# The Formation of Quinolin-2(*1H*)-ones via Electrocyclic Reaction of *o*-Isocyanatostyrenes Generated in situ from *o*-Isocyanostyrenes

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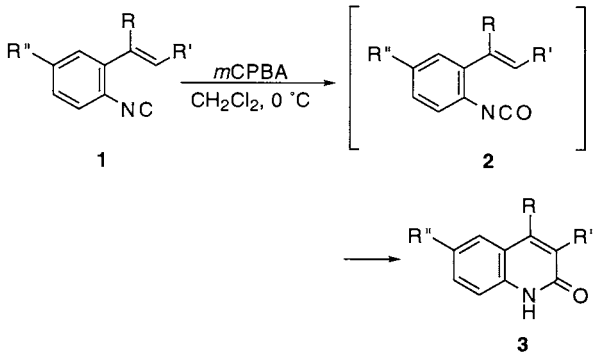
(Received April 6, 2000; CL-000321)

A convenient one-pot preparation of 4-substituted or 3,4-disubstituted quinolin-2(1*H*)-ones from 2-isocyanostyrene derivatives, which involves *m*CPBA oxidation to the corresponding isocyanate intermediates followed by electrocyclization, is described.

Quinolin-2(1*H*)-one derivatives have been of use in organic synthesis.[1] Moreover, some compounds having this skeleton have interesting biological profile,[2] exhibiting, for example, angiotensin II receptor[2b] and oxytocin[2c] antagonist activities. Therefore, a number of new methods for the synthesis of this class of molecules have recently appeared.[3] In this paper, we wish to describe the results of our investigation, which offer a facile route to 4-substituted or 3,4-disubstituted quinolin-2(1*H*)-ones **3** based on *m*CPBA oxidation of 2-isocyanostyrene derivatives **1**. As outlined in Scheme 1, this one-pot procedure involves initial formation of the corresponding isocyanate intermediates **2**, followed by *in situ* electrocyclic reaction.[4] Reports on the synthesis of quinolin-2(1*H*)-one derivatives by electrocyclization of 2-isocyanatostyrenes, generated *in situ* by Curtius rearrangements of the respective acyl azides, have been recorded.[5a–c] The kinetic and computational studies of this electrocyclic reaction in hexadueteriobenzene, have recently been reported by Dolbier, Jr. et al.[5d] The methods, however, involve tedious reaction conditions and/or incomplete generality.

The starting isocyanides **1** were prepared as follows. Treatment of the respective *o*-aminostyrenes, which were commercially available or readily prepared using the procedure of Smith and Livinghouse[6] or Bell et al.,[7] with formic acid in refluxing toluene gave the corresponding formamide, which were then dehydrated with phosphorous oxychloride in the presence of triethylamine in THF to give **1** in high overall yields.[8] While these isocyanides appeared to be somewhat unstable, most of them could be purified by column chromatography on silica gel and storable for prolonged periods at refrigerator temperature.

The isocyanides **1** were treated with an equimolar amount of *m*CPBA in dichloromethane at room temperature overnight. After usual workup, the residual products were recrystallized to give quinolin-2(1*H*)-ones **3**. The results are summarized in Table 1. The 4-substituted quinolin-2(1*H*)-one derivatives **3a–e** and **3h** were obtained in fair-to-good yields (Entries 1–5 and 8). α,β-Disubstituted 2-isocyanostyrenes **1f** and **1g** were also treated with *m*CPBA under the same conditions to obtain 3,4-disubstituted derivatives **3f** and **3g**, respectively. The reactions proceeded more slowly than those of the reactions forming 4-substituted derivatives and gave rather diminished yields of the expected products (Entries 6 and 7). The presence of the isocyanato intermediates in the reaction mixtures from **1f** or **1g** was confirmed on the basis of their IR spectra, which exhibited intense absorption bands (ν ca. 2250–2260 $cm^{-1}$) assignable to the isocyanato group. It should be noted that a similar treatment of 2-isocyanostilbene (**1**, R = R" = H, R' = Ph) with *m*CPBA unfortunately resulted in the formation of a mixture including the corresponding isocyanato derivative, as judged from its IR spectrum (ν ca. 2254 $cm^{-1}$). Heating of this mixture resulted in the formation of an intractable mixture of products, from which no trace amount of the expected 3-phenylquinolin-2(1*H*)-one was obtained. These results can probably be understood in terms of the strained hindrance of the transition state of isocyanate intermediates together with the results of kinetic studies by Dolbier, Jr. et al,[5] which indicated




**a** R=Me, R'=R"=H; **b** R=Ph, R'=R"=H; **c** R=2-$MeC_6H_4$, R'=R"=H; **d** R=4-$(MeO)C_6H_4$, R'=R"=H; **e** R=3,4-$(MeO)_2C_6H_3$, R'=R"=H; **f** R=Me, R'=Me, R"=H; **g** R=Ph, R'=Me, R"=H; **h** R=Ph, R'=H, R"=Cl

**Scheme 1.**

**Table 1.** Preparation of quinolin-2(1*H*)-ones **3**

| Entry | Isocyanide **1** | Product **3** (Yield/%)[a] |
|---|---|---|
| 1 | **1a** | **3a**[b] (70) |
| 2 | **1b** | **3b**[c] (63) |
| 3 | **1c** | **3c** (55) |
| 4 | **1d** | **3d**[d] (62) |
| 5 | **1e** | **3e** (74) |
| 6 | **1f** | **3f** (43) |
| 7 | **1g** | **3g** (22) |
| 8 | **1h** | **3h**[e] (74) |

[a]Isolated yields after recrystallization. [b]Commercially available. [c]Mp 270–273 °C (lit.,[1c] mp 264–265 °C). [d]Mp 237–240 °C (lit.,[1d] mp 239–241 °C). [e]Mp 261–264 °C (lit.[7] mp 262 °C).

that β-substituted *o*-isocyanatostyrenes requires high activation energies for cyclization.

A number of reagents,[9] such as ozone,[9a] halogens in the presence of dimethyl sulfoxide,[9b] nitrogen oxide,[9c] or pyridine oxide,[9d] have been reported to oxidize isocyanides to the corresponding isocyanates. These reagents, however, are undoubtfully unsuitable for the present transformation. To the best of our knowledge, this is the first report which indicates that *m*CPBA can oxidize isocyano group to isocyanato group.

A typical procedure is illustrated by the preparation of 4-methylquinolin-2(1*H*)-one (**3a**). To a stirred solution of **1a** (0.28 g, 2.0 mmol) in dichloromethane (10 mL) at 0 °C was added *m*CPBA (80%, purchased from Kanto Chemical Co., Inc.; 0.43 g, 2.0 mmol) in several portions. The reaction mixture was then allowed to warm to room temperature and stirred overnight at that temperature. The resulting mixture was transferred to a separating funnel using dichloromethane (20 mL), washed with saturated aqueous sodium carbonate, and dried over anhydrous sodium sulfate. After evaporation of the solvent, the crude solid material was purified by recrystallization from diethyl ether–hexane to afford the pure quinolinone **3a** (0.11 g, 70%) as a white solid; mp 217–220 °C; identified by a direct comparison with commercially available compound (purchased from Tokyo Kasei Kogyo Co., Ltd.) (mp 221–223 °C).[10]

In comparison to the previously described syntheses of quinolin-2(1*H*)-one derivatives,[6] the advantages of the synthesis described here are that the reaction procedure is simple and the products are readily obtained by recrystallization in high purity. Applications of the present process to the synthesis of related heterocycle–fused pyridone derivatives are now in progress in our laboratory.

Assistance in MS experiments by Mrs. Miyuki Tanmatsu of this Department is gratefully acknowledged.

**References and Notes**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8 **1a**: $R_f$ 0.78 (1:2 EtOAc–hexane); IR (neat) 2122 $cm^{-1}$; $^1H$ NMR (270 MHz, $CDCl_3$) δ 2.10 (3H, s), 5.07 (1H, s), 5.29 (1H, s), and 7.2–7.35 (4H, m); MS *m/z* (%) 143 ($M^+$, 20) and 117 (100). **1b:** $R_f$ 0.72 (1:2 EtOAc–hexane); IR (neat) 2122 $cm^{-1}$; $^1H$ NMR (270 MHz, $CDCl_3$) δ 5.40 (1H, s), 5.87 (1H, s), and 7.25–7.4 (9H, m); MS *m/z* (%) 205 ($M^+$, 87) and 204 (100). **1c**: $R_f$ 0.77 (1:2 Et2O–hexane); IR (neat) 2120 $cm^{-1}$; $^1H$ NMR (270 MHz, $CDCl_3$) δ 2.02 (3H, s), 5.55 (1H, d, *J* = 1.1 Hz), 5.69 (1H, d, *J* = 1.1 Hz), and 7.1–7.35 (8H, m); MS *m/z* (%) 219 ($M^+$, 22), 218 (29), and 204 (100). **1d**: $R_f$ 0.65 (1:2 EtOAc–hexane); IR (neat) 2123 and 1607 $cm^{-1}$; $^1H$ NMR (270 MHz, $CDCl_3$) δ 3.80 (3H, s), 5.27 (1H, d, *J* = 1.0 Hz), 5.77 (1H, d, *J* = 1.0 Hz), 6.84 (2H, d, *J* = 8.9 Hz), 7.18 (2H, d, *J* = 8.9 Hz), and 7.3–7.45 (4H, m); MS *m/z* (%) 235 ($M^+$, 100). **1e:** mp 79–81 °C ($Et_2O$–hexane–$CH_2Cl_2$); IR (KBr disk) 2124 and 1601 $cm^{-1}$; $^1H$ NMR (270 MHz, $CDCl_3$) δ 3.85 (3H, s), 3.88 (3H, s), 5.31 (1H, s), 5.79 (1H, s), 6.71 (1H, dd, *J* = 8.2 and 2.0 Hz), 6.79 (1H, d, *J* = 8.6 Hz), 6.87 (1H, d, *J* = 2.0 Hz), and 7.3–7.45 (4H, m); MS *m/z* (%) 265 ($M^+$, 100). **1f**: $R_f$ 0.85 (1:2 EtOAc–hexane); IR (neat) 2121 $cm^{-1}$; $^1H$ NMR (270 MHz, $CDCl_3$) δ 1.80 (3H, dd, *J* = 6.9 and 1.1 Hz), 2.03 (3H, t, *J* = 1.3 Hz), 5.63 (1H, qd, *J* = 6.9 and 1.3 Hz), and 7.15–7.35 (4H, m); MS *m/z* (%) 157 ($M^+$, 100). **1g**: $R_f$ 0.80 (1:2 EtOAc–hexane); IR (neat) 2121 $cm^{-1}$; $^1H$ NMR (270 MHz, $CDCl_3$) δ 1.92 (3H, d, *J* = 7.1 Hz), 6.02 (1H, q, *J* = 7.1 Hz), and 7.15–7.45 (9H, m); MS *m/z* (%) 219 ($M^+$, 43) and 218 (100). **1h:** mp 86–88 °C (hexane); IR (KBr disk) 2124 $m^{-1}$; $^1H$ NMR (270 MHz, $CDCl_3$) δ 5.40 (1H, d, *J* = 1.0 Hz), 5.88 (1H, d, *J* = 1.0 Hz), and 7.2–7.35 (8H, m); MS *m/z* (%) 241 (10), 239 ($M^+$, 31) and 204 (100).

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10 Physical and spectral properties for new quinolinones **3** follows. **3c:** mp 201–203 °C ($Et_2O$); IR (KBr disk) 3439 and 1651 $cm^{-1}$; $^1H$ NMR (270MHz, $CDCl_3$) δ 2.14 (3H, s), 6.62 (1H, s), 7.05–7.55 (8H, m), and 12.2 (1H, br); MS *m/z* (%) 235 ($M^+$, 100). **3e:** mp 243–246 °C ($Et_2O$–$CHCl_3$); IR (KBr disk) 3426 and 1651 $cm^{-1}$; $^1H$ NMR (270 MHz, $CDCl_3$) δ 3.91 (3H, s), 3.97 (3H, s), 6.70 (1H, s), 6.95–7.1 (3H, m), 7.17 (1H, t, *J* = 7.9 Hz), 7.45–7.6 (2H, m), 7.70 (1H, d, *J* = 7.9 Hz), and 11.6 (1H, br); MS *m/z* (%) 281 ($M^+$, 0.8), 237 (12), and 208 (100). **3f:** mp 265–268 °C ($CHCl_3$–$Et_2O$); IR (KBr disk) 3442 and 1649 $cm^{-1}$; $^1H$ NMR (270 MHz, $CDCl_3$) δ 2.32 (3H, s), 2.49 (3H, s), 7.15–7.7 (3H, m), 7.70 (1H, d, *J* = 7.9 Hz), and 11.2 (1H, br); MS *m/z* (%) 173 ($M^+$, 100). **3g**: mp 227–230 °C (hexane–$Et_2O$); IR (KBr disk) 3449 and 1654 $cm^{-1}$; $^1H$ NMR (270 MHz, $CDCl_3$) δ 2.07 (3H, s), 7.05–7.7 (2H, m), 7.2–7.3 (2H, m), 7.35–7.6 (5H, m), and 11.6 (1H, br); MS *m/z* (%) 235 ($M^+$, 57) and 234 (100).