A Noteworthy Improvement of the 3-Diazo-4-oxo-3,4-dihydroquinoline Photosynthesis of Indole-3-carboxamides

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Received February 23, 1977

The use of benzene, in place of methylene chloride as solvent, allows the synthesis of amides of indole-3-carboxylic acid *via* the photolysis of 3-diazo-4-oxo-3,4-dihydroquinoline to occur in significantly higher yield and requiring shorter reaction times. This modification makes unnecessary the time consuming and costly chromatographic purification step, and allows the synthesis of novel amides which could not be isolated using the previous method.

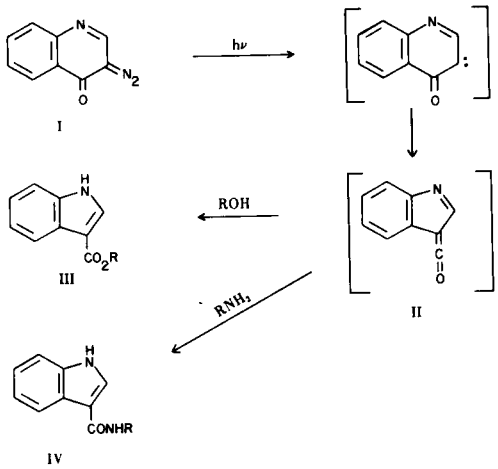
J. Heterocyclic Chem., 14, 519 (1977).

We have reported 3-diazo-4-oxo-3,4-dihydroquinoline to be an excellent synthon for indole-3-carboxylates (1) as well as indole-3-carboxamides (2) (see Scheme 1). Recent work in our laboratory has shown that this synthetic procedure can be vastly improved, the yields significantly increased, the expensive as well as time consuming chromatographic step eliminated, and the total reaction time reduced from ten to about four hours by using benzene as the solvent in place of methylene chloride as previously reported (1,2). Additionally, we have been able to synthesize certain novel amides using this benzene solvent modification which we, unexplainably, had not been able to obtain using our published methylene chloride procedure (2).

Benzene is useful as a solvent because it readily dissolves both starting material I and the amine. In addition, the amide product is not soluble so that the product either separates during irradiation or after some of the benzene is removed. This eliminates expensive and time consuming preparative thin layer separations that we have previosuly employed (1,2). We have rerun the reported amide preparations (2) and have obtained a much higher yield in every case (Table I). In addition, the reaction times were reduced from 10 to 4 hours. This reduction could be due to the sensitizing properties of benzene.

All attempts to synthesize the *N*,*N*-di-*n*-butyl-, the *N*-(2-methyl-4-methoxyphenyl)-, the *N*-(2,4-dimethylphenyl)-, and the *N*-(2-pyridyl)indole-3-carboxamides, using a methylene chloride solvent, were unsuccessful. However, when the reactions were carried out in benzene,

Scheme 1

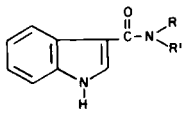


the products crystallized from the benzene in good yields (see Table I).

EXPERIMENTAL (3)

The following procedure can be applied to the syntheses of all indole-3-carboxamides described below. 3-Diazo-4-oxo-3,4-dihydroquinoline (200 mg.) was dissolved in 10 ml. of benzene and a 2.8 molar excess of amine was added. This mixture was then transferred to a pyrex test tube, lightly stoppered, and irradiated with a 450 watt Hanovia High Pressure mercury vapor lamp for four hours. After irradiation, the walls of the test tube were scraped to free any particulate matter and the entire contents of the tube were reduced in volume to 2 ml. under vacuum. This remaining solution was then chilled in an ice bath while the inside

Table 1



R	R'	Yield % (a) (methylene chloride)	Yield % (benzene)
Ethyl	Ethyl	39.4	63.7
H	*n*-Butyl	40.0	53.2
H	Phenyl	42.0	56.3
H	Benzyl	56.4	68.9
H	2-phenylethyl	58.9	66.0
H	*o*-chlorophenyl	64.1	70.0
H	*o*-bromophenyl	49.9	58.0
H	4-methoxy-2-methylphenyl	--	57.8
H	2,4-dimethylphenyl	--	69.9
H	2-pyridyl	--	65.3
n-Butyl	*n*-Butyl	--	60.1

(a) Reference (2).

walls of the tube were scratched to incude further crystallization. After twenty minutes, the contents of the tube were filtered, dissolved in 20 ml. of ethanol, boiled with 0.5 g. of norite, filtered, and 3-5 ml. of water was added to the filtrate, the volume of which was reduced under vacuum to incipient recrystallization. The product was then filtered and dried *in vacuo*.

N,N-Dibutylindole-3-carboxamide.

This compound had m.p. 103°; ir, 1590 (conjugated C=O), 3400 cm^{-1} (N-H); nmr (deuteriochloroform): 0.9 δ (t, J = 6 Hz, 6H), 1.2-1.7 δ (m, 8H), 3.5 δ (t, J = 6 Hz, 4H), 6.9 δ (d, J = 3 Hz, 1H), 7.2 δ (d, J = 3 Hz, 3H), 7.75 δ (t, J = 6 Hz, 1H), 10.19 δ (bs, 1H); mass spectra: m/e (relative abundance), 144 (100, acylium ion), 272 (26.2, m^+).

Anal. Calcd. for $C_{17}H_{24}N_2O$: C, 74.96; H, 8.88; N, 10.20. Found: C, 75.07; H, 8.87; N, 10.22.

N-(2-Pyridyl)indole-3-carboxamide.

This compound had m.p. 228-229°; ir: 1650 (conjugated C=O), 3400 cm^{-1} (N-H): nmr (DMSO-d_6): 7.1 δ (m, 2H), 7.45 δ (m, 2H), 7.7 δ (t, J = 6 Hz, 1H), 8.4 δ (m, 4H), 9.95 δ (S, 1H); mass spectrum: m/e (relative abundance), 144 (100, acylium ion), 237 (34.7, M+), 94 (19, $C_6H_4N_2H_2^+$). The elemental analysis of this compound was not satisfactory, even after four recrystallizations.

N-(2,4-Dimethylphenyl)indole-3-carboxamide.

This compound had m.p. 173-174°; ir: 1640 (conjugated C=O), 3400 cm^{-1} (N-H); nmr (DMSO-d_6): 2.25 δ (s, 3H), 2.3 δ (s, 3H), 6.9-7.5 δ (m, 6H), 8.2 δ (m, 2H), 9.1 δ (s, 1H), 12.0 δ (bs, 1H); mass spectrum (4): m/e (relative abundance), 121 (100, $C_8H_9NH_2^+$), 144 (51.2, acylium ion), 264 (39.5, M+).

Anal. Calcd. for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.34; H, 6.02; N, 10.59.

N-(4-Methoxy-2-methylphenyl)indole-3-carboxamide.

This compound had m.p. 200-201°; ir: 1615 (conjugated C=O), 3400 cm^{-1} (N-H); nmr (DMSO-d_6): 2.3 δ (s, 3H), 3.75 δ (s, 3H), 6.75 δ (d, J = 9 Hz, 2H), 7.2 δ (q, J = 3 Hz, 2H), 7.49 δ (d, J = 6 Hz, 2H), 7.95 δ (d, J = 3 Hz, 1H), 8.15 δ (q, J = 3 Hz, 1H), 8.35 δ (s, 1H), 11.0 δ (bs, 1H); mass spectrum (4): m/e (relative abundance), 137 (100, $C_8H_9ONH_2^+$), 144 (77.7, acylium ion), 280 (60.1, M^+).

Anal. Calcd. for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.84; H, 5.67; N, 9.94.

Acknowledgements.

One of us (JTC) was supported by a research fellowship from the Slovenian Research Community, Ljubljana, Yugoslavia, and by a Research Internship from the College of Physical and Mathematical Sciences of Brigham Young University. Dr. E. G. Paul of the Brigham Young University Chemistry Department is thanked for his many discussions of our nmr data.

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(1) B. Stanovnik, M. Tišler, and J. T. Carlock, *Synthesis*, 754 (1976).

(2) J. T. Carlock, J. S. Bradshaw, B. Stanovnik, and M. Tišler, *J. Org. Chem.*, in press.

(3) The following spectral instruments were used. Ir, (potassium bromide) Hilger and Watts H-1200 Mark II; nmr, Varian Associates EM-390, (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad); mass spectra, HP-5982A GC/MS operated at 70 EV interfaced with an HP-5934A data system. Elemental analyses were performed by Eisenhower Microanalytical Laboratories, P. O. Box 635, Holly Hill, Florida 32017. Melting points (uncorrected) were determined on a Thomas-Hoover capillary melting point apparatus.

(4) All prior amide spectra have given the acylium ion as the base peak, however on aromatic rings with Inductive disubstitution, the base peak becomes $RR'C_4H_6NH_2$ from cleavage of the amide bond and subsequent rearrangements. This is readily correlated with Hammet equation constants of substituents. See: Y. S. Nekrasov, P. A. Sharbatyan, R. S. Sagtullin, V. A. Puchkov, A. N. Kost, and N. S. Vul'fson, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2181 (1969); [*Chem. Abstr.*, 72, 36890r (1970)].