HIGH-PRESSURE SYNTHESIS OF 5,6-DIHYDRO-2H-PYRAN SYSTEM. Eu(FOD)$_3$ MEDIATED (4+2)CYCLOADDITION OF 1-METHOXYBUTA-1,3-DIENE TO N-PROTECTED α-AMINO ALDEHYDES

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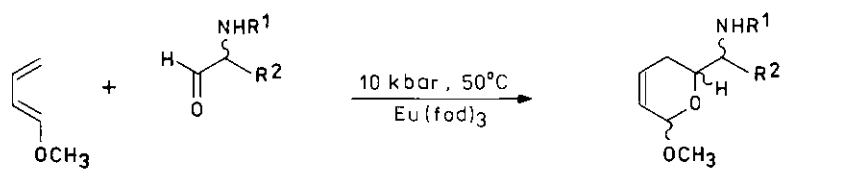
Abstract — High-pressure (4+2)cycloaddition of 1-methoxybuta-1,3-diene (1) to N-protected α-amino aldehydes (2) is described. The use of a lanthanide catalyst permits reduction of the required pressure to 10 kbar.

Several years ago we have demonstrated the ability of activated carbonyl compounds to undergo the Diels-Alder reaction with 1,3-dienes, forming 5,6-dihydro-2H-pyran derivatives.[1] Recently we have found that the use of high pressure with Eu(fod)$_3$ as a catalyst under 10 kbar[2] or without any catalyst under 20 kbar[3] extended the reactivity scope of non-activated carbonyl dienophiles.[4,5] During these studies, the application of various chiral aldehydes as dienophiles has been investigated.[6,7] α-Amino aldehydes prepared from α-amino acids[8] are a very convenient source of chirality, but due to their instability they are relatively rarely used.[9] The use of α-amino aldehydes as dienophiles in the Diels-Alder reaction offers an easy access to interesting precursors of the components of aminoglycoside antibiotics, difficult to obtain by other routes.[10]



1

2 a : R^1=Cbz , R^2=H
b : R^1=Cbz , R^2=CH_3
c : R^1=Boc , R^2=CH_3
d : R^1=Tos , R^2=CH_3
e : R^1=Cbz , R^2=$CH_2CH(CH_3)_2$
f : R^1=Boc , R^2=$CH_2CH(CH_3)_2$
g : R^1=Cbz , R^2=$CH_2C_6H_5$
h : R^1=Tos , R^2=$CH_2C_6H_5$

3

Cbz = $CO_2CH_2C_6H_5$
Boc = $CO_2C(CH_3)_3$
Tos = $SO_2C_6H_4CH_3$

Scheme

The goal of the present work was to introduce amino functionality on the C-7 carbon atom connected with a 5,6-dihydro-2H-pyran ring. For this purpose we selected eight representative N-protected α-amino aldehydes 2 in racemic form[11] and subjected them to (4+2)cycloaddition with 1-methoxybuta-1,3-diene 1 (Scheme). Reaction conditions[12] and yields of isolated products[13] are given in the Table.

Table. The reactions of 1-methoxybuta-1,3-diene with N-protected α-amino aldehydes

α-Amino aldehyde	Reaction conditions			Cycloadduct	Yield
	P (kbar)	T (°C)	Catalyst		(%)
2a	10	50	1% $Eu(fod)_3$	3a	50
2b	10	50	1% $Eu(fod)_3$	3b	41
2b	10	50	5% $Eu(fod)_3$	3b	63
2c	10	50	1% $Eu(fod)_3$	3c	27
2c	10	50	1% $Pr(fod)_3$	3c	27
2d	10	50	1% $Eu(fod)_3$	3d	35
2e	10	50	1% $Eu(fod)_3$	3e	40
2f	10	50	1% $Eu(fod)_3$	3f	20
2g	10	50	1% $Eu(fod)_3$	3g	65
2h	10	50	1% $Eu(fod)_3$	3h	67

$Eu(fod)_3$ mediated reactions of 1 with N-protected α-amino aldehydes (2), carried out at atmospheric pressure, are much too slow to be perceptible. The high-pressure reactions without catalyst generally fail. However, the combination of both methods: high pressure and use of lanthanide catalyst, gave the desired adducts in good yields, depending mainly on the kind of the protecting group. We found that the formyl group in 2c is so hindered that fails to react under very high-pressure conditions (1-2% yield at 24 kbar and 60°C). An addition of 1% $Eu(fod)_3$ increased the yield to 27% under milder conditions; analogous results were obtained for $Pr(fod)_3$ and $Yb(fod)_3$. Cbz-Protected alaninal (2b) gave under the same conditions a higher yield of 3b (41%), owing to reduction of steric hindrance of the formyl group. Further growth of yield can be obtained by either an increase in the amount of the lanthanide catalyst and/or by elevation of pressure.

The *cis:trans* isomer ratio of adducts 3 varied between 1:9 and 3:7.[14] This shift in favour of the *trans*-adduct, as compared with that observed for very high-pressure cycloaddition performed without catalyst, is due to slightly acidic equilibration of 3 during the reaction course.[15]

Summing up, mild Lewis acid mediated high-pressure (4+2)cycloaddition of 1-methoxybuta-1,3-diene (1) to N-protected α-amino aldehydes (2) provides a direct route to a 7-amino functionalized 5,6-dihydro-2H-pyran systems of type 3. Adducts 3 are promising intermediates in the total synthesis of complex monosaccharides, e.g. purpurosamines. Furthermore, a variaty of options for opening of the 5,6-

dihydro-2H-pyran ring can be used in the total synthesis of many unnatural amino acids, e.g. statine, 3-hydroxyproline, 4-amino-3-hydroxypentanoic acid, etc.

GENERAL PROCEDURE

The high-pressure apparatus[12] is charged with aldehyde 2b (2.07g, 0.01M), 1-methoxybuta-1,3-diene 1 (1.66g, 0.02M), methylene chloride (6ml), and $Eu(fod)_3$ (0.104g, 0.1mM). After closing the vessel with the mobile piston, the apparatus is placed between the pistons of a hydraulic press and the pressure is raised to 10 kbar. After stabilization of the pressure, the heater is switched on, whereupon the temperature is raised to 50°C. The reaction mixture is kept under these conditions for 20 h, then cooled to room temperature, and decompressed. After decompression, the solvent is evaporated under reduced pressure and the residue is chromatographed on silica gel (Merck Kieselgel 60, 230-400 mesh) using hexane/ethyl acetate (7:3) as eluent. The solvent is evaporated and the residue is dried under reduced pressure to provide a chromatographically pure mixture of adducts *cis*-3b and *trans*-3b as an oil; yield: 1.2g (41%). The mixture of *cis*-3b and *trans*-3b is finally separated by high performance liquid chromatography.

ACKNOWLEDGMENTS

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11. We synthesized racemic N-protected α-amino aldehydes 2 according to the known procedure (C. F. Stanfield, J. E. Parker, and P. J. Kanellis, J. Org. Chem., 1981, 46, 4797, 4799), followed by column chromatography on silica gel. Racemization of N-protected α-amino aldehydes on silica gel has been reported earlier: A. Ito, R. Tokahashi, and Y. Baba, Chem. Pharm. Bull., 1975, 23, 3081; D. H. Rich, E. T. Sun, and A. S. Boparai, J. Org. Chem., 1978, 43, 3624.

12. All reactions were carried out in methylene chloride as solvent. For high-pressure experiments we used the piston-cylinder type apparatus described earlier: J. Jurczak, Bull. Chem. Soc. Jpn., 1979, 52, 3438.

13. For all new compounds, satisfactory elemental analyses or exact masses and ^{1}H NMR (200 MHz) spectra were obtained.

14. Typical examples of ^{1}H NMR spectra (200 MHz, $CDCl_3$ as solvent, TMS as standard) for *cis*- and *trans*-adducts: *cis*-3b, δ (ppm): 7.35 (s, 5H, C_6H_5), 5.98 (m, 1H, CH=CH), 5.64 (m,1H, CH=CH), 5.13 (m, 1H, NH), 5.10 (s, 2H, CH_2Ph), 5.07 (s, 1H, O-CH-OMe), 3.9 - 3.6 (m, 2H, O-CH-C, N-CH-C), 3.47 (s, 3H, OCH_3), 2.2 - 1.8 (m, 2H, CH_2-C=C), 1.27 (d, 3H, CH_3); *trans*-3b, δ (ppm): 7.35 (s, 5H, C_6H_5), 5.97 (m, 1H, CH=CH), 5.72 (m, 1H, CH=CH), 5.11 (s, 2H, CH_2Ph), 5.09 (m, 1H, NH), 4.85 (bs, 1H, O-CH-OMe), 3.9 - 3.7 (m, 2H, O-CH-C, N-CH-C), 3.40 (s, 3H, OCH_3), 2.2 - 1.8 (m, 2H, CH_2-C=C), 1.28 (d, 3H, CH_3).

15. A *cis-trans* mixture of adducts 3 treated with PPTS in methanol, according to J. Jurczak, T. Bauer, and A. Golebiowski, Bull. Pol. Ac. Chem., 1985, 33, 397, provided pure *trans*-3 in quantitative yield.

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