# One-Pot Synthesis of 1-Oxo-1,2-dihydroisoquinolines (Isocarbostyrils) via $S_{RN}1$ (Ar) Reactions[1]

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1-Oxo-1,2-dihydroisoquinolines (isocarbostyrils) are of increasing importance in pharmaceutical chemistry[2,3] and as intermediates in isoquinoline alkaloid synthesis. There is, therefore, a permanent search for new and efficient synthetic methods for this system[4-7]. The $S_{RN}1$ (Ar) reaction[8] which, when extended to *ortho*-functionallized ($NH_2$, $OCH_3$) aryl halides, has led to indoles[1,9,10,12] and to benzofurans[11], also provides a straight forward and versatile access to isocarbostyrils.

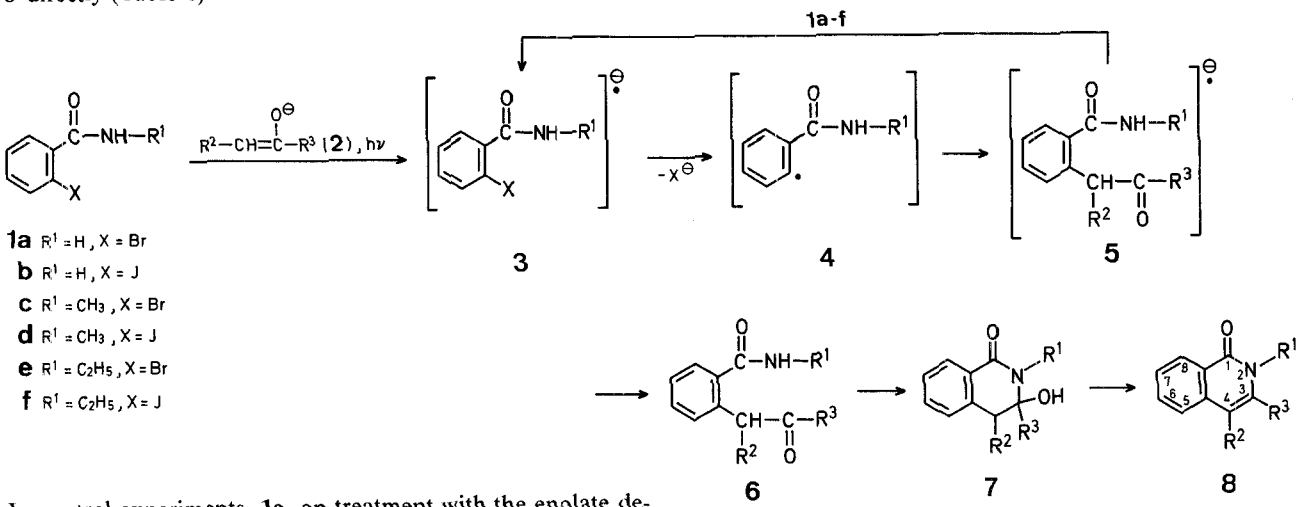
0039-7881/81/0932-0729 $ 03.00 

**Table 1.** Preparation of Isocarbostyrils **8**

| Substrate **1** | Enolate **2** of Ketone | Irradiation time [h] | Yield [%] of | | Product **8** | | | | Yield [%] |
|---|---|---|---|---|---|---|---|---|---|
| | | | recovered **1** | reduced **1** | No. | $R^1$ | $R^2$ | $R^3$ | |
| **1a** | $H_3C—CO—CH_3$ | 0.5 | 0 | 0 | **8a** | H | H | $CH_3$ | 90 |
| **1a** | $H_3C—CO—C_3H_7$-*i* | 0.5 | 0 | 0 | **8b** | H | H | *i*-$C_3H_7$ | 90 |
| **1a** | $H_3C—CO—C_4H_9$-*t* | 0.5 | 0 | 0 | **8c** | H | H | *t*-$C_4H_9$ | 90 |
| **1a** | $C_2H_5—CO—C_2H_5$ | 5 | 0 | 20 | **8d** | H | $CH_3$ | $C_2H_5$ | 70 |
| **1a** | $H_3C—CO—CH_2CH_2C_6H_5$ | 5 | 0 | 30 | **8e** | H | $CH_2C_6H_5$ | $CH_3$ | 30 |
| | | | | | **8f** | H | H | $CH_2CH_2C_6H_5$ | 15 |
| **1a** | cyclohexanone | 3 | 0 | 60 | **8g** | H | —$(CH_2)_4$— | | 30 |
| **1a** | $H_3C—CO—CH_2OCH_3$ | 5 | 45 | 0 | **8a** | H | H | $CH_3$ | 35 |
| **1a** | $H_3C—CO—CH(OCH_3)_2$ | 6 | 60 | 0 | **8h** | H | H | $CH_2OCH_3$ | 10 |
| **1a** | $H_3C—CO—C_6H_4—OCH_3$-4 | 6 | 86 | 0 | **8i** | H | H | $C_6H_4—OCH_3$-4 | 4 |
| **1b** | $H_3C—CO—C_6H_4—OCH_3$-4 | 6 | 0 | 0 | **8i** | H | H | $C_6H_4—OCH_3$-4 | 80 |
| **1c** | $H_3C—CO—CH_3$ | 5 | 13 | 23 | **8j** | $CH_3$ | H | $CH_3$ | 40 |
| **1d** | $H_3C—CO—CH_3$ | 3 | 0 | 43 | **8j** | $CH_3$ | H | $CH_3$ | 45 |
| **1e** | $H_3C—CO—CH_3$ | 4 | 10 | 40 | **8k** | $C_2H_5$ | H | $CH_3$ | 40 |
| **1f** | $H_3C—CO—CH_3$ | 3 | 0 | 42 | **8k** | $C_2H_5$ | H | $CH_3$ | 43 |

[a] Yield of pure isolated product.

We have found that treatment of primary (**1a, b**) or secondary (**1c-f**) *ortho*-halobenzamides with various ketone enolates **2** affords the corresponding 3- and 4-substituted isocarbostyrils **8** directly (Table 1).




In control experiments, **1a**, on treatment with the enolate derived from pinacolone, did not react at all in the dark, whereas, under U.V. illumination in the presence of galvinoxyl (0.25 mmol), the reaction was significantly retarded (incomplete after 5 h). These two experiments are consistent with an $S_{RN}1$ mechanism leading to **8** via **6** and **7** as depicted in the Scheme.

The product of the $S_{RN}1$ reaction is **6**, which under the reaction conditions undergoes a spontaneous cyclization to the $\alpha$-amino alcohol **7**. This unstable product [stability decreasing from $R^3 = t\text{-}C_4H_9$ to $R^3 = CH_3$] dehydrates readily at room temperature and in the presence of acid traces to give the isocarbostyril **8** and has, therefore, been isolated only in some cases, **7b, c,** [($R^1$, $R^2 = H$; $R^3 = i\text{-}C_3H_7$) and ($R^1$, $R^2 = H$; $R^3 = t\text{-}C_4H_9$)] for the sake of characterization.

The two classical limitations of the $S_{RN}1$ reactions are observed:

(a) The lack of regioselectivity for ketones which can produce two enolates leads to a mixture of isocarbostyrils whose ratio depends upon the ratio of the two enolates and of their relative reactivity toward the radical **4**.

(b) The reduction of the substrate **1a** by some enolates derived from ketones with $\beta$ hydrogen atoms, gives various amounts of benzamide. A quantitative reduction is observed by treatment of **1a** with the enolate derived from acetaldehyde. On the other hand, secondary amide substrates **1c-f** treated with nucleophiles which were perfectly suitable for reactions with **1a**, are reduced to a large extent (~50%) regardless the nature of the leaving group X; the reaction of **1d, f** (X = J) being only faster than the reaction with **1c, e** (X = Br).

A further limitation (c) is the fact that a rather poor nucleophile, such as the enolate derived from *p*-methoxyacetophenone gives **8** in very poor yield when treated with **1a** (X = Br) but on using **1b** (X = J) the desired isocarbostyril **8** is obtained in excellent yield.

In addition to the limitations a and b, it should be noticed that the reaction of **1a** with functionallized ketone enolates **2**, such those derived from methoxyacetone or from pyruvalde-

**Table 2.** Characterization of α-Amino Alcohols 7 and Isocarbostyrils 8

| Product | m.p. [°C] ($CH_2Cl_2$/hexane) | Molecular formula[a] or Lit. m.p. [°C] | M.S. *m/e* | $^1$H-N.M.R. ($CDCl_3$)[b] δ [ppm] |
|---|---|---|---|---|
| **7b** | —[c] | — | 205 ($M^+$); 187 (M − 18) | 1.00 (d, 6H); 1.9 (m, 1H); 2.80 (d, 1H); 3.10 (d, 1H, $J$ = 15 Hz); 4.30 (s, 1H); 6.70 (br. s, 1H); 7.0–8.0 (m, 4H) |
| **7c** | —[d] | — | 219 ($M^+$); 201 (M − 18) | 1.10 (s, 9H); 3.10 (d, 1H); 3.40 (d, 1H, $J$ = 15 Hz); 4.00 (s, 1H); 6.90 (br. s, 1H); 7.2–8.1 (m, 4H) |
| **8a** | 215° | 211°[15] | 159 ($M^+$) | 2.40 (s, 3H); 6.25 (s, 1H); 7.2–7.7 (m, 3H); 8.30 (d, 1H) |
| **8b** | 194–196° | 197°[16] | 187 ($M^+$); 172 | 1.37 (d, 6H); 3.0 (m, 1H); 6.40 (s, 1H); 7.3–7.7 (m, 3H); 8.30 (d, 1H) |
| **8c** | 190–192° | $C_{14}H_{15}NO$ (201.3) | 201 ($M^+$) | 1.35 (s, 9H); 5.30 (s, 1H); 7.2–7.7 (m, 3H); 8.30 (d, 1H) |
| **8d** | 190–193° | $C_{13}H_{13}NO$ (187.2) | 187 ($M^+$); 172; 158 | 1.30 (t, 3H); 2.75 (q, 2H); 2.26 (s, 3H); 7.4–8.0 (m, 3H); 8.43 (d, 1H) |
| **8e** | 215–220° | $C_{17}H_{15}NO$ (249.3) | 249 ($M^+$); 158 | 2.43 (s, 3H); 4.10 (s, 2H); 7.1–7.6 (m, 8H); 8.40 (d, 1H) |
| **8f** | 195–198° | $C_{17}H_{15}NO$ (249.3) | 249 ($M^+$); 172 | 3.0 (br s, 4H); 6.23 (s, 1H); 6.9–7.6 (m, 8H); 8.40 (d, 1H) |
| **8g** | 250–255° | $C_{13}H_{13}NO$ (199.2) | 199 ($M^+$); 171 | 1.9 (m, 4H); 2.7 (m, 4H); 7.4–7.8 (m, 3H); 8.60 (d, 1H) |
| **8h**[e] | 128–130° | $C_{11}H_{11}NO_2$ (189.2) | 189 ($M^+$); 159 | 3.43 (s, 3H); 4.40 (s, 2H); 6.40 (s, 1H); 7.1–7.7 (m, 3H); 8.35 (d, 1H) |
| **8i** | 243° ($CH_3OH/H_2O$) | 243°[17] | 251 ($M^+$); 236 | 3.90 (s, 3H); 6.70 (s, 1H); 7.00 (d, 2H); 7.4–7.8 (m, 5H); 8.40 (d, 1H) |
| **8j** | 103° ($CH_3OH/H_2O$) | 103°[7] | 173 ($M^+$); 158 | 2.36 (s, 3H); 3.60 (s, 3H); 6.33 (s, 1H); 7.2–7.8 (m, 3H); 8.40 (d, 1H) |
| **8k** | 59–60° | 55–59°[18] | 187 ($M^+$) | 1.33 (t, 3H); 2.45 (s, 3H); 4.25 (q, 2H); 6.45 (s, 1H); 7.4–7.8 (m, 3H); 8.40 (d, 1H) |

[a] Satisfactory microanalyses obtained: C ±0.40, H ±0.05, N ±0.05; exception **8h**.
[b] I.R. ($CHCl_3$) of **7**: $\nu$ = ~3500 $cm^{-1}$.
I.R. ($CHCl_3$) of **8**: $\nu$ = 3400–3150 (NH); 1650 $cm^{-1}$ (—N—CO—).
[c] $R^1$, $R^2$ = H, $R^3$ = $i$-$C_3H_7$; dehydrates on heating at 194–196 °C to **8b**.
[d] $R^1$, $R^2$ = H, $R^3$ = $t$-$C_4H_9$; dehydrates on heating at 190–192 °C to **8c**.
[e] Analyzed by high resolution mass spectrometry: *m/e* = 189.0792 ($M^+$ requires 189.2164).

hyde dimethyl acetal give **8a, h** ($R^3 = CH_3$ and $R^3 = CH_2OCH_3$), respectively, instead of the desired isocarbostyril **8** with $R^3$ = —$CH_2$—$OCH_3$ or —$CH(OCH_3)_2$. The loss of methoxide may occur by fragmentation of the radical anion **5** [$R^3 = CH_2OCH_3$ or $CH(OCH_3)_2$] similar to a mechanism suggested to take place when bromobenzene was treated with the enolate derived from methoxyacetone[13]. However, this is not a real limitation since the oxidation ($SeO_2$) of the 3-methylisocarbostyril is easy and gives high yields (80–90%) of the 3-formyl derivative from which various 3-functionalized (COOH; CN; $CH_2OH$, CH=CHCOOH) isocarbostyrils may be obtained[14].

Thus, our one-pot synthesis, compared with others, offers several interesting features (1) it starts with commercially or readily available materials, (2) it is carried out under mild basic conditions and often requires short reaction times, (3) it is versatile and gives, in several cases, the desired product in excellent yields.

**Preparation of Compounds 7 and 8; General Procedure:**
Ammonia (25 ml) is condensed at −33 °C in a three neck flask fitted with a Dry Ice condenser. The enolate **2** is formed using the ketone (4 mmol) and an equivalent amount of freshly sublimed potassium *t*-butoxide. The substrate **1** (1 mmol) is then added and the reaction mixture is irradiated (Rayonet RPR 204 from the SO New England Ultraviolet Co., equipped with 4 tubes RUL 3000). The reaction is quenched by addition of ammonium chloride (0.5 g) and the ammonia is evaporated. Water (50 ml) addition allows the extraction of α-amino alcohols **7** by dichloromethane (4 × 30 ml) whereas slight acidification with 2 normal hydrochloric acid (1 ml) before work up leads directly to the isocarbostyrils **8**.

Received: March 23, 1981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