AMINO ACID ACYLATION REAGENTS AND METHODS OF USING THE SAME

TECHNICAL FIELD

[1] This application claims priority to, and the benefit of, US Provisional Patent Application No. 62/134,065, entitled AMINO ACID ACYLATION REAGENTS AND METHODS OF USING THE SAME, which was filed March 17, 2015. The contents of this application are herein incorporated by reference in their entirety for all purposes.

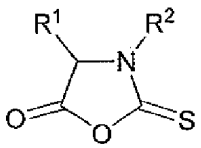
[2] The present disclosure relates to amino acid acylation reagents and methods of acylating nucleophiles with the same.

BACKGROUND

[3] α-Amino acids are the basic structural units of proteins and present in the chemical structures of many biologically important compounds. The alpha carbon of α-amino acids, when bonded to a non-hydrogen side chain, is a chiral center. Such amino acids, *e.g.*, alanine, can be one of two stereoisomers, designated L- and D-. An amino acid's stereochemistry can influence a compound's biological properties, including, for example, maytansinoid's properties. Maytansinoids are cytotoxic compounds structurally related to the natural product maytansine. Maytansinoids include C-3 esters of maytansinol, such as C-3 amino acid esters of maytansinol and derivatives of the same. It has been reported that certain C-3 N-methyl-L-alanine esters of maytansinol are more cytotoxic than those of the corresponding D- form. Current methods of synthesizing stereomerically pure C-3 amino acids esters of maytansinol require multiple steps, involve low-yielding reactions, require hard-to-access reagents, and/or require purification steps to remove undesired stereoisomers. Thus, there is need for synthetic methods that efficiently install amino acids, *e.g.*, to provide esters such as C-3 esters of maytansinol, with high stereomeric purity.

SUMMARY

[4] Disclosed herein are compounds of Formula (I):



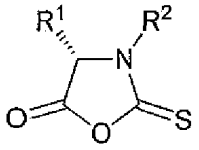
(I)

wherein:

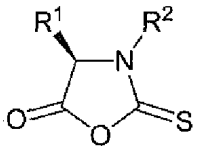
R^1 is alkyl, alkenyl, alkynyl, aryl, alkaryl, aralkyl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroaryl, or an amino acid side chain, and

R^2 is a hydrogen atom, alkyl, alkenyl, alkynyl, aryl, alkaryl, aralkyl, heteroalkyl, heteroalkenyl, heteroalkynyl, or heteroaryl.

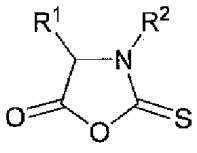
[5] Furthermore, disclosed herein are methods of acylating a nucleophile comprising contacting said nucleophile with a compound of Formula (I) in the presence of one or more Lewis acids and one or more bases. In some examples, the compound of Formula (I) is a compound of Formula (Ia) or (Ib):

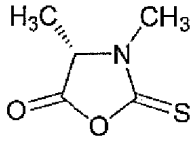


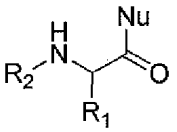
(Ia)

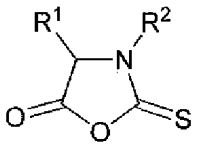


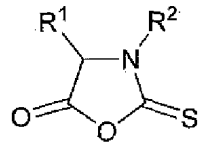
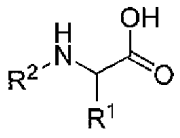
(Ib)

wherein R^1 and R^2 are as defined above. In certain examples, the methods provide an amino acid coupled product that is stereomerically pure. In one aspect, the present invention refers to a compound of Formula (I)  (I) or a salt thereof, wherein R_1 is alkyl and R_2 is alkyl. In another aspect, the present invention refers to a compound of Formula (Iaa)

 (Iaa) wherein the compound is stereomerically pure. In yet another aspect, the present invention refers to a method of preparing a compound of Formula (II)

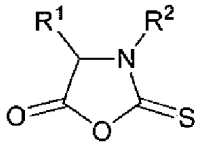


(II) comprising contacting a compound of Formula (I)  (I) with a nucleophile in the presence of one or more Lewis acids and one or more bases, wherein R^1 is alkyl, R^2 is alkyl, and Nu is an appended portion of the nucleophile, to form the compound of Formula (II). In a further aspect, the present invention refers to a method of preparing a compound of

Formula (I)  (I) or a salt thereof, wherein R_1 is alkyl, and R_2 is alkyl, comprising contacting a compound of Formula (III)  (III) with 1,1'-thiocarbonyldiimidazole in the presence of one or more bases.

DETAILED DESCRIPTION

[6] Provided herein are compounds of Formula (I):



(I)

wherein:

R^1 is alkyl, alkenyl, alkynyl, aryl, alkaryl, aralkyl, or an amino acid side chain containing at least one carbon, and

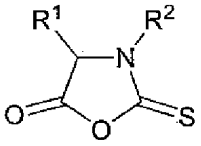
R^2 is a hydrogen atom, alkyl, alkenyl, alkynyl, aryl, alkaryl, or aralkyl.

[7] Furthermore, provided herein are processes for acylating a nucleophile comprising contacting said nucleophile with a compound of Formula (I) in the presence of one or more Lewis acids and one or more bases.

CLAIMS

We claim:

1. A compound of Formula (I):



(I)

or a salt thereof, wherein:

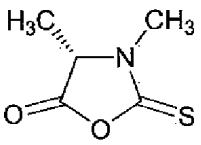
R^1 is alkyl and

R^2 is alkyl.

2. The compound of claim 1, wherein R^1 and R^2 are each, independently, unsubstituted $C_{1\text{-}20}$ alkyl.

3. The compound of claim 5, wherein R^1 and R^2 are each methyl.

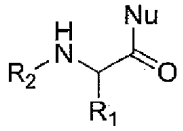
4. A compound of Formula (Iaa):



(Iaa)

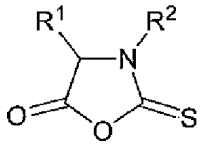
wherein the compound is stereomerically pure.

5. A method of preparing a compound of Formula (II):



(II)

comprising contacting a compound of Formula (I):



(I)

with a nucleophile in the presence of one or more Lewis acids and one or more bases,

wherein:

R^1 is alkyl,

R^2 is alkyl, and

Nu is an appended portion of the nucleophile,

to form the compound of Formula (II).

6. The method of claim 5, wherein nucleophile is an alcohol.

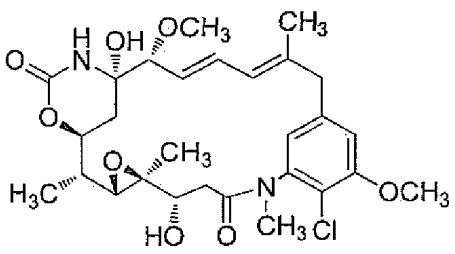
7. The method of claim 5 or 6, wherein the alcohol is a compound having the formula R^A-OH, wherein R^A is alkyl, alkenyl, alkynyl, alkaryl, aralkyl, aryl, heteroalkyl, heteroalkenyl, heteroalkynyl, or heterocycloalkyl.

8. The method of any of claims 5-7, wherein R^1 and R^2 are each, independently, unsubstituted C_{1-20} alkyl.

9. The method of any of claims 5-8, wherein R^1 and R^2 are methyl.

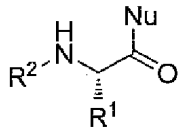
10. The method of any of claims 5-9, wherein the nucleophile is a maytansinoid having a C-3 hydroxyl group.

11. The method of any of claims 5-10, wherein the nucleophile is a compound of Formula (IV):



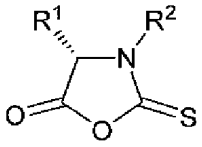
(IV).

12. The method of any of claims 5-11, wherein the compound of Formula (II) is a compound of Formula (IIa):



(IIa)

and the compound of Formula (I) is a compound of Formula (Ia):



(Ia),

wherein the compounds of Formula (Ia) and (IIa) are stereomerically pure.

13. The method of any of claims 5-12, wherein R^1 and R^2 are methyl.

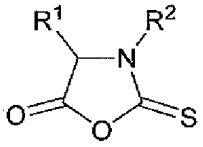
14. The method of any of claims 5-13, wherein the one or more Lewis acids are selected from the group consisting of $Zn(OTf)_2$, AgOTf, $Sc(OTf)_3$, $Cu(OTf)_2$, $Fe(OTf)_2$, $Ni(OTf)_2$, or $Mg(OTf)_2$.

15. The method of any of claims 5-14, wherein the one or more bases are selected from the group consisting of triethylamine, tributylamine, diisopropylethylamine, 1,8-diazabicycloundec-7-ene, and 2,6-di-tert-butylpyridine.

16. The method of any of claims 5-15, wherein the method is performed in a diluent comprising one or more polar aprotic solvents selected from the group consisting of diethyl ether, tetrahydrofuran, N,N-dimethylformamide, 2-methyltetrahydrofuran, 1,4-dioxane, and N,N-dimethylacetamide.

17. The method of any of claims 12-16, wherein the compound of Formula (Ia) prepared has an enantiomeric excess of at least 95%.

18. A method of preparing a compound of Formula (I):



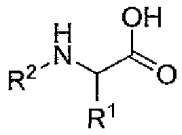
(I)

or a salt thereof, wherein:

R_1 is alkyl, and

R_2 is alkyl,

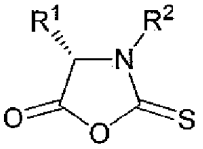
comprising contacting a compound of Formula (III):



(III)

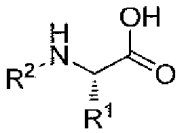
with 1,1'-thiocarbonyldiimidazole in the presence of one or more bases.

19. The method of claim 18, wherein the compound of Formula (I) is a compound of Formula (Ia):



(Ia)

and the compound of Formula (III) is a compound of Formula (IIIa):



(IIIa)

wherein the compound of Formula (IIIa) is stereomerically pure.

20. The method of any of claims 18-19, wherein R^1 and R^2 are each, independently, unsubstituted C_{1-6} alkyl.

21. The method of any of claims 18-20, wherein R^1 and R^2 are methyl.