

Preparation of 4-bromoaniline derivatives

The present invention provides a process for preparing
5 4-bromoaniline derivatives.

4-Bromoaniline derivatives are useful compounds which are used as intermediates in chemical industry. They are suitable, for example, for preparing active compounds used in the field of crop
10 protection, or for preparing pharmaceutically active compounds. WO 99/58509, for example, describes processes for preparing isoxazolin-3-ylacylbenzenes in which 4-bromoaniline derivatives are employed as intermediates for preparing herbicidally active compounds. WO 98/31681 describes these active compounds
15 (2-alkyl-3-(4,5-dihydroisoxazol-3-yl)acylbenzenes) as herbicidally active compounds.

It is known from the literature that the selective bromination of anilines in the para position is impossible, or possible only
20 with difficulty (Houben-Weyl 5/4, 241, 274 ff). In general, bromination with elemental bromine is not selective, but frequently associated with the formation of considerable amounts of dibromo compounds. According to experience, the selectivities for monobromo to dibromo compounds are in an order of magnitude
25 of about 9:1, i.e. the proportion of undesired dibromo compounds is about 10%. Thus, only with expensive reagents, such as tetrabutylammonium tribromide, the compound 4-bromo-2-(4,5-dihydroisoxazol-3-yl)-3-methylaniline, for example, was obtained at -30°C in a yield of about 50% (cf.
30 WO 99/58509).

It is an object of the present invention to provide an alternative process for preparing 4-bromoaniline derivatives. The preparation process described in WO 99/58509 for the
35 4-bromo-2-(4,5-dihydroisoxazol-3-yl)-3-methylaniline derivatives gives unsatisfactory yields and an unsatisfactory purity of the products. Accordingly, the process described in WO 99/58509 is only of limited use for the industrial preparation of such compounds.

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We have found that this object is achieved by a process for preparing 4-bromoaniline derivatives of the formula I

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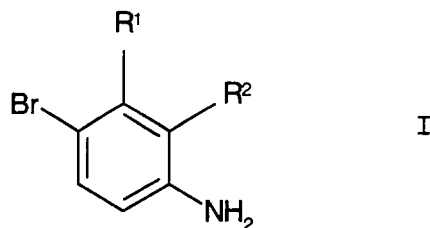
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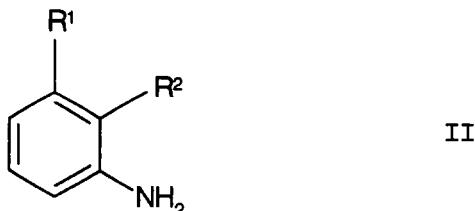


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where:

- 10 R^1 is C_1 - C_6 -alkyl, C_1 - C_6 -haloalkyl, C_1 - C_6 -alkoxy, C_1 - C_6 -haloalkoxy, C_3 - C_8 -cycloalkyl, halogen
 R^2 is C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy, C_3 - C_8 -cycloalkyl, C_2 - C_6 -alkenyl, cyano or a heterocyclic radical,

- 15 which comprises reacting a compound of the formula II



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- in which R^1 and R^2 are as defined above with a brominating agent in the solvent pyridine or in a solvent mixture comprising at
 25 least 55% by weight of pyridine.

With the aid of the process according to the invention, it is possible to obtain the aniline derivatives of the formula I in higher yields than with the prior-art preparation processes.

- 30 Thus, for example, the compound 4-bromo-2-(4,5-dihydroisoxazol-3-yl)-3-methylaniline can be obtained by the process described in WO 99/58509 (cf. Example 10 therein) in a yield of only 47%, whereas the yield in the process according to the invention is at least 60%, preferably at least
 35 70% or 80%, and in particular at least 90%.

- Moreover, the compounds of the formula I are obtained in higher purity. Here, the bromination takes place with high selectivity in the 4-position of the phenyl ring. The selectivity (ratio of
 40 monobromo to dibromo compound) is at least 92:8, in particular at least 95:5. Surprisingly, the proportion of impurities, such as, for example, dibromides (these dibromides are derivatives of the formula I which are substituted in the 5- or 6-position by a further bromine atom) which are difficult to remove from the
 45 resulting reaction mixture, or whose removal requires relatively high technical expenditure, is less than 5%. Accordingly, the number of further additional purification steps for isolation and

work-up of the compounds I prepared by the process according to the invention can be reduced. This is particularly advantageous for the industrial production of the compounds I, since an efficient and cost-effective process can be provided.

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Owing to the high selectivity and the small proportion of dibromo compounds, it is possible, if appropriate, to use the reaction product even without additional purification for the next process steps for further conversion into suitable end products.

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C₁-C₆-Alkyl is a straight-chain or branched alkyl group having 1 - 6 carbon atoms, such as, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl; preference is given to C₁-C₄-alkyl, such as, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl or tert-butyl.

C₁-C₆-Haloalkyl is a straight-chain or branched C₁-C₆-alkyl group as mentioned above which is partially or fully substituted by

20 fluorine, chlorine, bromine and/or iodine, i.e., for example, chloromethyl, dichloromethyl, trichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, chlorofluoromethyl, dichlorofluoromethyl, chlorodifluoromethyl, 2-fluoroethyl, 2-chloroethyl, 2-bromoethyl, 2-iodoethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 2-chloro-2-fluoroethyl, 2-chloro-2,2-difluoroethyl, 2,2-dichloro-2-fluoroethyl, 2,2,2-trichloroethyl, pentafluoroethyl, 2-fluoropropyl, 3-fluoropropyl, 2,2-difluoropropyl, 2,3-difluoropropyl, 2-chloropropyl, 3-chloropropyl, 2,3-dichloropropyl, 2-bromopropyl, 3-bromopropyl, 3,3,3-trifluoropropyl, 3,3,3-trichloropropyl, 2,2,3,3,3-pentafluoropropyl, heptafluoropropyl, 1-(fluoromethyl)-2-fluoroethyl, 1-(chloromethyl)-2-chloroethyl, 1-(bromomethyl)-2-bromoethyl, 4-fluorobutyl, 4-chlorobutyl, 4-bromobutyl, nonafluorobutyl, 5-fluoropentyl, 5-chloropentyl, 5-bromopentyl, 5-iodopentyl, 35 undecafluoropentyl, 6-fluorohexyl, 6-chlorohexyl, 6-bromohexyl, 6-iodohexyl or dodecafluorohexyl; preferably C₁-C₄-haloalkyl, such as chloromethyl, dichloromethyl, trichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, chlorofluoromethyl, dichlorofluoromethyl, chlorodifluoromethyl, 2-fluoroethyl, 2-chloroethyl, 2-bromoethyl, 2-iodoethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 2-chloro-2-fluoroethyl, 2-chloro-2,2-difluoroethyl, 2,2-dichloro-2-fluoroethyl, 2,2,2-trichloroethyl, pentafluoroethyl, 2-fluoropropyl, 2,3-difluoropropyl, 2,2-difluoropropyl, 2,3-difluoropropyl, 2-chloropropyl, 3-chloropropyl, 2,3-dichloropropyl, 2-bromopropyl, 3-bromopropyl, 3,3,3-trifluoropropyl,

3,3,3-trichloropropyl, 2,2,3,3,3-pentafluoropropyl, heptafluoropropyl, 1-(fluoromethyl)-2-fluoroethyl, 1-(chloromethyl)-2-chloroethyl, 1-(bromomethyl)-2-bromoethyl, 4-fluorobutyl, 4-chlorobutyl, 4-bromobutyl or nonafluorobutyl;

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C₁-C₆-alkoxy is a straight-chain or branched alkyl group having 1 - 6 carbon atoms, such as, for example, methoxy, ethoxy, n-propyloxy, isopropyloxy, n-butyloxy, isobutyloxy, tert-butyloxy, n-pentyloxy or n-hexyloxy; preferably C₁-C₄-alkoxy
 10 such as, for example, methoxy, ethoxy, n-propyloxy, n-butyloxy, isobutyloxy or tert-butyloxy;

C₁-C₆-haloalkoxy is a straight-chain or branched C₁-C₆-alkoxy group as mentioned above which is partially or fully substituted
 15 by fluorine, chlorine, bromine and/or iodine, i.e., for example, fluoromethoxy, difluoromethoxy, trifluoromethoxy, chlorodifluoromethoxy, bromodifluoromethoxy, 2-fluoroethoxy, 2-chloroethoxy, 2-bromoethoxy, 2-iodoethoxy, 2,2-difluoroethoxy, 2,2,2-trifluoroethoxy, 2-chloro-2-fluoroethoxy,
 20 2-chloro-2,2-difluoroethoxy, 2,2-dichloro-2-fluoroethoxy, 2,2,2-trichloroethoxy, pentafluoroethoxy, 2-fluoropropoxy, 3-fluoropropoxy, 2-chloropropoxy, 3-chloropropoxy, 2-bromopropoxy, 3-bromopropoxy, 2,2-difluoropropoxy, 2,3-difluoropropoxy, 2,3-dichloropropoxy, 3,3,3-trifluoropropoxy,
 25 3,3,3-trichloropropoxy, 2,2,3,3,3-pentafluoropropoxy, heptafluoropropoxy, 1-(fluoromethyl)-2-fluoroethoxy, 1-(chloromethyl)-2-chloroethoxy, 1-(bromomethyl)-2-bromoethoxy, 4-fluorobutoxy, 4-chlorobutoxy, 4-bromobutoxy, nonafluorobutoxy, 5-fluoropentoxy, 5-chloropentoxy, 5-bromopentoxy, 5-iodopentoxy,
 30 undecafluoropentoxy, 6-fluorohexoxy, 6-chlorohexoxy, 6-bromohexoxy, 6-iodohexoxy or dodecafluorohexoxy; preferably C₁-C₄-haloalkoxy, such as fluoromethoxy, difluoromethoxy, trifluoromethoxy, chlorodifluoromethoxy, bromodifluoromethoxy, 2-fluoroethoxy, 2-chloroethoxy, 2-bromoethoxy, 2-iodoethoxy,
 35 2,2-difluoroethoxy, 2,2,2-trifluoroethoxy, 2-chloro-2-fluoroethoxy, 2-chloro-2,2-difluoroethoxy, 2,2-dichloro-2-fluoroethoxy, 2,2,2-trichloroethoxy, pentafluoroethoxy, 2-fluoropropoxy, 3-fluoropropoxy, 2-chloropropoxy, 3-chloropropoxy, 2-bromopropoxy, 3-bromopropoxy,
 40 2,2-difluoropropoxy, 2,3-difluoropropoxy, 2,3-dichloropropoxy, 3,3,3-trifluoropropoxy, 3,3,3-trichloropropoxy, 2,2,3,3,3-pentafluoropropoxy, heptafluoropropoxy, 1-(fluoromethyl)-2-fluoroethoxy, 1-(chloromethyl)-2-chloroethoxy, 1-(bromomethyl)-2-bromoethoxy, 4-fluorobutoxy, 4-chlorobutoxy,
 45 4-bromobutoxy or nonafluorobutoxy;

C_3 - C_8 -cycloalkyl is an unsubstituted or substituted cycloalkyl ring having 3 - 8 carbon atoms, such as, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl. Suitable substituents are, for example: C_1 - C_6 -alkyl,
 5 C_1 - C_6 -alkoxy or halogen;

preference is given to unsubstituted C_3 - C_6 -cycloalkyl, such as, for example, cyclopropyl, cyclopentyl or cyclohexyl;

- 10 C_2 - C_6 -alkenyl is a straight-chain or branched alkenyl group having 2 - 6 carbon atoms, where the double bond is at the point of attachment, such as, for example, ethenyl, prop-1-en-1-yl, 1-methylethenyl, buten-1-yl, 1-methylprop-1-en-1-yl, 2-methylprop-1-en-1-yl, penten-1-yl, 1-methylbut-1-en-1-yl,
 15 2-methylbut-1-en-1-yl, 3-methylbut-1-en-1-yl, 1,2-dimethylprop-1-en-1-yl, hex-1-en-1-yl, 1-methylpent-1-en-1-yl, 2-methylpent-1-en-1-yl, 3-methylpent-1-en-1-yl, 4-methylpent-1-en-1-yl, 1,2-dimethylbut-1-en-1-yl, 1,3-dimethylbut-1-en-1-yl,
 20 2,3-dimethylbut-1-en-1-yl, 3,3-dimethylbut-1-en-1-yl, 1-ethylbut-1-en-1-yl, 2-ethylbut-1-en-1-yl or 1-ethyl-2-methylprop-1-en-yl;

Halogen is fluorine, chlorine, bromine, in particular chlorine or
 25 bromine.

- "Heterocyclic ring" is a saturated, unsaturated or partially unsaturated heterocycle having 3 - 8 ring atoms and one, two or three oxygen, sulfur or nitrogen atoms. Preference is given to
 30 heterocycles which contain at least one oxygen and/or one nitrogen atom. Preference is furthermore given to heterocycles having 5 or 6 ring atoms. The heterocycle can be attached to the phenyl ring at any site of the heterocycle, for example via a heterocyclic nitrogen ring atom or a carbon ring atom. The
 35 heterocycles are unsubstituted or mono-, di- or trisubstituted. Suitable substituents are radicals which are chemically inert under the chosen reaction conditions, such as, for example, C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy or halogen. Suitable heterocyclic rings in the context of the present invention are, for example, the
 40 following heterocycles: pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, piperidinyl, morpholinyl, oxazinyl, isoxazolinyl, isoxazolidinyl, etc. Preference is given to the following heterocycles: isoxazolyl, isoxazolinyl or isoxazolidinyl, in particular
 45 4,5-dihydroisoxazol-3-yl or 4,5-dihydroisoxazol-5-yl.

The process according to the invention is preferably suitable for preparing compounds of the formula I where the substituents are as defined below:

- 5 R^1 is C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy, C_3 - C_8 -cycloalkyl, halogen,
 R^2 is C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy, C_3 - C_8 -cycloalkyl, cyano or a heterocyclic radical.

The process according to the invention is furthermore preferably
10 suitable for preparing the following compounds of the formula I:

- 4-bromo-2-(4,5-dihydroisoxazol-3-yl)-3-methylaniline,
4-bromo-2-(4,5-dihydroisoxazol-3-yl)-3-ethylaniline,
4-bromo-2-(4,5-dihydroisoxazol-3-yl)-3-methoxyaniline,
15 4-bromo-2-(4,5-dihydroisoxazol-3-yl)-3-ethoxyaniline,
4-bromo-2-(3-methyl-4,5-dihydroisoxazol-5-yl)-3-methylaniline,
4-bromo-2-(3-methyl-4,5-dihydroisoxazol-5-yl)-3-ethylaniline,
4-bromo-2-(3-methyl-4,5-dihydroisoxazol-5-yl)-3-methoxyaniline,
4-bromo-2-(3-methyl-4,5-dihydroisoxazol-5-yl)-3-ethoxyaniline,
20 4-bromo-2-(isoxazol-3-yl)-3-methylaniline,
4-bromo-2-(isoxazol-3-yl)-3-ethylaniline,
4-bromo-2-(isoxazol-3-yl)-3-methoxyaniline,
4-bromo-2-(isoxazol-3-yl)-3-ethoxyaniline,
4-bromo-2-(5-methylisoxazol-3-yl)-3-methylaniline,
25 4-bromo-2-(5-methylisoxazol-3-yl)-3-ethylaniline,
4-bromo-2-(5-methylisoxazol-3-yl)-3-methoxyaniline,
4-bromo-2-(5-methylisoxazol-3-yl)-3-ethoxyaniline,
4-bromo-2-cyano-3-methylaniline,
4-bromo-2-cyano-3-methoxyaniline.

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The reaction of the compounds II with a brominating agent is preferably carried out by the following process steps:

- According to the invention, the reaction is carried out in the
35 solvent pyridine, or in solvent mixtures comprising at least 55% by weight, preferably 80% by weight of pyridine. In the case of solvent mixtures, suitable additional solvents in the mixture with pyridine are, for example, alcohols, such as methanol or ethanol, in particular methanol; esters, such as ethyl acetate or
40 butyl acetate, in particular ethyl acetate or butyl acetate; amides, such as, for example, N,N-dimethylformamide or N,N-dimethylacetamide; or water.

- Initially, the compound II is charged in pyridine or a
45 pyridine-containing solvent mixture, as solution or suspension. The brominating agent is then added over a period of 5 minutes -

5 hours. The brominating agent is added either directly, i.e. without solvent, or together with a suitable solvent.

Preferred brominating agents are elemental bromine or a mixture
5 of HBr and hydrogen peroxide. In the case of bromine, the bromine is preferably added together with a suitable solvent, such as, for example, pyridine, with formation of pyridinium perbromide. In this case, a particularly high selectivity in the ratio of monobromo to dibromo compound is achieved.

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In a preferred embodiment of the process, the brominating agent and the compound II are employed in a molar ratio of from 1:1 to 2:1. The brominating agent is preferably employed in equimolar amounts, or in a slight excess.

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The reaction is carried out at temperatures of from 20°C to the boiling point of the solvent, preferably in the range from 60°C to 85°C. In a further preferred embodiment, the reaction is carried out at temperatures of from 50°C to 100°C, preferably in the range
20 from 80°C to 100°C, with particular preference at about 100°C.

The reaction time is 1 - 24 hours, preferably 2 - 12 hours, in particular 5 - 8 hours. In a further preferred embodiment, the reaction time is 30 min - 10 h, preferably 30 min - 5 hours.

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If the brominating agent used is a mixture of HBr and hydrogen peroxide, the brominating agent is added to the solution of II over a period of preferably from 10 minutes to 3 hours. The molar ratio of HBr to compound II is preferably in the range from 1:1
30 to 1.5:1. The addition is carried out at temperatures of 0 - 50°C, preferably 20 - 40°C. The hydrogen peroxide is then added. The molar ratio of H₂O₂ to HBr is from 1:1 to 1.5:1. The addition is carried out at temperatures of from 10°C to the boiling point of the solvent, preferably from 50°C to 120°C, with preference from
35 80°C to 100°C, with particular preference at about 100°C; in a further preferred embodiment, the addition is preferably carried out at from 60°C to 85°C. The solution is then stirred for a period of 10 min - 36 hours, preferably 10 min - 8 hours. In a further embodiment, the solution is stirred for a period of 1 -
40 36 hours, preferably 2 - 8 hours. In a further embodiment, the solution is stirred for a period of from 10 min to 3 hours, preferably from 10 min to 2 hours. Subsequently, the product is worked up and purified. To this end, the solution is concentrated. The crude product is dissolved in a suitable
45 solvent, preferably pyridine or a solvent mixture comprising at least 50% pyridine, and water is added. Filtration and washing of

the residue or crystallization using a suitable solvent (for example water) gives the product in good yield and high purity.

However, it is also possible to take up the crude product in
5 dimethyl disulfide and to wash the product with water and/or aqueous sodium hydroxide solution. The organic solution can then be used for subsequent steps.

In a preferred embodiment, the compound of the formula II is
10 initially charged in pyridine or in a mixture of pyridine and water. In the latter case, the ratio of pyridine to water is in the range from 80 to 98% by weight to 20 to 5% by weight, preferably in a range of from 90 to 95% by weight to 10 to 5% by weight.

15 The ratio of the compound of the formula II to pyridine or pyridine/water is chosen such that a 5 - 25% strength solution, preferably a 10 - 15% strength solution, is formed. Above 0.8 to 1.1 molar equivalents, preferably 0.9 to 1.0 molar equivalents,
20 of HBr are then added to the resulting solution. The water is removed by azeotropic distillation and hydrogen peroxide is added to the solution that remains over a period of 1 - 3 hours, preferably 1.5 - 2.5 hours, at 50 - 120°C, preferably 80 - 110°C, in particular at about 100°C. The hydrogen peroxide is usually
25 employed in a 20% strength to 50% strength, preferably 30 to 50% strength, aqueous solution.

The mixture is then stirred for about 10 min to 2 h, preferably 30 min to 1 h.

30 This is followed by work-up of the product. To this end, the reaction solution is cooled to about room temperature and, if required, washed with aqueous sodium sulfite solution, and the organic phase is concentrated. The resulting product can be used
35 without further purification for subsequent reactions. However, it is also possible to take up the residue in dimethyl disulfide, to wash the resulting solution with water or aqueous sodium hydroxide solution and to use the resulting organic phase for subsequent reactions.

40 In a further embodiment, it is possible to add HBr to the pyridine which, if appropriate, comprises up to 10% of water, and then to remove the water azeotropically. The compound of the formula II is then dissolved in the reaction mixture and the
45 hydrogen peroxide is added dropwise. Both the quantitative ratios

of the substances employed and time and temperature conditions correspond to the conditions mentioned above.

In a further embodiment, it is also possible to use pyridinium
5 hydrobromide instead of pyridine and HBr.

If the brominating agent used is elemental bromine, the brominating agent is preferably added to the solution of II a little at a time or continuously over a period of from about 30
10 minutes to 6 hours. The molar ratio of bromine to the compound II is preferably in the range from 1:1 to 1.5:1. The addition is carried out at temperatures of 0 – 50°C, preferably at room temperature. The solution is then stirred for a period of 1 – 24 hours, preferably 2 – 8 hours. Subsequently, the product is
15 worked up and purified. To this end, the solution is concentrated and the crude product is dissolved in a suitable solvent, preferably pyridine or a solvent mixture comprising at least 50% pyridine, and admixed with water. Filtration and washing of the residue or crystallization using a suitable solvent (for example
20 water) gives the product in good yield and high purity.

Furthermore, the product can also be obtained from the reaction solution by extraction. To this end, the reaction solution is initially concentrated and the residue is taken up in a suitable
25 solvent or solvent mixture, the components being selected, for example, from water, ethyl acetate and dimethyl disulfide (DMDS), in particular water, ethyl acetate, water/ethyl acetate or water/DMDS. Suitable for the extraction are water-immiscible solvents or the corresponding solvent mixtures, such as, for
30 example, ethyl acetate, butyl acetate, toluene or methyl tert-butyl ether (MTBE). Concentration of the solution gives the product in good yield and high purity.

The crude product is purified either by washing the residue
35 obtained, or by crystallization. Suitable for washing are, for example, water and aqueous solvents. Suitable for recrystallization are, for example, toluene and benzene.

In principle, in the context of further reaction for preparing
40 active compounds, the crude product obtained can also be used for the next reaction step without further purification of the reaction solution. To this end, the reaction solution which contains the compounds of the formula I can be diluted with further solvents and thus be employed as crude solution for the
45 next process step. Alternatively, it is also possible to

concentrate the reaction solution and to transfer the resulting residue directly or as a melt into the next process step.

The compounds of the formula II to be used as starting materials
5 are known from the literature and/or commercially available. They can be prepared by processes known per se, such as, for example, described in more detail in WO 98/31681 or WO 99/58509.

The invention is illustrated in more detail in the working
10 examples below.

Example 1

4-Bromo-2-(4,5-dihydroisoxazol-3-yl)-3-methylaniline

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Brominating agent: HBr/H₂O₂

100.5 g of 2-(4,5-dihydroisoxazol-3-yl)-3-methylaniline are initially charged in 2000 g of pyridine, and 98.2 g of HBr are
20 added dropwise at 20-35°C. At 78-84°C, 64.6 g of hydrogen peroxide are then added dropwise over 0.5 h. The mixture is stirred at 25°C for a further 12 hours and then concentrated until an oily residue remains. The crude product is, at 50°C, dissolved in 100 ml of pyridine and admixed with 1000 ml of water. The mixture
25 is stirred at 0°C for 1 h and then filtered off, and the filter residue is washed twice with 200 ml of water and dried.

This gives 141 g (yield: 92%) of a yellow solid (HPLC: 94.6% of 4-bromo-2-(4,5-dihydroisoxazol-3-yl)-3-methylaniline, 1.8% of
30 6-bromo-2-(4,5-dihydroisoxazol-3-yl)-3-methylaniline, 3.4% of 4,6-dibromo-2-(4,5-dihydroisoxazol-3-yl)-3-methylaniline).

Example 2

35 4-Bromo-2-(4,5-dihydroisoxazol-3-yl)-3-methylaniline

Brominating agent: bromine

100 g of 2-(4,5-dihydroisoxazol-3-yl)-3-methylaniline are
40 initially charged in 1000 g of pyridine, and a solution of altogether 96.19 g of bromine in 1000 g of pyridine is added dropwise at 20°C in five freshly prepared portions, over 3 hours. The mixture is stirred for a further 12 hours. Pyridine is distilled off at 150 mbar and a bath temperature of 75°C. The
45 residue is dissolved in 2 l of water and extracted repeatedly with in each case 250 ml of ethyl acetate. Concentration gives 122.1 g of product (yield 81.6%; GC: 93.2% of

4-bromo-2-(4,5-dihydroisoxazol-3-yl)-3-methylaniline, 2.7% of
6-bromo-2-(4,5-dihydroisoxazol-3-yl)-3-methylaniline, 4.1% of
4,6-dibromo-2-(4,5-dihydroisoxazol-3-yl)-3-methylaniline).

5 Example 3

4-Bromo-2-(4,5-dihydroisoxazol-3-yl)-3-methylaniline

Brominating agent: bromine

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5 g of the compound 2-(4,5-dihydroisoxazol-3-yl)-3-methylaniline are initially charged in 50 g of pyridine, and a solution of altogether 4.89 g of bromine in 50 g of pyridine (mixture to be prepared at 0°C) is added dropwise at 20°C over 5 h. The mixture

15 is stirred at 25°C for a further 12 hours. The batch is poured into 250 ml of water and extracted three times with in each case 100 ml of MTBE. The combined organic phases are washed twice with in each case 100 ml of water, dried over sodium sulfate and concentrated.

20

This gives 6.0 g of product (yield 79.8%; 94.3% of 4-bromo-2-(4,5-dihydroisoxazol-3-yl)-3-methylaniline, 1.8% of 6-bromo-2-(4,5-dihydroisoxazol-3-yl)-3-methylaniline, 3.5% of 4,6-dibromo-2-(4,5-dihydroisoxazol-3-yl)-3-methylaniline).

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Example 4

4-Bromo-2-(4,5-dihydroisoxazole-3-yl)-3-methylaniline

30 Brominating agent: HBr, H₂O₂

500.0 g of 2-(4,5-dihydroisoxazol-3-yl)-3-methylaniline are initially charged in 4 500 g of pyridine, and at 25 - 35°C, 467.4 g of 47% strength HBr are added dropwise. Under reflux, the
35 water is distilled off azeotropically at atmospheric pressure. At 100°C, 199.2 g of 50% strength H₂O₂ are then added dropwise over a period of 2 hours. The reaction mixture is stirred for another hour and then cooled to room temperature and washed with sodium sulfite solution, and the solvent is then distilled off (T<100°C).

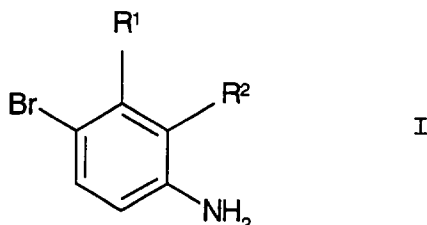
40 The residue is taken up in 3 220 g of dimethyl disulfide and, at 60°C, washed with 1 500 g of water. The resulting solution is used for a subsequent reaction.

This gives about 83% of the desired product.

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We claim:

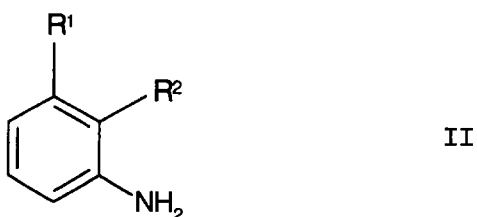
1. A process for preparing 4-bromoaniline derivatives of the
5 formula I



where:

- 15 R¹ is C₁-C₆-alkyl, C₁-C₆-haloalkyl, C₁-C₆-alkoxy,
C₁-C₆-haloalkoxy, C₃-C₈-cycloalkyl, halogen
R² is C₁-C₆-alkyl, C₁-C₆-alkoxy, C₃-C₈-cycloalkyl,
C₂-C₆-alkenyl, cyano or a heterocyclic radical,

- 20 which comprises reacting a compound of the formula II



in which R¹ and R² are as defined above with a brominating agent in the solvent pyridine.

- 30
2. A process as claimed in claim 1, wherein the brominating agent used is bromine.
3. A process as claimed in claim 1, wherein the brominating agent used is hydrogen bromide and hydrogen peroxide.
- 35
4. A process as claimed in any of claims 1 - 3, wherein the solvent used is pyridine.
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5. A process as claimed in any of claims 1 - 4, where R¹ is C₁-C₆-alkyl.
6. A process as claimed in claim 5, where R¹ is methyl or ethyl.
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7. A process as claimed in any of claims 1 - 6, where R² is a heterocyclic ring.

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8. A process as claimed in claim 7, where R² is an isoxazole, isoxazoline or isoxazolidine ring.
9. A process as claimed in claim 8, where R² is
5 4,5-dihydroisoxazol-3-yl or 4,5-dihydroisoxazol-5-yl.
10. A process as claimed in any of claims 1 - 8 for preparing
4-bromo-2-(4,5-dihydroisoxazol-3-yl)-3-methylaniline.

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