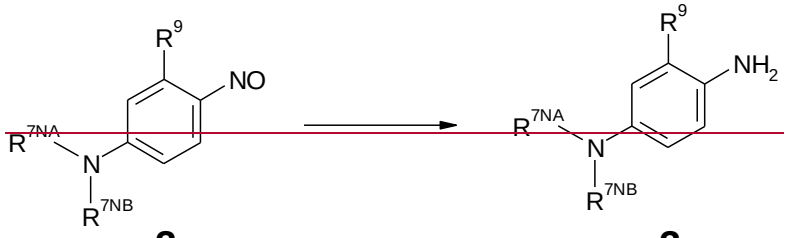
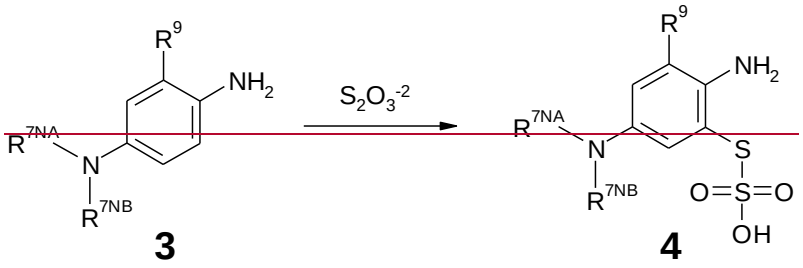
CLAIMS

1. A method of synthesis comprising the steps of, in order:

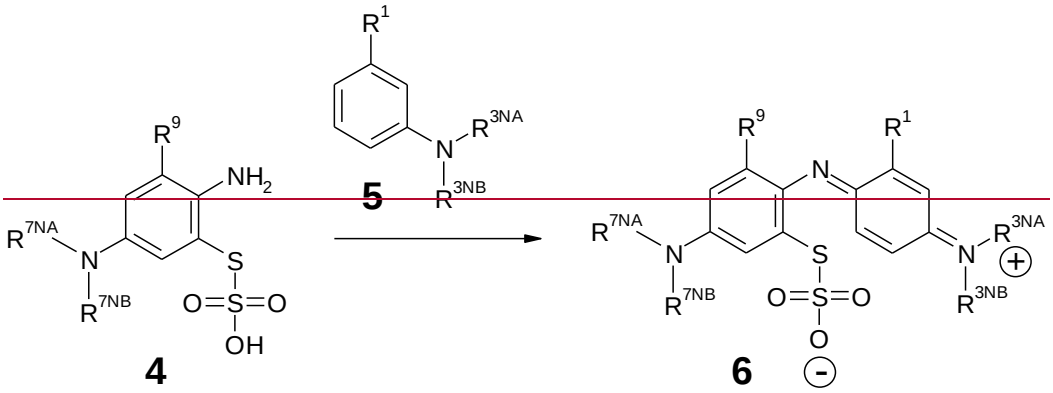
nitrosyl reduction (NR), in which an *N,N*-disubstituted-3-optionally substituted-4-nitrosyl aniline, **2**, is reduced to form said *N,N*-disubstituted-1,4-diamino-5-optionally substituted benzene, **3**:



thiosulfonic acid formation (TSAF), in which an *N,N*-disubstituted-1,4-diamino-5-optionally substituted benzene, **3**, is oxidized in the presence of a thiosulfate to give said thiosulfuric acid S-{2-(amino)-3-(optionally substituted)-5-(disubstituted-amino)-phenyl} ester, **4**:



oxidative coupling (OC), in which a thiosulfuric acid S-{2-(amino)-3-(optionally substituted)-5-(disubstituted amino)-phenyl} ester, **4**, is oxidatively coupled to an *N,N*-disubstituted-3-optionally substituted-aniline, **5**, using an oxidizing agent that is or comprises Cr(VI), to give a [4-{2-(thiosulfate)-4-(disubstituted amino)-6-(optionally substituted)-phenyl-imino}-3-(optionally substituted)-cyclohexa-2,5-dienylidene]-*N,N*-disubstituted ammonium, **6**:



wherein;

each of R^1 and R^9 is independently selected from: -H; C_{1-4}alkyl; C_{2-4}alkenyl; and halogenated C_{1-4}alkyl;

each of R^{3NA} and R^{3NB} is independently selected from: C_{1-4}alkyl; C_{2-4}alkenyl; and halogenated C_{1-4}alkyl;

each of R^{7NA} and R^{7NB} is independently selected from: C_{1-4}alkyl; C_{2-4}alkenyl; and halogenated C_{1-4}alkyl; and

and wherein;

the nitrosyl reduction (NR), thiosulfonic acid formation (TSAF), and oxidative coupling (OC) steps are completed in a single reaction vessel.

2. A method of synthesis according to claim 1, wherein said thiosulfate is or comprises $Na_2S_2O_3$.

3. A method of synthesis according to claim 1 or claim 2, wherein said oxidation in said thiosulfonic acid formation (TSAF) step is by reaction with an oxidizing agent that is or comprises Cr(VI).

4. A method of synthesis according to any one of the preceding claims, wherein said oxidation in said thiosulfonic acid formation (TSAF) step is by reaction with an oxidizing agent that is or comprises $Na_2Cr_2O_7$.

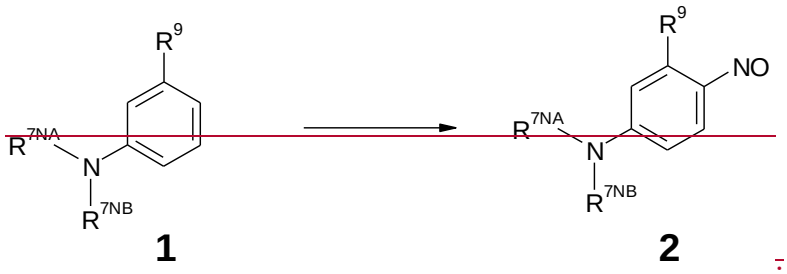
5. A method of synthesis according to claim any one of the preceding claims, wherein said reduction in said nitrosyl reduction (NR) step is by reaction with a reducing agent that is or comprises Fe(O).

6. A method according to any one of the preceding claims, wherein said reduction in said nitrosyl reduction (NR) step is by reaction with a reducing agent that is or comprises metallic iron.

7. A method according to claim 6, wherein metallic iron is used in excess, and wherein the excess metallic iron is not removed from the reaction mixture after reaction completion.

8. A method of synthesis according to any one of the preceding claims, wherein said reduction in said nitrosyl reduction (NR) step is performed in under acidic conditions.

9. A method of synthesis according to any preceding claim, further comprising, before said nitrosyl reduction (NR) step, the additional step of: nitrosylation (NOS), in which an *N,N*-disubstituted-3-optionally substituted aniline, **1**, is 4-nitrosylated to give said *N,N*-disubstituted-3-optionally substituted-4-nitrosyl aniline, **2**:



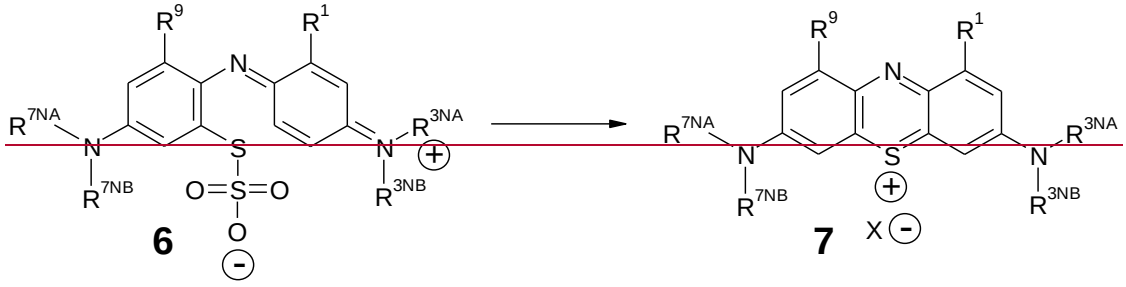
10. A method according to claim 9, wherein said nitrosylation is performed using a nitrite.

11. A method of synthesis according to claim 10, wherein said nitrosylation is performed using a sodium nitrite.

12. A method of synthesis according to any one of claims 9 to 11, wherein said nitrosylation is performed under acidic conditions.

13. A method according to any one of claims 9 to 12, wherein the nitrosylation step (NOS) is completed in the same reaction vessel as the nitrosyl reduction (NR), thiosulfonic acid formation (TSAF), and oxidative coupling (OC) steps.

14. A method according to any preceding claim further comprising after the step of oxidative coupling (OC), the step of ring closure (RC), in which said isolated and purified [4-(2-(thiosulfate)-4-(disubstituted amino)-6-(optionally substituted)-phenyl-imino)-3-(optionally substituted)-cyclohexa-2,5-dienylidene]-*N,N*-disubstituted ammonium, **6**, is subjected to ring closure to give a 3,7-bis(disubstituted-amino)-1,9-(optionally substituted)-phenothiazin-5-ium salt, **7**:



wherein X is one or more anionic counter ions to achieve electrical neutrality.

15. A method according to claim 14, wherein the ring closure (RC) step is completed in the same reaction vessel as the nitrosyl reduction (NR), thiosulfonic acid formation (TSAF), and oxidative coupling (OC) steps.

16. A method according to any one of claims 1 to 15, further comprising

after the step of oxidative coupling (OC), and

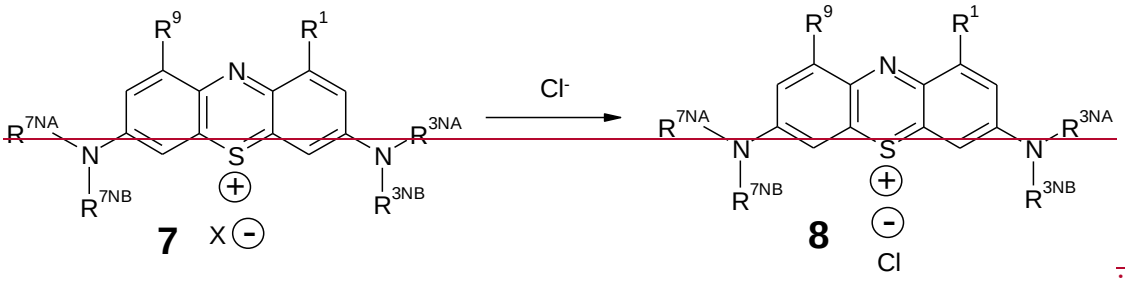
before the step of ring closure (RC) if present, the step of

isolation and purification of zwitterionic intermediate (IAPOZI), in which said [4-{2-(thiosulfate)-4-(disubstituted amino)-6-(optionally substituted)-phenyl-imino}-3-(optionally substituted)-cyclohexa-2,5-dienylidene]-*N,N*-disubstituted ammonium, **6**, is isolated and purified.

17. A method according to claim 16, wherein isolation and purification is by filtration followed by washing.

18. A method of synthesis according to any one of claims 14 to 17, comprising said ring closure (RC) step, and the subsequent additional step of:

chloride salt formation (CSF), in which said 3,7-bis(disubstituted-amino)-1,9-(optionally substituted)-phenothiazin-5-ium salt, **7**, is reacted with chloride, to give a 3,7-bis(disubstituted-amino)-1,9-(optionally substituted)-phenothiazin-5-ium chloride salt, **8**:



19. A method of synthesis according to claim 18, wherein the chloride is hydrochloric acid.

20. A method of synthesis according to claim 19, wherein chloride salt formation (CSF) is performed at a relatively low pH of 0 to 2.

21. A method of synthesis according to claim 20, wherein chloride salt formation (CSF) is performed at a relatively low pH of about 1.

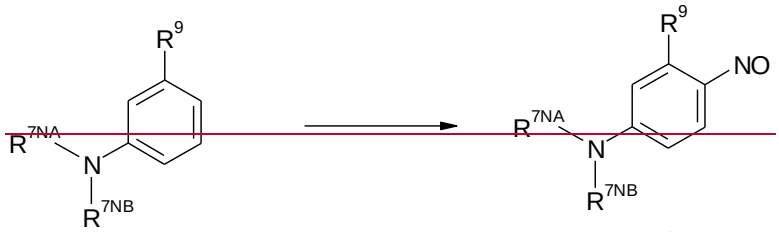
22. A method of synthesis according to any one of claims 19 to 21, wherein chloride salt formation (CSF) is performed at a relatively cool temperature of 20 to 30°C.

23. A method of synthesis according to claim 22, wherein chloride salt formation (CSF) is performed at a relatively cool temperature of about 25°C.

24. A method of synthesis according to claim 18, wherein said chloride is sodium chloride.

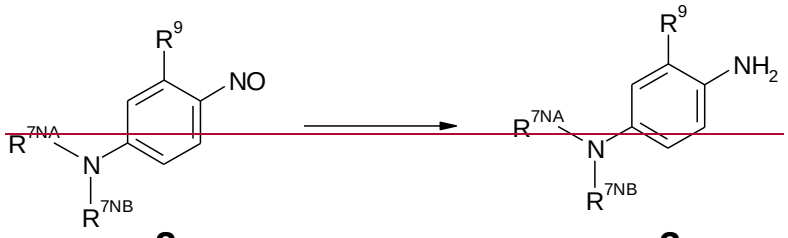
~~25. A method of synthesis comprising the steps of, in order:~~

~~nitrosylation (NOS), in which an *N,N*-disubstituted-3-optionally substituted aniline, **1**, is 4-nitrosylated to give said *N,N*-disubstituted-3-optionally substituted-4-nitrosyl aniline, **2**:~~



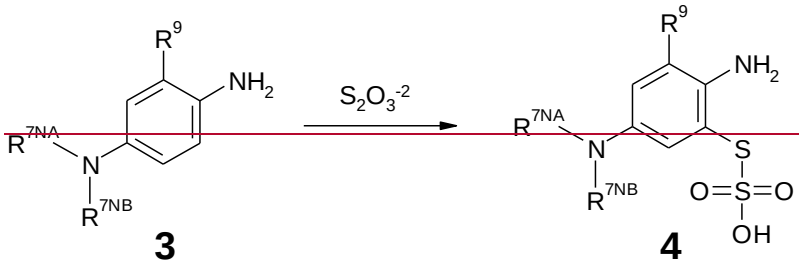
1 **2**

~~nitrosyl reduction (NR), in which an *N,N*-disubstituted-3-optionally substituted-4-nitrosyl aniline, **2**, is reduced to form said *N,N*-disubstituted-1,4-diamino-5-optionally substituted benzene, **3**:~~



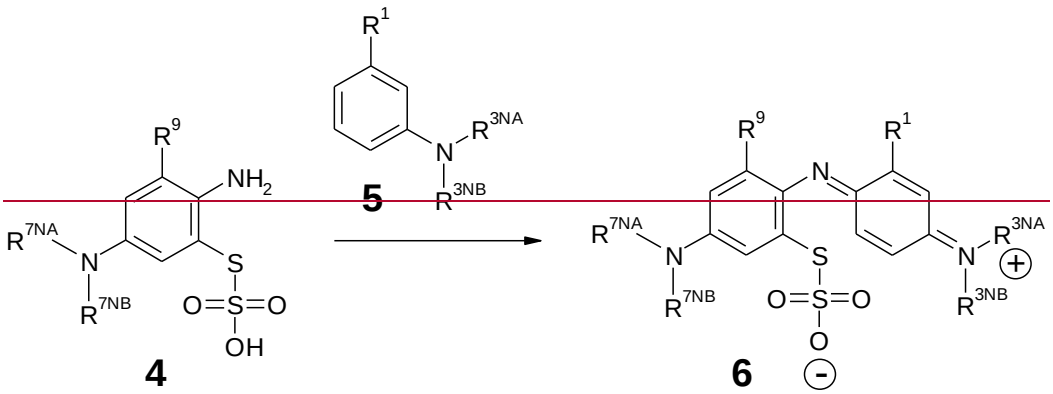
2 **3**

~~thiosulfonic acid formation (TSAF), in which an *N,N*-disubstituted-1,4-diamino-5-optionally substituted benzene, **3**, is oxidized in the presence of a thiosulfate to give said thiosulfuric acid S-{2-(amino)-3-(optionally substituted)-5-(disubstituted-amino)-phenyl} ester, **4**:~~



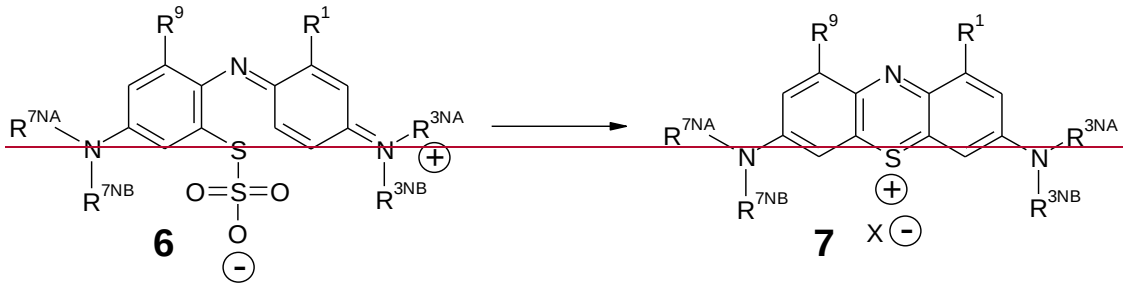
3 **4**

~~oxidative coupling (OC), in which a thiosulfuric acid S-{2-(amino)-3-(optionally substituted)-5-(disubstituted amino)-phenyl} ester, **4**, is oxidatively coupled to an *N,N*-disubstituted-3-optionally substituted-aniline, **5**, using an oxidizing agent that is or comprises Cr(VI), to give a [4-{2-(thiosulfate)-4-(disubstituted amino)-6-(optionally substituted)-phenyl-imino}-3-(optionally substituted)-cyclohexa-2,5-dienylidene]-*N,N*-disubstituted ammonium, **6**:~~

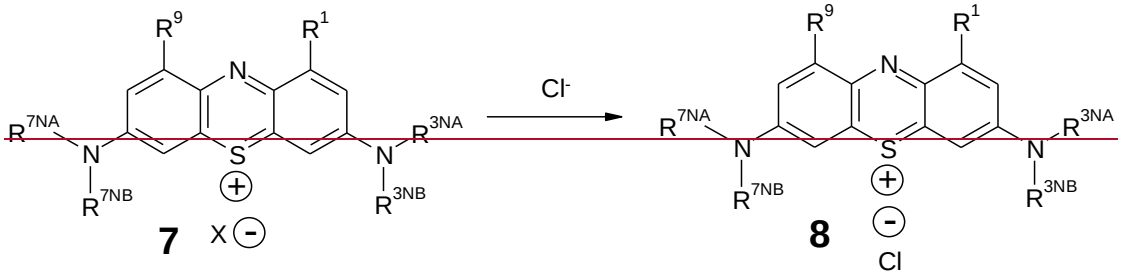


~~wherein all of the preceding steps are completed in the same reaction vessel,~~

~~ring closure (RC), in which said isolated and purified [4-(2-(thiosulfate)-4-(disubstituted amino)-6-(optionally substituted)-phenyl-imino}-3-(optionally substituted)-cyclohexa-2,5-dienylidene]-*N,N*-disubstituted ammonium, **6**, is subjected to ring closure to give a 3,7-bis(disubstituted-amino)-1,9-(optionally substituted)-phenothiazin-5-ium salt, **7**:~~

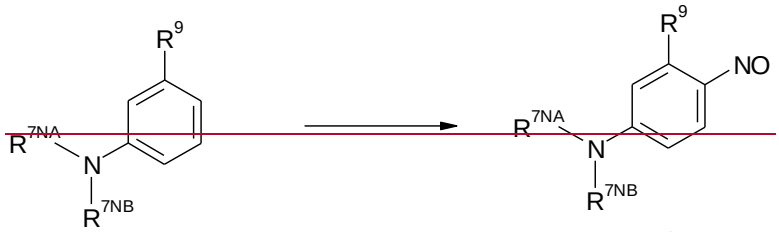


~~chloride salt formation (CSF), in which said 3,7-bis(disubstituted-amino)-1,9-(optionally substituted)-phenothiazin-5-ium salt, **7**, is reacted with chloride, to give a 3,7-bis(disubstituted-amino)-1,9-(optionally substituted)-phenothiazin-5-ium chloride salt, **8**:~~



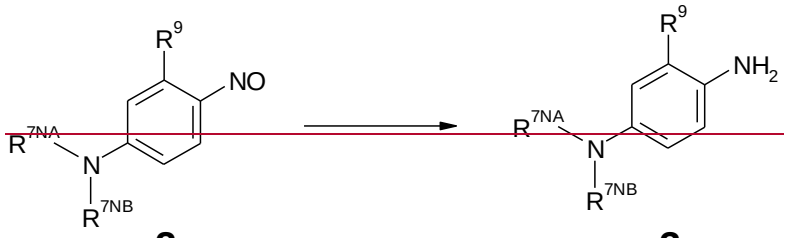
26. A method of synthesis comprising the steps of, in order:

nitrosylation (NOS), in which an *N,N*-disubstituted-3-optionally substituted aniline, **1**, is 4-nitrosylated to give said *N,N*-disubstituted-3-optionally substituted-4-nitrosyl aniline, **2**:



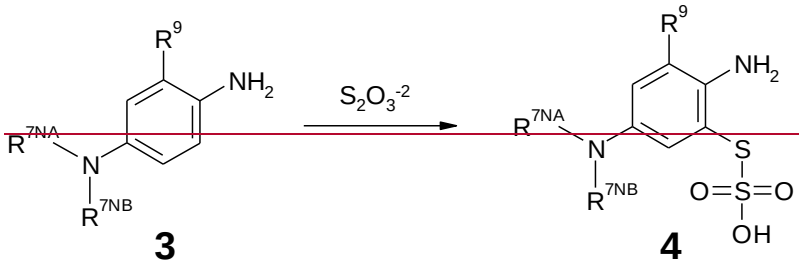
1 **2**

nitrosyl reduction (NR), in which an *N,N*-disubstituted-3-optionally substituted-4-nitrosyl aniline, **2**, is reduced to form said *N,N*-disubstituted-1,4-diamino-5-optionally substituted benzene, **3**:



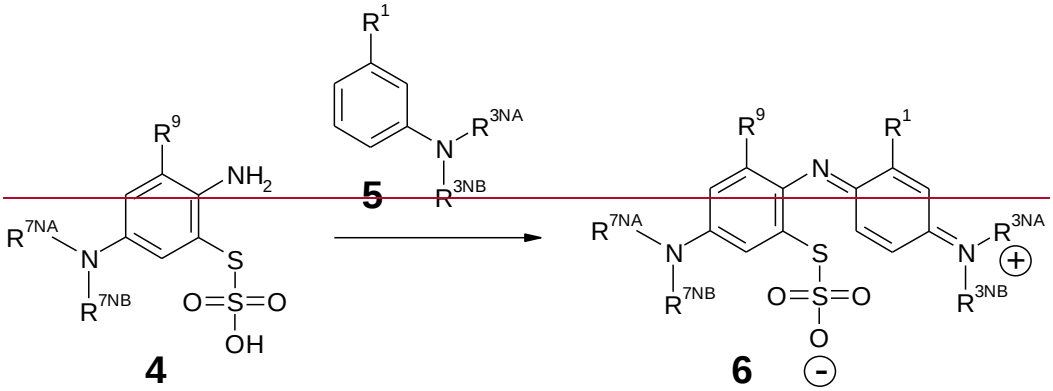
2 **3**

thiosulfonic acid formation (TSAF), in which an *N,N*-disubstituted-1,4-diamino-5-optionally substituted benzene, **3**, is oxidized in the presence of a thiosulfate to give said thiosulfuric acid S-{2-(amino)-3-(optionally substituted)-5-(disubstituted-amino)-phenyl} ester, **4**:

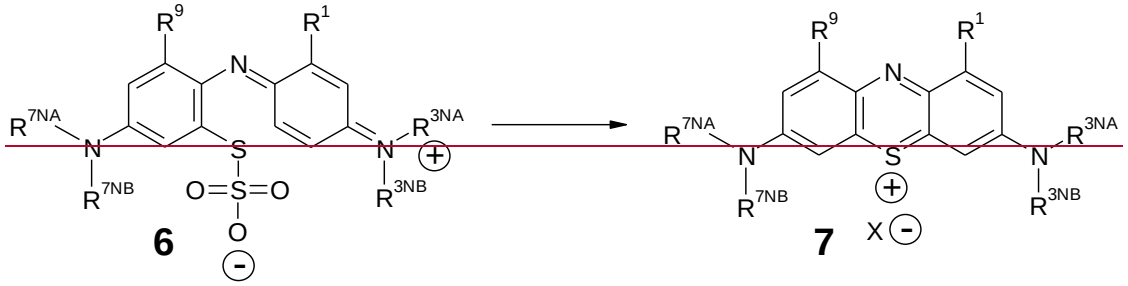


3 **4**

oxidative coupling (OC), in which a thiosulfuric acid S-{2-(amino)-3-(optionally substituted)-5-(disubstituted amino)-phenyl} ester, **4**, is oxidatively coupled to an *N,N*-disubstituted-3-optionally substituted-aniline, **5**, using an oxidizing agent that is or comprises Cr(VI), to give a [4-{2-(thiosulfate)-4-(disubstituted amino)-6-(optionally substituted)-phenyl-imino}-3-(optionally substituted)-cyclohexa-2,5-dienylidene]-*N,N*-disubstituted ammonium, **6**:

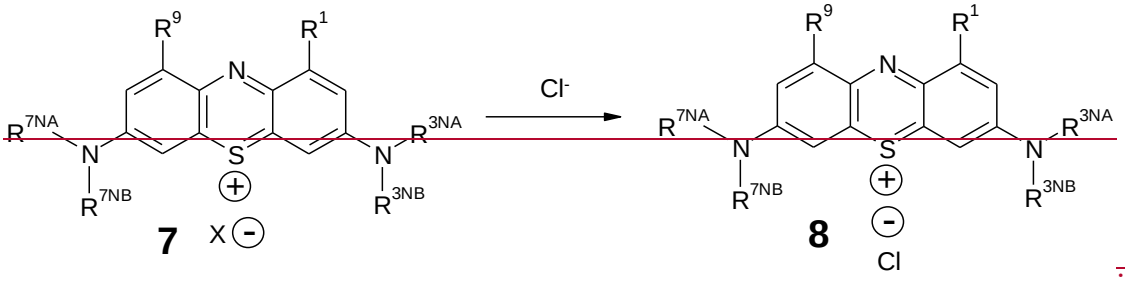


ring closure (RC), in which said isolated and purified [4-(2-(thiosulfate)-4-(disubstituted amino)-6-(optionally substituted)-phenyl-imino)-3-(optionally substituted)-cyclohexa-2,5-dienylidene]-*N,N*-disubstituted ammonium, **6**, is subjected to ring closure to give a 3,7-bis(disubstituted-amino)-1,9-(optionally substituted)-phenothiazin-5-ium salt, **7**:



wherein all of the preceding steps are completed in the same pot,

chloride salt formation (CSF), in which said 3,7-bis(disubstituted-amino)-1,9-(optionally substituted)-phenothiazin-5-ium salt, **7**, is reacted with chloride, to give a 3,7-bis(disubstituted-amino)-1,9-(optionally substituted)-phenothiazin-5-ium chloride salt, **8**:



27. A method according to any preceding claim, further comprising addition of an activating agent prior to or during the thiosulfonic acid formation (TSAF) step.

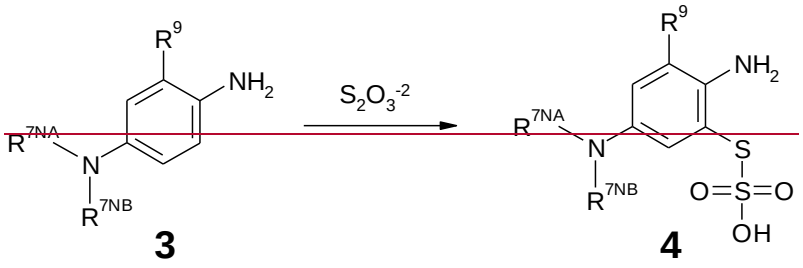
28. A method according to the preceding claim, wherein the activating agent comprises aluminium sulphate.

29. A method according to any preceding claim, wherein a filtration agent is added to the reaction vessel in which the nitrosyl reduction (NR), thiosulfonic acid formation (TSAF), and oxidative coupling (OC) steps are completed.

30. A method according to the preceding claim, wherein the filtration agent is or comprises cellulose.

31. A method of synthesis comprising the steps of, in order:

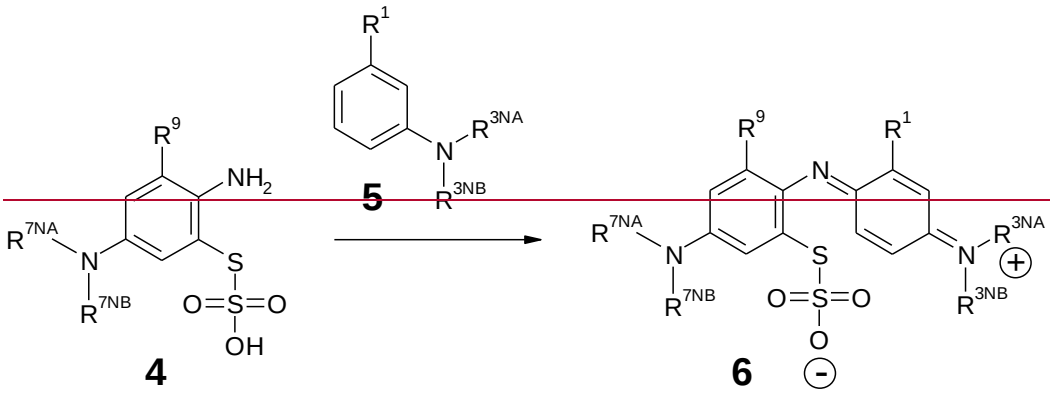
thiosulfonic acid formation (TSAF), in which an *N,N*-disubstituted-1,4-diamino-5-optionally substituted benzene, **3**, is oxidized in the presence of a thiosulfate to give said thiosulfuric acid S-{2-(amino)-3-(optionally substituted)-5-(disubstituted-amino)-phenyl} ester, **4**:



3 **4**

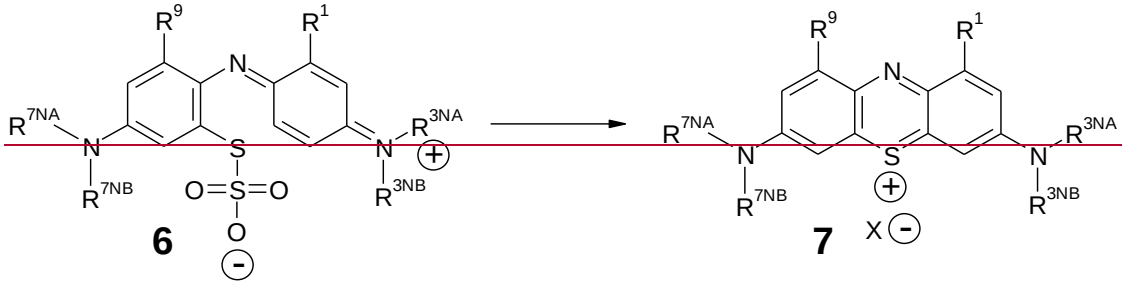
wherein during or prior to the thiosulfonic acid formation an activating agent is added,

oxidative coupling (OC), in which a thiosulfuric acid S-{2-(amino)-3-(optionally substituted)-5-(disubstituted amino)-phenyl} ester, **4**, is oxidatively coupled to an *N,N*-disubstituted-3-optionally substituted-aniline, **5**, using an oxidizing agent that is or comprises Cr(VI), to give a [4-{2-(thiosulfate)-4-(disubstituted amino)-6-(optionally substituted)-phenyl-imino}-3-(optionally substituted)-cyclohexa-2,5-dienylidene]-*N,N*-disubstituted ammonium, **6**:



4 **5** **6**

ring closure (RC), in which said isolated and purified [4-{2-(thiosulfate)-4-(disubstituted amino)-6-(optionally substituted)-phenyl-imino}-3-(optionally substituted)-cyclohexa-2,5-dienylidene]-*N,N*-disubstituted ammonium, **6**, is subjected to ring closure to give a 3,7-bis(disubstituted-amino)-1,9-(optionally substituted)-phenothiazin-5-ium salt, **7**:



6 **7**

wherein;

each of R^1 and R^9 is independently selected from: -H; C_{1-4}alkyl; C_{2-4}alkenyl; and halogenated C_{1-4}alkyl;

each of R^{3NA} and R^{3NB} is independently selected from: C_{1-4}alkyl; C_{2-4}alkenyl; and halogenated C_{1-4}alkyl;

each of R^{7NA} and R^{7NB} is independently selected from: C_{1-4}alkyl; C_{2-4}alkenyl; and halogenated C_{1-4}alkyl; and

X^- is a halide counter ion

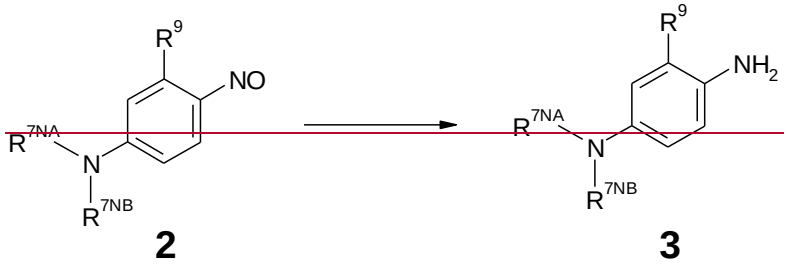
optionally with the proviso that the compound is **not** a $ZnCl_2$ mixed salt.

32. A method according to claim 31, wherein the activating agent is or comprises Al(III).

33. A method according to claim 32, wherein the activating agent is or comprises aluminium sulphate hexadecahydrate.

34. A method of synthesis according to any one of claims 31 to 33, further comprising, before said thiosulfonic acid formation (TSAF) step, the additional step of:

nitrosyl reduction (NR), in which an *N,N*-disubstituted-3-optionally substituted-4-nitrosyl aniline, **2**, is reduced to form said *N,N*-disubstituted-1,4-diamino-5-optionally substituted benzene, **3**:

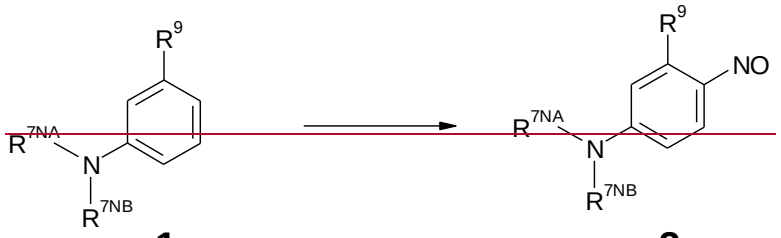


2 **3**

35. A method according to claim 34, wherein the nitrosylation (NOS) step, the thiosulfonic acid formation (TSAF) step and the oxidative coupling (OC) step are all completed in the same pot.

36. A method of synthesis according to claim 34 or claim 35, further comprising, before said nitrosyl reduction (NR) step, the additional step of:

nitrosylation (NOS), in which an *N,N*-disubstituted-3-optionally substituted aniline, **1**, is 4-nitrosylated to give said *N,N*-disubstituted-3-optionally substituted-4-nitrosyl aniline, **2**:



37. A method according to any one of claims 31 to 36 further comprising

after said oxidative coupling (OC) step, and

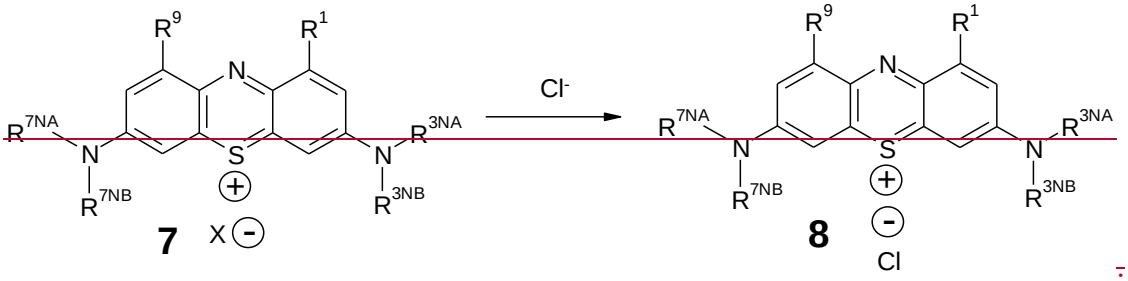
after said chromate reduction (CR) step if present, and

before said ring closure (RC) step,

isolation and purification of zwitterionic intermediate (IAPOZI), in which said [4-{2-(thiosulfate)-4-(disubstituted amino)-6-(optionally substituted)-phenyl-imino}-3-(optionally substituted)-cyclohexa-2,5-dienylidene]-*N,N*-disubstituted ammonium, **6**, is isolated and purified.

38. A method of synthesis according to any one of claims 31 to 37, further comprising, after said ring closure (RC) step, the additional step of:

chloride salt formation (CSF), in which said 3,7-bis(disubstituted-amino)-1,9-(optionally substituted)-phenothiazin-5-ium salt, **7**, is reacted with chloride, to give a 3,7-bis(disubstituted-amino)-1,9-(optionally substituted)-phenothiazin-5-ium chloride salt, **8**:

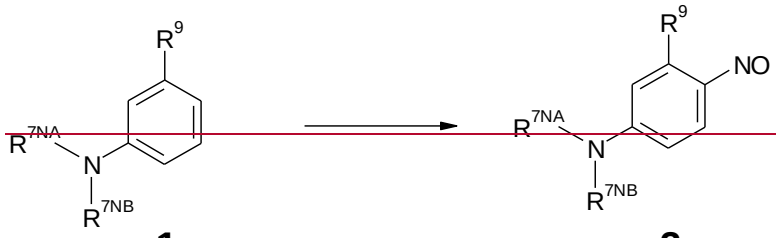


39. A method according to any one of claims 31 to 38, wherein the method comprises at least one filtration, and wherein a filtration agent is added to the reaction pot prior to that filtration.

40. A method according to claim 39, wherein the filtration agent is or comprises cellulose.

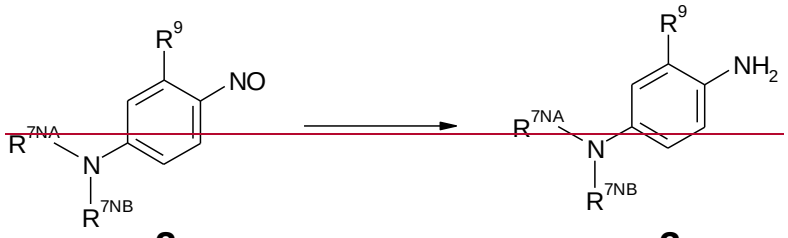
41. A method of synthesis comprising one or more of the steps of, in order:

nitrosylation (NOS), in which an *N,N*-disubstituted-3-optionally substituted aniline, **1**, is 4-nitrosylated to give said *N,N*-disubstituted-3-optionally substituted-4-nitrosyl aniline, **2**:



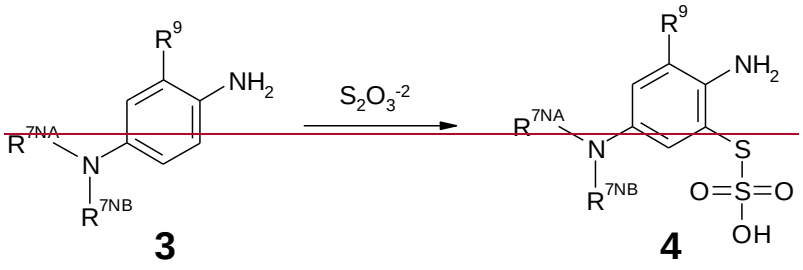
1 **2**

nitrosyl reduction (NR), in which an *N,N*-disubstituted-3-optionally substituted-4-nitrosyl aniline, **2**, is reduced to form said *N,N*-disubstituted-1,4-diamino-5-optionally substituted benzene, **3**:



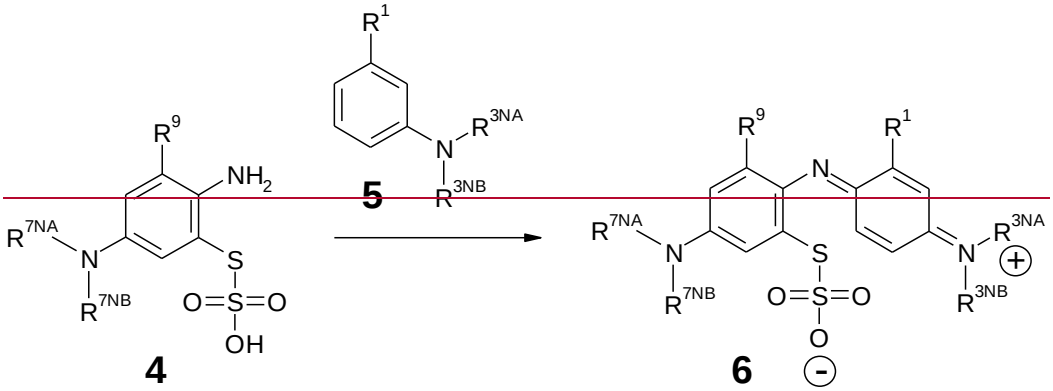
2 **3**

thiosulfonic acid formation (TSAF), in which an *N,N*-disubstituted-1,4-diamino-5-optionally substituted benzene, **3**, is oxidized in the presence of a thiosulfate to give said thiosulfuric acid S-{2-(amino)-3-(optionally substituted)-5-(disubstituted-amino)-phenyl} ester, **4**:



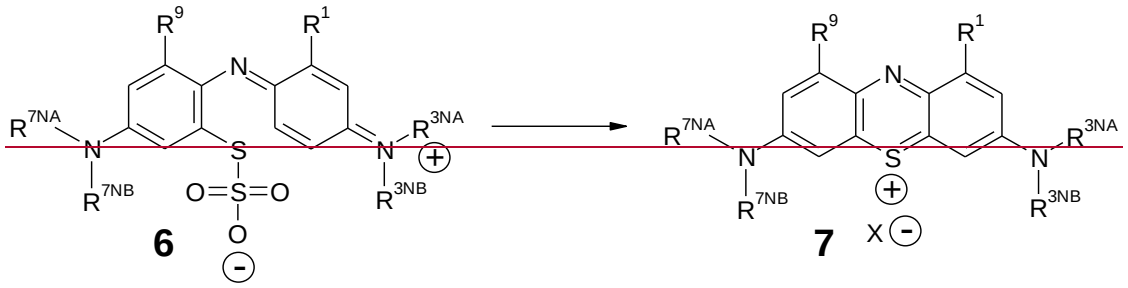
3 **4**

oxidative coupling (OC), in which a thiosulfuric acid S-{2-(amino)-3-(optionally substituted)-5-(disubstituted amino)-phenyl} ester, **4**, is oxidatively coupled to an *N,N*-disubstituted-3-optionally substituted-aniline, **5**, using an oxidizing agent that is or comprises Cr(VI), to give a [4-{2-(thiosulfate)-4-(disubstituted amino)-6-(optionally substituted)-phenyl-imino}-3-(optionally substituted)-cyclohexa-2,5-dienylidene]-*N,N*-disubstituted ammonium, **6**:

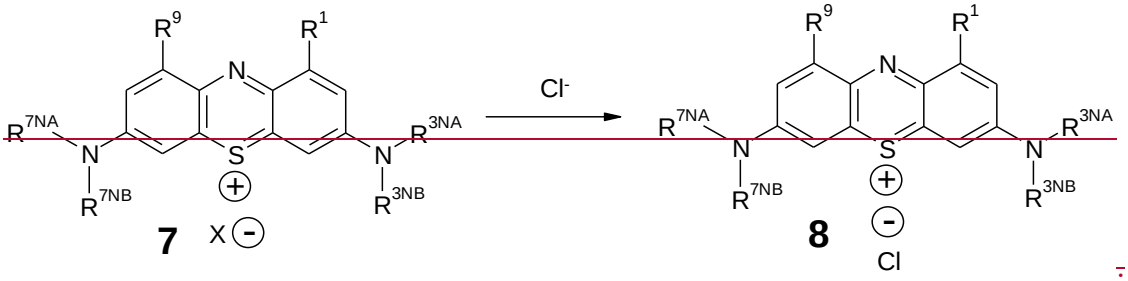


~~Cr(VI) Reduction (CR), in which the product of the oxidative coupling (OC) step is treated to convert residual Cr(VI) to Cr(III),~~

~~ring closure (RC), in which said isolated and purified [4-{2-(thiosulfate)-4-(disubstituted amino)-6-(optionally substituted)-phenyl-imino}-3-(optionally substituted)-cyclohexa-2,5-dienylidene]-*N,N*-disubstituted ammonium, **6**, is subjected to ring closure to give a 3,7-bis(disubstituted-amino)-1,9-(optionally substituted)-phenothiazin-5-ium salt, **7**:~~



~~chloride salt formation (CSF), in which said 3,7-bis(disubstituted-amino)-1,9-(optionally substituted)-phenothiazin-5-ium salt, **7**, is reacted with chloride, to give a 3,7-bis(disubstituted-amino)-1,9-(optionally substituted)-phenothiazin-5-ium chloride salt, **8**:~~



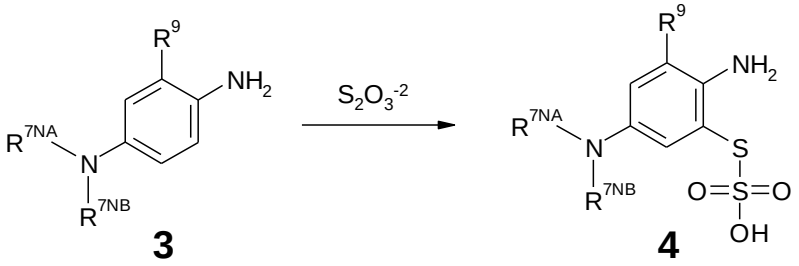
~~wherein the method comprises at least one filtration, and wherein a filtration agent is added to the reaction pot prior to that filtration.~~

~~42. A method according to claim 41, wherein the filtration agent is or comprises cellulose.~~

CLAIMS

1. A method of synthesis comprising the steps of, in order:

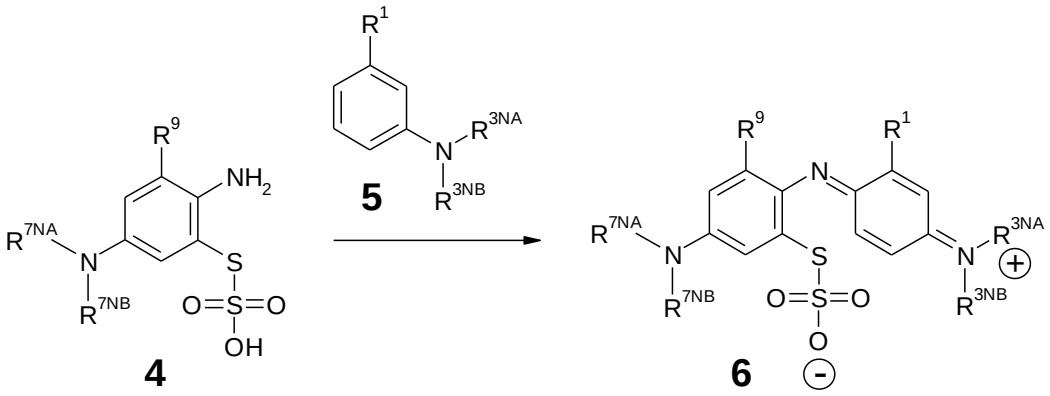
thiosulfonic acid formation (TSAF), in which an *N,N*-disubstituted-1,4-diamino-5-optionally substituted benzene, **3**, is oxidized in the presence of a thiosulfate to give said thiosulfuric acid S-{2-(amino)-3-(optionally substituted)-5-(disubstituted-amino)-phenyl} ester, **4**:



3 **4**

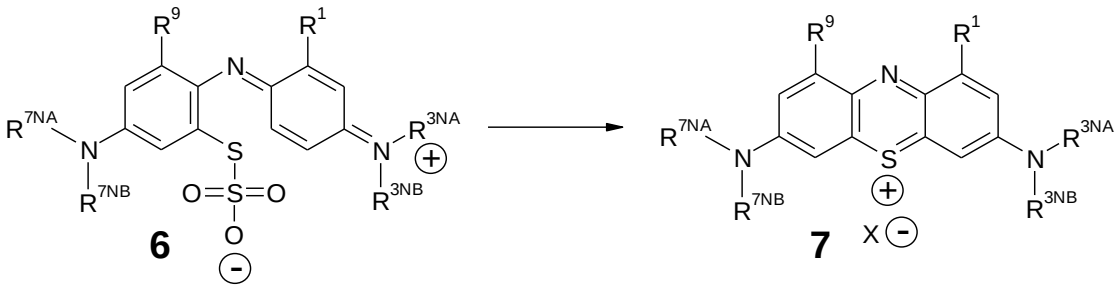
wherein during or prior to the thiosulfonic acid formation an activating agent is added,

oxidative coupling (OC), in which a thiosulfuric acid S-{2-(amino)-3-(optionally substituted)-5-(disubstituted amino)-phenyl} ester, **4**, is oxidatively coupled to an *N,N*-disubstituted-3-optionally substituted-aniline, **5**, using an oxidizing agent that is or comprises Cr(VI), to give a [4-{2-(thiosulfate)-4-(disubstituted amino)-6-(optionally substituted)-phenyl-imino}-3-(optionally substituted)-cyclohexa-2,5-dienylidene]-*N,N*-disubstituted ammonium, **6**:



4 **5** **6**

ring closure (RC), in which said [4-{2-(thiosulfate)-4-(disubstituted amino)-6-(optionally substituted)-phenyl-imino}-3-(optionally substituted)-cyclohexa-2,5-dienylidene]-*N,N*-disubstituted ammonium, **6**, is subjected to ring closure to give a 3,7-bis(disubstituted-amino)-1,9-(optionally substituted)-phenothiazin-5-ium salt, **7**:



wherein;

each of R^1 and R^9 is independently selected from: -H; C_{1-4}alkyl; C_{2-4}alkenyl; and halogenated C_{1-4}alkyl;

each of R^{3NA} and R^{3NB} is independently selected from: C_{1-4}alkyl; C_{2-4}alkenyl; and halogenated C_{1-4}alkyl;

each of R^{7NA} and R^{7NB} is independently selected from: C_{1-4}alkyl; C_{2-4}alkenyl; and halogenated C_{1-4}alkyl; and

X^- is a halide counter ion

wherein each of R^1 and R^9 is independently selected from: -H; C_{1-4}alkyl; C_{2-4}alkenyl; and halogenated C_{1-4}alkyl;

each of R^{3NA} and R^{3NB} is independently selected from: C_{1-4}alkyl; C_{2-4}alkenyl; and halogenated C_{1-4}alkyl;

each of R^{7NA} and R^{7NB} is independently selected from: C_{1-4}alkyl; C_{2-4}alkenyl; and halogenated C_{1-4}alkyl; and

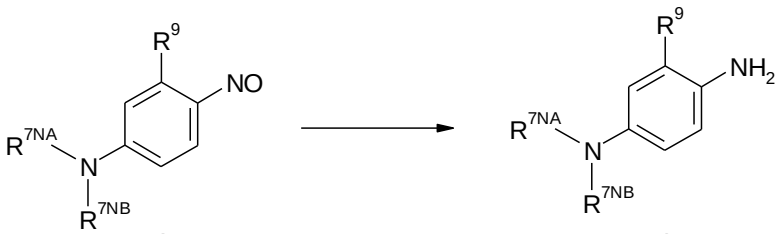
with the proviso that the compound is **not** a $ZnCl_2$ mixed salt.

2. A method according to claim 1, wherein the activating agent is or comprises Al(III).

3. A method according to claim 2, wherein the activating agent is or comprises aluminium sulphate hexadecahydrate.

4. A method of synthesis according to any one of claims 1 to 3, further comprising, before said thiosulfonic acid formation (TSAF) step, the additional step of:

nitrosyl reduction (NR), in which an *N,N*-disubstituted-3-optionally substituted-4-nitrosyl aniline, **2**, is reduced to form said *N,N*-disubstituted-1,4-diamino-5-optionally substituted benzene, **3**:

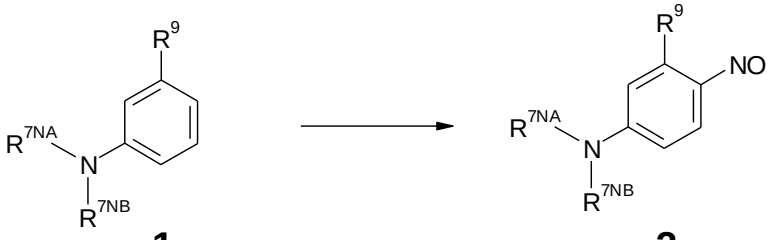


2 **3**

5. A method according to claim 4, wherein the nitrosylation (NOS) step, the thiosulfonic acid formation (TSAF) step and the oxidative coupling (OC) step are all completed in the same pot.

6. A method of synthesis according to claim 4 or claim 5, further comprising, before said nitrosyl reduction (NR) step, the additional step of:

nitrosylation (NOS), in which an *N,N*-disubstituted-3-optionally substituted aniline, **1**, is 4-nitrosylated to give said *N,N*-disubstituted-3-optionally substituted-4-nitrosyl aniline, **2**:



1 **2**

7. A method according to any one of the preceding claims further comprising

after said oxidative coupling (OC) step, and

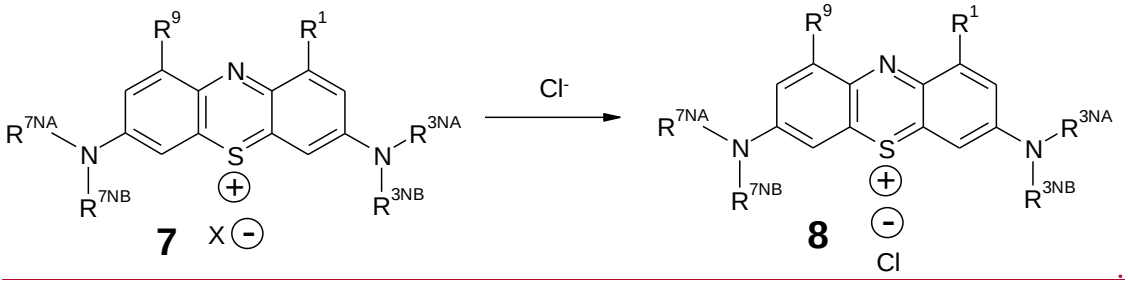
after said chromate reduction (CR) step if present, and

before said ring closure (RC) step,

isolation and purification of zwitterionic intermediate (IAPOZI), in which said [4-{2-(thiosulfate)-4-(disubstituted amino)-6-(optionally substituted)-phenyl-imino}-3-(optionally substituted)-cyclohexa-2,5-dienylidene]-*N,N*-disubstituted ammonium, **6**, is isolated and purified.

8. A method of synthesis according to any one of the preceding claims, further comprising, after said ring closure (RC) step, the additional step of:

chloride salt formation (CSF), in which said 3,7-bis(disubstituted-amino)-1,9-(optionally substituted)-phenothiazin-5-ium salt, **7**, is reacted with chloride, to give a 3,7-bis(disubstituted-amino)-1,9-(optionally substituted)-phenothiazin-5-ium chloride salt, **8**:



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9. A method according to any one of the preceding claims, wherein the method comprises at least one filtration, and wherein a filtration agent is added to the reaction pot prior to that filtration.

10. A method according to claim 9, wherein the filtration agent is or comprises cellulose.