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$CeCl_3 \cdot 7H_2O$/AcCl-catalyzed Prins–Ritter reaction sequence: a novel synthesis of 4-amido tetrahydropyran derivatives

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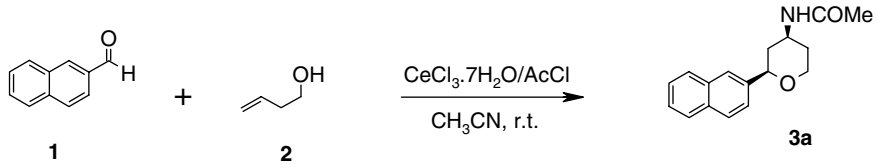
Abstract—Homoallylic alcohols, carbonyl compounds and nitriles undergo a smooth tandem Prins–Ritter type cyclization in the presence of $CeCl_3 \cdot 7H_2O$/AcCl at ambient temperature to produce 4-amido tetrahydropyrans in high yields with all cis-selectivity. Spirocyclic 4-amido tetrahydropyrans are obtained in the case of cyclic ketones.

Combining three or more components in a one-pot catalytic operation avoiding stoichiometric amounts of reagents, large volumes of solvents and extensive purification techniques is one target of modern organic synthesis.[1] The 4-amino tetrahydropyran ring system is a core unit 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] Although there have been some reports on the use of the Ritter reaction to terminate Prins-cyclizations, the scope of this process has not been explored extensively;[6] hence an efficient and practical methodology for a Prins–Ritter sequence would be of importance for natural product synthesis.[7] $CeCl_3 \cdot 7H_2O$ has received attention as a cost-effective, non-toxic, readily available and selective reagent for various organic transformations.[8] The mild Lewis acidity associated with cerium(III) chloride enhances its use at levels from stoichiometric to catalytic, as a powerful reagent for various organic transformations.[9]

We describe here an efficient Prins–Ritter reaction sequence for the direct synthesis of 4-amido tetrahydropyrans from homoallylic alcohols, carbonyl compounds and nitriles. Firstly, we carried out a three-component coupling reaction of 2-naphthaldehyde with but-3-en-1-ol in acetonitrile in the presence of 10 mol % of $CeCl_3 \cdot 7H_2O$ and 1.5 equiv of acetyl chloride at ambient temperature. The reaction went to completion in 7 h and the product, 4-acetamido tetrahydropyran **3a**, was obtained in 88% yield with cis-selectivity (Scheme 1).

Thus encouraged, we examined various substituted arylaldehydes and homoallylic alcohols. *p*-Methylbenzaldehyde, *p*-bromobenzaldehyde, 3,4,5-trimethoxybenzaldehyde and *p*-nitrobenzaldehyde reacted well with 3-buten-1-ol and acetonitrile to produce the corresponding 4-acetamido tetrahydropyrans in high yields (Table 1, entries b–e). Furthermore, substituted homoallylic alcohols such as 1-phenylbut-en-1-ol and 1-cyclohexylbut-3-en-1-ol also participated efficiently in this



Scheme 1.

Keywords: Prins-cyclization; Cerium reagents; Amido tetrahydropyrans.
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Table 1. Preparation of 4-acetamido tetrahydropyrans via Prins–Rittter reaction sequence

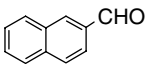
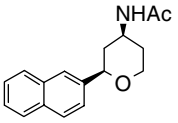
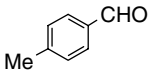
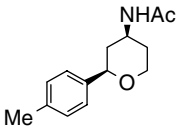
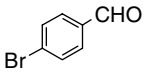
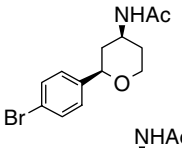
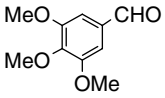
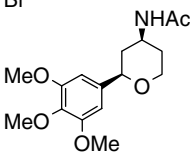
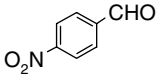
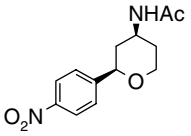
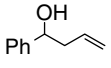
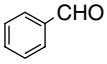
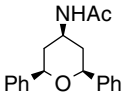
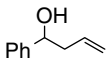
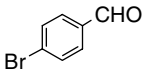
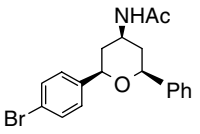
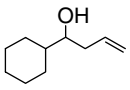
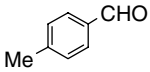
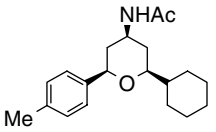
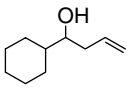
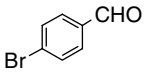
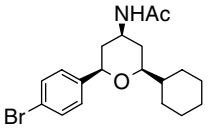
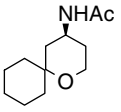
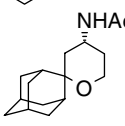
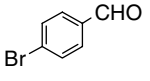
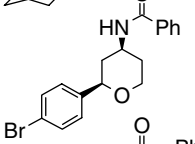
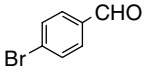
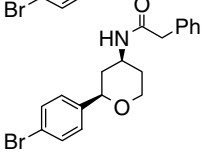
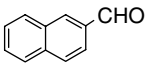
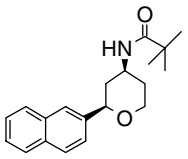
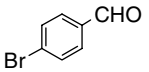
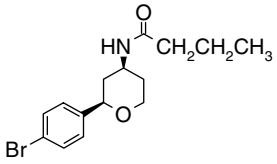
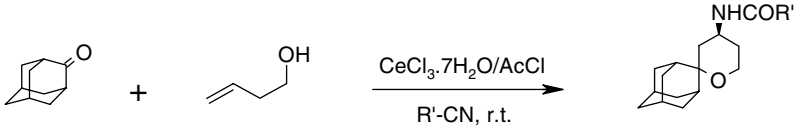
Entry	Homoallyl alcohol	Carbonyl compound	Nucleophile	Amidopyrans	Time[a] (h)	Yield[b] (%)
a			CH_3CN		7.0	88
b			CH_3CN		6.0	91
c			CH_3CN		6.5	90
d			CH_3CN		7.0	85
e			CH_3CN		7.5	80
f			CH_3CN		6.5	92
g			CH_3CN		6.0	90
h			CH_3CN		7.0	94
i			CH_3CN		6.5	91
j			CH_3CN		8.0	88
k			CH_3CN		8.5	85
l			PhCN		7.5	89
m			$PhCH_2CN$		8.0	86

Table 1 (*continued*)

Entry	Homoallyl alcohol	Carbonyl compound	Nucleophile	Amidopyrans	Time[a] (h)	Yield[b] (%)
n			Me_3CCN		7.0	90
o			$CH_3CH_2CH_2CN$		7.5	82

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

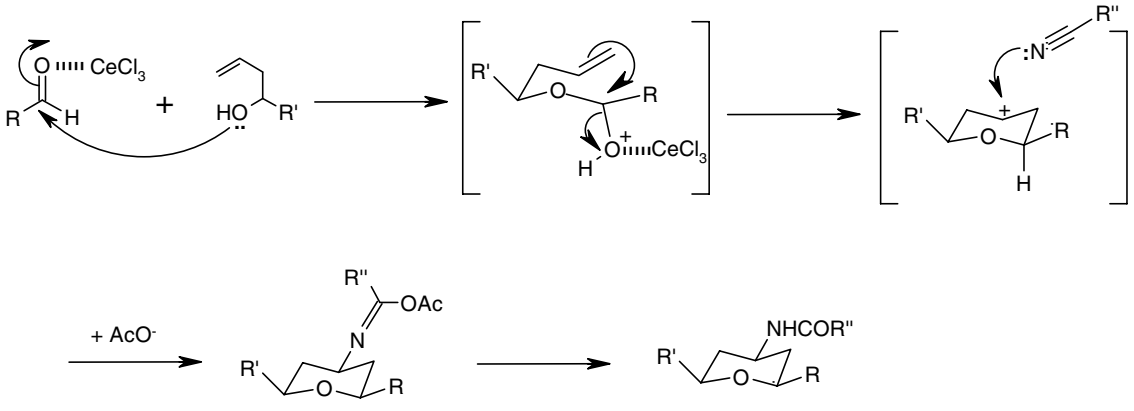


Scheme 2.

transformation (Table 1, entries f–i). Ketones such as cyclohexanone and 2-adamantanone reacted comparably giving spirocyclic 4-acetamido tetrahydropyrans in good yields (Table 1, entries j and k, Scheme 2).

The process also succeeded with benzonitrile, benzyl cyanide, *t*-butyl nitrile and *n*-butyronitrile (Table 1, entries l–o). Low conversions were obtained (20–45%) when the reactions were performed with CH_3COCl alone, the addition of 10 mol % of $CeCl_3{\cdot}7H_2O$ dramatically improving the reaction rates and yields. No reaction was observed in the absence of CH_3COCl even after a long reaction time (12 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. The substituents on the tetrahydropyranyl ring occupy equatorial positions, as confirmed by NOE experiments. Only one diastereoisomer was obtained in each case, the structure of which was confirmed by ^1H NMR studies. The formation of the products can be explained by hemi-acetal formation followed by Prins-cyclization and subsequent Ritter amidation (Scheme 3).

A rationale for the all cis-selectivity involves 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 favours equatorial attack of the nucleophile.[10] Other Lewis acid catalysts such as $InCl_3$, $InBr_3$, $BiCl_3$ and $ZrCl_4$ were tested, but $CeCl_3{\cdot}7H_2O$ was found to be most efficient in terms of conversion. The nature of the substituents on the aromatic ring had some effect on the conversion. Unactivated and moderately activated aryl aldehydes such as chloro- or bromo-substituted benzaldehyde gave higher yields of products compared to strongly activated



Scheme 3.

or deactivated aldehydes. 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.[11]

In summary, we have described a novel and efficient Prins–Ritter sequence to produce highly substituted 4-amido tetrahydropyrans in high yields with all cis-selectivity. The use of inexpensive and readily available $CeCl_3{\cdot}7H_2O/CH_3COCl$ makes this procedure simple, convenient and practical.

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11. *General procedure*: A mixture of homoallylic alcohol (1.2 mmol), carbonyl compound (1 mmol), acetyl chloride (1.5 mmol) and $CeCl_3{\cdot}7H_2O$ (10 mol %) in acetonitrile (5 mL) was stirred at 23 °C for a specified amount of 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 anhydrous Na_2SO_4. Removal of the solvent followed by purification on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 4:6) gave pure 4-amido tetrahydropyran. The products thus obtained were characterized by IR and NMR spectroscopy. The characterization data were found to be consistent with that of authentic samples.[6] Compound **3b**: *N-[2-(4-methylphenyl)-(2R,4S)-tetrahydro-2H-4-pyranyl]acetamide*: Solid, mp 166–168 °C. IR (KBr): ν 3294, 2956, 2926, 1648, 1553, 1366, 1087, 1042, 802, 730 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.41 (m, 2H), 1.94 (s, 3H), 1.96 (m, 1H), 2.16 (m, 1H), 2.32 (s, 3H), 3.64 (td, 1H, $J = 2.0$, 11.8 Hz), 4.16–4.19 (m, 2H), 4.34 (dd, 1H, $J = 1.7$, 11.3 Hz), 5.23 (d, 1H, $J = 7.5$ Hz), 7.12 (dd, 4H, $J = 8.1$, 14.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.3, 73.0, 59.4, 42.5, 40.1, 33.2, 29.9, 25.9, 23.3, 21.6, 21.2. LCMS: *m/z* (%): (M+Na) 256. HRMS calcd for $C_{14}H_{19}NO_2Na$: 256.1313. Found: 256.1320. Compound **3h**: *N-2-cyclohexyl-6-(4-methylphenyl)-(2S,4S,6R)-tetrahydro-2H-4-pyranyl]acetamide*: Solid, mp 188–190 °C. IR (KBr): ν 3314, 2923, 2852, 1646, 1543, 1368, 1083, 922, 804 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.96–1.24 (m, 5H), 1.39–1.52 (m, 5H), 1.61–1.78 (m, 3H), 1.93 (s, 3H), 2.04 (m, 1H), 2.16 (m, 1H), 2.32 (s, 3H), 3.28 (m, 1H), 4.12 (m, 1H), 4.35 (dd, 1H, $J = 1.5$, 11.3 Hz), 5.18 (d, 1H, $J = 8.3$ Hz), 7.04–7.22 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.2, 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. Compound **3j**: *N-[(4R)-1-oxaspiro[5.5]undec-4-yl]acetamide*: Solid, mp 148–150 °C. IR (KBr): ν 3350, 2954, 2922, 2851, 1632, 1536, 1367, 1206, 1083, 821, 743 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.20–1.71 (m, 12H), 1.85 (m, 1H), 1.93 (s, 3H), 2.04 (m, 1H), 3.68 (m, 2H), 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.