Pergamon

Tetrahedron Letters 41 (2000) 2671–2674

TETRAHEDRON LETTERS

Stereoselective radical bromination of α-chloro hydrocinnamic acid derivatives

Leh See Wong, Bun Chan and Eng Wui Tan *

Department of Chemistry, University of Otago, PO Box 56, Dunedin, New Zealand

Received 15 December 1999; accepted 3 February 2000

Abstract

Reaction of (*S*)-2-chloro-3-phenylpropanoic acid derivatives with NBS gave the corresponding 3-bromo-2-chloro derivatives with a preference for the formation of the (2*R*,3*S*) isomers over the (2*R*,3*R*) isomers. The stereoselectivity was affected by the nature of the carboxylic acid derivative. Reaction of ester derivatives was highly stereoselective while the reaction of amide derivatives showed varied stereoselectivity which depended on the nature of the amide. Theoretical studies at UHF/3-21G* level showed that the intermediate benzylic radical of the methyl ester, the methyl amide and the diisopropyl amide derivatives had different energy profiles with respect to rotation of the C2–C3 bond. The different stereoselectivity observed from reaction of the various acid derivatives could be attributed, at least in part, to different distribution of conformers of the radical intermediate.

1. Introduction

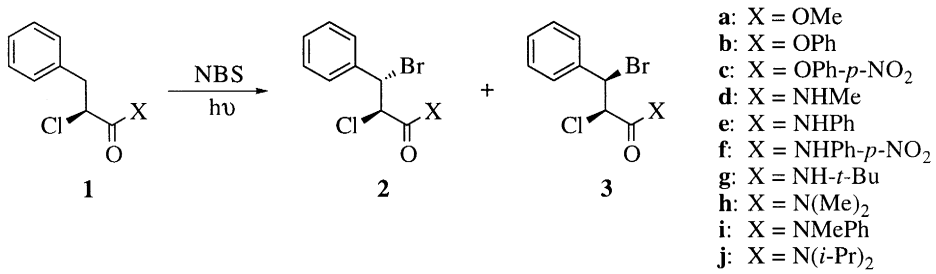
It has been reported that radical bromination of methyl (*S*)-2-chloro-3-phenylpropanoate **1a** gave predominantly the methyl (2*R*,3*S*)-3-bromo-2-chloro-3-phenylpropanoate **2a** (Scheme 1).[1] The result was attributed to the formation of a chloro bridge in the radical intermediate.[2] In this article we report experimental and theoretical studies of radical bromination of α-chloro carboxylic acid derivatives analogous to **1a**, as part of a detailed study of stereoselective radical bromination of α-chloro carboxylic acid derivatives.

2. Results and discussion

α-Chloro hydrocinnamic acid derivatives **1a**–**j** were prepared by converting the carboxylic acid[3] to the acid chloride, and reacting the acid chloride with the appropriate alcohol or amine.[4] Bromination

* Corresponding author.

0040-4039/00/$ - see front matter
PII: S0040-4039(00)00220-3



Scheme 1.

of the α-chloro acid derivatives was carried out with NBS in refluxing CCl_4, with irradiation from a 160 W mercury gas discharge lamp.[5] The reaction mixture was analysed by ^1H NMR spectroscopy to determine the extent of reaction and diastereomeric excess. In all cases, the crude mixture contained only the corresponding α-chloro β-bromo acid derivatives **2** and **3** and succinimide. The ratio of the two diastereomers **2** and **3** was determined from the relative integration of the α-proton and/or β-proton signals of the two isomers. The stereochemical configuration of the α-chloro β-bromo esters was assigned by comparing their ^1H NMR spectra to that of **2a** and **3a**. The major isomers from the reactions of the *p*-nitrophenyl amide **1f** and the diisopropyl amide **1j** were identified to be **2f** and **2j**, respectively, by X-ray crystallography.[6] The configuration of products from bromination of other amides was assigned by comparing their NMR spectra to the spectra of **2f** and **2j**. The diastereoselectivity observed is shown in Table 1.

Table 1
Ratio of diastereomeric α-chloro β-bromo acid derivatives **2** and **3** from NBS bromination of α-chloro acid derivative **1**

Reactant **1**	Acid Derivative	Ratio of Products **2** : **3**
a	OMe	10 : 1
b	OPh	10 : 1
c	OPh-*p*-NO_2	10 : 1
d	NHMe	2 : 1
e	NHPh	2 : 1
f	NHPh-*p*-NO_2	2 : 1
g	NH-*t*-Bu	3 : 1
h	$N(Me)_2$	4 : 1
i	NMePh	10 : 1
j	$N(i\text{-}Pr)_2$	> 20 : 1

Bromination of different α-chloro esters showed no significant difference in the diastereomeric ratio of the products. In contrast to the reported high diastereoselectivity of bromination of **1a**, the reaction of the corresponding methyl amide **1d** gave a low preference for the formation of the (2*R*,3*S*) isomer **2d**. The stereoselectivity achieved from the reaction of other amides remained close to that of the methyl amide. However, replacing a primary amide with a secondary amide significantly raised the preference for the formation of the (2*R*,3*S*) isomer **2**, and the selectivity increased with the bulkiness of the substituents.

Theoretical studies were carried out to determine the energy profile of C2–C3 bond rotation of the radical intermediates of **1a** (ester), **1d** (primary amide) and **1j** (secondary amide). Geometry optimisations were carried out on MacSpartan Plus™.[7] The dihedral angle 1 (DA1=C1–C2–C3–CPh) was fixed at a specific angle (0, 30, 60...330°) and the dihedral angle 2 (DA2=O(carbonyl)–C1–C2–C3) was changed from 0 to 330° with an interval of 30°. The energy of different conformers with a specific DA1 was obtained at SYBYL level to determine the preferred conformation of each DA1-fixed conformer. The geometry of each DA1-fixed conformer was then optimised at AM1 level and refined at UHF/3-21G* level. The results are shown in Fig. 1.

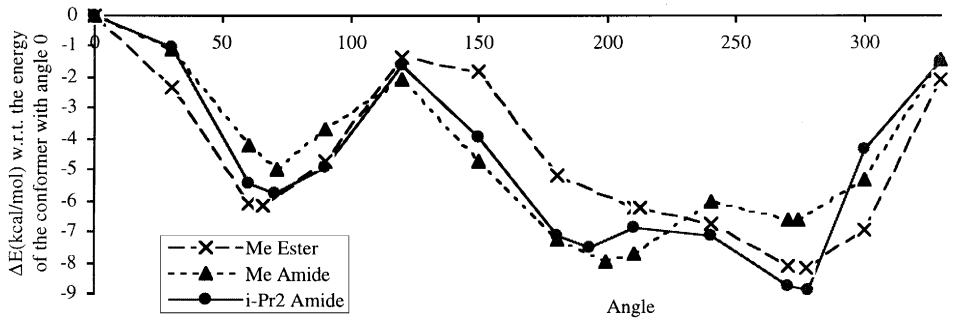


Fig. 1. Energy versus dihedral angle (Cl–C2–C3–CPh). Profile of the intermediate radical of the methyl ester **1a**, methyl amide **1d** and diisopropyl amide **1j**. Calculated at UHF/3-21G* level

The energy profile for the radical intermediate of the α-chloro methyl ester **1a** showed two local minima (DA1=60, 270°) (Fig. 2). The global minimum (DA1=270°) places the phenyl group and the ester in an *anti* configuration and the chlorine parallel to the *p*-orbital of the benzylic radical. Presumably, this conformation minimises steric interactions and maximises any potential stabilisation of the radical by neighbouring chlorine. Bromine atom transfer is more likely to occur on the less hindered *si* face. This leads to the formation of the (2*R*,3*S*) isomer. The local minimum at DA1=60° has the *si* face hindered by the chlorine and the *re* face hindered by the ester. There is no clear facial preference for bromine atom transfer. The α-chloro methyl amide **1d** showed three minima in its energy profile (DA1=60, 210 and 270°), and the minimum with DA1=210° was the global minimum. In this conformation, the amide is parallel to the *p*-orbital of the radical. In a related system, an amide neighbouring group effect has been suggested which could account for this preferred conformation.[8] Bromine atom transfer to this conformer would occur preferentially from the *re* face to give the (2*R*,3*R*) product and hence lower the overall preference for the formation of the (2*R*,3*S*) product. The energy profile of the α-chloro diisopropyl amide **1j** showed three local minima (DA1=60, 210 and 270°). However, while the global minimum of the methyl amide occurred at DA1=210°, that of the diisopropyl amide occurred at DA1=270°. This can be attributed to the bulkier amide experiencing more severe non-bonding interactions with the phenyl group, thus favouring an *anti* arrangement.

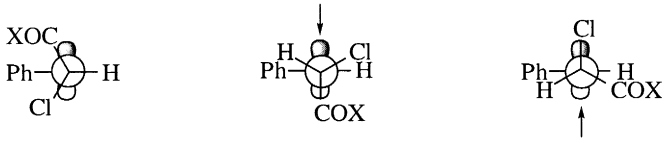


Fig. 2. Minimum energy C2–C3 rotation conformers of the intermediate radical

The difference in stereoselectivity of bromination cannot be explained solely by these bond conformer distributions. For instance, if bromine atom transfer to the radical intermediate of the α-chloro amide **1d** only occurred at the preferred face of each minimum energy C2–C3 rotation conformer at the same rate, the (2*R*,3*R*) isomer **3d** is expected to be the major product, in contrast to observation. It has been suggested that in addition to the relative population of minimum energy conformers, the relative energy of the transition states for atom transfer to the two prochiral faces of each minimum energy conformer is also important in determining the product distribution.[9] The calculation of transition state energies is beyond the scope of this communication.

3. Conclusion

The stereoselectivity of radical bromination of α-chloro hydrocinnamic acid derivatives was found to be affected by the nature of the acid derivative. α-Chloro esters consistently showed high preference for formation of the (2*R*,3*S*) α-chloro β-bromo derivative. Primary amide analogues showed low stereoselectivity. Bromination of secondary amides showed higher stereoselectivity than the primary amides, and the selectivity generally increased with the bulkiness of the amide. The difference in the outcome can be partly attributed to the different distribution of C2–C3 rotation conformers of the radical intermediate for each class of compound.

References

1. Shaw, J. P.; Tan, E. W. *J. Org. Chem*. **1996**, *61*, 5635.
2. For an overview, see: Skell, P. S.; Shea, K. J. In *Free Radicals*; Kochi, J. K., Ed. Bridged free radicals. John Wiley & Sons: New York, 1973; Vol. II, pp. 809–852.
3. For example, see: (a) Fisher, E.; Schoeller, W. *Liebigs Ann. Chem*. **1907**, *357*, 1. (b) Renard, M. *Bull. Soc. Chim. Biol*. **1946**, *28*, 497. (c) Karrer, P.; Reschofsky, H.; Kasse, W. *Helv. Chim. Acta* **1947**, *30*, 271.
4. Typical procedure for preparation of α-chloro acid derivatives **1**. A mixture of (*S*)-2-chloro-3-phenylpropanoic acid (4.0 g, 21.7 mmol) and PCl_5 (9.0 g, 43.4 mmol) in benzene (100 ml) was heated under reflux under an anhydrous atmosphere for 2 h. The resulting solution was cooled and washed with ice-water (1×50 ml). After drying (Na_2SO_4), aniline (2.0 g, 21.7 mmol) and triethylamine (4.4 g, 43.4 mmol) were added to the solution and the mixture was left stirring under an anhydrous atmosphere for 2 days. The solution was washed with 1 M HCl, satd $NaHCO_3$ and water and was then dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product recrystallised from hexane/ethyl acetate to give pure **1e** in 24% yield. All new compounds were fully characterised.
5. Typical procedure for bromination. A mixture of phenyl (*S*)-2-chloro-3-phenylpropanamide **1e** (20 mg, 77 mmol) and NBS (13 mg, 77 mmol) in CCl_4 (5 ml) was heated at reflux under nitrogen. The reaction was initiated by irradiation with a 160 W mercury lamp. After 2 h the mixture was cooled and the solvent was removed under reduced pressure. The composition of the crude product was determined by NMR spectroscopy. All new compounds were fully characterised.
6. Simpson, J.; Chan, B.; Wong, L. S.; Tan, E. W. *Acta Crystallogr.*, in preparation. Compound **2f** had ^{1}H NMR ($CDCl_3$) δ 4.94 (1H, d, *J*=8.2 Hz), 5.57 (1H, d, *J*=8.2 Hz), 7.33–7.42 (3H, m), 7.42–7.52 (2H, m), 7.71 (2H, d, *J*=9.2 Hz), 8.02 (1H, bs), 8.25 (2H, d, *J*=9.2 Hz) ppm. Compound **2j** had ^{1}H NMR ($CDCl_3$) δ 1.35 (6H, d, *J*=6.8 Hz), 1.48 (6H, d, *J*=6.8 Hz), 3.65 (1H, m), 4.16 (1H, m), 5.04 (1H, d, *J*=10.7 Hz), 5.55 (1H, d, *J*=10.7 Hz), 7.20–7.40 (5H, m) ppm.
7. MacSpartan Plus™, Wavefunction, Inc., 18401 Von Karman, Suite 370, Irvine, California, 92612, USA.
8. Easton, C. J.; Merrett, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 3035.
9. Caramella, P.; Rondan, N. G.; Paddon-Row, M. N.; Houk, K. N. *J. Am. Chem. Soc.* **1981**, *103*, 2438.