Pronounced Electronic Effects of the Allylic Amino Group on the π-Facial Stereoselectivity and Reactivity in Electrophilic Additions to Double Bonds

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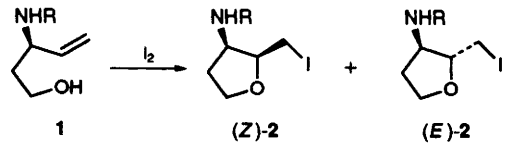
The selectivity of iodoetherification of *N*-substituted 3-aminopent-4-en-1-ols **1**, providing mixtures of *N*-substituted (*E*)- and (*E*)-3-amino-2-iodomethyltetrahydrofurans [(*Z*)-**2** and (*E*)-**2**], correlates well with the electronic effects of the *N*-substituents, increasing with an increase in the electron withdrawing effect of the substituents.

Stereoelectronic control of π-facial stereoselection in addition reactions to stereogenic unsaturated bonds has received considerable attention owing to its synthetic and theoretical interests.[1] For diastereoselective nucleophilic additions to carbonyl compounds, stereoelectronic effects of substituents in transition state stabilization have been well documented[2] and nicely rationalized by Anh and Eisenstein[3] and Cieplak hypotheses.[4] For electrophilic additions to allylically substituted alkenes, however, these effects have been studied less[1,5] and substituents have been confined to arylalkyl, silyl, hydroxy, alkoxy, and halogens.[6–12] Little attention has been paid to amino groups,[13] despite their interesting electronic characteristics.

Consequently we have targeted this area for study and discovered that R substituents on an amino group exert salient influences both on the reactivity and the selectivity for the iodoetherification of 3-aminopent-4-en-1-ols **1** (Scheme 1): with an increase in the electron attracting ability of R, the ratio of (*Z*)- to (*E*)-3-amino-2-iodomethyltetrahydrofurans [(*Z*)-**2**/(*E*)-**2**] increases, while the reactivity of **1** decreases.

Iodoetherification of **1a–g**[14] was undertaken at 0 °C by exposing **1** (1 mmol) to I_2 (2 mmol) and $NaHCO_3$ (2 mmol) in a given organic solvent and H_2O (5–2 cm^3) (Table 1).† The reaction was monitored by TLC, and for the slow reactions I_2 and $NaHCO_3$ (2 mmol each) were added at appropriate intervals.‡ Under similar conditions, the iodoetherification of *N*-phenyl and *N*-*p*-tolyl derivatives of **1** was unsuccessful and gave complex mixtures of **2** (R = Ph, *p*-tolyl), their iodination products on the aromatic ring, and many other unidentified products. The (*Z*)-**2**/(*E*)-**2** ratios were determined from their ^1H and ^{13}C NMR spectra. The resonances of CH_2I of (*Z*)-**2** appeared at δ 4.8–6.2 higher fields than those of the corresponding (*E*)-**2** in their ^{13}C NMR spectra.[15] Unfortunately, acyl derivatives (**1f–g**) were not soluble in ether in a sufficient concentration, and the cyclization of these substrates was examined in ethyl acetate. These solvents significantly affected the reaction rate, but much less the stereoselectivity (runs 4–5 and 6–7).

Table 1, arranged in order of decreasing electron attracting ability of R, reveals that there seem to be general trends both in reactivity and stereoselectivity. As for the reactivity, in the series of sulfonyl (runs 1–5) and acyl derivatives (runs 6–9), the reactions are markedly accelerated with a decrease in the electron attracting nature of R. As for the selectivity, the preponderance of (*Z*)-**2** over (*E*)-**2** gradually diminishes as going down the Table 1 from run 1 to 7, and is finally reversed in runs 8 and 9.



1 (*Z*)-**2** (*E*)-**2**

Scheme 1

The unique stereochemical outcome may be rationalized by taking steric and electronic factors into consideration (Scheme 2). Sterically, the cyclization *via* **I** may be favoured over the one *via* **II**, since the latter suffers from the C_1–N *gauche* and (approximate) C_5–N eclipsing interactions. Electronically, the C_4–C_5 bond of **II** is expected to be somewhat activated toward electrophilic additions owing to its high lying HOMO caused by a π–n_N interaction (homoallyl anion),[5] while the double bond of **I** may be deactivated owing to its low lying HOMO caused by a π–$\sigma^*_{C(3)-N}$ interaction.[1,5] The deactivation may become increasingly significant by an increase in the electron attracting ability of R, where the energy level of $\sigma^*_{C(3)-N}$ orbital becomes lower and the π–$\sigma^*_{C(3)-N}$ interaction more efficient. As a consequence, as going from run 9 to 1, the reactions gradually change from the *trans*-selective ones (steric control) to the *cis*-selective ones (electronic control).

Hitherto, it has been pointed out sporadically that allylic heteroatoms, especially highly electronegative ones such as O and F, play an outstanding role in determining the stereochemical course for the electrophilic addition reactions.[6–13] Most of these studies, however, have been devoted to clarify the structure–selectivity relationship, and none of them have successfully demonstrated the effect of the electronic modification of these heteroatoms on the selectivity.[8a,11b] In this context, this is the first investigation, which demonstrates that the stereoselectivity changes proportionally to the inductive effect of allylic substituents. The stereocontrol, based on the electronic modulation, ranges widely from (*Z*)-**2f**/(*E*)-**2f** = 0.32 to (*Z*)-**2a**/(*E*)-**2a** = 13.3 and may find wide application to the synthesis of amino sugars and related compounds.

Further study is in progress to examine other substituents R of **1**, the C_1–C_5 substitution derivatives of **1**, and the reactions of **1** with other electrophiles.

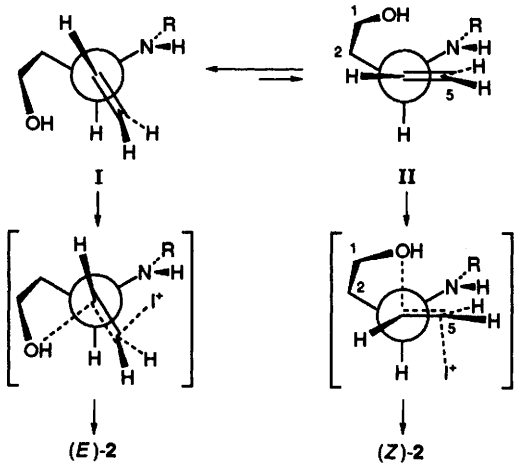
Table 1 Iodoetherification of *N*-substituted 3-aminopent-4-en-1-ols **1**

				2	
Run	**1** (R)	Solvent[a]	Reaction time[b]/h	(*Z*)-**2**:(*E*)-**2**[c]	Isolated yield[d] (%)
1	**1a**: R = SO_2CF_3	EtOEt	210[e]	93:7	49
2	**1b**: R = $SO_2CH_2CF_3$	EtOEt	67[f]	85:15	91
3	**1c**: R = SO_2Me	EtOEt	28	79:21	87
4	**1d**: R = SO_2-*p*-Tol	EtOEt	9	71:29	99
5	**1d**: R = SO_2-*p*-Tol	EtOAc	6	71:29	96
6	**1e**: R = $COCF_3$	EtOEt	59[g]	67:33	87
7	**1e**: R = $COCF_3$	EtOAc	36[h]	69:31	92
8	**1f**: R = COMe	EtOAc	3	24:76	51
9	**1g**: R = COPh	EtOAc	2	30:70	92

[a] **1** (1 mmol), I_2 (2 mmol) and $NaHCO_3$ (2 mmol) in water (2 cm^3) and a given solvent (5 cm^3) at 0 °C. [b] Approximate time required for the completion of reaction. [c] Determined from ^1H and ^{13}C NMR spectra. [d] Combined isolated yield of (*Z*)-**2** and (*E*)-**2**. [e] Further additions of I_2 (2 mmol) and $NaHCO_3$ (2 mmol) after 19 and 69 h. [f] Further additions of I_2 (2 mmol) and $NaHCO_3$ (2 mmol) after 7 and 33 h. [g] Further additions of I_2 (2 mmol) and $NaHCO_3$ (2 mmol) after 22 and 35 h. [h] Further addition of I_2 (2 mmol) and $NaHCO_3$ (2 mmol) after 20 h.

† All new compounds showed satisfactory spectral (^1H, ^{13}C NMR, IR, MS) and analytical data.

‡ Apparently **1** undergoes cyclization more slowly than the corresponding 3-hydroxy derivatives.[8b]



Scheme 2 Stereoselective iodoetherification of **1**

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