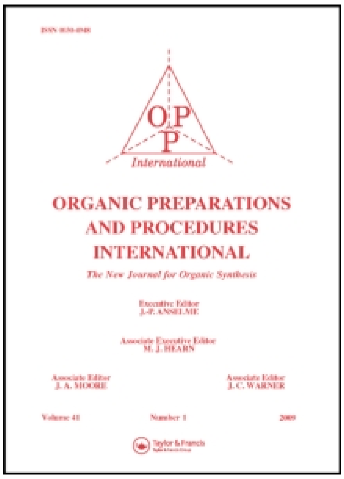

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IMPROVED SYNTHESIS OF *tert*-BUTYL 8-QUINOLYL CARBONATE

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IMPROVED SYNTHESIS OF tert-BUTYL 8-QUINOLYL CARBONATE

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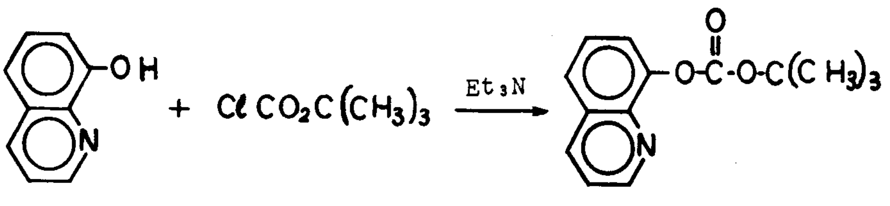
t-Butyl 8-quinolyl carbonate has found wide use for the synthesis of t-butyloxycarbonylamino acids.[1,2] Although several methods of synthesis of these derivatives are known,[3] there still exists a need of improvement of their methods of synthesis[4,5] as well as for the purification of the products.[6] Of the numerous mixed carbonates used for blocking of amino groups, those with an 8-quinolyl residue are among the best since very pure products are obtained in high yields.[1,7,8] The present paper describes an improvement of our own method[1] which permits the large scale preparation of very pure t-butyl 8-quinolyl carbonate in high yield. The method of Ovchinnikov was adapted for the preparation of t-butyl chloroformate.[9,10]



EXPERIMENTAL

t-Butyl chloroformate. - Metallic potassium (78 g, 2 g-atom) in 1700 ml anhydrous t-butanol was refluxed in a round bottom flask fitted with a reflux condenser equipped with a drying tube (NaOH). When conversion was complete, the excess butanol was evaporated in vacuo on a water bath at the water pump. The residue (373 g) was suspended in 500 ml anhydrous ether and poured into a 1.5 l. three necked round bottom flask fitted with a mechanical stirrer and a drying tube (NaOH). The suspension was thoroughly mixed for 2 hrs. and cooled to -70°. After that time, the suspension was siphoned in small portions into a 2.5 l. reactor by means of a Teflon tube reaching to the bottom. The flask cooled in a bath at -70° and fitted with a mechanical stirrer, thermometer and a $CaCl_2$ drying tube had previously been charged with a solution of phosgene of 495 g (5 moles) in 1 l. of anhydrous ether. An additional amount (2 x 100 ml.) of ether was used for a quantitative transfer of the salt. During the addition of potassium t-butylate, the temperature should not exceed -55°. After t-butylate addition, the solution was warmed to -30° and stirred at this temperature for an additional 3 hrs. The precipitated potassium chloride was filtered and the filtrate concentrated in vacuo to a weight about 370 g at temperatures not exceeding -10°. Analysis[11] indicated that the solution was ∿ 1.6 molar (80% yield based of potassium). This solution was used for further synthesis.

t-Butyl 8-quinolyl carbonate. - A 2.5 l. four-necked flask fitted with an efficient mechanical stirrer, dropping funnel, thermometer, and drying tube ($CaCl_2$) was charged with a solution of 232 g (1.6 mole) of 8-hydroxyquinoline and 222 ml (1.6 mole) triethylamine in 1050 ml. of anhydrous tetrahydrofuran and 250 ml anhydrous ether. To this solution cooled to -65°, a solution of t-butyl chloroformate pre-cooled to -65° was added dropwise at such a rate that the temperature did not exceed -60° Triethylamine hydrochloride began to separate and the solution became red-brown. The reaction mixture was diluted with 250 ml anhydrous ether and stirred for an additional 12 hrs. at -60°. The temperature was raised gradually to room temperature and stirring was continued for an additional 12 hrs. at that temperature; the solution finally became yellow. The precipitated triethylamine hydrochloride was filtered and washed with 1 l. of ether. The filtrate and washings were concentrated *in vacuo* to about 450 g and acidified with 0.5 N HCl solution to pH 2. This acidic solution was extracted with ethyl acetate (6 x 250 ml) and the combined extracts were washed with water and dried over anhydrous sodium sulfate. Evaporation of the solvent *in vacuo* left a residue (211 g, mp. 69-74°), which was dissolved in 420 ml hot (50°) ethanol. Crystallization was initiated by the gradual addition of 230 ml water. The crystals were collected and thoroughly washed with 300 ml 50% ethanol to give 257 g (53% yield based on potassium) of white crystals, mp. 75.5-76°, lit.[1] softening 67°, mp. 69.5-72°, were obtained.

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11. An excess of triethylamine was added to a small sample of the *t*-butyl chloroformate solution. The precipitated triethylamine hydrochloride obtained after evaporation of the solvent was dried to constant weight: 137.6 mg of hydrochloride corresponds to 1 mmole of *t*-butyl chloroformate.

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