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A Sakurai–Prins–Ritter reaction sequence for the diastereoselective synthesis of 4-amidotetrahydropyrans catalyzed by bismuth triflate

Gowravaram Sabitha [a,*], M. Bhikshapathi [a], Sambit Nayak [a], J. S. Yadav [a], R. Ravi [b], A. C. Kunwar [b]

[a] Organic Division I, Indian Institute of Chemical Technology, Hyderabad 500 007, India
[b] N M R Division, Indian Institute of Chemical Technology, Hyderabad 500 007, India

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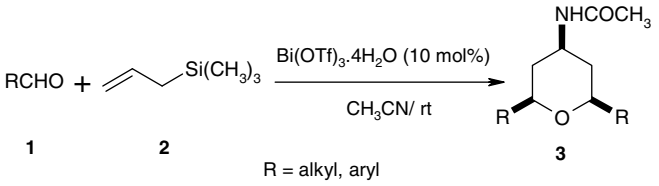
ABSTRACT

The synthesis of 4-amidotetrahydropyrans has been achieved by a single-step Sakurai–Prins–Ritter reaction sequence in a domino fashion by the reaction of an aldehyde and allyltrimethylsilane in acetonitrile using $Bi(OTf)_3$ as catalyst. The present synthesis is highly efficient and diastereoselective.

Functionalized tetrahydropyrans constitute key structural motifs of a large number of biologically active natural products.[1] They have been constructed in a wide variety of ways, with the most common strategies involving cyclizations onto oxacarbenium ions or epoxides, hetero Diels–Alder cyclizations, conjugate addition reactions, and the reduction of cyclic hemiketals.[2] Of the large range of permutations available, the 2,4,6-substitution pattern has been the most widely studied.[2,3] We have investigated the construction of trisubstituted tetrahydropyrans possessing a 4-halo substituent.[4] The synthetic utility of these cyclizations would be greatly extended if functional groups other than a halide could be introduced at C-4. Amino tetrahydropyrans are important structural motifs of a wide range of natural products[5] such as ambruticins, oligomers of glucoamino acids, sialic acid, and desyherbaine. These compounds are also used in photographic films[6] and host-guest chemistry.[7] Examples of the Sakurai–Prins–Ritter (three reactions) in a single step, for the synthesis of symmetric 2,6-disubstituted-4-acetamidotetrahydropyrans are limited[8] and it has not been explored extensively. Recently, $BF_3 \cdot OEt_2$ mediated synthesis of symmetrically substituted 4-aminotetrahydropyrans was reported, but stoichiometric amounts of catalyst and long reaction times it required (8–36 h).[9] Hence, there is still great demand for a new catalytic system with high efficiency and low catalytic loading.

We report herein an expedient direct synthesis of all *cis* 2,4,6-trisubstituted tetrahydropyrans via a Sakurai–Prins–Ritter reaction sequence mediated by $Bi(OTf)_3 \cdot 4H_2O$. Bismuth compounds have attracted recent attention due to their low toxicity, low cost, and high stability.[10] Bismuth salts have been reported as catalysts for opening of epoxides,[11] Mannich-type reactions,[12] formation and deprotection of acetals,[13] Friedel–Crafts reactions,[14] and Fries and Claisen rearrangements.[15] $Bi(OTf)_3$ is particularly attractive because it is commercially available or can be prepared easily from commercially available starting materials.[16,17]

Initially, 2 equiv of benzaldehyde was treated with 1 equiv of allyltrimethylsilane in acetonitrile in the presence of 10 mol % $Bi(OTf)_3 \cdot 4H_2O$ at room temperature, resulting in 4-acetamido-2,4-diphenyl tetrahydropyran in 85% yield with high diastereoselectivity (Scheme 1). The reaction was found to be very fast and was complete within 45 min. Under similar conditions, various



Scheme 1.

* Corresponding author. Tel./fax: +91 40 27160512.
E-mail address: gowravaramsr@yahoo.com (G. Sabitha).

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other aldehydes were reacted to afford the corresponding 4-acetamidotetrahydropyrans (Table 1). In all the cases studied, aliphatic aldehydes were found to react rapidly furnishing the corresponding products in excellent yields, whereas aromatic aldehydes reacted slowly. Among these, aromatic aldehydes containing electron withdrawing groups gave higher yields of products, compared to those having electron donating groups on the ring. Electron-rich *o*-methoxybenzaldehyde led to the desired product in moderate yield (Table 1, entry g). All the reactions are highly diastereoselective, and from the ^{1}H and ^{13}C NMR spectra it was apparent that a single product had been isolated in each reaction.

From NOE studies, it was confirmed that all three substituents occupied equatorial positions on the tetrahydropyranyl ring (Figure 1). For tetrahydropyrans **3a** and **3i**, ^{1}H NMR experiments were performed at 500 MHz in $CDCl_3$ solution. Assignments were made using DQFCOSY experiments. The presence of a plane of symmetry

Table 1
$Bi(OTf)_3{\cdot}4H_2O$-catalyzed synthesis of 4-amidotetrahydropyrans[a,b]

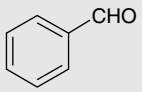
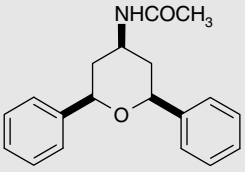
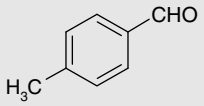
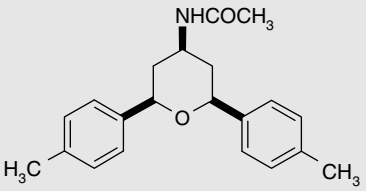
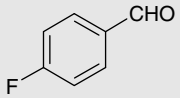
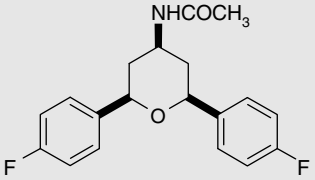
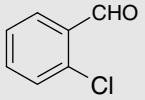
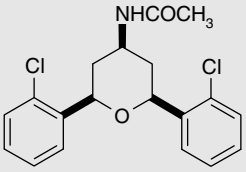
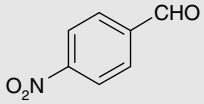
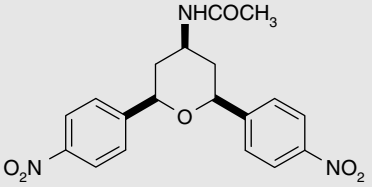
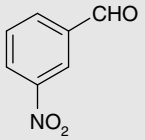
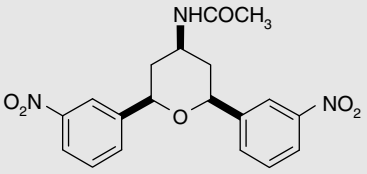
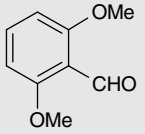
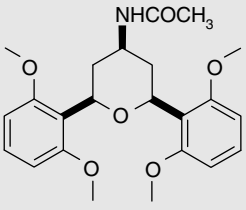
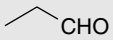
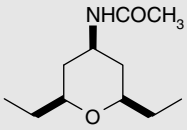
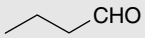
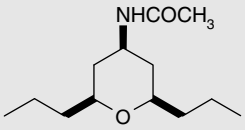
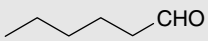
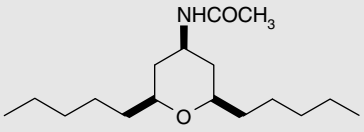
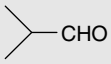
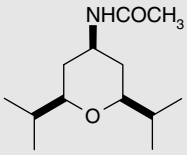
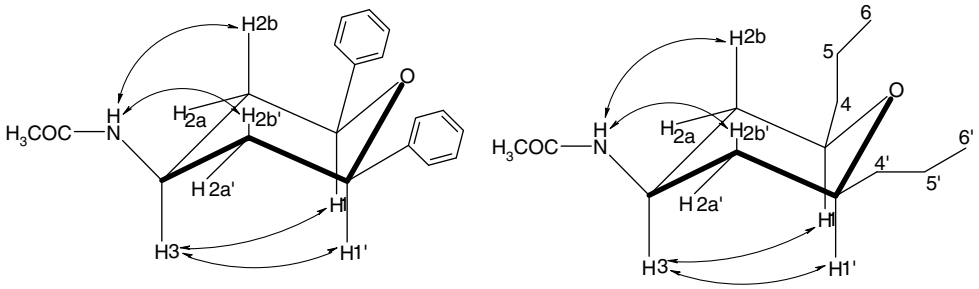
Entry	Aldehyde	Product	Time (h)	Yield (%)
a			0.75	85[9]
b			1.5	70[9]
c			1.0	88
d			1.0	86[9]
e			1.0	84[9]
f			1.25	80[9]
g			3.0	60

Table 1 (*continued*)

Entry	Aldehyde	Product	Time (h)	Yield (%)
h			0.5	98[9]
i			0.5	96
j			0.5	94
k			0.5	95

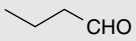
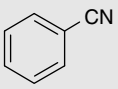
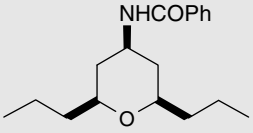
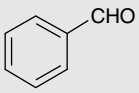
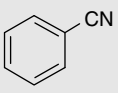
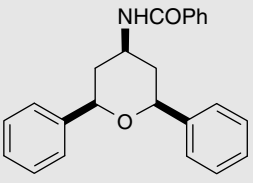
[a] All products were characterized by spectral data and confirmed by NOE studies.
[b] Isolated pure products.



3a **3i**

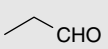
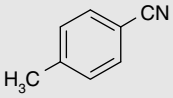
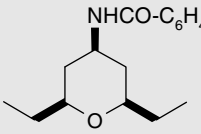
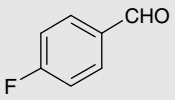
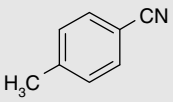
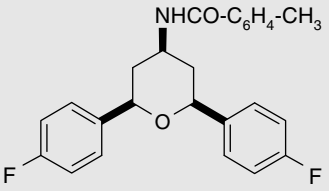
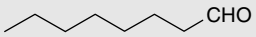
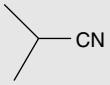
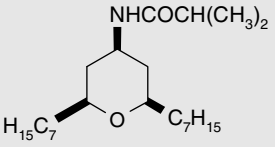
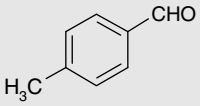
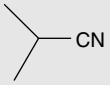
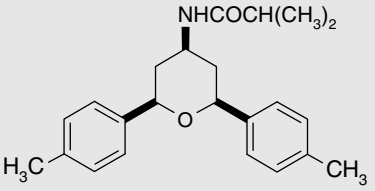
Figure 1. Schematic nOe diagram of **3a** and **3i.**

Table 2
$Bi(OTf)_3 \cdot 4H_2O$-catalyzed synthesis of 4-amidotetrahydropyrans using different nitriles[a,b]

Entry	Aldehyde	Nitrile	Product	Time (h)	Yield (%)
a				0.75	84
b				1.5	80

(*continued on next page*)

Table 2 (*continued*)

Entry	Aldehyde	Nitrile	Product	Time (h)	Yield (%)
c				0.75	82
d				1.25	78
e				0.75	84
f				2.0	64

[a] All products were characterized by spectral data and confirmed by NOE studies.
[b] Isolated pure products.

in the molecules was evident from the ^{1}H NMR spectra. We noticed that δH1 = δH1′, δH2a = δH2a′, and δH2b = δH2b′. For **3a**, an nOe cross peak between CH1/CH3 (CH1′/CH3) revealed that H1(H1′) and H3 are on the same side of the ring and adopt a *diaxial* orientation. The proposed structure of **3a** was further supported by the coupling constants $^3J_{CH1/CH2a}$ = 1.8, $^3J_{CH1/CH2b}$ = 11.7, $^3J_{CH2a/CH3}$ = 4.3, and $^3J_{CH2b/CH3}$ = 11.7 Hz. Thus, CH2b (CH2b′) is *antiperiplanar* to both CH1(CH1′), and C3H. Interestingly, we also observed a ω coupling of ~2 Hz between H2a and H2a′, further supporting their *equatorial* orientation. All these findings confirm that the pyran ring adopts a chair conformation, where the substituents at C1, C1′ and C3 are present in *equatorial* positions. The spectral parameters and nOes for **3i** are very similar to those for **3a** and imply a similar structure.

Similarly, the one-pot Sakurai–Prins–Ritter reaction of aldehydes and allyltrimethylsilane proceeded in the presence of other nitriles such as benzonitrile, 4-methylbenzonitrile, and *iso*-butyronitrile providing the corresponding products in good yields with high diastereoselectivity as determined from the ^{1}H NMR spectra of the crude products. In all cases, the three substituents occupied equatorial positions. The results are indicated in Table 2. This catalytic (10 mol %) method offers several advantages including mild conditions, rapidity, no formation of byproducts and does not require an inert atmosphere.

In conclusion, we have developed an efficient one-pot, Sakurai–Prins–Ritter reaction mediated by bismuth triflate to furnish 4-amidotetrahydropyrans.

Acknowledgment

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References and notes

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(e) *General procedure*: Allyltrimethylsilane **2** (0.6 mmol) was added to a mixture of aldehyde **1** (1.0 mmol) and $Bi(OTf)_3{\cdot}4H_2O$ (10 mol %) in nitrile (5 mL), and the reaction mixture was stirred at room temperature for the specified time. After completion of the reaction (as indicated by TLC), the reaction mixture was quenched with water and extracted with ethyl acetate (2×5 mL), the combined organics were washed with brine and water, dried (anhyd $NaSO_4$), and concentrated to leave a crude compound which was subjected to flash column chromatography using 4:1 hexane, ethyl acetate solvent as eluent to afford a pure compound **3**.

N1-(2,6-Diphenyltetrahydro-2H-4-pyranyl)acetamide **3a** (Table 1): white solid; mp: 220–222 °C; IR (KBr): cm^{-1} 3279, 3069, 2927, 2842, 1643, 1552, 747; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.41 (m, 4H), 7.34 (m, 4H), 7.26 (m, 2H), 5.43 (d, J = 8.4 Hz, 1H), 4.66 (dd, J = 1.8, 11.7 Hz, 2H), 4.39 (ttd, J = 4.3, 11.7, 8.4 Hz, 1H), 2.29 (dddd, J = 1.8, 2.0, 4.3, 13.0 Hz, 2H), 1.96 (s, 3H), 1.42 (td, J = 11.7, 13.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.3, 142.2, 128.8, 128.2, 126.2, 78.7, 46.0, 41.9, 23.9; HRMS (m/z): calcd: 318.1469; found: 318.1458 (M^++Na).

N1-[2,6-Di(4-fluorophenyl)tetrahydro-2H-4-pyranyl]acetamide **3c** (Table 1): Brown solid, mp: 176–178 °C; (KBr): cm^{-1} 3275, 3082, 2947, 2925, 2840, 1643, 1603, 835; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.65 (d, J = 7.5 Hz, 2H), 7.34–7.25 (m, 4H), 7.23–7.16 (m, 2H), 5.21 (d, J = 8.3 Hz, 1H), 5.02 (d, J = 9.8 Hz, 2H), 4.48–4.34 (m, 1H), 2.51–2.44 (m, 2H), 1.93 (s, 3H), 1.32–1.18 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 167.0, 161.3, 136.6, 125.8, 113.2, 112.9, 75.3, 44.1, 20.9; HRMS (m/z) calcd: 354.1281; found: 354.1270 (M^++Na).

N1-[2,6-Di(2,6-dimethoxyphenyl)tetrahydro-2H-4-pyranyl]acetamide **3g** (Table 1): Brown solid, mp: 226–228 °C; (KBr): cm^{-1} 3282, 3078, 2956, 2914, 2872, 1636, 1608; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.16 (d, J = 2.2 Hz, 2H), 6.72–6.70 (m, 4H), 5.22 (d, J = 8.3 Hz, 1H), 4.96 (d, J = 10.5 Hz, 2H), 4.45–4.34 (m, 1H), 3.81 (s, 12H), 2.43–2.33 (m, 2H), 1.95 (s, 3H), 1.26–1.13 (m, 2H); HRMS (m/z) calcd: 438.1892; found: 438.1824 (M^++Na).

N1-(2,6-Dipropyltetrahydro-2H-4-pyranyl)acetamide **3i** (Table 1): semi solid; IR (KBr): cm^{-1} 3287, 2929, 2869, 1647, 1561, 1146; ^1H NMR ($CDCl_3$, 500 MHz): δ 5.32 (d, J = 8.4, 1H), 4.00 (ttd, J = 4.3, 11.7, 8.4 Hz, 1H), 3.32 (m, 2H), 1.94 (s, 3H), 1.91 (dddd, J = 1.8, 2.0, 4.3, 13.0 Hz, 2H), 0.97 (td, J = 11.7, 13.0 Hz, 2H), 1.50 (m, 2H), 1.45 (m, 2H), 1.36 (m, 2H), 1.35 (m, 2H), 0.90 (m, 6H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.5, 76.2, 47.1, 38.8, 37.1, 22.8, 15.2, 13.7; HRMS (m/z) calcd: 250.1782; found: 250.1782 (M^++Na).

N1-(2,6-Dipentyltetrahydro-2H-4-pyranyl)acetamide **3j** (Table 1): white solid, mp: 80–82 °C; (KBr): cm^{-1} 3287, 3089, 2928, 2855, 1643, 1556; ^1H NMR ($CDCl_3$, 300 MHz): δ 5.60 (d, J = 7.5 Hz, 1H), 4.02–3.88 (m, 1H), 3.33–3.24 (m, 2H), 1.93 (s, 3H), 1.92–1.85 (m, 2H), 1.53–1.24 (m, 16H), 1.01–0.86 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.2, 76.0, 46.4,38.6, 36.1, 31.7, 25.2, 23.5, 22.6, 14.0; HRMS (m/z) calcd: 306.2408; found: 306.2421 (M^++Na).

N1-(2,6-Diisopropyltetrahydro-2H-4-pyranyl)acetamide **3k** (Table 1): semi solid; (KBr): cm^{-1} 3283, 3091, 2943, 2879, 1644, 1556; ^1H NMR ($CDCl_3$, 300 MHz): δ 5.62 (d, J = 7.5 Hz, 1H), 3.98–3.85 (m, 1H), 3.03–2.95 (m, 2H), 1.94 (s, 3H), 1.93–1.87 (m, 2H), 1.67–1.59 (m, 2H), 0.95–0.86 (m, 14H); HRMS (m/z) calcd: 250.1782; found: 250.1787 (M^++Na).

N1-(2,6-Dipropyltetrahydro-2H-4-pyranyl)benzamide **3a** (Table 2): white solid, mp: 126–128 °C; (KBr): cm^{-1} 3281, 3065, 2956, 2865, 1629, 1543; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.71 (dd, J = 8.0, 1.4 Hz, 2H), 7.43 (m, 3H), 5.84 (d, J = 8.8 Hz, 1H), 4.21–4.15 (m, 1H), 3.42–3.35 (m, 2H), 2.09–1.97 (m, 2H), 1.60–1.30 (m, 8H), 1.17–0.97 (m, 2H), 0.93 (t, J = 7.3 Hz, 6H); HRMS (m/z) calcd: 312.1939; found: 312.1950 (M^++Na).

N1-(2,6-Diphenyltetrahydro-2H-4-pyranyl)benzamide **3b** (Table 2): white solid, mp: 202–204 °C; (KBr): cm^{-1}3282, 3081, 2923, 2843, 1634, 1546; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.65 (d, J = 7.5 Hz, 2H), 7.48–7.42 (m, 6H), 7.35 (t, J = 8.3 Hz, 4H), 7.30–7.26 (m, 3H) 5.95 (d, J = 8.3 Hz, 1H), 4.76 (d, J = 10.5 Hz, 2H), 4.67–4.53 (m, 1H), 2.50–2.42 (m, 2H), 1.61–1.48 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 163.9, 140.6, 132.7, 129.1, 126.3, 126.2, 123.7, 75.8, 44.7.; HRMS (m/z) calcd: 380.1626; found: 380.1632 (M^++Na).

N1-(2,6-Diethyltetrahydro-2H-4-pyranyl)-4-methylbenzamide **3c** (Table 2): white solid, mp: 172–174 °C; (KBr): cm^{-1} 3290, 3037, 2959, 2920, 2875, 1632, 1541; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.60 (d, J = 8.3 Hz, 2H), 7.19 (d, J = 8.3 Hz, 2H), 5.81 (d, J = 8.3 Hz, 1H), 4.24–4.09 (m, 1H), 3.36–3.26 (m, 2H),2.41 (s, 3H), 2.09–2.01 (m, 2H), 1.62–1.42 (m, 4H), 1.12–0.99 (m, 2H), 0.93 (t, J = 7.5 Hz, 6H); HRMS (m/z) calcd: 298.1782; found: 298.1795 (M^++Na).

N1-[2,6-Di(4-fluorophenyl)tetrahydro-2H-4-pyranyl]-4-methylbenzamide **3d** (Table 2): white solid, mp: 212–214 °C; (KBr): cm^{-1} 3294, 3044, 2925, 2850, 1630, 1534; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.62 (d, J = 7.5 Hz, 2H), 7.43–7.37 (m, 4H), 7.22 (d, J = 8.3 Hz, 2H), 7.08–7.01 (m, 4H), 5.88 (d, J = 7.5 Hz, 1H), 4.72 (d, J = 11.3 Hz, 2H), 4.63–4.50 (m, 1H), 2.47–2.39 (m, 5H), 1.57–1.43 (m, 2H); HRMS (m/z) calcd: 430.1594; found: 430.1594 (M^++Na).

N1-(2,6-Diheptyltetrahydro-2H-4-pyranyl)-2-methylpropanamide **3e** (Table 2): white solid, mp: 103–105 °C; (KBr): cm^{-1} 3283, 2924, 2853, 1646, 1551; ^1H NMR ($CDCl_3$, 200 MHz): δ 5.10 (d, J = 8.0 Hz, 1H), 4.03–3.89 (m, 1H), 3.37–3.24 (m, 2H), 2.33–2.14 (m, 1H), 1.96–1.84 (m, 2H), 1.50–1.24 (m, 24H), 1.13 (d, J = 6.5 Hz, 6H), 0.98–0.85 (m, 8H); HRMS (m/z) calcd: 390.3347; found: 390.3353 (M^++Na).

N1-[2,6-Di(4-methylphenyl)tetrahydro-2H-4-pyranyl]-2-methylpropanamide **3f** (Table 2): white solid, mp: 254–256 °C; (KBr): cm^{-1} 3284, 3089, 2932, 28640, 1648, 1556; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.29 (d, J = 8.3 Hz, 4H), 7.13 (d, J = 8.3 Hz, 4H), 5.22 (d, J = 7.5 Hz, 1H), 4.64 (d, J = 10.5 Hz, 2H), 4.41–4.28 (m, 1H), 2.36 (s, 6H), 2.32–2.25 (m, 3H) 1.44–1.31 (m, 2H), 1.15 (d, J = 6.8 Hz, 6H).; HRMS (m/z) calcd: 374.2095; found: 374.2099 (M^++Na).