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LEWIS ACID INDUCED REACTIONS OF PROPARGYL TRIMETHYL SILANE WITH ω-ETHOXY LACTAMS SYNTHESIS OF γ-ALLENYL-GABA

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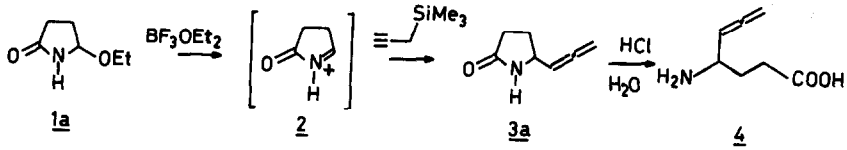
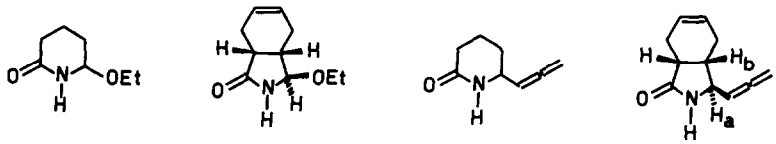
Abstract: Reactions of propargyl trimethyl silane with ω-ethoxy lactams 1a-c under the influence of boron trifluoride etherate afford ω-allenyl lactams 3a-c; 5-allenyl-2-pyrrolidinone is hydrolyzed to γ-allenyl-GABA.

N-Acyliminium ions are versatile intermediates for the synthesis of various nitrogen compounds, in particular alkaloids[1]. In the past several years we have been investigating ring closure reactions of cyclic N-acyl-iminium ions (e.g. 2), prepared in situ on treatment of ω-alkoxy lactams (e.g. 1a-c) with acid[1a]. Most attention was paid to reactions with π-nucleophiles like simple olefins and acetylenes. In certain cases, however, such reactions suffer from low regioselectivity and/or yield[2b]. Recently, we reported that allyl and propargyl silanes in a number of cases are to be preferred as π-nucleophiles, invariably giving complete regioselectivity and high yield in intramolecular reactions[2]. We now describe our results using propargyl trimethyl silane in an intermolecular fashion[3]. In addition, we show an interesting synthetic application of the products.



1a 2 3a 4



1b 1c 3b 3c

Reactions of ethoxy lactams with propargyl silane were carried out as follows. To a stirred mixture of ethoxy lactam (1a-c[4], 10 mmol), propargyl trimethyl silane[5] (4.5 ml, 30 mmol) and dichloromethane (20 ml) was added dropwise at 0°C boron trifluoride etherate (3.6 ml, 30 mmol). After 15 min the reaction mixture was allowed to warm up to r.t. over 30 min. It was then poured out into 25 ml of brine. Extractive work-up ($CHCl_3$) afforded the crude allenes 3a-c, which contained no isomeric contaminants according to ^1H NMR. Purification using flash chromatography furnished pure 3a-c in yields of about 50%[6,7] as colourless oils, which all of them solidified on standing. The assignment of the stereochemistry of 3c is based on mechanistic considerations and ^1H NMR evidence[8].

Amide hydrolysis of 3a was easily achieved by heating it at 80-90°C for 18 hr with 18% aqueous hydrochloric acid. Evaporation of the volatiles, followed by ion exchange chromatography (Amberlite resin IR 45, pyridine/water 1:4) afforded γ-allenyl-γ-aminobutyric acid (γ-allenyl-GABA, 4) as an oily substance, which crystallized to a white solid[10] (m.p. 171-172°C) on adding acetone to a concentrated aqueous solution.

γ-Allenyl-GABA is an amino acid with potentially interesting biological properties, since it is an analogue of the inhibitory neurotransmitter GABA[11]. Other analogues with similar structures as 4 (γ-vinyl-GABA, γ-acetylenic-GABA) have been found to be irreversible inhibitors of the GABA-catabolyzing enzyme GABA-T[12]. 5-Ethoxy-2-pyrrolidinones appear to be expedient starting materials for the synthesis of a variety of GABA analogues and further research is planned in this direction.

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References and notes

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6. 3a: yield 46%; IR (neat): 1958, 1690 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$): δ 7.0 (br s, NH), 5.1-5.3 (m, C=C=CH), 4.8-5.0 (m, C=C=CH_2), 4.1-4.4 (m, CHN), 1.7-2.6 (m, CH_2CH_2), ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 207.0 (s), 178.0 (s), 92.5 (d), 77.4 (t), 52.7 (d), 29.6 (t), 27.6 (t).
3b: yield 49%; IR (neat): 1960, 1660 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$): δ 6.6 (br s, NH), 5.1-5.3 (m, C=C=CH), 4.8-5.0 (m, C=C=CH_2), 3.9-4.2 (m, CHN), 2.2-2.7 (m, CH_2CO), 1.4-2.2 (m, remaining CH_2's); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 207.1 (s), 171.8 (s), 93.0 (d), 78.2 (t), 51.1 (d), 28.8 (2x t), 18.9 (t).
3c: yield 48%; IR (neat): 1956 and 1690 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$): δ 6.6 (br s, NH), 5.7-5.9 (m, CH=CH), 5.1-5.3 (m, C=C=CH), 4.8-5.0 (m, C=C=CH_2), 3.7-3.9 (m, CHN), 1.8-2.9 (m, remaining 6H's). ^{13}C NMR (62.9 MHz,

$CDCl_3$): δ 207.7 (s), 179.5 (s), 126.1 (d), 125.2 (d), 91.4 (d), 77.7 (t), 57.8 (d), 38.9 (d), 37.4 (d), 25.1 (t), 22.1 (t).

7. Yields have not yet been optimized. Tin tetrachloride as Lewis acid gives similar results, but is less convenient than BF_3OEt_2.

8. The propargyl silane molecule is expected to approach the acyliminium ion from the less hindered face, leading to the stereochemistry as shown in 3c with H_a and H_b trans. The coupling constant of these protons was found to be 3.5 Hz (determined after decoupling of the adjacent allene proton). The coupling constant between the corresponding protons in 1c has been determined to be 1.5 Hz and in the thermodynamically much less stable cis isomer of 1c 5.5 Hz. With the knowledge that oxygen substituents can substantially lower vicinal coupling constants[9] we also conclude from these NMR data that our bicyclic allene has the stereochemistry as drawn in 3c.

9. See e.g. H. Günther, "NMR Spektroskopie", Georg Thieme Verlag, Stuttgart, 1973, p. 117.

10. 4: yield 76%; IR(KBr): 1960, 1660, 1625, 1545 cm^{-1}; ^1H NMR (100 MHz, D_2O): δ 5.1-5.3 (m, C=C=CH), 4.9-5.1 (m, C=C=CH_2), 3.5-3.9 (m, CHN), 2.0-2.3 (m, CH_2CO), 1.7-2.0 (m, CH_2CN). ^{13}C NMR (62.9 MHz, D_2O): δ 210.2 (s), 183.7 (s), 90.3(d), 81.8 (t), 52.3 (d), 35.9 (t), 31.9 (t).

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