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SHORT COMMUNICATIONS

A Procedure for Preparation of 2-Methylquinoline-4-carboxylic Acids

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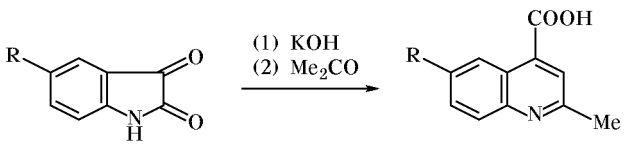
2-Methylquinoline-4-carboxylic acids are widely used in organic synthesis for the preparation of various derivatives possessing high biological activity [1–3]. These compounds are usually obtained by the Pfitzinger reaction, i.e., by heating a mixture of 5-substituted isatin with acetone in the presence of alkali. For example, 2-methylquinoline-4-carboxylic acid was synthesized in such a way in 50% yield [3–5], and 2,6-dimethylquinoline-4-carboxylic acid was obtained in 60% yield [6]. The yield of 6-bromo-2-methylquinoline-4-carboxylic acid was only 40%.

Presumably, the low yields of 2-methylquinoline-4-carboxylic acids prepared by addition of alkali to a mixture of 5-substituted isatin with acetone is explained by an appreciable contribution of the side reaction involving addition of acetone to isatin, which precedes opening of the isatin ring. The resulting unsaturated intermediate is likely to undergo tarring at elevated temperature, thus reducing the yield of the target product.

With a view to improve the yield and purity of 6-substituted 2-methylquinoline-4-carboxylic acids **IIa**–**IIc** we tried a different order of mixing of the reactants. According to the proposed procedure, a mixture of isatin **Ia**–**Ic** and a 28% solution of alkali was stirred for 5 min, and acetone was then added. As a result, we succeeded in increasing the product yield and minimizing formation of tars, the reactant ratio and reaction time remaining unchanged.



Ia–Ic **IIa–IIc**

R = H (**a**), Br (**b**), Me (**c**).

6-Bromo-2-methylquinoline-4-carboxylic acid (IIb). A mixture of 8 g (0.035 mol) of 5-bromoisatin (**Ib**) with a solution of 16 g (0.28 mol) of potassium hydroxide in 32 ml of water was stirred for 5 min at room temperature, 38.23 ml (0.836 mol) of acetone was added, and the mixture was heated for 8 h under reflux (on a water bath). The mixture was neutralized to pH 5–6 with 10% hydrochloric acid, and the precipitate was filtered off, washed with warm water, and dried. Yield 12.65 g (93%), mp 259–260°C.

Following a similar procedure, 2-methylquinoline-4-carboxylic acid (**IIa**) was synthesized in 91% yield, mp 238–240°C, and 2,6-dimethylquinoline-4-carboxylic acid (**IIc**) was obtained in 94% yield, mp 267–268°C. Acids **IIa**–**IIc** were identified by the IR spectra and melting points (no depression of the melting point was observed on mixing with an authentic sample).

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