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Synthesis and characterization of some new 1,2,3-thiadiazole and 1,2,3-selenadiazole triterpene derivatives from allobetulone and 2-oxoallobetulin

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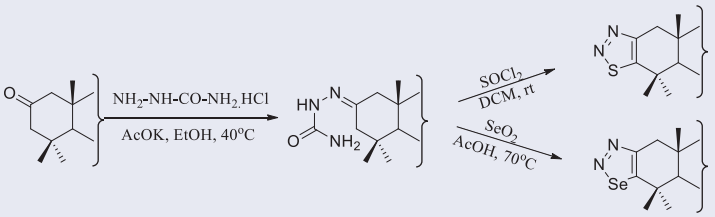
ABSTRACT

The synthesis of new 1,2,3-thiadiazole and 1,2,3-selenadiazole derivatives from triterpenoid ketones has been investigated via the corresponding semicarbazones. The intermediates **5**, **8** have also been isolated, separated and their structures identified. The Hurd–Mori reaction and Lalezari method have been applied to synthesize a series of new substances **6** and **7**. The regioselectivity of the functionalization mostly was centered at the C-3 position for the products **9** and **10**. The structures of these compounds were confirmed by 2D-NMR spectroscopy.

GRAPHICAL ABSTRACT



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KEYWORDS
Triterpenoid ketone; semicarbazone; Hurd–Mori reaction; Lalezari method

Introduction

Compounds containing 1,2,3-thiadiazole and 1,2,3-selenadiazole fragments in molecule are now being interested by scientists because they have interesting activities.[1,2] For example, derivatives of 1,3,4-thiadiazoles are known to exhibit antimicrobial activity,[3,4] antifungal activity,[5] anti-inflammatory,[6] antiviral,[7] analgesic,[8] while 1,2,3-selenadiazoles have been studied because of their potential activities as antibacterial, antimicrobial activity,[9,10] analgesic, and anti-inflammatory drugs,[11] anti HIV activity against HIV-I in MT-4 cells,[12] antitumor.[13] Although there are many routes to synthesize heterocyclic substances containing S and Se, there are only a few possible methods to synthesize these type substances. The Hurd–Mori reaction is the most widely used method in the research on 1,2,3-thiadiazoles,[14] and 1,2,3-selenadiazole derivatives are being followed by the Lalezari method.[15] Currently, few reports have appeared about the synthesis of 1,2,3-thiadiazoles

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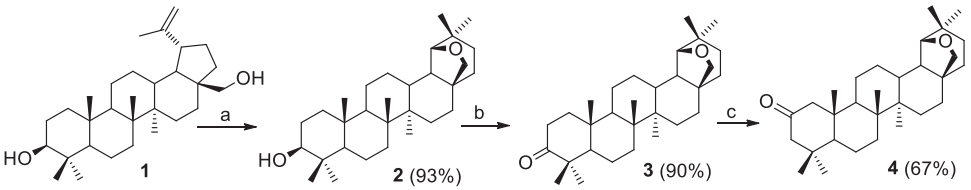


(a): *p*-TsOH, DCM, reflux; (b): Oxalyl chloride, DMSO, Et_3N, DCM, -78°C-0°C; (c): Sulfur, morpholine, reflux

Scheme 1. Synthesis of allobetulone and 2-oxoallobetulin.

and 1,2,3-selenadiazoles triterpene derivatives on the basis of naturally occurring compounds. Only limited data were reported about using the Hurd–Mori reaction for the synthesis of 1,2,3-thiadiazolo terpenoids starting from cyclopentanonopimaric and betulonic acid,[16] and using the Lalezari method for the synthesis of 1,2,3-selenadiazole derivatives of friedelin.[17]

Betulin **1** which is a triterpenoid based on the lupane skeleton, is found in high amounts in birch bark, and is now commercially available. Allobetulin **2** ((18α)-19β, 28-epoxyoleanan-3β-ol) is an isomer of betulin, obtained from betulin by a Wagner–Meerwein rearrangement in the presence of different acid catalysts.[18,19] Various derivatives were obtained from allobetulin and these possess many interesting biological properties[20] including antiviral,[21,22] antifeedant,[23] immunotropic,[24,25] antibacterial,[26] anti-inflammatory and anti-ulcer activities,[27] cytotoxicity,[28,29] and inhibition of glycogen phosphorylase.[30]

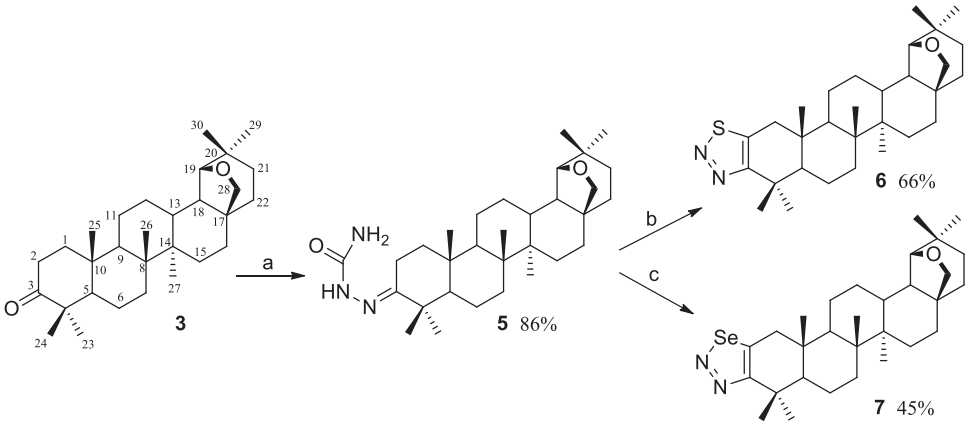
Allobetulin **2** can be transformed into valuable allobetulone **3** by reaction with various oxidative reagents.[31,32] Allobetulone was rearranged to 2-oxoallobetulin **4** by using Willgerodt–Kindler conditions in the presence of sulfur in morpholine.[33] In this study, a series of new triterpene derivatives have been synthesized from allobetulone **3** and 2-oxoallobetulin **4** by condensation of ketones group with semicarbazide and continuing to the thiadiazoles and selenadiazoles by the Hurd–Mori reaction and Lalezari method, respectively.

Results and discussions

Synthesis of starting substances was realized following the procedure of a previous study,[34] wherein betulin **1** can be transformed to allobetulin **2** (93%), and then allobetulone **3** (90%) and 2-oxoallobetulin **4** (67%) in high yields (Scheme 1).

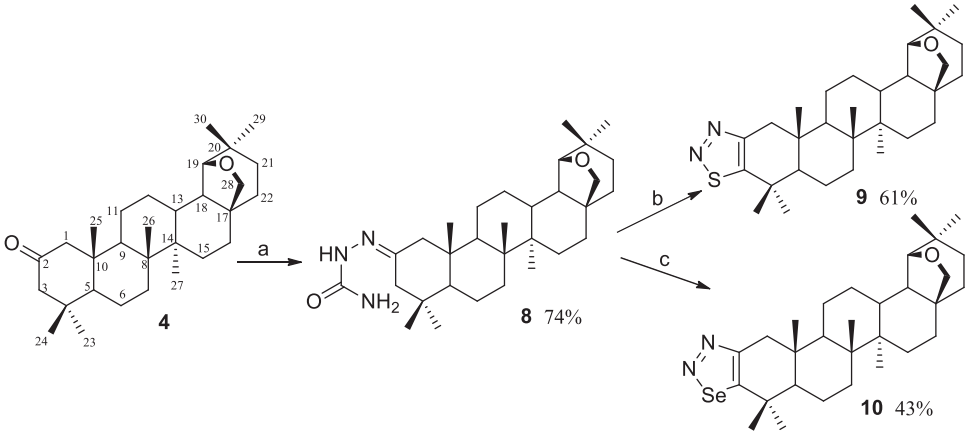
The reaction of allobetulone **3** with semicarbazide hydrochloride in the presence of potassium acetate in ethanol afforded allobetulone semicarbazone **5** in very high yields (86%). The reaction of **5** with thionyl chloride following the standard literature conditions of the Hurd–Mori synthesis gave 1,2,3-thiadiazole allobetulin **6** in a moderate yield (66%). Synthesis of 1,2,3-selenadiazole **7** by the reaction of **5** with selenium dioxide in acetic acid at 70 °C following the Lalezari method fused selenadiazole **7** with reasonable yield (45%) (Scheme 2).

Reaction of 2-oxoallobetulin **4** with semicarbazide hydrochloride in the presence of potassium acetate in ethanol leads to 2-oxoallobetulin semicarbazone **8** in very high yields (74%). The reaction of **8** with thionyl chloride following the Hurd–Mori synthesis afforded 1,2,3-thiadiazole derivative **9** in moderate yield (61%) (Scheme 3). However, only one product was obtained, this means that the semicarbazone derivative **8** could



(a): $NH_2NHCONH_2.HCl$, AcOK, EtOH, 40°C; (b): $SOCl_2$, DCM, rt; (c): SeO_2, AcOH, 70°C

Scheme 2. Synthesis of triterpene derivatives from allobetulone.



(a): $NH_2NHCONH_2.HCl$, AcOK, EtOH, 40°C; (b): $SOCl_2$, DCM, rt; (c): SeO_2, AcOH, 70°C

Scheme 3. Synthesis of triterpene derivatives from 2-oxoallobetulin.

exist in the *E* form. The structure of compound **9** was confirmed by 2D-NMR spectroscopy. Some correlations in 2 D-NMR of the obtained compounds are similar to those in the previous study because of the same skeleton in the lupane triterpene type.[34] In the HMBC spectra, the signals of the protons on the C-1 at 3.49 ppm and 2.46 ppm correlate with only one signal of C-25 at 16.5 ppm. According to the NOESY spectra, the signal of the proton on the C-1 at 3.49 ppm correlates with the signal of the proton on the C-25 at 0.84 ppm.

Synthesis of 1,2,3-selenadiazole **10** is carried out by reaction of **8** with selenium dioxide in acetic acid at 70 °C following the Lalezari method to give a product with reasonable yield (43%). Again, only one compound was obtained, and the structure of compound **10** was confirmed by 2D-NMR spectroscopy (Scheme 3).

In the HMBC spectra, the signals of the protons on the C-1 at 3.58 ppm and 2.58 ppm correlate with only one signal of C-25 at 16.4 ppm. According to COSY spectra, the signal of the proton on the C-1 at 2.58 ppm correlates with the signal of the

proton on C-25 at 0.88 ppm. In the NOESY spectra, the signal of the proton on the C-1 at 3.58 ppm correlates with the signal of the proton on the C-25 at 0.88 ppm.

Conclusions

Two semicarbazone triterpenoid substances **5**, **8** were prepared by condensation reactions. A series of new 1,2,3-thiadiazole derivatives **6, 9** and 1,2,3-selenadiazole derivatives **7**, **10** have been successfully obtained by the Hurd–Mori reaction and Lalezari method, respectively. This research direction will be continued and the synthesized substances could be investigated for further applications.

Experimental

General

Melting points were determined with a Reichert Thermovar with a microscope, and are uncorrected. Infrared spectra were measured and processed on a Bruker Alpha-T FT-IR spectrometer with a universal sampling module coupled to OPUS software. The ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker 300 (operating respectively at 300 MHz and 75 MHz), Bruker 400 Avance (operating respectively at 400 MHz and 100 MHz) (Bruker, Billerica, MA). Mass spectra were recorded on a Hewlett-Packard 5989 A mass spectrometer (EI or CI mode), coupled with an HP Apollo 900 series (Hewlett-Packard, Palo Alto, CA). High-resolution mass data were recorded on a Kratos MS50TC (Kratos, Manchester, UK), with an electron impact ionizer energy of 70 eV, at a temperature of 250 °C. Reagents and solvents were purchased from Sigma Aldrich, ABCR and Acros. Solvents were mostly dried and in some cases were used as received. Betulin was purchased from Kaden Chemicals GmbH and used as received. All reactions were carried out in flame-dried glassware, but no special precautions were taken to exclude moisture.

General procedures for the synthesis of allobetulin-3-semicarbazone (5) and allobetulin-2-semicarbazone (8)

A solution of allobetulone (2-oxoallobetulin) (100 mg, 0.227 mmol) in ethanol (3 ml) was stirred at 40 °C. Semicarbazide hydrochloride (304 mg, 2.72 mmol) and potassium acetate (89 mg, 0.908 mmol) in 3 ml water were added and the mixture was continuously stirred with TLC or mass spectral monitoring. After the reaction had finished, the mixture was poured into water (30 ml). The precipitate was filtered, washed with water, and dried over sodium sulfate. The crude product was purified by column chromatography on silica with eluent $CHCl_3$.

Allobetulin-3-semicarbazone (5): Yield: 97 mg (86%); mp 252–254 °C. ^{1}H-NMR ($CDCl_3$, 300 MHz, ppm): 3.77 (d, 1H, $J = 7.71$ Hz, H-28), 3.53 (s, 1H, H-19), 3.45 (d, 1H, $J = 7.80$ Hz, H-28), 2.33–2.22 (m, 2H, H-2), 1.81–1.28 (m, 25H-complex CH, CH_2), 1.25 (s, 3H, CH_3-23), 1.15 (s, 3H, CH_3-26), 1.04 (s, 3H, CH_3-24), 1.00 (s, 3H, CH_3-30), 0.93, (s, 3H, CH_3-27), 0.90 (s, 3H, CH_3-25), 0.79 (s, 3H, CH_3-29). ^{13}C-NMR ($CDCl_3$, 75 MHz, ppm): 205.43 (C = O), 159.12 (C-3), 87.91 (C-19), 71.26 (C-28), 55.26,

50.35, 46.76, 41.47, 41.26, 40.76, 40.59, 38.47, 37.04, 36.72, 36.27, 34.21, 33.36, 32.69, 29.70, 28.80, 28.43, 26.39, 26.23, 24.55, 23.51, 21.36, 19.55, 19.44, 15.87, 15.63, 13.41. HRMS: $C_{31}H_{51}N_3O_2$, calculated: 497.39813, found: 497.39803. IR (ATR, neat, cm^{-1}): 3471, 2926, 2859, 1692, 1581, 1468, 1452.

General procedures for the synthesis of 1,2,3-thiadiazolo[3,2-b] allobetulin (6) and 1,2,3-thiadiazolo[2,3-b] allobetulin (9)

A solution of allobetulin-3-semicarbazone (allobetulin-2-semicarbazone) (50 mg, 0.100 mmol) in dry DCM (3 ml) was stirred at room temperature under an argon atmosphere. Thionyl chloride (0.147 ml, 2.01 mmol) was added and the mixture was continuously stirred with TLC or mass spectral monitoring. After the reaction had finished, 3 ml water was added, the mixture was washed by Na_2CO_3 (3 × 3 ml) and water (3 × 3 ml), and dried over magnesium sulfate. The solvent was evaporated and the residue mixture was purified by column chromatography with heptane/EtOAc 9:1 to obtain the product.

General procedures for the synthesis of 1,2,3-selenadiazolo[3,2-b]allobetulin (7) and 1,2,3-selenadiazolo[2,3-b]allobetulin (10)

A solution of allobetulin-3-semicarbazone (allobetulin-2-semicarbazone) (50 mg, 0.100 mmol) and selenium dioxide (16.72 mg, 0.151 mmol) in AcOH (3 ml) was stirred at 70 °C under an argon atmosphere under mass or TLC monitoring. After the reaction had finished, the mixture was cooled to room temperature and filtered from the precipitated selenium. Water (6 ml) was added and the precipitate was isolated. The crude mixture was purified by column chromatography with heptane/EtOAc 9:1 to obtain the product.

Full experimental detail, ^{1}H-NMR and ^{13}C-NMR spectra of all the new compounds can be found via the "Supplementary Content" section.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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