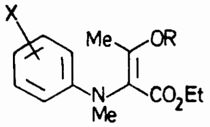
Heteroatom-directed Photoarylation: Synthesis of Indoles and 3-Hydroxyindolines

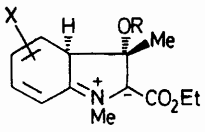
By Arthur G. Schultz* and William K. Hagmann
(*Department of Chemistry, Cornell University, Ithaca, New York* 14853)

Summary Preparative scale irradiation of 2-anilinoacetoacetates gives 3-hydroxyindolines, which suffer acid-catalysed dehydration to give indoles.

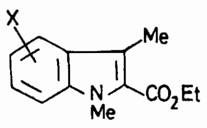
We report here an experimentally simple, high yield synthesis of the 3-hydroxyindolines (**3a**) and their conversion into indoles (**4**).[1] The procedure promises to be general for preparation of indoles with substituents that are useful in alkaloid synthesis and provides the first synthesis of the 2-alkoxycarbonyl-3-hydroxyindoline system. The key step in the synthesis involves photocyclization–rearrangement of 2-anilino-1,3-dicarbonyl compounds to give 3-hydroxyindolines [heteroatom directed photoarylation; *e.g.*, (**1a**) → (**3a**)].[2]



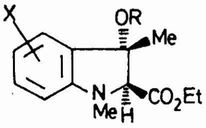
(1)
a; R = H
b; R = Me



(2)
a; R = H
b; R = Me



(4)
a; X = H
b; X = o-OMe
c; X = p-OMe
d; X = m-OMe
e; X = p-Br



(3)
a; R = H
b; R = Me

The required 2-anilinoacetoacetates are conveniently prepared in high yield by reaction of the appropriate aniline with ethyl-2-chloro- or ethyl-2-bromo-acetoacetate,[3] and exist predominantly in the enolic form (**1a**) in $CDCl_3$ solution (i.r. and n.m.r. analysis). Pyrex-filtered irradiation of (**1a**) in benzene–methanol–acetic acid solution (15:15:1, saturated with argon) produces indoles in nearly quantitative yield as shown in the Table. The photoreaction has been applied to large scale laboratory preparation and must occur with high photochemical efficiency; 20 g of (**4a**) was prepared in <8 h using conventional Hanovia equipment.

On the other hand, the 3-hydroxyindolines (**3a**) may be isolated in quantitative yield by irradiation of (**1a**) in the absence of acids. For example, irradiation of (**1a**; X = H) in n-pentane in the presence of solid sodium carbonate gives (**3a**; X = H) as the only detectable product (n.m.r. analysis). The n.m.r. spectrum of (**3a**; X = H) ($CDCl_3$, Me_4Si internal standard) reveals the presence of a single diastereoisomer [δ 1·30 (3H, t, J 7 Hz), 1·43 (3H, s), 2·7br (1H, s, exchangeable with D_2O), 2·78 (3H, s), 3·96 (1H, s), 4·26 (2H, q, J 7 Hz), and 6·4—7·4 (4H, complex m)]. The stereochemistry in (**3a**) is established from the i.r. spectrum which shows bands at $\nu(CS_2)$ 3560 (free OH) and 3440 (intermolecular hydrogen bonding; disappears with dilution) cm^{-1}.[4] Treatment of a solution of (**3a**; X = H) with acetic acid results in rapid and quantitative con version into the indole (**4a**).

Table. Isolated yields of indoles (**4**) from (**1**).

Compound	X	Yield/%	M.p./°C[a]
(**4a**)	H	92	76—77
(**4b**)	*o*-OMe	88	44—45
(**4c**)	*p*-OMe	86	95—96
(**4d**)	*m*-OMe	93	b
(**4e**)	*p*-Br	84	66—67

[a] Crystallized from ethanol. [b] A mixture of 6-methoxy- (m.p 116—117 °C) and 4-methoxy- (m.p. 56—57 °C) isomers (55:45) were produced which were separated by fractional crystallization.

We have shown that the enolic tautomer (**1a**) is most probably involved in the photosynthesis of (**3a**), presumably *via* the ylide (**2**).[5] Thus, treatment of (**1a**) with potassium hydride in tetrahydrofuran–hexamethylphosphoramide followed by addition of trimethyloxonium fluoroborate gives (**1b**) as a mixture of geometric isomers, which are separated by silica gel thick layer chromatography. Irradiation of either isomer of (**1b**) in n-pentane–sodium carbonate, results in double bond isomerization and rapid formation of (**3b**) as a mixture of diastereoisomers; subsequent acetic acid treatment gives (**4a**) in virtually quantitative yield from (**1b**). Furthermore, preparation and irradiation of ethyl-2-(*N*-methylanilino)-2-methylacetoacetate (enolization precluded) does not result in cyclization, but rather gives a complex mixture of photolysis products. Finally, the stereochemistry in (**1a**) and (**3a**) is consistent with a reaction mechanism involving conrotatory photocyclization of (**1a**) to give the intermediate ylide (**2**) followed by a suprafacial 1,4-hydrogen migration to give the indoline (**3a**).[6]

This work was supported by the National Institutes of Health.

(*Received*, 30*th June* 1976; *Com.* 732.)

---

[1] For recent indole synthetic methodology see: P. G. Gassman, T. J. van Bergen, D. P. Gilbert, and B. W. Cue, Jr., *J. Amer. Chem. Soc.*, 1974, **96**, 5495.

[2] A. G. Schultz and W. Y. Fu, *J. Org. Chem.*, 1976, **41**, 1483.

[3] W. R. Boehme, *Org. Synth.*, 1953, **33**, 45.

[4] J. Castells and J. Palau, *J. Chem. Soc.*, 1964, **4938**; B. Capon and M. I. Page, *J. Chem. Soc.* (*B*), 1971, **741**.

[5] The 'non-oxidative photocyclization' of *N*-aryl enamines has been reported: O. L. Chapman, G. L. Eian, A. Bloom, and J. Clardy, *J. Amer. Chem. Soc.*, 1971, **93**, 2918.

[6] A. G. Schultz and M. B. DeTar, *J. Amer. Chem. Soc.*, 1976, **98**, 3564.