Diastereoisomeric Imidazo[1,2-*a*]pyridines

Richard Kubík,[a] Jan Němeček,[b] Stanislav Böhm,[a] Martin Hradilek[c] and Josef Kuthan*[a]

[a] Department of Organic Chemistry, Prague Institute of Chemical Technology, 166 28 Prague 6, The Czech Republic.
Fax: +42 2 2431 1082; e-mail: stibori@vscht.cz
[b] Institute of Microbiology, Academy of Sciences of the Czech Republic, 141 20 Prague 4, The Czech Republic.
[c] Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, 162 06 Prague 6,
The Czech Republic.

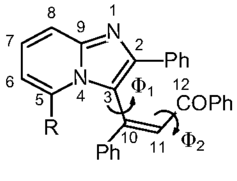
The axially chiral ketone **1** and its methyl derivative **2** have been reduced with sodium borohydride to the corresponding diastereoisomeric alcohols **3** and **4**.

Diastereoisomerism is obviously caused either by two asymmetric centres or by two atropoisomeric subsystems in a given molecule. We wish to report here a novel, less common case in which the diastereoisomeric couples containing only one asymmetric carbon are formed by reduction of a prochiral carbonyl group bound to the axially chiral molecular skeleton of sterically crowded imidazo[1,2-*a*]pyridinoic ketones.

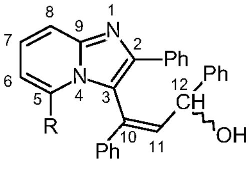
(*Z*)-1,3-Diphenyl-3-(2-phenylimidazo[1,2-*a*]pyridin-3-yl)prop-2-en-1-one **1** prepared by the ferricyanide oxidation[1,2] of 1-(pyridin-2-yl)-2,4,6-triphenylpyridinium perchlorate has been investigated by X-ray structure analysis which indicates the presence of two pairs of enantiomeric molecules in the unit cell.[3] To obtain a deeper insight into the enantiomerism in solution states as well, ^{1}H NMR spectra of ketone **1**[†] have been investigated in the absence as well as in the presence of achiral shift reagent Eu(FOD)$_3$. While expected chemically induced shifts (CISs) were only observed in these experiments, the use of chiral shift reagent Eu(hfbc)$_3$ resulted in a typical 1:1 splitting of certain proton signals indicating the racemic character of the substrate **1** in CDCl$_3$ solutions. For example, two separated H-6 proton signals clearly indicate this behaviour.[‡]

The molecular geometry optimization for various torsion angles ϕ_1 and ϕ_2 in **1** by the semiempirical PM3 method[4] predicts four conformers.[5] The calculated racemization barriers 13.5–23.5 kcal mol^{-1} suggest restricted rotations (mainly around the C3–C10 bond) of the side chain in molecules such as **1** as the reason for their axial chirality.

The reactions of ketones **1** and **2** with sodium borohydride in ethanol at 20 °C gave mixtures of diastereoisomeric (*Z*)-1,3-diphenyl-3-(2-phenylimidazo[1,2-*a*]pyridin-3-yl)prop-2-en-1-ols **3** or the corresponding methyl derivatives **4**, respectively.[§] Integral intensity consideration in the ^{1}H NMR spectra of **3** and **4** led to the approximate ratios 3:2 for the appropriate diastereoisomeric pairs **3a,b** and **4a,b**, respectively, which underwent no interconversions in the range 20–110 °C according to the spectral measurements. In the case of **4**, both species **4a** and **4b** were separated by preparative HPLC as well as by crystallization using their different solubility in diethyl ether.[¶]



1 R = H
2 R = Me



3a,b R = H
4a,b R = Me

According to our knowledge, diastereoisomeric molecules possessing a combination of central and axial chiralities have not yet been carefully investigated in heterocyclic chemistry except maybe for some recently investigated 5,11-dihydrodibenzo[*b*,*e*]azepin-6-ones.[6] On the other hand, similar diastereoisomers containing one atropoisomeric chiral system and one asymmetric carbon atom have been occasionally observed among molecules of quite different structures.[7,8]

Experiments with other compounds such as **1** and towards the study of diastereoisomeric alcohols such as **3** are in progress.

This research has been supported within the project no. 203/93/0320 of the Grant Agency of the Czech Republic.

[†] NMR spectra were recorded on Varian VXR-400 and Bruker AM-400 instruments at 298 K (standard 2D techniques). Methyl derivative **2** was prepared analogously to the parent compound **1** by ferricyanide oxidation of the corresponding quaternary pyridinium salt[1] (yield 76%): m.p. 191–192 °C; ^{1}H NMR (400 MHz, CDCl$_3$, standard TMS) δ 2.453 (s, 3H, Me), 6.437 (m, lH), 7.068 (dd, 1H, *J* 6.8, 9.0 Hz), 7.12 (m, 3H, 2-Ph *m*, *p*), 7.187 (dd, 2H, 12-Ph *m*, *J* 7.7, 7.7 Hz), 7.340 (m, 1H, 12-Ph *p*), 7.400 (m, 1H, 8-H), 7.470 (m, 2H, 10-Ph *o*), 7.520 (m, 2H, 12-Ph *o*), 7.694 (m, 2H, 2-Ph *o*); ^{13}C NMR δ 19.94 (Me), 113.19 (C-6), 115.21 (C-8), 117.71 (C-3), 127.17 (2-Ph *p*), 127.23 (10-Ph *o*), 127.68 (10-Ph *o*), 127.80 (2-Ph *m*), 127.85 (2-Ph *o*), 127.91 (12-Ph *m*), 129.15 (10-Ph *m*), 129.22 (C-11), 129.86 (10-Ph *p*), 132.26 (12-Ph *p*), 133.88 (2-Ph *ipso*), 136.44 (C-5), 137.30 (12-Ph *ipso*), 139.90 (10-Ph *ipso*), 143.37 (C-10), 144.15 (C-2), 146.70 (C-9), 191.28 (C-12); IR (CHCl$_3$) ν_{max}/cm^{-1} 1637, 1659 (C=C–C=O).

[‡] *Spectral data for* **1**: ^{1}H NMR δ (CDCl$_3$) 6.67 (ddd, 1H, 6-H, *J* 6.8, 6.8, 1.3 Hz); [CDCl$_3$, Eu(FOD)$_3$] 6.83 (t, 1H, 6-H); [CDCl$_3$, Eu(hfbc)$_3$] 6.76 (t, 6-H, first enantiomer) and 6.85 (t, 6-H, second enantiomer).

[§] The products **3** and **4** gave satisfactory elemental analyses. Only selected spectral data are reported.

For **3a,b**: m.p. 143–145 °C, yield 90%; IR ν_{max}/cm^{-1} (CHCl$_3$) 1635 (C=C), 3153 (br.), 3594 (O–H); ^{1}H NMR (400 MHz, CDCl$_3$) δ_H 4.94 (d, 1H, 12-H^b, *J* 9.2 Hz), 4.99 (d, 1H, 12-H^a, *J* 8.6), 6.51 (ddd, 1H, 6-H^a, *J* 6.7, 6.7, 1.0), 6.68 (ddd, 1H, 6-H^b, *J* 6.7, 6.7, 1.0), 6.70 (d, 1H, 11-H^a, *J* 8.6), 6.81 (d, 1H, 11-H^b, *J* 9.2), 7.62 (dd, 1H, 8-H^a, *J* 9.1, 1.0), 7.66 (dd, 1H, 8-H^b, *J* 9.1, 1.0), 7.80 (dd, 1H, 5-H^b, *J* 6.7, 1.0); ^{13}C NMR (100 MHz, CDCl$_3$) δ 72.20 (CH-12^b), 72.40 (CH-12^a), 112.34 (C-6^a), 112.57 (C-6^b), 117.45 (C-8^b), 117.48 (C-8^a), 123.85 (C-5^a), 124.10 (C-5^b), 124.90 (C-7^a), 124.95 (C-7^b), 136.99 (CH-11^b), 138.43 (CH-11^a).

For **4a,b**: m.p. 223–227 °C, quantitative yield; IR ν_{max}/cm^{-1} (CHCl$_3$) 1637 (C=C), 3562, 3595 (O–H); ^{1}H NMR and ^{13}C NMR spectral data, footnote ¶.

[¶] Stereoisomer **4a** (major), m.p. 245–247 °C (EtOH–CHCl$_3$): ^{1}H NMR (400 MHz, CDCl$_3$) δ 2.078 (s, 3H, Me), 5.025 (d, 1H, 12-H, *J* 8.4), 6.322 (m, 1H, 6-H), 6.667 (d, 1H, 11-H, *J* 8.4), 7.008 (m, 2H, 10-Ph *o*), 7.086 (dd, 1H, 7-H, *J* 6.8, 9.0), 7.15–7.22 (m, 3H, 12-Ph *m*, *p*), 7.28–7.41 (m, 8H, 2-Ph *m*, *p*; 10-Ph *o*, *m*, *p*), 7.582 (m, 1H, 8-H), 7.924 (m, 2H, 2-Ph *o*); ^{13}C NMR (100 MHz, CDCl$_3$) δ 19.51 (Me), 72.82 (C-12), 113.52 (C-6), 115.58 (C-8), 117.82 (C-3), 125.25 (C-7), 125.87 (12-Ph *o*), 126.36 (10-Ph *o*), 127.65 (12-Ph *p*), 127.91 (2-Ph *o*), 128.22 (10-Ph *p*), 128.41 (2-Ph *p*), 128.51 (12-Ph *m*), 128.76 (2-Ph *m*), 129.23 (10-Ph *m*), 132.41 (12-Ph *ipso*), 133.95 (2-Ph *ipso*), 136.71 (C-5), 137.68 (C-11), 140.72 (10-Ph *ipso*), 141.74 (C-10) 143.72 (C-2), 147.22 (C-9).

Stereoisomer **4b** (minor), m.p. 174–176 °C (Et$_2$O): ^{1}H NMR (400 MHz, CDCl$_3$) δ 2.639 (s, 3H, Me), 5.071 (d, 1H, 12-H, *J* 9.2), 6.460 (m, 1H, 6-H), 6.729 (d, 1H, 11-H, *J* 9.2), 6.801 (m, 2H, 12-Ph *o*), 7.0–7.2 (m, 6H, 12-Ph *m*, *p*; 2-Ph *m*, *p*), 7.119 (dd, 1H, 7-H, *J* 6.8, 9.0), 7.28–7.40 (m, 5H, 10-Ph *o*, *m*, *p*), 7.586 (m, 1H, H-8), 7.692 (d, 2H, 2-Ph *o*, *J* 8.1); ^{13}C NMR (100 MHz, CDCl$_3$) δ 20.12 (Me), 72.12 (C-12), 113.62 (C-6), 115.51 (C-8), 117.09 (C-3), 125.16 (C-7), 125.72 (12-Ph *o*), 126.51 (10-Ph *o*), 127.50 (12-Ph *p*), 127.53 (2-Ph *p*), 127.60 (2-Ph *o*), 128.25 (2-Ph *m*), 128.25 (12-Ph *m*), 128.37 (10-Ph *p*), 129.14 (10-Ph *m*), 133.40 (12-Ph *ipso*), 133.80 (2-Ph *ipso*), 135.70 (C–11), 137.23 (C-5), 140.17 (10-Ph *ipso*), 142.24 (C-10), 144.11 (C-2), 146.94 (C-9).

References

1 J. Kuthan, *Heterocycles*, 1994, **37**, 1347.
2 S. Böhm, R. Kubík, J. Novotný, J. Ondráček, B. Kratochvíl and J. Kuthan, *Collect. Czech. Chem. Commun.*, 1991, **56**, 2326.
3 S. Böhm, R. Kubík, M. Hradilek, J. Němeček, M. Hušák, S. Pakhomova, J. Ondráček, B. Kratochvíl and J. Kuthan, *Collect. Czech. Chem. Commun.*, in press.
4 J. J. P. Stewart, *Comput. Chem.*, 1989, **10**, 209, 221.
5 S. Böhm, R. Kubík, M. Hradilek, J. Němeček, M. Hušák, B. Kratochvíl and J. Kuthan, *Collect. Czech. Chem. Commun.*, in press.
6 J. Teixidó, Institut Químic de Sarrià, Barcelona, Spain, personal communication.
7 M. Oki, in *Topics in Stereochemistry*, eds. N. L. Allinger, E. L. Eliel and S. H. Wilen, J. Wiley and Sons, New York, 1983, vol. 14, p. 1.
8 T. H. Siddall, *Tetrahedron Lett.*, 1965, 4515; 1966, 2027.

Received: Cambridge, 29th September 1994
Moscow: 14th October 1994; Com. 4/05972G