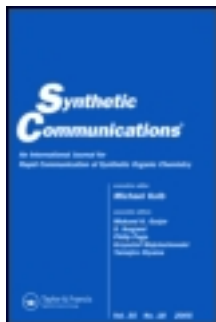


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A NEW EFFICIENT AND MILD SYNTHESIS OF 2-OXINDOLES BY ONE-
POT WOLFF-KISHNER LIKE REDUCTION OF ISATIN DERIVATIVES

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Tuscia", via S. Camillo de Lellis, 01100, Viterbo, Italy.

Abstract: Indole-2-one derivatives were prepared from the corresponding isatines
via one pot reduction in hydrazine hydrate.

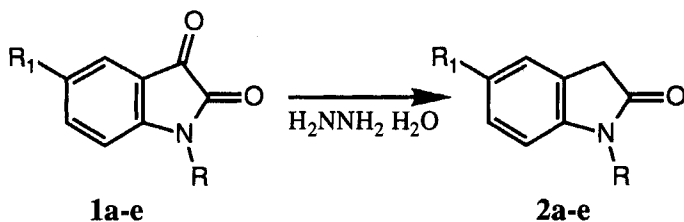
Hydrazine reduction of carbonyl compounds^{1,2} is an old and widely used
reaction for complete deoxygenation of carbonyl compounds. Unfortunately the
decomposition of hydrazone intermediates requires severe experimental conditions
which sometimes can not be compatible with other functional groups present in the
molecule to be reduced.

Because of the intermediate position of indole-2-one derivatives between
indoles and isatines in the indole series, the interconversion of these compounds
has been explored extensively, and several 2-oxindoles have been prepared by
reduction of indole-2,3-diones. This reduction by the classical Wolff Kishner
procedures, was precedently obtained by heating the hydrazone in a sealed tube
with a sodium ethoxide solution at 170-200°C during several hours or boiling the
hydrazone with potassium hydroxide in high boiling point solvents³.

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In connection with our studies on indole-2,3-dione derivatives, we unexpectedly found that 1-benzyl-1H-indole-2,3-dione **1a** reacted readily with hydrazine hydrate to give directly, without isolation of the intermediate hydrazone, the corresponding 1-benzyl-1H-indole-2-one **2a** in 75% yield (scheme 1, table).

SCHEME 1



a: R=CH₂C₆H₅, R₁=H; **b:** R=H, R₁=H; **c:** R=C₆H₅, R₁=H;

d: R=CH₃, R₁=H; **e:** R=H, R₁=OCH₃.

Although it is reported in literature that hydrazones of the α -dicarbonyl compounds 2,3-butanedione, diphenyl glyoxal and isatin may be decomposed in milder experimental conditions than hydrazones of other carbonyl compounds⁴, the one pot Wolff Kishner reduction of isatin has never been reported. In the case of isatin Seibert boiled the hydrazone in NaOH 2N during 2hrs and obtained 2-oxindole only in 13% yield.

The unexpected easy obtention of the 1-benzyl-1H-indole-2-one **2a** encouraged us to test this reaction on isatin **1b**, 1-phenyl-1H-indole-2,3-dione **1c**, 1-methyl-1H-indole-2,3-dione **1d** and 5-methoxy-1H-indole-2,3-dione **1e** in order to verify the generality of the reaction. In each case the corresponding 1H-indole-2-one **2b-d** was obtained in 15-30 min in high yield without isolation of the intermediate hydrazone.

TABLE

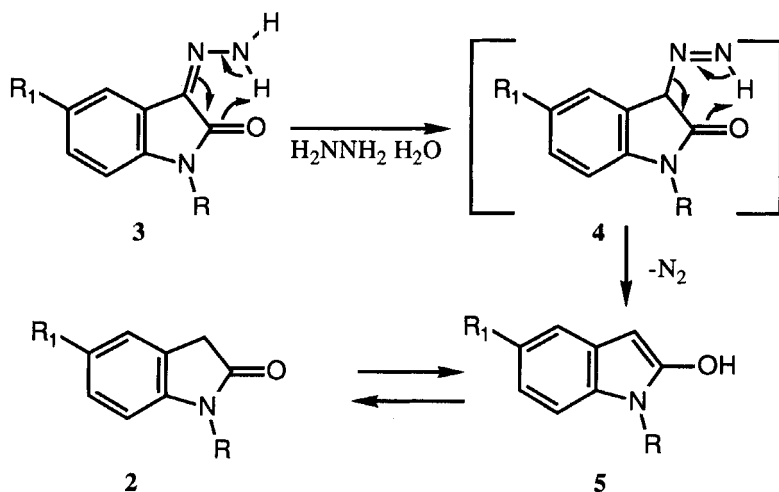
Compound	R	R1	Product	Yield (%)	Reaction Time (min)
1a	CH ₂ C ₆ H ₅	H	2a	88	30
1b	H	H	2b	76	30
1c	C ₆ H ₅	H	2c	92	15
1d	CH ₃	H	2d	85	30
1e	H	OCH ₃	2e	85	15
6	-	-	7	80	15

Probably the direct decomposition of isatin hydrazones **3** in hydrazine hydrate is, in this case, more efficient and faster than in the classical Wolff Kishner reduction method, due to the possibility of the α -ketoamide to give anchimeric assistance in the stage of decomposition of hydrazone. The reaction could be similar to the Kishner-Leonard elimination which occurs in α -substituted carbonyls, proceeding either through a diimide anion which fragments via elimination to an alkene, or via a vinyl diimide as reported by Leonard⁵ and Wharton⁶.

The carbonyl amide moiety can in fact form an hydrogen bond with the leaving proton on nitrogen with an intermediate six member ring **4**. The possibility of intramolecular hydrogen bonding could drive the formation of the intermediate **4** through the E form, as previously reported by Szmant⁷, and the proton shift can then proceed through the enol form of the final product **5** (scheme 2).

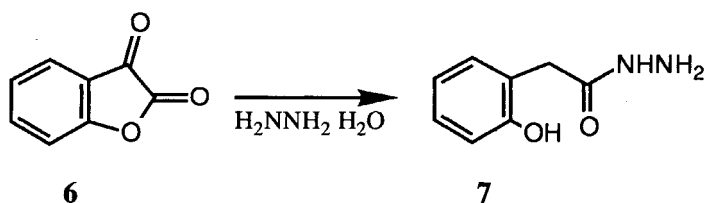
When the reaction was then carried out on the α -ketolactone moiety of coumarandione **6** under the same experimental conditions, the hydrazide of 2-(2-

SCHEME 2



hydroxy-phenyl)-acetic acid 7, the product of carbonyl reduction and ester hydrazinolysis was directly obtained (scheme 3, table).

SCHEME 3



Finally we wish to point out that the direct one pot reduction of several 1H-indole-2,3-dione derivatives in hydrazine hydrate represents an interesting synthetic method for the synthesis of 2-oxindole derivatives in good yield under mild experimental conditions and in short reaction times.

Experimental:

Nmr spectra were recorded on a varian XL 300 (300 MHz) spectrometer and are reported in δ values. Melting points were obtained on a Reichert Kofler apparatus

and are uncorrected. Microanalyses were performed by C. Erba 1106 analyzer. Infrared spectra were recorded on a Kratos MS80 spectrometer. All solvents were ACS reagent grade.

General procedure for the reduction of the 2-oxindoles **2a-e**

10 mmol of the appropriate isatin derivative **1a-e** were dissolved in 10ml of hydrazine hydrate 98% and refluxed for 15-30 min (table). The reaction mixtures were then poured in cold water, extracted in ethyl acetate and dried over Na₂SO₄. Evaporation of the solvent and subsequent recrystallization from hexane/ethyl acetate afforded the corresponding 2-oxindoles **2a-e**.

2a: 88%; mp 66-67°C (lit.⁸67°C); ir (v, cm⁻¹) (KBr) 1695, 1610; ¹Hnmr (δ, ppm) (CDCl₃) 3.60 (s, 2H, CH₂), 4.90 (s, 2H, CH₂), 6.67-7.29 (m, 9H, CH); ¹³Cnmr (δ, ppm) (CDCl₃) 35.6 (CH₂), 43.7 (CH₂), 108.9(CH), 122.3 (CH), 124.3 (CH), 127.4 (C), 127.5 (CH), 127.7 (CH), 128.6 (CH), 144.28 (C), 175.0 (C); ms +EI (m/z, M⁺) 223; Anal. Calcd. for C₁₅H₁₃NO: C 80.69, H 5.87, N 6.27. Found: C 80.58, H 5.80, N 5.99.

2b: 76%; mp 124-125°C (lit.⁹126°C); ir (v, cm⁻¹) (KBr) 3200, 1690, 1615, 1470; ¹Hnmr (δ, ppm) (CDCl₃) 3.52 (s, 2H, CH₂), 6.66-7.25 (m, 4H, CH), 9.78 (s, 1H, NH); ¹³Cnmr (δ, ppm) (CDCl₃) 36.4 (CH₂), 110.0 (CH), 122.3 (CH), 124.5 (CH), 125.4 (C), 127.9 (CH) 142.8 (C), 176.6 (C); ms +EI (m/z, M⁺) 133; Anal. Calcd. for C₈H₇NO: C 72.16, H 5.30, N 10.52. Found: C 71.94, H 5.19, N 10.33.

2c: 92%; mp 119-121°C (lit.¹⁰121); ir (v, cm⁻¹) (KBr) 1695, 1615; ¹Hnmr (δ, ppm) (CDCl₃), 3.55 (s, 2H, CH₂), 6.70-7.30 (m, 9H, CH); ¹³Cnmr (δ, ppm) (CDCl₃) 35.6 (CH₂), 108.5 (CH), 122.3 (CH), 124.3 (CH), 127.4 (CH), 127.5 (C), 127.6 (CH), 127.8 (CH), 143.7 (C), 175.6 (C); ms +EI (m/z, M⁺) 209; Anal. Calcd. for C₉H₉NO: C 73.45, H 6.16, N 9.52. Found: C 73.36, H 6.08, N 9.26.

2d: 85%; mp 85-87°C (lit.¹¹89°C); ir (v, cm⁻¹) (KBr) 3400,1705, 1615; ¹Hnmr (δ, ppm) (CDCl₃) 3.17 (s, 3H, CH₃), 3.48 (s, 2H, CH₂), 6.76-7.27 (m, 4H, CH); ¹³Cnmr (δ, ppm) (CDCl₃) 26.1 (CH₃), 35.7 (CH₂), 108.1(CH), 122.3 (CH), 124.3 (CH), 124.4 (C), 127.8 (CH), 145.23 (C), 175.0 (C); ms +EI (m/z, M⁺) 147; Anal. Calcd. for C₉H₉NO: C 73.45, H 6.16, N 9.52. Found: C 73.36, H 6.08, N 9.26.

2e: 85%; mp 151-153°C (lit.¹²153°C); ir (v, cm⁻¹) (KBr) 1695, 1600; ¹Hnmr (δ, ppm) (CDCl₃) 3.51 (s, 2H, CH₂), 3.77 (s, 3H, CH₃), 6.75-6.87 (m, 4H, CH), 9.24 (s, 1H, NH); ms +EI (m/z, M⁺) 163; Anal. Calcd. for C₉H₉NO₂: C 66.25, H 5.56, N 8.58. Found: C 66.47, H 5.48, N 8.71.

Procedure for the reduction of coumarandione 6

50 mmol of coumarandione **6** were dissolved in 50 ml of hydrazine hydrate 98% and refluxed for 15 min. The reaction mixture was then poured in cold water, extracted in ethyl acetate and dried over Na₂SO₄. Evaporation of the solvent and subsequent recrystallization from ethanol/ethyl acetate afforded the hydrazide of 2-(2-hydroxy-phenyl)-acetic acid **7**.

7: 80%; mp 154-155°C (lit.¹³154-155°C); ir (v, cm⁻¹) (KBr) 3500, 1690; ¹Hnmr (δ, ppm) (CDCl₃) 3.55 (s, 2H, CH₂), 6.73-7.14 (m, 4H, CH); ms +EI (m/z, M⁺) 166; Anal. Calcd. for C₈H₁₀N₂O₂: C 57.82, H 6.07, N 16.89. Found: C 57.70, H 5.98, N 16.73.

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References

1. Todd, D., The Wolff-kishner Reduction, in "Organic Reactions"; John Wiley and sons, inc., New York, 1948; pp. 378-422.

2. Hutchins, R.O.; Hutchins, M.K., Reduction of C=X to CH₂ by Wolff Kishner and other hydrazone methods, in "Comprehensive Organic Synthesis"; Trost, B.M.; Fleming, I.; Pergamon Press, Oxford, 1991, 8, pp.327-362.
3. Julian, P.L., Meyer, E.W., Printy, H.C.: The Chemistry of Indoles. In "Heterocyclic Compounds"; Elderfield, R.C.; Jhon Wiley and sons, Inc., New York, 1952, 3, p. 129.
4. Seibert, W., Chem. Ber., 1947, 80, 494.
5. Leonard, N.J.; Gelfand, S., J. Am. Chem. Soc., 1955, 3272.
6. Wharton, P.S.; Bohlen, D.H., J. Org. Chem., 1961, 26, 3615.
7. Szmant, H.H., Angew. Chem. Int. Edit., 1968, 7, 120.
8. Cornforth, J.W., Cornforth, R.H., Dagiiesh, C.E., Neuberger, A., Biochem .J., 1951, 48, 591.
9. Beil., 21, 282.
10. Kisteneva, M.S., Zhur. Obsheei Kim., 1956, 26, 1169.
11. Beil., 21, 283.
12. Wieland, T., Unger, O., Ber., 1963, 96, 253.
13. Lange, J., Urbansky, T., Diss. Pharm. Pharmacol., 1968, 20, 607.

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