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Aust. J. Chem. **2004**, *57*, 629–633

Highly Diastereoselective Radical Reactions of Substituted Methylideneimidazolidinones and Related Systems*

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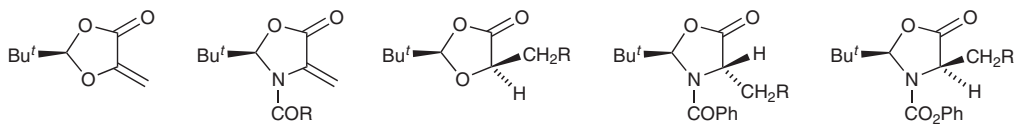
Stannane-mediated radical addition to methylideneimidazolidinones occurs with good to excellent diastereoselectivity. The stereochemical outcome of addition is highly dependent on the nature of the N1 substituent on the imidazolidinone ring.

Manuscript received: 27 February 2004.
Final version: 8 April 2004.

Recognition that organic free-radical reactions can proceed with high chemo-, regio-, and diastereoselectivity[1–4] has underpinned the development of radical-based methodologies, and they now occupy an important place in the arsenal available to the synthetic organic chemist. However, the rational exploitation of such reactions requires identification of the factors that underlie the nature and degree of selectivity. Although these are now reasonably well understood for many types of radical reactions including additions to acyclic olefinic compounds,[1,2,5] this is not the case for additions to more complex substrates in which small structural changes can result in large changes to the stereochemical outcomes of the reactions.[6–9] The radical chemistry of the *exo*-methylidene heterocycles **1** and **2** provides a case in point (Scheme 1). In a typical example, stannane-mediated cyclohexyl radical addition to dioxolanone **1** affords mainly the *cis* product **3** (*cis*/*trans*: 7).[6] Other related radical reactions of substrate **1** also exhibit high *cis* diastereoselectivity.[6,7] Conversely, treatment of oxazolidinone **2a** with cyclohexyl iodide and tributylstannane gives mainly the *trans* product **4** (*trans*/*cis*: >49).[6,8] Radical addition reactions of the *N*-naphthoyl compound **2b** also show *trans* diastereoselectivity,[8] as do those of **2a** with a variety of radicals such as methyl, adamantyl, isobutyl, perfluoropropyl, methoxymethyl, and tetra(*O*)acetylglucosyl (*trans*/*cis*: 7–49).[8]

The effect that small changes in substrate structure have on the diastereoselective outcome is dramatically illustrated by comparing the stereochemical outcomes of the radical addition reactions of *N*-benzoyloxazolidinone **2a** and *N*-phenoxycarbonyloxazolidinone **2d**. In contrast to the highly *trans* diastereoselective reactions that occur with *N*-benzoyloxazolidinone **2a**, the stannane-mediated reaction between the cyclohexyl radical and carbamate **2d** gives mainly the *cis* product **5** (*cis*/*trans*: 49).[8] Similar reactions with carbamates **2e** and **2f** are also very highly *cis* diastereoselective (*cis*/*trans*: >49).[8] As the pure enantiomers of compounds **1** and **2** are easily prepared, and their adducts



1 **2** **3** **4** **5**

a R = Ph
b R = 1-naphthyl
c R = CH_3
d R = OPh
e R = OCH_3
f R = OCH_2Ph

3: R = cyclohexyl
4: R = cyclohexyl
5: R = cyclohexyl

Scheme 1.

* Dedicated with affection and admiration to Professor Lew Mander on the occasion of his 65th birthday.

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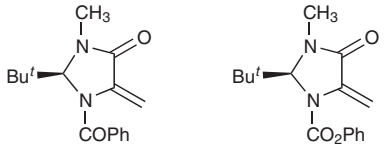
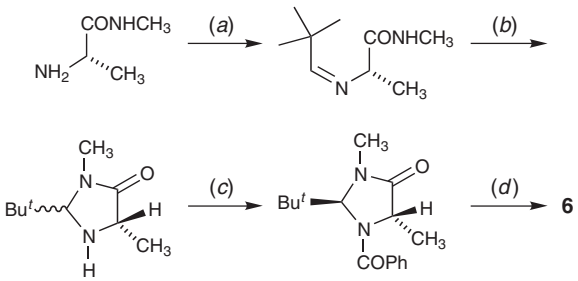
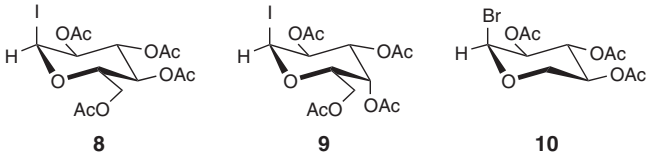


Scheme 2.



Scheme 3. Reagents and conditions: (*a*) Bu^{t}CHO, pentane, Dean–Stark, Δ, 3 h; (*b*) CF_3CO_2H, CH_2Cl_2, 0°C, 1 h, $NaHCO_3/H_2O$; (*c*) PhCOCl, CH_2Cl_2, Et_3N, room temp., 16 h, radial chromatography; (*d*) NBS, CCl_4, *hν*, then NaI, acetone, Δ, 4 h.



Scheme 4.

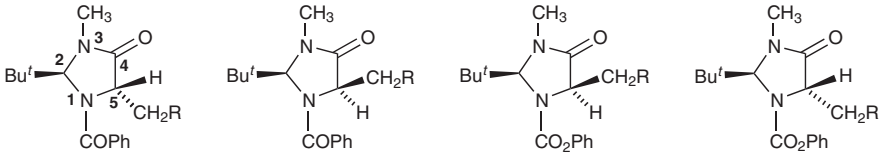
readily undergo hydrolysis, these reactions afford a useful method for the enantioselective preparation of α-substituted hydroxy- and amino-acids.[8,9]

In order to compare the above radical reactions with those of a related system, as well as to explore further opportunities for the enantioselective synthesis of substituted alanines and identify the mechanism by which the nature of the N1 substituent in compounds such as oxazolidinones **2a** and **2d** affects diastereoselectivity, we examined the behaviour of the related imidazolidinones **6** and **7** (Scheme 2).

Preparation of (2*S*)-methylideneimidazolidinone **6** from the *N*-methylamide of L-alanine (Scheme 3) is similar to the synthesis of oxazolidinones **2**,[8–11] and an analogous sequence of reactions affords the pure (2*S*)-carbamate **7**. As stannane-mediated radical reactions of sugar-derived radicals with oxazolidinones have been shown to proceed with high diastereoselectivity,[8] we conducted similar reactions with imidazolidinones **6** and **7**. The unstable iodides **8** and **9** (Scheme 4) to be used as the radical precursors were prepared from the appropriate pentaacetates.[12,13] As the analogous preparation of D-xylose triacetate iodide was unsuccessful, the unstable bromide **10**[14] was used instead.

Radical additions of cyclohexyl and isopropyl iodide to imidazolidinones **6** and **7** were conducted under 'catalytic tin' conditions,[15] whereby the substrate, the radical precursor, tributyltin chloride, sodium cyanoborohydride, and the initiator (AIBN) in acetonitrile were photolyzed at 30°C with a medium-pressure mercury lamp. The reaction mixture was treated with aqueous ammonia in order to remove the tin residues and was then filtered through a plug of silica using ethyl acetate as eluent. The *cis*/*trans* ratio of the products was determined by integration of the ^{1}H NMR spectra. For *N*-benzoyl compounds such as **11** and **12** (Scheme 5), for which the stereochemistry could be confirmed because we have X-ray or other data, the signals for the C2 and C5 protons of the *trans* isomer were found to be downfield of the comparable signals for the *cis* isomer. For example, the δ_H values for the C2 and C5 protons in the *trans* compound **11c** were 5.67 and 4.27 ppm, respectively, whereas those for the equivalent protons in the *cis* isomer **12c** were 5.60 and 3.83 ppm. For the carbamates **13** and **14** the C2 signal for the *trans* isomer was also downfield in comparison to that for the *cis* isomer, but the signal for the C5 proton was upfield. For example, **14c** displayed signals for the C2 and C5 protons at 5.18 and 4.20 ppm, while those for the *cis* isomer **13c** were at 5.05 and 4.41 ppm, respectively. The preferential formation of adducts **11a** and **11b** indicates that additions to the *N*-benzoyl substrate **6** are highly *trans* diastereoselective (**11a**/**12a**: 21 and **11b**/**12b**: 16). Conversely, stannane-mediated additions to carbamate **7** give mainly *cis* products (**13a**/**14a**: 6 and **13b**/**14b**: 6.8). The major product in each reaction was isolated by radial chromatography, and was characterized by mass spectrometry, IR, UV, and NMR spectroscopy, as well as elemental analysis. The isolated yields were 67% for the *trans* (2*S*,5*S*) compound **11a**, $[\alpha]_D^{22}$ +43.6° in CH_2Cl_2; 69% for the *trans* (2*S*,5*S*) compound **11b**, $[\alpha]_D^{22}$ +16.5° in CH_2Cl_2; 61% for the *cis* (2*S*,5*R*) compound **13a**, $[\alpha]_D^{22}$ −26.6° in CH_2Cl_2; and 63% for the *cis* (2*S*,5*R*) compound **13b**, $[\alpha]_D^{22}$ −33.3° in CH_2Cl_2.

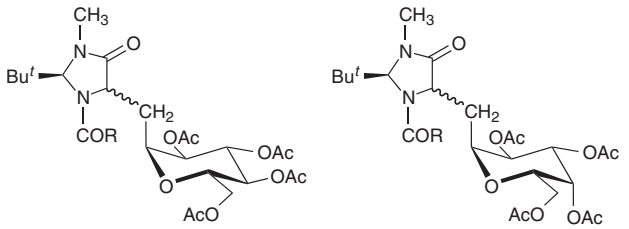
Reactions of imidazolidinones **6** and **7** with the radicals derived from the halo sugars **8**, **9**, and **10** were conducted either under catalytic tin conditions or by the slow addition of a stoichiometric amount of tributylstannane during the reaction. In most cases the catalytic method gave better yields of the addition adducts. In view of the potential sensitivity of the resultant products to aqueous ammonia, the workup procedure to effect the removal of tin residues was modified. In particular, the reaction mixture was partitioned between hexane, which preferentially dissolves tin compounds, and acetonitrile, which retains the more polar adducts.[16] In the reactions with glucosyl iodide **8** and galactosyl iodide **9** only a single product was isolated after careful analytical chromatography. Unfortunately, ^{1}H NMR spectroscopy could not be employed to assign the stereochemistry of each of the products as the protons on the sugar moiety obscured the diagnostic signals from the protons present on the imidazolidinone nucleus. Accordingly, we turned to circular dichroism (CD) measurements; these showed that the *trans* compounds **11a**–**11c** and **14c** gave very similar traces which were easily distinguishable from those of their *cis* isomers. As the CD traces for **15a** and **16a**, which were formed from the reaction of *N*-benzoyl substrate **6** with iodo sugars **8** and **9**, respectively, were very similar to those observed for related *trans* compounds **11a**–**11c** and **14c**, we tentatively assigned the *trans* stereochemistry to these products (Scheme 6). In addition, the stereochemistry of the anomeric sugar carbon was



11 **12** **13** **14**

a R = cyclohexyl
b R = isopropyl
c R = H

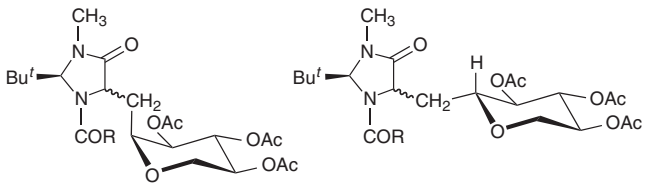
Scheme 5.



15 **16**

a R = Ph
b R = OPh

Scheme 6.



17 **18**

a R = Ph
b R = OPh

Scheme 7.

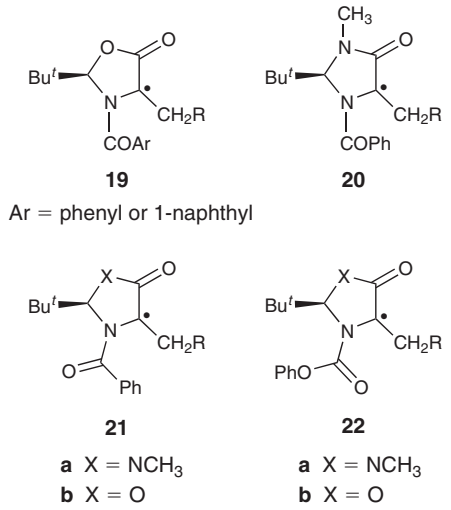
assigned as α because glucosyl and galactosyl radicals usually form α-anomeric adducts in their reactions with olefinic substrates.[17] The isolated yields of the pure compounds, which were characterized by mass spectrometry, UV, IR, and NMR spectroscopy, as well as elemental analysis, were 52% for the (2*S*,5*S*) compound *trans*-**15a**, $[\alpha]_D^{22}$ +91.2° in CH_2Cl_2; and 50% for the (2*S*,5*S*) compound *trans*-**16a**, $[\alpha]_D^{22}$ +71.0° in CH_2Cl_2.

Similarly, the adducts derived from *N*-carbamate substrate **7** were tentatively assigned as possessing the *cis* stereochemistry. The isolated yields of the pure compounds, which were characterized by mass spectrometry, UV, IR, and NMR spectroscopy, as well as elemental analysis, were 61% for the (2*S*,5*R*) product *cis*-**15b**, $[\alpha]_D^{22}$ +10.5° in CH_2Cl_2; and 56% for the (2*S*,5*S*) product *cis*-**16b**, $[\alpha]_D^{22}$ +21.1° in CH_2Cl_2.

Reactions of xylose bromide **10** with substrate **6** gave the best yields (57%) when a stoichiometric amount of tributylstannane was added during the reaction. Conversely, the best yield (47%) obtained for the same reaction with carbamate **7** occurred when the catalytic tin method was used. In each case two adducts were detected and isolated as gums. Unfortunately, the use of NMR spectroscopy to assign the stereochemistry of the products was unreliable due to diagnostic signal overlap and relatively poor resolution. However, on the basis of CD measurements and by analogy with the above results, we tentatively assigned the stereochemistry of the products from the *N*-benzoylimidazolidinone **6** as *trans* and those from the *N*-carbamate imidazolidinone **7** as *cis*. Differences in the shifts for the NMR signals assigned to the sugar moieties suggest that the two isomers from each reaction differ in stereochemistry at the anomeric position, and that the β-form is the major isomer. The formation of β-adducts has previously been reported for stannane-mediated addition reactions of xylosyl radicals.[18] On this basis, we believe that the two products from **6** detected in a ratio of 1 : 4.8, and characterized by mass spectrometry, UV, IR, and NMR spectroscopy, as well as elemental analysis, are the α-(2*S*,5*S*) compound *trans*-**17a**, $[\alpha]_D^{22}$ +21.2° in CH_2Cl_2, and the β-(2*S*,5*S*) compound *trans*-**18a**, $[\alpha]_D^{22}$ +38.9° in CH_2Cl_2 (Scheme 7). The two products isolated in a ratio of 1 : 1.6 from the reaction involving the carbamate **7** are believed to be the α-(2*S*,5*R*) compound *cis*-**17b**, $[\alpha]_D^{22}$ −33.9° in CH_2Cl_2, and the β-(2*S*,5*R*) compound *cis*-**18b**, $[\alpha]_D^{22}$ +62.2° in CH_2Cl_2. The mixture of anomers obtained in reactions with xylose bromide suggests that the conformational rigidity of the xylosyl radical is much less than that of the glucosyl and galactosyl radicals.[18]

In summary, present and previous results[6–9] show that stannane-mediated radical additions to methylidene-2-*tert*-butyl-1,3-dioxolanones, oxazolidinones, and imidazolidinones are highly diastereoselective. All reactions reported for dioxolanone **1** exhibit *cis* diastereoselectivity, whereas selectivity in reactions that involve methylideneoxazolidinones and imidazolidinones depends on the nature of the substituent on N1. In particular, reactions of *N*-aroyl substrates such as **2a** and **6** are highly *trans* diastereoselective, while those of *N*-aryloxycarbonyl substrates such as **2d** and **7** are highly *cis* diastereoselective. The nature of the addend radical, unlike that of the N1 substituent, appears to exert a relatively minor influence on the degree but not the direction of diastereoselectivity.

Equilibration experiments in which diastereoisomers **11c** and **12c** were treated with lithium *tert*-butoxide in refluxing *tert*-butanol indicated that they are of approximately equal thermodynamic stability, and empirical calculations on other pairs of *cis* and *trans* isomers such as **11a** and **12a** gave similar results. Therefore, we conclude that stereochemical outcomes must reflect the facial selectivity of hydrogen-atom transfer



Scheme 8.

from tributylstannane to the intermediate radicals **19** and **20** (Scheme 8), and that the relative rates of hydrogen-atom transfer to the *syn* and *anti* faces of the intermediate radicals are not under thermodynamic control. This view accords with the general assumption that hydrogen-atom transfers from tributylstannane to carbon-centred radicals have early transition states.[19]

Structural features of the intermediate radicals that may affect the facial selectivity of hydrogen-atom transfer include the degree of pyramidalization and the radical stabilization energies of the intermediates. We expect that captodative stabilization of phenoxycarbonyl-substituted radicals such as **22** will be less than that of their *N*-benzoyl counterparts.[20] However, the dramatic effect that the nature of the N1 substituent has on the stereochemical outcome of radical reactions that involve methylideneimidazolidinones suggests that the conformations adopted by the intermediates must be of prime importance. Therefore, we have commenced a theoretical study of radicals **19** and **20**, and related species. Thus far, the results of molecular mechanics and semi-empirical molecular orbital calculations lead to the same conclusion, namely that the preferred conformation of radicals that bear *N*-aroyl substituents involves the exocyclic *N*-carbonyl group lying close to the plane of the heterocyclic ring and the carbonyl oxygen pointing towards the 2-substituent, as in structure **21**. Conversely, the preferred conformation of the analogous species, which bears *N*-aryloxycarbonyl or *N*-acyloxycarbonyl substituents, is that the exocyclic carbonyl oxygen of the carbamate points away from the 2-substituent, as in structure **22**. It may be significant that the X-ray crystal structures of compounds **6** and **7**, as well as related compounds,[21] have a trigonal carbon at the 5-position, and show approximately the same orientation for the carbonyl oxygen as those predicted by theoretical calculations.

Another significant feature of the theoretically predicted intermediate radicals, and one which is also supported by X-ray studies, is that the phenyl ring in both structures **21a** and **21b** lies below the plane of the imidazolidone ring. However,

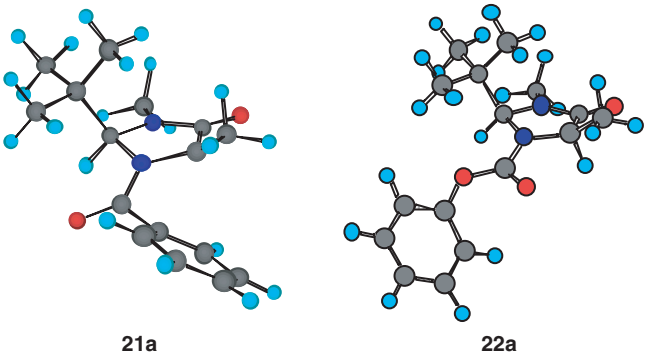


Fig. 1. Preferred conformations of radicals **21a** (R = H) and **22a** (R = H).

because of the disposition of the carbonyl group, the aryl group is close to the C5 radical centre in structure **21a**, while in structure **22a** it is close to C2. In both cases the phenyl ring is substantially twisted out of the plane of the heterocyclic ring and the N1 nitrogen is somewhat pyramidalized. Inspection of models of intermediate radicals similar to **21a** and **22a**, and which are based on the calculated structures and X-ray data for related species, reveals that the aryl substituent on the face of the heterocyclic ring *anti* to the *tert*-butyl group will substantially shield the C5 centre in **21a** and **21b**, and thereby hamper the approach of a hydrogen-atom transfer reagent (Fig. 1). Although the substituent in *N*-carbamate radicals **22a** and **22b** and related alkoxycarbonyl species also lies below the face of the ring *anti* to the *tert*-butyl group, it is situated too far from C5 to impede hydrogen-atom transfer.

In summary, we have shown that stannane-mediated radical addition to imidazolidinones **6** and **7** is highly diastereoselective and follows the pattern already established for related reactions of oxazolidinone **2**. Also, consideration of the structural features of the intermediate radicals in these reactions and those of dioxolanone **1** led us to the following conclusions.

1. The *tert*-butyl group in radicals derived from dioxolonane **1** sterically hinders the approach of the stannane, and thereby directs hydrogen-atom transfer to occur at the *anti* face of the ring to give *cis* products such as **3**.
2. The steric effect of the aryl substituent in proximity to the C5 centre in radicals of the general type **21a** and **21b** outweighs the steric effect exerted by the *tert*-butyl group, and hence the radical transfer occurs *syn* to the *tert*-butyl group to give *trans* products such as **4** and **11**.
3. As the alkyl or aryl substituent is relatively remote from the C5 centre in radicals such as **22a** and **22b**, the *tert*-butyl group directs hydrogen-atom transfer to occur at the *anti* face of the ring to afford *cis* products such as **5** and **13**.

A more precise determination of the structural and thermodynamic characteristics of the starting materials and radical intermediates, as well as the degree to which they effect the stereochemical outcome of these reactions awaits the results of further experiments and theoretical studies.

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