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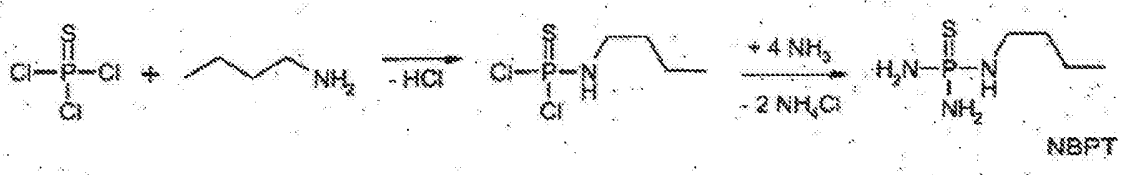
(54) **Eljárás aszimmetrikus (tio)foszforsavtriamidok előállítására**

Method for producing asymmetric (thio)phosphate triamides

The present invention relates to a method for preparing asymmetric (thio)phosphoric triamides from (thio)phosphoric trichloride and primary amines and ammonia.

Asymmetric (thio)phosphoric triamides, particularly N-(n-butyl)thiophosphoric triamide (NBPT), are inhibitors of the near ubiquitous enzyme urease, and are added as stabilizers to urea-containing fertilizers which would otherwise, due to urease, suffer decomposition to ammonia and carbon dioxide and thereby premature loss of efficacy (see e.g. EP0119487). Further applications are, for example, the stabilization of manure with respect to urease-dependent degradation of the urea present, described in WO 2000/061522, and also the addition to toiletries and hygiene articles to reduce odour nuisance in the sanitary sector according to WO 2008/022925 and WO 2008/022919.

The synthesis of NBPT (and related compounds) was first described in *Goehring et al.*, Chem. Ber. **1956**, *89*, 1760, in which n-butylammonium chloride was refluxed with a large excess of thiophosphoric trichloride, the N-butylthiophosphoric dichlorodiamide formed was isolated by fractional distillation and reacted with excess condensed ammonia. To isolate the pure substance, the solubility of the ammonium chloride occurring as by-product in the liquid ammonia was utilized.



Disadvantages of the technical implementation of this synthesis are the large excesses of (thio)phosphoric trichloride and ammonia (ca. 40 equivalents), which necessitate complex purification and recycling operations since disposal as waste would be uneconomic. Owing to the high toxicity and corrosivity of gaseous hydrogen chloride and (thio)phosphoric trichloride, a suitable plant ought to consist predominantly of special materials which withstand these compounds, even at reflux temperature.

A continuous industrial process for preparing NBPT and similar compounds is therefore proposed in WO 1998/031693 (cf. also WO 1998/031692 and WO 1998/013691) which avoids the major problems of the above preparation route. For this purpose, the reaction steps described above are operated continuously in an organic solvent in two reactors connected in succession, where the intermediate is not isolated and the reaction mixture from the first step is reacted in the second step with at least 16, preferably at least 20 eq. of ammonia. In the first step, which is preferably conducted at 0 to 15°C, a tertiary amine, for example a pyridine derivative or a trialkylamine, serves as auxiliary base which is recovered and recycled. To avoid removing ammonium chloride as a solid, this method uses the solubility of ammonium chloride in liquid ammonia as already described in *Goehring et al.* Part of the large excess of ammonia is reliquefied by vapour compression and cooling and fed back into the process. The auxiliary base and the solvent are separated from the product by distillation and likewise fed back into the process. The product is obtained in high yield of ca. 90-92.4% but only at a purity of 92.4 to 93.3%. The ammonia/ammonium chloride phase obtained in large amounts is dissolved in water and has to be cost-intensively processed. This method has the disadvantage – in addition to the low, often unsatisfactory product purity – that it cannot be implemented in customary multi-purpose plants due to implementation at 8-15°C and at elevated pressure (up to ca. 7 bar), but rather it requires an individually constructed, pressure-tight production plant and, because of the high process technology cost and the complexity of the plant required, high initial investments arise which are only amortized in the case of very high production amounts. The resulting large amount of ammoniacal ammonium chloride solution also necessitates a suitable disposal or processing route.

WO 2010/045895 describes a process for preparing the compounds specified, including NBPT, which may be carried out in standard apparatuses in a batch process, which consists of reacting two equivalents of the amine with (thio)phosphoric trichloride at room temperature in a non-polar organic solvent, preferably toluene, wherein the second equivalent binds the molecule of hydrogen chloride formed as the ammonium salt, which precipitates and is filtered off. The filtrate is then further reacted at 0°C with a large excess (ca. 15 eq.) of ammonia (liquid) or at room

temperature under pressure with an excess of ammonia (gaseous) to form the product, which partially precipitates, as does the ammonium chloride produced.

For the removal thereof, the reaction mixture is heated to 50 – 80°C, whereupon the product goes into solution and the ammonium chloride is filtered off. On cooling the filtrate, the product precipitates and may be filtered off. In order to achieve a commercially useful NBPT having a purity of >99%, the product must be repeatedly recrystallized usually from toluene. The yields stated for the crude product are 80-84% and for the recrystallized product 68% to 71% of theory (purification losses ca. 15%) at a batch size of 25 mmol, while at a batch scale-up to 2.05 mol the crude yield decreases to only 70%. In the industrial conversion, this method has the disadvantage, in addition to the low yield, that at least four solid separation steps by filtration are required in order to obtain a sufficiently pure product, which requires a very complex plant setup. This in turn results in high manufacturing costs. The use of toluene as solvent also leads to long drying times owing to the low melting point of NBPT.

WO 2007/054392 describes a preparation method in which, similar to that of WO 1998/031693, thiophosphoric trichloride is reacted with n-butylamine at 30°C in a polar organic solvent in the presence of an auxiliary base (e.g. tri-n-butylamine) and the product mixture is then reacted at 0°C with ammonia. For the work-up, the precipitated ammonium chloride is firstly dissolved in a sufficient amount of water, the homogeneous organic phase is separated and the solvent removed by distillation such that an organic biphasic system of liquid product phase and auxiliary base is formed which are immiscible with each other. The product phase is separated and precipitated by placing in water. The yield is 66% of theoretical yield of NBPT at a purity of only 76%. The reaction can be conducted batchwise or (semi-)continuously. This method, however, has the disadvantages of a low yield and a very low purity of the isolated product such that further purification steps are generally required in order to obtain a marketable product.

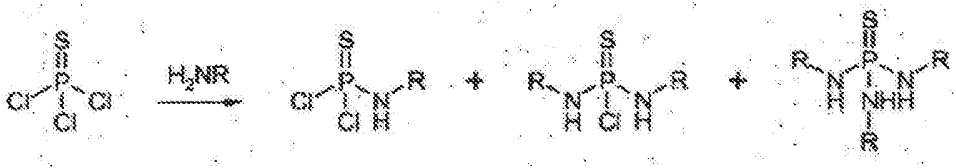
WO 2009/121786 discloses a method for preparing asymmetric thiophosphoric amides including NBPT starting from N-(n-alkyl)thiophosphoric dichloride which is characterized in that particularly few by-products are formed. This was achieved by

cooling the N-(n-alkyl)thiophosphoric dichloride as a solution to below 0°C and mixing in the shortest possible time with a similarly cooled excess of liquid ammonia (10 or 20 eq.) without backmixing such that no reaction takes place during the mixing. After mixing, the reaction mixture, via a tubular reactor, preferably a heat exchanger, was fed into a column which separated the reaction mixture. Overall yields between ca. 85% and 96.4% were specified for substance mixtures of NBPT with N-propylthiophosphoric triamide (likewise a urease inhibitor) where the maximum yield of NBPT was 70.5%. The process can be operated continuously or batchwise.

However, this method also requires an individually constructed, pressure-tight production plant having specific devices in order to ensure mixing of the reactants without backmixing. In addition, the method is designed for the preparation of substance mixtures and significantly excess amounts of 10 to 20 eq. of ammonia are required.

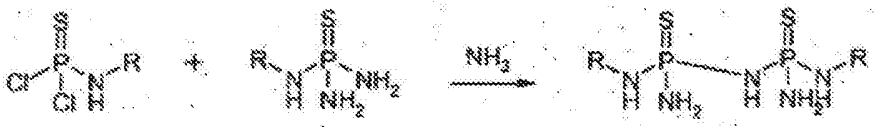
Therefore, all of the above methods have one or more disadvantages, to the effect that special plants of high complexity or highly elevated pressure resistance are required, highly contaminated crude products are obtained requiring very laborious purification, low yields of NBPT are obtained or large excesses of ammonia are required, particularly when using the same as co-solvent.

The low yields and poor product purities in the methods described are due in part to a low selectivity, especially in the first stage, in which, in addition to both the desired monoamide or diamide of the (thio)phosphoric acid, the undesired diamide or monoamide and also the triamide of the (thio)phosphoric acid are also formed in each case.



However, the by-products are formed to an even greater degree in the second stage, in which the monoamide or diamide formed in the first step can react with the triamide of the (thio)phosphoric acid, whereby dimeric and oligomeric (partly by subsequent

reactions with primary amine or ammonia and also phosphazene-like) by-products are formed (cf. also WO 2009/121786), e.g. according to the scheme below:



WO 2009/121786 evades this problem by means of complex technical measures by reacting the (thio)phosphoric dichloroamide with ammonia in a very short time without backmixing in a special plant in the continuous reaction proposed, in which the concentration of the (thio)phosphoric dichloroamide is kept very low. However, this is accompanied by the disadvantages already mentioned above.

A need therefore exists for a method for preparing asymmetric (thio)phosphoric triamides, particularly NBPT, which provides these substances in good yields, high purity and high space-time yields and can also be implemented with only minor adjustment in terms of apparatus to the customary multipurpose stirred tank plants in the fine chemical industry, ideally without the necessity of elevated pressures and large excesses of ammonia.

The object of the present invention, therefore, was to provide a method which can be carried out in conventional stirred tank-based typically fine chemical multipurpose plants, which in contrast to the prior art documented above is capable of affording asymmetric (thio)phosphoric triamides, particularly NBPT, in good yields and purities, without inconvenient purification steps (e.g. repeated recrystallization) or continuously operating special reactors being required, where particularly large excesses of ammonia should be avoided.

It has now been found, surprisingly, that in the reaction in the specified temperature range, the secondary reactions of the second stage can be largely suppressed, and the reaction of the (thio)phosphoric amidodichloride and/or (thio)phosphoric diamidomonochloride with ammonia still proceeds with an excellent space-time yield.

The object of the invention was achieved by a method for preparing asymmetric (thio)phosphoric triamides by reacting a primary amine with (thio)phosphoric

trichloride to give the corresponding (thio)phosphoric amidodichloride and/or (thio)phosphoric diamidomonochloride and subsequent reaction of the (thio)phosphoric amidodichloride or (thio)phosphoric diamidomonochloride formed with ammonia characterized in that the reaction of the (thio)phosphoric amidodichloride and/or (thio)phosphoric diamidomonochloride with ammonia is carried out at least partly, mainly, substantially or completely at a temperature below -30°C, preferably in the range of -80°C to -32°C, particularly preferably in the range of -60°C to -35°C and especially preferably in the range of -55°C to -40°C. The method according to the invention is carried out as a one-pot variant, i.e. the reaction of the primary amine with (thio)phosphoric trichloride to give the corresponding (thio)phosphoric amidodichloride and/or (thio)phosphoric diamidomonochloride and the subsequent reaction of the (thio)phosphoric amidodichloride or (thio)phosphoric diamidomonochloride formed with ammonia are carried out sequentially in the same reaction vessel, and the (thio)phosphoric amidodichloride and/or (thio)phosphoric diamidomonochloride obtained by reacting a primary amine with (thio)phosphoric trichloride is not isolated. At least partial implementation of the reaction is here understood to mean a reaction with ammonia of at least 20%, mainly is understood to mean at least 50% and substantially to mean at least 90%, of the acid chloride groups of (thio)phosphoric amidodichloride and (thio)phosphoric diamidomonochloride present at the start of the ammonia addition.

In the context of this application, the partial term (thio)phosphoric can be interpreted either as thiophosphoric or as phosphoric. The preferred interpretation is thiophosphoric. In the context of the present invention, asymmetric (thio)phosphoric triamides are understood to mean thiophosphoric triamides or phosphoric triamides in which the phosphorus atom bears two NH_2 groups and one NHR group or one NH_2 group and two NHR groups, where R is an organic residue. Since a mixture of thiophosphoric triamides or phosphoric triamides having one or two NHR groups on the phosphorus atom is also obtained, depending on the selection of the amounts used of primary amine and (thio)phosphoric trichloride, such mixtures also fall under the definition of asymmetric (thio)phosphoric triamides.

In a preferred embodiment, the present invention relates to the preparation of asymmetric (thio)phosphoric triamides by reacting a primary amine with (thio)phosphoric trichloride to give the corresponding (thio)phosphoric amidodichloride and subsequent reaction of the same with ammonia to give the asymmetric (thio)phosphoric triamide.

Particular preference is given to the preparation of thiophosphoric triamides by reacting a primary amine with thiophosphoric trichloride to give the corresponding thiophosphoric amidodichloride and subsequent reaction of the same with ammonia.

The primary amine used for the present method corresponds to the formula R-NH_2, where R is an organic residue, preferably an unsubstituted alkyl, cycloalkyl, aryl or heteroaryl residue or an alkyl, cycloalkyl, aryl or heteroaryl residue substituted with one or more groups inert under the reaction conditions. The alkyl, cycloalkyl, aryl or heteroaryl residue is preferably a C_1-C_{18} alkyl, C_3-C_{12} cycloalkyl, C_6-C_{14} aryl or C_4-C_{13} heteroaryl residue, particularly preferably a C_1-C_{10} alkyl residue, especially preferably an unsubstituted C_1-C_6 alkyl residue and most preferably n-butyl. Preferred inert groups are alkyl, aryl, heteroaryl, alkoxy, aryloxy, heteroaryloxy, alkylthio, arylthio, heteroarylthio, fluorine, chlorine, bromine, cyano, particularly preferably C_1-C_{18} alkyl, C_6-C_{14} aryl, C_4-C_{13} heteroaryl, C_1-C_{18} alkoxy, C_6-C_{14} aryloxy, C_4-C_{13} heteroaryloxy, C_1-C_{18} alkylthio, C_6-C_{14} arylthio, C_4-C_{13} heteroarylthio, fluorine, chlorine, bromine, cyano and especially preferably C_1-C_8 alkyl, C_6-C_{10} aryl, C_4-C_9 heteroaryl, C_1-C_8 alkoxy, C_6-C_{10} aryloxy, C_4-C_9 heteroaryloxy, C_1-C_8 alkylthio, C_6-C_{10} arylthio, C_4-C_9 heteroarylthio, fluorine, chlorine, bromine and cyano.

To prepare (thio)phosphoric amidodichloride using the present method, the primary amine is used preferably in an amount of 0.8 to 1.2, particularly preferably 0.98 to 1.05 equivalents and especially preferably 1 equivalent. To prepare (thio)phosphoric diamidomonochloride on the other hand, the primary amine is used preferably in an amount of 1.8 to 2.2, particularly preferably 1.96 to 2.1 equivalents and especially preferably 2 equivalents, based on (thio)phosphoric trichloride.

The reaction of the primary amine with (thio)phosphoric trichloride preferably takes place in the presence of an auxiliary base in order to bind the hydrogen chloride formed during the reaction. A tertiary amine preferably serves as auxiliary base, particularly preferably a tertiary trialkylamine, N-alkylpyrrolidine, N-alkylpiperidine, N-alkylmorpholine, dialkylaniline, a pyridine or a polycyclic tertiary amine with a heterocyclic structure such as DABCO, DBU or quinuclidine.

To synthesize (thio)phosphoric amidodichloride, the auxiliary base in the present method is advantageously used in an amount of 0.7 to 10, preferably 0.8 to 2, particularly preferably 0.98 to 1.2 equivalents and especially preferably of exactly 1 equivalent, and to synthesize (thio)phosphoric diamidomonochloride in an amount of 1.6 to 10, preferably 1.8 to 4, particularly preferably 1.96 to 2.4 equivalents and especially preferably exactly 2 equivalents, based on (thio)phosphoric trichloride.

Due to the particularly smooth course of the reaction in the conversion to (thio)phosphoric triamide in the temperature range mentioned above, it is sufficient to use not more than 10 equivalents, preferably not more than 8 equivalents of ammonia, based on (thio)phosphoric triamide. The use of larger amounts of ammonia is evidently possible, but usually not very attractive for ecological and economic reasons. The minimum amount of ammonia is apparent to those skilled in the art from the number of amide groups to be introduced and the binding of the resulting hydrogen chloride.

It is also possible to initially charge (thio)phosphoric amidodichloride and/or (thio)phosphoric diamidomonochloride or a reaction mixture comprising at least one of these compounds and to add ammonia, i.e. to operate the start of the reaction with a deficiency of ammonia.

The low reaction temperature in the reaction with ammonia also allows the method to be carried out at a low absolute pressure of less than 3, preferably in the range of 0.3 to 2 bar, especially preferably in the range of 0.8 to 1.5 bar. In a very particularly preferred from, the method is carried out "unpressurized", i.e. at atmospheric pressure.

In the present method, the reaction of the primary amine with (thio)phosphoric trichloride and/or the reaction of the (thio)phosphoric amidodichloride and/or (thio)phosphoric diamidomonochloride with ammonia is typically carried out in a polar aprotic organic solvent or solvent mixture which preferably comprises one or more of the following solvents or consists of these: ethyl acetate, propyl acetate, isopropyl acetate, butyl acetate, isobutyl acetate, tetrahydrofuran, 2-methyltetrahydrofuran, 1,4-dioxane, diethyl ether, diisopropyl ether, di-n-propyl ether, di-n-butyl ether, methyl tert-butyl ether, diisobutyl ether, dimethoxyethane, acetone or methyl isobutyl ketone.

The amount of solvent is selected advantageously so that the reaction mixture can be readily stirred at the reaction temperature but is not unnecessarily diluted. It is dependent on the nature of the starting materials and the type of solvent selected. In a preferred embodiment, the organic solvent or solvent mixture is used in such an amount that the concentration of (thio)phosphoric trichloride at the start of the reaction with the primary amine is in the range of 0.5 to 5 mol/kg.

Astonishingly, it has also been revealed that the first step in the present method, i.e. the reaction of the primary organic amine with (thio)phosphoric trichloride, proceeds at a very low temperature with very high selectivity such that the target compound ultimately obtained is also formed in high yield and purity in conventional batch mode.

The reaction of the primary amine with (thio)phosphoric trichloride is therefore preferably carried out partly, mainly, substantially or completely at a temperature below -20°C, preferably in the range of -80°C to -25, particularly preferably in the range of -50°C to less than -30°C. Partial implementation of the reaction is here understood to mean a conversion of at least 20 mol%, mainly is understood to mean at least 50 mol% and substantially to mean at least 90 mol% of the (thio)phosphoric trichloride.

For the work-up of the product mixtures comprising the asymmetric (thio)phosphoric triamides, the ammonium salts formed in the reaction can be removed from the reaction mixture by filtration or aqueous extraction. An extraction is preferably carried

out where particular preference is given to using the minimum amount of water required to dissolve the ammonium salts.

In an advantageous embodiment, (thio)phosphoric triamide is precipitated from the product mixture. The precipitation is typically done by adjusting the concentration of (thio)phosphoric triamide in the product mixture, either by dilution or concentration, preferably by removing some of the reaction solvent by distillation, and optionally by addition of a non-polar antisolvent consisting of or comprising one or more unbranched, branched or cyclic hydrocarbons, particularly preferably an alkane or alkane mixture, especially preferably pentane, hexane, heptane, cyclohexane, isohexane, isooctane (2,2,4-trimethylpentane) or petroleum ether or mixtures thereof, whereupon the product can be isolated by filtration. In this form of the purification, the intermediate isolation of the crude product can be omitted and (thio)phosphoric triamide can be obtained at a purity of >95%, preferably >97% and particularly preferably >98%.

At standard pressure the antisolvent preferably has a boiling point of less than 120°C, particularly preferably less than 90°C, especially preferably less than 70°C, to enable short drying times of the moist product isolated and to allow a simple removal by distillation of the reaction solvent and recycling into the process. With preference, either a) the antisolvent at a temperature in the range of <0°C to 60°C, preferably in the range of 50°C to 60°C, is added to the reaction mixture and then cooled to 0°C to 30°C, or b) the reaction mixture at a temperature in the range of 0°C to 60°C, preferably at 15°C to 35°C, is added to the antisolvent and the mixture then maintained at a temperature of 0°C to 30°C. The final temperature is preferably 15°C to 25°C in both cases. Variant a) is preferred if the asymmetric (thio)phosphoric triamide is to be isolated by means of a centrifuge and variant b) is preferred if isolation is by means of a suction filter.

In an advantageous configuration of the invention, the solvent and/or the antisolvent used for the precipitation is recovered and again fed into the process. The solvent is preferably recovered by distillation which is also effected in part or completely in the context of the increase in the product concentration by distillation, whereas in the

distillation of the mother liquors and filtrate washes in the product isolation an at least partial recovery of the solvent and/or antisolvent can also be effected. As an alternative, distillates, mother liquors and filtrate washes having a positive energy balance can be utilized thermally.

The auxiliary base can be recovered and fed again into the process. The recovery is preferably effected by distillation in the context of the recycling of the solvent and antisolvent and/or in the work-up of the aqueous extracts.

In contrast to the prior art documented above, the method described has the advantage of being able to be conducted at or virtually at standard pressure, i.e. of requiring no special apparatus, but rather of being able to be carried out in standard batch tank systems customary in the fine chemical industry without major adjustments to the configuration being necessary. In this case, the products can be obtained in good yields, high purities and high space-time yields at comparatively low excesses of ammonia.

Examples

The present method is illustrated by means of the examples below without being restricted to them.

Examples 1 to 4:

Preparation of NBPT at different temperatures:

1 eq. of thiophosphoric trichloride was dissolved in dry ethyl acetate with exclusion of air and moisture and the resulting solution was cooled to the lower limit of the specified temperature range. By addition of 1 eq. of triethylamine with stirring a yellow suspension was formed. Subsequently, 1 eq. of n-butylamine was metered in with stirring such that the temperature of the reaction mixture remained in the stated range. After the end of the reaction, 9.99 eq. of ammonia were introduced such that the temperature of the reaction mixture remained in the stated range. The white suspension

obtained was stirred for 1 h, the temperature then slowly increased to 10°C whereupon excess dissolved ammonia escaped as a gas. The reaction mixture was quenched with 35 eq. of water, the aqueous phase was separated, the organic phase washed with water and concentrated to dryness on a rotary evaporator. The purities determined by HPLC (w/w) and the yields corrected for purity are given in Table 1.

Table 1

Example	Temperature range	Crude product purity	Yield
1*	-13 to -5°C	74%	61%
2*	-25 to -18°C	81%	73%
3	-40 to -35°C	91%	89%
4	-55 to -50°C	91%	89%

*non-inventive

Example 5:

Preparation of NBPT and precipitation of the product by addition of an antisolvent

100 g of thiophosphoric trichloride were dissolved in 343.6 g of dry ethyl acetate with exclusion of air and moisture and the resulting solution was cooled to -50°C. By addition of 59.7 g of triethylamine with stirring a yellow suspension was formed and then 42.5 g of n-butylamine were metered in such that the temperature of the reaction mixture remained in the range of -50°C to -40°C. After the end of the reaction, 98.5 g of ammonia (9.99 eq.) were introduced with stirring such that the temperature of the reaction mixture remained in the range of -40 to -50°C. The white suspension obtained was stirred for 1 h at -50°C, the temperature was then slowly increased to 10°C whereupon excess dissolved ammonia escaped as a gas. The reaction mixture was quenched with 269.9 g of water and the aqueous phase was separated. The organic phase was washed with 50 g of water and the combined aqueous phases back-extracted twice with 100 g of ethyl acetate each time. The combined organic phases were freed from solvent by distillation under reduced pressure at <50°C until a ca. 50% solution of NBPT remained in the bottom. 125 g of hexane were added at a temperature of

40°C and the mixture was slowly cooled with stirring whereupon the product crystallized as needles. The mixture was further cooled to 10°C, the precipitated crystals were filtered off under suction on a suction filter and washed twice with 50 g of cold hexane each time. The filter cake was dried at room temperature under vacuum. The NBPT isolated was obtained at a purity of 98.7% and the yield was 85.7% of theory.

Example 6:

Preparation of NBPT using a reduced amount of ammonia

The method was carried out analogously to Example 5 but using only 78.8 g of ammonia (7.99 eq.) The NBPT isolated was obtained at a purity of >99.9% and the yield was 81.3% of theory.

Example 7:

Preparation of NBPT with anhydrous work-up

The method was carried out analogously to Example 6 but replacing the extractive work-up by filtering the precipitated ammonium salts from the reaction mixture followed by washing the filter residue with ethyl acetate. The NBPT isolated was obtained at a purity of 99.8% and the yield was 82.5% of theory.

Example 8:

Preparation of NBPT at elevated concentration

The method was carried out analogously to Example 6 but using only 300.6 g of ethyl acetate as solvent. The NBPT isolated was obtained at a purity of 98.0% and the yield was 79.7% of theory.

Szabadalmi igénypontok

1. Eljárás aszimmetrikus (tio)foszforsavtriamidok előállítására egy primer amin és (tio)foszforsavtriklorid reagáltatásával a megfelelő (tio)foszforsavamidodiklorid és/vagy (tio)foszforsavdiamidoklorid előállítása és ezt követően a képződött (tio)foszforsavamidodiklorid és/vagy (tio)foszforsavdiamidoklorid ammóniával való reagáltatása útján, **azzal jellemezve, hogy** a megfelelő (tio)foszforsavamidodiklorid és/vagy (tio)foszforsavdiamidoklorid előállítására a primer amin és (tio)foszforsavtriklorid reagáltatását és ezt követően a (tio)foszforsavamidodiklorid és/vagy (tio)foszforsavdiamidoklorid ammóniával való reagáltatását egyedényes változatként hajtjuk végre, továbbá hogy a (tio)foszforsavamidodiklorid és/vagy (tio)foszforsavdiamidoklorid ammóniával való reagáltatását részben, főleg vagy teljesen -30°C alatti, előnyösen -80°C és -32°C közötti, különösen előnyösen -60°C és -35°C közötti és a leginkább előnyösen -55°C és -40°C közötti hőmérsékleten végezzük, és hogy a (tio)foszforsavamidodikloridot és/vagy (tio)foszforsavdiamidokloridot nem különítjük el.

2. Az 1. igénypont szerinti eljárás, **azzal jellemezve, hogy** a primer amin az $R\text{-}NH_2$ képletnek felel meg, ahol R jelentése helyettesítetlen alkil-, cikloalkil-, aril- vagy heteroarilcsoport vagy olyan alkil-, cikloalkil-, aril- vagy heteroarilcsoport, amely helyettesítve van alkil-, aril-, heteroaril-, alkoxi-, ariloxi-, heteroariloxi-, alkiltio-, ariltio-, heteroariltio- vagy cianocsoporttal vagy fluor-, klór- vagy brómatommal, előnyösen C_1-C_{18} alkil-, C_6-C_{14} aril-, C_4-C_{13} heteroaril-, C_1-C_{18} alkoxi-, C_6-C_{14} ariloxi-, C_4-C_{13} heteroariloxi-, C_1-C_{18} alkiltio-, C_6-C_{14} ariltio-, C_4-C_{13} heteroariltio- vagy cianocsoporttal vagy fluor-, klór- vagy brómatommal, különösen előnyösen C_1-C_8 alkil-, C_5-C_{10} aril-, C_4-C_9 heteroaril-, C_1-C_8 alkoxi-, C_6-C_{10} ariloxi-, C_4-C_9 heteroariloxi-, C_1-C_8 alkiltio-, C_6-C_{10} ariltio-, C_4-C_9 heteroariltio- vagy cianocsoporttal vagy fluor-, klór- vagy brómatommal, és jelentése előnyösen C_1-C_{18} alkil-, C_3-C_{12} cikloalkil-, C_6-C_{14} aril- vagy C_4-C_{13} heteroarilcsoport, különösen előnyösen C_1-C_{10} alkilcsoport, méginkább előnyösen helyettesítetlen C_1-C_6 alkilcsoport és a leginkább előnyösen n-butilcsoport.

3. Az előző igénypontok bármelyike szerinti eljárás, **azzal jellemezve, hogy** a primer amin (tio)foszforsavtrikloriddal való reagáltatását segédanyagként egy bázis, előnyösen egy tercier amin, különösen előnyösen egy tercier trialkilamin, N-alkilpirrolidin, N-alkilpiperidin, N-alkilmorfolin, dialkilanilin, piridin vagy egy heterociklusos szerkezetű policiklusos tercier amin, például DABCO, DBU vagy kinuklidin jelenlétében hajtjuk végre.

4. Az előző igénypontok bármelyike szerinti eljárás, **azzal jellemezve, hogy** a (tio)foszforsavtriamidra vonatkoztatva legfeljebb 10 ekvivalens, előnyösen legfeljebb 8 ekvivalens ammóniát használunk.

5. Az előző igénypontok bármelyike szerinti eljárás, **azzal jellemezve, hogy** az ammóniával való reagáltatást 3 barnál kisebb, előnyösen 0,5 bar és 2 bar és különösen előnyösen 0,8 bar és 1,5 bar közötti abszolút nyomáson hajtjuk végre.

6. Az előző igénypontok bármelyike szerinti eljárás, **azzal jellemezve, hogy** a primer amin (tio)foszforsavtrikloriddal való reagáltatását és/vagy a (tio)foszforsavamidodiklorid és/vagy (tio)foszforsavdiamidoklorid ammóniával való reagáltatását egy poláros aprotikus szerves oldószerben vagy olyan oldószerelegyben hajtjuk végre, amely a következőkben felsorolt oldószerek közül egyből vagy többből áll: etilacetát, propilacetát, izopropilacetát, butilacetát, izobutilacetát, tetrahidrofurán, 2-metiltetrahidrofurán, 1,4-dioxán, dietiléter,

diizopropiléter, di-n-propiléter, di-n-butiléter, metil-terc-butil-éter, diizobutiléter, dimetoxietán, aceton és metil-izobutil-keton.

7. Az előző igénypontok bármelyike szerinti eljárás, **azzal jellemezve, hogy** a primer amin (tio)foszforsavtrikloriddal való reagáltatását -20°C alatti, előnyösen -80°C és -25°C közötti, különösen előnyösen -50°C és -30°C közötti hőmérsékleten hajtjuk végre.

8. Az előző igénypontok bármelyike szerinti eljárás, **azzal jellemezve, hogy** a reakció során képződött ammóniumsókat vizes extrakcióval a reakcióelegyből eltávolítjuk.

9. Az előző igénypontok bármelyike szerinti eljárás, **azzal jellemezve, hogy** a reakció során képződött ammóniumsókat szűréssel a reakcióelegyből eltávolítjuk.

10. Az előző igénypontok bármelyike szerinti eljárás, **azzal jellemezve, hogy** a terméket a reakcióközegből egy apoláros szerves oldószer, előnyösen egy vagy több egyenes vagy elágazó láncú vagy gyűrűs szénhidrogénből álló vagy ilyent vagy ilyeneket tartalmazó oldószer adagolása útján kicsapatjuk és szűréssel elkülönítjük.

11. Az előző igénypontok bármelyike szerinti eljárás, **azzal jellemezve, hogy** a (tio)foszforsavamidodiklorid és/vagy (tio)foszforsavdiamidoklorid ammóniával való reagáltatásához a (tio)foszforsavamidodikloridot vagy (tio)foszforsavdiamidokloridot vagy a (tio)foszforsavamidodikloridot vagy (tio)foszforsavdiamidokloridot tartalmazó reakcióelegyet tápláljuk be először és ezután hozzáadjuk az ammóniát.

12. Az előző igénypontok bármelyike szerinti eljárás, **azzal jellemezve, hogy** a primer amint (tio)foszforsavtrikloriddal reagáltatjuk és a képződött (tio)foszforsavamidodikloridot ammóniával (tio)foszforsavtriamiddá konvertáljuk.

13. A 12. igénypont szerinti eljárás, **azzal jellemezve, hogy** a (tio)foszforsavtriamidra vonatkoztatva 0,8-1,2 ekvivalens primer amint használunk.

14. A 12. igénypont szerinti eljárás, **azzal jellemezve, hogy** 0,8 – 1,2 ekvivalens bázist mint segédanyagot használunk a primer amin és a (tio)foszforsavtriklorid reagáltatásánál a megfelelő (tio)foszforsavamidodiklorid előállítására.