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Tautomerism of α,β-Ethylenic Imines and Their Reactivity toward Electrophilic Olefins

Ivan Jabin,*,† Gilbert Revial,‡ Michel Pfau,‡ Bernard Decroix,† and Pierre Netchitaïlo†

URCOM, Université du Havre, Faculté des Sciences et Techniques, 25 rue Philippe Lebon, BP 540, 76058 Le Havre Cédex, France, and ESPCI, Laboratoire de Chimie Organique associé au CNRS (ESA 7084), 10 rue Vauquelin, 75231 Paris Cédex 05, France

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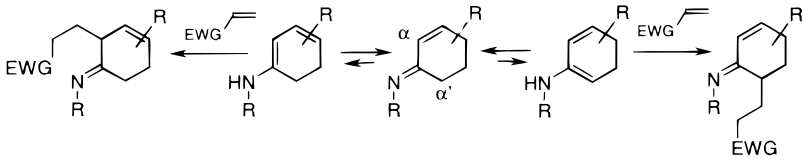
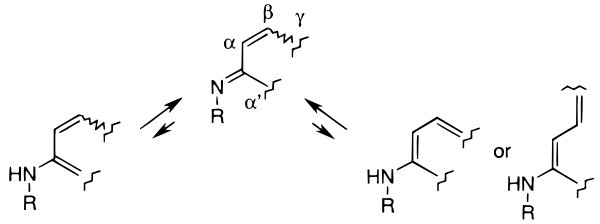
ABSTRACT



The equilibrium between α,β-ethylenic imines and their secondary enamine tautomer form has been demonstrated for the first time. These imines react with electrophilic olefins to give Michael adducts at either the α or the α′ position of the imine function.

It has been well known since the 1970s that the reaction of imines with electrophilic olefins can lead to Michael adducts.[1] However, the reactivity of their α,β-ethylenic counterparts toward Michael acceptors has not yet been studied. Only the Michael type reaction of imines conjugated with an aromatic system (i.e., dihydroisoquinoline[2] or substituted acetophenone imines[3]) has been reported.

Imines are known to react through their secondary enamine form (present in undetectable concentration at equilibrium) with electrophilic olefins.[4] In the interesting case of α,β-ethylenic imines, one can anticipate that appropriate imines can possess two different enamine tautomeric forms and therefore can give either Michael adducts at the α, α′, and γ position or Diels−Alder adducts.



Since our previous work dealt essentially with a general method of "deracemizing alkylation" involving enantioselective Michael addition of chiral cyclohexanone imines,[5] the present study was undertaken to see if our method can be extended to chiral cyclohexen-2-one imines. Consequently it seemed necessary to us to show evidence of the tautomerism of α,β-ethylenic imines and to investigate their reactivity toward electrophilic olefins.

† Université du Havre.
‡ Laboratoire de Chimie Organique associé au CNRS (ESA 7084).

(1) Pfau, M.; Ribière, C. *J. Chem. Soc., Chem. Commun.* **1970**, 66−67.
(2) Kametani, T.; Surgenor, S. A.; Fukumoto, K. *Heterocycles* **1980**, *14*, 303−310. Kametani, T.; Surgenor, S. A.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1981**, 920−925. Kessar, S. V.; Singh, P.; Sharma, S. K. *Tetrahedron Lett.* **1982**, *23*, 4179−4180. Bhattacharjya, A.; Bhattacharya, P. K.; Pakrashi, S. C. *Heterocycles* **1983**, *20*, 2397−2400. Kobor, J.; Lazar, J.; Fulop, F.; Bernath, G. *J. Heterocycl. Chem.* **1994**, *31*, 825−828. Kobor, J.; Sohar, P.; Fulop, F. *Tetrahedron* **1994**, *50*, 4873−4886.
(3) Hoberg, H.; Kieffer, R. *Justus Liebigs Ann. Chem.* **1972**, *760*, 141−150. Pfau, M.; Ughetto-Monfrin, J.; Joulain, D. *Bull. Soc. Chim. Fr.* **1979**, 627−632. Tsuge, O.; Hatta, T.; Kuwata, M.; Yamashita, T.; Kakehi, A. *Heterocycles* **1996**, *43*, 2083−2090.
(4) See ref 1. For a general reference on the chemistry of enamines, see: Rappoport, Z. *The Chemistry of Enamines (The Chemistry of Functional Groups)*; John Wiley and son: New York, 1994.
(5) Pfau, M.; Revial, G.; Guingant, A.; d'Angelo, J. *J. Am. Chem. Soc.* **1985**, *107*, 273−274. Jabin, I.; Revial, G.; Melloul, K.; Pfau, M. *Tetrahedron: Asymmetry* **1997**, *8*, 1101−1109 and references therein.

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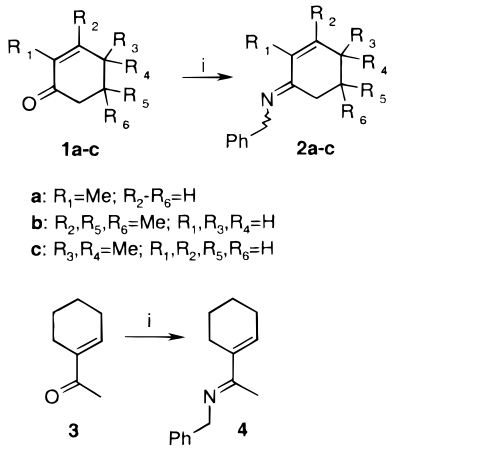
Thus, we prepared the imines **2a**−**c** and **4** from the corresponding enones[6] **1a**−**c** and **3** using the smooth $TiCl_4$ activation method[7] (Scheme 1).

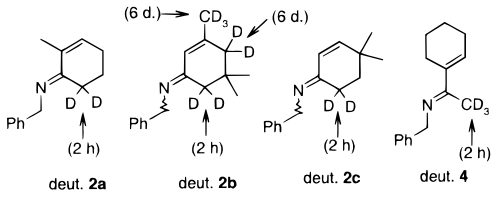
Scheme 1



The imines **2a**−**c** and **4** are temperature and light sensitive, and consequently attempts to purify them by distillation resulted in very low yields. However, ^{1}H and ^{13}C NMR and GC-MS data for the crude imines **2a**−**c** and **4** revealed in all cases the presence of a single compound[8] in accordance with the structure displayed. Therefore, they were used without further purification for the remaining part of this work.

An ^{1}H NMR study in CD_3OD of the imines **2a**−**c** and **4** was then undertaken to confirm that an imine−enamine tautomerism does occur and to see which enamine forms are involved in this equilibrium. Scheme 2 shows the

Scheme 2



deuterated compounds obtained after the times indicated to reach a total exchange.

This NMR study has clearly confirmed for the first time the tautomeric equilibrium between α,β-ethylenic imines and their secondary enamine forms. In all cases the α′ position relative to the imine group was deuterated in ca. 2 h. Deuteration at other positions was observed only in the case of imine **2b** and in a much longer time (ca. 6 days).[9] These results strongly suggest that electrophilic olefins should be reactive toward α,β-ethylenic imines. Moreover, in the case of a Michael type reaction, it should occur preferably at the α′ position.

In a first set of experiments, imines **2a**−**c** and **4** were reacted without solvent with phenyl acrylate[10] (1.0−1.3 equiv) and the reaction products were analyzed by GC-MS.[11] In all experiments, the structure of the major adducts (i.e., compounds **5**−**9** isolated by flash chromatography) results from a Michael alkylation of the starting imines. Indeed, under the reaction conditions, cyclization of the intermediate Michael adducts occurred spontaneously leading to lactams **5**−**9**.[12] No adducts resulting from a Diels−Alder reaction have been observed (Scheme 3).

The unsaturated imines **2a**−**c** and **4** show a low reactivity toward a very reactive Michael acceptor in comparison to the simple imines.[13] Indeed, we had to heat (55−70 °C) the reaction mixture for 16−24 h in order to obtain a total conversion of the imine. Even under these conditions (i.e., 70 °C, 24 h, 1.3 equiv of phenyl acrylate, neat), imine **2b** which bears a bulky *gem*-dimethyl group was not reactive enough toward phenyl acrylate, and isophorone **1b** (resulting from hydrolysis of imine **2b** during workup) was the major compound isolated after flash chromatography. Raising the temperature of the reactions resulted in degradation of the sensitive imines **2a**−**c** and **4**.

(6) Enones **1b**,**c** and **3** are commercially available while enone **1a** was prepared according to the literature: Warnhoff, E. W.; Martin, D. G.; Johnson, W. S. *Org. Synth. Collect. Vol. IV* **1967**, 162−165.

(7) White, W. A.; Weingarten, H. *J. Org. Chem.* **1967**, *32*, 213−214.

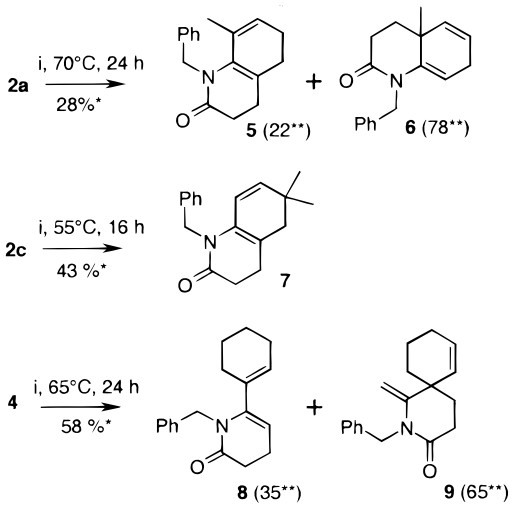
(8) ^{1}H and ^{13}C NMR spectra of compounds **2a**−**c** and **4** have shown that imines **2b** and **2c** consist of a mixture of *Z*:*E* isomers and that imines **2a** and **4** are single *E* isomers. The $A^{1,3}$ strain in imine **2a** prevents the formation of the *Z* isomer. **2a**: oil; EIMS *m*/*z* (rel int) 199 (M^+, 28), 91 (base), 65 (19) 51 (18); IR ($CHCl_3$) 1643, 1607, 1496, 1454 cm^{-1}; ^{1}H NMR (200 MHz, CD_3OD) δ 1.79 (tt, J_1 = 6.2 Hz, J_2 = 6.2 Hz, 2H), 1.87 (ddd, $J_1 \approx$ 1.5 Hz, $J_2 \approx$ 1.5 Hz, $J_3 \approx$ 1.5 Hz, 3H), 2.16 to 2.25 (m, 2H), 2.48 (t, J = 6.2 Hz, 2H), 4.65 (s, 2H), 6.33 to 6.36 (m, 1H), 7.15 to 7.33 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.66, 22.61, 25.32, 27.07, 53.87, 126.3, 127.4 (2C), 128.2 (2C), 134.8, 135.9, 140.9, 167.5. **2b** (mixture of *Z*:*E* isomers): oil; EIMS *m*/*z* (rel int) 227 (M^+, 17), 212 (45), 107 (10), 91 (base), 65 (15); IR (neat) 1636, 1607, 1495, 1453 cm^{-1}; ^{1}H NMR (200 MHz, CD_3OD) δ 0.99 (s, 6H), 1.87 and 1.91 (2s, 3H), 2.10 (d, J = 11.1 Hz, 2H), 2.27 (d, J = 10.3 Hz, 2H), 4.59 and 4.63 (2s, 2H), 6.02 and 6.44 (2q, J = 1.5 Hz, 1H), 7.10−7.35 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.04 and 24.61 (1C), 28.13, 28.62, 31.77, and 32.17 (1C), 39.54 and 44.73 (1C), 45.90 and 48.63 (1C), 53.81 and 54.56 (1C), 115.1, 126.4, 127.8 (2C), 128.3 (2C), 140.7 and 140.8 (1C), 146.3 and 150.3 (1C), 166.0 and 167.9 (1C). **2c** (mixture of *Z*:*E* isomers): oil; EIMS *m*/*z* (rel int) 213 (M^+, 19), 198 (11), 91 (base), 65 (17); IR (neat) 1632, 1607, 1495, 1454 cm^{-1}; ^{1}H NMR (200 MHz, CD_3OD) δ 1.10 and 1.12 (2s, 6H), 1.72 (t, J = 6.7 Hz, 2H), 2.59 (t, J = 6.7 Hz, 2H), 4.57 and 4.62 (2s, 2H), 6.03 and 6.31 (2d, J = 10.3 Hz, 1H), 6.24 and 6.47 (2d, J = 10.3 Hz, 1H), 7.10−7.38 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ (major isomer) 23.51, 28.10 (2C), 32.11, 35.73, 54.70, 125.2, 126.9 (2C), 128.1 (2C), 128.8, 140.3, 148.4, 166.8. **4**: oil; EIMS *m*/*z* (rel int) 213 (M^+, 43), 170 (38), 91 (base), 65 (19); IR ($CHCl_3$) 1655, 1614, 1495, 1451 cm^{-1}; ^{1}H NMR (200 MHz, CD_3OD) δ 1.51−1.78 (m, 4H), 2.04 (s, 3H), 2.14−2.40 (m, 4H), 4.62 (s, 2H), 6.42 (tt, J_1 = 1.5 Hz, J_2 = 4.1 Hz, 1H), 7.05−7.30 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.40, 21.93, 22.42, 24.66, 25.76, 54.67, 125.9, 127.1 (2C), 127.8 (2C), 130.2, 139.9, 140.8, 166.6.

(9) In the case of imine **2c**, only deuteration at the α′ position is possible.

(10) Reaction between methyl acrylate or methyl vinyl ketone and imines **2a**−**c** and **4** were also attempted but resulted in the degradation of the starting material. Consequently, much more reactive electrophilic olefins (i.e., phenyl acrylate and maleic anhydride) were tested. Phenyl acrylate was prepared according to the literature: Ahlbretch, A. H.; Codding, D. W. *J. Am. Chem. Soc.* **1953**, *75*, 984.

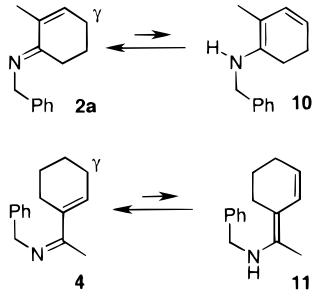
(11) This technique permits the separation of the regioisomers and the determination of their ratio. For further details, see the following reference: Jabin, I.; Revial, G.; Tomas, A.; Lemoine, P.; Pfau, M. *Tetrahedron: Asymmetry* **1995**, *6*, 1795−1812.

Scheme 3



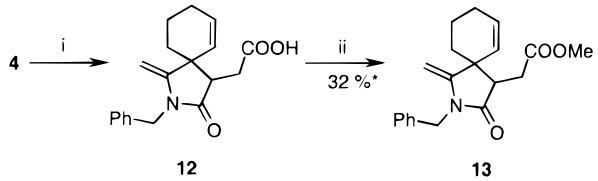
i: phenyl acrylate, neat.
*: overall yield calculated from the corresponding enone.
**: relative % by GC-MS determination.

The Michael alkylation took place either at the α′ position relative to the imine group (in the case of compounds **5**, **7**, and **8**) or at the α position (in the case of compounds **6** and **9**), but no alkylation at the γ position was observed. Formation of lactam **6** and spirolactam **9** is quite surprising since no deuteration at the γ position of imines **2a** and **4** was detected when the NMR study in CD_3OD was done.[14] This unexpected result indicates that tautomeric enamines **10** and **11** are present in the equilibrium even if deuteration at the γ position is too slow to be observed.



To confirm this result, another electrophilic olefin was tested with imine **4**. Thus, this latter was reacted with maleic anhydride and the resulting crude carboxylic acid **12** was directly esterified yielding after flash chromatography the spirolactam **13**[15] in 32% overall yield from enone **3** (Scheme 4).

Scheme 4



i: maleic anhydride (1.2 eq.), THF (*anh.*), rt, 16 h.
ii: DCC, DMAP, MeOH, rt, 16 h.
*: overall yield calculated from the corresponding enone **3**

GC-MS analysis of the crude spirolactam **13** revealed that it was the unique reaction product. In this case, Michael alkylation took place regioselectively at the α position, involving again addition of the secondary enamine **11** to the electrophilic olefin. Moreover, the reaction proceeds diastereoselectively since only one isomer was detected by GC-MS and NMR analyses.

In conclusion, we have shown that α,β-ethylenic imines are in equilibrium with their tautomeric secondary enamine forms. Under our reaction conditions, they react with electrophilic olefins, giving exclusively Michael adducts. The Michael addition occurs either at the α or α′ position relative to the imine group, and the regioselectivity at the α position was predicted by tautomeric deuteration.

(12) For further details on the mechanism, see the following references: Paulvannan, K.; Stille, J. R. *J. Org. Chem.* **1992**, *57*, 5319−5328. See also ref 5 and Pfau, M.; Jabin, I.; Revial, G. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1935−1936. Jabin, I.; Revial, G.; Tomas, A.; Lemoine, P.; Pfau, M. *Tetrahedron: Asymmetry* **1995**, *6*, 1795−1812. **5**: oil; EIMS *m*/*z* (rel int) 253 (M^+, 56), 162 (11), 91 (base), 65 (12); IR (neat) 1668, 1393 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.75−2.09 (m, 4H), 1.84 (s, 3H), 2.12−2.19 (m, 2H), 2.40−2.47 (m, 2H), 4.73 (s, 2H), 5.59−5.70 (m, 1H), 7.05−7.35 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.98, 22.26, 24.71, 27.58, 32.61, 48.10, 123.2, 124.2, 126.8, 127.5 (2C), 128.0 (2C), 128.9, 136.0, 137.8, 172.5. **6**: oil; EIMS *m*/*z* (rel int) 253 (M^+, 24), 238 (21), 160 (11), 91 (base), 65 (12); IR (neat) 1652, 1455, 1386 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.13 (s, 3H), 1.64 (ddd, $J_1 = 3.2$ Hz, $J_2 = 5.9$ Hz, $J_3 = 13.4$ Hz, 1H), 1.79−1.95 (m, 1H), 2.59−2.75 (m, 4H), 4.79 (d, $J = 16.0$ Hz, 1H), 5.01−5.08 (m, 1H), 5.09 (d, $J = 16.0$ Hz, 1H), 5.47 (ddd, $J_1 \approx 2$ Hz, $J_2 \approx 2$ Hz, $J_3 \approx 10$ Hz, 1H), 5.54−5.70 (m, 1H), 7.08−7.37 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.27, 26.28, 29.07, 32.33, 33.46, 46.91, 103.3, 121.8, 126.4 (2C), 126.6, 128.3 (2C), 133.7, 137.4, 140.5, 168.6. **7**: oil; EIMS *m*/*z* (rel int) 267 (M^+, 92), 252 (62), 224 (21), 91 (base); IR (neat) 1755, 1731, 1666, 1594 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.97 (s, 6H), 2.16 (s, 2H), 2.32 (t, $J = 7.5$ Hz, 2H), 2.66 (t, $J = 7.5$ Hz, 2H), 4.94 (s, 2H), 5.50 (d, $J = 10.2$ Hz, 1H), 5.82 (d, $J = 9.7$ Hz, 1H), 7.13 to 7.44 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.18, 27.32, 30.86, 31.54, 41.78, 45.02, 113.2, 117.6, 126.4 (2C), 126.7, 128.3 (2C), 130.3, 137.9, 138.2, 170.0. **8**: oil; EIMS *m*/*z* (rel int) 268 (22), 267 (M^+, base), 266 (31), 224 (15), 189 (17), 91 (67); IR (neat) 1755, 1713, 1660 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.54−1.59 (m, 4H), 1.79−2.09 (m, 4H), 2.20 (ddd, $J_1 \approx 6$ Hz, $J_2 \approx 6$ Hz, $J_3 \approx 9$ Hz, 2H), 2.49 (dd, $J_1 = 7.0$ Hz, $J_2 = 9.1$ Hz, 2H), 4.77 (s, 2H), 5.16 (t, $J = 5.4$ Hz, 1H), 5.58 (tt, $J_1 \approx 2$ Hz, $J_2 \approx 2$ Hz, 1H), 6.97−7.41 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.21, 21.80, 22.34, 24.99, 28.20, 32.09, 45.93, 107.2, 126.7, 127.1 (2C), 128.1 (2C), 129.3, 133.5, 138.7, 144.9, 171.7. **9**: oil; EIMS *m*/*z* (rel int) 268 (16), 267 (M^+, 92), 252 (21), 239 (50), 238 (24), 91 (base); IR (neat) 1660, 1614, 1454 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.29 to 2.05 (m, 8H), 2.61 to 2.75 (m, 2H), 4.28 (d, $J = 1.6$ Hz, 1H), 4.43 (d, $J = 1.1$ Hz, 1H), 4.95 (s, 1H), 4.97 (s, 1H), 5.30−5.40 (m, 1H), 5.80 (dt, $J_1 = 3.8$ Hz, $J_2 = 10.2$ Hz, 1H), 7.05−7.35 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.88, 25.18, 28.49, 31.49, 32.46, 38.77, 47.08, 96.60, 126.5 (2C), 126.7, 128.3 (2C), 128.5, 132.5, 137.3, 149.2, 169.1.

(13) See ref 5.

(14) No clear deuteration at the γ position occurred even after 12 days in CD_3OD.

(15) **13**: oil; EIMS *m*/*z* (rel int) 326 (22), 325 (M^+, base), 265 (24), 252 (22), 91 (88); IR (neat) 1732, 1644 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.10 to 2.10 (m, 6H), 2.41 (dd, $J_1 = 7.5$ Hz, $J_2 = 15.6$ Hz, 1H), 2.79 (dd, $J_1 = 7.5$ Hz, $J_2 = 16.1$ Hz, 1H), 3.15 (t, $J = 7.5$ Hz, 1H), 3.67 (s, 3H), 4.14 (d, $J = 1.6$ Hz, 1H), 4.31 (d, $J = 2.1$ Hz, 1H), 4.54 (d, $J = 15.6$ Hz, 1H), 4.71 (d, $J = 15.6$ Hz, 1H), 5.40 (dd, $J_1 = 1.6$ Hz, $J_2 = 10.2$ Hz, 1H), 5.92 (dt, $J_1 = 3.8$ Hz, $J_2 = 9.7$ Hz, 1H), 7.10 to 7.30 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.06, 24.30, 28.50, 29.82, 43.92, 45.93, 49.10, 51.73, 88.91, 127.2 (2C), 128.5 (2C), 129.4, 131.3, 136.0, 151.7, 172.3, 174.2.

Future efforts will be directed at the extension of this work to chiral imines of cyclohexen-2-ones.

Supporting Information Available: Detailed descriptions of experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org. This material is also available from the author.

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