[CONTRIBUTION FROM THE LABORATORIES OF LION OIL DIVISION OF THE MONSANTO CHEMICAL CO. AND MIDWEST RESEARCH INSTITUTE]

A New Synthesis of Ureas. III. The Reaction of Aromatic Amines with Carbon Monoxide and Sulfur

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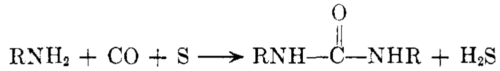
Previous papers in this series[3,4] describe the reaction of ammonia and aliphatic amines with carbon monoxide and sulfur giving urea and 1,3-dialkylureas and hydrogen sulfide.



$$RNH_2 + CO + S \longrightarrow RNH\text{—}\overset{\overset{\displaystyle O}{\|}}{C}\text{—}NHR + H_2S$$

Aromatic amines react only slightly under conditions which produce high yields of dialkylureas. However, in the absence of a solvent and with a tertiary amine catalyst, high yields of several diarylureas have been achieved. A study of the reaction conditions and the preparation of a variety of diaryl ureas are reported in this paper.

Reaction conditions. The location of optimum reaction conditions for the preparation of 1,3-diphenylurea is an example of the utility of statistically designed experiments for this purpose. Early work with this reaction showed very little promise of a satisfactory preparation of arylureas. Very low yields were obtained in the absence of a catalyst and even with a variety of basic catalysts and a wide range of reaction condition, yields no better than 50% were obtained.

An experiment was designed to study the effects of five reaction variables on the yield. The design was a one-half replicate of a 2^5 factorial experiment with four factor interactions confounded with main effects. It was intended that the second half of this design be run if interactions were important enough so that a more precise knowledge of the error term was needed. However, the results of the first block of 16 runs was conclusive enough to make the second block superfluous. The variables chosen for study were temperature, time, carbon monoxide pressure, amount of catalyst, and amount of sulfur.

The variables and their levels chosen for study were:

TABLE I

THE VARIABLES AND THEIR LEVELS

Temperature	100° to 160°
Time	1.5 and 3 hr.
Carbon monoxide pressure	300 to 600 p.s.i.g.
Triethylamine to aniline ratio	0.1:1 and 0.3:1
Amount of sulfur	1 and 2 times stoichiometry

Table II shows the yields for each run and the conditions under which it was made. The runs were made in a randomized order. Yields are based on the amount of aniline added. The exact procedure is described in the experimental section.

TABLE II

DIPHENYLUREA YIELDS, %

Catalyst Ratio	Sulfur	1.5 Hours 100°	1.5 Hours 160°	3.0 Hours 100°	3.0 Hours 160°
0.1:1	1:1	37.1[a]	24.8	46.1	25.5[a]
	2:1	45.6	31.9[a]	59.7[a]	30.8
0.3:1	1:1	34.7	38.8[a]	46.5[a]	24.3
	2:1	45.7[a]	37.0	52.9	39.0[a]

[a] CO pressure 600 p.s.i.g., other 300 p.s.i.g.

The results of the analysis of variance are shown in Table III.

TABLE III

ANALYSIS OF VARIANCE MEAN SQUARES[a]

	Temperature	Time	Sulfur	Cat. Ratio	Pressure
Temperature	993.8[b]				
Time	127.57[c]	96.16[d]			
Sulfur	1.09	1.80	351.60[b]		
Cat. ratio	37.60[d]	2.39	2.16	3.38	
Pressure	0.12	14.60	0.24	1.02	20.46

[a] Principal diagonal elements are main effects, others are first order interactions. [b] Significant at the 99.9% confidence level. [c] Significant at the 99% confidence level. [d] Significant at the 95% confidence level.

In the statistical analysis, the main effects were isolated and Cochran's test of the largest variance (time × temperature) was applied to the two factor interactions. This proved to be significant at the 5% level of significance. The remaining nine interactions had a mean square of 6.82. This compared favorably with the 6.51 (10 d.f.) error found previously for duplicate runs. Therefore, it was decided

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(1) Lion Oil Co.

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(3) R. A. Franz and F. Applegath, "A New Urea Synthesis: The Reaction of Ammonia, Carbon Monoxide, and Sulfur." Presented before the Southwest Regional Meeting of the American Society, December 1, 1960, Oklahoma City, Okla.

(4) R. A. Franz, F. V. Morriss, and F. Baiocchi, *A New Synthesis of Ureas: II. The Reaction of Primary Aliphatic Amines with Carbon Monoxide and Sulfur.* In press.

TABLE IV

DESIGN AND YIELDS (%)[a] FOR SERIES NO. 2

Time, Hr.	2:1 Sulfur				4:1 Sulfur			
	100°	115°	130°	145°	100°	115°	130°	145°
0.50				49.9				58.2
1.25			56.0	51.7			61.5	64.3
2.00		65.6	67.2	56.8		77.7	76.9	62.8
2.75	55.6	68.0	65.9		67.2	82.7	84.2	
3.50	62.3	70.2			71.9	86.2		
4.25	66.6				73.6			

[a] 95% confidence limits ± 8.13.

to use the 6.51 error for limits and tests of significance and on this basis the following conclusions were drawn.

There is no effect in tripling the catalyst ratio or doubling the CO pressure. Temperature interacted significantly with the catalyst ratio but the magnitude (3.9%) was small enough to possibly consider as due to experimental variation. In all cases, doubling of the sulfur increased the yield with an over-all average increase of 9.3%. Time, temperature, and their interaction were significant with the combination of 100° and 3.0 hr. giving the best yields in all cases. The sulfur effect appears completely additive with these factors.

Since the initial series had shown that only time, temperature and amount of sulfur were important variables, a second series was designed to find the optimum values for these factors. An orthogonal design not previously described in the literature was outlined (see Table IV). The design resembles a full replicate for one factor at four levels (temperature), one at six levels (time), and one at two levels (amount of sulfur). The major difference is in the omission of half the runs, namely those known to produce low yields, low temperature combined with short time, and high temperature combined with long time.

The yields produced in each run are shown in Table IV. Although the experimental times were not long enough to encompass the maximum, the results are quite conclusive. Increasing the sulfur ratio from 2:1 to 4:1 gave an average increase of 11% yield with 95% limits of 8.7 and 13.3 and the increase seemed to be independent of other conditions.

High and low temperatures (*e.g.*, 100° and 145°) are significantly less favorable to the reaction than either the 115° or 130° temperature.

The yield surface was adequately fitted by a quadratic function of the two variables; the maximum was found to be at about 116° for three hours thirty-three minutes. The yield at this point at a 4:1 sulfur level is estimated to be 83.2% with 95% confidence limits of 78.5 and 87.5%.

Further experiments indicated that extra time did not appreciably change these yields nor were larger amounts of sulfur beneficial.

Although the amount of catalyst was not effective in changing the yields of diphenylurea within the limits of these studies, later experimentation over a wider range of conditions showed that very small amounts of tertiary amine do not give satisfactory reaction rates. Very low yields were obtained if the catalyst to amine ratio was cut by a factor of ten and in general a ratio of about 1/10 was used. A variety of catalysts were investigated but only very basic, soluble compounds were effective. Besides the tertiary aliphatic amines the other catalysts which produced moderate yields were potassium hydroxide, and calcium oxide or magnesium oxide in methanol.

Solvents generally were detrimental to good yields. Methanol, petroleum ether, benzene, and pyridine all produced yields about 10% lower than similar runs without solvents.

The effect of substituents on yields. After the optimum conditions were obtained for preparing diphenylurea, a variety of aromatic amines were investigated under the same set of conditions. Table V summarizes the data from this study.

Five of the ureas have not previously been reported. The proof of structure depends upon elemental analysis, general similarity of physical properties to other ureas and in two cases, mixed melting points with the products prepared by better known methods.

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TABLE V

1,3-Diarylureas

Compound Prepared	Yield %	Melting Point Obsd.	Melting Point Lit.	Ref.	Carbon Calcd.	Carbon Anal.	Hydrogen Calcd.	Hydrogen Anal.	Nitrogen Calcd.	Nitrogen Anal.	Recrystallized from
1,3-Bis(2-pyridyl)urea	18	172	175	(5)							Methanol
1,3-Bis(3,4-dichlorophenyl)urea	20	277–279	(278–280 by synthesis)								—
1,3-Bis(2-chlorophenyl)urea	29	238	235–236	(6)							Methanol
1,3-Bis(3-chlorophenyl)urea	40	241	243	(6)							Methanol
1,3-Bis(4-chlorophenyl)urea	65	292–294	289–290	(7)							—
1,3-Diphenylurea	86	234–235	234	(8)							—
1,3-Bis(4-hydroxyphenyl)urea[a]	92	240 dec.	230 dec.	(9)							—
1,3-Bis(2-methoxy-5-chlorophenyl)urea	6	241–242	—		52.96	52.87	4.15	4.23	8.24	8.23	DMF-H_2O
1,3-Bis(4-carboxyphenyl)urea	34	>290	>270	(10)							—
1,3-Bis(2-methyl-5-chlorophenyl)urea	25	265–267	—								DMF-H_2O
1,3-Di-*o*-tolylurea	45	263–265	256	(11)							—
1,3-Di-*p*-tolylurea	79	260–262	260–261	(12)							—
1,3-Bis(4-methoxyphenyl)urea	63	232–234	234	(13)							Methanol
1,3-Di-2,4-xylylurea	23	sub. 260	262	(14)							—
1,3-Di-2,5-xylylurea	41	sub. 275	sub. 285	(15)							—
1,3-Di-2,6-xylylurea	8	>300	—		76.08	76.11	7.51	7.53	10.44	10.40	DMF
1,3-Bis(4-dimethylaminophenyl)urea	3	233–236	262 dec.	(16)							—
1,3-Bis(4-carbethoxyphenyl)urea	1	215–216	—	(10)	64.1	64.00	5.62	5.75	7.88	7.92	Methanol
1,3-Di-α-naphthylurea	14	289–292	296	(7, 17)	Also 8% yield of naphtho-1′,2′:4,5-thiazole, 298–299° m.p. (lit. 300°)						DMF Methanol
1,3-Di-β-naphthylurea	18	293–295	301–302	(18)	Also 22% yield of naphtho-2′,1′:4,5-thiazolone, 232–234° m.p.						—
1,3-Bis(4-diethylaminophenyl)urea[a]	27	212–215	223–224	(19)							—
1,3-Di-4-biphenylylurea	45	310–311	315	(20)							DMS

[a] No triethylamine used.

The yields ranged from 92% to zero. The major structural factors affecting the yields appear to be *ortho*-substitution and substitution with electronegative groups. In every case where an *ortho*-substituent was present low yields were obtained. A yield of 65% was obtained from *p*-chloroaniline but 3,4-dichloroaniline gave only a 20% yield. The reaction of 2,4- or 2,4,6-trichloroaniline produced no urea and no hydrogen sulfide.

No catalyst was required for the reaction of *p*-aminophenyl. The higher basicity may account for the reactivity of *p*-aminophenol but *N*,*N*-dimethyl-*p*-phenylenediamine gave only 3% yield without a catalyst and *N*,*N*-diethyl-*p*-phenylenediamine gave only a 27% yield.

The low yields of 1,2-di-α-naphthylurea and 1,3-di-β-naphthylurea are partly explained on the basis of side reactions which apparently produce amino thiols which react further to produce thiazolones. Further data on this side reaction will be presented in a future publication.

No evidence was obtained for direct interference in the reaction by carbonyl or carbalkoxy in the *para*-position but the urea yields were low in both cases. Several other substituents did enter into reaction in one way or another and these reactions will be reported in a subsequent paper.

The nitro, amino, aromatic hydroxyl, and thiol groups all were altered by the reaction under certain circumstances.

EXPERIMENTAL

The conditions for all the reactions reported duplicated those described for the best preparation of diphenylurea except that different solvents were used in purification.

Diphenylurea. Aniline (50 g.) and sulfur (34.4 g.) were placed in a 1-l. Magnedash autoclave with 4.4 g. of triethylamine. The autoclave was evacuated and then pressurized to 500 p.s.i.g. with carbon monoxide and heated rapidly to 130° for 3.5 hr. The pressure was released and the products rinsed from the vessel with ethanol. The ethanol was evaporated to about 50 ml., cooled and the solid filtered off. The white product (48.3 g.) melted at 235–238°. A second crop (0.9 g.) was obtained by evaporating the ethanol and washing the residue with dilute hydrochloric acid. It melted at 223–230° and this melting point was not lowered by mixing with pure diphenylurea. The total yield was 86.2% based on aniline.

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Aromatic Nitroso Compounds. I. A New 1,4-Rearrangement[1]

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2-Nitro-4-chloronitrosobenzene and 2-nitro-5-chloronitrosobenzene have been prepared. The nonidentity of these two compounds rules out a conceivable structure for this type of molecule in which the nitro and nitroso groups combine to give a symmetrical "benzofurazan dioxide" type of heterocycle. However, evidence has been obtained for the existence of this hitherto unknown heterocyclic configuration as an unstable intermediate or transition state in the high-temperature isomerization of either of these nitroso compounds to a mixture (approximately 1:1) of the two. This reaction is an example of a new type of 1,4-rearrangement involving the transfer of an oxygen atom between two nitrogen atoms.

It is generally accepted[2,3] that the crystalline, yellow compound with formula $C_6H_4N_2O_2$, originally thought[4] to be *o*-dinitrosobenzene, is better described as the *N*-oxide of the known compound benzofurazan (I), and may be named benzofurazan oxide (II). The question of the possible existence of benzofurazan dioxide[5] (III) has apparently not been previously investigated.

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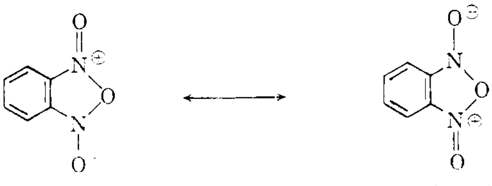
(5) Such a molecule would presumably be a resonance hybrid in which forms such as



might be expected to be of greater importance than the one designated as III. The dioxide formulation III was chosen as a symbol for this hybrid to emphasize the symmetry of this type of molecule.