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INTERMEDIATES IN THE LEUCKART REACTION OF BENZOPHENONE WITH FORMAMIDE

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Abstract: The isolation of benzhydrol and its ether in conjunction with N-formylbenzhydrylamine in the Leuckart reaction of benzophenone is reported; it is postulated that this alcohol is a possible intermediate in the reaction.

The Leuckart reaction,[1,2] about a century old, has remained one of the facile routes to the synthesis of a large number of amines.[3] Even though several intermediates such as carbinolamines, aldimines and ketimines have been postulated for this reaction, the actual species and the mechanism involved are still not quite well understood.[4-6] A recent hypothesis assumes the formation of esters of α-aminoalcohols and formic acid as intermediates which suffer reductive decarboxylation to give the usual Leuckart products.[7]

In order to gain more insight into the nature of this reaction, particularly with respect to the intermediates involved, we repeated the Lewis acid catalyzed benzophenone experiment of Bruce and Webers,[8] in which N-formylbenzhydrylamine was obtained in excellent yields. Our results are summarized in Table 1.

Benzophenone, when heated with formamide (99%) as usual, but in the dark, with or without anhydrous magnesium chloride (runs 1 and 2), and the water insoluble fraction resolved by preparative thin layer chromatography (TLC, SiO_2, acetone/benzene), gave N-formylbenzhydrylamine, unreacted ketone, and two additional products. The latter were identified as benzhydrol and benzhydryl ether, respectively (NMR, IR, mp comparison with the authentic samples). In no case was it possible to detect either a ketimine (or an aminoalcohol) intermediate in the total mixture.

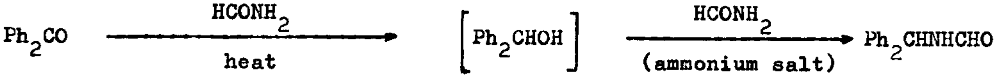
Table 1. Leuckart Reaction with Benzophenone and Benzhydrol

			Products		
			$Ph_2CHNHCHO$	Ph_2CHOH	$Ph_2CH)_2O$
Run	Conditions	Reagents(mol)	(%)	(mg)	(mg)
1	4 h, 180-195°C, dark	0.03, Ph_2CO; 0.18, $HCONH_2$	53	13.0	71.0
2	as in run 1 + 0.003 mol anhyd. $MgCl_2$	as in run 1	97	24.7	5.4
3	as in run 1	0.03, Ph_2CHOH; 0.18, $HCONH_2$	64		91.3
4	as in run 2	as in run 3	86		138.2

The above observations, not reported in previous investigations,[4,8] led us to suspect benzhydrol as a possible intermediate in the reaction. The versatility of this alcohol as an alkylating agent, in particular, has been well demonstrated in the work of Segrave[9] whereby a variety of triphenylmethanes were synthesized from anisole, benzene, toluene and the substituted and unsubstituted alcohol, respectively, in the presence of an acid catalyst.

Heating of benzhydrol with formamide, with or without catalyst (runs 3 and 4), gave in each case N-formylbenzhydrylamine and benzhydryl ether, respectively.

These facts indicate that the reduction of benzophenone to benzhydrol in formamide occurs and the subsequent reactions are simple alkylation of formamide or its derived ammonium salt to give the benzhydrylamine products, and could account for the presence of benzhydryl ether in the reaction mixture.



$$Ph_2CO \xrightarrow[\text{heat}]{HCONH_2} \left[Ph_2CHOH\right] \xrightarrow[\text{(ammonium salt)}]{HCONH_2} Ph_2CHNHCHO$$

Horii and coworkers[10] had earlier reported an unusual rearrangement in the Leuckart reaction of benzophenone when treated with diphenylurea and formic acid; the main product obtained was o-diphenylmethylaniline. It is possible that this was a simple case of C-alkylation of aniline by benzhydrol.[11]

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11. Partial reduction of benzophenone to benzhydrol was achieved with potassium formate (excess) in boiling o-xylene. Study of the isotopic effect (deuterium) in this reaction is in progress.

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