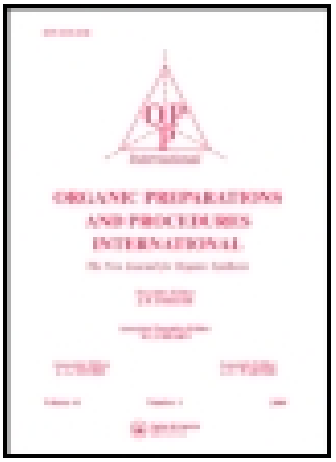

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A PRACTICAL LARGE-SCALE PREPARATION OF 5'-BROMOSPIRO(CYCLOHEXANE-1,3-[3H]INDOL)-2'(1'H)-ONE

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A PRACTICAL LARGE-SCALE PREPARATION OF 5'-BROMOSPIRO(CYCLOHEXANE-1,3'-[3H]INDOL)-2'(1'H)-ONE

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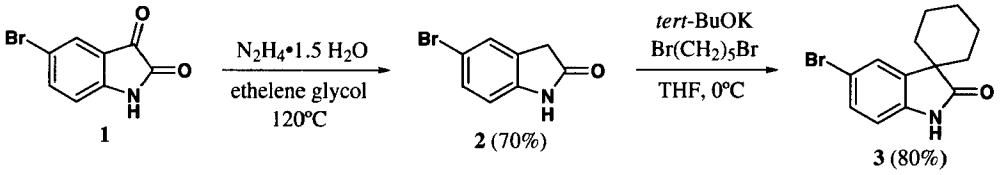
We were interested in a large-scale preparation of 5'-bromospiro(cyclohexane-1,3'-[3H]indol)-2'(1'H)-one (**3**), an intermediate in the synthesis of progesterone receptor modulators.[1] Initially, the compound was prepared from oxindole using the Kende procedure[2a] by alkylation followed by bromination with bromine in acetic acid/chloroform.[3] Unfortunately, this sequence gave multiple impurities in the alkylation product.[1a,4] On large scale, this was a serious problem and we had to resort to chromatography and recrystallization.[5] The subsequent bromination had to be carefully controlled to avoid over-bromination. In addition, brominated impurities were formed from the side-products generated in the alkylation step.



The regioselectivity and purity problems were overcome by simply changing the order of transformations, *i. e.* introduction of bromine in the oxindole core followed by alkylation of 5-bromooxindole (**2**),[3,6] which was prepared from inexpensive, technical grade 5-bromoisatin (**1**).[7] It was found that *n*-butyllithium could be replaced with potassium *tert*-butoxide and 1,5-diiodopentane with the more stable 1,5-dibromopentane at 0°C in tetrahydrofuran (THF) in the alkylation step.[8] In comparison to the initial sequence, the reaction was clean and the product crystallized out upon replacement of THF with acetonitrile.[9]

The new procedure is suitable for scale-up. In fact, six consecutive scale-up batches gave a total of 45 kg of 97.0-99.5% pure product. In addition, the alkylation proceeded with reproducible and consistent yields of 84-89%.

EXPERIMENTAL SECTION

Melting points were determined on a Mel-Temp II apparatus and are uncorrected. HPLC was performed using Phenomenex Luna C8(2), 3 μm, 150 x 4.60 mm column and acetonitrile - water mobile phase containing ammonium acetate modifier. The reagents were purchased from Aldrich and used without further purification; 5-bromoisatin (**1**) was purchased from Lancaster Synthesis, Inc.

5-Bromo-1,3-dihydroindol-2-one (2).- A 5-L, four-necked flask equipped with a nitrogen inlet, an addition funnel, an overhead mechanical stirrer, temperature controller, condenser, and a heating mantle was charged with 5-bromoisatin (**1**, 300 g, 1.30 mol, 98% pure) and ethylene glycol (2.0 L). Hydrazine hydrate, $N_2H_4 \cdot 1.5\ H_2O$ (150 mL) was added from the addition funnel at the rate of 13 mL/min. The orange suspension turned gradually to a brown solution. The mixture was heated to 120°C and stirred for 6 h. The suspension which formed, was cooled to ambient temperature and the solid was collected. The cake was washed with water (4 x 200 mL) and dried in a vacuum oven at 40°C/20 mmHg to give **2** (197 g, 70% yield; 97.0% purity, mp 218-222°C, *lit.*[3b] mp 220-221°C) as a tan solid. If needed, the product may be recrystallized from ethanol.[3b]

5'-Bromospiro(cyclohexane-1,3'-indolin)-2'-one (3).- A 5-L, four-necked flask was equipped with mechanical stirrer, condenser with nitrogen adapter, addition funnel, thermometer and cooling bath. Tetrahydrofuran (750 mL) was added to the flask followed by 5-bromo-1,3-dihydroindol-2-one (**2**, 150 g, 0.708 mol) and the mixture was cooled to –15°C. Potassium *tert*-butoxide (251 g, 2.12 mol, 3.0 equiv.) was dissolved in THF (1.5 L) and added dropwise within 30 min., while the temperature was maintained at –15°C. The contents of the addition funnel were rinsed into the flask with THF (250 mL). 1,5-Dibromopentane (119 mL, 199 g, 0.866 mol, 1.2 equiv.) was added dropwise with the temperature being maintained between –10 and –2°C. The contents of the addition funnel were rinsed with THF (100 mL) and the mixture was stirred at 0°C for 1 h. The reaction mixture was quenched with 3.5% hydrochloric acid (1.0 L). After 1 h of stirring, the layers were separated. The dark red, organic layer was washed with brine (250 mL) and transferred to a 5-L distillation flask. THF was distilled off and replaced with acetonitrile. During distillation, acetonitrile (1.0 L) was added gradually until the batch temperature reached 77-80°C and an orange slurry was formed. The heating mantle was replaced with a cooling pan and the slurry was gradually cooled to 0-5°C. The reaction mixture was stirred for an additional 30 min. at 0-5°C. The solid was collected, washed with cold (0-5°C) acetonitrile (3 x 150 mL) and dried in a vacuum oven at 50°C/20 mmHg to give **3** (158 g, 80% yield; 99.5% purity, mp 196-198°C, *lit.*[1b] mp 196-199°C) as an off-white solid.

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5. TMEDA, a complexing agent used in the Kende procedure, was later replaced with LiCl which simplified the work-up. Also, 1,5-dibromopentane, 1,5-ditosylpentane, and a 1:1 mixture of 1,5-dibromo- and 1,5-diiodopentane were tried with no apparent improvement in the yield and the purification procedure.

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9. Alkylation of oxindole under conditions described in Ref. 8 required extensive chromatographic purification.

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