

## Utilizing *o*-quinone methide chemistry: synthesis of sterically hindered acridin-4-ols

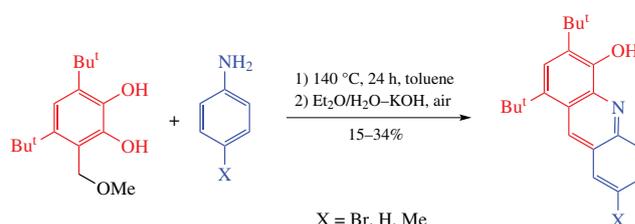
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Three new sterically hindered acridin-4-ols have been prepared by alkylation of anilines with 3,5-di-*tert*-butyl-6-methoxymethylcatechol followed by oxidation of the reaction mixture. Formation of the acridine moiety was found to occur in the course of oxidation of the intermediate (anilinomethyl)catechol on contact with air in the Et<sub>2</sub>O/H<sub>2</sub>O–KOH system. The molecular structure of two acridin-4-ols was determined by single-crystal X-ray diffraction.

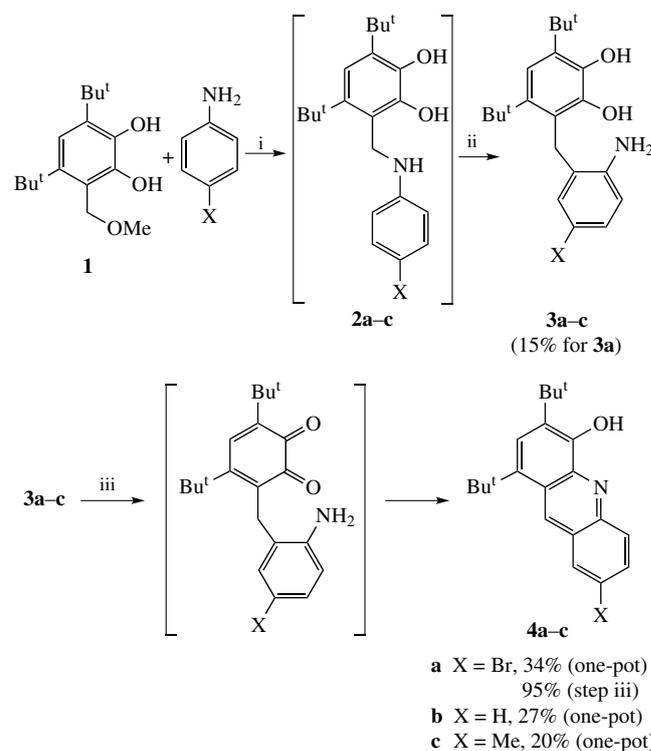


**Keywords:** acridines, heterocyclization, quinone methides, alkylation, catechols, anilines, X-ray diffraction analysis.

Acridines find application in the chemistry of dyes, sensors,<sup>1–3</sup> as starting reactants for the synthesis of polyaromatic compounds,<sup>4</sup> ligands in catalytic systems<sup>5</sup> and components of luminescent functional materials.<sup>4,6</sup> Recognized strategies for building an acridine backbone comprise the Friedländer synthesis,<sup>7</sup> preparation of acridinones with the subsequent reduction,<sup>8,9</sup> cycloisomerization of 3-alkynyl-2-arylpiperidines,<sup>10</sup> oxidative cyclization of *N*-(2-alkenylaryl)-substituted enamines<sup>11</sup> and transformation of 2-aminophenones.<sup>12</sup> 4-Hydroxyacridines hold a special place among this class of compounds since they may be regarded as 8-hydroxyquinolines with an expanded  $\pi$ -system.<sup>13,14</sup> Acridin-4-ols with additional alkyl substituents, e.g., *tert*-butyl, should possess improved solubility in organic solvents, which can promote their application in coordination chemistry and as ion metal extractants. Previously, copper(II) complex with 1,3-di-*tert*-butylacridin-4-ol was obtained in minor amounts,<sup>15</sup> however the synthetic details were not documented. Herein, we present utilizing *o*-quinone methide chemistry as a key step for the synthesis of sterically hindered 1,3-di-*tert*-butylacridin-4-ol derivatives (Scheme 1).

3,5-Di-*tert*-butyl-6-methoxymethylcatechol **1**<sup>16</sup> can act as a source of sterically hindered *o*-quinone methide in the alkylation of alcohols,<sup>17</sup> heterocycles,<sup>18</sup> thiols<sup>19</sup> as well as activated arenes.<sup>20</sup> On the other hand, anilines possess properties of both N- and C-nucleophiles. We have herein found that the reaction between catechol **1** and 4-bromoaniline under mild conditions (at temperatures up to 90 °C) both in the presence and in the absence of AcOH leads to the quantitative formation of (anilinomethyl)catechol **2a** as the N-alkylation product (see Scheme 1). A slow evaporation of toluene from the reaction mixture with further heating at 140 °C for 24 h leads to the accumulation of C-alkylation product **3a**. A similar tendency was previously observed during the thermolysis of aniline with unsubstituted *o*-quinone methide.<sup>21</sup> Catechol aniline **3a** has been

isolated in 15% yield. The specific signal for its methylene protons are observed at 3.80 ppm in <sup>1</sup>H NMR and at 29.06 ppm in <sup>13</sup>C NMR spectra. This compound is well soluble in DMSO and toluene and poorly soluble in *n*-hexane. Air oxidation of compound **3a** (vigorous stirring of its ethereal solution with

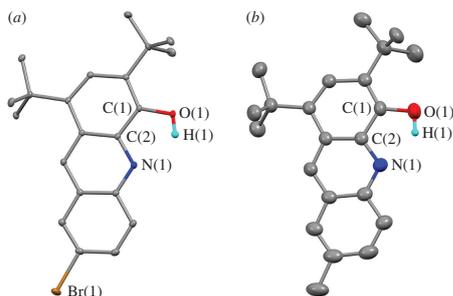


**Scheme 1** Reagents and conditions: i, PhMe, 90 °C; ii, evaporating, 90 → 140 °C, 24 h; iii, O<sub>2</sub> (air), KOH, Et<sub>2</sub>O/H<sub>2</sub>O.

H<sub>2</sub>O–KOH system on contact with air) was followed by further intramolecular condensation and rearrangement affording finally acridin-4-ol **4a** in quantitative yields (see Scheme 1). The attempted oxidation of compound **3a** with oxidants well-defined in catechol chemistry [HNO<sub>3</sub>, Ag<sub>2</sub>O,<sup>22</sup> KOH/K<sub>3</sub>Fe(CN)<sub>6</sub>],<sup>16,18</sup> led to the inseparable mixtures of products. The oxidation of the reaction mixture without isolation of **3a** made it possible to obtain product **4a** in 34% yield. The additional identified product was known catechol aldimine<sup>23</sup> resulted from catechol amine **2a** oxidation.<sup>†</sup> Acridin-4-ols **4b** and **4c** have been prepared analogously in 27 and 20% yields, respectively.

Single crystals of **4a** and **4c** suitable for X-ray study (Figure 1) were grown from *n*-hexane. The X-ray analysis<sup>‡</sup> revealed that compounds **4a** and **4c** had similar structures. The distances in the OCCN-fragments in heterocycles of **4a** and **4c** are in good agreement with each other and with those of previously published related compounds (Online Supplementary Materials, Table S1).<sup>30</sup> Three aromatic rings of compounds **4a** and **4c** form planes. The average deviations from the planes of non-hydrogen atoms with the exception of *tert*-butyl substituents are 0.020 and 0.023 Å in **4a** and **4c**, respectively. The hydrogen atom H(1) lies in the plane of the OCCN-fragments in both compounds. The N(1)⋯H(1) distance and the O(1)–H(1)⋯N(1) angle suggest the presence of intramolecular O–H⋯N interaction in **4a** and **4c**.<sup>31</sup>

The UV-absorptions of acridin-4-ols **4a–c** are very similar to those reported for acridines and polyfluorohydroxyacridines.<sup>30</sup> UV-VIS absorption spectra of **4a–c** were obtained in 2 × 10<sup>−5</sup> M solutions in MeCN [Figure 2(a)]. Along with the high-energy intense band at 270 nm (*p*-band) associated with the π–π\* transition mainly localized in the π-system of acridine, the spectra



**Figure 1** The X-ray structures of acridinols (a) **4a** at 100 K and (b) **4c** at 298 K. Thermal ellipsoids are given at the 30% probability level. Hydrogen atoms are omitted for clarity.

<sup>†</sup> 3-(2-Amino-5-bromobenzyl)-4,6-di-*tert*-butylcatechol **3a**. 3,5-Di-*tert*-butyl-6-(methoxymethyl)catechol **2a** (2.66 g, 0.01 mol) and *p*-bromoaniline (1.07 g, 0.01 mol) were dissolved in toluene (20 ml). The mixture was brought to boiling, and the solvent was slowly evaporated until still temperature reached 140 °C (24 h). The mixture was then cooled to 60 °C, and hexane (20 ml) was added. White-yellow solid was filtered off, washed with hexane and dried under vacuum. Yield 0.6 g (15%).

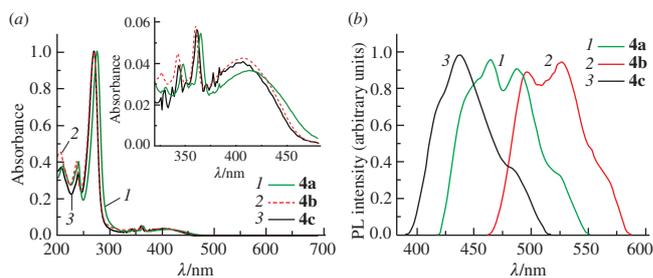
7-Bromo-1,3-di-*tert*-butylacridin-4-ol **4a**. Compound **3a** (0.20 g, 0.5 mmol) was dissolved in diethyl ether and stirred vigorously for 1 h with a KOH (0.002 mol) solution in H<sub>2</sub>O (5 ml). The mixture was extracted, washed with water and dried over Na<sub>2</sub>SO<sub>4</sub>. Product **4a** was isolated by column chromatography (hexane as the eluent) as yellow solid. Yield 0.18 g (95%). Synthesis of acridinol **4a** without isolation of **3a** provides a yield of 1.32 g (34%).

<sup>‡</sup> X-ray diffraction data were collected on a Bruker D8 Quest diffractometer (MoK $\alpha$  radiation,  $\omega$ -scan technique,  $\lambda = 0.71073$  Å). The intensity data were integrated by the CrysAlisPro (**4a**)<sup>24</sup> and SAINT (**4c**)<sup>25</sup> programs. SADABS (**4c**)<sup>26</sup> and SCALE3 ABSPACK (**4a**)<sup>27</sup> programs were used to perform absorption corrections. The structure was solved by dual method<sup>28</sup> and refined on  $F^2_{\text{hkl}}$  using SHELXTL package.<sup>29</sup> All non-hydrogen atoms were refined anisotropically. The H(1) hydrogen atom was found from Fourier syntheses of electron density. All other

also contain a low-energy absorption band at about 404 nm ( $\beta$ -band). Indeed, the conjugation of the nitrogen lone pair with the acridine  $\pi$ -system should give rise to an (intramolecular) charge transfer band in the absorption spectrum.<sup>32</sup> The intensity of this band is related to the degree of interaction of the solute and the solvents<sup>33,34</sup> and varies in polar and non-polar solvents.

Although acridines exhibit fairly intense luminescence both in solid state and in solution,<sup>30,34</sup> the fluorescence efficiency of acridinols is very low.<sup>35</sup> This is apparently due to a photoinitiated intramolecular proton transfer (ESIPT) between a phenolic hydrogen and a nitrogen atom of the pyridine ring in an excited state.<sup>36</sup> The fluorescence spectrum of unsubstituted acridin-4-ol **4b** has two bands with maxima at 496 and 526 nm. The photoluminescence spectrum of bromine-substituted acridinol **4a** is blue-shifted with photoluminescence maxima at 464 and 488 nm. The photoluminescence spectrum of methyl-substituted acridinol **4c** is even more shifted to shorter wavelengths and is a broadband with maximum at 437 nm [Figure 2(b)].

In summary, we have demonstrated that catechol anilines, products of C-alkylation of aniline with *o*-quinone methide, can be accessed in one stage without the use of protection groups of catechol fragment (earlier, analogous catechol aniline was prepared with the use of protection groups in several stages<sup>37</sup>). Oxidation of these catechol anilines provides new sterically hindered acridin-4-ols. Variation of the substituents in the acridine ring allows one to change the optical properties of these compounds. This new findings and an excellent solubility of 1,3-di-*tert*-butylacridin-4-ols in organic solvent should open the way for the design of new ion metal extractants, compounds for OLED, nonlinear optical and other materials.



**Figure 2** (a) The normalized absorption spectra of the acridin-4-ols (1)–(3) **4a–c** in MeCN solution and (b) photoluminescence spectra in DMSO solution,  $\lambda_{\text{ex}} = 405$  nm, at room temperature.

hydrogen atoms were placed in calculated positions and were refined in the riding model [ $U_{\text{iso}}(\text{H}) = 1.5U_{\text{eq}}(\text{C})$  for CH<sub>3</sub>-groups and  $U_{\text{iso}}(\text{H}) = 1.2U_{\text{eq}}(\text{C})$  for other groups].

*Crystal data for 4a.* C<sub>21</sub>H<sub>24</sub>BrNO,  $M = 386.32$ , monoclinic, space group  $P2_1/c$ , 100 K,  $a = 21.0450(5)$ ,  $b = 9.6964(3)$  and  $c = 9.0820(2)$  Å,  $\beta = 100.2020(10)^\circ$ ,  $Z = 4$ ,  $V = 1823.98(8)$  Å<sup>3</sup>,  $d_{\text{calc}} = 1.407$  g cm<sup>−3</sup>,  $F(000) = 800$ ,  $\mu = 2.261$  mm<sup>−1</sup>. Crystal size 0.29 × 0.15 × 0.10 mm. Total of 39408 reflections were collected [4389 independent reflections with  $I > 2\sigma(I)$ ,  $R_{\text{int}} = 0.0523$ ] and used in the refinement, which converged to  $wR_2 = 0.0609$ , GOF = 1.040 for all independent reflections [ $R_1 = 0.0243$  was calculated for 4389 reflections with  $I > 2\sigma(I)$ ].

*Crystal data for 4c.* C<sub>22</sub>H<sub>27</sub>NO,  $M = 321.44$ , orthorhombic, space group  $Pbca$ , 298 K,  $a = 9.3823(6)$ ,  $b = 11.9768(10)$  and  $c = 34.102(3)$  Å,  $\beta = 100.2020(10)^\circ$ ,  $Z = 8$ ,  $V = 3832.0(5)$  Å<sup>3</sup>,  $d_{\text{calc}} = 1.114$  g cm<sup>−3</sup>,  $F(000) = 1392$ , crystal size 0.50 × 0.27 × 0.17 mm,  $\mu = 0.067$  mm<sup>−1</sup>. Total of 12956 reflections were collected [4065 independent reflections with  $I > 2\sigma(I)$ ,  $R_{\text{int}} = 0.0455$ ] and used in the refinement, which converged to  $wR_2 = 0.2522$ , GOF = 1.015 for all independent reflections [ $R_1 = 0.2109$  was calculated for 4065 reflections with  $I > 2\sigma(I)$ ].

CCDC 2023832 and 2023833 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via <http://www.ccdc.cam.ac.uk>.

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#### Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2021.03.040.

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