Reactions of *N*-Acyl Imines with Dihydropyrans

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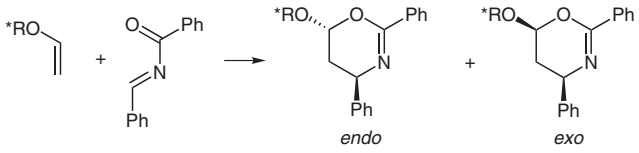
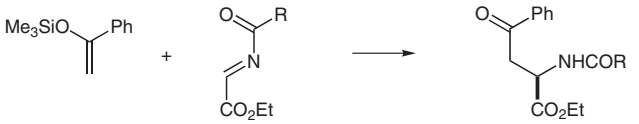
Abstract: A series of dihydropyranyl acetamides was synthesized by the TFA-catalyzed reaction of dihydropyrans with *N*-acyl imines.

Key words: *N*-acyl imines, dihydropyrans, dihydropyranyl acetamides, Mannich reaction, cycloaddition



Equation 1



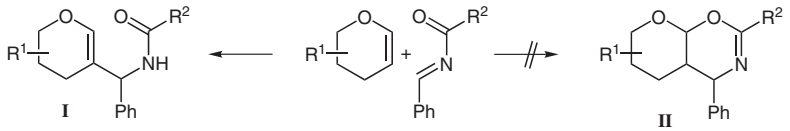
Equation 2

There has been a renewed interest in the use of *N*-acyl imines as intermediates for stereoselective synthesis.[1] Pertinent to our own work, we noted that a number of groups have studied the reactions of *N*-acyl imines and related derivatives with electron-rich olefins, with varying outcomes.[2–7] Until recently, only a handful of examples of [4+2]-cycloaddition reactions had been reported. Schmidt was an early pioneer of this work, and reported the isolation of cycloadducts in high yield from the reaction of vinyl acetates with in situ generated *N*-acyl imines.[7] Extending this concept, Dujardin and co-workers recently reported the [4+2] cycloadditions of *N*-acyl imines with chiral vinyl ethers as an enantioselective route to β-amido aldehydes (Equation 1).[3–5] Interestingly, it was observed that the stereochemistry, as well as the mechanism of formation, of the 1,3-oxazine cycloadducts was found to be heavily influenced by the choice of Lewis acid used to promote cycloaddition. In the presence of $SnCl_4$, reactions proceeded by a stepwise mechanism leading to the selective formation of *exo* products, whereas $Yb(fod)_3$ favored *endo* product formation via a concerted mechanism. In contrast, Kobayashi has reported that when a silyl ether is used as the donor, a Mannich-type reaction appears to be the favored route (Equation 2).[6]

Independent work in our laboratory prompted us to study related reactions of *N*-acyl imines with dihydropyrans as a route to some novel bicyclic acetals (Scheme 1). Our interest in this area stemmed from a broad focus on developing new methodologies for constructing polycyclic structures of interest in natural product synthesis. Specifically, our goal was to prepare a series of tetrahydropyrano-1,3-oxazines **II**[8] and study their behavior towards nucleophilic ring cleavage. Ikeda has reported the reaction of 2,3-dihydropyran with an *N*-methyl-*N*-acyl immonium ion, generated in situ from 1,3,5-trimethyl[1,3,5]triazinane under basic conditions.[9] However, the bicyclic cycloadduct in this case was an unstable immonium ion which did not survive the reaction conditions. We thought that the alternative use of an *N*-acyl imine would circumvent this problem and allow the isolation of the cycloadduct. To our surprise, however, the only product we observed in each case was the dihydropyranyl acetamide **I**.

As Table 1 shows, this reaction is general for a variety of donor–acceptor combinations, and showed a remarkable degree of stereoselectivity. In all cases involving a 4-phenyl substituted dihydropyran (entries 4–7), a single isomeric product formed, generally as a crystalline material. The relative stereochemistries assigned to products **4c–f** is based on the X-ray crystal structure analysis of compound **4d** (Figure 1). Not surprisingly, the reaction of dihydropyran **1d**[10] (entry 8) gave a diastereomeric mixture of products **4g**.

Two different procedures were employed in this study. In the first of these, the *N*-acyl imine was generated in situ



Scheme 1

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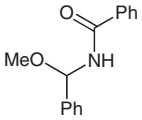
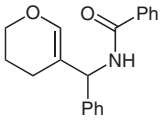
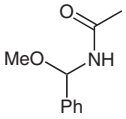
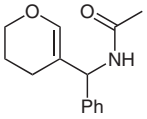
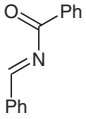
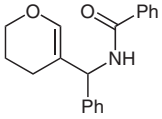
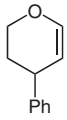
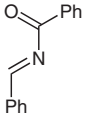
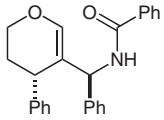
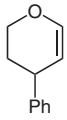
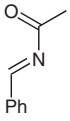
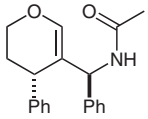
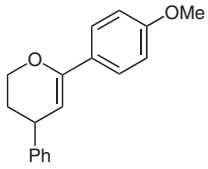
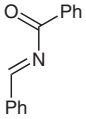
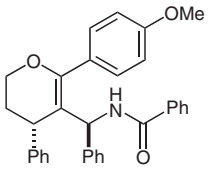
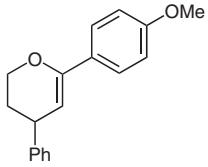
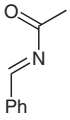
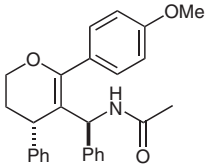
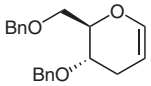
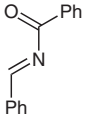
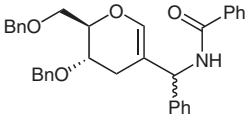
Table 1 Reactions of *N*-Acyl Imines with Dihydropyrans

Entry	DHP	Reagent	Conditions[a]	Product[b]	Yield (%)[c]
1	 **1a**	 **2a**	A	 **4a**	72
2	 **1a**	 **2b**	A	 **4b**	42
3	 **1a**	 **3a**	A	 **4a**	76
4	 **1b**	 **3a**	A	 **4c**	65
5	 **1b**	 **3b**	A	 **4d**	62
6	 **1c**	 **3a**	A	 **4e**	72
7	 **1c**	 **3b**	B	 **4f**	77
8	 **1d**[d]	 **3a**	A	 **4g**	68[e]

[a] Conditions A: TFA (0.2 equiv), CH_2Cl_2, 0 °C to r.t., 12 h; Conditions B: $BF_3{\cdot}OEt_2$ (0.2 equiv), CH_2Cl_2, 0 °C to r.t., 12 h.
[b] All products were identified by ^1H and ^{13}C NMR spectroscopy.
[c] Yields are based on isolated and purified materials.
[d] Synthesized according to the published procedure.[10]
[e] Diastereomeric ratio is 1:1.5 as determined by ^1H NMR spectroscopy.

from its *N*,*O*-acetal precursor in the presence of the donor component (entries 1 and 2). In the second approach, the *N*-acyl imine was separately prepared following literature procedures[4,11] and immediately reacted with the dihydropyran without purification (entries 3–8). Highest yields were found when catalytic TFA was employed. The use of other initiators such as $SnCl_4$ generally gave lower yields of the same products, as did the use of stoichiometric amounts of TFA. In contrast to the findings of Dujardin, when $Yb(fod)_3$ was used, no reaction was observed. The use of photolysis and ultrasound resulted in an equal lack of success. Predictably, yields increased slightly when

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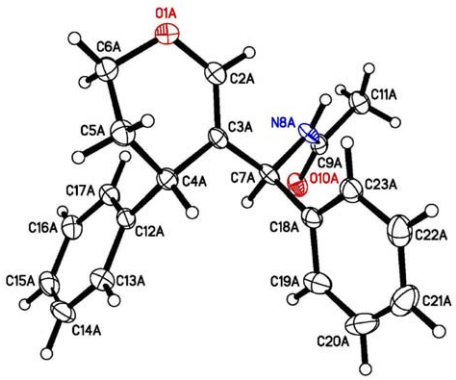

Figure 1 ORTEP diagram of compound **4d**

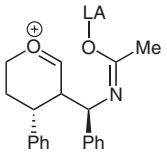

Figure 2 A zwitterion intermediate

electron-donating groups were present on the 2-position of the dihydropyran (entries 6 and 7).

Based on prior discussions of related reactions,[5] it is highly likely that these reactions proceed in a nonconcerted fashion via a zwitterion intermediate (Figure 2), which then loses a proton faster than ring-closure can occur. Unfortunately, attempts to trap this oxocarbenium ion with added nucleophiles (e.g., anisole, allylsilane) were unsuccessful.

In summary, a Mannich-type reaction was observed in the TFA-catalyzed reaction of dihydropyrans with *N*-acyl imines. Related beta substitution reactions of dihydropyrans have been documented.[12] However, we are aware of only one example of the use of a Michael acceptor in this context.[13]

^{1}H NMR: Bruker AMX 600 spectrometer (600 MHz); δ values in ppm relative to tetramethylsilane signal as internal reference; coupling constants *J* in Hz; ^{13}C NMR: Bruker AMX 600 spectrometer (150 MHz); δ values in ppm relative to the residual ^{13}C solvent signal ($CDCl_3$: δ = 77.0) as internal reference. The progress of all reactions was monitored by TLC, which was carried out on Merck silica gel plates with fluorescent indicator. Flash column chromatography was performed using 230–400 mesh silica gel. All commercially available reagents were used as received unless otherwise reported. Melting points are uncorrected. *N*-Acyl imines and *N*,*O*-acetal **2a** were prepared by using the reported procedures.[4,10]

Dihydropyranylacetamides 4a–g; General Procedure

To a solution of either *N*-acyl imine **3a/3b** or *N*,*O*-acetal **2a** (1.1 equiv) in CH_2Cl_2 was added dihydropyran **1a–d** (1.0 equiv) at 0 °C followed by trifloroacetic acid (0.2 equiv), unless otherwise indicated. The mixture was stirred overnight and then quenched with few drops of H_2O and dried ($MgSO_4$). After filtration and evaporation of CH_2Cl_2 in vacuo, the crude product was purified by flash column chromatography using hexane–EtOAc mixtures.

4a

Crystalline white solid; mp 121–122 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 7.4 Hz, 2 H), 7.79 (t, *J* = 7.4 Hz, 1 H), 7.36 (t, *J* = 7.7 Hz, 2 H), 7.32–7.22 (m, 5 H), 6.65 (d, *J* = 8.0 Hz, 1 H), 6.41 (s, 1 H), 5.70 (d, *J* = 8.2 Hz, 1 H), 3.89–3.87 (m, 2 H), 1.94–1.90 (m, 2 H), 1.81–1.78 (m, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 166.6, 142.6, 140.1, 134.4, 131.5, 128.5, 127.8, 127.3, 126.9, 112.1, 65.5, 56.0, 22.0, 21.0.

4b

Crystalline white solid; mp 142–144 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.21–7.30 (m, 5 H), 6.70 (d, *J* = 7.9 Hz, 1 H), 6.35 (s, 1 H), 5.47 (d, *J* = 8.6 Hz, 1 H), 3.88–3.90 (m, 2 H), 1.97 (s, 3 H), 1.84–1.78 (m, 4 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.2, 142.1, 140.3, 128.3, 127.0, 126.8, 112.2, 65.3, 55.4, 23.0, 21.9, 20.7.

4c

Crystalline white solid; mp 168–170 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.42–7.25 (m, 15 H), 6.50 (s, 1 H), 6.12 (d, *J* = 7.4 Hz, 1 H), 5.60 (d, *J* = 7.5 Hz, 1 H), 4.00–3.95 (m, 1 H), 3.91 (dt, *J* = 2.0, 10.9 Hz, 1 H), 3.27 (br s, 1 H), 2.21–2.15 (m, 1 H), 1.78–1.75 (m, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 166.1, 144.6, 143.1, 140.3, 131.3, 128.8, 128.3, 127.9, 127.2, 126.7, 112.6, 61.7, 56.2, 38.4, 31.1.

4d

Crystalline white solid; mp 130–131 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.34–7.19 (m, 8 H), 7.16 (d, *J* = 6.8 Hz, 2 H), 6.55 (s, 1 H), 5.83 (d, *J* = 7.7 Hz, 1 H), 5.39 (d, *J* = 8.0 Hz, 1 H), 3.94–3.91 (m, 1 H), 3.87 (dt, *J* = 2.2, 10.8 Hz, 1 H), 3.12 (t, *J* = 4.1 Hz, 1 H), 2.14–2.07 (m, 1 H), 1.73 (s, 4 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 168.6, 144.1, 142.3, 140.4, 128.6, 128.4, 128.3, 127.7, 127.6, 126.4, 112.9, 61.7, 55.1, 38.2, 31.2, 22.8.

Crystallographic Data:[14] $C_{20}H_{21}NO_2$, M = 307.38, monoclinic, space group P21/c, *a* = 15.7685 (8) Å, *b* = 8.9293 (5) Å, *c* = 24.4424 (13) Å, *a* = 90.00°, *b* = 105.38 (2)°, *g* = 90.00°, *V* = 3318.30 (3) Å^3, *Z* = 8, *F*(000) = 1312, crystal size = 0.33 × 0.17 × 0.02 mm. The crystals were very thin and consequently, diffraction was far too weak for a standard diffractometer. Crystallographic data were collected on a Bruker-Nonius X8 Proteum diffractometer equipped with multilayer-optic focused CuK (α) radiation (λ = 1.54178 Å) at 90 K ('CryoCool LN2', CryoIndustries of America.) The structure was solved by direct methods (SHELXS-97)[15] and refined by full-matrix least-squares against F^2 (SHELXS-97).[15] Hydrogen atoms were found in difference maps and refined using the appropriate riding model for each type of H atom.

4e

Crystalline white solid; mp 64–66 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.52 (d, *J* = 8.5 Hz, 2 H), 7.42–7.38 (m, 5 H), 7.33–7.21 (m, 6 H), 7.13 (d, *J* = 7.6 Hz, 2 H), 7.07 (d, *J* = 7.6 Hz, 2 H), 6.93 (d, *J* = 8.5 Hz, 2 H), 6.20 (s, 1 H), 4.20 (dt, *J* = 2.5, 10.7 Hz, 1 H), 4.15–4.12 (m, 1 H), 3.80 (s, 3 H), 3.37 (br t, *J* = 4.8 Hz, 1 H), 2.31–2.15 (m, 1 H), 1.85–1.80 (m, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 165.2, 159.9, 154.1, 145.7, 141.4, 133.9, 131.2, 130.0, 129.3, 128.8, 128.4, 128.1, 127.0, 126.7, 126.1, 113.9, 107.3, 62.6, 55.7, 55.2, 37.0, 31.8.

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4f
Oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.50 (d, *J* = 8.0 Hz, 2 H), 7.39 (t, *J* = 7.1 Hz, 2 H), 7.34–7.22 (m, 6 H), 7.12 (d, *J* = 7.5 Hz, 2 H), 6.90 (d, *J* = 8.0 Hz, 2 H), 5.97 (d, *J* = 8.6 Hz, 1 H), 5.31 (d, *J* = 8.4 Hz, 1 H), 4.20–4.11 (m, 2 H), 3.78 (s, 3 H), 3.30 (br s, 1 H), 2.29–2.20 (m, 1 H), 1.84–1.77 (m, 1 H), 1.47 (s, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 168.5, 159.8, 153.8, 145.4, 141.2, 130.0, 128.8, 128.5, 128.3, 126.9, 126.8, 126.1, 113.7, 113.3, 106.8, 62.3, 55.1, 54.7, 37.0, 31.6, 22.7.

4g
Isomeric mixture; oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ (major isomer) = 7.28 (t, *J* = 6.9 Hz, 2 H), 7.48–7.22 (m, 18 H), 6.50 (s, 1 H), 6.42 (d, *J* = 8.1 Hz, 1 H), 5.74 (d, *J* = 8.5 Hz, 1 H), 4.63–4.46 (m, 4 H), 3.97–3.91 (m, 1 H), 3.89–3.82 (m, 1 H), 3.79–3.74 (m, 2 H), 2.32 (td, *J* = 5.0, 16.0 Hz, 1 H), 2.03 (dd, *J* = 7.0, 16.0 Hz, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 166.5, 142.0, 141.4, 139.7, 138.0, 137.9, 137.88, 134.3, 131.6, 128.7, 128.6, 128.3, 127.74, 127.67, 127.6, 127.0, 126.9, 109.6, 76.5, 73.5, 71.1, 70.0, 68.7, 55.2, 27.8.

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