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Condensation of Chiral Imines and Chiral β-Enaminoesters with Maleic and Citraconic Anhydrides

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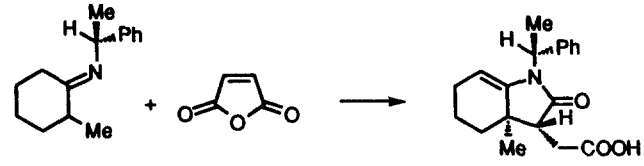
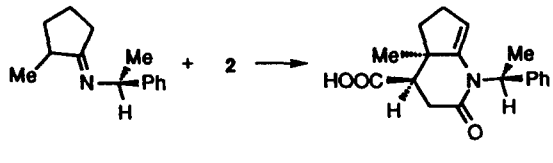
Abstract *: Condensations of chiral imines* **1** *and* **4**, *and chiral enaminoesters* **10** *and* **13**, *with maleic and citraconic anhydrides were reported. These experimental outcomes can be rationalized by invoking the compact, endo-approaches of the two reactants* **18**. © 1997 Published by Elsevier Science Ltd.

The Michael-type alkylation of chiral imines, and chiral enaminoesters, derived from optically active 1-phenylethylamine, has been documented for numerous examples.[1] In this respect, the use of very reactive maleic anhydride, and derivatives, as Michael acceptors, seemed highly promising. In a preliminary report, we have thus established that addition of imine **1** to maleic anhydride **2** afforded, with a high degree of stereocontrol, the bicyclic adduct **3**.[2] In this paper, we report the comparative reactivities of chiral imines **1** and **4**, and of chiral enaminoesters **10** and **13**, toward maleic and citraconic anhydrides. We show that these condensations are in general highly regio- and stereoselective, allowing the enantioselective access to various five- and six-membered, nitrogen-containing heterocycles. We show also that the stereochemical findings in these reactions can be readily interpreted, on the basis of the above mechanistic proposals.[1,2]

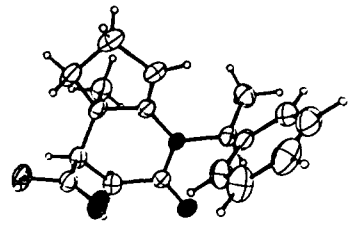


1 **2** **3**

When the five-membered chiral imine **4** was added to electrophile **2** (THF, 1 h at 20 °C), adduct **5**[3] was obtained as a single isomer, in an almost quantitative yield. The structure of **5** was unambiguously determined through an X-ray crystal structure analysis.



4 **5**



X-ray crystal structure of **5**

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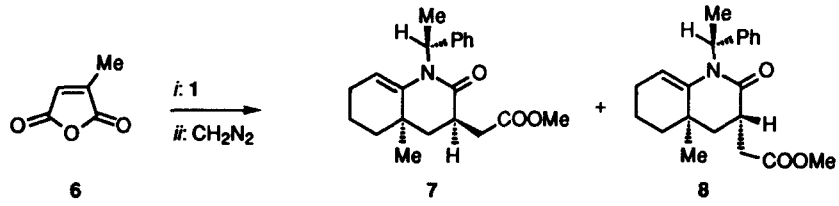
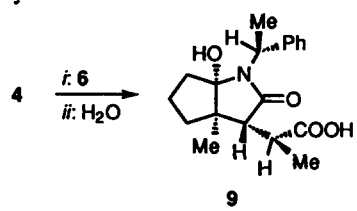
Addition of imine **1** to citraconic anhydride **6** (4 h in THF at reflux) furnished, after esterification of the crude with CH_2N_2, a mixture of adducts **7**[4] and **8**, in the ratio of 4:1, respectively, with a 65 % combined yield. The relative configuration at the two newly created stereogenic centers in **7** and **8** was established by ^1H NMR spectroscopy, including NOE experiments.

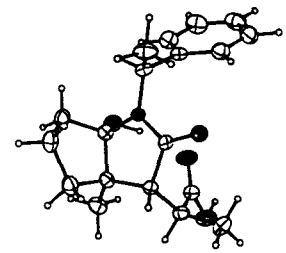


6 **7** **8**

When imine **4** was added to **6** (24 h in THF at reflux, followed by neutral aqueous treatment at 20 °C) the crystalline adduct **9**[5] was isolated with a 35 % yield, along with unidentified side compounds. The configuration at the four newly created, contiguous stereogenic centers in **9** was deduced from the X-ray diffraction analysis.

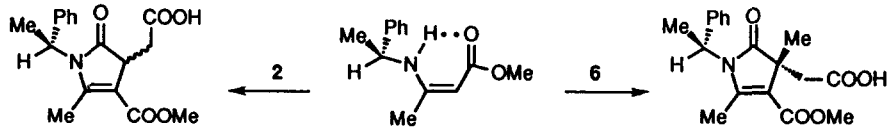


9



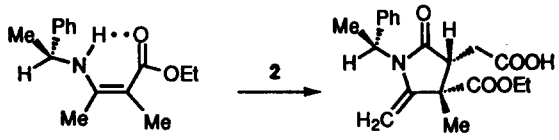
X-ray crystal structure of **9**

Condensation of chiral enaminoester **10**[6] with **2** (THF, 2 h at 20 °C) gave with a 69 % yield an equimolar mixture of diastereomeric acids **11**[7]. Addition of this enaminoester to anhydride **6** (12 h in refluxing THF) led with 73 % yield to adduct **12**[8]. The configuration depicted at the newly created stereogenic center in **12**, although not definitely established, rests on the putative mechanism of the present Michael process (*vide infra*).



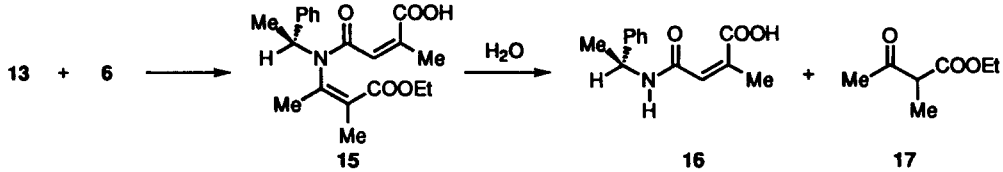
11 **10** **12**

When enaminoester **13**[9] was exposed to anhydride **2** (THF, 12 h at 20 °C), the monocyclic adduct **14**[10] was obtained as a single diastereomer with a 70 % yield. The relative stereochemical relationship between the two newly created stereogenic centers in **14** was established by ^1H NMR spectroscopy, including NOE experiments.



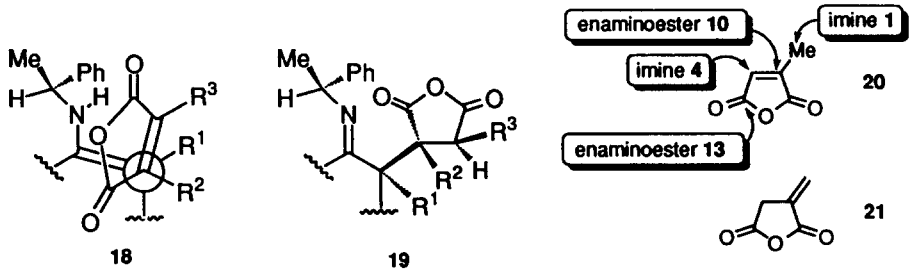
13 14

Addition of enaminoester **13** to citraconic anhydride **6** (5 h in refluxing THF) afforded water-sensitive adduct **15** (not fully characterized). Hydrolysis, in neutral conditions (10 min at 20 °C), of this crude adduct then furnished acid-amide **16**[11] (60 % yield) and ketoester **17** (40 % yield).



15 16 17

DISCUSSION. The Michael-type alkylation of chiral imines and chiral enaminoesters, derived from 1-phenylethylamine, constitutes one of the most efficient methods for the stereocontrolled elaboration of quaternary carbon centers.[1] Through this work, we have shown that one or two additional stereogenic centers can be also created by using maleic anhydride or citraconic anhydride as Michael acceptors. These addition reactions were in general highly regio-, enantio-, and diastereoselective, reflecting an *aza-ene-synthesis-like*, cyclic transition state.[2] With the exception of addition **1** + **6** → **7** + **8**, all the above outcomes can be rationalized by invoking the compact, "*endo*" approaches of the reactants **18**, in which the nucleophilic partners (more substituted secondary enamines: R^1 = Me, or enaminoesters: R^1 = COOR) and the anhydrides are *synclinal*, with a *syn*-arrangement of the carbonyl groups of the electrophiles and the nitrogen atom of enamines,[2] leading to intermediary derivatives **19**. Intramolecular nucleophilic attack of one of the two carbonyl groups of **19** by the imine nitrogen atom then delivered the observed adducts. Quite surprisingly, citraconic anhydride **6** exhibited four distinct electrophilic sites, the regioselectivity in their attack depending on the nature of the nucleophilic partner (**20**). In this respect, it should be pointed out that the electrophile involved in addition **1** + **6** → **7** + **8** (formal attack of the methyl group of **6**) was not citraconic anhydride itself, but the itaconic anhydride tautomer **21**.



18 19 20 21

NOTES AND REFERENCES

1 Reviews: d'Angelo, J.; Desmaële, D.; Dumas, F.; Guingant, A. *Tetrahedron: Asymmetry*, **1992**, *3*, 459-505. d'Angelo, J.; Cavé, C.; Desmaële, D.; Dumas, F. *Trends in Organic Synthesis*, Pandalai, S.G., Ed.; Trivandrum (India), **1993**, *4*, 555-616.

2 Cavé, C.; Desmaële, D.; d'Angelo, J.; Riche, C.; Chiaroni, A. *J. Org. Chem.*, **1996**, *61*, 4361-4368.

3 **5**: mp 168-170 °C (AcOEt); IR: 3446, 1727, 1595 cm^{-1}; $[\alpha]_D^{20}$ -17.8 (c 6.2, MeOH); ^1H NMR (200 MHz, $CDCl_3$) δ: 9.3 (broad s, 1H), 7.51-7.20 (m, 5H), 6.25 (q, *J* = 7.1 Hz, 1H), 4.46 (dd, *J* = 2.6, 1.9 Hz, 1H), 2.85-2,67 (m, 3H), 2.33-1.67 (m, 4H), 1.61 (d, *J* = 7.1 Hz, 3H), 1.25 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 178.2 (C), 168.3 (C), 140.9 (C), 140.7 (C), 128.2 (2 CH), 127.4 (CH), 126.2 (2 CH), 108.4 (CH), 50.1 (CH), 46.7 (CH), 46.1 (C), 34.0 (CH_2), 32.5 (CH_2), 28.1 (CH_2), 23.9 (CH_3), 15.1 (CH_3); Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 4.67. Found: C, 72.32; H, 7.10; N, 4.60.

4 **7**: amorphous solid; IR: 1742, 1669, 1640 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 7.32-7.18 (m, 5H), 6.18 (q, *J* = 7.1 Hz, 1H), 4.85 (dd, *J* = 5.5, 2.8 Hz, 1H), 3.70 (s, 3H), 2.97 (m, 1H), 2.83 (dd, *J* = 6.0, 4.0 Hz, 2H), 2.10-1.40 (m, 8H), 1.59 (d, *J* = 7.1 Hz, 3H), 1.17 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 172.6 (C), 170.4 (C), 142.4 (C), 139.3 (C), 128.3 (2 CH), 126.2 (CH), 125.7 (2 CH), 109.7 (CH), 51.6 (CH), 51.4 (CH_3), 40.6 (CH_2), 38.3 (CH_2), 36.9 (CH_2), 36.1 (CH), 33.2 (C), 24.8 (CH_2), 23.0 (CH_3), 17.9 (CH_2), 15.4 (CH_3).

5 **9**: mp 169-171 °C (AcOEt); IR: 3460, 3400-3100, 1721, 1658 cm^{-1}; $[\alpha]_D^{20}$ -37.1 (c 2.1, MeOH); ^1H NMR (200 MHz, $CDCl_3$) δ 12.0 (broad s, 1H), 7.35-7.15 (m, 2H), 7.05-6.90 (m, 3H), 4.65 (q, J = 7.1 Hz, 1H), 4.30 (broad s, 1H), 2.60-2.40 (m, 1H), 2.15 (d, J = 5.5 Hz, 1H), 1.80-1.30 (m, 6H), 1.45 (d, J = 7.1 Hz, 3H), 1.15 (d, J = 7.0 Hz, 3H), 0.75 (s, 3H); Anal. Calcd for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.22. Found: C, 68.59; H, 7.71; N, 4.19.

6 **10**: prepared from corresponding β-ketoester and (*S*)-1-phenylethylamine (THF, 12 h at reflux, 71 %); oil; IR: 3292, 1653, 1605 cm^{-1}; $[\alpha]_D^{20}$ + 589 (c 5.6, MeOH); ^1H NMR (200 MHz, $CDCl_3$) δ 8.8 (d, J = 6.0 Hz, 1H), 7.26-7.07 (m, 5H), 4.52 (q, J = 6.0 Hz, 1H), 4.38 (s, 1H), 3.55 (s, 3H), 1.65 (s, 3H), 1.40 (d, J = 6.0 Hz, 3H) ; ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.1 (C), 161.7 (C), 145.0 (C), 128.9 (2 CH), 127.2 (CH), 125.5 (2 CH), 82.9 (CH), 52.9 (CH_3), 50.1(CH), 25.0 (CH_3), 19.8 (CH_3); Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.23; H, 7.76; N, 6.39. Found: C, 71.33; H, 7.85; N, 6.42.

7 **11**: mp 137-139 °C (AcOEt); IR: 3600-3100, 1731, 1666, 1613 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 13.0 (broad s, 1H), 7.35-7.25 (m, 5H), 5.64 (q, J = 7.1 Hz, 1H), 3.70 (s, 3H), 3.52 and 3.46 (m, 1H), 3.24-3.10 (m, 2H), 2.17 and 2.16 (s, 3H), 1.75 and 1.74 (d, J = 7.1 Hz, 3H).

8 **12**: amorphous solid; IR: 3600-3100, 1730-1680, 1622 cm^{-1}; $[\alpha]_D^{20}$ - 55.2 (c 12.3, EtOH); ^1H NMR (200 MHz, $CDCl_3$) δ 10.0 (broad s, 1H), 7.40-7.15 (m, 5H), 5.70 (q, J = 7.0 Hz, 1H), 3.70 (s, 3H), 3.20 (d, J = 18.0 Hz, 1H), 2.95 (d, J = 18.0 Hz, 1H), 2.15 (s, 3H), 1.60 (d, J = 7.0 Hz, 3H), 1.40 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 181.9 (C), 175.7 (C), 164.5 (C), 155.5 (C), 140.1 (C), 128.6 (2 CH), 126.7 (CH), 126.1 (2 CH), 110.9 (CH), 51.5 (CH_3), 49.0 (CH), 46.5 (CH_2), 40.1 (C), 20.9 (CH_3), 15.0 (CH_3), 13.8 (CH_3).

9 **13**: prepared from corresponding β-ketoester and (*S*)-1-phenylethylamine (THF, 12 h at reflux, 69 %); oil; IR: 3292, 1653, 1607 cm^{-1}; $[\alpha]_D^{20}$ + 299 (c 5.5, MeOH); ^1H NMR (200 MHz, $CDCl_3$) δ 9.7 (d, J = 6.0 Hz, 1H), 7.40-7.20 (m, 5H), 4.70 (q, J = 6.0 Hz, 1H), 4.20 (q, J = 6.0 Hz, 2H), 1.80 (s, 3H), 1.75 (s, 3H), 1.55 (d, J = 6.0 Hz, 3H), 1.30 (t, J = 6.0 Hz, 3H) ; ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.9 (C), 158.9 (C), 145.6 (C), 128.5 (2 CH), 126.7 (CH), 125.3 (2 CH), 87.5 (C), 58.3 (CH_2), 53.0 (CH), 25.0 (CH_3), 15.6 (CH_3), 14.5 (CH_3), 12.4 (CH_3).

10 **14**: amorphous solid; IR: 3600-3100, 1740, 1722, 1643 cm^{-1}; $[\alpha]_D^{20}$ - 7.5 (c 1.8, EtOH); ^1H NMR (400 MHz, $CDCl_3$) δ 9.8 (broad s, 1H), 7.35-7.26 (m, 5H), 5.66 (q, J = 7.2 Hz, 1H), 4.24 (d, J = 3.0 Hz, 1H), 4.15. (q, J = 7.2 Hz, 2H), 4.10 (d, J = 3.0 Hz, 1H), 3.13 (dd, J = 5.5 Hz, J = 5.6 Hz, 1H), 2.96 (dd, J = 16.7 Hz, J = 5.6 Hz, 1H), 2.39 (dd, J = 16.7 Hz, J = 5.5 Hz, 1H), 1.70 (d, J = 7.2 Hz, 3H), 1.50 (s, 3H), 1.21 (t, J = 7.2 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 175.3 (C), 174.9 (C), 171.2 (C), 146.5 (C), 139.1 (CH_2), 128.6 (2 CH), 127.3 (CH), 126.4 (2 CH), 89.5 (C), 61.7 (CH_2), 51.5 (C) 49.8 (CH), 46.8 (CH), 31.4 (CH_2), 20.6 (CH_3), 14.2 (CH_3), 14.0 (CH_3).

11 **16**: mp 143-147 °C (AcOEt); IR: 3460, 3400-3100, 1721, 1658 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.4 (broad s, 1H), 7.3 -7.20 (m, 5H), 6.60 (broad s, 1H), 6.28 (q, J = 1.5 Hz, 1H); 5.16 (q, J = 7.1 Hz, 1H), 2.12 (d, J = 1.5 Hz, 3H), 1.58 (d, J = 7.1 Hz, 3H); Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.91; H, 6.49; N, 6.00. Found: C, 66.69; H, 6.53; N, 5.96.

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