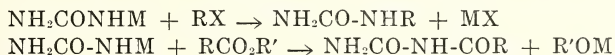


The Preparation and Reactions of Lithium Urea

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Acyl ureas, $R\text{-CO-NH-CO-NH}_2$, have usually been made by one of two general methods. In the first of these urea is treated with an acid chloride or anhydride, usually at a high temperature. This method is generally successful, but not infrequently gives poor yields, especially with derivatives of unsaturated acids (1). The second method consists of condensing urea with an ester in the presence of sodium ethylate. This method has been widely used in the preparation of barbiturates from substituted malonic esters; it can also be used with esters of monobasic acids (2).

A third method which should be applicable to the synthesis of both acyl and alkyl derivatives of urea appears to have been little studied. This is the treatment of an alkali salt of urea with a halide or an ester:



This reaction was investigated to some extent by Jacobson (3) who used sodium urea. He found that mono-sodium urea reacted readily, in liquid ammonia solution, with compounds containing an active halogen atom, such as benzyl chloride and benzoyl chloride, but that no reaction occurred with simple alkyl halides such as butyl iodide and butyl chloride. He also found that monosodium urea reacted, in the presence of acetone, with esters of monobasic acids, to yield monoacyl derivatives, and with esters of dibasic acids, such as glutaric and pimelic, to yield what appeared to be diacyl derivatives. Jacobson only made a few monoacyl ureas in this way, and he did not use esters of unsaturated acids. He was unable to prepare disodium urea from a liquid ammonia solution of urea and metallic sodium.

The present work was undertaken to extend the study to the lithium derivatives of urea, in the hope that the reaction would go more smoothly and have a wider application. In the course of the work, the reactions of sodium urea were also investigated further.

Both mono-lithium and mono-sodium urea can be prepared in good yield by adding one equivalent of the metal to a liquid ammonia solution of urea. The salts can be isolated by allowing the liquid ammonia solutions to evaporate to dryness under anhydrous conditions. The salts so obtained are greyish white powders which are stable for months, in the absence of moisture.

Monolithium urea reacts readily, in general, with esters of monobasic acids. The reaction is best carried out by the procedure of Jacobson, using acetone as a solvent. Esters of aliphatic acids react slowly

with lithium urea under these conditions, and the reaction mixture must stand for several hours in order to get an appreciable yield of the acyl urea. Esters of aromatic acids, and of substituted aliphatic acids, such as chloroacetic, acetoacetic and malonic, react rapidly, and in some cases almost violently. Methyl esters seem to give better yields than ethyl, although this point was not investigated in detail. As will be seen from Table I, the yields vary considerably; although the methyl chloroacetate and methyl acetoacetate reacted rapidly with lithium urea, no crystalline product could be isolated.

TABLE I.—Acyl Ureas from Alkali Ureas.

Compound used	Urea used	Yield of Acyl Urea	M.p. of Acyl Urea	Speed of Reaction
Et butyrate	Li	34%	165-167	slow
Me butyrate	Li	40	165-167	"
Me stearate	Li	60	174-175	"
Me benzoate	Li	42	213-215	rapid
Et benzoate	Na	25	212	"
Me salicylate	Li	50	187-188	"
Me caproate	Li	10	183-184	slow
Me oleate	Li	50	160	"
Me phenylacetate	Li	10	213-215	"
Me chloroacetate	Li	none		rapid
Me cinnamate	Li	40	205-207	slow
Me crotonate	Li	13	225-227	rapid
Et acetoacetate	Li	none		"
Et acetoacetate	Na	10	112-114	"
Et phthalate	Li	15	227-229	very slow
Me succinate	Li	20	245-255	slow
Me adipate	Li	25	255-265	"
Et malonate	Li	low	210	rapid
Et malonate	Na	low	211	"
Benzyl chloride	Li	low	147-148	
Benzyl chloride	Na	low	147-148	
Benzoyl chloride	Li	none		
Benzoyl chloride	Na	none		
Benzenesulfonylchloride	Li	low	173-173	
Benzenesulfonylchloride	Na	none		

With esters of dibasic acids, mixtures of mono and diacyl derivatives were obtained, regardless of the proportions of reactants used, except in the case of malonic ester where barbituric acid was the only product isolated.

Although Jacobson showed that sodium urea reacted with benzoyl chloride in liquid ammonia solution, we were unable to obtain any appreciable reaction of either lithium or sodium urea with acid halides or benzyl chloride in benzene solution, even after prolonged boiling. A

small amount of product was obtained under these conditions with benzenesulfonyl chloride, but the reaction does not seem to have any preparative value.

Experimental

Mono-lithium urea. One-half mole of lithium (3.5 g.), cut in small pieces was added slowly to a solution of one-half mole of urea (30 g.), dissolved in 500 cc. of liquid ammonia. The solution acquired a dark blue color as the lithium was added, and this gradually disappeared as the metal was used up. Occasionally, when the reaction proceeded too slowly, a small crystal of ferric nitrate was added as a catalyst. When all the lithium had been added the mixture was stirred for thirty minutes, and was then allowed to stand overnight to evaporate the ammonia. The residual solid was then heated, under anhydrous conditions, over a water-bath to drive off any remaining ammonia vapor. It was stored in a vacuum desiccator over calcium chloride. The greyish-white powder so obtained melted at 179-182° C.

Analysis: Calculated for $\text{CH}_3\text{N}_2\text{OLi}$, Li, 10.6%.

Found, Li, 10.3%.

Sodium urea was made by the same process, and was found to melt rather indefinitely at 150-155° C.

Reaction with esters of monobasic acids. These were all carried out in the same general way. Ten grams (0.15 moles) of lithium urea was treated with 0.3 moles of the ester and 19 cc. of dry acetone. The mixture frequently became warm at this stage, and gradually turned brown and pasty. It was allowed to stand overnight, and was then diluted with water and acidified with dilute hydrochloric acid. The precipitate was collected and recrystallized from 95% alcohol in most instances.

Reaction with esters of dibasic acids. These reactions were carried out as described above, except that 0.15 moles of ester were used. In some cases the reactions were repeated using 0.075 moles of ester to 0.15 moles of lithium urea, but this had no effect on the melting points of the products obtained.

Reaction with halides. A mixture of 0.15 moles of alkali urea and 0.3 moles of halide in 100 cc. of dry benzene was refluxed over a steam bath for several hours. The benzene was decanted, and the white solid was dissolved or suspended in water and the solution made faintly acid with dilute hydrochloric acid. The solid obtained from the aqueous solution was recrystallized. Usually, evaporation of the benzene yielded no solid product.

Summary

Monolithium urea has been prepared by the action of lithium on a liquid ammonia solution of urea.

Lithium urea reacts with an excess of an ester of a monobasic acid, in the presence of acetone, to yield the corresponding monoacyl urea.

Lithium urea reacts with esters of dibasic acids to give, apparently, a mixture of the mono and diacyl ureas.

Lithium urea does not react to an appreciable extent with compounds containing reactive halogen atoms, in benzene solution.

Bibliography

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