# A Novel Cascade Reaction of Aryl Aldoxime with Dimedone Under Microwave Irradiation: The Synthesis of *N*-Hydroxylacridine

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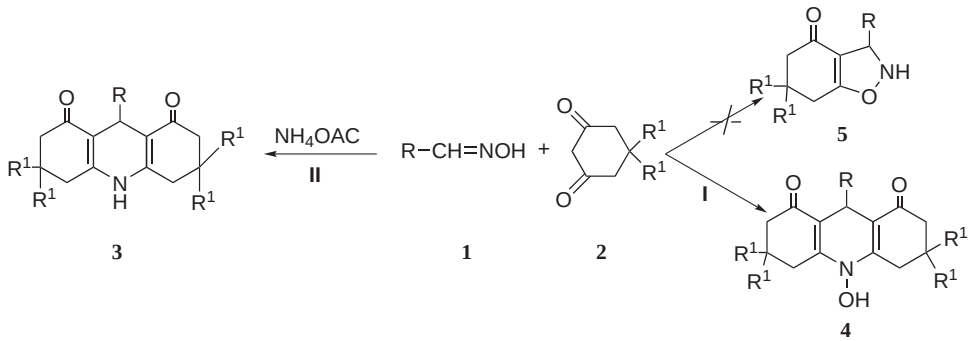
**Abstract:** A novel sequential addition, elimination and cyclization reactions took place when aldoxime and dimedone in glycol was subjected to microwave irradiation and a new type of *N*-hydroxylacridinedione derivatives was obtained in excellent yields (80–95%) within a short reaction time (4–8 min).

**Key words:** aryl aldoxime, dimedone, *N*-hydroxylacridine, microwave

1,4-Dihydropyridines (1,4-DHPs) are well-known compounds because of their pharmacological profile as calcium channel modulators.[1] The chemical modifications of the DHP ring such as the introduction of different substituents or heteroatoms[2] have allowed expansion of the research to structure-activity relationship to afford new insight into the molecular interactions at the receptor level. In fact, it is well-established that slight structural modification on the DHP ring may bring significant change in pharmacological activities.[3] Acridine belongs to a special class of compounds not only because of their interesting chemical and physical properties but also due to their immense utility in pharmaceutical and dye industry. With an 1,4-DHPs parent nucleus, acridines are well known atherapeutic agents.[4] The discovery of acridines as antimalarial and antitumor agents has attracted the attention of organic chemists and led to intensive interest in the synthesis of several drugs based on acridine.[5] The introduction of aryl on the nitrogen of acridine causes laser activity.[6] However, the introduction of a hydroxyl on the nitrogen atom of acridine has not been reported.

Oximes are important intermediates in organic synthesis such as in 1,3-dipolar cycloadditions,[7] and can be applied in the preparation of heterocycles.[8] It was recently found that these reactions can be accelerated by microwave irradiation (MW).[9] Since microwave heating was first used for organic synthesis by Gedye[10] in 1986, the MW assisted organic synthesis has been a topic of continuing interest.[11] The relative low cost of modern domestic microwave ovens makes them readily available to academic and industrial chemists.[12] In this paper, we report a novel cascade reaction of oximes with dimedone under microwave irradiation that leads to the synthesis of a new type of heterocyclic compounds, the *N*-hydroxylacridine derivatives (Scheme 1).

As a part of a research program directed towards the design and synthesis of lead compounds for potentially interesting drugs, aldoxime was taken into consideration as a possible starting point to obtain new substances with pharmacological activity. In our recent efforts aiming at synthesizing compound **5**, we treated **1** and **2** in glycol under microwave irradiation. However, instead of the desired compound **5**, a new compound 9-substituded-*N*-hydroxyl-1,2,3,4,5,6,7,8,9,10-decahydro-acridine-1,8-dione (**4**) was obtained.[13]




**Scheme 1**

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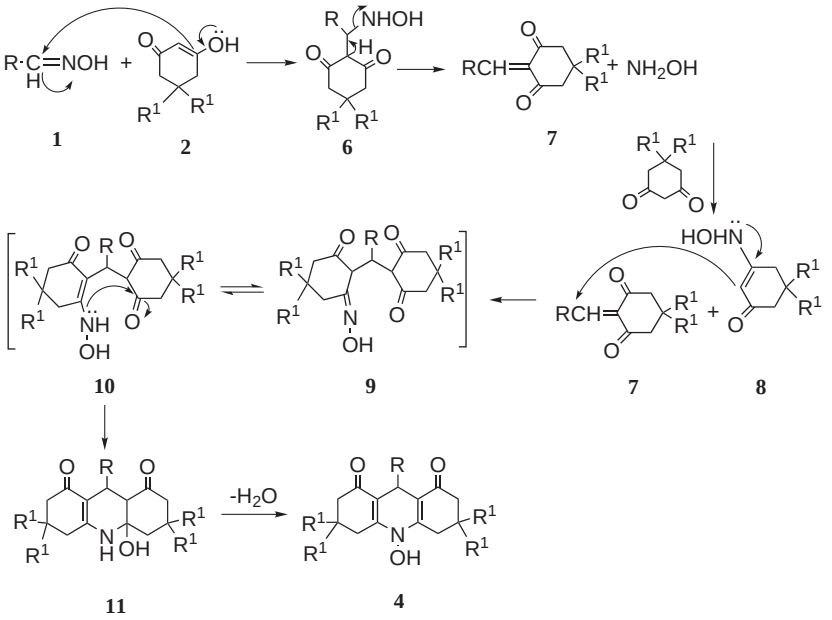

**Scheme 2**

This reaction may occur via the (addition, elimination, addition, cyclization) mechanism shown in Scheme 1. The Michael addition between aldoxime and 1,3-dicarbonyls gave the intermediate **6** which on elimination of $NH_2OH$ gave 2-aryllidene-1,3-cyclohexanedione (**7**). Michael addition between **7** and **8** (obtained from dimedone **2** and $NH_2OH$) then furnished the intermediate **9**, which isomerized to **10**. Intramolecular cyclodehydration of **10** gave **4** (Scheme 2). The structure of compound **4a** (containing a water molecule, Figure 2) was confirmed by an X-ray crystallographic analysis.[14]

When ammonium acetate was added to this reaction system under the same conditions, acridine derivatives **3** were obtained (Table 1). The structure of **3g** was also confirmed by X-ray diffraction study (Figure 1). In this case, a similar mechanism is involved. The nucleophilicity of ammonia (from ammonium acetate) was stronger than $NH_2OH$, which led to the formation of **3**. When ketoximes were used in place of aldeoximes, these reactions could not take place.

In summary, we have disclosed a novel reaction between aldoxime and dimedone and realized the introduction of the hydroxyl to the nitrogen atom of acridine derivatives, which provided a rapid, efficient and environmentally friendly method for the synthesis of *N*-hydroxyl acridine derivatives. This method not only could be applied to aromatic aldoxime but also to heterocyclic and aliphatic aldoxime. These *N*-hydroxylacridinedione derivatives are expected to exhibit interesting biological properties, which are currently under investigation.

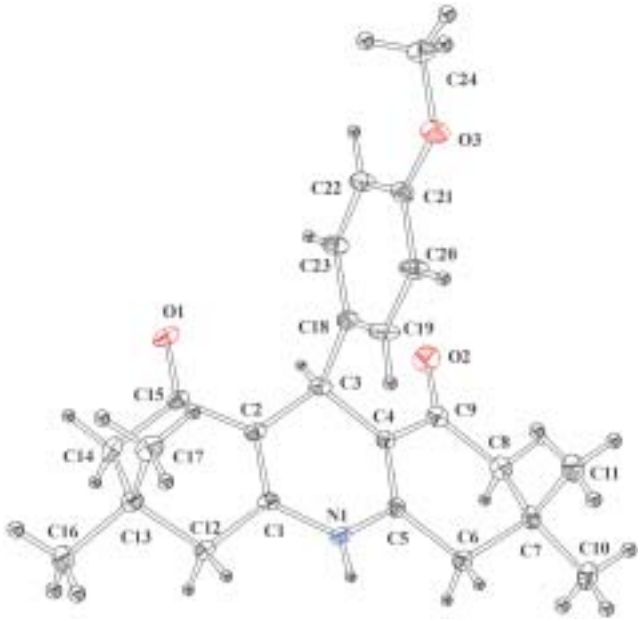


**Figure 1** The structure of **3g**

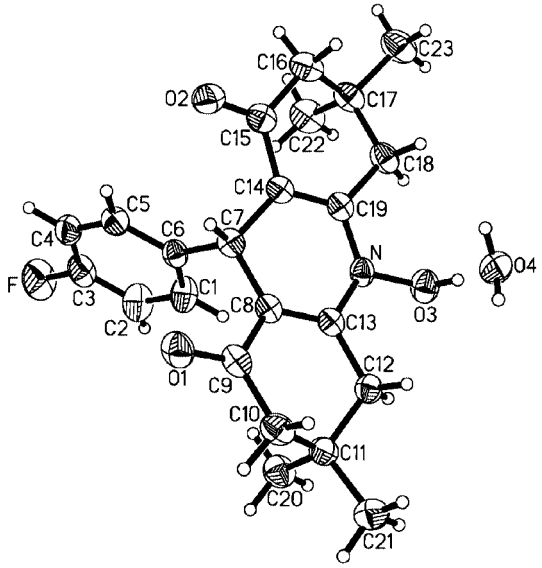


**Figure 2** The structure of **4a**

**Table 1** Synthesis of Acridine Derivatives **3** and **4**

| Entry | Oxime | $R^1$ | Time (min) | Yield (%) | Mp (°C) (literature) |
|---|---|---|---|---|---|
| **3a** | 3-$NO_2C_6H_4CH$=NOH | $CH_3$ | 6[a] (85)[b] | 80[a] (76)[b] | 284–285 (283–285)[15,16] |
| **3b** | 2-Cl $C_6H_4CH$=NOH | $CH_3$ | 5[a] (90)[b] | 86[a] (85)[b] | 221–223 (221–223)[16] |
| **3c** | 4-$ClC_6H_4CH$=NOH | $CH_3$ | 5[a] (70)[b] | 92[a] (88)[b] | 221–223 (221–223)[16] |
| **3d** | 4-$(CH_3)_2NC_6H_4CH$=NOH | $CH_3$ | 6 | 88 | 264–266 (264–266)[15,16] |
| **3e** | 3,4-$(CH_3O)_2C_6H_3CH$=NOH | $CH_3$ | 5 | 84 | 258–260 |
| **3f** | 3,4-$(OCH_2O)C_6H_3CH$=NOH | $CH_3$ | 5 | 80 | 324–326 |
| **3g** | 4-$CH_3$ °$C_6H_4CH$=NOH | $CH_3$ | 5 | 88 | 269–270 (269–270)[15] |
| **3h** | 1,4-$C_6H_4(CH$=NOH$)_2$ | $CH_3$ | 8 | 90 | >300 |
| **3i** | 2-furyl-CH=NOH | $CH_3$ | 5 | 85 | >300 |
| **3j** | $CH_3CH_2CH$=NOH | $CH_3$ | 4 | 89 | 282–283 |
| **3k** | $CH_3CH_2CH_2CH$=NOH | $CH_3$ | 4 | 91 | 286–287 |
| **3l** | $CH_3CH_2CH_2CH_2CH$=NOH | $CH_3$ | 4 | 92 | 227–228 |
| **3m** | $(CH_2)_3(CH$=NOH$)_2$ | $CH_3$ | 5 | 95 | >300 |
| **4a** | 4-$FC_6H_4CH$=NOH | $CH_3$ | 5 | 90 | 233–234 |
| **4b** | 2-$ClC_6H_4CH$=NOH | $CH_3$ | 6 | 88 | 222–223 |
| **4c** | 4-$ClC_6H_4CH$=NOH | $CH_3$ | 5 | 92 | 256–257 |
| **4d** | 3,4-$(OCH_2O)C_6H_3CH$=NOH | $CH_3$ | 4 | 93 | 248–249 |
| **4e** | 4-$CH_3OC_6H_4CH$=NOH | $CH_3$ | 6 | 90 | 146–147 |
| **4f** | 3-$NO_2C_6H_4CH$=NOH | $CH_3$ | 5 | 92 | 136–137 |
| **4g** | 4-$NO_2C_6H_4CH$=NOH | $CH_3$ | 5 | 95 | 134–135 |
| **4h** | 4-$(CH_3)_2NC_6H_4CH$=NOH | $CH_3$ | 7 | 88 | 159–160 |
| **4i** | 1,4-$C_6H_4(CH$=NOH$)_2$ | $CH_3$ | 6 | 92 | >300 |
| **4j** | 2-furyl-CH=NOH | $CH_3$ | 5 | 83 | 196–197 |
| **4k** | 4-$CH_3OC_6H_4CH$=NOH | H | 6 | 85 | >300 |
| **4l** | 4-$ClC_6H_4CH$=NOH | H | 4 | 86 | >300 |
| **4m** | 2-OH-4-$OCH_3C_6H_3CH$=NOH | H | 7 | 88 | 237–238 |
| **4 n** | $CH_3CH_2CH$=NOH | $CH_3$ | 5 | 81 | 204–205 |
| **4o** | $CH_3CH_2CH_2CH$=NOH | $CH_3$ | 4 | 85 | 152–153 |
| **4p** | $CH_3CH_2CH_2CH_2CH$=NOH | $CH_3$ | 4 | 86 | 115–116 |
| **4q** | $(CH_2)_3(CH$=NOH$)_2$ | $CH_3$ | 5 | 89 | 218–220 |
| **4r** | $C_6H_5C(CH_3)$=NOH | $CH_3$ | 8 | 0 | – |
| **4s** | 4-$ClC_6H_4C(CH_3)$=NOH | $CH_3$ | 8 | 0 | – |
| **4t** | $(CH_3)_2C$=NOH | $CH_3$ | 8 | 0 | – |

[a] Method A in glycol under the irradition of MW.
[b] Method A in glycol at 100 °C.

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(13) **The General Procedure is Represented Below**: The mixture of substituted aryl aldeoxime (2 mmol) and dimedone (4 mmol) in glycol (5 mL) was irradiated for 4–6 min. The reaction mixture was cooled to r.t. and poured into 50 mL of $H_2O$, filtered to give the crude product, which was further purified by recrystallization from 95% EtOH. All products are characterized by IR and $^1$H NMR spectral data. Typical spectral data: compound **3i**: IR (KBr): 3285, 3069, 2957, 2867, 1624, 1605, 1483, 1396, 1364, 1251, 1170, 1141, 1069, 1012, 981, 922, 886, 816, 773, 728, 599, 567 cm$^{-1}$. $^1$H NMR (DMSO-$d_6$): δ = 0.92 (s, 6 H, 2 × $CH_3$), 1.02 (s, 6 H, 2 × $CH_3$), 2.03–2.41 (m, 8 H, 4 × $CH_2$), 4.98 (s, 1 H, CH), 5.81 (d, 1 H, *J* = 3.00 Hz, furan H), 6.21 (dd, 1 H, *J* = 3.08 Hz, furan H), 7.35 (d, 1 H, *J* = 0.90 Hz, furan H), 9.36 (s, 1 H, NH). Compound **3j**: IR (KBr): 3280, 3209, 3068, 2959, 2930, 2871, 2721, 1645, 1600, 1488, 1381, 1309, 1273, 1244, 1225, 1188, 1169, 1143, 1121, 1065, 1006, 885, 870, 775, 733, 693, 648, 618, 572, 560 cm$^{-1}$. $^1$H NMR (DMSO-$d_6$): δ = 0.63 (t, 3 H, *J* = 7.56 Hz, $CH_3$), 1.02 (s, 12 H, 4 ´ $CH_3$), 1.24–1.26 (m, 2 H, $CH_2$), 2.02–2.27 (m, 8 H, 4 × $CH_2$), 3.80 (t, 1 H, *J* = 5.25 Hz, CH), 8.99 (s, 1 H, NH). Compound **4c**: IR (KBr): 3300, 2961, 2878, 2674, 1603, 1568, 1490, 1409, 1371, 1323, 1272, 1225, 1141, 1023, 902, 848, 565, 523 cm$^{-1}$. $^1$H NMR (DMSO-$d_6$): δ = 0.87 (s, 6 H, 2 × $CH_3$), 1.04 (s, 6 H, 2 × $CH_3$), 2.02–2.68 (m, 8 H, 4 × $CH_2$), 4.93 (s, 1 H, CH), 7.14 (d, 2 H, *J* = 6.3 Hz, Ar H), 7.25 (d, 2 H, *J* = 6.3 Hz, Ar H), 10.79 (s, 1 H, OH). Compound **4i**: IR (KBr): 3225, 2954, 2871, 1667, 1660, 1504, 1462, 1504, 1462, 1369, 1229, 1154, 1010, 808, 661, 582 cm$^{-1}$. $^1$H NMR (DMSO-$d_6$): δ = 0.82 (s, 12 H, 4 ´ $CH_3$), 1.02 (s, 12 H, 4 ´ $CH_3$), 2.00–2.65 (m, 16 H, 8 ´ $CH_2$), 4.47 (s, 2 H, 2 ´ CH), 6.95 (s, 4 H, Ar H), 10.73 (s, 2 H, 2 ´ OH). Compound **4j**: IR (KBr): 3308, 2958, 2930, 2867, 2728, 1605, 1562, 1501, 1469, 1359, 1324, 1262, 1220, 1142, 1072, 1007, 1072, 979, 951, 921, 884, 781, 727, 683, 616, 600, 566 cm$^{-1}$. $^1$H NMR (DMSO-$d_6$): δ = 0.94 (s, 6 H, 2 × $CH_3$), 1.05 (s, 6 H, 2 × $CH_3$), 2.07–2.61 (m, 8 H, 4 × $CH_2$), 5.12 (s, 1 H, CH), 5.84 (d, 1 H, *J* = 3.3 Hz, furan H), 6.25 (dd, 1 H, *J* = 3.0 Hz, furan H), 7.35 (d, 1 H, *J* = 0.81 Hz, furan H), 10.85 (s, 1 H, OH). Compound **4k**: IR (KBr): 3278, 3186, 3052, 2945, 1644, 1603, 1490, 1362, 1229, 1173, 1127, 1034 cm$^{-1}$. $^1$H NMR (DMSO-$d_6$): δ = 1.76–1.95 (m, 4 H, $CH_2$), 2.19–2.22 (m, 4 H, =C–$CH_2$–), 2.29–2.48 (m, 4 H, –CO–$CH_2$–), 3.67 (s, 3 H, $CH_3$), 4.85 (s, 1 H, CH), 6.72 (d, 2 H, *J* = 8.4Hz, Ar H), 7.05 (d, 2 H, *J* = 8.4 Hz, Ar H), 9.37 (s, 1 H, OH). Compound **4n**: IR (KBr): 3298, 2962, 2958, 2966, 2657, 1627, 1552, 1464, 1389, 1298, 1233, 1172, 1144, 1074, 1002, 934, 905, 887, 778, 740, 685, 612,3, 567 cm$^{-1}$. $^1$H NMR (DMSO-$d_6$): δ = 0.66 (t, 3 H, *J* = 7.50 Hz, $CH_3$,), 1.02 (s, 6 H, 2 ´ $CH_3$), 1.05 (s, 6 H, 2 ´ $CH_3$), 1.16–1.20 (m, 2 H, $CH_2$), 2.06–2.63 (m, 8 H, 4 × $CH_2$), 3.85 (t, 1 H, *J* = 5.25 Hz, CH), 10.60 (s, 1 H, OH).

(14) The sing-crystal growth was carried out in EtOH at r.t. X-ray crystallographic analysis was performed with a Siemens SMART CCD and a Siemens P4 diffractometer (graphite monochromator, $MoK_\alpha$ radiation $\lambda$ = 0.71073 Å). The crystal crystallizes with one water molecule. Crystal data for **3g**: $C_{24}H_{29}NO_3$, yellow, crystal dimension 0.80 × 0.80 × 0.30 mm, orthorhombic, space group Pca2 (1), *a* = 1.41862 (3), *b* = 1.51896 (3), *c* = 2.07611 (1) Å, $\alpha = \gamma = \beta = 90°$, *V* = 4.47366(13) Å$^3$, $M_r$ = 379.48, *Z* = 8, $D_c$ = 1.27 g/cm$^3$, $\lambda$ = 0.071073 Å, $\mu$ ($MoK_\alpha$) = 0.074 mm$^{-1}$, *F*(000) = 1632, *S* = 1.144, $R_1$ = 0.0652, $wR_2$ = 0.1510. Crystal data for **4a**: $C_{23}H_{28}ClFNO_4$, yellow, crystal dimension 0.58 × 0.58 × 0.40 mm, monoclinic, space group P2(1)/c, *a* = 12.638(2), *b* = 14.039 (3), *c* = 11.102 (2) Å, = 94.60 (1)°, *V* = 2140.2 (6) Å$^3$, $M_r$ = 401.46, *Z* = 4, *Dc* = 1.246 g/cm$^3$, $\lambda$ = 0.71073 Å, $\mu$ ($MoK_\alpha$) = 0.09 mm$^{-1}$, *F*(000) = 856, *S* = 0.906, $R_1$ = 0.0398, $wR_2$ = 0.0932.

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