DRUG SYNTHESIS METHODS AND MANUFACTURING TECHNOLOGY

4-IODOANTIPYRINE SYNTHESIZED BY MEANS OF SOLID-STATE MECHANICAL ACTIVATION

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Antipyrine and its benzenesulfonate were iodinated by solid-state mechanical activation (in the absence of solvent) under the action of iodine, iodine chloride, $Me_4N^+ICl_2^-$, and $Et_4N^+ICl_2^-$ with the formation of 4-iodoantipyrine. The proposed process does not require organic solvents and meets all Green Chemistry demands. The best results were achieved with the use of tetraalkylammonium salts $Me_4N^+ICl_2^-$ and $Et_4N^+ICl_2^-$.

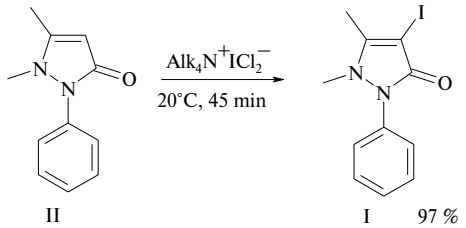
1-Phenyl-2,3-dimethyl-4-iodopyrazolone (4-iodoantipyrine, I) is a well-known drug possessing anti-inflammatory, interferon-inducing, and virus-neutralizing properties, which is also used in the radioactively labeled form [1, 2]. The wide use of this drug in the past decade is related to its unique effect in the prophylaxis and treatment of tick-borne encephalitis.

Traditional methods of the synthesis of 4-iodoantipyrine are based on the reaction of electrophilic iodination of antipyrine (II) in alcohol solutions, in particular, using iodine chloride or its complex salt $KICl_3$ [3, 4] or oxidative iodination systems [5]. One of the main trends in the development of modern organic synthesis is the search for new methods excluding the use of organic solvents [6]. This is a way to the new generation of technologies, which differ from the existing level by an increased ecological and technological safety and improved economic characteristics.

In the field of electrophilic iodination, there are very few examples of conducting reactions in the absence of solvents, under mechanical activation (MA) conditions. Recently, it was reported that the iodination of arenes without solvents was performed using reactants such as Me_4NINl_2 or metallic iodine in the presence of bismuth nitrate [7, 8]. Previously, we have studied the preparative potential of the well-known agents of electrophilic iodination such as ICl, N-iodosuccinimide, and iodophenyliodosodiacetate under MA conditions in the absence of solvents. It was concluded that solid-state methods offer a promising approach to the synthesis of iodinated arenes.

The aim of this investigation was to check for the possibility of iodinating antipyrine under MA conditions in the absence of solvents, using iodine (III), iodine chloride (IV), and complex iodine chloride salts $Me_4N^+ICl_2^-$ (V) and $Et_4N^+ICl_2^-$ (VI). Another goal was to use these data for the development of a convenient, ecologically safe method for the synthesis of 4-iodoantipyrine.

We have established for the first time that antipyrine (II) interacting with complex iodine chloride salts V and VI at room temperature in the absence of solvents is converted within a short time into 4-iodoantipyrine (I). When compound V (in contrast to VI) is used as the iodination agent, it is necessary to add 0.1 ml water to the reaction mass in order to ensure the complete conversion of the initial substrate (see Table 1).



Alk = Me (for V), Et (for VI)

Iodine chloride (IV) under MA conditions in the absence of solvents also produced iodination of antipyrine (II), but the process was accompanied by strong caking of the reac-

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tion mass, which was apparently the reason for incomplete conversion of the initial substrate even for prolonged (24 h) process duration (final yield, 63%). Low conversion of the initial substrate was also observed in the case where I_2 was used as the iodination agent, which was probably related to the weak electrophilicity of metallic iodine.

Thus, we have demonstrated for the first time the principal possibility of iodinating antipyrine under MA conditions in the absence of solvents under the action of iodine, iodine chloride, and its complex ammonium salts. The best iodination results are obtained with the complex iodine chloride salts V and VI, which ensured an almost quantitative yield of the target product (I).

The activity of the aforementioned iodination agents was also manifested in their reactions with antipyrine benzenesulfonate (VII). In this case, the alkylammonium reactants V and VI ensured the yield of 4-iodoantipyrine to a level of 82 – 88%. At the same time, the iodination of substrate VII under the action of agents III and IV proceeded with a yield of 44 and 50%, respectively.

The well-known methods of liquid-phase iodination of antipyrine involve certain technological operations in the stage of isolation and purification of the technical-purity product. These operations involve alkalinization of the reaction mass with sodium hydroxide (pH 9 – 10) and recrystallization from an appropriate organic solvent (usually, ethanol) [3, 4]. In this investigation, we used a more ecologically safe and cheaper alkali (sodium hydrocarbonate) and recrystallized the technical-purity product I from water.

Thus, we showed that antipyrine (II) can be iodinated under the action of complex iodine chloride salts V and VI under mild MA conditions in the absence of solvents into 4-iodoantipyrine with high (quantitative) yields. The proposed method of iodination, based on the solid-state process, fully excludes the use of organic solvents in all stages of synthesis. This shows a considerable advantage over traditional liquid-phase methods, and offers a yet rare example of such approach in practical organic synthesis.

EXPERIMENTAL PART

The course of the reactions was monitored and the purity of the target products was checked by TLC on Sorbfil PTsKh-P-A-UF plates eluted with a benzene – ethanol (8 : 2) mixture and developed by exposure to the UV light.

The ^1H and ^{13}C NMR spectra were recorded on a Bruker AC-300 (300 Mhz) spectrometer using TMS as the internal standard (for solvents, see the text below).

Tetramethylammonium iodide chloride (V). To 6.5 g of a 64% aqueous solution of tetramethylammonium chloride was added a mixture of 6.13 g (38 mmole) of iodine chloride with 5 ml of a 35% hydrochloric acid solution. The instantly formed yellow precipitate of tetramethylammonium iodide chloride was separated by filtration, washed sequentially on the filter (i) with a small amount of water and (ii) with ether, and dried at 50°C to obtain 8.55 g (83%) of a technical-purity product V in the form of a yellow crystalline powder; m.p., 210 – 212°C (published m.p., 198°C [7]); ^1H NMR spectrum in acetonuitrile-d_6 (δ, ppm): 3.1 (s, 12H, CH_3); ^{13}C NMR spectrum in acetonuitrile-d_6 (δ, ppm): 54.7.

Tetraethylammonium iodide chloride (VI) was obtained using a procedure analogous to that described above. Product VI is obtained in the form of a yellow crystalline powder; yield, 80%; m.p., 98 – 100°C (published m.p., 101 – 103°C [10]); ^1H NMR spectrum in acetonuitrile-d_6 (δ, ppm): 3.16 (q, 8H, CH_2), 1.2 (tt, 12H, CH_3); ^{13}C NMR spectrum in acetonitrile-d_6 (δ, ppm): 53.1, 7.6.

General method of iodination of antipyrine (II). A mixture of antipyrine (0.19 g, 1 mmole) and iodination agent VI (0.39 g, 1.2 mmole) was triturated in an agate mortar for 15 min and allowed to react for 30 min. To this mixture was added 60 ml of water and 0.12 g (1.4 mmole) of sodium hydrocarbonate, and the suspension was boiled for 15 min (until complete dissolution of the solid phase) and cooled (if necessary, sodium chloride is added). The precipitate was separated by filtration, washed on the filter with cold water, and dried to obtain 0.30 g (97%) of product I in the form of a white crystals; m.p., 160 – 161°C (published m.p., 160 – 161°C [12]); ^1H NMR spectrum in $CDCL_3$ (δ, ppm): 2.28 (s, 3H, CH_3); 3.08 (s, 3H, CH_3), 7.24 – 7.42 (m, 5H, C_6H_5); ^{13}C NMR spectrum in $CDCl_3$ (δ, ppm): 14.68, 36.57, 60.97, 124.0, 126.88, 129.12, 134.9, 157.45, 163.82.

General method of iodination of antipyrine benzenesulfonate (VII). A mixture of antipyrine benzenesulfonate (0.36 g, 1 mmole) and iodination agent VI (0.39 g, 1.2 mmole) was triturated in an agate mortar for 15 min and allowed to react for 30 min. To this mixture was added 60 ml of water and 0.20 g (2.4 mmole) of sodium hydrocarbonate, and the mixture was heated until complete dissolution of the solid phase and cooled (if necessary, sodium chloride is added). The precipitate crystals were separated by filtration, washed on the filter with cold water, and dried to obtain 0.28 g (88%) of product I; m.p., 160 – 161°C (published m.p., 160 – 161°C [11]).

TABLE 1. Iodination of Antipyrine with Various Reactants under MA Conditions in the Absence of Solvents for 45 min at 20°C at a Substrate/Reactant Ratio of 1 : 1.2

Substrate	Reactant	Yield of I, %
II	VI	97
VII	VI	88
II	V	96*
VII	V	82
II	IV	63
VII	IV	50
II	III	57
VII	III	44

* With addition of water.

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