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LESINURAD – THERE ARE MORE WAYS THAN ONE OF SYNTHESIZING THE DRUG

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This paper is dedicated to Professor Yasuyuki Kita on the occasion of his 77th birthday.

Abstract – Over the last several years significant efforts have been devoted, particularly in China, to develop new syntheses of Lesinurad. Virtually all key bonds in this molecule can now be created in many different ways, often in a very high yield. Although almost all of the chemistry examples presented in this review come from patent applications and as such have not been subjected to rigorous peer review, they may serve as an inspiration to solve analogous synthetic problems. However, the readers are encouraged to pay particular attention to the very recent trends in the literature which use multicomponent reactions and flow chemistry to minimize the environmental impact and achieve high yields of API at the same time.

CONTENTS:

1. INTRODUCTION

Lesinurad (**1**, RDEA594, *Zurampic*) is a first-in-class urate anion exchange transporter 1 (URAT1) inhibitor marketed as an oral therapy for the treatment of hyperuricemia associated with gout. It was approved by FDA at the end of 2015 and soon thereafter by EMA.[1,2] It is intended to be used in conjunction with either allopurinol or febuxostat due to an increased risk of acute renal failure.[3]

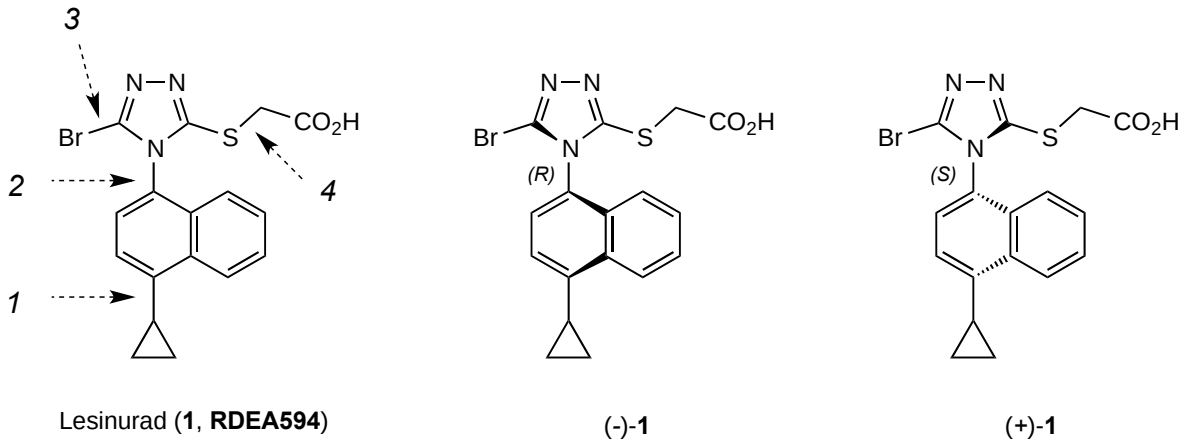


Figure 1. Lesinurad (**1**, RDEA594) and its enantiomeric forms (-)-**1** and (+)-**1**

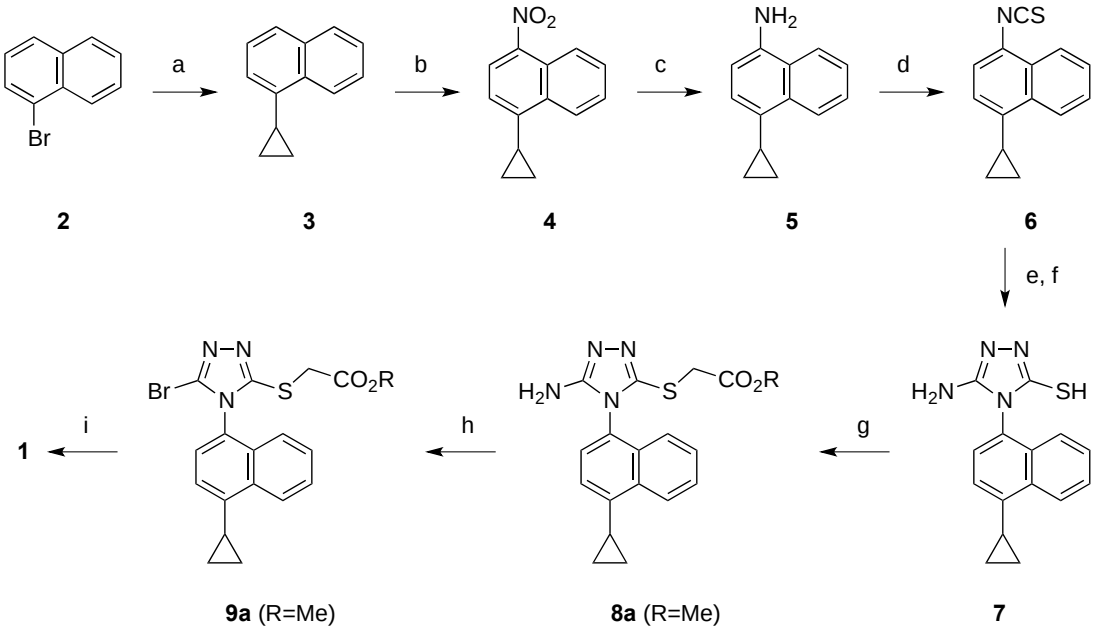
Lesinurad (**1**) exists as a mixture of stable atropisomers (-)-**1** and (+)-**1**[4,5] which can be separated either by chiral HPLC, SFC or by separation of diastereoisomeric esters with (*R*)-1-phenylethanol followed by hydrolysis.[4,6] Crystallization of salts with optically active amines has also been used for this purpose.[7,8] Interconversion between the atropisomers is slow at ordinary temperatures. The $t_{1/2}$ for isomerization is in excess of 275 days at 100 °C.[9]

The (+)-**1** isomer is more than three times more active against hURAT1 (IC_{50} 4.4 μM) than (-)-**1** (IC_{50} 15.1 μM) and is more metabolically stable in a human recombinant CYP2C9 assay.[4,9] It has been speculated that administration of a single isomer may help overcome side effects such as renal toxicity and serum creatinine elevation [4,5] but no enantiomerically pure form has reached the market, yet.

2. DISCUSSION OF SYNTHETIC STRATEGIES

2.1. The original synthesis

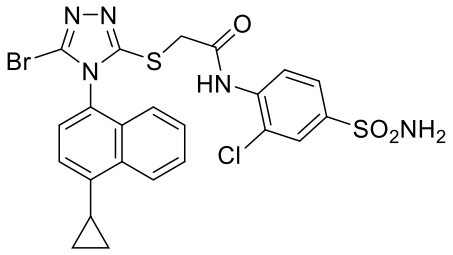
The original synthesis of racemic **1** involved derivatizing the naphthalene ring by sequential creation of the C-C, C-N, C-Br and C-S bonds (marked as *1*, *2*, *3* and *4* in Figure 1) as shown in Scheme 1.[10,11]



a) cyclopropyl-MgBr, $Cl_2Ni(dppp)_2$, THF, 0 °C to rt; 76% b) $NaNO_2$, 0 °C; 64% c) H_2, 10% Pd/C, EtOH; 73% d) $CSCl_2$, DIPEA, DCM, 0 °C; 86% e) aminoguanidine HCl, DIPEA, DMF, 50 °C, 15 h f) 2.0 M NaOH, 50 °C, 60 h; 49% g) $ClCH_2CO_2Me$, K_2CO_3, DMF, rt; 80% h) $NaNO_2$, $Et_3N^+BnBr^-$, $CHBr_3$, Cl_2CHCO_2H, rt, 3 h; 85% i) $LiOH_{aq}$, THF, EtOH, 0 °C, 45 min; 93%

Scheme 1. Original route of synthesis of Lesinurad (**1**) developed by Girardet *et al*. (Valeant Research&Development; Ardea Biosciences)[10]

Instead of the methyl ester **9a** (R=Me), the amide **10**[10] could also be hydrolyzed (NaOH, EtOH-water, reflux, 4 h; 82%)[11] to afford **1**.



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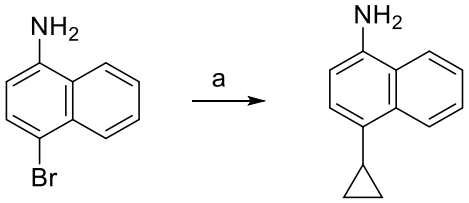
Reduction of the nitro group in **4** could also be achieved with Zn/NH_4Cl in 87% yield.[12]

2.2. Linking the cyclopropyl group with the naphthalene ring

The cyclopropyl substituent was introduced into **2** using the Kumada coupling reaction in 76% yield.[11] We found that a higher yield of 82% could be achieved via the Ni(dppp)Cl_2-catalyzed Negishi reaction.[13] A similar yield of 82% was reported recently by the scientists from Jiangxi Tonghe Pharmaceutical who used $FeCl_3$ as the catalyst in the Kumada reaction.[14] The cyclopropyl group can be incorporated directly into the skeleton using the Suzuki reaction (Scheme 2, cf Scheme 10).[15]

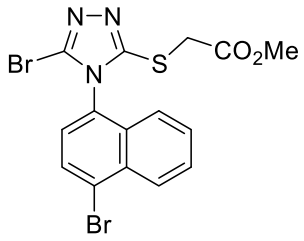


11 **5**

a) cyclopropyl-$B(OH)_2$ K_3PO_4, $Pd(PPh_3)_4$, toluene:water, 12 h, 100 °C; 84%

Scheme 2. Suzuki coupling for introduction of the cyclopropyl group[15]

A patent application by Zhao is directed at the introduction of the cyclopropyl group by reacting intermediate **12** with bromocyclopropane using a Suzuki coupling.[16]



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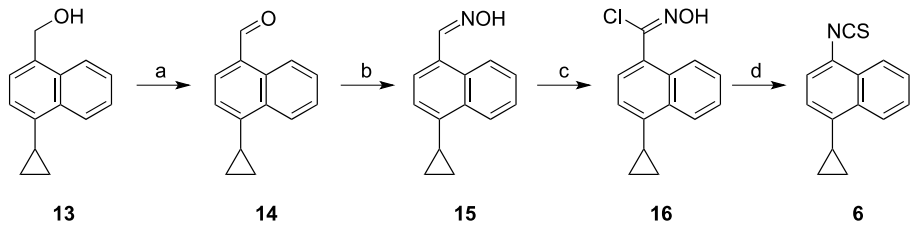
2.3. Formation of the triazole ring

Over the last 10 years or so, several improved approaches to the triazole ring have been published. For example, the original 86% yield of isothiocyanide **6** was increased to almost 95% just by replacing the base, DIPEA in $CSCl_2$-H_2CCl_2 with a biphasic aqueous system using NaOH (aq) and H_2CCl_2.[17]

The route shown in Scheme 1 is long, low-yielding (9.5%) and uses highly toxic reagents such as $CSCl_2$. However, the use of $CSCl_2$ to produce **6** can be avoided as demonstrated by inventors from Hwasun Pharmaceutical (Scheme 3).[18]

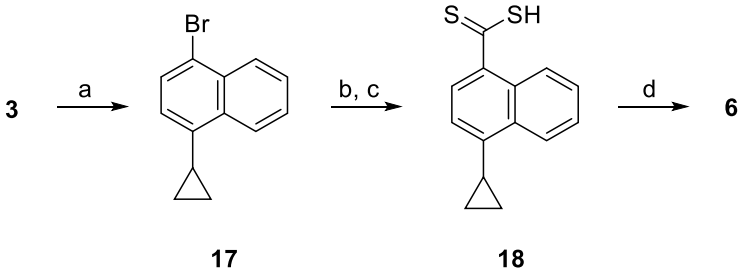


a) MnO_2, DCM, 12 h; quant b) NH_2OH•HCl, AcONa; 95% c) 1,3-dichloro-5,5-dimethylhydantoin, MeCN, 2 h; 92% d) thiourea, Et_3N, THF, 30 min; 94%.

Scheme 3. Hwasun's approach to intermediate **6**[18]

Another option for obtaining **6** by reacting **5** with di(1*H*-imidazol-1-yl)methanethione in an excellent yield of 96% was published by Meng *et al.*[15] A potentially simpler conversion of **5** into **6** with the use of NaSCN in xylenes at 140 °C was reported by scientists from Ardea Biosciences but no yields were given.[19]

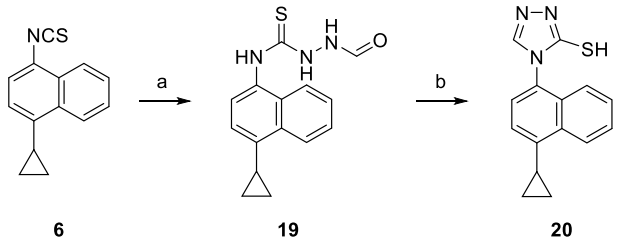
An alternative method to access thiocyanate **6** is based on the Curtius rearrangement of the azide derived from thioacid **18** (Scheme 4).[14]



a) 1,3-dibromo-5,5-dimethylhydantoin, H_2CCl_2, 30-50 °C; 91% b) Mg, THF, 2 h, 50-60 °C c) CS_2; 95% d) diphenylphosphoryl azide, Et_3N, toluene, 20 °C - reflux, 9 h; 94%

Scheme 4. An approach to intermediate **6** via Curtius rearrangement[14]

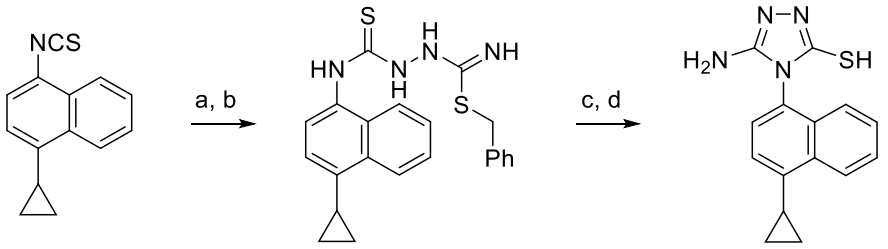
In Scheme 1 isothiocyanate **6** was used to synthesize the triazole ring in **7** in the reaction with aminoguanidine. Compound **6** can also serve as a key building block for producing triazole **20** as shown in Scheme 5.[17,19]



a) formylhydrazine, DMF, 50 - 55 °C b) K_2CO_3, DMF; no yield given

Scheme 5. Approach to intermediate **20**[17,19]

A similar approach has been used by scientists from Anhui Yixinming Pharmaceutical Technology (Scheme 6).[20]



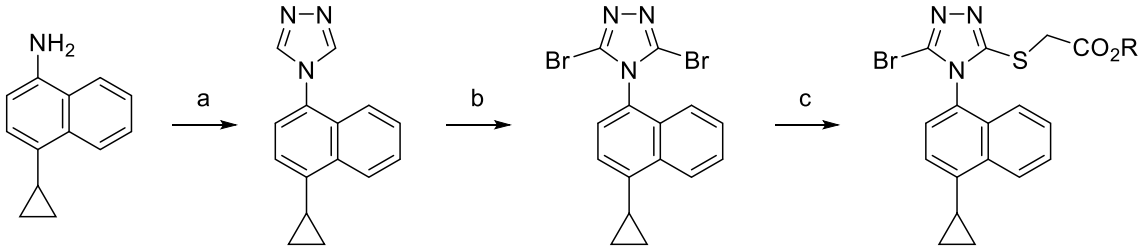
6 **21** **7**

a) $H_2NNHC(S)NH_2$, $PhCH_2Br$, EtOH, 0.5 h, reflux b) Na_2CO_3, water, overnight, rt c) EtOH, 0.5 h, reflux d) water; 77%

Scheme 6. Anhui Yixinming's approach to intermediate **7**[20]

Aminothiol **7** could be then reacted with methyl bromoacetate to afford **8a** (R=Me) in 98% yield (cf Scheme 1).

In fact, it is not necessary to use **6** since amino derivative **5** can be used directly to form the triazole ring in **21** as demonstrated by Li *et al.* (Scheme 7).[21,22]

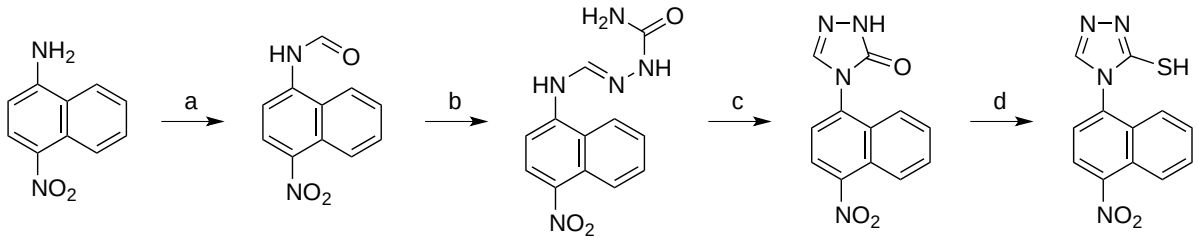


5 **21** **22** **9a** (R=Me)

a) $(HNCH_2CHO)_2$, pyridine, TMSCl, rt to reflux; 70% b) NBS, 40 °C; 85% c) $HSCH_2CO_2Me$, K_2CO_3, DMF, rt, 1 h; 50%

Scheme 7. Approach to triazole **21** by Li *et al.*[21,22]

An example of stepwise conversion of the amino group to the triazole ring via formamide **24** can be found in the patent application by Zhao (Scheme 8).[16]

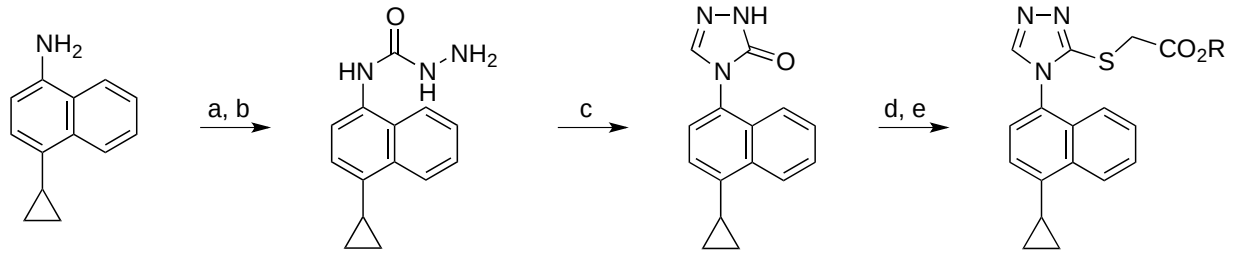


23 **24** **25** **26** **27**

a) HCO_2H, HCl, 50 °C, 2 h; 83% b) $H_2NNHC(O)NH_2$, Na_2CO_3, EtOH; 85% c) Na_2CO_3, EtOH; 95% d) SO_2, conc. H_2SO_4; 87%

Scheme 8. Approach to formamide **24** by Zhao *et al.*[16]

Another example of how the triazole ring can be assembled is shown in Scheme 9.[23]



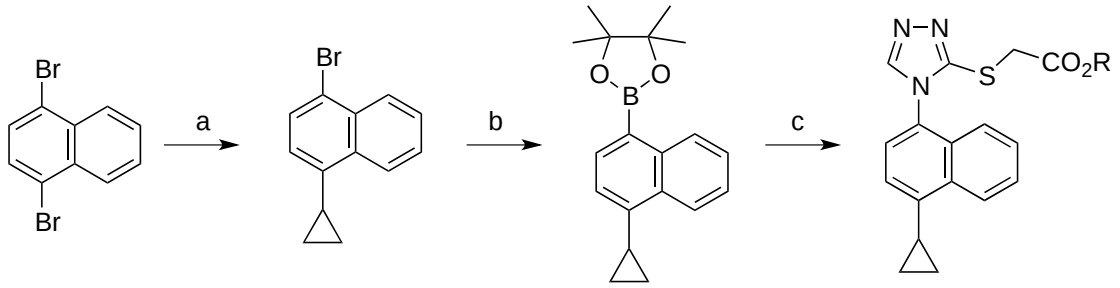
5 **28** **29** **30a** (R=Me)

a) $H_2NNHC(O)NH_2$, DABCO, DMF, 1.5 h, 45-60 °C; 2 h, 60 °C b) H_2O-MeOH 2 h, 10 °C; 85% c) $Me_2NCH(OMe)_2$, 12 h, 50 °C; 90% d) $HSCH_2CO_2Me$, DABCO, toluene, 2 h, 60 °C e) water-heptane-*t*-BuOMe, 2 h, 5-10 °C

Scheme 9. Another approach to triazole **29**[23]

2.4. Linking the triazole ring with the naphthalene core

The triazole ring in the synthetic routes shown in Schemes 1, 7, 8, 9 and 14 was built using amino derivatives (**5** or **23**) and then derivatized by adding the thioglycolic acid fragment. Chengdu Miracle Pharmaceutical proposed a different approach in which the already functionalized triazole ring is added to the naphthalene core using Chan-Lam - type chemistry (Scheme 10).[24]

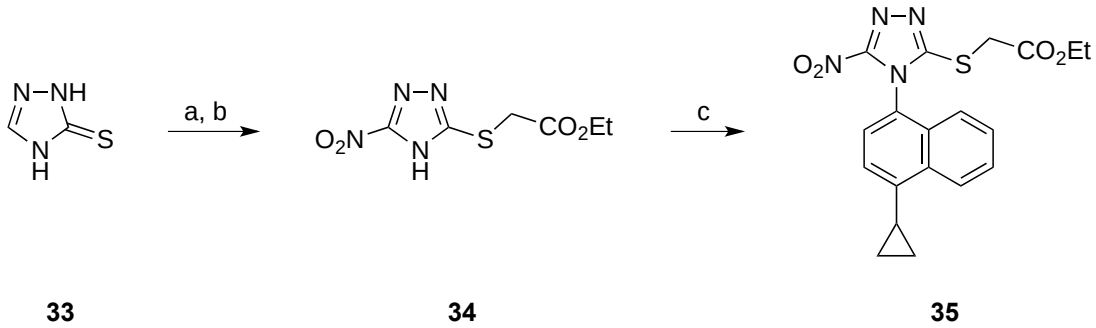


31 **17** **32** **30a** (R=Me)

a) cyclopropyl-$B(OH)_2$, K_2CO_3, $Pd(PPh_3)_4$, dioxane, 4 h, 100 °C; 87% b) bis(pinacolato)diboron, $Pd(dppf)_2$, dioxane, 18 h, 100 °C; 96% c) 2-(1*H*-1,2,4-triazol-5-ylthio)acetic acid methyl ester, CuCl, pyridine, rt; 82%

Scheme 10. Chengdu Miracle Pharmaceuticals approach to triazole **30a**[24]

Scientists from Anhui Wanbang Medical Technology proposed an approach based on Ullmann type coupling as shown in Scheme 11.[25]

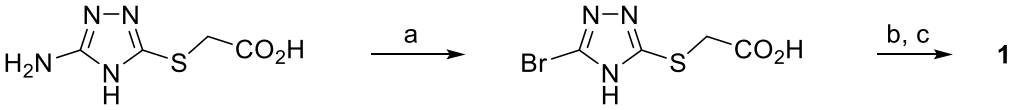


33 **34** **35**

a) $ClCH_2CO_2Et$, Et_3N, AcOEt, 1.5 h, rt to 50 °C; 95% b) $NaNO_2$, Ac_2O, 8 h, 0 °C; 75% c) **17**, CuI_2, K_3PO_4, 8-quinolinol, H_2O-toluene, 16 h, rt to reflux; 65%

Scheme 11. Anhui Wanbang's approach to triazole **35** via Ullmann type reaction[25]

A short variant of this method leading directly to **1** has been published by Xu (Scheme 12).[26]

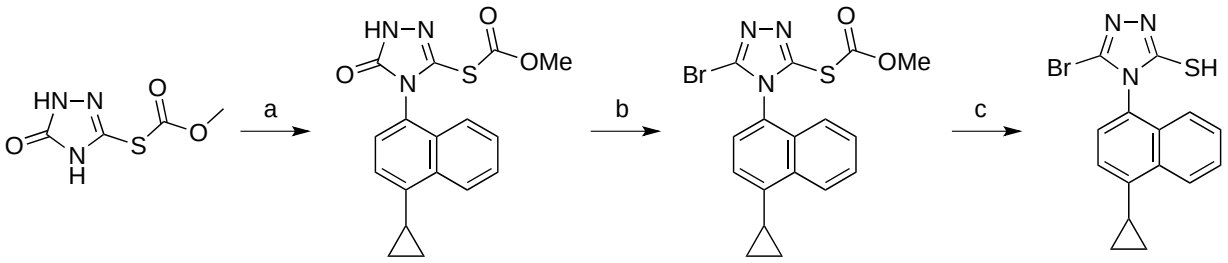


36 **37**

a) $NaNO_2$, HBr, 0.5 h, 5-10 °C b) **17**, CuBr, HBr, 5-10 °C; 30 min, rt; 63% c) K_2CO_3, $H_2NCH_2CH_2NH_2$, CuI, 8-quinolinol, DMF, rt to 100 °C; 5-7 h, 100 °C to 120 °C; 72%

Scheme 12. Recent route to Lesinurad (**1**) by Xu *et al*.[26]

Very recently, another version of the Ullmann coupling has been patented (Scheme 13).[27]



38 **39** **40** **41**

a) **17**, K_2CO_3, CuI, TMEDA, DMAC, 14-18 h, 120-130 °C; 87% b) $POBr_3$, 16 h, reflux; 90.3% c) NaOH, MeOH, 6 h, rt; 92%

Scheme 13. Recent approach to **39** via Ullmann type chemistry[27]

The thiol group in **41** was subsequently reacted with sodium chloroacetate in the presence of DIPEA to provide **1** in 92% yield.

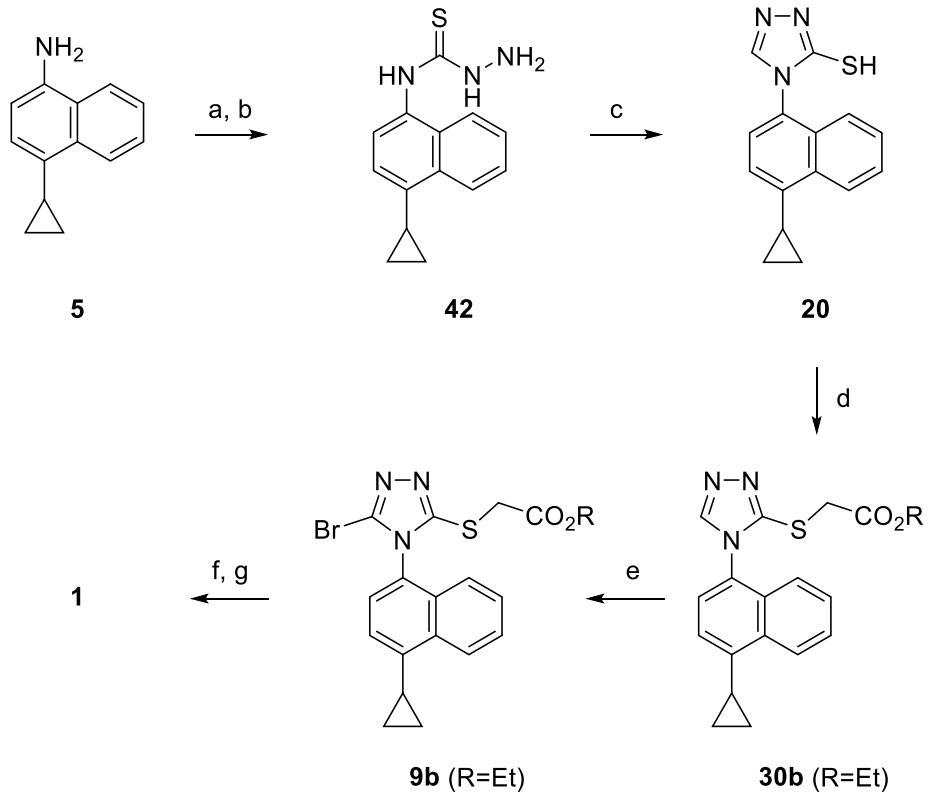
Recently, efficient *N*-arylation of azole compounds utilizing selective aryl-transfer TMP-iodonium(III) reagents has been described by Kita *et al*. but it has not been applied to the synthesis of Lesinurad, yet.[28]

2.5. Bromination of the triazole ring

The carbon-bromine bond on the triazole ring in Scheme 1 was formed using a Sandmeyer type reaction which uses toxic and corrosive reagents such as $CHBr_3$ and Cl_2CHCO_2H. An alternative involving $NaNO_2$, CuBr and HBr gave the relevant bromo derivative **37** (Scheme 12) in 63% yield.[26] A modification which uses an equimolar amount of $CuBr_2$ and KNO_2 in acetonitrile was also proposed but no yields were given.[19] However, while using less aggressive reagents, the latter process does not seem to be particularly cheap or environmentally friendly.

Another atom which could be replaced in high yield with -Br by using $POBr_3$, is oxygen (**39** to **40** in 90%; Scheme 13).[27] A lower yield of 65% was observed when the relevant oxy derivative **45a** (R=Me ; Scheme 17) was refluxed with NBS and PTSA.[29]

A shorter method patented by Suzhou Pengxu Pharmatech[30] (Scheme 14) is based on direct bromination of the triazole ring using Br_2 thus producing **9b** (R=Et).

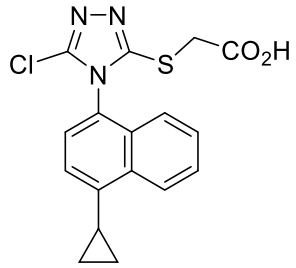


a) CS_2, NaOH, DMF, rt b) $N_2H_4.H_2O$, 60-70 °C; 50-70% c) $Me_2NCH(OMe)_2$, 1,4-dioxane; 70-80% d) $BrCH_2CO_2Et$, K_2CO_3, DMF, rt; 97% e) Br_2, pyridine, MeCN, rt; 76% or NBS, 60 °C, 2 h; 81% f) LiOH, H_2O, EtOH-THF, 0 °C g) HCl_{aq}; 99%

Scheme 14. Suzhou Pengxu Pharmatech's shorter approach to intermediate **9b**[30]

The yields are much better, but the method uses highly toxic (hydrazine, Br_2) and malodorous (CS_2) reagents. NBS can substituted for Br_2.[30] However, using an excess of NBS and elevated temperature efficiently double-brominates the triazole ring in **21** to give **22** (Scheme 7).[21]

The conditions for bromination of the triazole ring have significant impact on the quality of the final product. Researchers from Zentiva discovered that trace amounts of NCS present in commercially available NBS may lead to the formation of unacceptable amounts of impurity **43**.[31]



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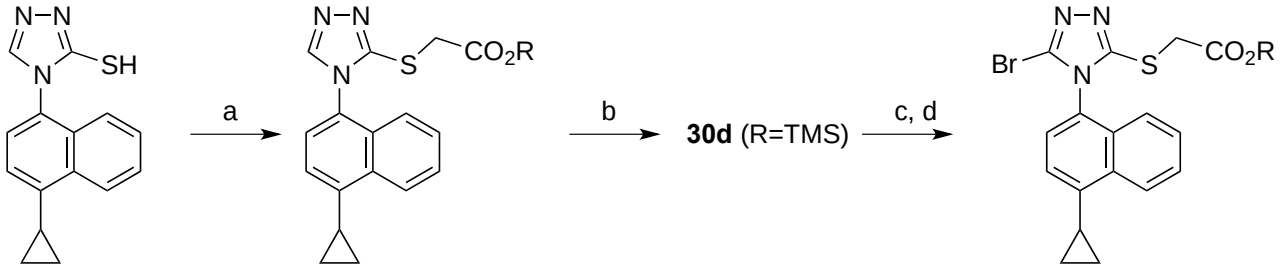
They proposed an improved bromination route starting from thiol **20** (Scheme 15).



20 **30c** (R=H) **9c** (R=*i*-PrNH$_3^+$)

a) $BrCH_2CO_2H$, $NaHCO_3$, 55 °C, 1 h; 91.9% b) *N,O*-bis(trimethylsilyl)acetamide, THF c) recrystallized NBS, THF, 55 °C, 3 h d) $^iPrNH_2$; 80%

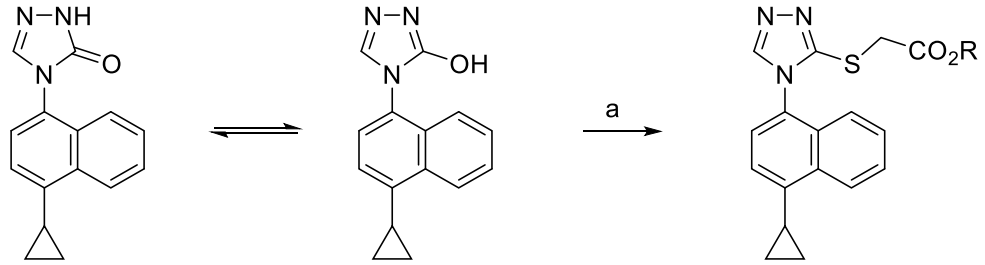
Scheme 15. Zentiva's approach to intermediate **9c** starting from **20**

The resulting ammonium salt **9c** (R=*i*-PrNH$_3$) was free of of impurity **43** and could be recrystallized to achieve 99.4% purity and converted to **1**.[31] Other brominating agents such as 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) could also be successfully used instead of NBS.[31]

2.6. Introduction of the thioglycolic acid side chain

The standard approach to the thioglycolic acid side chain is based on the reaction between the thiol group and haloacetic acid or its derivatives (Schemes 1, 14 and 15). Some improvements have been made to the way this reaction is run by using acetone-water instead of DMF as a reaction solvent.[17] Recently, esters of diols[32] and polyols were used as the substrates, allowing for a simpler workup and purification.[33]

Two alternative strategies to attach the side chain have been proposed. One involves substitution of bromo (Scheme 7)[21] or hydroxy group with thioglycolic acid residue (Scheme 16).[34]

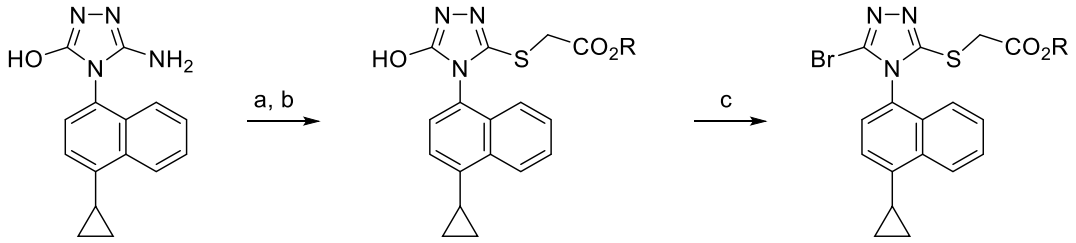


29 **30b** (R=Et)

a) $HSCH_2CO_2Et$, $H_2NCH_2CH_2CH_2NH_2$, toluene, 60 °C, 2 h; no yield given

Scheme 16. Alternative strategy to obtain intermediate **30b**

The second method utilizes the Sandmeyer type reaction (Scheme 17).[29]



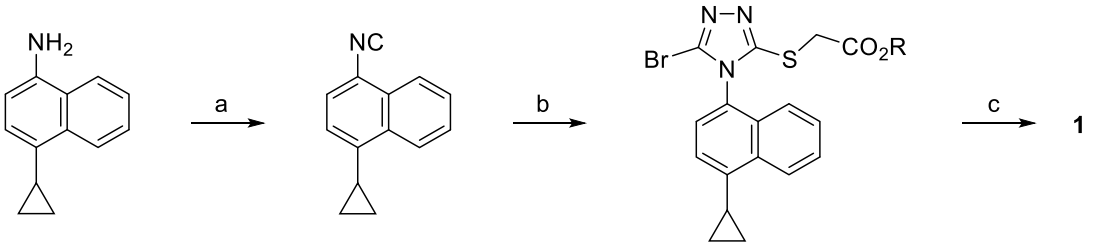
44 **45a** (R=Me) **9a** (R=Me)

a) HCl_{aq}, $NaNO_2$; 10 °C b) $HSCH_2CO_2Me$, rt, 3 h; 90% c) NBS, PTSA, H_2CCl_2, 8 h, reflux to rt; 65%

Scheme 17. Approach to **45a** (R=Me) via Sandmeyer type chemistry [29]

2.7. Application of one-pot, multicomponent and flow chemistry for the synthesis of Lesinurad

Recently, Lei *et al.* proposed a very short synthetic route leading to **1** (Scheme 18).[35]



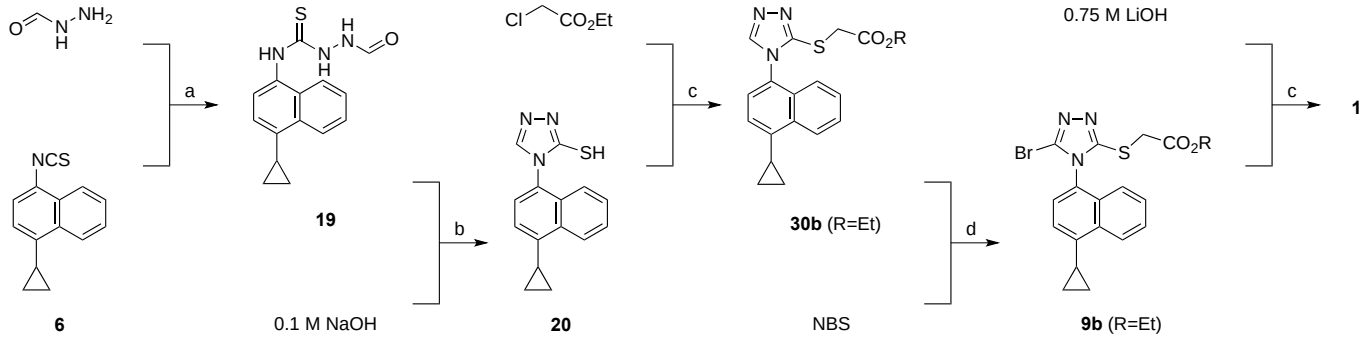
5 **46** **9a** (R=Me)

a) $CHCl_3$, NaOH, toluene; 75% b) $(SCH_2CO_2Me)_2$, TEMPO, NBS, $H_2NNHCHO$, DCE, rt; 52% c) LiOH, H_2O/EtOH; 92%

Scheme 18. Recent method to Lesinurad (**1**) by Lei *et al.*[35]

The key step is based on a three-component protocol which allowed the conversion of isocyanide **46** into Lesinurad precursor **9a** (R=Me) in 52% isolated yield.

Flow chemistry allows integration of several reaction steps and better control of reaction conditions.[36] This approach was applied by Damião *et al.* to the synthesis of Lesinurad **1** in 5 steps in 68% overall yield starting from isothiocyanate **6** and formylhydrazine (Scheme 19; cf Scheme 5).[37]



a) MeCN/DMF, 100 °C, 0.5 h b) 80 °C, 15 min c) MeCN, 100 °C, 10 min d) DCM, 80 °C, 60 min; 81% e) 60 °C, 5 min; 95%

Scheme 19. Recent method to Lesinurad (**1**) by Damião *et al*.[37]

3. CONCLUSIONS

Significant efforts have been devoted to the development of new syntheses of Lesinurad. Most of the work has been done in China which accounts for 2/3 of the references cited in this review. It is a reflection of a more general trend in the last decade.[38]

A wide variety of chemistries have been developed to create virtually all key bonds in the Lesinurad molecule, often in a high yield. Although almost all of the chemistry examples presented in this review come from patent applications and have not been subjected to rigorous peer review, they might serve as an inspiration to organic chemists when tackling analogous synthetic problems. However, the readers are encouraged to pay particular attention to the very recent trends in using multicomponent reactions[39,40] and flow chemistry[41,42] to minimize the environmental impact and simultaneously achieve high yields of API.

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