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A general strategy for the synthesis of oxoisoindolo[2,1-*a*]quinoline derivatives: the first efficient synthesis of 5,6,6a,11-tetrahydro-11-oxoisoindolo[2,1-*a*]-quinoline-10-carboxylic acids

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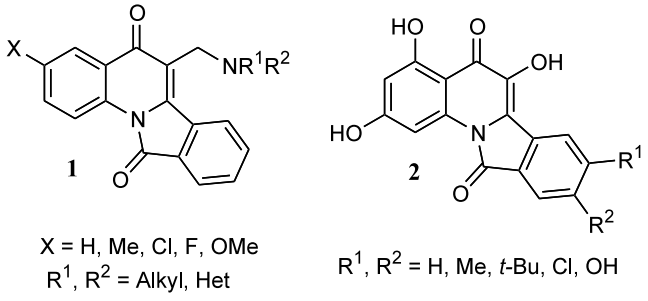
Abstract—An efficient two-step synthesis of new isoindolo[2,1-*a*]quinoline-10-carboxylic acids via [4+2] cycloaddition of the 4-α-furyl-4-*N*-arylaminobut-1-enes and maleic anhydride is described.

Isoindolo[2,1-*a*]quinolines are a class of molecules which possess an array of biological activities. In particular, the 5,11-dioxosubstituted isoindolo[2,1-*a*]quinolines **1** have protective effects against N_2-induced hypoxia,[1] and trihydroxyisoindolo[2,1-*a*]quinolines **2** show inhibitory activities against bacterial DNA-gyrase and human topoisomerase II (Scheme 1).[2]

Syntheses of 11-oxo- and 5,11-dioxoisoindolo[2,1-*a*]-quinolines are not numerous. For example, reductive cyclization of the *o*-(quinolyl-2)benzoic acid and its esters afford 6,6a-dihydro-11-oxoisoindolo[2,1-*a*]-quinolines.[3] Dioxo-analogs, the 5,11-dioxoisoindolo-quinolines have been prepared from 2-aryl-2,3-dihydro-3-oxo-1*H*-isoindole-1-acetic acids via intramolecular cyclization using $AlCl_3$.[1,4] In the presence of *p*-toluensulfonic acid, 2,3-dihydro-3*R*-3-hydroxy-2-[2-(1-methyl-prop-1-enyl)phenyl]-1*H*-isoindol-1-ones can be used to prepare either 6*H*-5-alkylidene-6,6a-dihydro-11-oxo-isoindolo[2,1-*a*]quinolines[5] or 5-mono- and 5,6a-disubstituted isoindolo[2,1-*a*]quinoline-11(6a*H*)-ones.[6] Condensation of substituted 2′-amino-2-methoxyacetophenones with phthalic anhydrides in refluxing toluene in the presence of triethylamine was also proposed as an effective method for the synthesis of benzoyl-substituted 5,11-dioxoisoindolo[2,1-*a*]quinoline.[2]



Scheme 1.

Earlier we prepared a series of substituted and spiroannulated tetrahydroquinolines,[7] benz-2-azepines[8] and 4-hydroxypiperidines[9] using homoallylamines as starting materials. Continuing our investigations on the synthetic properties of homoallyamines, we examined another possibility to prepare oxoisoindolo[2,1-*a*]-quinolines from these precursors. In this paper we describe a new synthesis of 5,5-dimethyl-11-oxoisoindolo[2,1-*a*]quinoline-10-carboxylic acids **5a**–**g** from the readily available α-furyl-substituted homoallylamines **3a**–**g** (Scheme 2).

Our starting materials, furyl substituted homoallylamines **3a**–**g**, are easily prepared in high yields by the reaction of methallylmagnesium chloride and furylaldimines obtained from the condensation of anilines with α-furylcarbaldehyde.[7,8]

Keywords: intramolecular Diels–Alder reaction; isoindoloquinoline; homoallylamine.

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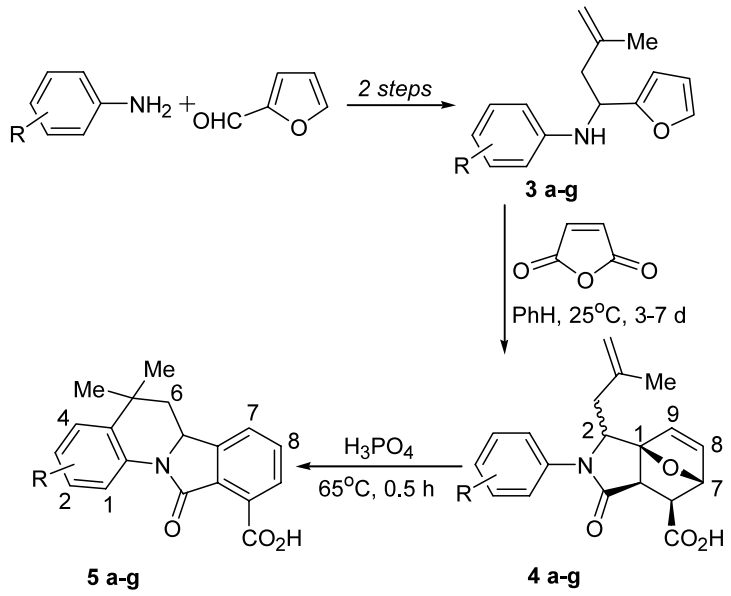

	Yield, %			
	R	**3**	**4**	**5**
a	H	87	96	68
b	*o*-Me	89	89	31
c	*o*-Bn	60	83	33
d	*o*-OMe	75	83	40
e	*p*-Et	84	84	61
f	*p*-OMe	89	91	64
g	*p*-F	78	95	55

Scheme 2.

The *N*-acylation of homoallylamines **3a**–**g** with maleic anhydride in benzene at room temperature and subsequent intramolecular Diels–Alder reaction provided the 3-aryl-2-methallyl-3-aza-10-oxatricyclo[5.2.1.$0^{1,5}$]dec-8-ene-6-carboxylic acids **4a**–**g** in high yields as *exo*-cycloadducts. ^{1}H NMR data, showed that these tricycles exist as a 1:1 mixture of isomers at C-2. Treatment of the epoxyisoindolines **4a**–**g** with an excess of phosphoric acid gave the isoindoloquinolinecarboxylic acids **5a**–**g** in 31–72% yield (Scheme 2) via aromatization (dehydration) of the oxabicyclo[2.2.1]-heptene fragment and intramolecular cyclization of the methallyl substituent.[10] The carboxylic acids **5a**–**g** are crystalline substances, sparingly soluble in most organic solvents and with high melting points. From the ^{1}H NMR spectra of compounds **5a**–**g**, the configuration of the proton H-6a was judged to be axial.

In summary, the synthetic method outlined is characterized by high yields and provides ready access to these tetracyclic alkaloid-type systems.

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5,5-Dimethyl-5,6,6a,11-tetrahydro-11-oxoisoindolo[2,1-*a*]quinoline-10-carboxylic acid **5a**: yield 68%; mp 237.5–240°C (chloroform); ν_{max} (KBr)/cm^{-1} 1727 (O–C=O), 1617 (N–C=O); EI-MS (70 eV) *m*/*z* (rel. int.): 307 (M^+, 92), 292 (65), 264 (21), 263 (100), 248 (18), 232 (11), 218 (15), 204 (12), 178 (3); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.47 (s, 3H), 1.54 (s, 3H), 1.72 (t, 1H, J=12.7 Hz), 2.41 (dd, 1H, J=12.7 and 2.6 Hz), 4.97 (dd, 1H, J=12.7 and 2.6 Hz), 7.23–7.39 (m, 2H), 7.48 (dd, 1H, J=7.5 and 1.9 Hz), 7.74–7.86 (m, 2H), 8.38 (dd, 1H, J=7.5 and 1.9 Hz), and 8.50 (dd, 1H, J=7.5 and 1.9 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 166.2 (C_{11}), 165.3 (COOH), 146.4 (C_{6b}), 136.6 (C_{10a}), 133.1, 132.9, 131.7, 129.5 (C_{10}), 128.9 (C_{12a}), 127.4, 126.6, 126.5, 125.6, 120.4 (C_8), 56.5 (C_{6a}), 42.0 (C_5), 33.5 (C_6), 31.7 (CH_3-5), 30.6 (CH_3-5). Anal. calcd for $C_{19}H_{17}NO_3$: C, 74.27; H, 5.54; N, 4.56. Found: C, 74.22; H, 5.57; N, 4.59.
1,5,5-Trimethyl-5,6,6a,11-tetrahydro-11-oxoisoindolo[2,1-*a*]quinoline-10-carboxylic acid **5b**: yield 31%; mp 209.5–

210°C (chloroform); ν_{max} (KBr)/cm^{-1} 1728 (O–C=O), 1619 (N–C=O); EI-MS (70 eV) m/z (rel. int.): 321 (M^+, 79), 306 (12), 288 (13), 275 (100), 262 (12), 221 (12), 152 (8), 130 (14), 115 (25), 91 (15), 77 (18), 65 (12); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.30 (s, 3H), 1.44 (s, 3H), 1.72 (dd, 1H, $J=13.4$ and 10.3 Hz), 2.39 (s, 3H), 2.42 (dd, 1H, $J=13.4$ and 4.7 Hz), 4.98 (dd, 1H, $J=10.3$ and 4.7 Hz), 7.20–7.30 (m, 3H), 7.77–7.79 (m, 2H), and 8.45 (dd, 1H, $J=5.8$ and 2.1 Hz). Anal. calcd for $C_{20}H_{19}NO_3$: C, 74.77; N, 5.92; H, 4.36. Found: C, 74.80; N, 5.96; H, 4.32.