

The Reaction of 2-Picoline *N*-Oxide with *o*-Substituted Benzoates and Isoatoic Anhydrides

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Received September 13, 1976

The reaction of 2-picoline *N*-oxide anion with *o*-substituted benzoates and isoatoic anhydrides to give synthetically useful 1-(2-methoxyphenyl)-2-(2-pyridinyl)ethanone *N*-oxides, 1-(2-hydroxyphenyl)-2-(2-pyridinyl)ethanone *N*-oxides and 1-(2-aminophenyl)-2-(2-pyridinyl)ethanone *N*-oxides is described.

J. Heterocyclic Chem., **14**, 139 (1977).

The addition of sodium methylsulfinylmethide to *o*-hydroxybenzoates and *o*-aminobenzoates to give good yields of *o*-hydroxy- ω -(methylsulfinyl)acetophenones and *o*-amino- ω -(methylsulfinyl)acetophenones, respectively, was described earlier (1,2). The subsequent transformations of these intermediates into a variety of heterocyclic systems has also been described (1,2,3,4,5). To extend this work to the preparation of heterocyclic systems containing pyridine *N*-oxide substituents, especially 3-substituted chromones and quinolones which may possess antiallergy (6) or CNS (7) activity, syntheses of 1-(2-hydroxyphenyl)-2-(2-pyridinyl)ethanone *N*-oxide and 1-(2-aminophenyl)-2-(2-pyridinyl)ethanone *N*-oxide were required.

The anions derived from 2-picoline and 2-picoline *N*-oxide were allowed to react with various substrates to determine which would give higher yields on the assumption that the 2-picoline intermediates could be oxidized to the corresponding *N*-oxides at any stage. The anions have been generated in a variety of ways (8,9,10,11). The most synthetically useful methods appear to be the generation of 2-picoline anion with phenyllithium in ether and the generation of 2-picoline *N*-oxide anion with sodium amide in liquid ammonia.

2-Picoline *N*-oxide anion failed to react with methyl salicylate or methyl anthranilate in contrast to the results obtained with dimethylsulfoxide anion. 2-Picoline anion reacted with methyl salicylate to give a very low yield of 1-(2-hydroxyphenyl)-2-(2-pyridinyl)ethanone, which had been previously prepared by demethylation of 1-(2-methoxyphenyl)-2-(2-pyridinyl)ethanone (7). The addition of 2-picoline *N*-oxide anion to isoatoic anhydrides (**1**, **2** and **3**) gave the desired amines (**5**, **6** and **7**) in adequate yields (12). 2-Picoline anion also reacted with *N*-methylisatoic

Scheme 1

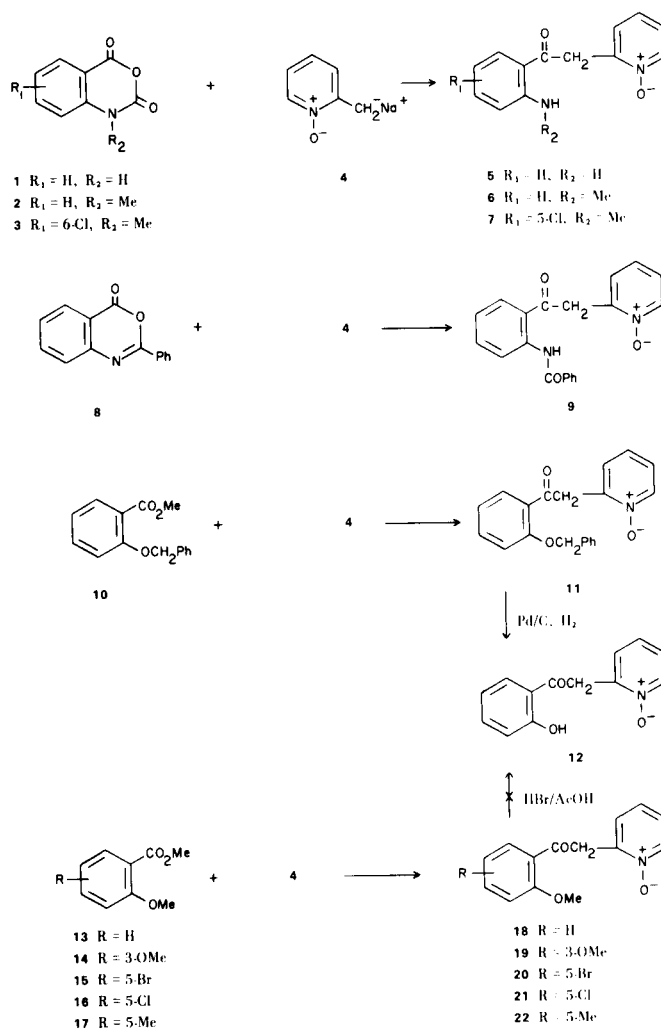
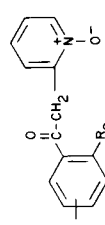


Table I



No.	R ₁	R ₂	M.p., (Recrystallization solvent)	Yield %	Formula	Calcd.			Found		
						C	H	N	C	H	N
5	H	-NH ₂	172-176 (a)	58	C ₁₃ H ₁₂ N ₂ O ₂	68.41	5.30	12.27	68.49	5.39	12.21
6	H	-NHMe	138-140 (b)	57	C ₁₄ H ₁₄ N ₂ O ₂	69.40	5.83	11.56	69.43	5.86	11.54
7	5-Cl	-NHMe	126-128 (b)	38	C ₁₄ H ₁₃ ClN ₂ O ₂	60.77	4.74	10.12	60.51	4.76	10.23
9	H	-NHCOPh	192-194 (a)	25	C ₂₀ H ₁₆ N ₂ O ₃	72.28	4.85	8.43	72.31	4.99	8.54
11	H	-OCH ₂ Ph	138-140 (b)	80	C ₂₀ H ₁₇ NO ₃	75.22	5.37	4.39	75.37	5.35	4.32
12	H	-OH	154-155 (b)	78	C ₁₃ H ₁₁ NO ₃	68.11	4.84	6.11	68.19	4.88	6.15
18	H	-OMe	116-118 (b)	50	C ₁₄ H ₁₃ NO ₃	69.12	5.39	5.76	68.84	5.55	6.00
19	3-OMe	-OMe	122-124 (b)	46	C ₁₅ H ₁₅ NO ₄	65.92	5.53	5.13	65.90	5.57	5.10
20	5-Br	-OMe	166-168 (a)	74	C ₁₄ H ₁₂ BrNO ₃	52.20	3.76	4.35	52.17	3.79	4.36
21	5-Cl	-OMe	119-123 (b)	67	C ₁₄ H ₁₂ ClNO ₃	60.55	4.36	5.04	60.34	4.42	4.90
22	5-Me	-OMe	98-100 (b)	33	C ₁₅ H ₁₅ NO ₃	70.02	5.88	5.44	69.98	5.94	5.35

(a) Recrystallized from ethanol. (b) Recrystallized from ethyl acetate.

anhydride to give 1-[2-(methylamino)phenyl]-2-(2-pyridinyl)ethanone. The synthesis of the various *N*-oxides by direct addition of 2-picoline *N*-oxide anion rather than addition of 2-picoline anion followed by oxidation was determined to be the route of choice.

The anion (4) was reacted with benzoxazinone (8) and *o*-ethers (10 and 13 to 17) to give the products shown in Scheme 1 and Table I.

1-(2-methoxyphenyl)-2-(2-pyridinyl)ethanone *N*-oxide (18) could not be used as an intermediate for the preparation of phenol (12). Conditions (refluxing hydrobromic acid in glacial acetic acid), which convert 1-(2-methoxyphenyl)-2-(2-pyridinyl)ethanone to 1-(2-hydroxyphenyl)-2-(2-pyridinyl)ethanone, transform *N*-oxide (18) into a 2-arylisoxazolo[2,3-*a*]pyridinium bromide (13). Phenol (12) was produced in good yield from benzyl ether (9) by catalytic hydrogenolysis.

Work is in progress on the conversion of the above intermediates into pyridine *N*-oxide substituted chromones, quinolones, cinnolones and coumarins.

EXPERIMENTAL

Melting points were measured with a Thomas-Hoover capillary melting point apparatus without correction. Nmr spectra were recorded on a Perkin-Elmer R 12 B spectrometer at 60 MHz with TMS as internal standard. Infrared spectra were recorded on a Beckmann IR-18A spectrometer. Ultraviolet spectra were recorded on a Beckmann DK-1 spectrometer.

1-[2-(Methylamino)phenyl]-2-(2-pyridinyl)ethanone.

A mixture of 2-picoline (18.6 g., 0.2 mole) and phenyllithium (0.2 mole) in anhydrous ether (250 ml.) was refluxed for 30 minutes. *N*-Methylisatoic anhydride (35.4 g., 0.2 mole) was added, and the resulting mixture was refluxed for an additional 30 minutes. The solid product was filtered off, dissolved in water, acidified with 5*N* hydrochloric acid and extracted with chloroform. The aqueous solution was neutralized with sodium carbonate and extracted with chloroform. The extracts were dried over sodium sulfate and evaporated to give a red-brown oil. The oil was chromatographed on a column of activated alumina. Elution with benzene gave a yellow oil which crystallized on standing (16 g., 35%). Recrystallization from hexane gave yellow crystals, m.p. 40-41°; uv (ethanol): λ max (ε) 228 mμ (ε 24,400), 261 (9600), 389 (6,700); ir (nujol): 3355 cm⁻¹ (N-H), 1665 cm⁻¹ (C=O); nmr (deuteriochloroform): δ 8.7 (s, 1, NH), 8.6-6.4 (m, 8, ArH), 4.43 (s, 2, CH₂) and 2.83 (d, 3, CH₃).

Anal. Calcd. for C₁₄H₁₄N₂O: C, 74.31; H, 6.24; N, 12.38. Found: C, 74.42; H, 6.31; N, 12.43.

1-(2-Hydroxyphenyl)-2-(2-pyridinyl)ethanone.

A mixture of 2-picoline (18.6 g., 0.2 mole) and phenyllithium (0.2 mole) in anhydrous ether (300 ml.) was refluxed for 30 minutes. Ethyl salicylate (10 g., 0.06 mole) was added, and the resulting mixture was refluxed for an additional 45 minutes. After cooling, the reaction mixture was poured onto ice and 6*N* hydrochloric acid. The organic layer was separated and extracted three times with 6*N* hydrochloric acid. The aqueous fractions were combined and the pH adjusted to 5 with 40% aqueous sodium

hydroxide solution and to 7 with sodium bicarbonate. The aqueous solution was extracted five times with ether (60 ml.). The extracts were dried over sodium sulfate and evaporated at reduced pressure to give an oil, which crystallized on standing. Recrystallization from absolute ethanol gave yellow crystals, m.p. 141-145°; uv (ethanol): λ max (ϵ) 208 (23,200), 254 (11,870), 332 (5,100), 410 (4,200); ir (nujol): 1635 cm^{-1} (C=O); nmr (DMSO): δ 13.9 (bs, 1, ArOH, exchanges with deuterium oxide), 8.6-6.5 (m, 8, ArH), 6.17 (s, 1, =C-OH, exchanges with deuterium oxide [compound exists as enol in DMSO]) and 4.60 (s, 1, =C-H, exchanges with deuterium oxide).

Anal. Calcd. for $\text{C}_{13}\text{H}_{11}\text{NO}_2$: C, 73.20; H, 5.17; N, 6.58. Found: C, 73.13; H, 5.28; N, 6.36.

1-(2-Methoxyphenyl)-2-(2-pyridinyl)ethanone *N*-Oxide (18).

2-Picoline *N*-oxide (240 g., 2.2 moles) was added to sodium amide (87 g., 2.2 moles) in anhydrous liquid ammonia (2000 ml.). The resulting deep red solution was stirred for 1 hour and then ethyl 2-methoxybenzoate (200 g., 1.1 moles) was added dropwise. The reaction mixture was stirred for one hour and then quenched by the careful addition of ammonium chloride (120 g.). The ammonia was allowed to evaporate. The solid residue was triturated with water, filtered, washed several times with water, dried under vacuum and recrystallized from ethyl acetate to give light beige crystals (134.8 g., 50%), m.p. 116-118°; uv (ethanol): λ max (ϵ) 211 (35,900), 253 (14,400), 303 (4,000); ir (nujol): 1680 cm^{-1} (C=O); nmr (deuteriochloroform): δ 8.3 to 6.8 (m, 8, ArH), 4.48 (s, 2, CH_2) and 3.88 (s, 3, OCH_3).

1-(2-Substitutedphenyl)-2-(2-pyridinyl)ethanone *N*-Oxides.

The compounds listed in Table I with the exception of **12** were prepared from the corresponding esters (**14**, **15**, **16** and **17**), isatoic anhydrides (**1**, **2** and **3**) and benzoylanthranil (**8**) by the same method and work-up described for **18**.

1-(2-Hydroxyphenyl)-2-(2-pyridinyl)ethanone *N*-Oxide (12).

A solution of 1-[2-(phenylmethoxy)phenyl]-2-(2-pyridinyl)ethanone *N*-oxide (50 g.) in acetic acid (125 ml.) was hydrogenated over 10% palladium on carbon catalyst (5 g.). When the uptake of

hydrogen ceased, the catalyst was filtered off. The filtrate was evaporated to give a black-green oil which crystallized on standing. Recrystallization from ethyl acetate gave white crystals (28 g., 78%), m.p. 154-155°; uv (ethanol): λ max (ϵ) 214 (36,300), 257 (19,700), 326 (4,000); ir (nujol): 1664 cm^{-1} (C=O); nmr (deuteriochloroform): δ 10.49 (s, 1, OH, exchanges with deuterium oxide), 8.5 to 6.7 (m, 8, ArH) and 4.61 (s, 2, CH_2).

Acknowledgment.

We would like to express our gratitude to Dr. R. C. Greenough, Mrs. D. Housman, Mr. W. C. Neumann and Mr. R. E. Saville for spectral data and Mrs. U. Zeek for elemental analysis.

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