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SYNTHESIS OF A NOVEL HEXAHYDROFURO[3,4-b]FURAN DERIVATIVE

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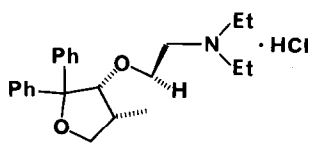
Summary: A facile, one-pot synthesis of an alkylated tetrahydrofuranone intermediate is applied to the synthesis of a novel hexahydrofuro[3,4-b]furan derivative.

As part of our program to synthesize semi-rigid probes for the muscarinic cholinergic receptor, we prepared the novel bicyclic analog 2-[(diethylamino)methyl]-6,6-diphenylhexahydrofuro[3,4-b]furan 1 to investigate the stereochemical requirements of the receptor.



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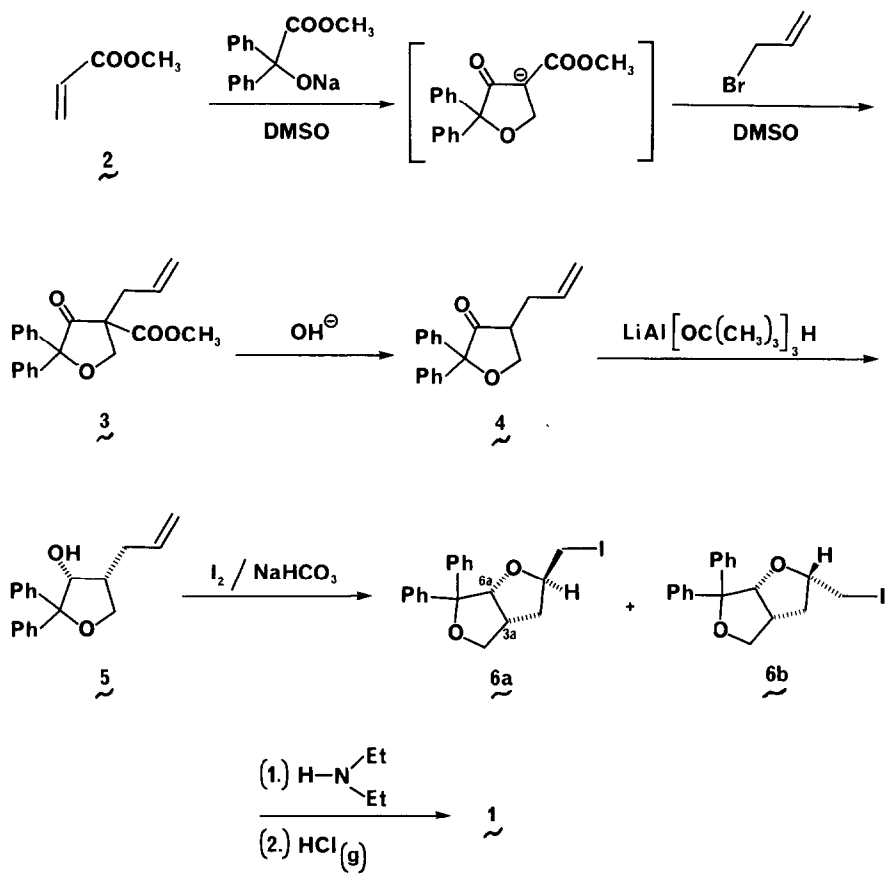
Our approach to the synthesis of 1 required a convenient preparation of the key intermediate 4-allyl-3-tetrahydrofuranone compound 4. The synthesis of 3-tetrahydrofuranone analogs by means of a Michael addition-Dieckmann cyclization sequence in DMSO has been reported.[1] The intermediate β-keto ester produced by this process is immediately converted to a β-keto ester carbanion by the alkoxide anion liberated during the Dieckmann cyclization (see scheme I). We now report a facile synthesis of 3 based on a one-pot Michael addition-Dieckmann cyclization followed immediately by alkylation of the resulting β-keto ester carbanion with allyl bromide.

Reaction of methyl acrylate 2 with methyl sodium benzilate in DMSO gave the intermediate β-keto ester carbanion which was alkylated with allyl bromide (25°C, 24h) to yield the tetrahydrofuranone derivative 3 in 65% overall yield; TLC R_f (benzene) 0.51; IR (neat) 1763, 1728, 1639 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 2.16-3.09 (m, 2H, CH_2-CH=CH_2), 3.66 (s, 3H), 4.02-4.78 (m, 2H, H-5), 4.82-6.09 (m, 3H, CH=CH_2), 7.19-7.60 (m, 10H); MS m/z 308 (M^+- C≡O), 105 (base peak).[2]

The subsequent hydrolysis and decarboxylation of the β-keto ester was accomplished by refluxing 3 in 5% NaOH for 7h. Ketone 4 was obtained as a colorless oil after flash chromatography[3] on silica gel (Baker)

SCHEME I



using benzene-petroleum ether (1:1) as the solvent (90% yield); TLC R_f (benzene) 0.70; IR (neat) 1755, 1640 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.54-3.01 (m, 3H, H-4 and CH_2-CH=CH_2), 3.74-4.60 (m, 2H, H-5), 4.82-5.77 (m, 3H, CH=CH_2), 7.17-7.60 (m, 10H); MS m/z 278 (M^+), 105 (base peak).[2]

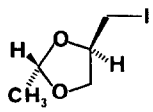
Reduction of 4 with lithium tri-tert-butoxyaluminohydride in ether (25°C, 24h) gave the cis-3-hydroxy-4-allyl compound 5 and the corresponding trans isomer (98:2).[4,5] The pure cis isomer was obtained as a white crystalline powder after several recrystallizations of the crude product from hexane (92% yield based on 4); mp 92-93.5°C; TLC R_f ($CHCl_3$) 0.41; IR ($CHCl_3$) 3575, 3440, 1640 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.41 (s, 1H, OH), 1.93-2.58 (m, 3H, H-4 and CH_2-CH=CH_2), 3.64-4.21 (m, 2H, H-5), 4.64-6.05 (m, 4H, H-3 and CH=CH_2), 7.07-7.57 (m, 10H); MS m/z 280 (M^+), 183 (base peak).[2]

Treatment of 5 with 5 equivalents of a 2.5% solution of iodine in ether and 10 equivalents of a saturated aqueous $NaHCO_3$ solution at 0°C for 4h afforded an 85:15 mixture of the iodo ethers 6a and 6b in 95% yield.[6] The crude product was recrystallized several times from hexane to give the pure exo isomer 6a as white

needles in 80% yield; mp 102-103.5°C; TLC R_f ($CHCl_3$) 0.59; ^{1}H NMR ($CDCl_3$, 180 MHz) δ 1.76-2.16 (m, 2H, H-3), 2.95-3.09 (m, 1H, H-3a), 3.13-3.21 (m, 2H, CH_2I), 3.76-4.09 (m, 3H, H-2 and H-4), 5.39 (d, 1H, J=5.8 Hz, H-6a), 7.10-7.50 (m, 10H); MS m/z 406 (M^+), 183 (base peak).[2]

The stereochemical assignment of the exo and endo isomers 6a and 6b was made using two lines of evidence. First, the stereochemical course of haloetherification reactions has been found to be influenced by steric interactions during the formation of products.[7] Construction of Dreiding molecular models suggests that the conformation leading to the production of the exo isomer 6a is favored due to fewer steric interactions during the cyclization process.[8] Since we obtained a product ratio of 85:15, the major product was tentatively assigned as the exo isomer 6a. In support of this, Johnson, et. al.[8] have unequivocally assigned the exo configuration to the major product formed from an iodoetherification reaction in which a product ratio of 95:5 was observed. The steric effects present during the cyclization reaction we performed were similar to those described by Johnson.

A second line of evidence for the correct assignment of the exo and endo isomers is based on the ^{1}H NMR spectra of the isomers of 6. To assist us in the interpretation of these spectra, we used the cis and trans-2,4-disubstituted 1,3-dioxolanes 7 and 8 as model compounds of 6a and 6b respectively. Borremans, et. al.[9] have made a detailed ^{1}H NMR study of isomers 7 and 8 and have found that the signal for H-2 of the



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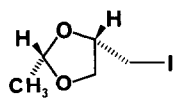

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trans isomer 7 is located 0.11 ppm downfield from the corresponding H-2 signal of the cis isomer 8.[10] From the ^{1}H NMR spectra of the isomers of 6, we observed the signal for H-6a of one isomer at 5.29 ppm and the same signal for the other isomer at 5.39 ppm. Based on the above model compounds, the signal located at 5.39 ppm should be due to the exo isomer 6a. Since the isomer with the H-6a signal at 5.39 ppm was also the major product of the iodoetherification reaction, our tentative assignment of this isomer as the exo isomer is consistent with both the stereochemical and spectroscopic arguments presented above.

Nucleophilic displacement of the iodo ether 6a with diethylamine was carried out in DMSO (45°C, 24h).[11] The resulting crude product was purified by preparative TLC on aluminum oxide plates (Merck) with ether-ammonium hydroxide (50:1) as the solvent. The pure amine was converted to the hydrochloride salt 1 to give a white powder which was recrystallized from ethyl acetate (60% yield from the iodo ether 6a); mp 131-133°C; ^{1}H NMR (D_2O, 60 MHz) δ 0.70-1.15 (t, 6H, J=7.2 Hz, CH_3), 1.72-2.20 (m, 2H, H-3), 2.50-3.15 (m, 7H, H-3a and N-CH_2), 3.56-4.20 (m, 3H, H-2 and H-4), 5.37 (d, 1H, J=5.8 Hz, H-6a), 7.03-7.50 (m, 10H); MS m/z 351 (M^+-HCl), 86 (base peak).[2]

Further studies to determine the scope of the one-pot synthesis of alkylated tetrahydrofuranones are currently in progress in our laboratory.

Acknowledgements. We wish to express our appreciation to the Campus Research Board for their support of this work. We also wish to thank Drs. D.L. Venton and N.I. Ghali for helpful discussions. We gratefully acknowledge Richard Dvorak for obtaining the mass spectra and Joseph Pan for assistance with the gas chromatographic analyses.

References and Footnotes

1. Gianturco, M.A., Friedel, P., and Giammarino, A.S., Tetrahedron, 20, 1763 (1964).
2. Satisfactory elemental analyses were obtained for all new compounds.
3. Still, W.C., Kahn, M., and Mitra, A., J. Org. Chem., 43, 2923 (1978).
4. A stereoselective reduction of a 1-keto-2-allyl analog similar to compound 4 has been reported by Fried, et. al. In their study, potassium tri-sec-butylaluminum hydride was used to stereoselectively produce the cis-1-hydroxy-2-allyl analog. The stereochemistry of the cis isomer was established by suitable spectroscopic means. See: Fried, J., Mitra, D.K., Nagarajan, M., and Mehrotra, M.M., J. Med. Chem., 23, 234 (1980). Our observations in the reduction of 4 are consistent with the observations presented in the above report.
5. The reduction of 4 was carried out at 25°C for 24 h using several reducing agents. The results of these reactions are summarized below. The ratio of isomers was measured by gas chromatographic analysis.

Reducing agent	Ratio of cis and trans isomers of compound 5 produced	
	cis-5	trans-5
$NaBH_4$/ethanol	57%	43%
$LiAlH_4$/ether	67%	33%
$LiAl[OC(CH_3)_3]_3H$/ether	98%	2%

6. Whittaker, N., Tetrahedron Lett., 2805 (1977).
7. Wong, H., Chapius, J., and Monkovic, I., J. Org. Chem., 39, 1042 (1974).
8. This observation is in agreement with work reported on a similar reaction in a synthesis of prostacyclin. See: Johnson, R.A., Lincoln, F.H., Nidy, E.G., Schneider, W.P., Thompson, J.L., and Axen, U., J. Amer. Chem. Soc., 100, 7690 (1978).
9. Borremans, F., Anteunis, M., and Anteunis-DeKetelaere, F., Org. Magn. Resonance, 5, 299 (1973).
10. In their synthesis of prostacyclin, Johnson, et. al. also report a similar downfield shift of the H-9 signal in the NMR spectrum of a PGI_1 isomer having the 6-exo configuration. See reference 8.
11. Monkovic, I., Perron, Y.G., Martel, R., Simpson, W.J., and Gylys, J.A., J. Med. Chem., 16, 403 (1973).

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