Pergamon

Tetrahedron Letters, Vol. 38, No. 52, pp. 9057-9060, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)10434-8

Regioselective 2*H*-3,6-Dihydropyran Synthesis with Tandem Oxo-Ene Formalism

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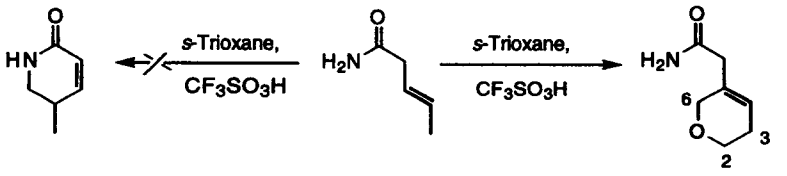
Abstract: Condensation of 3-alkenamides with *s*-trioxane in the presence of trifluoromethanesulfonic acid affords 2*H*-3,6-dihydropyrans.

Condensations of 3-alkenamides with carbonyl compounds, notably aromatic aldehydes, lead to a variety of lactams, often with high regio- and stereo-control.[1,2] Both γ- and δ-lactams,[1-3] either monocyclic or as part of a fused assembly, have been prepared from 3-alkenamides. The uniqueness of size and reactivity of formaldehyde (and its equivalents) can lead to reactions that are not observed when other aldehydes are used. Thus, with amidic nitrogen, a variety of aldehydes condense by an initial *N*-hydroxyalkylation.[1-3] By one such process, intramolecular attack of an *N*-(hydroxymethyl)amide derivative leads to 5,6-dihydro-2(1*H*)-pyridinones.[2] However, in contrast to hydroxyalkylation and cyclization we here report a new condensation of 3-alkenamides with *s*-trioxane to give 2*H*-3,6-dihydropyrans (Scheme 1).

A variety of 3-alkenamides and one thioalkenamide were reacted with *s*-trioxane in 20% trifluoromethanesulfonic acid-dichloromethane at 20 °C; dihydropyrans were isolated as shown in Table 1. In all cases, a single dihydropyran was isolated from a single alkenamide diastereoisomer, and in no case did the amidic unit undergo substitution or conversion into other functionality. From each pure alkenamide, a single regioisomeric 2*H*-3,6-dihydropyran was isolated.[4]



Scheme 1

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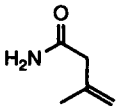
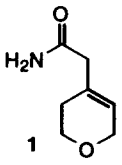
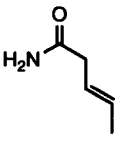
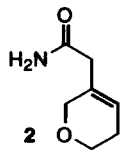
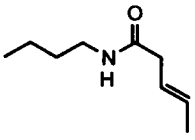
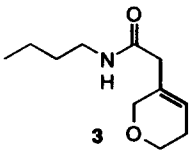
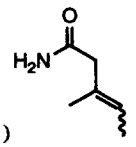
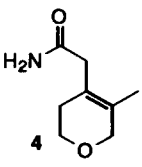
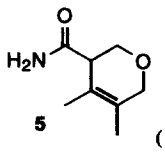
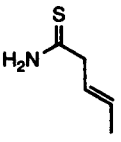
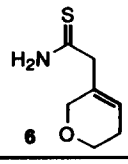
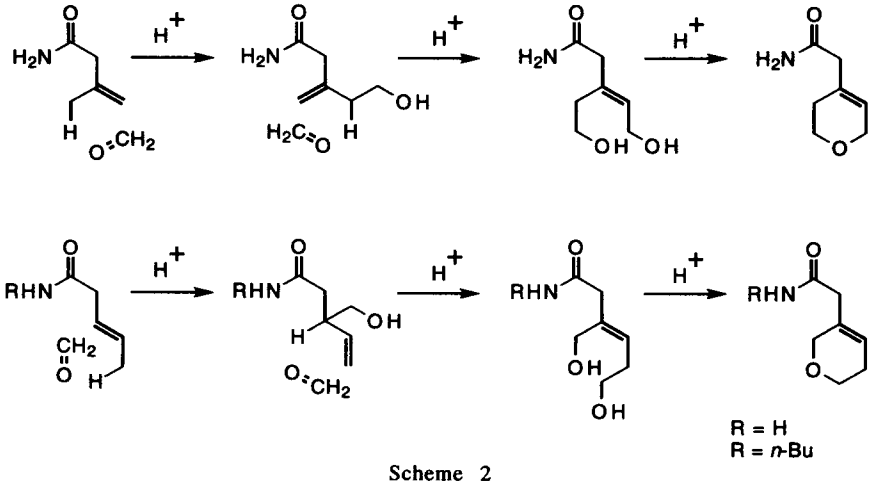
The results can be explained (Scheme 2) by an initial oxo-ene reaction involving the less (or least) sterically congested allylic hydrogen atom.[5] The homoallylic alcohol that results would itself undergo an oxo-ene reaction to give a 1,5-diol whose regiochemistry would be of no consequence, since protonation followed by loss of water would lead to but one allylic cation that would undergo cyclization giving a single dihydropyran.

Table 1. Reaction of 3-alkenamides with *s*-trioxane (1 eq.) in the presence of 20% V/V trifluoromethanesulfonic acid in dichloromethane at 20 °C

Entry	3-Alkenamide[2]	Time (h)	Dihydropyran	Yield (%)
1		4.5	 **1**	58
2		4	 **2**	55
3		3	 **3**	53
4	 (1:1)	20	 **4**  **5** (3:4)	71
5		3.5	 **6**	38

The 1:1 mixture of β,γ-unsaturated amides in entry 4 (Table 1) could not be separated, so it has not been demonstrated whether one isomer affords the disubstituted dihydropyran, and the other isomer the trisubstituted derivative. However, most probably the reaction is stereospecific, the *(E)*-amide affording the trisubstituted dihydropyran **5**, and the *(Z)*-isomer the disubstituted dihydropyran **4**. Involvement of an α-hydrogen atom of the *(E)*-isomer in the

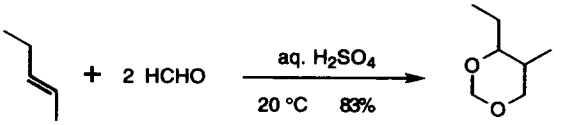
initial oxo-ene process is unsurprising in view of the bulk of the γ-methyl group which would hinder participation of the γ–β–γ'-unit in an ene reaction with HCHO.



Scheme 2

The present results can be distinguished from related reactions reported in the literature. Thus, Prins-type reactons[6-9] usually afford 1,3-dioxygenated compounds, including 1,3-dioxanes.[7] Whereas 3,4-dihydro-2*H*-pyrans are readily accessible *via* heterodiene synthesis (*e.g.* reaction of a vinyl ether with an α,β-unsaturated carbonyl compound),[10] the corresponding 3,6-dihydro-2*H*-pyrans would require the reaction of a 1,3-butadiene with a carbonyl compound. However, the latter process is not general; for example 1,3-butadiene itself gives a mixture including the 3,6-dihydro-2*H*-pyran, the mixture varying with temperature and catalyst.[11]

A limited sequential hydroxyalkylation involves the reaction of some terminal alkenes with formaldehyde in the presence of HCl to give 3-substituted-4-hydroxytetrahydropyrans, but as mixtures with 1,3-dioxane products.[12] Indeed, 1,3-dioxanes commonly result from the condensation of a simple alkene with formaldehyde (Scheme 3).[11,12] Thus, the synthesis of 3,6-dihydro-2*H*-pyrans from monounsaturated compounds by two hydroxalkylations appears to be without precedent.



Scheme 3

The rate of these new oxo-ene processes using CF_3SO_3H in CH_2Cl_2 is demonstrably faster than intramolecular cyclizations in the same medium; for example, in the absence of a carbonyl compound, *(E)*-3-pentenamide afforded 5-methylpyrrolidin-2-one in 91% yield.[3] Whether protonation of the amide group is sufficient to account for suppression of *N*-

hydroxymethylation must await further study, as must the rôle, if any, of the carboxamide group.[14]

In conclusion, these oxo-ene type reactions proceed at ambient temperatures and show that 3-alkenamides can form bonds to carbon electrophiles selectively at any of positions-2, -3, and -4, depending upon substitution of the alkenamide. The process of *N*-alkylation, whose synthetic applications have been demonstrated for other aldehydes,[1-3] has not been observed in reactions with *s*-trioxane, using the present reaction conditions. The resulting dihydropyrans containing a CH_2CONH- linkage have been attached to β-lactam rings for pharmaceutical applications.[13] Such versatility in regioselectivity, and its ability to be controlled has established a new synthetic utility of 3-alkenamides.

Acknowledgment. We are grateful to the Engineering and Physical Sciences Research Council for a Postdoctoral Fellowship (to A.F.).

References and Notes

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4. *Representative preparation of the 2H-3,6-dihydropyrans*: To a solution of 3-methyl-3-butenamide (5.0 mmol) and *s*-trioxane (0.45g, 5.0 mmol) in anhydrous CH_2Cl_2 (20 mL), CF_3SO_3H (4.0 mL) was added slowly, with stirring, at 20 °C. Progress of the reaction was followed by TLC. On completion (usually 3 h) the mixture was poured onto ice (10 g), neutralized with 20% aqueous NaOH and extracted with CH_2Cl_2 (3 x 30 mL). The combined extracts were dried and the solvent evaporated. The residue was recrystallized from 1:1 ethyl acetate: petroleum ether (40-40 °C) to give **5,6-dihydro-2*H*-pyran-4-yl acetamide** (0.41 g, 58%) as prisms, m.p. 105-106.5 °C; ^1H NMR ($CDCl_3$) δ_H 5.70 (3H, bd, =CH and NH_2), 4.18 (2H, m, $=CHCH_2$), 3.83 (2H, t, J = 6 Hz, CH_2CH_2O), 2.95 (2H, s, CH_2CO), 2.16 (2H, m, CH_2CH_2O); ^{13}C NMR ($CDCl_3$) δ_C 173.0, 130.5, 124.9, 65.3, 64.2, 44.8, 28.4. Found: C, 58.96; H, 7.71; N, 9.67. ($C_7H_{11}NO_2$ requires C, 59.55; H, 7.85; N, 9.92%). New compounds gave satisfactory elemental analyses or high resolution mass spectral data, and exhibited spectroscopic data (IR, ^1H NMR, and ^{13}C NMR) in agreement with their structures.
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14. A dihydropyran was not obtained from 2-methyl-3-phenylpropene.

(*Received in UK* 15 *September* 1997; *revised* 13 *October* 1997; *accepted* 17 *October* 1997)