. Abstr.*, 1977, **87**, 23000k).
4. S. Ueno, K. Sugihara, H. Hirayama, and M. Ichino, *Japan Kokai*, 76,101,985 (*Chem. Abstr.*, 1977, **86**,121169w).
5. E. Hayashi, T. Higashino, E. Oishi, C. Iijima, M. Yamagishi, C. Ota, Y. Miwa, A. Nakajima, and S. Iwata, *Yakugaku Zasshi*, 1978, **98**, 1560 (*Chem. Abstr.*, 1979, **90**, 152111h).
6. S. Ueno, K. Sugihara, H. Hirayama, and M. Ichino, *Japan Kokai*, 76,122,075 (*Chem. Abstr.*, 1977, **87**, 5822a).
7. J.T. Boyers and E.E. Glover, *J. Chem. Soc., Perkin Trans. 1*, 1977, 1960.
8. R.K. Howe and F.M. Schlepplnik, *J. Heterocycl. Chem.*, 1982, **19**, 721.

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