Bismuth-triflate-catalyzed Prins–Ritter reaction — An efficient synthesis of 4-amidotetrahydropyrans

J.S. Yadav, B.V. Subba Reddy, D.N. Chaya, G.G.K.S. Narayana Kumar

Abstract: Bismuth(III) triflate is found to be an effective Lewis acid in catalyzing a three-component reaction of homoallylic alcohol, carbonyl compound, and nitrile at ambient temperature via the Prins–Ritter sequence to furnish 4-amidotetrahydropyrans in high yields, all with cis selectivity. Spirocyclic 4-amidotetrahydropyrans are obtained in case of cyclic ketones.

Key words: Prins cyclization, bismuth(III) triflate, homoallyl alcohol, 4-amidotetrahydropyrans.

Résumé : On a trouvé que le triflate de bismuth(III) agit comme acide de Lewis efficace dans la catalyse de la réaction à trois composantes d'un alcool homoallylique, d'un composé carbonylé et d'un nitrile à la température ambiante, par le biais d'une séquence de Prins–Ritter, qui conduit à la formation de 4-amidotétrahydropyranes, avec des rendements élevés et une sélectivité complètement *cis*. Dans les cas où le produit de départ est une cétone cyclique, le produit obtenu est un 4-amidotétrahydropyrane spirocyclique.

Mots-clés : cyclisation de Prins, bismuth(III), triflate, alcool homoallylique, 4-amidotétrahydropyranes.

[Traduit par la Rédaction]

Introduction

Recently, multicomponent one-pot synthesis has received considerable attention because of its wide range of applications in medicinal chemistry for the production of structural scaffolds and combinatorial libraries in drug discovery (1). The 4-aminotetrahydropyran ring system is found in many biologically active natural products, such as ambruticins VS, glycamino acid, and others (2, 3). Tetrahydropyran derivatives are usually prepared by the Prins cyclization using acid catalysis (4, 5) or by intramolecular hetero-Michael reaction (6). However, the use of Ritter amidation to terminate Prins cyclization is scarce (7); hence, an efficient and practical methodology for the Prins–Ritter-type reaction would be of great importance for the synthesis of natural products (8).

Lanthanide triflates are unique Lewis acids that are currently of great interest (9). The high catalytic activity, low toxicity, moisture and air tolerance, and their recyclability make lanthanide triflates attractive alternatives to conventional Lewis acids (10). However, lanthanide triflates are rather expensive and their use in large-scale synthesis is limited. Therefore, cheaper and more efficient catalysts are desirable. In this direction, bismuth triflate has evolved as remarkable Lewis acid catalyst for effecting various organic transformations (11). Compared with lanthanide triflates, bismuth triflate is cheap and is easy to prepare, even on a multi-gram scale, from commercially available bismuth oxide and triflic acid (12). However, there have been no reports on the use of bismuth triflate for the synthesis of tetrahydropyrans.

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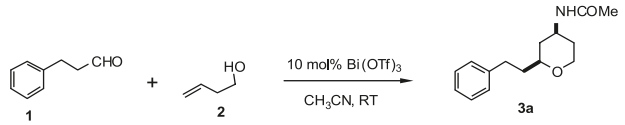
J.S. Yadav,[1] B.V. Subba Reddy, D.N. Chaya, G.G.K.S. Narayana Kumar. Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad 500 007, India.

[1]Corresponding author (e-mail: yadavpub@iict.res.in).

Scheme 1.



Results and discussion

In this article, we describe a direct and efficient method for the synthesis of 4-amidotetrahydropyrans via the Prins–Ritter sequence using bismuth triflate. In a preliminary study, 3-phenylpropanal (**1**) was treated with but-3-en-1-ol (**2**) in acetonitrile in the presence of 10 mol% of bismuth triflate. The reaction went to completion in 4.5 h at room temperature, and the product 4-acetamidotetrahydropyran **3a** was obtained, instead of tetrahydropyranyl-4-triflate, in 93% yield with cis selectivity (Scheme 1).

This result encouraged us to study the reaction with various aldehydes, homoallylic alcohols, and nitriles. Interestingly, 3-buten-1-ol reacted smoothly with cyclohexanecarboxaldehyde, isobutyraldehyde, *trans*-cinnamaldehyde, 1-naphthaldehyde, 3,4-dichlorobenzaldehyde, 3,4,5-trimethoxybenzaldehyde, and *m*-nitrobezaldehyde in acetonitrile to produce the corresponding 4-acetamidotetrahydropyrans in high yields (Table 1, entries **b**–**h**,). The substituted homoallylic alcohols like 1-phenylbut-en-1-ol and 1-cyclohexylbut-en-1-ol also participated well in this transformation (Table 1, entries **o** and **p**). This reaction proceeded well even with cyclic ketones such as cyclopentanone, cyclohexanone, and 4-phenyl-1-cyclohexanone to give spirocyclic-4-acet-

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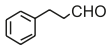
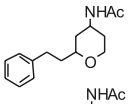
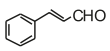
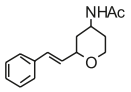
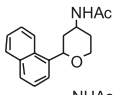
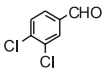
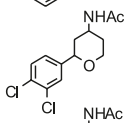
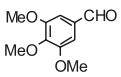
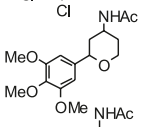
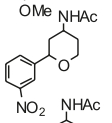
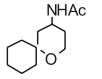
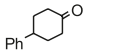
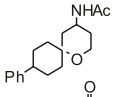
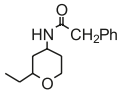
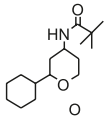
Table 1. Preparation of 4-amidotetrahdyropyrans via the Prins–Ritter reaction sequence.

Entry	Homoallyl alcohol	Carbonyl compound	Nucleophile	Amidopyrans	Time (h)[a]	Yield (%)[b]
a			CH_3CN		4.5	93
b			CH_3CN		5.0	90
c			CH_3CN		4.0	91
d			CH_3CN		4.5	88
e			CH_3CN		6.5	87
f			CH_3CN		7.0	85
g			CH_3CN		8.5	82
h			CH_3CN		8.5	80
i			CH_3CN		9.0	86
j			CH_3CN		7.5	88
k			CH_3CN		8.0	86
l			$PhCH_2CN$		7.0	86
m			Me_3CCN		7.5	88
n			PhCN		8.5	82
o			CH_3CN		7.5	90
P			CH_3CN		8.0	86

[a]All products were characterized by ^1H NMR, ^{13}C NMR, IR, and mass spectroscopy.
[b]Isolated and unoptimized yields.

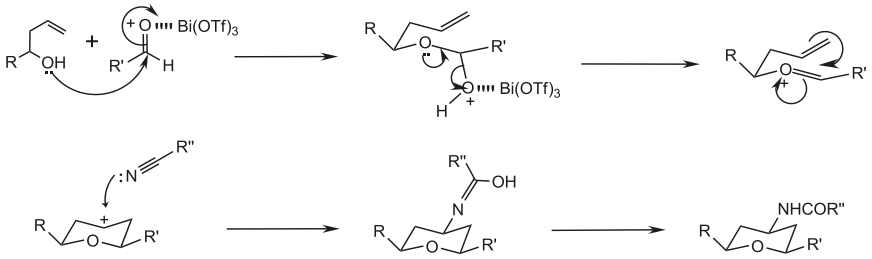
amidotetrahydropyrans comparably in good yields (Table 1, entries **i**–**k**; Scheme 2).

The reaction succeeded with other nitriles such as 2-phenyl acetonitrile, 3,3-dimethylbutanenitrile, and benzonitrile (Table 1, entries **l**–**n**). In the absence of bismuth triflate, the

Scheme 2.

3i

Scheme 3.



reaction did not proceed even after a long reaction time (16 h). The reactions were clean, and the products were obtained at room temperature in excellent yields and with high diastereoselectivity as determined from the NMR spectra of the crude products. Only one diastereoisomer was obtained in each case, the structure of which was confirmed on the basis of coupling constants and also by nOe experiments (8e). The formation of the products could be explained by hemi-acetal formation followed by Prins cyclization and subsequent Ritter amidation (Scheme 3).

A tentative reaction mechanism to realize the cis selectivity could be explained by assuming the formation of an (*E*)-oxocarbenium ion via a chairlike transition state, which has an increased stability relative to the open oxocarbenium ion owing to delocalization. The optimal geometry for this delocalization places the hydrogen atom at C-4 in a pseudo-axial position, which favours equatorial attack of the nucleophile (13). The effects of various metal triflates such as $In(OTf)_3$, $Yb(OTf)_3$, $Sm(OTf)_3$, $Dy(OTf)_3$, and $Ce(OTf)_3$ were examined in this reaction. Of these, bismuth triflate was found to be efficient in terms of conversion. The scope and generality of this process is illustrated with respect to various carbonyl compounds, homoallylic alcohols, and nitriles, and the results are presented in Table 1. It is noteworthy to highlight that both aromatic and aliphatic substrates worked well for this transformation.

Conclusion

In summary, we described a novel and efficient Prins–Ritter reaction to produce highly substituted 4-amidotetrahydropyrans in high yields, all with cis selectivity. The use of inexpensive and readily available bismuth triflate makes this procedure simple, convenient, and practical. In addition to its simplicity, efficiency, and milder reaction conditions, this method provides an easy access for 4-amidotetrahydropyran derivatives in a single-step operation.

Experimental

Melting points were recorded on Buchi R-535 apparatus and are uncorrected. IR spectra were recorded on a PerkinElmer FTIR 240-c spectrophotometer using KBr optics. ^{1}H, ^{13}C NMR spectra were recorded on Gemini-200 spectrometer in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV. TLC was monitored on 0.25 mm pre-coated silica-gel plates (60F-254).

General procedure

A mixture of but-3-en-1-ol (1 mmol), 3-phenylpropanal (1.2 mmol), and bismuth triflate (10 mol%) in acetonitrile (5 mL) was stirred at 23 °C for a specified time (Table 1). After completion of the reaction as indicated by TLC, the reaction mixture was quenched with water and extracted with ethyl acetate (2 × 10 mL). The combined organic layers were dried over anhyd. Na_2SO_4. Removal of solvent followed by purification on silica gel (Merck, 100–200 mesh, ethyl acetate/hexane, 4:6) gave pure 4-amidotetrahydropyran. The products thus obtained were characterized by IR and NMR spectroscopy. Characterization data was found to be consistent with that of authentic samples (6).

a: *N*-(2-phenethyltetrahydro-2*H*-4-pyranyl)acetamide

Pale yellow solid, mp 90–92 °C. IR (KBr) ν: 3308, 2923, 2852, 1648, 1543, 1368, 1083, 946, 745 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.26 (m, 2H), 1.31 (dq, 1H, *J* = 4.2, 12.2 Hz), 1.36 (q, 1H, *J* = 12.0 Hz), 1.85 (t, 2H, *J* = 7.5 Hz), 1.93 (s, 3H), 2.66 (ddt, 1H, *J* = 2.2, 4.2, 12.0 Hz), 2.74 (ddq, 1H, *J* = 2.2, 12.0, 12.0 Hz), 3.28 (m, 1H), 3.44 (dt, 1H, *J* = 1.5, 12.0 Hz), 3.89 (m, 1H), 4.13 (m, 1H), 5.28 (d, 1H, *J* = 8.3 Hz), 7.07–7.26 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.1, 31.4, 32.5, 37.7, 38.3, 45.9, 66.3, 75.4, 125.6, 127.8, 128.1, 141.7, 169.5. LC-MS: *m*/*z* (%): (M + Na) 270. HR-MS calcd. for $C_{15}H_{21}NO_2Na$: 270.1469. Found: 270.1478.

b: *N*-(2-cyclohexyltetrahydro-2*H*-4-pyranyl)acetamide

Colourless solid, mp 148–150 °C. IR (KBr) ν: 3280, 3089, 2944, 2930, 2822, 1648, 1543, 1422, 1373, 1091, 966, 804 cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.89–1.38 (m, 10H), 1.56–1.90 (m, 5H), 1.93 (s, 3H), 3.04 (m, 1H), 3.41 (dt, 1H, *J* = 2.0, 12.0 Hz), 3.86 (m, 1H), 3.90 (m, 1H), 5.36 (d, 1H, *J* = 7.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.4, 80.9, 66.2, 46.4, 35.6, 32.8, 32.7, 28.6, 28.4, 25.1, 23.2. LC-MS: *m*/*z* (%): (M + Na) 248. HR-MS calcd. for $C_{13}H_{23}NO_2Na$: 248.1626. Found: 248.1636.

c: *N*-(2-isopropyltetrahydro-2*H*-4-pyranyl)acetamide

Colourless solid. mp 74–76 °C. IR (KBr) ν: 3320, 2928, 2838, 1412, 1370, 1256, 1140, 1088, 1046, 986, 876 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.88 (d, 3H, *J* = 6.7 Hz), 0.91 (d, 3H, *J* = 6.7 Hz), 1.06 (m, 1H), 1.23–1.42 (m, 2H), 1.64 (m, 1H), 1.76–1.93 (m, 1H), 1.94 (s, 3H), 3.01 (dq, 1H, *J* = 1.5, 6.7 Hz), 3.41 (dt, 1H, *J* = 1.5, 12.0 Hz), 3.84–4.00 (m, 2H), 6.47 (d, 1H, *J* = 7.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.4, 81.4, 66.4, 46.3, 35.1, 32.8, 32.7, 23.1, 18.2, 18.0. LC-MS: *m*/*z*: (M + Na) 208. HR-MS calcd. for $C_{10}H_{19}NO_2Na$: 208.1313. Found: 208.1322.

d: *N*-2-[2-phenyl-(*E*)-1-ethenyl]tetrahydro-2*H*-4-pyranylacetamide

Yellow solid, mp 114–116 °C. IR (KBr) ν: 3294, 2956, 2926, 2230, 1648, 1553, 1366, 1087, 1042, 802, 730 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.18–1.50 (m, 2H), 1.94 (m, 1H), 1.98 (s, 3H), 2.13 (m, 1H), 3.60 (dt, 1H, *J* = 1.5, 12.0 Hz), 4.02–4.15 (m, 3H), 5.37 (d, 1H, *J* = 6.8 Hz), 6.14 (dd, 1H, *J* = 5.3, 15.8 Hz), 6.57 (d, 1H, *J* = 15.8 Hz), 7.18–7.40 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.4, 131.2, 130.3, 129.5, 128.3, 127.4, 126.1, 77.3, 66.6, 46.1, 38.9, 32.9, 23.2. LC-MS: *m*/*z*: (M + Na) 268. HR-MS calcd. for $C_{15}H_{19}NO_2Na$: 268.1313. Found: 268.1305.

e: *N*-[2-(1-naphthyl)tetrahydro-2*H*-4-pyranyl]acetamide

Pale yellow solid, mp 130–132 °C. IR (KBr) ν: 3294, 2956, 2926, 1648, 1553, 1366, 1087, 1042, 802, 730 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.42–1.67 (m, 2H), 1.97 (s, 3H), 2.04 (m, 1H), 2.42 (m, 1H), 3.84 (dt, 1H, *J* = 2.2, 12.0 Hz), 4.24–4.38 (m, 2H), 5.12 (dd, 1H, *J* = 1.7, 11.3 Hz), 5.27 (d, 1H, *J* = 7.5 Hz), 7.42 (m, 3H), 7.79 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.4, 137.4, 133.7, 130.2, 128.8, 128.1, 126.1, 125.5, 125.4, 123.1, 122.9, 75.9, 67.2, 46.6, 39.7, 33.0, 23.4. LC-MS: *m*/*z*: (M + Na) 292. HR-MS calcd. for $C_{17}H_{19}NO_2Na$: 292.1313. Found: 292.1320.

f: *N*-[2-(3,4-dichlorophenyl)tetrahydro-2*H*-4-pyranyl]acetamide

Pale yellow solid. mp 110–112 °C. IR (KBr) ν: 3316, 2945, 2852, 1643, 1543, 1376, 1077, 942, 812, 735 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.23–1.55 (m, 2H), 1.95 (m, 1H), 1.99 (s, 3H), 2.22 (m, 1H), 3.67 (dt, 1H, *J* = 2.2, 12.0 Hz), 4.07–4.23 (m, 2H), 4.38 (dd, 1H, *J* = 1.7, 11.3 Hz), 5.34 (d, 1H, *J* = 7.5 Hz), 7.24 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.8, 131.7, 131.2, 130.4, 130.2, 127.7, 124.9, 77.0, 66.8, 46.2, 40.4, 32.3, 23.2. LC-MS: *m*/*z*: (M + Na) 311. HR-MS calcd. for $C_{13}H_{15}Cl_2NO_2Na$: 310.0377. Found: 310.0380.

g: *N*-[2-(3,4,5-trimethoxyphenyl)tetrahydro-2*H*-4-pyranyl]acetamide

Yellow solid, mp 210–212 °C. IR (KBr) ν: 3296, 2944, 2936, 1648, 1548, 1376, 1078, 1042, 814, 720 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.32 (q, 1H, *J* = 12.4 Hz), 1.38 (dq, 1H, *J* = 4.5, 12.4 Hz), 1.93 (s, 3H), 2.06 (ddq, 1H, *J* = 12.6, 4.5, 2.2 Hz), 2.12 (ddt, 1H, *J* = 12.6, 4.5, 2.2 Hz), 3.63 (dt, 1H, *J* = 2.4, 12.2 Hz), 3.77 (s, 9H), 4.06 (m, 1H), 4.11 (m, 1H), 4.32 (dd, 1H, *J* = 2.0, 11.3 Hz), 5.30 (d, 1H, *J* = 7.5 Hz), 7.15–7.26 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.2, 153.0, 137.4, 137.1, 102.7, 78.3, 68.1, 66.2, 60.7, 55.9, 42.9, 35.2, 23.2. LC-MS: *m*/*z*: (M + Na) 332. HR-MS calcd. for $C_{16}H_{23}NO_5Na$: 332.1473. Found: 332.1484.

h: *N*-[2-(3-nitrophenyl)tetrahydro-2*H*-4-pyranyl]acetamide

Yellow solid, mp 188–190 °C. IR (KBr) ν: 3308, 2956, 2926, 1648, 1625, 1515,1456, 1102, 1032, 812, 726 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.22 (q, 1H, *J* = 12.3 Hz), 1.44 (dq, 1H, *J* = 4.4, 12.3 Hz), 1.95 (s, 3H), 2.20 (ddq, 1H, *J* = 12.3, 4.5, 2.4 Hz), 2.26 (ddt, 1H, *J* = 12.3, 4.5, 2.3 Hz), 3.67 (dt, 1H, *J* = 1.8, 12.0 Hz), 4.12 (m, 1H), 4.20 (m, 1H), 4.49 (dd, 1H, *J* = 2.0, 11.2 Hz), 5.23 (d, 1H, *J* = 7.0 Hz), 7.50–8.08 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.4, 148.2, 144.0, 131.7, 129.1, 122.3, 120.5, 77.1, 66.9, 46.1, 40.4, 32.2, 23.2. LC-MS: *m*/*z*: (M + Na) 287. HR-MS calcd. for $C_{18}H_{26}O_2Na$: 287.1007. Found: 287.1010.

i: *N*-(6-oxaspiro[4.5]dec-9-yl)acetamide

Light yellow solid, mp 112–114 °C. IR (KBr) ν: 3335, 2954, 2922, 2851, 1632, 1536, 1367, 1206, 1083, 821, 743 cm^{-1}.^1H NMR (200 MHz, $CDCl_3$) δ: 1.24–1.75 (m, 12H), 1.87 (s, 3H), 3.45–3.71 (m, 2H), 3.91 (m, 1H), 5.81 (d, 1H, *J* = 8.0 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 23.1, 24.5, 33.1, 41.1, 42.1, 44.3, 61.0, 83.9, 169.2 ppm. LC-MS: *m*/*z* (%): (M + H^+) 198. HR-MS calcd. for $C_{11}H_{20}NO_2$: 198.1494. Found: 198.1505.

j: *N*-[1-oxaspiro[5.5]undec-4-yl]acetamide

Colourless solid, mp 148–150 °C. IR (KBr) ν: 3350, 2954, 2922, 2851, 1632, 1536, 1367, 1206, 1083, 821, 743 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.20–1.71 (m, 12H), 1.85 (dq, 1H *J* = 4.6, 12.0 Hz), 1.93 (s, 3H), 2.04 (ddq, 1H, *J* = 12.0, 4.4, 2.2 Hz), 3.63 (dt, 1H, *J* = 2.2, 12.0 Hz), 3.68 (m, 1H), 4.11 (m, 1H), 5.10 (d, 1H, *J* = 6.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.3, 138.4, 137.2, 129.0, 125.6, 78.5, 66.9, 46.4, 40.6, 32.8, 23.4, 21.0. LC-MS: *m*/*z* (%): (M + Na) 234. HR-MS calcd. for $C_{12}H_{21}NO_2Na$: 234.1469. Found: 234.1476.

k: *N*-[9-phenyl-1-oxaspiro[5.5]undec-4-yl]acetamide

Colourless solid, mp 172–174 °C. IR (KBr) ν: 3434, 3320, 2926, 2860, 1645, 1543, 1446, 1375, 1078, 971, 759, 701 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 1.13–1.38 (m, 3H), 1.32–1.77 (m, 6H), 1.84–1.98 (m, 5H), 2.39–2.55 (m, 2H), 3.64 (dt, 1H, *J* = 2.2, 12.0 Hz), 3.77 (ddd, 1H, *J* = 1.5, 5.2, 12.0 Hz), 4.15 (m, 1H), 5.58 (d, 1H, *J* = 7.5 Hz), 7.08–7.25 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.3, 146.9, 128.1, 126.7, 125.7, 71.8, 59.3, 43.9, 43.5, 42.4, 39.8, 33.0, 29.4, 28.6, 28.0, 23.3. LC-MS: *m*/*z* (%): (M + Na) 310. HR-MS calcd. for $C_{18}H_{25}NO_2Na$: 310.1782. Found: 310.1788.

l: *N*-(2-ethyltetrahydro-2*H*-4-pyranyl)-2-phenylacetamide

Light yellow solid, mp 90–92 °C. IR (KBr) ν: 3434, 3320, 2926, 2860, 1645, 1543, 1446, 1375, 1078, 971, 759, 701 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 1.13–1.38 (m, 3H), 1.32–1.77 (m, 6H), 1.84–1.98 (m, 5H), 2.39–2.55 (m, 2H), 3.64 (dt, 1H, *J* = 2.2, 12.0 Hz), 3.77 (ddd, 1H, *J* = 1.5, 5.2, 12.0 Hz), 4.15 (m, 1H), 5.58 (d, 1H, *J* = 7.5 Hz), 7.08–7.25 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 179.6, 134.6, 130.8, 128.2, 127.0, 76.5, 66.4, 46.1, 38.1, 32.9, 28.9, 23.3, 9.6. LC-MS: *m*/*z* (%): (M + Na) 270. HR-MS calcd. for $C_{18}H_{25}NO_2Na$: 270.1469. Found: 270.1478.

m: *N*-(2-cyclohexyltetrahydro-2*H*-4-pyranyl)-2,2-dimethylpropanamide

Colourless solid, mp 136–138 °C. IR (KBr) ν: 3434, 3320, 2926, 2860, 1645, 1543, 1446, 1375, 1078, 971, 759, 701 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.13–1.38 (m, 3H), 1.32–1.77 (m, 6H), 1.84–1.98 (m, 5H), 2.39–2.55 (m, 2H), 3.64 (dt, 1H, *J* = 2.2, 12.0 Hz), 3.77 (ddd, 1H, *J* = 1.5, 5.2, 12.0 Hz), 4.15 (m, 1H), 5.58 (d, 1H, *J* = 7.5 Hz), 7.08–

7.25 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 177.7, 80.9, 66.6, 46.2, 35.5, 33.1, 28.8, 27.4, 26.4, 26.1, 26.0, 25.3. LC-MS: *m/z* (%): (M + Na) 290. HR-MS calcd. for $C_{18}H_{25}NO_2Na$: 290.2095. Found: 290.2089.

n: 2-cyclohexyl-4-phenylcarboxamidotetrahydro-2*H*-pyran

Pale brown solid, mp 112–114 °C. IR (KBr) ν: 3434, 3320, 2926, 2860, 1645, 1543, 1446, 1375, 1078, 971, 759, 701 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.13–1.38 (m, 3H), 1.32–1.77 (m, 6H), 1.84–1.98 (m, 5H), 2.39–2.55 (m, 2H), 3.64 (dt, 1H, *J* = 2.2, 12.0 Hz), 3.77 (ddd, 1H, *J* = 1.5, 5.2, 12.0 Hz), 4.15 (m, 1H), 5.58 (d, 1H, *J* = 7.5 Hz), 7.08–7.25 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.8, 134.4, 131.4, 128.4, 126.8, 80.9, 68.5, 46.8, 35.7, 35.4, 28.8, 26.1, 26.0, 25.2. LC-MS: *m/z* (%): (M + Na) 310. HR-MS calcd. for $C_{18}H_{25}NO_2Na$: 310.1782. Found: 310.1786.

o: *N*-[2-(4-bromophenyl)-6-cyclohexyltetrahydro-2*H*-4-pyranyl]acetamide

Pale yellow solid, mp 186–188 °C. IR (KBr) ν: 3278, 2923, 2848, 1643, 1553, 1488, 1369, 1154, 1085, 1010, 812 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.95–1.32 (m, 5H), 1.12 (m, 1H), 1.24 (m, 1H), 1.49 (m, 1H), 1.63– 1.85 (m, 5H), 1.94 (s, 3H), 2.00 (ddt, 1H, *J* = 2.0, 4.2, 2.0 Hz), 2.16 (ddt, 1H, *J* = 12.0, 4.2, 2.0 Hz), 3.30 (ddd, 1H, *J* = 11.0, 6.2, 2.0 Hz), 4.11 (ddt, 1H, *J* = 4.4, 8.5, 12.0 Hz), 4.35 (dd, 1H, *J* = 1.4, 11.0 Hz), 5.23 (d, 1H, *J* = 7.3 Hz), 7.18 (d, 2H, *J* = 8.5 Hz), 7.41 (d, 2H, *J* = 8.5 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 23.4, 26.2, 26.5, 28.7, 34.8, 40.4, 42.8, 46.7, 77.5, 80.7, 121.0, 127.3, 131.3, 141.6, 169.4 ppm. LC-MS: *m/z* (%): (M + H$^+$) 381. HR-MS calcd. for $C_{19}H_{27}BrNO_2$: 380.1225. Found: 380.1234

p: *N*-(2-pentyl-6-phenyltetrahydro-2*H*-4-pyranyl)acetamide

Pale yellow solid, mp 164–166 °C. IR (KBr) ν: 3434, 3320, 2926, 2860, 1645, 1543, 1446, 1375, 1078, 971, 759, 701 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.89 (t, 3H, *J* = 7.0 Hz), 0.98–1.64 (m, 10H), 1.94 (s, 3H), 2.02 (m, 1H), 2.19 (m, 1H), 3.53 (dt, 1H, *J* = 2.2, 12.0 Hz), 4.11 (m, 1H), 4.40 (m, 1H), 5.35 (d, 1H, *J* = 7.5 Hz), 7.14–7.33 (m, 5H). LC-MS: *m/z* (%): (M + Na) 312. HR-MS calcd. for $C_{18}H_{27}NO_2Na$: 312.1939. Found: 312.1944.

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