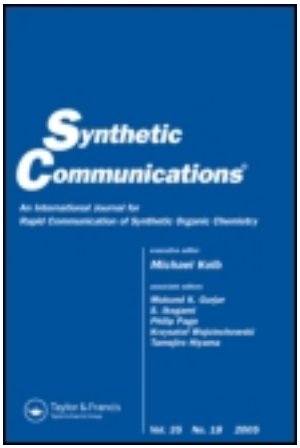

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Practical Synthesis of 3-Carboxyindazoles

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Abstract: A clean, high-yielding synthetic route to methyl 5-(bromomethyl)-1-tritylindazole 3-carboxylate **1** was needed. A principal intermediate was 5-methyl-3-carboxyindazole **2**. An analysis of a by-product found after executing Schad's 3-carboxyindazole synthesis led to undertaking this reaction with an inverse addition in the principal step. This simple modification gave **2** in excellent and reproducible yields.

Keywords: Carboxyindazole, indazole, indazole carboxylic acid, indazolone

A high-yielding synthesis of methyl 5-(bromomethyl)-1-tritylindazole-3-carboxylate (**1**) was needed. It was a key intermediate employed to build a subgroup of our HIV protease inhibitors.[1] A simple, efficient, scalable, and reliable synthesis of the 3-carboxyindazole precursor **2** was necessary (Scheme 1).

Philipp Schad reported an attractive one-pot synthesis of 3-carboxyindazoles from isatins in 1893.[2] However, subsequent papers have reported low and variable yields with laborious purifications upon repeating his procedure.[3] In our hands, Schad's methodology produced one major, and hard to separate, contaminant identified as 5-methyl-3-indazolone **4**. It accounted for up to 35% of our isatin **3** consumption. Baiocchi et al. reported isolating 3-indazolone by-products exclusively using Schad's reaction.[4] It was rationalized that an intramolecular cyclization of the azo

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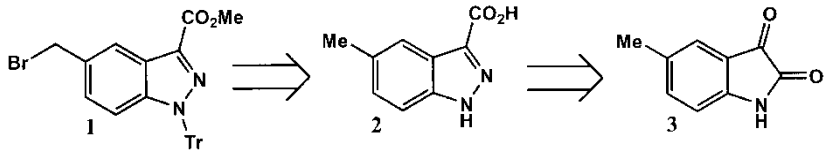


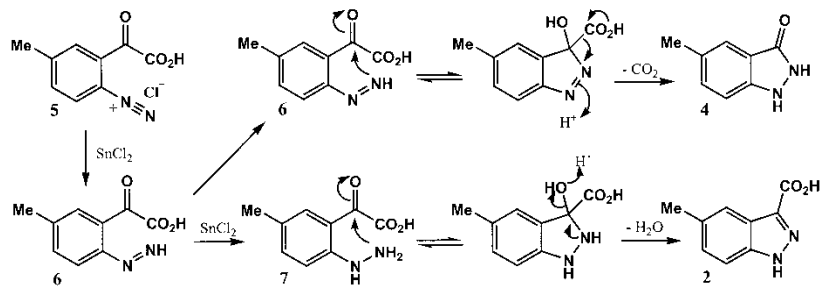
Scheme 1.

intermediate **6** gave the indazolone **4**, by way of decarboxylation, in competition with the desired reduction of **6** to the hydrazine **7** (Scheme 2). Accordingly, the formation of the by-product would increase with a slower addition of the reducing agent to the reaction. Naturally, unequal addition rates could account for the observed variability of the reaction.

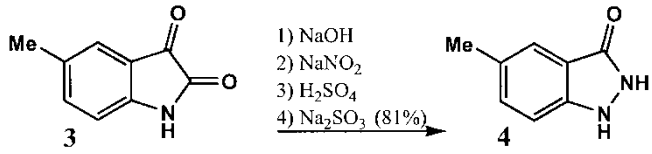
This hypothesis was tested by using a less-vigorous reducing agent. Enhanced indazolone formation was anticipated from a slower reduction of **6**. Sodium sulfite was employed in place of tin chloride, giving an 81% yield of **4** (Scheme 3). Only a trace of **2** was detected in the crude product. This reaction is a novel, selective, high-yielding, one-step synthesis of **4** from isatin.

In the preparation of **2**, the tin chloride mixtures had been added at slower rates to the diazonium solutions for larger reactions because this step was very exothermic and because it foamed excessively. Slower additions gave lower yields of **2** contaminated with more of **4**. Inverting this key step, by adding the diazonium solution to the tin chloride mixture, would maintain a high concentration of the reducing agent relative to the substrate for the duration of the reaction, thereby promoting the quick reduction of **6**. The formation of **2** would then be less dependent on the diazonium addition rate. In practice, the inverse addition reliably suppressed the formation of **4** and rendered **2** in 80% to 90% yields (Scheme 4).

In conclusion, an analysis of a by-product found when repeating Shad's 3-carboxyindazole synthesis led to inverting the addition of reactants in the key step. A diazonium solution was added to a tin chloride mixture. This



Scheme 2.



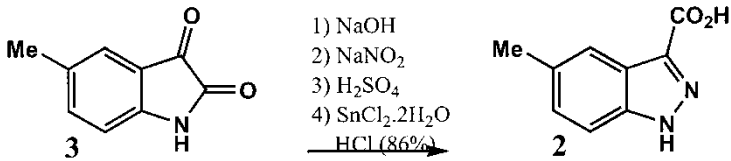
Scheme 3.

simple modification gave 5-methyl-3-carboxyindazole **2** in excellent and reproducible yields.

EXPERIMENTAL

Typical Procedure for the Preparation of 5-Methyl-3-carboxyindazole

A chilled (0°C) aqueous solution of $NaNO_2$ (2.2 g, 32 mmol, 10 mL of water) was added to a chilled (0°C) solution of commercially available 5-methylisatin (5.1 g, 32 mmol) in aqueous NaOH (1.3 g, 32 mmol, 10 mL of water). The combined solutions were added slowly to chilled (0°C) aqueous H_2SO_4 (3.4 mL of conc. H_2SO_4, 64 mmol, 60 mL of water) by means of an addition funnel with the tip below the surface of the acid solution. Ice was added to the reaction to maintain 0°C and ether was added to control foaming, as needed. After stirring an additional 10 min, the diazonium solution was added slowly to a chilled (0°C) mixture of $SnCl_2 \cdot 2(H_2O)$ (18 g, 80 mmol) in concentrated HCl (30 mL) by means of an addition funnel with the tip below the surface of the tin chloride mixture. Ice was again added to the reaction to maintain 0°C and ether was added to control foaming, as needed. After stirring an additional hour, the reaction was filtered. The golden yellow powder was dissolved in aqueous NaOH, washed with ether, precipitated with aqueous HCl, and crystallized from $AcOH/H_2O$ to give 4.8 g of **2** (86%) as very pale yellow needles, mp 340–342°C (lit.[3c] 343°C). ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.76 (bs, 1H), 7.87 (s, 1H), 7.55 (d, 1H, 8Hz), 7.27 (d, 1H, 8Hz), 2.44 (s, 3H).



Scheme 4.

Preparation of 5-Methylindazol-3-one

A chilled (0°C) aqueous solution of $NaNO_2$ (0.49 g, 7.0 mmol, 7.0 mL of water) was added to a chilled (0°C) solution of commercially available 5-methylisatin (1.0 g, 6.4 mmol) in aqueous NaOH (0.31 g, 7.7 mmol, 7.0 mL of water). The combined solutions were added slowly to chilled (0°C) aqueous H_2SO_4 (1.3 mL of conc. H_2SO_4, 24 mmol, 15 mL of water) by means of an addition funnel with the tip below the surface of the acid solution. Ice was added to the reaction to maintain 0°C and ether was added to control foaming, as needed. After stirring an additional 30 min, a chilled (0°C) aqueous solution of $NaHSO_3$ (3.3 g, 32 mmol, 15 mL of water) was added by means of an addition funnel with the tip below the surface of the diazonium solution. The reaction was stirred at room temperature for 12 h. The reaction was poured into water and the mixture was filtered. The orange powder was washed with ether and crystallized from ethanol to give 0.80 g of **4** (84%) as creamy white plates, mp 243–244°C (lit.[5] 240–242°C). ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.13 (bs, 1H), 7.39 (s, 1H), 7.15 (AB, 2H), 2.36 (s, 3H).

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