Enamide Photochemistry. A Convenient Synthesis of 3-Aryl-1-oxotetrahydro- and dihydro-Isoquinolines (Isocarbostyrils)

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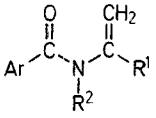
Irradiation of enamides **1** gave 3-aryl-1-oxotetrahydroisoquinolines **3** in good yields. Use of iodine led to the formation of dihydroisoquinolines **4**.

The photocyclization of aromatic enamides, a class of compounds possessing a marked degree of hexatrienic character, has been widely used by many groups, particularly by Ninomiya and coworkers who elegantly synthetized by this method a large variety of alkaloids[1].



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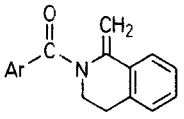

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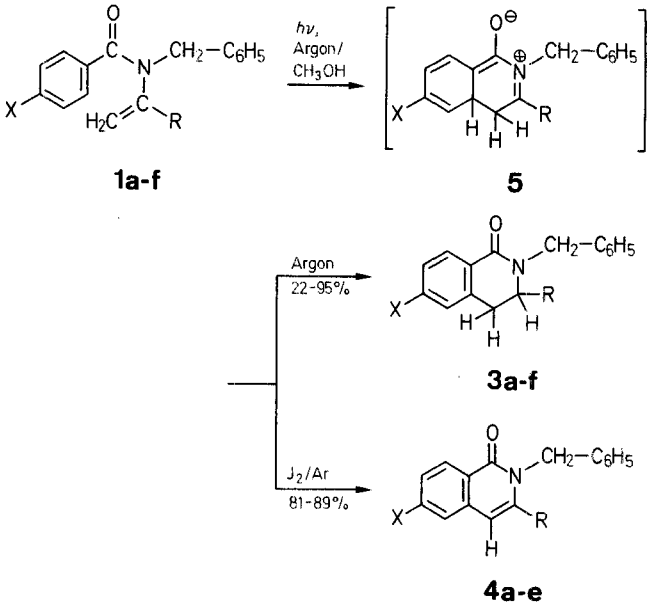
However a number of these systems fails to undergo this type of photocyclization: indeed the photolysis of aromatic enamides of general formula **1** (R^1 = alkyl) with an acyclic double bond gives rise mainly to enaminoketones, products of photo Fries rearrangement[2,3]. Since the main exception in this series concerns the bicyclic compounds **2** which photocyclize normally[4] we speculated that the photolysis of acyclic models **1** with R^1 = aryl could represent a new methodology for the construction of the isocarbostyril framework.

The stable[5] enamides **1a–f** are readily accessible by conventional methods[6]: acylation with benzoyl chloride or *p*-chlorobenzoyl chloride of ketone imines obtained by direct condensation of benzylamine with the appropriated aromatic ketones.

As anticipated, irradiation (Rayonet RPR 208, 2537 Å lamps, 3 h) of a carefully degassed methanolic solution of enamides **1a–e** affords the 3-aryl-2-benzyl-1-oxo-1,2,3,4-tetrahydroisoquinolines **3a–e** almost quantitatively. Under oxidative conditions (iodine) the corresponding isocarbostyrils **4a–e** can also be obtained with fairly good yields.
Owing to the hexatrienic character of the aromatic enamides **1a–e**, one can reasonably attribute the formation of the isocarbostyril derivatives to the photochemical ring closure of the 6π electron system (leading to **5**). Under anaerobic conditions the condensation is accompanied by a thermal [1, 5] hydrogen sigmatropic shift in compliance with the Woodward-Hoffman rules.



1a-f **5** **3a-f** **4a-e**

1,3,4	R	X
a		H
b	CH3	H
c	OCH3	H
d	F	H
e		Cl
f	N	H

Besides the limitation reported in the introduction (**1** with R^1 = alkyl), the photolysis of the pyridyl derivative under anaerobic conditions produces also the condensed heterocycle **3f**, but in a moderate yield (22%).

The photoreaction reported here represents therefore a new and efficient method for the elaboration of models possessing the isocarbostyril framework. Such compounds are of increasing interest in pharmaceutical chemistry[7,8] and can be regarded as intermediates in the synthesis of isoquinoline and dihydroisoquinoline ring systems, a class of compounds characterized by a large spectrum of biological activity[9,10].

Synthesis of Enamides 1a–f; General Procedure:

Ketone Imines: The appropriate ketone (50 mmol) is added dropwise to benzylamine (20 ml) and the mixture is gently refluxed for 4 h. After cooling potassium carbonate is added to the reaction mixture which is then stored in the refrigerator overnight. After filtration the unreacted amine and ketone are removed by distillation under vacuo (0.005 torr). The crude imine can be used without further purification.

Conversion of Ketone Imines to Enamides 1: To a solution of the ketone imine (50 mmol) and triethylamine (5.05 g, 50 mmol) in dry benzene (70 ml) is added benzoyl chloride or *p*-chlorobenzoyl chloride (50 mmol) in benzene (40 ml) at 5–8 °C under nitrogen with stirring. After the addition, the mixture is allowed to warm to room temperature for 1 h and then gently refluxed with continuous stirring for 0.5 h. The precipitated triethylamine hydrochloride is filtered off, the solvent removed and the residue is triturated with cold ethanol. The crude enamides **1a–e** are then recrystallized in ethanol before irradiation. Purification of enamide **1f** is carried out by column chromatography on silica gel (Merck, Kieselgel 60, 70–230 mesh) using the mixture ethylacetate/hexane (3/1) as eluent.

Table 1. *N*-(1-Acrylethenyl)-*N*-benzyl-N-benzamides **1a–f** prepared

Product No.	Yield [%]	m.p.[a] [°C]	Molecular Formula[b]	M.S. 70 ev) *m/e*[c]	^{1}H-N.M.R. ($CDCl_3$/TMS_{int})[d] δ[ppm]
1a	78	57–58°	$C_{22}H_{19}NO$ (313.4)	313 (M^+); 222; 208; 105; 91 (100); 77	4.6 (s, 1 H_{olefin}); 4.9 (s, 2 H, N—CH_2); 5.2 (s, 1 H_{olefin}); 7–7.7 (m, 15 H_{arom})
1b	76	99–100°	$C_{23}H_{21}NO$ (327.4)	327 (M^+); 236 (100); 222; 105; 91; 77	2.35 (s, 3 H, CH_3); 4.5 (s, 1 H_{olefin}); 4.7 (s, 2 H, N—CH_2); 5.2 (s, 1 H_{olefin}); 7–7.7 (m, 14 H_{arom})
1c	75	107–108°	$C_{23}H_{21}NO_2$ (343.4)	343 (M^+); 252; 238; 105; 91 (100); 77	3.9 (s, 3 H, O—CH_3); 4.6 (s, 1 H_{olefin}); 4.9 (s, 2 H, N—CH_2); 5.2 (s, 1 H_{olefin}); 6.85–7.7 (m, 14 H_{arom})
1d	75	156–157°	$C_{22}H_{18}FNO$ (331.4)	331 (M^+); 240; 226; 105; 91 (100); 77	4.5 (s, 1 H_{olefin}); 4.75 (s, 2 H, N—CH_2); 4.95 (s, 1 H_{olefin}); 6.9–7.7 (m, 14 H_{arom})
1e	81	100–101°	$C_{22}H_{18}ClNO$ (347.8)	349, 347 (M^-); 258, 256; 208; 139; 91 (100)	4.65 (s, 1 H_{olefin}); 4.9 (s, 2 H, N—CH_2); 5.3 (s, 1 H_{olefin}); 7.1–7.5 (m, 14 H_{arom})
1f	62	105–106°	$C_{21}H_{18}N_2O$ (314.3)	314 (M^+); 223; 209; 105; 91; 77 (100)	4.9 (br. s, 3 H, 1 H_{olefin} + N—CH_2); 5.4 (s, 1 H_{olefin}); 7.15–7.6 (m, 12 H_{arom}); 8.4–8.5 (br. d, 2 $H_{pyridine}$)

[a] Not corrected.
[b] Satisfactory microanalyses were obtained: C ±0.25, H ±0.25, N ±0.25, O ±0.17, F ±0.18, Cl ±0.17.
[c] M^+; $(M—CH_2C_6H_5)^+$; $(M—COR)^+$; $(RCO)^+$; $(C_6H_5CH_2)^+$; $(C_6H_5)^+$.
[d] I.R. (KBr): $\nu = 1650\ cm^{-1}$ (—N—CO—).

Table 2. 3-Aryl-2-benzyl-1-oxo-1,2,3,4-tetrahydroisoquinolines **3a–f** prepared

Product No.	Yield [%]	m.p.[a] [°C]	Molecular Formula[b]	M.S. (70 ev) *m/e*	^{1}H-N.M.R. ($CDCl_3$/TMS_{int})[c] δ[ppm]
3a	95	oil[d]	$C_{22}H_{19}NO$ (313.4)	313 (M^+); 91 (100)	2.95, 3.5 (dq, 2H, $J_{4,4'} = 16$ Hz, $J_{3,4} = 2$ Hz, $J_{3,4'} = 7$ Hz); 3.6, 5.8 (dd, 2H, $J = 15$ Hz, N—CH_2); 4.7 (m, 1H); 6.9–7.4 (m, 13 H_{arom}); 8.2 (m, 1 H_{peri})
3b	94	109–110°	$C_{23}H_{21}NO$ (327.4)	327 (M^+); 91 (100)	2.25 (s, 3H, CH_3); 2.95, 3.5 (dq, 2H, $J_{4,4'} = 16$ Hz, $J_{3,4} = 2$ Hz, $J_{3,4'} = 7$ Hz); 3.65, 5.8 (dd, 2H, $J = 15$ Hz, N—CH_2); 4.7 (m, 1H); 6.9–7.4 (m, 12 H_{arom}); 8.2 (m, 1 H_{peri})
3c	95	116–117°	$C_{23}H_{21}NO_2$ (343.4)	343 (M^+); 238 (100)	3.0, 3.55 (dq, 2H, $J_{4,4'} = 16.5$ Hz, $J_{3,4} = 2$ Hz, $J_{3,4'} = 7$ Hz); 3.8 (s, 3H, O—CH_3); 3.7, 5.85 (dd, 2H, $J = 15$ Hz, N—CH_2); 4.75 (m, 1H); 6.7 and 7.1 (dd, 4 H_{arom}, $J = 9$ Hz); 7.3–7.5 (m, 8 H_{arom}); 8.3 (m, 1 H_{peri})
3d	92	oil[d]	$C_{22}H_{18}FNO$ (331.4)	331 (M^+); 91 (100)	3.0, 3.6 (dq, 2H, $J_{4,4'} = 16$ Hz, $J_{3,4} = 2$ Hz, $J_{3,4'} = 7$ Hz); 3.7, 5.85 (dd, 2H, $J = 14.5$ Hz, N—CH_2); 4.8 (m, 1H); 7, 7.5 (dd, 4 H_{arom}, $J = 3$ Hz); 7–7.4 (m, 8 H_{arom}); 8.3 (m, 1 H_{peri})
3e	91	oil[d]	$C_{22}H_{18}ClNO$ (347.8)	349, 347 (M^+); 91 (100)	2.9, 3.45 (dq, 2H, $J_{4,4'} = 16$ Hz, $J_{3,4} = 4$ Hz, $J_{3,4'} = 7$ Hz); 3.65, 5.75 (dd, 2H, $J = 15$ Hz, N—CH_2); 4.75 (s, 1H); 6.9–7.4 (m, 12 H_{arom}); 8.15 (d, 1 H_{peri}, $J = 8.5$ Hz)
3f	22	oil[d]	$C_{21}H_{18}N_2O$[e] (314.3)	314 (M^+); 91 (100)	3.0, 3.7 (dq, 2H, $J_{4,4'} = 15.5$ Hz, $J_{3,4} = 2$ Hz, $J_{3,4'} = 7$ Hz); 3.8, 5.9 (dd, 2H, $J = 15$ Hz, N—CH_2); 4.8 (s, 1H); 7–7.7 (m, 10 H_{arom}); 8.3 (m, 1 H_{peri}); 8.55 (br. d, 2 $H_{pyridine}$)

[a] Not corrected.
[b] Satisfactory microanalyses were obtained: C ±0.28, H ±0.25, N ±0.18, O ±0.27, F ±0.09, Cl ±0.07.
[c] I.R. (KBr): $\nu = 1640\ cm^{-1}$ (—N—CO—).
[d] Analytical sample purified by preparative T.L.C.
[e] Analysed by high resolution mass spectroscopy: $m/e = 314.1415$ (M^+ requires 314.1419).

Preparation of compounds *3a–f* and *4a–e*; General Procedure:
A solution of the enamide **1** (2 mmol) in methanol (450 ml) is purged by bubbling argon through it for 0.5 h. Photolyses are carried out in water-cooled quartz reactors equipped with dry argon inlets and magnetic stirrers. The solution is placed in a Rayonet RPR 208 photochemical reactor containing eight Rul 2537 Å lamps. Degassing and stirring of the solution are maintained during the irradiation (3 h). The solvent is removed and the residual photoproduct is chromatographied on a silica gel column (Merck, Kieselgel 60, 70–230 mesh) using a mixture ethyl acetate/hexane (1/3) as eluent.

Table 3. 3-Aryl-2-benzyl-1-oxo-1,2-dihydroisoquinolines **4a–e** prepared

Product No.	Yield [%]	m.p.[a] [°C]	Molecular Formula[b]	M.S. (70 ev) *m/e*	^{1}H-N.M.R. ($CDCl_3$/TMS_{int})[c] δ [ppm]
4a	88	106–107°	$C_{22}H_{17}NO$ (311.4)	311 (M^+); 91 (100)	5.25 (s, 2H, N—CH_2); 6.45 (s, 1H); 6.75–7.8 (m, 13H_{arom}); 8.5 (m, 1H_{peri})
4b	89	134–135°	$C_{23}H_{19}NO$ (325.4)	325 (M^+); 91 (100)	2.45 (s, 3H, CH_3); 5.3 (s, 2H, N—CH_2); 6.5 (s, 1H); 7.05–7.8 (m, 12H_{arom}); 8.55 (m, 1H_{peri})
4c	84	140–141°	$C_{23}H_{19}NO_2$ (341.4)	341 (M^+); 91 (100)	3.8 (s, 3H, OCH_3); 5.25 (s, 2H, N—CH_2); 6.45 (s, 1H); 6.75–7.6 (m, 12H_{arom}); 8.5 (m, 1H_{peri})
4d	82	142–143°	$C_{22}H_{16}FNO$ (329.4)	329 (M^+); 91 (100)	5.3 (s, 2H, N—CH_2); 6.4 (s, 1H); 6.8–7.7 (m, 12H_{arom}); 8.55 (m, 1H_{peri})
4e	81	132–133°	$C_{22}H_{16}ClNO$ (345.8)	347, 345 (M^+); 91 (100)	5.2 (s, 2H, N—CH_2); 6.3 (s, 1H); 6.8–7.5 (m, 12H_{arom}); 8.55 (m, 1H_{peri})

[a] Not corrected.
[b] Satisfactory microanalyses were obtained: C ±0.29, H ±0.13, N ±0.29, O ±0.30, F ±0.18, Cl ±0.05.
[c] I.R. (KBr): $\nu = 1650\ cm^{-1}$ (—N—CO—).

Compounds **3b, c** are recrystallized from a mixture hexane/toluene (9/1). Purification of the oily products **3a, d, e, f** is effected by thin-layer chromatography on Merck silica gel 60 GF_{254} using the same eluent (except for **3f**, ethylacetate/hexane 3/1).

For the photolysis accomplished under oxidative conditions iodine (254 mg, 2 mmol) is previously added to the solution. After irradiation (3 h) as previously described, the solvent is removed, the residual photoproduct is dissolved in dichloromethane (50 ml) and washed with an aqueous solution of sodium thiosulfate (50 ml). The organic layer is then dried with magnesium sulfate. The crude photoproduct is treated by column chromatography as described above and compounds **4a–e** are recrystallized from ethanol.

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