Short Communication

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AN IMPROVED SYNTHESIS OF ISATIN

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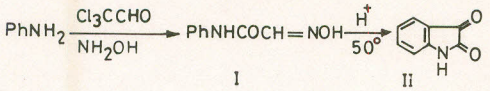
The interest in isatin derivatives as drugs [1] has led us to develop an economical two step process for the synthesis of isatin based on Marvel and Hiers method [2].



I II

A systematic study of reaction conditions showed that the replacement of sodium sulfate by ammonium sulfate gave better results and it was found that 63% less ammonium sulfate could be used as compared to sodium sulfate. This replacement was useful in two ways, firstly the solubility of ammonium sulfate in water is greater than that of sodium sulfate and permitted a reduction in the volume of water upto 35%. Secondly, the hard cake formation of hydrated sodium sulfate was avoided. The optimum mole ratio of hydroxylamine hydrochloride to aniline and chloral hydrate was 12.9:5.5:5.4, thus 20% less hydroxylamine hydrochloride could be used as compared to Marvel and Hiers method [2] and enhanced the yield of isonitrosoacetanilide (I) into isatin (II) in 85% yield was easily accomplished in conc. H_2SO_4 at 45-55° instead of 80°. The cyclization in polyphosphoric acid at 45-60° was almost as rapid as with conc. H_2SO_4. It has an advantage over conc. H_2SO_4 that there was no heat of reaction which could raise the reaction temperature. However, it is suggested that conc. H_2SO_4 is still a reagent of choice because it is inexpensive.

Optimum scaling up procedure. Isonitrosoacetanilide (I). To 76.3g (0.82 mole) of aniline in a 5 1 round bottom three neck flask fitted with a mechanical stirrer and thermometer, was added water (250 ml) and 50% v/v sulfuric acid (75 ml). Then a solution of chloral hydrate (135 g, 0.81 mole) and ammonium sulfate (750 g) in water (1.5 1) was added. The reaction mixture was heated to 60° till a clear solution was formed. A solution of hydroxylamine hydrochloride (135 g, 1.94 mole) in water (500 ml) was added drop wise in such a way that the addition of first half was made upto the temperature 90° and then the second half added at boiling temperature 103-105°. A solid product separated out within five minutes of vigorous boiling; at this stage, heating was stopped and the reaction mixture cooled to room temperature. The crystalline off-white product which separated out was collected and washed thoroughly with water (5 x 50 ml). It furnished 120.5 g (90%) of isonitrosoacetanilide, mp. 175°, lit[2]. mp. 175°. The product was almost pure and used as such for further conversion into isatin.

Isatin (II). 75 g. (0.45 mole) of isonitrosoacetanilide (I) was added gradually to the stirred conc. H_2SO_4 (400 ml) at 45-55°. After stirring for a further 30 min the reaction mixture was cooled to room temperature and poured into ice cold water (1.0 1). The precipitated solid was collected and washed with ice cold water (3 x 50 ml). It furnished 3.75 g (85%) of isatin which was recrystallised from ethanol to give red crystals, mp. 197-198°, lit[2]. mp. 196-197°.

In another experiment, 50 g of isonitrosoacetanilide (I) was allowed to cyclize in polyphosphoric acid (270 ml) at 45-60°. The mixture was worked up as described in the preceding paragraph to yield II (44.7 g), mp. 175°.

Keywords: Improved, Synthesis, Isatin.

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