ORGANIC LETTERS

2004
Vol. 6, No. 14
2421−2424

Asymmetric Michael Reaction Involving Chiral Imines/Secondary Enamines: Stereocontrolled Synthesis of 2,2-Disubstituted Tetrahydrothiophen-3-ones

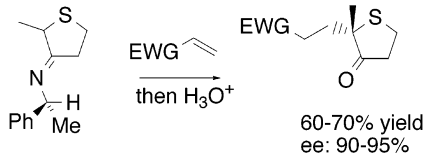
Didier Desmaële,*,† Sandrine Delarue-Cochin,† Christian Cavé,† Jean d'Angelo,† and Georges Morgant†,‡

Unité de Chimie Organique associée au CNRS (UMR 8076) and Laboratoire de Cristallographie Bioinorganique, Centre d'Etudes Pharmaceutiques, Université Paris-Sud, 5 rue J.-B. Clément, 92296 Châtenay-Malabry, France

didier.desmaele@cep.u-psud.fr

Received May 3, 2004

ABSTRACT



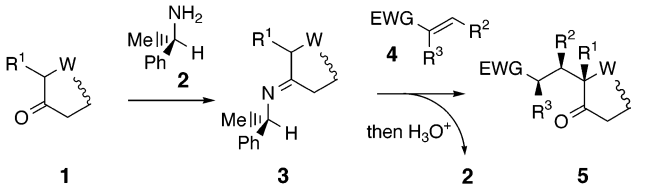
The asymmetric Michael reaction involving a chiral imine derived from 2-methyltetrahydrothiophenone-3-one and enantiopure (*R*)-1-phenylethylamine with a variety of electrophilic alkenes furnished 2,2-disubstituted tetrahydrothiophenone-3-ones with good yields and excellent stereoselectivity.

Since its discovery in 1985, the asymmetric Michael reaction involving chiral imines/secondary enamines derived from enantiopure 1-phenylethylamine has played a paramount role in organic synthesis, particularly for the stereoselective construction of quaternary carbon centers.[1] Besides outstanding regio- and stereochemical outcomes and a great tolerance regarding the nature of both reagents **1** and **4**, this reaction offers the advantage of using a simple experimental protocol associated with mild operating conditions and an inexpensive, readily available chiral auxiliary (Scheme 1).

Landmark examples of this reaction utilizing α-heterosubstituted imines, closely related to our synthetic objective detailed below, are reported in Scheme 2.[2,3,4]

As part of our program aimed at developing synthetic applications of the present methodology, we recently became interested in the stereocontrolled elaboration of 2,2-disubstituted tetrahydrothiophen-3-ones, which have become valuable intermediates in the synthesis of 17-thiasteroids,[5] thianucleosides,[6] and thiotetronic acids.[7] Preliminary results from this endeavor are reported herein.

Scheme 1. Asymmetric Michael Reaction Involving Chiral Imines



1 3 2 5

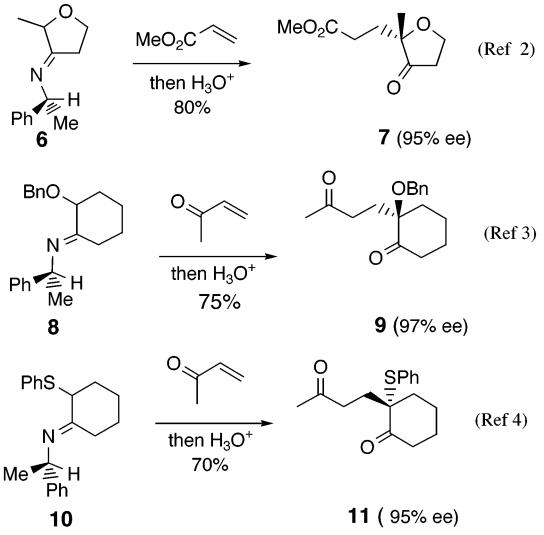
ee = 90-98%
de > 95%

R^1 = alkyl, OR, SR, CO_2R, CN
W = C, O
EWG = COR, CO_2R, CN, NO_2, SO_2R
R^2 = H, Me
R^3 = H, Me, OAc, NHAc, Cl

† Unité de Chimie Organique (UMR 8076).
‡ Laboratoire de Cristallographie Bioinorganique

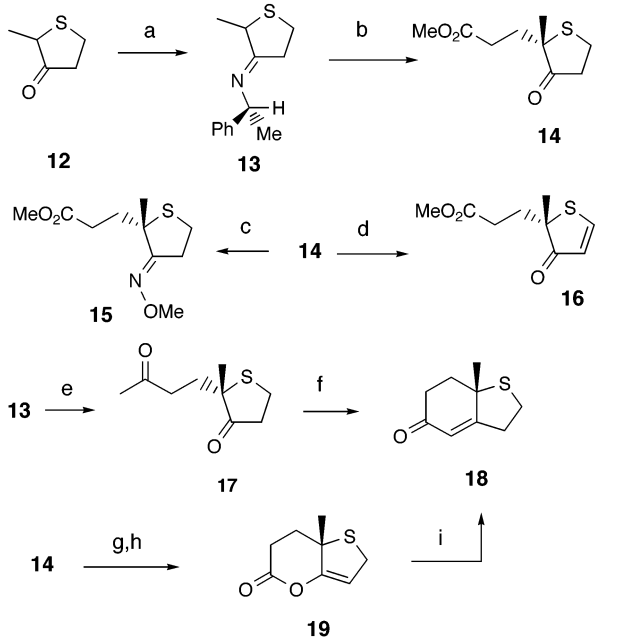
10.1021/ol0491944 CCC: $27.50
Published on Web 06/11/2004

Scheme 2. Michael Additions of α-Heterosubstituted Imines



We began our work with the preparation of chiral imine **13**, starting from commercially available 2-methyltetrahydrothiophen-3-one **12** and enantiopure (*R*)-1-phenylethylamine **2** (cyclohexane, 100 h at 20 °C, in the presence of a mixture of 5 Å molecular sieves, basic Al_2O_3, and SiO_2[1q]). Addition of crude imine **13** to methyl acrylate (neat, 70 h at 45 °C) furnished, after hydrolytic workup (20% aqueous AcOH, 20 °C), adduct (*S*)-**14** in 63% overall yield. The ee in **14** (≥95%) was determined by ^{1}H NMR spectroscopy, with addition of Eu(hfc)$_3$ as a shift reagent, at the level of

Scheme 3. Condensation of Imine **13** with Methyl Acrylate and Methyl Vinyl Ketone[a]



[a] Reagents and conditions: (a) **2**, catalyst, 20 °C. (b) H_2C=-$CHCO_2Me$, 45 °C, then 20% AcOH (63% for two steps). (c) $MeONH_3Cl$, AcONa (90%). (d) NCS, CCl_4 (83%). (e) MVK, 20 °C, then 20% AcOH (25%). (f) 3% KOH, MeOH, 60 °C. (g) (i) aq NaOH; (ii) 2 N HCl (quantitative). (h) Ac_2O, AcONa (70%). (i) 2 equiv of $LiCH_2PO(OMe)_2$, THF, −78 °C (57%).

the *O*-methyloxime derivative **15** (prepared as a single (*E*)-isomer by condensing **14** with $MeONH_3^+Cl^-$ in the presence of AcONa). The configuration of **14** was founded on the heuristic stereochemical rule we have proposed in this series.[1] Conversion of **14** into enone (*S*)-**16**, a potential intermediate in the synthesis of thiotetronic acids was achieved smoothly by subjecting **14** to *N*-chlorosuccinimide (CCl_4, 15 min at 20 °C, 83% yield). Condensation of **13** with methyl vinyl ketone (Et_2O, 24 h at 20 °C, then 20% aqueous AcOH) led to adduct (*S*)-**17** in 25% yield, along with a substantial amount of side products. This disappointing result can be interpreted by invoking a competitive retro-Michael process that possibly affects the regio- and stereochemical features of the reaction,[11] an assumption reinforced by the fact that the condensation of imine **6**, the oxygen counterpart of **13**, with methyl vinyl ketone led to a three-component mixture consisting of regioisomeric "monoalkylated" and "dialkylated" adducts.[2] Cyclization of **17** (3% KOH in MeOH, 2 h, 60 °C) next furnished bicyclic enone (*S*)-**18**, though contaminated by minor impurities. In view of the cumbersome separation of **17** from byproducts, an alternative synthetic route to **18**, a potential CD synthon for the construction of 17-thiasteroids, was developed, starting from keto ester (*S*)-**14**. Saponification of latter compound (NaOH, MeOH then 2 N HCl) gave the corresponding keto acid, which was then converted into enol lactone (*S*)-**19** (Ac_2O, AcONa, 2 h at 120 °C). Treatment of **19** with 2 equiv of $LiCH_2PO(OMe)_2$ (1 h, −78 °C, followed by 1 h at −20 °C,

(1) Reviews: (a) d'Angelo, J.; Desmaële, D.; Dumas, F., Guingant, A. *Tetrahedron: Asymmetry* **1992**, *3*, 459−505. (b) d'Angelo, J.; Cavé, C.; Desmaële, D.; Dumas, F. In *Trends in Organic Synthesis*; Pandalai, S. G., Ed.; Trivandrum: India, 1993; Vol 4, pp 555−615. For recent developments, see: (c) Desmaële, D.; Cavé, C.; d'Angelo, J.; Dumas, F. *Enantiomer* **2001**, *6*, 289−298. (d) Keller, L.; Camara, C.; Pinheiro, A.; Dumas, F.; d'Angelo, J. *Tetrahedron Lett.* **2001**, *42*, 381−383. (e) Tori, M.; Makino, G.; Hisazuni, K.; Sono, M.; Nakashima, K. *Tetrahedron: Asymmetry* **2001**, *12*, 301−307. (f) Schenato, R. A.; dos Santos, E. M.; Tenius, B. S. M.; Costa, P. R. R.; Caracelli, I.; Zukerman-Schpector, J. *Tetrahedron: Asymmetry* **2001**, *12*, 579−584. (g) Nour, M.; Tan, K.; Jankowski, R.; Cavé, C. *Tetrahedron: Asymmetry* **2001**, *12*, 765−769. (h) Christoffers, J.; Mann, A.; *Chem. Eur. J.* **2001**, *7*, 1014−1027. (i) Keller, L.; Dumas, F.; d'Angelo, J. *Tetrahedron Lett.* **2001**, *42*, 1911−1913. (j) Révial, G.; Jabin, I.; Redolfi, M.; Pfau, M.; *Tetrahedron: Asymmetry* **2001**, *12*, 1683−1688. (k) Ishizaki, M.; Iwahara, K.; Niimi, Y.; Satoh, H.; Hoshino, O. *Tetrahedron* **2001**, *57*, 2729−2738. (l) Tan, K.; Alvarez R.; Nour, M.; Cavé, C.; Chiaroni, A.; Riche, C.; d'Angelo, J. *Tetrahedron Lett.* **2001**, *42*, 5021−5023. (m) Jabin, I.; Révial, G.; Pfau, M.; Netchitaïlo, P. *Tetrahedron: Asymmetry* **2002**, *13*, 563−567. (n) Camara, C.; Joseph, D.; Dumas, F.; d'Angelo, J.; Chiaroni, A. *Tetrahedron Lett.* **2002**, *43*, 1445−1448. (o) Thominiaux, C.; Chiaroni, A.;. Desmaële, D. *Tetrahedron Lett.* **2002**, *43*, 4107−4110. (p) Christoffers, J.; Scharl, H. *Eur. J. Org. Chem.* **2002**, 1505−1508 (q) Keller, L.; Dumas, F.; d'Angelo, J. *Eur. J. Org. Chem* **2003**, 2488−2497. (r) Camara, C.; Keller, L.; Dumas, F. *Tetrahedron: Asymmetry* **2003**, *14*, 3263−3266. (s) Danet, M.; Normand-Bayle, M.; Mahuteau, J.; d'Angelo, J.; Morgant. G.; Desmaële, D. *Eur. J. Org. Chem.* **2004**, 1911−1922. (t) Hendra, F.; Nour, M.; Baglin, I.; Morgant, G.; Cavé, C. *Tetrahedron: Asymmetry* **2004**, *15*, 1027−1032.

(2) Desmaële, D.; d'Angelo, J.; Bois, C. *Tetrahedron: Asymmetry* **1990**, *1*, 759−762.

(3) Desmaële, D.; d'Angelo, J. *Tetrahedron Lett.* **1989**, *30*, 345−348.

(4) Nour, M.; Tan, K.; Cavé, C.; Villeneuve, D.; Desmaële, D.; d'Angelo, J.; Riche, C. *Tetrahedron: Asymmetry* **2000**, *11*, 2015−2021.

(5) Jogdeo, P. S.; Bhide, G. V. *Steroids* **1980**, *35*, 133−138. See also: Cachoux, F.; Ibrahim-Ouali, M.; Santelli, M. *Synlett* **2000**, 418−420.

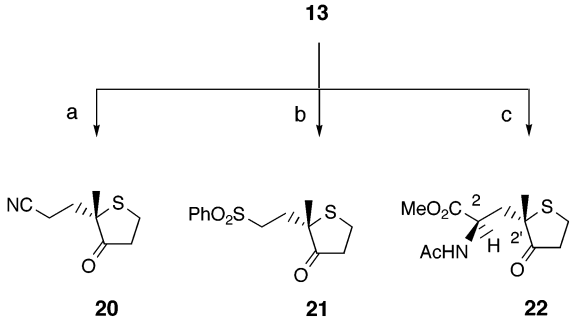
(6) Paquette, L. A. *Austr. J. Chem.* **2004**, *57*, 7−17.

(7) Jones, S. M.; Urch, J. E.; Brun, R.; Harwood, J. L.; Berry, C.; Gilbert, I. H. *Bioorg. Med. Chem.* **2004**, *12*, 683−692.

then NH_4Cl quench) furnished enone (*S*)-**18** (ee > 95%) with an overall yield of ca. 40%.[8] An attempt to improve this yield, adding 1 equiv of acetic acid according to the procedure described by Aristoff, was unsuccessful (Scheme 3).[9]

Coupling of imine **13** with acrylonitrile, phenyl vinyl sulfone, and methyl 2-acetamidoacrylate was also investigated. Employing the operating conditions developed for conversion [**13** → **14**] afforded the corresponding adducts in good yield and excellent stereoselectivity: (*S*)-**20** (69% yield, 90% ee), (*S*)-**21** (65% yield, >95% ee), and (2*R*,2′*S*)-**22** (58% yield, >95% de, >95% ee). The enantioselectivity in these adducts was established by ^{1}H NMR spectroscopy with addition of Eu(hfc)$_3$; Eu(fod)$_3$ was used to determine the de of **22** (Scheme 4).

Scheme 4. Condensation of Imine **13** with Various Electrophilic Alkenes[a]



[a] Reagents and conditions: (a) $H_2C{=}CHCN$, 45 °C, then 20% AcOH (69%); (b) $H_2C{=}CHSO_2Ph$, 45 °C, then 20% AcOH (65%); (c) $H_2C{=}C(NHAc)CO_2Me$, 45 °C, then 20% AcOH (58%).

The stereochemistry in compound **22** was determined by means of a single-crystal X-ray diffraction analysis,[10,11] including the absolute configuration, on the basis of the anomalous diffusion of the sulfur atom (Figure 1).[12]

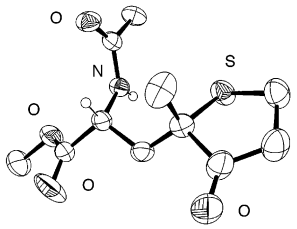
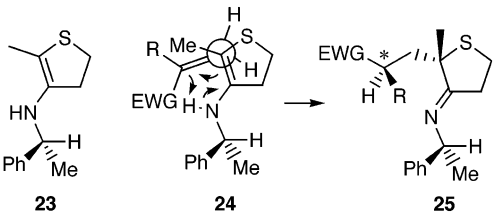


Figure 1. X-ray crystal structure of adduct **22** with labeled heteroatoms. All but hydrogen atoms attached to the tertiary carbon and nitrogen centers have been omitted for clarity.

As delineated below, the present Michael reaction involves a highly ordered transition state associated with a pericyclic process that ensures a predictable stereochemical course and a high level of stereoselectivity. It may be safely assumed that the nucleophilic partner implicated in these additions is the more substituted secondary enamine **23**, in tautomeric equilibrium with starting imine **13**. The remarkable stereochemical outcomes observed can be interpreted by invoking a syn approach between **23** and the electrophilic alkene partner and the related six-membered "aza-ene-synthesis-like" transition state **24**. According to such a model, the alkylation takes place predominantly on the less hindered (*Si*) π-face of enamine **23** (anti to the bulky phenyl group of the chiral amine moiety, portrayed in its energetically preferred conformation minimizing the A^{1,3} allylic strain, namely, the H atom eclipsing the five-membered ring).[13] This secures the (*S*)-configuration at the newly created quaternary carbon center in adducts **25**, which upon subsequent hydrolytic cleavage furnished products **14**, **17**, and **20**−**22**. Stereochemical control at the asterisked tertiary carbon center in adduct **25** (R = NHAc, EWG = CO_2Me), progenitor of product (2*R*,2′*S*)-**22**, originates from a concerted transfer of the proton borne by the N-atom of secondary enamine **23** to the α-carbon atom of methyl 2-acetamidoacrylate, the ester group of the latter facing the nitrogen atom of the enamine partner (endo arrangement) (Scheme 5).

Scheme 5. Stereochemical Course of the Asymmetric Michael Reaction



In summary, we have shown that the asymmetric Michael addition of chiral imine **13** to electrophilic alkenes provides a facile synthetic route to enantiopure 2,2-disubstituted

(8) Henrick, C. A.; Böhme, E.; Edwards, J. A.; Fried, J. H. *J. Am. Chem. Soc.* **1968**, *90*, 5926−5927.

(9) Aristoff, P. A. *J. Org. Chem.* **1985**, *50*, 1765−1766.

(10) Crystal data for **22**: white crystal with dimensions of 0.21 × 0.24 × 0.28 mm; mp = 99−100 °C (diethyl ether). $C_{11}H_{17}NO_4S$, M = 259.32: monoclinic, space group *P* 21, *Z* = 2, *a* = 8.252(2), *b* = 9.321(5), *c* = 9.521(2) Å, α = γ = 90°, β = 115.53(5)°, *V* = 660.1(7) Å^3, *d* = 1.300 g cm^{-3}, *F*(000) = 274, λ = 0.710693 Å (Mo Kα), μ = 0.248 mm^{-1}; 3795 reflections measured (−11 ≤ *h* ≤ 10, −12 ≤ *k* ≤ 13, 0 ≤ *l* ≤ 13) on a Nonius CAD4 diffractometer. The structure was solved with SIR92[11a] and refined with CRYSTALS.[11b,c] Hydrogen atoms riding. Refinement converged to *R* = 0.0467 for the 1592 reflections having *I* ≥ 2σ(*I*) (155 parameters), and w*R* = 0.0585, GOF *S* = 1.0901. Residual electron density: −0.32 and 0.48 e Å^3. The crystal cohesion is ensured by one hydrogen bond involving N [for N−H···O=C(Me)NH: 2.0145 Å, 176.53°, (symmetry code *i*: −*x*, *y* + 1/2, −*z* + 2)]. Crystallographic data is being deposited with Cambridge Crystallographic Data Centre (CCDC 235923).

(11) (a) *SIR92: A Program for Crystal Structure Solution*; Altomare, A.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A. *J. Appl. Crystallogr.* **1993**, *26*, 343−350. (b) *CAD4 Express Software*; Enraf-Nonius: Delft, The Netherlands, 1994. (c) *CAMERON: A Molecular Graphics Package*. Watkin, D. M.; Pearce, L.; Prout, C. K.; Chemical Crystallography Laboratory: University of Oxford, UK, 1993.

(12) FLACK X-PARAMETER: (a) Flack, H. D. *Acta Crystallogr., Sect. A* **1983**, *39*, 876−881. (b) Bernardinelli, G.; Flack, H. D. *Acta Crystallogr., Sect. A* **1985**, *41*, 500−511.

(13) Tran Huu Dau, M. E.; Riche, C.; Dumas, F.; d'Angelo, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1059−1064.

tetrahydrothiophen-3-ones. Such densely functionalized adducts could serve as chiral building blocks useful for access to a large variety of target molecules possessing biological/pharmacological activity. Further investigations in this area, including the study of the reactivity of imine **13** toward β-substituted Michael acceptors,[1n] are in progress.

Supporting Information Available: Preparation procedures and characterization data for **14**, **16**, **18**, and **20**−**22**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0491944