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IMPROVED YIELDS IN THE SYNTHESIS OF 4-NITRO[1-^{13}C]ANILINE

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Summary

4-Nitro[1-^{13}C]aniline has been prepared in overall yield of 54%, based on labeled acetone, by modification of a standard procedure (2).

Acetone labeled in its 1,3- or 2- positions is commonly used for the synthesis of 4-nitrophenol that is labeled in its 2,6- or 1-positions. The 4-nitrophenol is then an entry into specifically labeled 4-nitroaniline. The route to labeled 4-nitroaniline has been described by Swartz and Gulick (2), and is shown in Scheme I. In syntheses such as this it is desirable to obtain as large a yield as possible in order to cut down on the use of costly, labeled precursors. The costs of acetone needed in the synthesis of ^{13}C- and ^{14}C-labeled 4-nitroaniline are particularly high. Because of this we wish to report an improvement in the synthesis of 4-nitroaniline, specifically in the one-pass conversion of 4-nitrophenol into 4-nitroaniline, from the reported maximum of 40% to 85-87% yield.

Incorporation of labeled carbon into the ring of 4-nitrophenol is accomplished with condensation of labeled acetone and sodium nitromalonaldehyde. Swartz and Gulick found that week-long reaction in dilute base gave a low yield of 4-nitrophenol, but if the solution was next made strongly alkaline and kept a further 2 h, the yield reached 74%. We have used this procedure explicitly in preparing labeled 4-nitrophenol, but never reached, in any case, greater than 63-64% yield. We find now that the same yield, namely 63%, can be reached using only the shorter time of condensation in approx . 4 M sodium hydroxide. The optimum time in our hands, was 4.75 h; only 55% yield was obtained after 2 h of reaction.

The improvement we emphasize here, though, is in the conversion of 4-nitrophenol into 4-nitroaniline. This is achieved by thermal rearrangement of the phenol's 2-phenylquinazolinyl ether and

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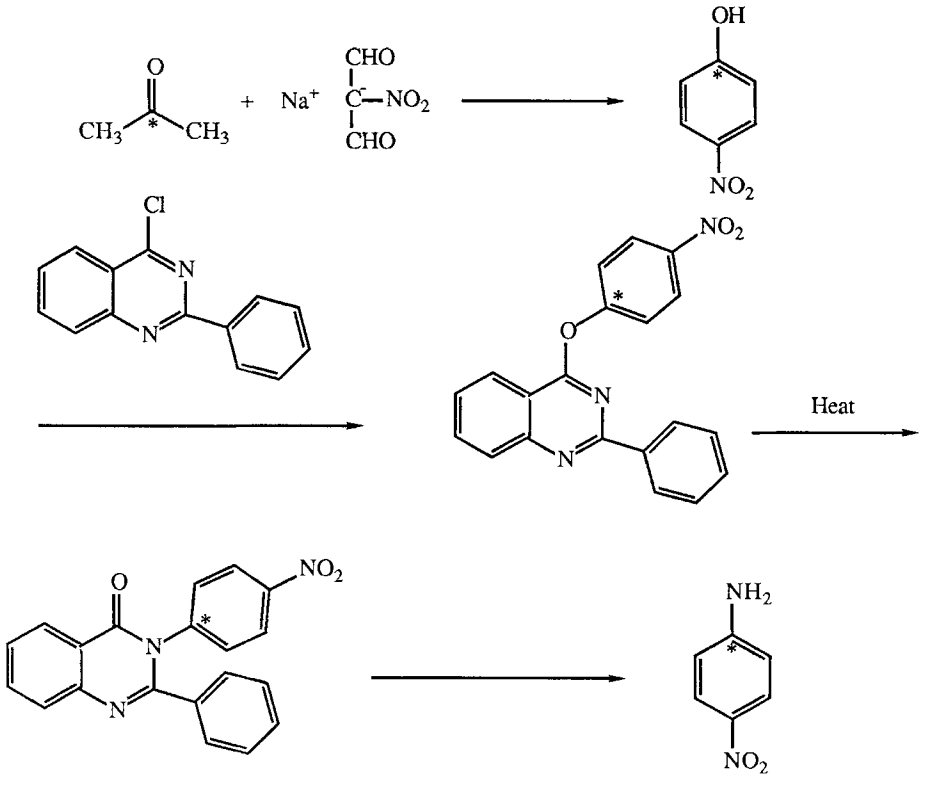
hydrolysis of the rearranged product. Like Swartz and Gulick we found that rearrangement in mineral oil failed, whereas "neat" thermal rearrangement proceeded smoothly. Contrary to the evidence of Swartz and Gulick, though, we were able to follow the rearrangement to completion by infrared spectroscopy.

Rearrangement of the ether, 4-(4-nitro[1-^{13}C]phenoxy)-2-phenylquinazoline (Scheme I), was carried out by heating at 290-320 °C. Rearrangement was followed by monitoring the changes in intensities of the carbonyl (1687 cm^{-1}) and ether-linkage (1221 cm^{-1}) peaks. Heating was stopped when the changes reached their maxima. This method, originally described by Morrow and coworkers (3), gave consistantly excellent results and is much to be preferred to that chosen by Swartz and Gulick, and which in our hands was unreliable, namely the visible appearance of the heated sample. Hydrolysis of the rearrangement product gave, eventually, 4-nitro[1-^{13}C]aniline.

SCHEME I



4-Nitrophenol

The procedure described here was worked out with unlabeled acetone. To a solution of 3.25 g (20.7 mmol) of sodium nitromalonaldehyde in 400 mL of 4.2 M sodium hydroxide cooled to 2 °C, was added dropwise with stirring a solution of 1.02 g (17.6 mmol) of acetone in 50 mL of 4.2 M sodium

hydroxide, over a period of 25 min. The mixture was stirred at 5 °C for 140 min, allowed to warm to room temperature and stirred for an additional 2 h. The mixture was acidified with conc. hydrochloric acid while keeping the temperature below 30 °C, and extracted continuously with ether for 24 h. The ether solution was dried over magnesium sulfate in the presence of activated carbon and worked up to give 1.53 g (11.0 mmol, 63%) of pale yellow 4-nitrophenol, mp 106-109 °C.

4-(4-Nitro[1-^{13}C]phenoxy)-2-phenylquinazoline

[2-^{13}C]acetone, diluted with unenriched acetone, was used to prepare 38.5% enriched 4-nitro[1-^{13}C]phenol (2). A mixture of 2.00 g (14.3 mmol), of 4-nitro[1-^{13}C]phenol, 3.64 g (15.2 mmol) of 4-chloro-2-phenyl-quinazoline, and 5.0 g of potassium carbonate was added in one portion to 300 mL of dry acetone which had been purged with nitrogen for 30 min. The mixture was purged for a further 10 min and boiled under reflux in a nitrogen atmosphere for 48 h. After being cooled to room temperature the mixture was poured into 400 mL of ice water, which was next stirred for 30 min. The white precipitate was collected, washed with water, and dried under vacuum to give 4.82 g (14.0 mmol, 38.5% enrichment, 98% yield) of the quinazolinyl ether, mp 218-220 °C.

4-Nitro[1-^{13}C]aniline

4-(4-Nitro[1-^{13}C]phenoxy)-2-phenylquinazoline (2.51 g, 7.30 mmol) was heated under nitrogen atmosphere in a Wood's metal bath at 290-320 °C. Heating was stopped after intervals of 10, 20, 30, and 30 min, and at each interval the reactant mixture was cooled and a sample was removed for infrared analysis (KBr pellet). Increase in the carbonyl peak (1687 cm^{-1}) and decrease in the ether-linkage peak (1221 cm^{-1}) were followed. After the total heating time of 90 min the mixture when cooled to room temperature became a brown gum. To this was added a mixture of 80 mL of methanol and 6 mL of water. After purging the mixture with nitrogen for 15 min, 6.0 g of potassium hydroxide was added. The mixture was boiled under reflux overnight, cooled to room temperature, acidified with conc hydrochloric acid, and heated again at 50-60 °C for 1 h. The resulting solution was cooled in an ice bath and made alkaline with 50% aqueous potassium hydroxide. The mixture was concentrated to a semi-solid in a rotary evaporator and diluted with 250 mL of water. The solution was extracted with 1 x 200 mL and 3 x 150 mL of ether. Workup of the ether solution gave 878 mg (6.34 mmol, 87%) of enriched 4-nitro[1-^{13}C]aniline, mp 145.5-147 °C.

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