Zen-ichi Horii, Tatsuo Sakai, and Takeshi Inoi: A Modified Leuckart Reaction. II.[1]

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In the preceding paper[1] it has been reported that a good result had been obtained in the Leuckart reaction by using a mixture of urea and formic acid instead of ammonium formate or formamide. In order to extend this method to the synthesis of N-methylamino compounds, we have investigated the reaction of a mixture of N,N′-dimethylurea and formic acid on carbonyl compounds. Fortunately, we succeeded in the conversion of carbonyl compounds into corresponding N-methylamino compounds by this method, but the yield obtained was rather low (40~50%) when compared with those of the Novelli's procedure[2] which used N-methylformamide in lieu of formamide in the Leuckart reaction and the reductive amination by the catalytic hydrogenation of carbonyl compounds in the presence of methylamine. However, as N,N-dimethylurea is available as a commercial product and also can be prepared easily from urea and methylamine, there is no difficulty in supplying starting materials. Moreover, this reaction can be carried out in an open vessel. From these points it can be concluded that this method is valuable for the synthesis of N-methylamino compounds directly from carbonyl compounds. Experimental data are given in the accompanying table.

Experimental

General Procedure—Following the method of our previous work,[1] carbonyl compound, HCOOH (85%), and N,N′-dimethylurea were mixed in the molar ratio of 1:4:2. This mixture was heated to 110~120° and kept at this temperature for 2 hrs. and then raised to 180° during 1 hr., and maintained between 180~190° for 3 hrs. After cooling, 15% HCl was added and heated to hydrolyze the N-formyl derivatives. After recovering the unreacted carbonyl compound by extraction with benzene, the solution was made alkaline and the separated N-methylamino compound was extracted with benzene and purified as usual.

Preparation of N-Methylbenzhydrylamine—Benzophenone (9.1 g.), 85% HCOOH (11.5 g.), and N,N′-dimethylurea (8.8 g.) were mixed and heated at 110~120° for 2 hrs., at 180° for 1 hr., and at 180~190° for 3 hrs. After cooling, the reaction mixture was heated with 35 cc. of 15% HCl for 1 hr. and extracted with benzene to remove the unchanged starting material. Making alkaline with 20% NaOH, separated N-methylamino compound was extracted with benzene. After drying over anhyd. Na_2SO_4, the benzene was evaporated and the residue was distilled under a reduced pressure. b.p.$_2$ 116~118°. Yield, 4.5 g. (45.9%). N-Methylbenzhydrylamine hydrochloride, m.p. 238°. *Anal.* Calcd. for $C_{14}H_{15}NCl$: C, 71.93; H, 6.90. Found: C, 71.72; H, 6.93.

Carbonyl compd.		Formic acid	N,N′-dimethylurea	Product									
						Yield		Hydrochloride					
								m.p.	lit. m.p.	Analysis			
										Found		Calcd.	
Formula	g.	g.	g.	Formula	b.p., °C/mm.	g.	%	°C	°C	C	H	C	H
$C_6H_5COCH_3$	6.0	11.5	8.8	$C_6H_5CH(NHCH_3)CH_3$	48~49/2	2.5	37.3	174	173	64.03	8.12	63.00	8.22
$C_6H_5COC_6H_5$	9.1	11.5	8.8	$C_6H_5CH(NHCH_3)C_6H_5$	116~118/2	4.5	45.9	238	238	71.72	6.93	71.93	6.90
$C_6H_4\left\{\begin{array}{l}-OCH_3(2)\\-CH_2-\\COCH_3(1)\end{array}\right.$	3.3	4.6	3.5	$C_6H_4\left\{\begin{array}{l}-OCH_3(2)\\-CH_2CH(NH-\\\quad CH_3)CH_3(1)\end{array}\right.$	79~81/1	0.8	22.0	128	129~132	61.31	8.32	61.24	8.41

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[1] Part I: J. Pharm. Soc. Japan, **72**, 1208(1952).

[2] Novelli: J. Am. Chem. Soc., **61**, 520(1939).