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Three-component, one-pot diastereoselective synthesis of 4-amidotetrahydropyrans via the Prins–Ritter reaction sequence

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Abstract

Three-component coupling of carbonyl compounds, homoallylic alcohols, and nitriles has been achieved using 20 mol % of phosphomolybdic acid (PMA) at ambient temperature via the Prins–Ritter sequence to furnish 4-amidotetrahydropyrans in high yields with all cis selectivity. Spirocyclic-4-amidotetrahydropyrans are obtained using cyclic ketones.

Keywords: Prins–Ritter sequence; Nitriles; Heteropolyacids; Amidotetrahydropyrans

1. Introduction

The multi-component one-pot synthesis has received great importance because of its wide range of applications in pharmaceutical chemistry for production of structural scaffolds and combinatorial libraries for drug discovery. In particular, three-component coupling (3CC) reactions have proven remarkably successful in generating molecular complexities in a single step operation.[1] The 4-aminotetrahydropyran ring system is a core structure in a number of natural products such as ambruticins VS, glycamino acid, and others.[2,3] Generally, tetrahydropyran derivatives are prepared via Prins cyclization using acid catalysis.[4,5] However, the use of Ritter amidation to terminate Prins cyclization is scarce,[6] hence an efficient and practical methodology for the Prins–Ritter type reaction would be of great importance for natural product synthesis.[7]

In recent years, heteropolyacids (HPAs) are environmentally friendly and economically viable solid acids owing to their ease of handling, high catalytic activities, and reactivities.[8] They are non-toxic and allow cleaner reactions in comparison to conventional catalysts. Also, heteropolyacids are promising solid acids and act as bifunctional catalysts in homogeneous as well as in heterogeneous conditions.[9] Among various heteropolyacids, phosphomolybdic acid (PMA, $H_3PMo_{12}O_{40}$) is one of the less expensive and commercially available solid acid catalysts.[10] However, there have been no reports on the use of phosphomolybdic acid for the synthesis of 4-amidotetrahydropyran derivatives via the Prins–Ritter sequence.

2. Results and discussions

In this paper, we describe a direct and efficient protocol for the synthesis of 4-amidotetrahydropyrans by means of Prins–Ritter sequence using PMA as solid acid catalyst. Initially, we attempted the coupling of cyclohexanecarboxaldehyde with but-3-en-1-ol in acetonitrile in the presence of 20 mol % of phosphomolybdic acid. Surprisingly, the reaction went to completion over 6.5 h and the product, 4-acetamidotetrahydropyran **3a** was obtained, instead of 4-hydroxytetrahydropyran, in 92% yield with cis selectivity (Scheme 1).

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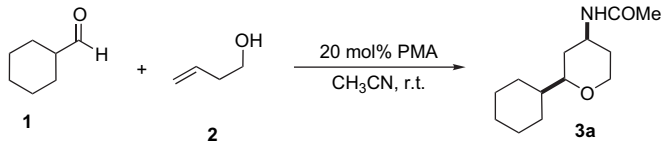


Scheme 1.

Encouraged by this result, we turned our attention to various aldehydes, homoallylic alcohols, and nitriles. Interestingly, propanaldehyde, hydrocinnamaldehyde, 2-naphthaldehyde, *p*-methylbenzaldehyde, *p*-methoxybenzaldehyde, and *p*-nitrobenzaldehyde reacted readily with 3-buten-1-ol and acetonitrile to produce the corresponding 4-acetamidotetrahydropyrans in high yields (entries b–g, Table 1). The structure of the 2, 4-disubstituted tetrahydropyran was established by NOE experiments (Fig. 1).

The structure of **3d** shown in Figure 1 was deduced from the NMR data, where the two substituents are shown to be cis to each other. The H2 proton has a large and small coupling of J=11.2 and 2.2 Hz. Presence of the large coupling indicates

Table 1
Preparation of 4-acetamidotetrahydropyrans via Prins–Ritter reaction sequence

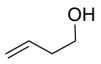
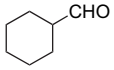
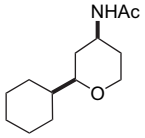
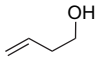
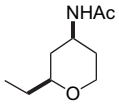
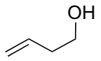
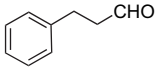
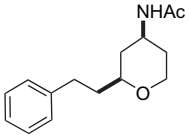
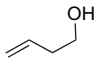
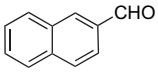
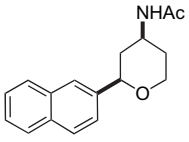
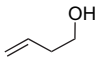
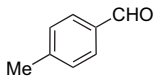
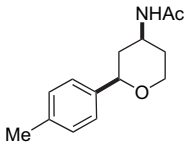
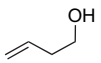
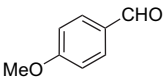
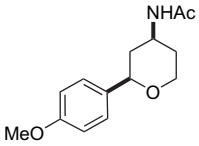
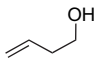
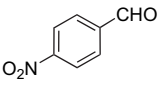
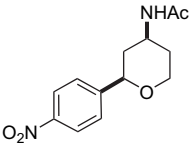
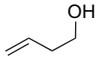
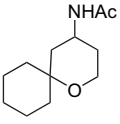
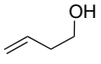
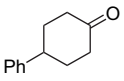
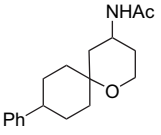
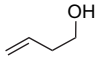
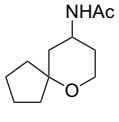
Entry	Homoallyl alcohol	Carbonyl compound	Nucleophile	Amidopyrans	Time[a] (h)	Yield[b] (%)
a			CH_3CN		6.5	92
b			CH_3CN		7.0	90
c			CH_3CN		7.0	89
d			CH_3CN		8.0	90
e			CH_3CN		7.5	92
f			CH_3CN		8.5	82
g			CH_3CN		8.5	80
h			CH_3CN		8.0	88
i			CH_3CN		7.5	84
j			CH_3CN		8.0	85

Table 1 (*continued*)

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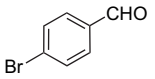
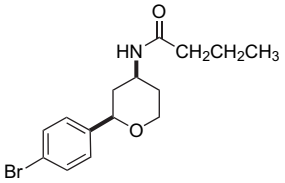
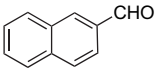
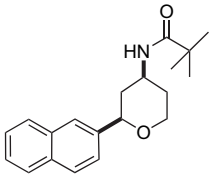
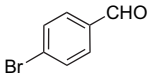
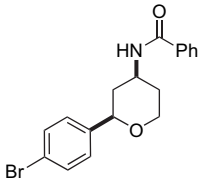
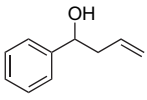
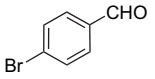
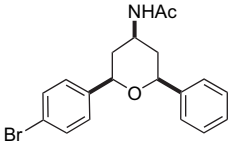
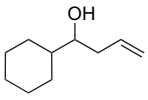
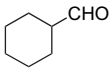
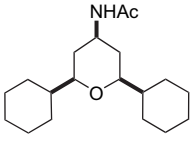
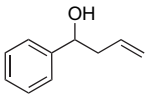
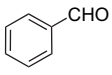
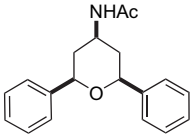
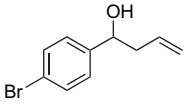
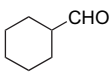
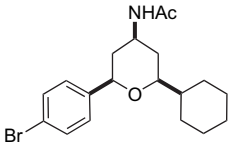
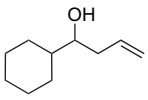
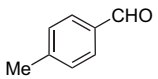
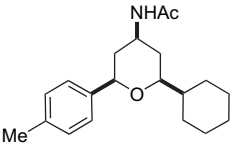
k			$CH_3CH_2CH_2CN$		7.0	88
l			Me_3CCN		7.5	87
m			PhCN		8.5	82
n			CH_3CN		8.0	85
o			CH_3CN		7.5	92
p			CH_3CN		7.5	91
q			CH_3CN		8.0	84
r			CH_3CN		7.5	86

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

that it is in axial position, with large diaxial coupling with H3a, which imply an equatorial position for the aromatic group at C2. Similarly the equatorial orientation of the substituent at C4 is suggested by the multiplicities of H3a and H5a protons (H3a (q) with $J\sim11.9$ Hz and H5a (dq) with $J=4.8$, ~11.9 Hz). The equatorial orientation of the substituents at C2 and C4 is also confirmed by NOESY cross peaks for H2 with H4 and H6. This structure was further confirmed by NOESY cross peaks for NH/H3a, NH/H3e, NH/H5a, NH/H5e, Ar/H3a, and Ar/H3e.

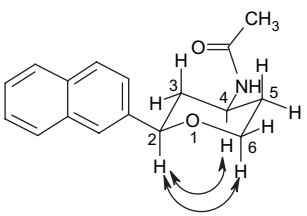


Figure 1. Characteristic NOE's of product **3d**.

The substituted homoallylic alcohols like 1-phenylbut-en-1-ol, 1-cyclohexylbut-3-en-1-ol, and 1-(4-bromophenyl)-3-buten-1-ol also participated well in this transformation (entries n–r, Table 1). The structure of the 2,4,6-trisubstituted tetrahydropyran was established by NOE experiments (Fig. 2). As

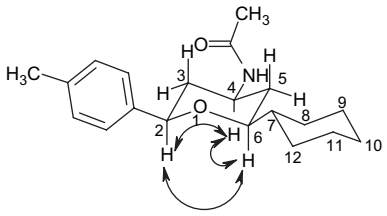
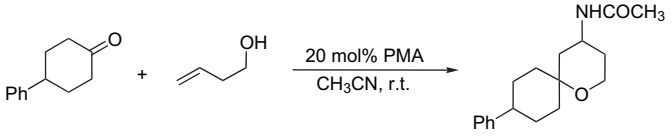


Figure 2. Characteristic NOE's of product **3r**.

expected, NMR data suggest that for **3r** all the three 2, 4, and 6 substituents are at equatorial position. The H2 and H6 protons show large vicinal couplings (J=11.3 Hz), corresponding to axial orientation of these protons, which was further confirmed by H2/H6. This implies equatorial orientation of the substituents at 2 and 6 positions. Equatorial orientation of the substituent at C4 position is confirmed by NOESY cross peak for H2/H4, and also H4/H6. Further, equatorial position of the aromatic group was confirmed by NOESY cross peaks, H-*ortho*/H3e, and also H-*ortho*/H3a.The structure was further confirmed by NOESY cross peaks for NH/H3a, NH/H3e, NH/H5a, NH/H5e, H7/H5a, and H7/H5e.

This reaction was also successful with cyclic ketones such as cyclohexanone, 4-phenyl-1-cyclohexanone, and cyclopetanone to give spirocyclic-4-acetamidotetrahydropyrans comparably in good yields (entries h–j, Table 1, Scheme 2).



Scheme 2.

The reaction was successful with other nitriles such as *n*-butyronitrile, *tert*-butyl nitrile, and benzonitrile (entries k–m, Table 1). In the absence of phosphomolybdic acid, the reaction did not proceed even after a long reaction time (12 h). The reactions were clean and the products were obtained at room temperature in excellent yields with high diastereoselectivity as determined from the NMR spectra of the crude products. In all cases, cis-isomer was obtained exclusively and the structure of which was confirmed by NOE experiments. The formation of the products could be explained by hemi-acetal formation followed by Prins cyclization and subsequent Ritter amidation (Scheme 3).

A rationale for the cis selectivity could be explained by assuming the formation of an (*E*)-oxocarbenium ion via a chair-like transition state, which has an increased stability relative to the open oxocarbenium ion due to delocalization. The optimal geometry for this delocalization places the hydrogen atom at C4 in a pseudo-axial position, which favors equatorial attack of the nucleophile.[11] Among other solid acid catalysts such as montmorillonite KSF, Amberlyst-15®, and phosphotungstic acid tested, phosphomolybdic acid was found to be efficient in terms of conversion. The scope and generality of this process are 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.

3. Conclusion

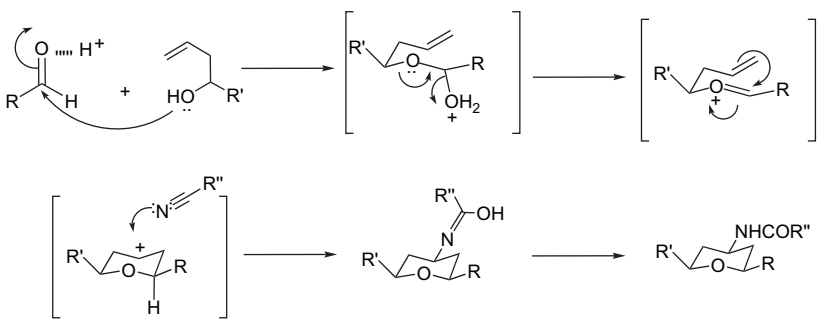
In summary, we have described an efficient Prins–Ritter reaction to produce highly substituted 4-amidotetrahydropyrans in high yields with all cis selectivity. The use of inexpensive and readily available phosphomolybdic acid makes this procedure simple, convenient, and practical. In addition to its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

4. Experimental section

4.1. General

Melting points were recorded on Buchi R-535 apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer FT-IR 240-c spectrophotometer using KBr optics. ^{1}H NMR and ^{13}C spectra were recorded on Gemini-200 and Varian Bruker-300 spectrometer in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV.

General procedure: A mixture of homoallylic alcohol (1.0 mmol), carbonyl compound (1.0 mmol), and phosphomolybdic acid (20 mol %) in nitrile (5 mL, used as a solvent) 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



Scheme 3. A plausible reaction mechanism.

(2×10 mL). The combined organic layers were dried over anhydrous 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 NMR, IR, and mass spectrometry.

*4.1.1. N-(2-Cyclohexyltetrahydro-2H-4-pyranyl)-acetamide (**3a**)*

Colorless solid, mp 148–150 °C. IR (KBr): ν 3280, 3089, 2944, 2930, 2822, 1648, 1543, 1422, 1373, 1091, 966, 804 cm^{-1}. ^1H 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). LCMS *m/z* (%): (M+Na) 248. HRMS calcd for $C_{13}H_{23}NO_2Na$: 248.1626. Found: 248.1636.

*4.1.2. N-(2-Ethyltetrahydro-2H-4-pyranyl)acetamide (**3b**)*

Colorless solid, mp 82–84 °C. IR (KBr): ν 3286, 3091, 2954, 2930, 2842, 1642, 1559, 1437, 1373, 1155, 1091, 977, 738 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.92 (t, 3H, J=7.3 Hz), 1.22–1.59 (m, 4H), 1.82–1.92 (m, 2H), 1.94 (s, 3H), 3.22 (m, 1H), 3.44 (dt, 1H, J=1.8, 12.0 Hz), 3.99 (m, 1H), 3.95 (m, 1H), 5.31 (d, 1H, J=8.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.4, 77.7, 66.3, 46.0, 37.9, 32.6, 28.8, 23.0, 9.5. LCMS *m/z* (%): (M+Na) 194. HRMS calcd for $C_9H_{17}NO_2Na$: 194.1156. Found: 194.1165.

*4.1.3. N-(2-Phenethyltetrahydro-2H-4-pyranyl)-acetamide (**3c**)*

Pale yellow solid, mp 90–92 °C. IR (KBr): ν 3308, 2923, 2852, 1648, 1543, 1368, 1083, 946, 745 cm^{-1}. ^1H 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. LCMS *m/z* (%): (M+Na) 270. HRMS calcd for $C_{15}H_{21}NO_2Na$: 270.1469. Found: 270.1478.

*4.1.4. N-[2-(2-Naphthyl)tetrahydro-2H-4-pyranyl]-acetamide (**3d**)*

Light yellow solid, mp 155–157 °C. IR (KBr): ν 3242, 3057, 2936, 2851, 1633, 1558, 1363, 1306, 1250, 1145, 1089, 964, 821, 738 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.81 (m, 4H, Ar), 7.45 (m, 3H, Ar), 5.37 (d, 1H, NH, J=8.3 Hz), 4.58 (dd, 1H, H2, J=11.2, 2.2 Hz), 4.24 (m, 1H, H4), 4.22 (m, 1H, H6e), 3.73 (dt, 1H, H6a, J=2.4, 12.2 Hz), 2.31 (ddt, 1H, H3e, J=12.8, 4.6, 2.2 Hz), 2.01 (ddq, 1H, H5e, J=12.8, 4.4, ~2.3 Hz), 1.97 (s, 3H, CO–Me), 1.55 (dq, 1H, H5a, J=4.8, ~12.4 Hz), 1.45 (q, 1H, H3a, J ~ 11.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.4, 32.7, 40.7, 46.5, 67.1, 78.7, 123.9, 124.3, 125.8, 126.1, 127.6, 128.0, 128.1, 132.9, 133.3, 139.4, 169.4. LCMS *m/z* (%): (M+Na) 292. HRMS calcd for $C_{17}H_{19}NO_2Na$: 292.1313. Found: 292.1321.

*4.1.5. N-[2-(4-Methylphenyl)tetrahydro-2H-4-pyranyl]-acetamide (**3e**)*

Pale yellow solid, mp 166–168 °C. IR (KBr): ν 3294, 2956, 2926, 1648, 1553, 1366, 1087, 1042, 802, 730 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.30 (q, 1H, J=12.0 Hz), 1.37 (dq, 1H, J=4.6, 12.4 Hz), 1.94 (s, 3H), 1.96 (ddq, 1H, J=12.7, 4.4, 2.2 Hz), 2.16 (ddt, 1H, J=12.7, 4.6, 2.2 Hz), 2.32 (s, 3H), 3.64 (dt, 1H, J=2.2, 12.2 Hz), 4.16 (m, 1H), 4.19 (m, 1H), 4.34 (dd, 1H, J=1.7, 11.3 Hz), 5.23 (d, 1H, J=7.5 Hz), 7.08 (d, 2H, J=8.1 Hz), 7.16 (d, 2H, J=8.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.3, 133.6, 129.4, 128.5, 125.6, 73.0, 59.4, 46.6, 42.5, 40.1, 23.3, 21.2. LCMS *m/z* (%): (M+Na) 256. HRMS calcd for $C_{14}H_{19}NO_2Na$: 256.1313. Found: 256.1320.

*4.1.6. N-[2-(4-Methoxyylphenyl)tetrahydro-2H-4-pyranyl]-acetamide (**3f**)*

Light green solid, mp 183–185 °C. IR (KBr): ν 3306, 2946, 2936, 1651, 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, 3H), 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), 6.80 (d, 2H, J=8.5 Hz), 7.15–7.26 (m, 2H, J=8.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.2, 156.6, 134.4, 128.5, 114.6, 73.6, 58.4, 54.6, 46.4, 42.6, 40.3, 23.2. LCMS *m/z* (%): (M+Na) 272. HRMS calcd for $C_{14}H_{19}NO_{32}Na$: 272.1262. Found: 272.1270.

*4.1.7. N-[2-(4-Nitrophenyl)tetrahydro-2H-4-pyranyl]-acetamide (**3g**)*

Yellow solid, mp 190–192 °C. IR (KBr): ν 3294, 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), 7.47 (d, 2H, J=8.6 Hz), 8.18 (d, 2H, J=8.6 Hz). LCMS *m/z* (%): (M+Na) 287. HRMS calcd for $C_{13}H_{16}N_2O_4Na$: 287.1007. Found: 287.1015.

*4.1.8. N-[1-Oxaspiro[5.5]undec-4-yl]acetamide (**3h**)*

Colorless 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. LCMS *m/z* (%): (M+Na) 234. HRMS calcd for $C_{12}H_{21}NO_2Na$: 234.1469. Found: 234.1476.

*4.1.9. N-[9-Phenyl-1-oxaspiro[5.5]undec-4-yl]acetamide (**3i**)*

Colorless 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. LCMS *m/z* (%): (M+Na) 310. HRMS calcd for $C_{18}H_{25}NO_2Na$: 310.1782. Found: 310.1793.

*4.1.10. N-(6-Oxaspiro[4.5]dec-9-yl)acetamide (**3j**)*

Light yellow solid, mp 112–114 °C. IR (KBr): ν 3335, 2954, 2922, 2851, 1632, 1536, 1367, 1206, 1083, 821, 743 cm^{-1}. ^{1}H 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. LCMS *m/z* (%): (M+H$^+$) 198. HRMS calcd for $C_{11}H_{20}NO_2$: 198.1494. Found: 198.1505.

*4.1.11. N-[2-(4-Bromophenyl)-tetrahydro-2H-4-pyranyl]-butanamide (**3k**)*

Colorless solid, mp 178–180 °C. IR (KBr): ν 3291, 2958, 2924, 2850, 1636, 1549, 1250, 1095 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.94 (t, 3H, *J*=7.55 Hz), 1.23 (m, 1H), 1.64 (m, 2H), 1.93 (m, 1H), 2.09 (t, 2H, *J*=7.5 Hz), 2.18 (m, 2H), 3.64 (dt, 1H, *J*=2.2, 12.0 Hz), 4.08–4.21 (m, 2H), 4.35 (dd, 1H, *J*=2.2, 11.3 Hz), 5.19 (d, 1H, *J*=7.5 Hz), 7.17 (d, 2H, *J*=8.3 Hz), 7.42 (d, 2H, *J*=8.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.2, 140.9, 131.3, 127.2, 121.1, 77.8, 66.8, 46.0, 40.6, 38.5, 32.5, 19.0, 13.5. LCMS *m/z* (%): (M+Na) 349. HRMS calcd for $C_{15}H_{20}BrNO_2Na$: 349.0575. Found: 349.0584.

*4.1.12. N-[2-(2-Naphthyl)tetrahydro-2H-4-pyranyl]-2,2-dimethylpropanamide (**3l**)*

Pale brown solid, mp 172–174 °C. IR (KBr): ν 3422, 3284, 3069, 2935, 2847, 1648, 1549, 1491, 1352, 1251, 1145, 1089, 825, 700 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.16 (s, 9H), 1.41 (q, 1H, *J*=12.0 Hz), 1.53 (dq, 1H, *J*=4.6, 12.4 Hz), 2.10 (ddq, 1H, *J*=2.3, 4.4, 12.6 Hz), 2.34 (ddt, 1H, *J*=2.2, 4.6, 12.6 Hz), 3.70 (dt, 1H, *J*=12.0, 2.4 Hz), 4.24 (m, 1H), 4.26 (m, 1H), 4.52 (dd, 1H, *J*=2.2, 11.2 Hz), 5.40 (d, 1H, *J*=8.3 Hz), 7.42 (m, 3H), 7.79 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.5, 33.0, 38.6, 40.9, 46.3, 67.1, 78.7, 101.6, 123.9, 124.2, 125.8, 126.0, 127.6, 128.0, 132.9, 133.3, 139.5, 178.2. LCMS *m/z* (%): (M+Na) 334. HRMS calcd for $C_{20}H_{25}NO_2Na$: 334.1782. Found: 310.1790.

*4.1.13. N-[2-(4-Bromophenyl)tetrahydro-2H-4-pyranyl]-benzamide (**3m**)*

Colouless solid, mp 206–208 °C. IR (KBr): ν 3278, 3064, 2939, 2848, 1632, 1539, 1487, 1399, 1145, 1085, 827, 700 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.52 (q, 1H, *J*=12.2 Hz), 1.66 (dq, 1H, *J*=4.8, 12.2 Hz), 2.16 (ddq, 1H, *J*=2.2, 4.4, 12.0 Hz), 2.32 (ddt, 1H, *J*=2.2, 4.6, 12.0 Hz), 3.66 (dt, 1H, *J*=2.0, 12.2 Hz), 4.16 (m, 1H), 4.24 (m, 1H), 4.50 (dd, 1H, *J*=2.0, 12.0 Hz), 5.86 (d, 1H, *J*=7.5 Hz), 7.11–7.76 (m, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 32.5, 40.8, 46.6, 67.1, 77.8, 121.2, 126.7, 127.3, 128.5, 128.6, 131.4, 131.5, 140.8, 172.2. LCMS *m/z* (%): (M+H$^+$) 361. HRMS calcd for $C_{18}H_{19}BrNO_2$: 360.0599. Found: 360.0606.

*4.1.14. N-[2-(4-Bromophenyl)-6-phenyltetrahydro-2H-4-pyranyl]acetamide (**3n**)*

Light yellow solid, mp 170–172 °C. IR (KBr): ν 3316, 2945, 2852, 1643, 1543, 1376, 1077, 942, 812, 735 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.25–1.39 (m, 2H), 1.94 (m, 3H), 2.22–2.32 (m, 2H), 4.33 (m, 1H), 4.56–4.66 (m, 2H), 5.30 (d, 1H, *J*=7.5 Hz), 7.21–7.39 (m, 7H), 7.41–7.46 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.4, 40.1, 40.3, 46.7, 77.7, 78.4, 125.7, 127.4, 127.6, 128.4, 131.5, 140.8, 141.8, 142.0, 169.6. LCMS *m/z* (%): (M+Na) 397. HRMS calcd for $C_{19}H_{20}BrNO_2Na$: 396.0575. Found: 396.0586.

*4.1.15. N-(2,6-Dicyclohexyltetrahydro-2H-4-pyranyl)-acetamide (**3o**)*

Colorless solid, mp 180–182 °C. IR (KBr): ν 3288, 3093, 2956, 2932, 2843, 1644, 1559, 1437, 1373, 1155, 1091, 977, 744 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.80–1.43 (m, 16H), 1.54–1.80 (m, 8H), 1.89–1.92 (m, 2H), 1.93 (s, 3H), 3.00 (ddd, 2H, *J*=11.0, 6.8, 1.2 Hz), 3.90 (m, 1H), 5.17 (d, 1H, *J*=7.9 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 23.5, 26.5, 28.8, 29.2, 35.8, 43.2, 46.8, 80.3, 169.2. LCMS *m/z* (%): (M+Na) 330. HRMS calcd for $C_{19}H_{33}NO_2Na$: 330.2408. Found: 330.27416.

*4.1.16. N-(2,6-Diphenyltetrahydro-2H-4-pyranyl)-acetamide (**3p**)*

Light yellow solid, mp 232–234 °C. IR (KBr): ν 3279, 3070, 2951, 2842, 1641, 1552, 1373, 1293, 1120, 747, 696 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.38 (q, 2H, *J*=12.0 Hz), 1.94 (s, 3H), 2.29 (td, 2H, *J*=2.2, 12.0 Hz), 4.35 (m, 1H), 4.64 (dd, 2H, *J*=1.5, 11.3 Hz), 5.24 (d, 1H, *J*=7.5 Hz), 7.20–7.40 (m, 10H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 23.4, 40.4, 46.7, 78.3, 125.7, 127.5, 128.3, 142.0, 169.4. LCMS *m/z* (%): (M+Na$^+$) 318. HRMS calcd for $C_{19}H_{21}NO_2Na$: 318.1469. Found: 318.1479.

*4.1.17. N-[2-(4-Bromophenyl)-6-cyclohexyltetrahydro-2H-4-pyranyl]acetamide (**3q**)*

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. LCMS *m/z* (%): (M+H$^+$) 381. HRMS calcd for $C_{19}H_{27}BrNO_2$: 380.1225. Found: 380.1234.

*4.1.18. N-[2-Cyclohexyl-6-(4-methylphenyl)-tetrahydro-2H-4-pyranyl]acetamide (**3r**)*

Pale yellow solid, mp 188–190 °C. IR (KBr): ν 3314, 2923, 2852, 1646, 1543, 1368, 1083, 922, 804 cm^{-1}. ^{1}H NMR

(500 MHz, $CDCl_3$): δ 7.22 (d, 2H, Ar-*ortho*, J=7.9 Hz), 7.12 (d, 2H, Ar-*meta*, J=7.9 Hz), 5.30 (d, 1H, NH, J=8.3 Hz), 4.38 (dd, 1H, H2, J=11.3, 2.0 Hz), 4.16 (dtt, 1H, H4, J=8.3, ~11.9, ~4.2 Hz), 3.31 (ddd, 1H, H6, J=11.3, 6.2, 1.8 Hz), 2.32 (s, 3H, Ar–Me), 2.19 (ddt, 1H, H3e, J=12.4, 4.3, 2.1 Hz), 2.00 (ddt, 1H, H5e, J=12.3, 4.2, 2.1 Hz), 1.96 (s, 3H, CO–Me), 1.92–1.66 (m, 5H, Cy), 1.48 (m, 1H, H7), 1.24 (m, 1H, H3a), 1.13 (m, 1H, H5a), 1.29–1.03 (m, 5H, Cy). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.2, 133.6, 129.8, 128.8, 125.5, 80.6, 46.8, 42.8, 40.4, 34.9, 28.9, 28.6, 26.5, 26.1, 23.4, 21.0. LCMS *m/z* (%): (M+Na) 338. HRMS calcd for $C_{20}H_{29}NO_2Na$: 338.2095. Found: 338.2106.

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