Chemistry

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1962

SovietRxiv

Abstract

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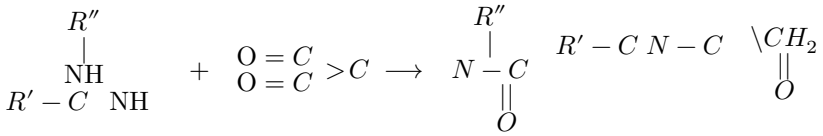
A Method for Preparing 1,2-Disubstituted 4,6-Dioxotetrahydropyrimidines

(Presented by Academician A. N. Nesmeyanov, January 22, 1962)

As the literature data show, malonyldichloride ([1]) and dialkyl diethyl malonates ([2,3]), reacting with unsubstituted amidines, can give low yields of 2-alkyl (or aryl)-5,5-dialkyl-(or diaryl)-4,6-dioxotetrahydropyrimidines.

Our previous works have shown that carbon suboxide, when there are groups in the reagent molecule equivalent in their basicity (for example, 2-aminopyridine ([4]), 2-aminothiazole and some of its substituted derivatives ([5])), enters into a cyclization reaction with formation of a 4,6-dioxopyrimidine ring. At first we carried out a series of experiments to study the interaction of carbon suboxide with amidines unsubstituted at the nitrogen atom. It proved that in this case the cyclization reaction does not occur, and the amidines with carbon suboxide give, according to a scheme analogous for most monoamines ([6–8]), N,N′-malonyl-bis-amidines. On the basis of the fact that N-substituted amidines possess imino and secondary-amino groupings, whose basicities are approximately the same, we decided to study the reaction of carbon suboxide with amidines of this kind. The reaction of carbon suboxide with N-substituted amidines proceeds in the cold and leads to satisfactory yields of the corresponding 1,2-disubstituted 4,6-dioxotetrahydropyrimidines:



The reaction is catalyzed by anhydrous aluminum trichloride and proceeds in anhydrous diethyl ether. As proof that the compounds obtained are 4,6-dioxotetrahydropyrimidines, their IR spectra were taken in the region of the intense band of the NH group (3200–3450 cm^{-1}). The absence of this band supports the fact that the products of the interaction of carbon suboxide with N-substituted amidines are 4,6-dioxotetrahydropyrimidines, since in other conceivable cases the presence of an NH band would be obligatory.

As a result of the interaction of carbon suboxide with N-phenylacetamidine (I), N-phenylphenacetamidine (II), N-phenylbenzamidine (III), N-*o*-tolylbenzamidine (IV), N-*p*-tolylbenzamidine (V), N-phenyl-*o*-toluamidine (VI), N-*p*-tolyl-*o*-toluamidine (VII), N-phenyl-*p*-toluamidine (VIII), N-*o*-tolyl-*p*-toluamidine (IX), and N-*p*-tolyl-*p*-toluamidine (X), respectively, the following were obtained: 1-phenyl-2-methyl-4,6-dioxotetrahydropyrimidine (XI), 1-phenyl-2-benzyl-4,6-dioxotetrahydropyrimidine (XII), 1,2-diphenyl-4,6-dioxotetrahydropyrimidine (XIII), 1-*o*-tolyl-2-phenyl-4,6-dioxotetrahydropyrimidine (XIV), 1-*p*-tolyl-2-phenyl-4,6-dioxotetrahydropyrimidine (XV), 1-phenyl-2-*o*-tolyl-4,6-dioxotetrahydropyrimidine (XVI), 1-*p*-tolyl-2-*o*-tolyl-4,6-dioxotetrahydropyrimidine (XVII), 1-phenyl-2-*p*-tolyl-4,6-dioxotetrahydropyrimidine (XVIII), 1-*o*-tolyl-2-*p*-tolyl-4,6-dioxotetrahydropyrimidine (XIX), and 1,2-di-*p*-tolyl-4,6-dioxotetrahydropyrimidine (XX).

For XI–XX, *p*-nitrobenzoyl derivatives were obtained, which indicates the existence of their monoenolic tautomeric forms. According to preliminary data, XI–XX possess biological activity and are inhibitors with respect to certain viruses. The reaction between carbon suboxide and I–X, obtained by known methods, proceeded uniformly. As an example we give the preparation of XIII.

1.0 g of III with m.p. 112–114° was dissolved in 50 ml of absolute diethyl ether, and several milligrams of anhydrous aluminum trichloride were added to the solution; the mixture was filtered, and the filtrate was gradually added to a vigorously stirred solution of a slight excess of carbon suboxide (ethereal solutions of carbon suboxide were prepared by the method described earlier ([9], [10]), and their concentration was determined by the anilide method ([11])). After about one third of the solution of III had been added, the reaction mixture took on the appearance of a milky-white emulsion, and toward the end of the addition small crystals appeared. The mixture was shaken for 30 min, allowed to stand for 1 hour, and the precipitated small white crystals were collected by suction on a Schott funnel. The yield of crude product was close to quantitative. For purification, the substance was dissolved in a small amount of hot chloroform, an equal volume of benzene was added, and the solution was evaporated on a boiling water bath until abundant crystallization appeared. After cooling, the precipitate was separated, washed with cold ether, and the purification operation was repeated 2 more times. XIII was then dried in a vacuum desiccator for several days. Yield of XIII about 75%. With the aid of *p*-nitrobenzoyl chloride, a *p*-nitrobenzoyl derivative with m.p. 194–195° (from ethanol) was obtained.

Table 1

Substance	Yield, %	M.p., °C	Formula	N, % found	N, % calc.	Mol. wt. found	Mol. wt. calc.
XI	58	260–261	$C_{11}H_{10}O_2N_2$	14.0	13.86	–	202.2

Substance	Yield, %	M.p., °C	Formula	N, % found	N, % calc.	Mol. wt. found	Mol. wt. calc.
XII	65	212–213	$C_{17}H_{14}O_2N_2$	10.00	10.06	275	278.28
XIII	75	212–213	$C_{16}H_{12}O_2N_2$	10.63	10.59	268	264.26
XIV	70	212–214	$C_{17}H_{14}O_2N_2$	10.11	10.06	284	278.28
XV	79	228–229	$C_{17}H_{14}O_2N_2$	9.83	10.06	272	278.28
XVI	80	246–247	$C_{17}H_{14}O_2N_2$	10.03	10.06	276	278.28
XVII	75	242–243	$C_{18}H_{16}O_2N_2$	9.32	9.57	295	292.31
XVIII	68	229–230	$C_{17}H_{14}O_2N_2$	10.24	10.06	279	278.28
XIX	63	234–235	$C_{18}H_{16}O_2N_2$	9.67	9.57	291	292.31
XX	60	230–231	$C_{18}H_{16}O_2N_2$	9.44	9.57	294	292.31

The yield, melting point, and chemical-analysis data for XI–XX are given in Table 1.

Leningrad Chemical-Pharmaceutical Institute

Received
15 I 1962

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Note: Figure translations are in progress. See original paper for figures.