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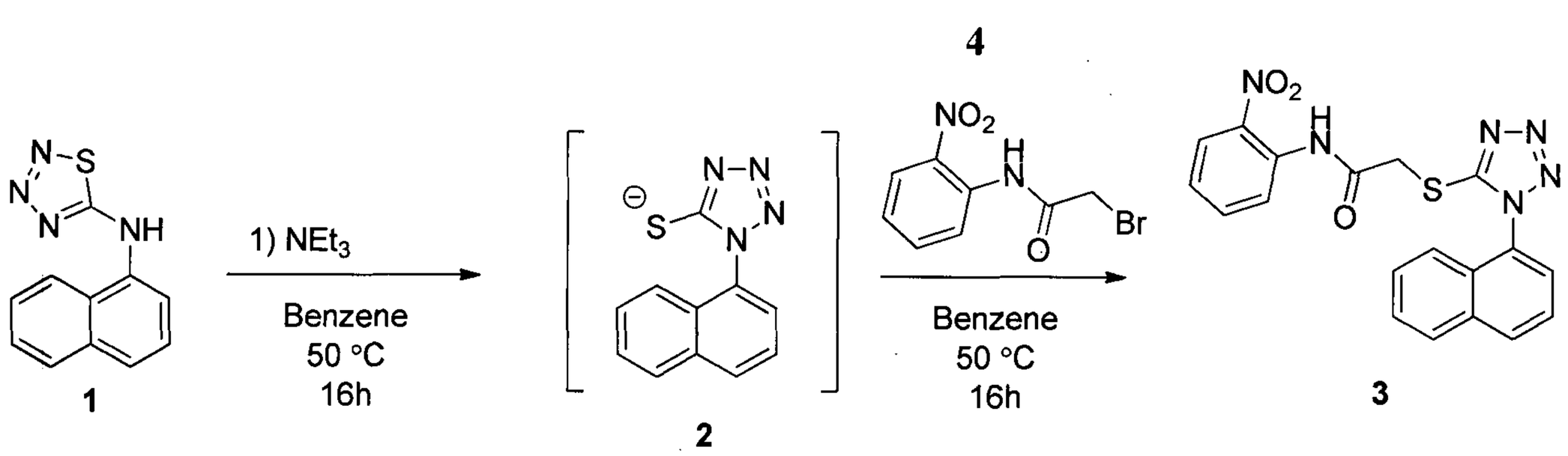
(54) **Titre : NOUVEAU PROCEDE POUR PREPARER DES INHIBITEURS DE TRANSCRIPTASE INVERSE NON NUCLEOSIDIQUE (ITINN) POUR LE TRAITEMENT DU VIH**

(54) **Title: NEW PROCESS TO MAKE NON NUCLEOSIDAL REVERSE TRANSCRIPTASE INHIBITORS (NNRTI) FOR THE TREATMENT OF HIV**



(57) **Abrégé/Abstract:**
A chemical process that can form pharmaceutically acceptable medicaments NNRTI's for the treatment of HIV starting from thiotriazole compounds. The chemical process can form thiotetrazoles such as 2-((1-(naphthalen-1-yl)-1H-tetrazol-5-yl)thio)-N-(2-nitrophenyl)actetamide that is. a potent NNRTI with nanomolar activity.

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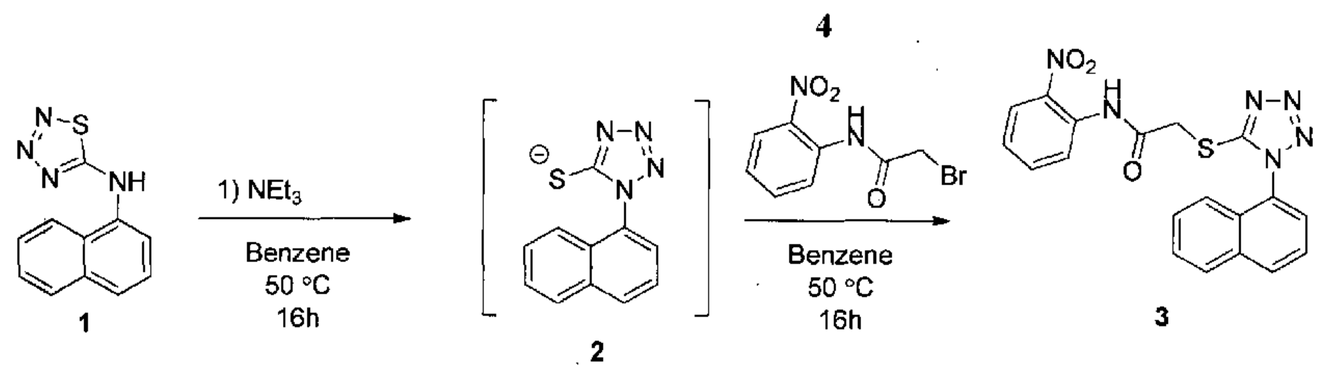
(54) Title: NEW PROCESS TO MAKE NON-NUCLEOSIDAL REVERSE TRANSCRIPTASE INHIBITORS (NNRTI) FOR THE TREATMENT OF HIV



(57) Abstract: A chemical process that can form pharmaceutically acceptable medicaments NNRTI's for the treatment of HIV starting from thiotriazole compounds. The chemical process can form thiotetrazoles such as 2-((1-(naphthalen-1-yl)-1H-tetrazol-5-yl)thio)-N-(2- nitrophenyl)actetamide that is. a potent NNRTI with nanomolar activity.

Title: New Process to make non nucleosidal reverse transcriptase inhibitors (NNRTI) for the treatment of HIV

Description:

The present invention is a new process to synthesize thiotetrazoles that can be used as non nucleosidal reverse transcriptase inhibitors (NNRTI's). The pharmaceutical acceptable salts of the thiotetrazole NNRTI's can be used for the treatment of human immunodeficiency virus (HIV) infection and for the prevention of HIV, in addition as a compliment with other therapies and medicaments used to treat HIV. It is known that compounds that inhibit the function of the HIV Reverse Transcriptase (HIV-RT) can inhibit the replication of the HIV virus in infected cells. Therefore, compounds that can inhibit HIV-RT can be useful for the treatment of HIV and be used for the prevention of contracting HIV. The thiotetrazole analogues made from the process have been shown to have nanomolar activity against HIV. In addition, thiotetrazoles and their pharmaceutical acceptable salts have been proposed to be useful molecules for the development of medicaments that can be used for the treatment of inflammatory arthritis and hyperuricemia. The thiotetrazoles and their pharmaceutical acceptable salts can also be used as research tools to develop new and/or improve current medicaments for the treatment of life altering diseases such as HIV, inflammatory arthritis, and hyperuricaemia.

The process involves the use of thiotriazoles to make a thiotetrazole anion that is trapped in situ by a suitable electrophile to form a thiotetrazole compound. Thiotriazoles are useful molecules and are used as the starting materials in this process because of their stability and safety associated with their use and storage. The thiotriazoles are converted to thiotetrazoles that can be combined with a suitable electrophile to form a molecule that can have therapeutic properties and/or can be used as a research tool to discover new medicaments in the areas of HIV infection and prophylaxis and/or inflammatory arthritis and hyperuricemia.

In one embodiment of the present invention, the process involves a solvent such as benzene, a substituted thiotriazole **1**, a base, and an electrophile that is trapped when the thiolate anion **2** is formed (Scheme 1). The thiotriazole is stirred in benzene at 60°C in the presence of triethyl amine for at least 1h and the electrophile is added and stirred for at least 1-24 hours at 60°C. The reaction is monitored using thin layer chromatography (TLC) or other analytical techniques. When the reaction is complete, the reaction has the solvent removed and is purified

using crystallization and/or silica gel chromatography to provide the product 2-((1-(naphthalen-1-yl)-1H-tetrazol-5-yl)thio)-N-(2-nitrophenyl)actetamide in 45% yield which has been shown to be a potent NNRTI with nanomolar activity against the wild type and mutated strains of HIV-1

In a second embodiment of the present invention, the process can use different bromide electrophiles and different thiotriazoles to make different NNRTI analogues that can be used as pharmaceutical preparations to treat HIV which causes Acquired Immunodeficiency Syndrome (AIDS).

In a third embodiment of the present invention is that the process has several advantages over other reported processes. For example, current processes to make thiotetrazole analogues use azides under high temperatures which can be explosive and isothiocyanates which are dangerous mutagens. This process is advantageous because it does not use these azides or nitriles.

For example, 2-((1-(naphthalen-1-yl)-1H-tetrazol-5-yl)thio)-N-(2-nitrophenyl)actetamide, compound **3** (Scheme 1), can be made by stirring in a batch flask by adding to a stirred solution of the thiatriazole **1** (50.0 mg, 0.219 mmol) in benzene (2.19 mL) and added triethylamine (40.0 µL, 0.262 mmol) forming a light yellow mixture. The reaction is then stirred for 18 h and then the bromide (56.0 mg, 0.219 mmol) was added and stirred for an additional 12 h. The reaction progress was monitored using thin layer chromatography and upon completion the reaction was quenched with water (20 mL), and extracted with dichloromethane (3 x 25 mL) and the organic layer dried over Na_2SO_4, filtered and evaporated in vacuo. The crude residue was purified using column chromatography (ethyl acetate in hexanes) to afford the pure product as a light yellow oil (25.0 mg, 45 %). IR (Thin film $CHCl_3$): 3322, 3066, 2924, 2355, 2325, 1701, 1604, 1585, 1498, 1434, 1396, 1341, 1275, 1242, 1149, 1088, 958, 913 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): 11.0 (1H, s, broad), 8.70 (1H, dd, J = 8.0, 1.0 Hz), 8.41 (1H, dd, J = 8.0, 1.0 Hz), 8.15 (1H, m), 8.01 (1H, dd, J = 8.0, 1.0 Hz), 7.54-7.52 (5H, m), 7.47 (1H, d, J = 8.0 Hz), 7.42 (1H, m), 4.28 (2H, s) ppm. ^{13}CNMR (400 MHz $CDCl_6$): 165.6, 156.1, 155.4, 136.0, 134.5, 134.0, 132.2, 129.0, 128.8, 128.7, 127.8, 126.0, 125.3, 124.4, 122.8, 128.8, 128.7, 122.0, 37.4 ppm. MS (EI) m/e (rel intensity): 407 (100), 243 (3), 230 (2), 213 (5), 211 (2), 186 (1), 169 (11), 139 (3) 113 (1) $C_{19}H_{15}N_5O_3S$. HRMS (EI) m/e $C_{19}H_{15}N_5O_3S$ calc'd mass = 407.0926, found = 407.0920.

Further, Thiotetrazole 1 can be made according to the following procedure. For example, N-(Naphthalen-1-yl)-1,2,3,4-thiatriazol-5-amine **1** was made using the general method

for thiatriazole synthesis and the crude residue was purified using silica gel chromatography (10-30% ethyl acetate in hexanes) affording the pure thiatriazole **1** as a light tan solid (1.20 g, 75 %, mp = 122 °C). IR (Thin film $CHCl_3$): 3391, 3046, 2986, 1550, 1499, 1470, 1424, 1351, 1263, 1220, 1155, 1118, 1050, 894, 741, 703 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): 11.2 (1H, s, broad), 8.12 (1H, m), 8.04 (1H, dd, J = 7.5, 1.0 Hz), 7.99 (1H, m), 7.84 (1H, d, J = 7.5 Hz), 7.64-7.56 (3H, m) ppm. ^{13}C NMR (400 MHz, DMSO-d_6): 177.5, 136.6, 134.6, 129.1, 127.3, 127.3, 127.0, 126.6, 126.6, 122.4, 119.1 ppm. MS (EI) m/e (rel intensity): 228 (4), 187 (6), 185 (100), 169 (12), 158 (17), 153 (26), 141 (22), 127 (86), 92 (6), 75 (5), 62 (2). HRMS (EI) m/e $C_{11}H_8N_4S$ calc'd mass = 228.0470, found = 228.0475.

Thiol **2** was made using the following procedure. To make 1-(Naphthalen-1-yl)-1H-tetrazole-5-thiol **2,** a stirred 50 °C solution of the napthyl triazole **1** (50.0 mg, 0.219 mmol) in benzene (2.19 mL) was added triethylamine (39.0 µL, 0.285 mmol). The reaction was stirred at 50 °C for 22 h and the quenched with water (25.0 mL) and ethyl acetate (50.0 mL), washed with 1M HCl (3 x 20 mL), water (3 x 20 mL) and brine (3 x 20 mL). The organic phase was dried over sodium sulfate and evaporated in vacuo to afford **2** as white light pink crystals (70.0 mg, 100% yield, mp = 120-122 °C). IR (Thin film $CHCl_3$): 3046, 2986, 1499, 1470, 1424, 1351, 1263, 1220, 1155, 1118, 1050, 894, 741, 703 cm^{-1}. ^1H NMR (400 MHz, DMSO-d^6): 8.21 (1H, d, J = 8.0 Hz), 8.01 (1H, d, J = 8.0 hz), 7.79-7.55 (4H, m) 7.39 (1H, d, J = 8.5 Hz) ppm. ^{13}C NMR (400 MHz, DMSO-d_6): 134.6, 132.0, 129.6, 129.0, 128.8, 128.3, 127.4, 126.4, 125.3, 122.2 ppm (missing 1 carbon). MS (ESI+) m/e (rel intensity): 229 (90), 228 (4), 227 (2), 217 (3), 213 (2), 212 (14), 204 (3), 201 (100), 200 (5), 197 (4),187 (4), 186 (6), 185 (2). HRMS (ESI) m/e $C_{11}H_9N_4S$ calc'd mass = 229.05479, found = 229.05525.

The 2-Bromo-N-(2-nitrophenyl)acetamide **4**, was made by adding to a stirred solution of o-nitro aniline (462.0 g, 2.52 mmol) in chloroform (25.0 mL) was added bromo acetyl bromide (242.0 µL, 2.77 mmol) dropwise forming a yellow precipitate. The reaction was stirred at room temperature for 12 h, then quenched with water (75 mL) and extracted with dichloromethane (3 x 50 mL). The organic washings were dried with sodium sulfate, filtered and evaporated in vacuo to afford a light brown solid (391.0 mg, 51 %). In the case that full consumption of the aniline was not achieved, the crude material was reacted again with bromo-acetyl bromide allowing for complete conversion of nitro aniline into the amide product. In this case purification was not necessary because of the high purity obtained and the quantitative yield with respect to the nitro

aniline. 'H NMR (400 MHz, Toluene-d_8): 11.2 (1H, s, broad), 8,74 (1H, d, J = 8.0 Hz), 8.26 (1H, d, J = 8.0 Hz), 7.71 (1H, t, J = 8.0 Hz), 7.27 (1H, t, J = 8.0 Hz) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): 165.1, 136.1, 134.0, 126.1, 124.4, 122.2, 29.6 ppm.

The NNRTI **3**, has been found to have nanomolar activity against the wild type strains of HIV. In a fourth embodiment of the present invention, the process is also useful for other bromides, R-Br,

R = *o*-nitro phenyl acetamide
m-nitro phenyl acetamide
p-nitro phenyl acetamide
o-methyl phenyl acetamide
m-methyl phenyl acetamide
p-methyl phenyl acetamide
o-chloro phenyl acetamide
m-chloro phenyl acetamide
p-chloro phenyl acetamide

In a fifth embodiment of the present invention, the process can use other suitable thiotriazoles that have an alkyl, or aryl, or heteroaryl group attached at the C1 position of the thiotriazole ring.

AMENDED CLAIMS
received by the International Bureau on 20 January 2015 (20.01.15)

1. A chemical process using a method selected from one of: a non-continuous method and a continuous method consisting essentially of forming thiotetrazoles using a solvent, thiotriazole, an amine, and a suitable electrophile.
2. The chemical process of claim 1 can form thiotetrazoles wherein the said thiotetrazoles comprise pharmaceutical compounds that are non-nucleosidal reverse transcriptase inhibitors (NNRTI).
3. Cancelled.
4. The chemical process of claim 1 wherein the forming step comprises an electrocyclization reaction that forms a thiolate that is trapped by the electrophile in situ.
5. The chemical process of claim 1 wherein the forming step is carried out in 1 step starting with the said thiotriazole.
6. The chemical process of claim 1 wherein the forming step is carried out in 2 steps starting with the said thiotriazole.
7. The chemical process of claim 1 wherein the solvent is benzene or any other suitable solvent.
8. The chemical process of claim 1 wherein the thiotriazole in claim 1 is a naphthalene derived thiotriazole or other C1 functionalized thiotriazole that is suitable.
9. The chemical process of claim 1 wherein the amine is triethyl amine.
10. The chemical process of claim 1 wherein the thiotetrazoles are formed after heating to at least 50°C.
11. The chemical process of claim 1 wherein the thiotetrazoles are non-nucleosidal reverse transcriptase inhibitors (NNRTI) that have inhibitory concentrations in the range of gram (g) to nanomolar (nm).
12. The chemical process of claim 1 forms pharmaceutical compounds that are non-nucleosidal reverse transcriptase inhibitors (NNRTI) wherein the thiotetrazoles are formed in chemical yields that range from 0.0001000% - 99.99%.
13. The chemical process of claim 1 wherein the method is a non-continuous method and the forming step is performed in a batch vessel that can be sealed.
14. The chemical process of claim 13 wherein the vessel holds an inert atmosphere.
15. The chemical process of claim 14 wherein the inert atmosphere is a noble gas.
16. The chemical process of claim 1 wherein the method is a continuous method and the forming step is performed in a micro flow reaction vessel comprising pre-fabricated channels and/or grooves with dimensions ranging from 0.100 micrometers to 200 micrometers.
17. The chemical process of claim 16 wherein chemical reaction solvent or fluid passes inside the said channels and/or grooves with distances travelled by the said fluid ranging from 1 cm to 1000 meters.
18. The chemical process of claim 16 wherein the said reaction vessel is capable of obtaining temperature ranges from -150°C to 400°C.

19. The chemical process of claim 16 wherein the said reaction vessel adjusts and regulates the rate of reaction fluid flow and the residence times within the said channels and/or grooves.
20. The chemical process of claim 19 wherein the said rate of reaction fluid flow in claim 19 is within the range of 0.0001000mL/minute-500.00 L/minute.
21. The chemical process of claim 19 wherein the said residence times in claim 19 are within the ranges of 0.00001 seconds-100 hours.
22. Cancelled.
23. Cancelled.
24. Cancelled.
25. Cancelled.
26. Cancelled.
27. Cancelled.
28. The chemical process of claim 1 wherein the forming step yields thiotetrazoles in at least 1% yield.
29. The chemical process of claim 1 wherein the forming step yields thiotetrazoles in at least 9% yield.
30. The chemical process of claim 1 wherein the forming step yields thiotetrazoles in at least 19% yield.
31. The chemical process of claim 1 wherein the forming step yields thiotetrazoles in at least 29% yield.
32. The chemical process of claim 1 wherein the forming step yields thiotetrazoles in at least 39% yield.
33. The chemical process of claim 1 wherein the forming step yields thiotetrazoles in at least 49% yield.
34. The chemical process of claim 1 wherein the forming step yields thiotetrazoles in at least 59% yield.
35. The chemical process of claim 1 wherein the forming step yields thiotetrazoles in at least 69% yield.
36. The chemical process of claim 1 wherein the forming step yields thiotetrazoles in at least 79% yield.
37. The chemical process of claim 1 wherein the forming step yields thiotetrazoles in at least 89% yield.
38. The chemical process of claim 1 wherein the forming step yields thiotetrazoles in at least 99% yield.
39. The chemical process of claim 1 wherein the electrophile is a bromide electrophile (R-Br), where R = is selected from the group containing: o-nitro phenyl acetamide, m-nitro phenyl acetamide, p-nitro phenyl acetamide, o-methyl phenyl acetamide, m-methyl phenyl acetamide, p-methyl phenyl acetamide, o-chloro phenyl acetamide, m-chloro phenyl acetamide, and p-chloro phenyl acetamide.

40. A chemical process that uses a solvent, an amine base, a C1 N-alkyl substituted thiotriazole and a reaction vessel to make a thiotetrazole comprising the steps of:
a) mixing the solvent and thiotriazole for any period of time,
b) adding the amine base into the reaction vessel and mixing for a period of time,
c) adding the electrophile,
d) heating the reaction vessel to a temperature between the range of 50°C and 150°C for a period of time greater than 12 hours.

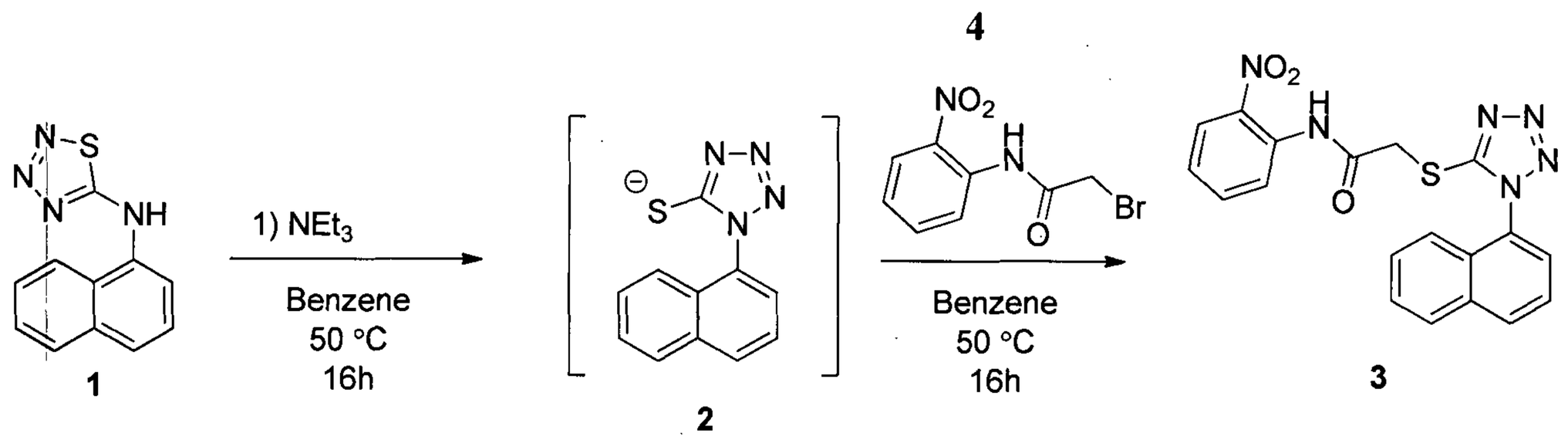
41. The chemical process of claim 40 wherein the amine base is triethyl amine.

42. The chemical process of claim 40 wherein the reaction vessel is selected from one of: a batch reactor and a micro flow reactor.

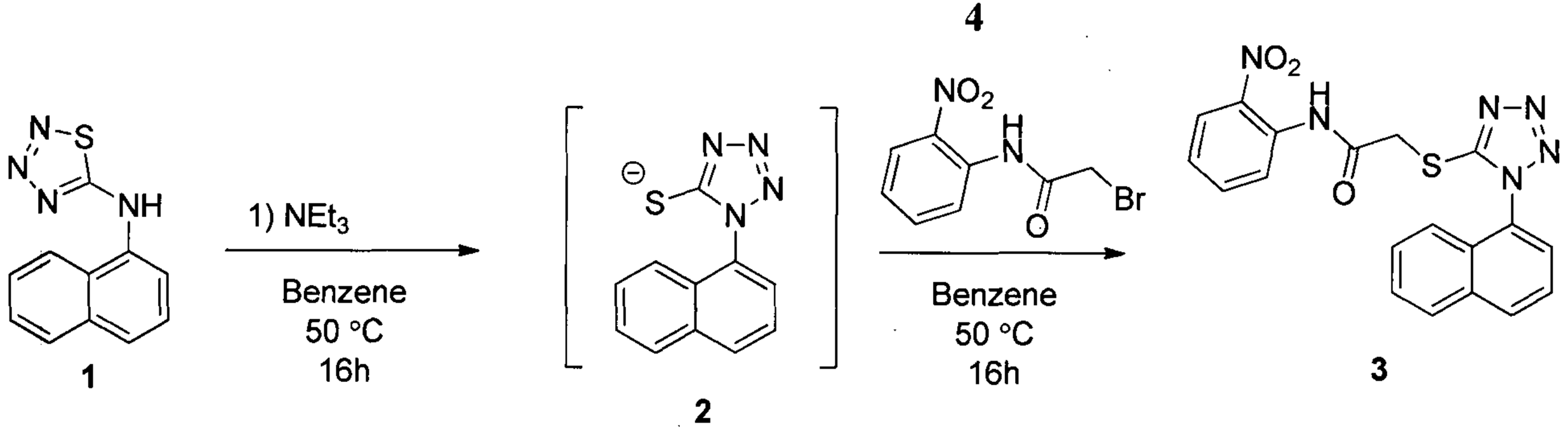
Figures

Scheme 1

Chemical process to form a NNRTI pharmaceutical compound **3** from **1**. The intermediate **2** is trapped by the bromide.



The invention is a new process to synthesize compounds effective against various strains of HIV reverse transcriptase. The thiotriazole **1** is heated in benzene at 50 °C in the presence of triethyl amine for 16h followed by addition of the bromide and stirring forming the tetrazole **3**.


4
1) NEt3
Benzene
50 °C
16h
Benzene
50 °C
16h
1
2
3