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Stereoselective One-Pot, Three-Component Synthesis of 4-Amidotetrahydropyran

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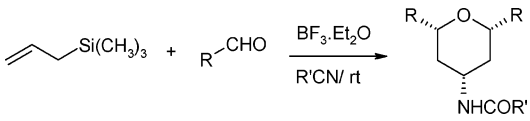
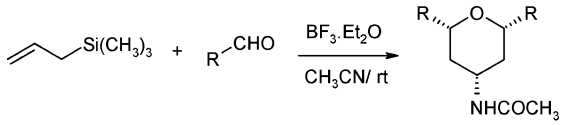


where R=R'= alkyl, aryl

The reaction of aldehyde with allylsilane in acetonitrile mediated by boron trifluoride etherate generated 4-aminotetrahydropyrans in good yields. The product is highly stereoselective.

Multicomponent reactions are gaining interest in organic synthesis due to its ability to form multiple bonds in a single step.[1] Substituted tetrahydropyrans are important targets because of their presence in many natural products.[2] These tetrahydropyrans are prepared by hetero-Diels−Alder methods,[3] manipulation of carbohydrates,[4] Prins cyclization,[5] and intramolecular Michael reactions.[6] Although there are a few methods for the synthesis of 4-halo-,[7] 4-thio-,[8] 4-azido-,[9] 4-aryl-,[10] and 4-hydroxytetrahydropyran,[5e,f,7d,11] methods for the synthesis of 4-aminotetrahydropyran are limited.[12] In this paper, an efficient method for the synthesis of 4 aminotetrahydropyran from aldehyde, trimethylallylsilane, and acetonitrile mediated by BF_3·Et_2O is disclosed (Scheme 1). Thus, when benzaldehyde was subjected to react with allyltrimethylsilane in acetonitrile in the presence of boron trifluoride etherate, 4-acetamido-2,6-diphenyltetrahydrofuran was obtained in 70% yield.

SCHEME 1. Synthesis of 4-Acetamidotetrahydropyran



where R= alkyl, aryl

The reaction is generalized in Table 1. In all of the cases studied, 4-acetamidotetrahydropyrans **1b**−**11b** could be obtained in high purity without any side products. Both aliphatic and aromatic aldehydes give good yields with high diasteroselectivity as determined from the ^{1}H and ^{13}C NMR spectrum of the crude product. The substituent on the aromatic ring has a promising effect on this reaction. The electron-withdrawing and simple aldehydes gave good yields compared to electron-donating groups on the ring. On the other hand, aliphatic aldehydes are better substituents than the aromatic aldehydes. Only a single diastereomer was obtained from each reaction, which was determined by ^{1}H and ^{13}C NMR and comparison of the authentic samples.[11a] The conformations of the compounds are in the chair form, and all three substituents are in the equatorial position. This was confirmed by NOE experiments and single-crystal X-ray analysis (ORTEP diagram of **1b** in the Supporting Information).[13]

Other nitriles such as dichloroacetonitrile and bezonitrile also gave the corresponding protected 4-aminotetrahydropyrans **1d**−**6d** in good yields (Table 2).

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(13) Crystallographic data for compound CMR-2 has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 658766.

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SCHEME 2. Mechanism of the Reaction

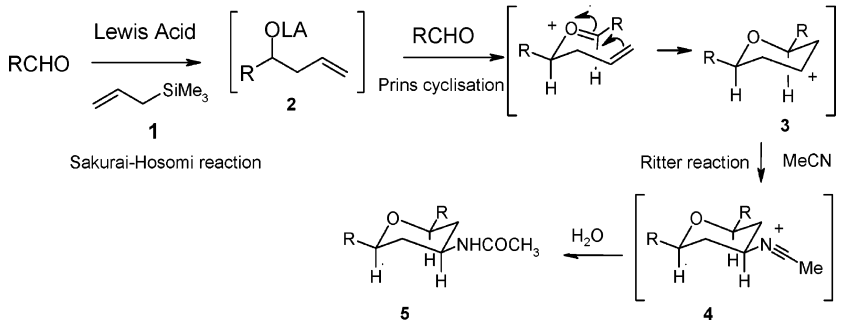

TABLE 1. Synthesis of 4-Aminotetrahydropyran

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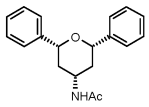
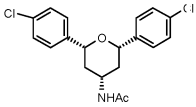
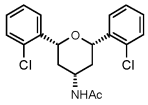
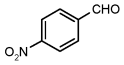
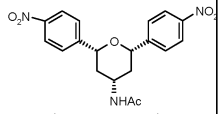
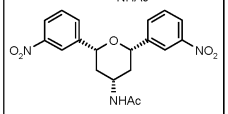
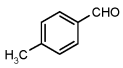
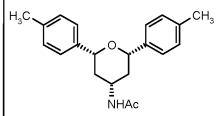
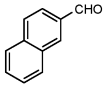
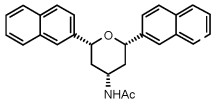
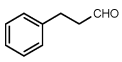
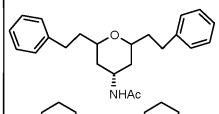
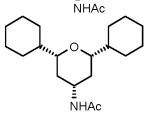
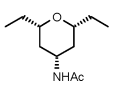
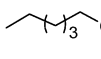
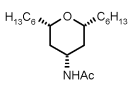
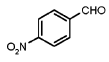
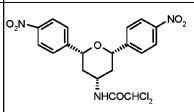
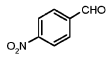
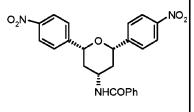
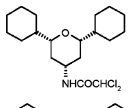
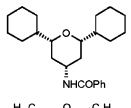
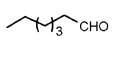
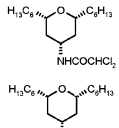
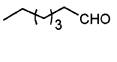
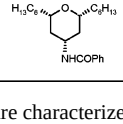
1		24		70
2		24		74
3		24		89
4		24		70
5		27		63
6		36		60
7		36		45
8		12		85
9		12		99
10		12		98
11		12		91

[a] Yields refer to isolated yield. Compounds are characterized by ^{1}H, ^{13}C NMR and IR spectra.

TABLE 2. Synthesis of 4-dichloroacetamido- and 4-benzamidotetra-hydropyran

Sl No.	Aldehyde (c)	Nitrile	time/h	Product (d)	Yield[a] (%)
1		Cl_2CHCN	12		92
2			12		67
3		Cl_2CHCN	8		65
4			8		61
5		Cl_2CHCN	8		76
6			8		65

[a] Yields refer to isolated yield. Compounds are characterized by ^{1}H, ^{13}C NMR and IR spectra.

The major advantage of this reaction is that in a single step, three reactions, primarily (i) Sakurai−Hosomi, (ii) Prins cyclization, and (iii) Ritter, can be performed without any difficulties. To our knowledge, this is the first single-step method for the synthesis of symmetric 2,6-disubstituted 4-acetamidotetrahydropyran. The mechanism of the reaction can be explained as follows. In the presence of Lewis acid, allyltrimethylsilane **1** reacts with aldehyde to afford intermediate **2** (Scheme 2). The intermediate **2** reacts with another molecule of aldehyde to give tetrahydropyranyl cation **3**, which in the presence of neucleophile, CH_3CN, gives intermediate **4**. The species **4** upon hydrolysis gives the 4-acetamidotetrahydropyran **5**.

This method will be of immense importance in organic synthesis, as the 4-aminotetrahydropyran skeleton is a core structure in a number of bioactive molecules[14] and natural products such as ambruticins VS, glycamino acid, sialic acid,

(14) (a) Gopalsamy, A.; Moore, W. J.; Kern, J. C.; Molinari, A. J.; Shi, M.; Welmaker, G. S.; Wilson, M. A.; Krishnamurthy, G.; Commons, T. J.; Webb, M. B.; Woodworth, R. P. PCT. Int. Appl. WO 2006124875 A2, 2006, 516 pp. (b) Braun, A.; Courtemanche, G.; Crespin, O.; Fett, E.; Pascal, C. Fr. Demande FR 2873690 A1, 2006, 59 pp. (c) Bandiera, T.; Lombardi Borgia, A.; Polucci, P.; Villa, M.; Nesi, M.; Angiolini, M.; Varasi, M. PCT. Int. Appl. WO 2007068619 A1, 2007, 238 pp. (d) Duan, J.; King, B. W.; Decicco, C.; Maduskuie, T. P.; Voss, M. E. US Patent Appl. US 2004072802 A1, 2004, 150 pp.

and others.[15] This type of skeleton is also used in photographic films[16] and host−guest chemistry.[17]

In summary, an efficient, highly diastereoselective one-pot method for the synthesis of 2,6-disubtituted 4-amidotetrahydropyran in good yields has been developed. The scope and synthetic applications of this novel reaction are under investigation in our laboratory.

Experimental Section

General Procedure. To a mixture of aldehyde (1.0 equiv), allyltrimethylsilane (0.6 equiv), and nitrile (5.0 mL) was added borontrifluoride etherate (1.2 equiv) drop by drop at rt. The reaction mixture was strirred at rt for specified time. The progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluents. After completion of the reaction, the product was extracted with ethyl acetate and washed with brine and water. The organic layer was dried (Na_2SO_4) and evaporated to leave the crude product, which was purified by short column chromatography over silica gel to give the title compounds.

4-Acetamido-2,6-diphenyltetrahydropyran (1b, Table 1). To a mixture of benzaldehyde, **1a** (0.10 mL, 1.0 mmol), allyltrimethylsilane (0.10 mL, 0.6 mmol), and acetonitrile (5.0 mL) was added boron trifluoride etherate (0.15 mL, 1.2 mmol) drop by drop at rt. The reaction mixture was strirred at rt for 24 h. Progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluents. After completion of the reaction, the product was extracted with ethyl acetate and washed with brine and water. The organic layer was dried (Na_2SO_4) and evaporated to leave the crude product, which was purified by short column chromatography over silica gel to give 4-acetamido-2,6-diphenyltetrahydropyran **1b** (207 mg, 70%) as a crystalline solid with mp 223−224 °C. The product **1b** is characterized by spectrometric methods. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38−1.48 (m, 2 H), 1. 96 (s, 3 H), 2.25−2.30 (m, 2 H), 4.32−4.44 (m, 1 H), 4.65 (dd, J=11.2 and 2.0 Hz, 2 H), 5.60 (d, J= 8.0 Hz, 1 H), 7.25−7.43 (m, 10 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.6, 40.6, 46.9, 78.5, 125.9, 127.7, 128.5, 142.2, 169.6. IR: 3296, 2922, 2846, 1640, 1543, 1493, 1446, 1282, 1114, 1064 cm^{-1}. Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.42; H, 7.20; N, 4.69.

***N*-[2,6-Bis-(4-nitrophenyl)tetrahydr-pyran-4-ylbenzamide (2d, Table 2).** To a mixture of nitrobenzaldehyde, **2c** (151 mg, 1.0 mmol), allyltrimethylsilane (0.10 mL, 0.6 mmol.), and benzonitrile (5.0 mL) was added borontrifluoride etherate (0.15 mL, 1.2 mmol) drop by drop at rt. The reaction mixture was strirred at rt for 12 h. Progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluents. After completion of the reaction, the product was extracted with ethyl acetate and washed with brine and water. The organic layer was dried (Na_2SO_4) and evaporated to leave the crude product, which was purified by short column chromatography over silica gel to give *N*-[2,6-bis(4-nitrophenyl)tetrahydropyran-4-ylbenzamide **2d** (300 mg, 67%) as a crystalline solid with mp 263−264 °C. The product **2d** was characterized by spectrometric methods. ^{1}H NMR (400 MHz, $CDCl_3$/DMSO-d_6): δ 1.52−1.61 (m, 2 H), 2.31−2.35 (m, 2 H), 4.30−4.45 (m, 1 H), 4.84−4.86 (m, 2 H), 6.10 (s, 1 H), 7.65−7.67(d, J = 8.8 Hz, 2 H), 8.24−8.25 (d, J = 8.8 Hz, 2 H), 8.35 (d, J = 6.4 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$/DMSO-d_6): δ 37.8, 46.1, 65.7, 76.2, 122.6, 125.7, 146.2, 148.1, 162.7. IR: 3274, 3087, 2923, 2840, 1673, 1602, 1558, 1516, 1350, 1284, 1207, 1127, 1084, 850, 809, 746 cm^{-1}. Anal. Calcd for $C_{19}H_{17}Cl_2N_3O_6$: C, 50.24; H, 3.77; N, 9.25. Found: C, 50.35; H, 3.81; N, 9.18.

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Supporting Information Available: Experimental procedures and full characterization data for all compounds, ^{1}H and ^{13}C NMR spectra of all compounds and X-ray crystallographic data and ORTEP diagram of **1b** are included. This material is available free of charge via the Internet at http://pubs.acs.org.

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