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# One-Pot Synthesis of 3-Substituted Isoquinolin-1-(2*H*)-ones and Fused Isoquinolin-1-(2*H*)-ones by $S_{RN}1$ Reactions in DMSO

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3-Substituted isoquinolin-1-(2*H*)-ones and fused isoquinolin-1-(2*H*)-ones have been obtained by the photostimulated $S_{RN}1$ reactions of 2-iodobenzamide with the enolates of aromatic (acetophenone, 1-(benzo[*d*][1,3]dioxol-5-yl)ethanone, 1- and 2-naphthyl methyl ketones, and 2-, 3-, and 4-acetylpyridine), aliphatic (1-adamantyl methyl ketone), and cyclic ketones (1- and 2-indanone, α- and β-tetralone, and 1-benzosuberone) in DMSO.


## Introduction

Derivatives of isoquinolin-1-(2*H*)-one compose an important class of heterocyclic compounds from both the synthetic and biological points of view. It is well known that their structures are incorporated in several alkaloids and other pharmacologically important compounds such as thalifoline,[1] dorianine,[2] narciclasine,[3] pancratistatin, and lycoricidine.[4]

Substituted isoquinolinones exhibiting antidepressant,[5] anti-inflammatory,[6] anti-ulcer,[7] analgesic,[5] hypolipidemic,[8] and antihypertensive[9] characteristics have also been described. In addition, it has been shown that some compounds of this family act on the central nervous system or behave as inhibitors of lipoxygenase, poly (ADP-ribose)-polymerase, and cholesterol biosynthesis among others. Isoquinolinones are also employed for the treatment of stomach tumors and diseases of human brain cells.[2]

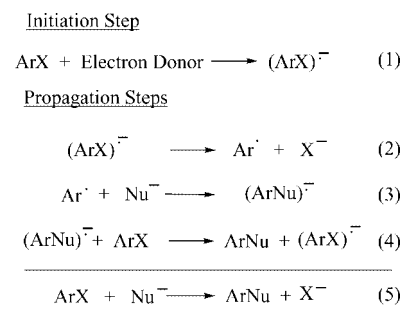
Considering their chemical stability, substituted isoquinolin-1-(2*H*)-ones are often used as building blocks in organic synthesis, as useful intermediates in the synthesis of indenoisoquinolines, protoberberines, and dibenzoquinolizines, and are also of interest in medicinal chemistry.[10]

There are several procedures to obtain isoquinolinones. The Bischler–Napieralski and Pictet–Spengler[2] reactions are classic methods for the synthesis of isoquinolinones.

The synthetic methods employed in the synthesis of these heterocycles involve the use of homophthalic anhydride [e.g. the base–promoted condensation reactions with 2-(bromomethyl)benzonitrile to the synthesis of indolo(3,2-*c*)isoquinolinone],[11] the transformation of isocoumarins by primary amines,[12] double metalation of an *N*-propenyl-2-methyl benzamide to give a cyclocondensation reaction with DMF,[13] $S_NAr$ reactions from 2-chlorobenzonitriles with β-keto esters followed by cyclization in acid conditions,[14] and intramolecular Diels–Alder reactions.[2] Recently, the synthesis of isoquinolinones has been improved by using transition-metal catalysts.[2,15]

Although many synthetic approaches toward isoquinolinone ring systems have already been reported, we describe herein an efficient synthesis of 3-substituted isoquinolin-1-(2*H*)-ones and fused isoquinolin-1-(2*H*)-ones in one step by the $S_{RN}1$ mechanism.

The $S_{RN}1$ mechanism is a chain process whose key steps are presented in Scheme 1. This mechanism is an important route to achieve the formation of a new C–C bond by the reaction of aromatic substrates with carbanions.[16]




Scheme 1.

The initiation step is the electron transfer (ET) from an electron donor to the substrate to afford the radical anion of the substrate [Scheme 1, Equation (1)]. Only a few systems are known to react by the $S_{RN}1$ mechanism in a thermal (or spontaneous) reaction. Most of these systems need to be initiated by different means. Photoinitiation, chemical initiation by alkali metals in liquid ammonia, or electro-

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chemical initiation at a cathode are the most frequently used techniques. However, other reagents to initiate the reactions, such as $Fe^{2+}$, $SmI_2$, or Na(Hg) are also known.[16]

In the propagation steps, the radical anion fragments into a radical and the anion of the leaving group [Equation (2)]. The radical reacts with the nucleophile to form the radical anion of the substitution product [Equation (3)]. The ET from this radical anion to the substrate affords the substitution product and the radical anion of the substrate, which propagates the chain reaction [Equation (4)]. Overall, Equations 2–4 depict a nucleophilic substitution in which radicals and radical anions are intermediates [Equation (5)].

A particularly useful application of the $S_{RN}1$ reaction is the synthesis of heterocycles from aromatic compounds that have an appropriate substituent *ortho*- to the leaving group.[16,17] Recently, this method has been applied to the synthesis of a new family of 2*H*-1,2-benzothiazine 1,1-dioxides[18] and 1-phenyl-1-oxazolino-indane derivatives containing quaternary carbon atoms.[19] In this field, an important example is the synthesis of 2-substituted and fused indoles by the reaction of 2-iodoaniline with ketone enolates.[20] Substituted isoquinolin-1-(2*H*)-ones have been obtained by reaction of *o*-iodo- or *o*-bromobenzamides with enolates of ketones in liquid ammonia under photostimulation.[21]

The reaction between substituted *o*-iodobenzamide and the enolate derived from the 2-acetyl homoveratric acid sodium salt leads to tricyclic isoquinolinones that can be readily converted to either berberine or benzo[*c*]phenanthridone ring systems, affording a versatile access to both families of alkaloids.[22] In addition, there is only one report of the synthesis of 1- and 2-naphthylisoquinoline derivatives, which consists of the reaction of *o*-bromobenzamide with enolates derived from 1- or 2-naphthyl methyl ketones under photostimulation in DMSO. The isoquinolinones were not isolated but were transformed into isoquinoline derivatives.[23]

Although isoquinolinones are important compounds, little effort has been devoted to the synthesis of these compounds by the $S_{RN}1$ mechanism in DMSO. In the present study, we undertake the synthesis of 3-substituted isoquinolinones with acyclic aromatic and aliphatic ketones, and for the first time, we report the synthesis of fused isoquinolinones by the photostimulated $S_{RN}1$ reactions of the enolates of cyclic ketones with *o*-iodobenzamide under irradiation in DMSO.

## Results and Discussion

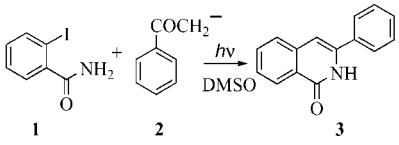
### 3-Substituted Isoquinolin-1-(2*H*)-ones

The photostimulated reaction of *o*-iodobenzamide (**1**) with the enolate of acetophenone (**2**) affords the 3-phenylisoquinolin-1-(2*H*)-one (**3**) in 91% yield [Equation (6)]. This reaction does not occur in the dark and is partially inhibited by *p*-dinitrobenzene (*p*-DNB), a known radical anion scavenger (Table 1, Experiments 1–3). These results provide strong experimental evidence that this reaction proceeds through the $S_{RN}1$ mechanism.

Table 1. Reactions of **1** with ketone enolates.[a]

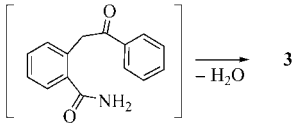
| Expt. | Nucleophile | % $I^-$[b] | Products[c] (%) | % Benzamide |
|---|---|---|---|---|
| 1 | **2** | 100 | **3** (91) | – |
| 2[d] | **2** | <2 | – | – |
| 3[e] | **2** | 67 | **3** (68) | – |
| 4 | **4** | 100 | **5** (87) | – |
| 5 | **6a** | 90 | **7a** (83) | – |
| 6 | **6b** | 78 | **7b** (68) | 7 |
| 7[f] | **8a** | 92 | **9a** (81) | – |
| 8 | **8b** | 88 | **9b** (79) | – |
| 9 | **8c** | 94 | **9c** (72) | – |
| 10 | **10** | 97 | **11** (71) | 20 |
| 11 | **12a** | 86 | **13a** (51) | 23 |
| 12 | **12b** | 93 | **13b** (42) | 44 |
| 13 | **12c** | 96 | **13c** (88) | – |
| 14 | **14a** | 90 | **15a** (70) | – |
| 15 | **14b** | 93 | **15b** (80) | – |

[a] Reactions carried out under $N_2$ in 10 mL of DMSO [**1** (1 mmol), ketone (4 mmol) and *t*BuOK (4.04 mmol)]. Irradiation time: 180 min. [b] Determined potentiometrically. [c] Isolated yield in parentheses. [d] Reaction in the dark. [e] *p*-DNB (20 mol-%) was added. [f] Quantified by GLC.



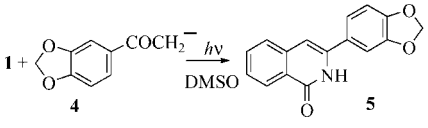

1 2 3 (6)

It should be noted that the intermediate formed by the $S_{RN}1$ reaction cyclizes spontaneously by polar intramolecular reaction to give corresponding product **3** [Equation (7)].




(7)

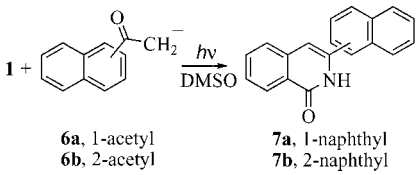
A related nucleophile, the enolate of 1-(benzo[*d*][1,3]dioxol-6-yl)ethanone (**4**), gives the ring closure product **5** in similar yields under irradiation with **1** [Equation (8) and Table 1, Experiment 4].




4 5 (8)

3-(Naphthalen-1-yl)isoquinolin-1-(2*H*)-one (**7a**) is obtained by a photostimulated reaction of **1** with the enolate of 1-naphthyl methyl ketone (**6a**) in 83% yield in DMSO. In the photostimulated reaction of **1** with 2-naphthyl methyl ketone (**6b**), 3-(naphthalen-2-yl)isoquinolin-1-(2*H*)-one (**7b**) is obtained in 68% yield together with the reduced product benzamide in 7% yield [Equation (9) and Table 1, Experiments 5 and 6].

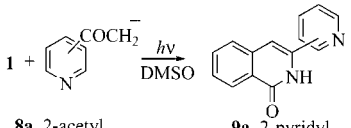



**6a**, 1-acetyl
**6b**, 2-acetyl

**7a**, 1-naphthyl
**7b**, 2-naphthyl

(9)

Excellent yields of 3-pyridyl-substituted isoquinolinones are obtained when heteroaromatic ketone enolates are employed as nucleophiles. Thus, the enolates of 2-, 3-, and 4-acetylpyridines (**8a**–**c**) react with **1** under photostimulation in DMSO to afford the 3-pyridinyl-isoquinolin-1-(2*H*)-ones (**9a**–**c**) in 72–81% yield [Equation (10) and Table 1, Experiments 7–9].

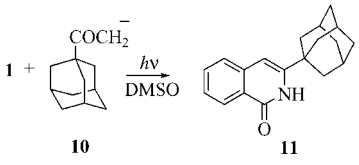



**8a**, 2-acetyl
**8b**, 3-acetyl
**8c**, 4-acetyl

**9a**, 2-pyridyl
**9b**, 3-pyridyl
**9c**, 4-pyridyl

(10)

The lipophilic adamantyl moiety has been used to improve the pharmacological activities of certain compounds, and hence, we considered the possibility of obtaining the 3-adamantyl-substituted isoquinolinone. In the photostimulated reaction of the enolate of 1-adamantyl methyl ketone with **1**, 3-(adamantan-1-yl)isoquinolin-1-(2*H*)-one (**11**) was obtained in high yield [Equation (11) and Table 1, Experiment 10].

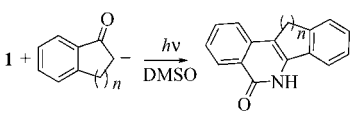



**10** **11**

(11)

### Fused Isoquinolin-1-(2*H*)-ones

6*H*-Indeno[1,2-*c*]isoquinolin-5-(11*H*)-one (**13a**) and 11,12-dihydrobenzo[*c*]phenanthridin-6-(5*H*)-one (**13b**) are obtained by photostimulated reactions of **1** with the enolates of 1-indanone (**12a**) and α-tetralone (**12b**), respectively, [Equation (12) and Table 1, Experiments 11 and 12]. The reduction product benzamide was formed together with the target fused isoquinolinones. On the other hand, the enolate of 1-benzosuberone (**12c**) reacts with **1** to give the tetracyclic isoquinolinone **13c** in 88% yield, uncontaminated with benzamide [Equation (12) and Table 1, Experiment 13].

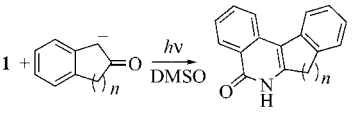



**12a**, $n = 1$
**12b**, $n = 2$
**12c**, $n = 3$

**13a**, $n = 1$
**13b**, $n = 2$
**13c**, $n = 3$

(12)

6*H*-Indeno[2,1-*c*]isoquinolin-5-(7*H*)-one (**15a**) is obtained by a photostimulated reaction of **1** with the enolate of 2-indanone (**14a**) in 70% yield. Under the same conditions, the reaction of **1** with the enolate of β-tetralone (**14b**) furnishes 80% of **15b** [Equation (13) and Table 1, Experiments 14 and 15]. The reduction product benzamide was not observed in these reactions.




**14a**, $n = 1$
**14b**, $n = 2$

**15a**, $n = 1$
**15b**, $n = 2$

(13)

## Conclusions

The photostimulated reactions of several acyclic enolates of aromatic (acetophenone, 1-(benzo[*d*][1,3]dioxol-5-yl)ethanone, 1- and 2-naphthyl methyl ketones, and 2-, 3-, and 4-acetylpyridine), aliphatic (1-adamantyl methyl ketone), and cyclic ketones (1- and 2-indanone, α- and β-tetralone, and 1-benzosuberone) with substrate **1** in DMSO afford 3-substituted isoquinolinones and fused isoquinolinones in very good yields (42–91%) by the $S_{RN}1$ mechanism.

Considering the availability and simplicity of the starting materials and the readiness and mild conditions of the procedure, we have demonstrated that this methodology becomes a general technique for the synthesis of isoquinolin-1-(2*H*)-ones.

## Experimental Section

### General Methods and Materials

**Methods:** $^1$H NMR (200 MHz) and $^{13}$C NMR (50 MHz) spectra were obtained in $CDCl_3$ or [$D_6$]DMSO as solvents. The purification of the products was performed by column chromatography on silica gel. Irradiation was conducted in a photochemical reactor equipped with two 400-W Hg lamps emitting maximally at 350 nm (air- and water-refrigerated). Potentiometric titration of iodide ions was performed with a pH meter using a $Ag/Ag^+$ electrode. Melting points were performed with an Electrothermal 9100 instrument.

**Materials:** *t*BuOK was commercially available and used as received. DMSO was distilled under vacuum and stored under molecular sieves (4 Å). Acetophenone, 1- and 2-naphthyl methyl ketones, 1-(benzo[*d*][1,3]dioxol-5-yl)ethanone, 1-adamantyl methyl ketone, 2-, 3-, and 4-acetypyridine, α- and β-tetralone, 1- and 2-indanone, and 1-benzosuberone were commercially available and distilled under reduced pressure. *o*-Iodobenzamide (**1**) was prepared from 2-iodobenzoic acid according to the literature procedure.[24]

**Photostimulated Reaction of Acetophenone Enolate (2) with *o*-Iodobenzamide (1) in DMSO:** The following procedure is representative of all these reactions. They were carried out in a 20-mL three-neck round-bottomed flask equipped with a nitrogen inlet and magnetic stirrer at room temperature. To dry and deoxygenated DMSO (10 mL) under nitrogen was added *t*BuOK (0.453 g, 4.04 mmol) and acetophenone (0.468 mL, 4.00 mmol). After 15 min, **1** (0.247 g, 1 mmol) was added, and the reaction mixture was irradiated for

180 min. The reaction was quenched with excess ammonium nitrate and water. The precipitate formed was removed by filtration and dried under vacuum to give **3** as light-colored crystals. The filtrate was extracted with dichloromethane, and the organic extract was washed with water and dried with anhydrous $MgSO_4$, and benzamide was purified and quantified by column chromatography on silica gel. The concentration of iodide ions in the aqueous solution was determined potentiometrically.

**Isolation and Identification of Products**

**3-Phenylisoquinolin-1-(2*H*)-one (3):** Compound **3** (201 mg, 91%) was obtained according to the general procedure and recrystallized from acetone as white needles. M.p. 199–200 °C (lit m.p.[25] 205 °C). $^1$H NMR (200 MHz, [D$_6$]DMSO): $\delta$ = 11.49 (br. s , 1 H, NH), 8.21 (d, $J$ = 8.0 Hz, 1 H, CH), 7.82–7.70 (m, 4 H, CH), 7.55–7.44 (m, 4 H, CH), 6.91 (s, 1 H, CH) ppm. $^{13}$C NMR (50 MHz, [D$_6$]-DMSO): $\delta$ = 162.69, 140.00, 137.87, 133.83, 132.53, 129.16, 128.70, 126.60, 126.31, 124.82, 103.15 ppm. MS: *m*/*z* (%) = 222 (15), 221 (100), 194 (8), 165 (16), 143 (9), 89 (16), 82 (9), 77 (8), 63 (9).

**3-(Benzo[*d*][1,3]dioxol-6-yl)isoquinolin-1-(2*H*)-one (5):**[26] Compound **5** (230 mg, 87%) was obtained according to the general procedure and recrystallized from methanol as white needles. M.p. 251–252 °C. $^1$H NMR (200 MHz, [D$_6$]DMSO): $\delta$ = 11.36 (br. s, 1 H, NH), 8.18 (d, $J$ = 8.0 Hz, 1 H, CH), 7.74–7.64 (m, 2 H, CH), 7.50–7.30 (m, 3 H, CH), 7.03 (d, $J$ = 8.0 Hz, 1 H, CH), 6.85 (br. s, 1 H, CH), 6.10 (s, 2 H, $CH_2$) ppm. $^{13}$C NMR (50 MHz, [D$_6$]-DMSO): $\delta$ = 162.66, 148.16, 147.70, 139.67, 137.98, 132.53, 127.84, 126.58, 126.49, 126.06, 124.58, 120.81, 108.44, 106.95, 102.48, 101.48 ppm. MS: *m*/*z* (%) = 266 (17), 265 (100), 264 (9), 206 (6), 178 (11), 152 (11), 151 (9), 132 (13), 89 (18), 76 (21), 63 (16). HRMS: (EI) calcd. for $C_{16}H_{11}NO_3$ 265.0739; found 265.0748.

**3-(Naphthalen-1-yl)isoquinolin-1-(2*H*)-one (7a):**[27] Compound **7a** (225 mg, 83%) was obtained according to the general procedure and recrystallized from acetone as white needles. M.p. 222–224 °C. $^1$H NMR (200 MHz, [D$_6$]DMSO): $\delta$ = 11.62 (br. s, 1 H, NH), 8.27 (d, $J$ = 8.0 Hz, 1 H, CH), 8.08–7.90 (m, 3 H, CH), 7.79–7.49 (m, 7 H, CH), 6.66 (s, 1 H, CH) ppm. $^{13}$C NMR (50 MHz, [D$_6$]-DMSO): $\delta$ = 162.23, 139.51, 137.76, 133.15, 132.80, 132.48, 130.91, 129.27, 128.30, 127.36, 126.79, 126.63, 126.44, 126.36, 126.17, 125.28, 125.07, 124.98, 105.98 ppm. MS: *m*/*z* (%) = 272 (17), 271 (100), 270 (99), 269 (14), 252 (15), 241 (14), 240 (10), 127 (15), 126 (14), 121 (27), 107 (14), 106 (11), 89 (10). HRMS: (EI) calcd. for $C_{19}H_{13}NO$ 271.0997; found 271.1002.

**3-(Naphthalen-2-yl)isoquinolin-1-(2*H*)-one (7b):** Compound **7b** (184 mg, 68%) was purified by column chromatography on silica gel eluting with a dichloromethane/diethyl ether gradient (100:0→0:100) and recrystallized from acetone as white needles. M.p. 238–239 °C. $^1$H NMR (200 MHz, [D$_6$]DMSO): $\delta$ = 11.60 (br.s, 1 H, NH), 8.43 (br. s, 1 H, CH), 8.24 (d, $J$ = 8.0 Hz, 1 H, CH), 8.06–7.90 (m, 4 H, CH), 7.76–7.70 (m, 2 H, CH), 7.61–7.47 (m, 3 H, CH), 7.1 (s, 1 H, CH) ppm. $^{13}$C NMR (50 MHz, [D$_6$]-DMSO): $\delta$ = 162.72, 139.75, 137.89, 132.99, 132.69, 132.61, 130.97, 128.41, 128.27, 127.49, 126.90, 126.71, 126.63, 126.44, 125.82, 124.93, 124.15, 103.67 ppm. MS: *m*/*z* (%) = 272 (21), 271 (100), 215 (18), 143 (11), 127 (11), 120 (10), 115 (11), 108 (10), 107 (12). HRMS: (EI) calcd. for $C_{19}H_{13}NO$ 271.0997; found 271.0996.

**3-(Pyridin-2-yl)isoquinolin-1-(2*H*)-one (9a):** Compound **9a** (91%) was quantified by GLC, purified by column chromatography on silica gel eluting with an *n*-hexane/dichloromethane gradient (100:0→0:100) and recrystallized from *n*-hexane/dichloromethane as light yellow crystals. M.p. 140–142 °C (lit m.p.[28] 136–137 °C). $^1$H NMR (200 MHz, [D$_6$]DMSO): $\delta$ = 10.74 (br. s, 1 H, NH), 8.70 (br. d, $J$ = 4.4 Hz, 1 H, CH), 8.26–8.17 (m, 2 H, CH), 8.02–7.93 (m, 1 H, CH), 7.81–7.72 (m, 2 H, CH), 7.59–7.45 (m, 3 H, CH) ppm. $^{13}$C NMR (50 MHz, [D$_6$]DMSO): $\delta$ = 161.37, 149.05, 148.92, 137.65, 137.49, 136.39, 132.77, 127.25, 126.76, 126.00, 124.23, 120.16, 103.69 ppm. MS: *m*/*z* (%) = 223 (16), 222 (100), 194 (17), 193 (14), 118 (21), 90 (14), 89 (21), 78 (11), 63 (10), 51 (13), 43 (11). HRMS: (EI) calcd. for $C_{14}H_{10}N_2O$ 222.0793; found 222.0801.

**3-(Pyridin-3-yl)isoquinolin-1-(2*H*)-one (9b):** Compound **9b** (176 mg, 79%) was purified by column chromatography on silica gel eluting with an *n*-hexane/acetone gradient (75:25→0:100) and recrystallized from acetone/water as light yellow crystals. M.p. 234–235 °C. $^1$H NMR (200 MHz, [D$_6$]DMSO): $\delta$ = 11.66 (br. s, 1 H, NH), 8.99 (d, $J$ = 2.6 Hz, 1 H, CH), 8.64 (dd, $J$ = 4.8, 1.5 Hz, 1 H, CH), 8.25–8.16 (m, 2 H, CH), 7.73–7.72 (m, 2 H, CH), 7.55–7.49 (m, 2 H, CH), 7.00 (s, 1 H, CH) ppm. $^{13}$C NMR (50 MHz, [D$_6$]DMSO): $\delta$ = 162.64, 149.89, 147.57, 137.60, 137.33, 134.20, 132.64, 129.70, 126.74, 126.60, 125.07, 123.50, 104.12 ppm. MS: *m*/*z* (%) = 223 (15), 222 (100), 221 (13), 194 (10), 193 (12), 139 (9), 118 (21), 90 (13), 89 (22), 63 (14), 51 (12), 43 (16). HRMS: (EI) calcd. for $C_{14}H_{10}N_2O$ 222.0793; found 222.0795.

**3-(Pyridin-4-yl)isoquinolin-1-(2*H*)-one (9c):** Compound **9c** (160 mg, 72%) was obtained according to the general procedure as light-colored crystals and recrystallized from acetone as white crystals. M.p. 265–266 °C. $^1$H NMR (200 MHz, [D$_6$]DMSO): $\delta$ = 11.64 (br. s, 1 H, NH), 8.69 (dd, $J$ = 4.5, 1.8 Hz, 2 H, CH), 8.24 (dd, $J$ = 8.0, 0.7 Hz, 1 H, CH), 7.82 (dd, $J$ = 4.5, 1.8 Hz, 2 H, CH), 7.76 (dd, $J$ = 4.5, 0.7 Hz, 2 H, CH), 7.61–7.49 (m, 1 H, CH), 7.18 (d, $J$ = 0.7 Hz, 1 H, CH) ppm. $^{13}$C NMR (50 MHz, [D$_6$]DMSO): $\delta$ = 162.56, 150.13, 140.70, 137.27, 137.19, 132.77, 127.30, 127.14, 126.68, 125.60, 120.65, 105.01 ppm. MS: *m*/*z* (%) = 223 (16), 222 (100), 221 (13), 194 (12), 193 (14), 139 (8), 90 (10), 89 (21), 78 (8), 63 (14), 51 (11), 43 (12). HRMS: (EI) calcd. for $C_{14}H_{10}N_2O$ 222.0793; found 222.0795.

**3-(Adamantan-1-yl)isoquinolin-1-(2*H*)-one (11):** Compound **11** (198 mg, 71%) was purified by column chromatography on silica gel eluting with a petroleum ether/diethyl ether gradient (90:10→50:50) and recrystallized from dichloromethane/diethyl ether as white needles. M.p. 271–273 °C. $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ = 10.19 (br. s, 1 H, NH), 8.36 (d, $J$ = 8.0 Hz, 1 H, CH), 7.62 (ddd, $J$ = 8.0, 6.8, 1.4 Hz, 1 H, CH), 7.52–7.49 (m, 1 H, CH), 7.42 (ddd, $J$ = 8.0, 6.8, 1.4 Hz, 1 H, CH), 6.32 (d, $J$ = 1.4 Hz, 1 H, CH), 2.16 (m, 3 H, CH), 2.02 (d, $J$ = 2.9 Hz, 6 H, $CH_2$), 1.83 (t, $J$ = 2.9 Hz, 6 H, $CH_2$) ppm. $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ = 164.22, 149.55, 138.80, 132.57, 127.34, 126.37, 126.02, 124.78, 100.90, 40.77, 36.70, 36.30, 28.54 ppm. MS: *m*/*z* (%) = 280 (21), 279 (100), 278 (11), 222 (18), 91 (7), 89 (12), 79 (6), 77 (8), 41 (13). HRMS: (EI) calcd. for $C_{19}H_{21}NO$ 279.1623; found 279.1632.

**6*H*-Indeno[1,2-*c*]isoquinolin-5-(11*H*)-one (13a):**[11] Compound **13a** (118 mg, 51%) was obtained according to the general procedure and recrystallized from DMF as light yellow crystals. M.p. 376–378 °C. $^1$H NMR (200 MHz, [D$_6$]DMSO): $\delta$ = 12.30 (br. s, 1 H, NH), 8.26 (d, $J$ = 8.0 Hz, 1 H, CH), 8.03–7.99 (m, 1 H, CH), 7.76–7.75 (m, 2 H, CH), 7.64–7.60 (m, 1 H, CH), 7.51–7.31 (m, 3 H, CH), 3.91 (s, 2 H, $CH_2$) ppm. $^{13}$C NMR (50 MHz, [D$_6$]DMSO): $\delta$ = 162.69, 143.04, 139.43, 136.79, 135.66, 132.69, 127.82, 126.93, 126.76, 125.66, 124.80, 123.26, 119.43, 115.74, 32.78 ppm. MS: *m*/*z* (%) = 234 (17), 233 (100), 232 (51), 204 (23), 203 (14), 102 (15), 88 (13), 76 (11). Compound **13a** exhibits spectral and analytical data in accordance with that in ref.[11]

**11,12-Dihydrobenzo[*c*]phenanthridin-6-(5*H*)-one (13b):**[29] Compound **13b** (104 mg, 42%) was obtained according to the general procedure as light-colored crystals and recrystallized from acetone

as white crystals. M.p. 273–275 °C. $^1$H NMR (200 MHz, [D$_6$]-DMSO): $\delta$ = 11.37 (br. s, 1 H, NH), 8.31–8.26 (m, 1 H, CH), 7.95–7.86 (m, 2 H, CH), 7.76 (ddd, $J$ = 8.0, 6.8, 1.5 Hz, 1 H, CH), 7.55–7.47 (m, 1 H, CH), 7.33–7.28 (m, 3 H, CH), 2.91 (s, 4 H, CH$_2$) ppm. $^{13}$C NMR (50 MHz, [D$_6$]DMSO): $\delta$ = 161.99, 137.06, 136.87, 132.88, 132.64, 128.65, 128.49, 127.79, 127.14, 126.66, 126.17, 125.42, 123.02, 110.19, 27.53, 20.90 ppm. MS: *m*/*z* (%) = 248 (18), 247 (100), 246 (63), 232 (20), 228 (31), 217 (14), 115 (9), 114 (14), 109 (12). Compound **13b** exhibits spectral and analytical data in accordance with that in ref.[29]

**5,11,12,13-Tetrahydro-5-aza-benzo[3,4]cyclohepta[1,2-*a*]naphthalen-6-one (13c):** Compound **13c** (230 mg, 88%) was obtained according to the general procedure and recrystallized from acetone as a white solid. M.p. 243–245 °C. $^1$H NMR (200 MHz, [D$_6$]DMSO): $\delta$ = 11.39 (br. s, 1 H, NH), 8.30 (dd, $J$ = 8.0, 1.8 Hz, 1 H, CH), 7.93 (br. d, $J$ = 8.4 Hz, 1 H, CH), 7.80–7.72 (m, 1 H, CH), 7.54–7.37 (m, 5 H, CH), 2.59–2.48 (m, 4 H, overlapped, CH$_2$), 2.25–2.15 (m, 2 H, CH$_2$) ppm. $^{13}$C NMR (50 MHz, [D$_6$]DMSO): $\delta$ = 161.83, 140.29, 137.03, 136.66, 134.55, 132.56, 128.89, 128.73, 128.11, 127.25, 126.36, 125.85, 125.47, 122.88, 111.54, 33.37, 31.06, 22.22 ppm. MS: *m*/*z* (%) = 262 (20), 261 (100), 260 (16), 246 (36), 233 (22), 232 (28), 228 (14), 115 (12), 114 (11), 102 (12). HRMS: (EI) calcd. for $C_{18}H_{15}NO$ 261.1154; found 261.1148.

**6*H*-Indeno[2,1-*c*]isoquinolin-5-(7*H*)-one (15a):** Compound **15a** (163 mg, 70%) was purified by column chromatography on silica gel eluting with a dichloromethane/diethyl ether gradient (100:0→0:100). White solid. M.p. 316–318 °C. $^1$H NMR (200 MHz, [D$_6$]DMSO): $\delta$ = 12.16 (br. s, 1 H, NH), 8.41–8.32 (m, 2 H, CH), 8.05 (br. d, $J$ = 7.7 Hz, 1 H, CH), 7.85 (td, $J$ = 7.5, 1.1 Hz, 1 H, CH), 7.58–7.51 (m, 2 H, CH), 7.42–7.34 (m, 1 H, CH), 7.23–7.15 (t, $J$ = 7.3 Hz, 1 H, CH), 3.85 (s, 2 H, CH$_2$) ppm. $^{13}$C NMR (50 MHz, [D$_6$]DMSO): $\delta$ = 161.77, 146.41, 140.78, 138.38, 134.12, 132.94, 128.11, 126.95, 125.60, 124.90, 124.34, 123.64, 122.61, 119.65, 113.10, 35.40 ppm. MS: *m*/*z* (%) = 234 (7), 233 (100), 232 (13), 204 (15), 177 (6), 176 (7), 102 (6), 88 (7). HRMS: (EI) calcd. for $C_{16}H_{11}NO$ 233.0841; found 233.0844.

**7,8-Dihydrobenzo[*a*]phenanthridin-5-(6*H*)-one (15b):**[29] Compound **3** (198 mg, 80%) was obtained according to the general procedure and recrystallized from acetone/water as white needles. M.p. 279–280 °C. $^1$H NMR (200 MHz, [D$_6$]DMSO): $\delta$ = 11.65 (br. s, 1 H, NH), 8.30 (dd, $J$ = 8.0, 1.5 Hz, 1 H, CH), 8.19 (br. d, $J$ = 8.0 Hz, 1 H, CH), 7.79–7.70 (m, 2 H, CH), 7.50 (td, $J$ = 7.5, 1.1 Hz, 1 H, CH), 7.34–7.14 (m, 3 H, CH), 2.80–2.65 (m, 4 H, CH$_2$) ppm. $^{13}$C NMR (50 MHz, [D$_6$]DMSO): $\delta$ = 161.18, 140.81, 135.98, 135.01, 132.34, 132.02, 127.79, 127.46, 126.25, 125.77, 125.47, 125.31, 123.53, 108.52, 27.50, 26.61 ppm. MS: *m*/*z* (%) = 248 (17), 247 (100), 246 (29), 232 (12), 228 (15), 218 (10), 217 (10), 203 (7), 202 (8), 189 (7), 109 (8), 95 (9), 43 (19). Compound **15b** exhibits spectral and analytical data in accordance with that in ref.[29]

**Supporting Information** (see footnote on the first page of this article): $^{13}$C- and $^1$H NMR spectroscopic data of compounds **3**, **5**, **7a**, **7b**, **9a**, **9b**, **9c**, **11**, **13a**, **13b**, **13c**, **15a**, and **15b**.

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[1] M. S. Chern, W. R. Li, *Tetrahedron Lett.* **2004**, *45*, 8323–8326.
[2] V. A. Glushkov, Y. V. Shklyaev, *Chem. Heterocycl. Compd.* **2001**, *37*, 663–687.
[3] D. Gonzalez, T. Martinot, T. Hudlickly, *Tetrahedron Lett.* **1999**, *40*, 3077–3080.
[4] R. C. Thompson, J. Kallmerten, *J. Org. Chem.* **1990**, *55*, 6076–6078.
[5] S. Senda, O. Ohtani, E. Katho, H. Miyake, K. Fujiwara, *Ger. Offen*. 3031574, **1981** [*Chem. Abstr.* **1981**, *95*, 132692].
[6] K. Kubo, N. Ito, I. Souzu, Y. Isomura, H. Homma, *Ger. Offen.* 2828528, **1979** [*Chem. Abstr.* **1979**, *90*, 168468].
[7] S. Senda, O. Ohtani, E. Katho, M. Nagasaka, H. Miyake, K. Fujiwara, M. Tanaka, *Fr. Demande* 2502619, **1983** [*Chem. Abstr.* **1983**, *98*, 71955].
[8] M. Hasegava, K. Shirai, K. Matsumoto, Y. Suzuki, I. Takahasi, *US Patent* 5441962, **1994** [*Chem. Abstr.* **1994**, *121*, 912].
[9] S. Senda, O. Ohtani, E. Katho, M. Nagasaka, H. Miyake, K. Fujiwara, M. Tanaka, *Ger. Offen*. 3211501, **1982** [*Chem. Abstr.* **1983**, *98*, 198048].
[10] F. Coelho, D. Veronese, E. C. S. Lopes, R. C. Rossi, *Tetrahedron Lett.* **2003**, *44*, 5731–5735.
[11] P. G. Jagtap, E. Baloglu, G. Southan, W. Williams, A. Roy, A. Nivorozhkin, N. Landrau, K. Desisto, A. L. Salzman, C. Szabó, *Org. Lett.* **2005**, *7*, 1753–1756.
[12] S. Otha, S. Kimoto, *Tetrahedron Lett.* **1975**, *16*, 2279–2282.
[13] L. E. Fisher, J. M. Muchowski, R. D. Clark, *J. Org. Chem.* **1992**, *57*, 2700–2705.
[14] R. J. Snow, T. Butz, A. Hammach, S. Kapadia, T. M. Morwick, A. S. Prokopowicz, H. Takahashi, J. D. Tan, M. A. Tschantza, X. Wangb, *Tetrahedron Lett.* **2002**, *43*, 7553–7556.
[15] K. Cherry, A. Duchêne, J. Thibonnet, J. L. Parrain, M. Abarbri, *Synthesis* **2005**, 2349–2355.
[16] For reviews, see: a) R. A. Rossi, A. B. Pierini, A. B. Peñéñory in *The Chemistry of Functional Groups* (Eds.: S. Patai, Z. Rappoport), Wiley, Chichester, **1995**, Supplement D2, ch. 24, pp. 1395–1485; b) R. A. Rossi, A. B. Pierini, A. N. Santiago, "Aromatic Substitution by the $S_{RN}1$ Reaction" in *Organic Reactions* (Eds.: L. A. Paquette, R. Bittman), John Wiley & Sons, New York, **1999**, vol. 54, pp. 1–271; c) R. A. Rossi, A. B. Pierini, A. B. Peñéñory, *Chem. Rev.* **2003**, *103*, 71–167.
[17] R. A. Rossi, M. T. Baumgartner, "Synthesis of Heterocycles by the $S_{RN}1$ Mechanism" in *Targets in Heterocyclic Systems: Chemistry and Properties* (Eds.: O. A. Attanasi, D. Spinelli), Societa Chimica Italiana, Rome, **1999**, vol. 3, pp. 215–243.
[18] W. J. Layman, T. D. Greenwood, A. L. Downey, J. F. Wolfe, *J. Org. Chem.* **2005**, *70*, 9147–9155.
[19] M. D. Roydhouse, J. C. Walton, *Chem. Commun.* **2005**, 4453–4455.
[20] S. M. Barolo, A. E. Lukach, R. A. Rossi, *J. Org. Chem.* **2003**, *68*, 2807–2811, and references therein.
[21] R. Beugelmans, M. Bois-Choussy, *Synthesis* **1981**, 729–731.
[22] R. Beugelmans, M. Bois-Choussy, *Tetrahedron* **1992**, *48*, 8285–8294.
[23] R. Beugelmans, M. Bois-Choussy, *J. Org. Chem.* **1991**, *56*, 2518–2522.
[24] R. A. Moss, S. Chatterjee, W. Boguslawa, *J. Org. Chem.* **1986**, *51*, 4303–4307.
[25] E. Bisagni, C. Landras, S. Thirot, C. Huel, *Tetrahedron* **1996**, *52*, 10427–10439.
[26] W. J. Cho, M. J. Park, B. H. Chung, C. O. Lee, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 41–46.
[27] Although this compound was synthesized, no product characterization was reported, see: W. J. Cho, S. Y. Min, T. N. Le, T. S. Kim, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4451–4454.
[28] E. M. Brun, S. Gil, M. Parra, *Arkivoc* **2002**, *X*, 80–89.
[29] J. H. Rigby, D. D. Holsworth, K. James, *J. Org. Chem.* **1989**, *54*, 4019–4020.

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