We Claim:

1. A method of preparing a hydrazide from hydrazine and an acyl chloride comprising the steps of:

   (a) preparing a stirred substantially uniform slurry comprising hydrazine and an inert solvent; and

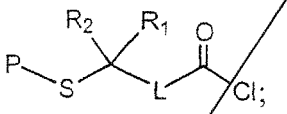
   (b) adding an acyl chloride continuously to said slurry.

2. The method according to claim 1 wherein the acyl chloride is added substantially drop wise to the slurry.

3. The method according to claim 1 or 2 wherein the acyl chloride further comprises a protected thiol.

4. The method according to claim 3 wherein the acyl chloride comprises a benzyl thioether.

5. The method according to claim 1 or 2 wherein the acyl chloride has the structure:



   wherein P is a thiol protecting group;

   R_1 and R_2 are each selected from the group consisting of C_1-C_5 alkyl;

   L is an alkylene linker.

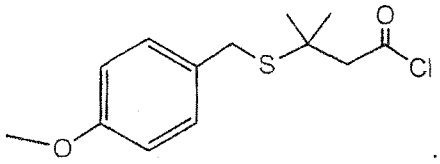
6. The method according to claim 5 wherein L is $-CH_2-$.

7. The method according to claim 5 or 6 wherein R_1 and R_2 are each independently methyl.

8. The method according to claim 5, 6 or 7 wherein P is a benzyl group, optionally substituted on the phenyl ring.

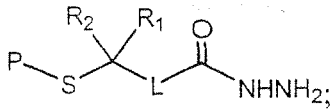
9. The method according to claim 8 wherein P is *p*-methoxybenzyl group.

10. The method according to claim 1 or 2 wherein the acyl chloride has the structure:



11. The method according to any one of claims 1 to 10 wherein the inert solvent is methylene chloride.

12. The method according to claim 1, 2 or 11 wherein said hydrazide product has the structure:



wherein P is a thiol protecting group;

R_1 and R_2 are each selected from the group consisting of C_1-C_5 alkyl;

L is an alkylene linker.

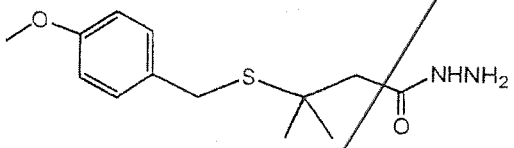
13. The method according to claim 12 wherein L is $-CH_2-$.

14. The method according to claim 12 wherein R_1 and R_2 are each independently methyl.

15. The method according to claim 12 wherein P is a benzyl group, optionally substituted on the phenyl ring.

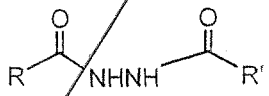
16. The method according to claim 15 wherein P is *p*-methoxybenzyl group.

17. The method according to claim 12 wherein the desired hydrazide is



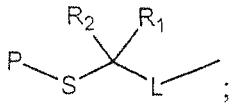
or a salt thereof.

18. The method according to any one of claims 1 to 16 wherein the hydrazide contains less than 5% of a bis-hydrazide by-product having the structure:



wherein R and R' are optionally substituted alkyl, heteroalkyl, or heteroalkaryl groups.

19. The method according to claim 18 wherein R and R' are

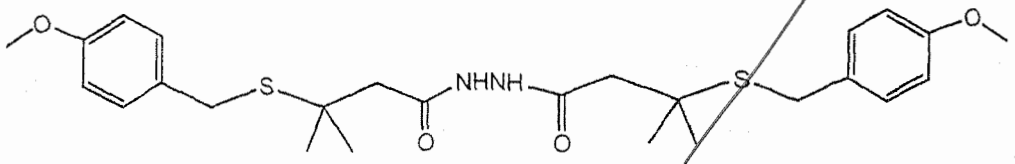


wherein P is a thiol protecting group;

R_1 and R_2 are each selected from the group consisting of C_1-C_5 alkyl;

L is an alkylene linker.

20. The method according to claim 19 wherein L is $-CH_2-$.
21. The method according to claim 20 wherein R_1 and R_2 are each independently methyl.
22. The method according to claim 19 wherein P is a benzyl group, optionally substituted on the phenyl ring.
23. The method according to claim 22 wherein P is *p*-methoxybenzyl group.
24. The method according to claim 23 wherein the bis-hydrazide by-product has a structure:



25. The method according to any one of claims 1 to 24 wherein the continuous addition of acid chloride solution is adjusted to maintain reaction temperature of about -68 °C to about -75°C.
26. The method according to any one of claims 1 to 25 wherein the hydrazine slurry is substantially uniform.
27. A method of preparing a compound containing a hydrazide linkage comprising the steps of:

(a) cooling a reaction vessel comprising a stirred inert solvent to a desired low temperature;

(b) adding hydrazine in a continuous fashion to said reaction vessel thereby preparing a stirred substantially uniform slurry comprising the hydrazine and the inert solvent;

(c) adding an acid chloride to said slurry in a continuous fashion, thereby forming a hydrazide linkage.

28. The method of claim 27 wherein the inert solvent is methylene chloride.
29. A method of preparing a hydrazine slurry comprising the steps of:

(a) chilling an inert solvent to a temperature of about –68 °C to about –75 °C;

and

(b) adding hydrazine dissolved in an inert solvent drop wise to the cold inert solvent.

30. The method according to claim 29 wherein the inert solvent is methylene chloride.

31. The method according to claim 29 or 30 wherein the hydrazine slurry is stirred at a speed of about 270 to about 400 rpm.

32. A method of preparing 3-methyl-3-mercaptobutanoic acid hydrazide comprising the step of preparing a hydrazide according to the method of claim 16.

33. A method of preparing an immunoconjugate of a member of the family of calicheamicins with a monoclonal antibody as carrier, which comprises preparing a monoacylated hydrazine where the acyl group contains an S-protected mercapto function. according to a method as claimed in claim 3, removing the protecting group of the S-protected mercapto function. and using the resultant hydrazide for preparing said immunoconjugate.

34. A method as claimed in claim 33 wherein said resultant hydrazide is 3-methyl-3-mercaptobutanoic acid hydrazide.

35. A method as claimed in claim 34 wherein 3-methyl-3-mercaptobutanoic acid hydrazide is used as linker to make gemtuzumab ozogamicin or inotuzumab ozogamicin.

CLAIMS

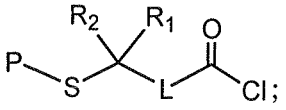
1. A method of preparing a hydrazide from hydrazine and an acyl chloride, comprising
(a) a step of preparing a stirred uniform slurry comprising hydrazine and an inert solvent; and
(b) a step of adding an acyl chloride continuously to said slurry.

2. The method according to claim 1 wherein the acyl chloride is added drop wise to the slurry.

3. The method according to claim 1 or 2 wherein the acyl chloride further comprises a protected thiol moiety.

4. The method according to claim 3 wherein the acyl chloride comprises a benzyl thioether moiety.

5. The method according to claim 1 or 2 wherein the acyl chloride has the structure:



wherein P is a thiol protecting group;
R_1 and R_2 are each selected from the group consisting of C_1-C_5 alkyl;
L is an alkylene linker.

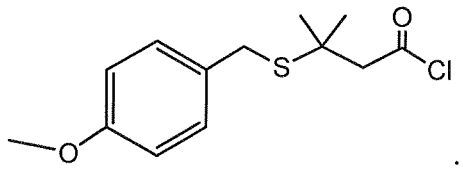
6. The method according to claim 5 wherein L is $-CH_2-$.

7. The method according to claim 5 or 6 wherein R_1 and R_2 are each independently methyl.

8. The method according to claim 5, 6 or 7 wherein P is a benzyl group, optionally substituted on the phenyl ring.

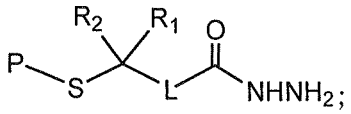
9. The method according to claim 8 wherein P is *p*-methoxybenzyl group.

10. The method according to claim 1 or 2 wherein the acyl chloride has the structure:



11. The method according to any one of claims 1 to 10 wherein the inert solvent is methylene chloride.

12. The method according to claim 1, 2 or 11 wherein said hydrazide product has the structure:



wherein P is a thiol protecting group;
R_1 and R_2 are each selected from the group consisting of C_1-C_5 alkyl;
L is an alkylene linker.

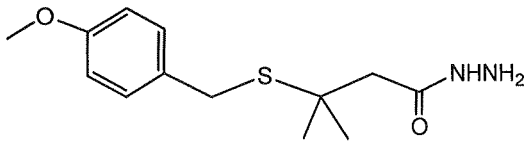
13. The method according to claim 12 wherein L is $-CH_2-$.

14. The method according to claim 12 wherein R_1 and R_2 are each independently methyl.

15. The method according to claim 12 wherein P is a benzyl group, optionally substituted on the phenyl ring.

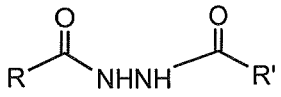
16. The method according to claim 15 wherein P is *p*-methoxybenzyl group.

17. The method according to claim 12 wherein the desired hydrazide is



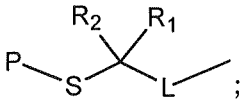
or a salt thereof.

18. The method according to any one of claims 1 to 16 wherein the hydrazide contains less than 5% of a bis-hydrazide by-product having the structure:



wherein R and R' are optionally substituted alkyl, heteroalkyl, or heteroalkaryl groups.

19. The method according to claim 18 wherein R and R' are



wherein P is a thiol protecting group;
R_1 and R_2 are each selected from the group consisting of C_1-C_5 alkyl;
L is an alkylene linker.

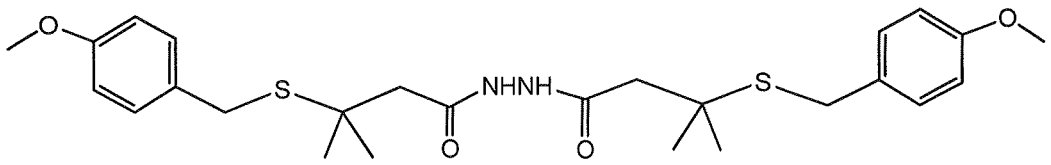
20. The method according to claim 19 wherein L is $-CH_2-$.

21. The method according to claim 20 wherein R_1 and R_2 are each independently methyl.

22. The method according to claim 19 wherein P is a benzyl group, optionally substituted on the phenyl ring.

23. The method according to claim 22 wherein P is *p*-methoxybenzyl group.

24. The method according to claim 23 wherein the bis-hydrazide by-product has a structure:



25. The method according to any one of claims 1 to 24 wherein the continuous addition of acyl chloride solution is adjusted to maintain reaction temperature of -68°C to -75°C.

26. The method according to any one of claims 1 to 25 wherein the hydrazine slurry is uniform.

27. A method of preparing a compound containing a hydrazide linkage, comprising
(a) a step of cooling a reaction vessel comprising a stirred inert solvent to a low temperature;
(b) a step of adding hydrazine in a continuous fashion to said reaction vessel thereby preparing a stirred uniform slurry comprising the hydrazine and the inert solvent;
(c) a step of adding an acyl chloride to said slurry in a continuous fashion, thereby forming a hydrazide linkage.

28. The method of claim 27 wherein the inert solvent is methylene chloride.

29. A method of preparing a hydrazine slurry, comprising
(a) a step of chilling an inert solvent to a temperature of -68°C to -75°C;
and
(b) a step of adding hydrazine dissolved in an inert solvent drop wise to the cold inert solvent.

30. The method according to claim 29 wherein the inert solvent is methylene chloride.

31. The method according to claim 29 or 30 wherein the hydrazine slurry is stirred at a speed of 270 to 400 rpm.

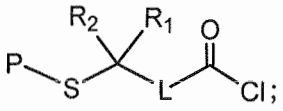
32. A method of preparing 3-methyl-3-mercaptobutanoic acid hydrazide comprising the step of preparing a hydrazide according to the method of claim 16.

33. A method of preparing an immunoconjugate of a member of the family of calicheamicins comprising a monoclonal antibody as carrier, which comprises a preparing a monoacylated hydrazide where the acyl group contains an S-protected mercapto function, according to a method as claimed in claim 3, removing the protecting group of the S-protected mercapto function, and using the resultant hydrazide for preparing said immunoconjugate.

34. A method as claimed in claim 33 wherein said resultant hydrazide is 3-methyl-3- mercaptobutanoic acid hydrazide.

35. A method as claimed in claim 34 wherein 3-methyl-3-mercaptobutanoic acid hydrazide is used as linker to make gemtuzumab ozogamicin or inotuzumab ozogamicin.

36. A method of preparing a hydrazide compound from hydrazine and an acyl chloride, comprising
(a) a step preparing a stirred uniform slurry comprising hydrazine and an inert solvent, and
(b) a step of continuously adding an acyl chloride to said slurry, wherein said acyl chloride has the following structure



in which P is a thiol protecting group;
R_1 and R_2 are each selected from the group consisting of C_1-C_5 alkyl;
L is an alkylene linker;
wherein said continuous addition of acyl chloride solution is adjusted to maintain reaction temperature of -65°C to -75°C.