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THE REACTION OF N-ARYL NITRONES WITH DICHLOROKETENE: A NEW SYNTHESIS OF ISATINS

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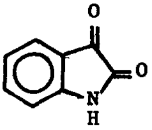
As part of our continuing study of the use of N-aryl nitrones in ortho-selective aromatic substitution reactions[1-3], we have investigated the reaction of a number of such nitrones with dichloroketene. These reactions lead to adducts which can be hydrolysed by boiling water or aqueous acid to isatin (1) or a derivative of isatin.

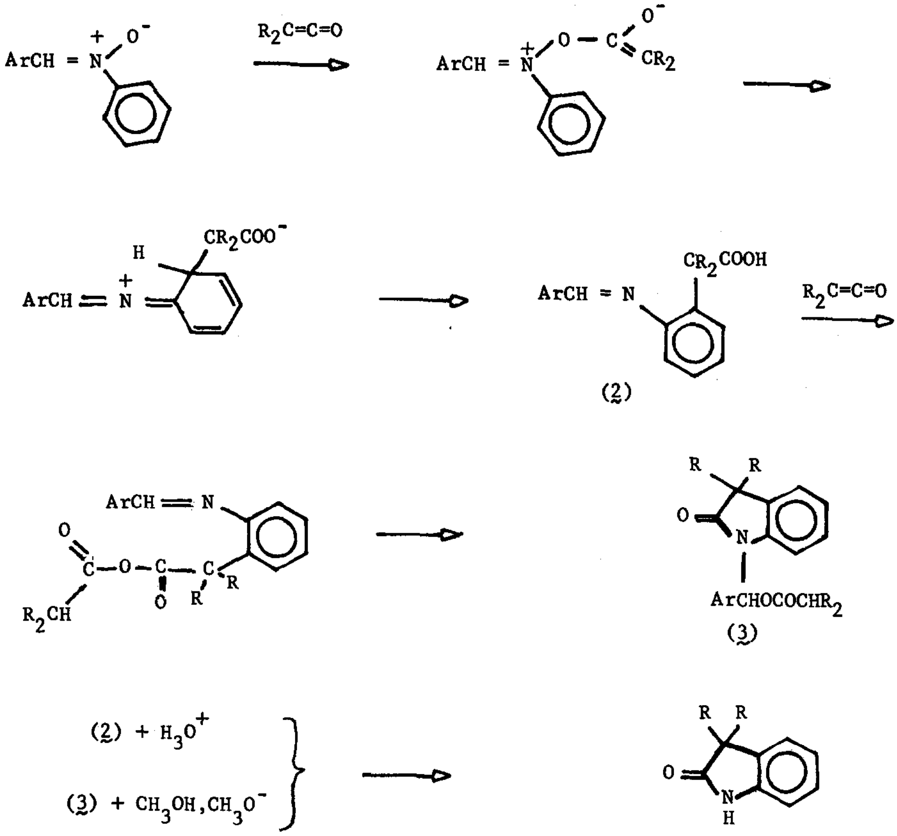


(1)

This new isatin synthesis seems of significance because of its simplicity, few steps, and good yields. Isatins are valuable intermediates in the preparation of pharmaceuticals and dyes, adding to the usefulness of the reaction. While this manuscript was in preparation, an account of another new isatin synthesis (based on sulfur ylid chemistry) was published[4]; this drew attention to the shortcomings of existing routes to the isatin system.

Our method, as mentioned above, involves the reaction of N-aryl nitrones with dichloroketene. Although this reaction has not been investigated previously, other workers have investigated the reactions of nitrones with dialkyl and diaryl ketenes. Staudinger and Miescher were the first to report on the reactions of diphenylketene with various nitrones[5], noting the formation of a 1:1 adduct with diphenylnitrone and a 1:2 adduct (nitrone:ketene) with triphenylnitrone. Later workers, notably Hassall and Lippman[6], and Taylor and co-workers[7], reinvestigated the work of Staudinger and Miescher. Taylor and his associates also worked with variously substituted N-aryl nitrones, and with dimethylketene in place of diphenylketene. Based on this work, it appears that two types of product, the imino acid (2) or the oxindole (3) can normally be expected from nitrone/ketene reactions. Both can be hydrolyzed to the same oxindole (Scheme I).

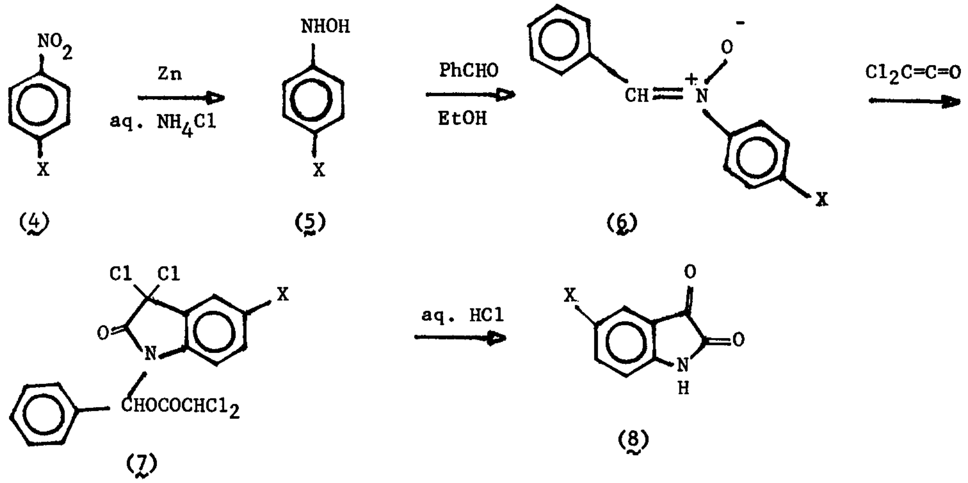
Scheme I



Thus, we expected that in the case where R = Cl in Scheme I (i.e., in the reaction of dichloroketene with an N-aryl nitrone) an adduct would be obtained which could ultimately be hydrolysed to an isatin derivative. This expectation was borne out by experiment. Initially, we determined whether our adduct was of the 1:1 or 1:2 variety. In an exploratory experiment, we treated N-aryl nitrones with a molar equivalent of dichloroketene, thereby optimizing conditions for the maximum yield of 1:1 adduct. However, we found that even under these conditions, a 1:2

adduct was favored, an observation in keeping with Taylor's studies of the dimethylketene/N-aryl nitrone system. Thus, in all future experiments we used slightly in excess of 2 molar equivalents of ketene for each molar equivalent of nitrone in order to favor the formation of 1:2 adduct in the highest possible yield. These 1:2 adducts (7) are white crystalline materials which give correct elemental analyses and spectroscopic data for the structure suggested. Hydrolysis proceeds smoothly to the corresponding isatins (8) which were found to be identical with authentic materials. Thus, it is possibly to convert appropriate aromatic nitro-compounds into isatins in four steps (Scheme II), or more conveniently in two consecutive "one-pot" reactions since it is not necessary to isolate the aryl hydroxylamines (5) or the adducts.

Scheme II



X	% Yields		Melting Points, °C	
	(6)→(7)	(7)→(8)	(7)	(8)
H	81	85	138-140	201-203
CH$_3$	75	70	149-150	183-185
Cl	65	77	160-162	249-251
Br	65	70	159-161	251-253

The synthesis is limited at present by the difficulty of preparing some nitrones (6) by the route indicated. For example when X = CO$_2$Et or OMe, the initial reduction of the nitro compound did not give a viable yield of hydroxylamine in our experiments. It is therefore desireable that alternative routes to N-aryl nitrones be developed. We also note that dichloroketene reacts with carboxylic acid and nitro groups[8], posing difficulties for the conversion of (7) to (8) if these groups are present.

The reactions were carried out by adding a dilute (5-10%) solution of dichloroacetyl chloride to a cold, stirred solution (0 - 10°C) of the nitrone in dry tetrahydrofuran to which enough triethylamine had been added to dehydrohalogenate the dichloroacetyl chloride. The whole reaction mixture was maintained under a blanket of dry nitrogen. After addition was complete, triethylamine hydrochloride was filtered off, and tetrahydrofuran evaporated from the filtrate, whereupon the adduct was obtained. Hydrolysis of the adducts was accomplished by boiling with water or (more rapidly) with 1M hydrochloric acid. Optimum yields of isatins were obtained in experiments in which the adduct was not isolated. In these preparations, the filtrate remaining after removal of triethylamine hydrochloride was evaporated to a dark colored syrup, and this was then subjected to hydrolysis with 1M hydrochloric acid.

Treatment of nitrones with dichloroacetyl chloride in the absence of triethylamine causes rearrangement of the nitrone to an amide, in accord with earlier observations of nitrone/acid chloride reactions[9].

ACKNOWLEDGEMENT

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FOOTNOTES AND REFERENCES

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